Acid and Base Catalysis of Urea Synthesis: Nonlinear Brønsted Plots consistent with a Diffusion-controlled Proton-transfer Mechanism and the Reactions of Imidazole and *N*-Methylimidazole with Cyanic Acid

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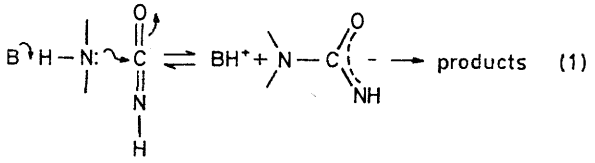
Brønsted plots for general acid and general base catalysis of the synthesis of phenylurea from aniline and cyanic acid are nonlinear. The maximum values of the rate constants for general acid and for general base catalysis are similar and the value of β_{nuc} for the buffer catalysed reaction is *ca.* 1·0. The data are consistent with a mechanism involving a zwitterionic intermediate and a rate-limiting proton-transfer step that is close to diffusion controlled in the thermodynamically favourable direction. Proof that proton transfer to the leaving nitrogen is complete before C–N bond breaking takes place in the cleavage of a substituted urea is provided by the similar rate and equilibrium constants for the reversible reaction of imidazole and *N*-methylimidazole with cyanic acid.

THE first step in the synthesis of substituted ureas from amines and cyanic acid, the formation of a zwitterionic intermediate, was described in the preceding paper.[1] In this paper we consider the mechanism of the subsequent proton-transfer step(s) that give the uncharged urea product; urea hydrolysis must proceed through the same steps in the reverse direction. The existence of a change in rate-determining step and an intermediate already rules out a fully concerted mechanism of acid–base catalysis or cyclic proton transfer synchronous with C–N bond formation and breakdown, and the observed values of β_{nuc}, 0·3 and 0·8 for strongly and weakly basic amines, respectively, as well as the diffusion-controlled limit for reaction rates, rule out mechanisms involving free amine anion and protonated cyanic acid as intermediates [equations (1), (2), and (4) of ref. 1]. It remains to distinguish between possible stepwise mechanisms of catalysis and concerted mechanisms that involve a single molecule of catalyst [*e.g.* equation (1)].



With the exception of the independent work of Hegarty on the decomposition of *N*-phenylcarbamoylimidazole,[2] clear-cut evidence for general acid or base catalysis of the reaction of amines with cyanic acid or of the hydrolysis of ureas in aqueous solution has not been described previously.[3] The importance of the proton transfer steps is shown, however, by the presence of catalysis by tertiary amines, acids, and other proton-transferring agents in non-aqueous media.[4] It has been suggested that catalysis by tertiary amines involves nucleophilic catalysis with the intermediate formation of an *N*-carbamoylated tertiary ammonium ion;[4-6] the evidence supporting this interpretation is subject to alternative interpretations [7a] and it might be expected that this intermediate would be less reactive toward nucleophilic attack than cyanic acid itself. The experiments described here were undertaken because a consideration of structure–reactivity relationships in general acid–base catalysed reactions [8] led to the prediction that general acid–base catalysis might be detectable for the reactions of weakly basic nucleophiles with cyanic acid or with isocyanates that contain a basic amine. Further, a comparison of the reactions of imidazole and of *N*-methylimidazole with cyanic acid in both directions was carried out. It was hoped that by substitution of a (non-transferable) methyl group for a proton on the attacking or leaving amine it would be possible to determine whether proton transfer to and from this amine occurs in a stepwise or a concerted manner.

EXPERIMENTAL

Materials and methods are described in the preceding paper; [1] kinetic measurements were made at 25° and ionic strength maintained at 1·0M with sodium chloride, unless noted otherwise. Rate constants for general acid and base catalysis of the reaction of aniline with cyanic acid were generally obtained from six runs in the presence of increasing concentrations of buffers up to *ca.* 1·0M; the detailed conditions for some of the reactions are given in Supplementary Publication No. SUP 21137 (8 pp.).† Values or limits for the catalytic constants of some weak acids were determined only at pH 4, well below the pK_a of the acid; spot checks at pH 5 indicated no significant contribution of catalysis by the basic species under these conditions. Similarly, catalysis by some weak bases was measured at a single pH value well above the pK_a of the conjugate acid, at which acid catalysis would not be expected to be significant as estimated from the known catalytic constants for stronger acids. Two consecutive runs with cyanate in the same chloroacetate buffer con-

† For details of Supplementary Publications see Notice to authors No. 7 in *J.C.S. Perkin II*, 1973, Index issue. Items less than 10 pp. are supplied as full-size copies.

[1] A. Williams and W. P. Jencks, preceding paper.

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

[3] I. A. Kemp and G. Kohnstam, *J. Chem. Soc.*, 1956, 900; T. Mukaiyama, S. Ozaki, and T. Hoshino, *Bull. Chem. Soc. Japan*, 1954, **27**, 578; T. Hoshino, T. Mukaiyama, and H. Hoshino, *ibid.*, 1952, **25**, 392.

[4] C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, 1935, **18**, 142; J. Bunkus, *J. Org. Chem.*, 1961, **26**, 779; E. Dyer and J. F. Glenn, *J. Amer. Chem. Soc.*, 1957, **79**, 366; *J. Org. Chem.*, 1961, **26**, 2919; J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 1947, 713; J. W. Baker and J. Gaunt, *ibid.*, 1949, 9, 19, 27; J. W. Baker, M. M. Davies, and J. Gaunt, *ibid.*, p. 24.

[5] M. Pestemer and D. Lauerer, *Angew. Chem.*, 1960, **72**, 612; S. L. Reegen and K. C. Frisch, *J. Polymer Sci.*, 1970, **8**, 2883.

[6] Y. Furuya, S. Gsto, K. Itoho, I. Urasaki, and A. Morita, *Tetrahedron*, 1968, **24**, 2367.

[7] (*a*) A. Farkas and G. A. Mills, quoted in A. Farkas and P. F. Strohm, *Ind. and Eng. Chem.* (*Fundamentals*), 1965, **4**, 32; K. C. Frisch, S. L. Reegen, W. V. Floutz, and J. P. Oliver, *J. Polymer Sci. A-1*, 1967, **5**, 35; (*b*) J. M. Lowenstein, *J. Chem. Soc.*, 1956, 4665.

[8] W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705.

taining aniline gave identical rate constants, showing that a reaction of aniline with the buffer does not interfere significantly. The existence and approximate magnitude of the catalytic constant for the solvated proton were determined from twelve runs in the pH range 0·9—2·0 in which the proton-catalysed reaction, after correction for other terms, accounted for 13—28% of the total observed rate (SUP 21137).

Reaction of imidazole with cyanate was followed at 240 nm using quartz cells; imidazole buffer (2·5 ml) was equilibrated to 25° and potassium cyanate (0·02 ml; 0·4M) added. A gradual increase in absorbance was observed in the synthetic reaction but a decrease in the hydrolysis of *N*-carbamoylimidazole (prepared by the method of Lowenstein [7b]) in imidazole buffers. Owing to the high background u.v. absorbance of *N*-methylimidazole the change in absorbance at 240 nm in the presence of potassium cyanate in *N*-methylimidazole buffers could only be observed by using 3 ml quartz cells (1 cm path length) fitted with quartz 'spacers' to give an effective path length of 0·2 cm. *N*-Methylimidazolium chloride was adjusted to pH 3·5—4·0 and added to buffer of the same pH. This solution (1 ml) was pipetted into the cell and potassium cyanate stock (0·02 ml; 0·4M) added, the 'spacer' inserted, and the reaction followed at 240 nm in the thermostatted cell compartment of a Beckman-DU–Gilford spectrophotometer. Essentially the same procedure was followed using short pathlength cells except that mixing was effected prior to adding to the cell. Knowledge of zero time enabled the overall extinction change to be calculated by extrapolation.

Although attempts to synthesise pure *N*-carbamoyl-*N'*-methylimidazolium ion were unsuccessful, a solution containing this compound was prepared by adding 3M-HCl (5 ml) to *N*-methylimidazole (0·82 g) and potassium cyanate (0·82 g) in water (5 ml) at 0° and allowing the mixture to stand for 10 min at 0°. Portions (0·005 ml) of this solution were added to reaction mixtures (3 ml) to follow the hydrolysis or approach to equilibrium of *N*-carbamoyl-*N'*-methylimidazolium ion at 240 nm.

Product Analysis.—In order to determine the possible contribution of nucleophilic catalysis of cyanate disappearance by attack of acetate ion on cyanic acid to form a mixed anhydride followed by attack of aniline on the reactive acetyl group to give acetanilide,[9,10] the products of the reaction were examined spectrophotometrically. It was found that <5% of the product was acetanilide at the highest concentration of acetate buffer that was examined; the same result was found for the possible formation of chloroacetanilide in chloroacetate buffers. However, in the presence of formate buffers the formation of formanilide was detected spectrophotometrically and the observed rate constants did not level off with increasing buffer concentration. This suggests that nucleophilic catalysis involving attack of aniline on the highly reactive formyl group of the mixed anhydride is significant and, accordingly, formate buffers were not used for kinetic experiments.

RESULTS

General Acid and Base Catalysis of Phenylurea Synthesis.—The observed pseudo-first-order rate constants for the reaction of aniline with cyanate increase with increasing concentration of the buffer (k_u, Figure 1). The data were corrected for (*a*) a small increase in the rate of cyanate hydrolysis caused by buffer in the absence of aniline, (*b*) a 'depletion' rate constant caused by nucleophilic reaction of primary and secondary amine buffers with cyanic acid, calculated from the data of Table 1 of ref. 1 and illustrated by k_n in Figure 1, and (*c*) curvature of the plots caused by partial change in the rate-determining step,

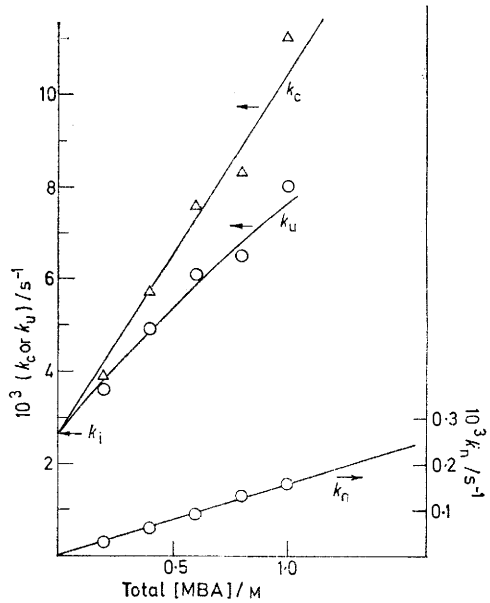


FIGURE 1 Reactivity of aniline with cyanic acid at pH 4·05 in the presence of increasing concentrations of methyl β-alaninate (MBA). Circles, k_u, represent the uncorrected data; triangles are the data corrected for change in rate-limiting step as described in the text. Circles, k_n, represent depletion of cyanic acid caused by reaction with MBA (Table 1, of ref. 1); k_i is the calculated intercept from hydrolysis of cyanate and reaction of aniline with cyanic acid (Table 1 of ref. 1)

using the known buffer-independent rate constant $k_{max.}$ for the aniline reaction (Table 1 of ref. 1) and equation (2),[11]

$$k_{corr} = (k_{obs} - k_0)/[1 - (k_{obs} - k_0)/(k_{max.} - k_0)] \quad (2)$$

in which k_0 is the rate constant at zero buffer concentration.[1,6] The triangles in Figure 1 illustrate typical corrected data and the slope of the lines in the Figure give the estimated corrected catalytic constant at this buffer ratio. There is no indication of a second-order term in buffer concentration, such as might be expected if both acid and base catalysis were occurring in the same transition state.

The rate constants k_A and k_B, for general acid and general base catalysis, respectively, were evaluated by plotting the catalytic constants at each buffer ratio, after division by the concentration of free amine and the fraction of free cyanic acid, against the fraction of the buffer as the free base (B/T). The intercepts at zero and 100% free base give k_A and k_B, respectively, as illustrated in Figure 2 for catalysis by the dication and monocation of DABCO; * again the lines indicate the estimated upper and lower limits of the data. It is evident from Figure 1 that the catalytic constants are not of high precision, but we believe that they are adequate to establish the existence of both

* Abbreviations used here are: DABCO, diaminobicyclooctane or triethylenediamine; CIm, *N*-carbamoylimidazole; $CImMe^+$, *N*-carbamoyl-*N'*-methylimidazolium ion; Im, imidazole; MeIm, *N*-methylimidazole; AN, aniline.

[9] G. R. Stark, *Biochemistry*, 1965, **4**, 1030.
[10] P. M. Mader, *J. Org. Chem.*, 1968, **33**, 2253.
[11] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 1973, **95**, 5637.

acid and base catalysis and to draw conclusions from their relative magnitudes on a logarithmic scale. The rate constants and error limits are summarised in Table 1.

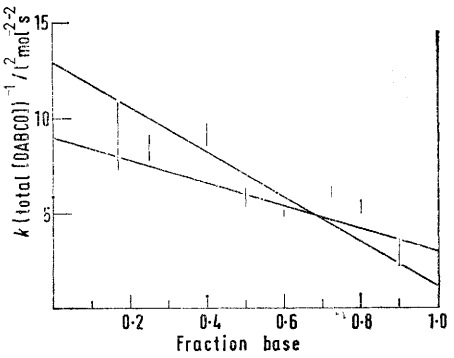


FIGURE 2 Dependence of buffer catalysis of the reaction of aniline and cyanic acid on the fraction of DABCO monocation. Lines yield maximal and minimal values for k_A and k_B; k is derived from k_{obs} corrected for a hydrolysis term and divided by total free aniline and the fraction of cyanic acid. Data are from SUP 21137

TABLE 1

Acid–base parameters for the buffer catalysed reaction of aniline with cyanic acid [a]

Catalyst [b]	pH [f]	pK_a	k_A/ l^2 mol^{-2} s^{-1} [e]	k_B/ l^2 mol^{-2} s^{-1} [e]	N [d]
Aniline		4·75	7·4 (0·6)	1·8 (0·9)	33
DABCO		3·6	11 (2)	2·0 (0·8)	35
Acetate		4·55	2·4 (0·6)	3·7 (0·3)	12
Chloroacetate		2·65	7·8 (1·0)	3·2 (0·6)	21
Water		−1·7	230 (100)	0·028 (0·006) [c]	13
N-Propargylmorpholine	4·05	5·55	2·4 (0·4)		9
Dichloroacetate	4·89	1·12		0·41 (0·29)	6
Ethoxyacetate	5·01	3·32		5·7 (0·4)	4
Trifluoroacetate	5·04	0·26		<0·2	5
N-Chloroethylmorpholine	4·05	6·3	2·4 (0·1)		5
N-Methylmorpholine	4·04	7·8	3·4 (0·3)		6
Ethyl glycinate	4·05	7·6	7·3 (0·9)		6
Methyl β-alaninate	4·05	9·25	6·4 (0·7)		6
Ethylamine	4·07 [g]	10·85	1·4 (0·1)		12
Quinuclidine	4·05	11·55	0·49 (0·26)		6
Piperidine	4·05	11·35	<0·113		6
Acetamidine	4·05	12·52	<0·081		6
Guanidine	4·05	13·6	<0·081		6
Borate	4·05	9·2	4·6 (0·5)		6

[a] 25°; ionic strength maintained at 1·0M with sodium chloride. [b] The base species is given; k_A refers to the action of the conjugate acid. [c] This is calculated from k for aniline (Table 1 of ref. 1) by division by 55·5 mol l^{-1}. [d] Number of points. [e] Error limits of the values are given in parentheses. [f] Absence of a pH value indicates measurements carried out over a series of buffer ratios (SUP 21137). [g] Rates also checked at pH 5·04.

Increasing the ionic strength of the medium lowers the rate constant for the reaction of aniline with cyanic acid, but the effects of added solutes including quaternary ammonium salts (with constant ionic strength) are small (SUP 21137).

Catalytic constants for DABCO buffers, in the form of 50% dication, were determined for the reactions of a series of substituted anilines with cyanic acid (SUP 21137). These catalytic constants correspond to ($k_A + k_B$) and are plotted logarithmically in Figure 3 against the pK_a of the substituted aniline; the line in Figure 3 is drawn with a slope of 1·0. Although a complete kinetic analysis was not carried out, this result shows that the sensitivity of the catalytic constants to the basicity of the attacking amine is large; in fact, the sensitivity is somewhat larger than indicated by the Figure because the catalytic constants are not corrected for the k_1 step, which becomes kinetically significant and decreases the observed catalytic constants for the more basic anilines.

Formation and Breakdown of Carbamoylimidazoles.— The dependence on pH of the pseudo-first-order rate constants for the hydrolysis of dilute solutions of carbamoylimidazole and *N*-carbamoyl-*N*′-methylimidazolium ion is shown in Figure 4. The hydrolysis of CIm follows the rate

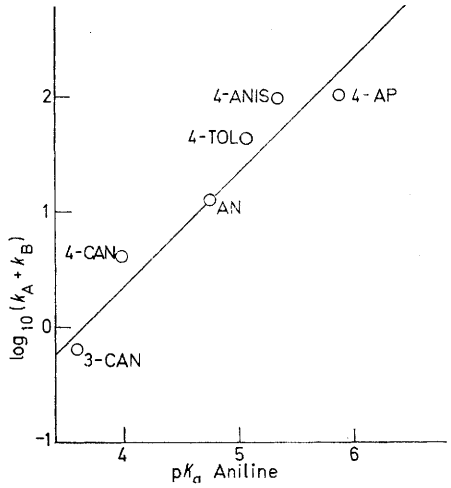


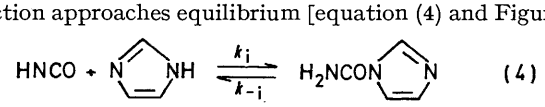
FIGURE 3 Effect of aniline structure on $k_A + k_B$ for reaction with cyanic acid catalysed by DABCO buffer (SUP No. 21137). Abbreviations are: 3-CAN = 3-chloroaniline, 4-CAN = 4-chloroaniline, 4-TOL = 4-toluidine, 4-ANIS = 4-anisidone, 4-AP = 4-aminophenol; slope of line is 1·0

law (3) with k_{-i} 1·05 × 10^{-2} s^{-1} and pK_a for protonated carbamoylimidazole 4·15, in agreement with the results of

$$k_{obs} = k_{-i}[CIm] = k'_{-i}[CImR^+][OH^-] \quad (3)$$
(R = H or Me)

Stark.[12] The rate of hydrolysis of *N*-carbamoyl-*N*′-methylimidazolium ion, which cannot lose a proton to give the uncharged compound, is very similar to that of protonated carbamoylimidazole at low pH and is proportional to hydroxide ion activity between pH 3 and 5 with k'_{-i} 9·3 × 10^7 l mol^{-1} s^{-1}.

At pH 7·21 the cleavage of a dilute solution of carbamoylimidazole in phosphate buffer proceeds to completion, but in the presence of imidazole buffers the reverse reaction of imidazole with cyanic acid becomes significant and the reaction approaches equilibrium [equation (4) and Figure 5].



(4)

The hydrolysis of cyanate is relatively slow at this pH and

[12] G. R. Stark, *Biochemistry*, 1965, **4**, 588.

the equilibrium constant $K_a = [NCO^-][ImH^+]/[CIm]$ was found to be 1·33 l mol^{-1} from equation (5), in which A_0 and

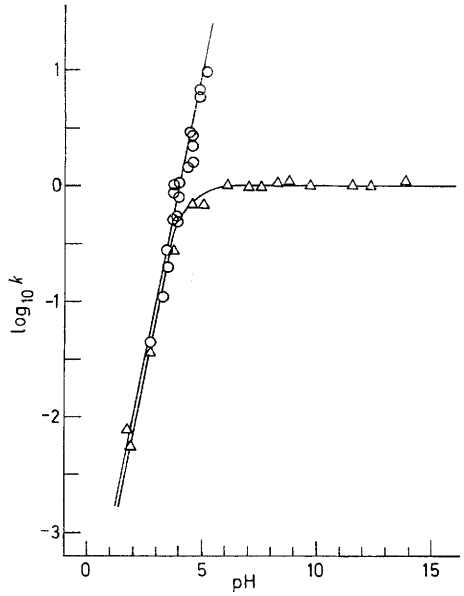


FIGURE 4 pH-Dependence of hydrolysis of *N*-carbamoylimidazole (△) and *N*-carbamoyl-*N'*-methylimidazole (○). Lines are theoretical from parameters in Table 4

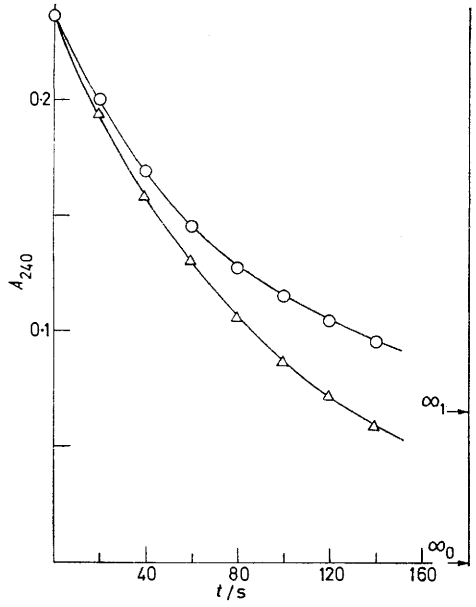


FIGURE 5 Decomposition and approach to equilibrium at pH 7·21 of a solution of *N*-carbamoylimidazole in phosphate buffer (△) and in imidazole buffer (○; 1·0M); A_{240} is the absorbance at 240 nm; ∞_0 and ∞_1 represent infinity values of A_{240} for phosphate and imidazole buffers respectively

A_{eq} are the measured absorbances of carbamoylimidazole at zero time and at equilibrium, respectively.

$$K_c = [ImH^+](A_0 - A_{eq})/A_{eq} \quad (5)$$

The approach to equilibrium of dilute solutions of potassium cyanate or carbamoylimidazole in imidazole buffers is (pseudo) first order and follows the rate law (6).

$$k_{obs} = k_i[Im]f(HNCO) + k_{-i} \quad (6)$$

The values of k_i and k_{-i} were obtained from the slopes and intercepts, respectively, of plots of k_{obs} against $[Im]f(HNCO)$ based on a series of experiments with varying imidazole buffer concentrations in the pH range 6·22—7·21 (Table 2).

TABLE 2

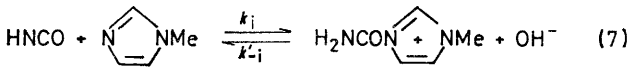
Interaction of cyanic acid with imidazole [a,e]

Fraction base	pH [d]	k_i/l mol^{-1} s^{-1} [b]	$k_{-i} \times 10^2$/ s^{-1}	K_c/l mol^{-1} [c]
0·1	6·22	68 (11)	0·98	1·6
0·125	6·33	67 (7)	0·83	1·48
0·2	6·5	77 (4)	1·05	1·39
0·2	6·5	77 (9)	0·88	1·18
0·5	7·17	65 (7)	0·96	1·55
0·5	7·17	68 (5)	0·99	1·6

[a] 25°; ionic strength maintained at 1·0M with sodium chloride; numbers in parentheses are numbers of kinetic runs. [b] Average value k_i = 71 l mol^{-1} s^{-1}. [c] Average value K_c = 1·4 l mol^{-1}. [d] pH Of lowest imidazole concentration. [e] At fraction base = 0·5, $[ImH^+]$ = 0·25M. [CIm]/[total cyanate] = 0·158. Optical density change for a 0·304 × 10^{-2}M solution in total cyanate is 0·310. Thus $\Delta\varepsilon_{240}$ = 0·310/0·304 × 10^{-2} × 0·158 = 645; direct value obtained from Figure 5 is 780.

The average equilibrium constant K_c = 1·4 l mol^{-1} and the rate constant for hydrolysis k_{-i} = 9·5 × 10^{-3} s^{-1} are in good agreement with the directly measured values. The value of K_c is smaller than previously reported values in the range 2·4—4·2 l mol^{-1} obtained at a lower ionic strength by a titrimetric procedure near neutral pH in the presence of imidazole buffers.[12] The discrepancy between the mean value of k_i = 71 l mol^{-1} s^{-1} and an earlier value of k_i = 7·8 l mol^{-1} s^{-1} calculated from K_c and k_{-i} is a consequence of this difference in K_c and a different value of the ionisation constant that was used to calculate the concentration of free cyanic acid. The observed rate constants were found to be independent of the concentration of acetate buffers from 0·1 to 1·0M at pH 5·50.

The formation of *N*-carbamoyl-*N'*-methylimidazolium ion from cyanic acid and *N*-methylimidazole [equation (7)] can be demonstrated at low pH values where the reaction is thermodynamically most favourable; however at low pH the competing hydrolysis of cyanic acid becomes fast and the concentration of free *N*-methylimidazole decreases



so that kinetic measurements become difficult. The reaction may be followed by measuring the increase in absorption of the product at 240 nm upon the addition of cyanic acid to 1·0M-*N*-methylimidazolium ion at pH 4·20 (Figure 6); the rapid formation of *N*-carbamoyl-*N'*-methylimidazolium ion is followed by a slow decomposition caused by the hydrolysis of cyanic acid, which displaces the equilibrium and eventually leads to disappearance of the product. The rate constants for the initial approach to equilibrium were determined at a series of concentrations of *N*-methylimidazolium ion as shown in Figure 7. The reaction was followed in the forward direction by adding cyanic acid (circles) and in the reverse direction by adding a small portion of a solution of product that had been prepared by mixing concentrated solutions of cyanic acid and *N*-methylimidazolium ion (triangles). The two experiments gave similar results and the intercept at zero *N*-methylimidazolium ion concentration agrees with the directly measured rate of hydrolysis of *N*-carbamoyl-*N'*-methylimidazolium ion. The observed rate was found to be independent of the concentration of

acetate buffer from 0·1 to 1·0M at pH 4·00. The values of k_i and k'_{-i} are given by equation (8) and were obtained

$$k_{obs} = k_i[MeIm]f(HNCO) + k'_{-i}[OH^-] \quad (8)$$

from the slope and intercept, respectively, of a series of plots similar to that of Figure 7 after correction for the

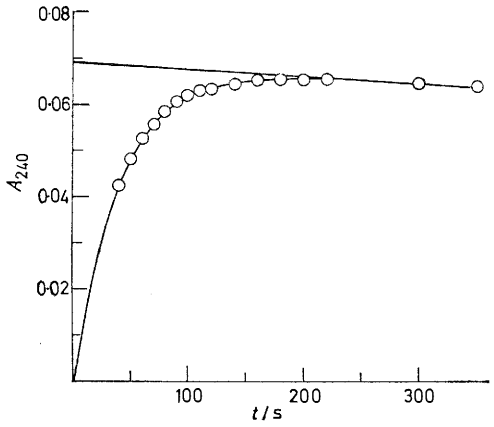


FIGURE 6 Formation and decay of *N*-carbamoyl-*N'*-methylimidazole from addition of potassium cyanate to acetate buffer containing *N*-methylimidazolium ion: conditions, pH 4·20; [MeImH$^+$] 0·8M; 0·1M-acetate buffer; 0·02 ml 0·4M-KNCO per 1 ml buffer; 0·1 cm path length cells

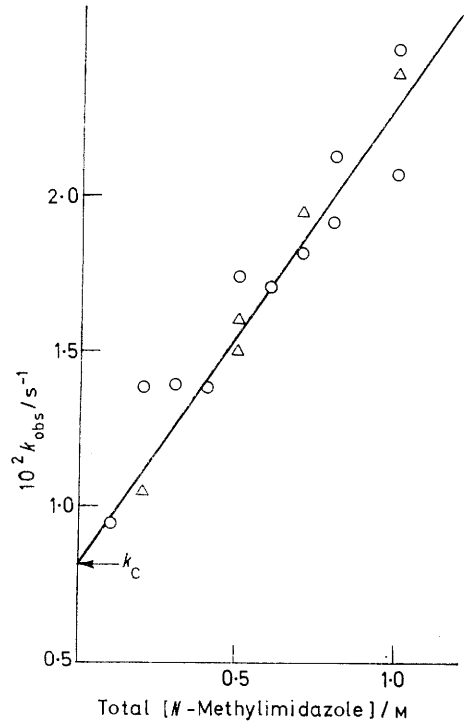


FIGURE 7 Dependence of the rate constant for reaction of *N*-methylimidazole with cyanic acid on the concentration of *N*-methylimidazole: $k_c = k'_{-i}$ [OH$^-$] + cyanate hydrolysis rate constant. Approach to equilibrium is *via* synthesis (○) and decomposition (△); data at pH 4·00 from Table 3

concentrations of the reactive ionic species as described in Table 3. The equilibrium constant K' = [HNCO][MeImH$^+$]/[CImMe$^+$] = 0·093 l mol^{-1} was calculated from $K' = k'_{-i}K_w/k_iK_{MeImH^+}$. The several rate and equilibrium constants for the reaction of cyanic acid with imidazole and with *N*-methylimidazole are summarised in Table 4.

TABLE 3

Interaction of *N*-methylimidazole with cyanic acid [a]

[MeImH$^+$]	ΔA_{240}	10^2k/s^{-1}
pH 3·50 [g] slope [d] 0·89 (0·11) × 10^{-2} l mol^{-1} s^{-1}		
0·5	1·52	0·68 (0·03)
0·375	1·2	0·46 (0·01)
0·25	0·9	0·42 (0·01)
0·125	0·435	0·33 (0·01)
0		0·2 [c]
k_i [e,h]/l mol^{-1} s^{-1} 120 (10); K' [f,i]/l mol^{-1} 0·087 (0·011)		
pH 3·8 [g] slope [d] 1·3 (0·1) × 10^{-2} l mol^{-1} s^{-1}		
1·0	1·3	2·0 (0·1)
0·75	1·0	1·65 (0·05)
0·5	0·72	1·3 (0·02)
0·5	0·72	1·31 (0·01) [b]
0·25	0·39	0·84 (0·02)
0		0·55 [c]
k_i [e,h]/l mol^{-1} s^{-1} 140 (10); K' [f,i]/l mol^{-1} 0·10 (0·01)		
pH 4·00 [g] slope [d] 1·5 (0·1) × 10^{-2} l mol^{-1} s^{-1}		
1·0	2·1, 2·5	2·4 [j]
0·8	1·9, 2·1	
0·7	1·8	1·95 [j]
0·6	1·7	
0·5	1·7	1·5,[j] 1·6 [j]
0·4	1·3	
0·3	1·3	
0·2	1·3	1·1 [j]
0·1	0·94	
0	0·82 [c]	
k_i [e,h]/l mol^{-1} s^{-1} 145 (15); K' [f,i]/l mol^{-1} 0·091 (0·008)		

[a] 25°; 1·1M ionic strength maintained with sodium chloride; acetate concentration 0·1M. [b] Acetate at 0·5M. [c] Hydrolysis of CImMe$^+$ from data of Figure 3 and SUP 21137. [d] k *versus* [MeImH$^+$]. [e] k_i = slope × $[a_H]/[K_{a(MeIm)}f(HNCO)]$. [f] K' = [MeImH$^+$][HNCO]/[CImMe$^+$]. [g] pH Of solutions did not vary by >0·01 from the quoted value. [h] Average k_i = 133 l mol^{-1} s^{-1}. [i] Average K' = 0·093 l mol^{-1}.

TABLE 4

Summary of equilibrium and rate constants for the reaction of imidazole and *N*-methylimidazole with cyanic acid at 25° and ionic strength 1·0M [a]

Parameter	Imidazole [d]	*N*-Methylimidazole
k_i/l mol^{-1} s^{-1}	71	135
k_{-i}/s^{-1}	9·5 × 10^{-3} [c]	
k'_{-i}/l mol^{-1} s^{-1}	6·7 × 10^7	9·3 × 10^7
K_c/l mol^{-1}	1·4	
K/l mol^{-1} [b]	1·34 × 10^{-4}	
K'/l mol^{-1}	0·20	0·093

[a] The constants are defined in the text. [b] K = [HNCO][Im]/[CIm]. [c] Value by direct measurement 1·05 × 10^{-2} s^{-1}. [d] pK_a of CImH$^+$ = 4·15.

DISCUSSION

The Brønsted plots for general acid catalysis (Figure 8) and general base catalysis (Figure 9) of the reaction of aniline with cyanic acid are non-linear and approach similar limiting values of the rate constants for acid and base catalysis. These results provide additional evidence for a stepwise reaction mechanism with a kinetically significant proton-transfer step and are consistent with rate-determining proton transfer to or from the catalyst that is close to diffusion controlled in the thermodynamically favourable direction.[8,13,14] For general acid catalysis these conclusions are based on the close similarity of the catalytic constants for substituted

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

[14] M. Eigen, *Angew. Chem. Internat. Edn.*, 1964, **1**, 1; M. Eigen and L. DeMaeyer in 'Techniques of Organic Chemistry,' ed. A. Weissberger, Interscience, New York, 1963, vol. VIII, part II, p. 1031.

ammonium ions of pK_a up to 9, followed by a sharp downward deviation for less acidic catalysts (Figure 8). The *N*-alkylmorpholines (propargyl, methyl, and 2-chloroethyl) exhibit almost the same values of k_A over a pK_a range of 2 but are less effective than other amines, as has been observed and discussed previously for other systems.[11,15,16] The enhancement by *ca.* 30-fold of catalysis by the proton is consistent with the known faster reaction of the hydronium ion by 10- to 30-fold in diffusion-controlled proton transfers.[13,14] The non-linearity of the Brønsted plot for general base catalysis is based on the similar rate constants for three basic

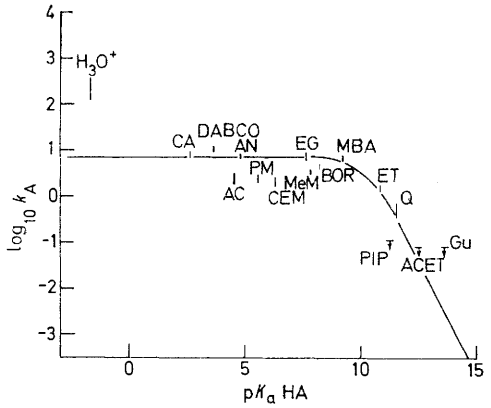


FIGURE 8 Brønsted dependence of k_A; line is theoretical for a simple proton transfer: pK_a 10·2; $k_{plateau}$ 6·3 l² mol⁻² s⁻¹. Data are from Table 1 and abbreviations are: CA = chloroacetic acid, AC = acetic acid, PM = *N*-propargylmorpholine, CEM = *N*-(2-chloroethyl)morpholine, MeM = *N*-methylmorpholine, EG = ethyl glycinate, BOR = borate, MBA = methyl β-alaninate, ET = ethylammonium ion, Q = quinuclidine, PIP = piperidine, ACETˆ = acetamidine, GUˆ = guanidine

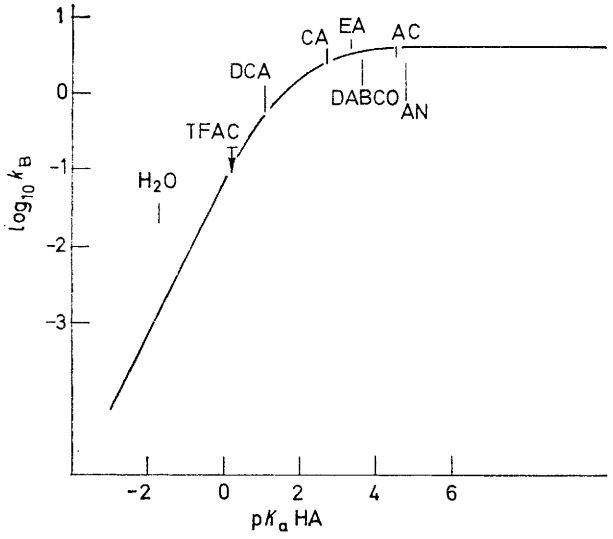
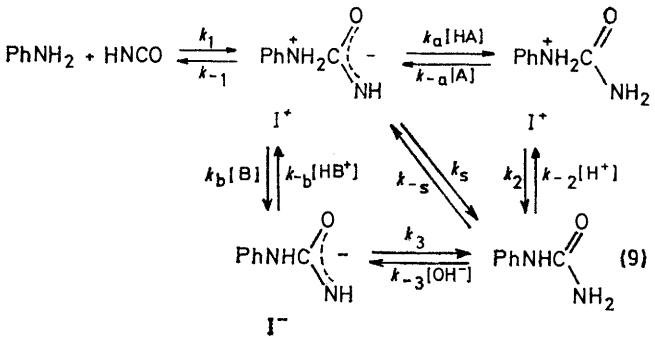


FIGURE 9 Brønsted dependence of k_B; line is theoretical for a simple proton transfer: pK_a 1·8, $k_{plateau}$ 4·0 l² mol⁻² s⁻¹. Data are from Table 1 and abbreviations are: TFAC = trifluoroacetate, DCA = dicyloroacetate, EA = ethoxyacetate

carboxylate anions and the lower values for dichloroacetate and trifluoroacetate (Figure 9). Water shows a positive deviation from the descending limb of the curve.

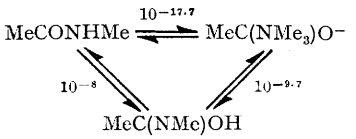
The simplest interpretation of these results is given by the mechanism of equation (9), in which k_a and k_b are the rate constants for simple proton transfer reactions from or to the catalyst, respectively, and are



close to the diffusion-controlled limit in the thermodynamically favoured direction; k_s represents a proton switch in which the initially formed zwitterion $I^{\pm}$ is converted directly to the uncharged urea, probably with the help of one or more water molecules. One or more water molecules may also be involved in the other proton transfer steps. This mechanism is closely similar to that for ester aminolysis,[8,17] except that no further cleavage of bonds between heavy atoms after the proton transfer step is necessary to form product in the urea synthesis reaction.

The position of the break points in the Brønsted plots should be within approximately one unit of the pK_a of the substrate site that is involved in the proton transfer.[8,14,15] Although precise estimates are not possible, a rough estimate [18,*] of the pK_a of $I^{\pm}$ of 12 ± 2

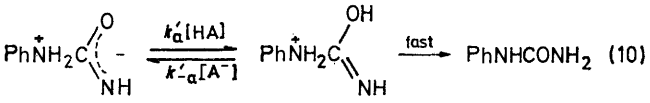
* The three microscopic pK_a values of $PhNH_2C(NH)O^-$ can be calculated using linear free energy relationships (see appendix of ref. 15): using the known pK_a for *N*-methylacetamide [19a] and the equilibrium constant for the formation of the isoimide [19b] the pK_a of the hydroxy-group of MeC(HMe)OH is calculated to be 9·7. Using ρ_I 8·4 and σ_I 0·1 [15] the introduction of a non-resonating nitrogen



instead of Me should reduce the pK_a by *ca.* 0·84 units and the positive charge on the nitrogen should reduce it by a further 4·7 units (ref. 15, appendix) to yield a calculated pK_a of 4 ± 2. Similar arguments yield a pK_a of 12 ± 2 for protonated isoimide $PhNH_2C(NHMe)O^- \longrightarrow PhNH_2C(NMe)O^- + H^+$ starting from the pK_a of the amide (17·7). Another method using Charton's σ_I [18] for RNH_2 of *ca.* 0·6 reduces the pK_a of the methyl species by 8·4 × 0·6 = 5 units to 4·7 and 12·7 respectively. The errors in estimating the microscopic pK_a values are probably larger than ±2 because of this uncertainty and because of a 10-fold difference between estimates of the tautomeric equilibrium constant.[19] The pK_a of the ammonium proton $MeNH_2C(NH)O^- \longrightarrow MeNHC(NH)O^- + H^+$ may be estimated from the pK_a of *N*-methylurea protonated on N.[19a] Allowing 4·7 units for the presence of a full negative charge the microscopic pK_a should be 1 ± 2.

[15] J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 1436.
[16] J. Hine and J. Mulders, *J. Org. Chem.*, 1967, **32**, 2200.
[17] A. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, submitted for publication.
[18] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.
[19] (*a*) R. S. Molday and R. G. Kallen, *J. Amer. Chem. Soc.*, 1972, **94**, 6739; (*b*) A. R. Fersht, *ibid.*, 1971, **93**, 3504.

is consistent with the break point of the plot for general acid catalysis near pK_a 10. We hesitate to estimate the pK_a of I$^{\pm}$ that should correspond to the break point for general base catalysis near pK_a 1·8, but it appears reasonable that it should be below the pK_a of anilinium ion of 4·8 and above that of *N*-protonated *N*-methylurea of −3·9.[19a] Protonation of the oxygen atom of I$^{\pm}$ gives a hydroxy-group with an estimated pK_a[18] of 4 ± 2 [equation (10)]. If the probability of proton



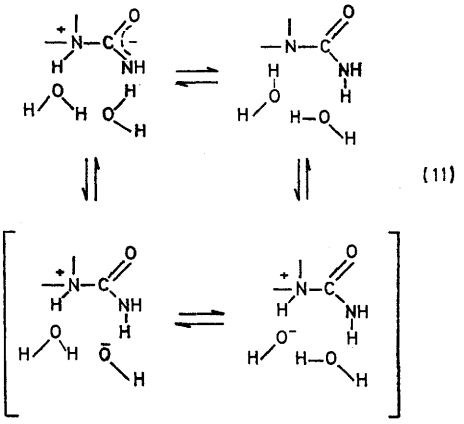
(10)

transfer to the basic nitrogen atom of I$^{\pm}$ on each encounter with an acid is <1·0,[15,20] protonation on oxygen by acids of pK_a <4 can provide an alternative route to products [equation (10)]. This provides a possible explanation for the larger catalytic constant for chloroacetic acid than for acetic acid. Since the pK_a of the substituted anilinium ion is certainly lower than that of the hydroxy-group in the intermediate of equation (10), subsequent proton transfer will occur more readily from this nitrogen atom so that the intermediate is expected to go on to form products more rapidly than it reverts to I$^{\pm}$. Similarly, the subsequent proton transfers of the k_a and k_b steps in equation (9) are strongly favourable thermodynamically and are expected to occur rapidly with the solvent or with the original catalyst molecule in a ' one-encounter ' mechanism.

The larger catalytic constants of ammonium cations than of acetic acid for general acid catalysis and of the more basic carboxylate anions than of aniline or DABCO monocation for general base catalysis are in the expected direction for small favourable electrostatic effects in the transfer of a proton to the anionic portion of I$^{\pm}$ and in the abstraction of a proton from the cationic nitrogen atom of I$^{\pm}$. The slightly smaller maximum values of the rate constants for general base compared with general acid catalysis may reflect steric hindrance to the removal of a proton from the substituted anilinium ion.[14,20]

The proton switch that accounts for the proton transfers in the ' water ' reaction can occur directly or, more probably, in a stepwise manner with the intermediate formation of a solvated hydroxide ion in the vicinity of the substrate [equation (11)]. The latter mechanism is essentially the same as that proposed for the corresponding step in ester aminolysis and is consistent with the values of β_{nuc} *ca.* 0·8 that are observed for both reactions when this step is believed to be rate determining.[17]

The rate constants for the reactions of a series of anilines catalysed by DABCO buffers, in the form of 50% dication, exhibit an even greater sensitivity to aniline basicity with a value of β_{nuc} of at least 1·0 (Figure 3). This means that the observed rate constants have a sensitivity to polar substituents on the aniline that is similar to that for protonation to give the


(11)

anilinium ion. Since k_a and k_b are presumably limiting rate constants that are close to diffusion controlled and insensitive to aniline structure, this value of β_{nuc} should reflect the effect of substituents on the equilibrium formation of I$^{\pm}$. A value of β_{nuc} = 1·0 is expected for the equilibrium formation of a cationic anilinium group in I$^{\pm}$ and is the same as has been observed in several aminolysis reactions for the formation of analogous intermediates.[15,17,21] ' Pre-association ' or ' spectator ' mechanisms, in which the catalyst is present in a reaction cage during the formation or cleavage of bonds between heavy atoms,[21,22] are possible in principle for urea synthesis but are inconsistent with the value of β_{nuc} *ca.* 1·0 for the catalysed reaction and with the observed change in rate-determining step with increasing buffer concentration.

The observation of a change in rate-determining step with increasing buffer concentration makes possible the estimation of approximate values for the individual rate and equilibrium constants in the mechanism of equation (9). The steady state expression for the general acid and base catalysed and ' water ' reactions is given in equation (12). The value of k_1 is given by the limiting value of k_{obs} at high acid concentration when the attack step becomes rate determining; from the

$$k_{obs} = \frac{k_1(k_s + k_a[HA] + k_b[B])}{k_a[HA] + k_b[B] + k_s + k_{-1}} \qquad (12)$$

data of Figure 3 of ref. 1, k_1 for 4-anisidine is 27·5 l mol^{-1} s^{-1}. When $k_{obs} = 0{\cdot}5k_1$, $(k_a[HA] + k_b[B] + k_s) = k_{-1}$. If k_a and k_b are taken[14] as 10^9 l mol^{-1} s^{-1} and knowing the relative values of k_a and k_s, the value of k_{-1} for the anisidine reaction is then $3{\cdot}4 \times 10^8$ s^{-1} and $k_1/k_{-1} = 8{\cdot}1 \times 10^{-8}$ l mol^{-1}. The value of k_s is 10^8 s^{-1}, which is comparable to the rate constant of $4{\cdot}8 \times 10^7$ s^{-1} for the analogous proton switch of acetic acid in water.[23]

[20] E. F. Caldin, J. E. Crooks, and D. O'Donnell, *J.C.S. Faraday I*, 1973, 993, 1000; K. J. Ivin, J. J. McGarvey, E. L. Simmons, and R. Small, *ibid.*, p. 1016; D. Grimshaw, P. J. Heywood, and E. Wyn-Jones, *J.C.S. Faraday II*, 1973, 756.

[21] M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 8828.

[22] (*a*) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, 1971, **93**, 2014; (*b*) W. P. Jencks and K. Salvesen, *ibid.*, p. 1419.

[23] E. Grunwald and S. Meiboom, *J. Amer. Chem. Soc.*, 1963, **85**, 2047; E. Grunwald, C. F. Jumper, and S. Meiboom, *ibid.*, p. 522; Z. Luz and S. Meiboom, *ibid.*, p. 3923.

Based on the observed value of $\beta_{nuc} = 1{\cdot}0$, which corresponds to the effect of polar substituents on the equilibrium constant k_1/k_{-1}, the value of k_1/k_{-1} for ammonia addition to cyanic acid may be estimated to be of the order of $1{\cdot}1 \times 10^{-3}$ l mol^{-1}. Since the overall equilibrium constant for urea formation from ammonia and cyanic acid [24] is $1{\cdot}1 \times 10^{11}$ l mol^{-1}, the equilibrium constant for the formation of urea from the zwitterionic intermediate may then be estimated to be of the order of 10^{14}. Thus, the slow hydrolysis of urea (k has the value $8{\cdot}3 \times 10^{-10}$ s^{-1} at 25°) [24] may be accounted for by the unfavourable equilibrium formation of the dipolar intermediate $I^{\pm}$ (*K ca.* 10^{-14}) followed by the breakdown of this intermediate to cyanic acid and ammonia with a rate constant k_{-1} *ca.* 8×10^4 s^{-1}.

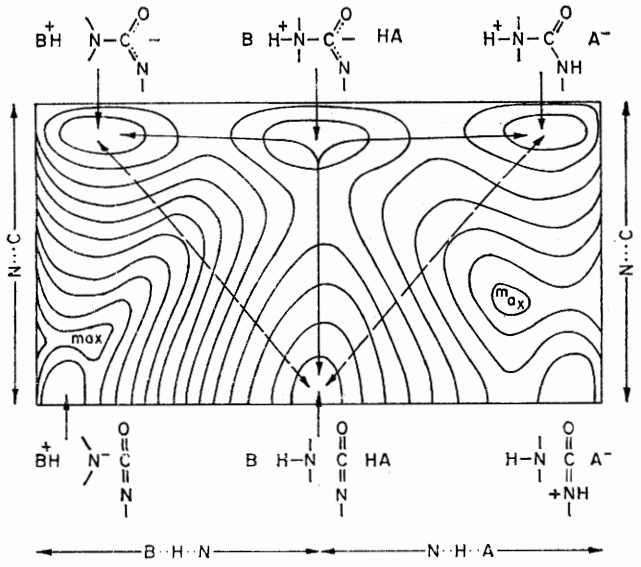
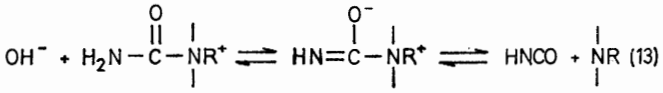


FIGURE 10 Representation of energy surfaces for urea formation from cyanic acid and aniline *via* a zwitterionic intermediate and mediated by acids (HA) of pK_a *ca.* 10 and bases (B) of pK_a *ca.* 2 (see text for details)

The occurrence of stepwise rather than concerted general acid and base catalysis in urea synthesis is expected in view of the small or negligible free energy of the proton-transfer step for many of the catalysts; concerted catalysis requires that there be a large favourable free energy of proton transfer to or from the catalyst to overcome the additional energy and entropy requirements of such a mechanism.[8,25] The situation may be illustrated by the three-dimensional reaction co-ordinate diagram of Figure 10, in which the vertical co-ordinate represents the formation and cleavage of the N–C bond and the horizontal co-ordinate represents proton transfer to or from a base catalyst (left side) or an acid catalyst (right side). The contour lines are drawn to represent the relative energies of intermediates or transition states when these can be estimated and the cross sections along the horizontal and vertical axes are drawn with small barriers for proton transfer and for N–C bond formation or cleavage; however, the essential features of the diagram are not changed if, for example, it is assumed that there is no barrier for a proton transfer that is strongly favoured thermodynamically. The catalysts are taken with pK_a values close to the break points of the respective Brønsted plots, so that the free energy of proton transfer to or from the addition intermediate is zero. The stepwise mechanisms (solid lines) are favoured over the concerted mechanisms (dashed lines) for both acid and base catalysed reactions. This is expected to be the case for any reaction in which the free energy of the proton transfer step is zero, provided that the intermediates have a finite existence; in this reaction the stepwise path is especially favourable because of the very high energy of the amine anion and *N*-protonated cyanic acid [26] intermediates in the lower left and right corners of the diagrams. The diagram is for the reaction of a weakly basic amine, for which the proton transfer step is rate determining. For a more strongly basic amine the addition intermediate $I^{\pm}$ will be more stable and have a larger barrier for decomposition, so that N–C bond formation and cleavage will become rate determining. With a sufficiently weakly basic nucleophile and a strongly basic or acidic catalyst the free energy of proton transfer becomes favourable and a concerted mechanism of catalysis may become significant.

Reactions of Imidazole and N-*Methylimidazole.*—The use of the (non-transferable) methyl group as a model for the (transferable) proton provides a convenient method for identifying the position of a proton in the transition state of a reaction.[27] If the pH-independent hydrolysis of a substituted urea actually involves the hydroxide ion catalysed breakdown of the species that is protonated on the leaving nitrogen atom [equation (13; R = H)], a similar rate constant should be observed for the species with a methyl group instead of a proton on the leaving group [equation (13; R = Me)], whereas if the proton is on some other atom or is only partially transferred to the nitrogen atom in the transition state the *N*-methyl group is not a model for the proton in the transition state and similar rate constants for the two species are not expected.



It was possible to apply this technique to the reversible reactions of imidazole and *N*-methylimidazole with cyanic acid. The almost identical rate constants for the hydroxide ion catalysed breakdown of *N*-carbamoyl-*N'*-methyl- and *N*-carbamoyl-imidazolium ions at low pH (Figure 4) show that the rapid equilibrium

[24] H. L. Welles, A. R. Giaquinto, and R. E. Lindstrom, *J. Pharm. Sci.*, 1971, **60**, 1212 (essentially zero ionic strength).
[25] W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 4731; W. H. R. Shaw and D. G. Walker, *ibid.*, 1958, **80**, 5337.
[26] G. A. Olah, J. Nishimura, and P. Kreienbühl, *J. Amer. Chem. Soc.*, 1973, **95**, 7672.
[27] R. W. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 1961, **83**, 4390; J. E. Reimann and W. P. Jencks, *ibid.*, 1966, **88**, 3973; W. P. Jencks and M. Gilchrist, *ibid.*, 1968, **90**, 2622; D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *ibid.*, 1971, **93**, 188.

protonation of the leaving imidazole group accounts for both the hydrolysis of protonated carbamoylimidazole at low pH and the pH-independent hydrolysis of the unprotonated species at higher pH, which is described by the same rate law and rate constant (Figure 4 and Table 4).[12] Conversely, the similar rate constants for the reaction of imidazole and *N*-methylimidazole with cyanic acid (k_1, Table 4) show that there is no significant amount of proton removal from the attacking imidazole in the transition state of the synthetic reaction. There is a further similarity and that is between the value of k_1 for attack of imidazole and *N*-methylimidazole on cyanic acid and the bimolecular rate constant k' (Table 1 of ref. 1) for a hypothetical primary amine of pK_a 7 with cyanic acid. These results provide further support for a stepwise reaction mechanism involving complete protonation of the leaving group before C–N cleavage occurs in urea decomposition and no proton removal from the attacking amine when the C–N bond is formed in urea synthesis.

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