the layers were separated. On evaporation, the organic phase afforded 1 g of a brown liquid which by glpc analysis showed no unchanged starting material.

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Reactions of General Bases and Nucleophiles with Bis(*p*-nitrophenyl) Methylphosphonate

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Abstract: Primary, secondary, and tertiary amines react with bis(*p*-nitrophenyl) methylphosphonate (b-*p*-NPMP) (I) *via* general base catalysis of water attack (eq 1). The rate law is first-order in substrate and in amine. One mole of b-*p*-NPMP yields quantitatively 1 mol of *p*-nitrophenyl methylphosphonate (VI) and 1 mol of *p*-nitrophenol (*p*-NP) or its anion depending on pH. The rates of formation of VI and *p*-NP are identical. Solvent deuterium isotope effects, $k_2(H_2O)/k_2(D_2O)$, are greater than 2 for amine reactions. Different classes of amines follow a Brønsted relation with a slope of 0.38. *s*-Collidine falls below the Brønsted line but is as reactive as pyridine. Fluoride ion and several oxyanions react with I by a nucleophilic mechanism. At high fluoride ion concentration, 2 mol of *p*-NP is released in a first-order process. At lower fluoride concentrations less than 2 mol of *p*-NP is produced. II, a product of initial fluoride ion attack, can react with a second mole of fluoride *or* other bases in solution. *p*-Methoxyphenolate anion reacts with I in two kinetically separable reactions, releasing 2 mol of *p*-NP. Benzohydroxamate anion releases 2 mol of *p*-NP in a first-order process. Phosphate and hydroxide anions produce 1 mol of *p*-NP and VI probably in nucleophilic processes. $k_2(H_2O)/k_2(D_2O)$ for the reactions of fluoride and phosphate ions with b-*p*-NPMP $\cong$ 1.00–1.15. Steric crowding in the transition state can be invoked to explain the reactions of amines with I *via* a general base mechanism and the reactions of fluoride anion and oxyanions with I *via* a nucleophilic mechanism.

The question of the relative importance of general base and nucleophilic catalysis in displacement reactions at the tetrahedral organophosphorus center is most intriguing. Reactions of neutral esters have been shown to proceed by both pathways.[1–5] The factors which determined whether a nucleophilic or general base mechanism obtains have only just begun to be assembled.[1–5] Of particular interest are the reactions of amino groups in enzyme-catalyzed reactions.[6] We will demonstrate that the reactions of nitrogen bases with bis(*p*-nitrophenyl) methylphosphonate (I) occur by general base catalysis of water attack, while fluoride ion and oxyanions react *via* a nucleophilic mechanism.

Experimental Section

Bis(*p*-nitrophenyl) methylphosphonate (b-*p*-NPMP) and *p*-nitrophenyl methylphosphonate (*p*-NPMP) were synthesized as previously reported:[7] b-*p*-NPMP, mp 127–129°; nmr ($CDCl_3$) δ 1.98 (d, 3), 7.82 (q, 8); *p*-NPMP, mp 112–113°; nmr ($CDCl_3$) δ 1.63 (d, 3), 7.71 (q, 4), 12.18 (s, 1).

Commercial piperidine hydrochloride was recrystallized from absolute ethanol, *n*-butylamine hydrochloride from ethanol–hexane, and imidazole from benzene. *s*-Collidine hydrochloride was prepared by bubbling hydrogen chloride gas through *s*-collidine dissolved in hexane. The hydrochloride was filtered and recrystallized from 1-butanol. Pyridine was distilled from potassium hydroxide under reduced pressure (2 mm) and aziridine (Dow Chemical Co.) was distilled from potassium hydroxide at atmospheric pressure. Hydrazine dihydrochloride and ammonia (0.1 *M* standardized) were Fisher Certified Reagents and used without further purification. Benzohydroxamic acid (Aldrich Chemical Co.) was recrystallized from ethyl acetate[8] and *p*-methoxyphenol from 1-butanol. Deuterium oxide, 99.8% purity, was obtained from Bio-Rad Laboratories. Acetonitrile was Mallinckrodt Nanograde. All other materials were of reagent grade and used without further purification.

Phosphate and carbonate buffers were prepared according to the procedures in the Biochemists Handbook.[9] For amines, partially neutralized solutions (usually 0.5 or 0.1 neutralized) of the nitrogen bases were used as buffers. Standardized hydrogen chloride and sodium hydroxide solutions were used to neutralize amines as the free base or as the hydrochloride, respectively. Potassium chloride was employed to maintain ionic strength at 0.5 *M*. Approximately 10^{-4} *M* EDTA was added to all solutions. pH measurements were made on a Radiometer Model 26 pH meter. Desired pH values were easily maintained since low substrate concentrations were used.

Spectra. Nmr spectra were recorded on a Varian T-60 instrument. Ultraviolet spectra were obtained on a Cary 14 spectrophotometer. A pK_a value of 7.15 for *p*-nitrophenol was employed;[10] spectra of *p*-nitrophenol[11] and *p*-nitrophenolate anion[7] yielded absorbance maxima at 317 nm (ε 9500) and 400 (18,200), respectively. *p*-Nitrophenyl methylphosphonate had a maximum

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(1) J. R. Cox and O. B. Ramsey, *Chem. Rev.*, 64, 317 (1964).

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 6.

(3) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, Chapter 10.

(4) S. A. Khan and A. J. Kirby, *J. Chem. Soc. B*, 1172 (1970), and references cited therein.

(5) A. Williams and R. A. Naylor, *ibid.*, 1967 (1971).

(6) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971, Chapter 16.

(7) E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3063 (1970).

(8) C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 67.

(9) S. P. Datta and A. L. Grzybowski, "Biochemists Handbook," C. Long, Ed., Van Nostrand, New York, N. Y., 1961, p 19.

(10) J. Bjerrum, F. Schwarzenbach, and L. G. Sillen, *Chem. Soc., Spec. Publ.*, No. 6, 1 (1957).

(11) L. Lang, Ed., "Absorption Spectra in the Ultraviolet and Visible Region," Academic Press, New York, N. Y., 1962.

Table I. General Base Catalysis of the Hydrolysis of Bis(*p*-nitrophenyl) Methylphosphonate (b-*p*-NPMP) at 25.5° [a]

Amine	pK_a[b]	[Amine], M[c]	pH[d]	k_2, M^{-1} sec^{-1} [e]	$k_2(H_2O)/k_2(D_2O)$
Pyridine	5.35	0.149–0.894	5.31–5.42[f]	7.25×10^{-4}	
		0.152–0.912	6.25–6.38[f]	8.00×10^{-4}	
	5.85	0.167–0.449	5.42–5.48[f,g]	3.14×10^{-4} [h]	2.30
Imidazole	7.19	0.0324–1.00	7.19	3.03×10^{-3}	
		0.333–1.00	8.20	3.08×10^{-3}	
	7.65	0.167–1.00	7.25[g]	1.47×10^{-3} [h]	2.06
	7.65	0.333–1.00	8.31[g]	1.30×10^{-3} [h]	2.37
s-Collidine	7.45	0.139–0.416	7.35–7.59[f]	8.15×10^{-4}	
Hydrazine	7.93[i]	0.0833–0.250	8.23	2.38×10^{-3} [i]	
	8.43[i]	0.0833–0.250	8.23[g]	1.06×10^{-3} [h,i]	2.19
Aziridine	8.10	0.167–1.00	9.90	6.40×10^{-3}	
Ammonia	9.42	0.015–0.090	9.63	1.11×10^{-2}	
n-Butylamine	10.83	0.100–0.500	10.83	6.31×10^{-2}	
Piperidine	11.35	0.0835–0.500	11.35	1.54×10^{-1}	
		0.0835–0.500	10.42	1.62×10^{-1}	

[a] Concentration of b-*p*-NPMP = $2.20–2.80 \times 10^{-5}$ M; ionic strength = 0.5 M with added KCl. [b] Of amine conjugate acid; pK_a values are observed pH values for amines in solution as 50% acidic–50% basic forms, established by quantitative addition of standard HCl or NaOH. For pyridine and *s*-collidine, an average value was taken (see footnote *f*). pK_a values are in agreement with literature values: R. C. Weast, Ed., "Handbook of Biochemistry," Chemical Rubber Publishing Co., Cleveland, Ohio, 1968. pK_a values in D_2O are taken as observed pH values + 0.40 for solutions of half-neutralized amine.[26] [c] Total amine concentration; fraction of free base present in solution is dependent on pH values. [d] The amine and its hydrochloride were used as buffers in all cases. [e] k_2 values were determined from the slope of the plots of pseudo-first-order rate constants *vs.* concentrations of amine existing in the free base form. [f] pH values of 0.5 and 0.1 neutralized solutions of pyridine and 0.5 neutralized solutions of *s*-collidine were dependent on amine concentration. This is consistent with self-association at high amine concentration as previously reported (ref 4 and 19). [g] Observed "pH" values in D_2O. [h] In D_2O. [i] Statistically corrected.

in water at 288 nm (ε 9560). b-*p*-NPMP in acetonitrile yielded a maximum at 274 nm (ε 19,400).

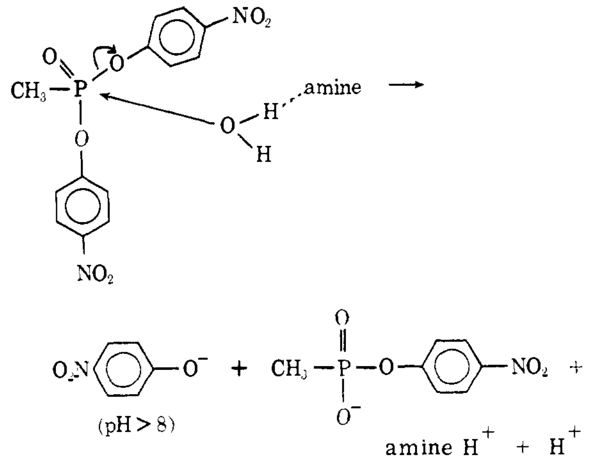
Kinetics. Reactions of b-*p*-NPMP were performed by measuring the rate of appearance of *p*-nitrophenol or its anion, depending on pH, and in some cases the appearance of *p*-NPMP. A Cary 14 recording spectrophotometer equipped with a thermostated cell holder and 0–1 and 0–0.1 slide wires was used. The reaction medium consisted of the reagent at the desired concentration and pH. Exactly 3 ml of this solution was pipetted into a 1-cm cuvette and thermostated for *ca.* 15 min. The reaction was initiated by the addition of 1–10 μl of a stock solution of substrate dissolved in acetonitrile, using a flat-top plastic stirring rod. Final ester concentrations were ~$2.20–2.80 \times 10^{-5}$ M; acetonitrile was ≤0.5% v/v. Depending on reaction rate, spectrophotometer measurements were made within 2–10 sec after mixing. Times were measured using the Cary 14 recorder which was independently calibrated. Reactions were run under pseudo-first-order conditions with catalyst in excess and in all cases followed first-order kinetics. Most reactions were allowed to proceed to infinity (at least 10 half-lives) and rate constants were calculated using the usual first-order expression for a reaction to completion.[12] For some slower reactions the methods of Guggenheim[13] or Kezdy[14] were employed. Data were analyzed in these cases using a computer-calculated least-squares Guggenheim or Kezdy plot. b-*p*-NPMP reactions with *p*-methoxyphenol anion were complicated by phenol oxidation. For this nucleophile, buffer solutions were deoxygenated by allowing nitrogen gas to bubble through them. Oxidation was thus minimized and the data were treated by the Kezdy method.

Second-order rate constants were determined by plotting observed pseudo-first-order constants against catalyst concentration. The slope was taken as the second-order rate constant and the intercept as the first-order constant in the absence of added catalyst.

The rates of reaction of *p*-NPMP in the presence of imidazole in borate buffers were followed by the rate of *p*-nitrophenolate anion formation at 400 nm as previously described.[15] Pseudo-first-order rate constants were treated in the same way as the first-order constants for b-*p*-NPMP reactions.

Results

Amines. Data for the reactions of amines with bis(*p*-nitrophenyl) methylphosphonate, b-*p*-NPMP, are given in Table I. A Brønsted plot for the data in Table I is shown in Figure 1. The rate-determining step for these reactions is represented in eq 1. Evidence



(1)

for general base catalysis by amines of water attack is as follows.

a. The free base form is the only kinetically active amine species detected. The rate law at the pH values examined is given in eq 2, where k_2, k_2', and k_2'' are the

$$\text{rate} = [\text{b-}p\text{-NPMP}] \times \{k_2[\text{amine}] + k_2'[\text{OH}^-] + k_2''[\text{H}_2\text{O}]\} \quad (2)$$

second-order rate constants for the reaction of amine, hydroxide ion, and water, respectively. Using partially neutralized amine solutions as buffers, k_2 values are obtained from the slope of the observed pseudo-first-order rate constants plotted as a function of amine existing in the free base form. The intercept yields the $k_2'[\text{OH}^-]$ and $k_2''[\text{H}_2\text{O}]$ quantities. Values of k_2 are independent of pH, which excludes specific acid and base-catalyzed pathways as being kinetically important. No evidence could be found for rate terms greater than first order in amine free base, nor was the rate found to be dependent on protonated amine.

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(12) K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1965, p 7.

(13) E. D. Guggenheim, *Phil. Mag.*, 2, 538 (1926).

(14) F. J. Kézdy, J. Jay, and A. Bruylants, *Bull. Soc. Chim. Belg.*, 67, 687 (1958).

(15) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, 92, 4675 (1970).

Table II. Reactions of Imidazole with *p*-NPMP[a]

[*p*-NPMP], M	[Imid],[b] M	pH	k_2, M^{-1} sec^{-1}	$k_2(H_2O)/k_2(D_2O)$
1.02×10^{-3}	0.0966–0.199	9.22[c]	1.30×10^{-6}	1.04
1.03×10^{-3}	0.100–0.200	9.37[c,d]	1.25×10^{-6} [e]	
2.47×10^{-5} [f]	0.597	8.74[g]	1.50×10^{-6} [h]	

[a] T = 60.9°. [b] Total imidazole concentration. [c] 0.133 M sodium borate solution; pH observed at 25°. [d] Observed "pH" in D_2O. [e] In D_2O. [f] *p*-NPMP concentration based on initial concentration of b-*p*-NPMP. [g] 0.200 M boric acid–sodium hydroxide; pH observed at 25°. [h] Determined under pseudo-first-order conditions.

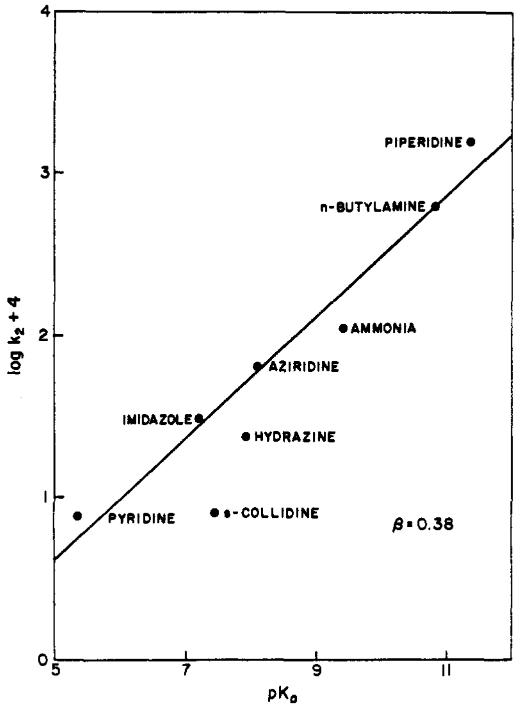

Figure 1. Brønsted plot for the general base-catalyzed reactions of amines with b-*p*-NPMP at 25.5°.

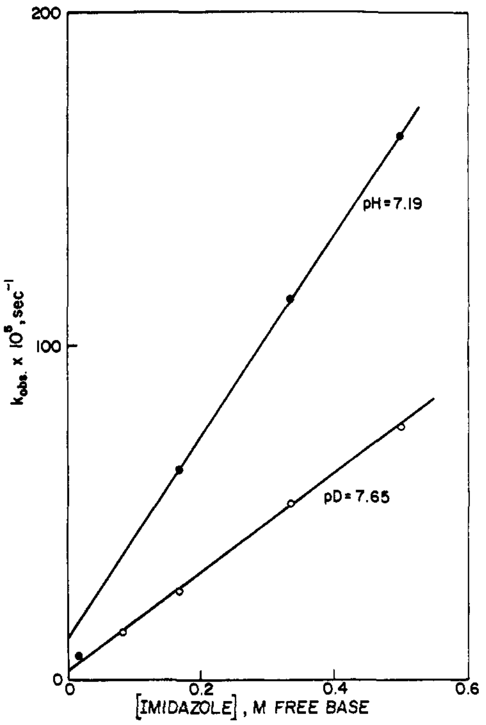

Figure 2. Plot of the observed rate constants in H_2O and D_2O for the reaction of imidazole with b-*p*-NPMP *vs.* the concentration of imidazole in the free base form.

b. For all amines listed in Table I, 1 mol of *p*-nitrophenyl methylphosphonate (*p*-NPMP) and 1 mol of *p*-nitrophenol (or its anion, depending on pH) are formed. *p*-NPMP has an absorbance maximum at 288 nm (ε 9560). Above pH 9, spectra due to *p*-nitrophenolate anion at 400 nm and *p*-NPMP are easily separable. *p*-NPMP once formed is much less reactive than b-*p*-NPMP[7,15,16] and can be considered stable. For five amines, imidazole, hydrazine, ammonia, *n*-butylamine, and piperidine, the rates of formation of *p*-nitrophenolate anion (*p*-NP) and *p*-NPMP were identical. The rate of *p*-NPMP formation was followed at 310 nm by difference spectroscopy.[17]

c. Most amines in Table I follow a Brønsted relation (Figure 1) with a slope of 0.38 (r = 0.97) except for *s*-collidine which falls considerably below the line. These amines have widely differing steric environments about the nitrogen center; one would expect considerably more scatter if a nucleophilic mechanism obtained[4,15,18–24] (see Discussion).

d. *s*-Collidine, although falling below the Brønsted line in Figure 1, is as reactive as pyridine. In nucleophilic substitution reactions at phosphorus a sterically hindered amine such as *s*-collidine would be expected to show no or low reactivity.[4,15,18] Where general base catalysis is observed, *s*-collidine shows appreciable reactivity and often is approximately as reactive as pyridine.[4,18,25]

e. The deuterium solvent isotope effects, $k(H_2O)/k(D_2O)$, for the reactions of pyridine, imidazole, and hydrazine are in the range 2.06–2.37. Figure 2 shows the reactivity of b-*p*-NPMP with half-neutralized imidazole in H_2O (pH 7.19) and D_2O (pD 7.65).[26] The value of the isotope effect is as expected for general base catalysis.[4,5,25,27] Nucleophilic catalysis would yield an isotope effect near unity.[4,15,19–22]

Data for the reaction of imidazole with *p*-NPMP at 60.9° are given in Table II. The solvent isotope effect

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[16] E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3069 (1970).

[17] In kinetic studies the absorption maxima of *p*-NPMP is not useful owing to the strong absorbance of b-*p*-NPMP, $\lambda_{max}(H_2O)$ = 270 nm.

[18] Reference 2, pp 59–61, and ref 3, pp 317–322 and references cited therein.

[19] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965).

[20] W. P. Jencks and M. Gilchrist, *ibid.*, **87**, 3199 (1965).

[21] G. DiSabato and W. P. Jencks, *ibid.*, **83**, 4393 (1961).

[22] A. J. Kirby and M. Younas, *J. Chem. Soc. B*, 1165 (1970).

[23] G. J. Lloyd, C.-M. Hsu, and B. S. Cooperman, *J. Amer. Chem. Soc.*, **93**, 4889 (1971).

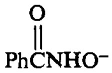
[24] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 511, 516 (1953).

[25] F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).

[26] pD = pH + 0.40; T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961); P. K. Glasoe and F. A. Long, *ibid.*, **64**, 188 (1960).

[27] Reference 3, p 306.

Table III. Data for the Reactions of Nucleophiles with b-*p*-NPMP[a]

Nucleophile	pK_a[b]	[N], *M*[c]	pH	k_2, M^{-1} sec^{-1}
F^-	3.45	0.001–0.03	7.09[d]	2.65
		0.001–0.05	9.14[e]	2.38
 $\mathrm{Ph\overset{\overset{O}{\|}}{C}NHO^-}$	8.80[f]	0.00178–0.09	7.50[d]	33.8
CH_3OPhO^-	10.20	0.0274–0.0977	9.08–9.21	$k_2(1) = 1.48$[g] $k_2(2) = 8.88 \times 10^{-2}$[g]
OH^-	15.74		8.90–11.35	35
HPO_4^{2-}	7.21	0.05–0.15	8.89–9.05[h]	1.22×10^{-2}
		0.05–0.15	8.85–9.12[h,i]	1.07×10^{-2}[j]

[a] [b-*p*-NPMP] = 2.50–2.58 × 10^{-5} *M*; ionic strength equals 0.5 *M* with KCl. [b] pK_a of the conjugate acid. Values are from ref 15 unless noted. [c] Total nucleophile concentration; fraction of free base is dependent on pH values. [d] In 0.2 *M* phosphate buffer. [e] In 0.2 *M* carbonate buffer. [f] R. Swidler, R. F. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81**, 327 (1959). [g] Second-order rate constants for each step of the two-step reaction. Rate constants are calculated by a computer-assisted Kezdy method.[12] [h] pH established by KH_2PO_4 and added KCl. This is an unbuffered system and pH was slightly dependent on HPO_4^{2-} concentration. This method is acceptable since the rate of reaction in the absence of phosphate is small. [i] Observed "pH" in D_2O. [j] In D_2O; $k_2(H_2O)/k_2(D_2O) = 1.15$.

equals 1.04 which is consistent with a nucleophilic mechanism for amine–*p*-NPMP reactions as shown previously.[15] b-*p*-NPMP, in the presence of imidazole, produces 1 mol of *p*-NPMP as determined by spectrophotometric methods (Table I). When the resulting solution is allowed to react further at 60.9° the second phenolate moiety is released in a slow pseudo-first-order process. A second-order rate constant is calculated (Table II), which within experimental error equals that obtained for the *p*-NPMP–imidazole reaction, using *p*-NPMP as substrate.

Nucleophiles. The reactions of fluoride ion and most oxyanions studied can be shown to proceed by a nucleophilic pathway. Data for these reagents are given in Table III. Each reagent will be discussed separately.

Fluoride Ion. At high fluoride ion concentrations reaction with b-*p*-NPMP releases 2 mol of *p*-nitrophenol in a first-order process. This is interpreted on the basis of an initial nucleophilic attack by fluoride ion at phosphorus in a slow step forming *p*-nitrophenyl methylphosphonofluoridate (II) (Scheme I, reaction a). This is followed by a faster nucleophilic attack producing III (reaction b). However, at lower fluoride ion concentrations, less than the theoretical amount of *p*-nitrophenol (*p*-NP) was released (also in a first-order process) corrected for reaction of buffer. It will be shown that carbonate and phosphate buffers in the absence of fluoride ion react with b-*p*-NPMP, producing 1 mol of *p*-NP.

Equations b–d of Scheme I show the possible reactions of II. None of the reactions were followed kinetically. A rate expression can be written, however, for the disappearance of II which is given in eq 3

$$-\mathrm{d(II)}/\mathrm{d}t = k_b[\mathrm{II}][\mathrm{F}^-] + k_c[\mathrm{II}][\mathrm{B}] + k_d[\mathrm{II}][\mathrm{B}] \quad (3)$$

where B is a base in solution and can be buffer, hydroxide ion, or water.[28] The reactions are each first order in II and eq 3 can be transformed to eq 4, where

$$k'_{\mathrm{obsd}} = k_b[\mathrm{F}^-] + k_c[\mathrm{B}] + k_d[\mathrm{B}] \quad (4)$$

k'_{obsd} is a first-order rate constant. The k_b and k_c steps result in the release of 2 mol of *p*-NP, while only 1 mol of *p*-NP is released as a result of k_d. Equation 5

$$(k_b[\mathrm{F}^-] + k_c[\mathrm{B}])/k_d[\mathrm{B}] = (A_\infty - A_1)/(2A_1 - A_\infty) \quad (5)$$

can be derived from eq 4, where A_1 is the infinity value for the release of 1 mol of *p*-NP at a given substrate concentration, and A_∞ is the infinity value for reaction in the presence of fluoride ion at the same concentration of substrate.

Table IV presents data for the reaction of fluoride ion with b-*p*-NPMP in various buffer systems. The slow step, k_{slow}, is independent of pH and buffer as expected for a rate-determining nucleophilic attack of fluoride ion on b-*p*-NPMP. Consistent with this interpretation is the value for the solvent isotope effect which is near unity. Equation 5 leads to the prediction at constant [B] that $((A_\infty - A_1)/(2A_1 - A_\infty))$ be proportional to fluoride ion concentration. Figure 3 shows this to be the case. Data for *s*-collidine in water are not plotted

Table IV. Data for the Reactions of b-*p*-NPMP with Fluoride Ion[a]

Conditions	A_∞	$\dfrac{A_\infty - A_1}{2A_1 - A_\infty}$	[F⁻], *M*	k_{slow}, M^{-1} sec^{-1}[b]
I = 0.2 *M* phosphate, pH 7.09	0.495	49.0	0.300	
	0.481	12.2	0.03	
	0.473	8.26	0.02	2.65
	0.450	4.00	0.01	
	0.435	2.85	0.01	
	0.398	1.45	0.005	
	0.380	1.08	0.003	
	0.329	0.462	0.001	
	0.250		0.000	
I = 0.2 *M* carbonate, pH 9.13	0.880	3.99	0.05	
	0.780	1.47	0.0167	2.38
	0.660	0.646	0.01	
	0.665	0.562	0.005	
	0.500	0.058	0.001	
	0.489		0.000	
I = 0.2 *M* *s*-collidine, pH 7.52	0.698	115.6	0.0272	
	0.695	57.3	0.00906	2.88
	0.666	8.75	0.00453	
	0.639	4.57	0.00181	
	0.580	1.87	0.000906	
	0.351		0.000	
I = 0.2 *M* *s*-collidine, pH 7.6, 92% D_2O[c]			0.00405	2.46
			0.0243	

[a] 0.3 *M* KCl added in all experiments, I = 0.5 *M*; [b-*p*-NPMP] = 2.58 × 10^{-5} *M*. [b] Second-order rate constant for reaction a, Scheme I; $k_{\mathrm{slow}} = k_2$ in Table III. [c] Observed "pH" value.

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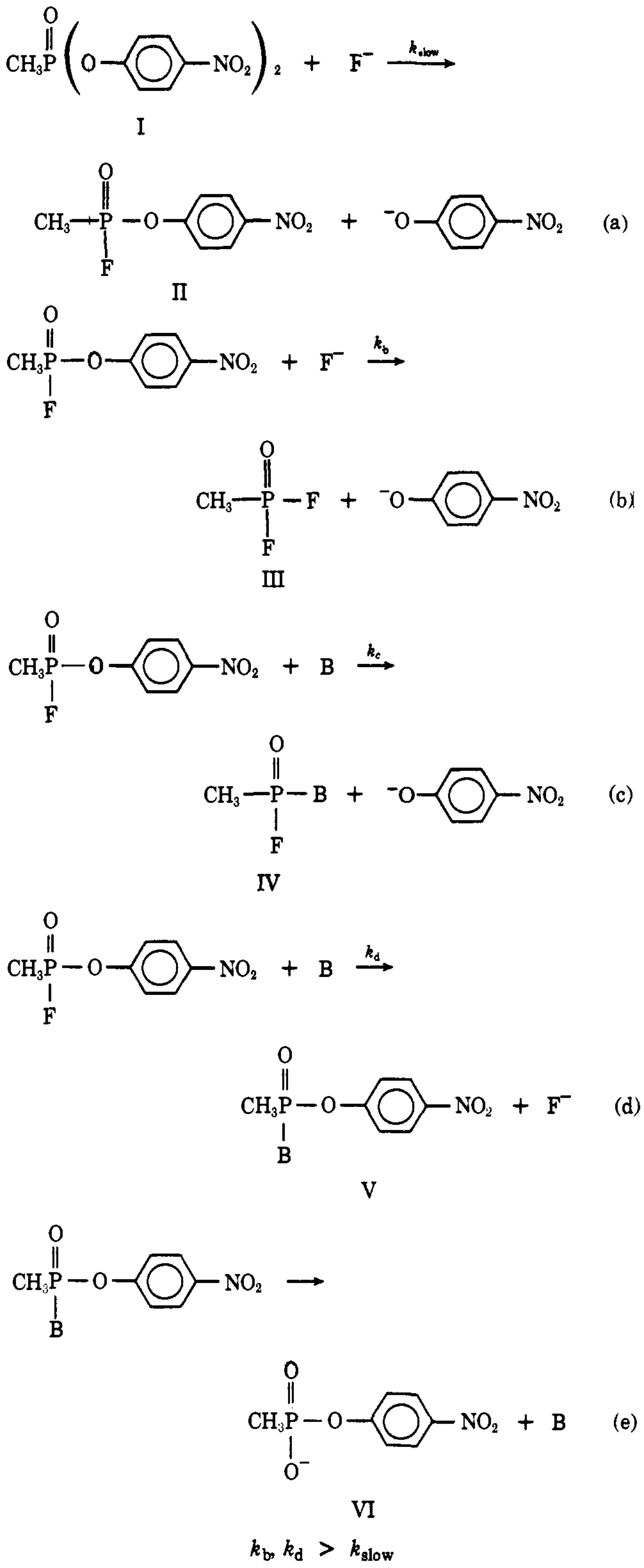
[28] A rate term for the reaction of II with *p*-nitrophenolate anion regenerating I has been omitted. Such a rate term would be expected to be small on the basis of the concentrations of II and *p*-nitrophenol present and on the low nucleophilicity of the *p*-nitrophenolate anion.

Scheme I



since at the fluoride ion concentrations used, the values of $(A_\infty - A_1)/(2A_1 - A_\infty)$ are large and yield a line with a good deal of scatter. The plots for phosphate and carbonate buffers (Figure 3) pass through the origin; thus the quantity $k_c[B]$ in eq 4 and 5 is small and can be neglected. The slope in Figure 4 is greater in phosphate than in carbonate buffers. The values of $(A_\infty - A_1)/(2A_1 - A_\infty)$ in *s*-collidine (pH 7.52) buffer are greater than in phosphate (pH 7.09) buffer at comparable fluoride concentrations. This is consistent with phosphate (as HPO_4^{2-} and $H_2PO_4^-$) and carbonate (as CO_3^{2-} and HCO_3^-) acting as nucleophiles[29] in the k_d step (reaction d, Scheme I). A general base path cannot be excluded, however. *s*-Collidine would be expected to be a weak nucleophile or act as a general base.

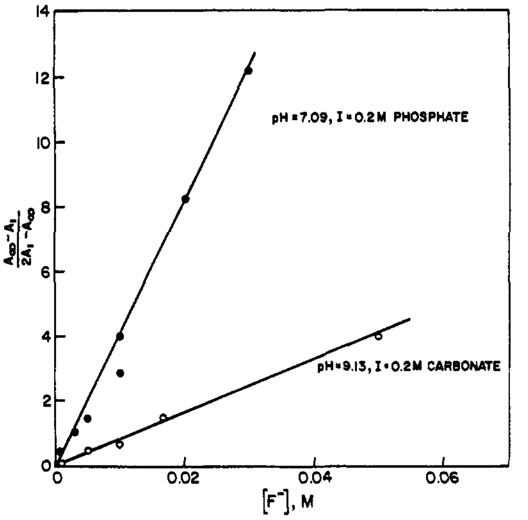


Figure 3. Plot of $(A_\infty - A_1)/(2A_1 - A_\infty)$ *vs.* fluoride ion concentration for phosphate and carbonate buffers.

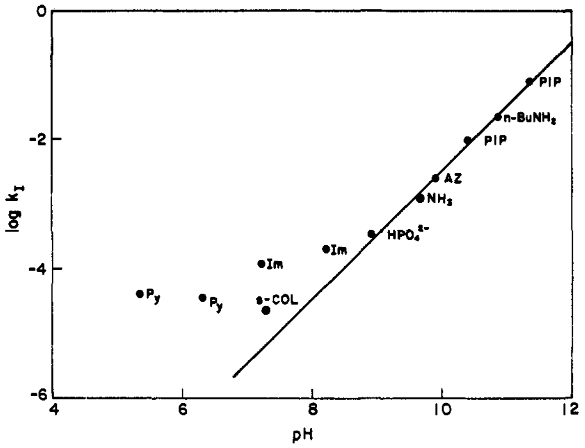


Figure 4. Plot of log k_1 *vs.* pH. Each point represents the observed rate in the presence of the labeled amine or HPO_4^{2-}, extrapolated to 0 *M* amine or HPO_4^{2-} concentration.

Further information can be obtained from spectral data after the reaction of b-*p*-NPMP in the presence of fluoride ion. These data are presented in Table V. In carbonate buffer *p*-nitrophenyl methylphosphonate ion (*p*-NPMP) can be detected as a reaction product. Based on the extinction coefficients for *p*-NPMP and *p*-nitrophenolate ion, the quantity of *p*-NPMP found is exactly equal to the amount of the second mole of *p*-NP in b-*p*-NPMP that is unreleased. V (Scheme I, reaction e) likely decomposes to *p*-NPMP. If a general base path is operative, *p*-NPMP would be produced directly from II.

Hydroxamate Ion. The reaction of benzohydroxamate ion with b-*p*-NPMP releases 2 mol of *p*-NP in a first-order process. This is explained on the basis of

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[29] It should be noted that by varying phosphate and carbonate concentrations, values of k_a and k_c could be obtained. This was not done in this investigation.

Table V. Spectral Data for the Reaction of b-*p*-NPMP with Fluoride Ion[a]

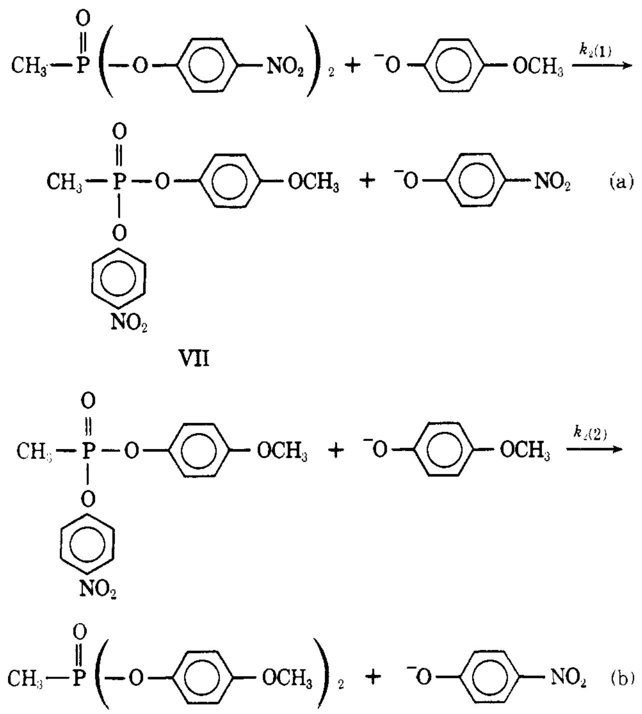
$[F^-]$, M	$A_{\infty(400\ nm)}$	$A_{\infty(288\ nm)}$	[*p*-nitrophenolate], M, unreleased	[*p*-NPMP], M
0.3	0.960	0.074	0	0.75×10^{-5} (max)
0.01	0.660	0.142	1.53×10^{-5}	1.45×10^{-5}
0.001	0.500	0.228	2.41×10^{-5}	2.35×10^{-5}
0	0.470	0.250	2.58×10^{-5}	2.61×10^{-5}

[a] [b-*p*-NPMP] = 2.58×10^{-5} M; 0.2 M carbonate, I = 0.5 M with KCl, pH 9.14; $A_{max\ 400} = 0.470$ for 1 mol of *p*-nitrophenolate anion released.

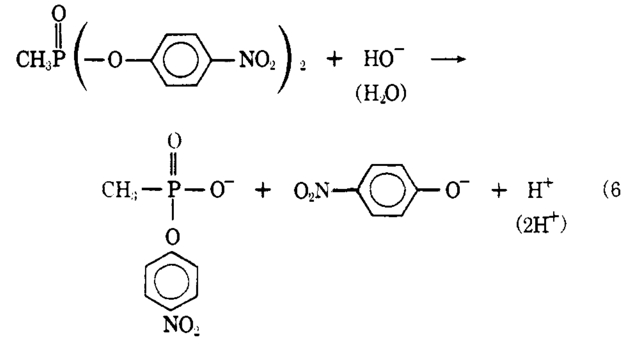
two consecutive displacements by benzohydroxamate ion at phosphorus, the first step being rate determining. The rate constant for the initial bimolecular displacement is given in Table III.

***p*-Methoxyphenolate Ion.** Reaction of this reagent with b-*p*-NPMP produces 2 mol of *p*-NP. However, the reaction was biphasic. It could be analyzed on the basis of two consecutive first-order reactions as shown in Scheme II, yielding a second-order rate constant for each step (Table III).

Scheme II



Hydroxide Ion (and Water). The reactions of hydroxide ion and water with b-*p*-NPMP proceed according to eq 6.[16] Rate constants for the hydrolysis of b-*p*-NPMP due to the reactions of hydroxide ion and water can be obtained from intercepts of the amine and phosphate dianion data. Figure 4 plots log k_I against pH, where k_I is the first-order rate constant at 0 M amine (or HPO_4^{2-}) for the data in Table I. Above pH 9 the slope in Figure 4 is unity, showing a first-order dependence on hydroxide ion. A value of k_2 for hydroxide ion of 35 M^{-1} sec^{-1} is calculated (Table III). Below pH 9, the water reaction becomes kinetically important.



Phosphate Dianion. The reactions of b-*p*-NPMP in phosphate and carbonate buffers produce 1 mol of *p*-NP and 1 mol of *p*-NPMP in a first-order process. The reaction of HPO_4^{2-} was studied; data are in Table III. The deuterium solvent isotope effect equals 1.15. At 0.05–0.15 M HPO_4^{2-}, the rate of *p*-NPMP formation at 310 nm is always slower than *p*-NP production. These data suggest that phosphate dianion acts as a nucleophile toward b-*p*-NPMP forming pyrophosphate[30] which then decomposes to *p*-NPMP and HPO_4^{2-}.

Discussion

Reactions of reagents with b-*p*-NPMP proceed *via* attack at the phosphorus center. Attack at aromatic carbon can be excluded on the grounds that it would yield smaller rate constants than those observed in this investigation.[19]

Substitution reactions at phosphorus can take place by direct nucleophilic displacement *or* general base catalysis of water attack. Thus, reactions of amines with diisopropyl phosphorochloridate,[24] *p*-nitrophenyl phosphate dianion,[19] phosphoramidate monoanion,[20] *p*-nitrophenyl methylphosphonate,[15] phosphorylimidazole,[23] and aryl methyl phosphate monoanions[22] proceed by direct displacement. Hydrolysis of diisopropyl phosphorofluoridate,[31,32] diethyl phosphorofluoridate,[33] isopropyl methylphosphonofluoridate (Sarin) in water[34] and methanol,[35] methyl ethylene phosphate,[25] and aryl diphenylphosphinates[5] proceeds *via* general base catalysis. Reactions of some 2-aryloxy-2-oxo-1,3,2-dioxaphosphorinanes[4] with amines proceed by competing nucleophilic and general base mechanisms. Most of the above substrates react with active oxyanions and fluoride ion[2,3] by a nucleophilic pathway. Weakly basic oxyanions such as acetate react with certain "phosphorinanes"[4] by general base catalysis.

b-*p*-NPMP is useful in distinguishing nucleophilic and general base mechanisms. Reactions of b-*p*-NPMP with neutral or monoanionic nucleophiles can yield a neutral phosphorus molecule, which should react further with excess reagents at measurable rates. However, water attack catalyzed by a general base produces *p*-nitrophenyl methylphosphonate ion which is unreactive at 25° compared to b-*p*-NPMP. *p*-NPMP has an ultraviolet absorption, making it easily detectable.

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(30) Reference 2, Chapter 7.

(31) M. Kilpatrick and M. L. Kilpatrick, *J. Phys. Chem.*, 53, 1371 (1949).

(32) R. F. Hudson and R. Greenhalgh, *J. Chem. Soc. B*, 325 (1969).

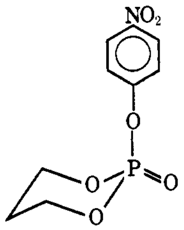
(33) T. Wagner-Jauregg and B. E. Hackley, *J. Amer. Chem. Soc.*, 75, 2125 (1953).

(34) J. Epstein, P. L. Cannon, Jr., and J. R. Sowa, *ibid.*, 92, 7390 (1970).

(35) M. A. Weinberger, R. Greenhalgh, and P. M. Lutley, *Can. J. Chem.*, 48, 1358 (1970).

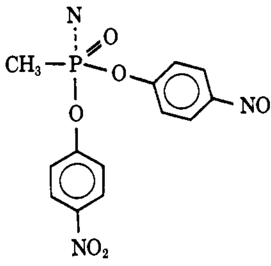
Amines. Reactions of b-*p*-NPMP with amines proceed exclusively by a general base pathway. The stoichiometry (eq 1), rate law (eq 2), Brønsted correlation, and solvent deuterium isotope effect are completely consistent with this interpretation. The kinetically equivalent general acid–hydroxide ion reaction can be excluded. b-*p*-NPMP is one of the few examples of an acyclic organophosphorus ester showing general base behavior in its reactions with amines. The fit and slope of the Brønsted plot are of interest. General base catalyzed reactions as well as nucleophilic displacements are subject to steric effects about the nitrogen center.[36] Steric effects are more marked for the nucleophilic cases. The apparent fit to a Brønsted plot (Figure 1) of amines of widely varying structure is likely fortuitous. Small deviations of ammonia, piperidine, and hydrazine as well as the larger one of *s*-collidine are consistent with this interpretation. However, the fit that is obtained would not be expected if a nucleophilic path obtained.

The magnitude of the Brønsted slope, *ca.* 0.38, is consistent with a general base mechanism. It has been shown that toward the same or similar neutral substrates a nucleophilic mechanism yields a higher value of the Brønsted slope than a general base path.[37] For example, the reactions of substituted pyridines with 2-(2,4-dinitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (VIII) proceed by a nucleophilic mechanism yielding a Brønsted β of *ca.* 0.70, while amines reacting with VIII by a general base path appear to yield a lower β value.[4] Sarin[34] reacts with amines in water *via* a general base mechanism; the β value is 0.51.


VIII

Hydrazine falls slightly below the drawn Brønsted line (Figure 1). The hydrazine reaction with Sarin[34] falls on the Brønsted line. In cases where a nucleophilic pathway occurs, hydrazine is usually more reactive than would be expected on the basis of its basicity and thus displays an α effect.[4,38] It seems likely that general base catalysis of water attack at the tetrahedral organophosphorus center does not show an α effect by hydrazines.[39]

General base catalysis by amines seems to depend on "the relative basicity of the nucleophile and the leaving group."[4] Low amine basicity and/or a poor leaving group in the substrate favor it. However, b-*p*-NPMP provides a good leaving group and some of the amines examined are quite basic. An explanation can be offered based on steric crowding that would occur if an amine attacked directly at phosphorus. Courtauld models show that a trigonal-pyramidal transition state, IX (or pentacovalent intermediate), produced by attack of any nucleophile on b-*p*-NPMP, is crowded. The smaller water molecule can, *via* the general base path, attack phosphorus more easily than an amine nitrogen. This approach is offered to explain the general base reactions of imidazole with a series of aryl diphenylphosphinates.[5] A similar explanation has been advanced to explain a general base mechanism for reaction of sterically hindered amine with a sulfinyl sulfone.[40] One might expect that aziridine and ammonia attack b-*p*-NPMP nucleophilically since the nitrogen atom is not hindered by adjacent carbon atoms. Yet they do not and one must conclude that specific effects determine the mode of attack at phosphorus.


IX

Examples of general base catalysis are restricted principally to neutral phosphorus substrates. Anionic substrates undergo direct displacement by nitrogen nucleophiles. In the transition state an incoming nitrogen nucleophile develops a partial positive charge, which is alleviated by primary and secondary amines by eventual loss of a proton. Development of a partial positive charge on nitrogen *may* favor attack by the amine at a phosphorus molecule which has a net negative charge.[41]

Nucleophiles. The reactions of fluoride ion and oxyanions with b-*p*-NPMP proceed by way of a nucleophilic pathway. Release of 2 mol of *p*-nitrophenol from b-*p*-NPMP (with fluoride, benzohydroxamate, or *p*-methoxyphenolate ions) and solvent deuterium isotope effects (near unity for fluoride ion and phosphate dianion) are in agreement with this interpretation. The relative reactivities of the reagents listed in Table III are similar to the order of their reactivities with other organophosphorus substrates where a nucleophilic mechanism has been shown.[2,4,16]

Fluoride, *p*-Methoxyphenolate, and Benzohydroxamate Ions. Fluoride ion has been shown to be a remarkably reactive nucleophile toward neutral[2,3,38,42] and anionic[16,21,22,43] organophosphorus esters. The strength of the phosphorus–fluorine bond is documented.[32] Fluoride ion should be a weak general base and its reaction with b-*p*-NPMP by a nucleophilic pathway is clear. Further evidence can be presented. The reactions of VIII with hydroxide and fluoride ions are probably nucleophilic in nature.[4] The ratio of their second-order rate constants is 110, while this same ratio for hydroxide and fluoride ions with b-*p*-NPMP is 140.

[36] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapters 2 and 3.

[37] Reference 6, pp 176–179.

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

[39] Hydroxylamine does show an apparent α effect where general base catalysis obtains. However, this may be due to oxygen attack: H. J. Brass and M. L. Bender, unpublished results.

[40] J. L. Kice and J. D. Campbell, *J. Org. Chem.*, **36**, 2291 (1971).

[41] G. W. Jameson and J. M. Lawlor, *J. Chem. Soc. B*, 53 (1970).

[42] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 508 (1953).

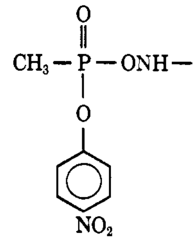
[43] A. J. Kirby and A. G. Varvoglis, *ibid.*, 135 (1968).

Details of the reactions of *p*-nitrophenyl methylphosphonofluoridate (II) (Scheme I, reactions b–e) must be carefully interpreted. Data for the reactions of II are obtained by quantities of product (*p*-NP) produced rather than direct kinetic measurements. The reactions in Scheme I are reasonable and consistent with previously reported data.[44] A nucleophilic mechanism is favored for the reaction of II with carbonate and phosphate species.[4] However, a general base path cannot be excluded and is reasonable for the *s*-collidine reaction.

The question arises as to why reaction a is the slow step in Scheme I. Two *p*-nitrophenyl moieties in b-*p*-NPMP (I) should make it a more reactive substrate than II. The steric crowding argument invoked for amine reactions can be applied. Crowding in the transition state makes fluoride ion attack on b-*p*-NPMP difficult. Such crowding is not present in II and its reactions with fluoride ion and other bases proceed more rapidly.

Further substantiation of the steric crowding approach is derived from the reaction of *p*-methoxyphenolate ion with b-*p*-NPMP. Two consecutive first-order reactions are observed. The initial product upon nucleophilic substitution is *p*-methoxyphenyl *p*-nitrophenyl methylphosphonate (VII) (Scheme II, reaction a). Replacement of a *p*-methoxy group for a *p*-nitro group produces a substrate (VII) with approximately the same steric environment about the phosphorus center as in b-*p*-NPMP. The reactivity of VII should be less than that of b-*p*-NPMP based on electronic factors; this is precisely the case.

The reaction of benzohydroxamate ion with b-*p*-NPMP is rapid owing to the α effect displayed by this nucleophile.[2,16,38,45] With benzohydroxamate ion in excess two consecutive displacements on b-*p*-NPMP appear to occur, the first being the slow step producing X. However, we cannot discount the possibility that an internal displacement in X takes place by loss of a proton bonded to nitrogen, followed by attack of the anion produced at phosphorus, releasing the second mole of *p*-nitrophenol.[46]



X

Hydroxide Ion and Water. The reactions of hydroxide ion and water with b-*p*-NPMP produce *p*-NPMP, which is stable under reaction conditions. The rate–pH profile in Figure 4 is typical of many neutral phosphorus esters.[4] With a strong oxyanion such as hydroxide ion a nucleophilic pathway possibly obtains. The reaction of water becomes important below pH *ca.* 9. Our data below pH 9 are limited and subject to error in intercept estimation in plots of the form k_{obsd} *vs.* general base or nucleophile concentration. However, it appears that the water reaction involves general base catalysis by a second (or more) water molecule(s). The intercepts in Figure 2 for the imidazole reaction with b-*p*-NPMP in H_2O and D_2O yield an isotope effect of approximately 2 for the water/deuterium oxide reaction. A solvent isotope effect of 2 is also observed for the reactions of pyridine at pH 5.35 and pD 5.45. General base catalysis of water attack has been reported for substrate VIII.[4] From Figure 4 an estimate of the second-order rate constant for water attack of 7×10^{-7} M^{-1} sec^{-1} can be made. It is calculated by dividing the first-order rate constant by 55 *M*. If the Brønsted line in Figure 1 is extended, it passes near the point for water ($\text{p}K_a(H_3O^+) = -1.74$) based on this second-order rate constant. Extrapolating to the pK_a of water (15.74), the second-order rate constant for the reaction of hydroxide ion falls only slightly above the Brønsted line. Thus a general base mechanism for hydroxide ion cannot be excluded.

The data in this investigation are consistent with concerted reactions at the phosphorus center, *i.e.*, for water attack catalyzed by amines, for the water reaction catalyzed by water, and for SN2(P) bimolecular reactions of nucleophilies. No direct evidence has been obtained to indicate the existence of a pentacoordinate intermediate, though it cannot be excluded. Jencks[47] has pointed out for displacements at tetrahedral carbon that an asymmetric transition state can be involved rather than a tetrahedral intermediate in some cases. This would mean that "the tetrahedral intermediate could be close to a transition state rather than a discrete intermediate."[45] We wish to point out that reaction coordinates for displacements at phosphorus (or carbon) may represent a continuum depending on substrate and nucleophile. This continuum can range from the pure SN2(P) case (or the concerted trimolecular general base case), to an asymmetric transition state, to a stable pentacoordinate intermediate. One can speculate that a sterically crowded substrate such as b-*p*-NPMP would favor the asymmetric transition state rather than a pentacoordinate intermediate if a pure SN2(P) case does not obtain.

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(44) Further comment on the reactions of II with fluoride ion and buffer can be made. The reactivity of II with F^- is much greater than with B producing *p*-NP (Scheme I, reactions b and c). Yet, F^- and B react with II at comparable rates producing *p*-NP and F^-, respectively (reactions b and d). The question of a pentacoordinate intermediate or positions of groups attached to phosphorus in an SN2(P) transition state can be speculated. However, our data are not definitive enough to warrant such a speculation.

(45) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

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

(47) Reference 35, pp 486–487.