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General Acid Catalyzed Addition of Anilines to Dicyanamide Ion through a Concerted Mechanism

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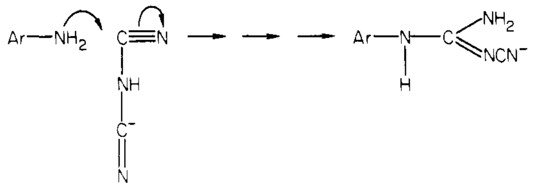
The addition of anilines to dicyanamide ion in aqueous solution is shown to be general acid catalyzed. The Brønsted exponent for the reaction where aniline substituent is varied and the acid is retained constant is $\beta_{\text{nuc}} = 0.63$ for acetic acid and $\beta_{\text{nuc}} = 0.66$ for oxonium ion. The Brønsted exponent for varying the general acid when the aniline is kept constant is −0.54 for 4-sulfanilic acid. The data are consistent with a mechanism where neutral aniline attacks the anionic dicyanamide assisted by concerted proton transfer from the general acid to the substrate nitrogen.

The aminolysis of cyanamides has been used synthetically to yield anti-bacterial guanidine type derivatives.[1] The reaction of anilines with dicyanamide is an example of such a process which is quite easily measured under mild aqueous conditions (eq 1).

$$\text{ArNH}_2 + \text{HN(CN)}_2 \rightarrow \text{Ar—NH—C(NH}_2\text{)=N—CN} \quad (1)$$

The addition of the amine nucleophile to the cyanamide moiety poses some intriguing problems which involve the mechanism by which a proton is effectively transferred from the nucleophile to the nitrile. It is possible that the transfer could be via a bridging mechanism or through the intervention of an acid or base transporter molecule as in the addition of anilines to isocyanic acid.[2] A ramification of the problem is that proton transfer could be concerted with the heavy atom reorganization in the reaction or it could be a stepwise process. A further complication to the addition of amines to cyanamides with electron-withdrawing side chains is that they could participate as their anionic species where the repulsive effect of the negative charge could be swamped by its spread into a resonating system (eq 2). Attendent on the reactivity of the neutral cyanamide is the possibility that the reaction flux is carried mainly by the carbodiimide tautomer (eq 3).



(2)

$$\text{RNH—C≡N} \rightleftarrows \text{R—N=C=NH} \quad (3)$$

So far as we are aware there has been little work carried out on mechanistic problems in the reactions of cyanamides with nucleophiles[3] and in particular none with the synthetically useful dicyanamide. It is possible to envisage a large number of possible mechanisms for the addition of amines to cyanamides; in order to elucidate these and provide data which could be helpful in the industrial synthesis of cyanoguanidines we studied the addition of anilines to dicyanamide using aqueous media. The results are also relevant to the aqueous degradation and shelflife of cyanoguanidines through the dicyanamide pathway.

Experimental Section

Materials. Substituted anilines were obtained commercially as free bases or as hydrochlorides and were distilled or recrystallized. Dicyanamide was obtained from Aldrich as the sodium salt. All buffers were of analytical grade or were purified from bench grade reagents and water was double distilled from glass. *N*-4-Chlorophenyl-*N′*-cyanoguanidine was prepared by dissolving 4-chloroaniline hydrochloride (1.6 mmol) and sodium dicyanamide (1.7 mmol) in water (20 mL) and stirring the mixture overnight. The product, obtained by filtration, was recrystallized from ethanol to give white needles, mp 205–206 °C (lit.[1d,4] mp 204–205 °C). Anal. Found: C, 33.0; H, 5.0; N, 38.2. Calculated for $C_8H_7ClN_4$: C, 32.8; H, 4.8; N, 38.2.

Methods. Kinetics of the reaction between anilines and dicyanamide (used in excess) were measured as follows. An aliquot of the stock solution of aniline in acetonitrile (50 μL) was added to 2.5 mL of a fully temperature equilibrated solution of acid buffer containing dicyanamide (at approximately 0.2 M) to give a final concentration of about 1 mM in the aniline. A blank cell containing all the above ingredients except the aniline was employed to compensate for any background hydrolysis of the dicyanamide (less than 1% of the aniline rate). Pseudo-first-order rate constants were measured spectrophotometrically at constant wavelength previously determined by a repetitive scanning experiment on the reaction solution. The same spectrophotometer (Pye-Unicam SP 800) was utilized in the scanning and constant wavelength studies and was coupled with a Servoscribe potentiometric recorder. The aniline was added to the buffer on the flattened tip of a glass rod. Three rapid vertical strokes of the glass rod in the silica cell effected complete mixing and the servoscribe recorder was activated at the instant of addition. Pseudo-first-order rate constants were calculated from the slopes of linear plots of $A_t - A_\infty$ vs. time on two cycle semilogarithmic graph paper.

Measurements of aniline p*K*'s were carried out spectrophotometrically using the stirred cell apparatus previously described.[5] The absorption was measured using a Unicam SP 800 instrument at a fixed wavelength previously determined to give the largest absorption change. The p*K* was obtained from the linear plot of $\log(\Delta_t - \Delta_{\text{pH}})/\Delta_{\text{pH}}$ vs. pH (eq 4). The terms Δ_t and Δ_{pH}

$$\log(\Delta_t - \Delta_{\text{pH}})/\Delta_{\text{pH}} = \text{pH} - \text{p}K \quad (4)$$

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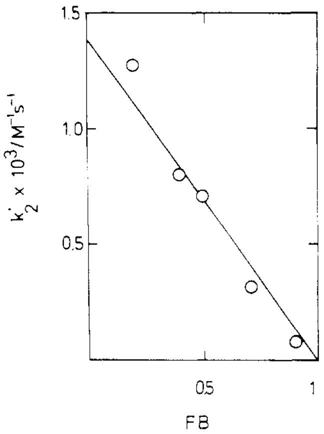


Figure 1. Apparent second-order rate constants (k'_2) for the reaction of 4-sulfanilic acid with dicyanamide (at a concentration 0.23 M) as a function of the fraction of acetate base (FB). Data from supplementary Table II for 40 °C and 1 M ionic strength. Line is calculated from the parameter in Table I.

Table I. Reaction of 4-Sulfanilic Acid in Acetate Buffer with Increasing Concentrations of Dicyanamide[a]

$[NaN(CN)_2]$, M	$k_{obsd} \times 10^3$, s^{-1}	$k_{obsd} \times 10^3/[NaN(CN)_2]$, $M^{-1}\ s^{-1}$
0.37	1.90	5.14
0.23	1.13	4.91
0.13	0.67	5.15
0.05	0.26	5.20

[a] Conditions: 40 °C, 1 M acetate buffer at pH 3.80, ionic strength maintained at 1.5 M with KCl.

represent the change in optical density respectively for total protonation of the aniline and partial protonation to the measured pH.

Analysis was carried out on the product of the kinetic reactions using an HPLC apparatus comprising a Pye-Unicam LC-XPD pump (Altex), PU 4020 UV detector, and single pen recorder (PM 8251). The analytical column (4.6 × 200 mm^2) was packed with Lichrosorb RP 8 10 m (Merck) reversed phase support and the eluent was 50% methanol/water containing 0.1% H_3PO_4. *N*-(4-Chlorophenyl)-*N'*-cyanoguanidine was shown to have a retention time of 6 min on the above column with a flow rate of 2.00 mL/min. The samples were added to the column directly from the product solution from the kinetic reactions.

Results

The product of the reaction of 4-chloroaniline with dicyanamide in acetate buffers was found to be *N*-(4-chlorophenyl)-*N'*-cyanoguanidine in essentially 100% yield by comparison of peak heights with the authentic material using the HPLC apparatus.

The reactions of anilines with dicyanamide were found to obey excellent pseudo-first-order kinetics in aniline concentration and these rate constants are proportional to the dicyanamide concentration (Table I). The existence of a tight isosbestic wavelength (at 278 nm) for the reaction of sulfanilic acid with dicyanamide confirms the simple stoichiometry of the reaction. The catalytic effectiveness of general acids for the latter reaction was measured from kinetics for increasing concentrations of buffer at several pH's. The fraction of base species (FB) may be calculated from eq 5 where K_a is the ionization constant of the acid

$$FB = 1/(1 + a_H/K_a) \qquad (5)$$

determined under the conditions of the kinetic experiments. The pseudo-first-order rate constants are linear in buffer concentration and the slopes of the derived lines represent the apparent second-order rate constants k_2' for the buffer. Values of k_2' for a given buffer are linear in fraction of base (FB) and no indication of base catalysis is seen (for example, Figure 1). Division of the second-order rate constant (from the intercept at FB = 0) by the concentration of the dicyanamide anion gives a third-order rate constant k_{HA} which predicts the rates according to the empirical rate law (eq 6). A value of k_H may be obtained

$$\text{rate} = k_{HA}[HA][ArNH_2][N(CN)_2^-] \qquad (6)$$

from a plot of the pseudo-first-order rate constant at zero buffer vs. the hydrogen ion concentration (see Figure 2). No allowance was made in the above calculations for the acid base property of the dicyanamide; this species has a p*K* less than unity and is effectively present only as its anion at all the pH's employed. Of course, as will be discussed later, the dicyanamide could react through the very small concentration of neutral form.

Results for the reaction of sulfanilic acid with dicyanamide catalyzed by general acids are recorded in Table II and those for 3-chloroaniline in Table III.

The effect of changing the substituent in the aniline was studied with acetic acid and the oxonium ion as the acid catalysts and assuming that eq 6 holds; these investigations

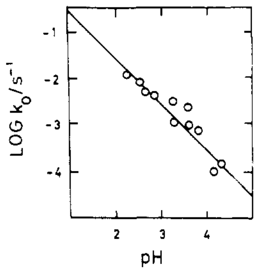


Figure 2. Dependence on pH of the intercept (k_0) at zero buffer concentration for the reaction of 4-sulfanilic acid with dicyanamide (0.23 M, 40 °C, 1 M ionic strength). The line is calculated from the parameter in Table I.

Table II. Third-Order Rate Constants for the Reaction of 4-Sulfanilic Acid with Dicyanamide Catalyzed by General Acids[a]

acid	p*K*	$k_{HA} \times 10^2$, $M^{-2}\ s^{-1}$ [b]
1 oxonium ion	−1.70	1150 (11)
2 chloroacetic acid	2.88	5.83 (36)
3 formic acid	3.66	1.63 (28)
4 ethoxyacetic acid	3.62	2.57 (10)
5 acetic acid	4.55	0.58 (30)
6 propionic acid	4.84	0.30 (6)
7 isobutyric acid	4.85	0.75 (8)
8 maleic acid	1.63	30 (10)
9 (dimethylamino)-acetonitrile	4.33	0.26 (8)

[a] Conditions: 40 °C, ionic strength 1 M maintained with KCl, wavelength for kinetic study 270 nm.
[b] Number of data points, including duplicates, are given in parentheses.

Table III. Reaction of 3-Chloroaniline with Dicyanamide in the Presence of General Acids[a]

acid	p*K*	$k_{HA} \times 10^2$, $M^{-2}\ s^{-1}$ [b]
acetic acid	4.55	1.96 (38)
oxonium ion	−1.70	5900 (5)
(dimethylamino)-acetonitrile	4.3	1.09 (8)

[a] Conditions: 40 °C, 1 M ionic strength maintained with KCl, kinetics measured at 270 nm. [b] Number of data points, including duplicates, given in parentheses.

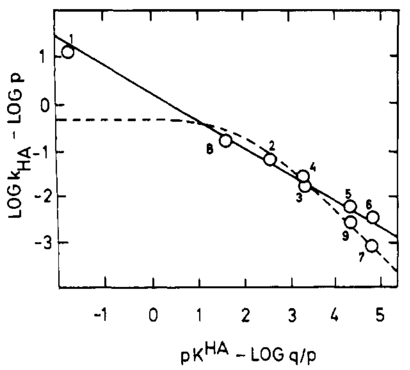


Figure 3. Brønsted plot, corrected statistically, for the third-order rate constant for attack of 4-sulfanilic acid on dicyanamide catalyzed by general acids at 40 °C, 1 M ionic strength. The line is calculated from the following equation. The dashed line is an

$$\log k_{HA} - \log p = -0.54 \pm 0.06\ (pK - \log p/q) + 0.23 \pm 0.24\ (r = 0.983)$$

"eigen" plot (Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1) drawn for a p*K* of 1.9 and $k_{max} = 0.5\ M^{-2}\ s^{-1}$ which seems to best fit the data—see text.

Table IV. Reaction of Substituted Anilines with Dicyanamide in the Presence of Oxonium Ion and Acetic Acid Catalyst[a]

aniline	p*K*	N^d	$k_{HA} \times 10^2$, M^{-2} s^{-1} [b]	$k_H \times 10^{-2}$, M^{-2} s^{-1} [c]
3-chloro[e]	3.11		2.00	0.59
parent	4.58	8	2.61	3.10
4-methoxy	5.29	8	29.1	5.40
3-nitro	2.45	8	0.23	0.05
4-chloro	3.88	8	2.48	0.62
4-hydroxy	5.50	8	32.6	6.94
4-sulfonato[e]	2.82		0.58	0.115

[a] Conditions: 40 °C, 1 M ionic strength maintained with KCl, 0.23 M sodium dicyanamide. [b] Catalytic rate constants from the slopes of plots vs. buffer concentration. [c] Rate constants from the intercepts at zero concentration of the buffer plots. [d] Data points. [e] From Tables II and III.

were carried out at a constant pH. It was necessary to allow for the fraction of aniline present in its conjugate acid form using p*K*'s determined under the conditions of the kinetics. The k_{HAc} and k_H terms for aniline attack are recorded in Table IV.

The results of the above experiments were used to construct Brønsted type plots for the reactions which are illustrated in Figures 3 and 4. The Brønsted equations are recorded in the legends to the appropriate figures.

Discussion

The reaction of anilines with dicyanamide catalyzed by general acids obeys the empirical eq 6 which is kinetically equivalent to eq 7 and 8. Further ambiguities exist as the dicyanamide in eq 8 could be reacting in its tautomeric carbodiimide form.

$$\text{rate} = k'[N(CN)_2^-][ArNH_3^+][A^-] \qquad (7)$$

$$= k''[HN(CN)_2][ArNH_2][A^-] \qquad (8)$$

We can exclude eq 7 because aniline will not react in its protonated form as a nucleophile. It could be argued that general base catalysis by A^- removes protons from the conjugate acid of the aniline assisting its attack. This mechanism could not compete with that where the conjugate base reacts directly especially as this species is present in substantial proportion at the pH of the experiments. The role of the conjugate base A^- other than as a general base would be unprecedented.

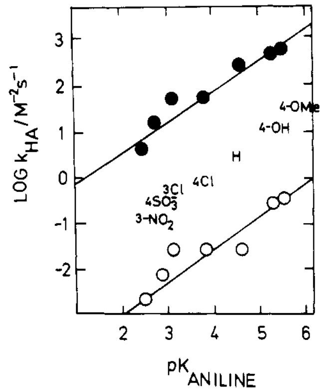
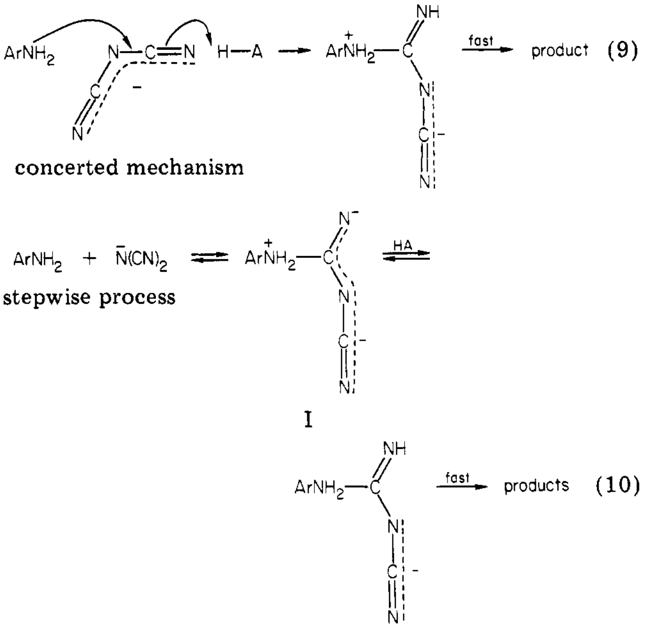


Figure 4. Brønsted type plots for the attack of anilines on dicyanamide catalyzed by the proton (●) and by acetic acid (0) at 40 °C and 1 M ionic strength. The lines are calculated from the following equations.

$$\log k_H = 0.66 \pm 0.08\ pK^{\text{aniline}} - 0.68 \pm 0.32 (r = 0.966)$$

$$\log k_{HA} = 0.63 \pm 0.09\ pK^{\text{aniline}} - 4.01 \pm 0.38\ (r = 0.949)$$

We prefer the rate law of eq 6 which could involve either a concerted or a stepwise attack (eq 9 and 10). There is no observable general acid catalysis in the attack of amines on carbodiimides.[6a] When the nucleophile is changed to carboxylate in the latter system general acid catalysis is seen and the proton transfer is concerted with C–N bond formation.[6a] The concerted mechanism is likely for the addition to the cyanamide. The stepwise process would involve general acid catalysis of the second step (eq 10). Such a mechanism would yield a classical eigen type Brønsted relationship (Figure 3) where the k_{HA} term becomes independent of the structure of the catalytic acid when its p*K* is less than the p*K* of the conjugate acid of the acceptor base.[6b] Attempting to fit the equation of the eigenline to the data in Figure 3 gives a tolerable correlation for a p*K* of 1.9 for the imino nitrogen of the conjugate acid of I. The proton term lies about 20- to 50-fold above the p*K* independent rate constant ($0.5\ M^{-2}\ s^{-1}$) which



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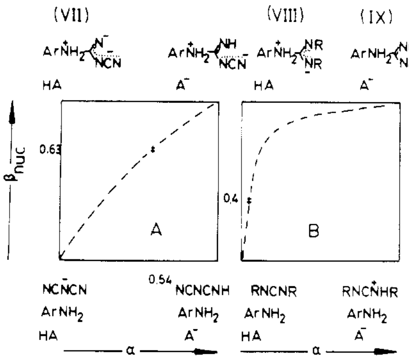
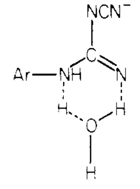


Figure 5. Three-dimensional potential energy diagrams for acid-catalyzed attack of aniline on dicyanamide (A) and carbodiimide (B). The extent of reaction vertically is measured by β_{nuc} for aniline attack and horizontally by α for the assistance of acid catalyst. Energy contours are omitted for clarity and reaction coordinates are denoted by dashed lines. The horizontal coordinate (α) for the transition state for the carbodiimide reaction is taken as between 0 and 0.1 since such low values represent the upper limit for observation of general acid catalysis (see text).

agrees well with the considerations of Barnett[6b] who indicates that the proton has an enhanced activity in diffusion-controlled reactions. Since the pK of >C=NH is very unlikely to be as low as 1.9 even with the attached $ArNH_2^-$– and NC^-N– groups we can exclude the stepwise process.

The absence of an uncatalyzed addition of anilines to dicyanamide indicates that the intramolecular transport of the proton direct or through a water bridge is not occurring in either a stepwise process (structure II) or in a



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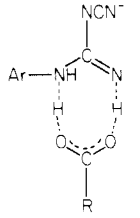
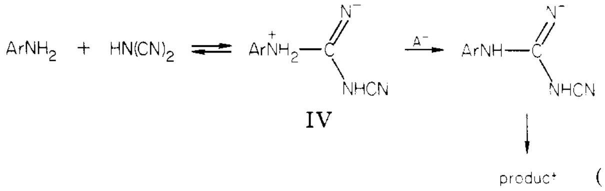


III

process concerted with nucleophilic attack. The intramolecular transport of the proton by a bifunctional transfer agent such as carboxylic acids (III) is unlikely because the reaction is also catalyzed to the same extent by ammonium ions (of similar pK) which cannot act bifunctionally (see Tables II and III). Mechanisms for eq 8 could also be stepwise or concerted (eq 11 and 12). A Brønsted plot



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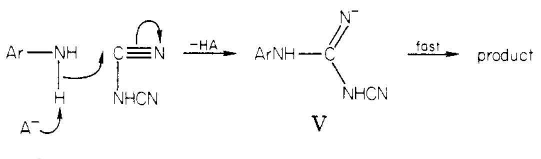
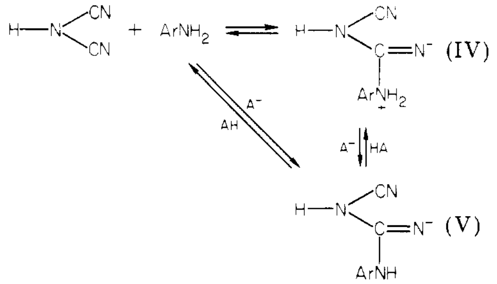


(12)

for k'' of eq 8 is linear from pK −1.7 to 5. In order to obtain the Brønsted slope for k'' it is not necessary to know the pK of $HN(CN)_2$ as this does not alter as the catalyzing base changes; the pK of this species is less than unity but has not been experimentally determined.

The stepwise mechanism (eq 11) would exhibit an eigen type Brønsted plot characterized by an inflexion at the pK of the catalytic base species equivalent to that of the anilinium proton of IV. At pK values below that of the donor acid the slope of the Brønsted plot would be +1 whereas for higher pK's the value of k'' would be independent of base structure due to diffusion-controlled proton transfer. The anilinium proton in IV would be required to have a pK greater than 5 because the Brønsted plot is linear up to this value. The pK of the anilinium proton is expected to be much smaller than 5 particularly as sulfanilic acid is a much stronger acid than the parent anilinium ion. If the mechanism of eq 11 involved a preassociation or spectator catalysis by the buffer the apparent pK of the break could be shifted to a value higher than that of the anilinium ion. Such a mechanism would involve a ternary complex ($A^-{\cdot}ArNH_2{\cdot}HN(CN)_2$) prior to the N–C bond-forming step to yield ($A^-{\cdot}ArNH_2$–$C(N^-)$–NHCN). Such a spectator catalysis should give a linear Brønsted plot in pK^{AH} of unit slope when the proton-transfer step is rate limiting. This is not consistent with the observed slope of +0.46.

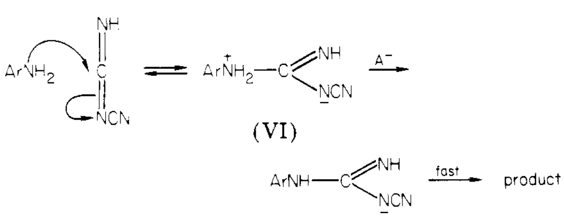
The concerted mechanism (eq 12) can be excluded because the rate constant for protonation of the anion V to yield IV in eq 13 would be at a diffusion-controlled rate



(13)

especially for the more acidic conjugate acids. (This depends on the pK of IV → V being similar to that for the corresponding anilinium ion. This is reasonable because the R–C(N⁻)– group is not expected to be electron withdrawing relative to the hydrogen group (H–).) Since decomposition of IV to reactants is faster than that of V to reactants (because the former reaction represents departure of a fully protonated amine) then the reaction flux must take the route to reactants through IV from V. By the principle of microscopic reversibility the forward route for the reaction must pass through IV; since this route has already been excluded we conclude that eq 8 does not hold for the nitrile tautomer.

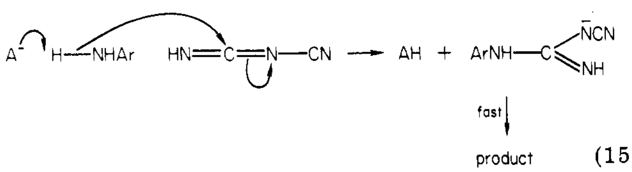
Equation 8 could still hold when the neutral dicyanamide reacts as its carbodiimide tautomer (cf. eq 3). Trapping of the zwitterion (eq 14) by the general base



(14)

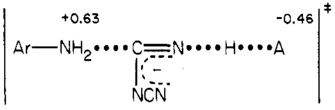
accepting a proton would be possible as both the acidic and basic nitrogens in the intermediate VI should have pK values between −1.7 and 15.7. We might expect to see curvature in the buffer plot as the concentration is increased due to a change in rate-limiting step; curvature is not observed even up to the concentration of 1 M in buffer. The Brønsted plot of log k_{A^-} vs. pK^{HA} does not exhibit classical eigen type curvature and the line is straight over a large pK^{AH} range with slope (0.46) much less than the required unity. Moreover, since the pK of -NH-CN is less than that for water a general acid component of eq 8 would be expected (rate = $k[HN(CN)_2][ArNH_2][HA]$).

A further possibility is that concerted proton transfer occurs (eq 15) but this may be excluded by consideration of an argument similar to that used (cf. eq 13) against the concerted process in eq 12.

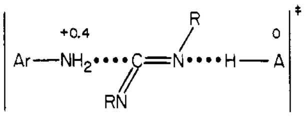


(15)

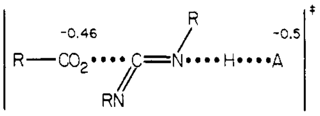
We can estimate the effective charge distribution for the concerted proton transfer reaction from the Brønsted parameters and this is represented in eq 16A. It is necessary to assume that the substituent effect on the aryl nucleus for the equilibrium formation of the zwitterion VII is unity in order to obtain the charge illustrated on the attacking nitrogen. This is not too difficult an assumption. In comparison with the attack of anilines on carbodiimide (where β_{nuc} = 0.4)[6] the change in effective charge is high, consistent with fairly advanced bond formation between nitrogen and carbon (eq 16B). This is consistent with the requirement for acid catalysis which is not seen in the aminolysis of carbodiimides. The position of the transition state on the three-dimensional potential energy surface is illustrated in Figure 5 and is defined by the horizontal and vertical axes which correspond to the various Brønsted parameters. The carbodiimide, which does not require general acid catalysis for attack of aniline,[7] has a transition state in the bottom left corner. Whereas the carbodiimide surface is skewed due to the relative stability of the intermediate VIII compared with the product IX the dicyanamide reaction has an unstable intermediate VII compared with the product. It may of course be the case that the α value for the carbodiimide reaction is too small for general acid catalysis to be measurable against that by the proton; this is almost certainly the case because a change in charge on the intermediate corresponding to VII for *carboxylate* ion attack leads to measurable general acid catalysis[7] (see eq 16C).



(16A)



(16B)



(16C)

Relationship of the Present Study to Degradation. The conclusion that the addition of anilines to dicyanamide involves general acid catalysis requires that the microscopic reverse of the synthetic path, namely the degradation of cyanoguanidines to anilines and dicyanamide, has proton removal concerted with fragmentation. (We do not imply here that the degradation of *N*-phenyl-*N'*-cyanoguanidines is *required* to go through the dicyanamide as an intermediate.) No such catalysis is seen in an analogous reaction, the degradation of imidates to nitriles recently studied by Gilbert and Jencks[8] and found to require only specific base catalysis by the hydroxide ion. This mechanism can readily be explained if the p*K* of the "imidate" in the dicyanamide system is very much higher than that in the imido ester system; this might be expected as ionization in the former case places two negative charges on a conjugated system. The reverse of the dicyanamide addition mechanism appears to be an example of a concerted E2 type of reaction involving a multiple CN bond. Other examples of this mechanism are the reverse of carboxylate addition to carbodiimides[7] and amine formation from carbinol amine derivatives[9] where departure of the leaving group is concerted with proton transfer.

With regard to degradation of the phenylcyanoguanidines under physiological or storage conditions the mechanism indicated by the microscopic reverse of eq 9 indicates that a proton switch must occur to yield a zwitterionic intermediate which will react in a rate-limiting step with a basic species. The pH dependence of the zwitterion concentration will be "bell" shaped with a pH maximum likely to be near pH 2–3 between the p*K* of the anilinium species and that of the cyanamide. Thus we might expect degradation to dicyanamide to occur most efficiently in the acid region of pH especially as increasing the basicity of the base is not likely to compensate for the lower concentration of zwitterion at the high pH for full activity of the general base catalyst; this is because the Brønsted β for base structure variation will be 0.46.

A referee pointed out that the Brønsted α value for general acid catalysis is apparently independent of the p*K* of the attacking aniline. This behavior indicates weak coupling between proton transfer and bond formation whereas in analogous E2 mechanisms bond cleavage (formation) is strongly coupled with proton transfer. Such behavior might be expected in the present system which is closely related to others such as addition of amines to isocyanates where proton transfer is a step separate from the bond-formation step.

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Registry No. $NaN(CN)_2$, 1934-75-4; $3\text{-}ClC_6H_4NH_2$, 108-42-9; $C_6H_5NH_2$, 62-53-3; $4\text{-}MeOC_6H_4NH_2$, 104-94-9; $3\text{-}O_2NC_6H_4NH_2$, 99-09-2; $4\text{-}ClC_6H_4NH_2$, 106-47-8; $4\text{-}HOC_6H_4NH_2$, 123-30-8; $4\text{-}HO_3SC_6H_4NH_2$, 121-57-3; oxonium ion, 13968-08-6; chloroacetic acid, 79-11-8; formic acid, 64-18-6; ethoxyacetic acid, 027-03-2; acetic acid, 64-19-7; propionic acid, 79-09-4; isobutyric acid, 79-31-2; maleic acid, 110-16-7; (dimethylamino)acetonitrile, 926-64-7; *N*-(4-chlorophenyl)-*N'*-cyanoguanidine, 1482-62-8.

Supplementary Material Available: Tables of the experimental rate constants supplementary to Tables II, III, and IV (6 pages). Ordering information is given on any current masthead page.

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[7] Ibrahim, I. T.; Williams, A. *Ibid.* **1982**, 1459.

[8] Gilbert, H. F.; Jencks, W. P.; *J. Am. Chem. Soc.* **1979**, *101*, 5774.

[9] (a) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353. (b) Sayer, J. M.; Peskin, M.; Jencks, W. P. *Ibid.* **1973**, *95*, 4277. (c) Sayer, J. M.; Jencks, W. P. *Ibid.* **1977**, *99*, 464.