consistent with a change in the structure of the transition state for a concerted reaction with changing basicity of the nucleophile or a stepwise preassociation mechanism in which there is weak nucleophilic interaction with the attacking pyridine in *both* steps, with β_{nuc} = 0.1 and 0.2, for example.

3-Methoxypyridine was synthesized by the method of Prins.[6] Phosphorylation of 3-methoxypyridine was effected by the forceful injection of a solution containing 0.3 M 3-methoxypyridine in 0.90 M KOH into a small tube containing 1 equiv of $POCl_3$. All solutions were at 4 °C. An aliquot of this synthesis mixture was applied immediately to the side of a quartz cell in the spectrophotometer cell holder, and the reaction was initiated by forceful injection of a solution containing the desired concentration of nucleophile, 0.050 M carbonate buffer, and 1.0 M KCl at pH 10.3 and 25 °C. Disappearance of the phosphorylated 3-methoxypyridine was monitored by following the decrease in absorbance at wavelengths in the range 290–307 nm. Good first-order kinetics were observed for more than 3 half-lives in each case. Second-order rate constants were obtained from the slopes of plots of values of k_{obsd} vs. the concentration of nucleophile in the range 0–0.2 M; the observed increase in k_{obsd} was always >100%. The rates of reaction with 4-morpholinopyridine and 4-(dimethylamino)-pyridine were determined by spectrophotometric analysis of the ratio of products. No catalysis by buffers was observed.

Acknowledgment. We appreciate correspondence with Dr. A. Williams.

Registry No. 3-Cyanopyridine, 100-54-9; 4-cyanopyridine, 100-48-1; 3-chloropyridine, 626-60-8; 3-pyridinecarboxamide, 98-92-0; 4-pyridinecarboxamide, 1453-82-3; 3-pyridinecarboxylate, 3308-39-2; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-morpholinopyridine, 2767-91-1; 4-(dimethylamino)pyridine, 1122-58-3; 3-methoxypyridine, 7295-76-3.

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The Question of Concerted or Stepwise Mechanisms in Phosphoryl Group ($-PO_3^{2-}$) Transfer to Pyridines from Isoquinoline-*N*-phosphonate

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Received December 13, 1982

The existence of the metaphosphate monomer as an intermediate has been the subject of considerable scrutiny in the hydrolysis and transfer reactions of monophosphate esters and amides.[1-3] Recent studies on the methanolysis of phenyl phosphates bearing an asymmetric phosphorus atom[3] have indicated inversion of configuration at phosphorus, consistent with either a concerted mechanism or a preassociation stepwise mechanism where metaphosphate monomer reacts in the encounter complex before it can escape into bulk solution. It is possible that inversion observed in enzyme-catalyzed phosphonyl group transfer reactions[4] could be due to a mechanism similar to the latter with the metaphosphate group reacting at the active site before it can "tumble" and hence cause racemization.

We decided to study phosphonyl group transfer from a pyridine-*N*-phosphonate donor to a series of unhindered pyridine acceptors because the reaction must be symmetrical when acceptor and donor basicities are identical. The preassociation mechanism (eq 1) predicts a curved Brønsted plot and has a theoretical rate

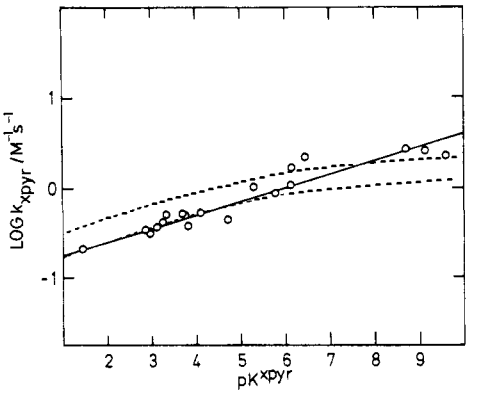

Figure 1. Reactivity of pyridines against isoquinoline-*N*-phosphonate as a function of the pK of the pyridine; 25 °C, ionic strength 0.2 M. Identity of the pyridines in increasing order of pK: 3-CN, 3-Br, 3-Cl, 3-MeOCO, 3-Ac, 3-CHO, 4-Br, 4-Cl, 3-CH_2CN, 4-CHO, H, 3-Me, 4-Me, 3,5-Me_2, 3,4-Me_2, 4-morpholino, 4-NH_2, 4-Me_2N. The line is calculated from the equation $\log k_{xpyr} = (0.15 \pm 0.01)pK^{xpyr} - (0.87 \pm 0.07)$ (r = 0.946), which is the best linear fit to the data points. The dashed curves are theoretical (see equation in text) for β_N = 0.2 drawn to fit either high or low pK points.

$$^{+}isq\text{–}PO_3^{2-} + xpyr \underset{}{\overset{k_1}{\rightleftharpoons}} {}^{+}isq\text{–}PO_3^{2-}\cdot xpyr \overset{k_2}{\rightleftharpoons} isq\cdot xpyr\cdot PO_3^{-} \overset{k_3}{\rightleftharpoons} isq\cdot {}^{+}xpyr\text{–}PO_3^{2-} \overset{k_4}{\rightleftharpoons} isq + {}^{+}xpyr\text{–}PO_3^{2-} \quad (1)$$

law $k/k_0 = 1/(1 + 10^{\Delta pK\beta_N})$ where $\Delta pK = pK^{isq} - pK^{xpyr}$, k_0 is the value of k when k_2 is rate limiting, and β_N is the Brønsted exponent when attack of acceptor pyridine is rate limiting (k_3). The mechanism assumes that k_2 and k_3 are independent of the "spectator" pyridines xpyr and isq in the respective steps.

The Brønsted relationship for the theoretical equation gives a family of normalized theoretical curves for log k/k_0 dependent only on β_N and ΔpK and these are illustrated in the following paper.[5] The concerted mechanism would give a linear Brønsted plot consistent with a transition state that does not change its structure over the range in question for a series of structurally related nucleophiles.[6]

The pyridinolysis of isoquinoline-*N*-phosphonate[7] was conveniently measured spectrophotometrically at 350 nm[8] by using buffers composed of hindered amines at low concentrations at pHs between 8 and 12. Isoquinoline-*N*-phosphonate was prepared in solution by mixing 0.5 mL of a stock of 0.5 mL of isoquinoline in 40% acetonitrile/water (v/v, 10 mL) with 10 mg of ammonium phosphoramidate; the stock was used directly in kinetics without attempting to isolate a solid product and was discarded after 2 h. The reaction with pyridines obeys good first-order kinetics and the rate law is $k_{obsd} = k_{intercept} + k_{xpyr}[xpyr]$ and is independent of the acid form of the pyridine. The value of $k_{intercept}$ is composed of buffer and water reaction; amines possess a significant reactivity toward pyridine-*N*-phosphonates.[9] The second-order rate constant (k_{xpyr}) obeys an excellent linear Brønsted-type relationship (Figure 1).

The dependence of the rate constant for phosphonyl group transfer on the concentration of the acceptor nucleophile excludes

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(7) The rate constant for the aqueous decomposition of the stock solution (k_{H_2O}) as measured by the decay at 350 nm agreed well with the value predicted from the Brønsted relationship for the hydrolysis of substituted pyridine-*N*-phosphonates;[9] we are thus confident that we are measuring the degradation of isoquinoline-*N*-phosphonate. It is not possible to characterize reactive pyridine-*N*-phosphonates in the normal way.
(8) The pyridine concentrations were kept below 0.05 M to prevent complications due to self-association. Experiments at different pHs with basic pyridines confirmed that only the base form was reacting.
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0002-7863/83/1505-3357$01.50/0

a simple dissociative path where metaphosphate monomer escapes from the encounter complex and has a significant lifetime. The data do not fit any curve of the family predicted from the theoretical equation of the stepwise process; since the equation is normalized, the horizontal position of a member of the family of curves is fixed by the pK of the donor pyridine and only the vertical position varied to fit the experimental data. The limiting slope of the curve predicted for the stepwise mechanism is reasonably expected to be similar to the β for the attack of pyridines on phosphoramidate (+0.2) where expulsion of ammonia from the preassociation complex would be rate determining. The theoretical line for $\beta_N = 0.2$ is shown fitting the points at high pK where close examination suggests a limiting rate constant. This line deviates grossly from the low pK points (as illustrated), and fitting the same line (by vertical displacement) to the low pK points yields similar deviations for those at high pK. Curvature for β_N values higher than 0.2 is very pronounced (see the following paper[5]) and would be clearly visible in the data. A nontheoretical "curve" may be fitted to the data, but this necessitates a break at a pK ($\sim$7) that is not theoretically possible as the system is chosen so that the stepwise process, if operating, would be symmetrical at the pK of isoquinoline (5.42). Force fitting the theoretical equation for the stepwise process gives a best fit to a least-squares program where $\beta_N = 0.3$. The "residuals" for this fitting possess a nonrandom variation with pK consistent with a poor fit unlike those for the linear equation (see figure), which have a random distribution.

Jameson and Lawlor[9] observed that morpholine, piperazine, piperidine, and piperazine monocation reacted with 4-methylpyridine-N-phosphonate with a reactivity range of 3-fold. These amines are close structural analogues of each other, and if the stepwise path were operating, the dissociative step involving formation of the ternary complex would be rate limiting because the amines are more powerful nucleophiles than is 4-methylpyridine.

The present results indicate an essentially constant transition-state structure for phosphonyl group transfer over a wide range of acceptor basicities. Data for the β_{EQ} for transfer of the phosphate between pyridines[10] taken with the present data point to weak charges on the pyridine nitrogens in the transition state similar to those in the analogous sulfonate group transfer.[5] The transition site is symmetrical.

There is incontrovertible evidence from trapping and reactivity studies[11] that discrete metaphosphorimidate intermediates are formed in some transfer reactions in aqueous solution. Conditions must therefore exist for a system involving a preassociation mechanism that bridges the gap between concerted and the $S_N1(P)$ process where the intermediate is free. This has yet to be demonstrated in monophosphate reactions although the zero Brønsted exponent[12] in the aminolysis of 2,4-dinitrophenyl phosphate is indicative of such a mechanism.

Acknowledgment. We thank the SERC and ICI Organics Division for financial support, Dr. R. B. Moodie for a gift of 4-morpholinopyridine, and Professor W. P. Jencks and Dr. M. Skoog for disclosing their work prior to publication.

Registry No. 3-Cyanopyridine, 100-54-9; 3-bromopyridine, 626-55-1; 3-chloropyridine, 626-60-8; 3-methoxycarbonylpyridine, 93-60-7; 3-acetylpyridine, 350-03-8; 3-formylpyridine, 500-22-1; 4-bromopyridine, 1120-87-2; 4-chloropyridine, 626-61-9; 3-cyanomethylpyridine, 6443-85-3; 4-formylpyridine, 872-85-5; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 3,5-dimethylpyridine, 591-22-0; 3,4-dimethylpyridine, 583-58-4; 4-morpholinopyridine, 2767-91-1; 4-aminopyridine, 504-24-5; 4-dimethylaminopyridine, 1122-58-3; isoquinoline-N-phosphonate, 85370-61-2; isoquinoline, 119-65-3; ammonium phosphoramidate, 18299-52-0.

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Preassociation Concerted Mechanism for Sulfate Group ($-SO_3^-$) Transfer between Isoquinoline-N-sulfonate and Substituted Pyridines[1a]

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Received December 13, 1982

There has been much discussion of the existence of preassociation stepwise processes in phosphoryl group transfer reactions[1b,2,3] in particular in relation to the central role of this reaction in biochemistry. Transfer of the analogous sulfate group from a nitrogen or oxygen donor involving free sulfur trioxide in the ternary complex with donor and acceptor may occur;[1b] transfer reactions of this group ($-SO_3^-$) have biological importance in the initial steps of inorganic sulfate utilization.[4]

Studies of the reaction of pyridine-N-sulfonates with aryl oxide ions have established that the transition state is symmetrical[5] with little bonding between sulfur and the entering or departing atoms. Although the symmetrical transition state is consistent with the concerted transfer of the sulfate group, it is difficult to distinguish between concerted and stepwise preassociation mechanisms for this reaction.

A Brønsted-type study of the reaction of substituted pyridines with isoquinoline-N-sulfonate[6] should be able to diagnose a concerted preassociation mechanism (eq 1) from a stepwise preas-

$$^+\text{isq}{-}SO_3^- + \text{xpyr} \rightleftarrows [^+\text{iso}{-}SO_3^-\cdot\text{xpyr}] \rightarrow |\text{isq}\cdots SO_3\cdots\text{xpyr}|^{\ddagger} \rightarrow [\text{isq}\cdot{}^+\text{xpyr}{-}SO_3^-] \rightleftarrows \text{isq} + {}^+\text{xpyr}{-}SO_3^- \quad (1)$$

sociation mechanism (eq 2). The former mechanism predicts a substantially linear relationship, whereas the stepwise mechanism predicts a break at a pK corresponding to that of isoquinoline.

Isoquinoline-N-sulfonate was prepared by passing SO_3 in a carrier stream of nitrogen through a solution of isoquinoline in dichloroethane.[6] Reaction of isoquinoline-N-sulfonate with pyridines was measured spectrophotometrically at 350 nm in aqueous buffers at 25 °C and 0.1 M ionic strength. The reaction, followed at pHs between 7 and 8, obeys good pseudo-first-order kinetics and has the rate law $k_{obsd} = k_{buffer} + k_{H_2O} + k_{xpyr}[\text{xpyr}]$, where the pyridine reacts in its basic form as determined from measurements with the basic pyridines. General base catalysis is excluded by the use of hindered pyridines (see caption to Figure 1), and water and the buffers, which are composed of hindered amines, contribute to the background reaction. The experimental data are shown in the figure, and the second-order rate constants obey an excellent linear plot: $\log k_{xpyr} = (0.23 \pm 0.002)pK^{xpyr} - (1.92 \pm 0.04)$ ($r = 0.995$). The observation of a linear relationship excludes the preassociation stepwise process and is consistent with a concerted one.

The theoretical equation for the stepwise mechanism (eq 2) has

$$^+\text{isq}{-}SO_3^- + \text{xpyr} \rightleftarrows [^+\text{isq}{-}SO_3^-\cdot\text{xpyr}] \rightleftarrows [\text{isq}\cdot\text{xpyr}\cdot SO_3] \rightleftarrows [\text{isq}\cdot{}^+\text{xpyr}{-}SO_3^-] \rightleftarrows \text{isq} + {}^+\text{xpyr}{-}SO_3^- \quad (2)$$

the form $k = k_0/(1 + 10^{\Delta pK\beta_N})$ where $\Delta pK = pK^{isq} - pK^{xpyr}$ and k_0 is the overall rate constant when formation of ternary complex is rate limiting ($\Delta pK < 0$). When decomposition of the ternary complex is rate limiting ($\Delta pK > 0$), the Brønsted-type plot becomes linear with slope β_N. The insert to the figure (B) illustrates

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(5) Hopkins, A.; Day, R. A.; Williams, A., submitted for publication in *J. Am. Chem. Soc.*
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