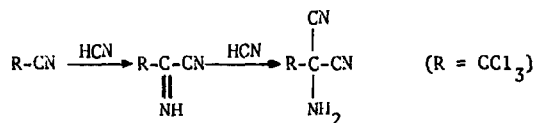


SYNTHESIS OF AMINO ACIDS FROM NITRILES

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The reaction of hydrogen cyanide with nitriles to give the substituted  $\alpha$ -amino malononitrile has been reported for trichloroacetonitrile.



A similar reaction with malononitrile gave only tars.<sup>1</sup>

We have been interested in the generality of this reaction since the  $\alpha$ -aminodinitriles would give  $\alpha$ -amino acids after hydrolysis and decarboxylation. Because there is a marked inductive effect in the base hydrolysis of nitriles,<sup>2</sup> a similar effect might be expected for the addition of cyanide. The addition of cyanide to the nitrile must therefore compete with its addition to the added hydrogen cyanide (R = H) to give the dimer, followed by oligomerization and polymerization to the cyanide polymer.<sup>3</sup>

It has been shown that nitriles are major products of prebiotic synthetic experiments such as the action of electric discharges on mixtures of methane and ammonia.<sup>4</sup> If the above reaction were general, this could have accounted for a significant fraction of the amino acids synthesized in the primitive ocean.

We have investigated the reaction under the more dilute conditions that are considered reasonable for prebiotic syntheses. An aqueous solution of  $3 \times 10^{-2}$  M nitrile,  $7.5 \times 10^{-2}$  M HCN, 0.15 M  $\text{NH}_4\text{Cl}$  was brought to pH 8 and heated at 100° for 40 days. The ammonia was added to avoid conversion of the amino nitrile to the hydroxy nitrile. The solution was hydrolyzed with 3 M HCl for 24 hrs, desalted, and analyzed on the amino acid analyzer. (In the case of succinodinitrile, the sample was acid hydrolyzed after desalting to hydrolyze and pyroglutamic acid formed during the desalting process.) The yields are given in Table 1.

The aspartic acid, glutamic acid and iminodiacetic acid were identified by collecting the corresponding peaks from the amino acid analyzer, desalting, and preparing the trifluoroacetyl amino acid n-butyl esters.<sup>5</sup> The GC-MS analysis (OV-1 1% on Chromosorb W 1/4' x 6' column LKB 9000) of the unknowns showed the same retention time and mass spectrum as the known compounds.

Table 1. Yields of Amino Acids from Nitriles

Nitrile	Amino acid formed	Yield (%)
Malononitrile	Aspartic acid	9.5
Succinonitrile	Glutamic acid	1.9
Benzyl cyanide	Phenylalanine	<0.01 <sup>a</sup>
3-Indolylacetonitrile	Tryptophan	<0.01 <sup>a,b</sup>
Propionitrile	$\alpha$ -Aminobutyric acid	0.04
Glycolonitrile	Serine	0.02 <sup>c</sup>
Aminoacetonitrile	Diaminopropionic acid	0 <sup>d</sup>

<sup>a</sup>The insolubility of the nitrile may account for the extremely low yield. <sup>b</sup>Basic hydrolysis. <sup>c</sup>All the runs gave about 0.12% of serine. Therefore less than one half of the serine in this run is due to the addition of cyanide to glycolonitrile. <sup>d</sup>26% of iminodiacetic acid was obtained due to the reaction  $2\text{NH}_2\text{CH}_2\text{CN} \longrightarrow \text{NH}(\text{CH}_2\text{CN})_2 + \text{NH}_3$  and hydrolysis.

The aspartic acid reached the same maximum yield after 1 day at 100° and 25 days at 60°. The glutamic acid reached its maximum yield after 15 days at 100°. At room temperature the respective yields of aspartic and glutamic acids are 3% and 0.2% after 120 days.

These results show that the attack of  $\text{CN}^-$  on the nitrile is indeed sensitive to the inductive effect of the R group. Only those nitriles with strong electron withdrawing groups will be able to add cyanide in competition to the addition of cyanide to HCN. Under organic synthetic conditions this problem might be overcome in cases where R is electron donating if the HCN is added slowly, thereby keeping its concentration low during the reaction. The addition of  $\text{CN}^-$  to the nitrile would then be relatively more favorable than the self-condensation.

The prebiotic synthesis of amino acids by this reaction does not appear feasible except in the case of aspartic acid and glutamic acid where the inductive effect of  $\text{R} = \text{CN}$  and  $\text{R} = \text{CH}_2\text{CN}$  results in the addition of cyanide at a rate that is rapid on the geological time scale. In these cases the yields are sufficiently high that this process might compete with the alternative prebiotic syntheses of aspartic and glutamic acids from electric discharges and cyanide polymerizations of aspartic acid from cyanoacetylene.<sup>6</sup>

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