the purines in acetone and DMSO, in which, as aprotic solvents, base association is less significant.[7]

We conclude that the selectivity observed in the photochemical reactions of the heterocyclic bases for the purines is a result of the suppression of the reactivity of the pyrimidines due to the presence of the purines, and we assume that base association (stacking) is responsible for this effect. These findings are now being studied further and extended to associates of heterocyclic bases with amino acids. The possible "protection" of sensitive sites in biopolymers through the appropriate association agent is also under investigation.

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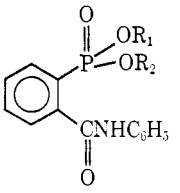
Interaction of Amides and Phosphates. Intramolecular Catalysis of Amide Hydrolysis by a Phosphonic Acid

Sir:

The association of nucleic acids and proteins has been recognized to be of biochemical significance.[1] We have sought evidence for chemical interactions between the functional groups serving as linkages in these molecules and have recently demonstrated the reactivity of an amide functionality toward a phosphate center in acid solution.[2] We have now observed a reaction due to a complementary interaction, catalysis of the hydrolysis of an amide brought about by the presence of a neighboring phosphate derivative.

Compound **1**, 2′-phosphonobenzanilide, was prepared by hydrolysis of the diethyl ester, **2**, in acetone–



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = C_2H_5$

water (1:1) containing 6 *M* hydrogen chloride.[2] Crystals of **1** (colorless plates, mp 213–214°) precipitate from the solution in over 99% yield. Spectral characteristics are consistent with the proposed structure (nmr m, δ 7.0–8.9; ir (KBr) 1600 (C=O), 1160 cm^{-1} (P=O)) as is the elemental analysis. *Anal.* Calcd for $C_{13}H_{12}NO_4P$: C, 56.32; H, 4.36; N, 5.05; P, 11.17. Found: C, 55.99; H, 4.48; N, 5.07; P, 11.19. The hydrolysis of the amide to 2-carboxyphenylphosphonic acid[4] and aniline hydrochloride (products were determined in a large scale preparative reaction) was followed by monitoring the decrease in absorbance due to the starting material at 270 nm. All kinetics were performed using stoppered quartz cells to hold solutions in the constant-temperature cell housing of a Unicam SP1800A spectrophotometer at 50 ± 0.10°. All acid concentrations were confirmed by titration; NBS buffers were used.[5]

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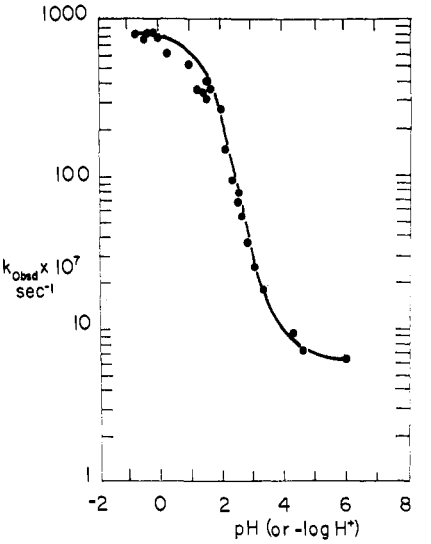

Figure 1. Observed rate constants for hydrolysis of **1** at 50.0°. The curve is a plot of eq 1. Experimentally determined points are indicated. Substrate concentration was 10^{-6} *M*. From pH 1 to pH 6 ionic strength was maintained at 0.5 *M*.

Figure 1 is a compilation of the observed first-order (buffer independent) rate constants for hydrolysis of **1** as a function of the acidity of the hydrolysis medium. The empirical kinetic equations for the reaction involving participation of the phosphonic acid do not involve an explicit term in solvent lyonium ion concentration at acidities up to 5 *M*. The plotted curve is of the equation

$$k_{obsd} = k(H_2A)/(H_2A + HA^-) + k'(HA^-)/(HA^- + H_2A) \quad (1)$$

where H_2A and HA^- are **1** and its conjugate base, respectively; $k = 8.6 \times 10^{-5}$ sec^{-1} and $k' = 6.9 \times 10^{-7}$ sec^{-1}. The pK' for **1** that gives a best fit for the curve is 1.6 and this agrees with values obtained by extrapolation from related literature values.[6] The corresponding para-substituted compound monoethyl ester[2] (prepared by hydrolysis of the para isomer of **2** in lithium hydroxide) hydrolyzes (without involvement of a plateau region) at a much slower rate, according to the equation

$$k_{obsd} = k''(H+) \quad (2)$$

at 50° where $k'' = 1.5 \times 10^{-6}$ sec^{-1} M^{-1}. Similar behavior is observed for benzanilide ($k'' = 1.1 \times 10^{-6}$ sec^{-1}) so that the phosphonate group has only a small inductive effect. For comparison, the diacid form of **1** hydrolyzes with $k = 8.5 \times 10^{-5}$ sec^{-1} M^{-1}. In 1.0 *M* acid at 50° the hydrolysis of **1** proceeds with a value for k_{obsd} greater than that for benzanilide by a factor of 74. However, at pH 6, where reaction of **1** occurs through the monoanion in the plateau asso-

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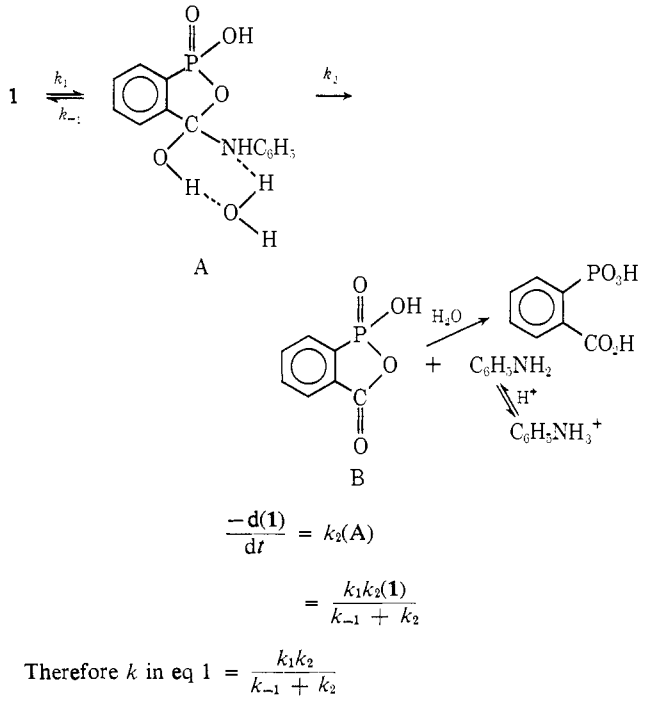
ciated with **1'**, k_{obsd} exceeds the extrapolated k_{obsd} for benzanilide by a factor of 6×10^5. The rate constant for the bimolecular reaction between phosphate and **3** is very small. No reaction of **3** in 1 *M* potassium phosphate buffer (pH 6) was observed when the solution was maintained at 90° for 1 month. Therefore, comparison of the rate of the intramolecular reaction of the internal phosphonate residue with the amide with that of external phosphate and **3** can only be estimated to favor the internal reaction by an apparent concentration of more than 10^3 *M*, assuming we could detect a concentration change of 3%. The solvent isotope effect in both plateau regions (below pH 2 and above pH 5), k_{H_2O}/k_{D_2O}, is 1.0, indicative of nucleophilic catalysis.[7]

We propose the mechanism in Scheme I as a likely

Scheme I



$$\frac{-d(\mathbf{1})}{dt} = k_2(A) = \frac{k_1k_2(\mathbf{1})}{k_{-1} + k_2}$$

Therefore k in eq 1 $= \dfrac{k_1k_2}{k_{-1} + k_2}$

route for the hydrolysis reaction of **1** which is consistent with the experimental data and kinetic forms (an analogous route can be written for the monoanion). The proposed cyclic acyl phosphonate intermediate (B) is a compound known to hydrolyze rapidly under the conditions of the amide hydrolysis reaction.[8,9] In Scheme I, hydrolysis of the acyl phosphonate B occurs after the aniline molecule has left the addition intermediate and thus after the chromophore being observed has been eliminated.

Nucleophilic catalysis by neighboring un-ionized carboxyl functions (or the zwitterionic equivalent) is a favored mechanism in the hydrolysis of amides[10-16] although a mechanism involving electrostatic catalysis has also been considered.[12,14,16] The observed rate constant for hydrolysis of these compounds shows a plateau region similar to that which we have observed for **1**, where the plateau ends as dissociation of the carboxylic acid occurs. Solvent isotope effects on these rate constants for carboxyl participation are also near unity. This argues for a similarity of mechanism between the phosphoric and carboxylic acid cases. Since dissociation of the proton from the phosphonate monoacid occurs at higher pH than does the corresponding carboxylic acid, the phosphonate group is an apparently more effective internal catalyst in neutral solution. Our finding further emphasizes that the amide functionality is reactive toward noncarboxylic functional groups as well as carboxylic acids. The very large rate ratio of the inter- and intramolecular reactions of phosphate with the amide gives further indication of a mechanism involving nucleophilic rather than general acid or base catalysis.[17]

We are examining the requirements for interaction of phosphates and amides in further detail and are extending our kinetic studies on these and related systems.

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Experimental Solvation Energies of Aliphatic Alkoxide Ions and Hydroxide Ions

Sir:

We wish to report here (for the first time to our knowledge) the relative solvation enthalpies for a series of aliphatic alkoxide ions and hydroxide ion from the gas phase to dimethyl sulfoxide (DMSO). Several years ago Brauman and Blair[1] demonstrated that the gas-phase order of acidity for a few common aliphatic alcohols is exactly the reverse of that reported previously from condensed phase studies. The inescapable conclusion is that the observed acidity order for aliphatic alcohols (and presumably some others) in solution is determined primarily by solvation factors. It has been realized for many years that a quantitative evaluation of solvation energies would be practical if only accurate gas-phase equilibrium constants for ion–molecule reactions were available. Recent advances in mass spec-

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