



RESEARCH ARTICLES

Kinetics of *trans*-Cinnamic Anhydride Reactions Catalyzed by Pyridine, 4-Dimethylaminopyridine, and *N*-Methylimidazole

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Abstract □ The kinetics of hydrolysis of *trans*-cinnamic anhydride and of its reactions with hydroxy compounds were studied in the presence of pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole as catalysts. The absolute rates of the catalyzed hydrolysis decreased with increasing acetonitrile content (decreasing solvent polarity), but the catalytic efficiency of *N*-methylimidazole and 4-dimethylaminopyridine relative to pyridine increased as the solvent polarity decreased. The relative catalytic rates for the cinnamoylation of *n*-propanol in acetonitrile were 1:259:16,000 for pyridine, *N*-methylimidazole, and 4-dimethylaminopyridine, respectively.

Keyphrases □ Kinetics—hydrolysis of *trans*-cinnamic anhydride catalyzed by pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole □ *trans*-Cinnamic anhydride—hydrolysis kinetics catalyzed by pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole □ Hydrolysis kinetics—*trans*-cinnamic anhydride, catalyzed by pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole

The cinnamoyl group, $C_6H_5CH=CHCO$, is a powerful chromophore and, therefore, of analytical interest. A quantitative method for aliphatic amines (1, 2) is based on their reaction with *trans*-cinnamic anhydride to give the corresponding cinnamamides. These reactions are rapid and quantitative, but aromatic amines and alcohols, which are relatively weak nucleophiles, react too slowly for practical use of the published procedure.

Pyridine is a widely used acylation catalyst; recently, the more powerful 4-dimethylaminopyridine (3, 4) and *N*-methylimidazole (5, 6) have been introduced as catalysts for analytical acetylations. Therefore, the application of these catalysts to the cinnamoylation of aromatic amines and alcohols may be of analytical utility. This paper describes kinetic measurements on the hydrolysis of cinnamic anhydride and its reactions with some hydroxy compounds using pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole as the catalysts.

EXPERIMENTAL

Materials—*trans*-Cinnamic anhydride was prepared by a modified published procedure (7). A mixture of 30 g of *trans*-cinnamic acid and 50 g of acetic anhydride, protected from atmospheric moisture, was refluxed for 2 hr. Acetic acid and acetic anhydride were removed by distillation, and the solid residue was recrystallized three times from benzene, in the presence of activated charcoal, to give colorless needles, mp 136–137° [lit. (7) mp 136°]. The molar absorptivity in acetonitrile solution at λ_{max} 294 nm was 4.23×10^4 [lit. (8) 4.32×10^4].

Pyridine¹ and *N*-methylimidazole² were used directly. 4-Dimethylaminopyridine² was recrystallized from petroleum ether, mp 113° [lit. (9) mp 112–113°]. Acetonitrile³ was a spectrophotometric grade solvent. Phenol⁴ was recrystallized from benzene, mp 40.9° [lit. (10) mp 40.85°]. Alcohols were reagent grade products and were used directly. Buffers were prepared from reagent grade materials and water that was redistilled from alkaline permanganate in an all-glass system. Ionic strength was brought to a constant value with potassium chloride.

Procedures—*Hydrolysis Kinetics*—All kinetic runs were carried out at 25.0°. The ionic strength in the hydrolysis studies was 0.10 *M*. The rate measurements were made in one of three ways, depending on the reaction half-life. If the half-life was <2 min, 50 μ l of 3.3×10^{-5} *M* *trans*-cinnamic anhydride in acetonitrile was stirred rapidly into 3.0 ml of the aqueous buffer contained in a rectangular 1-cm spectrophotometer cell positioned in the spectrophotometer⁵ cell compartment. Absorbance, monitored at 305 nm, was recorded as a function of time beginning within 10 sec of initiation of the reaction.

For reactions with half-lives of 2–15 min, 2.0 ml of 1.7×10^{-4} *M* cinnamic anhydride in acetonitrile was delivered into 50.0 ml of aqueous buffer. The mixed solution was transferred to a 10-cm cell for absorbance measurements at 305 nm. With both procedures, the data were interpreted by means of plots of $\log(A_t - A_\infty)$ versus t , where A_t is the absorbance at time t and A_∞ is the absorbance when the reaction is essentially complete (at least 10 half-lives). From the slopes of the linear plots, the apparent first-order rate constants were evaluated.

¹ Fisher Scientific Co.

² Aldrich Chemical Co.

³ Burdick & Jackson Laboratories.

⁴ Mallinckrodt Chemical Works.

⁵ Cary model 14.

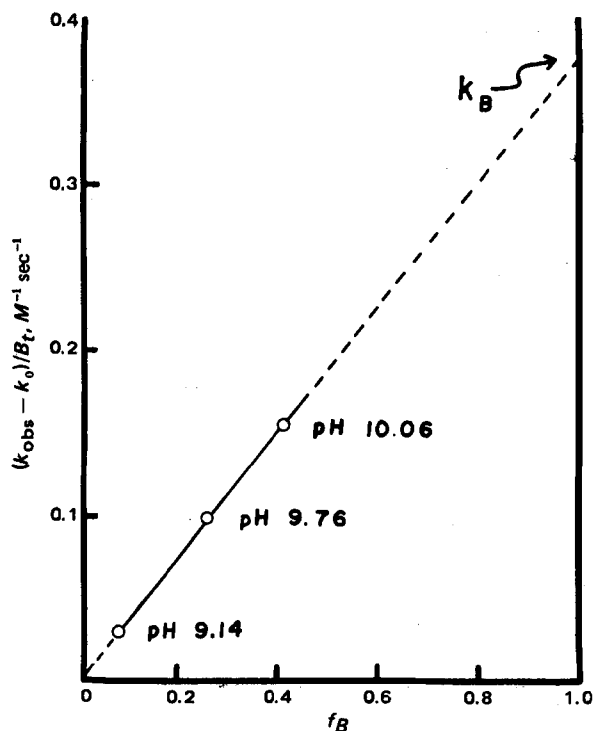


Figure 1—Plot according to Eq. 4 for *trans*-cinnamic anhydride hydrolysis in carbonate buffers at 25°.

If the half-life was >15 min, an initial rate method was used. The absorbance of the reaction mixture (prepared as for reactions having half-lives of 2–15 min) at 305 nm was a linear function of time initially. By writing the rate equation as $V_0 = k_{\text{obs}}C_A^0$ at essentially zero time, k_{obs} can be calculated as the ratio of the initial rate V_0 (in moles per liter second) to the initial anhydride concentration C_A^0 . The initial rate V_0 is obtained from the initial slope V_0 of absorbance versus time by $V_0 = V_0/b(\epsilon_R - 2\epsilon_p)$, where b is the path length and ϵ_R and ϵ_p are the molar absorptivities of reactant cinnamic anhydride and product cinnamic acid anion, respectively. At 305 nm, $\epsilon_R = 3.60 \times 10^4$ and $\epsilon_p = 1.34 \times 10^3$.

Esterification Kinetics—Appropriate volumes of acetonitrile solutions of the hydroxy compound and the catalyst (the volumes depend on the reactivities of the hydroxy compound and the catalyst) were mixed in a

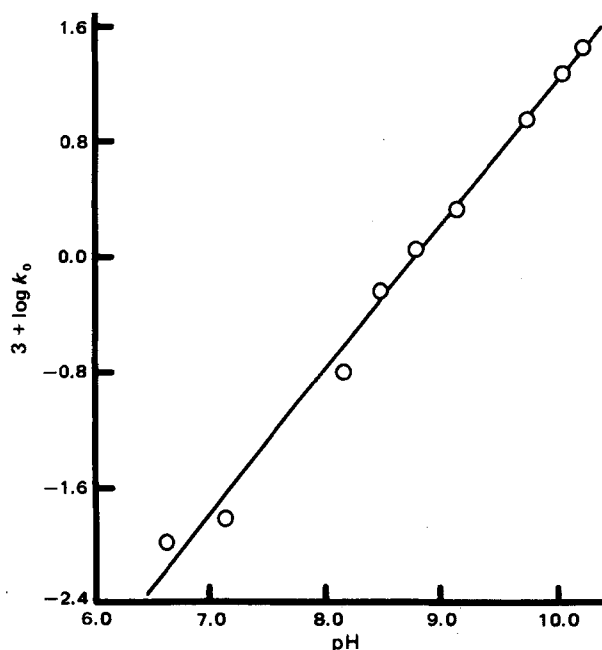


Figure 2—The pH-rate profile for the hydrolysis of *trans*-cinnamic anhydride at 25°, ionic strength 0.10 M, and zero buffer concentration. Data were taken from Table I.

Table I—Rate Constants for Hydrolysis of *trans*-Cinnamic Anhydride at 25°

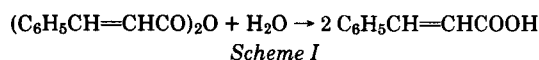
pH	Buffer	$10^3 k_0$, sec ⁻¹	k_B , M ⁻¹ sec ⁻¹
10.23	Carbonate	29.07	0.381 ^a
10.06	Carbonate	18.84	
9.76	Carbonate	8.95	
9.14	Carbonate	2.14	0.332 ^a
8.80	Tris(hydroxymethyl)- aminomethane	1.13	
8.48	Tris(hydroxymethyl)- aminomethane	0.582	
8.17	Tris(hydroxymethyl)- aminomethane	0.158	0.00254 ^a
7.14	Phosphate	0.0160	
6.64	Phosphate	0.0111	

^a Mean values.

beaker. An acetonitrile solution of cinnamic anhydride was added, and the absorbance was followed at 305 nm in a 1-cm cell.

RESULTS AND DISCUSSION

Cinnamic Anhydride Hydrolysis Kinetics—The hydrolysis reaction shown in Scheme I:



is accompanied by a decrease in absorbance at 305 nm. Pseudo-first-order kinetics were observed at constant pH, temperature, and ionic strength. Reproducibility was excellent, as indicated by this typical result at pH 8.8 (mean \pm SD): $k_{\text{obs}} = 6.75 \pm 0.04 \times 10^{-3} \text{ sec}^{-1}$ ($n = 3$).

Buffer Catalysis and pH-Rate Profile—The pseudo-first-order rate constants were measured as a function of total buffer concentration at constant pH, temperature (25°), and ionic strength (0.10 M), over the pH range of 6.64–10.23 in phosphate, tris(hydroxymethyl)aminomethane, and carbonate buffers. The rate constants increased with buffer concentration and were interpreted as follows. Letting k_{obs} represent the observed pseudo-first-order rate constant:

$$k_{\text{obs}} = k_0 + k_B[B] + k_A[A] \quad (\text{Eq. 1})$$

where [A] and [B] are the molar concentrations of buffer species in the conjugate acid and base forms, respectively, k_A and k_B are the second-order rate constants for buffer catalysis by A and B, respectively, and k_0 is the first-order rate constant for hydrolysis at zero buffer concentrations, with the entire equation referring to constant pH. The buffer species concentrations can be related to the total buffer concentration B_t by:

$$[A] = f_A B_t \quad (\text{Eq. 2})$$

$$[B] = f_B B_t \quad (\text{Eq. 3})$$

where f_A and f_B are the fractions of buffer in the indicated form. Combining Eqs. 1–3 gives:

$$\frac{k_{\text{obs}} - k_0}{B_t} = k_A + (k_B - k_A)f_B \quad (\text{Eq. 4})$$

If the experiment is carried out at several pH values (with the same buffer), a plot of $(k_{\text{obs}} - k_0)/B_t$ against f_B is predicted to be linear, with

Table II—Rate Constants for Catalyzed Hydrolysis of Cinnamic Anhydride at pH 8.45 and 25°

Catalyst	$10^4 C_t^a$, M	$10^4 [C]$, M	$10^3 k_{\text{obs}}$, sec ⁻¹	k_C , M ⁻¹ sec ⁻¹
Pyridine	12.1	12.1	8.60	2.77
	19.4	19.4	10.28	2.60
	24.2	24.2	11.85	2.72
<i>N</i> -Methylimidazole	2.94	2.79	9.06	13.69
	4.90	4.64	11.60	13.70
	6.86	6.51	14.09	13.61
4-Dimethylamino- pyridine	0.117	0.00639	6.48	1.88×10^3
	0.195	0.01073	7.42	1.99×10^3
	0.274	0.01507	8.27	1.97×10^3

^a Total catalyst concentration.

Table III—Catalytic Rate Constants for the Hydrolysis of Cinnamic Anhydride at 25°

pH	$k_C, M^{-1} \text{sec}^{-1}$		
	Pyridine	<i>N</i> -Methylimidazole	4-Dimethylamino-pyridine
8.45	2.70	13.66	1.95×10^3
8.78	3.02	14.22	1.85×10^3
9.17	3.75	14.95	1.82×10^3

intercepts of k_A when $f_B = 0$ and of k_B when $f_B = 1$. The quantity k_0 is obtained at each pH by plotting k_{obs} versus B_t and extrapolating to $B_t = 0$; the fraction f_B is calculated with $f_B = K_a / ([H^+] + K_a)$, where K_a is the buffer acid dissociation constant.

The thermodynamic pKa values of bicarbonate, protonated tris(hydroxymethyl)aminomethane, and monobasic potassium phosphate at 25° are 10.33, 8.06, and 7.20, respectively (11). The apparent pKa values at ionic strength 0.10 M, calculated by Davies' method (12), are 10.22, 8.18, and 7.09, respectively. Plots of k_{obs} versus B_t at constant pH were linear. Figure 1 shows the plot according to Eq. 4 for carbonate buffer, showing negligible catalytic effect by the conjugate acid form of the buffer. The same behavior was observed for the other buffers. Since $k_A = 0$, Eq. 1 shows that k_B also can be evaluated by plotting k_{obs} versus $[B]$. Table I summarizes these studies, listing the k_0 and k_B values found.

The k_B quantities for carbonate and phosphate probably describe a general base catalysis of the hydrolysis, but k_B for tris(hydroxymethyl)aminomethane undoubtedly includes a nucleophilic attack on the anhydride since the absorption spectrum of the reaction product is not identical with that of the expected product cinnamic acid.

Figure 2 is a pH-rate profile for the anhydride hydrolysis. The slope of 1.00 shows the expected first-order dependence on the hydroxide ion. From the relationship $k_0 = k_{\text{OH}} a_{\text{OH}}$, the second-order rate constant for alkaline hydrolysis of cinnamic anhydride is $k_{\text{OH}} = 169 M^{-1} \text{sec}^{-1}$.

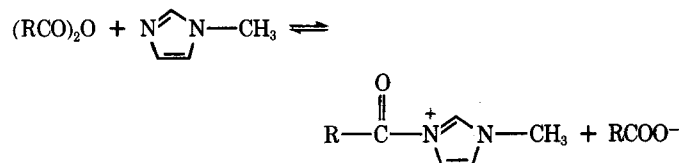
Catalysis by Pyridine, 4-Dimethylaminopyridine, and *N*-Methylimidazole—The hydrolysis of cinnamic anhydride catalyzed by pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole was studied in carbonate, tris(hydroxymethyl)aminomethane, and phosphate buffer. The catalyzed reaction was first order in the conjugate base form of the catalyst. Therefore, at any given pH, the observed pseudo-first-order rate constant is given by:

$$k_{\text{obs}} = k_0 + k_B[B] + k_C[C] \quad (\text{Eq. 5})$$

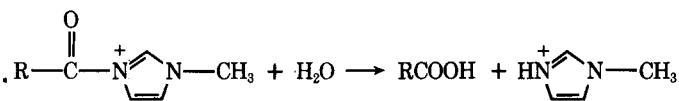
where k_C is the catalytic rate constant and $[C]$ is the molar concentration of the base form of the catalyst. Since k_0 and k_B are known, k_C can be calculated. The pKa values at 0.10 M ionic strength and 25° are 5.29 for pyridine, 9.68 for 4-dimethylaminopyridine (11), and 7.19 for *N*-methylimidazole (13). Table II gives typical results, showing the constancy of k_C and its reproducibility, at several catalyst concentrations. The k_C values obtained at several pH values are listed in Table III.

In view of the reproducibility of k_C at a given pH (Table II), the data of Table III indicate a pH dependency of k_C for pyridine and *N*-methylimidazole. Over the limited pH range studied, k_C can be described by $2.45 + 8.5 \times 10^4 a_{\text{OH}} M^{-1} \text{sec}^{-1}$, $13.50 + 1.01 \times 10^5 a_{\text{OH}} M^{-1} \text{sec}^{-1}$, and $1.87 \times 10^3 M^{-1} \text{sec}^{-1}$ for pyridine, *N*-methylimidazole, and 4-dimethylaminopyridine, respectively.

Although the mechanisms of these reactions have not yet been elucidated, it appears probable, based on the similar acetic anhydride reaction (14), that the catalysis occurs via the formation of an intermediate as shown for *N*-methylimidazole in Schemes II and III.



Scheme II



Scheme III

The pH-independent component of k_C describes the attack of water on the intermediate, whereas the pH-dependent component represents

Table IV—Effect of Acetonitrile on the Catalytic Rate Constant for the Hydrolysis of Cinnamic Anhydride^{a,b}

Acetonitrile Content, % v/v	$k_C, M^{-1} \text{sec}^{-1}$		
	Pyridine	<i>N</i> -Methylimidazole	4-Dimethylaminopyridine
3.9	3.51	13.89	1.96×10^3
13.5	1.89	10.53	1.91×10^3
23.1	0.90	6.22	1.73×10^3
32.8	0.40	3.70	1.46×10^3
42.4	0.17	1.96	0.86×10^3

^a At pH 8.86 and 25°; the buffer contained 0.004 M protonated tris(hydroxymethyl)aminomethane, 0.017 M of the buffer base, and 0.096 M KCl. ^b The concentrations of catalysts in their base forms were: pyridine, $1.21 \times 10^{-3} M$; *N*-methylimidazole, $2.89 \times 10^{-4} M$; and 4-dimethylaminopyridine, $1.38 \times 10^{-6} M$.

Table V—Third-Order Rate Constants for *N*-Methylimidazole-Catalyzed Reaction of Cinnamic Anhydride with Hydroxy Compounds in Acetonitrile at 25°^a

Hydroxy Compound ^b	$10^2 k_3, M^{-2} \text{sec}^{-1}$	
	Mean	SD ^c
Phenol	96.4	0.1
Isoamyl alcohol	10.7	0.2
<i>n</i> -Amyl alcohol	9.22	0.04
Isobutyl alcohol	7.88	0.05
<i>n</i> -Butyl alcohol	3.47	0.06
<i>n</i> -Propyl alcohol	3.24	0.03
Isopropyl alcohol	0.72	0.03
<i>sec</i> -Butyl alcohol	0.65	0.09
<i>tert</i> -Butyl alcohol	0.58	0.03

^a Initial anhydride concentration was $2.67 \times 10^{-5} M$. ^b Initial phenol concentration was 0.105 M, initial alcohol concentrations were 1.02–2.37 M, and the catalyst concentration was 0.14–1.12 M. ^c Six determinations for *n*-propyl alcohol; three determinations for the other compounds.

the attack by hydroxide ion. The magnitudes of the latter quantity, particularly for 4-dimethylaminopyridine, are uncertain because of the restricted pH range studied.

Medium Effects—The alkaline hydrolysis rate of cinnamic anhydride was decreased sharply by the addition of acetonitrile to the aqueous medium, as illustrated by these pseudo-first-order rate constants ($10^3 k_{\text{obs}}/\text{sec}^{-1}$) at 25° in a pH 8.86 buffer in the absence of added acetonitrile: 3.9% acetonitrile, 6.14; 13.5%, 3.72; 23.1%, 1.74; 32.8%, 0.96; and 42.4%,

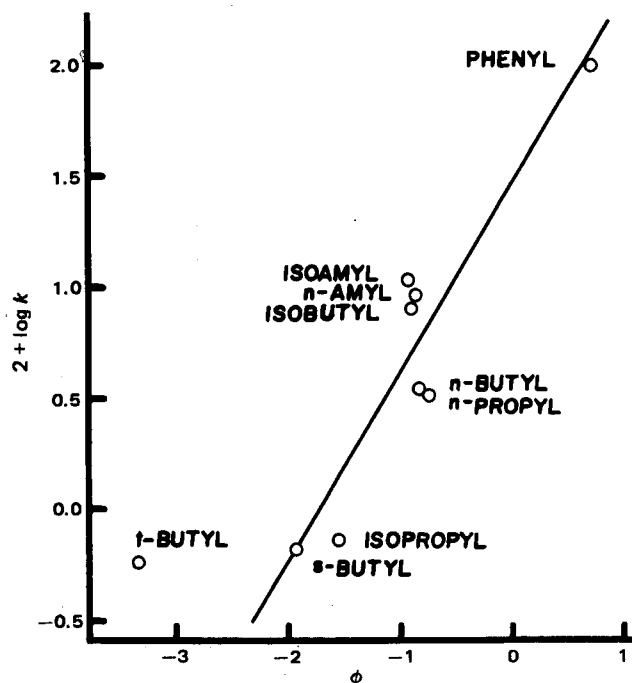


Figure 3—Correlation of rates of cinnamylation of hydroxy compounds (Table V) with substituent constant ϕ (17).

Table VI—Relative Catalytic Effectiveness of *N*-Methylimidazole and 4-Dimethylaminopyridine in Some Acylation Reactions (Pyridine = 1.00)

Reactants	Solvent	Relative Rate	
		<i>N</i> -Methylimidazole	4-Dimethylaminopyridine
Cinnamic anhydride + water	3.9% aqueous acetonitrile	3.96	558
Cinnamic anhydride + water	13.5% aqueous acetonitrile	5.57	1011
Cinnamic anhydride + water	23.1% aqueous acetonitrile	6.91	1922
Cinnamic anhydride + water	32.8% aqueous acetonitrile	9.25	3650
Cinnamic anhydride + water	42.4% aqueous acetonitrile	11.5	5058
Cinnamic anhydride + <i>n</i> -propanol	Acetonitrile	259	1.6×10^4
Acetic anhydride + isopropanol ^a	<i>N,N</i> -Dimethylformamide	362	1.7×10^4

^a Taken from Ref. 18.

0.60. Higher acetonitrile concentrations were not studied because of buffer insolubility.

The second-order catalytic rate constant k_C was measured for pyridine, *N*-methylimidazole, and 4-dimethylaminopyridine in water-acetonitrile mixtures (Table IV). All of the constants decreased as the organic component of the solvent increased, with the decrease being relatively greater the weaker the catalyst. This behavior (*i.e.*, reduction in reactivity as the solvent polarity decreases) indicates that the transition state is more polar than the initial state of the rate-determining step of the reaction. Rate-limiting formation of the onium-ion intermediate in Scheme II is consistent with this result.

This dependence of the rate on solvent polarity observed with the catalyzed hydrolysis of cinnamic anhydride in mixed aqueous solvents contrasts with the finding (15) that the rate of the *N*-methylimidazole-catalyzed reaction of acetic anhydride with isopropanol is relatively insensitive to solvent polarity for a series of organic solvents.

Cinnamoylation of Hydroxy Compounds—Kinetic studies of the reaction of cinnamic anhydride with *n*-propanol catalyzed by *N*-methylimidazole in acetonitrile solution showed that it was first order in the alcohol and in the catalyst. Therefore, the pseudo-first-order rate constant for the loss of anhydride may be written as:

$$k_{\text{obs}} = k_3[\text{alcohol}][\text{catalyst}] \quad (\text{Eq. 6})$$

Table V lists k_3 values for the *N*-methylimidazole-catalyzed cinnamoylation of some hydroxy compounds.

For *n*-propanol, k_3 was also measured with pyridine and 4-dimethylaminopyridine as the catalysts, yielding $1.25 \pm 0.003 \times 10^{-4} M^{-2} \text{sec}^{-1}$ for pyridine and $2.01 \pm 0.01 M^{-2} \text{sec}^{-1}$ for 4-dimethylaminopyridine.

The k_3 values of Table V correlate roughly with the basicity of the hydroxy compound as measured by the pK_a of the conjugate acid ROH₂⁺ (16). They are not correlated well by the Taft polar substituent constant σ^* perhaps because of a steric influence. Robinson and Matheson (17) defined a substituent constant ϕ , which includes the steric effect in the alkyl portion of esters. Figure 3 shows the correlation of k_3 values with ϕ . The equation of the regression line is:

$$\log k_3 = 0.844\phi - 0.56 \quad (\text{Eq. 7})$$

with correlation coefficient $r^2 = 0.93$ and a standard deviation about the regression line of 0.28 log k unit. (The value for *tert*-butyl alcohol is not included in the regression.) In general, this acylation reaction is faster for primary alcohols than for branched alcohols, probably for steric reasons; among the primary alcohols, the reaction rates parallel alcohol basicity.

Relative Catalytic Activity—Table VI collects relative rate data for several acylation reactions in various solvents for pyridine, *N*-methylimidazole, and 4-dimethylaminopyridine. For each entry (line) in Table VI, the relative rate is expressed as the ratio k_C (catalyst)/ k_C (pyridine) for that particular reaction and solvent.

In summary, the most important findings were that the reaction rate decreases as the solvent polarity decreases and that the catalytic activities of *N*-methylimidazole and of 4-dimethylaminopyridine relative to pyridine increase as the solvent polarity decreases. Both observations are consistent with the formation of the ionic onium intermediates (Scheme II). The intermediates formed from *N*-methylimidazole and 4-dimethylaminopyridine are capable of extensive charge delocalization relative to the acylpyridinium intermediate. As the solvent polarity decreases, the transition state leading to the intermediate is destabilized for all catalysts, but this effect is greatest for pyridine. Thus, the relative rate increases for the more powerful catalysts. This finding is indirect evidence for the intermediacy of the onium ion.

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