The Key Role of Zwitterionic Species in the Conversion of Ureas into Isocyanates in Aqueous Solution. Hydrolysis of 1-Phenylcarbamoylimidazole

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

N-Phenylcarbamoylimidazole (2) is converted into aniline and imidazole near neutral pH but is relatively unreactive in acidic and basic solution. The rate of hydrolysis of (2) varies in a complex way as the pH of the medium [H_2O; 30°; μ = 1·0 (KCl)] is changed, reaching two maxima at pH *ca.* 4·5 and 10·0. It is proposed that the zwitterionic tautomer (4) of (2) is the reactive species over the entire pH range [except in highly basic solution where the conjugate base of (2) reacts]. The rate of decomposition of the zwitterion (to imidazole and phenyl isocyanate initially) is so rapid ($t_{\frac{1}{2}}$ *ca.* 10^{-4} s) that the diffusion-controlled proton transfers involved in the formation of the zwitterion become rate limiting in the pH region 4—10. Addition of sufficient concentration of general acids or bases (except imidazole) can cause a change in the rate-limiting step to zwitterion decomposition in this pH region. Data are also presented for 1-phenylcarbamoylbenzimidazole (14), 1-(*p*-bromophenylcarbamoyl)imidazole (11), and 3,5-dimethyl-1-phenylcarbamoylpyrazole (12) and are interpreted similarly. The catalysis of the diffusion-controlled proton transfer steps by primary, secondary, and tertiary amine catalysts is investigated in detail for the hydrolysis of (14). Addition of low concentrations ($<5 \times 10^{-5}$M) of imidazole in neutral solution initially increases the rate of hydrolysis of (2) (imidazole acting as a general acid–base) but high concentrations of imidazole actually retard the overall rate of hydrolysis of (2). This is interpreted in terms of imidazole acting as an efficient trap for the phenyl isocyanate intermediate, thus regenerating the substrate.

THE hydrolysis of simple ureas has been thoroughly investigated under acidic, basic, and neutral conditions.[1-6] Much of the study of this reaction has been prompted by its possible relevance as a model system for urease catalysed hydrolysis. In concentrated acid the rate of reaction varies in a complex way with hydrogen ion activity and there is no consensus on the reactive species involved. Moodie and his co-workers [1] have suggested from detailed kinetic studies in concentrated sulphuric acid solution that the major reaction occurs *via* the diprotonated urea in the more acidic solutions. On the other hand O'Connor and Barnett [2] concluded that the data are best interpreted in terms of a single mechanism, unimolecular decomposition of the free base. In dilute acid solution, the rate of hydrolysis becomes pH independent.[3,4] The basic hydrolysis of urea has also been the subject of some investigation;[5,6] in this region ammonia and cyanate are the initial products formed. The kinetic form observed is complex and several reports suggest that the reaction does not proceed through a simple bimolecular pathway.[5]

All these studies have been hampered by the extremely low reaction rates encountered, *e.g.* $t_{\frac{1}{2}}$ >5 h for urea at 100° in water. We have found that by the incorporation of one nitrogen atom of a ureido-function into a heterocyclic system, the rates of hydrolysis can be increased enormously. It was thus possible to investigate in detail the various steps in the hydrolysis of such ureas and also to define the catalytic species which are involved in each step.

RESULTS AND DISCUSSION

The initial compound investigated was 1-phenylcarbamoylimidazole (2), which was synthesised by the reaction of phenyl isocyanate with imidazole in dry ether. In aqueous solution compound (2) is rapidly hydrolysed, the final products of hydrolysis being aniline and imidazole. At pH <9 and >11, repetitive scans of the u.v. spectrum of (2) show a clean reaction in which there is no build-up of intermediates; this resulted in tight isosbestic points being held in these regions. Between pH 9 and 11, however, another reaction intervened since repetitive scans of the u.v. region showed the build-up and decay of an intermediate. The first reaction [disappearance of (2)] could, however, be followed either at longer wavelength (290 nm) or at an isosbestic point for the subsequent reaction; similarly the subsequent reaction could be studied at suitable wavelengths, particularly at pH >10·5 where it was appreciably slower than the first step. The rate of the subsequent reaction was specifically acid-catalysed in the pH region 9—11·5 suggesting that the intermediate was the *N*-phenylcarbamic acid anion (5) which is known to hydrolyse by such a mechanism.[7,8] This was confirmed when the rate constants obtained for the subsequent reaction were compared with the values recently reported for the decarboxylation of (5).[7] Thus at pH >9 (and possibly over the entire pH range), (5) is most probably an intermediate in the hydrolysis of (2).

pH–*Rate Profile for* 1-*Phenylcarbamoylimidazole* (2).—The rate constants for the hydrolysis of (2) were determined over a wide pH range in the absence of added buffer species; the results are summarised in Table 1 and shown as a plot of k_{obs} against pH in Figure 1. It is seen from these values that (2) is remarkably reactive particularly in neutral solution where $k_{obs} = 8 \times 10^{-3}$ s^{-1}. In contrast (2) is relatively unreactive even in strongly

[1] D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1971, 407.
[2] C. J. O'Connor and J. W. Barnett, *J.C.S. Perkin II*, 1973, 1457.
[3] W. H. R. Shaw and J. J. Bordeau, *J. Amer. Chem. Soc.*, 1955, **77**, 4729.
[4] W. H. R. Shaw and D. G. Walker, *J. Amer. Chem. Soc.*, 1958, **80**, 5337.
[5] K. R. Lynn, *J. Phys. Chem.*, 1965, **69**, 687.
[6] R. C. Warner, *J. Biol. Chem.*, 1942, **142**, 705.
[7] S. L. Johnson and D. L. Morrison, *J. Amer. Chem. Soc.*, 1972, **94**, 1323.
[8] M. Caplow, *J. Amer. Chem. Soc.*, 1968, **90**, 6795.

basic solution and is stable (at 30°) in acid. This behaviour is just the opposite to that normally observed for the hydrolysis of related substrates such as simple ureas, esters, and amides, which are stable in neutral solution and hydrolysed (sometimes rapidly, though this is dependent largely on structure) in acid and base.[9]

accurate values for these constants are vital to the argument developed below, the measurements were repeated at several wavelengths and using different buffer solutions and samples of the substrate. In general, the experimental values obtained followed closely the theoretical curves and were in excellent internal agreement.

TABLE 1

Observed rate constants for the hydrolysis of 1-phenylcarbamoylimidazole (initially 5×10^{-5}M) in water at 30° and $\mu = 1{\cdot}00$ (KCl)

pH	2·81	3·28	3·62	4·00	4·40	4·85	5·04	5·30
$10^3 k_{obs}/s^{-1}$	2·40	5·75	10·7	14·8	15·8	14·7	13·2	11·2
pH	6·00	6·68	7·30	8·20	8·75	9·15	9·20	9·58
$10^3 k_{obs}/s^{-1}$	8·50	7·90	7·90	8·80	13·2	18·0	17·0	23·5
pH	9·72	9·94	10·10	10·20	10·45	10·90	11·25	11·50
$10^3 k_{obs}/s^{-1}$	28·4	28·8	30·2	27·5	23·5	15·3	8·65	5·34
pH	12·00	12·40	13·00	13·50				
$10^3 k_{obs}/s^{-1}$	3·34	0·85	0·32	0·31				

The urea (2) therefore provides an exception to this general behaviour; its reactivity in neutral solution is more akin to (but still greater than) that shown by aroyl chlorides [10] and acylimidazoles.[11] The observed rate of hydrolysis of (2) is at a maximum in the pH region 5—10.

The u.v. spectrum of (2) (measured rapidly before appreciable hydrolysis took place) showed two distinct changes at pH *ca.* 4 and 10. It was possible, therefore, to measure two pK_a values for (2) at suitable wavelengths. The data obtained are summarised as plots of

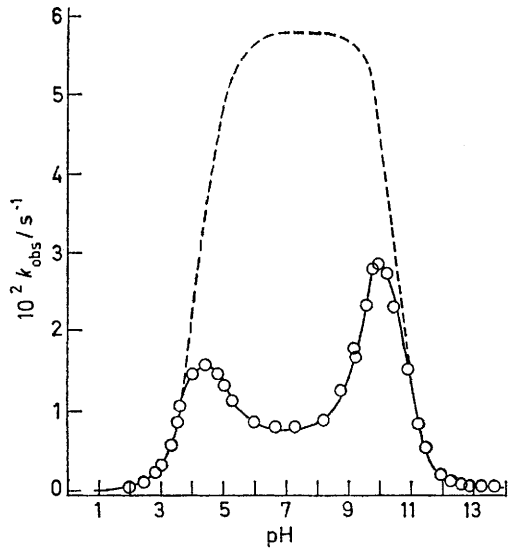


FIGURE 1 Plot of the observed first-order rate constants for the hydrolysis of 1-phenylcarbamoylimidazole in water at 30° (open circles). The broken line has been drawn using equation (1) with p$K_{a_1} = 4{\cdot}25$, p$K_{a_2} = 10{\cdot}62$, and $k_5 K_T = 5{\cdot}80 \times 10^{-2}$ s^{-1}. The solid line has been drawn using equation (2 + 9) with the values of the constants listed in equations (3)—(8)

absorbance against pH in Figures 2 and 3; the calculated pK_a values are 4·25 and 10·62 for (2). Because

The conjugate acids of acetylimidazole and *N*-methoxycarbonylimidazole have reported pK_a values of 3·8 and 3·6 respectively.[11,12] The pK_a value (which we shall

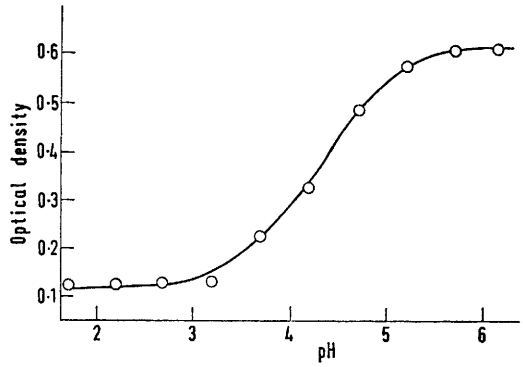


FIGURE 2 Plot of optical density of urea (2) at 290 nm against pH at 30° [H_2O; μ 1·0 (KCl)]; pK_{a_1} 4·25

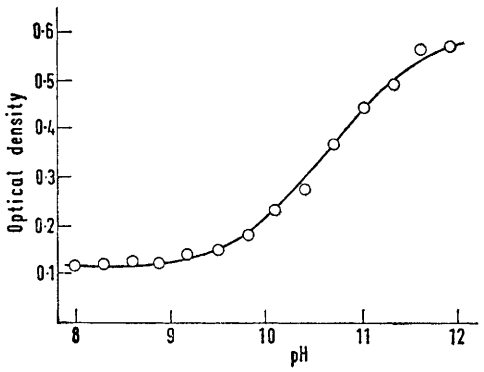
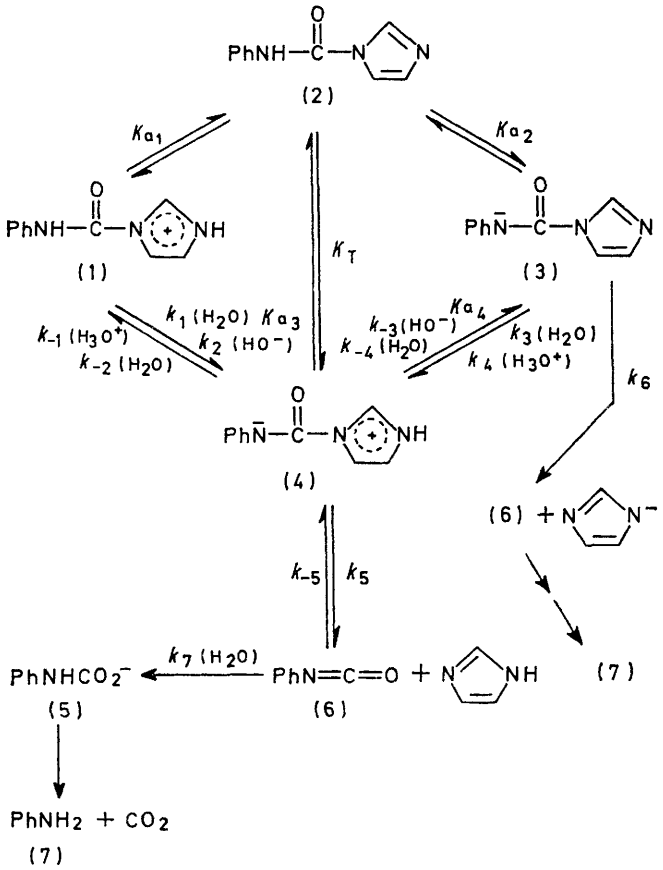


FIGURE 3 Plot of optical density of urea (2) at 288 nm against pH at 30° [H_2O; μ 1·0 (KCl)]; pK_{a_2} 10·62

designate pK_{a_1}) of 4·25 can therefore be assigned with a fair degree of certainty to the protonation of the imidazole group in (2) [formation of (1)]. It is more difficult to find models for the higher pK_{a_2} value; however trifluoro- and dichloro-acetanilide have reported [13] pK_a

[9] S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.
[10] M. L. Bender and M. C. Chen, *J. Amer. Chem. Soc.*, 1963, **85**, 30, 37.
[11] D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, 1971, **93**, 178.
[12] R. B. Moodie and R. Towill, *J.C.S. Perkin II*, 1972, 184.
[13] A. M. Segretain, M. Bengelmans-Verrier, and M. Laloidiard, *Bull. Soc. chim. France*, 1972, 3367.

values of 9·51 and 10·88 respectively. On this basis the pK_{a_3} value for (2) is assigned to the ionisation of the NH *proton* [formation of (3)]. The imidazole group in (2) is thus apparently strongly electron withdrawing.



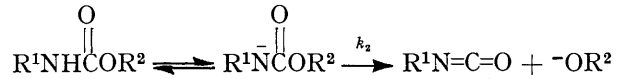
SCHEME 1

Although few quantitative measurements have been made, there is ample qualitative evidence to support this; it has been attributed to the involvement of the lone pair of electrons on nitrogen in the aromatic sextet of the heterocycle.[14,15]

Thus in the pH region $<$ *ca.* 4, the substrate (2) is present almost entirely as its conjugate acid (1); in the region 5—10, the neutral substrate (2) is the major species present while at pH $>$11, (2) is converted largely into the anion (3). On this basis it is seen that the substrate shows maximum solvolytic reactivity when (2) is the major species present while the decrease in reactivity corresponds approximately to the conversion of (2) into (1) and (3) in acidic and basic solution.

However, it is difficult to visualise how the neutral urea (2) could itself undergo such rapid spontaneous or water-assisted hydrolysis. Johnson and Giron [16] have reported that the methyl(phenyl)carbamoyl analogue of (2) is unreactive except in acid solution [where it is still hydrolysed slowly relative to (2) in neutral solution]. Clearly then, it is unreasonable that (2) itself should undergo rapid water attack; moreover the presence of the NH group in (2) is an essential structural feature which results in the rapid neutral hydrolysis.

We therefore propose that the neutral substrate (2) is in equilibrium with a tautomer (4) which is the reactive species for hydrolysis. This is an attractive alternative *a priori* since the concentration of the tautomer (or zwitterion) (4) is also governed by the magnitude of the equilibrium constants K_{a_1} and K_{a_2} and also (4) is expected to undergo very rapid reaction. Thus a recent study [17,18] of carbamates of type (8) has established that substrates with good leaving groups (pK_a of $HOR^2 < ca.$ 12) undergo *E*1cB elimination from the anion (9) to give isocyanate intermediates (10) (the latter are rapidly hydrated in a subsequent step). Since the transition state for the loss of alkoxide ion from the anion (9) is reached with a large degree of acyl–oxygen bond cleavage, the reaction shows a very high sensitivity to the nature of the leaving group. The carbamate with a *p*-nitrophenoxide leaving group (8; $R^1 = R^2 = p\text{-}NO_2C_6H_4$) reacted so rapidly that k_2 was not directly measurable, even using stopped-flow techniques. However, k_2 can be estimated [from



SCHEME 2

data for (9; $R^1 = p\text{-}NO_2C_6H_4$, $R^2 = m\text{-}NO_2C_6H_4$)] as 10^4 s^{-1} (at 25°), using the pK_a value of 7·15 for *p*-nitrophenol. The zwitterion (4) bears a structural similarity to the anion (9); in the case of (4) the leaving group is neutral imidazole. Since the conjugate acid of the leaving group of (4) (protonated imidazole) also has a pK_a of *ca.* 7·2,[19] one might expect that the specific rate constant for the reaction of the zwitterion (k_5 in Scheme 1) would be of the same order of magnitude.[20] Since this represents a reaction with $t_{\frac{1}{2}} < 10^{-4}$ s, clearly (4) is sufficiently reactive to account for the overall reactivity of (2), even if (4) is present in a relatively low equilibrium concentration.

If the four forms of the substrate present in solution [(1)—(4)] are assumed to be in equilibrium at each pH, then the expression (1) can be derived for the variation of k_{obs} with pH. Although four different pK_a values are involved in Scheme 1, these are not independent; once three are known, the fourth is also defined since the tautomeric constant K_T ($= K_{a_3}/K_{a_1} = K_{a_2}/K_{a_4}$). Equation (1) predicts that the observed rate–pH profile

$$k_{obs} = \frac{(k_5 K_T) K_{a_1} a_H}{a_H + a_H K_{a_1} + K_{a_1} K_{a_2}} \qquad (1)$$

[14] T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, 1972, **94**, 1250.
[15] H. A. Staab, *Angew. Chem. Internat. Edn.*, 1962, **7**, 351.
[16] S. L. Johnson and H. M. Giron, *J. Org. Chem.*, 1972, **37**, 1383.
[17] A. F. Hegarty and L. N. Frost, *J.C.S. Chem. Comm.*, 1972, 500.
[18] A. F. Hegarty and L. N. Frost, *J.C.S. Perkin II*, 1973, 1719.
[19] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. 1.
[20] See however, B. Capon, *Org. Reaction Mech.*, 1972, 422.

would be bell shaped.[21] However the observed data (solid line, Figure 1) clearly show two maxima. Moreover, the pK_a values estimated from the rate data (using the relationship pH = pK_{a_1} or pK_{a_2} when the observed rate is half the maximum value [21]), are *ca.* 3·5 and 11·4, significantly different from those determined spectrophotometrically. If, however, one uses the values already obtained for pK_{a_1} and pK_{a_2} (4·25 and 10·65 respectively) and varies the magnitude of (k_5K_T) to obtain the best fit to the observed rate constants at high and at low pH then the theoretical plot of k_{obs} against pH predicted by equation (1) is shown by the broken line in Figure 1.

Since the rate of reaction at pH 7 is *lower* than that predicted by equation (1), the observed rate constants cannot be correlated by the addition of *extra* terms to equation (1). Three possible reasons for such negative deviations from pH–rate profiles have been described by Jencks and his co-workers [22] as (*a*) change in the step which is rate-determining for the overall reaction, (*b*) association of the substrate molecules, which reduces their effective concentration in solution, and (*c*) reversal of an equilibrium by one or more of the products of the reaction.

The steps involved in the formation of the zwitterion (4) from the neutral species (2) only involve proton transfers; the possibility therefore arises that one or more of these becomes rate determining under certain conditions. Assuming a steady state concentration of the zwitterion (4), equation (2) can be derived which relates

$$k_{obs} = \frac{k_5(k_1 + k_2[HO^-])a_H/K_{a_1} + k_5(k_3 + k_4a_H)K_{a_2}/a_H}{k_{-1}a_H + k_{-2} + k_{-3}[HO^-] + k_{-4} + k_5} \cdot \frac{a_HK_{a_1}}{a_H + a_HK_{a_1} + K_{a_1}K_{a_2}} \quad (2)$$

the observed rate constant to a_H [but detailing the proton transfer steps involved in the formation and reactions of (4)].

Proton transfer reactions in aqueous solution to or from oxygen or nitrogen are extremely fast. Eigen,[23] using a large variety of organic acids and bases, has demonstrated that the rates of such reactions (in the thermodynamically favoured direction) are diffusion controlled, *i.e.*, the activation energy is so low that the reaction rate is determined merely by the diffusion together of the proton donor and acceptor. In aqueous solution at 25° the diffusion-controlled rate limit is *ca.* 10^{10} l mol^{-1} s^{-1}.

Normally therefore, the zwitterion (4) would be in equilibrium with (1) and (3), since (4) would return to (1) or (3) (*via* the fast proton transfer steps governed by $k_{-1}[H_3O^+]$ or $k_{-3}[HO^-]$) many times more rapidly than it would go on to products (*via* k_5). Under these conditions $(k_{-1}[H_3O^+] + k_{-3}[HO^-]) \gg k_5$; also $k_1/k_{-1} = K_{a_2}$ [$= k_2(K_w)/k_{-2}$] and $k_{-4}/k_4 = K_{a_4}$ [$= k_{-3}(K_w)/k_3$], and equation (2) reduces to (1). If, however, the reverse is true and k_5 is faster than the proton transfer steps to re-form (1) and (3) from (4) then the formation of (4) [from (1) and/or (3)] will be rate determining. This would imply that the observed rate would be slower than that predicted by equation (1) in neutral solution (as observed, see Figure 1).

TABLE 2

Observed rate constants for hydrolysis of 1-phenylcarbamoylimidazole in glycine ethyl ester buffers at 30° in water and μ = 1·00 (KCl)

10^3[Amine] /M	10^2k_{obs}/s^{-1} pH 6·70	pH 7·20	pH 7·70	pH 8·20	pH 8·70
2·7	3·90	3·71	3·97	2·88	4·04
5·4	4·26	4·61	4·26	3·34	4·19
8·1		4·70			
10·8		5·01	4·70	4·51	
13·5	4·80	5·50			
16·2			5·01		5·12
27·0		5·35	5·36	5·12	5·35

The view that the proton transfer steps are rate limiting in the neutral pH region is also supported by the observation of non-linear buffer catalysis for the hydrolysis of (2) in this region. Tables 2—4 show the results obtained for the amines, glycine ethyl ester, morpholine, and *N*-ethylmorpholine at various pH values. In each case the rate of hydrolysis of (2) was investigated in the presence of the amine–amine hydrochloride, which also acted as a buffer to maintain pH. It is seen that k_{obs} increases in each case non-linearly as the total amine concentration is increased (Figure 4 gives an example). At low [amine], k_{obs} rises steeply with increasing [amine] but then levels out and eventually becomes independent of [amine] at high values. The maximum rate of hydrolysis, which is not exceeded no matter how much amine is present, could be determined either by measuring k_{obs} in the presence of 0·1—1·0M-amine, or better, by extrapolation of plots of $1/k_{obs}$ against $1/[amine]_T$ (which are linear, see below) to infinite total amine concentration (*i.e.* $1/[amine]_T = 0$). In each case this proved to be $5·8 \times 10^{-2}$ s^{-1} (within experimental error) between pH 6·7 and 8·7. Similar results were obtained using

TABLE 3

Observed rate constants for hydrolysis of 1-phenylcarbamoylimidazole in morpholine buffers at 30° in water and μ = 1·00 (KCl)

10^3[Amine] /M	10^2k_{obs}/s^{-1} pH 7·53	pH 8·53	pH 9·53
1000	6·54	6·00	6·00
500	5·54	5·14	5·14
250	5·14	5·05	5·14
125	4·80	5·14	4·96
62	4·50	4·64	4·36
31	4·00	4·50	4·50
10		3·70	
5·0		2·95	
2·5		2·01	
1·25		1·70	

[21] R. A. Alberti and V. Massey, *Biochim. Biophys. Acta*, 1954, **13**, 347.

[22] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, ch. 10.

[23] M. Eigen, *Angew. Chem. Internat. Edn.*, 1964, **3**, 1.

primary, secondary, and tertiary amines and the maximal rate in the presence of ' infinite ' buffer was also essentially the same ($6{\cdot}0 \times 10^{-2}$ s^{-1} for morpholine). The value of k_5K_T is therefore the same as that predicted by equation (1) (see Figure 1).

TABLE 4

Observed rate constants for hydrolysis of 1-phenylcarbamoylimidazole in *N*-ethylmorpholine buffers at 30° in water and μ = 1·00 (KCl)

10^3[Amine] /M	10^2k_{obs}/s^{-1}			
	pH 6·50	pH 7·5	pH 8·00	pH 8·50
0·27	1·34	1·28	1·15	1·645
0·54	1·535	1·56	1·60	1·92
0·81	1·84	1·80	1·92	2·35
1·08	2·09	2·00	2·09	2·48
1·35	2·30	2·09	2·35	
2·7	2·44	2·19	2·56	2·65
5·4	3·20	2·88	3·15	3·07
8·1	3·38	3·15		3·49
10·8	3·97	3·77	4·00	3·84
13·5	4·26	3·90	4·00	3·60
27·0		4·90	4·70	4·30

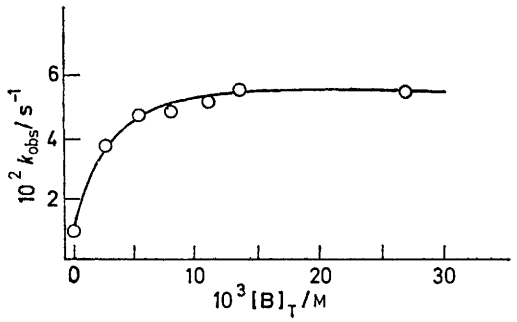


FIGURE 4 Dependence of observed rates of hydrolysis of urea (2) in glycine ethyl ester buffers at pH 7·20 at 30° (H_2O; μ 1·0)

The hydrolysis of (2) was only catalysed by the addition of general acids or bases in the pH region 4—10, *i.e.*, where the observed rates of hydrolysis of (2) fall below the broken ' theoretical ' line of Figure 1. Thus similar rates of hydrolysis were obtained in the presence and absence of 0·1M-*N*-ethylmorpholine at pH 4·0 and 11·0. Also by measuring the pH–rate profile for the hydrolusis of (2) in the presence of a sizeable ($2{\cdot}7 \times 10^{-2}$M), though admittedly, not quite ' infinite ', concentration of *N*-ethylmorpholine, the k_{obs} values obtained over the entire range are close to those predicted from equation (1).

A clearer picture of the mechanism of hydrolysis of (2) now emerges. Equation (1) [or equation (2), making the assumption that k_5 is rate determining] is closely followed by the observed rate constants in the presence of proton transfer catalysts; moreover, the kinetic and spectrophotometric pK_a values (pK_{a_1} and pK_{a_2}) are then identical. Since $k_5K_T = 5{\cdot}8 \times 10^{-2}$ s^{-1} and k_5 can be estimated as *ca.* 10^4 s^{-1} then K_T, the equilibrium constant for the zwitterion (4) can be estimated as $5{\cdot}8 \times 10^{-6}$. Since K_{a_1} and K_{a_2} are known (from both kinetic and spectrophotometric data) values for K_{a_3}, K_{a_4}, the acidity constants for the zwitterion can be estimated. The values calculated are $3{\cdot}2 \times 10^{-10}$ and $5{\cdot}2 \times 10^{-6}$ respectively for K_{a_3} and K_{a_4} (or pK_{a_3} = 9·49 and pK_{a_4} = 5·27). This is a particularly satisfactory result since, on purely intuitive grounds, one would expect that the value of pK_{a_1} would be close to pK_{a_4} (the observed values are 4·25 and 5·27) and pK_{a_2} would be similar to pK_{a_3} (observed values 10·62 and 9·49) (see Scheme 1), the ionisations involved being similar. In purely aqueous solution in the absence of added buffers the situation is more complex since it appears that in the pH region 4—10, there is a changeover in the rate-determining step from breakdown of the zwitterion (k_5) to its formation (k_1, k_2, k_3, and/or k_4). Although it would appear *a priori* highly unlikely that a reaction as rapid as a proton transfer could control the overall rate of reaction, it is in competition with a demonstrably very rapid reaction, breakdown of the zwitterion *via* k_5. Moreover, several mechanisms have been recently proposed which involve a rate-limiting, diffusion-controlled proton transfer to oxygen, nitrogen, or sulphur; these have been reviewed by Barnett.[24]

The experimental data are certainly consistent with this interpretation since by an appropriate choice of constants, it is possible using equation (2), to fit closely the observed rate constants in Table 1 over the entire pH range; the solid line in Figure 1 which shows the two maxima was drawn using equation (2) with the values for the constants taken from equations (3)—(8).

$$k_{-1} = 1{\cdot}5 \times 10^4 k_5 \quad (3)$$

$$k_{-3} = 1{\cdot}0 \times 10^4 k_5 \quad (4)$$

$$k_2K_w/K_{a_1} + k_4K_{a_2} = 8{\cdot}0 \times 10^{-3}\ \text{s}^{-1} \quad (5)$$

$$k_5K_T = \frac{k_5k_1}{k_{-1}K_{a_1}} = \frac{k_5k_3K_{a_2}}{k_{-3}K_w} = 5{\cdot}8 \times 10^{-2}\ \text{s}^{-1} \quad (6)$$

$$k_{-1} = 4{\cdot}9 \times 10^{-2}\ \text{s}^{-1} \quad (7)$$

$$k_3 = 2{\cdot}8 \times 10^{-1}\ \text{s}^{-1} \quad (8)$$

The best fit of the experimental data to equation (2) was obtained using a program written for the Olivetti–Underwood Programma 101 desk computer. The spectrophotometrically determined values for K_{a_1}, K_{a_2}, and equations (5) and (6) were used and the best values of k_{-1} and k_4 in terms of k_5 estimated using a successive iteration technique. From these, values of k_1 and k_3 can be determined [equations (7) and (8)]. The values of k_{-1}, k_5, and k_{-3} themselves cannot be determined except in terms of other constants; however, the shape of the curve obtained is quite sensitive to the relative values used. Therefore, the key equations (3)—(8) derived from the experimental data are unique.

One final modification has to be made in Scheme 1 [and consequently to equation (2)]. This arises since the rate of hydrolysis of (2) does not decrease as the pH is increased in the region pH 13—14 as predicted by equation (2); instead k_{obs} becomes almost independent of pH (see Table 1) at high pH. This is best explained in

[24] R. E. Barnett, *Accounts Chem. Res.*, 1973, **6**, 41.

terms of the occurrence of an additional mode of reaction of the anion (3) which undergoes unimolecular loss of imidazole anion (k_6) to give phenyl isocyanate initially. Since the substrate (2) is largely in the form of the anion (3) above pH 11, increasing pH in this region will not change the rate of elimination. To complete

$$k_{obs} = k_6 K_{a_2}/(K_{a_2} + a_H) \quad (9)$$

the rate expression for the behaviour of (2) in aqueous solution in the absence of added buffer species, equation (9) should be added as an extra term to equation (2). [This was taken into account when the values in equations (3)—(8) were computed].

The rate of reaction of (3) in basic solution is quite close to that of an analogous carbamate (8; $R^1 = p$-$NO_2C_6H_4$, R^2 = Me) [$k_{obs} = 2{\cdot}4 \times 10^{-4}$ s^{-1} for (3); $= 1{\cdot}5 \times 10^{-4}$ s^{-1} at pH 14 for (8)], where the leaving group, methoxide ion, has a leaving ability similar to that of imidazole anion.

Thus, it has been established that equation (2 + 9) closely fit the observed complex dependence of the rate of hydrolysis of (2) over the entire pH range using the values of the constants given in the text. The proposed reaction (Scheme 1) involves the zwitterion (4) as the principal reactive species; either its formation or decomposition can be rate determining, depending on the presence or absence of catalysts for the competing proton transfers. The rate-determining step thus changes with pH as follows: pH <4, k_5; 4—6, k_1; 6—8, $k_2 + k_4$; 8—10, k_3; 10—12, k_5; >12, k_6.

Identification of the Isocyanate (6) *in the Reaction Pathway.*—Since imidazole is one of the products of solvolysis of (2), it is possible that its increasing concentration in solution as the reaction progresses might affect the rate of reaction of the remaining substrate (2). From the

TABLE 5

Observed rate constants for the hydrolysis of 1-phenylcarbamoylimidazole (2) in imidazole buffers in water at pH 7·20 at 30° and μ = 1·00 (KCl)

10^4[Im]/M	5·0	8·0	27	54	81	109
$10^3 k_{obs}$/s^{-1}	13·5	12·5	5·48	3·10	2·17	1·65

results (Table 5) it is clear that k_{obs} does in fact decrease markedly as the total imidazole concentration is increased. This inhibition of the rate of hydrolysis of (2) by added imidazole is a general phenomenon and was also noted at pH >7·0 and also at lower pH (although the effect was less marked in the latter case); this will be dealt with in detail elsewhere.[25]

This observation is important since it helps to define a further step in the overall reaction sequence. If the zwitterion (4) reacts analogously to the carbamate conjugate base (9) then phenyl isocyanate (6) will also be an intermediate on the reaction pathway (see Scheme 1). The observed decrease in k_{obs} as the imidazole concentration is increased can be explained in these terms since the intermediate phenyl isocyanate can either react with imidazole, *via* k_{-5}, regenerating the starting material (4) [and thus (2)], or alternatively react with H_2O (or possibly HO^-), ultimately giving the normal hydrolysis products aniline and imidazole. Assuming that (1)—(4) are in equilibrium and a steady-state concentration of phenyl isocyanate, equation (10), which relates the observed rate to the imidazole concentration, can be derived. This implies that $1/k_{obs}$ should be proportional to the imidazole concentration (or $[Im]_T$) at constant pH. An example of such a plot is shown in Figure 5 and it is

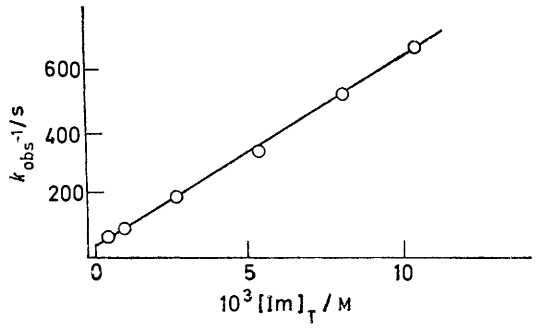


FIGURE 5 Plot of the reciprocal of the observed rate of hydrolysis of urea (2) at pH 7·20 against the total imidazole buffer concentration

seen that this relationship is closely followed. Similar linear plots were obtained at all pH values studied,[25] adding support to the proposed mechanism in Scheme 1.

$$k_{obs} = k_5 K_T(k_7[H_2O])/(k_{-5}[Im] + k_7[H_2O]) \quad (10)$$

Equation (10) also implies that when the plot of $1/k_{obs}$ is extrapolated to [Im] = 0, the intercept will be equal to k_5K_T. When this was done at pH 6·0—9·0, the value of k_5K_T obtained was $5{\cdot}8 \times 10^{-2}$ s^{-1}, justifying the assumption that (1)—(4) are in equilibrium in the presence of large quantities of imidazole. At lower imidazole concentrations (10^{-4}—10^{-3}M) the observed rate of hydrolysis initially rises as the imidazole concentration is increased (see Figure 6); apparently the effect of imidazole acting as a general acid–base is dominant at these concentrations.

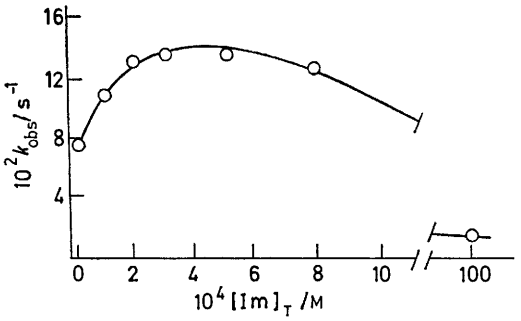


FIGURE 6 Observed first-order rate constants for the hydrolysis of urea (2) in imidazole buffers at pH 7·20 in water at 30°

This latter observation also makes it unlikely that the dip in the pH–rate profile observed (Figure 1) is due to the back reaction with imidazole formed in the course of the reaction. Also association between substrate molecules is unimportant since the same rate constants were

[25] A. F. Hegarty and C. N. Hegarty, unpublished results.

observed when an initial substrate concentration of $2\cdot5 \times 10^{-6}$M was used (*ca.* 20-fold less than that used in Table 1).*

Estimation of K_{a_3} *and* K_{a_4}.—An estimate of the pK_a values of the zwitterion (4) can be made on the basis of the constants calculated from equation (2). Since both k_1 and k_3 are known, if any of the constants k_5, k_{-1}, or k_{-3} can be estimated, then values for all the remaining constants become available [from equations (3), (4), and then (6)]. When this is attempted, however, a dilemma arises. (*a*) If it is assumed that $k_5 = 10^4$ s^{-1} then $pK_{a_3} = 9\cdot49$ and $pK_{a_4} = 5\cdot27$. As mentioned previously, these are reasonable values, based on a comparison of pK_{a_1} with pK_{a_4} and pK_{a_2} with pK_{a_3}. However, the values of k_{-1} and k_{-3} calculated are unexpectedly *ca.* 10^2-fold less than the well-established [23] diffusion limit of *ca.* 10^{10} l mol^{-1} s^{-1}. This discrepancy also appears to be in k_2 and k_4 since from equation (5) if k_2 and k_4 are of the same magnitude, then each has a value of *ca.* $2\cdot75 \times 10^8$ l mol^{-1} s^{-1}. (*b*) If, alternatively, it is assumed that k_{-1} and k_{-3} *do* have their expected values of *ca.* 10^{10} l mol^{-1} s^{-1} then $k_5 = 10^6$ s^{-1}; $K_{a_3} = 3\cdot25 \times 10^{-12}$ ($pK_{a_3} = 11\cdot5$); and $K_{a_4} = 5\cdot25 \times 10^{-4}$ ($pK_{a_4} = 3\cdot3$). The value of k_5 *could* of course be as high as 10^6 s^{-1} since the preferred value of 10^4 s^{-1} was only based on a model substrate; however, the calculation that $pK_{a_4} < pK_{a_1}$ and $pK_{a_3} > pK_{a_2}$ appears unsound on chemical reasoning. Thus, for example, protonation of the imidazole group in (1) and (4) should make (1) a stronger acid (for loss of an anilino hydrogen atom) than (2). A possible factor which might just alter the relative magnitude of the pK_a values has been observed in related materials by Jencks and his co-workers,[26] who have presented evidence that *N*-methylacetylimidazolium ion is stabilised by resonance by *ca.* 2·7 kcal mol^{-1} relating to similar materials.

Such an effect could make the imidazolylcarbonyl group in (2) and (4) *less* electron withdrawing than expected and thus possibly reverse the expected order of pK_{a_3} and pK_{a_2} (note that the neutral *N*-imidazolyl group has already been shown on the basis of the low pK_{a_2} value to be itself powerfully electron withdrawing). However, even if this explanation were accepted as reasonable, equation (5) still requires that k_2 and k_4 are $\ll 10^{10}$ l mol^{-1} s^{-1}.

Thus either the mechanism presented in Scheme 1 is incorrect (and this is unlikely in view of all the other evidence already presented and further material below) or else the proton transfer steps are indeed occurring at *ca.* 10^2-fold less than those measured by Eigen.[2] Very recently, it has been reported [27] that the rate of the proton transfer to 1,8-bisdimethylaminonaphthalene in the thermodynamically favoured direction is $1\cdot9 \times 10^5$ l mol^{-1} s^{-1}, *i.e.* 10^5-fold less than the ' normal ' diffusion controlled limit. This has been attributed to the stabilisation of the protonated form by hydrogen bonding and steric hindrance in the free base form. A similar effect was noted by Bernasconi [28] in the deprotonation of Meisenheimer complexes by hydroxide ion where the rates of deprotonation were 2×10^8 l mol^{-1} s^{-1} or *ca.* 10^2-fold less than the diffusion limit. It is just possible that such a factor also operates in the present instance; resonance stabilisation and/or hydrogen bonding in the zwitterion (4) may reduce the rate of proton transfer to (1) and (3) by the observed factor of *ca.* 10^2.

Substituent Effects.—(a) N-*Aryl*. The rate constants for hydrolysis of the *p*-bromophenyl compound (11) are summarised in Figure 7. It is seen that the observed

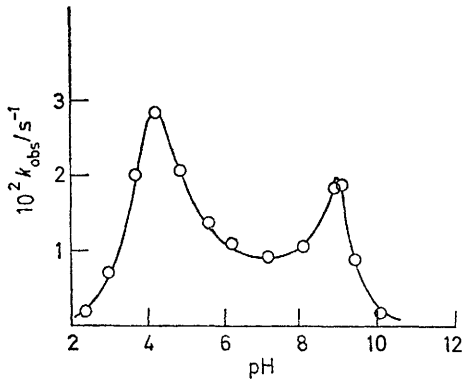
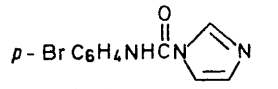
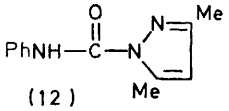


FIGURE 7 Plot of the observed rates of hydrolysis of 1-*p*-bromophenylcarbamoylimidazole (11) against pH in water (μ 1·0) at 30°



(11)



(12)

pH rate profile is very similar to that for (2) (Figure 1) with maxima at pH 4·1 and 8·9 (although the relative magnitudes of the maxima are reversed). The *p*-bromo-group has the largest effect on pK_{a_3}, being too remote to effect pK_{a_1}. Thus, although K_T is therefore larger (more zwitterion present) the zwitterion is also less reactive (k_5 is smaller) so that k_5K_T is approximately the same as for (2). The overall effect, therefore, is that the substituent has a relatively small effect on reactivity. However, the change in the constants observed is that expected on the basis of the proposed mechanism of hydrolysis of (2).

(b) *Leaving group*. The hydrolysis of 1-phenylcarbamoylbenzimidazole (14) was also investigated. Again, the pH–rate profile shows two maxima (Figure 8) and the observed data were closely correlated (solid line) using equation (2 + 9) with the following values of the constants: $K_{a_1} = 2\cdot0 \times 10^{-3}$ ($pK_{a_1} = 2\cdot70$); $K_{a_2} = 2\cdot82 \times 10^{-11}$ ($pK_{a_2} = 10\cdot55$); $k_{-1} = 1\cdot39 \times 10^4 k_5$; $k_{-3} = 1\cdot43 \times 10^4 k_5$; $k_2K_w/K_{a_1} + k_4K_{a_2} = 2\cdot14 \times 10^{-3}$; k_5K_T

* The possibility also arises that ' dip ' in the pH–rate profile could be due to a changeover in the reaction studied to the subsequent hydration of (6); however, this latter reaction (studied independently) is significantly faster and is accompanied by a spectral change which occurs in a direction opposite to that observed.

[26] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432.
[27] F. Hibbert, *J.C.S. Chem. Comm.*, 1973, 463.
[28] C. F. Bernasconi, *J. Phys. Chem.*, 1972, **75**, 3636.

$= k_5k_1/k_{-1}K_{a_1} = k_5k_3K_{a_2}/k_{-3}K_w = 1{\cdot}25 \times 10^{-2}$; $k_1 = 3{\cdot}47 \times 10^{-1}$; $k_3 = 9{\cdot}3 \times 10^{-2}$; $k_6 = 5{\cdot}6 \times 10^{-3}$.

The pK_{a_1} and pK_{a_2} values were also measured spectrophotometrically at 275 nm and had the same values as those determined from the kinetic data.

Since benzimidazole is less basic than imidazole (the pK_a values of the conjugate acids are 5·27 and 7·20 respectively),[29] the value of pK_{a_1} obtained (2·70) is consistent with that already reported for (2) (4·25); as expected pK_{a_2} is almost the same in both systems. Since k_5K_T is thus smaller for (14), the overall rate of hydrolysis is slower; moreover, the pH–rate profile looks different (Figure 8) since the decomposition of (15) at high pH is relatively more important. This is reflected in the larger value of k_6 obtained for (15), which in turn is a result of the better leaving group (benzimidazole anion) involved (the pK_a values of the conjugate acids, imidazole and benzimidazole, are 14·2 and 13·1 respectively).[28,29]

Interestingly, the values calculated for the other constants are also in accord with those reported above for (2). Thus, if it is assumed that k_2 and k_4 are of the same magnitude then each is *ca.* 6×10^7 l mol^{-1} s^{-1}. Also, if a reasonable value is assumed for $K_{a_3}(>K_{a_2})$, then k_{-1} and k_{-3} are each calculated to be $<10^{10}$ l mol^{-1} s^{-1} [as in the case of (2)]. Presumably, therefore, the same explanation of the dilemma is valid in the case of (14).

The observed pH–rate profile for the hydrolysis of 3,5-dimethyl-1-phenylcarbamoylpyrazole (12), which is

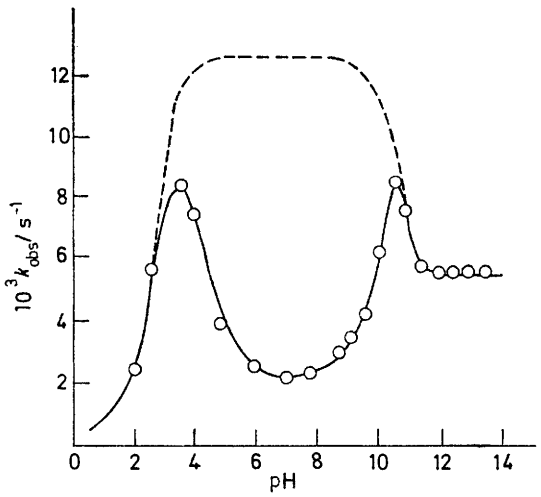


FIGURE 8 Plot of the observed rate constants for the hydrolysis of 1-phenylcarbamoylbenzimidazole (14) against pH in water at 30° (μ 1·0). The broken line has been drawn using equation (2) with $pK_{a_1} = 2{\cdot}70$, $pK_{a_2} = 10{\cdot}55$, and $k_5K_T = 1{\cdot}25 \times 10^{-2}$ s^{-1}. The solid line has been drawn using equation (2 + 9) with the values of the constants given in the text

presented in Figure 9 can also be understood in these general terms. This k_{obs} against pH plot is broadly of the same type as Figure 1 except that the reduction in k_{obs} in acid and in base is not as marked. This arises since (12) is both a weaker acid (pK_{a_1} *ca.* 13·4), and also weaker base ($pK_{a_1} < 0$), than either (2) or (14). The urea derivatives (2), (11), (12), and (14) are therefore most likely all hydrolysed by a similar mechanism involving a proton transfer as the rate-limiting step in neutral solution.

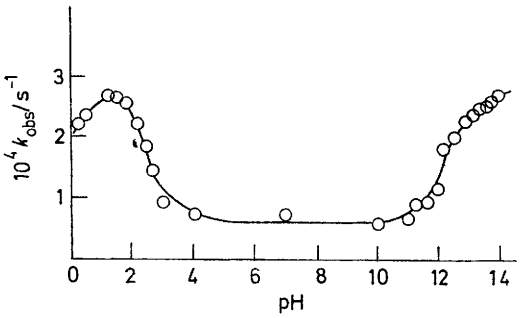


FIGURE 9 Plot of the observed rate of hydrolysis of 3,5-dimethyl-1-phenylcarbamoylpyrazole (12) in water at 30° [μ 1·0 (KCl)]

Catalysis of Proton Transfer.—The fact that buffer species catalyse the hydrolysis of (2) has already been mentioned.

Surprisingly, the three amines studied with (2) as substrate (Tables 2—4) do not appear to show any great variation in catalytic ability from one to another or as the pH of the solution (and thus the relative amounts of the free and protonated amine) is varied. This may be in part an artefact of the experimental determinations since the observed rate rises very rapidly at low buffer concentration.

Greater differences were observed when the catalysis of the hydrolysis of 1-phenylcarbamoylbenzimidazole (14) was examined. The following amines were used: glycine, glycine ethyl ester, and *N*-ethylmorpholine; the results obtained {k_{obs} for hydrolysis of (14) as a function of pH and total buffer concentration $[B]_T$} are summarised in Tables 6—8. The k_{obs} against total buffer

TABLE 6

Observed pseudo-first-order rate constants for the hydrolysis of 1-phenylcarbamoylbenzimidazole in *N*-ethylmorpholine buffers at various pH values in water at 30° and μ = 1·00 (KCl)

[Amine] /M	$10^3k/s^{-1}$ pH 7·00	pH 7·50	pH 8·00	pH 8·50	pH 9·00	pH 9·50
0·0		2·30				
0·0027	3·29	3·63	4·11			
0·0054		4·27	5·48			
0·0081		5·43	6·12			
0·0162	6·77	7·43	8·50	9·53	8·86	8·93
0·0270		8·86	10·5			
Slope	2·5	1·9	1·3	1·15	1·1	1·1

TABLE 7

Observed pseudo-first-order rate constants for the hydrolysis of 1-phenylcarbamoylbenzimidazole in glycine buffers at various pH values in water at 30° and μ = 1·00 (KCl)

[Amine] /M	$10^3k/s^{-1}$ pH 6·50	pH 7·30	pH 7·70	pH 8·10	pH 8·50	pH 9·00
0·0027			2·68		3·20	4·43
0·0162	3·15	3·50	3·88	4·23	5·62	7·88
Slope	15	10	10·5	9·5	4·6	2·25

[29] J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and J. C. Turner, *J.C.S. Perkin II*, 1973, 432.

concentration plots are of the same shape as for the catalysis of hydrolysis of (2) (see Figure 4) rising to a maximum value ($1\cdot25 \times 10^{-2}$ s^{-1}) which is independent of $[B]_T$.

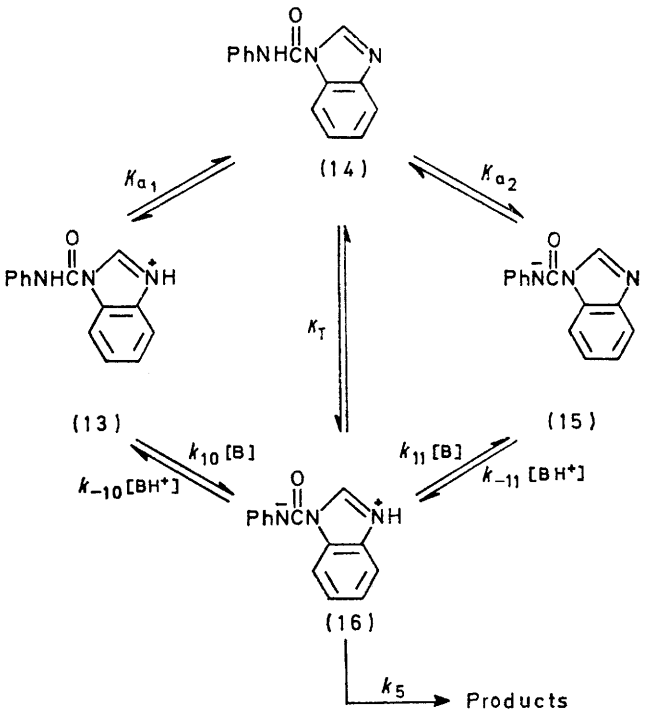
TABLE 8

Observed pseudo-first-order rate constants for the hydrolysis of 1-phenylcarbamoylbenzimidazole in glycine ethyl ester buffers at various pH values in water at 30° and $\mu = 1\cdot00$ (KCl)

	$10^3k/s^{-1}$						
[Amine] /M	pH 4·40	pH 5·50	pH 6·50	pH 6·90	pH 7·30	pH 7·70	pH 8·10
0·0027		4·43			5·19	5·00	
0·0054						6·95	
0·0081	7·94	7·48	7·94	8·11	8·53	8·22	8·53
Slope	2·15	0·91	0·60	0·57	0·48		

These results can be interpreted in terms of the mechanism in Scheme 3; the formation of (16) from (13) and (15) is catalysed by the free amine (B) and its conjugate acid BH^+ respectively while the reverse reactions are catalysed by BH^+ and B. Note that the buffer species are not involved in any other reaction, *e.g.* direct nucleophilic attack on (13) or (14) or catalysis of k_5. From Scheme 3, equation (11) may be derived by assuming a steady-state concentration of (16). The portion of the hydrolytic rate due to catalytic reaction (k_{cat}) was determined by the difference between the observed rate (k_{obs}) and the hydrolytic rate at the same pH (k_0). Since all the measurements were made in the pH region between pK_{a_1} and pK_{a_2}, this reduces to equation (12). Since $K_{a_3} = a_H[B]/[BH^+]$ and $[B]_T = [BH^+] + [B]$, equation (12) can be inverted and rewritten as (13), which implies that plots of $1/k_{cat}$ against $1/[B]_T$ would be linear; this was in fact observed at all pH values for both substrates (2) and (14). The intercept of these plots (when $1/[B]_T = 0$, *i.e.* at ' infinite ' buffer concentration) gives $k_{obs} = k_5K_T$; this is perhaps the most accurate method of determining this constant. The values of k_5K_T were, within experimental error, the same for all amine buffers used and at all pH values [$5\cdot8 \times 10^{-2}$ s^{-1} for (2) and $1\cdot25 \times 10^{-2}$ for (14)].

The slopes of the plots of $1/k_{cat}$ against $1/[B]_T$ [$= (a_H + K_{a_3})/(k_{10}K_{a_3}a_H/K_{a_1} + k_{-11}K_{a_2})$] are a measure of the ability of the amine to act as a catalyst. The values of these ' slopes ' are summarised in Tables 6—8. It is seen that the slope does not vary greatly for the amines glycine ethyl ester and *N*-ethylmorpholine as the pH is changed. This remarkable result which implies that the catalytic ability of the amine is independent of whether the protonated or free amine is present, is explicable qualitatively as follows. Since the amine



SCHEME 3

pK_{a_3} value lies midway between pK_{a_1} and pK_{a_2} (and thus also midway between the zwitterion pK_{a_3} and pK_{a_4} values), catalysis of formation of (16) from (13) by free base species B and from (15) by BH^+ is equally efficient. Therefore, changing the pH of the solution which decreases the importance of one pathway brings about an exactly corresponding increase in the rate of the other.

$$k_{cat} = \frac{k_5(k_{10}[B]a_H/K_{a_1} + k_{-11}[BH^+]K_{a_3}/a_H)}{k_5 + k_{-10}[BH^+] + k_{11}[B]} \cdot \frac{a_HK_{a_1}}{a_H + a_HK_{a_1} + K_{a_1}K_{a_2}} \quad (11)$$

$$k_{cat} = \frac{k_5(k_{10}[B]a_H/K_{a_1} + k_{-11}[BH^+]K_{a_3}/a_H)}{k_5 + k_{-10}[BH^+] + k_{11}[B]} \quad (12)$$

$$\frac{1}{k_{cat}} = \frac{(a_H + K_{a_3})}{\frac{K_{10}a_HK_{a_3}}{K_{a_1}} + k_{-11}K_{a_2}} \cdot \frac{1}{[B]_T} + \frac{k_{-10}a_H + k_{11}K_{a_3}}{\frac{k_5k_{10}a_HK_{a_3}}{K_{a_1}} + k_{-11}K_{a_2}k_5} \quad (13)$$

In the more general case, the slopes of plots of $1/k_{cat}$ against $1/[B]_T$ *do* vary with pH. It is then possible to solve for the two unknowns k_{10} and k_{-11} and the values obtained which best fit the data are summarised in Table 9.

TABLE 9

Summary of k_{10} and k_{-11} values obtained for 1-phenylcarbamoylbenzimidazole (14)

Amine	pK_a	k_{10}	k_{-11}
Glycine	9·60	$5\cdot2 \times 10^5$	$2\cdot0 \times 10$
Glycine ethyl ester	7·75	$1\cdot1 \times 10^4$	$3\cdot2 \times 10^2$
N-Ethylmorpholine	7·80	$4\cdot4 \times 10^4$	$5\cdot4 \times 10^2$

It is seen that catalysis of proton transfer by the

pathways represented by k_{10} and k_{-11} are both sensitive to the nature of the amine used. This implies that neither of these steps is diffusion controlled (which would result in the rates of both steps being equal for each catalyst); it is clear that neither k_{10} or k_{-11} will be diffusion controlled so long as $pK_{a_3} > pK_{a_5} > pK_{a_4}$.

If k_{-10} and k_{11} (the diffusion controlled processes) are assumed to be of the order of 5×10^8 l mol^{-1} s^{-1} (as expected for a reaction between general acids–bases in aqueous solution) [25] then K_{a_3} and K_{a_4} can be calculated from these values (Table 9) and the equations given above. The best values obtained are $pK_{a_3} = 12{\cdot}1$ and $pK_{a_4} = 1{\cdot}8$. Thus, the dilemma observed above with the estimated values of pK_{a_3} and pK_{a_4} of (2) and (14) (obtained from data in the absence of added buffer species) is exactly reproduced here. That is, pK_{a_3} is apparently greater than pK_{a_2} and pK_{a_4} is apparently smaller than pK_{a_1} (which, as previously pointed out, is opposite to the expected order). Of course, if the other assumption is made (*i.e.* that $pK_{a_3} < pK_{a_2}$ and $pK_{a_3} > pK_{a_1}$) then the values calculated for k_{10} and k_{-11} are *ca.* 5×10^6 l mol^{-1} s^{-1}, *i.e. ca.* 10^2-fold less than expected for a diffusion controlled process.

Since $k_{10}/k_{-11} = K_{a_3}/K_{a_5}$ it is implied that k_{10} would change from being proportional to the nature of the amine when $pK_{a_5} < pK_{a_3}$ to a diffusion controlled process (and thus independent of the amine used) when $pK_{a_5} > pK_{a_3}$. Using this technique it might then be possible to estimate k_{10} directly even when this is diffusion controlled. However, no observable catalysis of the hydrolysis of (14) was found in the presence of 0·01M-triethylamine or -piperidine at pH 7·2. This is consistent with a changeover occurring for these amines; since k_{10} no longer increases with the pK_a of the amine (being diffusion controlled) the reduced concentration of free base at low pH is not offset by its higher reactivity. A further difficulty in studying stronger amine bases is that at high pH (where the important k_{-11} term would become dominant), no catalysis is observed since the various species in Scheme 3 are in equilibrium. This arises from the unique symmetry of the systems [(2) and (14)] under study. Since the pK_a values of the substrates are relatively close together, catalysis by both acid and base species are effective, the relative importance of each changing (often in a compensatory fashion) with pH.

In conclusion, therefore, the hydrolysis of the ureas (2) and (14) [and also most probably of (11) and (12)] occurs in neutral solution *via* rate-determining loss of a proton from the protonated substrate [(1) or (13)] or donation of a proton to the anion [(3) or (15)] to form the zwitterion [(4) or (16)]. The zwitterion undergoes rapid unimolecular reaction to form phenyl isocyanate and imidazole (or benzimidazole) initially. This has an important implication also for the reverse reaction between phenyl isocyanate and amines. By the principle of microscopic reversibility, the rate-determining step should also be the proton transfer step in which the initially formed zwitterion is converted into the urea. It is interesting to note that in previous studies of this reverse reaction (in non-aqueous solvents) strong catalysis (and bifunctional catalysis [30]) was observed.[31] Since even in aqueous solution the proton transfer steps can be rate limiting it is clear that the catalytic reagent acts on this step. It is also likely that the addition of a tertiary amine (for example triethylamine) which is commonly done to catalyse the addition of alcohols to aryl isocyanates has a similar effect. These results are supported by a recent study by Williams and Jencks on the mechanism of the reaction of isocyanic acid with amines (in aqueous solution).[32] A sharp break was noted in a plot of reaction velocity against the pK_a of the amine and it was concluded that a changeover in the rate-determining step occurred, from nucleophilic attack (with strong amine bases) to possibly proton transfer from the zwitterion formed (for weak amines). Imidazole, although not examined in detail, has a pK_a of 7·20 and should lie close to the point where the changeover in mechanism occurs. This is entirely consistent with our results involving phenyl isocyanate and imidazole since we have demonstrated that the addition of relatively small concentrations of general acids or bases can bring about a change in the rate-determining step.

EXPERIMENTAL

Substrates.— *3,5-Dimethyl-1-phenylcarbamoylpyrazole.* 3,5-Dimethylpyrazole (9·6 g, 0·1 mol) was dissolved in dry diethyl ether (100 ml) at 30°. Phenyl isocyanate (11·9 g, 0·1 mol) in dry diethyl ether (20 ml) was added and the solution stirred vigorously. A white *solid*, m.p. 64° (20 g, 92%), separated, and was removed by filtration, and washed with dry diethyl ether. Recrystallisation from ethanol–diethyl ether raised the m.p. to 66·0—66·5° (Found: C, 66·8; H, 6·2; N, 19·4. $C_{12}H_{13}N_3O$ requires C, 66·95; H, 6·1; N, 19·5%).

1-Phenylcarbamoylimidazole. Imidazole (6·8 g) in dry diethyl ether (100 ml) was added to a solution of phenyl isocyanate (11·9 g) also dissolved in dry diethyl ether (50 ml) with stirring. A white solid separated and was removed by filtration. The *urea* (15 g, 80%) was washed with dry diethyl ether and was used without further purification. It had m.p. 111—112°, and the i.r. and n.m.r. spectra were consistent with the assigned structure (Found: C, 64·2; H, 4·9; N, 22·7. $C_{10}H_9N_3O$ requires C, 64·2; H, 4·85; N, 22·45%). The urea could be stored for several weeks over P_2O_5 *in vacuo*. Eventually, however, some diphenylurea was formed; a new sample of the substrate was therefore prepared at least once a month for kinetic studies.

1-Phenylcarbamoylbenzimidazole. This was similarly prepared in 75% yield and had m.p. 153—153·5° (Found: C, 70·7; H, 4·7; N, 17·6. $C_{14}H_{11}N_3O_1$ requires: C, 70·9; H, 4·7; N, 17·7%).

1-p-Bromophenylcarbamoylimidazole. This was prepared in 80% yield by the same general procedure, m.p. 147—

[30] See, for example, S. A. Lammiman and R. S. Satchell, *J.C.S. Perkin II*, 1972, 2300.

[31] J. M. Briody and D. Narinesingh, *Tetrahedron Letters*, 1971, 4143.

[32] A. Williams, personal communication.

148° (Found: C, 45·5; H, 3·1; N, 16·3. $C_{10}H_8BrN_3O$ requires C, 45·1; H, 3·0; N, 15·8%).

Kinetic Experiments.—All rate data were measured on a Cary 14 recording spectrophotometer which was fitted with a Radiometer pH-stat assembly: this comprised a Radiometer pH meter (type PHM 26), a titrator (type TTT 2B), and an autoburette (type ABU 1C) and has already been described in detail.[18] A Metrohm EA 125U electrode, which was standardised at 30° using Radiometer aqueous buffer solutions, was used. The water used was deionised and then twice distilled from alkaline potassium permanganate. The ionic strength was maintained throughout at 1·0 by the addition where appropriate of potassium chloride. Separate experiments however showed that the hydrolysis of (2) is not sensitive to the ionic strength of the reaction medium; thus the same rate of hydrolysis of (2) was observed (within an experimental error to ±2%) in the presence and absence of 1·0M-KCl at pH 7·0.

Measurement of pH–*Rate Profiles.*—In a typical experiment an aqueous solution of 1M-potassium chloride (36·5 ml) was pipetted into the thermostatted cell (at 30°) in the spectrometer. The contents of the cell were 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 (*ca.* 10^{-2}M) in acetonitrile or dioxan was then added to initiate reaction and the kinetics were followed by observing the decreasing optical density at a suitable wavelength. The analytical wavelengths used are noted as appropriate in the Tables and Figures. The pH was maintained constant by the pH-stat assembly. The rate constants were measured at 0·5 pH unit intervals in the range 3—11 by this method. Below pH 3, solutions of the desired pH were prepared by mixing the appropriate quantities of 1M-hydrochloric acid solution and 1M-potassium chloride solution and the pH checked on the pH meter. Above pH 11, appropriate quantities of 1M-potassium hydroxide solution and 1M-potassium chloride solution were mixed to give solutions of the required pH. In all cases the optical density against time plots were strictly pseudo-first-order to >95% reaction and the first-order rate constants were calculated using the experimental infinity value.

Catalysis of the Hydrolysis of 1-*Phenylcarbamoyl-imidazole and -benzimidazole by Amine and Amino-acid Buffers.*—In a typical experiment, an aqueous solution of potassium chloride (36·5 ml; μ 1·00) was pipetted into the thermostatted cell (30°) in the spectrometer. A portion (0·1 ml) of a 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 of a solution of the substrate in acetonitrile or dioxan was then added as before to initiate reaction and the kinetics followed by observing the decreasing optical density at a suitable wavelength. A pseudo-first-order rate constant was then calculated from these data. The procedure was repeated several times, using various portions (0·2, 0·3, 0·4 ml, *etc.*) of added amine and the rate constants calculated in each case.

pK_a *Determinations.*—Since the substrates were reactive in the pH regions close to their pK_a values it was necessary to use a sampling technique to estimate the optical density of the unchanged substrate as a function of pH. The technique used has already been described in detail.[18]

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