If the variance is constant at each point C, a fit of ln C *versus* time would require weighting each point proportional to the reciprocal of the variance, approximately C^2 in the case of constant CV. With constant variance, a zero-order plot would require no weighting.

From similar considerations, an estimate of σ^2 (equal to CV^2 in the case of constant CV and a first-order reaction) can be obtained from replicate determinations of the rate constant using the formula:

$$\Sigma w(k - \bar{k}_w)^2/(n - 1)$$

Where $\bar{k}_w$ is the weighted mean, n is the number of replications and w is $\Sigma(t - \bar{t})^2$. (Term w is equal to $k^2\Sigma(t - \bar{t})^2$ in the case of ln k). A shortcut formula for $\Sigma w(k - \bar{k})^2$ is $\Sigma wk^2 - \Sigma w(\bar{k}w)^2$.

An example of some calculations for the combination ab follows. The duplicate determinations of the rate constants were 5.86 and 8.22, and $\Sigma(t - \bar{t})^2$ was 0.0125 for each determination:

(1) The weighted average, $\bar{k}_w$, = [(0.0125)5.86 + (0.0125)8.22]/(0.025 + 0.025) = 7.04 (since the weights are equal, the weighted average equals the ordinary arithmetic average).

(2) σ^2 (One degree of freedom) from the duplicates = $[\Sigma wk^2 - \Sigma w(\bar{k}_w)^2]/(n - 1)$ = [(0.0125)(5.86)^2 + (0.0125)(8.22)^2 − 0.025 (7.04)^2]/1 = 0.0348

(3) The weighted average of ln k = ln k_w = [(5.86)^2(0.0125) ln 5.86 + (8.22)^2(0.0125)ln 8.22]/[(5.86)^2(0.0125) + (8.22)^2(0.0125)] = 1.99

The approximations inherent in the method should be kept in mind, namely the transformation to logs and the fact that observed values are used rather than true values in the weighting. However, if the CV is not large, the reliability of any conclusions from this analysis should not be in doubt.

REFERENCES

(1) J. A. Plaizier-Vercammen and R. E. De Neve, *J. Pharm. Sci.*, **69**, 1403 (1980).

(2) D. E. Fonner, Jr., J. R. Buck, and G. S. Banker, *ibid*, **59**, 1587 (1970).

(3) S. Dincer and S. Ozdurmus, *ibid*, **66**, 1070 (1977).

(4) O. L. Davies, "Design and Analysis of Industrial Experiments," Hafner, New York, N.Y., 1963.

Kinetics and Mechanism of Hydroxy Compound Cinnamoylation in Acetonitrile Catalyzed by *N*-Methylimidazole and 4-Dimethylaminopyridine

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Abstract □ The kinetics of reaction of the acylating agents *trans*-cinnamic anhydride and *trans*-cinnamoyl chloride with the hydroxy compounds *n*-propyl alcohol and water in the presence of *N*-methylimidazole and 4-dimethylaminopyridine were studied spectrophotometrically in acetonitrile solution at 25°. The acid chloride reacted *via* the intermediate formation of the *N*-acyl catalyst, which underwent general base-catalyzed reaction with the hydroxy compound. The anhydride did not form the *N*-acyl intermediate, but instead underwent direct general base catalysis. In the presence of water, all systems formed the *N*-acyl intermediate. The mechanistic route followed by the system was determined by the nucleophilicity of the catalyst, the ability of the leaving group, and the polarity of the solvent.

Keyphrases □ Cinnamoylation—hydroxy compounds in acetonitrile, catalyzed by *N*-methylimidazole and 4-dimethylaminopyridine, kinetics □ Kinetics—cinnamoylation of hydroxy compounds in acetonitrile □ 4-Dimethylaminopyridine catalysis—cinnamoylation of hydroxy compounds, kinetics □ *N*-Methylimidazole catalysis—cinnamoylation of hydroxy compounds, kinetics

Acylation is an important synthetic and analytical reaction. Pyridine is the classical acylation catalyst, but during the past decade more powerful catalysts have been introduced, most notably 4-dimethylaminopyridine, which has been used in synthesis (1–4) and analysis (5–8). More recently this laboratory introduced *N*-methylimidazole as an analytical acylation catalyst (9–13).

Acylation reactions are usually carried out in nonaqueous solvents. Although the mechanisms of acyl transfer in aqueous systems have been well studied (14–16), the nature of these reactions in nonhydroxylic solvents is not yet understood. Among the features that have been suggested as important in determining the kinetics and mechanisms of these reactions are the balance between nucleophilic and general base catalysis, the complex nature of rate equations (17–19), the possibility of kinetically significant ion-pair formation (3, 20, 21), competing reactions (22), and formation of molecular complexes (23). Some of these factors were addressed in a recent study on the kinetics of acetylation of alcohols by acetic anhydride and acetyl chloride, catalyzed by *N*-methylimidazole and 4-dimethylaminopyridine, in acetonitrile solution (24).

Since the cinnamoyl group, $C_6H_5CH{=}CHCO$, is a powerful UV chromophore, it is an interesting analytical acyl group (25, 26). An earlier study (27) reported the kinetics of hydrolysis of *trans*-cinnamic anhydride and of its reactions with some alcohols, catalyzed by pyridine, 4-dimethylaminopyridine, and *N*-methylimidazole, but the study was not designed to explore the detailed nature of the mechanism. In the present paper the reactions of *trans*-cinnamic anhydride and *trans*-cinnamoyl chloride with *n*-propyl alcohol and water, in acetonitrile solution, are described. The catalysts were *N*-methylimidazole and 4-dimethylaminopyridine; the reactions were studied by UV spectrophotometry.

EXPERIMENTAL

Materials—*trans*-Cinnamoyl chloride[1] was distilled under reduced pressure to give colorless crystals, mp 34–35° [lit. mp 35–36° (28)]. The molar absorptivity at 298 nm, in acetonitrile, was 2.42 × 10^4 liter/mole cm. *trans*-Cinnamic anhydride was synthesized as previously described (27), mp 136–137° [lit. mp 136° (29)]. Its molar absorptivity at 294 nm was 4.26 × 10^4 liter/mole cm. *N*-Methylimidazole[1] was distilled under

[1] Aldrich Chemical Co.

0022-3549/83/0400-0366$01.00/0

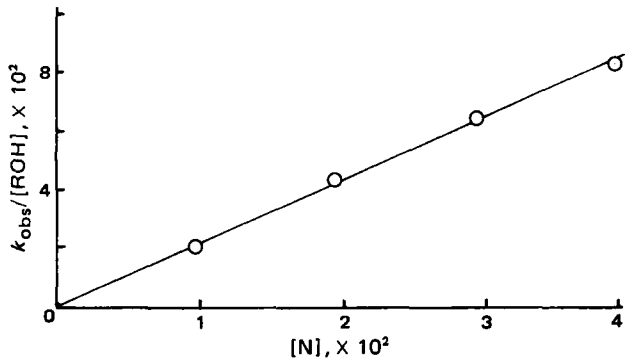


Figure 1—*Plot of Eq. 1 for the cinnamoyl chloride–dimethylaminopyridine–n-propyl alcohol system. Initial cinnamoyl chloride concentration was 2.71 × 10^{-5} M and the alcohol concentrations ranged from 0.08 to 0.61* M.

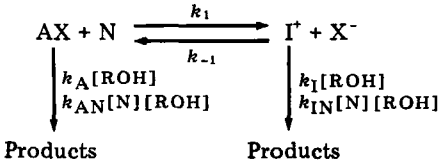
reduced pressure, bp 55° at 14–16 mm Hg. 4-Dimethylaminopyridine[1] was recrystallized from *n*-hexane, mp 113.5° [lit. 112–113° (3)]. Acetonitrile[2] was spectrophotometric grade.

Procedures—A typical kinetic run was carried out as follows. Solutions of the acylating agent, the catalyst, and the hydroxy compound were prepared in acetonitrile. Appropriate portions of the catalyst and hydroxy compound were mixed to give a volume of 4.8 ml; this solution was equilibrated at 25°. Reaction was initiated by adding 0.2 ml of the acylating agent solution. The progress of the reaction was followed by recording the absorbance, at a wavelength suitable for the particular system, as a function of time[3]. The absorbance at the completion of the reaction was measured after the lapse of at least 10 half-lives. In all cases the catalyst and hydroxy compound were in large excess to establish pseudo first-order conditions with respect to the acylating agent.

For the measurement of the rate of intermediate formation in the cinnamic anhydride–dimethylaminopyridine system in aqueous acetonitrile, 3.5 ml of a mixture of catalyst, water, and acetonitrile was equilibrated in a 1-cm spectrophotometer cell in the thermostated cell compartment. Fifty microliters of a solution of cinnamic anhydride in acetonitrile was added to the cell and the mixture was stirred. The absorbance was monitored at 350 nm; recording of the absorbance began <10 sec after adding the acylating agent. All data reported are at 25.0 ± 0.1°.

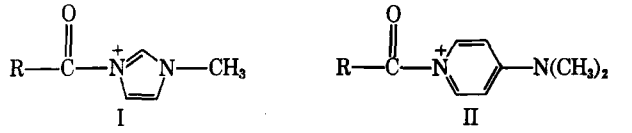
RESULTS AND DISCUSSION

Kinetic Scheme—The reactions of acetic anhydride and acetyl chloride in acetonitrile, in the presence of *N*-methylimidazole or 4-dimethylaminopyridine, were previously described (24). This same kinetic scheme (Scheme I) was used in the present study to analyze the kinetic data.



Scheme I

In Scheme I, AX represents the acylating agent (cinnamic anhydride or cinnamoyl chloride), N is the catalyst (*N*-methylimidazole or 4-dimethylaminopyridine), ROH is the hydroxy compound (*n*-propyl alcohol or water), X^- is the leaving group (cinnamate or chloride ion), and I^+ is the *N*-cinnamoylated catalyst, *i.e.*, I or II, where R is $C_6H_5CH{=}CH$.



Scheme I includes several possible kinds of kinetic behavior, dependent on the relative values of the rate constants (especially the ratio k_1/k_{-1},

[2] Burdick and Jackson.

[3] Cary Model 14 spectrophotometer equipped with a thermostated cell compartment.

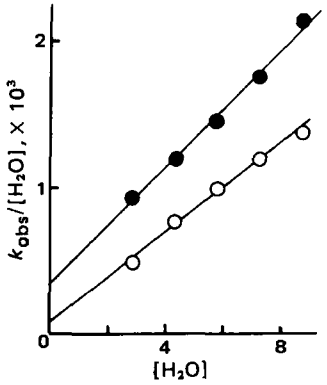


Figure 2—*Plot of Eq. 2 for the hydrolysis of cinnamoyl chloride in acetonitrile with 4-dimethylaminopyridine as catalyst. Initial cinnamoyl chloride concentration: 8.05 × 10^{-5}* M. *Catalyst concentrations: (○) 7.81 × 10^{-3}* M, *(●) 13.02 × 10^{-3}* M.

which largely determines the level of intermediate I^+ in the system). The rate constants for product formation can be described as: (k_A) the uncatalyzed reaction, (k_{AN}) general base catalysis, (k_I) nucleophilic reaction, and (k_{IN}) general base catalysis of the nucleophilic reaction.

The general experimental approach was to examine the reaction mixture spectrophotometrically for evidence of the presence of I^+. The kinetics were followed by observing the decrease in concentration of either AX or I^+ on reaction with ROH. Rate constants were evaluated from semi-logarithmic pseudo first-order plots. Derivations for those systems that can be described by the same rate equations developed for the acetylation kinetics (24) are not presented in this paper.

Cinnamoyl Chloride–Dimethylaminopyridine–*n*-Propyl Alcohol—A mixture of cinnamoyl chloride and dimethylaminopyridine exhibited UV absorption at longer wavelengths than either of the solution components. The new spectrum is ascribed to *N*-cinnamoyl dimethyl aminopyridinium chloride. In the presence of excess catalyst, the intermediate was formed very rapidly; in the presence of excess cinnamoyl chloride, up to several minutes was required. Quantitative conversion to the intermediate was demonstrated by using various amounts of catalyst and cinnamoyl chloride. The intermediate shows λ_{max} 350 nm, log ϵ_{max} 4.6. This system belongs to the special case $k_1 >>> k_{-1}$ in Scheme I; so, as shown previously (24), the kinetics may be described by:

$$\frac{k_{obs}}{[ROH]} = k_I + k_{IN}[N] \qquad \text{(Eq. 1)}$$

In Eq. 1, k_{obs} is the observed first-order rate constant and [N] is the free catalyst concentration. Since the intermediate is quantitatively formed, $[N] = [N]_0 - [AX]_0$, where the subscripted quantities are initial concentrations.

Pseudo first-order behavior was observed for >3 half-lives, with reactions monitored at 350 nm. The k_{obs} values were linearly dependent on the *n*-propyl alcohol concentration at constant $[N]_0$. Figure 1 shows the plot according to Eq. 1. The estimates $k_I = 0.14 \times 10^{-3}\ M^{-1}\ sec^{-1}$ (*SD*

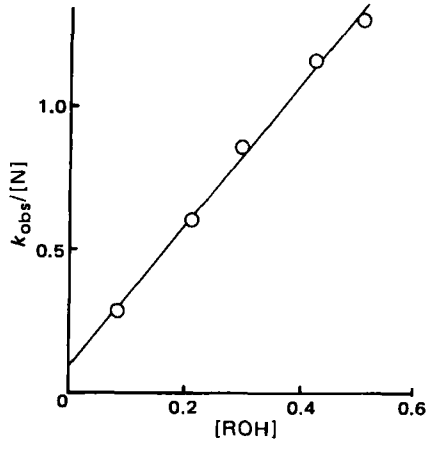


Figure 3—*Plot of Eq. 3 for the cinnamic anhydride–dimethylaminopyridine–n-propyl alcohol system. Catalyst concentration: 0.0125* M, *initial anhydride concentration: 3.50 × 10^{-4}* M.

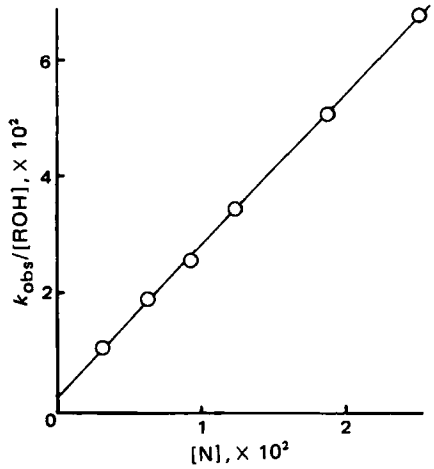


Figure 4—*Plot of Eq. 4 for the cinnamic anhydride–dimethylaminopyridine–n-propyl alcohol system. Alcohol concentration: 0.426* M.

2.6×10^{-3}) and $k_{IN} = 2.18\ M^{-2}\ sec^{-1}$ (*SD* 0.10) were obtained from this plot, thus k_I is not significantly different from zero.

Cinnamoyl Chloride–*N*-Methylimidazole–*n*-Propyl Alcohol—This system also gave quantitative intermediate formation, with λ_{max} 340 nm. The data were analyzed using Eq. 1, yielding $k_I = 5.3 \times 10^{-3}\ M^{-1}\ sec^{-1}$ (*SD* 1.6×10^{-3}) and $k_{IN} = 0.229\ M^{-2}\ sec^{-1}$ (*SD* 0.007).

Cinnamoyl Chloride–Dimethylaminopyridine–Water—Since the intermediate was formed quantitatively in this system, the loss of intermediate on reaction with water was followed at 350 nm. The water concentration ranged from 2.8 to 8.8 *M*. First-order kinetics were observed for the higher water concentrations, but significant deviations were seen at low water concentrations. The pseudo first-order rate constants were linearly dependent on the catalyst concentration, but did not vary linearly with the water concentration. The dependence suggested a rate equation both first- and second-order in water:

$$k_{obs} = (k_I + k_{IN}[N])[H_2O] + (k_I^W + k_{IN}^W[N])[H_2O]^2 \quad \text{(Eq. 2)}$$

If Eq. 2 describes the system, a plot of $k_{obs}/[H_2O]$ *versus* $[H_2O]$ should be linear and, from the dependence of the intercept and slope on [N], the individual constants can be estimated (Fig. 2). The rate constants found were $k_I = -2.8 \times 10^{-3}\ M^{-1}\ sec^{-1}$ (*SD* 3.2×10^{-3}), $k_{IN} = 0.045\ M^{-2}\ sec^{-1}$ (*SD* 0.012), $k_I^W = 7.2 \times 10^{-5}\ M^{-2}\ sec^{-1}$ (*SD* 8.1×10^{-5}), and $k_{IN}^W = 0.010\ M^{-3}\ sec^{-1}$ (*SD* 0.001). Thus k_I and k_I^W are not significantly different from zero. Scheme I requires modification for this system to include catalysis of the "IN" route by a molecule of water.

The cinnamoyl chloride–*N*-methylimidazole–water system was also examined. At low water concentrations the kinetic behavior was similar to that described for dimethylaminopyridine, but at high water concentrations serious deviations from first-order kinetics were seen. This may be a consequence of the formation of cinnamic anhydride *in situ*, as postulated for the analogous acetyl system (24).

Cinnamic Anhydride–Dimethylaminopyridine–*n*-Propyl Alcohol—The mixture of cinnamic anhydride and dimethylaminopyridine in acetonitrile exhibited an absorption spectrum that nearly could be accounted for as the sum of the spectra of the two solutes. But at high concentrations (~0.2 *M* for each solute), some absorption at longer wavelength was seen, presumably a consequence of the formation of a small amount of the intermediate. In this system, therefore, $k_1 \ll k_{-1}$. Reaction may take place *via* AX, I^+, or both. This kinetic system was described previously and (24) leads to:

$$\frac{k_{obs}}{[N]} = k_I + \left(\frac{k_A}{[N]} + k_{AN}\right)[ROH] \quad \text{(Eq. 3)}$$

and

$$\frac{k_{obs}}{[ROH]} = k_A + \left(\frac{k_1}{[ROH]} + k_{AN}\right)[N] \quad \text{(Eq. 4)}$$

If [N] is held constant and [ROH] is varied, Eq. 3 is plotted; if [ROH] is constant and [N] varies, Eq. 4 is used. From the slopes and intercepts the rate constants can be evaluated.

The reaction was followed at 320 nm, and good first-order kinetics were followed for >3 half-lives. Figures 3 and 4 show the plots according to Eqs. 3 and 4, respectively. The values found were: $k_1 = 0.096\ M^{-1}\ sec^{-1}$ (*SD* 0.039); $k_A = 0.33 \times 10^{-2}\ M^{-1}\ sec^{-1}$ (*SD* 0.16×10^{-2}); and $k_{AN} = 2.18\ M^{-2}\ sec^{-1}$ (*SD* 0.09). Evidently this reaction occurs mainly by the general base (k_{AN}) route; k_A is essentially zero, as verified in the corresponding *N*-methylimidazole system.

Table I—Mechanisms of Cinnamoylation Reactions in Acetonitrile [a]

Catalyst	Leaving Group: Chloride	Leaving Group: Cinnamate
N-Methylimidazole	*Via* I^+	*Via* AX
4-Dimethylaminopyridine	*Via* I^+	Mainly *via* AX

[a] Symbols as defined in Scheme I.

Cinnamic Anhydride–*N*-Methylimidazole–*n*-Propyl Alcohol—This system displayed the same kinetic behavior as the preceding system and Eqs. 3 and 4 were applied. The kinetics were first-order for >3 half-lives. The rate constants were $k_1 = 0.029 \times 10^{-2}\ M^{-1}\ sec^{-1}$ (*SD* 0.037×10^{-2}), $k_A = 0.69 \times 10^{-4}\ M^{-1}\ sec^{-1}$ (*SD* 0.96×10^{-4}), and $k_{AN} = 2.16 \times 10^{-2}\ M^{-2}\ sec^{-1}$ (*SD* 0.12×10^{-2}). Clearly k_1 and k_A are not significantly different from zero.

Cinnamic Anhydride–*N*-Methylimidazole–Water—On the addition of cinnamic anhydride to a solution of *N*-methylimidazole in aqueous methanol, light absorption was observed at wavelengths longer than the spectra of the added solutes, implying that the increased polarity of the medium (relative to dry acetonitrile) promotes formation of the intermediate. This behavior was seen also in the corresponding acetic anhydride system (24), which was described by:

$$k_{obs} = \left[\frac{k_I' + R'k_A'}{1 + R'}\right][H_2O] \quad \text{(Eq. 5)}$$

where $k_I' = k_1 + k_{IN}[N]$, $k_A' = k_A + k_{AN}[N]$, and $R'\ [X^-]/K[N] + k_I'[H_2O]/k_1[N]$ with $K = k_1/k_{-1}$. As the water concentration increases, both K and k_1 will increase and R' will decrease. At high water concentrations R' approaches zero and k_{obs} approaches $k_I'[H_2O]$: the reaction proceeds solely *via* the intermediate. At extremely low water concentration, R' becomes very large and k_{obs} approaches $k_A'[H_2O]$; the reaction then occurs solely *via* the anhydride. At intermediate water concentrations where R' is finite, both routes may be involved. According to Eq. 5, moreover, if R' is finite and varies during the course of a reaction, deviations from first-order kinetics may be observed.

The reaction was monitored at 340 nm. At low water concentrations (0.56–2.56 *M*) significant deviations from first-order kinetics were seen. The k_{obs} values estimated from the first half-life were linearly dependent on [N] and $[H_2O]$. At high water concentrations (11.1–27.8 *M*), the reactions were strictly first-order and k_{obs} was directly dependent on [N]. The dependence on water concentration in this region, however, was not linear, suggesting the possible involvement of a second molecule of water.

Cinnamic Anhydride–Dimethylaminopyridine–Water—This system showed spectral and kinetic behavior very similar to that observed with the *N*-methylimidazole system. During the very early stage after mixing the components, the absorbance at 350 nm (attributed to the intermediate) increased on a time scale accessible to measurement. At time zero, the concentrations $[I^+]$ and $[X^-]$ are very small, so the back-reaction (k_{-1} step) and reaction with water (k_I' step) are negligible. Hence the initial rate, measured as the absorbance change per sec, is equal to $\epsilon_I k_1[N]_0[AX]_0$, where ϵ_I is the molar absorptivity of I^+. Over the first 20 sec of reaction the absorbance was a linear function of time. Experiments were carried out at several water concentrations, with these results: $[H_2O]$ 5.65 *M*, k_1 46.5 M^{-1} sec−1; $[H_2O]$ 10.9 *M*, k_1 57.5 $M^{-1}\ sec^{-1}$; $[H_2O]$ 16.4 *M*, k_1 69.7 $M^{-1}\ sec^{-1}$; $[H_2O]$ 21.9 *M*, k_1 82.0 $M^{-1}\ sec^{-1}$; and $[H_2O]$ 27.3 *M*, k_1 106.4 $M^{-1}\ sec^{-1}$.

Catalytic Mechanisms—Table I summarizes the qualitative observations of this study. The acid chloride reacts by forming the intermediate

Table II—Comparison of Rate Constants for Some Acylation Reactions in Acetonitrile at 25°

Catalyst [a]	Alcohol	Acyl Group [b]	Acid Chloride [c] k_{IN}	Anhydride [c] k_{AN}
NMIM	*n*-Propyl Alcohol	Acetyl	0.50	0.0403
NMIM	*n*-Propyl Alcohol	Cinnamoyl	0.23	0.0216
DMAP	*n*-Propyl Alcohol	Cinnamoyl	2.18	2.18
NMIM	Isopropyl Alcohol	Acetyl	0.053	0.0041
DMAP	Isopropyl Alcohol	Acetyl	1.3	0.5

[a] NMIM = *N*-methylimidazole, DMAP = 4-dimethylaminopyridine. [b] Acetyl data from Ref. 24. [c] Units are $M^{-2}\ sec^{-1}$.

acylammonium ion (I^+ in Scheme I), whereas the anhydride does not form the intermediate unless the catalyst is very powerful. When the solvent polarity is increased by adding water, intermediate formation is favored even in the anhydride systems. These conclusions are identical with those reached in the study of acylations with acetyl chloride and acetic anhydride (24). This insensitivity of mechanistic pathway to the nature of the acyl group suggests that the mechanism is determined primarily by three factors: the catalyst nucleophilicity, the leaving group ability, and the solvent polarity. Increases in any of these factors will promote the formation of intermediate and the possibility of product formation through the k_I and k_{IN} routes. That the acid anhydrides react mainly by the general base catalyzed (k_{AN}) route, even in the presence of strong nucleophilic catalysts, has been an unexpected finding of these studies.

Table II lists rate constants for the cinnamoylation reactions reported here and includes, for comparison, some data (24) on acetylation reactions. Several patterns can be seen. In comparable systems, the general base catalysis quantities k_{AN} and k_{IN} are larger for 4-dimethylaminopyridine than for *N*-methylimidazole, reflecting the greater base strength of the former catalyst. The acetyl substrates are two-fold more reactive than the corresponding cinnamoyl compounds. For a given acyl group and alcohol, the chloride–anhydride (k_{IN}/k_{AN}) ratio is >10 for *N*-methylimidazole and close to unity for 4-dimethylaminopyridine. Since k_{IN} describes the reaction of the intermediate, this indicates that *N*-methylimidazole is a better leaving group than is a carboxylate, whereas 4-dimethylaminopyridine is about as good a leaving group as a carboxylate. These relationships are not expected on the basis of the leaving group basicities, but they may reflect a relatively greater resonance stabilization of the *N*-acyl-4-dimethylaminopyridinium intermediate.

REFERENCES

(1) W. Steglich and G. Höfle, *Angew. Chem. Int. Ed.*, **8**, 981 (1969).

(2) G. Höfle and W. Steglich, *Synthesis*, **1972**, 620.

(3) G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem. Int. Ed.*, **17**, 569 (1978).

(4) S. S. Wang, J. P. Tam, B. S. Wang, and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **18**, 459 (1981).

(5) K. A. Connors and K. S. Albert, *J. Pharm. Sci.*, **62**, 845 (1973).

(6) E. L. Rowe and S. M. Machkovech, *ibid.*, **66**, 273 (1977).

(7) V. Fell and C. R. Lee, *J. Chromatogr.*, **121**, 41 (1976).

(8) F. de Fabrizio, *J. Pharm. Sci.*, **69**, 854 (1980).

(9) K. A. Connors and N. K. Pandit, *Anal. Chem.*, **50**, 1542 (1978).

(10) R. Wachowiak and K. A. Connors, *ibid.*, **51**, 27 (1979).

(11) S. L. Wellons, M. A. Carey, and D. K. Eider, *ibid.*, **52**, 1374 (1980).

(12) A. S. Bittner, L. E. Harris, and W. F. Campbell, *J. Agr. Food Chem.*, **28**, 1242 (1980).

(13) N. K. Pandit, A. O. Obaseki, and K. A. Connors, *Anal. Chem.*, **52**, 1678 (1980).

(14) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N.Y., 1966.

(15) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N.Y., 1969.

(16) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N.Y., 1971.

(17) S. A. Lapshin, V. A. Dadali, Y. S. Simanenko, and L. M. Litvinenko, *Zh. Org. Khim.*, **13**, 586 (1977).

(18) V. A. Dadali, I. A. Tsupilo, and L. M. Litvinenko, *ibid.*, **13**, 211 (1977).

(19) I. H. Pitman and T. Higuchi, *J. Org. Chem.*, **40**, 378 (1975).

(20) E. M. Cherkasova, S. V. Bogatkov, and Z. P. Golivina, *Russ. Chem. Rev. (Engl. Transl.)*, **46**, 246 (1977).

(21) L. M. Litvinenko, V. A. Savelova, V. A. Shatskaya, and T. N. Sadovskaya, *Dokl. Akad. Nauk SSSR*, **198**, 844 (1971).

(22) A. Hassner, L. R. Krepski, and V. Alexanian, *Tetrahedron*, **34**, 2069 (1978).

(23) E. Guibe-Jampel, G. Le Corre, and M. Wakselman, *Tetrahedron Lett.*, **1979**, 1157.

(24) N. K. Pandit and K. A. Connors, *J. Pharm. Sci.*, **71**, 485 (1982).

(25) W. H. Hong and K. A. Connors, *Anal. Chem.*, **40**, 1273 (1968).

(26) K. A. Connors and W. H. Hong, *Anal. Chim. Acta*, **43**, 334 (1968).

(27) S.-F. Lin and K. A. Connors, *J. Pharm. Sci.*, **70**, 235 (1981).

(28) R. Adams and L. H. Ulrich, *J. Am. Chem. Soc.*, **42**, 605 (1920).

(29) J. D. M. Simpson and S. S. Israelstam, *J. S. African Chem. Inst.*, **2**, 170 (1949).

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Solvent Effects on the Cinnamoylation of *n*-Propyl Alcohol Catalyzed by *N*-Methylimidazole and 4-Dimethylaminopyridine

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Abstract □ The kinetics of reaction of *trans*-cinnamic anhydride or *trans*-cinnamoyl chloride with *n*-propyl alcohol, catalyzed by *N*-methylimidazole or 4-dimethylaminopyridine, were studied spectrophotometrically at 25° in methyl ethyl ketone, ethylene dichloride, methylene chloride, and toluene. The acid chloride reacted in all solvents *via* the intermediate formation of the *N*-acyl catalyst, which underwent reaction with the alcohol catalyzed by another molecule of the base. The anhydride did not form the intermediate in any of the solvents, but underwent direct general base catalysis. The rate of the anhydride reactions was not sensitive to solvent polarity, whereas the rate of the chloride reactions tended to increase as the solvent polarity decreased. A kinetic analysis is given of the effect of ion-pair formation on the kinetics of acyl transfer in systems where the charged *N*-acyl catalyst intermediate is formed.

Keyphrases □ Cinnamoylation—of *n*-propyl alcohol, catalysis by *N*-methylimidazole and 4-dimethylaminopyridine, solvent effects □ 4-Dimethylaminopyridine—catalyses, cinnamoylation of *n*-propyl alcohol □ *N*-methylimidazole—catalyses, cinnamoylation of *n*-propyl alcohol

Although the kinetics and mechanisms of acyl transfer reactions in water have been carefully studied (in large part because such reactions serve as models for enzyme-catalyzed reactions), acyl transfers in nonaqueous media are less well understood despite their great importance in synthesis and analysis. The relatively recent introduction of powerful acylation catalysts like 4-dimethylaminopyridine (1) and *N*-methylimidazole (2) has stimulated in-

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