The Reactivity of Phenyl Isocyanate in Aqueous Solution

By **Anthony F. Hegarty,*** **Con N. Hegarty,** and **Francis L. Scott,** Chemistry Department, University College, Cork, Ireland

The rate of hydrolysis of 1-phenylcarbamoylimidazole (3) in water at 30° is markedly depressed by the addition of imidazole in the pH region 6–10. This is rationalised in terms of the formation of a small equilibrium concentration of phenyl isocyanate in solution. Phenyl isocyanate, besides reacting with imidazole to regenerate (3), can also be competitively trapped by H_2O, HO^-, and other nucleophiles: the relative rates of reaction of HO^- and H_2O with phenyl isocyanate are $7 \times 10^5 : 1$. Phenyl isocyanate also shows a low sensitivity to the nature of primary amine nucleophiles with a Brønsted β value of 0.30. Secondary and α-effect amines lie on the same correlation line as primary amines, consistent with a transition state in which there is little bond formation. In all cases, urea formation shows simple second-order kinetics (first order each in amine and phenyl isocyanate) and no catalysis by general acids or bases (or by products formed) is observed: this contrasts with the results of previous studies which have been carried out in non-aqueous solution.

ARYL ISOCYANATES (1) react readily with a wide variety of nucleophilic reagents to form addition products. Thus both amines and alcohols give substituted ureas and carbamates (2; Y = NHR or OR). These reactions have been widely studied from a synthetic

$$\underset{(1)}{Ar{-}N{=}C{=}O} \longleftrightarrow Ar{-}N{=}\overset{+}{C}{-}\overset{-}{O} \xrightarrow{+HY} \underset{(2)}{Ar{-}NH{-}\overset{O}{\overset{\|}{C}}{-}Y}$$

standpoint and have been the subject of two recent reviews.[1,2]

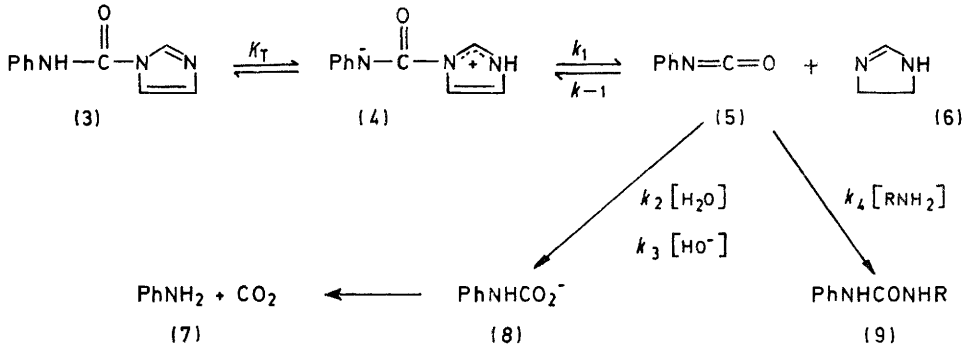
The kinetics of the reactions of phenyl isocyanate with alcohols, amines, and water in non-aqueous solvents were extensively studied by Baker and his co-workers in a classic series of experiments.[3-10] The reaction followed complex second-order kinetics with the added complication that the rate constant obtained depended on the ratio of the alcohol–isocyanate concentration. In addition, catalysis by the products formed was also noted in some cases. Recently Satchell

[1] R. G. Arnold, J. A. Nelson, and J. J. Verbane, *Chem. Rev.*, 1957, **57**, 47.
[2] S. Ozaki, *Chem. Rev.*, 1972, **72**, 457.
[3] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 1947, 713.
[4] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 1949, 9.
[5] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 1949, 19.
[6] J. W. Baker, M. M. Davies, and J. Gaunt, *J. Chem. Soc.*, 1949, 24.
[7] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 1949, 27.
[8] J. W. Baker and D. N. Bailey, *J. Chem. Soc.*, 1957, 4649.
[9] J. W. Baker and D. N. Bailey, *J. Chem. Soc.*, 1957, 4652.
[10] J. W. Baker and D. N. Bailey, *J. Chem. Soc.*, 1957, 4663.

and his co-workers [11] have criticised the techniques used by previous workers (particularly Baker) in estimating the rate constants in these reactions. Satchell has proposed that reaction may occur between the isocyanate and dimers or trimers of the alcohol at high alcohol concentrations.[11]

The solvents typically employed (benzene, hexane, ether) for these studies are of low dielectric constant which promotes association between substrate, reagents, and products.[12,13] Few studies have been carried out in water, possibly because phenyl isocyanate reacts rapidly with water over the entire pH range. We have used 1-phenylcarbamoylimidazole (3) in aqueous solution and have thus been able to measure the reactivity of isocyanate under these conditions for the first time.

The technique used depends on the observation [14] that (3) is hydrolysed in neutral solution *via* the zwitterion (4) to give initially phenyl isocyanate (5) and imidazole (6) (Scheme 1). It has been shown [14] that the substrate (3) is in equilibrium with the zwitterion (4) when sufficient concentrations of general acids or bases are present; under these conditions k_{obs} [for hydrolysis of (3)] $= k_1K_T$. The addition of imidazole to the reaction



SCHEME 1

solution has a dual result: (*a*) imidazole, by acting as a general acid–base brings about a true equilibrium between (3) and (4) and (*b*) imidazole also reacts with the isocyanate formed to regenerate (4) and ultimately the substrate (3). At high imidazole concentrations (>0.01M) the effect of (*b*) is dominant with the result that the rate of hydrolysis of (3) actually decreases markedly as the imidazole concentration in solution is increased (Table 1).

TABLE 1

Observed rate constants for the hydrolysis of (3) in imidazole buffers [H_2O, 30 °C, μ = 1.00 (KCl)]

pH	10^3 Total imidazole concentration (M)	$10^3 k_{obs}$ (s^{-1})
5.10	2.84	31.1
5.10	5.68	27.4
5.10	8.52	24.5
5.10	11.36	20.5
6.00	2.84	20.5
6.00	5.68	15.2
6.00	8.52	9.6
6.00	11.35	7.9
6.00	14.20	6.6
6.70	2.84	5.97
6.70	5.68	5.76
6.70	8.52	4.23
6.70	11.36	2.98
7.20	2.84	5.50
7.20	5.68	3.10
7.20	8.52	2.17
7.20	11.36	1.64
7.70	2.84	3.58
7.70	5.68	2.08
7.70	11.36	1.06
8.00	8.52	1.46
9.00	8.52	2.87
9.25	8.52	3.62
9.70	8.52	6.67
10.08	8.52	11.11

These results can be interpreted in terms of equation (1) which was derived on the assumptions that (i) (3) and (4) are in equilibrium; (ii) in the presence of excess of imidazole, (5) is present in a small steady-state concentration; and (iii) the isocyanate (5) may react with nucleophiles, neutral imidazole, water, or hydroxide (Scheme 1). Equation (1) implies [see equation (2)]

$$k_{obs} = \frac{k_1K_T(k_2[H_2O] + k_3[HO^-])}{k_{-1}[Im]_T \cdot K_a/(a_H + K_a) + k_2[H_2O] + k_3[HO^-]} \quad (1)$$

that a plot of $1/k_{obs}$ against total imidazole concentration ($[Im]_T = [Im] + [ImH^+]$) would be linear at each pH and this is actually observed (Figure 1). When $1/k_{obs}$ is plotted against free imidazole concentration then the slope obtained $\{= k_{-1}/k_1K_T(k_2[H_2O] + k_3[HO^-])\}$ is independent of pH in the region 6.0—7.7. Since imidazole itself has a pK_a of 7.20, this implies that neutral water and imidazole free base are the only species which react

$$\frac{1}{k_{obs}} = \frac{k_{-1}}{k_1K_T(k_2[H_2O] + k_3[HO^-])}[Im] + \frac{1}{k_1K_T} \quad (2)$$

presence of excess of imidazole to generate a small equilibrium concentration of phenyl isocyanate in

[11] S. A. Lammiman and R. S. Satchell, *J.C.S. Perkin II*, 1972, 2300.

[12] A. E. Oberth and R. S. Bruenner, *J. Phys. Chem.*, 1968, **72**, 845.

[13] A. Farkas and G. A. Mills, *Adv. Catalysis*, 1962, **13**, 393.

[14] A. F. Hegarty, C. N. Hegarty, and F. L. Scott, *J.C.S. Perkin II*, 1974, 1258.

with the isocyanate (5) in this pH region (*i.e.* $k_2[H_2O] \gg k_3[HO^-]$). Figure 2 presents a summary of the inverse slopes $\{= k_1K_T(k_2[H_2O] + k_3[HO^-])/k_{-1}\}$ of these plots as a function of pH. It is seen that at pH >8.0, the value of this function increases with pH and eventually becomes proportional to the hydroxide ion concentration (*i.e.* at pH >9, $k_3[HO^-] \gg k_2[H_2O]$). Under these

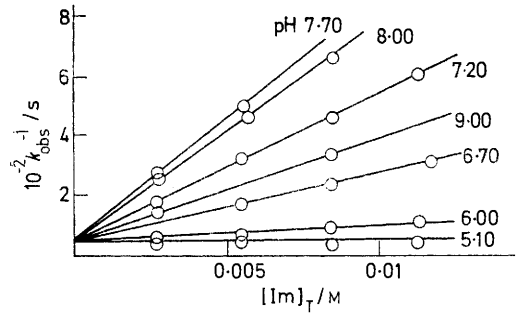


FIGURE 1 Plots of the inverse of the observed rate constant for the hydrolysis of (3) (H_2O, 30°, μ = 1.0) against total imidazole concentration at pH 5.10—9.00. The slopes of these plots increase from 5.10 to 7.70 as the fraction of free imidazole present is increased; at pH >8.0 the slopes decrease due to more effective trapping of phenyl isocyanate by hydroxide ion

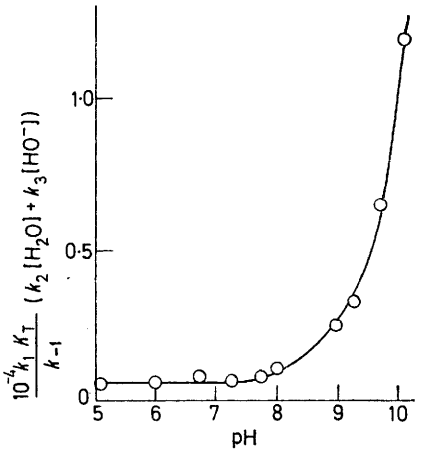


FIGURE 2 Plot of the inverse of the slope of plots of $1/k_{obs}$ against [Im] (data from Table 1) against pH

conditions therefore hydroxide ion (rather than water) is the principal competitor for the isocyanate.

Using these data it is possible therefore to calculate the relative efficiencies of water and imidazole as reactants for phenylisocyanate. Since k_1K_T for (3) has previously been reported [14] as 5.8×10^{-2} s^{-1}, and using $[H_2O] = 55.5$M, it is possible to estimate (from Figure 2) k_{-1}/k_2 as 3.5×10^4. This implies that imidazole is *ca.* 3.5×10^4-fold more reactive than water towards phenyl isocyanate. From data at higher pH (Figure 2) (where attack by HO^- is dominant) it is possible to calculate that k_3/k_{-1} is 20. Thus HO^- reacts with (5) 20-fold more rapidly than does free imidazole. This is the correct order based on the expected nucleophilicities of the two reagents but the difference is surprisingly small. However, the two nucleophiles are not really of the same type, having different charges and nucleophilic atoms; moreover hydroxide ion normally shows large negative deviations from Brønsted plots which include other oxyanions.[15,16] With these reservations, since HO^- reacts with (5) 7×10^5-fold more rapidly than does H_2O, the Brønsted β value for nucleophilic attack can be estimated as *ca.* 0.33.

This technique can also be extended to the study of other nucleophiles with phenyl isocyanate in water. By following the reaction of (3) in the presence of a large (constant) concentration of imidazole at fixed pH, we can essentially generate a small equilibrium concentration of phenyl isocyanate (5) in solution. The addition of another nucleophile (for example, an amine RNH_2) speeds the overall rate of disappearance of (3) by reacting with (5) to give inert products [the ureas (9)]. A good nucleophile competes most effectively with imidazole for (5), increasing the apparent rate of reaction of (3) (Scheme 1). This is best understood in terms of the kinetic equation (3) which relates the rate enhancement in the presence of added amine to the free imidazole concentration. For simplicity the reaction of (5) with H_2O and HO^- is eliminated by subtracting from k_{obs} the rate observed (k_0) when $[RNH_2] = 0$.

$$k_N = k_{obs} - k_0 = \frac{k_1K_Tk_4[RNH_2]}{k_{-1}[Im] + k_4[RNH_2]} \quad (3)$$

$$1/k_N = \frac{k_{-1}[Im]}{k_1k_Tk_4} \cdot \frac{1}{[RNH_2]} + \frac{1}{k_1K_T} \quad (4)$$

$$k_N = \frac{k_1K_T \cdot k_4}{k_{-1}[Im]} \cdot [RNH_2] \quad (5)$$

The results obtained using morpholine are summarised in Table 2. A constant imidazole concentration (usually total imidazole = 0.02M) was used in all cases while the rate of reaction of (3) was determined in the

TABLE 2

Observed first-order rate constants for the solvolysis of (3) in 0.02M-imidazole$_T$ in the presence of added morpholine at various pH at 30° (μ = 1.00, KCl)

	[Morpholine]				
pH	0.0027M	0.0054M	0.0081M	0.0108M	k_4/k_{-1}
6.90		6.50	9.75	13.1	7.00
7.20	5.00	9.10	13.0	16.8	7.05
7.51	7.51	14.0	21.0	22.7	7.00
7.80	10.5	20.0			7.10

presence of increasing concentrations of morpholine. Plots of $1/k_N$ against 1/[morpholine] are linear (see Figure 3) as implied by equation (4) [which is derived by inversion of equation (3)]. The slopes of these plots yield a single value for k_4/k_{-1} (= 7.0) which is pH independent. This confirms that imidazole and amine free bases are the only species which react with phenyl

[15] T. C. Bruice and S. J. Benkovic, ' Bioorganic Mechanisms,' Benjamin, New York, vol. 1, 1956.

[16] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

isocyanate (5); neither reaction is acid or base catalysed over the pH region studied.

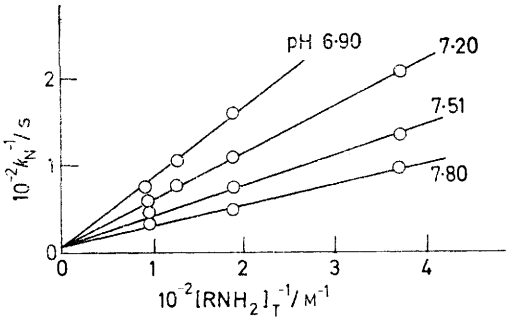


FIGURE 3 Double reciprocal plot of $1/k_{obs}$ against $1/k_N$ for the hydrolysis of (3) (H_2O, 30°, μ = 1.0, 0.02M added imidazole); the amine used is morpholine

Similar results were obtained using glycine, glycine ethyl ester, glycylglycine, hydrazine, ammonia, methylamine, dimethylamine, piperidine, and methoxylamine; the results obtained are summarised in Table 3. It is

TABLE 3

Summary of observed first-order rate constants for the reaction of (3) measured in 0.02M-imidazole$_T$ (30°; H_2O; μ = 1.0) in the presence of added amines

		10^3k_{obs} (s^{-1}) $10^3[RNH_2]$ (M)				
RNH_2	pH	2.7	5.4	8.1	10.8	k_4/k_{-1}
Glycine	7.20 [a]		2.42	3.20	3.95	17.4
Glycine ethyl ester	7.20		22.0	34.5	45.3	4.36
Glycylglycine	7.20	8.00	15.0	22.0	30.4	5.75
Hydrazine	7.20	15.0	30.0	45.0	60.0	5.01
Morpholine	7.20	5.0	9.1	13.0	16.8	7.05
Ammonia	7.20		29.0	44.5	58.0	12.6
Methylamine	9.00 [b]		12.0	18.5	23.8	30.2
Dimethylamine	9.00		14.1	20.5	27.1	36.3
Piperidine	9.00	18.5	33.0	51.5	67.3	54.9
Methoxylamine	7.20 [c]		5.50	7.00	10.44	0.44

[a] Rate of solvolysis of (3) in 0.02M-imidazole at pH 7.20 is 9.60×10^{-4} s^{-1}. [b] Rate of solvolysis of (3) in 0.02M-imidazole at pH 9.00 = 1.31×10^{-3} s^{-1}. [c] Measured in the presence of 0.05M added imidazole.

possible in some cases to use a simplified plotting technique to estimate k_4/k_{-1} values. Thus when the imidazole concentration is much higher than that of the amine, the isocyanate reacts more rapidly to regenerate (4) than to go on to give products (*i.e.* k_{-1}[Im] $\gg$ k_4[RNH_2]). Under these conditions equation (3) reduces to (5) which implies that k_N (or k_{obs}) should rise linearly as the amine concentration is increased; such a plot is shown in Figure 4. It was particularly convenient to determine the ratios k_4/k_{-1} under these conditions, since the slopes of plots of k_{obs} against [RNH_2] give the ratio directly. It must be emphasised that the same ratio was obtained independent of pH, [Im], or [RNH_2] used to study the reaction; the concentrations and pH used were chosen to give conveniently measureable rates over a reasonable range of reaction.

The results obtained are summarised in Figure 5 which shows a Brønsted type plot of log (k_4/k_{-1}) against the pK_a of the conjugate acid of the amine nucleophile. The relative nucleophilicities of the primary amines are excellently correlated by a line with slope (or β value) = 0.30. No serious deviations are observed, which is notable in a correlation of such a shallow slope. Note that this type of simple result (good second-order kinetics, absence of catalysis, direct correlation of rate constants with nucleophilicity) is in marked contrast to the earlier work in this field (see above).

The small β value observed suggests that the transition state is reached early on the reaction pathway;

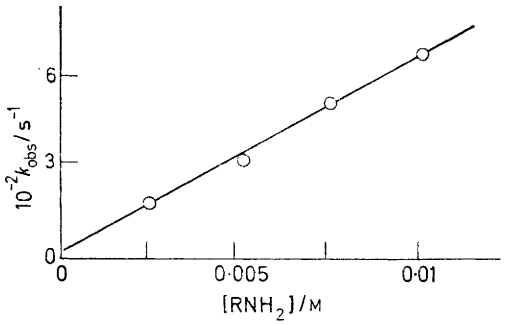


FIGURE 4 Plot of k_{obs} for the hydrolysis of (3) in the presence of 0.02M-imidazole at pH 9.0 as a function of added morpholine; the plot is linear at low [morpholine] and gives the competition ratio k_4/k_{-1} directly

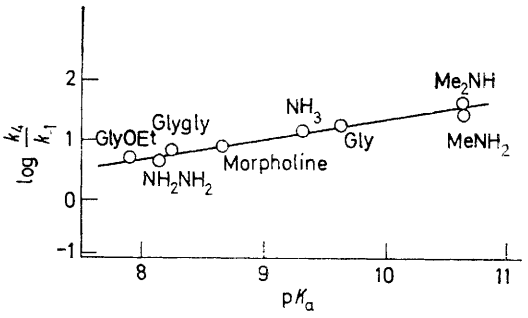
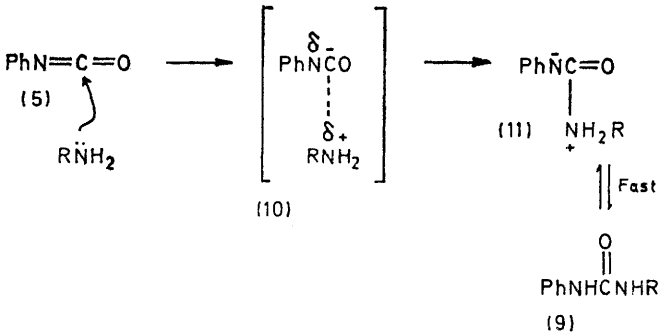


FIGURE 5 Brønsted plot of log k_4/k_{-1} against the pK_a of the conjugate acids of the amines used; the slope (or β value) is 0.30

there is little C–N bond formation and consequently the nitrogen of the attacking amine does not have to



SCHEME 2

bear much positive charge in the transition state (Scheme 2). Thus, little sensitivity to the nature of the

amine is shown. The maximum value of β has been estimated by Jencks and his co-workers as +1.74 for a reaction involving nucleophilic attack by an amine on an acyl centre.[17] Thus, on an approximate basis, we can conclude that the transition state (10) represents *ca.* 20% bond formation between carbon and nitrogen. Since no catalysis by a second mole of the amine was observed in the present instance, the subsequent proton transfer steps [(11) ⇌ (9)] are not rate limiting.

In the Brønsted plot (Figure 5) it is noted that secondary amines (morpholine, piperidine, and dimethylamine) do not deviate greatly from the line which correlates the primary amines. This is unusual behaviour for amine attack on an acyl centre [18] but most likely arises from the small degree of bond formation observed in the transition state. Since the C–N bond remains long in the transition state the more encumbered secondary amines can be accommodated without difficulty. Also notable is the observation that the data for both hydrazine and methoxylamine (not shown) lie close to the correlation line. These are amines which normally show an 'α-effect,' *i.e.* their reactivity toward acyl (though not necessarily sp^3) [19] carbon is enhanced relative to other amines. However, a recent report by Dixon and Bruice [20] has shown that the magnitude of the α-effect is not invariant and depends on the nature of the unsaturated sp^2 carbon centre involved. A direct relationship was observed between the magnitude of the effect and the Brønsted β value for the reaction. Thus, when β is large (>1), which implies a transition state with a large degree of bond formation, the observed α-effect is also large; presumably in such a reaction the demand for delocalisation of the accumulated charge in the transition state is largest. In the present instance the opposite effect is operative. Since β is small, the demand for delocalisation of charge in the transition state is relatively less important; consequently, the α-effect nucleophiles do not show enhanced reactivity.

It is interesting that tertiary amines, which cannot form stable urea adducts with phenyl isocyanate, do not speed up the rate of reaction of (3) (measured in the presence of an excess of imidazole). Thus, the rate of disappearance of (3) is the same in the presence or absence of added *N*-ethylmorpholine or triethylamine (0.01M). The tertiary amines can theoretically also react with phenyl isocyanate but the adduct formed in this case, unlike (11), cannot tautomerise to the stable urea (9). By analogy with the zwitterion (4), it is expected that the adduct formed from tertiary amines would be highly reactive, dissociating to regenerate the starting isocyanate.

It was shown previously [14] that the rate-determining steps for the hydrolysis of (3) in purely aqueous solution (in the absence of added buffer species) in the pH region 4—10 were the proton transfer reactions by means of which the zwitterion (4) is formed from (3). This has the important consequence that in the reverse reaction (by the principle of microscopic reversibility) the same step is rate determining. The reverse reaction involves nucleophilic attack by the amine imidazole on phenyl isocyanate to give ultimately the urea (3). It is clear that in this reaction (pH 4—10, aqueous solution) the conversion (4) ⟶ (3) is the slow step. In the presence of larger quantities of imidazole, of course, the proton transfer (4) ⟶ (3) is speeded up to such an extent that the nucleophilic attack step (6) + (5) ⟶ (4) is rate controlling. It has been shown that a similar change-over in mechanism from rate-determining amine attack [(5) ⟶ (10), Scheme 2] to tautomerism to the urea [(11) ⟶ (9)] may occur generally in the case of the weaker amine bases with cyanic acid.[21]

The likelihood that the proton transfer step is generally rate determining in non-aqueous solvents is supported by some recent work reported by Briody and his co-workers.[22] Acetonitrile was used as solvent to study the reaction of aniline with phenyl isocyanate. In support of a rate-limiting proton transfer in this case was the observation of a primary isotope effect (k_H/k_D = 1.3—2.0) and the fact that sterically hindered amines (such as 2,6-dimethylpyridine) are effective catalysts.

Because of the rapid reaction of phenyl isocyanate with hydroxide ion above pH *ca.* 10 it was not possible to obtain reliable data for other nucleophiles in this region. Also since only free imidazole (and not its conjugate acid) is able to trap phenyl isocyanate to reform (3), the rate of hydrolysis of (3) is not significantly depressed by added imidazole at pH <*ca.* 6. This limits the effective pH range in which measurements can be made with (3) to the region 6—10; this is not too restrictive since most amine nucleophiles either have pK_as in this range or exist partly in the free base form. Moreover the lower limit at which measurements can be made can be reduced to pH *ca.* 3 by the use of 1-phenylcarbamoylbenzimidazole in the presence of benzimidazole; the k_1K_T value for this substrate is also known (= 1.25×10^{-2} in water at 30°).[14]

EXPERIMENTAL

Materials.—Standard solutions (1.0M) of glycine, glycine ethyl ester hydrochloride, methylamine hydrochloride, dimethylamine hydrochloride, morpholine hydrochloride, piperidine hydrochloride, ammonium chloride, imidazole, hydrazine hydrate, *N*-ethylmorpholine, trimethylamine hydrochloride, and methoxylamine in twice-distilled water were prepared at 30°. A standard solution (0.2M) of glycylglycine in twice-distilled water was also prepared (this compound has limited solubility in water). Glycine, glycylglycine, glycine ethyl ester hydrochloride, and

[17] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.
[18] T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265.
[19] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, 1967, **89**, 2327.
[20] J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2052.
[21] A. Williams and W. P. Jencks, *J.C.S. Perkin II*, 1974, 1753, 1760.
[22] J. M. Briody and D. Narinesingh, *Tetrahedron Letters*, 1971, 4143.

ammonium chloride were AnalaR grade. Methylamine, dimethylamine, morpholine, trimethylamine, and piperidine were converted into their hydrochlorides before use and then recrystallised from ethanol–ether and dried in a vacuum desiccator over P_2O_5. Hydrazine hydrate, *N*-ethylmorpholine, and methoxylamine were used without further purification.

Kinetic Experiments.—All rate data were measured on a Cary 14 recording spectrophotometer which was fitted with a Radiometer pH-stat assembly, which comprised a Radiometer PHM 26 pH meter, a titrator (type TTT 2b), and an autoburette (type ABU 1C). A Metrohm EA 125U electrode, which was standardised using Radiometer aqueous buffer solutions, was also used. A thermostatted cell (36.5 ml) (Pyrex with quartz windows) was mounted in the cell compartment of the spectrometer and the contents were stirred magnetically. Into the cell (but above the light beam) dipped a Metrohm EA 125U pH electrode which recorded the pH of the solution and provided feedback to the titrator to control the addition of the acid–base used to maintain the pH of the solution; the acid–base was added *via* a Teflon capilliary tube which was adjacent to the pH electrode. The kinetics of hydrolysis of the substrate (3) were studied by following the change in optical density of the substrate at a suitable wavelength (usually 250 nm); further details have previously been described.[14]

In a typical kinetic experiment, an aqueous solution of 0.02M-imidazole (36.5 ml) (μ = 1.00, KCl) was pipetted into the thermostatted cell at 30° in the spectrometer. A portion (0.1 ml) of the standard solution of the amine under investigation was then pipetted into this solution and the contents of the cell allowed to reach thermal equilibrium. Acid or base was then added (*via* the pH-stat) to bring the solution to the desired pH. A drop (*ca.* 10 μl) of a solution of the substrate (3) in acetonitrile or dioxan was then added to initiate reaction and the kinetics followed by observing the decrease in optical density at a suitable wavelength. A pseudo-first-order rate constant was then calculated from the data. The procedure was repeated several times using various portions of added amine (0.2, 0.3, 0.4 ml *etc.*) and the rate constants calculated from the pseudo-first-order plots obtained for each case. A plot of the dependence of the observed rate constant on the concentration of the added amine was thus obtained, from which could be calculated the relative abilities of the amine and imidazole to trap the phenyl isocyanate liberated in the reaction.

This procedure was then repeated for each of the other amines under investigation; the exact conditions (concentration of imidazole, pH, concentration of added amine) were selected for each amine to give the greatest possible range of variation in the observed rate.

[4/2203 *Received, 25th October,* 1974]