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ON THE MECHANISM OF THE REACTION OF CYANIDE ION WITH CYSTINE

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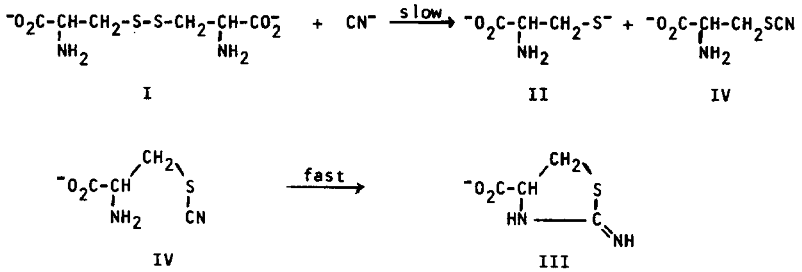
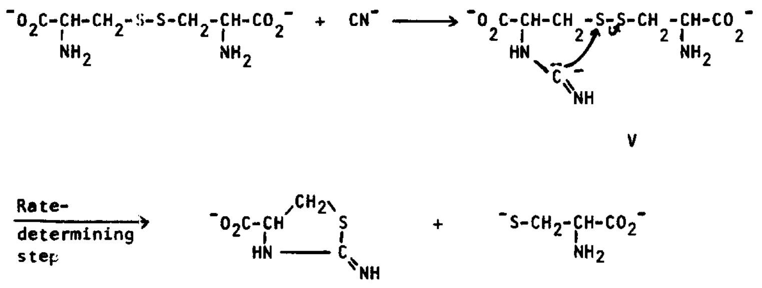
Cystine dianion (I) is known to react with cyanide ion in basic medium to yield the cysteine dianion (II) and the 2-imino-4-thiazolidinecarboxylate ion (III).[1,2] At pH 12.5 the reaction was found to be second order overall and first order with respect to both cystine dianion and cyanide ion. On the basis of this work a mechanism involving uncomplicated attack of cyanide ion on the disulfide bond of the cystine dianion to form the cysteine dianion and the thiocyanate (IV) in the rate-determining step was proposed. The thiocyanate (IV) then underwent rapid ring closure to yield the 2-imino-4-thiazolidine carboxylate ion (III).[2]



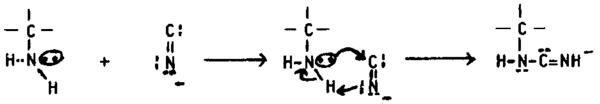
$$^{-}O_2C\text{-}\underset{NH_2}{CH}\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}\underset{NH_2}{CH}\text{-}CO_2^- + CN^- \xrightarrow{slow} {}^{-}O_2C\text{-}\underset{NH_2}{CH}\text{-}CH_2\text{-}S^- + {}^{-}O_2C\text{-}\underset{NH_2}{CH}\text{-}CH_2SCN$$

More recently, Davis and co-workers, in an attempt to correlate the sulfur-sulfur bond distance of cystine with the activation energy for this process, reinvestigated the kinetics of the reaction using N^{15}-labeled cystine. An isotope effect, $k_{14}/k_{15} = 1.0094$, was found, the 95% confidence limits being ±0.05%.[3,4] A new mechanism, involving the $(-NH-\ddot{C}=NH)^-$ ion (V), was proposed to accomodate this effect.


V

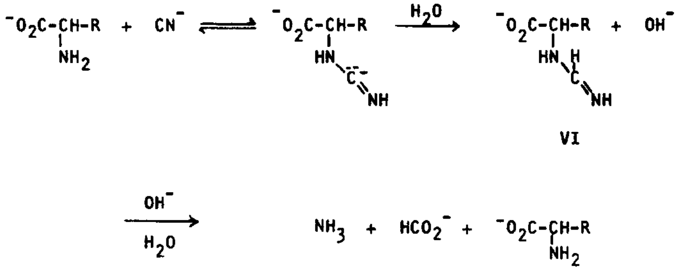
Rate-determining step

We wish to report here our observations concerning this mechanism. Formation of the $(-NH-\ddot{C}=NH)^-$ ion necessitates nucleophilic attack of the amino group on the cyanide ion (or <u>vice versa</u>) with concomitant or subsequent "transfer" of hydrogen from the amino nitrogen to the cyano nitrogen. Such a step appears unlikely to us. In view of the electron-rich nature of both the amino group and cyanide ion, it is reasonable to expect rather strong repulsive interaction between them, although formation of the $(-NH-\ddot{C}=NH)^-$ ion can be rationalized if the ambident form of the cyanide ion is utilized.



In this form the carbon atom of the cyanide ion would be electron deficient and possibly subject to nucleophilic attack by the amino group.

Since the formation of the $(\text{-NH-}\ddot{C}\text{=NH})^-$ ion would occur before the rate-determining step in the reaction, and the rate of the reaction itself is reasonably fast, the $(\text{-NH-}\ddot{C}\text{=NH})^-$ ion would be formed rapidly, even if in equilibrium with the initial reactants. It is therefore reasonable to expect that this ion would form readily in an amino acid not containing the disulfide group. The ion formed, since it could not undergo ring closure, would then abstract a proton from the solvent to form a substituted formimidine (VI), which under the conditions employed would decompose to form ammonia and formate ion and regenerate the amino acid. In effect, the amino acid would act as a catalyst for the decomposition of cyanide ion.



$$^{-}O_2C\text{-}\underset{NH_2}{CH}\text{-}R + CN^- \rightleftharpoons {}^{-}O_2C\text{-}\underset{HN\text{-}\ddot{C}^{-}\text{=}NH}{CH}\text{-}R \xrightarrow{H_2O} {}^{-}O_2C\text{-}\underset{HN\text{-}CH\text{=}NH}{CH}\text{-}R + OH^-$$

VI

$$\xrightarrow[H_2O]{OH^-} NH_3 + HCO_2^- + {}^{-}O_2C\text{-}\underset{NH_2}{CH}\text{-}R$$

We have investigated this possibility using the amino acid glycine. In a typical experiment (KCN:glycine = 39.5:1) a 2.38×10^{-3}M solution of glycine in 0.034M KOH was prepared and thermostated at 40°. Similarly, a solution of 0.094M KCN in 0.025M KOH was prepared, standardized for CN^- with $AgNO_3$, and thermostated. A solution of 0.034M KOH was also thermostated for use in preparation of a blank. All solutions were purged with nitrogen before use. For the kinetic runs, equal volumes of KCN and glycine solutions were mixed, and the disappearance of CN^- ion was followed by titration with $AgNO_3$ over the course of six days. At the same time, a blank consisting of equal volumes of KCN and 0.034M KOH solutions was prepared and followed similarly.

Three different KCN:glycine ratios were studied: 478:1 (3 days)[*], 39.5:1 (6 days), and 4.6:1 (10 days). The data thus obtained[**] indicated that, within experimental error, no cyanide ion was consumed, even over long periods of time at relatively high glycine concentrations. A small loss of cyanide ion observed in both sample and blank was attributed to loss of HCN from the solutions.[***]

In another experiment an attempt was made to detect possible evolved ammonia. Samples of the KCN:glycine = 4.6:1 mixture and the corresponding blank solution were prepared and heated at 40° C for one hour, during which time a stream of dry, deoxygenated nitrogen was passed through each sample, then through a tube containing anhydrous KOH, and finally into a solution of Nessler's reagent. Comparison of the resulting solutions indicated that no ammonia was evolved during this time. A sample of glycine in KOH solution gave a negative test when treated in this manner.

From these data we conclude that a mechanism involving the $(\text{-NH-}\ddot{\text{C}}\text{=NH})^-$ ion is, in all probability, not operative. Other conceivable mechanisms, other than an uncomplicated nucleophilic attack of cyanide ion on the sulfur atom in the disulfide group, are not particularly attractive. Work is currently underway in these laboratories in an attempt to further elucidate the mechanism of this reaction.

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[*] Indicates length of run

[**] Three runs were made at each ratio

[***] The HCN/CN^- ratio under these conditions is about 1/1000

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REFERENCES

(1) A. Schoberl, M. Kawohl, and R. Hamm, Ber., **84**, 571 (1951); CA **46**, 3532.

(2) O. Gawron and J. Fernando, J. Am. Chem. Soc., **83**, 2906 (1961).

(3) R. E. Davis, J. B. Louis, and A. Cohen, J. Am. Chem. Soc., **88**, 1 (1966).

(4) E. S. Wagner and R. E. Davis, J. Am. Chem. Soc., **88**, 7 (1966).