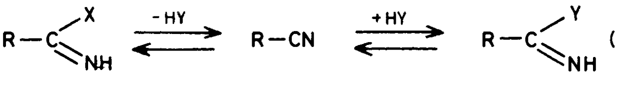
Acid-catalysed Hydrolysis of Cyanamides: Estimates of Carbodi-imide Basicity and Tautomeric Equilibrium Constant between Carbodi-imide and Cyanamide

Stephen V. Hill and Andrew Williams *
University Chemical Laboratories, Canterbury, Kent CT2 7NH
Jethro L. Longridge
ICI Pharmaceuticals Division, Alderley Park, Macclesfield

N-Cyanourea is demonstrated as an intermediate in the hydrolysis of dicyanamide which is shown to react as its carbodi-imide tautomer. The hydrolysis of *N*-cyanourea, dicyanamide, and *NN'*-dimethylcyanoguanidine is specific acid-catalysed. General acid catalysis is demonstrated for the hydrolysis of *NN'*-dimethylcyanoguanidine and is considered to be specific acid-nucleophilic. Assuming the carbodi-imide mechanism also holds for the specific acid-catalysed hydrolysis of cyanamide the tautomeric equilibrium constant for formation of the parent carbodi-imide in water at 25° is estimated to be 0.6×10^{-7} and the pK of the protonated carbodi-imide ($H_2\overset{+}{N}{=}C{=}NH \rightleftharpoons H^+ + HN{=}C{=}NH$) is estimated to have a value within one unit of zero. Rate constants are reported for alkaline hydrolysis of cyanamides.

We are interested in the addition of nucleophiles to electrophilic acceptors in the context of our extended study of dissociative mechanisms of acyl group transfer.[1] The addition of nucleophiles to nitriles is the microscopic reverse of the dissociative step in an elimination–addition mechanism for imidoyl group transfer [equation (1)]. Studies on the addition step will therefore be pertinent to the mechanism of the reaction depicted in equation (1). Nitriles, however, are reluctant to add non-activated nucleophiles under mild conditions of temperature and solvent [2] and we therefore undertook the investigation of the hydrolysis of dicyanamide (I), *N*-cyanourea (II), and *NN'*-dimethylcyanoguanidine (III) as these offered faster reactions and therefore more reliable data concerning mechanism.



(1)

Previous studies have indicated that general acids increase the rate of decomposition of cyanamide [3] and the present work extends this observation to the cyanoguanidine (III).

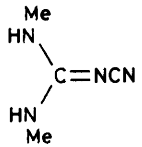
Experimental

Materials.—Sodium dicyanamide and sodium *N*-cyanourea were obtained from Aldrich Chemical Company and *NN'*-dimethylcyanoguanidine was prepared by the following procedure (we are grateful to Mr. J. M. Wardleworth, ICI Pharmaceuticals Division, for this work). Ethanolic methylamine (36 ml, 33% w/v) was added to a solution of *SS'*-dimethyldithiocyanoimidocarbonate [4a] (10.5 g) in ethanol (80 ml) and the product stirred at room temperature for 18 h. Methanethiol was removed by purging for 2 h with nitrogen and the residual solution evaporated to dryness. The residue was recrystallised from ethanol to give *NN'*-dimethylcyanoguanidine (4.43 g), m.p. 183—185° (lit.,[4b] 174—175°). (Found: C, 42.8; H, 7.3; N, 50.1. Calc. for $C_4H_8N_4$: C, 42.9; H, 7.1; N, 50.0%).

Methods.—The hydrolyses of dicyanamide, and of *N*-cyanourea and *NN'*-dimethylcyanoguanidine in acid, were followed using 1 cm silica cells placed in the thermostatted cell holder of a Pye-Unicam SP 800 spectrophotometer. Rate constants were obtained from first-order plots (using experimental infinity readings) or from initial rate measurements. Optimum wavelengths are given in the Table .

NCNHCN
(I)

$NH_2CONHCN$
(II)


(III)

Rate data for the degradation of dicyanamide at pH >2 were measured using solutions where the pH was maintained with a pH-stat apparatus; this consisted of a Pye-Unicam SP 500 spectrophotometer which had been modified so that the contents of a silica cell could be stirred with a magnetic follower.[5] A Radiometer pH probe (GK 2321c) and a microdelivery tube were inserted into the solution above the light path. The pH was initially adjusted by adding a small portion of dilute HCl through the delivery tube by manual operation of the Radiometer ABU 11 autoburette. A Radiometer digital pH-meter (PHM 62) monitored the pH to ±0.01 units and during the reaction activated the burette to maintain the pH at the required level by addition of dilute HCl. The concentration of the ionic species was only a small percentage of the total ionic concentration (1M).

Whereas at acid pH the cyanourea hydrolysis exhibits a large change in absorbance in the u.v. there is only a small change at alkaline pH. The reaction was therefore measured by taking 50µl portions of the solution and measuring the change in absorption in 1M-HCl solution (where the degradation is fast); the change in absorption is proportional to the cyanurea unchanged at the alkaline pH.

The degradation of *NN'*-dimethylcyanoguanidine at pH >2 was followed by h.p.l.c. analysis of the reaction solution. Portions of the solution were taken at intervals and diluted with methanol thus quenching the reaction. Samples of the diluted solution were then analysed chromatographically. The chromatographic system consisted of a constant-volume pump delivering 1 ml min^{-1} together with a Cecil u.v. detector and a Chessel chart recorder. The column (19 cm × 4.6 mm i.d.) was packed with Spherisorb S5 ODS ' reverse phase ' packing and the sample introduced *via* a Rheodyne syringe sample loader fitted with a 20µl loop. The *NN'*-dimethylcyanoguan-

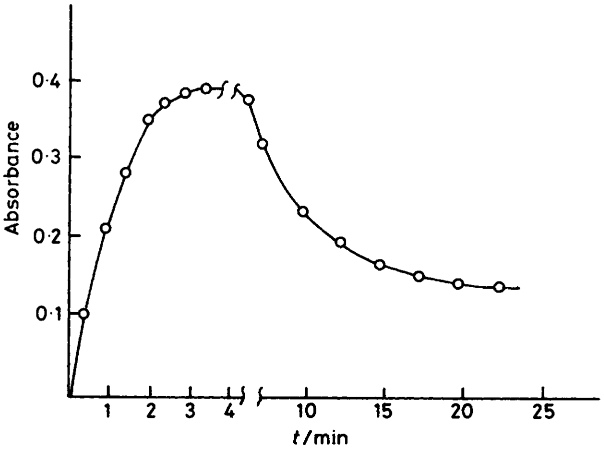


Figure 1. Demonstration of an intermediate in the degradation of dicyanamide at 1M-HCl, 40° (wavelength for study 275 nm)

idine had a retention time of 5 min and was eluted with a mixture of acetonitrile (far-u.v. grade), 5%; water, 95%; and AnalaR phosphoric acid, 0.1%, v/v. The wavelength was set at 225 nm. The *NN'*-dimethylcyanoguanidine peak was measured against a standard and the concentration thus obtained plotted *versus* time on semi-logarithmic graph paper to obtain pseudo-first-order rate constants.

Product Analysis.—Application of the biuret test [6] to the products of the hydrolysis of the dicyanamide and cyanourea was used to detect the yield of biuret. The reagent solution of $CuSO_4 \cdot 5H_2O$ (1.5 g) and $NaKC_4H_4O_6 \cdot 4H_2O$ (6 g) in water (500 ml) and 10% NaOH (300 ml) was made up to 1 l. The reagent (4 ml) and test sample (1 ml) was allowed to stand for 3 min and the absorbance read at 550 nm. The products of the *NN'*-dimethylcyanoguanidine hydrolysis were analysed by h.p.l.c.

Results

The degradation of dicyanamide in aqueous solution gave biuret in essentially theoretical yield as the only final product. When the reaction was followed spectrophotometrically at 275 nm the formation and decay of an intermediate was immediately apparent as shown in Figure 1. The intermediate is demonstrated to be *N*-cyanourea by comparison of the decomposition rate constants of the intermediate in acid with those of authentic cyanourea (Figure 2). The change in absorbance from dicyanamide to intermediate varies with pH and the formation rate constant is greater than that for decomposition of the intermediate. The $pK_{apparent}$ value derived for the cyanourea from the pH-dependence of the absorbance change (4.00) agrees with that previously measured (3.66).[6b]

Hydration of *NN'*-dimethylcyanoguanidine is catalysed by undissociated formic and acetic acid. The plots of pseudo-first-order rate constants *versus* total buffer acid concentration are linear. Several kinetic runs were carried out at a variety of pH values corresponding to differing fractions of base. The slopes of the linear plots of pseudo-first-order rate constant against total buffer concentration are proportional to the fraction of the acid component of the buffer. The rate law for the reaction is $k_{obs} = k_H + [H^+] + k_{HA}[HA]$. Dicyanamide, cyanourea, and *NN'*-dimethylcyanourea react with hydroxide ion; the second-order rate constants are recorded in the Table.

The acid- and hydroxide-catalysed rate constants for hydrolysis of dicyanamide, *N*-cyanourea, and *NN'*-dimethylcyanoguanidine are recorded in the Table. The dicyanamide hydrolyses follow the rate law (2) where λ_1 corresponds to the

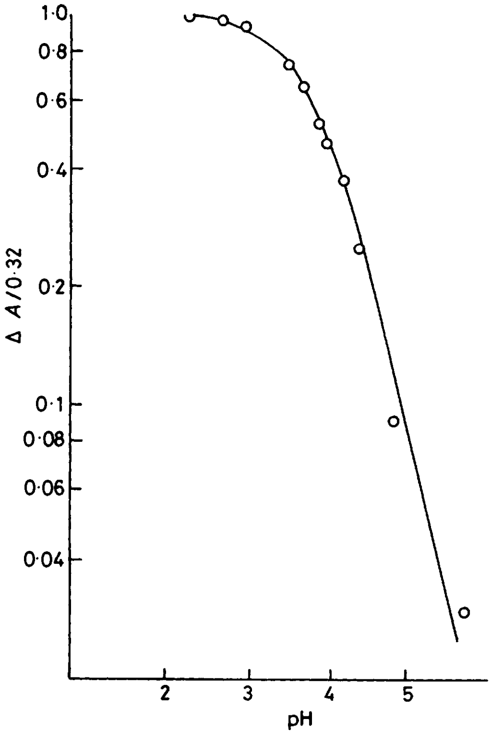


Figure 2. Titration as a function of pH of the change in absorbance at 235 nm (40°, ionic strength 1M) for the formation of *N*-cyanourea from dicyanamide. The line is calculated for p*K* 4.0 and the values of the change in absorbance are normalised by division by the maximal change (0.32 units)

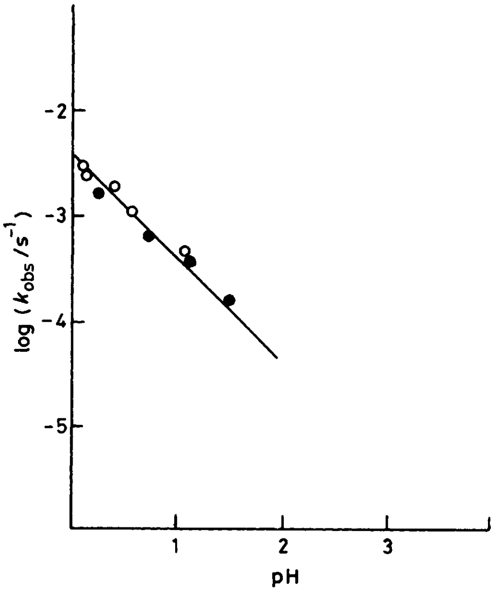


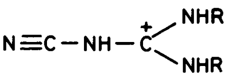
Figure 3. The pH-dependence of the rate constants for degradation of the intermediate (●) for dicyanamide hydrolysis and *N*-cyanourea (○). The line is calculated from the parameters in the Table

$$A = a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda t} \qquad (2)$$

Table. Rate parameters for the degradation of some nitriles [a]

Nitrile	k_{H^+}/l mol^{-1} s^{-1}	k_{OH^-}/l mol^{-1} s^{-1}	λ/nm [g]
$N\cdots\bar{C}\cdots NCN$ (40°) [b]	1.4×10^{-2}(8)	3.6×10^{-2}(6)	240
$NH_2CONHCN$ (40°) [b]	2.4×10^{-3}(11)	1.8×10^{-4}(5) [c]	240
$(NHMe)_2\overset{+}{C}{-}NCN$ (80°) [b,f]	2.4×10^{-3}(9)	1.6×10^{-4}(11) [d,e]	224
$(NH_2)_2\overset{+}{C}{-}NCN$		9.6×10^{-4}(100°) [7]	
NH_2CN	3.8×10^{-5}(25°) [13]		
MeCN	8.3×10^{-8}(65°) [l,m]	1.2×10^{-4}(25°) [j]	
PhCN	1.5×10^{-6}(100°) [l,m]	3.1×10^{-4}(60°) [k]	
HCN	2.7×10^{-7}(65°) [h]		

[a] Ionic strength maintained at 1M with $NaClO_4$ (*NN'*-dimethylcyanoguanidine) and with KCl for the dicyanamide and *N*-cyanourea. Values in parentheses are temperatures (°C) and number of data points. [b] This work. [c] Followed indirectly by u.v. spectroscopy of the degradation of the remaining dicyanamide at acid pH. [d] This result was kindly obtained by Mr. R. Button of ICI Pharmaceuticals Ltd. [e] These measurements were made by h.p.l.c. analysis of the product. [f] Values of k_{AcOH} and k_{CHOOH} are 1.6×10^{-5}(8) and 9.3×10^{-5}(14) l mol^{-1} s^{-1} respectively; measurements were made between pH 4.2 and 5 and 3.2 and 4.1 for acetate and formate buffers. [g] Wavelength for the kinetic experiments carried out using the spectrophotometric method. [h] V. K. Krieble and J. G. McNally, *J. Am. Chem. Soc.*, 1929, **51**, 3368; V. K. Krieble and A. L. Peiker, *ibid.*, 1933, **55**, 2326. [i] V. K. Krieble and C. I. Noll, *J. Am. Chem. Soc.*, 1939, **61**, 560. [j] S. Wideqvist, *Arkiv. Kemi*, 1956, **10**, 265. [k] K. B. Wiberg, *J. Am. Chem. Soc.*, 1955, **77**, 2519. [l] C. J. Hyland and C. J. O'Connor, *J. Chem. Soc., Perkin Trans. 2*, 1973, 223. [m] Rate constants increase non-linearly with acid concentration. Second-order rate constants taken from the lowest acid concentration quoted (<1M).


(IV)

rate constant for formation and λ_2 to that for decay of the intermediate. The value of λ_2 was evaluated by plotting log $A_t - A_\infty$ against time; this plot was linear with an initial curved part. The slope was recorded for the linear portion (at large time values). Extrapolating back to zero time gives a 'running infinity' ($A_{r\infty}$) from which it is possible to obtain λ_1 by plotting log $A_t - A_{r\infty}$ *versus* time. Since the intermediate, *N*-cyanourea, does not revert to dicyanamide the mechanism is a simple consecutive reaction [equation (3)] and λ_1 and λ_2 the observed parameters correspond to the rate constants k_1 and k_2; these are processed to yield the parameters in the Table.

$$\text{dicyanamide} \xrightarrow{k_1} N\text{-cyanourea} \xrightarrow{k_2} \text{biuret} \qquad (3)$$

Eloranta [7] showed that the alkaline hydrolysis of dicyandiamide (*N*-cyanoguanidine) gave guanidine, carbon dioxide, and ammonia passing through guanylurea as an intermediate. A single small product peak appears in the h.p.l.c. trace for hydrolysis of (III); this was shown not to be *NN'*-dimethylurea, *N*-methylurea, or *NN'*-dimethylcarbamoylguanidine by comparison with standards. By analogy with Eloranta's work we expect the product to be the symmetrical dimethylguanidine.

Discussion

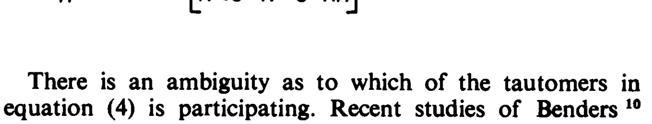
Kinetic analysis of the hydrolysis of dicyanamide demonstrates for the first time that *N*-cyanourea is an intermediate. The observation may be added to that of Eloranta [7] who showed that urea is an intermediate in the hydrolysis of cyanamide and that *N*-guanylurea is an intermediate in the hydrolysis of dicyandiamide (*N*-cyanoguanidine).

Compounds in which a nitrile group is attached to a nitrogen atom are more acid labile than alkyl or aryl nitriles. The effect is probably due to the increased basicity of the species which enables a greater concentration of the more reactive conjugate acid to be maintained. The effect of the nitrogen-containing groups is to increase the reactivity of the nitrile except in the case of the cyanoguanidine which possesses a predominantly basic character and takes on structure (IV) in acid pH. In base the $NC(NHR)_2$ group in (III) would feed electrons into the nitrile from the basic amino groups *via* the imino conjugation and hence reduce the reactivity towards hydroxide ion.

The $\overbrace{N{=}C{-}\bar{N}}$– group is more effective in activation of the nitrile to reaction with hydroxide ion than are the phenyl, methyl, or $NH_2CO\bar{N}$ group (Table). The presence of negative charge on the substituent would be expected to reduce reactivity below that for the neutral group. Previous work has shown that the effect of the charge can be swamped by the electropositivity of the rest of the substituent group.[8] For example the CO_2^- group is net electron withdrawing [9] as is the $CONH^-$ group.[8]

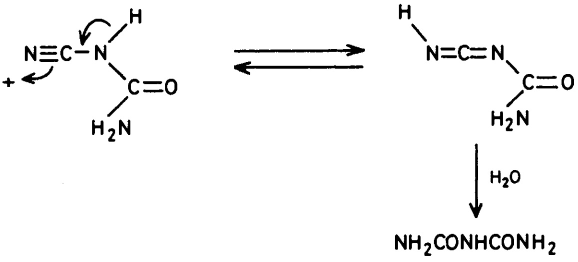
In both of these cases the ability of the anionic acyl group to withdraw electrons is largely a function of the ability of the groups to disperse charge through resonance forms. Although the σ_I (a measure of pure inductive effect) is unknown for the carbamate ion that for CO_2^- has a negative value. The nitrile group must be very much more effective in electron withdrawal, due to resonance dispersal, than is the negative charge as a donor in order to explain the exceptional reactivity of the dicyanamide anion towards hydroxide ion (Table) compared with that of other nitriles.

Comparison of the reactivity in acid-catalysed hydrolysis shows that the N≡C–NH– group enhances the rate compared with a regular nitrile such as acetonitrile. The dicyanamide monoanion is presumably reacting as its protonated form in the rate-limiting step because the acid-catalysed reaction is dependent on unit power of the proton concentration and not on its square.

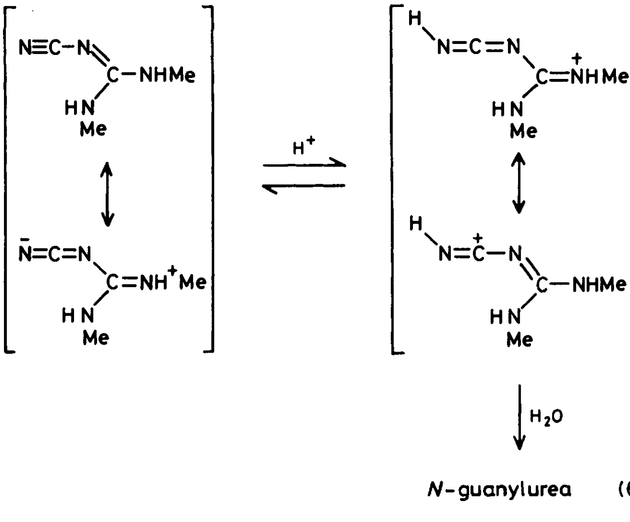

(4)

There is an ambiguity as to which of the tautomers in equation (4) is participating. Recent studies of Benders [10] indicate that the analogue NCNRCN, where R is an alkyl group such as methyl, needs strongly acidic media for its hydrolysis. Thus the NC–NH–CN tautomer will not sustain a rapid hydrolysis at weakly acidic pH values; moreover a second proton would be required in the rate equation from the conjugate base (NC–$\bar{\text{N}}$–CN). The overall rate constant for attack of water on the dicyanamide will include the ionisation constant of NC–NH–CN, the tautomeric equilibrium constant between cyanamide and carbodi-imide forms and the rate constant for attack of water on cyanocarbodi-imide. The latter rate parameter is expected to be extremely high as electron-withdrawing acyl substituents are known to activate carbodi-imide functions.[11a]

Hydrolysis of the *N*-cyanourea would involve by analogy the corresponding carbamoylcarbodi-imide intermediates which are known to be reactive species.[11b] The stability of *N*-cyano-alkylureas in sulphuric acid at 50° at concentrations of up to 10 M [10b,c] confirms the mechanism of equation (5).

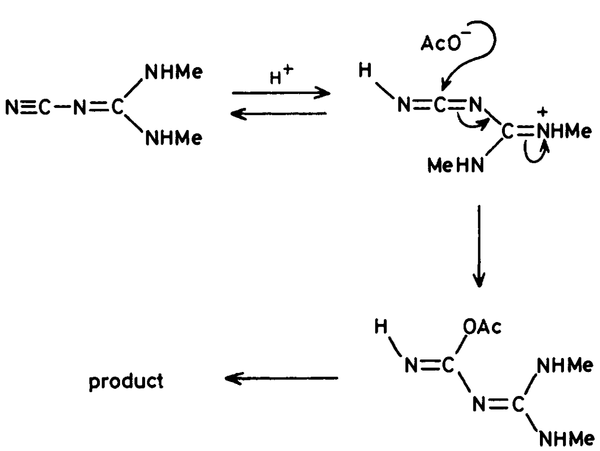

(5)

Cyanoguanidine hydrolysis under acid conditions has a rate constant proportional to unit power of the proton concentration. Protonation would be most effective on the nitrile nitrogen as shown in equation (6) where we favour a carbodi-imide-type mechanism.


(6)

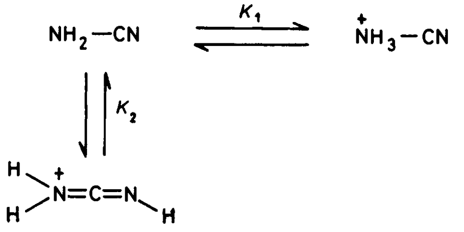
Hydrolysis of the dimethylcyanoguanidine is also catalysed by buffer acids acetic and formic acid, and by comparison with the proton-catalysed reaction this probably involves the carbodi-imide tautomer. Catalysis of regular nitrile hydrolysis by weak acid is a very poor reaction if known at all.[2]

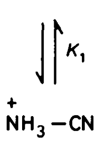
Comparison with the reaction of carboxylic acids with carbodi-imides [12] indicates that the most favoured reaction mechanism for general acid-catalysed hydrolysis of the dimethylcyanoguanidine should be specific acid-nucleophilic catalysis passing through an *O*-acylisourea intermediate [equation (7)]. Attack of the carboxylate ion on carbodi-imides is acid catalysed but in the present case the carbodi-imide is already activated to nucleophilic attack by the positively charged guanidino-function.


(7)

The tentative results of this work on the effect of structure variation of the carboxylic acid indicate a low selectivity for attack of the carboxylate anion on the protonated cyanoguanidine; this is consistent with the known low selectivity for attack of nucleophiles on carbodi-imides.[12]

Tillett [13] and Kilpatrick [14] found that the hydrolysis of cyanamide is acid catalysed and at relatively low proton concentration the rate is first order in substrate and proton concentration. At higher acidities the cyanamide protonates and exhibits a pK of -0.6.[3,14] Application of Hall's equations [15] for primary amines using as a standard pK that of ethylammonium ion gives a calculated value for pK_1 of -1.72 [equation (8)]. The equation used is a slight modification of Hall's derived by Fox and Jencks [15b] and utilises σ_I values. The nearness of the calculated and observed values indicates that the value of -0.6 refers to amine protonation; the use of σ_I values for the calculation neglects a possible resonance interaction between the amino-function and the nitrile in the conjugate base.


(8)

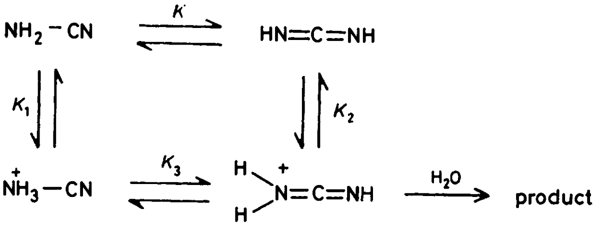

(9)

The carbodi-imide mechanism for acid-catalysed hydrolysis of cyanamide [equation (9)] was preferred by Kilpatrick [14] and this is consistent with the carbodi-imide mechanism shown by us for the dicyanamide and cyanourea hydrolyses. The overall acid-catalysed rate constant for the carbodi-imide scheme [equation (9)] is given by equation (10). Since

$$k_{obs} = K\cdot k_{H^+}\cdot[H]/(1 + [H^+]/K_1)\ (=[H^+]K\cdot k_{H^+} \text{ at } [H^+] < K_1) \quad (10)$$

we know the value of $K\cdot k_{H^+}$ from the second-order rate constant for proton catalysis at low proton concentration (3.8 10^{-5} l mol^{-1} s^{-1} at 25°)[13] we may estimate the tautomeric equilibrium constant K provided we have an estimate of k_{H^+}. The latter value we can take to be no more than an order of magnitude from 630 l mol^{-1} s^{-1} from that for di-n-propylcarbodi-imide;[16] this leads to a value of K of 0.6×10^{-7}. This value is very much greater than that calculated from molecular orbital studies for the gas-phase equilibrium (10^{-19})[17] as might be expected due to solvation of the tautomers. We do not believe that there is much error in the assumption that the acid-catalysed rate constant for the propylcarbodi-imide is the same as that for the parent. There is a possibility however that solvation of the parent carbodi-imide could make a difference in the rate constants.

We can estimate to within narrow limits the basicity of the parent carbodi-imide from the results of the present and previous work[16] assuming that the carbodi-imide mechanism holds for the acid-catalysed hydrolysis of cyanamide [equation (11)]. Within the scheme, where the rate constant is given by equation (12), all the species are stabilised by conjugation

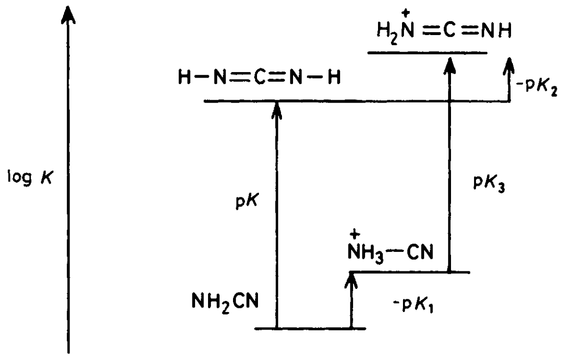


(11)

$$k_{obs} = KK_1k_{H_2O}/K_2(1 + K_1/[H^+]) = K_3k_{H_2O}/(1 + K_1/[H^+]) \quad (12)$$

except NH_3^+CN; we may thus make the reasonable assumption that $K_3 > K$ because both of these equilibria are between similar systems. The species NH_3^+CN is not conjugated and therefore is less stabilised towards its tautomer than is NH_2-CN. Since the equilibrium constant $K_2 = K\cdot K_1/K_3$ the value of K_2 must be less than K_1, *i.e.* $pK_2 > -0.6$. Previous work from this laboratory[16] gave an upper limit for the pK of a carbodi-imide as 1 derived from studies on acid-catalysed hydrolysis. We therefore conclude, allowing for a margin of error, that the pK of a regular carbodi-imide lies between *ca.* −1 and +1.

It may appear paradoxical that the value for carbodi-imide basicity comes close to that of cyanamide. This is not so surprising since there is no common cation [equation (11)]. The position is further clarified by the free energy diagram [equation (13)].



(13)

The pK of a ketimine approximates to 7.[18] Introduction of an adjacent ketimine group will lower this value and a pK for a carbodi-imide of approximately zero is consistent with this. It is impossible to estimate the pK closer than this on theoretical grounds as there are no suitable models. It is not possible to measure the pK of regular carbodi-imides, although the value should be in an accessible range, because carbodi-imides hydrolyse in aqueous solution too rapidly in the acid region.[16]

It is possible that the electron-withdrawing groups force different mechanisms on the hydrolysis of cyanamide and dicyanamide and cyanourea. The pK of the protonated carbodi-imide parent and the tautomeric equilibrium constant derived from the analogy should therefore be treated with the appropriate caution.

We hope to study hindered carbodi-imides in the future to confirm our pK estimate.

References

1 A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 627.
2 Z. Rappoport, 'The Chemistry of the Cyano Group,' Interscience, London, 1970.
3 M. J. Sullivan and M. L. Kilpatrick, *J. Am. Chem. Soc.*, 1945, **67**, 1815.
4 (*a*) A. Hantzch and M. Wolvekamp, *Liebig's Ann. Chem.*, 1904, **331**, 265; (*b*) S. Birtwell, F. H. S. Curd, J. A. Hendry, and F. L. Rose, *J. Chem. Soc.*, 1948, 1650.
5 S. Thea and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1981, 72.
6 (*a*) F. Kurzer, *Chem. Rev.*, 1956, **56**, 95; (*b*) Y. I. Muskin and A. I. Finkelstein, *Zh. Obshch. Khim.*, 1963, **33**, 1883 (*Chem. Abstr.*, 1964, **60**, 3618f).
7 J. Eloranta, *Suomen Kemi.*, 1960, **B33**, 193.
8 H. Al-Rawi and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 2671.
9 C. K. Sauers, W. P. Jencks, and S. Groh, *J. Am. Chem. Soc.*, 1975, **97**, 5546.
10 (*a*) P. H. Benders, *Rec. J. Royal Neth. Chem. Soc.*, 1976, **95**, 217; (*b*) P. H. Benders and J. Th. Hackmann, *ibid.*, 1972, **91**, 343; (*c*) P. H. Benders, *Tetrahedron Lett.*, 1973, 3653.
11 (*a*) A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589; (*b*) J. Goerdeler and S. Raddatz, *Chem. Ber.*, 1980, **113**, 1095.
12 I. T. Ibrahim and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1455, 1459.
13 B. R. Mole, J. P. Murray, and J. G. Tillett, *J. Chem. Soc.*, 1965, 802.
14 M. L. Kilpatrick, *J. Am. Chem. Soc.*, 1945, **67**, 1815.
15 (*a*) H. K. Hall, *J. Am. Chem. Soc.*, 1957, **79**, 5441; (*b*) J. P. Fox and W. P. Jencks, *ibid.*, 1974, **96**, 1436.
16 A. Williams and I. T. Ibrahim, *J. Am. Chem. Soc.*, 1981, **103**, 7090.
17 B. T. Hart, *Aust. J. Chem.*, 1973, **26**, 461, 477.
18 W. Bruyneel, J. J. Charette, and E. De Hoffmann, *J. Am. Chem. Soc.*, 1966, **88**, 3808.

Received 1st *August* 1983; *Paper* 3/1333