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Solvent Effects on Displacement of Fluoride Ion from Isopropyl Methylphosphonofluoridate

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Abstract: Studies have been made on the rate of displacement of fluoride ion from isopropyl methylphosphonofluoridate (I) by oxygen nucleophiles in dipolar aprotic solvents and methanol. (Comparable data in aqueous solution are available.) In dipolar aprotic solvents the reaction between a nucleophile which forms a stable phosphonylated product and I can be written as simple equilibrium: $I + A \rightleftharpoons \text{ester} + F^-$. The equilibrium lies far to the left if the anion is *m*- or *p*-nitrophenolate or 4-nitrocatecholate and only slightly to the right with an anion as basic as phenolate. Displacement of fluoride ion is mediated by the addition of a proton donor such as the conjugate acid of the nucleophile or a protic solvent. The reaction is termolecular, involving the attacking anion, a proton donor, and I, and the termolecular rate constant is related to the strength of the proton donor (acidity of the solvent or conjugate acid). In aqueous medium, water is a proton donor in displacement of fluoride ion from I by nucleophiles which form stable phosphonylated products; with nucleophiles such as the anion of benzhydroxamic acid, water not only provides a proton but also serves to provide an ionizing medium for the transition state. Fluoride ion is a potent nucleophile for formation of I from phosphorus esters; the cation associated with the fluoride has a marked effect on the rate of formation of I.

In aqueous solution, P–F splitting in isopropyl methylphosphonofluoridate (I) by reaction with oxygen anions such as phenolates, catecholates, pyrogallates, anions of hydrated aldehydes, keto oximes, and hydroxamic acids occurs by nucleophilic attack on the phosphorus atom and results in the formation of phosphonylated esters of varying hydrolytic stability. Phosphonylated phenols are relatively stable, reacting only slowly with water to produce isopropyl methylphosphonic acid and the corresponding phenolate anion. The phosphonylated monocatecholate ion is also hydrolytically stable; it, however, decomposes slowly *via* an intramolecular mechanism to isopropyl alcohol and catechol methylphosphonate.[1]

Phosphonylated hydrated aldehydes, keto oximes, and hydroxamic acids are unstable; the first hydrolyzes very rapidly to isopropyl methylphosphonic acid, regenerating the hydrated aldehyde,[2] whereas the latter two undergo Beckmann or Lossen type rearrangements.[3,4] The rate of reaction of I with phenols,[5] catechols,[6,7] pyrogallols,[7] keto oximes,[4,8] hydrated aldehydes,[8] and hydroxamic acids[9–12] can be expressed as a simple bimolecular displacement, *i.e.*

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(1) T. Higuchi, personal communication.

(2) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 368 (1961).

(3) R. Swidler and G. M. Steinberg, *J. Amer. Chem. Soc.*, **78**, 3594 (1956).

(4) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

(5) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964).

(6) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *ibid.*, **78**, 341 (1956).

(7) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, R. A. Stephani, and E. Cook, *ibid.*, **86**, 4959 (1964).

(8) J. Epstein, P. L. Cannon, Jr., H. O. Michel, B. E. Hackley, Jr., and W. A. Mosher, *ibid.*, **89**, 2937 (1967).

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(10) R. Swidler and G. M. Steinberg, *ibid.*, **78**, 3594 (1956).

(11) M. A. Stolberg and W. A. Mosher, *ibid.*, **79**, 2618 (1957).

(12) (a) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958); (b) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959); (c) R. Swidler, R. E. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959).

$$-\frac{d[I]}{dt} = k_2[A^-][I]$$

where $[A^-]$ is the concentration of the anion (monoanion in the case of catechols, pyrogallols, and hydrated aldehydes).

For each class of reactant, a linear free energy equation, $\log k_2 = \alpha pK_a + C$, where K_a is the ionization constant of the conjugate acid of the reactive anion, adequately describes the relation between the rate and the proton basicity of the nucleophile.

The slopes and intercepts for several classes of nucleophiles are given in Table I. The positive α values indicate that the ease of displacement of fluoride ion from I in aqueous solution by oxyanions is related to the proton basicity of the nucleophile. However, the importance of basicity varies with the class of nucleophile, and basicity is not the only factor of importance. There are large differences in rates among nucleophiles of different classes of the same basicity. (Compare, for example, the bimolecular rate constants of the anion of a phenol and the anions of a pyrogallol and a hydroxamic acid of the same basicity; Table I, column 4.) Also, it has been found that cation-bearing phenolates, catecholates, and pyrogallates are as reactive in displacing fluoride from I as their noncationic counterparts, although the former have much lower basicities.[5,7]

Table I. Slopes (α) and Intercepts (C) in Displacement Reactions of Isopropyl Methylphosphonofluoridate in Aqueous Solution

Nucleophile (conjugate bases)	α	C	Log k_2 for pK_a = 9 (temp, °C)
Hydrated aldehydes	0.46	−2.95	1.15 (25)
Phenols	0.59	−4.17	1.13 (25)
Keto oximes	0.64	−3.25	2.53 (30)
Pyrogallols	0.76	−3.70	3.12 (25)
Catechols	0.81	−4.88	2.38 (25)
Hydroxamic acids	0.80	−3.87	3.35 (30)

The higher reactivities of the anions of hydroxamic acid over those of the phenolates of like basic strengths have been attributed to the "α" effect,[13] an explanation which, however, cannot be used to explain the disparity in reactivities among phenols, catechols, and pyrogallols. The differences found among the hydroxybenzenes are presumed to be due to the presence of undissociated *o*-hydroxy groups which can hydrogen bond to the phosphonyl oxygen (or fluorine), thus facilitating bond formation in the transition state.

In contrast to oxygen nucleophiles, amines are general base catalysts in the hydrolysis of I. Also, monoprotonated diamines (charged amines) or hydrazine (an α-amine) is not significantly better than uncharged or non-α primary amines of like basicity as hydrolysis catalysts.[14]

From these and other studies in displacement rates, several investigators[15–17] have summarized the important factors in nucleophilicity in displacement reactions on phosphorus esters. Although it is stated that alteration of the solvent can affect the order of nucleophilic reactivity, the role of water in these reactions is not clearly defined. In this connection, the hydrolysis rate of dialkyl phosphorofluoridates is acid catalyzed,[18] and it has been postulated that the acid-catalyzed hydrolysis involves a simultaneous push on the phosphorus atom by a water molecule and a pull on the fluorine by a hydronium ion.[19] Extending this concept, one can visualize water as the proton donor in the reaction of I with anions in aqueous medium. On the other hand, it has been observed that "bimolecular reactions between anions and uncharged species are often much faster in dipolar than in protic solvents."[20] It was thought that a better understanding of the role of water in displacement of fluoride ion from I could be obtained from studies on the rates of displacement by anions in dipolar aprotic and other protic solvents.

Studies on displacement rates of I by nucleophiles (or other fluorinated phosphorus esters) in nonaqueous protic or aprotic solvents are meager, but some understanding of the nature of the P–F bond and its stability in nonaqueous media can be gained from the studies of Dostrovsky and Halmann.[21] The order of displacement of chloride from diisopropyl phosphorochloridate (DCIP) by anionic reagents in ethanol solution was found to be $F^- > EtO^- > PhO^- > EtOH > PhS^- > CH_3C(=O)O^-$. The fluoride ion reaction was observed to be about six times slower in 60% ethanol than in dry ethanol, which led to the conclusion that the charge is more highly dispersed in the bipyramidal transition state than in the reactants.[21] Also, from the fact that diisopropyl phosphorofluoridate reacts more slowly than its chlorine analog, it was concluded that "the bond between the halogen and phosphorus is involved in the transition state."

A basic difference between the P–F and P–Cl bonds is found in the reactions of phosphonofluoridates and -chloridates with amines in nonaqueous media. In acetonitrile, it was found in this laboratory that there was no discernible reaction of I with 1 *M* β-phenylethylamine over a period of 18 hr at 25°, whereas amines were found to react with comparative ease with phosphorochloridates.[21] Greenhalgh and Weinberger[22] report that in the reaction of I with ethanolamine in chloroform only the oxygen-phosphonylated product is formed; with the chlorine analog of I under the same conditions about 90% of the product yield is the nitrogen-phosphonylated compound.

In this paper, we report our studies on the anionic displacement of fluoride ion in aprotic solvents and in methanol, of acid catalysis in nonaqueous media and of nucleophilicity of F^- in various solvents.

Results

1. Reactions of Anions and I in Aprotic Solvents. (a) Bimolecular Rate Constants in Dimethylform-

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

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[15] J. O. Edwards, "Inorganic Reaction Mechanisms," W. A. Benjamin, New York, N. Y., 1964, pp 68 ff.

[16] R. F. Hudson, *Chimia*, **16**, 173 (1962).

[17] J. F. Bunnett, *Annu. Rev. Phys. Chem.*, **14**, 271 (1963).

[18] See, *e.g.*, W. A. Waters and C. G. M. de Worms, *J. Chem. Soc.*, 926 (1949); M. Kilpatrick and M. Kilpatrick, *J. Phys. Colloid Chem.*, 53, 1371, 1385 (1949). Also, the solvolysis of various alkyl and benzyl fluorides is acid catalyzed; see W. T. Miller, Jr., and J. Bernstein, *J. Amer. Chem. Soc.*, 70, 3600 (1948); N. B. Chapman and J. L. Levy, *J. Chem. Soc.*, 1673 (1952).

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[21] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 1004 (1956).

[22] R. Greenhalgh and M. A. Weinberger, *Can. J. Chem.*, **45**, 495 (1967).

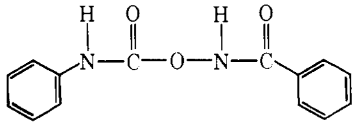
Table II. Reaction Rates of I with Benzhydroxamate, Phenolate, and Biacetyl Monooximate Anions in Different Solvents at 25°

Solvent[a]	Anion	Concn range, M	k_2, M^{-1} sec^{-1}	No. of runs
Dimethylformamide (26.6)	Benzhydroxamate	0.05–0.100	$(1.2 \pm 0.2) \times 10^{-3}$	3
Dimethyl sulfoxide (47)	Benzhydroxamate	0.05–0.100	$(3.2 \pm 0.2) \times 10^{-3}$	2
Acetonitrile (36)	Benzhydroxamate	0.025–0.100	$(4.3 \pm 0.7) \times 10^{-3}$	3
	Phenolate	0.002–0.003	0.19[b]	5
Acetone (21)	Benzhydroxamate	0.05–0.100	$(2.03 \pm 0.13) \times 10^{-3}$	3
Nitromethane (38.6)	Benzhydroxamate	0.05–0.10	$(1.50 \pm 0.04) \times 10^{-2}$	3
	Biacetyl monooximate	0.02–0.04	$(5.02 \pm 0.54) \times 10^{-2}$	3

[a] Dielectric constant in parentheses. [b] Determined from k_2 of reaction between F^- and phenolate ester of isopropyl methylphosphonic acid and equilibrium constant calculated from equilibrium concentrations of products and reactants. This value is considered to be only an approximate value.

amide, Dimethyl Sulfoxide, Acetonitrile, Acetone, and Nitromethane. Bimolecular rate constants of the reaction of I with (a) benzhydroxamate[23] anion in five aprotic solvents, (b) biacetyl monooximate in nitromethane, and (c) phenol anion in acetonitrile are shown in Table II. No significant reaction between nitrocatecholate anion and I, *p*-nitrophenolate anion and I, or *m*-nitrophenolate anion and I,[24] involving formation of the esters, could be found in these solvents. The rate constant of the reaction of phenolate ion with I was calculated from the bimolecular rate constant for the displacement of the phenolate group from the phenolate ester of isopropyl methylphosphonic acid by fluoride ion ($k_2 = (4.0 \pm 1.8) \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$) and the equilibrium constant determined from the equilibrium concentrations of the reactants and products ($K = 4.9 \pm 0.8$).

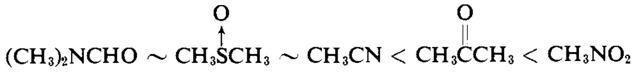
The reaction between benzhydroxamate anion and I produced IV, which results from a reaction of the rearrangement product of the phosphonylated benzhydroxamic acid and unreacted benzhydroxamic acid.



IV

It appears that to produce stable phosphonylated products from I in aprotic solvents, the attacking anion must have a basicity of the order of that of the phenolate anion: displacement reactions occurring in a mixture of I with phenolates or catecholates of lower basicity are due most probably to traces of water or hydroxide ion.

The data in Table II are arranged in what is assumed to be increasing acidity of the solvent,[25] *i.e.*



$$(CH_3)_2NCHO \sim CH_3\overset{O}{\overset{\uparrow}{S}}CH_3 \sim CH_3CN < CH_3\overset{O}{\overset{\|}{C}}CH_3 < CH_3NO_2$$

and show an increasing rate constant as the acidity of the solvent increases. On the other hand, there appears to be no relationship between the dielectric constant of the solvent and the bimolecular rate constant of the reaction between benzhydroxamate ion and I (dielectric constants are given in parentheses in Table II).

(b) Acid Catalysis in Aprotic Solvents. The observation of the effect of solvent acidity on the reaction rate suggested a study to determine the effect of addition of the conjugate acid of the reactive anion on the displacement rate of F^- from I in an aprotic solvent. Tables III and IV contain the data of runs made on the

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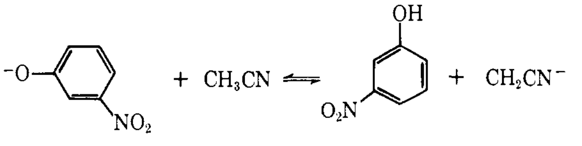
(23) The values of bimolecular rate constants of the benzhydroxamate–I reaction in Table II are based on the rate of formation of fluoride ion. The rate of subsequent reaction involving the rearranged product and the benzhydroxamate anion was not determined.

(24) Very comprehensive studies were made of this reaction in acetonitrile because initial results using the rate of fluoride ion appearance to determine the rate of the reaction between the anion and I gave a bimolecular rate constant of $1.2 \times 10^{-3}\ M^{-1}$ sec^{-1} *with theoretical quantities* of fluoride ion being produced. However, the rate constant for the reverse reaction was found to be ~35 M^{-1} sec^{-1} (see Table X). If a simple equilibrium was assumed, then, under the experimental conditions used, a theoretical yield of fluoride ion was inconsistent with the quantities predicted from the rate data. Subsequent nmr studies showed no formation of the *m*-nitrophenolate ester of isopropyl methylphosphonic acid; the only product found (proceeding from either reaction direction) by nmr and gas chromatographic techniques was isopropyl methylphosphonate anion, which could have been formed by water or hydroxide ion attack on I. Attack by water or hydroxide ion was also qualitatively consistent with the rates found for the reactions between the *m*-nitrocatecholate and *m*- and *p*-nitrophenolate ions with I in several aprotic solvents (*i.e.*, the rate increased in the order nitrocatecholate < *p*-nitrophenolate < *m*-nitrophenolate) if one assumes that hydroxide ion is formed in the equilibrium $A^- + H_2O \rightleftharpoons OH^- + HA$, where A^- is the *m*-nitrocatecholate or *m*- or *p*-nitrophenolate anion. Obviously, the equilibrium constant (and hence equilibrium concentration of the hydroxide ion) will increase with increasing proton basicity of A^-. However, the explanation involving water or hydroxide ion is not completely satisfactory in view of the following.

First, analysis of the H_2O content of the reaction mixture showed that the water content was less than 0.001%. This quantity of water is insufficient to decompose 25% of the GB in the sample, let alone 100%. Also the reaction rate, after passing the reaction mixture through a molecular sieve to remove water, was the same as that attained prior to passage through the sieve. Moreover, if the reaction were with OH^-, then other phenols of the same proton basicity but sterically hindered for reaction with I (1), would be expected to give similar rate data. Tests with the sterically hindered anion of 2,6-dimethyl-4-acetylphenol, $pK_a = 8.2$ [A. Fischer, *et al.*, *J. Chem. Soc. B*, 782 (1966)] showed that the rate was only 0.1 to 0.2 that of *m*-nitrophenolate anion.

It was also considered possible that the destruction of I was due to a reaction with the solvent anion, which could be formed in small quantities *via* the equilibrium



but the proposed product of the reaction, *viz.*, cyanomethylisopropyl methylphosphonate could not be isolated from the reaction mixture. Negative tests were also obtained for *m*-nitrofluorobenzene, eliminating a mechanism of decomposition of I involving displacement of phenolic oxygen by fluoride (see, *e.g.*, A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1961, pp 184–204).

(25) The order is based upon the ionization constants of the solvents (or closely related solvents) in water as determined by R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, 75, 2439 (1953). These are: CH_3NO_2, $pK_a \sim 10$; $(CH_3)_2C{=}O$, $pK_a \sim 20$; $(CH_3)_2SO_2$, $pK_a \sim 23$; and CH_3CN and $CH_3C({=}O)NH_2$, $pK_a \sim 25$. It is recognized that acidities determined in water may not be an accurate reflection of the acidities in the systems studied.

Table III. Acid Catalysis in Nitromethane by Benzhydroxamic Acid in the Reaction of Benzhydroxamate Anion with I at 25°

Run no.	[Benzhydroxamate], *M*	[Benzhydroxamic acid], *M*	k_{obsd}, sec^{-1}
1	0.0500		7.5×10^{-4}
2	0.0500	0.00502	1.9×10^{-3}
3	0.0500	0.0100	2.79×10^{-3}
4	0.0500	0.0201	4.84×10^{-3}
5	0.0500	0.0501	1.08×10^{-2}
6	0.0203	0.0101	1.21×10^{-3}

Table IV. Acid Catalysis in Acetonitrile by Benzhydroxamic Acid in the Reaction of Benzhydroxamate Anion with I at 25°

Run no.	[Benzhydroxamate], *M*	[Benzhydroxamic acid], *M*	k_{obsd}, sec^{-1}
1	0.0250		1.38×10^{-4}
2	0.0496		1.91×10^{-3}
3	0.1000		3.85×10^{-3}
4	0.0250	0.00502	1.60×10^{-3}
5	0.0250	0.0100	2.25×10^{-3}
6	0.0250	0.0251	3.59×10^{-3}
7	0.0250	0.0500	5.46×10^{-3}

reaction of I with benzhydroxamate anion in nitromethane and acetonitrile to which had been added varying quantities of benzhydroxamic acid.

In nitromethane, the data are consistent with the interpretation that two simultaneously occurring reactions take place whose overall rate describing the destruction of I can be written as

$$-\frac{d[I]}{dt} = k_2[A^-][I] + k_3[A^-][I][HA]$$

The value of k_2, the bimolecular rate constant of the reaction between the anion and I, is 1.5×10^{-2} M^{-1} sec^{-1} (see Table II); k_3, a termolecular constant, is 4.0 M^{-2} sec^{-1}. The latter value is calculated from the experimentally determined first-order rate constant, k_{obsd} (obtained from a plot of the logarithm of I remaining *vs.* time) and the relationship $k_{\text{obsd}} = k_2[A^-] + k_3[A^-][HA]$. It is obvious that, in this case, acid catalysis contributes significantly to the overall rate (approximately 20%) even when the acid concentration is as low as 1×10^{-3} *M;* with acid concentration 5×10^{-3} *M*, the acid-catalyzed reaction is dominant.

In acetonitrile, while the data indicate the existence of an acid-catalyzed reaction, a plot of $k_{\text{obsd}}/[A^-]$ *vs.* [HA] is approximately linear with a slope of 3.0 only between the acid concentrations of 0.01 and 0.05. Extrapolation of the linear portion to zero acid concentration gives a higher value for the bimolecular rate constant of hydroxamate ion with I than is experimentally determined.

2. Reaction of I with Anions in Methanol. (a) ***m*- and *p*-Nitrophenolate.** In methanol alone, there is no or a negligible reaction between I and the alcohol; in methanol containing the anions of *m*- or *p*-nitrophenols but no added *m*- or *p*-nitrophenol, I is converted almost entirely to the methyl ester of isopropyl methylphosphonic acid. In methanol containing the anion and the acid form of *m*-nitrophenol, only 44% of the initial amount of I is converted to the methyl isopropyl methylphosphonate. It is assumed that the remainder of I is converted to the *m*-nitrophenolate ester whose identity in the reaction mixture was established by gas chromatographic techniques. The data are summarized in Table V.

Table V. Product Analysis of Reaction of Two Anions with I in Methanol

Nucleophile	[Anion], *M*	[Conjugate acid], *M*	% of I^a found as methyl isopropyl methylphosphonate
m-Nitrophenolate	0.020		88.0
m-Nitrophenolate	0.050	0.050	44.4
p-Nitrophenolate	0.100		75.4

^{a} Analysis ±10%.

Table VI. Bimolecular Rate Constant for Reaction of Methoxide Ion with I

μ	pK_B^{a}	B/BH$^+$	[OCH$_3^-$], $M \times 10^6$	k_0, sec^{-1} $\times 10^4$	k_2, M^{-1} sec^{-1}
0.0200	5.56	3.958	11.0	3.82	34.7
0.0200	5.56	1.979	5.50	2.24	40.7
0.0100	5.72	1.979	3.80	1.72	45.3
0.00735	5.78	1.816	3.57	1.45	40.6
0.00735	5.78	1.816	3.57	1.45	40.3
				Av	40.3 ± 2.3

^{a} $pK_B = pK_B' - 4.0\sqrt{\mu}$; $pK_B' = 6.12$.

Table VII

Run no.	[Anion], *M*	[Conjugate acid], *M*	k_{obsd}, sec^{-1}
(a) Reaction of *m*-Nitrophenolate Anion with I in CH$_3$OH			
1	0.00205		2.92×10^{-3}
2	0.00215		2.92×10^{-3}
3	0.0255		3.70×10^{-3}
4	0.0260		4.88×10^{-3}
5	0.0508		3.37×10^{-3}
6	0.0504	0.0522	1.93×10^{-3}
7	0.1004	0.1004	3.13×10^{-3}
(b) Reaction of *p*-Nitrophenolate Anion with I in CH$_3$OH			
1	0.1008		2.41×10^{-2}
2	0.0501	0.0503	2.48×10^{-4}
3	0.1001	0.1001	4.01×10^{-4}

The bimolecular rate constant for the reaction between I and methoxide ion in methanol was determined in separate experiments to be 40.3 ± 2.3 M^{-1} sec^{-1} (Table VI). From this value and the values of the first-order rate constants for the reaction between I and *m*- and *p*-nitrophenolate anions in the presence of their conjugate acids (Table VIIa, runs 6 and 7; Table VIIb, runs 2 and 3) as well as an estimate of the methoxide concentration under the experimental conditions of Table VII using the equation

$$[OCH_3^-] = (K_{\text{met}}/K_a)([A^-]/[HA])$$

where K_{met}, the ion product of methanol in methanol, is 1.95×10^{-17} [26] and K_a, the ionization constant of the

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(26) E. J. King, "The International Encyclopedia of Physical Chemistry and Chemical Physics," Vol. 4, "Acid Base Equilibria," Pergamon Press, New York, N. Y., 1965.

Table VIII. Reaction of Benzhydroxamate Anion with I in CH_3OH at 25°

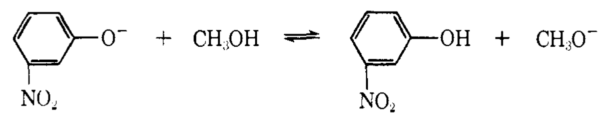
Run no.	[Anion], M	[Conjugate acid], M	k_0, sec^{-1}
1	0.001055		7.34×10^{-3}
2	0.001055		7.94×10^{-3}
3	0.01124		16.85×10^{-3}
4	4.03×10^{-3}	0.200	3.22×10^{-3}
5	2.00×10^{-3}	0.200	1.85×10^{-3}
6	2.01×10^{-3}	0.100	2.03×10^{-3}

conjugate acid in methanol, was experimentally determined to be 6.76×10^{-13} for m-nitrophenol and 6.46×10^{-12} for p-nitrophenol, the bimolecular rate constants[27] for the reaction of I with m- and p-nitrophenolate anions in methanol are calculated to be $(1.80 \pm 0.17) \times 10^{-2}$ M^{-1} sec^{-1} and $(2.65 \pm 0.14) \times 10^{-3}$ M^{-1} sec^{-1}, respectively.

Using the calculated bimolecular rate constants, one would predict that 55% of I would be converted to the methyl ester in run 2 of Table V, a value in reasonable agreement with the found 44%.

First-order plots of runs 1–5, Table VIIa, and run 1, Table VIIb, showed a slight curvature with a steady decline in the observed rate, whereas such plots were linear for those runs in which conjugate acid was added. (The first-order constants reported in Table VII were calculated from the initial slopes.)

These observations are consistent with displacement by methoxide ion being the primary course of the reaction. The curvature of the plots of runs 1–5, with a concomitant decrease in the observed rate, is due to the formation of m-nitrophenol, which represses methoxide formation in the equilibrium



Since initial concentrations of methoxide ion are higher in unbuffered than buffered solutions, higher first-order rates are observed in the absence of conjugate acid than in its presence, especially at low conjugate acid concentrations (*cf.* Table VIIa, run 6, with runs 3 and 4).

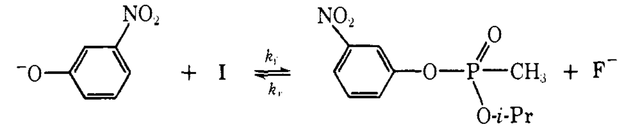
(b) Benzhydroxamate. Table VIII contains data on the observed first-order rates of reaction of I with benzhydroxamate anion alone and with added conjugate acid. As previously, using an experimentally determined pK_a for benzhydroxamic acid in methanol of 12.97, the bimolecular rate constant for the benzhydroxamate ion–I reaction in methanol is calculated to be 0.86 ± 0.07 M^{-1} sec^{-1}.

Table IX. Rate and Equilibrium Constants for Reaction of I with m-Nitrophenolate Anion in H_2O, MeOH, and CH_3CN at 25°

Solvent	k_f, M^{-1} sec^{-1}	k_r, M^{-1} sec^{-1}	K_R	K_E
H_2O	0.255	$(2.90 \pm 0.01)^b \times 10^{-3}$	88	96.8 ± 11.8
CH_3OH	0.018 ± 0.0017^a	$(8.84 \pm 0.28)^a \times 10^{-3}$	2	
CH_3CN	$<0.01^d$	33.4 ± 1.5^c		$<3 \times 10^{-4}$

[a] Two determinations. [b] Five determinations. [c] Seven determinations. [d] See text for explanation of how this value was obtained.

3. Equilibria and Rate Studies of the Reaction of m-Nitrophenolate Anion and I in Water, Methanol, and Acetonitrile. Cationic Effects in Acetonitrile. Table IX gives the bimolecular rate constants for the forward (k_f) and reverse (k_r) reactions, the equilibrium constants calculated from the rate constants (K_R), and the equilibrium constants calculated from the experimentally measured concentrations of products and reactants at equilibrium (K_E) for the reaction



NIMP

The value of k_f in water is from ref 5; the value of k_f in acetonitrile was estimated from the value of k_r and K_E estimated from data on (a) the equilibrium concentration of F^- in a mixture initially 0.002 M with respect to F^- and NIMP and (b) the quantity of I isolated from an equilibrium mixture initially 0.02 M with respect to F^- and NIMP. The value k_r in acetonitrile was found to be highly dependent upon the nature and concentration of the cation associated with the attacking nucleophile. Table X gives the results of studies on the rate of displacement of the m-nitrophenolate group of NIMP by fluoride ion, where the cations were tetraethyl- and tetrabutylammonium. The value shown in Table IX is an average of the seven experiments at low concentration of cation ($\leq 10^4$ M).

Discussion

1. General. Reactions of anions in aprotic solvents are often difficult to interpret because of interactions among the anions with solvents, their cations, and their conjugate acids. Tetraalkylammonium salts were chosen for these studies because they are less likely to form ion pairs in dipolar aprotic solvents than are alkali metal salts. Tetrabutylammonium salts, for example, are strong electrolytes in acetonitrile.[28]

However, it has also been amply demonstrated that homoconjugative associations take place readily in acetonitrile.[29] The nonlinearity observed in the plot of $k_{obsd}/[A^-]$ *vs.* [HA] (Table IV) for the reaction of the

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(27) The reaction is most probably termolecular, involving I, the anion, and conjugate acid or solvent molecules (or both) as proton donors to the fluorine. The participation of the conjugate acid was considered to be small as compared with solvent molecules on the following bases. First, correction for the methoxide contribution to the first-order rate gave values which indicated that there was a first-order dependency on one of the reactants (*i.e.*, either the anion or conjugate acid) and a zero-order dependency on the other. Secondly, as will become evident from the analysis in the discussion of this report, the termolecular rate constant would be expected to increase less than two orders of magnitude with a change of acidity of the proton donor of 6 pK_a units (12.17 for m-nitrophenolate and 18.1 for methanol), whereas the ratio of concentration of methanol to m-nitrophenol was between 10^2 and 10^3. Since the contribution to the overall rate is due to the product of the termolecular rate constant and the concentration of the proton donor, the major contribution will be due to methanol.

(28) J. F. Coetzee and G. P. Cunningham, *J. Amer. Chem. Soc.*, **87**, 2529 (1965).

(29) J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).

Table X. Data on the Rate of Reaction between F^- and NIMP in CH_3CN at 25°

Run no.	No. of runs	Ester concn range, *M*	F^- concn range, *M*	Cation[a]	k_2, M^{-1} sec^{-1}
1	4	$(1.94–3.88) \times 10^{-4}$	$4.2–8.2) \times 10^{-5}$	$(C_2H_5)_4N^+$	33.5 ± 1.8
2	1	3.90×10^{-5}	1.72×10^{-4}	$(C_2H_5)_4N^+$	33.3
3	2	5.82×10^{-5}	4.11×10^{-4}	$(C_2H_5)_4N^+$	39.9 ± 2.2
4	3	2.06×10^{-4}	4.02×10^{-3}	$(C_2H_5)_4N^+$	41.6 ± 3.6
5	3	2.06×10^{-4}	1.00×10^{-2}	$(C_2H_5)_4N^+$	74.4 ± 5.1
6	2	2.06×10^{-4}	8.0×10^{-3}	$(C_4H_9)_4N^+$	526.3 ± 1.7
7	1	2.06×10^{-4}	8.0×10^{-2}	$(C_4H_9)_4N^+$	851.4

[a] Concentration of cation the same as concentration of F^-.

benzhydroxamate ion and I in acetonitrile might be due to an incorrect assumption that the added concentrations are the concentrations actually present in solution. There are no published homoconjugation data of benzhydroxamate anion with its conjugate acid in acetonitrile. However, if a formation constant of 10–10^2 is assumed[30] and is used to calculate the concentrations of A^- and HA in the runs shown in Table IV (assuming the anion–conjugate acid species is inactive), then the plot is much more linear, with the value of the intercept approaching much more closely the experimentally determined bimolecular rate constant.

It is also thought probable that homoconjugation of the benzhydroxamate anion with its conjugate acid in nitromethane is much less than that in acetonitrile (and hence can be neglected) owing to the competition for the anion provided by the solvent.[31]

2. Comparison of Rates of Reaction of I in Aprotic Solvents and Water. Role of Water in Nucleophilic Displacement of I. The demonstrated acid catalysis of hydroxamic acid in the displacement of fluoride ion by hydroxamate anion suggests the possibility that, in aqueous media, water acts as an acid catalyst in a termolecular reaction involving an anion and I. If this is the mechanism, then it might be expected that the termolecular rate constant would be related to the pK_a's of the conjugate acids or proton-donating solvents. Termolecular rate constants for the reaction of I, benzhydroxamate anion, and (a) H_2O, (b) CH_3OH, (c) benzhydroxamic acid, and (d) CH_3CN were therefore calculated or estimated from available data and the equation

$$k_3 = k_2/[\text{acid}]$$

where [acid] refers to the solvent or benzhydroxamic acid concentrations. For the reaction between benzhydroxamate anion and I in water, k_3, calculated from a previously determined bimolecular rate constant of 17 M^{-1} sec^{-1},[12a] is *ca.* 0.3 M^{-2} sec^{-1}. For the reaction in methanol, k_3 = 0.3 M^{-2} sec^{-1} (calculated from k_2 = 0.86 M^{-1} sec^{-1}). The termolecular constant for the reaction of I with benzhydroxamate anion and benzhydroxamic acid (in nitromethane solvent) was found to be 4.0 M^{-2} sec^{-1} (Table III). For the reaction in acetonitrile, $k_3 = 2 \times 10^{-4}$ M^{-2} sec^{-1} (calculated from $k_2 = 3.6 \times 10^{-3}$, Table II).

The pK_a's of benzhydroxamic acid in nitromethane,[32] water in water, methanol in methanol,[26] and acetonitrile in acetonitrile[33] are *ca.* 11, 15.75, 18, and 27.2, respectively.

A plot of the pK_a *vs.* the log of the termolecular rate constant is shown in Figure 1. The approximate equation for the solid line[34] is log k_3 = $-0.28\text{p}K_a + 3.8$. The plot shows the role of an acid in displacement reactions of I by benzhydroxamate ion; the relatively small negative-slope value shows that the sensitivity of the reaction to acidic components is not very high and that the rate will increase with increasing acidity of the proton donor. Points are also shown on the graph of the k_3 values and the pK_a's of the solvent molecules for the reaction of *m*-nitrophenolate anion and I. A line (dotted) connecting the two points produces a slope close in magnitude to that obtained using benzhydroxamate anion data, and suggests that there will be similar sensitivities to acids in reactions of dissimilar anions with I.

These data support the postulate that one role of water is as an acid catalyst in displacement reactions of I by anions. However, there appears to be a second role attributable to water which is discussed below.

Reactions of Anions in Methanol. The bimolecular rate constants for the reaction of I with various anions in methanol and the pK_a's of their conjugates in methanol are shown in Table XI. A semilog plot of the bimolecular rate constants of the reactions of I with *m*- and *p*-nitrophenolate, benzhydroxamate, and methoxide ions *vs.* the pK_a's of the respective conjugate

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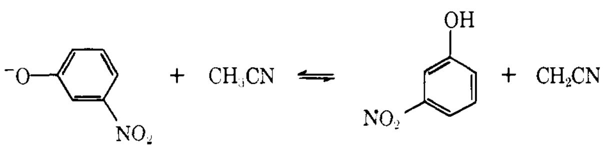
(30) A value of 10–10^2 appears reasonable since O. Exner and B. Kakač, *Collect. Czech. Chem. Commun.*, **28**, 1656 (1963), have concluded from infrared studies of benzhydroxamic acid and its alkyl derivatives in dioxane solution that the anion exists in the form



Such a structure could be expected to exhibit significantly less homoconjugation than, for example, phenol and its meta and para derivatives due to internal hydrogen bonding, and perhaps a homoconjugation tendency similar to that of an ortho-substituted phenol such as *o*-nitrophenol. The formation constants for the homoconjugative complexes of phenol, *p*-nitrophenol, and *o*-nitrophenol in acetonitrile are approximately 10^6, 10^5, and 10^2, respectively: J. F. Coetzee and G. R. Padmanabhan, *J. Phys. Chem.*, **69**, 3193 (1965). The lower value of the constant for *o*-nitrophenol, relative to the other phenols, has been attributed to intramolecular hydrogen binding

(31) Although in classification of dipolar aprotic solvents acetonitrile and nitromethane are grouped together, nitromethane is considered to be one of the less dipolar aprotic solvents (see ref 20).

(32) To our knowledge, the acidity of benzhydroxamic acid in nitromethane has not been measured; an estimate of the pK_a based upon the difference in dielectric constants of H_2O (78.5) and CH_3NO_2 (38.6) would be between 10 and 11.

(33) J. F. Coetzee, *Progr. Phys. Org. Chem.*, 4, 55 (1967).

(34) It is difficult to fully rationalize the existence of this correlation, since it is not corrected by inclusion of appropriate activity coefficients. Unfortunately, these are not available. The form of the correlation after choice of a standard state would be

$$\log k^{\text{s}} = \alpha \log \text{p}K_{\text{a}}^{\text{s}} + \left(\log \frac{\gamma_{\text{n}}^{\text{s}}\gamma_{\text{n}}^{\text{s}}\gamma_{\text{HA}}^{\text{r}}}{\gamma_{\text{s}}^{\text{s}}} - \log \frac{\gamma_{\text{H}^+}^{\text{s}}\gamma_{\text{A}^-}^{\text{s}}}{\gamma_{\text{HA}}^{\text{s}}}\right) + C$$

In order for the relationship to hold precisely, the term in brackets would have to vanish.

Table XI. Bimolecular Rate Constants of Reaction of I with Various Anions in Methanol and pK_a's of Conjugate Acids at 25°

Anion	pK_a	k_2, M^{-1} sec^{-1}
p-$NO_2C_6H_4O^-$	11.19	2.65×10^{-3}
m-$NO_2C_6H_4O^-$	12.17	1.80×10^{-2}
$PhC(=O)NHO^-$	12.97	0.86
OCH_3	18.1	40.3

acids in methanol shows that a reasonably good line of slope 0.57 can be drawn using the *m*- and *p*-phenolate and methoxide values.[35] The slope is close to the 0.59 value observed for reaction of phenolates with I in aqueous solution.[5]

The reaction of benzhydroxamate ion is about one order of magnitude higher than would be anticipated from its pK_a.

From the plot, it could be predicted that the bimolecular rate constant of the phenolate anion (pK_a = 14.1[36]) and I in methanol is 0.18 M^{-1} sec^{-1}.

The ratios of the reactivities of the benzhydroxamate to the phenolate ion in water, methanol, and acetonitrile are approximately 60:5:0.02. Since the susceptibility of the displacement rate to the acidity of the solvents appears to be similar for the two ions, it is tempting to speculate that the differences among the ratios of the reactivities in different solvents are due to solvent effects rather than to acidity. The ratios decrease as the "ionizing power" of the solvent decreases.[37] At least qualitatively, they parallel the relative rates of solvolysis of *p*-methoxyneophyl *p*-toluenesulfonate in the three solvents (39:0.9:0.03), which suggests that an ionization is involved in the transition state of the benzhydroxamate–I interaction. Thus, it appears that solvent water can play a dual role in displacement reactions of I: as an acid catalyst and to provide a medium for ionization of the transition-state intermediate. The latter action facilitates bond formation between the phosphorus and the oxygen of the attacking anion. It is thought that the high reactivity of hydroxamate anions and other "α" nucleophiles such as the anions of isonitroso ketones and hypochlorous acid in aqueous solution can be explained on this basis.

Nucleophilicity of Fluoride Ions. Effect of Cation on the Nucleophilicity of F$^-$. The activity of F$^-$ increases with decreasing hydrogen-bonding ability of the solvent; F$^-$ is about 10^4 times as active in displacement of the *m*-nitrophenolate group from NIMP in acetonitrile as in water. A reasonable explanation for this fact is that F$^-$ is much more highly solvated in the protic solvents and an additional input of energy is required to dissociate the water (or methanol molecule) for the displacement to take place.

However, a significant difference in rates in acetonitrile is found, depending upon the concentration and nature of the cations added with the F$^-$, which cannot be rationalized by an explanation such as solvation of the fluoride ion. *Higher* rates are found with *higher* concentrations of the cationic species; a greater amount of ion pairing, which is to be expected with higher salt concentrations, should result in lower bimolecular rate constants. This suggests that there could be involvement of the cation in the formation and stabilization of the transition state. Further studies on cationic effects in polar solvent systems are planned.

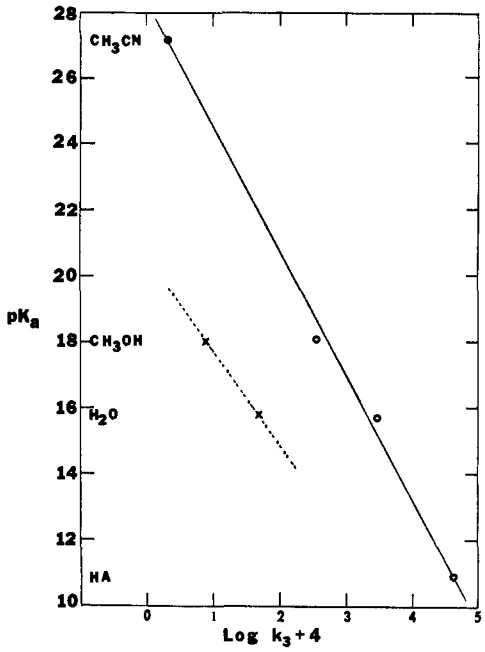
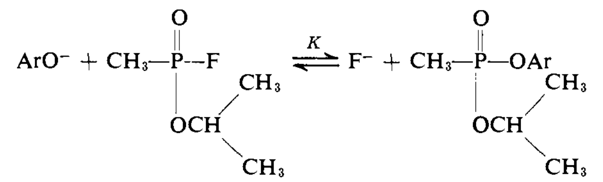


Figure 1. Plot of the logarithm of the termolecular rate constants of the reaction of I *vs.* pK_a of the solvent: ○, with hydroxamate anion; ×, with *m*-nitrophenolate.

Values of the equilibrium constant for the reaction



$$ArO^- + CH_3-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH(CH_3)_2}{|}}{P}}-F \xrightleftharpoons{K} F^- + CH_3-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH(CH_3)_2}{|}}{P}}-OAr$$

can be used to obtain the ratio of activity coefficients of the aryloxide ion to fluoride ion for the solvents in which the equilibrium constant is available. (This is valid to the extent that the ratio of activity coefficients of the aryloxyphosphonate esters to that of GB is unity for the various solvents.) Table XII contains the derived ratio of activity coefficients for *m*-nitrophenoxide and phenoxide ions. Note that the change in

Table XII. Derived Change in Ratio of Activity Coefficients of Aryloxide Anions Relative to F$^-$

Solvent	ArO^-	K	$\gamma_{ArO^-}/\gamma_{F^-}$
Water	*m*-Nitro	88	1.00[a]
Methanol	*m*-Nitro	2	0.022
Acetonitrile	*m*-Nitro	$<3 \times 10^{-4}$	$<3 \times 10^{-6}$
Water	–H	2×10^{4} [b]	1.00[a]
Methanol	–H	$\sim 2 \times 10^{4}$	~1
Acetonitrile	–H	4.9	2.5×10^{-4}

[a] By definition. Water is the standard-state solvent. [b] Derived using the constant for phenoxide and GB reported in ref 5.

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(35) In justification of this procedure, T. C. Bruice, *et al.*, *Biochemistry*, 1, 7 (1962), observed that phenols and aliphatic alcohols fall on the same line in a Brønsted plot of the log k_2 values *vs.* the pK_a's of the conjugate acids of the attacking nucleophiles.

(36) B. D. England and D. A. House, *J. Chem. Soc.*, 4421 (1962), gave a pK_a of phenol in methanol of 14.2; according to I. M. Kolthoff and L. S. Guss, *J. Amer. Chem. Soc.*, 60, 2516 (1938), the pK_a is 14.0.

(37) An alternative explanation for the observed order is that the activity coefficient ratio, $\gamma_{PhO^-}/\gamma_{PhC(=O)NHO^-}$ *increases* as the solvent becomes a poorer hydrogen bonder. This would be expected in view of the previously cited structure of benzohydroxamate ion (ref 30), whose internal hydrogen bond would render the anion activity coefficient less susceptible to changes due to relative solvent hydrogen bonding abilities.

Table XIII. Table of Analytical Data for Tetrabutylammonium Salts of Nucleophiles

		Calcd, %				Found, %				
Anion	Formula	C	H	N	O	C	H	N	O	Mp, °C
m-Nitrophenolate	$C_{22}H_{40}N_2O_3$	69.4	10.6	7.4	12.6	69.2	10.8	7.4	12.6	163–167
p-Nitrophenolate	$C_{22}H_{40}N_2O_3$	69.4	10.6	7.4	12.6	69.1	10.7	7.2	12.7	149
Biacetyl oximate	$C_{20}H_{42}N_2O_2$	70.1	12.4	8.2		70.5	12.4	7.9		140–141
Benzohydroxamate	$C_{23}H_{42}N_2O_2$	73.0	11.2	7.4	8.5	72.5	12.4	7.5	8.8	
4-Nitrocatecholate	$C_{22}H_{40}N_2O_2$	66.6	10.0	7.1		66.6	10.1	7.3		139–139.5
2,6-Dimethylacetophenoxide	$C_{26}H_{47}O_2$	77.0	11.7	3.5	7.9	76.9	11.5	3.6	8.2	180–183

activity coefficient for phenoxide ion is two orders of magnitude less than the change for *m*-nitrophenoxide on transfer from water to acetonitrile. This is in the expected direction.[20]

The values are consistent with the explanation that fluoride is very much more poorly solvated in acetonitrile than either *m*-nitrophenoxide or phenoxide anion, in agreement with the approximation that its energy in aprotic solvents is determined by the Born equation.[20] The *m*-nitrophenoxide and phenoxide ions may be considered to have appreciable dispersion energy relative to fluoride ion in their dipolar aprotic solvation in addition to lower Born energies because of charged delocalization in these ions.[20]

Experimental Procedures

Materials. Tetrabutylammonium salts of nucleophiles were prepared by reaction of aqueous solutions or methanolic solutions of tetrabutylammonium hydroxide (prepared from tetrabutylammonium iodide and silver oxide) with stoichiometric amounts of the conjugate acid. Analytical data for these salts are given in Table XIII. The benzohydroxamate salt, dissolved in acetone, was dried over Drierite and precipitated by addition of ether. It was purified three times by crystallization from acetone with addition of ether and then dessicated *in vacuo* over phosphorus pentoxide at room temperature. The *m*-nitrophenoxide and *p*-nitrophenoxide salts were purified by precipitating three times from acetone solutions by addition of ether. They were obtained initially as monohydrate salts on drying *in vacuo* at room temperature. Drying at 100° for 12 hr at 1 mm gave the anhydrous salts. The 2,6-dimethyl-4-acetophenol was prepared by the method of Benington, *et al.*,[38] mp 151–153°. Conversion to the tetrabutylammonium salt, crystallization several times from acetone, and drying *in vacuo* over phosphorus pentoxide at 56° gave material with mp 180–183°. The 4-nitrocatechol was prepared by the method of Rosenblatt, Epstein, and Levitch.[39] The tetrabutylammonium salt was recrystallized from concentrated acetone and dried *in vacuo* at 56° over phosphorus pentoxide to give material with mp 139–139.5°. The biacetyl oximate salt was recrystallized three times from acetone and dried *in vacuo* over calcium chloride at room temperature to give material with mp 140–141°.

The *O*-methyl *O*-isopropyl methylphosphonate was prepared by reaction of Sarin (*O*-isopropylmethyl phosphonofluoridate) with sodium methoxide, or solvolysis of *O*-isopropylmethyl phosphonochloridate with methanol. The product had bp 121° (10 mm).

O-Isopropyl *O*-*m*-nitrophenyl methylphosphonate was prepared by reaction of *O*-isopropylmethyl phosphonochloridate with the stoichiometric quantities of *m*-nitrophenol and triethylamine in ether solution. The product had bp 143–156° (0.5–0.7 mm) and mp 44–46°. *Anal.* Calcd for $C_{10}H_{14}NO_5P$: C, 46.3; H, 5.4; N, 5.4; P, 12.0. Found: C, 46.1; H, 5.3; N, 5.4; P, 12.1.

O-Isopropyl *O*-phenyl methylphosphonate, prepared similarly to the *m*-nitrophenyl ester, had bp 85–86.0° (1.0 mm). *Anal.* Calcd for $C_{10}H_{15}O_3P$: C, 56.1; H, 7.1; P, 14.3. Found: C, 56.0; H, 7.0; P, 14.3.

Authentic *O*-phenylcarbamyl benzohydroxamate and diphenylurea were prepared as described by Stolberg, *et al.*:[40] *O*-phenylcarbamyl benzohydroxamate, mp 176–177°; diphenylurea, mp 238°.

Triethylamine was distilled from phenyl isocyanate, then redistilled from potassium hydroxide pellets. Triethylamine hydrochloride was recrystallized three times from ethanol and dried *in vacuo* over phosphorus pentoxide. Solutions of triethylamine in methanol (made up gravimetrically) were standardized by neutralization with excess standardized 0.1 *N* hydrochloric acid and back-titration of excess acid with 0.1 *N* standardized sodium hydroxide to the bromothymol blue end point.

Diisopropyl phosphonite was prepared by dropwise addition of 19.7 g of dichloromethylphosphine (*Caution:* spontaneously flammable in air) in 60 ml of 30–60° petroleum ether (at 0 to −5°), with stirring, to 45 g of triethylamine and 26 g of isopropyl alcohol in 200 ml of petroleum ether under a nitrogen atmosphere. After filtration to remove triethylamine hydrochloride and drying over sodium sulfate, the petroleum ether was removed by distillation under nitrogen. The residue was distilled under nitrogen to give 8.35 g (30%) of water-white product, bp 43–45° (30 mm).[41]

O-Isopropylcyanomethyl methylphosphonate was prepared under nitrogen by the Michaelis–Arbuzov rearrangement. Addition of 3.9 g of chloroacetonitrile to 8.35 g of diisopropyl phosphonite in a 100-ml three-necked flask, with stirring, was followed by heating at 135–140° for 1 hr while the evolved isopropyl chloride was allowed to distill off through an upright condenser into a cooled receiver. The residue was then distilled under nitrogen at reduced pressure, bp 160–161° (30 mm). The yield was 5.12 g (62%) of water-white material with infrared peaks at 2250 (-C≡N), 1379 and 1390 (isopropyl), 998 (P—O—C), 1249 cm^{-1} (P=O). *Anal.* Calcd for $C_6H_{12}NO_2P$: C, 44.7; H, 7.5; N, 8.7. Found: C, 44.5; H, 7.5; N, 8.4.

A sample of *m*-nitrophenyl isopropyl ether was prepared by reaction of isopropyl iodide with *m*-nitrophenol in the presence of anhydrous potassium carbonate in refluxing acetone. The product had bp 109–110° (4.5 mm).

A sample of *m*-nitrofluorobenzene was prepared by the Schiemann reaction of *m*-nitrobenzenediazonium fluoroborate.

Sarin (GB; *O*-isopropyl methylphosphonofluoridate) was a redistilled sample of purity 97% minimum, stored in sealed ampoules in a freezer. (Nuclear magnetic resonance showed absence of the characteristic decomposition impurities of this material.)

Solvents were of the highest purities commercially available. Acetonitrile, dimethylformamide, and nitromethane were redistilled from phosphorus pentoxide through a Vigreux column. Mid-cuts were obtained for kinetic use. Methanol was distilled from magnesium methoxide and refractionated through a Vigreux column. Dimethyl sulfoxide was distilled at reduced pressure from potassium hydroxide pellets. Acetone was fractionated from Drierite. Storage of some of the solvents over molecular sieves did not alter rate constants obtained without such storage.

Tris buffers were made from the highest purity materials available from Sigma Chemical Co.

Benzohydroxamic acid was commercial material, recrystallized three times from ethyl acetate. The *m*- and *p*-nitrophenols were purified by recrystallization from aqueous hydrochloric acid solutions followed by final recrystallization from carbon tetrachloride.

Tetraethylammonium fluoride (Eastman White Label) was used without further purification after dessication for several days over phosphorus pentoxide *in vacuo*.

Tetrabutylammonium fluoride was prepared from silver fluoride and tetrabutylammonium iodide. After several recrystallizations from water of the polyhydrate salt, the material was dessicated for a week *in vacuo* over phosphorus pentoxide. The initial liquid substance crystallized on long standing.[42]

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(38) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).

(39) D. H. Rosenblatt, J. Epstein, and M. Levitch, *J. Amer. Chem. Soc.*, **75**, 3277 (1953).

(40) M. A. Stolberg, R. C. Tweit, G. M. Steinberg, and T. Wagner-Jauregg, *ibid.*, **77**, 765 (1955).

(41) *Cf.* P. Mastalesy, *Roc. Chem.*, **38** (1), 61 (1964).

Kinetic Methods. Fluoride Analysis. The method was adapted from Yamamura, Wade, and Sikes.[43] The following stock solutions were prepared.

(A) **Cerium Nitrate.** A 0.0167 *M* solution was prepared by dissolving 1.813 g of cerium nitrate in water in a 250-ml volumetric flask, and diluting to the mark.

(B) **Alizarin Dye Solution.** In a 50-ml volumetric flask, 0.3215 g of 3-aminomethylalizarin-*N*,*N*-diacetic acid (K and K Laboratories) was dissolved in dimethylformamide and diluted to mark with this solvent.

(C) **Acetate Buffer** (pH 4). Sodium acetate (20.2 g, anhydrous) was dissolved in 250 ml of distilled water. Then 58 ml of glacial acetic acid was added. The solution was diluted to a volume of 500 ml with distilled water.

(D) **Composite Alizarin Complexone Reagent.** In a 500-ml volumetric flask was mixed, in order, 330 ml of acetone, 68 ml of solution C (buffer), 10 ml of alizarin dye solution B, and 10 ml of cerium reagent A. This solution was diluted to volume and mixed. (It is reasonably stable for several days.)

For kinetics, reaction solutions were customarily made up to be 0.05–0.1 *M* in nucleophile and 2×10^{-3} in Sarin. For analysis, 0.500-ml volumetric aliquots were taken at various time intervals from the thermostated (25°) reaction vessel and discharged into 15 ml of the solution (D) in 25-ml volumetric flasks (which served to quench the reaction, as well as to develop absorption due to fluoride). The solutions were then diluted to the mark. The absorbancy was read after 15 min at 620 mμ and compared with a blank. If infinity solutions could not be conveniently obtained, "mock infinity" solutions were made by hydrolyzing an identical aliquot of Sarin with aqueous hydroxide solution, then adding the complexone reagent (D) and diluting to 25 ml as before. Occasionally, more dilute nucleophile strengths (0.01 *M*, etc.) were employed. In order to preserve pseudo-first-order conditions, the concentration of Sarin was then reduced to 2×10^{-4} *M*, and 5-ml aliquots were treated exactly as previously described. Plots of log $(A_\infty - A_t)$ *vs.* time were linear, where A_∞ = absorbancy at infinite time and A_t = absorbancy at the time of sample discharge into the quenching solution. Multiplication of slopes by 2.303 gave pseudo-first-order constants. Second-order coefficients were obtained in the usual manner.

Reactions of fluoride with *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate in acetonitrile were followed in a Cary Model 14 spectrophotometer at 470 mμ in a 10-cm cell for the slower runs. The volume of the cell was ~30-ml capacity, and reaction solutions were made up directly from stock reactants to give total volumes of 25 ml in the cell. After rapid shaking, the absorbancy was recorded. Pseudo-first-order plots were made as described above and translated to second-order coefficients. The order was established as first order in each reaction component by variation of each reaction component. Superimposed upon the normal concentration effect upon rates was a smaller salt effect which was detected by wide variation of the tetraalkylammonium fluoride concentrations. Faster runs were followed on an Aminco-Morrow stopped-flow apparatus with oscillographic readout. The instrument was equipped with a thermostated 1-cm mixing cell and had a mixing time of less than 5 msec. Photographic recordings of the traces were enlarged and converted to absorbancy readings. Tetraalkylammonium fluoride concentrations were employed in large excess over the ester concentration (2.05×10^{-4} *M*) so as to obtain pseudo-first-order kinetics. First-order plots were made in the usual way. Thermostating in the Cary Model 14 was checked directly in the sample compartment with a quartz thermometer. Temperatures recorded for the stopped-flow apparatus were the temperatures measured by a thermometer in the circulating water bath which functioned at ± 0.02°. The fastest half-lives followed were of the order of 15 msec.

The aqueous reaction of fluoride ion with *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate was followed in a Cary Model 14 spectrophotometer at 420 mμ in a 10-cm cell of maximum capacity 30 ml. The reaction solutions were made up directly in the cell to give final Tris buffer concentrations of 0.0500 *M*, with appropriate concentrations of potassium fluoride and the phosphonate ester. Mock infinity solutions were made up from identical concentrations of buffer, potassium fluoride, and with the ester replaced by *m*-nitrophenol. pH was read directly on the reaction solutions at the ends of the runs. Runs at 0.100 and 0.500 *M* KF went essentially to completion, giving first-order plots. Data from the literature[44] allowed calculation of an equilibrium constant for the reversible reaction of *m*-nitrophenolate ion with *O*-isopropyl methylphosphonofluoridate (Sarin).

Independent Determination of Aqueous Equilibrium for Reaction of *m*-Nitrophenolate Ion with Sarin. In a 10-cm reaction cell thermostated at 25°, a reaction mixture in 0.05 Tris buffer was made up to contain 1.674×10^{-4} *M* initial O-isopropyl *O*-*m*-nitrophenyl methylphosphonate, 0.500 *M* initial potassium fluoride (F^-), and 3.424×10^{-3} *M* initial GB (G_0). The reaction was allowed to proceed to give an asymptotic reading at 420 mμ. (After reaching an asymptotic value, the absorbancy underwent a very slow decay which is not understood.) The ester absorbancy coefficient was determined to be 3.11×10^2 and the total *m*-nitrophenol absorbancy coefficient was determined to be 4.871×10^3 at pH 7.96 (the pH of the reaction mixture). The extinction coefficient for *m*-nitrophenolate *ion* was determined to be 1.248×10^4 M^{-1} cm^{-1} at 420 mμ. Then, $A = (3.11 \times 10^2)(a - x) + (4.871 \times 10^3)(x)$, where A = measured absorbancy = 0.668, a = initial ester concentration = 1.674×10^{-4}, x = reacted ester = reacted fluoride. The value of x was then calculated, giving the total *m*-nitrophenolate (as phenolate and phenol). The absorbancy due to *m*-nitrophenolate was then calculated by subtracting the ester correction, $A_p = (A + (3.11 \times 10^2)x - (3.11 \times 10^2)a)$. This absorbancy, A_p, was then divided by 1.248×10^4 (the extinction coefficient for *m*-nitrophenolate) to obtain the concentration of *m*-nitrophenolate, [P⁻], in the reaction mixture. Then

$$K = \frac{[\mathrm{F^-}][\mathrm{E}]}{[\mathrm{GB}][\mathrm{P^-}]} = \frac{(0.500)(a - x)}{(G_0 + x)[\mathrm{P^-}]} = 85.0$$

In a similar way, reaction of 0.500 *M* potassium fluoride, 1.674×10^{-4} *M* ester, and 6.466×10^{-3} *M* GB gave a final reading of 0.542 at pH 7.93, which gave a calculated $K = 109$.

Determination of Dissociation Constants in Methanol. The triethylamine pK_a was redetermined at 25.6 ± 0.2° by making up triethylamine–triethylamine hydrochloride buffers in methanol in the presence of *p*-nitrophenol as indicator, whose pK_a has been accurately determined to be 11.19.[45] The extinction coefficient of *p*-nitrophenolate was measured in 0.04 *M* sodium methoxide at 425 mμ to be 8.05×10^3 M^{-1} cm^{-1}. Solutions of buffer and indicator contained concentrations of *p*-nitrophenol of 6×10^{-5} *M*, with varying total concentrations of buffer. The extinction coefficient of free *p*-nitrophenol was 45.0 M^{-1} cm^{-1} at 425 mμ. Concentrations of the anion of *p*-nitrophenol were determined by the following formula, utilizing a cell of 10-cm path length.

$$[\mathrm{A^-}] = \frac{\mathrm{OD} - 450C_0}{80{,}500}$$

where [A⁻] = concentration of *p*-nitrophenolate ion, C_0 = initial concentration of *p*-nitrophenol = 6×10^{-5} *M*, OD = measured optical density of the mixture. The ionic strength was varied from 2×10^{-3} to 2×10^{-2}. The amine buffer ratio was close to 1:1 for amine and amine hydrochloride. The ΔpK_a for *p*-nitrophenol and triethylamine was calculated as

$$\Delta \mathrm{p}K_\mathrm{a} = \log \frac{[\mathrm{B}]}{[\mathrm{BH^+}]} + \log \frac{[\mathrm{HA}]}{[\mathrm{A^-}]}$$

where ΔpK_a = pK_a(*p*-nitrophenol) − pK_a(triethylamine), [B] = triethylamine concentration, [BH⁺] = triethylamine hydrochloride concentration = μ (ionic strength), [HA] = *p*-nitrophenol concentration; [A⁻] = concentration of *p*-nitrophenolate ion. Plot of ΔpK_a *vs.* $\sqrt{\mu}$ gave ΔpK_a at infinite dilution = 0.60. (The slope was −3.3, whereas the theoretical Debye–Hückel slope is −4.0.) Thus, the pK_a of triethylamine was determined to be 10.59. Data for this determination are given in Table XIV.

In a similar way, the pK_a of *m*-nitrophenol was measured in methanol, employing triethylamine–triethylamine hydrochloride buffers and employing pK_a = 10.59 for triethylamine. Measurements were made at 420 mμ with ε 1.389×10^3 M^{-1} cm^{-1} for *m*-nitro-

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[42] *Cf.* A. Allerhand and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 1233 (1963), who were unable to obtain crystalline material.

[43] S. S. Yamamura, M. A. Wade, and J. H. Sikes, *Anal. Chem.*, **34**, 1308 (1962).

[44] J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964).

[45] J. Juilliard, *Bull. Soc. Chim. Fr.*, 1727 (1966).

Table XIV. Data for Triethylamine pK_a Determination at 25.6°

Initial [B], M	Initial [BH$^+$], M	OD (425 mμ)	μ	[B]/[BH$^+$]	Log ([B]/[BN$^+$])	[HA], M	[A$^-$], M	[HA]/[A$^-$]	Log ([HA]/[A$^-$])	ΔpK_a
0.01968	0.0200	1.968	0.0200	0.984	$\bar{1}.9930$	3.59×10^{-5}	2.411×10^{-5}	1.489	0.173	0.166
0.01378	0.0140	1.830	0.0140	0.984	$\bar{1}.9930$	3.76×10^{-5}	2.240×10^{-5}	1.679	0.225	0.218
0.00984	0.0100	1.722	0.0100	0.980	$\bar{1}.9912$	3.89×10^{-5}	2.106×10^{-5}	1.847	0.266	0.258
0.003936	0.0040	1.408	0.0040	0.975	$\bar{1}.9890$	4.28×10^{-5}	1.716×10^{-5}	2.494	0.397	0.386
0.001968	0.0020	1.224	0.0020	0.975	$\bar{1}.9890$	4.51×10^{-5}	1.487×10^{-5}	3.033	0.482	0.471

phenolate and 16.4 M^{-1} cm^{-1} for *m*-nitrophenol. The plot of ΔpK_a *vs.* $\sqrt{\mu}$ gave a slope of −3.1, whereas the theoretical slope is −4.0.

In determination of the pK_a of benzohydroxamic acid (25.4°), benzohydroxamate–benzohydroxamic acid buffers were employed in excess over *p*-nitrophenol indicator. Measurements were made at 425 mμ similarly to the triethylamine determination. With this system, simple Debye–Hückel theory predicts ΔpK_a to be invariant with ionic strength. No extrapolation was performed owing to the fact that [HA]/[A$^-$] ratios for benzohydroxamic acid had to be 5–10 at the more dilute buffer strengths, and high conversions of *p*-nitrophenol to *p*-nitrophenolate were obtained ([A$^-$]/[HA] of 6–27). Thus the determination was limited to two values obtained at μ = 0.0020 and μ = 0.0040, which gave ΔpK_a = 1.78 ± 0.02. This value should be a good approximation to the ΔpK_a at infinite dilution.

Kinetics in Methanol. Owing to the interfering reaction of methoxide with GB which competed with nucleophilic anions, buffered media were employed. Reactions of anions with GB were followed by fluoride analyses (see above). Using triethylamine buffers, the methoxide rate coefficient was determined. The methoxide concentrations were determined using the Debye–Hückel limiting law for methanol (*i.e.*, $pK_B = pK_B' - 4.0\sqrt{\mu}$ for amine buffers). Values calculated in this way gave good agreement for varying ionic strengths, buffer concentrations, and buffer ratios.

Tetrabutylammonium salts of nucleophiles were used, except in the case of fluoride, when the tetraethylammonium salt was employed. The observed pseudo-first-order coefficients for anions were corrected for methoxide contributions by the following method: The pK_B of the nucleophilic buffer species was calculated from the thermodynamic pK_a and the ion product of methanol. According to the Debye–Hückel first approximation, this pK_B is invariant with ionic strength. From the buffer ratio, the concentration of methoxide was calculated. This concentration was multiplied by the second-order coefficient of methoxide ion attack to obtain the methoxide contribution. The contribution was then subtracted from the pseudo-first-order coefficient to obtain the corrected pseudo-first-order coefficient for attack by the anion of the buffer species. Division of the corrected pseudo-first-order coefficient by the anion concentration gave the second-order coefficient for the nucleophile. Possible acid catalysis by the conjugate acid appeared to be small and was neglected.

For the reaction of fluoride and methoxide with *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate in methanol, reactions were followed in triethylamine buffers ([B]/[BH$^+$] = 2) at 410 mμ. Tetraethylammonium fluoride was employed in large excess over the ester.

The reaction with fluoride was followed to about 80% reaction, and that of methoxide to about 4% reaction. The ester was employed at 4×10^{-4}–1×10^{-3} M concentration in a 10-cm cell. Mock infinity absorbances were calculated from measured adsorption of *m*-nitrophenol in solutions more dilute than the ester concentrations employed, with added nucleophile and buffer present at the same concentrations as the reaction solutions. Pseudo-first-order kinetics were obtained, and were converted to second-order kinetics in the usual way.

Reaction Products in Methanol. Reactions of nucleophiles in methanol were found to produce substantial quantities of *O*-isopropyl *O*-methyl methylphosphonate. *O*-Isopropyl *O*-methyl methylphosphonate was detected by vapor-phase chromatography and determined relative to an authentic sample. Chromatograms were run on an F & M biomedical gas chromatograph isothermally at 102°. The column was 4-ft 15% QF-1 on 80–100 silanized Chromosorb W. A flame ionization detector was employed. Under these conditions, Sarin had a retention time of 1.6 min and *O*-isopropyl *O*-methyl methylphosphonate had a retention time of 4.9 min. Reaction mixtures were made up with the appropriate concentrations of tetrabutylammonium salt and conjugate acid and with 2×10^{-3} M Sarin. After standing at room temperature for 60 min, 10-μl samples were analyzed as described above. Analyses in this system were reproducible to about ±10%.

Reaction of 0.1903 g of tetrabutylammonium *m*-nitrophenolate, 0.0696 g of *m*-nitrophenol, and 0.0282 ml of Sarin in 5 ml of methanol for 30 min gave a detectable amount of *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate, identified by gas chromatography. Although the peak was poor and could not be quantitated owing to interference by the tetrabutylammonium *m*-nitrophenolate decomposition peaks, the peak was identified by the characteristic retention time of 8.7 min and the appearance of a green hydrogen flame in the flame ionization detector (associated with phosphorus compounds). Chromatography was conducted isothermally at 155° on a 6-ft 5% SE-30 on 80–100 silanized Chromosorb W column. Samples injected were of 10-μl size.

Reaction of 0.3626 g of tetrabutylammonium benzohydroxamate, 0.13714 g of benzohydroxamic acid, and 0.140 ml of Sarin in 10 ml of methanol for 30 min was quenched by addition of 0.2 ml of concentrated hydrochloric acid with shaking. Thin-layer chromatography was conducted on Eastman silica chromatograms with fluorescent background (Table XV). The reaction mixture showed benzohydroxamic acid (starting material) and substantial conversion to *O*-phenylcarbamyl benzohydroxamate. No diphenylurea was detected (*cf.* ref 40). Ultraviolet light of 2557 Å was used for visualization of the migrated spots.

Table XV. Thin-Layer Chromatographic System for Identification of Products from Sarin and Benzohydroxamate in Methanol[a]

Compound	Solvent	R_f
Diphenylurea	10% MeOH–90% CCl_4	0.328
	5% MeOH–95% CCl_4	0.25
O-Phenylcarbamyl benzohydroxamate	10% MeOH–90% CCl_4	0.509
	5% MeOH–95% CCl_4	0.30
Benzohydroxamic acid	10% MeOH–90% CCl_4	0.182
	5% MeOH–95% CCl_4	0.10

[a] Eastman silica chromatograms.

Product Studies of Reaction of Fluoride Ion with *O*-Isopropyl *O*-*m*-Nitrophenyl Methylphosphonate and Sarin (GB) with *m*-Nitrophenoxide in Acetonitrile. Fluoride Ion Disappearance. Reaction of 2×10^{-3} M tetraethylammonium fluoride with 2×10^{-2} M *m*-nitrophenyl ester showed that 98.4% of the fluoride was consumed before 40 sec of reaction time using the fluoride analysis described above.

Sarin (GB) Production. Sarin was measured by gas chromatography on the apparatus described above using the 6-ft 5% SE-30 column described previously, isothermally at 74°. The retention time was 1.1 min. Stock 0.04 M tetraethylammonium fluoride in acetonitrile (1 ml) was mixed with 1 ml of stock 0.04 M *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate. The reaction was immediately analyzed and gave a 93% yield of Sarin (GB).

Absence of *O*-Isopropylcyanomethyl Methylphosphonate in Reaction of GB with *m*-Nitrophenolate in Acetonitrile. A reaction mixture 0.1 M in tetrabutylammonium *m*-nitrophenolate and 4×10^{-3} M GB in acetonitrile was sampled at various times, 1-ml aliquots being quenched with 0.1 ml of formic acid; 10-μl samples were then analyzed at 150° isothermally on the 6-ft 5% SE-30 column previously described. None of the samples showed (over 2.5 hr) any evidence of the cyanomethyl methylphosphonate (retention time 0.6 min).

Absence of *O*-Isopropyl *O*-*m*-Nitrophenyl Methylphosphonate in Reaction of GB with *m*-Nitrophenolate. A reaction run as above failed to show the ester (retention time 9.8 min) even after overnight reaction at room temperature.

Absence of Isopropyl *m*-Nitrophenyl Ether in Reaction of GB with *m*-Nitrophenolate. Thin-layer chromatography of the ether and free phenol showed good separation on Eastman silica chromatograms with fluorescent background using either carbon tetrachloride or petroleum ether as eluent. A reaction mixture prepared as above showed none of the *m*-nitrophenyl isopropyl ether (visualization by 2557-Å ultraviolet light).

Nmr Studies of Reaction of *m*-Nitrophenolate with Sarin (GB) in Acetonitrile. Reactions of tetraalkylammonium salts of *m*-nitrophenolate ion with GB were conducted (0.1 *M* in each component in deuterioacetonitrile dried over molecular sieves (4 A)). Similar reactions were conducted between tetraalkylammonium salts of fluoride ion and *O*-isopropyl *O*-*m*-nitrophenyl methylphosphonate. Each reaction solution was examined soon after mixing, and again after about 24 hr. The former reactions were slow, as expected, and provided evidence for an exchangeable proton, possibly the phosphonic acid or phosphonate of Sarin (from *hydrolysis*), though the aromatic multiplet did not resemble authentic samples of *m*-nitrofluorobenzene or *m*-nitrophenol after acidification. The latter reactions produced GB, but on standing overnight gave spectra identical with those of the former systems. No water could be detected in the deuterioacetonitrile or in the salts utilized. Reaction proceeded in identical fashion in Teflon-lined reaction tubes. Karl Fisher analysis of acetonitrile or acetonitrile with 0.1 *M* tetrabutylammonium *m*-nitrophenolate showed no detectable water ($<2 \times 10^{-4}$ *M*) in solutions dried over molecular sieves. Yet, these same solutions reacted to liberate nearly quantitative amounts of fluoride ion from Sarin (GB) and gave a reproducible rate constant.

Reaction of Tetrabutylammonium 2,6-Dimethyl-4-acetophenoxide with GB in Acetonitrile. This substance was run at 0.1 *M* anion concentration and 2×10^{-3} *M* GB concentration in freshly dried acetonitrile with precautions to exclude water. It gave an apparent $k_2 = 1.6 \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$. A parallel run with *m*-nitrophenolate ion at identical concentrations gave $k_2 = 1.17 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$. Thus, even though the former phenol has aqueous pK_a almost identical with that of *m*-nitrophenol,[46] it reacts only 13% as fast as the latter phenol in what is presumably (*vide infra*) a hydrolysis reaction.

Reaction of Tetrabutylammonium 2,6-Dimethyl-4-acetophenoxide with *O*-Isopropyl *m*-Nitrophenyl Methylphosphonate in Acetonitrile. The reaction was followed at 470 mμ using 0.016 *M* anion and 8.00 $\times 10^{-5}$ *M* ester in a 10-cm cell. The reaction was very slow and showed curvature (probably due to the back-reaction of a reversible system). A mock infinity solution was prepared and the initial rate was obtained, giving $k_2 = 3.23 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$.

Column Chromatography and Derivatization of Products of Reaction of GB with *m*-Nitrophenolate. In 100 ml of dry acetonitrile was placed 3.684 g of tetrabutylammonium *m*-nitrophenolate and 1.2 ml of GB (Sarin, about 1.2 g). After 40 hr of reaction in a polyethylene bottle, the material was neutralized to a light yellow color by dropwise addition of hydrochloric acid. The mixture was then evaporated in a hood. The oily residue was taken up in 50% methanol-50% carbon tetrachloride and chromatographed on a 1-ft column of Fisher alumina. Elution was with 50% methanol-50% carbon tetrachloride. The first few fractions contained no material, then four fractions were obtained which on evaporation gave yellow oils, crystallizing on scratching to give violet solids. (The solids redissolved in various solvents to give yellow solutions.) Nmr examination showed evidence of the tetrabutylammonium cation and an aromatic multiplet. Acetylation of a small quantity of the material gave *m*-nitrophenyl acetate, mp 55-56°. Thus, the reaction seems to involve hydrolysis to give a difficultly separable mixture of tetrabutylammonium salts and *m*-nitrophenol which crystallized together in some form of complex or clathrate.

Products of Reaction of Benzohydroxamate with Sarin (GB) in Nitromethane and Acetonitrile. Tlc on Eastman chromatogram silica strips gave the following R_f values (fluorescent background used with 2257-Å ultraviolet detection).

Solvent	Diphenylurea	Benzo-hydroxamic acid	Carbamate
Abs ethanol	0.81	0.32	0.82
Concd ammonia	0.00	0.05 dec	0.7

Tetrabutylammonium benzohydroxamate (5 ml, 0.1 *M*) and 5 ml of 0.04 *M* GB in nitromethane were mixed and allowed to stand for 2 hr. Then 1 ml was quenched with 0.1 ml of glacial acetic acid.

Two-dimensional migration with ethanol of 1 − γ spots showed a product spot (either diphenylurea or *O*-phenylcarbamyl benzohydroxamate).

Two-dimensional migration with concentrated ammonia from a reaction of 0.05 *M* benzohydroxamate with 0.02 *M* GB showed *O*-phenylcarbamyl benzohydroxamate and no diphenylurea.

Similarly, in acetonitrile, reaction of 0.05 *M* benzohydroxamate with 0.02 *M* GB gave *O*-phenylcarbamyl benzohydroxamate (after 60 min of reaction).

Reaction of *O*-Isopropyl *O*-Phenyl Methylphosphonate with Fluoride Ion in Acetonitrile. The reaction was followed by the fluoride technique previously described. Reactions did not go to completion using excesses of the ester over the fluoride ion. (The ester concentration was varied from 0.05 to 0.02 *M*; the fluoride was relatively constant at about 2×10^{-3} *M*). An attempt was made to analyze the data in terms of the equilibrium

$$K = \frac{[\mathrm{F}^-][\mathrm{E}]}{[\mathrm{P}^-][\mathrm{G}]}$$

where $[\mathrm{F}^-]$ = final fluoride concentration, [E] = final ester concentration, $[\mathrm{P}^-]$ = final phenoxide concentration, and [G] = final Sarin concentration. Reasonably constant equilibrium constants were obtained. However, kinetic analysis according to

$$\Delta x/\Delta t = k_1[\mathrm{E}]\overline{[a - x]} - k_1K[\bar{x}^2]$$

$$\Delta x/\Delta t = k_1[\mathrm{E}]\overline{[a - x]} - [\bar{x}]^2K$$

where [E] = ester concentration, $\overline{[a - x]}$ = mean value of fluoride concentration over the time interval, $[\bar{x}]$ = mean value of reacted fluoride over the time interval, and $\Delta x/\Delta t$ = change in fluoride over a small time interval *t*, gave variables for k_1 and $k_1K (= k_{-1})$. It thus seems that this reaction is more complicated than the simple analysis we have attempted.

Reaction of Fluoride Ion with *O*-Phenyl *O*-Isopropyl Methylphosphonate. The reaction was studied in water and in methanol by observing the increase in absorption at 278 mμ due to phenol production. The high concentration of fluoride ion employed gave aqueous pH readings of 8.2–8.8 after addition of acetic acid to bring the "added acetic acid" concentration in the final medium to about 2–4 $\times 10^{-3}$ *M*. No evidence for the back-reaction between Sarin and phenol was encountered, as good pseudo-first-order kinetics was obtained. The *O*-phenyl *O*-isopropyl methylphosphonate was employed at a concentration of 1×10^{-4} *M* and the reactions were followed in a 10-cm thermostated cell on a Cary recording spectrophotometer. In the slow runs (in methanol), mock infinity solutions were made up from the required quantities of tetraethylammonium fluoride and phenol. The latter runs were followed to 30% completion and to 1% completion (for the slowest run). A summary of results is given in Tables XVI and XVII.

Table XVI. Reaction of Aqueous KF with *O*-Phenyl *O*-Isopropyl Methylphosphonate

pH	Temp, °C	k_0, min^{-1}	[KF], *M*	k_2, M^{-1} sec^{-1}
8.22	25.06	5.72×10^{-3}	3.20	2.98×10^{-5}
8.84	25.16	3.47×10^{-3}	2.40	2.41×10^{-5}
8.28	25.06	3.19×10^{-3}	1.63	3.26×10^{-5}
8.53	24.97	5.87×10^{-3}	3.26	3.00×10^{-5}
			Mean	$2.91 \pm 0.24 \times 10^{-5}$

Table XVII. Reaction of Methanolic Tetraethylammonium Fluoride with *o*-Phenyl *o*-Isopropyl Methylphosphonate

[Fluoride], *M*	Temp, °C	k_0, min^{-1}	k_2, M^{-1} sec^{-1}
0.0476	25.2	2.33×10^{-5}	8.2×10^{-6}
0.3392	25.2	1.87×10^{-4}	9.2×10^{-6}

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(46) A. Fischer, *et al.*, *J. Chem. Soc. B*, 782 (1966), gave a pK_a of 8.22 for the 3,5-dimethyl-4-hydroxyacetophenone.