Kinetics of the Reactions of Pentacyanonitrosylferrate(II) with Mono- and Diamino Acids

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The reactions of $Fe(CN)_5NO^{2-}$ with glycine, α-alanine, β-alanine, γ-aminobutyric acid, ornithine and lysine were gas-volumetrically studied in a weakly-alkaline medium. The kinetic data show that the reactivity of the amino group depends on the basicity of the amine, on the behaviour of nucleophilic centers of the carbon chain, and on their steric positions.

The kinetic results are compared to the data of the reactions of amino acids with nitrous acid and of the complex with aliphatic amines.

Introduction

Our earlier results show that the diazotization of aliphatic amines by pentacyanonitrosylferrate(II) takes place in neutral or weakly-basic solutions [1]. It is suggested that the biological activity [2] may be connected with the deamination of the amino compounds of the organism. According to the features of analogous reactions, carcinogenic N-nitroso compounds or its precursors can be formed, so the medical applications of the complex require investigations of these reactions in detail.

Furthermore these nitrosation processes appear promising from the preparative point of view, as we observed the formation of heterocyclic compounds from diamino acids [3, 4].

The effect of the substituents on the reactivity of the amino groups were also studied by means of systematic investigation of reactions with mono- (glycine, α and β-alanine and γ-aminobutyric acid) and diamino acids (ornithine, lysine).

Experimental

Materials

$Na_2Fe(CN)_5NO{\cdot}2H_2O$ (Reachim) and the amino acids (Reanal) – diamino acids as their chloride salts – were reagent-grade commercial products. The ionic strength was adjusted by $NaClO_4$ which was twice recrystallized from methanol. Boric acid, as buffer, and the other reagents were analytical grade.

Methods and instruments

The gaseous product was analysed by an ATOMKI NZ 850 quadrupole mass spectrometer. The organic products were identified by paper-, thin layer- and gas-chromatography, and in case of diamino acids were separated from the solution. The reactions were followed by gas volumetry using a home-made gas burette system [5], and in some cases by spectrophotometry using a Beckman Acta III spectrophotometer.

Results

Stoichiometry of the Reactions

Similar to the reactions of aliphatic amines, N_2 gas evolution was observed in these reactions. In excess of amino acids one mol of N_2 forms for one mol complex, and in excess of complex also one mol N_2 forms for one mol reactant even in the reactions of diamino acids (Table I). This is a significant difference from the nitrosation with nitrous acid: the latter reacts with both of the amino groups of diamino acids [6]. In contrast with this the complex reacts selectively with the ω-amino group forming ω-OH– α-amino compound or/and N-heterocyclic derivatives. In the case of ornithine the main organic product is proline (the yield is 73%, separated as its benzyloxycarbonyl derivate) while in the reactions with lysine the ratio of ω-hydroxy and N-heterocyclic products is approximately 1:1 (39.2% of pipecolic acid was separated). Formation of γ-butyrolactone was detected in the reaction of γ-aminobutyric acid (Table II).

The spectral change is due to the formation of $Fe(CN)_5X^{3-}$ complexes, where X = H_2O, amino acid

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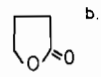
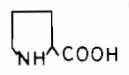
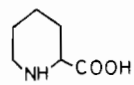
TABLE I. The Amount of N_2 Formed in the Reactions (T = 298 K, pH = 9.8, $V_{calculated}$ = 5.03 mol).

Amino acid	c_A (mol dm^{-3})	c_K (mol dm^{-3})	V (ml)
Glycine	0.02	0.50	4.88
α-alanine	0.02	0.50	5.00
	0.80	0.02	4.96
β-alanine	0.02	0.45	4.54
γ-aminobutyric acid	0.02	0.45	4.60
Ornithine	0.02	0.45	4.48
Lysine	0.02	0.45	4.42

TABLE II. The organic Products of the Reactions.

AMINO ACID	PRODUCT	
	acyclic	cyclic
NH_2-CH_2-COOH glycine	HO-CH_2-COOH [a] glycolic acid	
NH_2-CH(-CH_3)-COOH α-alanine	HO-CH(-CH_3)-COOH [a] lactic acid	
NH_2-CH_2-CH_2-COOH β-alanine	HO-CH_2-CH_2-COOH [a] hydracrilic acid	
NH_2-CH_2-CH_2-CH_2-COOH γ-aminobutyric acid		 [b] γ-butyrolactone
NH_2-CH_2-CH_2-CH_2-CH(-NH_2)-COOH ornithine		 [c] proline
NH_2-CH_2-CH_2-CH_2-CH_2-CH(-NH_2)-COOH lysine	HO-CH_2-CH_2-CH_2-CH_2-CH(-NH_2)-COOH [c] 6-OH-2-amino-capric acid	 [c] pipecolic acid

[a]Thin layer and/or paper chromatographic experiments with the product and the standard. The Rf values and color of spots are compared. [b]The product was identified by GC and IR spectra. [c]The products were separated by chromatography and analysed by IR and NMR spectra.

and the product [7a,b]. The equilibria of these complexes were not analysed.

According to this the stoichiometry of these reactions is:

$$Fe(CN)_5NO^{2-} + OH^- + RNH_2 = \\ = Fe(CN)_5X^{3-} + N_2 + \text{organic products} \qquad (1)$$

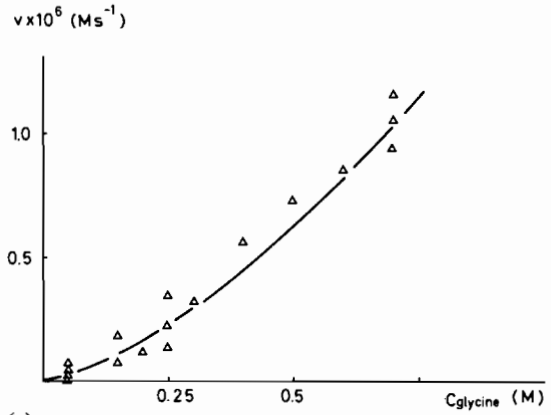
where

$R = -(CH_2)_m-COOH$ $\quad m = 1, 2, 3$

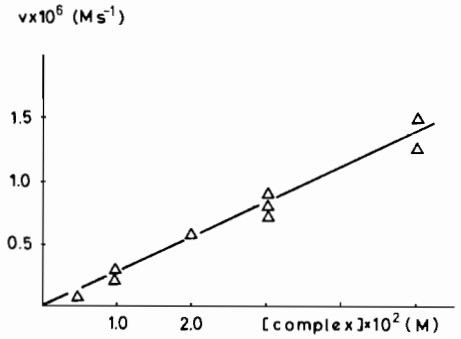
$R = -(CH_2)_n-CH(-NH_2)-COOH$ $\quad n = 3,4$

Kinetic Measurements

The reactions were followed only gas-volumetrically because the spectrophotometric measurements were less exact due to the formation of N_2 bubbles. Another problem of the spectrophotometry is the reaction between $[Fe(CN)_5H_2O]^{3-}$ and the excess amine or organic products which affects the absorbance.



(a)



(b)

Fig. 1. Dependence of the initial rates on the concentrations of a) glycine (c_k = 0.02 mol·dm^{-3}); b) complex (c_A = 0.5 mol·dm^{-3}), T = 298 K, pH = 9.00.

The gas volumetric measurements were evaluated by means of equation (2):

$$v_o = \frac{dV}{dt}\frac{1000}{V_M V_R} \qquad (2)$$

where V_M is the volume of 1 mol N_2 gas on the given temperature and pressure, V_R is the volume of the solution (cm^3), dV/dt is the limiting slope of a plot of V *vs.* t at zero time, and v_o is the initial rate.

In the experiments the concentrations of α-amino acids were varied in the range 0.1–1.1 mol dm^{-3} and those of PNF were between 0.02 and 0.05 mol dm^{-3}. The pH range was 9.0–10.7. In the other cases the concentration ranges of amino acids were between 0.025–0.8 mol dm^{-3} (c_{PNF} = 0.01 mol dm^{-3}) at pH 9. The ionic strength in the reactions of monoamino and diamino acids was adjusted to 1.0 and 1.5, respectively. The measurements were carried out at T = 293, 298, 303 and 308 K, but in the case of glycine and α-alanine only at T = 298 K.

Except in the reactions of α-amino acids the orders in the complex and in the amino acids determined by the van't Hoff method were found to be one for both

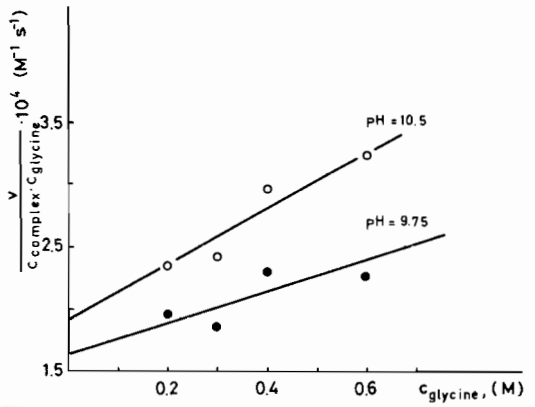


Fig. 2. Determination of the apparent rate constants in the reactions of glycine (c_k = 0.02 mol·dm^{-3}). 1. pH = 9.75; 2. pH = 10.50.

reactants. In the case of α-amino acids the order was higher than one (Fig. 1).

According to these the dependence of the initial rates on the initial concentrations can generally be described by equation (3):

$$v = k_1' c_A c_K + k_2' c_A^2 c_K \qquad (3)$$

where c_A and c_K are the concentrations of amino acids and of the complex, respectively. The apparent rate constants of the α-amino acids were determined graphically (Fig. 2).

As an explanation for the dependence of the rate constants on pH we assumed that the reactive form is the unprotonated amino acid [A], so the rate law is:

$$v = k_1 [A] c_K + k_2 [A] c_A c_K \qquad (4)$$

where

$$\underset{A}{NH_2{-}(CH_2)_n{-}COO^-} + H^+ \overset{K_p}{\rightleftharpoons} \underset{HA}{NH_3^+{-}(CH_2)_n = COO^-} \qquad (5)$$

From a comparison of eqns. (3) and (4) it follows

$$k_1' = k_1(1 + K_p[H^+])^{-1} \qquad (6)$$

$$k_2' = k_2(1 + K_p[H^+])^{-1} \qquad (7)$$

The k_2 values calculated by eqn. (7) decrease with increasing pH (Fig. 3). We assume that the zwitterionic forms of amino acids [HA] also take part in the reactions, so eqn. (4) can be written:

$$v = k_1 [A] c_K + k_2^{HA} [A] [HA] c_K + k_2^{A} [A]^2 c_K \qquad (8)$$

From a comparison of (4) and (8):

TABLE III. The Rate Constant Values at T = 298 K.

Amino compounds	$K_p \cdot 10^{-10}$	$Fe(CN)_5NO^{2-}$			N_2O_3
		$k_1 \cdot 10^4$ (mol^{-1} dm^3 s^{-1})	$k_2^{HA} \cdot 10^4$ (mol^{-2} dm^6 s^{-1})	$k_2^{A} \cdot 10^4$ (mol^{-2} dm^6 s^{-1})	$k_s \cdot 10^{-6}$ (mol^{-2} dm^6 s^{-1})
Glycine	0.37	1.8	8.1	1.2	2.6
α-alanine	0.49	1.6	2.8	1.0	1.1
β-alanine	1.26	44			1.0
γ-aminobutyric acid	3.60	91			7.3
Ornithine	3.31	145			
Lysine	4.57	196			
Benzylamine	0.29	7.5			
c-hexylamine	4.37	18.5			
ethylamine	4.57	50			
n-butylamine	5.01	55			
n-propylamine	5.50	59			

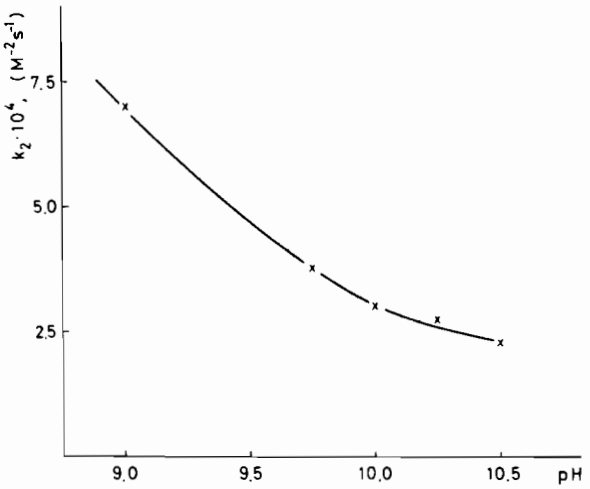


Fig. 3. The apparent rate constants as a function of pH in the reactions of glycine.

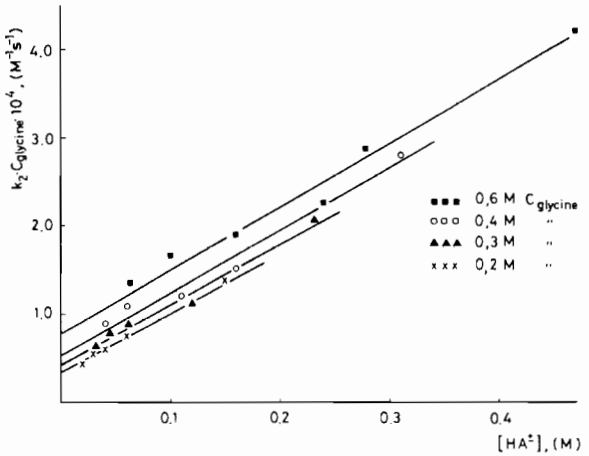


Fig. 4. Determination of the third order rate constants in the reactions of glycine.

$$k_2 c_A = k_2^{A}[A] + k_2^{HA}[A] \quad (9)$$

Taking into account that in the given range of pH

$$c_A = [A] + [HA] \quad (10)$$

the values of k_2^{HA} and that of k_2^{A} were determined by equation (11):

$$k_2 c_A = (k_2^{HA} - k_2^{A})[HA] + k_2^{A} c_A \quad (11)$$

as is shown in Fig. 4.

The graphically-determined rate constants at T = 298 K are summarized in Table III, while the k_1 values measured at different temperatures are collected in Table IV.

Except for the α-amino acids the k_1 values are much higher than $k_2^{HA}[HA]$ and $k_2^{A}[A]$. From a comparison of these values it follows that the amino group reacts faster when it is in remote position from the carboxylic group. Therefore the values determined for diamino acids characterize the reactivity of the ω-amino group.

Discussion

The experimental results suggest a mechanism which is analogous to that proposed for diazotization in acidic media.

TABLE IV. Rate Constants at Different Temperatures.

T (K)	$k_1 \cdot 10^3$ (mol^{-1} dm^3 s^{-1})			
	β-alanine	γ-aminobutyric acid	ornithine	lysine
288				27.9
293	3.75	9.9	14.8	25.5
298	3.92	9.1	14.7	19.6
303	3.71	10.2	14.6	15.7
308	3.70	9.7	14.9	15.4

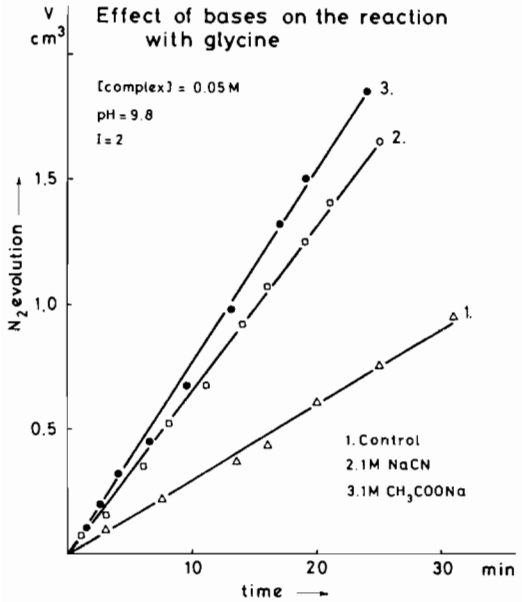


Fig. 5. The effect of the anions on the reactions of glycine (c_A = 0.4 mol·dm^{-3}).

The first step is the attack of the amino group on the electrophilic NO^+:

$$RNH_2 + [Fe(CN)_5NO]^{2-} \overset{K}{\rightleftharpoons} [Fe(CN)_5NORNH_2]^{2-} \quad (12)$$

The decomposition of this compound proceeds via several steps, including proton migration, dehydration and evolution of dinitrogen. Bowden *et al.*, studying the reactions of $Ru(bpy)_2(NO)Cl^{2+}$ with aromatic amines, came to similar conclusions [8]. Moreover some evidence was presented for the intermediates and the diazo compound was isolated. It was supposed that the proton transfer steps are probably promoted by unreacted amines.

According to this we investigated the effect of the nucleophilic compounds on the reaction rates (Fig. 5). The rate increases with the concentration of the

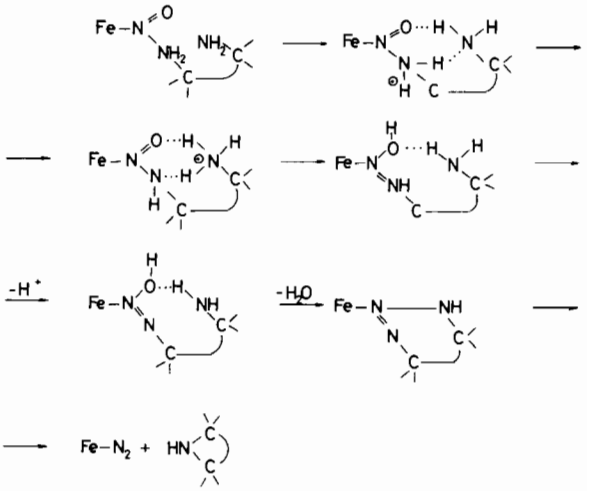


Fig. 6. The proposed mechanism for the formation of cyclic products.

nucleophiles. However no exact relation was observed between the catalytic effect and the basicity.

On the basis of this we assume that the adduct is converted to the N-nitroso compound on the effect of a nucleophilic catalyst:

$$[(CN)_5FeN(O)NH_2R]^{2-} + S \xrightarrow{k} [(CN)_5FeN(O)NHR]^{3-} + SH^+ \quad (13)$$

$$[(CN)_5FeN(O)NHR]^{3-} \xrightarrow[\text{fast}]{H^+} [(CN)_5FeN_2R]^{3-} + H_2O + S$$

Finally the diazo complex is transformed into the aqua complex.

As the reactivity of amino groups is influenced considerably by the quality and the position (relative to $-NH_2$) of other substituents of the particular amino acids, it is supposed that these groups also take an active part in the rate-determining step as catalytic centers ('inner catalysis'). The formation of the cyclic products is supported by the proposed mechanism (Fig. 6). Thus, the rate equation is of the form

$$v = Kk_S c_K [A] \quad (14)$$

and the rate constant is defined by equation (15):

$$k_S = k_i + k_{H_2O}[H_2O] + k_{HA}[HA] + k_A[A] + k_B[B] \quad (15)$$

where k_{HA}, k_A are the self-catalytic constants, k_i the 'inner-catalytic' constant and k_B is connected with the effect of buffer anions.

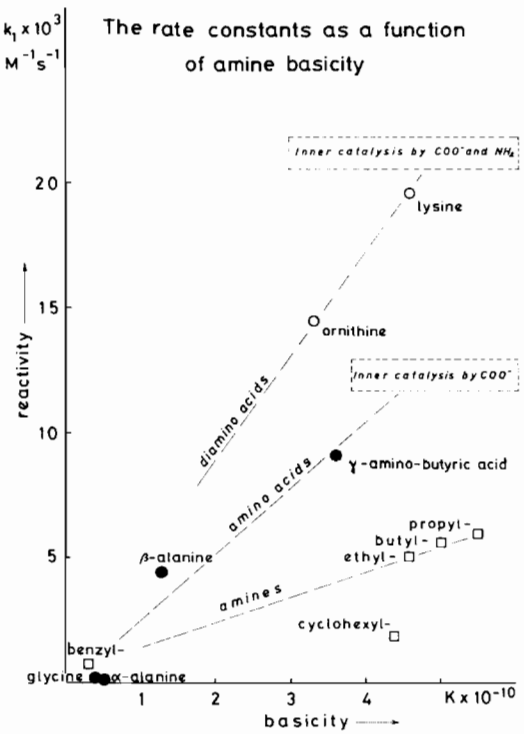


Fig. 7. The relation between the rate constants (k_1) and the basicity of amino group.

From a comparison of equations (8) and (14) it follows that each of the empirical rate constants, including k_1, contains an equilibrium constant:

$$k_1 = (k_i + k_{H_2O}[H_2O] + k_B[B])K \quad (16)$$

$$k_2^{HA} = k_{HA}K \quad (17)$$

$$k_2^{A} = k_AK \quad (18)$$

The temperature coefficient of the associative equilibrium constant is usually a negative value, which explains why the rate constants decrease with increasing temperature.

This constant, K, depends on the basicity of the reactive amino group as a parallel trend was observed between the rate constants and the basicity constants of the aliphatic amines (Table III).

The fact that the amino acids react faster than the amines is interpreted by 'inner catalysis' (Fig. 7).

This appears from the comparison of the rate constants of the mono-amino acids and that of the corresponding decarboxylic derivates. While the amino groups of the amino acids are less basic, they react faster. In the cases of α-amino acids the role of the self-catalysis is higher as a result of steric hindrance of the carboxyl group. The relatively fast reactions of diamino acids can be interpreted by the simultaneous effect of the carboxyl and amino group.

The increase of reactivity with the number of substituents is clearly shown by the examples of propyl amine (decarboxylic derivative of γ-aminobutyric acid), γ-aminobutyric acid and ornithine. The rates increase in the same sequence and this is in contrast to that which would be expected on the basis of the basicity values of their amino groups.

Our data can be compared with the results of the diazotization reactions of the same compounds with nitrous acid in acidic conditions (Table III) [9].

The rate constants of these reactions are much higher and are practically independent of the relative position of the amino group to the carboxylic one. A self-catalytic feature was also observed; however not the amine but the nitrite ion acts as a catalyst.

The most important difference (including the different medium) is the fact that in the reactions with the complex N-heterocyclic amino acids are formed in one step synthesis without change of configuration.

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