EQUILIBRIUM OF α-AMINOACETONITRILE FORMATION FROM FORMALDEHYDE, HYDROGEN CYANIDE AND AMMONIA IN AQUEOUS SOLUTION: INDUSTRIAL AND PREBIOTIC SIGNIFICANCE

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The equilibrium constant, $K_{an(H_2CO)}$, for the formation of α-aminoacetonitrile from formaldehyde, ammonia and hydrogen cyanide was evaluated at 25 °C. A first estimation of $K_{an(H_2CO)}$ was obtained from extrathermodynamic relationships of the type log K' vs $\Sigma\sigma^*$. The final value was then obtained from a comparison of the experimental and calculated pH dependences of α-hydroxy- and α-aminoacetonitrile concentrations. From these results, it appears that, after equilibrium, the ratio between the concentrations of the two precursors glycine and hydroxyethanoic acid, is a linear function of the concentration of free ammonia, i.e. $[CH_2(OH)CN]/[CH_2(NH_2)CN] = 21[NH_3]$ at 25 °C.

1. INTRODUCTION

Ethylenediamine and glycine, two basic industrial compounds, are usually not synthesized from α-aminoacetonitrile,[1,2] even though several attempts have been published.[3] A survey of the literature[4,5] and our knowledge of analogous systems[5] show that the difficulties with these syntheses are probably due not to a slow and unselective reduction or hydration of the nitrile, but to the formation of α-aminoacetonitrile from its precursors (HCN, H₂CO and NH₃). No fundamental investigation has been carried out on the equilibria involved in α-aminoacetonitrile formation in aqueous solution. The only work published so far[6] describes interactions between two compounds of this system, formaldehyde and hydrogen cyanide.
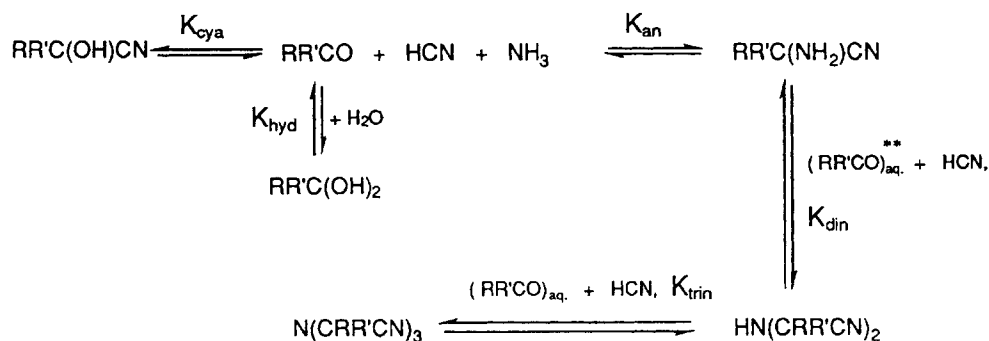
In this paper, a thermodynamic and kinetic study of the complete system, H₂CO–HCN–NH₃–H₂O, is reported. In addition to the synthetic interest in the results, a better understanding of the possible prebiotic

synthesis of glycine can be obtained. The latter is generally considered as the first and most abundant amino acid formed on the primitive Earth. Our first approach was to relate the equilibrium constants of cyanohydrins[6a] to those of α-aminonitriles in extrathermodynamic relationships. By extrapolation, an approximate value for the equilibrium constant of α-aminoacetonitrile was obtained. This value was then refined by comparing experimental and calculated plots of concentration of the different species present as a function of the pH. The most accurate value was reached when the best agreement between the two plots was obtained.

RESULTS AND DISCUSSION

According to data on previously investigated systems,[5] the carbonyl compound–hydrogen cyanide–ammonia system can be described by the equilibria shown in Scheme 1. The several equilibrium are defined in equations (1)–(5). In these equations, $[(RR'CO)_{aq.}]$ is the sum of the concentrations of the carbonyl compound, $RR'CO$, and of its hydrated derivative,

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$$RR'C(OH)CN \xrightleftharpoons{K_{cya}} RR'CO + HCN + NH_3 \xrightleftharpoons{K_{an}} RR'C(NH_2)CN$$

$$K_{hyd} \Big\Uparrow + H_2O$$

$$RR'C(OH)_2$$

$$(RR'CO)^{**}_{aq.} + HCN,$$

$$K_{din}$$

$$(RR'CO)_{aq.} + HCN, K_{trin}$$

$$N(CRR'CN)_3 \xrightleftharpoons{\hspace{3cm}} HN(CRR'CN)_2$$

<div align="center">Scheme 1</div>

$RR'C(OH)_2$.

$$K_{hyd} = \frac{[RR'CO]}{[(RR'C(OH)_2]} \tag{1}$$

$$K_{cya} = \frac{[RR'C(OH)CN]}{[(RR'CO)_{aq.}][HCN]} \tag{2}$$

$$K_{an} = \frac{[RR'(NH_2)CN]}{[(RR'CO)_{aq.}][HCN][NH_3]} \tag{3}$$

$$K_{din} = \frac{[HN(CRR'N)_2]}{[(RR'CO)_{aq.}][HCN][RR'C(NH_2)CN]} \tag{4}$$

$$K_{trin} = \frac{[N(CRR'CN)_3]}{[(RR'CO)_{aq.}][HCN][HN(CRR'CN)_2]} \tag{5}$$

When the carbonyl compound is formaldehyde, CN^- must always be in excess with respect to the substrate to avoid the presence of stabilized species resulting from the attack of amines on H_2CO (examples of these species are NH_2CH_2OH and $CNCH_2NHCH_2OH$). Moreover, to prevent oligomerization ($HOCH_2-O-CH_2OH$, etc.), formaldehyde is used in dilute solutions.

Evaluation of K_{an} by extrathermodynamic relationships

Quantitative information on cyanohydrin formation can be obtained from the literature. The hydration constants of the carbonyl compound and the equilibrium constants are shown in Table 1. K'_{cya} is the equilibrium constant of cyanohydrin formation related to the concentration of the non-hydrated carbonyl compound Schlesinger and Miller[6a] showed the existence of a Hammett-type linear relationship between log K'_{cya} and $\Sigma\sigma^*$. The slope of this Hammet–Taft relationship gives a ρ^* value of 7.98. $\Sigma\sigma^*$ is the sum of the Taft con-

stants of the aliphatic substituents of carbonyl compounds ($\sigma^*_{Me} = 0$, $\sigma^*_H = 0.49$). K'_{cya} is related to the equilibrium constant K_{cya} by

$$K'_{cya} = K_{cya}\left(\frac{1 + K_{hyd}}{K_{hyd}}\right) \tag{6}$$

To study the equilibrium constants for the formation of α-aminonitriles, we assumed an analogously linear relationship between log K'_{an} and $\Sigma\sigma^*$, where K'_{an} is the equilibrium constant of α-aminoacetonitrile formation related to the non-hydrated carbonyl compound.

From the available equilibrium constants for the formation of α-aminonitriles from acetaldehyde and acetone (Table 2)[5b,d], the value for the equilibrium constant of formaldehyde is evaluated by extrapolating the log K'_{an} vs $\Sigma\sigma^*$ relationship to $\Sigma\sigma^* = 0.98$ (Figure 1). This gives log $K'_{an(H_2CO)} = 10.9$ and $K'_{an(H_2CO)} = 7.94 \times 10^{10}$ mol^{-2} l^2.

Since $K'_{an(H_2CO)}$ is the value related to the equilibrium for the non-hydrated aldehyde and $K'_{an(H_2CO)}$ is available, application of equation (6) gives $K'_{an(H_2CO)} = 4 \times 10^7$ mol^{-2} l^2.

The slope of the log K'_{an} vs $\Sigma\sigma^*$ relationship is slightly higher but, however, similar to that for cyanohydrins ($\rho^* = 8.16$).

Table 1. Logarithms of the equilibrium constants for the formation of $RR'C(OH)CN$ relative to the unhydrated carbonyl compounds (K'_{cya}), hydration constants (K_{hyd}) and Taft constants ($\Sigma\sigma^*$) of the carbonyl compounds

Compound	Log K'_{cya}[a]	K_{hyd}	$\Sigma\sigma^*$
$R = R' = CH_3$	1·15	$7·2 \times 10^2$	0
$R = CH_3$, $R' = H$	4·56	0·94	0·49
$R = R' = H$	8·96	5×10^{-4}	0·98

[a] Equilibrium constants for the formation of cyanohydrins, which are the reciprocals of values given by Schlesinger and Miller[6a] for the dissociation of cyanohydrins.

Table 2. Equilibrium constants for the formation of α-aminonitriles relative to the unhydrated (K'_{an}) and hydrated (K_{an}) carbonyl compounds, hydration constants (K_{hyd}) and Taft constants ($\Sigma\sigma^*$) of the carbonyl compounds

Parameter	R = R' = CH$_3$	R = H, R' = CH$_3$	R = R' = H
K_{an}	8.3×10^2	3.8×10^6	4×10^{7a}
K_{hyd}	7.2×10^2	0.94	5×10^{-4}
$K'_{an} = K_{an}\left(\dfrac{1 + K_{hyd}}{K_{hyd}}\right)$	8.3×10^2	7.6×10^6	7.94×10^{10a}
LogK'_{an}	2.9	6.9	10.9^a

[a] Calculated in this work

Regarding the formation of the α-aminodinitrile, the only known equilibrium constant is relative to acetaldehyde,[5d] since α-aminodinitrile is never formed from acetone. From this value and assuming again the linear relationship, with the same slope as for α-aminonitriles, an approximate value for $K_{din(H_2CO)}$ of 5×10^6 can be obtained.

$K'_{an(H_2CO)}$ has been estimated to be 10^5, since no data on equilibrium constants for the formation of trinitriles are available. (We shall see later that this value has no influence on the results.)

To verify the extrapolated values of these equilibrium constants, we calculated the concentrations of the several species involved in the system, at various pH values, and compared them with the experi-

mental values (see the last section for detailed calculations).

However, a careful verification of the method was necessary. Systems in which the carbonyl compound was acetaldehyde or acetone had already been studied and their respective equilibrium constants are known.[5b,d] The good agreement obtained between the calculated and experimental pH–concentration plots (Figure 2) was an indication of the reliability of our calculation.

We were then able to calculate the pH dependences of α-aminonitrile, dinitrile, trinitrile and cyanohydrin concentrations for two sets of initial concentrations in formaldehyde–hydrogen cyanide and ammonia.

With equimolar initial concentrations of formaldehyde–hydrogen cyanide and ammonia (Figure 3), α-aminoacetonitrile formation will attain, around pH 10–10.5, a maximum representing 55–60% of the initial concentration of formaldehyde. The dinitrile formation will attain its maximum at pH ≈ 8 (25–30%), the trinitrile formation being negligible (1–2% at pH ≈ 7).

When the formaldehyde–hydrogen cyanide and ammonia concentrations were in a ratio of 1 : 9 (Figure 4), the formation of α-aminoacetonitrile was theoretically favoured (ca 95% at pH ≈ 10), while less than 8% of dinitrile at pH ≈ 8 was formed. In such proportions, the formation of trinitrile was negligible.

Experimental verification of K_{an}

Under equimolar conditions ($[H_2CO]_0 = [HCN]_0 = [NH_3]_0 = 1$ M), rapid degradation of the medium was observed, with several unassigned peaks appearing on the chromatograms. The experimental evolution of this complex system, calculated in Figure 3, could not then be studied.

Satisfactory experimental results were obtained, however, when the formaldehyde–hydrogen cyanide and ammonia concentrations were in the ratio of 1 : 9.
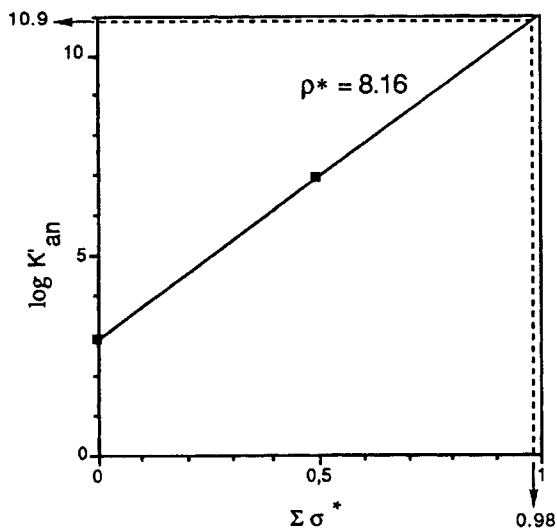

Figure 1. Plot of log K'_{an} vs $\Sigma\sigma^*$ (———). The value of log $K_{an(H_2CO)} = 10.9$ is obtained by extrapolation of the slope to $\Sigma\sigma^* = 0.98$

Acetone

$K_{cya} = 13.96$ $[CH_3CO]_0 = 0.2\ M$
$K_{an} = 830$
$K_{din} = K_{trin} = 0$ $[HCN]_0 = 0.2\ M$

$[NH_3]_0 = 0.2\ M$

Acetaldehyde

$K_{cya} = 17700$ $[CH_3CHO]_0 = 0.2\ M$
$K_{an} = 3800000$
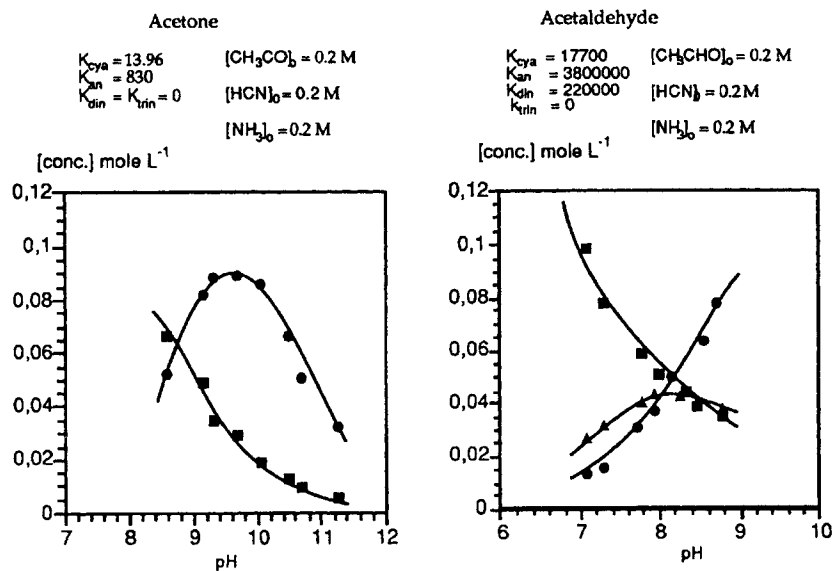$K_{din} = 220000$ $[HCN]_0 = 0.2\ M$
$K_{trin} = 0$

$[NH_3]_0 = 0.2\ M$

Figure 2. Experimental pH dependence of the different concentrations of cyanohydrin (■), α-aminonitrile (●) and α-aminodinitrile (▲) in acetone and acetaldehyde. (———) calculated plots
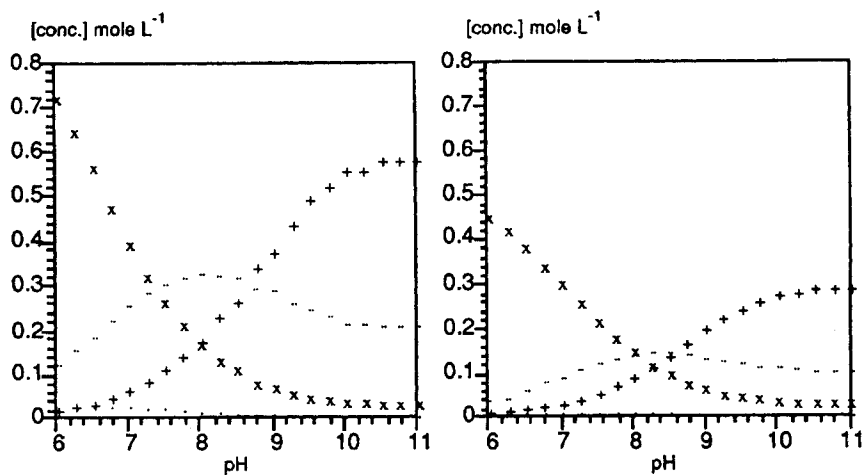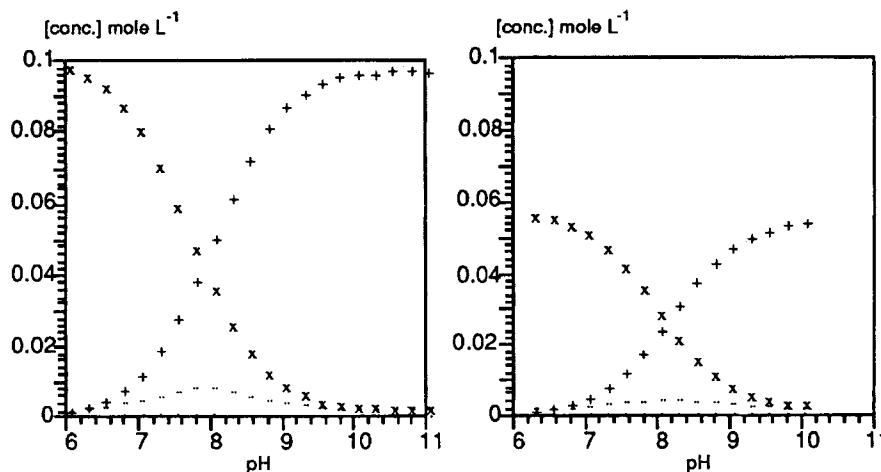

Figure 3. Calculated pH dependence of the different concentrations of glycolonitrile (x), α-aminonitrile (+), α-aminodinitrile (–) and α-aminotrinitrile (·) from formaldehyde. Equilibrium constants used: $K_{cya} = 4.76 \times 10^5$ (Ref. 6a), $K_{an} = 4 \times 10^7$ (this work), $K_{din} = 5 \times 10^6$ (this work) and $K_{trin} = 10^5$ (this work). Initial concentrations : $[NH_3]_0 = 1\ M$ and $[HCN]_0 = [H_2CO]_0 = 1\ M$ (left), $[NH_3]_0 = 0.5\ M$ and $[HCN]_0 = [H_2CO]_0 = 0.5\ M$ (right plot)

Figure 4. Calculated pH dependence of the different concentrations of glycolonitrile (x), α-aminonitrile (+), α-aminodinitrile (−) and α-aminotrinitrile (·) from formaldehyde. Equilibrium constants used: $K_{cya} = 4.76 \times 10^5$ (Ref. 6a), $K_{an} = 4 \times 10^7$ (this work) $K_{din} = 5 \times 10^6$ (this work) and $K_{trin} = 10^5$ (this work). Initial concentrations: $[NH_3]_0 = 0.9$ M and $[HCN]_0 = [H_2CO]_0 = 0.1$ M (left), $[NH_3]_0 = 0.514$ M and $[HCN]_0 = [H_2CO]_0 = 0.057$ M (right plot)

with these proportions, the kinetics of the system could be studied at various pH values for several hours. The equilibrium is reached when no evolution is observed in the kinetics of the formation of α-aminoacetonitrile and of the disappearance of glycolonitrile.

Although the kinetics of these systems were not the major aim of this study, it can be noticed, however, that
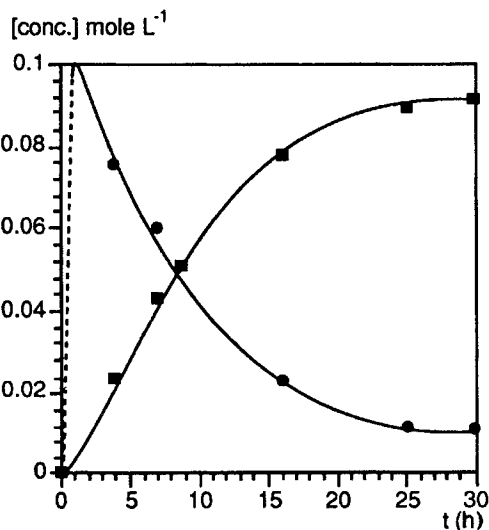

Figure 5. Time evolution, at 25 °C, of the system 0·1 M HCN–0·9 m NH₃–0·1 M H₂CO at pH 9·25, as followed by measuring the concentrations of α-aminoacetonitrile (■) formation and glycolonitrile (●) disappearance

when formaldehyde and hydrogen cyanide, in stoichiometric proportions, are added to aqueous ammonia solutions (The same proportions as indicated in Figure 4), the glycolonitrile is rapidly formed (less than 10 min) at any pH (kinetic control). An example is given in Figure 5.

The formation of α-aminoacetonitrile is slower, since the equilibrium is reached after about 30 h (thermodynamic control). The same phenomenon was observed when ketones were used as carbonyl compounds.[5a] The concentrations glycolonitrile (■) and α-aminoacetonitrile (●) at equilibrium are obtained from these kinetic plots (Figure 6).

Slight variations around the predetermined values, $K_{cya(H_2CO)}$, $K_{hyd(H_2CO)}$ and $K_{an(H_2CO)}$, lead to the best agreement between the experimental points (■, ●) and calculated curves (——) for the following values:

$$K_{cya(H_2CO)} = \frac{[H_2C(OH)CN]}{[(H_2CO)_{aq.}][HCN]} = 4.76 \times 10^5 \text{ mol}^{-1} \text{ l}$$

$$K_{hyd(H_2CO)} = \frac{[H_2CO][H_2O]}{[(H_2C(OH)_2]} = 5 \times 10^{-4} \text{ mol l}^{-1}$$

$$K_{an(H_2CO)} = \frac{[H_2C(OH)CN]}{[(H_2CO)_{aq.}][HCN][NH_3]}$$

$$= 1 \times 10^7 \text{ mol}^{-2} \text{ l}^2$$

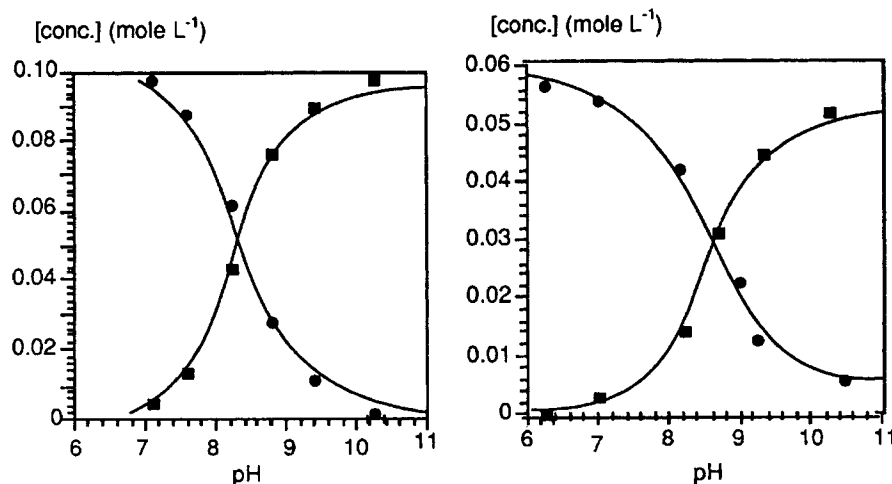The first two values were given by Schlesinger and Miller.[6a] We should therefore consider that the equili-

Figure 6. Experimental pH dependence of glycolonitrile (●) and α-aminoacetonitrile (■) concentrations, $[H_2CO]_0 = [HCN]_0 = 0 \cdot 1$ M and $[NH_3]_0 = 0 \cdot 9$ M (left); $[H_2CO]_0 = [HCN]_0 = 0 \cdot 057$ M and $[NH_3]_0 = 0 \cdot 514$ M (right). (———) Calculated plots with $K_{cya} = 4 \cdot 76 \times 10^5$ and $K_{an} = 1 \times 10^7$.

brium constant for the formation of α-aminoacetonitrile is 1×10^7 mol^{-2} l^2.

DISCUSSION AND CONCLUSION

The reactions for the formation of glycolonitrile (H$_2$C(OH)CN) and α-aminoacetonitrile (H$_2$C(NH$_2$)CN) in aqueous solutions containing formaldehyde, hydrogen cyanide and ammonia can be represented by the three equilibria given in scheme 2.

Industrial significance

α-Aminoacetonitrile is an interesting industrial intermediate compound. It leads to at least two basic compounds in the chemical industry, namely glycine, by hydration of the CN group, and ethylenediamine, by reduction of the same group. Attempts to obtain these two compounds from α-aminoacetonitrile lead to poor yields.[1,2] It seems that the thermodynamic and kinetic aspects of this system have not been taken into account.

This work should now be reconsidered, taking account of the present results.

Prebiotic significance

Prebiotically, the equilibrium between glycolonitrile and α-aminoacetonitrile is of great importance, owing to their major role in biological systems.
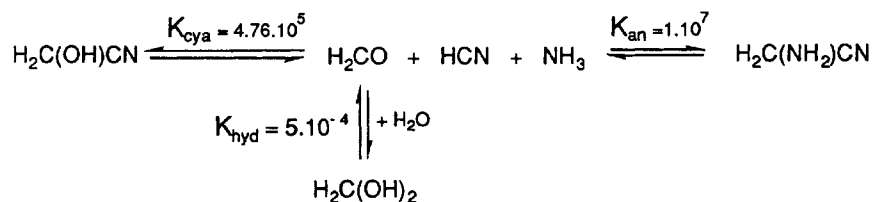
From the values of the equilibrium constants of glycolonitrile and α-aminoacetonitrile, the relative stabilities of the two compounds can be estimated:

$$\frac{K_{an(H_2CO)}}{K_{cya(H_2CO)}} = \frac{[CH_2(NH_2)CN]}{[CH_2(OH)CN][NH_3]} = 21$$

i.e.

$$\frac{[CH_2(NH_2)CN]}{[CH_2(OH)CN]} = 21[NH_3] \text{ at } 25 \,^{\circ}C$$

This equation implies that the proportion of the potential glycine precursor with respect to the hydrox-

$$H_2C(OH)CN \underset{\xrightarrow{\hspace{1cm}}}{\overset{K_{cya} = 4.76.10^5}{\rightleftharpoons}} H_2CO + HCN + NH_3 \underset{\xrightarrow{\hspace{1cm}}}{\overset{K_{an} = 1.10^7}{\rightleftharpoons}} H_2C(NH_2)CN$$

$$K_{hyd} = 5.10^{-4} \Bigg\Updownarrow +H_2O$$

$$H_2C(OH)_2$$

Scheme 2

yethanoic acid precursor is, independently of all kinetic aspects, a linear function of the concentration in free ammonia. In fact, the concentration of free and total ammonia, which could have been present in the primitive ocean, is actually the subject of discussion.

Miller and co-workers[7] estimated that the concentration of total ammonia could have been *ca* 0·1 M More recently, Summers and Chang[6b] reported much lower values, $3·6 \times 10^{-6}$–70×10^{-6} M. From these values and assuming the pH of the primitive ocean to be close to 8, the proportion of the glycine precursor with respect to the continuously formed hydroxyethanoic acid precursor varies, at 25 °C, from 1 to 0·001%. The reactions leading to cyanohydrin formation are under kinetic control (Figure 5), which means that, at prebiotic pH (probably basic, PH ~ 8), the almost instantaneous formation of glycolonitrile protected H_2CO and HCN, both highly energetic molecules formed in a continuous way, from irreversible degradation, which would have ended the evolutive process. The progressive elimination of these two molecules from their protected form leads to α-aminoacetonitrile (under thermodynamic control) and thus allowed for the appearance of amino acids.

To explain how the amino acids could be synthesized from α-aminoacetonitriles, despite the very low concentrations of ammonia[6,7] in prebiotic media, we can assume the presence and action of some reactants which react specifically with α-amino, rather than α-hydroxynitriles.[8-10] The chemical and kinetic aspects of this high selectivity will be reported in a subsequent paper.

EXPERIMENTAL

General. NMR spectra were recorded on a Bruker AC 250 (250 MHz) instrument; chemical shifts (δ) are reported relative to tetramethylsilane as an internal standard. To verify experimentally the calculated plots, several analytical methods were used. The method which gave the more satisfactory results was HPLC using a refractive index detector. HPLC was canned out on a Shimadzu LC-9A chromatograph with a Bio SiL C_{18} 'A/B' column (5 μm, 15 cm), a Shimadzu RID-6A refractive index detector (sensitivity $2·5 \times 10^{-9}$) and a Shimadzu C-R6A integrator. The element was almmonium chloride (0·05 M)–ammonia buffer solution adjusted to pH 7·5. The internal standard used for the calculation of concentrations was ethanol. Melting points were recorded on a Büchi 510 apparatus and are not corrected.

Materials. All solvents and reagents were of guaranteed grade from commercial sources and used without further purification, except in HPLC, where the solvents and reagents used were of HPLC grade.

Glycolonitrile. A 4·35 mol amount of anhydrous HCN (generated by reaction of a solution of NaCN with sulphuric acid, then dried on $CaCl_2$ and condensed at −10 °C) is slowly added to 4·7 mol of paraformaldehyde in suspension in 240 ml of dichloromethane, with 2 g of KCN present as catalyst. The initial temperature is set to 22 °C and stabilized at 25–30 °C, since the reaction is exothermic. At the end of the reaction (the reaction mixture is colourless), the temperature is lowered to 22 °C. A 400 ml volume of water is added to the medium, since the partition cofficient of glycolonitrile is more favourable to water than dichloromethane. The product is then stabilised by adding phosphoric acid until pH < 3. Pure glycolonitrile can be obtained, in 85% yield, by evaporating the solvent and distilling. $Eb_{0·4} = 86$ °C; δ_H (250 MHz, DMSO-d_6) 4·32 (d, 2H), 6·08 ppm (t, 1H); ν (CHCl$_3$) 3200–3600, 2250 cm^{-1}.

α-Aminoacetonitrile. An aqueous ammonia solution (32%, w/w) is added dropwise to pure glycolonitrile in molar proportions 9 : 1. The reaction is followed by TLC [elutent propan-2-ol–ammonia, (70:30)]. The product is extracted from the aqueous phase by continuous extraction from diethyl ether for 16 h. The solvent is evaporated under reduced pressure and pure α—aminoacetonitrile is obtained by distillation in 40% yield. $Eb_{0·5} = 50$–52 °C; δ_H (250 MHz, CDCl$_3$) 2·07(s, 2H), 3·52 ppm (s, 2H); δ_C (50·3 MHz, [1 M NH$_3$–D$_2$O (30%) buffer solution at pH 9] 146·1, 121·3, 29·7 ppm; ν (CHCl$_3$) 2100, 1615 cm^{-1}.

Iminodiacetonitrile (α-aminodiacetonitrile). A 7·81 g amount of pure α-aminoacetonitrile and 7·95 g of pure glycolonitrile are added to 150 ml of ethanol. After refluxing for 2·5 h, the reaction is maintained at −20 °C for 10 h. At the end of the reaction, the precipitate formed is filerted and pure iminodiacetonitrile is obtained by recrystallization from ethanol–light petroleum in 30% yield. Melting point 75 °C; δ_H(250 MHz, CDCL$_3$) 3·40 (m, 2H), 3·75 ppm (d, 2H); δ_C (50·3 MHz, [1 M NH$_3$–D$_2$O (30%) buffer solution at pH9] 148·2, 117·7, 35·6 ppm; ν (CHCl$_3$) 2225, 3335 cm^{-1}.

α-Aminotriacetonitrile. A solution of 100 g (0·07 mol) of hexamethylenetetramine in 500 ml water is added to 4·2 mol of hydrogen cyanide. At the end of the addition, HCl (35%, w/w) is added in 20 min. After 10 h at 22 °C, a yellowish solid is formed in the medium. Filtration and recrystallization from ethanol give pure nitrilotriacetonitrile in 22% yield with respect to hexamethylenetetramine. Melting point 126 °C; δ_H (250 MHz, CDCl$_3$) 4·05 ppm (s, 6H); δ_C (50·3 MHz, [1 M NH$_3$–D$_2$O (30%) buffer solution at pH 9] 148·1, 115·1, 41·7 ppm; ν(CHCl$_3$)2250 cm^{-1}.
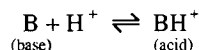
DEFINITIONS AND CALCULATIONS

Definition of apparent constants

κ = acidity constant

K_X = equilibrium constant for the formation of X.

Note: concentration of species in an acid-base equilibrium.

$$B + H^+ \rightleftharpoons BH^+$$
$$\text{(base)} \qquad \text{(acid)}$$

$$[B] + [BH^+] = C_t \text{ (total concentration)}$$

$$\kappa = \frac{[B][H^+]}{[BH^+]} \text{ (acidity constant)}$$

$$[B] + \frac{[B][H^+]}{\kappa} = C_t$$

$$[B] = \frac{\kappa}{\kappa + [H^+]} C_t \text{ (concentration of base)}$$

$$[BH^+] = \frac{[H^+]}{\kappa + [H^+]} C_t \text{ (concentration of acid)}$$

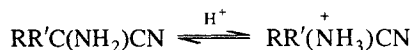In our systems, the formation of α-aminonitriles is represented by the following equilibrium:

$$RR'CO + HCN + NH_3 \xrightarrow{K_{an}} RR'C(NH_2)CN + H_2O$$
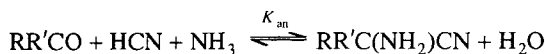
$$R = H, CH_3 \text{ etc.; } R' = H, CH_3 \text{ etc.}$$

The equilibrium constant for the formation of α-aminonitrile is

$$K_{an} = \frac{[RR'C(NH_2)CN]}{[RR'CO][HCN][NH_3]}$$

The α-aminonitrile exists in an acid–base equilibrium:

$$RR'C(NH_2)CN \xrightarrow{H^+} RR'(\overset{+}{N}H_3)CN$$

Assuming that only the basic forms of α-aminonitrile and ammonia react:

$$K_{an} = \frac{[RR'C(NH_2)CN]_t \dfrac{\kappa_{an}}{\kappa_{an} + [H^+]}}{[RR'CO][HCN][NH_3]_t \dfrac{\kappa_{NH_3}}{\kappa_{NH_3} + [H^+]}}$$

$[RR'C(NH_2)CN]_t$
    = total concentration of α-aminonitrile

$[NH_3]t$ = total concentration of ammonia

The formation of cyanohydrins results from the follow-

ing equilibrium:

$$RR'CO + HCN \xrightarrow{K_{cya}} RR'C(OH)CN$$
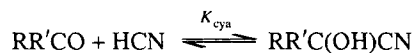
The product $[RR'CO][HCN]$ is related to $[RR'C(OH)CN]$ by

$$[RR'CO][HCN] = \frac{[RR'C(OH)CN]}{K_{cya}}$$

The equilibrium constant K_{an} becomes

$$K_{an} = \frac{[RR'C(NH_2)CN]_t \dfrac{\kappa_{an}}{\kappa_{an} + [H^+]} K_{cya}}{[RR'C(OH)CN][NH_3]_t \dfrac{\kappa_{NH_3}}{\kappa_{NH_3} + [H^+]}}$$

The apparent constant of the equilibrium, defined as

$$K_{a(an)} = \frac{[RR'C(NH_2)CN]_t}{[RR'C(OH)CN][NH_3]_t}$$

is related to $[H^+]$ by the following relationship:

$$K_{a(an)} = \frac{K_{an}}{K_{cya}} \frac{\kappa_{NH_3}}{\kappa_{NH_3} + [H^+]} \frac{\kappa_{an} + [H^+]}{\kappa_{an}}$$

The equilibrium for the formation of α-aminodinitriles can be represented by the reaction

$$RR'CO + HCN + RR'C(NH_2)CN$$
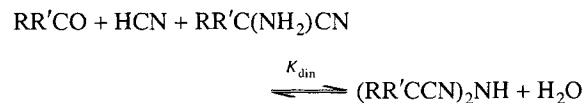
$$\xrightarrow{K_{din}} (RR'CCN)_2NH + H_2O$$

$$K_{din} = \frac{[(RR'CCN)_2HN]}{[RR'CO][HCN][RR'C(NH_2)CN]}$$

where K_{din} is the equilibrium constant for the formation of α-aminodinitriles. Assuming that only the basic form of the α-aminonitrile reacts, that the basicity of the α-aminodinitrle is weak, and since

$$[RR'CO][HCN] = \frac{[RR'C(OH)CN]}{K_{cya}}$$

$$K_{din} = \frac{[(RR'CCN)_2NH]K_{cya}}{[RR'C(OH)CH][RR'C(NH_2)CN]_t \dfrac{\kappa_{an}}{\kappa_{an} + [H^+]}}$$

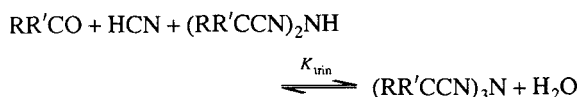The apparent equilibrium constant for the formation of

α-aminodinitriles given by

$$K_{(a)din} = \frac{[(RR'CCN)_2NH]}{[RR'C(OH)CH][RR'C(NH_2)CN]_t}$$

which is related to $[H^+]$ by

$$K_{a(din)} = \frac{K_{din}}{K_{cya}} \frac{\kappa_{an}}{\kappa_{an} + [H^+]}$$

The equilibrium for the formation of α-aminotrinitriles can be represented by the reaction

$$RR'CO + HCN + (RR'CCN)_2NH$$

$$\xrightleftharpoons{K_{trin}} (RR'CCN)_3N + H_2O$$

where

$$K_{trin} = \frac{[(RR'CCN)_3N]}{[RR'CO][HCN][(RR'CCN)_2NH]}$$

Since

$$[RR'CO][HCN] = \frac{[RR'C(OH)CN}{K_{cya}},$$

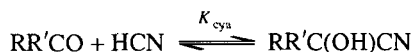$$K_{trin} = \frac{[(RR'CCN)_3N] K_{cya}}{[RR'C(OH)CN][(RR'CCN)_2NH]}$$

The apparent constant

$$K_{(a)trin} = \frac{[(RR'CCN)_3N]}{[RR'C(OH)CN][(RR'CCN)_2NH]},$$

is related to K_{trin} by

$$K_{(a)trin} = \frac{K_{trin}}{K_{cya}}$$

Finally, for cyanohydrins, the equilibrium of formation is represented by the reaction

$$RR'CO + HCN \xrightleftharpoons{K_{cya}} RR'C(OH)CN$$

where

$$K_{a(cya)} = \frac{[RR'C(OH)CN]}{[RR'CO][HCN]_t}$$

Since

$$K_{cya} = \frac{[RR'C(OH)CN]}{[RR'CO][HCN]} = \frac{[RR'C(OH)CN]}{[RR'CO][HCN]_t \dfrac{[H^+]}{[H^+] + \kappa_{HCN}}}$$

then

$$K_{a(cya)} = K_{cya} \frac{[H^+]}{[H^+] + \kappa_{HCN}}$$

Definition of concentrations

By fixing the concentration of cyanohydrin, the concentrations of carbonyl compound [RR'CO], α-aminonitrile [RR'C(NH_2)CN], α-aminodinitrile [(RR'CCN)_2NH] and α-aminotrinitrile [(RR'CCN)_3N] can be evaluated.

Let $[X]_0$ = initial concentration of X. The sum of CRR' groups is

$$[RRC(OH)CN]_0 = [RRC(OH)CN] + [RR'CO]$$
$$+ [RR'C(NH_2)CN]$$
$$+ 2[(RR'CCN)_2NH]$$
$$+ 3[(RR'CCN)_3] \quad (7)$$

and that of CN groups is

$$[RRC(OH)CN]_0 + [HCN]_0 = [RR'C(OH)CN] + [HCN]$$
$$+ [RRC(NH_2)CN]$$
$$+ 2[(RR'CCN)_2NH]$$
$$+ 3[(RR'CCN)_3] \quad (8)$$

Subtraction of equation (7) from equation (8) gives

$$[HCN]_0 = [HCN] - [RR'CO]$$
$$[HCN] = [HCN]_0 + [RR'CO]$$

Since

$$K_{a(cya)} = \frac{RR'C(OH)CN]}{[RR'CO][HCN]}$$

$$K_{a(cya)} = \frac{[RR'C(OH)CN]}{[RR'CO]([RR'CO] + [HCN])}$$

and

$$[RR'CO]^2 + [HCN]_0[RR'CO] - \frac{[RR'C(OH)CN]}{K_{a(cya)}} = 0$$

then

$$[RR'CO] = \frac{-[HCN]_0 + \sqrt{[HCN]_0 - \dfrac{4[RR'C(OH)CN]}{K_{a(cya)}}}}{2}$$

Let

$$B = [RR'C(OH)CN]_0 - [RR'CO] - [RR'C(OH)CN]$$
$$= [RR'C(NH_2)CN] + 2[(RR'CCN)_2NH]$$
$$+ 3[(RR'CCN)_3]$$

as

$$[(RR'CCN)_3N)]$$
$$= K_{a(trin)}[RR'C(OH)CN][(RR'CCN)_2NH]$$

and

$$[(RR'CCN)_2NH]$$
$$= K_{a(din)}[RR'C(OH)CN][RR'C(NH_2)CN],$$

then

$$B = [RR'C(NH_2)CN]$$
$$\times \{1 + K_{a(din)}[RR'C(OH)CN]$$
$$\times (2 + 3K_{a(trin)}[RR'C(OH)CN])\}$$

$$[RR'C(NH_2)CN]]$$

$$= \frac{B}{1 + K_{a(trin)}[RR'C(OH)CN](2 + 3K_{a(trin)}[RR'C(OH)CN])}$$

$$[(RR'CCN)_2NH] = \frac{B - [RR'C(NH_2)CN]}{2 + 3K_{a(trin)}[RR'C(OH)CN]}$$

$$[(RR'CCN)_3N] = \frac{B - [RR'C(NH_2)CN] - 2[(RR'CCN)_2NH]}{3}$$

Finally,

$$[NH_3] = [NH_3]_0 - [RR'C(NH_2)CN]$$
$$- [(RR'CCN)_2NH] - [(RR'CCN)_3N]$$

The objective of these equations is to determine, at equilibrium, the pH dependence of cyanohydrin, α-aminonitrile, α-aminodinitrile and α-aminotrinitrile concentrations, for given initial concentrations of cyanohydrin ($[RR'C(OH)CN]_0$), ammonia ($[NH_3]_0$) and hydrogen cyanide ($[HCN]_0$). The procedure consists in the calculation, at a given pH, of the apparent equilibrium constants for the different equilibria related to the concentrations of cyanohydrin, α-aminonitrile, α-aminodinitrile and α-aminotrinitrile, from the different known (or calculated in the case of formaldehyde) equilibrium constants.

By iterative calculations, the cyanohydrin concentration is modified and via the apparent equilibrium constants of cyanohydrin, α-aminonitrile, α-aminodinitrile and α-aminotrinitrile, the concentrations of the other compounds present in the medium are modified. When the concentrations in ammonia, hydrogen cyanide, carbonyl compound and α-aminonitrile, thereby calculated, lead to a value of the equilibrium constant for the formation of α-aminonitrile (K), close to the known (or calculated in the case of formaldehyde) value ($0.9\,K_{an} < K < 1.1\,K_{an}$), the equilibrium conditions are obtained.

For a group of values of $[RR'C(OH)CN]_0$, $[NH_3]_0$ and $[HCN]_0$, the other species can be expressed as a function of the actual concentration cyanohydrin ($[RR'C(OH)CN]$).

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