Reactions of Phosphonic Acid Esters with Nucleophiles. III. Reactivity of Amines toward *p*-Nitrophenyl Methylphosphonate[1]

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Abstract: The rate constants for the reactions of a series of amines with *p*-nitrophenyl methylphosphonate monoanion (*p*-NPMP) in water have been determined. The reaction is second order, first order each in amine and *p*-NPMP. Attack at aromatic carbon has been detected only for the reaction of piperidine. Pyridine reactivity follows a Brønsted relation with a slope $\beta = 0.35$ and a Hammett relation with a slope $\rho = -2.1$. With certain exceptions, other amines fall close to the Brønsted line. Apparent correlation by amines in general may be fortuitous since reactions of organophosphorus esters in general and *p*-NPMP in particular appear to be governed in part by the steric nature of the attacking nucleophile. The reactivities of aziridine, pyrrolidine, and piperidine are discussed.

The nucleophilic reactivity of amines toward phosphate monoester dianions has been reported in some detail;[3,4] the monoanion and neutral phosphorus ester reactivities have been less thoroughly investigated.[5-7] Summaries of the data obtained have been presented.[8-10] In this study, the reactions of amines with *p*-nitrophenyl methylphosphonate monoanion (*p*-NPMP) have been examined. This provides a direct comparison of the relative reactivities of phosphorus ester mono- and dianions; comparison can also be made with the neutral ester data.

Experimental Section

Synthesis of *p*-nitrophenyl methylphosphonic acid has been previously described.[1] Liquid amines were distilled at reduced pressure under nitrogen, which was continuously bubbled through a capillary tube into the distilling pot. The only exception was aziridine which was distilled at atmospheric pressure. No rigorous methods for removal of water from the liquid amines were used since water is the solvent for the reaction. Solid amines were recrystallized from *n*-hexane except for trimethylamine hydrochloride where 95% ethanol was the solvent. pH readings were made either on a Beckman Model G pH meter or on a Leeds and Northrup Model 7401 pH meter. Optical densities were measured at 400 mμ on a Beckman Model DU spectrophotometer using a tungsten lamp. A water blank was used in the spectrophotometer. Stock solutions, 0.2 *M*, in sodium borate and boric acid, were used in varied proportions to establish pH values between 7 and 9.5. Similarly, when pH values greater than 9.5 were needed, 0.2 *M* sodium hydroxide and 0.2 *M* boric acid stock solutions were used. Maintaining desired pH values during the reactions presented no problem, since low concentrations of substrate were employed.

Kinetic Experiments. Experiments were carried out in stoppered volumetric flasks thermostated at either 60.0 ± 0.10° or 30.0 ± 0.05° depending on the temperature desired; all solutions were freshly prepared. The nucleophile was dissolved in a small volume of the appropriate buffer solution. This solution was then transferred to the volumetric flask and further diluted with buffer solution to a volume which, upon subsequent addition of substrate solution, would be just below that of the final volume. This solution was then thermostated for 0.5 hr. Substrate (*p*-NPMP dissolved in water) was added and the flask was brought to volume with buffer. A timer was activated. The reaction was allowed to proceed for 10 min so that the solution could come to temperature before the first aliquot was withdrawn for analysis. The *p*-nitrophenolate ion in the aliquot was determined spectrophotometrically to obtain the rate; it was the only absorbing species at 400 mμ except when substituted *p*-nitroaniline formation was observed.

The amine nucleophiles, in all cases except one, were added as the free base. The exception was trimethylamine where the hydrochloride was used since trimethylamine has a boiling point of 4°; an amount of aqueous sodium hydroxide solution was added to the reaction flask sufficient to neutralize the hydrochloride. A sodium hydroxide–boric acid solution was then added as diluent to bring the reaction flask to the desired pH. It was noted that the trimethylamine free base liberated upon addition of sodium hydroxide remained in aqueous solution even at 60°.

p-Nitrophenol has a pK_a of 7.15[11] and the *p*-nitrophenolate ion absorbs at 400 mμ with an extinction coefficient of 18,200.[1] The techniques of *p*-nitrophenolate determination in solutions having pH values less than 9 have been discussed.[1]

In addition to amine attack at phosphorus, displacement at aromatic carbon is possible. The substituted anilines formed by attack of primary and secondary amines on carbon (C–O cleavage) also absorb at 400 mμ,[3,12] the wavelength used in following the attack on phosphorus (P–O cleavage). Attack by tertiary amines would form quaternary ammonium salts which would not absorb at 400 mμ.[3,12] One would expect the rate of formation and hydrolysis of these quaternary ammonium salts to be slower than the attack by the corresponding tertiary amines under the reaction conditions used in this study;[5] thus the observed rate is taken to be due to attack at phosphorus. The technique used by Kirby and Jencks[3,12] was employed in this study to determine the ratio of P–O to C–O attack for primary and secondary amines.

Rate constants were determined under pseudo-zero-order conditions using initial rates with the amine concentration in excess over that of the substrate, by following the first 1–4% of the reaction. Under these conditions the plot of absorbance against time was linear. Several experiments were performed under pseudo-first-order conditions, with amine in excess, to test the validity of the rate constant under pseudo-zero-order conditions. In all cases the value of k_2, the second-order rate constant corrected for hydrolysis, obtained under pseudo-first-order conditions, agreed with the value of k_2 obtained under pseudo-zero-order conditions. Second-order rate constants were independent of initial amine and/or substrate concentrations. An exception was 3-picoline

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[1] Papers I and II in the series: E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, in press.

[2] (a) Portions of the material contained herein were submitted to the Graduate School, Brown University, Providence, R. I., in partial fulfillment of requirements for the M.S. degree of H. J. B. (b) To whom inquiries should be addressed.

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

[4] J. D. Chanley and E. Feageson, *ibid.*, **85**, 1181 (1963).

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[6] P. Cannon, private communication.

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

[8] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

[9] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapters 5–6.

[10] A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967, Chapter 10.

[11] J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, "Stability Constants, Part I. Organic Ligands," The Chemistry Society, London, Special Publication No. 6, 1957.

[12] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3217 (1965).

Table I. Data for Amines Reacting with *p*-Nitrophenyl Methylphosphonate Ion

Nucleophile	T, °C	pK_a 25° [a]	pH	[N], M	[*p*-NPMP] × 10^4, M	k_2, M^{-1} min^{-1}	No. of expt
Pyridazine	60	2.04[b]	9.00–9.10	0.276–0.532	13.7	2.02×10^{-5b}	2
Pyrazole	60	2.54	7.70–8.89	0.518–1.07	9.40	1.38×10^{-5}	4
3-Chloropyridine	60	2.84	7.62–7.69	0.168–0.210	20.9	1.62×10^{-5}	2
Aniline	60	4.53	6.7	0.3	13.0	$\leq 7 \times 10^{-7}$	3
Pyridine	60	5.23	8.82	0.0495–0.0988	14.1	1.61×10^{-4}	4
	60	5.23	9.40	0.494	0.705	1.72×10^{-4c}	1
	30	5.23	8.70	0.414–0.0745	13.5–24.7	6.71×10^{-6}	3
Piperazine (monobasic)	60	5.68	7.40–7.80	0.102–0.140	10.4–13.8	3.15×10^{-4}	3
3-Picoline	60	5.78	8.90			1.75×10^{-4d}	
3-Aminopyridine	60	5.89	8.90	0.116–0.219	13.4	2.37×10^{-4}	2
	30	5.89	8.88	0.127–0.635	22.4	8.22×10^{-6}	3
2-Picoline	60	6.20	9.15	1.0	10.4	$\leq 8 \times 10^{-6}$	3
4-Picoline	60	6.26	9.30	0.0416–0.104	14.1	3.33×10^{-4}	2
2-Aminopyridine	60	6.86	9.10	0.498–0.949	13.4	1.06×10^{-5}	2
Hydrazine	60	7.81[b]	9.69–10.31	0.074–0.185[e]	9.40	1.93×10^{-3b}	4
Aziridine	60	8.01	10.10–10.42	0.0771–0.193	13.8	1.24×10^{-2}	3
Morpholine	60	8.70	10.05–10.20	0.0458–0.160	13.0	1.08×10^{-3}	3
4-Aminopyridine	60	9.17	11.31	0.0824–0.157	13.4	2.65×10^{-3}	2
2-Aminoethanol	60	9.51	10.48–11.30	0.0333–0.100	9.39–13.8	1.30×10^{-3}	4
Piperazine (dibasic)	60	9.62[b]	11.57–11.65	0.0770–0.385	6.50	4.94×10^{-3b}	2
Trimethylamine	60	9.91	11.58–11.71	0.100–0.195	1.19	3.50×10^{-3}	2
N-Methylpiperidine	60	10.08	11.25–11.30	0.165–0.340	1.08	1.16×10^{-3}	3
n-Propylamine	60	10.60	11.60–11.71	0.121–0.726	1.18	3.66×10^{-3}	7
2-Methylpiperidine	60	11.05	11.60–11.70	0.168	1.18	4.92×10^{-4f}	2
Piperidine	60	11.12	11.60–11.80	0.0978–0.336	1.18	4.77×10^{-3g}	3
Pyrrolidine	60	11.20	12.4	0.0147–0.0488	5.57–5.75	2.85×10^{-2}	3
	30	11.20	12.4	0.0814–0.163	19.2	2.27×10^{-3}	2

[a] Reference 13. [b] Both pK_a values and k_2 values are statistically corrected. [c] Determined under pseudo-first-order conditions. [d] See Table VI and section on 3-picoline. [e] Concentrations of hydrazine were determined by titration with a standardized solution of HCl. [f] Rate constant in doubt since hydroxide ion–water attack is 80% of the total rate. [g] Corrected for attack at aromatic carbon.

which displayed an increase in k_2 with a decrease in initial amine concentration.

Results

Kinetics. Amines reacting with *p*-NPMP generate *p*-nitrophenolate ion as a product; the appearance of this ion was used in following the kinetics. The reaction follows second-order kinetics and is first order each in amine and substrate concentrations. Rate constants and other data for a series of amine nucleophiles attacking *p*-NPMP are shown in Table I.[13] The constants were corrected for hydroxide ion and water attack on the substrate. For the case of piperidine where amine attack at aromatic carbon was observed, the rate constant was corrected for this side reaction. The rate law for amines reacting at the phosphorus site of *p*-NPMP is given in eq 1.

$$\text{rate} = k_2[p\text{-NPMP}][\text{amine}] \qquad (1)$$

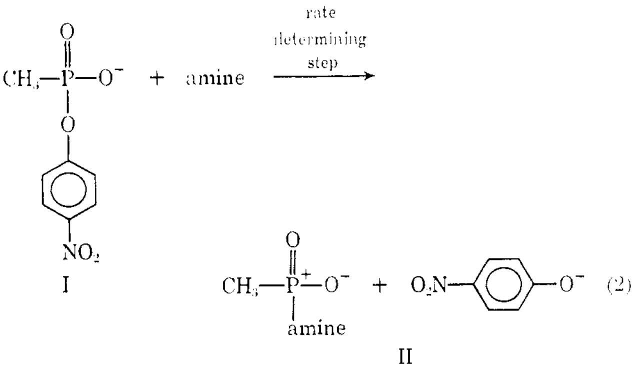
Table II gives data relevant to the solvent isotope effect $k_2(H_2O)/k_2(D_2O)$, which for the reaction of pyridine with *p*-NPMP is 1.17; this indicates that amine attack is directly at phosphorus rather than the kinetically indistinguishable attack by water at phosphorus catalyzed by amines. A mechanism involving water should yield a primary solvent isotope effect of approximately two.[14]

In the rate-determining step 1 mol of amine reacts with 1 mol of *p*-NPMP (eq 2) and 1 mol of *p*-nitrophenolate ion is formed. Evidence to support this is the rate law (eq 1)[15] and the observation that when the reaction of *p*-NPMP with three amines (pyridine,

Table II. Second-Order Rate Constants for the Reaction of Pyridine with *p*-NPMP[a–e]

[Pyridine], M	[*p*-NPMP] × 10^3 M	Solvent	$k_2 \times 10^4$ M^{-1} min^{-1}	$k_2(H_2O)/k_2(D_2O)$
0.124	1.18	H_2O[f]	1.56	
0.0496	1.18	H_2O[f]	1.59	1.17
0.199	2.06	D_2O	1.34	

[a] In H_2O and D_2O. [b] All reactions run in 0.05 M $Na_2B_4O_7$ buffer. [c] For H_2O experiments pH = 9.10; in D_2O "pH" observed = 9.28. [d] T = 60°. [e] The extinction coefficient for *p*-nitrophenolate was not determined; ε 18,200 was used, which is the value in water. [f] pK_a of pyridinium ion in H_2O = 4.88, at 60°.[11]



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(13) Amine pK_a values at 25 and 60° were obtained from the following sources: (a) reference 11; (b) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, 79, 5444 (1957); (c) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961); (d) J. M. Pagano, D. F. Goldberg, and W. C. Fernelius, *J. Phys. Chem.*, 65, 1062 (1961); (e) J. O. Edwards, L. B. Clapp, and C. E. O'Rourke, *J. Amer. Chem. Soc.*, 78, 2159 (1956).

(14) Reference 10, p 306.

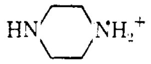
(15) The reaction of amide anions of primary and secondary amines with neutral *p*-NPMP is kinetically indistinguishable from that of neutral amine and substrate anion. The former reaction can be excluded on the grounds that the value of its rate constant would be greater than the rate constant of a diffusion-controlled reaction.

Table III. Effect of Ionic Strength on the Rate of Substitution of 4-Picoline on *p*-NPMP[a,b]

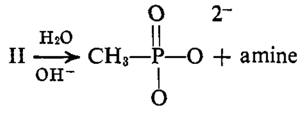
pH	Buffer	Ionic strength	[N],[c] *M*	[*p*-NPMP] × 10^3, *M*	$k_2 \times 10^4$, M^{-1} min^{-1}
9.30	Borate	0.049	0.104	1.41	3.20
9.30	Borate	0.049	0.0416	1.41	3.46
8.95	Borate	0.0049	0.0988	1.35	2.98
8.98	Borate	0.0049	0.0495	1.35	2.89

[a] T = 60°. [b] pK_a of conjugate acid is 6.26 at 25°. [c] N = 4-picoline.

3-aminopyridine, and monobasic piperazine) was allowed to go to completion, approximately 100% of the theoretical amount of *p*-nitrophenol was released. An exception is the case of piperidine which is discussed below. The rate was not dependent on pH between pH 7 and 12; thus there was no rapid preequilibrium protonation step. Both specific acid and base catalysis are excluded by these data. In addition there was no dependence of rate on buffer concentration except for a small ionic strength effect (Table III); thus general acid and base catalysis also are excluded.



The possibility that further reaction of the methylphosphoramidate[16] (II) with water or hydroxide ion to yield the methylphosphonate (III) (protonated depending on pH) does exist;[3,9,10] such reactions are



$$\mathrm{II} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O}} \mathrm{CH_3{-}P(=O)(O){-}O}^{2-} + \text{amine} \qquad (3)$$

III

expected to be rapid, and the kinetic analysis is not influenced. No analysis for the methylphosphonate was done in this study, since the prime purpose was to determine the rate constants for the rate-determining step (eq 2).

Activation parameters for three amine nucleophiles are found in Table IV. The activation energies (E_a) are calculated based on kinetic experiments performed at 30 and 60°. The entropies of activation ($\Delta S^{\ddagger}$) are calculated at 60°.

Table IV. Activation Parameters for Three Amine Nucleophiles Attacking *p*-NPMP

Nucleophile	E_a, kcal/mol	$\Delta S_{60°}^{\ddagger}$, eu
Pyridine	21.3	−22
3-Aminopyridine	22.5	−18
Pyrrolidine	16.9	−25

The range of the pK_a values of the amine nucleophiles is from 2.04 for the conjugate acid of pyridazine to 11.20 for the conjugate acid of pyrrolidine. It is to be noted that the pK_a values listed in Table I are values at 25°.

For the reaction of a neutral particle with an ion, one expects the effect of changes in ionic strength on rate to be small.[17] In Table III it can be seen that, by varying the ionic strength from 0.0049 to 0.049, the second-order rate constant is increased by approximately 10%. Therefore in this investigation ionic strength was not adjusted to a constant value; however it was usually ~0.05 and not below 0.040 or above 0.100.

Brønsted and Hammett Plots. A Brønsted plot using the amine data in Table I is given in Figure 1; where appropriate, the data have been statistically corrected.

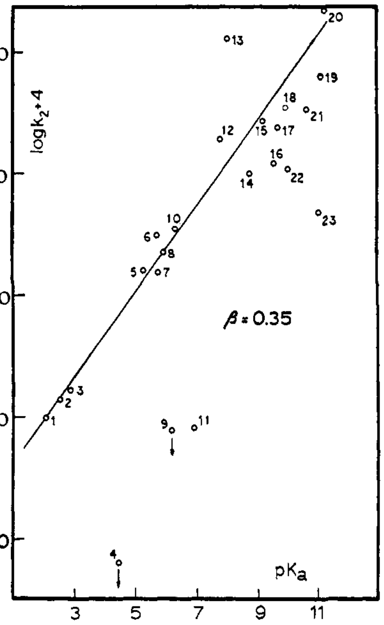


Figure 1. Brønsted plot for amines reacting with *p*-NPMP at 60° (pK_a values at 25°). Arrow indicates reaction rate is equal to or less than the hydroxide–water rate at the pH value employed (Table I): 1, pyridazine; 2, pyrazole; 3,3-cyclopyridine; 4, aniline; 5, pyridine; 6, piperazine (monobasic); 7, 3-picoline; 8, 3-aminopyridine; 9, 2-picoline; 10, 4-picoline; 11, 2-aminopyridine; 12, hydrazine; 13, aziridine; 14, morpholine; 15, 4-aminopyridine; 16, 2-aminoethanol; 17, piperazine (dibasic); 18, trimethylamine; 19, piperidine; 20, pyrrolidine; 21, *n*-propylamine; 22, N-methylpiperidine; 23, 2-methylpiperidine.

The line drawn is through the points for substituted pyridines and has a slope of 0.35. The pK_a values used in this plot are at 25°, while the reactions were examined at 60°. It was assumed that the heats of ionization for the amines studied would be sufficiently similar so that the pK_a values at 25° could be used. Table V lists those amines whose pK_a values have been reported at 60° or whose heats of ionization are known permitting calculation of pK_a values at 60°. Also included in Table V are the pK_a values at 25°. Figure 2 contains a Brønsted plot for the amines whose rate constants are given in Table I and whose pK_a values at 60° are given in Table V. The slope β = 0.29 in Figure 2. If a line is drawn in Figure 1 through those amines

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[16] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 87, 3199 (1965).

[17] K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1965, pp 220–221.

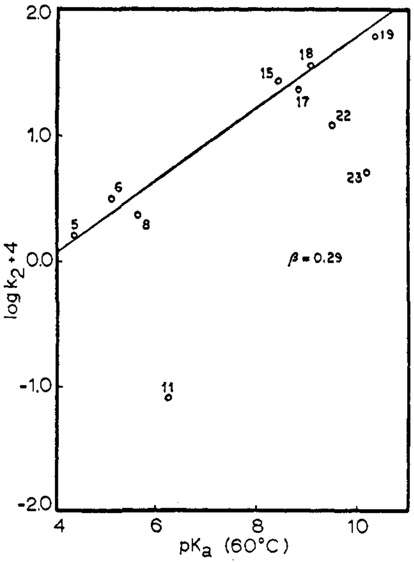

Figure 2. Brønsted plot for amines, whose pK_a values at 60° are known, reacting with *p*-NPMP. The numbers of points refer to the same amines as in Figure 1.

whose pK_a values at 60° are known, a slope of $\beta = 0.32$ would give the best fit. The difference in β of 0.03 is not considered to be significant.

Table V. pK_a Values for Conjugate Bases of Amines at 60 and 25°

Amine[a]	pK_a, 25°[b]	pK_a, 60°[b]
Pyridine (5)	5.23	4.88
Piperazine (6) (monobasic)	5.68	5.08
3-Aminopyridine (8)	6.03	5.63
2-Aminopyridine (11)	6.71	6.19
4-Aminopyridine (15)	9.18	8.35
Piperazine (17) (dibasic)	9.82 (20°)	8.82
Trimethylamine (18)	9.72	9.04
Piperidine (19)	11.12	10.26
N-Methylpiperidine (22)	10.08	9.48
2-Methylpiperidine (23)	11.05	10.16

[a] The numbers in parentheses are those for individual amines used in Figures 1 and 2. [b] Reference 13.

Of the 23 points in Figure 1, 18 fall relatively close to the line drawn. The exceptions are aniline, 2-picoline, 2-aminopyridine, and 2-methylpiperidine which fall below this line and aziridine which falls above it. Several amines, including morpholine, 2-aminoethanol, N-methylpiperidine, *n*-propylamine, and piperazine (dibasic), fall noticeably below the line, but yet are still quite close to it. Among the 18 amines that fit the correlation line as drawn reasonably well are aromatic amines and cyclic and acyclic aliphatic amines. The presence of a second heteroatom in the nucleophile such as oxygen or a second nitrogen atom does not for these cases cause a significant deviation from the line. Hydrazine, which might be expected to show a positive deviation due to an α effect,[18] falls only slightly above the line and the α effect is seen to be small for this compound.

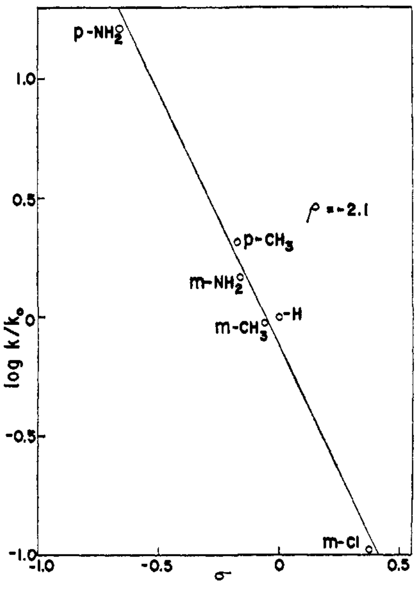

Figure 3. Hammett plot for six substituted pyridines reacting with *p*-NPMP.

A Hammett plot[19] using the six substituted pyridines (Table I) is seen in Figure 3; an excellent fit is obtained. The slope ρ (-2.1) indicates that the reaction rate decreases with an increase in electron-withdrawing power of the substituents. Such an effect is expected for nucleophiles in a bimolecular displacement reaction.[20] The magnitude of ρ is consistent with the reacting site being nitrogen in the aromatic ring.

3-Picoline. For the reaction of 3-picoline with *p*-NPMP, the second-order rate constant was found to increase with decreasing initial 3-picoline concentration (Table VI). A similar effect has been observed for the reaction of several pyridines with the *p*-nitrophenyl phosphate dianion.[3] The observation has been attributed to a self-association by the pyridines, producing an unreactive dimer.

Table VI. Kinetic Experiments Showing an Increase in Second-Order Rate Constants with Decreasing 3-Picoline Initial Concentration[a-c]

3-Picoline concn, *M*	$k_2 \times 10^4$, M^{-1} min^{-1}
1.00	0.96
0.80	1.12, 1.08
0.60	1.32, 1.30
0.40	1.41

[a] All experiments run in 0.16 *M* boric acid–sodium borate; buffer pH = 8.9. [b] Temperature = 60°. [c] Substrate concentration ranged from 1.37×10^{-3} *M* to 1.56×10^{-3} *M*.

It was found that by plotting k_2 *vs.* initial 3-picoline concentration, a straight line was obtained (Figure 4). Extrapolating to zero concentration of 3-picoline a k_2 value of 1.75×10^{-4} M^{-1} min^{-1} was obtained. This k_2 value falls close to the Brønsted plot (Figure 1), and the Hammett plot (Figure 3) and was used in these free-energy relations.

Aromatic Carbon Attack. It has been reported that primary and secondary amines attack the aromatic

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

[19] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

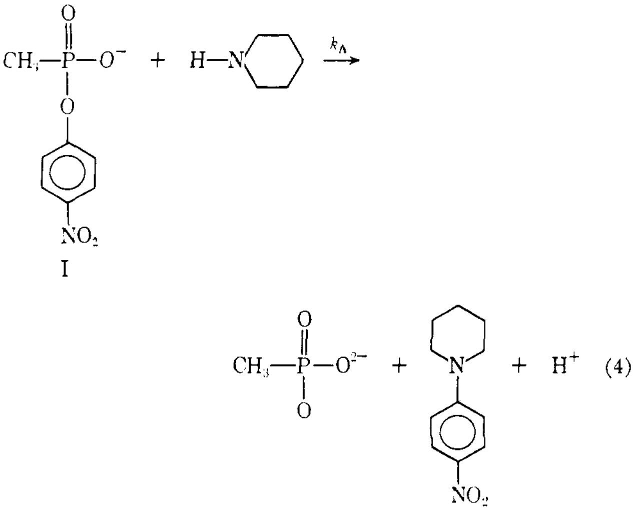
[20] H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

Table VII. Rate Constants for Aromatic Carbon Attack by Piperidine on *p*-NPMP[a]

[Piperidine], *M*	[*p*-NPMP] × 10^3, *M*	pH of reaction	$k_2 \times 10^3$, M^{-1} min^{-1}
0.195	0.118	11.61	2.61
0.0978	0.118	11.60	2.64
0.195	0.118	11.50	2.64

[a] T = 60°.

carbon site in both the *p*-nitrophenyl phosphate dianion[3,12] (*p*-NPP^{2-}) and the analogous *p*-nitrophenyl sulfate monoanion (*p*-NPS)[21] to produce substituted anilines. Using *p*-NPMP, piperidine was the only amine showing a significant amount of aromatic carbon attack, approximately 35% of the total reaction (Tables I and VII). The reaction of piperidine with the aromatic site of *p*-NPMP is shown in eq 4 to give methylphosphonate and 1-*p*-nitrophenylpiperidine. Data for the aromatic carbon rate constant are given in Table VII. The reaction of piperidine with the aromatic carbon site of *p*-NPP^{2-} was found to be catalyzed by hydroxide ion.[12] The pH was not varied in our experiments to study possible hydroxide ion catalysis. At 60°, k_2 for the attack by piperidine at phosphorus is 4.77 × 10^{-3} (Table I) while k_2 for attack by piperidine at aromatic carbon is 2.62 × 10^{-3}. Checks for aromatic attack by aziridine, pyrrolidine, 2-aminoethanol, and *n*-propylamine were made. At most 2% of aromatic attack was found for these amines.



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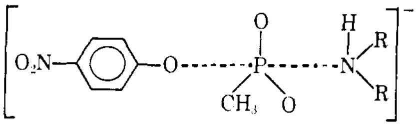
(4)

Discussion

The reaction of amines with *p*-NPMP appears to proceed by way of a bimolecular S$_N$2(P) mechanism. Except for the case of piperidine where aromatic carbon attack also occurs, our evidence indicates that attack is at phosphorus. The transition state for phosphorus attack can be pictured as in IV. (A secondary amine is used for illustrative purposes.) The values for the energies of activation (15–20 kcal/mol) and the entropies of activation (−15 to −25 eu) (Table IV) are consistent with this interpretation.[3,5,8,22] The solvent isotope effect of 1.17 (Table II) is also consistent with amine attack at phosphorus. Isotope effects near unity were found for amine attack at the phosphorus sites of *p*-NPP^{2-} [3] and the acetylphosphate anions.[23] The deviations from linearity in the Brønsted relation (Figure 1) are also indicative of an S$_N$2(P) mechanism, in particular, the decreased reactivity of *ortho*-substituted six-membered ring heterocycles. Such a reduced reactivity by these compounds has been found in those cases where nucleophilic attack occurs at the phosphorus sites.[3,16,23,24] Where general base catalysis by amines is observed the reduced reactivity by *ortho*-substituted amines is less pronounced.[24,25]



IV

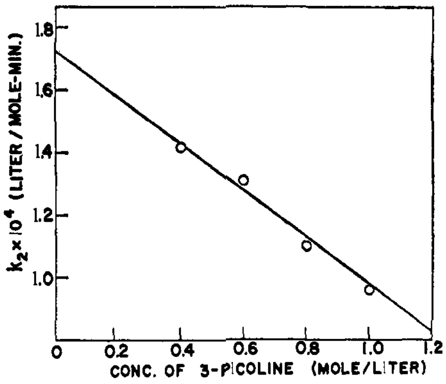


Figure 4. Plot of k_2 *vs.* intial 3-picoline concentration for the reaction of 3-picoline with *p*-NPMP.

The values of the Brønsted slope (β) of 0.35 and the Hammett slope ρ of −2.1 give a measure of the degree of bond formation between incoming amine nucleophile and phosphorus in the transition state. The amine–*p*-NPMP reaction is not as close to the borderline between unimolecular and bimolecular mechanisms as are the reactions of *p*-NPP^{2-} ($\beta \cong 0.13$)[3] and the 2,4-dinitrophenyl phosphate dianion ($\beta \cong 0$)[5] with amines. The value of the Brønsted slope in the pyridines–*p*-NPMP reactions is between the values mentioned above as determined for phosphate ester dianions reacting with amines and those for neutral phosphorus esters reacting with hydroxamate anions,[26,27] β = 0.5–0.9; for amines reacting with isopropyl methylphosphorofluoridate, β = 0.49.[6] The β value obtained here is reasonable considering the monoanionic nature of *p*-NPMP. The value of 0.35 is below the value of 0.56 reported for the amine–*p*-nitrophenyl phosphate (*p*-NPP) monoanion reactions.[5] No conclusions about this difference can be made at this time, since the number of amines studies in the *p*-NPP case was limited.

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(21) S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, **88**, 5504 (1966).

(22) Reference 10, p 302.

(23) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4393 (1961).

(24) Reference 10, pp 321–22, and references therein.

(25) Reference 9, pp 59–61, and references therein.

(26) R. Swidler, R. E. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959).

(27) β values for neutral phosphorus esters must be used for anion–substrate reactions since a detailed study with amines has not been reported except *via* a private communication.[6] The β value for the reaction of diisopropyl phosphorochloride with amines is probably ≥0.5, however.[7]

With certain exceptions amines of varying classes fall close to the Brønsted correlation line. This is in contrast to the cases of *p*-NPP^{2-} and the analogous *p*-NPS where the order of reactivity of amines is tertiary > secondary > primary, with parallel lines being drawn for each class of amine. The fact that several primary and secondary amines fall somewhat below the correlation line (Figure 1) is probably a result of reduced reactivity displayed by these compounds; this reduced reactivity is reported in other cases to a greater extent. Amine reactions with tetrahedral organophosphorus esters in general appear to be governed by both basicity and steric effects of the amine.[7,9,10,28] The validity of the Brønsted plot (Figure 1) for pyridines is confirmed by the good fit obtained in the Hammett plot, Figure 3. The fact that both 3- and 4-aminopyridine fit on the Hammett plot is evidence that the reactive site for nucleophilic attack at phosphorus is the ring nitrogen. This agrees with the observation that aniline is a poor nucleophile.

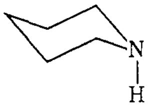
The dibasic form of piperazine falls slightly below the Brønsted line as drawn. The monobasic, cationic form falls slightly above the line. The latter may represent the expected rate enhancement[3,23] due to the presence of a positive charge in the nucleophile and a negative charge in the substrate.

The fact that the reactions of amines with tetrahedral organophosphorus compounds are governed at least in part by steric effects in the amines makes it important to discuss the reactivity of certain amines in some detail.

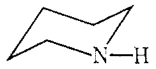
When pyridines and piperidines are substituted in the *ortho* position, the rate constants fall below the Brønsted line. Examples are 2-picoline, 2-aminopyridine, and 2-methylpiperidine. When 2-picoline was the nucleophile, the observed rate was equal to that of the combined hydroxide–water rate at pH 9.15; therefore, the rate of attack by this amine is less than that measurable under the conditions used. Reduced reactivities by these types of amines have been reported toward similar substrates.[3,16,23,24] The decreased reactivity of *ortho*-substituted six-membered cyclic ring compounds is found for *p*-NPMP, *p*-NPP^{2-},[3] the 2,4-dinitrophenyl phosphate dianion,[5] and the analogous *p*-NPS;[21] it is not found with diethyl phosphorofluoridate (DEFP).[29] Some of the reactions of DEFP in the presence of amines, however, probably proceed by general-base catalysis rather than nucleophilic attack by the amine. N-Methylpiperidine, while being less reactive than expected from the Brønsted line, shows a greater reactivity than 2-methylpiperidine. One might expect a decrease in reactivity by N-methylpiperidine of comparable magnitude to that of the *ortho*-substituted amines, yet the facts indicate otherwise and we conclude that the rate constants are determined by specific steric factors rather than by general bulkiness of the groups adjacent to the nitrogen.

If one takes into account, by correction using the Brønsted β values, the fact that basicity is one of the factors determining amine–*p*-NPMP reactivity, the reactivity order aziridine > pyrrolidine > piperidine is observed. Pyrrolidine reactivity is considerably greater than that of other secondary amines examined (except for aziridine) and we feel that its reaction rate is greater than would be ordinarily expected from the position of the other secondary amines on the Brønsted plot.

Enhanced reactivities by aziridines and phenylazetidines in nucleophilic displacement reactions have been reported.[30] The explanation given does not adequately explain the fact that pyrrolidine is more reactive than piperidine. The pK_a of pyrrolidine (11.20 at 25°) is roughly the same as the pK_a of piperidine (11.12 at 25°) and approximately tetrahedral bond angles exist at the nitrogen center in both;[31,32] yet pyrrolidine is ~sixfold more reactive than piperidine. The ring structure of pyrrolidine[31,32] is thought to assume a "half-chair" form with the heteroatom located on the axis of symmetry. The puckering of the ring in pyrrolidine is not nearly as great a deviation from planarity as would be found with piperidine. In order to achieve tetrahedral bond angles, with a minimum amount of C–C and H–H interactions, piperidine assumes a chair conformation. There are two forms of this chair conformation, however; in one, the H bonded to N is axial (Va) and in the other the H bonded to N is equatorial (Vb). Recent studies indicate that both forms are substantially populated, though there is uncertainty as to the relative amounts of each.[33-35] For piperidine reacting in conformer Va, the 2- and 6-axial hydrogens can hinder the approach of the nitrogen site to phosphorus. In Vb, the 3- and 5-axial hydrogens may similarly affect the reaction. For the case of pyrrolidine, hydrogen atoms bound to carbon atoms cannot hinder the reaction in the same fashion. Thus, enhanced reactivity of pyrrolidine relative to piperidine may possibly be explained in terms of the accessibility of the ring nitrogen to attack the phosphorus site.



Va



Vb

The increased nucleophilic reactivity of aziridine and pyrrolidine is displayed to a greater extent for phosphorus attack than aromatic carbon attack. Piperidine showed about 35% attack at carbon whereas about 2% attack was observed for aziridine and pyrrolidine. Recently it was reported that toward 1,3,5-trinitrobenzene in a 90% water–10% dioxane system pyrrolidine is more reactive by a factor of less than three than piperidine.[36] Clearly, attack at phosphorus must be more dependent upon the structural differences in these amines than is attack at aromatic carbon. The rate of amine substitution reactions of *trans*-dichloro(diethylamine)(tri-*n*-propylphosphino)platinum(II)[37] is determined by the effective size of the incoming

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(28) I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 516, (1953).

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

(30) L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966).

(31) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 248–252.

(32) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1966, pp 200–203.

(33) P. J. Buckely, C. C. Costain, and J. F. Parkin, *Chem. Commun.*, 668 (1968).

(34) H. Booth, *ibid.*, 802 (1968).

(35) G. A. Yausif and J. D. Roberts, *J. Amer. Chem. Soc.*, 90, 6428 (1968).

(36) C. Bernasconi, *ibid.*, **92**, 129 (1970).

(37) A. L. Odell and H. A. Raethel, *Chem. Commun.*, 1323 (1968).

nucleophile. For this, complex reactivity is in the order aziridine > pyrrolidine ≫ piperidine. This also suggests that the increased rate of reaction between pyrrolidine and *p*-NPMP is a steric phenomenon.

The reduced reactivity of aniline toward *p*-NPMP is more difficult to explain. The rate constant for aniline reaction with *p*-nitrophenyl acetate[38] falls on the Brønsted correlation. However, when tetrahedral phosphorus is the reactive site,[3] low aniline reactivity is observed.

From the data accumulated in this study and prior investigations it is clear that steric effects and their interpretations in amine reactivity toward tetrahedral phosphorus are indeed complicated. Aside from dependence on basicity, previous studies appear to show that amine reactivity is dependent on steric interference by the approaching amine nitrogen toward the phosphorus atom. Such effects are not totally dependent on the degree of bond formation in the transition state. *p*-NPP^{2-} and phosphoramidate monoanion which have low Brønsted slopes and diisopropyl phosphorochloridate[7] (DClP) which would be expected to have a high Brønsted slope are sensitive to the steric nature of the amine. The latter involving a greater degree of bond formation in the transition state displays a greater dependence on the structure of the amine than does the former.

Reactions of particular amines appear to show steric effects, the causes of which are not the same. Aziridine (and presumably pyrrolidine) show a high reactivity toward both tetrahedral phosphorus (*p*-NPMP) and carbonyl carbon (phenyl acetate). However, aniline shows reduced reactivity toward tetrahedral phosphorus but a "normal" reactivity toward carbonyl carbon. The case of *p*-NPMP is unusual. Most of the varied classes of amines studied fall close to the Brønsted line with several individual amines falling either above or below the line as drawn (Figure 1). Amines of similar structure to those falling close to the line will themselves also probably correlate with it. However, since data for other phosphorus substrates, including ones having both higher and lower β values than *p*-NPMP, show dependence on steric interference by reacting amines, the correlation observed in Figure 1 probably is in part fortuitous. Amine nucleophiles of different structural composition than those studied here may or may not fall on the *p*-NPMP Brønsted line.

Aromatic Carbon Attack. Piperidine was the only amine for which we have found evidence of attack at aromatic carbon. It seems reasonable that attack on carbon is less likely with monoanionic *p*-NPMP than with the dianionic *p*-NPP^{2-}. For the *n*-butylamine reaction with *p*-NPP^{2-}, 27% of the total absorbance at 400 mμ is caused by aromatic attack.[3] For the *n*-propylamine–*p*-NPMP reaction negligible aromatic attack is observed.[39]

Since aromatic carbon attack is known to be catalyzed by OH^-, one would expect amine–*p*-NPMP reactions studied at high pH values to display the greatest amount of aromatic attack. Yet with 2-aminoethanol, *n*-propylamine, and pyrrolidine the amount of aromatic carbon attack was $\leq 2\%$.

Acknowledgment. We acknowledge the support of the Department of Defense which made this work possible.

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[38] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

[39] The pH of the reaction of *n*-propylamine with *p*-NPMP was greater than the highest pH value for the reaction of *n*-butylamine with *p*-NPP^{2-}