Nucleophilic Reactions of 1-(N,N-Dimethylcarbamoyl)pyridinium Chloride[1a]

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A detailed kinetic study of nucleophilic reactions of 1-(N,N-dimethylcarbamoyl)pyridinium chloride (I) in water at 25° has been carried out. Direct nucleophilic displacements characterize the reactions of I with nucleophiles as determined by kinetic and product analyses. Only hydroxide and water terms were found in the buffer concentration independent rate constants (k_0) at various pH values; no hydronium ion catalysis was found up to 1 M HCl. The water term is not due to a SN1 mechanism, but rather is due to a direct nucleophilic interaction of water with I because of: (1) the moderate kinetic solvent isotope effect of 2.26; (2) a ΔS^* value of -27 e.u.; (3) the lack of a mass law effect in pyridine buffers. A linear free-energy correlation of the reactivity of neutral and anionic nucleophiles to I compared to p-nitrophenyl acetate in water at 25° indicates that anionic nucleophiles do not show a special reactivity to the cationic substrate, I, as compared to the neutral p-nitrophenyl acetate substrate.

1-(N,N-Dimethylcarbamoyl)pyridinium chloride (I) was prepared in this laboratory[2] in order to investigate the solvolytic properties of stable acylpyridinium compounds. Although I is not stable in nonhydroxylic solvents (ionic decomposition takes place forming dimethylcarbamoyl chloride and pyridine), it is relatively stable in neutral or acidic hydroxylic solvents.[2]

In view of previous work on acylpyridinium compounds and carbamoyl derivatives containing good leaving groups, several mechanisms are feasible for the solvolysis of I. A general base catalyzed hydrolysis of I would not be an unreasonable expectation as evidence has been obtained which suggests that the acetylpyridinium ion undergoes general base catalyzed hydrolysis.[3] The large solvent kinetic isotope effect[4] of 5.5 for the hydrolysis of acetylpyridinium ion also suggests a general catalysis, although Bunton and Shiner[5] have proposed an alternate explanation based on a model for secondary solvent isotope effects.

Dimethylcarbamoyl chloride hydrolyzes *via* a SN1 mechanism as demonstrated by its lack of reactivity to hydroxide ion, its small ΔS^* value, its independence of rate of disappearance on the concentration of added strong nucleophiles, and the trapping of dimethylcarbamoyl derivatives by added nucleophiles.[6]

Mechanistic studies on carbamoyl phosphate hydrolysis have been carried out, but conflicting results and interpretations have been reported. Halmann, et al.,[7] claim that mainly C–O bond breaking occurs over the pH range 0–5 by carrying out the reaction in H_2O^{18} and analyzing for the O^{18} content of the phosphate released. In later work Allen and Jones[8] claim that C–O cleavage occurs for the neutral ($pK_1 = 1.1$)[8] and dianionic species, and that P–O cleavage occurs for the monoanionic species ($pK_2 = 4.9$). These latter studies were also carried out in H_2O^{18}, and the amount of O^{18} incorporation into phosphate was measured.

On the basis of low ΔS^* values ($+12.3$ to 4.1 e.u.) for the hydrolysis of the neutral, mono-, and dianionic forms of carbamoyl phosphate, the low solvent kinetic isotope effects for these three forms, the nearly equal rate of solvolysis of the mono- and dianionic forms of carbamoyl phosphate, the finding of C–O bond cleavage, and the isolation of carbamoyl azide by added azide which does not increase the rate of disappearance of carbamoyl phosphate, Halmann, et al.,[7] proposed a SN1 mechanism of hydrolysis for carbamoyl phosphate in its neutral, mono-, and dianionic forms with mono-anionic, dianionic, and trianionic phosphate as the leaving groups. Also, Halmann, et al., present evidence for the capture of the carbamoyl cation with azide ion. On the basis of this earlier work we were led to investigate the mechanism of the solvolysis of the 1-(N,N-dimethylcarbamoyl)pyridinium ion, as pyridine is a good leaving group with a pK_a of 5.2 which lies between the pK of monoanionic phosphate (2.1) and dianionic phosphate (7.2) and is considerably less basic than trianionic phosphate ($pK_a = 12.3$). It might be expected on the basis of Halmann's work, therefore, that I might undergo hydrolysis by a SN1 mechanism. In the case of phenyl and p-nitrophenyl dimethylcarbamate, however, specific base catalyzed hydrolysis is important as demonstrated by the sizeable hydroxide ion terms in the rate equation.[9] In this latter case, the pK_a values of the leaving groups are 9.98 and 7.15, respectively. These reactions, however, were not studied at pH values less than 12.6 so the mechanism and relative magnitude of the water reaction remain unknown.

In the later work by Allen and Jones[8] it was concluded that carbamoyl phosphate does not undergo SN1 hydrolysis in the monoanionic form because of their finding of P–O bond cleavage, which has a pH profile very similar to the pH profile of the concentration of the monoanionic substrate. Additional work by these authors on azide trapping contests Halmann's[7] view that azide traps the carbamoyl cation. The result of

(1) This investigation was supported in part by Public Health Service Grant G. M. 11834–02 from the National Institutes of Health; (b) author to whom inquiries should be addressed.

(2) S. L. Johnson and K. A. Rumon, *J. Phys. Chem.*, **68**, 3149 (1964).

(3) C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, Jr., *Tetrahedron Letters*, **14**, 458 (1961).

(4) V. Gold and A. R. Butler, *J. Chem. Soc.*, 4362 (1961).

(5) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 3207 (1961).

(6) H. K. Hall, Jr., *ibid.*, **77**, 5993 (1955).

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(8) C. M. Allen, Jr., and M. E. Jones, *Biochemistry*, **3**, 1238 (1964).

(9) L. W. Dittert, Ph.D. Thesis, University of Wisconsin, School of Pharmacy, 1961.

their experiments with carbamoyl phosphate, using cyanate and carbamoyl azide in control experiments, indicates that azide is trapping cyanate. The amount of trapping of an intermediate at pH <3 is 4% or less, and as the pH increases above 3 the amount of trapping increases as the concentration of monoanionic phosphate decreases. These authors prefer an internal elimination by P–O bond cleavage giving metaphosphate and the carbamate ion (which rapidly gives ammonia and carbon dioxide) for the monoanionic carbamoyl phosphate, and an elimination by C–O bond cleavage giving cyanate and phosphate for the dianionic carbamoyl phosphate.

A mechanistic study of N,N-diethylcarbamoyl phosphate hydrolysis has been conducted by Lapidot and Samuel.[10] The monoanion in this case was found to have much greater reactivity than the neutral species or the dianion; C–O bond cleavage was found for the mono- and dianion and P–O bond cleavage was found for the acid-catalyzed hydrolysis of the neutral species. A low solvent kinetic isotope effect and a low ΔS^* value was found for the monoanionic species, which, coupled with the C–O bond cleavage, led the authors to suggest a SN1 solvolytic mechanism.

Experimental Section

Materials. Dimethylcarbamoylpyridinium chloride was prepared as previously described.[2] Reagent grade inorganic salts were used without further purification. Fisher Certified potassium chloride, hydroxylamine hydrochloride, monobasic and dibasic potassium phosphate, and sodium formate, Baker reagent grade sodium nitrite, potassium acetate, sodium fluoride, potassium carbonate, and potassium bicarbonate, Eastman White Label sodium azide, and Fisher primary standard tris(hydroxylmethyl)aminomethane (Tris) were used. Baker reagent grade pyridine was refluxed overnight over calcium hydride and distilled. Aldrich imidazole was recrystallized from ethanol and sublimed. The water used in the experiments was distilled water passed through an Illco-Way research model deionizer. Stuart Oxygen Co. 99.5% deuterium oxide and Merck and Co. deuterium chloride (>99.4% isotopic purity) in deuterium oxide were used.

Buffer Solutions. The buffer solutions were prepared by dissolving the appropriate salts in water, or by partially neutralizing a salt with HCl. The ionic strength was maintained at 1.0 by adding potassium chloride to the buffers. The following buffers were used: carbonate, Tris, phosphate, acetate, and formate. Potassium salts were used for all the buffers except formate. The pH values of the buffers were measured with a Beckman Zeromatic pH meter using a Beckman general-purpose glass electrode.

Kinetic Measurements. The disappearance of I was followed at 2600 Å. using a Beckman DU spectrophotometer, equipped with a thermostated cell compartment capable of maintaining constant temperature to ±0.01°. The faster reactions were initiated in a quartz cell; the slower reactions were initiated in volumetric flasks placed in a constant temperature bath; the very slow reaction solutions were placed in sealed ampoules. The reactions were all studied at 25.0 ± 0.1°; the water reactions were also studied at 50.0

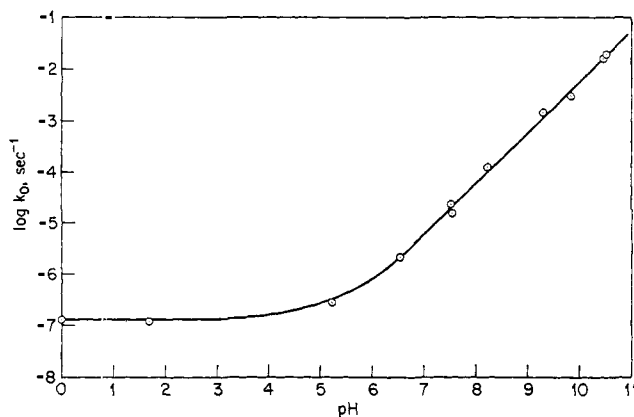(10) A. Lapidot and D. Samuel, *J. Chem. Soc.*, 1931 (1964).

Figure 1. Log k_0 vs. pH, where k_0 is the intercept value obtained from a plot of log k_{obsd} vs. buffer concentration at constant pH.

± 0.1°. The kinetics were followed to 80–90% reaction in most cases; good pseudo-first-order kinetics were obtained. In the case of the slow water reaction at 25°, a kinetic run with the same reaction solution used at 25° was carried out at 50°. The end point obtained in the 50° run was used as the end point in the 25° run. The rate constants, k_{obsd}, were obtained as previously described.[11] The initial concentration of I was 1.50–1.78 $\times$ 10^{-4} M. A plot of k_{obsd} vs. the concentration of the basic component in buffers of constant buffer ratio gives a straight line with the rate coefficient k_2 as the slope and $k_w + k_{OH}(OH^-) = k_0$ as the intercept where k_w is the water term and k_{OH} is the hydroxide ion term. Figure 1 is a plot of log k_0 vs. pH. No hydronium catalysis is seen in the pH range studied.

Hydroxylamine hydrochloride, imidazole, sodium azide, sodium fluoride, and sodium nitrite were added, in varying concentrations to Tris or phosphate buffers of constant buffer concentration, which were at least 2 pH units greater than the pK_a of the addend, the ionic strength being maintained at 1.0 with potassium chloride. A plot of k_{obsd} vs. addend concentration gives the rate coefficient as the slope. Linear relationships were obtained in all cases.

In order to measure pyridine catalysis, a polarographic method using a Leeds and Northrup Electro-chemograph Type E polarograph with a dropping mercury electrode, was used. The half-wave potential of I occurs at −0.98 v. vs. s.c.e., while the half-wave potential for a 1:1 pyridine–pyridine hydrochloride solution occurs at a more negative value. The wave height is a linear function of I concentration in this system. Initial concentrations of I in the kinetic runs were 8.07 $\times$ 10^{-3} M. A plot of log $(h_t - h_\infty)$ at −1.10 v. vs. time gives the pseudo-first-order rate constant, where h_t is the current at time t, and h_∞ is the infinity time current reading.
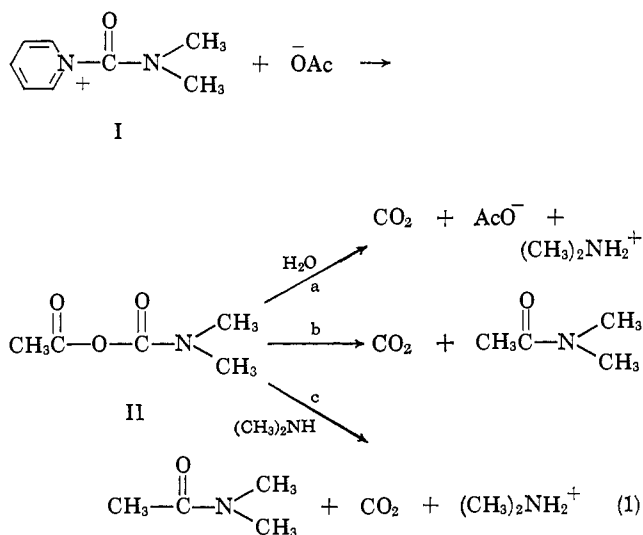
Other Measurements. The n.m.r. signals from solutions containing I in 0.6–1.0 M buffers in heavy water containing *t*-butyl alcohol as an internal standard were followed at 37°, using a Varian A-60 spectrometer operating at 59.8 Mc.p.s. A Cary Model 11 recording spectrophotometer was used in scanning the reaction mixtures.

(11) S. L. Johnson, *J. Am. Chem. Soc.*, **84**, 1729 (1962).

Results

Product Studies. The ultraviolet spectrum of the completed kinetic runs in carbonate, Tris, phosphate, and acetate buffers, and in the HCl solutions showed that pyridine was produced. Assuming the formation of 100% pyridine, the predicted optical density readings at 2600 Å. were obtained, asc alculated from the extinction coefficients of pyridine in the same buffers in which the kinetics were carried out.

An n.m.r. study of the course of the reaction of 0.37 M I in an acetate buffer (1.60 M NaOAc–0.40 M HOAc) shows that pyridine,[12] dimethylamine (as $(CH_3)_2NH_2^+$), and dimethylacetamide are produced as I is consumed. The concentration ratio of dimethylacetamide/dimethylamine is 1.0. Comparison of the product signals with those of authentic dimethylacetamide and dimethylamine hydrochloride, or spiking the product solution with the probable products substantiate the product assignments. Tetramethylurea is not produced in the reaction; the signals for tetramethylurea and dimethylamine (protonated) are quite distinguishable in the acetate buffer used. Also, tetramethylurea could not be found in the products by vapor phase chromatography. A gas (presumably CO_2) is given off during the reaction, but not after completion of the reaction. No unstable intermediate could be detected during the consumption of I. Apparently an unstable intermediate (II) is formed, which decomposes to the products, as indicated by eq. 1. The interaction of dimethylcar-

bamoyl chloride (neat) and sodium acetate results in nearly quantitative yields of dimethylacetamide[13]; presumably this reaction proceeds *via* the unstable intermediate II. Unstable mixed anhydrides of the type RCOOCONHR′ decompose in organic solvents to give RCONHR′ as in path b in eq. 2, and to give $(RCO)_2O$ and $(R′NH)_2CO$ by a disproportionation path.[14] Apparently, under the conditions of the experiment, the intermediate II does not disproportionate to give tetramethylurea, but rather, reacts with water to produce the unstable[15] dimethylcarbamic acid which then decomposes to dimethylamine and CO_2. Alternatively,

dimethylacetamide could result from the interaction of dimethylamine with II, providing that II, but not I, is extremely selective in its reaction with the extremely small amounts of dimethylamine present at the low pH of the reaction mixture. A similar n.m.r. investigation using a formate buffer shows that dimethylformamide–dimethylamine in a *ca.* 0.25:1 yield ratio is formed. No unstable intermediate or tetramethylurea could be detected.

The reaction of a solution of sodium fluoride (0.8 M) and I (0.32 M) in heavy water, followed by the n.m.r. technique shows that pyridine and dimethylcarbamoyl fluoride are produced as I is consumed. The dimethylcarbamoyl fluoride assignment was based upon a comparison of the n.m.r. spectrum of authentic dimethylcarbamoyl fluoride,[16] which has a very characteristic n.m.r. spectrum consisting of four peaks (due to fluorine splitting of the methyls and hindered rotation of the dimethylamino group) centered at –104 c.p.s. from the *t*-butyl alcohol standard in heavy water. The dimethylcarbamoyl fluoride slowly decomposes to yield tetramethylurea. The tetramethylurea and dimethylcarbamoyl fluoride were also identified by vapor phase chromatography.

Additional n.m.r. studies were carried out in sodium azide, phosphate buffer, and 3,5-dimethylpyridine solutions. A product with a split methyl signal (–100 c.p.s. from *t*-butyl alcohol), presumably dimethylcarbamoyl azide, and pyridine are the sole products in the azide solution; the dimethylcarbamoyl azide produced is hydrolytically stable over a 3-month period. In the phosphate buffer, pyridine and an intermediate (presumably dimethylcarbamoyl phosphate) with a single unsplit methyl signal at –101 c.p.s. from the *t*-butyl alcohol standard are produced. The intermediate slowly decomposes to dimethylamine (protonated) over a period of 2 weeks. In the 3,5-dimethylpyridine buffer, an equilibrium mixture of I and the 3,5-dimethylpyridinium[2] ion are produced.

A 0.99 M carbonate buffer at pH 10.3 which is 0.26 M in I yields 98 ± 7% pyridine and 90 ± 7% tetramethylurea as determined by vapor phase chromatography.

Kinetic Results. The second-order rate constants for the rate of disappearance of I in water at 25° are given in Table I. The rate coefficients are dependent only on the more basic component of the acetate and phosphate buffers. The Tris buffers show a moderate increase of rate coefficient with increasing pH. The carbonate buffers show an even stronger increase of k_2 with pH giving a OH^- independent term and a OH^- dependent term. This effect is currently unexplained. The hydroxylamine and imidazole reactions are nearly independent of pH (Table I). The nucleophiles studied include water, hydroxide, nitrite, imidazole, azide, Tris, phosphate, carbonate, hydroxylamine, bromide, acetate, formate, fluoride, and triethylamine. No bromide, nitrite, or triethylamine reaction was observed; no proton catalysis was apparent in HCl solutions up to 1 M (Figure 1).

The k_{H_2O} term was measured both at 25 and 50°; the resulting ΔS^* and ΔH^* values are –27 e.u. and 20.8 kcal./mole, respectively.

(12) The signals of I and pyridine in the ring proton region are well separated; see ref. 2.

(13) J. K. Lawson and J. A. T. Croom, *J. Org. Chem.*, **28**, 232 (1963).

(14) (a) W. Dickmann and F. Breest, *Ber.*, **39**, 3052 (1906); (b) C. Nageli and A. Tyabji, *Helv. Chim. Acta*, **18**, 142 (1953).

(15) C. Faurhold, *J. chim. phys.*, **22**, 1 (1925).

(16) We greatly appreciate the generous gift of dimethylcarbamoyl fluoride supplied by Dr. D. D. Coffman, Central Research Dept., E. I. DuPont de Nemours and Co.

Table I. Rates of Reaction of Nucleophiles with Dimethylcarbamoylpyridinium Chloride[a]

Nucleophile	pK_a	Buffer[b] ratio	Buffer concn. range,[h] M	pH[i]	Number of determinations	$k_{int}{}^g \times 10^4$ sec.$^{-1}$	$k_2{}^j \times 10^2$ M^{-1} sec.$^{-1}$	k_H/k_{DM}
CO_3^{2-}	10.36	1	0.05–0.25	9.81	11	33.0	4.56	
CO_3^{2-}	10.36	0.1	0.05–0.50	9.49	7	13.4	4.65	
CO_3^{2-}	10.36	1	0.025–0.15, $\mu = 0.6$	9.88	4	36.0	5.86	
CO_3^{2-}	10.36	3	0.025–0.15, $\mu = 0.6$	10.37	4	79.6	12.4	
CO_3^{2-}	10.36	10	0.025–0.10, $\mu = 0.6$	10.91	3	61.5	28.55	
Tris	8.20	1	0.02–0.40	8.21	7	1.20	0.155[k]	
Tris[c]	8.20	1	0.125–0.50	8.97[d]	3	1.25	0.145	1.07
Tris	8.20	10	0.0002–0.40	9.35	10	12.91	0.322[k]	
HPO_4^{2-}	7.20	1	0.025–0.15	6.48	4	0.020	0.0445	
HPO_4^{2-}	7.20	10	0.01–0.175	7.54	9	0.14	0.0546	
OAc^-	4.76	2	0.04–0.20	5.05	5	e	0.0136	
OAc^-	4.76	10	0.025–0.27	5.76	6	e	0.0115	
OAc^- [c]	4.76	2	0.045–0.21	5.50[d]	4	e	0.0174	0.78
HCO_2^-	3.75	1.69	0.10–0.50	3.98	5	e	0.0108	
H_2O	−1.6	In 0.20 M HCl, 25°		1.70			0.000810[f]	
H_2O	−1.6	In 1.00 M HCl, 25°		0.1			0.000806[f]	
D_2O		In 0.0206 M DCl, 25°		...			0.000358[f]	2.26
H_2O	−1.6	In 0.020 M HCl, 50°		...			0.0115[f]	
H_2O	−1.6	In 1 M HCl, 50°		...			0.0131[f]	
D_2O		In 0.0206 M DCl, 50°		...			0.00575[f]	2.14
Imidazole	7.04	1	0.01–0.10	7.32	6	e	1.86	
Imidazole	7.04	In 0.24/0.024 Tris buffer	0.01–0.10	9.4	5	18.8	1.50	
NO_2^-	3.4	In 0.5/0.5 Tris buffer	0.01–0.06	8.31	5		0	
F^-	3.1	In 0.5/0.5 Tris buffer	0.01–0.05	8.31	4	8.70	0.180	
F^- [c]	3.1	In 0.5/0.5 Tris buffer	0.01–0.05	8.97[d]	5	8.13	0.168	1.07
NH_2OH	5.75	In 0.10/0.01 Tris buffer	0.005–0.02	9.29	4	16.4	100	
NH_2OH	5.75	In 0.5/0.5 Tris buffer	0.005–0.02	8.31	3	13.0	93	
N_3^-	4.0	In 0.5/0.5 Tris buffer	0.005–0.02	8.31	5	8.68	12.7	
N_3^- [c]	4.0	In 0.5/0.5 Tris buffer	0.005–0.03	8.94[d]	4	9.0	12.2	1.04
Br^-	...	In 0.5/0.5 Tris buffer	0.5	8.31	1		0	
OH^-	15.7		0.05–0.5	10.8	5	440	10,000	
Et_3N	10.9	In 10% acetonitrile–90% water (v./v.), $\mu = 0.6$	0.05–0.5	10.8	5	440	0	

[a] In water at 25°, μ equals 1.0 (KCl) unless otherwise noted. [b] Refers to the ratio of the basic form of the buffer to its conjugate acid. [c] In heavy water. [d] pD value = meter reading + 4.0. [e] Too small to be determined. [f] The observed rate constant for the water reaction. [g] k_{int} refers to the intercept obtained by plotting k_{obsd} vs. buffer concentration at constant pH. [h] Concentration of the more basic component of the buffer mixture. [i] Constant to 0.15 pH unit in the most unfavorable cases and to 0.01 pH unit in the most favorable cases, as the buffer concentration varies. [j] k_2 refers to the slope obtained from a plot of k_{obsd} vs. the concentration of the more basic component of the buffer. For the carbonate and Tris buffers the k_2 values are not independent of the pH. [k] $k_2 = 0.00129 + 869$ [OH$^-$].

The following solvent deuterium isotope effects were observed at 25°; water, 2.26; azide, 1.04; acetate, 0.78; Tris, 1.07; and fluoride, 1.07. These were calculated from solutions containing the same buffer ratio in order to minimize specific salt effects.

In 1:1 pyridine–pyridine hydrochloride buffers a 250% rate increase is observed as the pyridine concentration is increased to 1 M. In a plot of k_{obsd} vs. buffer concentration a linear relationship is obtained, resulting in a catalytic coefficient of 6.43×10^{-7} M^{-1} sec.$^{-1}$ for pyridine. In 10:1 pyridine–pyridine hydrochloride buffers the rate increase is only 5% as the pyridine concentration is increased to 1 M due to the increased k_0 value. The pyridine term in the 10:1 buffer is 3×10^{-7} M^{-1} sec.$^{-1}$, but in this case the catalytic coefficient is determined with less accuracy due to the larger k_0 value. None of the ring-opened product (to be discussed later) could be seen by ultraviolet analysis in this buffer in which it is known to be stable.

In the more alkaline solutions (pH >10) a small amount (~0.01–2%) of ring opening occurs, the kinetics of which will be the subject of a future publication.

Discussion

The N,N-dimethylcarbamoylpyridinium ion undergoes direct nucleophilic substitution reactions as is evident by the product studies. The rates of the nucleophilic reactions are fairly well correlated with rates of nucleophilic reactions with p-nitrophenyl acetate[17] with a slope of 1.00 and a correlation coefficient of 0.973 by least-squares analysis (Figure 2). For the calculation of the slope, the pyridine term was not used, as the large negative deviation of the pyridine term in Figure 2 is due to the different mechanism of hydrolysis in pyridine-catalyzed hydrolysis of I and pyridine-catalyzed hydrolysis of p-nitrophenyl acetate. There seems to be no great separation of nucleophiles according to their charge types in Figure 2, which indicates that anions show no special reactivity to the cationic substrate I, as compared to the neutral p-nitrophenyl acetate substrate. Fluoride ion, however, deviates considerably even though the reaction is

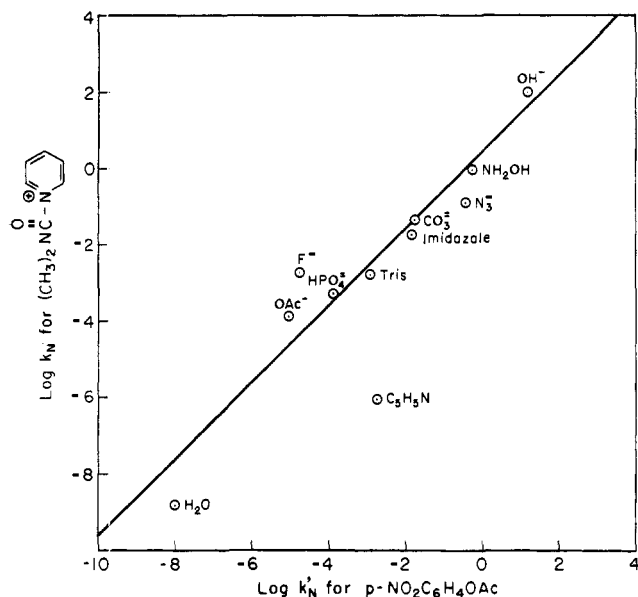(17) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).

Figure 2. Log k_N vs. log k_N' where k_N' is the nucleophilic reaction rate of a reactant to p-nitrophenyl acetate (W. P. Jencks and S. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960); W. P. Jencks, *ibid.*, **80**, 4585 (1958); M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1665 (1957)) in units of M^{-1} sec.$^{-1}$ and k_N is the nucleophilic reaction rate of the same reactant to I in units of M^{-1} sec.$^{-1}$.

entirely due to a nucleophilic interaction of F⁻ with the substrate as determined by the products. Nitrite, which has significant reactivity to p-nitrophenyl acetate, has no reactivity to I. Triethylamine, however, has negligible reactivity to both I and p-nitrophenyl acetate.

The solvent isotope effects observed in the reaction of water (2.26), azide (1.04), acetate (0.78), Tris (1.07), and fluoride (1.07) with I are reasonable, for direct nucleophilic reactions[18,19] on a carboxyl group. A maximum isotope effect of 1.18 would be expected for the fluoride reaction at 25° on the basis of the secondary solvent isotope effects proposed by Swain and Bader[20] due to a change in librational frequencies of the water molecules in proceeding from ground state (fully solvated fluoride ion) to transition state (partly covalent fluoride).

A general base catalyzed acetate hydrolysis of I shown in eq. 2 might be expected to be at least partially contributory to the acetate term on the basis that a general base catalysis has been demonstrated for the acetate reaction with p-nitrophenyl acetate.[21] The solvent isotope effect for this reaction is 1.8.[19] The

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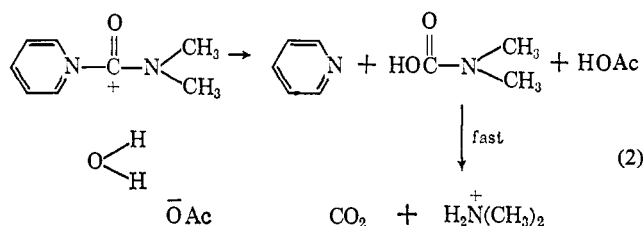
production of dimethylamine and CO_2 are consistent

(18) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Am. Chem. Soc.*, **84**, 595 (1962).
(19) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).
(20) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960).
(21) V. Gold and A. R. Butler, *J. Chem. Soc.*, 1334 (1962).

with eq. 2 as well as eq. 1. The correlation of nucleophilicities of various reactants including acetate to I and p-nitrophenyl acetate (Figure 2) are consistent with contributions from a general base process for the acetate reaction with I. However the inverse solvent isotope effect observed for the acetate reaction makes it appear unlikely that a general catalysis is of much importance.

The pyridine catalysis of the hydrolysis of I must be due to a general base catalysis, as the catalyst is identical with the leaving group making nucleophilic catalysis impossible. The Brønsted β value for this reaction assuming that the water term is entirely due to general catalysis is 0.7–0.8. Another mechanistic possibility for the pyridine term is catalysis of the ring opening reaction, which is known to be a very small portion of the total course of the reaction. This possibility, however, is ruled out on the basis that no ring-opening product can be detected after 10% reaction under conditions where the ring-opened product is stable.[22] The concentration of the ring-opened product would have been 8×10^{-3} M in this case and would easily have been detected by its ultraviolet spectrum at 3350 Å. Also, the ring-opening reaction is first order in general base *and* first order in hydroxide.[22] The catalytic coefficient of the pyridine term does *not* contain a hydroxide ion term, which would have been very easy to detect, as the pyridine term in the 10:1 buffer would be ten times greater than the pyridine term in the 1:1 buffer. The transition state in this case must contain I and at least one water molecule and pyridine. The magnitude of the catalytic coefficient for pyridine is very small accounting for the large negative deviation in Figure 2. Therefore, it is most probable that the rate constants for the interactions of other nucleophiles with I listed in Table I contain negligible contributions from general base catalysis. The product studies in the case of the fluoride, azide, and phosphate reactions bear this out. The acetate and formate product results are ambiguous on this account, however, as previously discussed.

A S_N1 type of mechanism for the hydrolysis of I is unlikely on the basis of the lack of a mass law effect of pyridine on the water term. Increasing amounts of pyridine in a 1:1 pyridine buffer, $\mu = 1$ with KCl, give a linear rate increase consistent with a general catalysis of pyridine, k_p, and inconsistent with the trapping of the carbamoyl cation with pyridine as in eq. 3. Such trapping should be important, since

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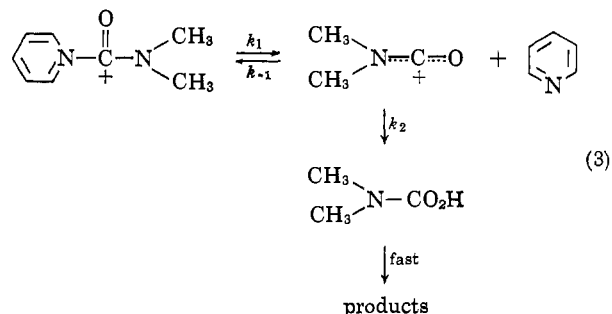
pyrrolidine and chloride at fairly low concentrations can trap the dimethylcarbamoyl cation in water.[6] The water rate constant according to scheme 3 should be

(22) S. L. Johnson and K. A. Rumon, unpublished results.

$$k_{H_2O} = \frac{k_1 k_2}{k_{-1}(C_5H_5N) + k_2} \qquad (4)$$

given by eq. 4. Since $k_{-1}(C_5H_5N)$ should be of comparable value as k_2 in the pyridine concentration range used here, the total observed reaction rate in the presence of pyridine should give a rate proportional to the pyridine concentration, k_p, as well as an inverse term for pyridine at high pyridine concentrations where it might be expected that $k_{-1}(C_5H_5N) \gg k_2$. The linearity of the k_{obsd} vs. pyridine concentration plot makes it seem unlikely that the water reaction of I via a Sn1 mechanism is important. The pH in this series of runs is 5.2–5.3, therefore the water reaction is the main contributing factor to k_0 (Figure 1).

The ΔS^* value of -27 e.u. for the water reaction indicates that the reaction is nucleophilic in nature, and not ionic, as Sn1 ester hydrolyses characteristically have activation entropies in the range 0–10 e.u. while reactions which involve the direct nucleophilic participation of water have large negative entropies in the range -15 to -30 e.u.[23] Possibly a general base mechanism prevails. This would be consistent with the large negative entropy of activation as well as the moderate solvent kinetic isotope effect.

The large negative entropy of activation for the water reaction obtained from this study should be contrasted with the small ΔS^* value of -0.4 e.u. obtained for the hydrolysis of monoanionic diethylcarbamoyl phosphate[10] and similarly low values for the hydrolysis of the various ionic states of carbamoyl phosphate.[7] The solvent isotope effect for the hydrolysis of I (2.26) is also in marked contrast to the small solvent isotope effects (≤ 1.33) obtained for the hydrolysis of diethylcarbamoyl phosphate[10] and carbamoyl phosphate.[7] Another striking chemical difference between carbamoyl phosphate and I is that carbamoyl phosphate is not sensitive to nucleophilic catalysis,[7] while I reacts almost exclusively directly with nucleophiles. In the case of carbamoyl phosphate, even the strong nucleophile, azide, did not increase the rate of phosphate appearance.[7,8] A comparison of the hydrolysis rate of monoanionic diethylcarbamoyl phosphate[24] where the leaving group has a pK_a of 7.2 with I where the leaving group has a pK_a of 5.2 indicates that the phosphate derivative hydrolyses faster by a factor of 190 at 50° and 118 at 25°. This reactivity order is just the reverse of the water reactions of acetyl phosphate on acetyl phenylphosphate[25] compared to N-methyl-N'-acetylimidazolium ion[26] or protonated N-acetylimidazole.[27] The latter three compounds undergo direct nucleophilic reactions with water. In this comparison the positively charged N-substituted acetyl derivatives are more reactive by a factor $>10^3$ than the anionic phosphate derivatives.

The comparison of the hydrolytic properties of N,N-diethylcarbamoyl phosphate or carbamoyl phosphate to the hydrolytic properties of I is very similar to the comparison of the hydrolytic properties of acetyl phosphate to those of acetyl phenylphosphate. Acetyl

phenylphosphate is believed to undergo hydrolysis by direct nucleophilic interaction of water while acetyl phosphate is believed to undergo hydrolysis by the metaphosphate path.[25] The solvent kinetic isotope effects for acetyl phenylphosphate and acetyl phosphate are 2.5 and ca. 1.0, respectively; the ΔS^* values are -28.8 e.u. and nearly 0, respectively. Acetyl phenylphosphate reacts with added anionic nucleophiles while acetyl phosphate does not. Furthermore acetyl phosphate is more reactive in its monoanionic form than in its dianionic form. Other phosphate esters believed to undergo hydrolysis by a metaphosphate path are also more reactive in their monoanionic forms.[28a] The same effect has been observed for diethylcarbamoyl phosphate.[10]

Secondary kinetic isotope effect data, product analysis, and H_2O^{18} data have given evidence that t-butyl phosphate in its protonated and neutral forms undergoes a Sn1 hydrolysis resulting in C–O bond cleavage, and by alternative mechanisms involving P–O bond cleavage in its mono- and dianionic forms.[28b] The protonated and neutral species are more reactive than the mono- and dianionic species. As a result no pH–rate maximum is observed at pH 4 as is observed for diethylcarbamoyl phosphate hydrolysis.[10] Since C–O bond cleavage was found[10] for monoanionic diethylcarbamoyl phosphate hydrolysis, and since the ΔS^* and solvent kinetic isotope effect values are consistent with a Sn1 rather than a direct nucleophilic mechanism, it is not clear why a pH–rate maximum was observed in this case. The less basic monoanionic phosphate would certainly be expected to be a better leaving group than the dianionic phosphate in a Sn1 reaction.

Perhaps a metaphosphate pathway for the hydrolysis of monoanionic diethylcarbamoyl phosphate as suggested by Allen and Jones[8] for carbamoyl phosphate might be seriously considered. The ΔS^* and k_H/k_D data on this compound could agree equally well with a metaphosphate path or a Sn1 path. In view of the conflicting evidence of Halmann, et al., and Allen and Jones on carbamoyl phosphate, additional studies should probably be carried out with diethylcarbamoyl phosphate to establish with certainty whether P–O or C–O bond cleavage takes place. Adequate control experiments over the pH range in question are necessary in H_2O^{18} work to determine whether there is O^{18} incorporation into reactants or separately into products, especially if positive results are obtained. A thorough investigation of this possibility was not reported in the conflicting reports of Halmann, et al.,[7] and Allen and Jones.[8]

Our results on I are not in disagreement with the Sn1 hypothesis of Lapidot and Samuel[10] for diethylcarbamoyl phosphate. Even though pyridine is a better leaving group than dianionic phosphate, a greater Sn1 reactivity of I compared to diethylcarbamoyl phosphate would probably not be expected. For example, neutral t-butyl phosphate[28] is ca. 100 times more reactive than t-butyldimethyl sulfonium[29] ion in water at 50°. Both of these reactions are believed to occur by a Sn1 mechanism. In this case dimethyl sulfide is a much weaker

(23) F. A. Long in "Advances in Physical Organic Chemistry," Vol. I, V. Gold, Ed., Academic Press Inc., New York, N. Y., 1963.
(24) Extrapolated from the rate data given in ref. 10.
(25) G. Di Sabato and W. P. Jencks, J. Am. Chem. Soc., 83, 4400 (1961).
(26) R. Wolfenden and W. P. Jencks, ibid., 83, 4390 (1961).
(27) W. P. Jencks and J. Carriuolo, J. Biol. Chem., 234, 1272 (1959).

(28) (a) J. R. Cox, Jr., and O. B. Ramsay, Chem. Rev., 64, 317 (1964); (b) A. Lapidot, D. Samuel, and M. Weiss-Broday, J. Chem. Soc., 637 (1964).
(29) C. G. Swain, L. E. Kaiser, and T. E. C. Knee, J. Am. Chem. Soc., 80, 4092 (1958).

base than monoanionic phosphate. If the dissociation of I is a higher energy process compared to diethylcarbamoyl phosphate ionization, then it would be expected that if a lower energy direct nucleophilic interaction path were available, it would be taken.

In their criticism of the work of Halmann, et al.,[7] Jones and Allen[8] proposed that the method of measuring carbamoyl phosphate hydrolysis by ammonia evolution in Halmann's experiments[7] measures the cyanate decomposition rather than carbamoyl phosphate decomposition, as supported by indirect cyanate determinations and kinetic measurements. A related erroneous concept present in Halmann's work will now be mentioned. In the pH range 5–7, the rate of production of ammonia is much lower than the rate of production of cyanate measured titrimetrically. The lowered rate of production of ammonia is not due to a lowered concentration of the monoanion in this pH range. The *observed* rate constants for the evolution of both cyanate and ammonia should be the same if both products are formed in a rate-determining step from a common precursor or set of equilibrium-related precursors. This observed rate constant should be the *sum* of the individual rate constants giving rise to each product. The individual rate constants can only be evaluated by additional data on the product ratio which is equal to the ratio of the individual rate constants. The lack of equality of the rate constants for the formation of ammonia and cyanate is a good indication that the rate constant for ammonia evolution is due to some other process unrelated to the decomposition of the carbamoyl phosphate monoanion, such as the hydrolysis of the cyanate product.

A major point of difference in ref. 7 and 8 is the interpretation of trapping experiments with azide. Halmann, et al.,[7] were able to isolate a 30% yield of carbamoyl azide from carbamoyl phosphate and sodium azide in the pH range 4.0–4.5. Since sodium azide has no effect upon the rate of disappearance of carbamoyl phosphate, it was proposed that azide was trapping [$H_2NC=O^+$], which is merely a protonated form of cyanic acid. However, it seems unreasonable to us that azide could really trap a protonated species such as [$H_2NC=O^+$] because the rate of deprotonation of such a species should be far greater than the rate of combination of azide with it in aqueous solvents.[30] If anything, it seems reasonable that azide should trap HCNO or CNO^- ($pK = 3.7$).[31] Trapping experiments would be more meaningful for N,N-disubstituted carbamic acid derivatives.

In conclusion: (1) I does not undergo SN1 hydrolysis; (2) I does undergo direct nucleophilic interactions with added nucleophiles in marked contrast to carbamoyl phosphate[7,8] or dimethylcarbamoyl chloride[5]; (3) I does undergo a very small amount of general base catalyzed solvolysis (with a minimum β value of 0.7–0.8 indicating that specific base catalysis or direct nucleophilic reaction is of much greater importance than general catalysis), in analogy with the acetylpyridinium ion[3]; and (4) the nucleophilicities of neutral and anionic nucleophiles towards I are well correlated with the reactivities of the same nucleophiles toward *p*-nitrophenyl acetate.

(30) (a) The deprotonation of H_2N^+ C=O would be expected to be diffusion controlled[30b] while a C–N bond-making reaction should be much slower. For example, the rate constant[26] for the reaction of the very strong base OH$^-$ with the positively charged carbonyl carbon of N-acetyl-N'-methylimidazolium ion is 1.5×10^5 mole^{-1} sec.$^{-1}$, while diffusion-controlled rate constants are $>10^4$ larger. (b) M. Eigen in "Techniques of Organic Chemistry," Vol. VIII, Part 2, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1031.

(31) A. R. Amell, *J. Am. Chem. Soc.*, 78, 6234 (1956).

Configurational Problems in Conjugated Systems.
I. Benzil Anion Radical and Dianion[1]

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The cis–trans configurational distributions and configurational stabilities of benzil anion radical (Bz_2^-) and dianion (Bz_2^{2-}), formed by successive electron transfers to benzil (Bz_2), have been studied in several solvents. Alkali metal transfer agents give cis–trans-Bz_2^- mixtures which are thermodynamically controlled owing to rapid electron exchange between the latter species and its configurationally labile parent (Bz_2). Addition of Bz_2 to various anion radicals and dianions gives a kinetically controlled Bz_2^- composition. In either case the cis configuration of Bz_2^- is favored, especially in nonpolar solvents. Bz_2^- undergoes cis–trans isomerization but less rapidly than it is converted to Bz_2^{2-}, when sufficient electron-transfer agent is present; thus the isomer composi-
tion of Bz_2^{2-} is the same as for Bz_2^-. Unlike Bz_2^-, Bz_2^{2-} is configurationally quite stable, a contrast which is easily rationalized in terms of π-electronic rotational barriers. The enolate (Bz_3^-) formed by addition of one mole of benzoyl chloride to Bz_2^{2-} also undergoes cis–trans isomerization, but again at a rate less than that of the second benzoylation step whenever excess benzoyl chloride is present.

Introduction

Configurational and conformational problems have been extensively investigated for conjugated dienes and diones. However, little is known about this aspect of the corresponding anion radicals and dianions. A study of some configurational aspects of the benzil