

Decreasing Reactivity with Increasing Nucleophile Basicity. The Effect of Solvation on β_{nuc} for Phosphoryl Transfer to Amines¹

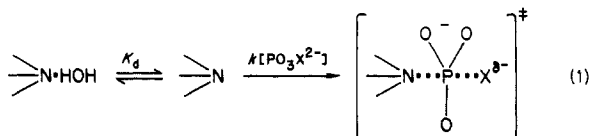
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Abstract: Rate constants for the reactions of substituted quinuclidines with *p*-nitrophenyl phosphate, 2,4-dinitrophenyl phosphate, 2,4-dinitrophenyl phosphate complexed with calcium, and phosphorylated pyridine decrease with increasing $\text{p}K_{\text{a}}$ of the amine. Plots of $\log k$ against $\text{p}K_{\text{a}}$ give slopes of $\beta_{\text{nuc}} = -0.05, -0.10, -0.11,$ and $-0.10,$ respectively, for these compounds; $\beta_{\text{nuc}} = -0.01$ for phosphorylated 4-morpholinopyridine. These negative slopes are attributed to a requirement for desolvation of the amine before nucleophilic attack, which is more difficult with more basic amines; a value of $\beta_{\text{d}} = -0.2$ for the desolvation step is suggested.

Nucleophilic reagents are likely to be hydrogen bonded to hydroxylic solvents, so that structure-reactivity correlations may reflect the behavior of the desolvation step as well as nucleophilic attack. The dependence of the reaction rate on the basicity of an attacking nucleophile is given by the slope, β_{nuc} , of a plot of $\log k$ against the $\text{p}K_{\text{a}}$ of the protonated nucleophile, BH^+ . The observed value of β_{nuc} includes the dependence of desolvation as well as nucleophilic attack on the basicity of the nucleophile, so that the amount of nucleophilic attack in the transition state may be underestimated if desolvation is neglected. The desolvation step will have a small or negligible influence on the observed value of β_{nuc} when there is a large amount of bond formation in a late transition state that resembles BH^+ , which is the reference compound for the Brønsted correlation and corresponds to the development of a full positive charge on the amine.^{2,3} However, for early transition states, in which the nucleophilic attack step has only a small dependence on basicity, the increase in the strength of hydrogen bonding to the solvent with increasing basicity can cause a significant decrease in the observed dependence of the rate on the basicity of the nucleophile if an initial desolvation step is required. Conversely, in the reverse reaction or in any reaction in which there is a large amount of bond breaking in the transition state, incomplete solvation of the leaving group may cause an increase in $-\beta_{\text{lg}}$ and an overestimation of the amount of bond breaking.

We report here several reactions of monosubstituted phosphates with substituted quinuclidines that decrease in rate with increasing basicity of the quinuclidine; i.e., β_{nuc} is negative. The reaction requires desolvation of the attacking amine, with the equilibrium constant K_{d} in eq 1, before nucleophilic attack of the free amine, with the rate constant k . A negative value of β_{nuc} will be observed



when the dependence on amine basicity for the desolvation step is more important than β for nucleophilic attack, i.e., when the negative value of β_{d} for K_{d} causes a rate decrease that is larger than the rate increase from β_{nuc} for reaction of the desolvated amine (k in eq 1). It is believed that there is little bond formation to the nucleophile in the open, "exploded", transition states for reactions of phosphate ester dianions and phosphorylated pyri-

dines,⁴⁻⁸ in fact, the rate constants for reactions of substituted pyridines with the dianion of 2,4-dinitrophenyl phosphate show no dependence on amine basicity. Nevertheless, these second-order reactions are much faster than hydrolysis, so that there must be a significant amount of bond formation to the nucleophile in the transition state in spite of the fact that the observed value of β_{nuc} is zero.⁵ Similar behavior has been observed for reactions of two quinuclidines with phosphorylated 4-morpholinopyridine and the statistically corrected rate constants for the reactions of triethylenediamine ($\text{p}K_{\text{a}} = 9.2$) with 2,4-dinitrophenyl phosphate and phosphorylated 3-methoxypyridine are larger than those for quinuclidine ($\text{p}K_{\text{a}} = 11.5$).^{5,8} Several diamine monocations are known to be more reactive toward monosubstituted phosphate derivatives than the more basic free diamines, but this difference has been ascribed to an electrostatic effect.^{4,5}

In addition to its inherent interest and its effects on structure-reactivity parameters, desolvation is of interest because it is one of the mechanisms by which enzymes can utilize noncovalent binding interactions with specific substrates to increase reaction rates.⁹

Experimental Section

Substituted quinuclidines, pyridine, and disodium *p*-nitrophenyl phosphate were purified by distillation or recrystallization. 4-Morpholinopyridine and phosphorylated 4-morpholinopyridine were prepared as described previously⁸ and 2,4-dinitrophenyl phosphate was kindly donated by Prof. David Chipman. Glass-distilled water was used throughout.

Pseudo-first-order rate constants were determined spectrophotometrically. The ionic strength was maintained at 1.0 with potassium chloride, unless noted otherwise. The reactions were usually carried out with use of the amine nucleophile, 95% free base, as the buffer. Some experiments in the presence of calcium ion were carried out at lower fractions of free base, in order to avoid precipitation of calcium hydroxide, and the fast reactions of phosphorylated pyridines were carried out in the presence of 0.05 M potassium carbonate or potassium hydroxide, in order to neutralize excess acid from the synthesis mixture.

Initial rates of reactions of *p*-nitrophenyl phosphate dianion at 39 °C were followed at 410 or 400 nm, as described previously.⁴ First-order rate constants for reactions of 2,4-dinitrophenyl phosphate at 39.1 ± 0.2 °C were determined at 360 nm. Rate constants for reactions of phosphorylated 4-morpholinopyridine at 25 °C were determined at 300 nm (295 nm for 3-quinuclidinone) and reactions of phosphorylated pyridine at 25 °C were followed at 270 nm. The phosphorylated pyridine was

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Table I. Second-Order Rate Constants ($M^{-1} s^{-1}$) for Reactions of Substituted Quinuclidines with *p*-Nitrophenyl Phosphate and 2,4-Dinitrophenyl Phosphate Dianions at 39 °C and with Phosphorylated Pyridine and 4-Morpholinopyridine Monoanions at 25 °C^a

amine	pK_a^b	<i>p</i> -nitrophenyl phosphate 10^7k	2,4-dinitrophenyl phosphate 10^4k	2,4-dinitrophenyl phosphate with 0.28 M calcium 10^4k	2,4-dinitrophenyl phosphate complex with calcium ^c 10^4k	phosphorylated 4-morpholinopyridine 10^3k	phosphorylated pyridine k
3-quinuclidinone	7.30 ^d	4.0	8.1	22.1 ^e 24.4 ^f	30.4 34.1 ^{f,g}	5.7	7.4 ^h
triethylenediamine ⁱ	8.92 ^j	4.4 4.2 ^k	8.2	17.6 18.6 ^j	23.2 24.7 ^{f,g}	4.8	5.7 ^h
3-chloroquinuclidine	9.09 ^j	4.4	7.3			5.2	4.7 ^l
3-hydroxyquinuclidine	10.13 ^j	3.2	5.1	11.2 ^m	14.8	6.3	4.3 ^l
quinuclidine	11.50 ^j	2.5 2.2 ⁿ	3.5	7.8 ^{f,o}	10.4 ^{f,g}	4.8	2.7 ^l
triethylenediamine monocation	3.47 ^p	4.2 ^q	7.1 ^r 8.0 ^s	16.7 ^r	22.4 ^f		

^aThe ionic strength was maintained at 1.0 with potassium chloride and the rate constants were determined with 95% free base except where noted. ^b25 °C, ionic strength 1.0. ^cCalculated from the observed rate constant with 0.28 M calcium and an association constant of $6.0 M^{-1}$.¹⁰ ^dEwing, S. P.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084. ^eMeasured at 37, 74, and 95% free base. ^fIonic strength 1.5. ^gCalculated by using the rate constant for 2,4-dinitrophenyl phosphate at ionic strength 1.0. ^hIn 0.05 M potassium carbonate. ⁱThe rate constants and K_a are statistically corrected by a factor of 2. The rate constants are based on the total concentration of buffer, 95% free base (except for phosphorylated pyridine). This introduces a negligible error, because the rate constant for triethylenediamine monocation is similar to that for triethylenediamine.^{4,5} ^jSayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353–6361. ^kIonic strength 0.03–0.05. ^lIn 0.01 M potassium hydroxide. ^mDetermined at 74% free base. ⁿIonic strength 0.05. ^oDetermined at 35% free base. ^pJencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. ^qKirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209–3216. ^rMeasured with 5% free base and extrapolated to 100% monocation. ^sKirby, A. J.; Varvoglis, A. G. *J. Chem. Soc. B* **1968**, 135–141.

prepared from phosphorus oxychloride and pyridine immediately before the addition of amine buffer, as described previously for phosphorylated 3-methoxypyridine.⁸ End points for reactions followed to completion were determined after >10 half-lives. The pH was measured at the end of the kinetic runs.

Results

Second-order rate constants for the reactions of substituted quinuclidines with *p*-nitrophenyl phosphate, 2,4-dinitrophenyl phosphate, phosphorylated 4-morpholinopyridine, and phosphorylated pyridine were determined from the slopes of linear plots of observed pseudo-first-order rate constants against the concentration of amine base and are reported in Table I. Rate constants are also reported for the reactions of quinuclidines with the dianion of 2,4-dinitrophenyl phosphate in the presence of 0.28 M calcium chloride and for the reactions with the calcium–dinitrophenyl phosphate complex, based on an association constant of $K_A = 6.0 M^{-1}$ for the formation of this complex.¹⁰ The rate constants for reactions of the calcium–dinitrophenyl phosphate complex are about threefold larger than those for dinitrophenyl phosphate.

Rate constants were determined at four or more concentrations of amine, usually in the range of approximately 0.05–0.4 M. Rate constants for the rapid reactions of phosphorylated pyridine were determined in duplicate at four amine concentrations in the range 1–4 mM. The rate constants were determined at ionic strength 1.0, maintained with potassium chloride; two experiments at ionic strength 0.03–0.05 gave rate constants that were 5–12% smaller.

The reactions of quinuclidine and the monocation of triethylenediamine with 2,4-dinitrophenyl phosphate in the presence of calcium were carried out at ionic strength 1.5, in order to obtain adequate concentrations of amine buffers. It was shown that there is no significant difference in the rate constants for the reactions of 3-quinuclidinone and triethylenediamine with 2,4-dinitrophenyl phosphate in the presence of 0.28 M calcium at ionic strength 1.5 compared with 1.0. The same rate constant for reaction of the free amine was obtained with quinuclidinone buffers containing 37, 74, and 95% base.

The rate constants for the reactions of triethylenediamine with 4-nitrophenyl phosphate,⁴ 2,4-dinitrophenyl phosphate,⁵ phosphorylated pyridine,¹¹ and phosphorylated 4-morpholinopyridine^{8,11} and for the reactions of quinuclidine with 2,4-dinitrophenyl phosphate⁵ and phosphorylated 4-morpholinopyridine⁸ show

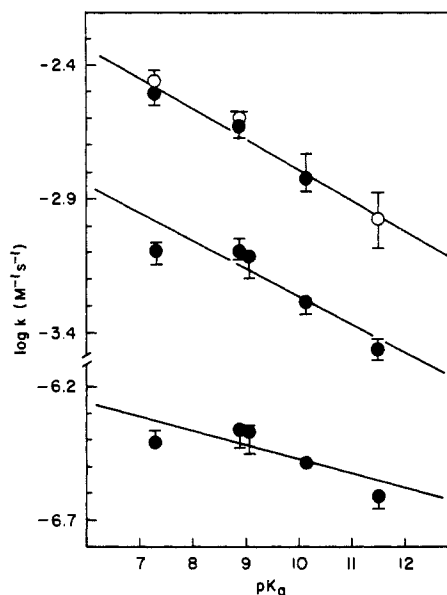


Figure 1. Brønsted-type plots for the reactions of substituted quinuclidines with the dianions of 2,4-dinitrophenyl phosphate complexed with calcium (upper line); 2,4-dinitrophenyl phosphate (middle line), and *p*-nitrophenyl phosphate (lower line) at 39 °C, ionic strength 1.0 (KCl) (●) and 1.5 (KCl) (○).

satisfactory agreement with previously reported values.

Discussion

The Brønsted-type plots of Figures 1 and 2 show the dependence on amine basicity of the second-order rate constants for the reactions of substituted quinuclidines with phosphate monoester dianions and phosphorylated pyridines, respectively. There is a decrease in the observed rate constants as the quinuclidines become more basic in the reactions with 2,4-dinitrophenyl phosphate and *p*-nitrophenyl phosphate (Figure 1) and with phosphorylated pyridine (Figure 2). The lines in the figures are drawn with (least-squares) slopes of $\beta_{nuc} = -0.10$ for 2,4-dinitrophenyl phosphate and phosphorylated pyridine, -0.05 for *p*-nitrophenyl phosphate, and -0.01 for phosphorylated 4-morpholinopyridine. The calcium-catalyzed reaction of 2,4-dinitrophenyl phosphate with quinuclidines follows a line with a negative slope of $\beta_{nuc} = -0.11$ (upper line, Figure 1), which does not differ significantly from the slope for the uncatalyzed reaction. A correlation of log k for the reactions with 2,4-dinitrophenyl phosphate and with the

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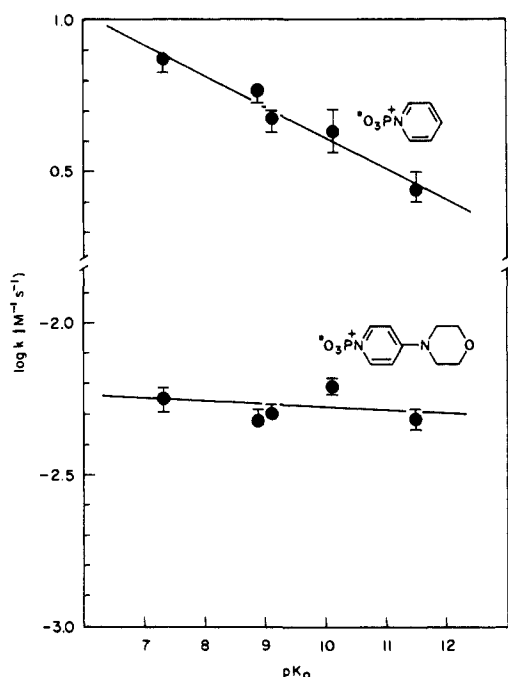


Figure 2. Brønsted-type plots for the reactions of substituted quinuclidines with phosphorylated pyridine and 4-morpholinopyridine at 25 °C, ionic strength 1.0 (KCl).

calcium-2,4-dinitrophenyl phosphate complex gives a good straight line that is consistent with a slope of 1.0, except for a small deviation of the point for 3-quinuclidinone (not shown).

These negative slopes are consistent with a desolvation step that must occur before nucleophilic attack by the amine (eq 1) and becomes more difficult as the amine becomes more basic. The data require a value of $-\beta_d \geq 0.10$ for desolvation that is equal to or greater than the value of β_{nuc} for attack by the desolvated amine. It is probable that there is some development of positive charge on the amine in the transition state for nucleophilic attack and that β_{nuc} for the desolvated amine is positive. Therefore, a limit of $-\beta_d \geq 0.2$ can be set for the desolvation step.

Electrostatic interactions should also be considered as a possible explanation for the negative values of β_{nuc} .^{4,11,12} An electron-withdrawing group on the attacking reagent could give a favorable electrostatic effect through a charge-dipole interaction with the negative charges on the substrate. This could give an increased rate constant for weakly basic nucleophiles and a decreased value of β_{nuc} .

This interpretation is excluded by the following: (1) Similar negative values of β_{nuc} are observed for the reactions of quinuclidines with the dianion of a phosphate ester and the monoanion of phosphorylated pyridine. (2) The values of β_{nuc} are positive for reactions of phosphorylated pyridines and *p*-nitrophenyl phosphate with pyridines and primary amines, although the less basic nucleophiles contain strongly electron-withdrawing substituents.^{4,8,11} (3) The calcium-catalyzed reactions of quinuclidines with 2,4-dinitrophenyl phosphate, in which the negative charges of the phosphate ester are neutralized by the positive charges of the calcium ion, follow essentially the same negative value of β_{nuc} as the uncatalyzed reactions (upper lines, Figure 1; $\beta_{\text{nuc}} = -0.11$ and -0.10).

Negative values of β_{nuc} will be observed only for reactions in which there is a small amount of bond formation in the transition state, so that β_{nuc} for attack of the unsolvated amine is smaller than $-\beta_d$ for the desolvation step. The reactions of monosubstituted phosphate derivatives with nucleophiles provide one example of this behavior because the driving force for expulsion of the leaving group arises largely from the two negative charges on the phos-

phoryl group. However, the reactions are clearly second order and are much faster than solvolysis; they involve a significant component of nucleophilic attack. There is evidence that the reactions of pyridines with phosphorylated pyridines occur through a concerted mechanism in which there is a small, but significant amount of bond formation to the nucleophile and a large amount of bond breaking to the leaving group in the transition state, which resembles the monomeric metaphosphate monoanion.⁶⁻⁸ These reactions are symmetrical, so that desolvation of the nucleophile before attack means that the leaving group becomes solvated after bond cleavage and the observed values of β_{lg} may provide an overestimate of the amount of bond breaking in the transition state. The reactions of phosphate monoester dianions show similar properties and probably proceed through similar transition states.^{4,5} In both series there is a decrease in β_{nuc} as the leaving group becomes better, so that negative values of β_{nuc} are most likely to be observed with leaving groups of low pK_a .^{4,5,8}

There is other evidence that the desolvation step can be kinetically significant in nucleophilic reactions. For example, the relatively small limiting rate constants for the reactions of anionic oxygen nucleophiles with carbocations suggest that there is a kinetic barrier for the desolvation of oxygen anions that must be overcome before reaction.¹³ The small values of β_{nuc} for attack on acyl compounds and of β for proton removal from carbon acids by basic alkoxide ions have been attributed to a requirement for partial desolvation of RO^- before nucleophilic attack, which becomes more difficult with increasing basicity of RO^- .^{2,3,14,15}

The curved Brønsted plots for catalysis of the ionization of acetylacetone by substituted acetate ions in Me_2SO :water mixtures can also be explained by a requirement for desolvation of the more basic catalysts.¹⁶ The linear Brønsted plots for catalysis of this reaction by primary amines are consistent with this explanation; furthermore, an increase in β with decreasing water content could be accounted for by a reduced requirement for desolvation of the amines in the less aqueous solutions. The decrease in the value of β_{nuc} from 0.41 in acetonitrile to 0.21 in methanol for the reactions of substituted quinuclidines with methyl iodide (based on pK_a values in methanol) provides another example of a reaction in which solvation of the nucleophile by a hydroxylic solvent appears to decrease the observed value of β_{nuc} .¹⁷ The decrease in β_{nuc} is consistent with the estimate of $-\beta_d \sim 0.2$ for quinuclidines.

A theoretical study has led to the conclusion that desolvation of the chloride anion, which has several electron pairs available to interact with the solvent, contributes almost half of the activation energy for its reaction with methyl chloride in water; however, the desolvation does not require a separate step with a potential minimum.¹⁸

Amines are less strongly solvated than oxygen anions, so that complete desolvation would require a much larger barrier for an oxygen anion than for an amine. However, amines have only a single electron pair, so that complete desolvation is required before nucleophilic attack is possible. There is evidence for a significant solvation energy of amines in water and the absolute change in Gibbs free energy for breaking the hydrogen bond between water and pyridine has been estimated to be 4.3 kcal mol⁻¹.¹⁹ Although basic alkoxide ions are solvated by three hydroxylic solvent molecules,²⁰ they do not require complete desolvation in order to

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undergo nucleophilic reaction. Desolvation in a separate, initial step, such as K_d of eq 1, is probably not required for most nucleophiles that have several electron pairs, unless access to the attacking atom is completely blocked by solvation.

The limited data that are available suggest that amines become more strongly hydrated with increasing amine basicity, although the importance of hydration of the free amines is considerably less than that of protonated amines.¹⁹ The Gibbs free energies for hydration from the gas phase differ by 0.87 kcal mol⁻¹ for 4-methylpyridine ($pK_a = 6.0$) and 3-chloropyridine ($pK_a = 2.8$)²¹ and by 1.7 kcal mol⁻¹ for 4-(dimethylamino)pyridine ($pK_a = 10.1$) and 4-cyanopyridine ($pK_a = 1.9$),²² which correspond to values of $\beta_d = -0.2$ and -0.15 , respectively. The free energies for hydrogen bonding of pyridines to 4-fluorophenol and for protonation in water give $\beta = 0.24$ for hydrogen bonding.¹⁹ The enthalpies of hydration of trifluoroethylamine ($pK_a = 5.9$) and ethylamine ($pK_a = 11.0$) are -1.8 and -4.5 kcal mol⁻¹, respectively, which would correspond to a value of $\beta_d = -0.4$ if there were a corresponding difference in the Gibbs energies of hydration.²³ These values suggest that an estimate of $\beta_d = -0.2 \pm 0.1$ is reasonable. This is similar in magnitude to the value of $\beta_d = 0.25$ for breaking the hydrogen bond of substituted alcohols to water, which becomes easier as the alcohol becomes less acidic.²⁴

We conclude that in order to obtain an estimate of the amount of charge development on the nucleophile as it forms a bond to the substrate in the transition state, the observed value of β_{nuc} should be corrected for the desolvation step. When β_{nuc} is small, a correction of 0.2 appears to be reasonable. The effect of the solvation correction is to enlarge the scale of possible values for β_{nuc} by the amount of $-\beta_d$; i.e., if the observed value of β_{eq} is 1.0 for complete addition of the nucleophile at equilibrium and β_d is -0.2 the range for β_{nuc} is 1.2 units. If the scale is normalized to a value of $\beta = 1.0$ for development of a full positive charge on the nucleophile, as in the reference protonation reaction, observed values of β_{nuc} can be corrected for the desolvation step according to eq 2, taking $\beta_d = -0.2$.²⁵ The correction decreases

$$\beta_{corr} = 0.2 \pm 0.8\beta_{obsd} \quad (2)$$

with increasing β_{obsd} and becomes negligible as β approaches 1.0 because the scales for both β_{obsd} and β_{corr} are based on the protonated nucleophile, BH^+ , with a charge of 1.0.

Values of β_{nuc} that are negative or close to zero can only be detected when the second-order rate constant for reaction with water is much smaller than the rate constants for the series of nucleophilic reagents being examined. We do not know why water is much less reactive than amines of comparable pK toward phosphoryl groups, in spite of the high affinity of phosphorus for oxygen.

The values of β_{nuc} for the reactions of monosubstituted phosphate derivatives with quinuclidines are significantly more negative than those for reactions with pyridines and primary amines, which are in the range of $\beta_{nuc} = 0-0.3$.^{4,8,11} This difference is not caused by the high basicity of the quinuclidines because the larger β_{nuc} values for pyridines and primary amines are observed in the same range of amine basicity.^{5,8} A possible explanation for the observed difference in β_{nuc} is that the value of β_{nuc} for the desolvated amine is smaller for quinuclidines than for other amines because of an earlier transition state for nucleophilic attack. This may be the result of steric hindrance and the unfavorable solvation effect that arises from close approach of the anionic phosphate oxygen atoms

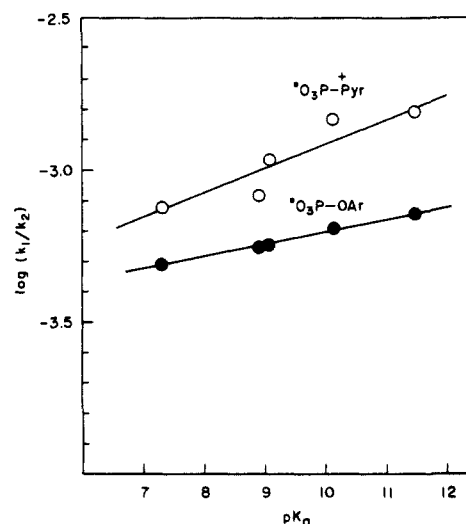


Figure 3. Brønsted-type plots to show the effect of the leaving group on β_{nuc} for the reactions of quinuclidines with phosphorylated pyridines and phosphate ester dianions. The logarithm of the rate constant ratio for two leaving groups is plotted against the pK_a of the nucleophile; k_1 refers to the leaving group with the larger pK_a .

to the hydrocarbon of the tertiary amine.

Grunwald and co-workers have found that the rate constants for the separation of solvating water from amines are considerably smaller for tertiary amines than for primary amines and ammonia. They have attributed this difference to a favorable interaction between the tertiary amine and the solvent through dispersion forces.²⁶ This suggests that desolvation will be more difficult for quinuclidines than for most other amines.

The observed effects of the desolvation step on rate constants for nucleophilic reactions in aqueous solution are relatively small, in part because the unfavorable desolvation of the attacking electron pair is largely compensated by interaction with the electrophile in the transition state. The much larger effects that are observed with changing solvents reflect the overall changes in charge and solvation of several reacting groups between the reactants and the transition state.²⁷

It was suggested previously that the rate constant for the reaction of triethylenediamine monocation with the dianion of *p*-nitrophenyl phosphate is abnormally high because of a favorable electrostatic interaction of the cation with the dianion.⁴ This conclusion was based on the similar rate constants for reaction of the monocation and the free base (after statistical correction) and the value of $\beta_{nuc} \sim 0.13$ for reactions of other amines, which predicts a smaller rate constant for the less basic monocation. The finding that β_{nuc} is negative for quinuclidines removes the basis for this conclusion; furthermore, the similar rate constants for the calcium-catalyzed reactions of 2,4-dinitrophenyl phosphate with the monocation and the free base of triethylenediamine (Table I) show that there is no significant electrostatic effect with the monocation. The reactions of other, noncyclic, diamine monocations with the dianion of *p*-nitrophenyl phosphate are faster than expected from their basicity.⁴ It is possible that this arises from a direct interaction of the charged group with dianionic phosphate esters, which may involve hydrogen bonding to anionic oxygen atoms.

Changes in Structure-Reactivity Parameters and Transition-State Structure. The less negative observed values of β_{nuc} for the less reactive substrates (Figures 1 and 2) represent "Hammond effects" and an increase in β_{nuc} for compounds with poorer leaving groups, which have been observed previously for the reactions of pyridines and primary amines with phosphate esters and phosphorylated pyridines.^{4,5,8} This behavior is shown more clearly by

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the plots of $\log(k_1/k_2)$ for the two different leaving groups in Figure 3, which have slopes of 0.08 and 0.04 for the phosphorylated pyridines and phosphate esters, respectively. This behavior can be described by the cross-interaction coefficient $p_{xy} = \partial\beta_{\text{nuc}}/\partial pK_{\text{lg}} = \partial\beta_{\text{lg}}/\partial pK_{\text{nuc}}$. The values of p_{xy} are 0.023 and 0.013, from the slopes of Figure 3, and the changes in pK_a of the leaving groups of 3.5 and 3.0 for the phosphorylated pyridines and phosphate esters, respectively. These are comparable to previously reported values of $p_{xy} = 0.014-0.020$ for reactions of amines with phosphorylated pyridines but are smaller than a value of $p_{xy} = 0.043$ for reactions of pyridines with phosphate esters, based on data from two different studies (one of which involved only three pyridines).^{4,5,8} The small value of p_{xy} for the phosphate esters removes the basis for the suggestion that the structure of the transition state changes more easily for reactions of phosphate esters than for phosphorylated pyridines.⁸

Insufficient data are available to determine whether there is curvature in the Brønsted plots for reactions of quinuclidines with phosphate compounds (Figures 1 and 2). However, the Brønsted plots for reactions of pyridines and primary amines with phosphorylated pyridines and with 2,4-dinitrophenyl phosphate are linear within experimental error; there is no curvature over 8 pK units for the reactions of pyridines with 2,4-dinitrophenyl phosphate.⁵ The upper limit for curvature in the reactions of pyridines and primary amines with phosphorylated pyridines corresponds to a direct interaction coefficient of $p_x = \partial\beta_{\text{nuc}}/-\partial pK_{\text{nuc}} \leq 0.006$.⁸ This would give a decrease in β_{nuc} of only 0.03 for a 5 unit change in pK_a of the nucleophile between pyridines and quinuclidines,

which would decrease β_{nuc} from 0.22 to 0.19 and from 0.17 to 0.14 for the reactions with phosphorylated 4-morpholinopyridine and 3-methoxypyridine, respectively. Thus, there is no significant Hammond effect with changing basicity of the nucleophile and the maximum change in β_{nuc} with increasing basicity would not give a negative value of β_{nuc} for the quinuclidines. Furthermore, the Brønsted line for the reactions of primary amines with phosphorylated 4-morpholinopyridine⁸ overlaps the pK range for the quinuclidines that react with this compound. The different classes of amines fall on different straight lines, some of which have different slopes, for reactions with phosphate compounds.^{4,5,8}

It may appear surprising that there is a significant change in β_{nuc} with changing pK_a of the leaving group, which corresponds to a positive cross coefficient p_{xy} , but no significant curvature in the Brønsted correlations, which means that there is no measurable change in β_{nuc} with changing pK_a of the nucleophile and the direct coefficient p_x is ~ 0 . However, this behavior is predicted by the expected movements of the transition state parallel and perpendicular to the reaction coordinate, with changing pK_a of the nucleophile and leaving group, on a reaction surface that is defined by the observed structure-reactivity coefficients.⁸

Registry No. 3-Quinuclidinone, 3731-38-2; triethylenediamine, 280-57-9; 3-chloroquinuclidine, 42332-45-6; 3-hydroxyquinuclidine, 1619-34-7; quinuclidine, 100-76-5; triethylenediamine monocation, 33937-19-8; *p*-nitrophenyl phosphate, 36199-67-4; 2,4-dinitrophenyl phosphate, 18962-96-4; calcium 2,4-dinitrophenyl phosphate, 99618-15-2; phosphorylated 4-morpholinopyridine, 26322-06-5; phosphorylated pyridine, 26322-03-2.

Chiral Allenylboronic Esters as a Practical Reagent for Enantioselective Carbon-Carbon Bond Formation. Facile Synthesis of (-)-Ipsenol

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Abstract: A stereospecific synthetic route to (-)-ipenol is described. The synthesis illustrates a new asymmetric synthetic reaction using chiral allenyl boronic esters. The scope of the synthesis as a general route to either (*R*)- or (*S*)-3-alkynol is further illustrated by several cases.

Recently we had envisioned the synthesis of a number of natural products which contain arrays of stereocenters in an open-chain arrangement. The methods of creating these stereocenters in the particular relative configuration have been termed "acyclic stereoselection".¹ Of the many potentially useful methods to this problem, addition of chiral nucleophiles to carbonyl compounds should offer the advantages of widespread applicability to a unique degree.² Among them, the asymmetric addition of allylic nucleophiles to the carbonyl compounds is one of the most powerful and useful synthetic methods in modern synthetic chemistry.³ On the other hand, the propargylic reagent has never been developed to a useful level due to the lack of a satisfactory chiral system. The even greater versatility of propargylic systems⁴ compared to

allylic systems encouraged us to study the former type compounds in detail. Whereas it is usually difficult to differentiate the two reactive centers of allylic system, it is relatively easy to achieve reaction specifically at either one of the two reactive centers in a propargylic system.⁵

Prior to our work, efforts to find an efficient asymmetric synthesis using allenyl anion had produced very limited success. Thus, the reaction with carbonyl compounds has been extensively studied with magnesium,⁶ aluminum,⁷ zinc,⁸ titanium,⁵ and boron⁹ reagents with much discussion on diastereoselectivity. Although a cyclic mechanism has generally been proposed for such a re-

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