distilled from lithium aluminum hydride and passed through 3A molecular sieves prior to use. Each carbonyl compound was dried overnight under vacuum prior to use in oxonium ion synthesis.

Coumarin (Eastman), 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (Aldrich), 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclopenten-5-one (Aldrich), 4,4'-dimethoxybenzophenone (Aldrich), 2,6-dimethyl-γ-pyrone (Aldrich), flavone (Aldrich), methyl fluorosulfate (Aldrich), perinaphthenone (Aldrich), trimethyloxonium hexafluorophosphate (Cationics), and xanthone (Aldrich) were used as received after spectroscopic characterization (NMR, IR). Acetophenone (Baker) was distilled prior to use. Diphenylcyclopropenone [mp 120.5–121.5 °C (lit.[46] mp 119–120 °C)] and 1,2-diphenyl-3-ethoxycyclopropenyl tetrafluoroborate [mp 185–186 °C (lit.[46] mp 195–196 °C)] were synthesized by the method of Breslow et al.[46] Bis(*p*-methylphenyl)cyclopropenone [mp 175–176 °C (lit.[56] mp 176–177 °C)] was prepared according to the procedure of Eicher and Hansen.[56] 4,6-Dimethyl-α-pyrone [mp 49–50 °C (lit.[57] mp 50–51 °C)] was prepared by decarbonylation of coumalic acid according to the method of Smith and Wiley.[57] 4-Methylcoumarin [mp 82–83 °C (lit.[58] mp 83–84 °C)] was prepared from phenol and ethyl acetoacetate by the method of Woodruff.[58] 4-Ethoxy-2,6-dimethylpyrylium tetrafluoroborate [mp 90–91 °C (lit.[47] mp 90–91 °C)] was synthesized by the method of Meerwein et al.[47] Triethyloxonium tetrafluoroborate was prepared by the method of Meerwein.[59] Trimethyloxonium tetrafluoroborate was prepared according to the procedure of Curphey.[60]

Carboxonium Ion Synthesis. Carboxonium ion derivatives of the carbonyl bases were prepared by reaction of trialkyloxonium tetrafluoroborate salts with the carbonyl bases in an inert atmosphere. A typical procedure for alkylation of coumarin is illustrated below. To a Schlenk vessel protected from light and charged with 1.21 g (7.58×10^{-3} mol) of trimethyloxonium tetrafluoroborate was added a solution of 1.40 g (9.58×10^{-3} mol) of coumarin in 25 mL of CH_2Cl_2. The mixture was stirred for 48 h, and then 20 mL of diethyl ether was added to precipitate the pyrylium salt **2**. The collected solid was washed successively with CH_2Cl_2 (20 mL) and diethyl ether (2 × 20 mL) and was then dried in vacuo to yield 1.38 g (73%) of **2** as a white solid, mp 121–122 °C dec.

Anal. Calcd for $C_{10}H_9O_2BF_4$: C, 48.43; H, 3.66. Found: C, 48.42; H, 3.64.

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Physical property data for all of the oxonium ions prepared in the course of this research are listed in Table I. All carboxonium ions were characterized by elemental analyses (supplementary material available), infrared spectra, ultraviolet–visible spectra, and ^1H NMR spectra.

Equilibrations. The carbonyl base (ca. 0.1 mol) was added under a blanket of dry nitrogen to an NMR tube which contained a weighed amount (ca. 0.1 mol) of an alkoxycarbenium ion salt; the solvent (generally SO_2) was condensed into the tube (ca. 0.5 mL). After being thoroughly degassed, the NMR tube was sealed under vacuum. The equilibration at 25 °C was monitored by periodic ^1H NMR observations; when the ratio of appropriate resonance signals was constant with time, it was judged that equilibrium had been established. In general, side products were not observed by ^1H NMR during these equilibrations. When small, extraneous peaks were observed, their presence did not seem to affect the calculated equilibration constants as deduced from the reproducibility obtained for several runs. Complete equilibration required several days to weeks, depending on the equilibration system. Between 8 and 15 consecutive electronic integrations per sample were utilized to determine the relative concentrations of the various species present in solution.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial financial support of this work. Charles R. Gambill was the recipient of a National Institutes of Health Fellowship, 1969–1973. We also express our deep appreciation to Professor Bing-Man Fung at the University of Oklahoma for his assistance in obtaining the ^{13}C NMR spectra.

Registry No. **2** BF_4^-, 77902-74-0; **2** PF_6^-, 77902-75-1; **2** FSO_4^-, 77902-76-2; **3** BF_4^-, 77902-78-4; **3** FSO_4^-, 77902-79-5; **5** BF_4^-, 77902-57-9; **5** PF_6^-, 77902-58-0; **5** FSO_3^-, 66633-47-4; **6** BF_4^-, 77902-60-4; **7** BF_4^-, 29531-31-5; **8** BF_4^-, 77902-81-9; **8** PF_6^-, 77902-82-0; **8** FSO_3^-, 77902-83-1; **9** BF_4^-, 13938-87-9; **9** PF_6^-, 77924-72-2; **9** FSO_3^-, 52912-00-2; **10** BF_4^-, 77902-85-3; **11**, 45952-21-4; **12**, 46185-86-8; **16** HSO_4^-, 77902-86-4; **17** $CF_3CO_2^-$, 77902-61-5; 4,4'-dimethoxybenzophenone, 90-96-0; diphenylcyclopropenone, 886-38-4; bis(*p*-methylphenyl)-cyclopropenone, 38377-57-0; 4,6-dimethyl-α-pyrone, 675-09-2; 2,6-dimethyl-γ-pyrone, 1004-36-0; 4-methylcoumarin, 607-71-6.

Supplementary Material Available: Figures 1 and 2, initial and final ^1H NMR spectra for equilibration of α-methoxy-4-methylbenzopyrylium tetrafluoroborate (**3**) with 4,4'-dimethoxybenzophenone in liquid SO_2; Table IV, solvent effects on the ^1H NMR parameters of several oxonium ions (**5**, **11**, **12**); Table V, supplementary elemental analysis data for new compounds (4 pages). Ordering information is given on any current masthead page.

Hydrolysis of Formamide at 80 °C and pH 1–9[1]

Jack Hine,* Richard S.-M. King, W. Robert Midden, and Ashoke Sinha

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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The rate of hydrolysis of formamide in hydrochloric acid and in various aqueous buffers was studied over the pH range 1–9 at 80 °C. The reaction is subject to general catalysis in cacodylate, acetate, propionate, and probably methoxyacetate and succinate buffers. Data extrapolated to zero buffer concentration or obtained under conditions where general catalysis should be relatively minor show that hydroxide ions are about 10 times as effective as hydrogen ions in bringing about hydrolysis. The water term in the rate equation is so small that it never contributes more than about 50% to the total reaction rate, but it appears to be real.

The kinetics and mechanism of hydrolysis of amides have been studied extensively in acidic and basic aqueous solution.[2-10] Studies in the intermediate pH range are much less common, however. In fact, it has been stated

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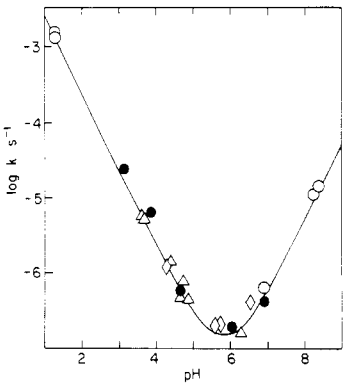

Figure 1. Logarithmic plot of first-order rate constants for hydrolysis of formamide in water at 80 °C vs. pH. The line is based on the application of eq 2 to the data represented by the open symbols, for which general catalysis is believed to be negligible. See the text for the rest of the key to the symbols.

that "hydrolyses of carboxylic acid amides...generally do not take place in neutral media".[8] Morawetz and Otaki studied the kinetics of amide formation and hydrolysis from carboxylic acids and excess amine in aqueous solution, but under these basic conditions the hydrolysis reaction arises almost entirely from the hydroxide ion induced process.[9] The only example we know of in which the nonenzymatic hydrolysis of a simple amide (one in which only hydrogen atoms or saturated aliphatic radicals are attached to the amide group) in aqueous solution has been clearly shown to arise from anything other than hydrogen ion or hydroxide ion catalysis is the study of the hydrolysis of *N*-*n*-butylacetamide in the presence of acetate buffers at 220 °C.[10] Wyness showed that this reaction is subject to general-acid catalysis by acetic acid but to no appreciable catalysis by acetate ions. That part of the reaction not due to acetic acid was not discussed. We have studied the hydrolysis of the simplest possible amide, formamide. In order to obtain reaction half-lives substantially less than 1 year in neutral solution, we have used an elevated temperature, 80 °C. We have covered the pH range 1–9, pH 6.3 being a neutral solution at 80 °C.

Results

Our first kinetic measurements were made with an initial formamide concentration around 0.055 M. In the presence of hydrochloric acid and of formate buffers the reactions were assumed to be second order, first order in formamide and first order in hydrogen ions. In the presence of ammonia buffers the reaction was assumed to be first order in formamide and first order in hydroxide ions. In each of these runs, where the pH changed by from 0.11 to 1.7 units because of the acidity of the ammonium ions or the basicity of the formate ions produced, the experimental data agreed better with the second-order rate equation used than with a first-order rate equation. The reaction was also studied in the presence of acetate and cacodylate buffers where the change in pH during a run was between 0.02 and 0.20 units, and the reaction was treated as first order. For each run the first-order rate constant is plotted logarithmically, as a circular point, against the average pH for the run in Figure 1. The first-order rate constants for the hydrochloric acid, formate, and ammonia runs were obtained by multiplying the calculated second-order rate constant by the hydrogen ion concentration or hydroxide ion concentration at the average pH.

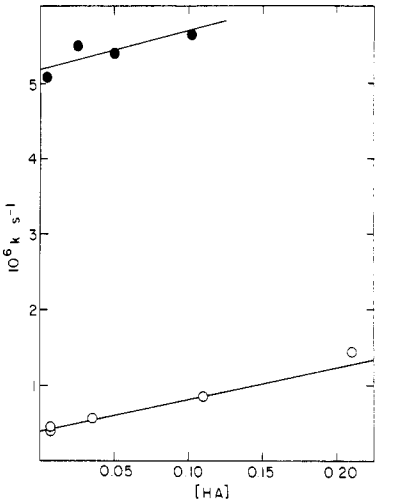

Figure 2. Plot of first-order rate constants for hydrolysis of formamide in water at 80 °C vs. concentration of buffer acid: ●, methoxyacetate buffers at pH 3.67 ± 0.01; ○, acetate buffers at pH 4.85 ± 0.05.

Table I. Kinetic Data in Various Buffers for Formamide Hydrolysis at 80 °C[a]

buffer	pH	$10^7 k_0$[b]	$10^7\sigma$[c]	$10^7 k_2$[d]	$10^7\sigma$[c]	μ[e]
cacodylate	6.29	1.64	0.22	2.58	0.26	0.13
acetate	4.85	4.11	0.17	4.13	0.41	0.30
propionate	4.64	4.82	0.22	2.47	0.20	0.20
propionate	4.37	14.6	1.4	2.2	0.8	0.81
succinate	4.71	7.5	1.7	0.8[f]	2.2	0.20
succinate	3.61	5.3	0.6	3.0[g]	3.4	0.10
$MeOCH_2$-CO_2H	3.67	51.9	1.4	4.9	2.8	0.14

[a] In aqueous solution. [b] In s^{-1}. [c] Estimated standard deviation. [d] In M^{-1} s^{-1}. [e] Ionic strength. [f] Based on the principal acid present, the monoanion of succinic acid. [g] Based on the principal acid present, undissociated succinic acid.

A second set of runs was made with use of initial formamide concentrations around 0.0004 M so that the effect of the ammonium formate produced on the pH and the reaction rate would be minimized. Runs were made with use of acetate, cacodylate, propionate, succinate, and methoxyacetate buffers. The first-order rate constants obtained at constant pH (±0.05) were plotted against the concentration of buffer acid. In Figure 2 are the plots of methoxyacetic acid at pH 3.67 (solid circles) and acetic acid at pH 4.85 (open circles). With propionic acid, runs were made at two different buffer ratios. The fact that the slopes of these two plots were the same within the estimated standard deviation shows that the observed catalysis arises largely, at least, from the buffer acid. This agrees with the results of Wyness using *N*-*n*-butylacetamide and acetate buffers and suggests that the same is true with methoxyacetic acid and acetic acid, which are stronger acids than propionic acid.

The data were fit to eq 1 by least-squares treatments

$$k = k_0 + k_2[\mathrm{HA}] \quad (1)$$

and the values of k_0 and k_2 obtained are listed in Table

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Table II. Kinetics of Formamide Hydrolysis in Water at 80 °C[a]

buffer	[buffer],[b] M	pH[c]	10^2k_2, M^{-1} s^{-1}	10^7k_1, s^{-1}	ionic strength[c]
HCl	0.100	1.29 ± 0.17	1.9	13 000	0.100
HCl	0.100	1.29 ± 0.17	2.2	15 000	0.100
HCO_2H	0.574	3.16 ± 0.08	2.5	240	0.124 ± 0.026
HCO_2H	0.195	3.85 ± 0.09	3.3	64	0.124 ± 0.026
HCO_2H	0.060	4.61 ± 0.12	1.9	6.0	0.072 ± 0.022
AcOH	0.056	5.57 ± 0.10		1.9	0.072 ± 0.015
Me_2AsO_2H	0.206	6.04 ± 0.01		1.9	0.062 ± 0.012
Me_2AsO_2H	0.058	6.97 ± 0.09		4.0	0.068 ± 0.020
NH_3	0.108	6.92 ± 0.06	24	6.3	0.114 ± 0.016
NH_3	0.010	8.24 ± 0.85	22	110	0.028 ± 0.018
NH_3	0.111	8.37 ± 0.23	21	150	0.044 ± 0.023

[a] Using about 0.055 M initial formamide. [b] Total initial concentration of both forms. [c] Covers the entire range for as far as the reaction was followed. The plus or minus figure for ionic strength shows how far these reactions were followed.

I. The general catalysis observed with cacodylate buffers may arise from cacodylate anions as well as from cacodylic acid.

Table I and Figure 2 both indicate that with the strongest acid studied, methoxyacetic, the buffer is so acidic that the hydrogen ion catalyzed reaction is so fast that the catalysis constant obtained is of reduced reliability. For some reason the rate constants obtained with use of succinate buffers were particularly erratic. The catalysis constants obtained were smaller than the estimated standard deviations. Thus we are not sure how small this constant may be, but, at least, the data indicate that the bifunctional succinic acid and succinate monoanion do not possess any remarkably great catalytic activity.

The rate constants extrapolated to zero buffer concentration (k_0 values from Table I) are also plotted in Figure 1 as triangles. Also plotted (as diamonds) are four other rate constants obtained with use of about 0.0004 M initial formamide in individual runs in which neither component of the acetate nor cacodylate buffer was present at a concentration larger than 0.017 M. In this concentration range there should be no major amount of general-acid or -base catalysis. We have assumed that general catalysis is negligible in the 0.055 M initial formate runs in hydrochloric acid and in those where ammonia buffers were used. The conclusion that there is no significant general catalysis by the components of ammonium buffers follows from our observation that in the run with 0.01 M initial ammonia and an average pH of 8.24 the observed second-order rate constant is slightly larger than in the run with a 0.10 M initial ammonia concentration and an average pH of 8.37. It is also relevant that Morawetz and Otaki, who used much higher ammonia and amine concentrations, observed no general catalysis in the hydrolysis and formation of several simple primary amides, as well as *N*-methylformamide and *N*-isopropylformamide.[9] Therefore, we fit the 15 data plotted as open symbols in Figure 1 to eq 2, minimizing the sum of the squares of the

$$k_{obsd} = k_H[H^+] + k_{OH}[OH^-] + k_w \quad (2)$$

logarithmic deviations. The resulting values of 0.0178 and 0.211 M^{-1} s^{-1} for k_H and k_{OH}, respectively, and of 8.4×10^{-8} s^{-1} for k_w fit the log k_{obsd} values with a standard deviation of 0.09 and gave an average deviation of 0.07 for the five log k values obtained between pH 5 and 7. The line in Figure 1 is based on these parameter values at an ionic strength of 0.10. When the k_w term is omitted, values of 0.0205 and 0.270 M^{-1} s^{-1} are obtained for k_H and k_{OH}, the standard deviation of the log k_{obsd} values increases to 0.13, and the average deviation of the five values obtained between pH 5 and 7 jumps to 0.15. We therefore believe that the k_w term is probably real, even though it is never large enough to contribute more than about 50% to the total reaction. The first-order rate constants for the hydrolysis of *N*-*n*-butylacetamide at 220 °C[10] extrapolated to zero acetate buffer concentration at pH 5.0, 5.2, and 5.7 are all equal to $(1.0 \pm 0.1) \times 10^{-5}$ s^{-1}. This is consistent with a significant contribution by a k_w term.

Experimental and Data Treatment Section

Kinetic Runs. Reactions carried out with about 0.055 M initial formamide were followed by formol titrations. In a typical run, 19 mL of aqueous buffer was heated to 80 °C in a 30-mL glass vial, and 1 mL of about 1.1 M aqueous formamide was injected through the rubber serum cap. At a recorded time the vial was removed from the constant-temperature bath and cooled in an ice bath. A 4-mL aliquot was titrated with standard sodium hydroxide to the phenolphthalein end point. After 5 mL of 37% (wt) formaldehyde had been added to the neutralized solution, the acid liberated by the formaldehyde was titrated with standard sodium hydroxide to the phenolphthalein end point. A small correction was made for acidic impurities in the formaldehyde solution. The runs in basic solution were carried out similarly except that formaldehyde or formaldehyde and standard acid were injected into the cooled reaction vial before it was opened. A run taken to be carried out in the presence of 0.010 M initial ammonia with use of about 0.045 M initial formamide was conducted by employing 0.010 M initial sodium hydroxide and the usual 0.055 M initial formamide. The hydroxide ion rate constant shows that more than 99% of the sodium hydroxide would be used up in 21 s. Half of the remaining formamide was not hydrolyzed until after about 40 h. Neglect of the first 21 s of the reaction is therefore justified.

The runs with about 0.0004 M initial formamide were followed by using ninhydrin to determine the amount of ammonium ions formed. In a typical run, 10 mL of buffer and 40 μL of 0.1 M formamide in a serum-stopped glass vial were placed in an 80 °C constant-temperature bath at zero time. At recorded times, 0.60-mL samples were withdrawn by syringe and mixed with 0.60 mL of ninhydrin reagent solution. The mixture was heated in a boiling water bath for 10 min and diluted to 5 mL with 50% aqueous ethanol, and its absorbance at 570 nm was determined by using a Cary 16 spectrophotometer. Blanks were run on the reagents; reference determinations using known concentrations of ammonium chloride gave a straight-line relationship between absorbance and ammonium ion concentration. The ninhydrin solution was usually made by dissolving 0.2 g of ninhydrin in 7.5 mL of dimethyl sulfoxide, 2.5 mL of 4 M pH 5.2 lithium acetate buffer, and 0.04 mL of 15% titanous chloride. In other cases, 0.03 g of hydrinantin (Pierce Chemical) was used instead of the titanous chloride solution and appeared to be better in some respects.

pH and p*K* Measurements. In the runs carried out with about 0.0004 M initial formamide, the pH of the reaction solution was measured at room temperature and at 80 °C by using a Radiometer PHM-26 pH meter with 2401B combination electrodes. In the runs with about 0.055 M initial formamide, the pH at 80 °C was calculated from the known composition of the solution and the p*K* values of the components at 80 °C. Equation 3, where K is the ionization constant and T is the absolute tem-

$$\log K = A/T + B \log T + C \quad (3)$$

perature, was used to obtain K values for formic acid, acetic acid, and ammonia at 80 °C. The method of least squares was used to obtain values of the constants from data over the range 0–60 °C.[11a] This gave pK_a values of 3.89 and 4.88 for formic and acetic acids, respectively, and a pK_b value of 4.77 for ammonia at 80 °C. The pK_w value for water at 80 °C is 12.62[11b] (on a molarity basis). The pH values were taken as $-\log a_{H^+}$ values and activity coefficients were calculated from the Davies equation[12] (eq 4) by

$$\log \gamma = -0.5739(\mu^{1/2}/(1 + \mu^{1/2}) - 0.2\mu) \quad (4)$$

using the Debye–Hückel constant of 0.5739 at 80 °C.[11c]

From the pH of solutions of cacodylate buffers at 80 °C is calculated a thermodynamic pK_a for cacodylic acid of 6.42 ± 0.02 for ionic strengths (sodium chloride) from 0.004 to 0.30 if the sodium cacodylate concentration is below 0.02 M. As the sodium cacodylate concentration increases to 0.30 M, the calculated pK_a increases to 6.52.

Treatment of Data. A nonlinear least-squares treatment[13] was used to obtain the rate constant that minimized the sum of the unweighted $(mL_{obsd} - mL_{calcd})^2$ values for the runs carried out with about 0.055 M formamide or $(Abs_{obsd} - Abs_{calcd})^2$ values for the runs carried out with about 0.0004 M initial formamide. A simple first-order or second-order rate equation was used for all the runs except those with formate or ammonia buffers and about a 0.055 M initial formamide concentration. The concentrations of formic acid and formate ions in the formate buffers were so much larger than the hydrogen ion (or hydroxide ion) concentration that they were not significantly affected by the small amount of transformation of formic acid to formate ions that accompanied the decrease in acidity of the reaction solution during the reaction. Thus we write differential rate equation shown in eq 5, in which A, B, and C are the initial concentrations of formamide, formic acid, and formate ions, respectively, t is the time, x is the change in formamide concentration, k_2 is the second-order rate constant, and K is the ionization constant of formic acid. The increase in ionic strength causes K to increase slightly during the reaction, but if it is taken as a constant (the value calculated at the average ionic strength), eq 5 can be integrated to give eq 6.

$$dx/dt = k_2KB(A - x)/(C + x) \quad (5)$$

$$k_2KBt = (A + C) \ln [A/(A - x)] - x \quad (6)$$

We calculated k_2 as that value that minimized the sum of the squares of $x_{obsd} - x_{calcd}$. Since we could not solve eq 6 for x, we used an iterative procedure to obtain x_{calcd}. Rate constants in the runs with ammonia buffers were obtained analogously.

Registry No. Formamide, 75-12-7.

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Model Studies Concerning the First Step in the Hydrolysis of Ribonucleic Acids by RNase A

Dirk van Aken,* Luud M. C. Paulissen, and Henk M. Buck

Eindhoven University of Technology, Department of Organic Chemistry, Eindhoven, The Netherlands

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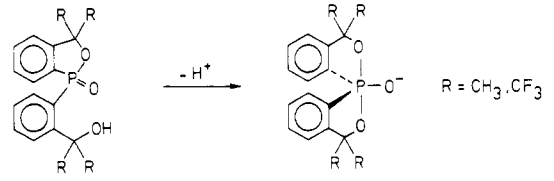
Low-temperature NMR measurements of the reaction of two cyclic oxyphosphoranes with FSO_3H in $CHCl_2F$ are described. An equilibrium is observed of the ring-opened phosphonium ions with the neutral oxyphosphoranes. From the activation parameters it is concluded that the rigidity introduced by a five-membered ring facilitates ring closure of the phosphonium ion, whereas a six-membered ring is less effective. Similarly, ring closure is found to occur in the solvolysis of a bicyclic phosphate where a five-membered ring makes the ring-opened product relatively rigid. This results in exocyclic ester cleavage to a greater extent than predicted by a pseudorotation mechanism. The reactions suggest that intramolecular phosphorylation of the 2'-OH group in RNA is facilitated by the ribose ring.

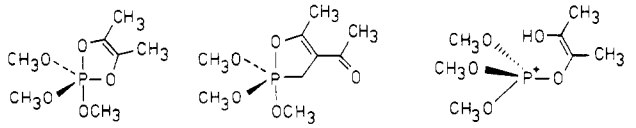
Introduction

It is generally accepted that phosphorylation reactions involve intermediates in which phosphorus is five-coordinated.[1] Examples of these intermediates have recently been isolated by making use of an intramolecular phosphorylation, e.g., in the phosphinate shown in Scheme I.[2] In addition, we have shown that structural factors which promote intramolecular phosphorylation can be conveniently detected by low-temperature NMR measurements of stable, cyclic oxyphosphoranes in strong acid solution.[3] Thus, it was demonstrated that a small amount of acid induces an equilibrium of the phosphorane, e.g., **1** or **2**, with a phosphonium ion, e.g., **1'**. This equilibrium involves a bimolecular proton transfer from the phosphonium ion to a neutral phosphorane molecule[3] (Scheme II). The equilibrium is fast when the ring contains a double bond

Scheme I



Scheme II



$$1 + {}^*1' \rightleftharpoons 1' + {}^*1$$

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