After 4 h at −78 °C the mixture was warmed rapidly to ambient temperature, quenched cautiously with water, and stirred for a further 10 min. The THF was evaporated and the product extracted into ether. The ether extract was dried (anhydrous magnesium sulfate), filtered, and evaporated to give a colorless oil. Column chromatography[9] (gradient elution, 0–30%, ether/*n*-pentane) gave the title product, **14**, as a colorless oil (0.167 g, 95% yield).

GC (150 °C) showed two peaks, ratio 4:1. The ^{1}H NMR spectra of **14–17** were consistent with the assigned structures but were complex due to the fact that these intermediates were 4:1 mixtures of diastereoisomers at C-2.

Anal. Calcd. for $C_{19}H_{40}SiO_3$: C, 66.22, H, 11.70. Found: C, 65.94; H, 11.64.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(3′-[(*tert*-butyldimethylsilyl)oxy]-1′-methylbut-1′-oxy)oct-7-ene (15). A sample of the crude acetylation product was purified by column chromatography[9] (gradient elution, 0–20% ether/*n*-pentane) to give **15** as a colorless oil.

Anal. Calcd for $C_{21}H_{42}SiO_4$: C, 65.24; H, 10.95. Found: C, 65.35; H, 10.66.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(3′-hydroxy-1′-methylbutoxy)oct-7-ene (16). The crude desilylation product was purified by column chromatography[9] (gradient elution, 0–30% ether/*n*-pentane) to give **16** as a colorless oil.

Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.29; H, 10.27.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(1′-methyl-3′-oxobutoxy)oct-7-ene (17). The crude oxidation product was purified by column chromatography[9] (gradient elution, 0–30% ether/*n*-pentane) to give **17** as a colorless oil.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.49; H, 9.58.

(2*RS*,4*R*)-2,4-Dihydroxyoct-7-ene (18). Column chromatography[9] of the crude product of base treatment of **17**[4a] (gradient elution, 10–70% ether/*n*-pentane) gave (2*S*,4*R*)-**18** (75% yield) and (2*R*,4*R*)-**18** (19% yield). (2*S*,4*R*)-**18** was a pale yellow oil with the following characteristics:

$[\alpha]^{25}_D$ +18.4 (*c* 1.0, CCl_4); IR (film) 3350 (OH), 1640, 910 cm^{-1} (CH_2=CH). ^{1}H NMR 1.19 (d, J = 6.2 Hz, 3, CH_3CH), 1.39–1.66 (m, 4, CH_2CH_2), 2.04–2.24 (m, 2, OCHCH_2CHO), 3.19 (br s, 2, 2 × OH), 3.83–3.91 (m, 1, CHO), 3.98–4.08 (m, 1, CHO), 4.96 (ddt, J = 10.2, 1.9, 1.2 Hz, 1, H_EH_ZC=CHCH$_2$), 5.03 (dq, J = 17.1, 1.9 Hz, 1, H_EH_ZC=CHCH$_2$), 5.75–5.88 (m, 1, CH$_2$=CH).

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. We also thank Professor P. A. Bartlett for supplying us with a specimen of the cyclic carbonate of the 2(*R*),4(*S*)-diol (enantio-**18**).[13]

Evidence for a Single Transition State in the Transfer of the Phosphoryl Group ($-PO_3^{2-}$) to Nitrogen Nucleophiles from Pyridino-*N*-phosphonates[1a]

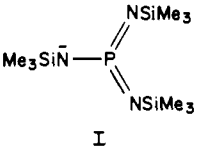
Nicholas Bourne and Andrew Williams*

Contribution from the University Chemical Laboratories, Canterbury, England.
Received April 17, 1984

Abstract: The reaction of pyridinio-*N*-phosphonates with pyridines in aqueous buffers has been demonstrated to involve nucleophilic attack at phosphorus. The second-order rate constants obey the equation log k_{xpy} = 0.15pK_{xpy} − 0.86 for attack on isoquinolinio-*N*-phosphonate over a wide range of pyridine basicity indicating a *single* transition state; this is consistent with a concerted transfer of the phosphoryl group rather than with a stepwise mechanism involving metaphosphate ion in a ternary encounter complex with donor and acceptor. Transfer of the phosphoryl group to pyridine from substituted pyridinio-*N*-phosphonates obeys the equation log k = −0.92pK_{xpy} + 5.24 and leads to a β_{eq} of 1.07 for substituent effect on the equilibrium constant for transfer. The effective charge at nitrogen, in the transition state, indicated by these values favors weak P–N bonding. An imbalance of −0.77 effective charge units between entering and leaving nitrogen in the transition state is proposed to derive from the charge on the PO_3 atoms, which therefore do not bear a full negative charge in the transition state. Transfer of the phosphoryl group from isoquinolinio-*N*-phosphonate to amines has been investigated kinetically, and the results are also consistent with weak bonding between phosphorus and nitrogen in the transition state.

The existence of unsaturated, metaphosphate-like, intermediates has been established for many phosphyl-transfer reactions.[1b–k]

The isolation and characterization of such intermediates are not so far advanced, and we know of only two well-characterized compounds: a nitrogen (I)[2] and a sulfur (II)[3] analogue of monomeric metaphosphate. The transfer of the phosphoryl group ($-PO_3^{2-}$)[4] between nucleophiles has been studied recently for enzyme and model systems using stereochemical probes.[5] Single phosphoryl transfers, such as from donor to enzyme or donor to acceptor,[6] have been found in all cases to exhibit inversion at the phosphorus. It is possible that in the enzyme reactions a meta-



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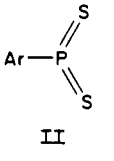

II

(1) (a) A preliminary communication of this work has appeared: Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 3357. (b) Satterthwait, A.; Westheimer, F. H. "Phosphorus Chemistry Directed toward Biology"; Stec, W., Ed.; Pergamon Press: New York, 1980; p 117. (c) Westheimer, F. H. *Spec. Publ.—Chem. Soc.* **1957**, *No. 8*, 180. (d) Traylor, P. S.; Westheimer, F. H. *J. Am. Chem. Soc.* **1965**, *87*, 553. (e) Gerrard, A. F.; Hamer, N. K. *J. Chem. Soc. B* **1968**, 539; **1967**, 1122. (f) Harvan, D. J.; Hass, J. R.; Busch, K. L.; Bursey, M. M.; Ramirez, F.; Meyerson, S. *J. Am. Chem. Soc.* **1979**, *101*, 7909. (g) Crunden, E. W.; Hudson, R. F. *Chem. Ind. (London)* **1958**, 1478; *J. Chem. Soc.* **1962**, 3591. (h) Williams, A.; Douglas, K. T. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1454. (i) Williams, A.; Douglas, K. T. *Ibid.* **1973**, 318. (j) Williams, A.; Douglas, K. T.; Loran, J. S. *Ibid.* **1975**, 1011. (k) The recent work of Westheimer's group and that of other groups on metaphosphate intermediates is summarized in: Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313.

(2) (a) Niecke, E.; Flick, W. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 134. (b) Scherer, O. J.; Kuhn, N. *Chem. Ber.* **1974**, *107*, 2123. (c) Pohl, S.; Niecke, E.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 261.

(3) Navech, J.; Majoral, J. P.; Kraemer, P. *Tetrahedron Lett.* **1983**, 5885.

(4) Strictly this group is the phosphonato, but it is better known as the phosphoryl, see: Bourne, N.; Williams, A. *J. Org. Chem.* **1984**, *49*, 1200–1204.

(5) Lowe (Lowe, G. *Acc. Chem. Res.* **1983**, *16*, 244) and Frey (Frey, P. A. *Tetrahedron* **1982**, *38*, 1541) have collected the important data on this topic.

(6) Buchwald, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 1438.

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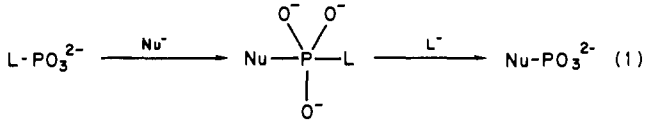
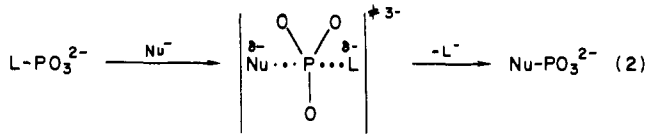
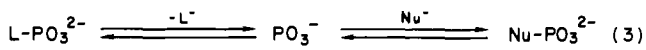
phosphate intermediate could be "held" by forces acting from the enzyme for sufficient time for reaction to occur in a stereochemically defined way. It is difficult to conceive that a free metaphosphate ion produced in a nonenzymatic reaction could rotate more slowly than it would react with a neighboring nucleophile.[6] Retention of configuration was observed by Knowles[7] for an intramolecular transfer of a phosphoryl group. Such a reaction is sterically constrained so that the neighboring nucleophile cannot attack "in line", presumably the favored path for the concerted process.

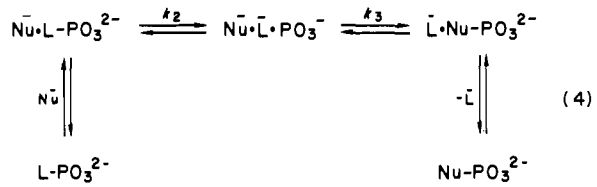
There are a number of discrete mechanisms that are available to describe phosphoryl group transfer between donor (L) and acceptor (Nu) nucleophiles. These include formation of an addition intermediate (eq 1), the intervention of a concerted process





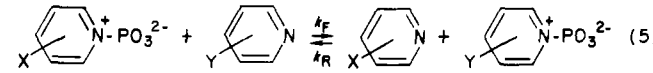


(eq 2), and metaphosphate formation (eq 3). Except for transfer to water or organic solvent all the phosphoryl-transfer reactions exhibit second-order kinetics, thus effectively excluding eq 3. All bimolecular reactions must involve some preassociation of reagents in an encounter complex (equivalent to "solvent-separated ion pair" in carbenium ion chemistry) prior to reaction. A "preassociation" stepwise mechanism (eq 4) and second-order kinetics would be



observed if the metaphosphate ion were sufficiently reactive that it scavenged a nucleophile present in the encounter complex faster than it could diffuse into the bulk solvent. In order to form product the phosphate ($L-PO_3^{2-}$) must dissociate in an encounter complex containing the nucleophile. If the nucleophile is not present the dissociation will not be productive as the products would either hydrolyze or revert to reagent.

Distinction between the extreme types of mechanism (eq 1, 2, and 4) should be possible using substituent effects to investigate differences arising from changes in rate-limiting step. It is necessary that donor and acceptor nucleophiles be of similar structure and that the acceptor basicity range above and below that of the donor; the break point in a linear free energy plot vs. pK of the acceptor may then be predicted accurately to be where the basicity of the acceptor nucleophile is equal to that of the donor. Pyridine-type donors and acceptors proved to be the most suitable. These are known to have a wide range of basicity for a single structural type[8,9] which has relatively little steric change provided ortho substituents are avoided. Jameson and Lawlor[10] followed the reaction of pyridinio-N-phosphonates with a number of nucleophiles including pyridines and showed that the reactions could easily be followed spectrophotometrically. We exploit the methods of these workers to study the transfer of the phosphoryl group between pyridine donors and acceptors (eq 5).



Experimental Section

Materials. Pyridines were dried over KOH pellets and redistilled before use. Amines were used as their hydrochlorides, which were recrystallized from suitable solvents. Buffer and other reagents were of analytical reagent grade or were recrystallized or redistilled from bench-grade materials. Ammonium hydrogen phosphoramidate was prepared by adding phosphoryl chloride (18 mL) to ice-cold 10% NH_3 (300 mL) during 10 min and stirring the mixture for a further 15 min. Acetone (1 L) was then added and the bottom (aqueous) layer separated and neutralized to pH 6 with glacial acetic acid. The mixture was cooled in ice and the crystalline product isolated, washed with ethyl alcohol and ether, and then dried under vacuum. The product had N 24.4%, H, 6.3%. Calcd for $NH_4^+NH_3PO_3^-$: N 24.6%, H 6.1%.

Pyridinio-N-phosphonates were prepared in solution and used without isolation. Most were prepared by adding an aliquot (0.5 mL) of a stock solution of the pyridine to solid ammonium hydrogen phosphoramidate (~10 mg) and swirling in ice. The compositions of the stock solutions were as follows: isoquinoline, 0.2 mL in acetonitrile/water (10 mL, 1:4 v/v); 3-picoline, 0.2 mL in water (10 mL); 3,5-lutidine, 0.2 mL in acetonitrile/water (10 mL, 1:9 v/v); 3-aminopyridine, 0.1 g in water (25 mL); 3,4-lutidine, 0.15 mL in acetonitrile/water (5 mL, 1:5 v/v). (4-Aminopyridinio)-N-phosphonate was prepared by dissolving 4-aminopyridine (50 mg) in acetonitrile (2 mL) and adding phosphoryl chloride (0.15 mL) with stirring in an ice bath. The mixture was stirred for an extra 15 min and then basified with KOH (5 M) to pH 8. Pyridinio-N-phosphonates may not be isolated and characterized in the normal fashion. Jameson and Lawlor[10] carefully investigated the structures of their materials using NMR techniques and demonstrated their identity as pyridinio-N-phosphonates. In the present study we show that the materials, prepared by us and presumed to be N-phosphonates, hydrolyze with first-order rate constants close to those found in and predicted from the previous study.[10] Further, we can predict the rate constant for reaction of (3-methoxypyridinio)-N-phosphonate with pyridine from our studies (from eq 8 the value is 3.05 M^{-1} s^{-1}), and this compares very well with that determined by Skoog and Jencks[11a] for material prepared in an entirely different way. The small difference between our predicted result and that of the other workers can be ascribed to the very different ionic strengths employed in the two laboratories.

Acetonitrile was purified by the method of Lewis and Smyth[11b] and then redistilled from calcium hydride. Water used throughout the investigation was doubly distilled from glass.

Methods. The reaction of nucleophiles with pyridinio-N-phosphonates was followed spectrophotometrically under conditions quoted in the results section. A typical reaction involved adding an aliquot of the phosphonate (~25 μL to give a final concentration of ca. 10^{-3} M) on the flattened tip of a glass rod to a 1-cm path length silica cell containing buffer solution (2.5 mL) in the thermostated cell holder of a Perkin-Elmer Model 124 spectrophotometer. The absorbance at the appropriate wavelength, obtained by repetitive scanning of a test reaction, was monitored against time. Reactions were normally followed over 7 half-lives and pseudo-first-order rate constants were obtained from plots of $A_t - A_\infty$ against time on two-cycle semilogarithmic graph paper. The measurement of pH was carried out using a Radiometer (PHM 26) instrument calibrated to ±0.02 pH units with E.I.L. standard buffers. Temperature was maintained to ±0.1° in the buffer solutions in the cell housing by using an external water-circulating thermostat.

Measurement of pK values was carried out by potentiometric titration in the usual manner with a Radiometer pH-titration set comprising REC Servograph, REA titratigraph, pH meter (PHM 26), Titrator TTT 60, and autoburette ABU 11. Brønsted correlations of the various kinetic parameters were made with a Texas Instruments T1-51 III calculator.

Results

The degradation of pyridinio-N-phosphonates in buffers containing pyridines exhibited mostly excellent first-order kinetics to over 90% of the reaction. In the majority of cases the extinction coefficients of the absorption of the various pyridinio-N-phosphonates are such that only one such species is able to be observed in the reaction. Fortuitously, this is not the case with the degradation of 4-methylpyridinio-N-phosphonate in pyridine

(7) Buchwald, S. L.; Pljura, D. H.; Knowles, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 845.
(8) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828.
(9) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.
(10) Jameson, A. W.; Lawlor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1970**, 53.
(11) (a) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 3356. (b) Lewis, G. L.; Smyth, C. P. *J. Chem. Phys.* **1939**, *7*, 1085.

Table I. Reaction of Pyridine with Substituted Pyridinio-*N*-phosphonates at 25 °C and 0.2 M Ionic Strength[h]

leaving group	pK^{xpy}	$k_{xpy}/M^{-1}\ s^{-1}$ [a,d]	N[d]	pH[g]	[py][c]	$k_{H_2O}/s^{-1}\ d,f_x\ 10^3$	λ/nm[e]
3-methylpyridine	5.81	0.81 ± 0.05 (0.82)	6	12	0.008	5.1 ± 0.3 (3.6)	280
3,5-dimethylpyridine	6.15	0.34 ± 0.1 (0.31)	10	12	0.012	1.9 ± 0.2 (1.5)	285
3-aminopyridine	6.03	0.78 ± 0.05 (0.39)	8	12	0.012	2.1 ± 0.25 (2.1)	338
3,4-dimethylpyridine	6.46	0.26 ± 0.05 (0.16)	6	12	0.02	0.60 ± 0.03 (0.69)	276
4-aminopyridine	9.14	6.24 ± 1.310^{-4} (5.49 × 10^{-4})	6	12	0.1		297
isoquinoline	5.46	1.43 ± 0.05 (1.31)	6	12	0.008	6.5 ± 0.34 (8.8)	350

[a] The quoted error is half the difference between the maximum and minimum possible slopes of the observed rate constants vs. pyridine concentration plots. [b] Number of data points including duplicates. [c] Maximum concentration of pyridine used. [d] Value in brackets is that calculated from the equation of Jameson and Lawlor.[10] [e] Wavelength used to follow the kinetics. [f] Quoted error is half the difference between maximum and minimum possible intercepts. [g] Maintained with KOH. [h] Ionic strength maintained with KCl.

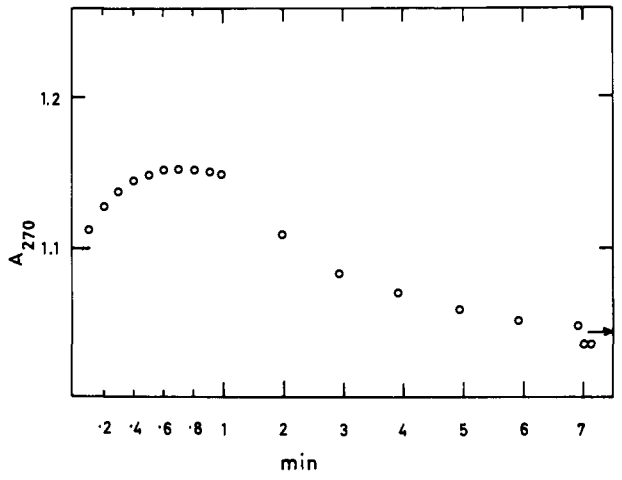


Figure 1. Formation and decay of pyridinio-*N*-phosphonate from (4-methylpyridinio)-*N*-phosphonate in pyridine buffer under conditions given in the text.

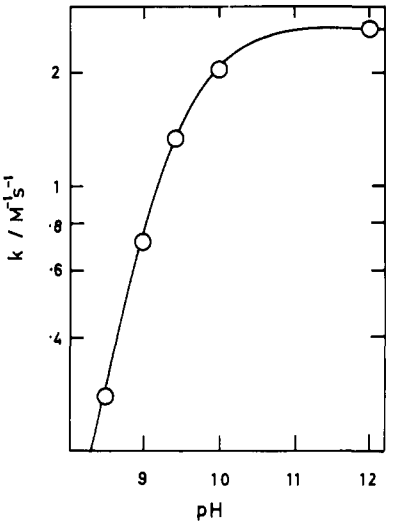


Figure 2. Dependence on pH of the pseudo-second-order rate constant for reactions of isoquinolinio-*N*-phosphonate with 4-aminopyridine. Each point is obtained from the slope of the pseudo-first-order rate constants vs. total 4-aminopyridine concentration. Conditions as in Table II. The pH was maintained with 0.02 M boric acid buffer, and the line is calculated from data in Table II.

buffers (0.025 M pyridine, pH 7.84, [tris(hydroxymethyl)-amino]methane at 0.01 M, ionic strength maintained at 0.1 M with KCl) where an initial increase in absorption at 270 nm was followed by a slower first-order decay (Figure 1). The decay rate constant (7.53 × 10^{-3} s^{-1}, 25 °C) is very close to that for the hydrolysis of pyridinio-*N*-phosphonate, prepared separately, in an identical buffer solution (7.66 × 10^{-3} s^{-1}). Jameson and Lawlor[10] found 9.3 × 10^{-3} s^{-1} for 0.2 M ionic strength and 25 °C. It is concluded that the pyridine buffer reacts with the 4-methylpyridinio-*N*-phosphonate in the initial reaction to form the pyridinio-*N*-phosphonate intermediate which undergoes the subsequent decomposition. It is likely that wavelengths exist for observing the formation of an intermediate in other pyridine systems, and we note that the reaction of 3-methylpyridine with pyridinio-*N*-phosphonate gave similar evidence for the nucleophilic reaction. Control experiments were carried out using only ammonium phosphoramidate (at the concentration in the original experiment) as the substrate. No change in absorption was noted, indicating that the original change was not due to reaction of the pyridine buffer with the phosphoramidate but to its reaction with the isoquinolinio-*N*-phosphonate.

The pseudo-first-order rate constants for reaction of pyridinio-*N*-phosphonates with buffers containing added nucleophile (N) obey eq 6, where k_{int} yields the rate constant for spontaneous

$$k_{obsd} = k_{int} + k_N[N] \quad (6)$$

hydrolysis of the substrate (Table I). The reaction of isoquinolinio-*N*-phosphonate with 4-aminopyridine over a pH range is illustrated in Figure 2 and demonstrates that the pseudo-first-order rate constant depends on the base form of the nucleophile as in eq 6. It is reasonably assumed that this is so for all the reactions studied here. The change in observed first-order rate constant caused by addition of nucleophile was significant and usually greater than 100% of the intercept at zero buffer concentration. The nucleophile concentration was, in most cases, kept below 0.05 M (Tables I–III) to obviate corrections due to curvature. The return reaction to the pyridinio-*N*-phosphonate reactant was checked by repeating the kinetics in the presence of a small concentration of the *product* pyridine equivalent to that in the substrate. The absence of a significant change in rate constant indicated that the "return" reaction could be neglected

Table II. Pyridinolysis of Isoquinolinio-*N*-phosphonate at 25 °C, 0.2 M Ionic Strength, and 10% v/v Ethanol/Water[e]

pyridine	p*K*	$k_F/M^{-1}\ s^{-1}$ [a]	*N*[b]	pH[c]	xpy[d]
3-CN	1.45	0.21 ± 0.03	14	8	0.10
3-Br	2.84	0.35 ± 0.04	5	8	0.025
3-Cl	2.98	0.30 ± 0.01	5	8	0.05
3-CH_3OCO	3.13	0.36 ± 0.03	6	8	0.10
3-CH_3CO	3.18	0.51 ± 0.01	5	8	0.025
4-CH_3OCO	3.26	0.42 ± 0.01	6	8	0.05
4-Br	3.78	0.49 ± 0.04	5	8	0.025
4-Cl	3.84	0.37 ± 0.03	7	8	0.05
3-CHO	3.70	0.53 ± 0.05	10	8	0.02
3-CH_2CN	4.1	0.51 ± 0.03	6	8	0.025
4-CHO	4.7	0.44 ± 0.04	9	8	0.02
H	5.32	1.02 ± 0.04	14	8	0.01
3-CH_3	5.81	0.88 ± 0.13	10	8	0.012
4-CH_3	6.15	1.67 ± 0.15	9	8	0.005
3,5-Me_2	6.15	1.15 ± 0.14	7	8	0.004
3,4-Me_2	6.46	2.28 ± 0.12	14	8	0.011
4-morpholino	8.7	2.70 ± 0.05	8	8	0.005
4-NH_2	9.14	2.60 ± 0.03	16	8.4–12	0.005
4-NMe_2	9.6	2.28 ± 0.17	12	12, 10.5	0.005
2,6-Me_2	6.77	<0.01	6	8	0.10
isoquinoline	5.46	<0.05	8	8	0.01

[a] Quoted error as described in footnote *a* of Table I. [b] Number of data points including duplicates. [c] Maintained pH 6 with [tris(hydroxymethyl)amino]methane (0.01 M), pH 10.5 with carbonate buffer (0.01M) and pH 12 with KOH; other buffers for 4-aminopyridine are given in the caption to Figure 2. [d] Maximum concentration of pyridine used. [e] Wavelength for kinetic study 350 nm; ionic strength maintained with KCl.

Table III. Aminolysis of Isoquinoline-*N*-phosphonate at 25 °C, 0.2 M Ionic Strength, and 10% v/v Ethanol/water[a,f]

amine	p*K*	$k/M^{-1}\ s^{-1}$ [b]	*N*[c]	pH[d]	amine[e]
piperidine	11.22	2.14 ± 0.05	4	13	0.009
piperazine	9.82	4.90 ± 0.05	6	12	0.003
morpholine	8.36	2.42 ± 0.05	6	12	0.012
piperazine-H^+	5.68	2.54 ± 0.16	10	6	0.01
NH_3	9.25	0.33 ± 0.01	6	12	0.025
NH_2NH_2	8.07	5.60 ± 0.08	8	12	0.01
$EtNH_2$	10.63	1.21 ± 0.03	6	12	0.012
n-$BuNH_2$	10.59	1.13 ± 0.11	8	12	0.012
n-$PrNH_2$	10.53	1.20 ± 0.07	4	12	0.02
$NH_2CH_2CH_2CO_2^-$	10.19	0.81 ± 0.03	6	12	0.02
$NH_2CH_2CH_2NH_2$	9.98	2.63 ± 0.15	8	12	0.015
$PhCH_2,cH_2NH_2$	9.78	1.08 ± 0.06	8	12	0.02
$NH_2CH_2CO_2^-$	9.60	0.94 ± 0.07	6	12	0.02
$HOCH_2CH_2NH_2$	9.50	1.48 ± 0.03	6	12	0.02
$PhCH_2NH_2$	9.34	0.96 ± 0.03	5	12	0.02
$NH_2CH_2CO_2Et$	7.75	0.69 ± 0.07	6	9	0.02
$NH_3^+CH_2CH_2NH_2$	7.52	1.25 ± 0.07	8	7.3	0.012
$CF_3CH_2NH_2$	5.7	0.16 ± 0.01	7	8	0.05
NH_2CH_2CN	5.34	0.36 ± 0.03	10	8	0.05
$N(CH_2CH_2)_3N$	8.80	8.40 ± 0.40	10	12	0.001

[a] Primary amines, except ammonia and hydrazine, fitted the equation $\log k/q = (0.13 \pm 0.03)(pK_{RNH_2} + \log(p/q)) - (1.36 \pm 0.32)$ (r = 0.882). [b] Quoted error as for footnote *a* in Table I. [c] Number of data points including duplicates. [d] pH maintained above 12 with KOH, pH 9 with boric acid (0.01 M), pH 8 with [tris(hydroxymethyl)amino]-methane (0.01 M), and pH 7.3 with phosphate (0.04 M). [e] Maximum concentration of amine used. [f] Wavelength for kinetic study 350 nm; ionic strength maintained with KCl.

under the conditions of the experiment. At relatively high concentrations of nucleophile in the buffer, curvature was sometimes observed possibly due to pyridine self-association; all the data collected were for linear concentration plots and are recorded in Tables I–III. Pseudo-second-order rate constants obtained from the slope of k_{obsd} against total nucleophile concentration were converted by division by the fraction of the nucleophile present in its basic form (frB). The value of frB was obtained from the pH of the solution and the p*K* of the nucleophile obtained under the conditions of the experiment.

The reactivity of 2,6-dimethylpyridine against isoquinolinio-*N*-phosphonate is over 100-fold *less* than that of an unhindered pyridine of similar basicity (Table II), indicating that the reaction is very sensitive to steric effects. Isoquinoline as a nucleophile was observed to have *no* effect on the hydrolysis of isoquinolinio-*N*-phosphonate (Table II); utilizing the experimental error leads to a reactivity smaller than that of a pyridine of similar p*K* by more than 20 times. These experiments and the observation of an intermediate demonstrate that the reactions being studied here are *nucleophilic* and not general-base catalyzed hydrolysis.

Hydrolysis rate constants for the pyridinio-*N*-phosphonates obey a good Brønsted relationship (eq 7). Our data is in excellent

$$\log k_{H_2O} = (-1.11 \pm 0.18)pK_{xpy} + (3.99 \pm 1.05)\ (r = 0.999) \quad (7)$$

agreement with that of previous workers as shown in Table I, and the Brønsted equation is similar.

The reaction of pyridine with substituted pyridinio-*N*-phosphonates obeys a Brønsted equation (8), and where com-

$$\log k_{py} = (-0.92 \pm 0.02)pK_{xpy} + (5.24 \pm 0.16)\ (r = 0.998) \quad (8)$$

parison is possible the data are in good agreement with those of previous workers.

Isoquinolinio-*N*-phosphonate reacts with substituted pyridines according to eq 9, and this is illustrated in Figure 3. The the-

$$\log k_{xpy} = (0.15 \pm 0.01)pK_{xpy} - (0.86 \pm 0.07)\ (r = 0.946) \quad (9)$$

oretical equation for the mechanism involving a preassociation stepwise path (eq 4) is given by eq 10 where $\Delta pK = pK_{isq} - pK_{xpy}$.

$$\log k/k_o = 1/(1 + 10^{(\Delta pK)\beta}) \quad (10)$$

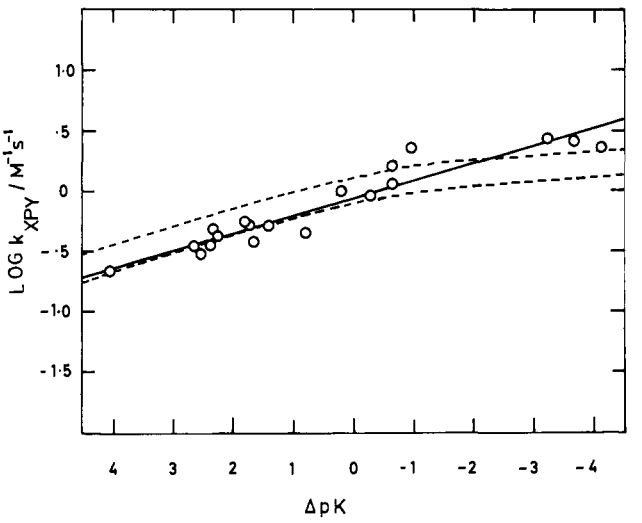


Figure 3. Reactivity of pyridines against isoquinolinio-*N*-phosphonate as a function of the difference in p*K* between attacking pyridine and isoquinoline. Conditions are as in Table II, and the line is calculated from equation (9). The dashed curves are calculated from eq 10 for $\beta = 0.2$ drawn to fit either high or low p*K* points. Identity of the pyridines may be obtained from Table II where they are listed in order of p*K*.

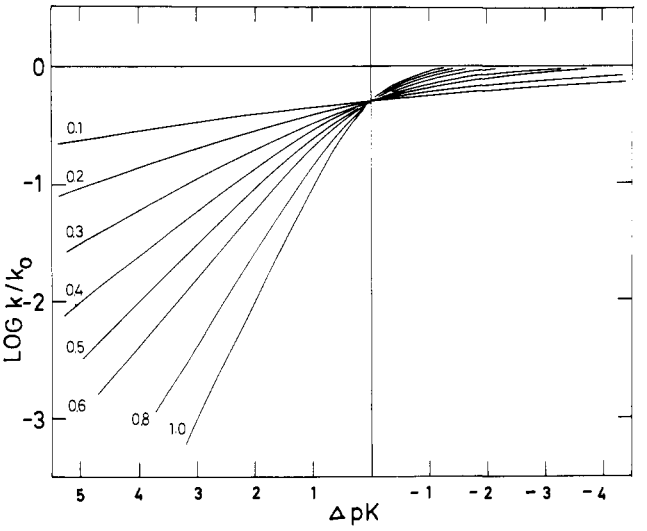


Figure 4. Family of normalized curves (log k/k_o) vs. ΔpK for the theoretical rate law governing the preassociation stepwise mechanism (eq 10). Numbers refer to the chosen value of β for the rate law.

This is derived from a simple steady-state treatment of eq 4 and applies specifically to a reaction where nucleophile and leaving group reactivity on PO_3^- in the ternary complex is governed by the same Brønsted equation. The value k_o is that of the observed second-order rate constant when the decomposition of the encounter complex $[Nu^-{\cdot}L{-}PO_3^{2-}]$ to the ternary encounter complex $[Nu^-{\cdot}L^-{\cdot}PO_3^-]$ is the rate-limiting step. The Brønsted coefficient, β, is the exponent for rate-limiting attack of the acceptor nucleophile (Nu^-) in the ternary complex. The mechanism assumes that both rate-limiting steps are independent of their respective "spectator" nucleophiles (xpy for the k_2 step and isq for the k_3 step) and that the complexes are essentially "encounter" complexes. Equation 10 gives a family of normalized theoretical curves (Figure 4) for log k/k_o dependent only on β and ΔpK. The best fit of the theoretical expression to the data is where $\beta = 0.3$; this leads to an acceptable correlation coefficient but examination of the "residuals" (log k_{xpy} − log $k_{xpy(calcd)}$) as a function of p*K* reveals a *nonrandom* variation. The residuals for the linear correlation (eq 9) however, exhibit a *random* variation consistent with good fit. Assuming a reasonable value of $\beta = 0.2$[10,12] gives a very poor

(12) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1965**, *87*, 3199.

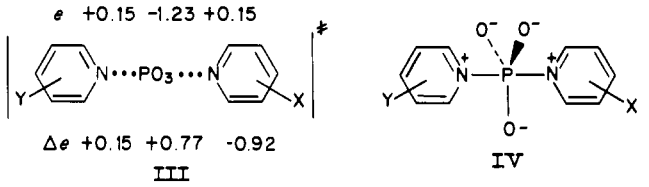
fit as judged from the nonrandomness of the residuals and two possible "fits" are shown in Figure 3, one that fits the upper points well and one that fits the lower.

The points of Figure 3 nevertheless possess a little curvature which is not predicted by the theoretical equation 10. It is not possible to judge whether this curvature is due to random microscopic medium effects on individual substituents even though a large number of nucleophiles have been employed and possible deviant points carefully checked.

Discussion

The definitive result of this work is that the electronic nature of the transition state for the reaction (eq 5) is almost completely independent of the basicity of the nucleophile over a range of pK where a change in rate-limiting step is predicted for the stepwise process. The linear or slightly curved Brønsted relationship for the reaction of pyridines with isoquinolinio-N-phosphonate indicates a single transition state for the range of nucleophiles. Thus the mechanisms of eq 1, 3, and 4 are ruled out except when the putative intermediate is exceptionally reactive and exists only in a shallow well at the top of an energy maximum. A nonlinear relationship is expected with a break at $\Delta pK = 0$ for a stepwise process with two electronically distinct transition states.

Since there is only one transition state for the reaction of eq 5, which is a symmetrical reaction, the donor and acceptor P–N bonds must be of the same order in the transition state. The value of β_L for attack of pyridine on substituted pyridinio-N-phosphonates (−0.92) coupled with β_N for attack of substituted pyridines (+0.15) yields a $\beta_{eq} = 0.15 + 0.92 = 1.07$. Thus the effective charge changes on attacking and departing nitrogen are +0.15 and −0.92 in a total change of 1.07.[13] The imbalance of −0.77 effective charge unit is presumably accommodated by the PO_3 grouping. Structure III illustrates the change in effective



III IV

charge on the various groupings. Provided effective charge is conserved then that on the PO_3 will be −1.23 in the transition state consistent with a structure close to the metaphosphate anion. A structure for the transition state close to that represented by IV is not consistent with the observed charges nor is one where there is full P–N bonding for either entering or leaving groups. The charge distribution implies that the transition state is in the bottom right corner of the three-dimensional potential energy diagram (Figure 5) where corners represent encounter complexes rather than free solvated species.

The symmetrical transition state can be neither "early" nor "late"; if treated by the valence-bond configuration mixing model,[14] the transition state should be made up of configurations other than the two "equal" ones represented by $py{:}PO_3^{2-}{\cdot\cdot}py^+$ because the charge "seen" on the nitrogen is considerably less than 0.5. Such a configuration would be $py{:}PO_3^{-}{:}py$ corresponding to the carbenium ion used in discussing the transfer of the alkyl group.[14]

The present method can exclude the possibility that the putative metaphosphate ion could be formed in the encounter complex faster than it can rotate out of plane (and racemize if the oxygens are not equivalent). Indeed analogous reactions thought to proceed via carbenium ions can involve inversion at the carbon.[15] The

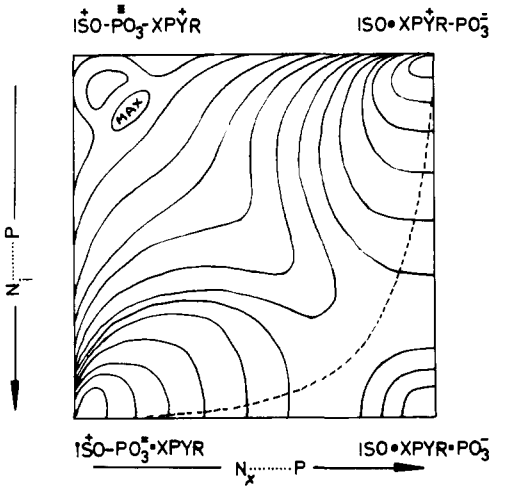


Figure 5. Diagrammatic potential energy surface for reaction of isoquinolinio-N-phosphonate with pyridines. The species at the corners are reaction complexes representing the closest distance where two or more molecules do not interact. The species at the top left is essentially structure IV, and reactants and products are bottom left and top right, respectively. The contour lines are not exact and are to indicate the general shape of the surface.

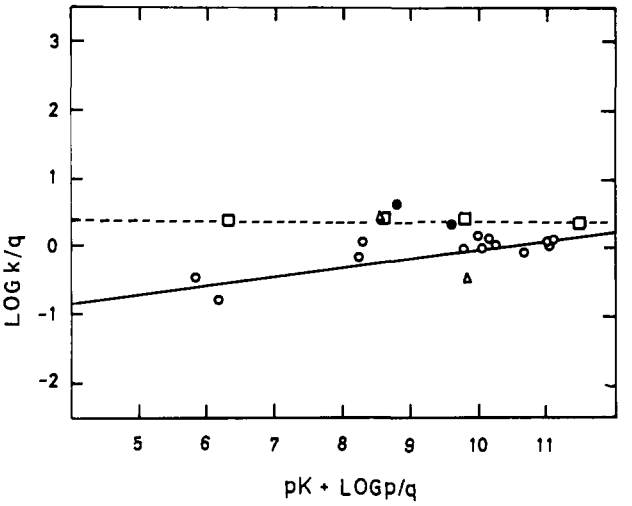


Figure 6. Reaction of amines with isoquinolinio-N-phosphonate. Data and conditions from Tables II and III. The identity of the species may be obtained from Tables II and III where the nucleophiles are arranged in order of their pK: primary amines (○), secondary amines (□), tertiary amines (●), and ammonia and triethylenediamine (△). The line is calculated from the equation in footnote *a* of Table III, and the dashed line is of zero slope for the cyclic secondary amines.

"rate constant" associated with such rotational motion depends considerably on the solvation factors: liquid water has a value of about 10^{10} s^{-1} whereas glycerol has 10^8 s^{-1} at 0 °C,[16] and rotation observed in the complex between 2,4-dinitrophenol and tertiary amines, limiting the proton transfer, was found to be less than 4×10^9 s^{-1}.[17]

The second-order rate constant for reaction of primary amines with isoquinolinio-N-phosphonate has a very shallow linear Brønsted line (Figure 6). The hydrazine point lies above the line in accord with its known activity as an α-nucleophile, but it is not exceptionally reactive compared with an amine of similar basicity; this is in agreement with the results of other workers[18] who point

(13) This value is close to that estimated by Benkovic and Schray (Benkovic, S. J.; Schray, K. J. "The Enzymes"; Boyer, P. D., Ed.; Academic Press: New York, 1973; Vol. 8, p 201) from the work of Jencks and Gilchrist[12] and Jameson and Lawlor[10] (+1.2) for transfer of the phosphoryl group between pyridines and ammonia. Effective charge on pyridinium nitrogen is independent of the constant acceptor atom. However, the data from the two laboratories refer in one case to 39 °C and 1 M ionic strength and in the other to 25 °C and 0.2 M ionic strength.

(14) Pross, A.; Shaik, S. S. *Acc. Chem. Res.* **1983**, *16*, 363.

(15) (a) Goering, W. von E.; Zeiss, H. H. *J. Am. Chem. Soc.* **1953**, *75*, 4733. (b) A detailed modern account of this subject is given in: Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper and Row: New York, 1981; Chapter 4.

(16) Powles, J. G. *Spec. Publ.—Chem. Soc.* **1966**, *20*, 127.

(17) Ivin, K. J.; McGarvey, J. J.; Simmons, E. L.; Small, R. *J. Chem. Soc., Faraday Trans. 1* **1973**, *69*, 1016.

(18) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.

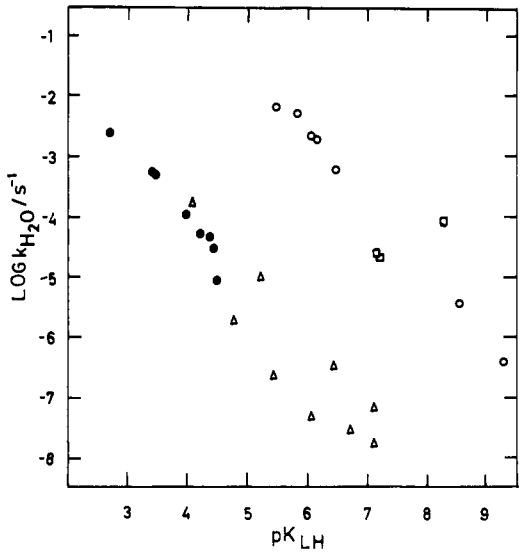


Figure 7. Hydrolytic reactivity of phosphonates L–PO_3^{2-} as a function of the leaving group LH. The data for the pyridines (○) are taken from Table I, and those for 4-morpholino- and 4-(dimethylamino)pyridine (pK 8.7 and 9.6, respectively) are from ref 10. The species (□) imidazolium N-phosphonate,[22] N'-methylimidazolium N-phosphonate,[22] and NH_3^+-PO_3^{2-} [12] are in increasing order of pK. Phenyl phosphates (△) in increasing order of pK are 2,4-dinitro-, pentachloro-, 2-nitro-4-acetyl-, 2-chloro-4-nitro-, 2,4,6-trichloro-, 2-nitro-4-chloro-, 3,5-dinitro-, 2-nitro-, and 4-nitro- (A. J.; Kirby, Varvoglis, A. G. *J. Am. Chem. Soc.* **1967**, *89*, 415). Acyl phosphates (●) in increasing order of pK are 3,5-dinitrobenzoyl, 4-nitrobenzoyl, 3-nitrobenzoyl, 4-chlorobenzoyl, benzoyl, 4-methylbenzoyl, 4-methoxybenzoyl, and acetyl (DiSabato, G.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4400). Conditions for these data are mostly 39° and 1 M ionic strength. The pyridines were at 25 °C and a lower ionic strength.

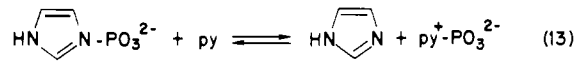
out that the α-nucleophile effect becomes smaller as β_N decreases. The reactivity of ammonia is a little below the line, consistent with its carrying a larger solvation shell than that for primary amines.[19] Six-membered ring secondary amines where the structure variations are not large exhibit a good Brønsted relationship with zero slope (Figure 6) over a pK range of over 5 units. Part of this result could arise from an electrostatic effect from the positive charge on the least basic amine. This would tend to cause a rate-constant increase and distort the β_N value. It is possible that the energy surface (Figure 5) with amine as acceptor has been skewed by the presence of the more reactive amine nucleophile to place the transition state closer to the bottom right corner. Estimates of metaphosphate ion reactivity[20,21] indicate that the species cannot have a deep energy well; the energy surface (Figure 5) in the vicinity of the intermediate ($Nu^-{\cdot}PO_3^-{\cdot}L^-$) will thus have shallow contours. Movement of the transition state in the vicinity of the bottom right corner will thus not cause a large change in energy, and any differences are unlikely to allow a practical distinction to be made. In our opinion, such mechanisms in the borderline region can hardly be called "discrete", and attempts to distinguish between them will be of little use.

Provided there is no change in β_L or β_N respectively for different pyridine nucleophiles or leaving groups, the rate constant for the reaction (eq 5) is given by the eq 11 and the equilibrium constant

$$\log k_F = +0.15pK^{xpy} - 0.92pK^{ypy} + 4.3 \quad (11)$$

for formation of ypy^+–PO_3^{2-} by eq 12. The equilibrium constant

$$\log K = (pK^{ypy} - pK^{xpy}) \quad (12)$$



(13)

for formation of pyridinio-N-phosphonate from imidazolio-N-phosphonate (eq 13) can be determined (with a little allowance for different conditions) from literature data for the reaction in both directions.[10,12] The value obtained (2.19×10^{-3}) is reasonably close to that (8.2×10^{-3}) calculated from eq 12. This agreement might be expected on the grounds that pyridines and imidazoles have similar structures. Calculation of the equilibrium constants for transfer between amines and pyridines should not be possible through eq 12, and that calculated for the formation of pyridinio-N-phosphonate from phosphoramidate (3.9×10^{-5}) is much smaller than the value estimated from forward[12] and reverse[10] rate constants (1.77×10^{-2}). Formation of 4-methylpyridinio-N-phosphonate from phosphoramidate has a similar difference (estimated 1.1×10^{-1}, calcd 3.17×10^{-4}). The larger observed equilibrium constants for transfer from ammonia reside largely in the leaving ability of the ammonium compared with a pyridine of similar pK (Figure 6). Only a small effect is obtained from the nucleophilicity of ammonia which is only slightly below that of a pyridine in attack on isoquinolinio-N-phosphonate. The leaving ability of the ammonia must to a large extent be the result of favorable solvation effects. Such leaving ability is indeed valuable, as without it we should not have been able to synthesize the present pyridinio-N-phosphonates with such ease. Phosphoramidate's use as a phosphorylating agent presumably resides in the exceptional leaving ability of the ammonia.

Acknowledgment. We thank the SERC and ICI Organics Division for financial support, Dr. R. B. Moodie for a kind gift of 4-morpholinopyridine, and Professor W. P. Jencks and Dr. M. Skoog for disclosing results from their independent work prior to its publication.[11a,23] Part of this work was carried out at the University of Genoa with the aid of a NATO travel grant (RG 115.80) and a Ciba-Geigy Senior Fellowship (A.W.).

Registry No. NH_3, 7664-41-7; NH_2NH_2, 302-01-2; $EtNH_2$, 75-04-7; n-$BuNH_2$, 109-73-9; n-$PrNH_2$, 107-10-8; $NH_2CH_2CH_2CO_2^-$, 23297-31-6; $NH_2CH_2CH_2NH_2$, 107-15-3; $PhCH_2CH_2NH_2$, 64-04-0; $NH_2CH_2CO_2^-$, 23297-34-9; $HOCH_2CH_2NH_2$, 141-43-5; $PhCH_2NH_2$, 100-46-9; $NH_2CH_2CO_2Et$, 459-73-4; $NH_3^+CH_2CH_2NH_2$, 26265-69-0; $CF_3CH_2NH_2$, 753-90-2; NH_2CH_2CN, 540-61-4; $N(CH_2CH_2)_3N$, 280-57-9; $NH_4^+NH_3PO_3^-$, 13566-20-6; 3-methylpyridino-N-phosphonate, 92670-25-2; 3,5-diethylpyridino-N-phosphonate, 92670-26-3; 3-aminopyridino-N-phosphonate, 92670-27-4; 3,4-dimethylpyridino-N-phosphonate, 92670-28-5; 4-aminopyridino-N-phosphonate, 28595-43-9; isoquinoline-N-phosphonate, 85370-61-2; 3-methoxypyridino-N-phosphonate, 92670-30-9; pyridine, 110-86-1; 3-cyanopyridine, 100-54-9; 3-bromopyridine, 626-55-1; 3-chloropyridine, 626-60-8; methyl 3-pyridinecarboxylate, 93-60-7; methyl 4-pyridnecarboxylate, 2459-09-8; 3-acetylpyridine, 350-03-8; 4-bromopyridine, 1120-87-2; 4-chloropyridine, 626-61-9; 3-pyridinecarboxaldehyde, 500-22-1; 3-(cyanomethyl)pyridine, 6443-85-2; 4-pyridinecarboxaldehyde, 872-85-5; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 3,5-dimethylpyridine, 591-22-0; 3,4-dimethylpyridine, 583-58-4; 4-morpholinopyridine, 92670-29-6; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; 2,6-dimethylpyridine, 108-48-5; isoquinoline, 119-65-3; piperidine, 110-89-4; piperazine, 110-85-0; morpholine, 110-91-8; piperazine-H^+, 22044-09-3; phosphoryl chloride, 10025-87-3; 3-aminopyridine, 462-08-8.

(19) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1973.
(20) (a) Loew, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 1630. (b) Loew, L. M.; MacArthur, W. R. *Ibid.* **1977**, *99*, 1019.
(21) (a) Guthrie, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3991; **1978**, *100*, 5892. (b) Haake, P.; Allen, G. W. *Bioorg. Chem.* **1980**, *9*, 325.
(22) Lloyd, G. J.; Hsu, C. M.; Cooperman, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 4889.
(23) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.*, following paper in this issue.