tetrahydropyran was determined by glpc using cyclohexane as an internal standard.

Reaction of 1 with Benzyl Alcohol. Samples of **1** were mixed with benzyl alcohol, mole ratio 1:10 at room temperature, 1:5 at −20°, and 1:20 at 0°. In all cases decomposition of **1** occurred with the formation of trialkyl phosphate. Glpc analysis showed that dibenzyl ether was formed. Formation of benzyl ethyl ether could not be detected because of its similar retention time to that of benzyl alcohol.

Reaction of Tribenzyl Phosphite with Diethyl Peroxide. Tribenzyl phosphite, 7.04 g (0.02 mol), and diethyl peroxide, 2.7 g (0.0274 mol), were mixed with cooling. The flask and its contents were cooled to −60°, evacuated, and flushed with argon three times. The course of the reaction was monitored by ^{31}P nmr spectroscopy. After 4 days there was found 32% phosphate, 59% phosphite, and 9% phosphorane, +68. After 15 days only phosphate, 88%, and phosphite, 12%, were present. Glpc analysis showed dibenzyl ether and benzyl ethyl ether had been formed.

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Structure–Reactivity Correlation for the Hydrolysis of Phosphoramidate Monoanions

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Abstract: The structure–reactivity relationship which correlates the rate constants for the hydrolysis of phosphoramidate monoanions with the pK_a of the leaving amine is nonlinear. The inflection point in the data which occurs at $pK_a \approx 8$ is attributed to changes in the nonsteady-state zwitterion concentration which are directly proportional to the pK_a of the parent amine. The equilibrium favors the zwitterionic species in aqueous solution for those phosphoramidates whose second dissociation constant is greater than 7.2. On the basis of these data, a semiquantitative description of the transition state for nucleophilic attack on phosphoramidates is developed which features bond cleavage to the departing group as greatly exceeding bond formation to the incoming nucleophile. This finding in conjunction with data for *O*- and *S*-phosphate mono- and diesters suggests that pentacovalent intermediates probably do not occur on the reaction pathways for acyclic mono- and diester hydrolysis.

The involvement of various phosphoramidates either as substrates or intermediates in the enzyme-catalyzed phosphorylation of hexose and adenosine triphosphate is well established.[3–6] Two examples follow. Phosphoramidate–adenosine diphosphate phosphotransferase facilitates the interconversion of adenosine di- and triphosphate utilizing *N*-phosphorylglycine, *N*-phosphorylhistidine, or phosphoramidate as the $[PO_3^{2-}]$ source.[3] Glucose 6-phosphatase catalyzes the transfer of $[PO_3^{2-}]$ from glucose 6-phosphate to water or inorganic phosphate through an enzymic *N*-phosphorylhistidine intermediate.[4] Several quantitative studies have dealt with the nonenzymic hydrolysis of phosphoramidate and various *N*-acyl and *N*-aryl derivatives.[7–9] In addition it has been demonstrated that the hydrolysis of phosphoramidate monoanion[7,10] and a series of phosphorylpyridinium ions[11] is subject to nucleophilic catalysis by various amines, especially pyridines and in the case of phosphoramidate, the hydrolysis is accelerated by electrophilic catalysts including formaldehyde and nitrous and hypochlorous acid. Collectively these studies posed a problem concerning the description of the transition state for the catalyzed and spontaneous hydrolysis of the ester monoanion. The proposal of a "borderline" unimolecular elimination reaction, not involving a "free" metaphosphate species, for the phosphoramidates, in contrast to the metaphosphate mechanism suggested for *O*-phosphate monoesters, stemmed from investigations of product distribution in various mixed alcohol–water solvents.[7,10,12] The results indicated that the solvolysis proceeded *via* a species that was selective toward nucleophilic reagents, *e.g.*, methanol is tenfold more reactive than water. Moreover, interpretation of the low Brønsted β value (0.2) for nucleophilic catalysis by pyridines implied a transition state with minor but not negligible bond formation between the nucleophile and phosphorus atom. Left unspecified, however, is the degree of bond cleavage between phosphorus and the departing group.

The present study of the hydrolysis of a series of phosphoramidate monoesters was initiated in order to establish a structure–reactivity correlation for this

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system. Such a relationship may serve to answer the above inquiry and in conjunction with other pertinent data may lead to a more quantitative description of the transition state for displacement reactions on phosphoramidates.

Experimental Section

All melting points are uncorrected. Microanalyses for nitrogen were performed by Midwest Microlab and for phosphate by the method of Martin and Doty (see below). Infrared spectra were obtained with a Perkin-Elmer 137 spectrometer. Methanol (Baker reagent grade), D_2O (99.8% Diaprep), $H_2{}^{18}O$ (1.5 atom %, Biorad), and twice-distilled deionized water were employed as solvents. Reagent grade salts, solvents, and acids (Fisher, Baker) were used without further purification, except where noted. Descending paper chromatograms were run on Schleicher and Schuell orange ribbon 589c paper in 0.1 *M* aqueous K_2CO_3–ethanol (3.5:6.5) and developed with Hanes and Isherwood Spray.[13] Amines were distilled prior to use. Nmr spectra were measured on a Varian Associates A-60 spectrometer using tetramethylsilane ($CDCl_3$) and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O) as internal standards. Mass spectra were measured on an MS-902 AEI spectrometer.

Materials. The monopotassium salts of *N*-(*n*-butyl)-, *N*-(methoxyethyl)-, *N*-(benzyl)-, and *N*-(phenethyl)phosphoramidates were prepared by an adaptation of the method of Stokes.[14] Diphenyl phosphorochloridate (0.05 mol) was added dropwise to a rapidly stirring, ice cold solution of amine (0.10 mol) in 200 ml of chloroform. The solution was stirred at room temperature for 4 hr and washed with 150-ml portions of 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to a clear oily residue. After all traces of chloroform had been removed, a white solid crystallized upon standing in the cold. The yields were approximately 60%.

***O,O*-Diphenyl *N*-(*n*-butyl)phosphoramidate** showed ir (KBr) 3.05 (m), 3.40 (w), 6.30 (m), 6.73 (s), 8.05 (s), 8.44 (s), 10.65 (s), 12.96 (m), 13.25 (m), and 14.50 μ (m); nmr δ ($CDCl_3$) 0.60–1.65 (complex m, 7, $CH_3CH_2CH_2C$), 3.05 (m, 2, $-CH_2N$), 4.06 (m, 1, $-NHP$), and 7.26 (s, 10, phenyl); mol wt of $C_{16}H_{21}N_1P_1O_3$, 305 (calcd, 305); mp 57–58°.

***O,O*-Diphenyl *N*-(phenethyl)phosphoramidate** showed ir (KBr) 3.07 (m), 3.50 (w), 6.30 (m), 6.75 (s), 8.05 (s), 8.45 (s), 10.75 (s), 13.20 (s), and 14.58 μ (m); nmr δ ($CDCl_3$) 2.65 (t, 2), 3.22 (m, 2), 4.33 (m, 1, CN*H*P), and 7.24 (m, 15, phenyl); mol wt of $C_{20}H_{20}N_1P_1O_3$, 353 (calcd, 353); mp 77.5–78.0°.

***O,O*-Diphenyl *N*-(benzyl)phosphoramidate** showed ir (KBr) 3.16 (m), 3.47 (w), 6.30 (m), 6.75 (s), 8.06 (s), 8.42 (s), 9.06 (m), 10.64 (s), 12.93 (s), 13.41 (m), and 14.50 μ (m); nmr δ ($CDCl_3$) 4.22 (m, 3, $-CH_2NH-$) and 7.20 (s, 15, phenyl); mol wt $C_{19}H_{18}N_1P_1O_3$, 339 (calcd, 339); mp 101–102°.

***O,O*-Diphenyl *N*-(methoxyethyl)phosphoramidate** showed ir (KBr) 3.10 (w), 3.46 (w), 6.30 (m), 6.74 (s), 8.41 (s), 9.04 (m), 10.80 (s), 13.00 (m), and 14.52 μ (m); nmr δ ($CDCl_3$) 3.28 (d, 7, $CH_3OCH_2CH_2N$), 4.58 (m, 1, $-NHP$), and 7.26 (s, 10, phenyl); mol wt of $C_{15}H_{18}N_1P_1O_4$, 307 (calcd, 307); mp 33–35°.

The monopotassium salt of the corresponding phosphoramidate was prepared by dissolving 4 g of the diphenyl derivative in 15 ml of refluxing 10 *N* potassium hydroxide. After exactly 10 min, the reaction was quickly cooled in ice and titrated to pH 5 with 17.5 *N* acetic acid. The reaction solution was then diluted to 150 ml with absolute ethanol. Precipitation of the desired salt was accomplished by the addition of ethyl acetate (300–400 ml). The product was isolated by filtration and twice purified by dissolving in absolute methanol followed by precipitation with acetone. The compounds were dried *in vacuo* over KOH and stored at −10°. The overall yields were approximately 40%. No attempts were made to maximize the yield.

The monopotassium salt of *N*-(*n*-butyl)phosphoramidate showed ir (KBr) 2.90–4.00 (broad multiplet), 6.13 (m), 7.09 (m), 8.30–9.00 (broad multiplet), 10.11 (m), 13.46 (m), and 14.50–14.90 μ (broad); nmr δ (D_2O) 0.67–2.10 (complex m, 7, $CH_3CH_2CH_2C$) and 3.00 (m, 2, CCH_2N); R_f 0.68.

Anal. Calcd for $C_4H_{11}N_1P_1K_1 \cdot 1CH_3OH$: N, 6.28; P, 13.90. Found: N, 6.41; P, 14.08.

The monopotassium salt of *N*-(phenethyl)phosphoramidate showed ir (KBr) 2.90–4.10 (broad multiplet), 6.20 (m), 7.10 (m), 8.45–8.74 (broad multiplet), 10.21 (s), 13.32 (m), and 14.32 μ (s); nmr δ (D_2O) 2.96–3.70 (complex m, 4, $-CH_2CH_2N$) and 7.60 (s, 5, phenyl); R_f 0.72.

Anal. Calcd for $C_8H_{11}N_1P_1O_3K \cdot 1CH_3OH$: N, 5.17; P, 11.44. Found: N, 5.14; P, 11.88.

The monopotassium salt of *N*-(benzyl)phosphoramidate showed ir (KBr) 2.88–4.13 (broad multiplet), 6.14 (m), 7.07 (m), 8.35–9.75 (broad multiplet), 10.18 (s), 13.67 (m), and 14.45 μ (m); nmr δ (D_2O) 4.22 (d, 2, $-CH_2N$) and 7.50 (s, 5, phenyl); R_f 0.66.

Anal. Calcd for $C_7H_9N_1P_1O_3K \cdot 1CH_3OH$: N, 5.45; P, 12.06. Found: N, 5.53; P, 12.25.

The monopotassium salt of *N*-(methoxyethyl)phosphoramidate showed ir (KBr) 2.88–4.15 (broad multiplet), 6.19 (m), 6.30–6.87 (broad multiplet), 10.19 (s), and 14.10–14.50 μ (broad); nmr δ (D_2O) 3.28 (m, 2), 3.48 (s, 3, CH_3O-), and 3.77 (t, 2) R_f 0.63.

Anal. Calcd for $C_3H_9N_1P_1O_4K \cdot 1CH_3OH$: N, 6.22; P, 13.77. Found: N, 6.01; P, 13.96.

The monoanilinium salt of *N*-(2,2,2-trifluoroethyl)phosphoramidate was prepared by the method of Todd[15] as modified by Chanley.[16] Trifluoroethylamine hydrochloride (0.05 mol), solubilized by triethylamine (0.10 mol), in 50 ml of chloroform was dropwise added to a rapidly stirring solution of dibenzyl phosphorochloridate (prepared from 0.05 mol of dibenzyl phosphite) in 150 ml of chloroform. The solution was stirred at room temperature for 6 hr and washed with 100-ml portions of 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to a clear oily residue. After all traces of chloroform had been removed the oil began to solidify and finally crystallized with the addition of *n*-hexane. The product isolated by filtration was satisfactory for hydrogenation without further purification.

***O,O*-Dibenzyl *N*-(2,2,2-trifluoroethyl)phosphoramidate** showed ir (KBr) 3.14 (m), 3.40 (w), 7.73–8.14 (broad multiplet), 8.60–8.80 (broad), 9.65–10.00 (broad multiplet), 13.40 (m), and 14.40 μ (m); nmr δ ($CDCl_3$) 3.33 (broad m, 2, CF_3CH_2N), 4.91 (d, 5, benzylic $-CH_2-$ and $-CNH-$), and 7.25 (s, 10, phenyl); mol wt of $C_{16}H_{17}F_3N_1P_1O_3$, 359 (calcd, 359); mp 50–53°.

A solution of 3 g of the dibenzyl derivative in 75 ml of absolute ethanol was hydrogenated in the presence of 50 mg of a 5% Pd/C catalyst. After 2 mol of hydrogen had been adsorbed (1.5 hr), the catalyst was removed by filtration, and the filtrate cooled in ice. Immediate precipitation occurred with the addition of 0.78 ml of aniline. The precipitate was removed by filtration and washed successively with cold absolute ethanol (10 ml) and absolute ether (25 ml). The product was dried *in vacuo* over KOH and stored at −10°, yield 1.0 g.

Monoanilinium *N*-(2,2,2-trifluoroethyl)phosphoramidate showed ir (KBr) 2.95 (m), 3.45–3.85 (broad doublet), 7.74 (m), 7.86 (m), 8.51–9.02 (broad multiplet), 9.65 (m), 10.44 (m), 13.39 (m); R_f 0.64.

Anal. Calcd for $C_8H_{12}F_3N_1P_1O_3 \cdot 1CH_3CH_2OH$: N, 9.15; P, 10.13. Found: N, 9.74; P, 9.88.

Dissociation Constants. Values for the dissociation constants for the phosphoramidates prepared above were determined titrimetrically in a Metrohm cell (EA 662) at 20°, μ = 0.2, KCl. Hydrogen and hydroxide ion corrections were applied as described in Albert and Serjeant[17,18] (Table I).

Apparatus. Instrumentation used in this study has been described previously.[19] Kinetic runs were carried out in Kimax (No. 45066) screw cap tubes maintained at reaction temperature (± 0.1°) by immersion in a circulating water bath.

Kinetics. Kinetic runs were initiated by the addition of the N-substituted phosphoramidate (5–6 mg) to 20 ml of the pre-equilibrated buffer solution or by the addition of a 1-ml aliquot from a freshly prepared stock solution (5 mg/ml) adjusted to the desired pH. The hydrolysis was monitored at 660 mμ by analysis for

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Table I. Dissociation Constants (μ = 0.2, 20°)

Phosphoramidate	pK_{a1}	pK_{a2}
N-(*n*-Butyl)	2.92 ± 0.06 (3.00)[a]	9.88 ± 0.10 (9.45)[a,b]
N-(Phenethyl)	2.91 ± 0.10	9.14 ± 0.04
N-(Benzyl)	2.89 ± 0.07	8.84 ± 0.05
N-(Methoxyethyl)	2.80 ± 0.06	8.73 ± 0.07
N-(2,2,2-Trifluoroethyl)	2.52 ± 0.20	7.03 ± 0.03

[a] Values (μ = 0.2, 55°) used in calculation of rate constants in Table II. [b] Calculated from the apparent heats of ionization for phosphoramidic acid (see ref 18).

orthophosphate by the method of Martin and Doty[20] as modified by Jencks.[10] Accurate determination of inorganic phosphate was hindered by the rapid hydrolysis of the phosphoramidates under the conditions of the development procedure. The catalysis was attributed to the high acidity and the presence of molybdate involved in the first step of the method and proved to be directly related to the time of exposure to these conditions. By carefully standardizing the development time, catalysis during the development procedure was restricted to a small constant fraction which does not affect the determination of a first-order rate constant. This was checked by measuring the OD produced by the development procedure for various phosphoramidate concentrations. Corrections of the OD values for the actual kinetic runs by applying such standard curves yielded rate constants that were not significantly different than the uncorrected runs. The hydrolyses followed first-order kinetics, and the observed rate constants were calculated from slopes of log $[(OD_\infty - OD_0)/(OD_\infty - OD_\tau + OD_{corr})]$ or log $[OD_\infty - OD_\tau]$ against time where OD_{corr} is the correction applied for catalysis observed in the development procedure. Plots were generally linear to at least three half-lives. Duplicate runs agreed within ±2%.

Buffers employed were hydrochloric acid (pH <2.8), formate (0.2 *M*, pH 3.2–4.5), acetate (0.2 *M*, pH 5.0–6.0), Tris (0.2 *M*, pH 6.5–8.5), and carbonate (0.067 *M*, pH 9.0–10.5). All of the kinetic runs were carried out at μ = 0.2, KCl. Acceleratory buffer effects were observed in the hydrolysis of *N*-(*n*-butyl)phosphoramidate with formic acid (pH 3.2–4.5) and trishydroxyaminomethane (pH 6.5–8.5) buffers. Rates which varied with buffer concentration were extrapolated to zero buffer concentration. The pH was measured at the temperature of the kinetic runs (glass electrode) upon initiation and after completion of the runs; those exhibiting pH drift greater than ±0.03 unit were discarded. Deuterium oxide buffers were *ca.* 98% D_2O after correction for addition of hydrogen acids and bases. The solvent isotope effect (pH 5.7) was calculated utilizing rates measured in identical H_2O and D_2O buffers in the plateau region. The buffer pK_a's are perturbed similarly to substrate pK_a's, thus allowing direct comparison of observed rates. The contribution by the neutral species at this pH is negligible.

^{18}O Tracer Experiments. The monopotassium salt of *N*-(*n*-butyl)phosphoramidate (15 mg) was dissolved in 1.5% ^{18}O-enriched acetate buffer (5 ml) at pH 5.6, μ = 0.2. The sample was allowed to hydrolyze to completion at 55° (7 days). The solution was then evaporated under vacuum to 0.5 ml, saturated barium hydroxide (1 ml) added, and the pH adjusted to 12 by the addition of 2 *M* sodium hydroxide (0.5 ml). The resulting white precipitate ($BaPO_4$ and $BaCO_3$) was isolated by centrifugation, washed twice with 95% ethanol and absolute ether, and dried *in vacuo*. The barium phosphate was converted to potassium dihydrogen phosphate by the method of Haake and Westheimer.[21] The oxygen of potassium dihydrogen phosphate was converted to carbon dioxide according to the method of Boyer, *et al.*[22] The relative isotopic abundances occurring in the carbon dioxide were determined in an MS-902 AEI mass spectrometer by measuring peak heights directly from the instrument's collector. Tank carbon dioxide was run as a standard prior to all determinations.

Products. Cleavage of the P–N bonds is the general mode of bond fission for phosphoramidates.[23] Paper chromatography of the hydrolysis products of *N*-(*n*-butyl)phosphoramidate and *N*-(2,2,2-trifluoro)phosphoramidates, utilizing pyrophosphate and orthophosphate as reference standards, revealed only orthophosphate; no pyrophosphate was detected. The picrate salt of benzylamine, mp 197° (lit.[24] mp 196°), was prepared from the products of hydrolysis of *N*-(benzyl)phosphoramidate in 1 *N* hydrochloric acid.

Product studies for the solvolysis of *N*-(*n*-butyl)phosphoramidate in varying mole fractions of methanol–water were conducted at 35°, and at pH values where the concentration of the monoanion was greater than 99%, μ = 0.2, KCl. The per cent methyl phosphate was calculated from the ratio of orthophosphate concentrations measured at t_∞ in the mixed solvents to the known value of orthophosphate concentration at t_∞ in aqueous solution. In practice this was accomplished by measuring the OD_∞ at t_∞ of aliquots of the methanol–water mixture containing known concentrations of the phosphoramidates by the development procedure of Martin and Doty, as described previously.[9] Paper chromatography of the solvolysis of *N*-(*n*-butyl)phosphoramidate in methanol–water utilizing orthophosphate, pyrophosphate, and methylphosphate as reference standards revealed methyl phosphate and orthophosphate as the solvolytic products.

Results

The pH–rate profile for the hydrolysis of *N*-(*n*-butyl)-phosphoramidate is shown in Figure 1. Pertinent kinetic data are summarized in Table II. The following kinetic equation describing the rate profile has previously been derived by assuming all species to be subject to hydrolysis excluding the species in which the phosphoryl oxygens and amine functions are completely dissociated (experimentally shown to be very stable)[9]

Table II. Rate Constants for the Hydrolysis of *N*-(*n*-Butyl)- and Selected Phosphoramidates

Phosphoramidate	$k_{H^+} \times 10^2$,[a] M^{-1} min^{-1}	$k_1 \times 10^2$,[a] min^{-1}	$k_2 \times 10^2$,[a] min^{-1}	$k_3 \times 10^2$,[a] min^{-1}
N-(*n*-Butyl)-[b]	91.7	1.42	0.164	
N-(*p*-Carboxyphenyl)-[c]	9.00	3.50	3.32	2.72
N-(*p*-Chlorophenyl)-[d]	1.47	0.383	0.057	
Phosphoramidate[e]	55.5	0.700	0.420	

[a] k_H is the second-order rate constant associated with hydronium ion catalyzed hydrolysis of the neutral species, k_1, k_2, and k_3 are first-order rate constants for the hydrolysis of the neutral, mono-, and dianion species, respectively. [b] (55°, μ = 0.2). [c] From the data of Benkovic and Benkovic[9] (35°, μ = 0.2). [d] From the data of Chanley and Feageson[7] (0°, μ = 2.0). [e] From the data of Chanley and Feageson[7] (36.8°, μ = 0.2).

$$k_{obsd} = \frac{a_H(k_H a_H + k_1) + k_2 K_{a1}}{a_H + K_{a1}(1 + K_{a2}/a_H)} \quad (1)$$

where k_H, k_1, and k_2 are defined in Table II. The values of k_{obsd} calculated from eq 4 utilizing the rate constants and dissociation constants listed in Tables I and II are in satisfactory agreement with the experimentally determined points (see Figure 1).

The S-shaped pH–rate profile for the model aliphatic phosphoramidate, *N*-(*n*-butyl)phosphoramidate, is typical of the profiles observed in the aqueous hydrolysis of *N*-(phenyl)-,[16] *N*-(*p*-chlorophenyl)-,[16] *N*-(*p*-methoxyphenyl)-,[16] *N*-(*p*-carboxyphenyl)phosphoramidates,[9] and of phosphoramidate itself.[10] It is apparent that successive protonation of the substrate results in an increase in k_{obsd}, the order of the rate constants being

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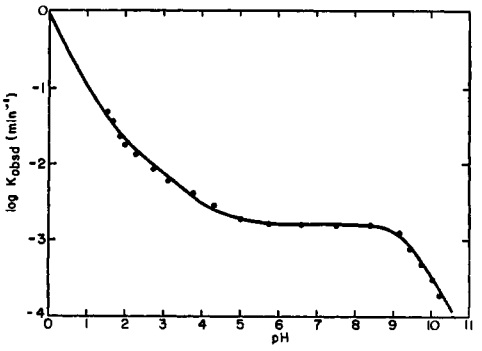


Figure 1. The log k_{obsd}–pH rate profile for the hydrolysis of *N*-(*n*-butyl)phosphoramidate at 55°, μ = 0.2. Solid line is theoretical curve calculated from values listed in Table II.

$k_{H^+} > k_1 > k_2$.[25] Calculations based on the pK_a values reported in Table I indicate that the plateau regions visible in the pH–rate profiles, *e.g.*, *N*-(*n*-butyl)-phosphoramidate, pH 5.5–9.0, and *N*-(*p*-chlorophenyl)-phosphoramidate (pK_a *ca.* 6.8), pH 3.5–5.5,[16] result primarily from hydrolysis of the labile monoprotonated form. The extended pH range over which the monoanion concentration is maximal for the aliphatic relative to the aryl phosphoramidates is a direct consequence of the increased difference between pK_{a1} and pK_{a2} for the aliphatic series.

A comparison of the effects of various solvent mixtures on the product distribution and rates of solvolysis of the monoanion for several phosphoramidates including *N*-(*n*-butyl)phosphoramidate and phosphoryl-*N*-methylimidazolium ion[26] are listed in Table III.

Table III. Solvolysis of the Monoanions of Phosphoramidates[f] (μ = 0.2)

Phosphoramidate	Solvent	% methyl phosphate	$k_{obsd} \times 10^3$, min^{-1}
N-(*n*-Butyl)	H_2O		1.64[a]
	D_2O		1.51[a]
	CH_3OH–H_2O (50 v/v)	74[b]	
N-Methylimidazole[c]	CH_3OH–H_2O (50 v/v)	78	
N-(*p*-Carboxyphenyl)[d]	CH_3OH–H_2O (50 v/v)	71	
Phosphoramidate[e]	H_2O		4.02
	D_2O		3.48
	CH_3OH–H_2O (50 v/v)	73	4.71
	Dioxane–H_2O (50 v/v)		5.25
N-(*p*-Chlorophenyl)[e]	H_2O		11.5
	D_2O		15.2
	CH_3OH–H_2O (50 v/v)	68	8.33
	Dioxane–H_2O (50 v/v)		6.73

[a] 55°. [b] 35°. [c] Reference 26, 35°. [d] Reference 9, 35°. [e] Reference 7; phosphoramidate, 37°, and *N*-(*p*-chlorophenyl), 25°. [f] See ref 15.

The important features of these collective data are that (1) the partitioning of phosphoramidates in mixed methanol–water solvents leads to a relatively large preponderance of methyl phosphate over inorganic phosphate, (2) the selectivity for methanol to water is independent of the phosphoramidate solvolyzed, (3) the rate of solvolysis of phosphoramidate is increased in less polar solvents relative to purely aqueous media while the rates of solvolysis of *N*-(*p*-carboxyphenyl)-

(25) The exception is *N*-(*p*-carboxyphenyl)phosphoramidate in which the order of the rate constants is $k_{H^+} > k_1 \approx k_2 \approx k_3$.

(26) S. J. Benkovic and S. M. Clough, unpublished results.

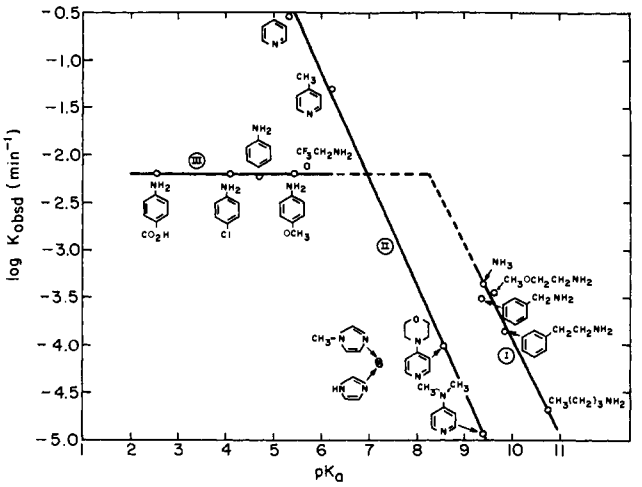


Figure 2. Plot of log k_{obsd} (min^{-1}) for the hydrolysis of phosphoramidate monoanions at 20°, μ = 0.2, *vs.* the pK_a of the leaving amine.

and *N*-(*p*-chlorophenyl)phosphoramidates are decreased, and (4) no significant kinetic deuterium solvent isotope effect is observed.

Data for the rates of hydrolysis of 16 phosphoramidates are presented in Table IV. Rate constants

Table IV. Rate Constants for the Hydrolysis of Phosphoramidates (20°, μ = 0.2)[a]

Amine	pK_a	$k_{obsd} \times 10^4$, min^{-1}
p-Carboxyphenyl	2.54[b]	63.1[g]
p-Chlorophenyl	4.07[b]	62.8[h]
Phenyl	4.69[b]	58.3[h]
p-Methoxyphenyl	5.44[b]	61.7[h]
2,2,2-Trifluoroethyl	5.7[c]	79.2
Pyridine	5.37[d]	2780[d]
4-Methylpyridine	6.21[d]	497[d]
4-Morpholinopyridine	8.53[d]	1.02[d]
4-Dimethylaminopyridine	9.39[d]	0.117[d]
N-Methylimidazole	7.20[b]	0.67, (0.54)[i]
Imidazole	7.20[b]	0.65[i]
Ammonia	9.38[e]	4.42[i]
Methoxyethyl	9.61[b]	3.52
Benzyl	9.33[b]	3.07
Phenethyl	9.83[f]	1.46
n-Butyl	10.77[b]	0.212

[a] Rate constants measured at temperatures other than 20° were calculated from the Arrhenius equation employing an appropriate value for E_a, where $E_a = \Delta H^{\ddagger} + RT$. [b] B. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth, London, 1965. [c] E. R. Bissel and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959). [d] Reference 11 (25°), $\Delta H^{\ddagger}$ = 23.6 kcal. [e] "Handbook of Chemistry and Physics," 44th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1963, p 1752. [f] W. H. Carothers, C. F. Bickford, and G. J. Herwitz, *J. Amer. Chem. Soc.*, **49**, 2908 (1927). [g] Reference 9, $\Delta H^{\ddagger}$ = 19.8 kcal. [h] Reference 16. [i] Reference 10, $\Delta H^{\ddagger}$ = 29.0 kcal. [j] Reference 7, $\Delta H^{\ddagger}$ = 23.6 kcal.

for the hydrolysis of *N*-monosubstituted phosphoramidates were measured at pH values where the compounds exist *ca.* 100% in the monoanionic form. The logarithm of the first-order rate constant is plotted against the pK_a of the leaving amine in Figure 2.

The total hydrolysis of *N*-(*n*-butyl)phosphoramidate in 1.5% ^{18}O enriched water (pH 5.6, μ = 0.2) resulted in the incorporation of 1.5 ± 0.1% ^{18}O into the inorganic phosphate (statistically corrected for the four oxygens

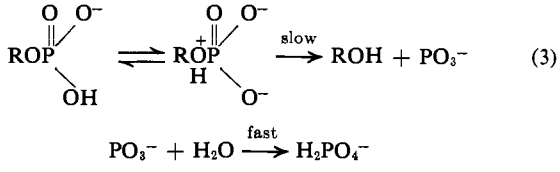
on inorganic phosphate), which we interpret as indicating the incorporation of one oxygen atom of solvent per molecule of inorganic phosphate. A control experiment with *n*-butylamine and inorganic phosphate revealed that no exchange occurred with the solvent during the time of the hydrolysis.

Discussion

It is convenient to discuss the free-energy relationship for the hydrolysis of phosphoramidates in terms of the three classes indicated in Figure 2. The hydrolytic rates for esters in classes I and II exhibit a high sensitivity to the pK_a of the leaving amine ($\beta = 1.0$), while the rates in class III are nearly invariant to the nature of the leaving group ($\beta = 0$). These results have not been encountered in previous studies on the hydrolysis of *O*- and *S*-phosphate monoesters.[27,28] The monoanions of *O*-phosphate monoesters were found to obey the linear relationship

$$\log k_{obsd} = 0.91 - 0.27pK_a \qquad (2)$$

over a ΔpK_a range of *ca.* 12 units. The small slope is consistent with a mechanism which involves loss of alcohol or phenol rather than alkoxide or phenoxide. This observation in conjunction with other physical-chemical data, *i.e.*, partitioning to products in mixed alcohol–water solvents, entropies of activation, and deuterium kinetic solvent isotope effects, has led to the formulation of a mechanism which may involve rapid preequilibrium generation of a steady-state zwitterion followed by expulsion of monomeric metaphosphate in the rate-determining step[27]



A similar hydrolytic mechanism has been postulated for *S*-phosphate monoester monoanions where the rate of hydrolysis is less sensitive to the pK_a of the departing thiol than for the oxygen case.[28]

The decomposition of a monoanionic zwitterion intermediate is also implicated in the hydrolysis of the monoanion phosphoramidates. However, unlike the *O*- and *S*-phosphate monoanions, the zwitterions derived from phosphoramidates are readily isolable species, *e.g.*, phosphoramidate itself (X-ray crystallography)[29,30] and the chloride salt of phosphoryl *N*-methylimidazolium ion.[31] Thermodynamic measurements of the heats of ionization of the neutral and monoanionic species of phosphoramidate in aqueous solution have been assigned to the dissociation of a hydroxyl and an ammonium function, respectively.[18] The intermediacy of the monoanionic zwitterions in hydrolysis is supported by the observation that phosphorylpyridinium and phosphoryl-*N*-methylimidazolium ions retain their reactivity in alkaline solution under conditions where the dianions of phosphoramidates derived from primary amines are unreactive. Moreover, the recent demonstration that the monoanion of *O*-methyl phosphoramidate is stable under conditions where the unsubstituted derivative is hydrolyzed rules out attack by hydroxide ion on the neutral form of phosphoramidate as a mechanism for apparent monoanion hydrolysis.[32] The stability of the *O*-methyl derivative further implies that hydrolysis of the monoanion of phosphoramidate must proceed *via* preequilibrium zwitterion formation with expulsion of the more favorable leaving group, the neutral amine rather than amine anion.

There is much less information available concerning the position of the equilibrium between non- and zwitterionic species in various *N*-substituted phosphoramidates. In class III, one may surmise that the phosphoryl oxygen is the thermodynamically favored site for protonation, with the nonzwitterionic form as the excess species in aqueous solution. This assignment was deduced by comparing the dissociation constant for the parent amine with pK_{a2} (7.2) for orthophosphate. For esters in class III ($pK_{a2} = 6.8$–7.0), the pK_a of the parent amine is less than that for orthophosphate so that addition of a second proton would favor the oxygen sites. For esters in class I ($pK_{a2} = 8.2$–9.9), similar arguments lead to the conclusion that the concentration of the monoanionic zwitterion is in excess. Moreover, in class I the experimentally determined pK_{a2} (Table I) is directly proportional to the amine pK_a with a slope of -1. The effect of the phosphoryl moiety on the latter pK_a is to lower this value by *ca.* one pK_a unit for the esters studied. Defining K_{zw} = [zwitterion]/[nonzwitterion], a semiquantitative estimate of K_{zw} for phosphoramidates in class I may be calculated from the relationship

$$\log K_{zw} = pK_{a2} - 7.2 \qquad (4)$$

By definition the value of pK_{a2} (7.2) should roughly correspond to K_{zw} equal to unity. A sample calculation reveals that K_{zw} is *ca.* 10^2 for *N*-(butyl)phosphoramidate. The above equation, however, should not be applied to class III esters, since the experimentally determined values for pK_{a2} are essentially invariant. This observation is in accord with the relatively small transmission of electronic effects through the phosphorus atom. A relevant case is the minor differences observed in pK_{a2} for phosphate monoesters over a wide range of alcohol substituents.[33]

The following equation for k_{obsd} may be derived, assuming a preequilibrium formation of a monoanionic zwitterionic species[9,16]

$$k_{obsd} = k_r K_{zw}/(K_{zw} + 1) \qquad (5)$$

where k_r is the rate of hydrolysis of the monoanionic zwitterion and $K_{zw}/(K_{zw} + 1)$ represents the mole fraction of monoanionic zwitterion. Consequently, for phosphoramidates in class I where $K_{zw} \gg 1$, $k_{obsd} = k_r$, so that k_r depends on the pK_a of the leaving amine with a slope, β, of -1.00. For the phosphoramidates in class III where $K_{zw} \ll 1$, $k_{obsd} = K_{zw}k_r$. The structure–reactivity correlation for these esters is the sum of

(27) A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, **89**, 415 (1967).
(28) S. Milstien and T. H. Fife, *ibid.*, **89**, 5820 (1967).
(29) E. Hobbs, D. E. C. Corbridge, and B. Raistrick, *Acta Crystallogr.*, **6**, 621 (1953).
(30) D. E. C. Corbridge and E. J. Lowe, *J. Chem. Soc.*, 493 (1954).
(31) E. Jampel, M. Wakselmann, and M. Vilkas, *Tetrahedron Lett.*, **31**, 3533 (1968).
(32) I. Oney and M. Caplow, *J. Amer. Chem. Soc.*, **89**, 6972 (1967).
(33) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 24.

the Brønsted slope for k_r (−1.00) and the dependency of K_{zw} on the pK_a of the amine (+1.0). As a consequence the observed rate remains relatively constant. In accord with this analysis is the observation that phosphorylpyridinium ion hydrolyzes *ca.* 40-fold more rapidly than the monoanion of *N*-(*p*-methoxyphenyl)-phosphoramidate (Figure 2) in spite of the fact that the pK_a values of the corresponding amines are *ca.* 5.4. A rationale for the solvent effects reported in Table III readily follows. Since for class III esters $k_{obsd} = K_{zw}k_r$, solvolysis in less polar solvents would result in a depression of K_{zw} compensated for by an increase in k_r. In the case of aliphatic amino acids it is known that K_{zw} is solvent sensitive decreasing from *ca.* 10^5 in water to unity in ethanol.[34] On electrostatic grounds k_r should increase upon transfer to less polar media owing to a transition state that features charge dispersal or neutralization relative to the ground state.[35,36] For esters of class I, $k_{obsd} = k_r$ and the solvent effect would be acceleratory as observed as long as $K_{zw} \gg 1$.

The equations for the plots obtained for classes I, II, and III in Figure 2 are given below (min^{-1}, 20°). Re-

$$\log k_{obsd} = 6.08 - 1.00pK_a \quad (6)$$

$$\log k_{obsd} = 5.64 - 1.13pK_a{}^{11} \quad (7)$$

$$\log k_{obsd} = -2.20 \quad (8)$$

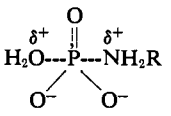
calling that the observed rates of hydrolysis for class I phosphoramidates are directly proportional to k_r, the high sensitivity of the rate of hydrolysis to the pK_a of the leaving amine is indicative of a transition state in which bond breaking between nitrogen and phosphorus is well advanced. Similar interpretations have been suggested in the hydrolysis of mono-, di-, and trisubstituted phosphate esters where the observed β values were −1.23 (dianion), −0.97, and −0.99, respectively.[27,37,38] The near identity in β values, however, should not be construed as indicative of a common mechanism in these cases. The data for the rates of hydrolysis of the phosphorylpyridinium ions (class II) fall on a separate but parallel line to the data for class I, the former being *ca.* 50-fold less reactive. The data, however, should not be viewed as electron delocalization increasing the stability of the pyridinium derivatives since there is an inherent problem in comparing aliphatic and tertiary amines owing to unequal hydration effects on their dissociation constants.[39] Increased delocalization, however, might be a factor with the phosphoryl-*N*-methylimidazolium and imidazolium ions. These two esters hydrolyze *ca.* 50 times more slowly than anticipated relative to class II. Similarly, Fersht and Jencks have shown that acetylimidazolium ion deviates (*ca.* 20-fold slower) from the structure-reactivity correlation for the hydrolysis of a series of acetylpyridinium ions.[40] Delocalization effects are not a significant factor in the hydrolysis of class III phosphoramidates, since *N*-(2,2,2-trifluoroethyl)phosphoramidate hydrolyzes at a rate comparable to the four aryl derivatives.

The mechanism of hydrolysis of phosphoramidates *a priori* may proceed by initial dissociation into a metaphosphate intermediate or *via* a bimolecular displacement of the amine by a molecule of solvent. The lack of involvement of a proton transfer in the rate-determining step is suggested by (1) the absence of a substantial deuterium solvent kinetic isotope effect in the hydrolysis of phosphoramidates in classes I and III (Table III) (although this by itself is not conclusive)[41] and (2) the identity of the rates of hydrolysis of phosphorylimidazolium ion and the model phosphoryl-*N*-methylimidazolium ion (Table IV), inferring that proton transfer to form the zwitterion is complete. The partitioning of the monoanions of phosphoramidates in mixed alcohol-water solvents in the absence and presence of electrophilic reagents[10] which favors the formation of phosphate monoesters over inorganic phosphate by a factor of approximately 10 (Table III) and less conclusively, the entropies of activation, *e.g.*, *N*-(*p*-chlorophenyl)phosphoramidate, −6.3 eu,[16] and phosphoramidate, −1.6 eu,[7] do not support a "free metaphosphate" intermediate.

A more exact description of the transition state for phosphoramidate hydrolysis can be constructed from the Brønsted type relations depicted in Figure 2. Lawlor has shown that the rate of nucleophilic attack on phosphorylpyridinium ions by a variety of aliphatic and aromatic amines (pK_a 2–11) can be correlated with a Brønsted coefficient, $\beta = 0.25$.[11] This coefficient is similar to those reported earlier ($\beta = 0.2$) for nucleophilic catalyzed hydrolysis of phosphoramidate by a limited series of substituted pyridines.[10] The β values may be calibrated for the complete transfer of $[PO_3^{2-}]$ from the donor, phosphoramidate, to a series of pyridines of varying basicity by utilizing the kinetic data of Jencks and Gilchrist[10] and Lawlor[11] which yields a $\beta = 1.2$ for the equilibrium process. The equilibrium value for the addition of a phosphoryl group to an amine acceptor, therefore, is considerably less than that for the transfer of an acyl group to alcoholate ions or amines ($\beta = 1.6$–1.7) and only slightly greater than the addition of a proton which by definition is unity.[39,42] Thus the phosphoryl moiety $[PO_3^{2-}]$ approximates the electropositive character of a proton. This type of analysis is, however, subject to the provisions expressed in ref 42 and is not precise. Nevertheless, the fractional positive charge transferred to the nucleophile may be approximated as 0.2/1.2 units with a concomitant loss of positive charge 1.0/1.2 units from the departing amine. This is in accord with the above arguments. As a result much of the driving force for the transfer of $[PO_3^{2-}]$ from phosphoramidate to an amine nucleophile apparently is derived from the excess electron density on the anionic oxygens. This is manifested in the unimolecular aspect of these reactions alluded to in earlier studies. Assuming the same Brønsted coefficient may be applied to oxygen nucleophiles (H_2O), it is apparent

(34) J. T. Edsall and M. H. Blanchard, *J. Amer. Chem. Soc.*, **55**, 2337 (1933).
(35) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 346.
(36) K. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 374.
(37) (a) A. J. Kirby and M. Younas, *J. Chem. Soc. B*, 510 (1970); (b) A. J. Kirby and M. Younas, *ibid.*, 1165 (1970).
(38) S. A. Khan and A. J. Kirby, *ibid.*, 1172 (1970).
(39) (a) H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957); (b) F. E. Condon, *ibid.*, **87**, 4481 (1965).
(40) (a) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5432 (1970); (b) *ibid.*, **92**, 5442 (1970).
(41) *E.g.*, a relevant discussion of deuterium solvent kinetic isotope effects may be found in the study of salicyl sulfate; see S. J. Benkovic, *ibid.*, **88**, 5511 (1966).
(42) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

that bond breaking ($\beta \cong 1.0$) is far more advanced than bond formation ($\beta = 0.2$). Some justification for the latter assumption is derived from the ratio of nucleophilic attack on 2,4-dinitrophenyl methyl phosphate by oxyanions and nitrogen bases which correlate with identical Brønsted coefficients ($\beta = 0.3$),[37] although evidence is scarce on this point. Thus the description that emerges features a loose, noncoupled transition state, *i.e.*, the degree of bond cleavage is not directly proportional to bond formation. There is no evidence



at present for general base catalysis of the attack step, although the slight buffer effects observed in the hydrolysis of the *n*-butylamine ester may preview such catalysis (see Experimental Section).

This result is paralleled in several other phosphoryl transfer reactions involving mono- and disubstituted esters for which β values are available for both the attacking and leaving groups.[37,43] These constants are compiled in Table V and have been calculated from data

Table V. A Comparison of β Values for the Incoming and Leaving Groups for Phosphate Esters

Type of reaction	β nucleophile	β leaving group
Phosphoramidates + amines	0.2[a]	−0.9 to −1.1[b]
Phosphate monoester dianions + amines	0–0.1[c]	−1.2[d]
Phosphate diester monoanions + amines	0.3–0.4[e]	−0.9 to −1.0[e]
Phosphate triesters + oxyanions	0.3–0.6[f]	−0.3 to −0.6[f]

[a] Reference 10 and 11. [b] Reference 11. [c] Reference 43 and A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965). [d] Reference 43. [e] Reference 37. [f] Reference 38.

that do not significantly deviate from the Brønsted correlation over the range of reactivities (log k_{obsd}) and pK_a values investigated. Again, the β values reported for nucleophilic displacements on mono- and diesters suggest that the transition state for these esters closely resembles that pictured above for the phosphoramidates. Note, however, that with the trisubstituted *O*-esters, the β values for entering and departing groups are approximately equal, suggesting that bond formation and cleavage are now coupled as in SN2 displacement reactions and, as recently demonstrated, in acyl transfer reactions.[39] The unimolecular aspect, as anticipated, has disappeared. That the increase in β for nucleophilic attack on triesters actually manifests increased bonding is supported by the greater reactivity of imidazole relative to amines of similar pK_a as the phosphoryl oxygens are successively esterified.[11,38] This observation is consistent with a progressive decrease in the free energy of the transition state as it approaches more closely the resonance stabilized phosphorylimidazolium ion. Although we have not considered within our analysis the possibility of a pentacovalent intermediate along the reaction path, it is obvious that

(43) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. B*, 135 (1968).

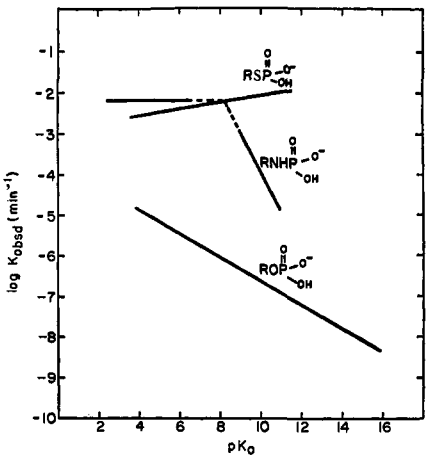


Figure 3. Plots of log k_{obsd} (min^{-1}) for the hydrolysis of *S*-, *N*-, and *O*-phosphate ester monoanions at 20° *vs.* the pK_a of the leaving group. Data were taken from ref 27 and 28.

regardless of the location of the rate-determining step leading to and from such an intermediate, β for the leaving group should not exceed β for the nucleophile.[44] For these reasons we have chosen to interpret the break in the structure–reactivity correlation (Figure 2) as arising from alterations in zwitterion concentration rather than a change in the rate-determining step for the partitioning of a pentacovalent intermediate. Moreover, if one employs a criteria based on enhanced reactivity as a probe for pentacovalent intermediacy, it is not evidenced by the plot of Figure 3 for the hydrolysis of the *O*-, *N*-, and *S*-phosphate monoester monoanions.[45] The order of reactivity is S− > N− > O− at $pK_a \approx 10$, but N− > S− > O− at $pK_a \approx 4$. The total range in hydrolytic rate is 10^4 at $pK_a \approx 10$ and 10^2 at $pK_a \approx 4$. Values as high as 10^9 recently have been cited as the kinetic acceleration obtained upon comparison of reactions proceeding through metastable pentacovalent species relative to a direct displacement transition state. Furthermore, there is no evidence for preequilibrium exchange for the $H_2{}^{18}O$ data for any of these reactions.[12] We do not deny, however, that metastable pentacovalent intermediates will be encountered in acyclic ester reactions but believe such observations will be restricted to special cases, *e.g.*, triesterified with strongly electron withdrawing substituents including F, Cl, or CN.[46]

An unusual facet of phosphoramidate chemistry is their high reactivity with amines relative to oxygen nucleophiles (H_2O or methanol). This ratio is in order of 10^3–10^4 for the attack of *n*-butylamine *vs.* water on phosphorylpyridinium or phosphoryl-*N*-methylimidazolium ions.[11,26] This is not a consequence of differing nucleophile sensitivity to the nature of the leaving group since the Brønsted coefficient is *ca.* −1.0 for the attack of either nucleophile on a series of phosphorylpyridinium ions but may be attributed mainly to differences in pK_a between amine nucleophiles and water. For example, a β value as low as 0.3 corresponds to a reactivity ratio of roughly 10^3 since $\Delta pK_a \approx 11$. This means of course that a common Brønsted

(44) L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 3035 (1970).

(45) W. A. Pryor and K. Smith, *ibid.*, 92, 2731 (1970).

(46) Observations consistent with this postulate recently have been reported; see R. F. Hudson and R. Greenhalgh, *J. Chem. Soc. B*, 325 (1969).

relationship applied to both types of nucleophiles. In this sense these results strikingly parallel the attack of amines on acetylpyridinium ions.[39] For oxygen nucleophiles (H_2O and methanol) the increased selectivity for methanol with the phosphoramidates apparently is the result of achieving the transition state earlier along the reaction coordinate than with *O*-phosphate monoesters.

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Synthesis and Base-Catalyzed Exchange of Dihydrobenzazocines[1a]

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Abstract: Benzo[2,3]tropone oxime (**10**) undergoes Beckmann rearrangement to 2-benzazocin-1(2*H*)-one (**11a**) which upon methylation followed by hydride reduction affords 1-methyl-1,2-dihydro-1-benzazocine (**2**). In potassium *tert*-butoxide–dimethyl sulfoxide, **2** isomerizes to the dienamine, 1-methyl-1,6-dihydro-1-benzazocine (**3**). The relative rates of deprotonation (*i.e.*, sum of NCH_2 exchange and isomerization) in the amine series, **2**, *trans*-*N*-methyl-*N*-cinnamylaniline (**20**), *cis*-*N*-methyl-*N*-cinnamylaniline (**21**), 1-methyl-1,2-dihydroquinoline (**18**), are 1.0:8.4:7.6:0.012 in potassium *tert*-butoxide–dimethyl-d_6 sulfoxide–*tert*-butyl alcohol-*O*-*d*. In the enamine series, **3**, *trans*-*N*-methyl-*N*-(3-phenyl-1-propenyl)aniline (**22**), 1-methyl-1,4-dihydroquinoline (**19**), the relative exchange rates of the methylene groups are 1.0:0.59:0.035. In the dibenz series, 5-methyl-5,6-dihydrodibenz[*b*,*f*]azocine (**1**), 5-methyl-5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine (**6**), *N*-methylphenanthridine (**7**), *N*-methyl-*N*-benzylaniline (**8**), the relative exchange rates in potassium *tert*-butoxide–dimethyl-d_6 sulfoxide are $1.0:0.13:0.51 \geq \sim 100$. Although no appreciable aromatic stabilization is detected in the kinetic data from the dibenz series, the moderately enhanced kinetic acidity of the benzazocines **2** and **3**, as compared to the dihydroquinoline models **18** and **19**, is attributed to a small degree of aromatic stabilization in the incipient 10π electron anion.

According to Huckel's $4n + 2$ rule, a fully conjugated, monocyclic orbital network containing 10π electrons should be "aromatic."[2-4] In recent years, molecules with 10π electrons in eight-,[5] nine-,[6-8] and ten-membered[4,9] carbocycles have been prepared, and in all cases except the cyclodecapentaenes, evidence demonstrating "aromatic" character has been obtained despite the severe angle strain associated with these medium-sized rings. The apparent stabilization of the cyclooctatetraene dianion[5] is especially striking, considering the additional electron repulsion present. On the other hand, the information available on the isoelectronic seven-,[10] eight-,[11,12] and nine-membered[13] heterocycles, in which the heteroatom contributes a lone pair to the formal count of 10π electrons, seems to indicate little of the special stability expected of an "aromatic" species.

We became interested in the properties of the potentially aromatic heterocyclic anologs of cyclooctatetraenide. Such molecules would contain the required 10π electron core but need carry only a single negative charge.[12,14] While the reduced net charge might confer an extra degree of stability compared to the cyclooctatetraene dianion, the chemical changes attending the heteroatom substitution would also open the way to reaction paths inaccessible to the hydrocarbon parent.

(1) (a) Taken in part from the Ph.D. Thesis of E. F. J., University of Illinois, Urbana, Ill., 1969; (b) National Institutes of Health Predoctoral Fellow, 1968–1969.

(2) (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, Chapter 10; (b) M. E. Vol'pin, *Russ. Chem. Rev.*, **29**, 129 (1960).

(3) R. Breslow, *Chem. Eng. News*, 90 (June 28, 1965).

(4) (a) F. Sondheimer, *et al.*, *Chem. Soc. Spec. Publ.*, No. 21, 75 (1967); (b) E. Vogel, *ibid.*, No. 21, 113 (1967).

(5) (a) T. J. Katz and H. L. Strauss, *J. Chem. Phys.*, **32**, 1873 (1960); (b) T. J. Katz, *J. Amer. Chem. Soc.*, **82**, 3784, 3785 (1960); (c) T. J. Katz, W. H. Reinmuth, and D. E. Smith, *ibid.*, **84**, 802 (1962); (d) H. L. Strauss, T. J. Katz, and G. K. Fraenkel, *ibid.*, **85**, 2360 (1963).

(6) T. J. Katz and P. J. Garratt, *ibid.*, **86**, 5194 (1964); E. A. LaLancette and R. E. Benson, *ibid.*, **87**, 1941 (1965); P. J. Garratt and K. A. Knapp, *Chem. Commun.*, 1215 (1970).

(7) M. Ogliaruso, R. Rieke, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 4731 (1966).

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