Nucleophilic Reactivity to Diphenylcarbamoyl Derivatives. The Unimolecular Nature of Diphenylcarbamoyl Chloride Hydrolysis

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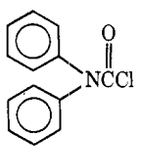
The nucleophilic reactivity of the fluoride, chloride, imidazole, pyridine, and *p*-nitrophenyl diphenylcarbamoyl derivatives have been investigated. The pyridinium ion is reactive to nucleophiles, following closely the reactivity sequence of these nucleophiles to *p*-nitrophenyl acetate. On the other hand, except for amine nucleophiles, diphenylcarbamoyl chloride is insensitive to nucleophiles, reacting instead with water. The $\Delta S^{\ddagger}$ of -5 eu for the water reaction and the small deuterium solvent isotope effect of 1.2 strongly suggest that diphenylcarbamoyl chloride hydrolyzes by an ionization reaction.

Diphenylcarbamoyl chloride (**1**) is known to specifically inactivate chymotrypsin[3,4] and cholinesterase.[5] This fact is very interesting because carbamoyl chlorides are thought to undergo hydrolysis by an ionization mechanism[6] and therefore to be insensitive to nucleophilic attack. If this is so, then the enzyme must be able to alter the mechanism of displacement reactions with the acid chloride, so that the ionization mechanism is bypassed by a lower energy process of direct reaction with the enzyme. For this reason we have studied in detail the sensitivity of the acid chloride and of the pyridinium derivative to nucleophilic attack. Diphenylcarbamoylpyridinium ion (**2**) has been found to be a good irreversible inhibitor of a variety of serine esterases and proteinases as well as of urease.[7]



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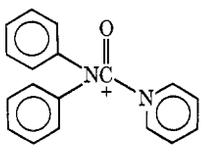

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Results

Diphenylcarbamoyl Chloride.—**1** has no reactivity to acetate, sulfite, phosphate, or formate, as demonstrated by the identical rate constants obtained in the presence or absence of these agents (Table II). No acid-catalyzed hydrolysis is observed in 1 *M* HCl or $HClO_4$. Concentrations of phosphate or acetate as high as 0.9 or 1 *M* give rise to quantitative yields of diphenylamine with identical rates. Had diphenylcarbamoyl phosphate been produced, then diphenylamine would not be produced in quantitative yield, because separate experiments with diphenylcarbamoylpyridinium ion, which reacts rapidly with phosphate to produce the phosphate derivative with a λ_{max} at 248 nm, demonstrate that the intermediate yields diphenylamine only slowly over the period of a week.

On the other hand, diphenylcarbamoyl chloride reacts readily with amine-containing buffers. In the case of imidazole the diphenylcarbamoylimidazole product, λ_{max} 233 nm, can be spectrophotometrically detected as well as the diphenylamine (λ_{max} 280 nm) product. In addition diphenylcarbamoylimidazole can be isolated from aqueous solutions containing imidazole and 1. (See Experimental Section.) The yield of the diphenylamine decreases as the yield of diphenylcarbamoylimidazole increases and the total rate increases with the increasing imidazole concentration in the buffer. These results are displayed in Table I. Similar product results are obtained in glycine containing buffers, 0.4 *M* in Tris, pH 8.3, in which the glycine concentration varies from 0.1×10^{-3} to 5×10^{-3} to 10×10^{-3} *M*. The yield of diphenylamine determined at 280 nm decreases in this series from 100 to 67 to 29%. These results are in accord with eq 1, which describes

TABLE I

YIELD OF DIPHENYLAMINE FROM DIPHENYLCARBAMOYL CHLORIDE IN IMIDAZOLE BUFFERS[a]

Buffer composition	Yield, % diphenylamine	Calcd,[b] % diphenylamine
0.05 *M* Im, 0.05 *M* ImH	52	48
0.10 *M* Im, 0.02 *M* ImH	36	31
0.15 *M* Im, 0.03 *M* ImH	22	23
0.10 *M* Im, 0.01 *M* ImH	46	31
0.20 *M* Im, 0.02 *M* ImH	24	18

[a] Constant ionic strength of 0.20 *M* maintained with KCl. Temperature is 25°. [b] Calculated from eq 1 substituting imidazole for glycine and using 0.0020 min^{-1} for k_b and 0.045 M^{-1} min^{-1} for k_g.

$$100/\%\ \text{diphenylamine} = 1 + k_g(\text{glycine})/k_b \qquad (1)$$

the expected yield of diphenylamine in terms of the kinetic constant observed in a separate set of experiments. Diphenylcarbamoyl chloride is known to react with amino acids, including glycine, in water–ethanol mixtures to give high yields of crystalline diphenylcarbamoyl derivatives.[8] In eq 1 k_g is the apparent catalytic coefficient of glycine in the buffer, and k_b is the constant buffer term. The derivation of eq 1 was made assuming that competitive kinetics[9a] give rise to diphenylamine as the hydrolysis product and diphenylcarbamoylglycine as the product of nucleophilic attack by glycine. The latter urea derivative is assumed to be optically transparent at 280 nm in analogy with 1,1-diphenylurea, which has a λ_{max} at 235 nm. A plot of eq 1 yields a straight line with a value of 50 M^{-1} for

(1) This work was supported by Grant GM-11834 from the U. S. Public Health Service.

(2) Taken in part from the M.S. thesis of H. M. G., Vassar College, 1965.

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(6) H. K. Hall, Jr., and C. H. Lueck, *J. Org. Chem.*, **28**, 2818 (1963).

(7) S. L. Johnson, unpublished work.

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(9) (a) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 161; (b) p 66.

TABLE II
KINETICS OF DIPHENYLCARBAMOYL CHLORIDE IN AQUEOUS SOLUTIONS[c] AT 25°

Reactant solution[b]	μ, M[a]	pH	k_o, min^{-1}	k_n, M^{-1} min^{-1}
0.20 M $HClO_4$	0.20–1.0[i]		0.00226 ± 0.00011	
1.0 M HCl	1.0		0.0017	
0–0.20 M $HClO_4$[g]	0.20		0.00225 ± 0.00015	
0–0.20 M HCl[h]	0.20		0.00193 ± 0.00020	k_{H_2O}/k_{D_2O} = 1.17
0–0.2 M DCl[j]	0.20		0.00165 ± 0.00011	
0.01 M HCl at 25°	0.01		0.00182	
0.01 M HCl at 48.8°	0.01		0.0308	
10% MeCN	0		0.0015	
1.0 M KCl, 10% MeCN	1.0		0.00148	
2.45 M KCl, 10% MeCN	2.45		0.00109	
0.20 M Na formate, 0.20 M formic acid, and five dilutions	0.20	3.81	0.0020	<0.002
0.20 M NaOAc, 0.10 M HOAc, and five dilutions	0.20	4.78	0.0018	<0.002
1.0 M NaOAc, 0.08 M HOAc in 10% MeCN	1.0	5.58	0.0014	<0.0002
0.05 M Na_2HPO_4, 0.05 M NaH_2PO_4, and five dilutions	0.20	6.85	0.0017	<0.007
0.90 M Na_2HPO_4, 0.10 M NaH_2PO_4, 0.10 M NaCl in 10% MeCN	2.45	7.51	0.0005	<0.0001
Hydrazine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.2 M K_2CO_3 buffer	0.20	10.3	0.0018	0.70
Hydroxylamine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.2 M K_2CO_3 buffer	0.20	10.3	0.0016	0.24
Hydroxylamine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.4 M Tris buffer	0.20	8.4	0.0025	0.26
0.2 M Na_2SO_3	0.60	9.71	0.0014	<0.001
0.2 M NaN_3	0.20	9.5		0.063
Butylamine, 10^{-4}, 5×10^{-4}, 10^{-3} M in 0.2 M K_2CO_3 buffer	0.20	10.3		0.55[f]
Glycine, 10^{-4}, 5×10^{-4}, 10^{-3}, 5×10^{-2}, 10^{-1} M in 0.40 M Tris buffer	0.20	8.4	0.0025	0.14[e]
Glycine, 10^{-3}, 5×10^{-3}, 10^{-2}, 10^{-1} M in 0.2 M K_2CO_3 buffer	0.20	10.4	0.0015	0.18[e]
0.18 M Im, 0.18 M ImH, and five dilutions	0.20	7.45	0.0020	0.036
0.08 M Im, 0.008 M ImH, and four dilutions	0.20	8.08	0.0022	0.052
0.70 M Im, 0.10 M ImH, and five dilutions	0.20	7.83	0.0020	0.052
0.20 M Im, 0.04 M ImH, and five dilutions	0.20	7.90	0.0016	0.048
1.0 M Imidazole		10.1		0.049
0.60 M MeIm, 0.20 M MeImH, and one dilution	0.20	7.4	0.003	0.022
0.20 M Tris, 0.20 M TrisH	0.20	8.29	0.0018	<0.0018
0.20 M KF	0.20		0.0021	<0.001
$NaNO_2$, 10^{-3}, 10^{-2}, 5×10^{-2} M in 0.2 M K_2CO_3 buffer		10.3	0.0022	0.008
Mercaptoethanol, 0.063 and 0.016 M in 0.1 M phosphate buffer, 10% MeCN	0.20	7.78	0.015	<10[d]
0.90 M pyridine, 0.09 M pyridineH in 10% MeCN	0.09	6.2		0.045
NaOH, 0.01, 0.04, 0.06, 0.08, 0.10, 0.14, 0.20 M	0.20		0.0019	1.04

[a] Ionic strength maintained with KCl unless otherwise noted. [b] Abbreviations used: Im, imidazole; MeIm, *N*-methylimidazole; *HOAc, acetic acid;* MeCN, *acetonitrile;* Tris, *tris(hydroxyethyl)aminomethane.* [c] Concentration of diphenylcarbamoyl chloride is 4×10^{-5} M. The substrate was dissolved in acetonitrile and introduced into the reaction medium to initiate the reaction. The final concentration of acetonitrile is 0.3% unless otherwise noted. k_o refers to the water term and k_n refers to the second order nucleophile term. [d] Calculated using a value of 9.5 for the pK_a of mercaptoethanol. [e] Calculated using a value of 9.6 for the pK_a of glycine. [f] Calculated using a value of 10.6 for the pK_a of butylamine. [g] Five separate determinations. [h] Nine separate determinations. [i] Five separate determinations in $NaClO_4$–$HClO_4$ mixtures. [j] Three separate determinations in 0.05, 0.10, and 0.20 M DCl, μ = 0.20.

k_g/k_b, the slope. This is in good agreement with the value of 0.071 M^{-1} min^{-1}/0.0025 min^{-1} = 28 M^{-1} obtained in the separate kinetic experiments.

The kinetics of the disappearance of **1** in various buffers are given in Table II. The salt effects and cosolvent effects are fairly small, as demonstrated by the less than 10% rate effect in the perchloric acid buffers of ionic strength varying from 0.02 to 1.0 M and the

TABLE III

KINETICS OF DIPHENYLCARBAMOYLPYRIDINIUM ION IN AQUEOUS SOLUTIONS AT 25°[e]

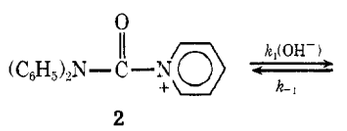
Reactant solutions	pH	k_{obsd}, min^{-1}	k_2, M^{-1} min^{-1}
H_2O–10^{-3} M HCl[a]		4.95×10^{-4}	
OH^-, determined[b] in 0.12 M Na_2CO_3 buffer and four dilutions	9.75	1.40 ± 0.25	$0.25 \pm 0.05 \times 10^5$
OH^-, determined[b] in 0.20 M Na_2CO_3 buffer and three dilutions	9.43	2.2 ± 0.2	$0.8 \pm 0.08 \times 10^5$
1.0 M NaOAc, 0.10 M HOAc[c]	5.68	0.17, 0.18	0.17, 0.18
0.50 M NaOAc, 0.05 M HOAc	5.65	0.079	0.16
1.0 M Na formate, 0.10 M formic acid[c]	4.58	0.18	0.18
1.0 M Na formate, 0.10 M formic acid[a]	4.58	0.21, 0.18	0.21, 0.18
0.50 M Na formate, 0.05 M formic acid[a]	4.55	0.13	0.26
0.02 M Sodium phosphate buffer[d]	7.0	0.0167, 0.0168	1.2
0.10 M Sodium phosphate buffer	7.56	0.069	0.78
0.02 M Tris buffer	7.28	0.0038	2.0
0.02 M Tris buffer[d]	9.0	1.16	3.6
Mercaptoethanol 0.0135 M in 0.02 M phosphate buffer[d]	7.0	20	4.7×10^5 [d]
Mercaptoethanol, 0.0068 M in 0.2 M phosphate buffer[d]	7.0	11	5.2×10^5
Mercaptoethanol, 0.000138 M in 0.02 M phosphate buffer[d]	7.0	0.20, 0.26	5.6×10^5, 4.2×10^6

[a] Followed at 280 nm. [b] Followed at 340 nm. [c] Followed by alkaline quenching method. [d] Based on a pK_a value of 9.5 for mercaptoethanol. [e] Abbreviations: Tris, tris(hydroxymethyl)aminomethane; AcO, acetate.

25% rate decrease obtained by adding 10% acetonitrile to the aqueous medium. The reaction of **1** with hydroxide is relatively slow, with the result that the alkaline hydrolysis term does not become important until the pH is raised to 12.2. The activation parameters for the hydrolysis of **1** determined in 0.01 M HCl at 48.8 and 25° are $\Delta H^{\ddagger} = 22$ kcal and $\Delta S^{\ddagger} = -5$ eu. Diphenylcarbamoyl chloride hydrolyzes at nearly the same rate in heavy water as in light water, giving a value of 1.2 for the solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}.

No terms second order in imidazole or first order in imidazole and first order in hydroxide ion could be detected for the interaction of diphenylcarbamoyl chloride with imidazole, when the reaction is carried out in a 1.0 M imidazole solution at pH 10.9.

Diphenylcarbamoylpyridinium Chloride.—In contrast to **1**, **2** is very sensitive to attack by nucleophiles, as demonstrated by the kinetic results in Table III. Also, **2** undergoes a ring-opening reaction in more alkaline solution to produce the Schiff base of 1,1-diphenylurea and glutacondialdehyde **3**, which absorbs maximally at 422 nm in its anionic form and 340 nm in its neutral form, $pK_a = 12$ according to eq 2. This



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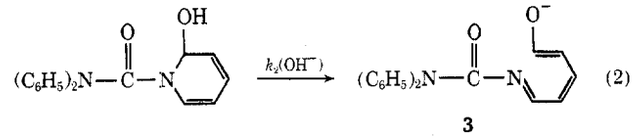

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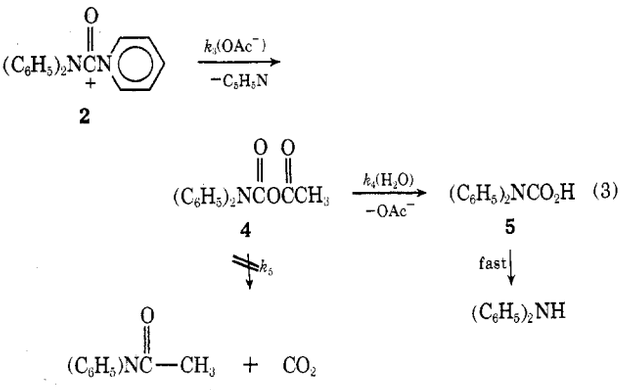
reaction is second order in hydroxide with a specific rate constant of k_1k_2/k_{-1} of 10^9 M^{-2} min^{-1}, as determined by using the same techniques as were used with dimethylcarbamoylpyridinium ion.[10]

(10) S. L. Johnson and K. A. Rumon, *Biochemistry*, **9**, 847 (1970).

The products of the reaction of nucleophiles with diphenylcarbamoylpyridinium ion have varying degrees of stability. The acetate derivative is only stable enough to be detected as a kinetic intermediate in the reaction given by eq 3. The intermediate diphenyl-



2 **4** **5** (3)

carbamoyl acetate **4** yields diphenylamine quantitatively in the k_4 step with a rate comparable to the rate of attack of 0.5 or 1.0 M acetate with **2** in the k_3 step. The kinetics of diphenylamine production followed at 280 nm are not first order, but rather show a lag period and therefore were treated by the method of consecutive kinetics. The rate constant for the interaction of acetate with **2** is 0.17 min^{-1} M^{-1}, as determined separately by the alkaline quenching method which measures directly the substrate concentration. The rate constant for the production of diphenylamine from **4** is estimated to be 0.25 min^{-1} when the absorbance changes at 280 nm are treated according to eq 4. A similar treatment

$$\frac{[(C_6H_5)_2NH]_t}{[(C_6H_5)_2NH]_0} = 1 + \frac{1}{k_3 - k_4}(k_4e^{-k_3t} - k_3e^{-k_4t}) \quad (4)$$

of the reaction in 0.5 M acetate buffer yields a nearly identical value of 0.20 min^{-1} for k_4, indicating that the intermediate **4** is not subject to nucleophilic or general base-catalyzed decomposition under these conditions. The decomposition rate of diphenylcarbamic acid **5**

under the conditions used here (pH 5.7) is much greater than the rate of formation of **5**, so that k_4 is rate limiting in the production of diphenylamine. The rate constant for this process is 10^2 min^{-1}.[11] The properties of diphenylcarbamoyl acetate can be compared with those of dimethylcarbamoyl acetate ($k_4 + k_5 > 0.08$ min^{-1}), which is produced from the reaction of dimethylcarbamoylpyridinium ion with acetate at a lower rate than its decomposition rate.[12] The acetate derivative yields 50% dimethylacetamide by rearrangement and 50% dimethylamine by hydrolysis at pH 5.4.[12] In contrast **4** does not internally rearrange (the k_5 step in eq 3), but rather quantitatively yields diphenylamine in the k_4 hydrolysis step.

The intermediate diphenylcarbamoyl formate, produced from the interaction of formate with **2**, decomposes with a rate constant which is at least five times greater than the rate constant for its production in the presence of 0.5 and 1.0 M formate. This is demonstrated by the identical first-order kinetics obtained from measuring either the amount of substrate present by the method of alkaline quenching, or by measuring the amount of diphenylamine produced by observing the reaction at 280 nm. A quantitative yield of diphenylamine was obtained, indicating that the intermediate diphenylcarbamoyl formate hydrolyzes only to diphenylamine rather than internally rearranging to diphenylformamide, which would be expected if its behavior were similar to that of dimethylcarbamoyl formate.[12]

The reaction of **2** with mercaptoethanol yields a stable thiol ester of diphenylcarbamic acid which absorbs maximally at 241 nm and does not hydrolyze to diphenylamine at pH 7.0 in a 0.1 M phosphate buffer over a period of 1 week. That **2** reacts with thiol to yield thiol esters, rather than other products such as pyridine ring addition products, is demonstrated by the isolation in high yield of the mercaptoethanol thiol ester upon treatment of **2** with mercaptoethanol in aqueous solution. (See Experimental Section.) The phosphate derivative of **2** absorbs maximally at 237 nm and decomposes very slowly at pH 7.56 to diphenylamine with an estimated half-life of 3–4 days. The hydroxylamine derivative of **2** or of **1** is very rapidly formed in a 0.1 M hydroxylamine solution, pH 6.3, and absorbs maximally at 237 nm, slowly decomposing overnight to give nearly quantitative amounts of diphenylamine as determined spectrally at 280 nm. Sodium sulfite reacts exceedingly rapidly with **2** to form a highly absorbing intermediate, λ_{max} 276 nm, which slowly decomposes over a week's time to the lesser absorbing diphenylamine. The sulfite reaction is too fast to measure using conventional techniques at pH 7 when quantities of sulfite as low as 10^{-4} M are used. The azide derivative of **2** is quite stable at pH 7.3, decomposing exceedingly slowly over a period of 1 week to give only slightly increased absorption at 280 nm. The above products from the interaction of **2** with nucleophiles are assumed to be the diphenylcarbamylated products by analogy with the corresponding dimethylcarbamylation of nucleophiles by dimethylcarbamoyl pyridinium ion.[12] Also, we have prepared diphenylcarbamoyl fluoride by treatment of **2** with KF in 10% aqueous acetonitrile. (See Experimental Section.)

Diphenylcarbamoylimidazole.—Because of the possibility that enzyme inhibition could involve histidyl residues, the chemical properties of diphenylcarbamoylimidazole were investigated. This compound represents an exceedingly stable acylimidazole derivative. Its spectrophotometrically determined pK_a value is 3.5. The rate of diphenylamine production followed in a 0.55 M formate buffer at pH 2.36 and in a 0.60 M formate buffer at pH 2.72 gives rate constants of 1.12×10^{-5} and 1.58×10^{-5} min^{-1} at 26°, respectively. These results can be analyzed according to eq 5. In contrast to its unreactivity to water and carboxylate ion, a rapid reaction of diphenylcarbamoylimidazole is observed with hydroxide ion, the specific rate constant from which is 3.6 M^{-1} min^{-1}, determined in 0.01–1.0 M NaOH solutions at 25°. This value is three times greater than the corresponding value for diphenylcarbamoyl chloride.

$$\text{rate} = [5.6 \times 10^{-5} + (\text{formate})\ 9.2 \times 10^{-5}] \times [(C_6H_5)_2NCOImH^+]\ min^{-1} \quad (5)$$

Other Diphenylcarbamoyl Derivatives.—The rate of the alkaline reaction of the p-nitrophenyl ester and of the alkaline and water reactions of the fluoride were determined. These results are summarized in Table IV with the alkaline and water reactions of the chloride, imidazole, and pyridinium derivatives.

TABLE IV

RATE CONSTANTS FOR THE HYDROXIDE AND WATER REACTIONS OF DIPHENYLCARBAMOYL DERIVATIVES AT 25°

Derivative	k_w, min^{-1}	k_{OH}, M^{-1} min^{-1}
Fluoride	3.8×10^{-6} [a]	77[b]
Chloride	1.8×10^{-3}	1.04
p-Nitrophenol		0.018[c]
Pyridine	4.95×10^{-4}	$2.5–8.0 \times 10^5$
Imidazole		3.6

[a] Determined in 10^{-1}–10^{-3} M HCl, 10% acetonitrile. [b] Determined in 10^{-2} M NaOH. [c] Determined in 0.88 M NaOH.

Discussion

The sensitivity of diphenylcarbamoyl chloride to reaction with nucleophiles is very small. This lack of sensitivity is most apparent in the low value of k_{OH}/k_w, the ratio of the hydroxide rate constant and the water rate constant, 500 M^{-1} for this substrate. The fluoride, on the other hand, has a k_{OH}/k_w value of 2×10^8 M^{-1}. Typical values of k_{OH}/k_w for most esters, both reactive and unreactive, is 10^9–10^{10} M^{-1}. Examples are 1.7×10^9 M^{-1} for diphenylcarbamoylpyridinium ion found here, 7×10^9 M^{-1} for p-nitrophenyl acetate, 20×10^{10} M^{-1} for phenyl acetate, 3.6×10^9 M^{-1} for 1-acetoxy-4-methoxypyridinium perchlorate, 2.2×10^9 M^{-1} for acetyl-4-methylpyridinium ion, and 3.9×10^8 for methyl chloroacetate.[13–15] No reaction of anionic nucleophiles with diphenylcarbamoyl chloride could be detected in the case of carboxylates, sulfite, phosphate, and carbonate. The value of 678 M^{-1} min^{-1} for k_{OH}

(11) S. L. Johnson and D. L. Morrison, *J. Amer. Chem. Soc.*, **94**, 1323 (1972).
(12) S. L. Johnson and K. A. Rumon, *ibid.*, **87**, 4782 (1967).
(13) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).
(14) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5442 (1970).
(15) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).

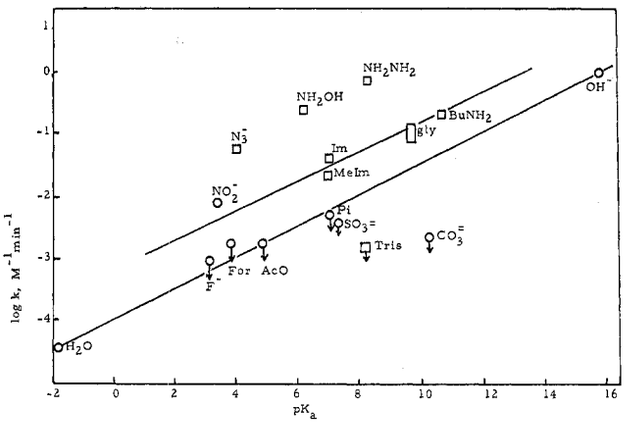


Figure 1.—Rate coefficients for nucleophilic reactions of diphenylcarbamoyl chloride *vs.* pK_a of the nucleophile. Abbreviations: gly, glycine; For, formate; AcO, acetate; Tris, tris(hydroxymethyl)aminomethane; Im, imidazole; MeIm, *N*-methylimidazole; Pi, phosphate; ○, oxygen nucleophiles; □, nitrogen nucleophiles. Data from Table II.

(32°, 25% acetonitrile) reported by Erlanger, *et al.*,[16] is in error, because this value was determined at a single pH value of 7.6 where there is no significant hydroxide reaction with diphenylcarbamoyl chloride. Because of the insensitivity to nucleophilic attack the hydroxide reaction does not become important until pH 11 due to its low value of 1 M^{-1} min^{-1}.

On the other hand, diphenylcarbamoyl chloride does react directly with amines forming the corresponding *N*,*N*-diphenylurea derivatives, and with the reactive anionic nucleophiles azide and nitrite. Greater reactivity to the "α effect" nucleophiles hydrazine and hydroxylamine than to primary amines of similar basicity is displayed, as shown in Figure 1, where the rate constants for the nucleophilic reactions are plotted against the pK_a of the nucleophile. The plot separates into two distinct lines; the amines are more reactive for their basicity than the oxygen nucleophiles water and hydroxide. The sensitivity to nucleophilic attack is small with the slope of the lines (the β values) being 0.25. The reactivity of nucleophiles to diphenylcarbamoyl chloride can be correlated with their nucleophilic reactivity to *p*-nitrophenyl acetate as shown in Figure 2 where also nucleophilic reactivity to diphenylcarbamoylpyridinium ion is shown. The slope for this plot is 0.5 for diphenylcarbamoyl chloride and 1.1 for diphenylcarbamoylpyridinium ion. The slope of 0.5 is considerably smaller than the slopes of unity for most reactions,[17] thereby suggesting very little bond making in the transition state for diphenylcarbamoyl chloride. The small negative entropy of activation of −5 eu and the solvent deuterium isotope effect of 1.2 for the water reaction of diphenylcarbamoyl chloride is in contrast to the large negative entropies of activation of −20 to −30 eu[18] and the sizable solvent isotope effects of >2 observed in the water reactions of most carboxylic acid derivatives.[17] These results, combined with the low sensitivity (low β) in nucleophilic displacement reactions, suggest that the transition state for the reaction

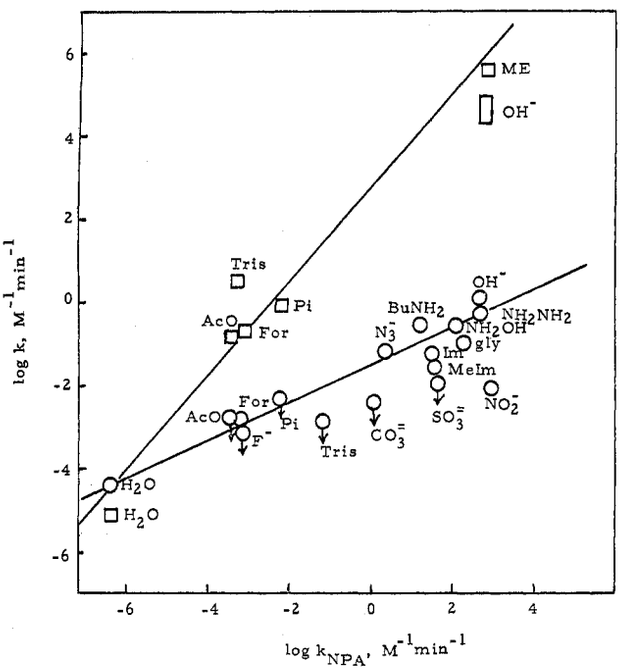
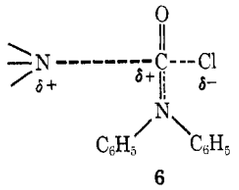


Figure 2.—Logarithmic plot of rate constants for the reactions of nucleophiles with *p*-nitrophenyl acetate, k_{NPA}, *vs.* the reactions of nucleophiles with diphenylcarbamoyl chloride, ○, and diphenylcarbamoylpyridinium ion, □. ME is mercaptoethanol; For, formate; AcO, acetate; Im, imidazole; MeIm, *N*-methylimidazole; Pi, phosphate. The formate rate constant for *p*-nitrophenyl acetate was estimated from the data of Fersht and Kirby[15a] for nucleophilic reactions of 2,4-dinitrophenyl acetate assuming a similar relative reactivity to *p*-nitrophenyl acetate. The other rate constants for *p*-nitrophenyl acetate has been summarized by Johnson.[17]

of diphenylcarbamoyl chloride with water and with other nucleophiles is very loose and nearly unimolecular. An even more extreme carbamoyl chloride reaction is that of dimethylcarbamoyl chloride, which exhibits an entropy of activation of 5 eu and is insensitive to reaction with added amine nucleophiles.[19,20]

In acyl transfer reactions from acyl compounds with good leaving groups Ferscht and Jencks found low sensitivity to the nucleophile basicity as well as low sensitivity to the basicity of the leaving group.[14] A very reactantlike transition state was suggested. The behavior of diphenylcarbamoyl chloride to nucleophilic reagents represents a very extreme example of low sensitivity to the reactivity of the nucleophile and can be accounted for by transition state **6**. The maintenance



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of sensitivity to factors other than basicity in the reactivity of diphenylcarbamoyl chloride to the "α nucleophiles" hydrazine and hydroxylamine as well as to azide ion, a situation similar to the reactions of acylpyridinium ions, suggests that highly reactive nucleophiles do not require much bonding in transition state **6** to exert their special reactivity.[14]

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Experimental Section

Materials.—Diphenylcarbamoylimidazole was prepared by allowing 1 *M* imidazole to react with 0.025 *M* diphenylcarbamoyl chloride in 30% aqueous dioxane at room temperature for 24 hr. Crystals were collected and recrystallized from ethanol, mp 119.3–122.5°, $\nu_{C=O}$ 1695 cm^{-1}. Analysis was performed by Schwarzkopf Analytical Service, Woodside, N. Y. *Anal.* Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.90; H, 4.93; N, 15.68. Diphenylcarbamoyl chloride 1,1-diphenylurea, ethyl diphenylcarbamate, and diphenylamine are from Distillation Products Industries. *p*-Nitrophenyl diphenylcarbamate is from Sigma Chemical Co. Dimethylcarbamoylpyridinium chloride was prepared by the method of Johnson and Rumon.[21] Diphenylcarbamoylpyridinium chloride, mp 107.5–108.5°, was prepared by the method of Herzog.[22] Diphenylcarbamoyl fluoride, mp 81.8–82.0°, was prepared by allowing equimolar KF and diphenylcarbamoylpyridinium chloride to react in 10% acetonitrile, and twice recrystallized from ethanol. This product has the same melting point as the diphenylcarbamoyl fluoride obtained by treatment of diphenylcarbamoyl chloride with SbF_3 in xylene.[5] The mercaptoethanol thiol ester of diphenylcarbamic acid was prepared from the treatment of II, 0.10 *M*, with 0.2 *M* mercaptoethanol, pH 8.0, for 5 min. The product was isolated in 89% yield in the crude form and recrystallized from ethanol, mp 77.5–78.5°. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 65.91; H, 5.53; N, 5.13; S, 11.71. Found: C, 65.38; H, 5.59; N, 5.03; S, 13.23. The infrared spectrum of this compound (taken with a Beckman IR-4 spectrometer) shows an OH stretching frequency at 3450 cm^{-1}, a carbonyl stretching frequency at 1666 cm^{-1}, and a single carbonyl stretching frequency at 1666 cm^{-1}. The latter frequency is in contrast with the 1724 cm^{-1} frequency of ethyl diphenylcarbamate, and serves to rule out the formation of the isomeric oxygen ester in the reaction. The presence of the OH stretching frequency confirms this structure because the isomeric product would have only a weak band due to SH stretching at *ca.* 2400 cm^{-1}. The thiol ester product absorbs maximally at 241 nm in the uv.

Chemical Kinetics.—The hydrolysis rate of diphenylcarbamoyl chloride, fluoride, -imidazole, and -pyridinium ion was followed by measuring the increase in absorption produced at 280 nm by the diphenylamine product. In case of acetate, phosphate, Tris, and thiol-containing buffers which react directly with diphenylcarbamoylpyridinium to form products which do not rapidly liberate diphenylamine, the disappearance of the substrate was measured by utilizing the ability of carbamoylpyridinium ions to undergo ring-opening reactions which produce chromophoric materials.[20] In this case diphenylcarbamoylpyridinium ion is allowed to react with the desired buffer, and 1-ml aliquots are removed at timed intervals and placed in 5 0-ml portions of 1 *M* NaOH. The absorbances of these solutions are then measured at 422 nm. At this pH the chromophoric material disappears only slowly with a specific rate constant of 0.012 min^{-1}.

The reaction of diphenylcarbamoylpyridinium ion with more basic buffers was followed at 340 or 422 nm, which is a measure of the concurrent ring-opening process. The alkaline hydrolysis of diphenylcarbamoyl chloride was followed at 245 nm in 0.01–1 *M* NaOH. Diphenylcarbamate, λ_{max} 245 nm, is the stable product from this reaction from diphenylcarbamoyl chloride, λ_{max} 227 nm. The reaction of diphenylcarbamate to produce diphenylamine depends only on hydrogen ion and has a specific rate constant $k_H = 0.45 \times 10^8\ M^{-1}\ min^{-1}$ at 25°.[11] The result is that this carbamate is the stable product of diphenylcarbamoyl chloride in alkaline solutions. The alkaline hydrolysis of diphenylcarbamoyl chloride and fluoride and of diphenylcarbamoylimidazole was also followed by a quenching procedure, in which appropriate amounts of 1 *M* acetic acid are added to aliquots from the alkaline reacting solutions. This gives a pH 4–6 solution, depending upon the conditions, in which diphenylcarbamate from the alkaline hydrolysis reaction readily produces diphenylamine which can be monitored at 280 nm. The pK_a of diphenylcarbamoylimidazole was measured by placing known quantities of the substrate in buffers of various pH values and measuring the absorbance of the acid form at 226.5 nm and the basic form of the substrate at 233 nm. The relationship $pK = pH + \log A_u - A/(A - A_i)$ was used, where A_i, A_u, and A are optical absorbances of the fully ionized form the unionized form, and observed form, respectively.

Analysis of Kinetics.—Semilog plots of $A_t - A_\infty$ *vs.* time were made, where the *A*'s refer to the optical absorbances. Good linearity is achieved to past 90% reaction in most cases. The rate constant is calculated from the slope of the line divided by 2.303. The observed rate constants are plotted against the buffer concentration if a series of buffers of constant pH and varying concentration is used. The slope of such a plot is taken as the specific rate constant, k_2, for the interaction of the substrate with the buffer component. The intercept, k_1, is equal to $k_w + k_{OH^-}(OH^-)$, the sum of the water and hydroxide terms. In the case where hydroxide is the variable buffer component k_o refers to the water term, k_w.

Registry No.—1, 83-01-2; 2, 33712-38-8; diphenylcarbamoyl fluoride, 10055-41-1; *p*-nitrophenyl diphenylcarbamate, 3848-46-2; diphenylcarbamoylimidazole, 2875-79-8; mercaptoethanol thiol ester of diphenylcarbamic acid, 33712-42-4.

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Micellar Effects upon the Decarboxylation of 3-Bromo and 2-Cyano Carboxylate Ions[1]

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The decarboxylation of 2-cyano-2-phenylacetate ion *via* an intermediate carbanion is catalyzed *ca.* 660-fold by micelles of cetyltrimethylammonium bromide, CTABr, but that of 3-bromo-3-phenylpropionate ion *via* an intermediate carbonium ion is retarded by cationic micelles. The micellar-catalyzed decarboxylation of the 2-cyano acetate ion is enhanced by added inorganic salts, but added salts reduce the micellar inhibition of the decarboxylation of the 3-bromo propionate ion.

Decarboxylation of the 6-nitrobenzisoxazole-3-carboxylate ion (I) is strongly catalyzed by cationic micelles of cetyltrimethylammonium bromide (CTABr).[3] This implies that the transition state with its delocalized negative charge interacts more strongly than I with the cationic micelle. We were therefore interested in examining micellar effects upon decarboxylations of other carboxylate ions. Two reactions, having different mechanisms, were examined.

The decarboxylation of 2-cyanocarboxylate ions (II)

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