Urea Synthesis from Amines and Cyanic Acid: Kinetic Evidence for a Zwitterionic Intermediate

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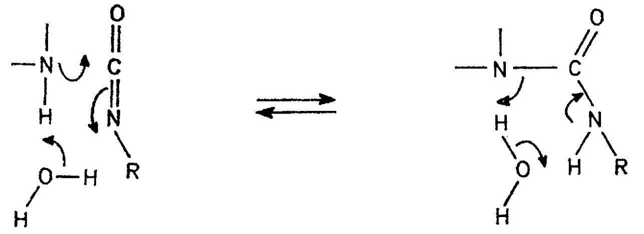
The following evdence supports the conclusion that the reaction of amines with cyanic acid and the hydrolysis of urea occur through a stepwise mechanism with the formation of an intermediate zwitterion. (1) The Brønsted type plot of $\log_{10}k'$ *versus* ammonium ion pK_a has a slope β_{nuc} 0·3 for basic amines and exhibits a break to a slope β_{nuc} 0·8 for weakly basic amines; the two segments are assigned to rate-determining nucleophilic attack and proton-transfer steps, respectively. (2) General acid–base catalysis is observed only with weakly basic amines, for which the proton-transfer step is rate determining. (3) A change in rate-determining step with increasing buffer concentration is observed as the uncatalysed attack step becomes rate determining.

We are interested in the problem of how a proton is removed from one nitrogen atom and added to the leaving nitrogen atom in urea decomposition and the equivalent problem of how proton transfer from the attacking amine to the nitrogen atom of cyanic acid takes place in the reverse reaction. Mechanisms for this proton transfer include the following. The proton transfer may occur intramolecularly, either directly or through one or more water molecules, at the same time as the C–N bond formation and cleavage [equation (1)].[1] Proton transfer may be brought about by a general base and/or a general acid catalyst in a concerted manner [equation (2)].[2] The reaction may occur through a stepwise mechanism in which proton transfer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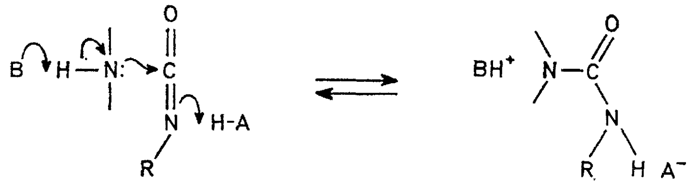

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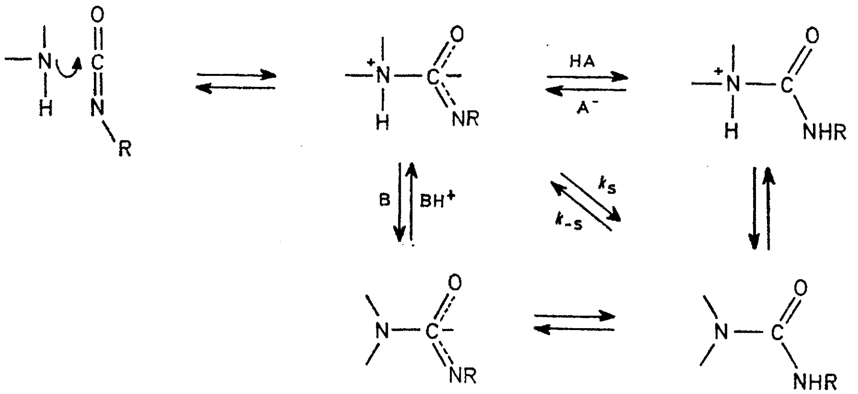

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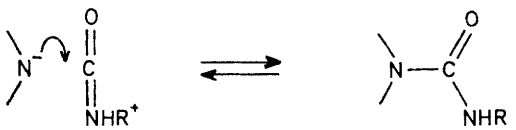
(4)

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[1] W. H. R. Shaw and D. G. Walker, *J. Amer. Chem. Soc.*, 1958, **80**, 5337.

[2] T. Hoshino, T. Mukaiyama, and H. Hoshino, *Bull. Chem. Soc. Japan*, 1952, **25**, 392.

is mediated by general base, general acid, and/or water after the formation of a zwitterionic intermediate in the synthetic reaction [equation (3)]; in the decomposition reaction this mechanism requires that the two proton transfers to form the zwitterionic intermediate be complete before C–N bond cleavage occurs.[3] If urea decomposition takes place with no proton transfer the immediate products will be the amine anion and *N*-protonated cyanic acid; microscopic reversibility then requires that the synthetic reaction proceed by the combination of these species [equation (4)].

It is known that the decomposition of urea occurs through a transition state with no net charge and that the synthetic reaction may be described by the two kinetically equivalent forms of the rate law (5).[4] The effects of salts and solvents on the rate of the synthetic

$$v = k[\mathrm{H}\overset{|}{\underset{|}{\mathrm{N}}}\mathrm{H}^+][\mathrm{NCO}^-] \qquad (5a)$$

$$= k'[\mathrm{HN}{<}][\mathrm{HNCO}] \qquad (5b)$$

reaction show that the transition state is less polar than the ionic reactants.[4] The similar behaviour of the rate constants for the reactions of free amines with cyanic acid, according to equation (5b), and with methyl isocyanate suggests that the ions $\mathrm{H}\overset{|}{\underset{|}{\mathrm{N}}}\mathrm{H}^+$ and NCO^- are not the reacting species.[5] Catalysis by general acids and bases in aqueous solution has not been detected in either direction.

Calculation from an earlier report[6] suggested that the bimolecular rate constant k' for the reaction of amines with cyanic acid increases with increasing amine basicity with a slope, β_{nuc}, of $\log_{10}k'$ against the pK_a of the ammonium ion of *ca.* 0·5. A lower slope, β_{nuc} 0·3, was found later for basic amines,[5] suggesting that the steeper slope resulted from the inclusion of the weakly basic aniline molecule in the correlation. In this paper we report the rate constants for a wide range of amines, which show a break in this correlation that suggests a change in the nature of the rate-determining step, and other evidence that supports the stepwise reaction (3).

EXPERIMENTAL

Materials.—Commercially available amines were purified by crystallisation of the hydrochlorides or by distillation of the free amine. Potassium cyanate was purified by dissolving a commercial sample in water and then adding one volume of ethanol.[7] The crystals were filtered off, washed with ethanol–water (5 : 1) and stored over P_2O_5 under vacuum to prevent decomposition to ammonia. Ethyl isothiocyanate was distilled before use.

Methods.—The pK_a of cyanic acid was determined under the conditions of the kinetics by adding a known quantity of hydrochloric acid to a known quantity of potassium cyanate solution and extrapolating the variations of pH to zero time. A plot of pH (at zero time) *versus* the logarithm of the ratio of cyanate to cyanic acid $\{\mathrm{pH} - \mathrm{p}K_a = \log_{10}([\mathrm{NCO}^-]/[\mathrm{HNCO}])\}$ gives a value of 3·29.[8] The pK_a values of various base/acid and reactant species were calculated using this equation and pH values for known buffer ratios.

Unless otherwise stated kinetic measurements were made at 25° with ionic strength made up to 1·0M with sodium chloride. Reaction of aniline with cyanic acid was measured spectrophotometrically since the product of the reaction, *N*-phenylurea, has an absorption at 235 nm; background absorption due to unchanged aniline was removed by quenching in 1·0M-HCl which also stops the reaction. The extinction coefficient of *N*-phenylurea in 1·0M-HCl was found to be 11,380.[9] Typically a reaction was started by adding 0·4M stock solution (0·01 ml) of potassium cyanate to a solution (2·5 ml) of aniline in buffer. Portions (0·01 ml) were removed at intervals and diluted with 1·0M-HCl (2 ml) The optical density was then measured in a Zeiss PMQ II spectrophotometer or a Beckman DU instrument fitted with a Gilford detector.

Synthesis of ureas from aliphatic amines gives no useful spectral change in the u.v. and the disappearance of cyanate was assayed by treating portions with aniline, quenching the aniline in 1·0M-HCl, and measuring the absorbance at 235 nm. The method is not suitable for reactions which are faster than the reaction of cyanate with aniline but at the pH of maximal rate cyanate in a 1·0M solution of anilinium hydrochloride has a half-life of *ca.* 10 s. The method consists of mixing potassium cyanate [0·4M stock (0·05 ml)] in solution (2·5 ml) containing amine buffer. Portions (0·1 ml) are then added at regular intervals to 1·0M-anilinium hydrochloride solution (0·1 ml) and incubated for *ca.* 5 min, diluted (0·05 ml in 2 ml) in 1·0M-HCl, and the absorption read at 235 nm.

We estimate that in the cyanate assay a concentration of 10^{-4}M of cyanate can easily be measured accurately. Concentrations much lower than this are measurable in the assay of *N*-phenylurea formation because it involves fewer operations and dilutions. These assays can be modified for any isocyanate which has a poor absorption change in the u.v. spectrum.

A Radiometer pH-stat was used to follow the hydrolysis of cyanate and isocyanates over a pH range because alkali is released which can be titrated with acid. Reaction of cyanic acid with aniline over a pH range was followed using the pH-stat to keep the pH constant by delivering acid taking portions of the reaction mixture to assay for *N*-phenylurea.

Reaction of ethyl isothiocyanate with amines and hydrolysis of alkyl isocyanates was followed spectrophotometrically (methyl isocyanate, 230; n-butyl isocyanate, 235; ethyl isothiocyanate, 255 nm).

Kinetics.—Reactions were followed to about two or three half-lives and infinity values read after about six half-lives. Pseudo-first-order rate constants were calculated from

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[3] (*a*) T. Mukaiyama, S. Ozaki, and T. Hoshino, *Bull. Chem. Soc. Japan*, 1954, **27**, 578; (*b*) J. A. Schmitt and F. Daniels, *J. Amer. Chem. Soc.*, 1953, **75**, 3564; (*c*) I. A. Kemp and G. Kohnstam, *J. Chem. Soc.*, 1956, 900.

[4] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism, Wiley, New York, 1961, 2nd edn., p. 307.

[5] G. R. Stark, *Biochemistry*, 1965, **4**, 1030.

[6] M. B. Jensen, *Acta Chem. Scand.*, 1959, **13**, 289.

[7] L. A. Brooks and L. F. Audrieth, *Inorg. Synth.*, 1946, **2**, 289.

[8] (*a*) M. B. Jensen, *Acta Chem. Scand.*, 1958, **12**, 1657, finds 3·54 (18°); (*b*) R. Caramazza, *Gazzetta*, 1958, **88**, 308, finds 3·47 (25°).

[9] This value agrees with those quoted in ' Organic Electronic Spectral Data,' ed. M. J. Kamlet, Interscience, New York, 1960, vol. 1, p. 147.

TABLE 1

Reaction of amines with cyanic acid and of isocyanates with water and hydroxide [a]

No.	Amine		pK_a	k'/l mol^{-1} s^{-1} [l]
1	Carbazoylmethyltrimethylammonium chloride (Girard T reagent)		2·18	2·1 [h]
2	Tyrosine		10·1	1550 [d]
3	Acetohydrazide		3·08	3·4 [h]
4	Ethyl carbazate		3·43	7·1 [h]
5	Azide ion		4·63	17
6	*O*-Methylhydroxylamine		4·75	18
7	Phenylhydrazine		5·28	33 [h]
8	Hydrazine		8·27	1500
9	Piperazine [n]		5·46	5·0
10	Morpholine		8·32	316
11	Piperazine [o]		9·84	2800
12	Dimethylamine		10·96	4200
13	Piperidine		11·35	3700
14	Pyrrolidine		11·34	3300
15	Trifluorethylamine		5·84	3·6
16	Aminoacetonitrile		5·56	13
17	Ethylenediamine [n]		7·49	71
18	Ethyl glycinate		7·65	70
19	β-Cyanoethylamine		8·20 [b]	142
20	Triglycine		8·10	140
21	Diglycine		8·33	160
22	1,3-Diaminopropane		9·10	270
23	Methyl β-alaninate		9·25	290
24	Ethanolamine		9·71	310
25	Ammonia		9·49	56
26	Glycine		9·80	560
27	β-Alanine		10·25	580
28	Methylamine		11·00	1300
29	Ethylamine		10·88	840
30	n-Propylamine		10·76	510
31	n-Butylamine		10·77	670
32	s-Butylamine		10·67	200
33	Isobutylamine		10·54	400
34	Cyclohexylamine		10·63	300
35	t-Butylamine		10·82	130
36	Trishydroxymethylaminomethane		8·23	3·00
37	4-Cyanoaniline		1·74 [c]	8·2 $\times 10^{-3}$ [e,i,]
38	3-Chloroaniline		3·60	0·14 [e,i]
39	4-Chloroaniline		3·98 [c]	1·0 [e,i,l]
40	Aniline		4·75	1·55 [e]
41	4-Toluidine		5·07 [c]	5·0 [e,i]
42	4-Anisidine		5·34 [c]	5·7 [e,i]
43	4-Aminophenol		5·88	20 [e,i]
44	4-Phenylenediamine		6·30 [c]	52 [e,i]
45	Aniline	Fraction base	0·5	13 [m,i]
		Fraction base	0·75	17 [m,i]
46	4-Anisidine	Fraction base	0·5	33 [m,i]
		Fraction base	0·5	34 [m,h]

Isocyanate hydrolysis

	k_H/l mol^{-1} s^{-1}	k_{H_2O}/s^{-1}	k_{HO}/l mol^{-1} s^{-1}
Cyanic acid	0·16 [j]	$7{\cdot}9 \times 10^{-2}$ [f]	$9{\cdot}8 \times 10^{2}$ [g]
Methyl isocyanate	0·10	$1{\cdot}47 \times 10^{-3}$	$5{\cdot}8 \times 10^{3}$
n-Butyl isocyanate		$5{\cdot}5 \times 10^{-4}$	
t-Butyl isocyanate		$5{\cdot}1 \times 10^{-4}$	

[a] 25°; ionic strength made up to 1·0M with sodium chloride; except where stated, buffering is by the amine; concentrations of buffer and amine species varied from 0·05 to 1·0M; pH of the measurements was close to the pK_a of the buffering species. [b] pK_a From M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 8828. [c] pK_a From B. Riddle and W. P. Jencks, *J. Biol. Chem.*, 1971, **246**, 3250. [d] Carbamoylation on the phenolic group; value calculated from D. G. Smyth, *Acta Chim. Hung.*, 1965, **44**, 197. [e] Reaction catalysed by amine or buffer. [f] Calculated from the kinetic data assuming a rate law: rate = k_{H_2O}[HNCO]. [g] Calculated from the data of Jensen [8a] extrapolated to 25° and using K_a for cyanic acid and K_w. [h] Acetate buffer. [i] DABCO [12] buffer. [j] Jensen [8a] finds a value of $6{\cdot}0 \times 10^{-2}$ l mol^{-1} s^{-1} at 18°. [l] Where comparisons are possible the data here agree well with those of other workers.[5,6] Error limits are less than 5% but for 4-cyanoaniline k' ranges from 6 to 11 $\times 10^{-3}$. [m] Buffer independent rate constants. [n] Monocation. [o] Neutral species.

linear plots of $\log_{10}(A_t - A_\infty)$ against time and for each reaction a maximum and minimum value obtained. We quote a mean value for rate parameters obtained from maximum and minimum values of slopes and intercepts.

RESULTS

Amines and Cyanic Acid.—Pseudo-first-order rate constants for the reaction of strongly basic amines are related linearly to amine concentration (Table 1 and Figure 1). Bimolecular rate constants for reaction of amine with cyanic acid were obtained by division of the first-order rate constants by concentration of free amine and by the fraction of cyanic acid [f(HNCO)] present at the pH of the reaction. Measurements of urea formation or cyanate depletion were made over a range of concentrations of amine buffer where pH does not vary significantly; correction for cyanate hydrolysis is therefore unnecessary and in the case of strongly basic amines measured at high pH hydrolysis was negligible. For the weakly basic amines the hydrolysis manifests itself as an intercept on the plot of rate constants *versus* buffer concentration. The observed absorbance changes from individual assays indicated that *N*-phenylurea formation and cyanate depletion went to completion. Various reports give the equilibrium constant for urea formation from cyanate and ammonium ions in the range 3·0—6·7 $\times 10^4$ l mol^{-1} around room temperature [10] confirming reaction to completion.

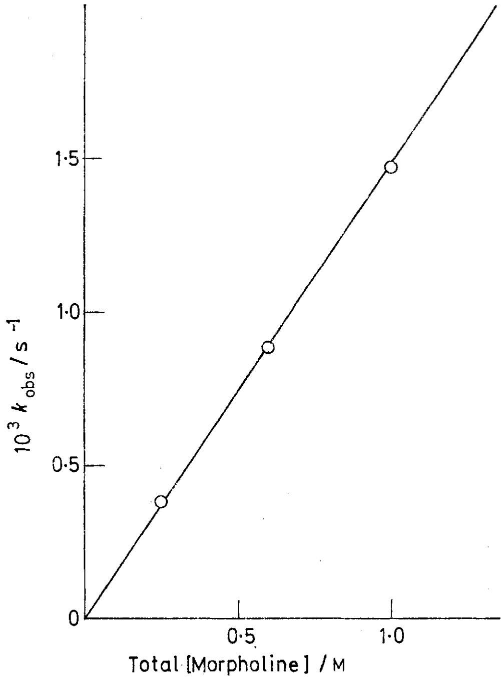

FIGURE 1 Rate constant for disappearance of cyanate as a function of morpholine buffer concentration: conditions, pH 8·32, fraction base 0·5

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[10] H. L. Welles, A. R. Giaquinto, and R. E. Lindstrom, *J. Pharm. Sci.*, 1971, **60**, 1212; G. N. Lewis and M. Randall, 'Thermodynamics,' McGraw-Hill, New York, 1923, p. 587; G. R. Stark, W. H. Stein, and S. Moore, *J. Biol. Chem.*, 1960, **235**, 3177; an equilibrium constant may be calculated from rate constant for urea formation (Table 1 and ref. 6) and urea hydrolysis data: W. H. R. Shaw and J. J. Bordeaux, *J. Amer. Chem. Soc.*, 1955, **77**, 4729.

Weakly basic amines such as anilines have rate constants depending on a power of the amine concentration greater than unity (Figure 2) and obey the kinetic equation (6). Division by the free amine concentation gives an equation which was utilised to obtain parameters from the data and an example of the linear plots is shown in Figure 2 where the intercept gives k' and the slope gives $k_B[RNH_3^+] + k_A[RNH_2]$. Only aniline itself was thoroughly analysed using a series of buffer ratios to obtain k_A and k_B (see Table 1 of ref. 11); the k_A and k_B terms for the other amines were not measured and only k' is recorded for these (Table 1).

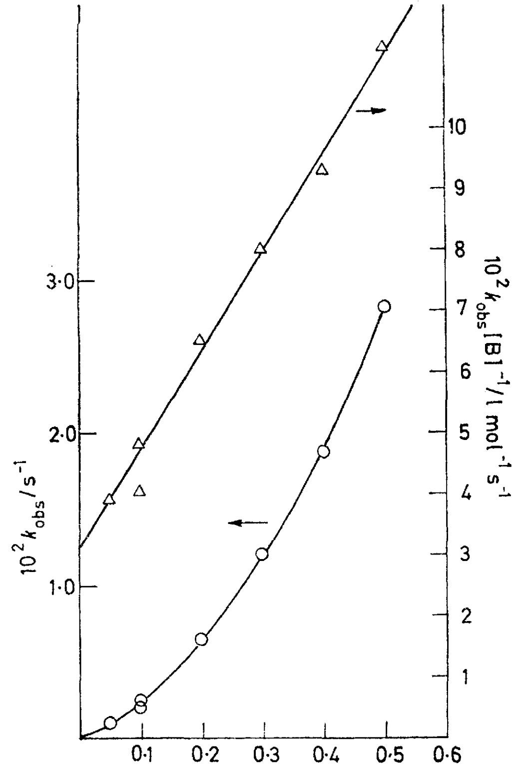

FIGURE 2 Rate constant for disappearance of cyanate as a function of piperazine buffer concentration (○) and a linearised plot of the data (△, see text): conditions, pH 5·46, fraction of monocation 0·5; the reaction is predominantly cyanic acid with monocation

The pH dependence for the rate constant for hydrolysis and *N*-phenylurea formation in a system containing aniline * and cyanate obeys the complex equation (6). Table 2 illustrates the agreement between the observed rate constant and that calculated using parameters from Table 1, Table 1 of ref. 11 (for k_A and k_B), and equation (6). The The first two terms of equation (6) are the acid and neutral hydrolysis rate constants for cyanic acid; a term involving the proton catalysed reaction of aniline with cyanate ($k_{H_2O}[AN][a_H]$) is not significant at the pH values employed and is therefore neglected.

$$k_{obs}/f(HNCO) = k_H[a_H] + k_{H_2O} + k'[AN] + k_A[AN][ANH^+] + k_B[AN]^2 \quad (6)$$

Reaction of Aniline and Cyanate in the Presence of Increasing Concentrations of Buffer.—At a given pH and cyanate concentration but with increasing concentrations of acetate or DABCO [12] the rate constant for reaction with aniline or 4-anisidine is not linear in buffer concentration. The maximal concentration of DABCO is 1·0M at 2·0M ionic strength but with acetate a 2·0M concentration is attained at 1·0M ionic strength. The data (see for example Figure 3) fit a saturation rate law analogous to the Michaelis–Menten equation and using the

TABLE 2

Reaction of aniline with cyanic acid over a pH range [a]

pH	$10^3 k_{obs}/s^{-1}$	$10^3 k_{calc}/s^{-1}$ [b]
3·00	2·37	2·34
	2·48	
3·45	2·56	2·61
	2·35	
3·95	2·34	2·75
	2·26	
4·00	2·40	2·74
	2·49	
4·50	1·70	2·16
	1·61	
5·00	0·893	1·18
	0·941	
	0·925	
	0·853	
6·00	0·449	0·451
	0·430	

[a] 25°, 0·05M-aniline used throughout, ionic strength made up to 1·0M with sodium chloride. [b] Calculated from data in Table 1 and in Table 1 of ref. 11 using expression (6) in the text.

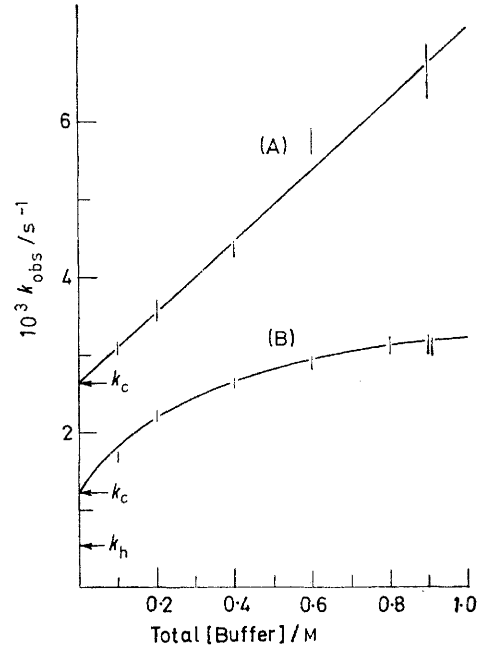

FIGURE 3 Effect of increasing DABCO buffer concentration on reaction of (A) *p*-chloroaniline and (B) *p*-anisidine with cyanic acid; k_h is the calculated rate constant for cyanate hydrolysis at this pH; k_c is the calculated rate constant for reaction of aniline with cyanic acid at zero buffer plus the hydrolysis rate constant for cyanate: conditions, pH 3·40, fraction DABCO monocation 0·5. Maximal rate constant for 3-chloroaniline is $4·7 \times 10^{-2}$ s^{-1} calculated as in the text

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* Abbreviations used in this paper are: DABCO, triethylenediamine or diaminobicyclo-octane; TRIS, trishydroxymethylaminomethane; AN, aniline.

[11] A. Williams and W. P. Jencks, following paper.

[12] A. Williams, 'Introduction to the Chemistry of Enzyme Action,' McGraw-Hill, London, 1969, p. 17.

Hofstee method[12] a maximal value for the rate constants was calculated. Division by aniline concentration and by the fraction of cyanic acid gives the limiting bimolecular rate constant. Similar limiting values were obtained for the aniline reaction in DABCO buffers at two different buffer ratios (Table 1, item 45); the 4-anisidine reaction in both acetate and DABCO buffers (Table 1, item 46) also gave similar limiting rate constants. In all cases the intercepts on the ordinate at zero buffer concentration were identical within the experimental limits with those calculated. Details of the kinetic data are collected in Supplementary Publication No. SUP 21136 (5 pp.).* Over the same concentration range of DABCO buffer 3-chloroaniline gave no indication of a saturation effect (Figure 3).

Curvature in the buffer catalysed reaction is argued later to be the result of a change in rate-determining step and complicates the analysis of buffer catalysis into acid and base components. We can neglect the effect of buffer curvature because this paper is concerned with parameters derived from intercepts at zero buffer concentration. In the case of aniline the effect of curvature was corrected for in determining the parameters of Table 1 using a published equation.[13a] The corrections are discussed more fully in the following paper because they are relevant to acid–base catalysis.[11]

Buffer catalysis was not observed with the strongly basic amines: no rate constant increase was observed with ethanol–amine in the presence of trimethylamine buffer (base/acid = 1) from 0·1 to 1·0M in total buffer concentration. Figure 1 also illustrates the absence of buffer catalysis (in this case self buffer catalysis).

Amines and Ethyl Isothiocyanate.—This reaction gives pseudo-first-order rate constants which are proportional to amine concentration. No buffer catalysis is observed and bimolecular rate constants (Table 3) were derived by division of first-order rate constants by free amine concentration; a hydrolysis correction is negligible.

TABLE 3

Reactivity of ethyl isothiocyanate towards amines[a, c]

Amine	pK_a	$10^4k'$/l mol^{-1} s^{-1} [b]
Ethyl glycinate	7·60	46
Glycine	9·80	170
Methylamine	10·85	420
Aniline	4·75	6·5
Semicarbazide	3·76	3·5
Hydrazine	8·27	1030
O-Methylhydroxylamine	4·75	5·8

[a] 25°; ionic strength made up to 1·0M with sodium chloride. [b] Reaction followed by observing the increase in absorbance at 255 nm. [c] Up to four measurements were made for each amine over a concentration range in amine buffer of 0·1 to 1·0M; pH was close to the pK_a of the amine; error limits were <5%.

Isocyanate Hydrolysis.—The pH-stat and cyanate assay methods for following cyanate hydrolysis give first-order rate constants (SUP 21136). The derived values for k_H and k_{H_2O} (Table 1) agree with the values obtained by by earlier workers.[3c, 8a, 13b]

DISCUSSION

Amines and Cyanic Acid.—A Brønsted type plot of $\log_{10}k'$ against pK_a for the nucleophilic reactions of a large series of amines with cyanic acid (Figure 4) exhibits a sharp break at pK_a 6. Basic primary amines and secondary amines follow correlation lines with a slope β_{nuc} 0·3, whereas weakly basic amines, mainly substituted anilines, follow a line with slope β_{nuc} 0·8. The existence of this break provides an explanation for the higher β_{nuc} from the more limited earlier work.[6] The change in slope does not represent merely a difference in behaviour of the different classes of amines[14] because it is observed within the series of aliphatic primary amines (for trifluoroethylamine) and secondary amines (for piperazine monocation); other evidence that will be described shortly confirms this conclusion. Secondary amines are *ca.* 3-fold more reactive than primary amines,[6, 15] as they are also toward saturated carbon.[16] TRIS, cyclohexylamine, isobutylamine, s-butylamine, n-butylamine, and t-butylamine, which

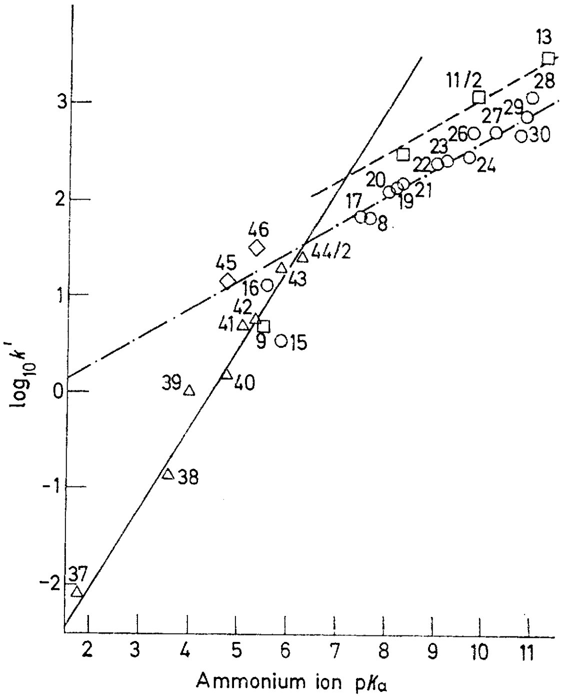

FIGURE 4 Brønsted type dependence of the reactivity of amines with cyanic acid (k', Table 1) on the pK_a of the ammonium ion: ○, primary amines; □, six-membered cyclic secondary amines; △, anilines; ◊ buffer-independent rate constants for reaction of anilines with cyanic acid; numbers refer to items in Table 1. The rate constant for symmetrical diamines is halved but the corresponding pK_a is not corrected. The dotted line is arbitrary representing k_1 and has slope 0·3; the full line has slope 0·8

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* 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.

[13] (*a*) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 1973, **95**, 5637; (*b*) M. W. Lister, *Canad. J. Chem.*, 1955, **33**, 426.

[14] E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc.* (*B*), 1971, 2187; L. Senatore, E. Ciuffarin, and L. Sagramora, *ibid.*, p. 2191; L. Senatore, E. Ciuffarin, A. Fava, and G. Levita, *J. Amer. Chem. Soc.*, 1973, **95**, 2918.

[15] P. Johncock, G. Kohnstam, and D. Speight, *J. Chem. Soc.*, 1958, 2544.

[16] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, 1967, **89**, 4400.

are not shown on the plot, exhibit slower rates that are attributed to steric effects. The so-called ' α-effect ' compounds, mainly hydrazine derivatives, generally react more rapidly than simple amines and follow a line with β_{nuc} 0·4 (Figure 5); there is no definite evidence for a break with these compounds.

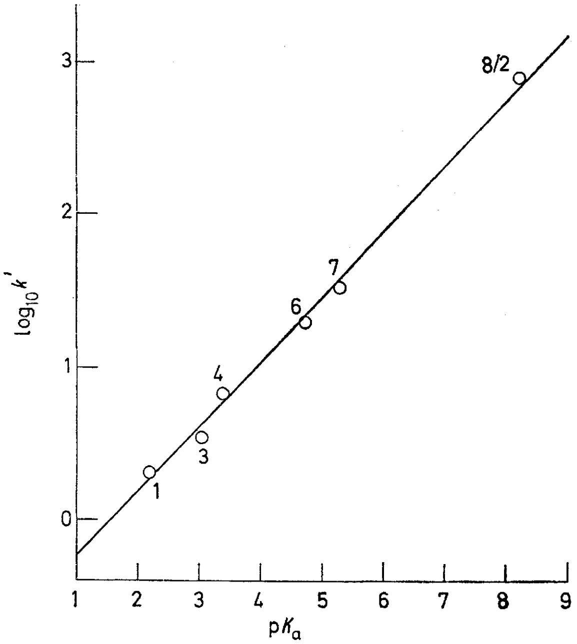
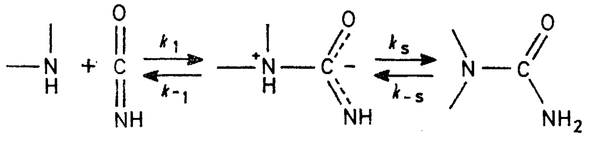


FIGURE 5 Brønsted type dependence of reactivity of ' α-effect ' amines with cyanic acid (k', Table 1). The rate constant for hydrazine is halved but no correction for the pK_a is made; numbers refer to items in Table 1 and the line has slope 0·4

The change in β_{nuc} means that there is a change in the nature of the rate-determining step with decreasing basicity of the attacking amine, from a transition state with relatively little charge on the attacking nitrogen atom and a small sensitivity to polar substituents for basic amines (β_{nuc} 0·3) to one with a large development of charge on the attacking nitrogen and a correspondingly large sensitivity to polar substituents for weakly basic amines (β_{nuc} 0·8). The simplest explanation of this result is that there is a change in rate-determining step, from amine attack for the basic amines [k_1, equations (7)] to a proton-transfer step that makes possible the conversion of the initially formed zwitterionic intermediate into the uncharged urea product for weakly basic amines [k_s, equation (7)]. The transition state for amine attack is expected to have relatively little charge development on the attacking nitrogen atom, whereas the dipolar intermediate has a full charge on this atom. This interpretation is supported by the fact that the change in rate-determining step corresponds to the appearance of buffer catalysis of the reaction. Strongly basic amines, for which amine attack is rate determining exhibit no general acid or base catalysis, whereas the reactions of weakly basic amines, for which proton transfer is rate determining, are catalysed by a second molecule of amine or ammonium ion as well as by added buffers. The mechanism of the proton transfer steps is discussed in the following paper.[11] This change in β_{nuc} and in rate-determining step is similar to the behaviour observed in ester aminolysis.[17]



(7)

The change in rate-limiting step may be regarded as a consequence of the variation in leaving ability of the ammonium ion in the k_{-1} step. In the case of the strongly basic amines the zwitterionic intermediate has a sufficient lifetime for proton transfer to occur before the amine is expelled so that $k_s > k_{-1}$ and k_1 is rate determining. With weakly basic amines the leaving group is better and k_{-1} is larger so that amine is expelled to regenerate starting materials more rapidly than proton transfer can occur and k_s becomes rate limiting; *i.e.* $k_{obs} = (k_1/k_{-1})k_s$. It is possible that the absence of evidence for a break or for buffer catalysis with ' α-effect ' amines reflects a rapid intramolecular proton transfer mechanism and/or a relatively low value of k_{-1} for these compounds. The absence of evidence for a break in the Brønsted type plot for ethyl isothiocyanate (Figure 6) may reflect a relatively small value

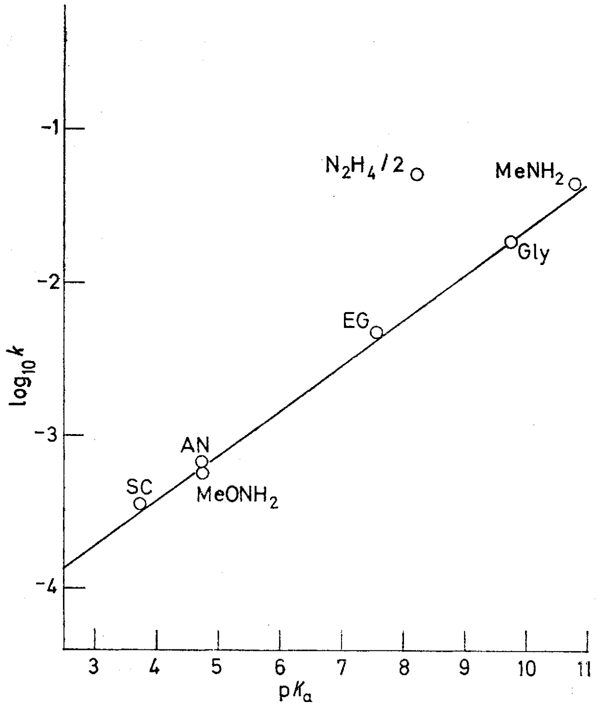


FIGURE 6 Brønsted type dependence of amine reactivity with ethyl isothiocyanate (Table 3); the line has a slope of 0·28; abbreviations, SC semicarbazide, EG ethyl glycinate, Gly glycine. Rate constant for hyrazine is halved but no correction is made for the pK_a

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[17] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622; A. Satterthwait and W. P. Jencks, *ibid.*, submitted for publication.

of k_{-1} in these reactions because of the relatively small driving force provided by the thiol anion to form C=S from the zwitterionic intermediate. The value of β_{nuc} 0·28, is similar to that for the reaction of cyanic acid with basic amines and supports a similar transition state; the ρ value of 0·84—1·0 for the reaction of glycine with substituted *N*-phenyl isothiocyanates is also consistent with this transition state.[18] The fact that the point for aniline falls on the same correlation line as other amines in the isothiocyanate reaction suggests that the negative deviation of aniline in the cyanic acid reaction does not reflect some peculiarity of aniline as a nucleophile.

The ^{13}C isotope effect, k^{12}/k^{13} 1·050 ± 0·005, for urea decomposition in water is consistent with rate-determining C–N bond cleavage in the reaction.[3b,19] There is no reason to expect that the rate-determining step should be similar in propionic acid and in water as solvents, but the decreasing isotope effects, k^{12}/k^{13} 1·027, 1·021, 1·016, and 1·008 for the decomposition of *NN'*-dimethyl-, unsubstituted, phenyl-, and *NN'*-diphenyl-ureas in propionic acid,[3b] are consistent with partial or complete change to rate-determining proton transfer in this solvent as electron withdrawing substituents are added to the urea.

Change in Rate-determining Step with Increasing Buffer Concentration.—If the upper line of Figure 4 represents rate determining amine attack and the lower line the rate-determining proton transfer, it should be possible to observe a change in rate-determining step for an amine that falls on the lower line near the break point if the rate of proton transfer is increased by increasing the buffer concentration. This is observed for the reactions of aniline and 4-anisidine in acetate and DABCO buffers, as illustrated in Figure 3. The rate is increased by low concentrations of added buffers that facilitates proton transfer, but as the buffer concentration and the observed rate increase the attack step, k_1, becomes progressively more rate determining and the rate levels off. The maximum reaction rates, extrapolated to infinite buffer concentration, give values of k_1 that fall close to the correlation line of Figure 4 for rate-determining attack of the more basic amines; these rate constants are identified as items 45 and 46 in Table 1 and Figure 4. The fact that the same values of k_1 are found for different buffer ratios and for different types of buffer, including the DABCO monocation–dication (see Table 1 and SUP 21136) shows that this curvature is not a consequence of buffer association. Furthermore, no significant curvature is observed for DABCO catalysis of the reaction with 3-chloroaniline (Figure 3); this is consistent with the predicted maximal buffer independent rate constant for this less basic amine that is calculated from the Brønsted type line for strongly basic amines (Figure 4). A similar change in rate-determining step has been suggested to account for the non-linear increase in rate with increasing buffer concentration in the decomposition of ethyl [(n-butyl)thiocarbamoylthio]formate[20] and *N*-phenylcarbamoylimidazole.[21]

There are some notable similarities but also important differences in the published results and interpretations for the reversible synthesis of carbamates, compared with ureas.[6,22] In view of the complexities of the former reaction,[22] we believe that it is premature to attempt a detailed comparison at this time.

Isocyanate Hydrolysis.—As in urea synthesis the problem of which ionic species are reacting is present for cyanate hydrolysis in neutral and alkaline media. Table 1 indicates that the rate constants for the acid catalysed hydrolysis of methyl isocyanate and cyanic acid are similar and thus alkyl isocyanates should be useful non-protonic models for the hydrolysis of cyanic acid. The rate constants $k_{\mathrm{H_2O}}$ and $k_{\mathrm{HO^-}}$ for methyl isocyanate are more than adequate to account for the corresponding reactions of cyanic acid, so that it may be concluded that the neutral and alkaline hydrolysis of cyanic acid involve the uncharged species and not reactions of the proton or water with the cyanate ion.

This work was supported by grants from the National Science Foundation and the National Institute of Child Health and Human Development of the National Institutes of Health. The University of Kent is thanked for a travel grant. We are grateful to Dr. A. F. Hegarty for keeping us informed of his work on the hydrolysis of *N*-phenylcarbamoylimidazole.

[4/914 *Received*, *7th May*, 1974]

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