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The Kinetics and Mechanism of the Cyanohydrin Reaction
in Aqueous Solution

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THE KINETICS AND MECHANISM OF THE CYANOHYDRIN REACTION IN AQUEOUS SOLUTION

By

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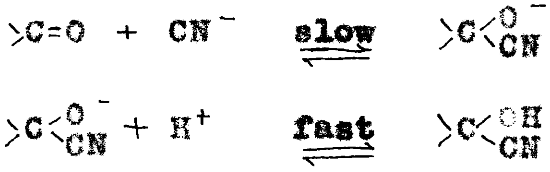
INTRODUCTION

The theory of carbonyl addition reactions has long been a subject of considerable interest. Numerous investigations and speculations have been undertaken to elucidate, if possible, a generalized mechanism for this type of reaction. However, on final analysis, it can be said that the answer has not yet been obtained.

The most generally accepted mechanism for the cyanohydrin reaction is based upon the qualitative studies of Lapworth[1]. The Lapworth mechanism is of particular interest because it has been widely regarded as exemplifying the manner in which most carbonyl addition reactions occur[2,3]. It is also of interest because it is considered as the first convincing evidence for the stepwise nature in which bimolecular reactions may occur[4].

Lapworth's studies were of such a qualitative nature that they did not permit either the evaluation of rate constants or of the order of the reaction. By modern standards his results can not be accepted as unequivocal evidence for the mechanism proposed. The mechanism involves a slow initial attack of cyanide ion on the carbonyl linkage, followed by a rapid attachment of a proton:



$$\begin{aligned} &>C=O + CN^- \overset{\text{slow}}{\rightleftharpoons} >C\begin{smallmatrix}O^-\\CN\end{smallmatrix} \\ &>C\begin{smallmatrix}O^-\\CN\end{smallmatrix} + H^+ \overset{\text{fast}}{\rightleftharpoons} >C\begin{smallmatrix}OH\\CN\end{smallmatrix} \end{aligned} \qquad (1)$$

It is noteworthy to observe that this mechanism does not involve catalysis in the sense that there is either a protolytic reaction between a catalyst and the substrate carbonyl molecule or the formation of an intermediate complex between these two entities. This feature of the mechanism is surprising when one considers other carbonyl reactions such as semicarbazone, oxime and phenylhydrazone formation, which are generally conceded to proceed through an addition compound analogous to a cyanohydrin. Quantitative studies on these latter reactions have demonstrated a pronounced generalized catalysis[5,6]. The phenomenon of generalized catalysis in carbonyl reactions is interpreted to imply a protolytic reaction directly between the substrate and the catalyst[7].

The cyanohydrin reaction is readily subject to basic catalysis. If the catalysis in this reaction was generalized catalysis, the Lapworth mechanism would be incompatible with the kinetics. None of the studies conducted by Lapworth or any of the subsequent investigators of the cyanohydrin reaction provide data which could be used to ~~clearly~~ examine clearly the possibility of generalized catalysis.

Therefore, it was deemed desirable to make a quantitative study of the cyanohydrin reaction in order to ~~further~~ elucidate further the mechanism, if possible, particularly with reference to the nature of the catalysis involved. Previous studies have shown that it is a simple, reversible reaction free from the complication of side reactions.

The kinetics of propionaldehyde, acetaldehyde and acetone cyanohydrin formation have been studied at one temperature under various conditions of ionic strength and buffer composition. This represents the first kinetics investigation of a cyanohydrin reaction in aqueous solution.

HISTORICAL

Although the literature is abundant with references on various aspects and applications of the cyanohydrin reaction, this brief survey will be limited primarily to the more pertinent studies which bear some relation to the mechanism of the reaction.

As early as 1886, Kiliani[8] had observed that substances of a basic nature, such as ammonia, had a remarkable accelerating influence on the formation of cyanohydrins.

In 1903, Lapworth[1] undertook the first systematic study of cyanohydrin formation. He investigated the reaction of camphorquinone with HCN in dilute aqueous and alcoholic solution. He found that in the absence of added catalytic agents the reaction went practically to completion in about 8-10 hours, while the addition of small amounts of base caused a comparable amount of reaction in a matter of seconds. The addition of small amounts of mineral acid arrested the rate to the extent that no perceptible reaction occurred within 14 days. Mainly on the basis of these results, Lapworth examined the following possible mechanisms and concluded that (D) was the only reasonable explanation:

$$\text{(A)} \quad >C{=}O + HCN \rightleftharpoons >C(OH)CN$$

$$\text{(B)} \quad >C{=}O + H^+ + CN^- \rightleftharpoons >C(OH)CN$$

$$\text{(C)} \quad >C{=}O + H^+ \overset{\text{slow}}{\rightleftharpoons} >\overset{+}{C}OH + CN^- \overset{\text{fast}}{\rightleftharpoons} >C(OH)CN \tag{2}$$

$$\text{(D)} \quad >C{=}O + CN^- \overset{\text{slow}}{\rightleftharpoons} >C(CN)\overset{-}{O} + H^+ \overset{\text{fast}}{\rightleftharpoons} >C(OH)CN$$

On consideration of the effects of acids and bases on the rate, all but (D) were ~~was~~ rejected by Lapworth.

In 1912 Bredig and Fiske[9] commenced an investigation of the reaction between benzaldehyde and HCN in chloroform and toluene solution, in the presence of the optically active catalysts quinine and quinidine. Their results indicated that a partial asymmetric synthesis had been achieved, as follows:

$$\begin{tikzcd} & C_6H_5CHOHCN\ \text{(levo)} \\ C_6H_5CHO \arrow[ur, "HCN"] \arrow[ur, "\text{Quinidine}"'] \arrow[dr, "HCN"] \arrow[dr, "\text{Quinine}"'] & \\ & C_6H_5CHOHCN\ \text{(dextro)} \end{tikzcd} \qquad (3)$$

The same effect was observed in the case of five other aromatic and aliphatic aldehydes[10]. Although these authors do not offer any substantial explanation relative to an exact interpretation of the mechanism involved, the implications are of importance. Most partial asymmetric syntheses which have resulted from the formation of an asymmetric carbon atom appear to depend on the presence of another optically active center either in the molecule itself or in another molecule actively involved in the reaction mechanism. Thus it is difficult to see how the Lapworth mechanism could be operative in these nonpolar solvents because it makes no allowance for the participation of the optically active base in influencing the configuration of the asymmetric carbon created in the reaction. According to the Lapworth mechanism, the base would serve only to increase and govern the cyanide ion concentration. Langenbeck[11] has commented briefly that the catalyst must have a function in the reaction beyond that of increasing the hydroxyl (actually the cyanide) ion concentration.

In 1914 Jones[12] conducted a quantitative investigation of the equilibrium constants of acetone and acetaldehyde cyanohydrin formation in dilute aqueous and alcoholic solution. He also performed some very approximate experiments on the influence of basic substances upon the rate of the reactions and concluded that his results were in accord with Lapworth's postulations.

The studies of Bredig and coworkers[9,10] on the asymmetric synthesis using optically active catalysts parallel~~s~~ markedly the asymmetric synthesis achieved by the use of the enzyme, emulsin, in which almost pure optically active antipode is produced[13]. This similarity stimulated considerable stereochemical investigations by biochemists in an attempt to relate the enzymatic and the non-enzymatic reactions. For the most part, these researches resulted in the formulation of possible intermediates in the non-enzymatic asymmetric synthesis without rendering any exact exposition of the mechanism. An excellent review of these studies is presented by Albers[13] and Möller[14].

In 1928 Albers[13] demonstrated that primary, secondary and tertiary amines are capable of catalyzing the benzaldehyde cyanohydrin reaction in nonpolar solvents. He also showed that, with the exception of aniline, no Schiff's bases are formed between benzaldehyde and the bases employed as catalysts. This would seem to indicate that the Schiff's base is not an intermediate in the cyanohydrin reaction.

In 1929 Möller[14] conducted the first really quantitative investigation of the kinetics of a cyanohydrin reaction. She studied the reaction of benzaldehyde and HCN in chloroform* solution in the presence of the alkaloid catalyst hydrocinchonine. The kinetics of the reaction followed a third order law, which was somewhat surprising. When the concentrations of the reactants and catalyst were varied, it was found that the rate constant was independent of the initial concentration of benzaldehyde but was directly proportional to the square of the ratio of initial base: HCN concentrations. The reader is referred to Möller's dissertation for more details. Taking into account the method of expression of concentrations which was employed in the rate equations, Möller concluded that the results could be interpreted by the following mechanism:

$$(BH)^+ + (CN)^- + RCHO \longrightarrow (B\ldots Cy) \longrightarrow Cy \qquad (4)$$

This mechanism involves the assumption that the base interacts completely with HCN and the product is entirely

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* Throughout this thesis, using the arbitrary division set up by Stewart[18], this solvent will be classified with nonpolar solvents.

dissociated into $(BH)^+$ and $(CN)^-$ ions. These ions in turn react simultaneously with the aldehyde to produce a loose molecular complex which then decomposes to give the product cyanohydrin. Möller attempted to validate the postulated mechanism as follows:

(a) A distinct temperature increase occurs almost instantaneously when chloroform solutions of HCN and quinine are mixed. This was taken to indicate an interaction of base and HCN.

(b) The conductivity of chloroform HCN solution, though small, is increased noticeably by the addition of hydrocinchonine. This was interpreted to indicate that ionic products were formed.

With respect to some of the intermediates or molecular species which might occur and influence the studies conducted, Möller considered the possibility of the formation of a compound or a complex between the aldehyde and the base catalyst. In order to prove that these substances do not form a compound, she measured the heat changes accompanying the union of the components in chloroform solution, and the freezing point depressions of corresponding benzene solutions. From the results of all the attempted experiments, it appeared as though no influence of the catalyst on the aldehyde was manifested. She concludes that a compound or complex of catalyst-aldehyde does not exist and therefore does not occur as an intermediate in the cyanohydrin synthesis. The reaction mechanism postulated by Möller to explain the kinetics is given by equation (4) above.

In 1932 Albers and Hamann[16] conducted the first quantitative study of the kinetics of a cyanohydrin reaction in a polar solvent. They were interested fundamentally in an explanation of the enzymatic asymmetric synthesis of cyanohydrins and were motivated by the fact that all the previous investigations along these lines had yielded no clear comprehension of the process involved. In order to obtain clues to the enzymatic reaction, they felt it was first necessary to establish the nature of the non-enzymatic mechanism. It is probable that these authors elected to study the non-enzymatic kinetics in a polar solvent because studies on the enzymatic reaction were always conducted in such a medium. In surveying the suggestions of other investigators as to the reaction mechanism, they make no reference to the work of Möller (perhaps because Möller's studies were in nonpolar solvents), and instead consider chiefly the postulations of Lapworth, which they sought to subject to quantitative verification.

Albers and Hamann studied the reaction of benzaldehyde and HCN in 50% alcoholic acetate buffers. They found that the reaction followed a second order rate law and that the rate constant was independent of the initial concentrations of benzaldehyde and HCN at a fixed pH, i.e. a fixed hydroxyl ion concentration. They also investigated the reaction in acetate buffers of three different pH's and found that the rate constant varied in direct proportion to the hydroxyl ion concentration. Taking into account the hydrolysis equilibrium of cyanide ion, the authors concluded that the kinetics was in exact agreement with the Lapworth mechanism. No attempt was made to investigate specifically ~~investigate~~ the possibility of generalized catalysis or to make allowance for the possible influence of ionic strength upon the reaction rate.

The rate of the enzymatic reaction was also studied in the same medium except for the presence of the enzyme. Contrary to previous assertions that the only effect of the enzyme was to influence the optical activity of the cyanohydrin, it was found that the enzyme accelerated the reaction significantly. It behaved like an ideal catalyst.

Stewart and coworkers[17,18], commencing in 1937, reported an investigation of the dissociation of acetone cyanohydrin in a wide variety of solvents including water, methanol, ethanol, propanol, butanol, 2-methylpropanol, 1,1-dimethylethanol, acetone, carbon tetrachloride, benzene, dioxane and chloroform. They found that the dissociation of acetone cyanohydrin into acetone and HCN is catalyzed by amines in all solvents. The catalyzed reaction is immeasureably fast in water and in the lower alcohols, while it is measureable in butanol and the nonpolar solvents and extremely slow in dioxane. Most of their studies were concentrated on the determination, in the various solvents, of the equilibrium constant for cyanohydrin dissociation as given by:

$$R_2C(OH)CN \overset{K_1}{\rightleftharpoons} R_2CO + HCN \qquad (5)$$

It was found that the K_1 value for the reaction in water in the presence of a catalyst varied considerably from the value in the absence of catalytic bases, which represented an apparent shift in the equilibrium. The variation observed depended both on the concentration and the species of the catalyst. The deviation was ascribed to the interaction of the base with HCN,

$$B + HCN \rightleftharpoons BH^{+} + CN^{-} \qquad (6)$$

To make allowance for this reaction, the overall equilibrium expression should be written as:

$$R_2C(OH)CN + R_3N \overset{K_2}{\rightleftharpoons} R_2CO + R_3NH^{+} + CN^{-} \qquad (7)$$

K_2 may then be related to K_1 by the dissociation constants of B and HCN in water and, in this manner, fairly consistent values for the equilibrium constant K_1 were obtained.

In all the alcohols and acetone, on the other hand, consistent values of K_1 could be obtained entirely by the use of equation (5), i.e. the degree of dissociation is unaffectby amine. This means that while in water there is evidence of interaction between amine and HCN, in the other polar solvents there is no experimentally detectable evidence of such interaction. In the nonpolar solvents the situation is apparently complex; the degree of dissociation is decreased by the addition of amine and the results do not lend themselves to any quantitative correlation. The authors conclude that the simple Lapworth dissociation mechanism may be true only in water solutions.

A study was also conducted on the relative rates of dissociation of acetone cyanohydrin in several solvents. The presentation given is largely qualitative. In discussing his results, Fontana[19] states, "the mechanism of the dissociation in both polar and nonpolar solvents is apparently quite complex as indicated by the fact that the kinetic data do not fit any simple rate law." It may be recalled at this point that, in the case of benzaldehyde cyanohydrin formation, Albers and Hamann[16] and Möller[15] reported kinetic data, in polar and nonpolar solvents respectively, which conformed to an integral rate law.

Baker and Hemming[20], in 1942, investigated the kinetics of the reaction of a series of p-alkylbenzaldehydes with HCN in constant boiling alcohol. The standard catalyst employed was a mixture of 0.01M pyridine and 0.01M pyridinium benzoate, which effectively constituted a buffer system. In their work they were not primarily interested in explicitly elucidating the mechanism of the cyanohydrin reaction. Rather they sought to obtain velocity constants for the various compounds in a standard medium in order to test the Baker-Nathan hypothesis as to the relative electron releasing abilities of different alkyl groups in compounds of the type studied.

The kinetic data, in every case, ~~was~~ were found to satisfy a second order law relative to a reversible bimolecular reaction. In order to test the validity of the concepts previously developed on the polar effects of alkyl groups, it was necessary to assume a representation for the activated transition complex. The representation used was in accord with the Lapworth formulation except for the assumption of resonating forms. Values were then assigned for the relative reductions in energy levels in the ground state of the aldehyde and in the activated state of the transition complex caused by the +I and +M effects. The differ$\overset{e}{a}$nces between the values of the two states for the various reactions were then compared with the rate constants and the two sequences were in exact agreement. Although not discussed by the authors, it may be pointed out that if their treatment is entirely valid, it could be inferred that the Lapworth mechanism is in accord with the results obtained. This, however, would not constitute a unique verification because other representations for the activated transition complex, which were not considered, might also yield the same theoretical sequence of reactivities.

In summary, it may be observed that the work of Möller[15] and of Albers and Hamann[16] constitute the only quantitative investigations of the kinetics of the cyanohydrin reaction. Their results, in nonpolar and polar solvents respectively, have been interpreted to indicate a different mechanism in each case, depending on the conditions of the study. The possibility of generalized catalysis and its implications has not heretofore been purposefully examined.

THEORY

Evaluation of the Rate Constants

If the rate of a reaction is proportional to the product of the first power of the concentrations of the two reacting substances, the reaction is of the second order. For the case in which there is no significant reverse reaction, the rate of formation of product is

$$\frac{dx}{dt} = kC_AC_B \tag{8}$$

If the two substances are present in unequal concentrations, equation (8) can be integrated to

$$kt = \frac{2.303}{a-b} \log \frac{a-x}{b-x} + C \tag{9}$$

where C is the constant of integration, k is the specific rate constant, a and b are the initial concentrations and (a-x) and (b-x) are the existing concentrations at any time t. A plot of log (a-x)/(b-x) vs. t should be a straight line, the slope of which is equal to k(a-b)/2.303. Thus the determination of the slope makes it possible to evaluate k.

For the case in which there is a significant reverse reaction of the first order, the expression for the rate constant may be derived as follows:

$$\begin{array}{ccccc} A & + & B & \underset{k_2}{\overset{k_1}{\rightleftharpoons}} & C \\ x & & x+c & & x_0-x \end{array}$$

x_o = initial concentration of reactant A

x = concentration of A at any time t

$x+c$ = concentration of B at any time, where c is a constant and is the differance between the concentrations of A and B at t = 0

The equilibrium constant $K = k_1/k_2$

x_o-x = concentration of product C at any time

The rate of disappearance of A will be

$$-\frac{dx}{dt} = k_1x(x+c) - k_2(x_o-x) \tag{10}$$

Substituting for k_2 and rearranging,

$$-k_1dt = \frac{dx}{x(x+c) - (x_o-x)/K} \tag{11}$$

If x_e is the equilibrium concentration of A, then

$$K = \frac{x_o - x_e}{x_e(x_e+c)} \tag{12}$$

Substituting the value of x_o from equation (12) and rearranging,

$$-k_1dt = \frac{dx}{x^2 + x(c+1/K) - x_e^2 - x_ec - x_e/K} \tag{13}$$

This may be integrated using the appropriate standard integral form to give

$$k_1t = \frac{2.303}{2x_e + c + 1/K} \log \frac{x + (c+x_e+1/K)}{x - x_e} + C' \tag{14}$$

where C' is the constant of integration. All terms are constants except x and t. A plot of log $x+(c+x_e+1/K)/\ (x - x_e)$ vs. t should be a straight line, the slope of which is equal to $k_1(2x_e+c+1/K)/\ 2.303$. Thus k_1 may be evaluated from the slope.

Generalized Acid-Base Catalysis

In its earliest days, the theory of acid-base catalysis in homogeneous solution was based largely on the premise that catalysis was due entirely to hydrogen or hydroxyl ions. Gradually, however, experimental evidence was accumulated which indicated that acid catalysis, for instance, could be effected by undissociated molecules of acid as well as by hydrogen ions. From 1923 onward, as result of the work of Bronsted, Lowry and Dawson, the theory of generalized catalysis evolved. According to this theory, it is possible for a reaction to be subject to the simultaneous catalytic influence of all the acids* present and/or all the bases* present in the solution. Thus if we have a reaction in which the mechanism involves in the rate determining step the reaction of a substrate with acids in general,

$$A + HA \longrightarrow \text{products}$$

$$k = \sum_i k_i(HA_i) \qquad (15)$$

---

* Acids and bases as defined by the Bronsted-Lowry proton theory of acids and bases.

where k is the overall rate constant, k_i the molar catalytic constant of the "i"th acid and $(HA)_i$ is the molar concentration of that acid. It is probable that reaction occurs simultaneously with the various species of acid which are in the solution. Equation (15) is of the form which would be expected for simultaneous side reactions.

To show that a reaction is subject to general acid catalysis, the method of Bronsted and Guggenheim[21] is generally employed. Consider the acid HA. Neglecting activity coefficients,

$$HA + H_2O \overset{k_a}{\rightleftharpoons} H_3O^+ + A^-$$

$$pk_a = pH + \log \frac{HA}{A^-} \qquad (16)$$

In this method the rate is determined in a series of buffers in which the oxonium ion concentration is constant, but the concentration of the acid component of the buffer is varied. This is accomplished by maintaining a fixed ratio of acid to base concentrations and a constant ionic strength in the series of buffer solutions. The ionic strength is maintained constant by the addition of neutral salts, which effectively suppresses salt effects.

If the rate varies in proportion with the concentration of HA, generalized acid catalysis is manifested; if the rate is constant in these circumstances, the reaction is subject to specific oxonium ion catalysis. The same considerations apply to basic catalysis. The literature is replete with experimental verification of reactions exhibiting generalized catalysis. Several reactions have been investigated which simultaneously exhibit both generalized acid and base catalysis and here the same fundamental considerations are involved. By suitable comprehensive investigation it is possible to evaluate the molar catalytic constants for different catalysts in a particular reaction[22].

Bronsted Catalytic Law

The mechanism of reactions which exhibit generalized catalysis is widely accepted as being characterized by a proton transfer between the substrate and the catalyst. Since dissociation equilibria of acids and bases in water also involve proton transfers, we would expect a correlation between the dissociation constants of a series of acids, for instance, and their molar catalytic constants in an acid catalyzed reaction. Such a relation has been proposed and verified by Bronsted and is known as the Bronsted catalytic law. The relation, which has an essentially empirical basis, is:

$$\begin{aligned} k_a &= G_a K_a^{\alpha} && \text{for acid catalysis} \\ k_b &= G_b K_b^{\beta} && \text{for basic catalysis} \end{aligned} \qquad (17)$$

where G_a or G_b and α or β are constants for a particular reaction in a given solvent and at a particular temperature. Subsequent modifications have been applied to this relation, but these will not be considered here. This type of relation has proved satisfactory for a number of reactions, considering that very often the catalysts studied represent an extremely wide range of dissociation constants. Several illustrations are cited by Bell[23].

Specific vs. Generalized Catalysis

The question of whether there is any fundamental differance between specific and generalized catalysis has not as yet been conclusively answered. Bronsted and Wynne-Jones[24] have made several interesting calculations, assuming the validity of the catalytic law, on the possibility of detecting generalized catalysis. Considering, for example, acid catalysis in 0.1N acetate buffer, several conclusions are possible from the following table.

	Proportion of catalysis due to		
Exponent	H_3O	H_2O	CH_3COOH
$\alpha = 0.1$	0.002%	98%	2%
$\alpha = 0.5$	3.6%	0.01%	96.4%
$\alpha = 1.0$	99.8%	5×10^{-12}	0.2%

It may be seen that if

(a) $\alpha = 0.1$, the reaction will appear to be uncatalyzed.

(b) $\alpha = 0.5$, the reaction will exhibit catalysis largely by undissociated acid molecules.

(c) $\alpha = 1.0$, the reaction will be a case of specific oxonium catalysis.

It is apparent that intermediate values of α, which can vary from 0 to 1, are most favorable for the experimental detection of generalized catalysis. Thus it may be that the real differance between generalized and specific catalysis is only a quantitative one and both are manifestations of the same phenomenon. Similar considerations may be extended to the case of basic catalysis.

Another point of interest is the possible influence of the substrate itself on the type of catalysis exhibited. The work of Bell and Lidwell[25] offers perhaps the best indication of the relative importance of this factor. They investigated the catalytic constants of a number of base catalysts for a particular substrate and evaluated α for the series of catalysts relative to that substrate. They studied each member of a series of closely related ketones in the same way, using the base catalyzed halogenation reaction in each case. It was found that α varied from 0.89 to 0.48 in the series of eight ketones investigated, and decreased in value as the reactivity of the ketone increased. Since the value of α may be regarded as an index of the extent of generalized catalysis, this result may be interpreted as implying that the amount of generalized catalysis for a particular reaction may vary markedly with the reactivity of the compound studied. Unfortunately, similar studies of other series of compounds have not been conducted and it is doubtful whether one may be justified in concluding that it is a general principle that the proportion of generalized catalysis is increased with the increasing reactivity of the substrate. Some such principal could be of value as a guide in the investigation of catalytic mechanisms. By an extrapolation of the results above, a series of substrates might exist for some reaction which would exhibit a complete transition from specific to generalized catalysis. This would, of course, be of value in correlating the two types of catalysis.

Formulation of Cyanohydrin Kinetics

According to the Bronsted theory of reactions in solution, the reacting particles form an intermediate complex which is in equilibrium with the reactants and which can decompose to give the reaction products.

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X \overset{k_2}{\rightleftharpoons} C \qquad (18)$$

Considering activity coefficients,

$$K_1 = \frac{k_1}{k_{-1}} = \frac{C_X}{C_A C_B} \cdot \frac{f_X}{f_A f_B} \qquad (19)$$

The rate of the reaction is considered proportional to the concentration of the intermediate complex,

$$\frac{dx}{dt} = k_2\, C_X = K_1\, k_2\, C_A C_B \frac{f_A f_B}{f_X} \qquad (20)$$

Defining $K_1\, k_2$ as k_o,

$$\frac{dx}{dt} = k_o\, C_A C_B \frac{f_A f_B}{f_X} \qquad (21)$$

Comparing this with the classical equation (8),

$$k = k_o \frac{f_A \, f_B}{f_X} \tag{22}$$

According to the Debye-Huckel theory,

$$- \ln f_i = Az_i^2\sqrt{u} + B\,u \tag{23}$$

for the range of ionic strength of about 0.01 to 0.1. B is an empirical constant depending essentially on the nature of the ion i.

Combining equations (22) and (23),

$$\ln k = \ln k_o + 2AZ_A Z_B\sqrt{u} + (B_X - B_A - B_B)\,u \tag{24}$$

This equation expresses the dependence of the rate constant on ionic strength in a fixed medium and at a particular temperature. The addition of neutral salts to change the ionic strength, and thereby the activity coefficients, is seen to influence the value of the rate constant. This is known as the primary salt effect. In the case of the reaction of a neutral molecule with an ion, the $2AZ_A Z_B\sqrt{u}$ term is zero (since Z signifies the charge of the particle) and the magnitude of the primary salt effect will depend largely on the relative values of B for the various species. For the majority of reactions of this type the primary salt effect rarely exceeds a few percent in the dilute range (0.01 to 0.1 ionic strength).

Now let us consider the formulation of the kinetic rate law of the cyanohydrin reaction according to the Lapworth mechanism (1) and according to the Bronsted theory. Since the rate determining step in the Lapworth mechanism involved a neutral molecule and an ion, the primary salt effect should be small and it will, for the present purposes be ignored. The rate equation should then be,

$$\frac{dx}{dt} = k_o \, C_{AC} \, C_{CN^-} \tag{25}$$

in which AC designates the carbonyl compound, and in which we will assume no significant reverse reaction. We shall consider the case in which the reaction is run in acetate buffers and define the following equilibrium constants,

$$K_2 = \frac{C_{H^+} C_{CN^-}}{C_{HCN}} \cdot \frac{f_{H^+} \, f_{CN^-}}{f_{HCN}} \tag{26}$$

$$K_3 = \frac{C_{H^+} \, C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{H^+} \, f_{OAc^-}}{f_{HOAc}} \tag{27}$$

Combining (25), (26), and (27),

$$C_{CN^-} = \frac{K_2}{K_3} \, C_{HCN} \, \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{HCN} \, f_{OAc^-}}{f_{HOAc} \, f_{CN^-}} \tag{28}$$

$$\frac{dx}{dt} = k_o \frac{K_2}{K_3} C_{AO} C_{HCN} \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{HCN} f_{OAc^-}}{f_{HOAc} f_{CN^-}} \qquad (29)$$

In order to simplify this equation, it is best to consider the experimental conditions. If experiments are run at a constant ionic strength and in a buffer where the ratio of C_{OAc^-}/ C_{HOAc} is constant, then equation (29) becomes

$$\frac{dx}{dt} = k' \; C_{AO} \; C_{HCN} \qquad (30)$$

where $\quad k' = k_o \frac{K_2}{K_3} \cdot \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{HCN} \; f_{OAc^-}}{f_{HOAc} \; f_{CN^-}}$

The experimentally determined rate constant relative to the concentrations of the species AO and HCN will be k' and k' may be experimentally evaluated by the use of equation (9). At the same constant ionic strength, the value of k' should be strictly proportional to the ratio C_{OAc^-}/ C_{HOAc}. These predictions should not be influenced by any salt effects since the condition of constant ionic strength is imposed.

Now let us consider equations (28) and (29) to examine possible secondary salt effects* if the ionic strength was varied. The activity coefficients of nonionic HCN and HOAc

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* The secondary salt effect is a change in the concentration of a reacting species, i.e. cyanide ion, which would be caused by changes in ionic strength.

may be set equal to 1 in dilute solution, and moreover, it may reasonably be assumed that the ratio f_{OAc^-} / f_{CN^-} will be practically constant in dilute solution. Thus the influence of the secondary salt effect should be negligible.

Now let us postulate a hypothetical mechanism for the cyanohydrin reaction which involves the hydroxyl ion catalyzed addition of molecular HCN to the carbonyl compound,

$$AO + HCN + OH^- \longrightarrow X \longrightarrow \text{products} \tag{31}$$

The rate equation for this mechanism, again neglecting the primary salt effect (which makes the Bronsted formulation equivalent to the classical) would be

$$\frac{dx}{dt} = k_o \, C_{AO} \, C_{HCN} \, C_{OH^-} \tag{32}$$

The dissociation constant of water may be written

$$K_W = \frac{C_{H^+} \, C_{OH^-}}{C_{H_2O}} \cdot \frac{f_{H^+} \, f_{OH^-}}{f_{H_2O}} \tag{33}$$

Combining equations (27), (32) and (33),

$$C_{OH^-} = \frac{K_W}{K_3 \, C_{H_2O}} \cdot \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{OAc^-}}{f_{OH^-}} \tag{34}$$

$$\frac{dx}{dt} = k_o \frac{K_W}{K_3 \, C_{H_2O}} \cdot C_{HCN} C_{AO} \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{OAc^-}}{f_{OH^-}} \qquad (35)$$

Considering the same corresponding conditions as were applied to the derivation of the rate equation for the Lapworth mechanism, equation (35) may be simplified to

$$\frac{dx}{dt} = k'' \, C_{HCN} \, C_{AO} \qquad (36)$$

where
$$k'' = k_o \frac{K_W}{K_3 \, C_{H2O}} \cdot \frac{C_{OAc^-}}{C_{HOAc}} \cdot \frac{f_{OAc^-}}{f_{OH^-}}$$

It is immediately apparent that equation (36) is identical in form to equation (30). The same effects of ionic strength and buffer composition upon the experimentally observed rate constants are predicted. Thus both the Lapworth and the postulated catalytic mechanism lead to the same rate law, making them kinetically indistinquishable. Although the reverse reaction of the rate determining step has been ignored in the above derivations, it may easily be shown that both mechanisms also give rise to the same rate equation when the reverse reactions are considered.

EXPERIMENTAL

Reagents

Baker's C.P. KSCN was purified according to the recommendations of Kolthoff and Lingane[26]. The salt was recrystallized from water, collected on a Buchner funnel and dried by suction. It was then placed in a desiccator and dried over P_2O_5 for several hours at room temperature. The salt was subsequently dried in an oven at 120°C for several hours and then finally fused in a furnace at about 190°C. After such treatment, the KSCN is suitable for use as a primary standard in argentimetric determinations.

Baker's C.P. $AgNO_3$ was dried in an oven at 120°C and then fused in a furnace at about 230°C. Pure NaCl was prepared by filtering a saturated solution of General Chemical Co. C.P. NaCl and treating the filtrate with C.P. concentrated HCl. The NaCl was collected, dried in an oven at 120°C, and then in furnace at 550°C for one hour.

0.1000N solutions of $AgNO_3$, KSCN and NaCl were prepared. The normality of the $AgNO_3$ was ascertained by a Mohr titration and by a Volhard titration. The results of the two methods were in excellent agreement, confirming the suitability of the KSCN as a primary standard. Thereafter, solutions of KSCN were prepared from the solid reagent treated as stated above, while solutions of $AgNO_3$ were prepared from reagent which had only been dried in an oven at 120°C. The $AgNO_3$ solutions were standardized against the KSCN. All solutions were kept in brown bottles and stored in the dark.

The $AgNO_3$ was checked from time to time and it was found that its normality did not change perceptibly over a period of several months.

Liquid HCN was made according to the method described in Organic Syntheses[27]. A solution approximately 0.2N in HCN was immediately prepared from the liquid HCN, and placed in a brown bottle and stored in the dark. The absence of substances capable of forming silver precipitates (other than cyanide) in the HCN solution was shown by the fact that when the cyanide is quantitatively removed from the solution, the addition of acidified $AgNO_3$ results in no precipitation.

The acetate buffers were prepared from solutions of HOAc and carbonate-free NaOH. The NaOH solution was standardized against a National Bureau of Standards standard sample of potassium acid phthalate, and the HOAc solution titrated against the NaOH solution. Then quantities of the acid and base were mixed to yield the desired buffer composition. The HOAc content of the buffer was determined by titration with the standardized NaOH. The normality thus obtained was in excellent agreement with the value calculated from the amounts of acid and base mixed, indicating little volume change had occurred on mixing. Several months later the buffer was again analyzed in the same way and the change in HOAc content amounted to less than 1%.

Eimer and Amend C.P. KNO_3 was used as inert electrolyte. The salt was dried in an oven at 120°C and weighed out in an atmosphere of less than 91% relative humidity, under which condition it is not appreciably hygroscopic.

Technical grades of the carbonyl compounds were purified as follows:

(a) Matheson Co. propionaldehyde was dried over $CaCl_2$ and then distilled in an atmosphere of nitrogen using a fractionating column 90 cm. long with about 10 theoretical plates. A constant boiling middle fraction was retained which boiled at 47.4°C (uncorr.) and had a refractive index, n_D^{20}, of 1.3632.

(b) U. S. Industrial acetone was refluxed over dry $KMnO_4$ for about ten hours, and then allowed to stand over the $KMnO_4$ for a day. The mixture was then filtered and the filtrate shaken with anhydrous K_2CO_3 and distilled through the fractionating column. A middle, constant boiling fraction was collected, boiling at 55.8°C (uncorr.) and with a refractive index, n_D^{20}, of 1.3587.

(c) Eastman Kodak acetaldehyde was dried over $CaCl_2$ and then fractionated in a small column in an atmosphere of nitrogen. The condenser was cooled with a glycol-water solution which was maintained at 0°C by a refrigeration unit. The receiver consisted of a 10 ml burette which was fitted with a ground glass joint and a jacket connected in series to the condenser. A middle fraction of distillate was reserved.

Boiled distilled water was used in the preparation of all solutions.

Apparatus

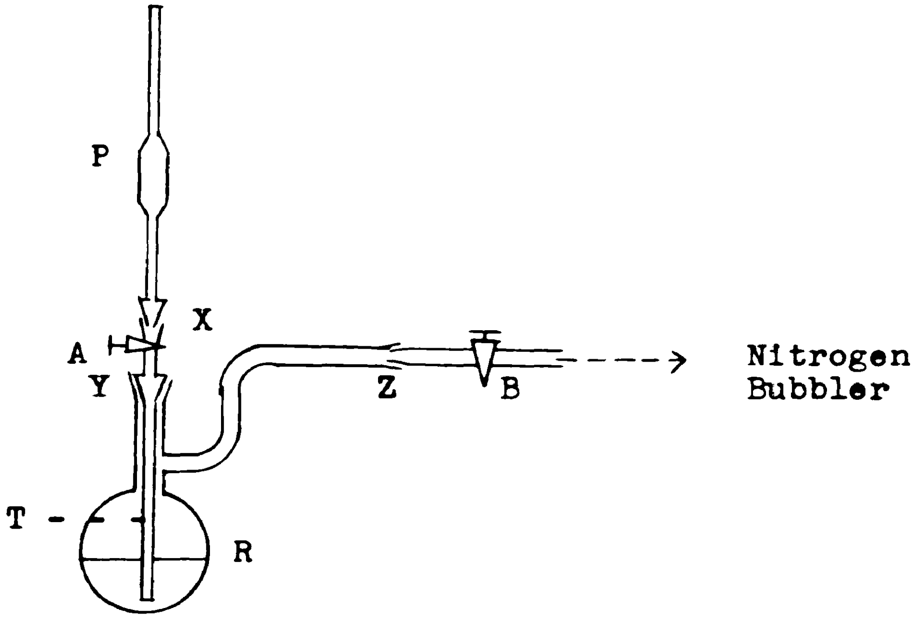
All titrations were conducted at 25°C in water-jacketed burets. Water from the thermostat bath was circulated through the jacket by means of a water pump. All volumetric apparatus was carefully calibrated using distilled water at 25°C.

The rate measurements were carried out in a glass apparatus similar to that used by Baker and Hemming[20]. A slight modification was employed, in that the gas bottle and manometer were eliminated and a gas bubbler filled with H_2SO_4 was inserted between the nitrogen source and the three-way stopcock. The apparatus used is illustrated in Figure 1. The nitrogen pressure was closely regulated by a pinchclamp on the rubber hose connecting the nitrogen tank with the gas bubbler. This apparatus permits the reaction to be run and the samples to be removed in an atmosphere of nitrogen with practically no exposure to air. Thus losses of HCN and the volatile carbonyl compounds as well as oxidation of the aldehydes are minimized. The sampling pipet delivered approximately 9 ml samples of reaction mixture. Due to the ground glass tip on this pipet, delivery procedure must be very carefully standardized to insure reproducibility of 0.01 ml.

The thermostat bath contained a stirrer, cooling coil, mercury thermoregulator and a mercury relay. The temperature was maintained at 24.97 ± 0.02°C. The thermometer in the bath could be read to the nearest hundreth of a degree and was standardized against a thermometer calibrated by the National Bureau of Standards.

FIGURE 1

REACTION VESSEL



P - Reaction pipet

A - Twoway stopcock

B - Threeway stopcock

T - Taphead

R - Reaction flask

X,Y,Z - Ground glass joints

All watches used in rate experiments were checked with the National Bureau of Standards time signal and it was ascertained that their error was wholly insignificant (of the order of 5 seconds a day).

Procedure

Prior to the initiation of a run, a solution of the carbonyl compound was prepared. Whenever initial concentrations of carbonyl were desired (sometimes for propionaldehyde and always for acetone), the freshly distilled compound was immediately transferred to a weight pipet and a definite amount was weighed into a volumetric flask which contained some of the solvent medium, either water or buffer solution. The flask was then filled to the mark with solvent at the proper temperature, 25°C. Whenever initial concentrations of carbonyl were not required (most of the propionaldehyde runs and all of the acetaldehyde runs), approximate amounts of the compound were delivered into a volumetric flask and the contents were, in this case also, filled to the mark. Propionaldehyde and acetone were delivered by means of the weight pipet, whereas acetaldehyde was delivered directly from the distillation receiver (due to its extreme volatility). With the aldehydes, precaution was exercised to maintain an atmosphere of nitrogen as much as possible.

For the experiments which required the addition of neutral salt to adjust the ionic strength to a desired value, the appropriate amount of KNO_3 was weighed out and transferred to the volumetric flask prior to the introduction of solvent.

The reaction vessel was placed in the thermostat bath and flushed out with a continuous stream of nitrogen. 50 ml of the stock HCN solution was pipetted into the reaction flask and then the flask was stoppered. Whenever it was necessary to determine initial HCN concentrations (for some of the propionaldehyde and all of the acetone runs), several samples of the stock HCN solution were analyzed immediately before the introduction of the 50 ml into the reaction flask. When the HCN and carbonyl solutions had come to temperature in the thermostat bath, 50 ml of the carbonyl solution was pipetted into the reaction flask. The time of half delivery was recorded as the starting point of the reaction. Then the taphead with its pipet was inserted. The reaction flask, which was mounted in a swivel clamp, was shaken immediately and vigorously to insure mixing. Samples of the reaction mixture were then removed at selected time intervals. The samples were forced into the reaction pipet by means of a current of nitrogen. After the removal of a sample, the pressure in the flask was released momentarily through the three-way stopcock and then the liquid remaining in the stem of the taphead receded into the bottom of the flask.

The analysis of samples was based on the findings of Ultee[28] who demonstrated that cyanohydrins are stable and do not give any silver cyanide precipitate in acidified $AgNO_3$. Unreacted cyanide, on the other hand, does form a precipitate and this permits one to follow the course of the reaction by the changes in concentration of cyanide in the reaction mixture. Samples were delivered into 25 ml of 0.1N $AgNO_3$ (an excess) which had been previously acidified with 6 ml of 6N HNO_3. The precipitate was filtered through Whatman No. 40 filter paper and thoroughly washed with several portions of water. The excess $AgNO_3$ was determined by titration with 0.1N KSCN. 2 ml of a saturated ferric alum solution was used as the indicator. The same general procedure was used in the analysis of pure HCN solutions.

The reaction was stopped by the addition of samples to the acidified $AgNO_3$, since strong acid completely inhibits the further formation of cyanohydrin. The reaction pipet had a delivery time of about 7 seconds and the time of half delivery was recorded as the time corresponding to the cyanide concentration of a particular sample. Samples were removed over an interval which generally represented 50-70% of the reaction. The reaction was then allowed to come to equilibrium and two or more samples were removed to determine the equilibrium concentration of cyanide. The time allowed for the reaction to come to equilibrium varied with the carbonyl compound and with the conditions of the experiment. When the concentration of HCN of several samples at succeeding time intervals reached a steady value, equilibrium was assumed. The time allowed was always considerably greater than the value which was calculated by the use of equations (9) and (14) for the time necessary for the HCN concentration to reach 99.9% of its equilibrium value. ~~This~~ This calculation could be made, at least to the nearest hour or so, once approximate values of the rate constant were either determined or could be estimated from other data.

In validating the foregoing procedure, it was found necessary to observe several particular precautions. Stewart and Fontana[18] report washing their silver cyanide precipitates with 0.25N HNO_3. It was found, however, on analyzing the HCN stock solution, that the results were more consistent when the precipitates were washed with water than with 0.25N HNO_3. With the acid wash, the filtrate became noticeably turbid, indicating that the acid had dissolved some of the precipitates. Therefore water washes were used in all subsequent filtrations. When cyanide solution is added to acidified $AgNO_3$, the solution should be stirred vigorously to prevent any local depletion of silver in the solution. Such depletion may delay the immediate precipitation of the cyanide and thereby afford an opportunity for small losses of the volatile HCN. This is most important when dealing with the more concentrated HCN-containing solutions, i.e. the stock solution.

In removing successive samples of HCN with the same pipet, it is necessary to clean and dry the pipet for each sample. Otherwise, apparently the small amount of solution remaining in the pipet loses HCN to the atmosphere and effectively dilutes the next sample withdrawn.

Owing to the volatility of HCN, experiments were performed to determine whether any losses of HCN from the reaction vessel would occur in the sampling process during the course of a run. HCN solution of approximately the same concentration as would be employed in the rate measurements was placed in the reaction flask. Then 5 or 6 samples were removed and analyzed in the manner already described. No drift in the values of HCN concentration was observed and the titration values were reproducible to ±0.03 ml. It was concluded that HCN losses are insignificant.

The rate of the reaction is extremely sensitive to changes in pH. In the early investigations with propionaldehyde, it became apparent that even small amounts of oxidation would alter the pH sufficiently to affect the rate. Consequently, in order to obtain concordant results, it is necessary that aldehydes be freshly distilled for each run.

Most of the rate measurements were conducted in buffer solutions. It was necessary to ascertain whether the addition of HCN would have any influence on the pH of the buffer. The pH of a buffer consisting of 0.0341N HOAc and 0.0342N NaOAc was measured at 25°C with a Coleman pH electrometer and found to be 4.62. This value is in agreement with the value obtainable from the interpolation tables of Cohn, Heyroth and Menkin[29]. The pH of a solution of 0.0341N HOAc, 0.0342N NaOAc, and 0.1N HCN was found to be identically 4.62. Thus the addition of HCN caused no perceptible change in the pH of the buffer.

CALCULATIONS AND DATA

The method of calculation of rate constants varied somewhat with the circumstances of the experiment.

All of the reactions studied occurred in a pH range of about 4.0 to 5.0. From the dissociation constant of HCN[30], 4.0×10^{-10}, it can be calculated that in a solution of this pH range over 99.9% of the cyanide exists as undissociated HCN. Thus the analytically determined cyanide is taken to represent the species, HCN.

It was found that the reaction of propionaldehyde and acetaldehyde goes virtually to completion. This fact was demonstrated by several experiments conducted for each of the aldehydes. When aldehyde concentration was initially in excess of HCN, it was invariably observed that, at equilibrium, the addition of a sample of reaction mixture to acidified $AgNO_3$ produced no precipitate whatsoever. Moreover, when the $AgNO_3$ was filtered and titrated with KSCN, the titration value corresponded exactly to all of the $AgNO_3$ used. This implies a vanishingly small HCN concentration and, for all practical purposes, the reaction may be regarded as proceeding to completion.

In several experiments where the initial HCN and propionaldehyde concentrations and the final HCN concentration were determined, it was found that the amount of HCN which disappeared corresponded, within experimental error, to the amount of propionaldehyde initially present. Thus it was assumed that the HCN and propionaldehyde had reacted mole for mole. The calculation of the rate constants is based on the changes in concentrations of the species, HCN and carbonyl compound. Changes in HCN concentration are determined analytically and changes in carbonyl concentration are assumed to occur on the mole for mole basis.

As to the order of the reaction, calculations were made for a first, second and third order reaction. Only the second order equation yielded consistent results. All subsequent calculations of rate constants were in accord with a reaction of the second order, first order relative to HCN and first order relative to the carbonyl compound.

In view of the foregoing, the rate constants for the propionaldehyde and acetaldehyde reactions were calculated using equation (9). Experiments 1,2,3, and 7 were calculated on the basis of initial HCN concentration, a, and initial propionaldehyde concentration, b. All of the other experiments with aldehyde were calculated on the basis of the equilibrium concentration of HCN. The HCN was initially in excess of aldehyde and therefore the equilibrium concentration of HCN represented a-b. Usually no initial concentrations of HCN or aldehyde were determined. Having a-x and a-b, one may calculate the concentration of aldehyde at any time, b-x. This latter scheme seemed preferable because all analyses would involve~~s~~ removal of samples from the reaction flask in identically the same manner, whereas the method of determination of initial concentrations would not. It also yielded somewhat more accurate results because of the difficulties encountered in the accurate analysis of the more concentrated HCN stock solution.

All buffer compositions given in the thesis are the concentrations existing in the reaction medium. The ionic strength is taken to be equal to the salt concentration of the buffer except where neutral salt has been added.

The rate constant was evaluated by a plot of log a-x/b-x vs. t. Time was always expressed in minutes. The actual plots were made on large sheets of graph paper. An illustration of the calculations involved using equation (9) is contained in Table 1 and Figure 2.

Table 1

Propionaldehyde
Experiment #14
Buffer composition: 0.1010N HOAc and 0.0509N NaOAc
u = 0.0509
Volume of 0.0999N $AgNO_3$ to stop reaction = 24.98 ml
Volume of sampling pipet = 8.78 ml
Equil. concentration of HCN (a-b) = 0.0424N

Sample	1	2	3	4	5
ml 0.1000N KSCN	16.29	17.04	17.71	18.80	19.27
Buret correction	-	-.01	-.02	-.02	-.02
ml KSCN (corrected)	16.29	17.03	17.69	18.78	19.25
m.equiv. $AgNO_3$ pptd.	*.869	.795	.729	.620	.573
HCN normality, a-x	**.0990	.0906	.0830	.0706	.0653
Aldehyde norm.,b-x	***.0566	.0482	.0406	.0282	.0229
Log a-x/b-x	.243	.274	.311	.399	.455
t, minutes	2.78	5.33	8.17	15.23	19.80

* 24.98x0.0999 - 16.29x0.1000 = .869 m.eq. $AgNO_3$ (or HCN) precipitated

** .869m.eq./8.78ml = 0.0990N HCN

*** 0.0990 - 0.0424 = 0.0566N aldehyde

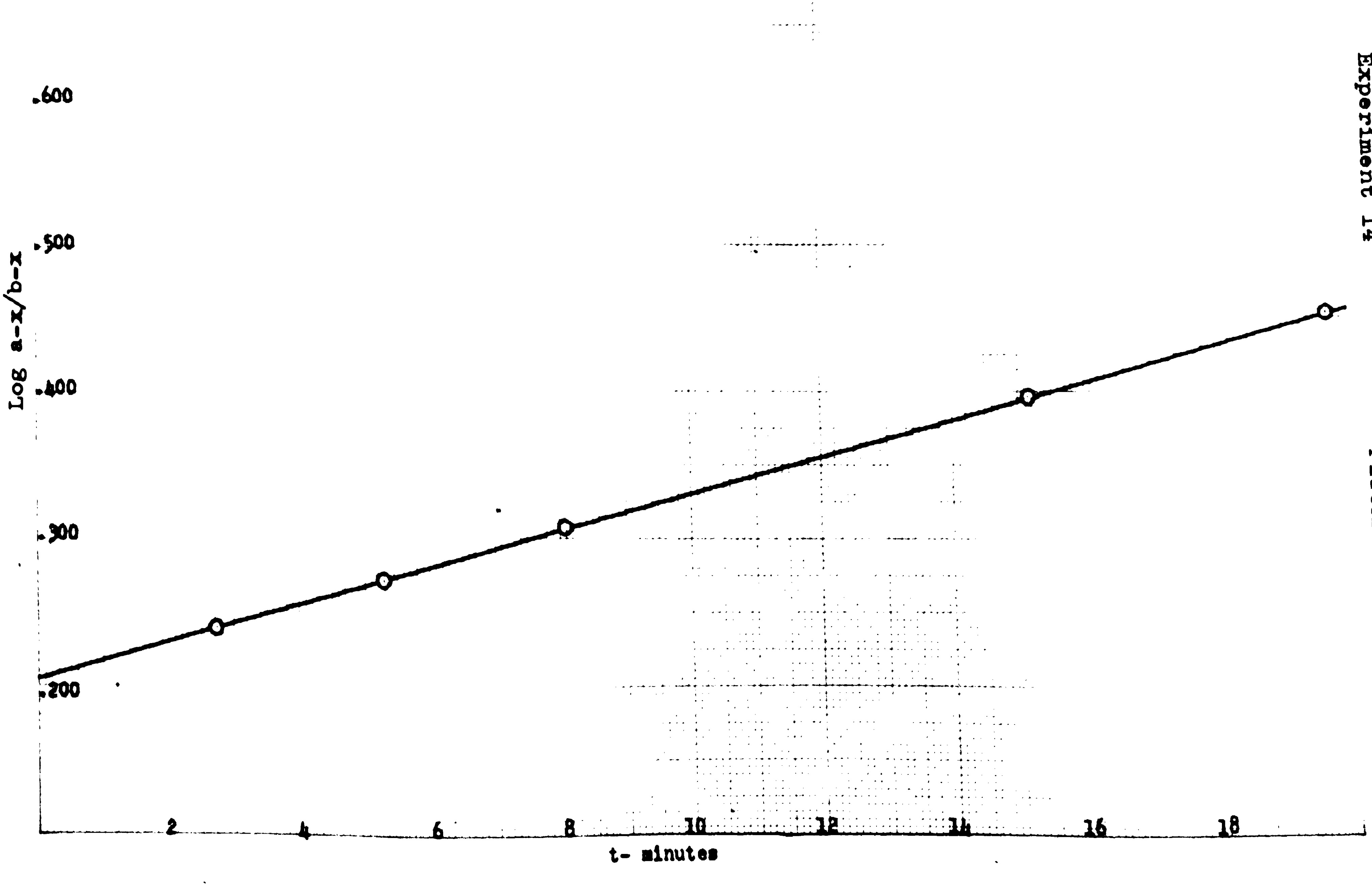
Slope of log a-x/b-x vs. t = 0.01244 min^{-1} (see Figure 2)

$$k = \frac{2.303 \times 0.01244}{0.0424}$$

k = 0.676 min^{-1} $(mol/liter)^{-1}$

FIGURE 2

Experiment 14



The reaction of acetone with HCN does not go to completion and it was necessary to take into account the back reaction. Equation (14) was therefore used to evaluate the rate constants. It was necessary in this case to determine the initial concentrations of the reactants. In the calculation of each run, except Experiment #37, the value of the equilibrium constant determined by that particular experiment was used. With Experiment #37, it was apparent that the value of the equilibrium concentration of HCN was greatly in error and the average of three other values of the equilibrium constant was used.

An illustration of the calculations involved using equation (14) is given in Table 2 and Figure 3. The calculation of the HCN concentrations, x, are similar to those given in Table 1 for a-x and will be omitted. By the graphical method indicated, the rate constant of the forward reaction, k_1, is evaluated. The point represented by initial concentrations at zero time was not included in any of the plots, due to the lack of adequate mixing at that time.

In Tables 3 through 20 are given the time-concentration data for all kinetics experiments and the calculated values of the rate constants. Data are given for the reaction of propionaldehyde,acetaldehyde and acetone under various conditions . The units of k are minutes^{-1} (moles/liter)$^{-1}$.

Table 2

Acetone
Experiment #35
Buffer composition: 0.0441N HOAc, 0.0496N NaOAc
u = 0.0496
Volume of 0.1000N $AgNO_3$ to stop reaction: 25.01 ml
Volume of sampling pipet: 9.21 ml

Initial HCN concentration, x_o = 0.0758N
Equil. conc. of HCN after five days, x_e = 0.0366N
Grams of acetone in 500 ml: 6.758
Initial acetone concentration = 0.1164N
Equil. conc. of acetone = 0.0772N
Equilibrium constant, K = 13.87 $(\text{mole/liter})^{-1}$
1/K = 0.0721 mol/liter
c = 0.0406N
$c+x_e+1/K$ = Q = 0.1493 mol/liter
$2x_e+c+1/K$ = 0.1859 mol/liter

Sample	x	$x+Q/x-x_e$	log $x+Q/x-x_e$	t
1	0.0748	0.2241/0.0382	0.768	4.37
2	0.0710	0.2203/0.0344	0.806	73.23
3	0.0655	0.2148/0.0289	0.871	172.52
4	0.0610	0.2103/0.0244	0.935	265.38
5	0.0584	0.2077/0.0218	0.979	346.70
6	0.0557	0.2050/0.0191	1.031	434.37

Slope of log $x+Q/x-x_e$ vs. t = 0.000628 min^{-1} (see Figure 3)

k = 0.00778 minutes^{-1} $(\text{mol/liter})^{-1}$

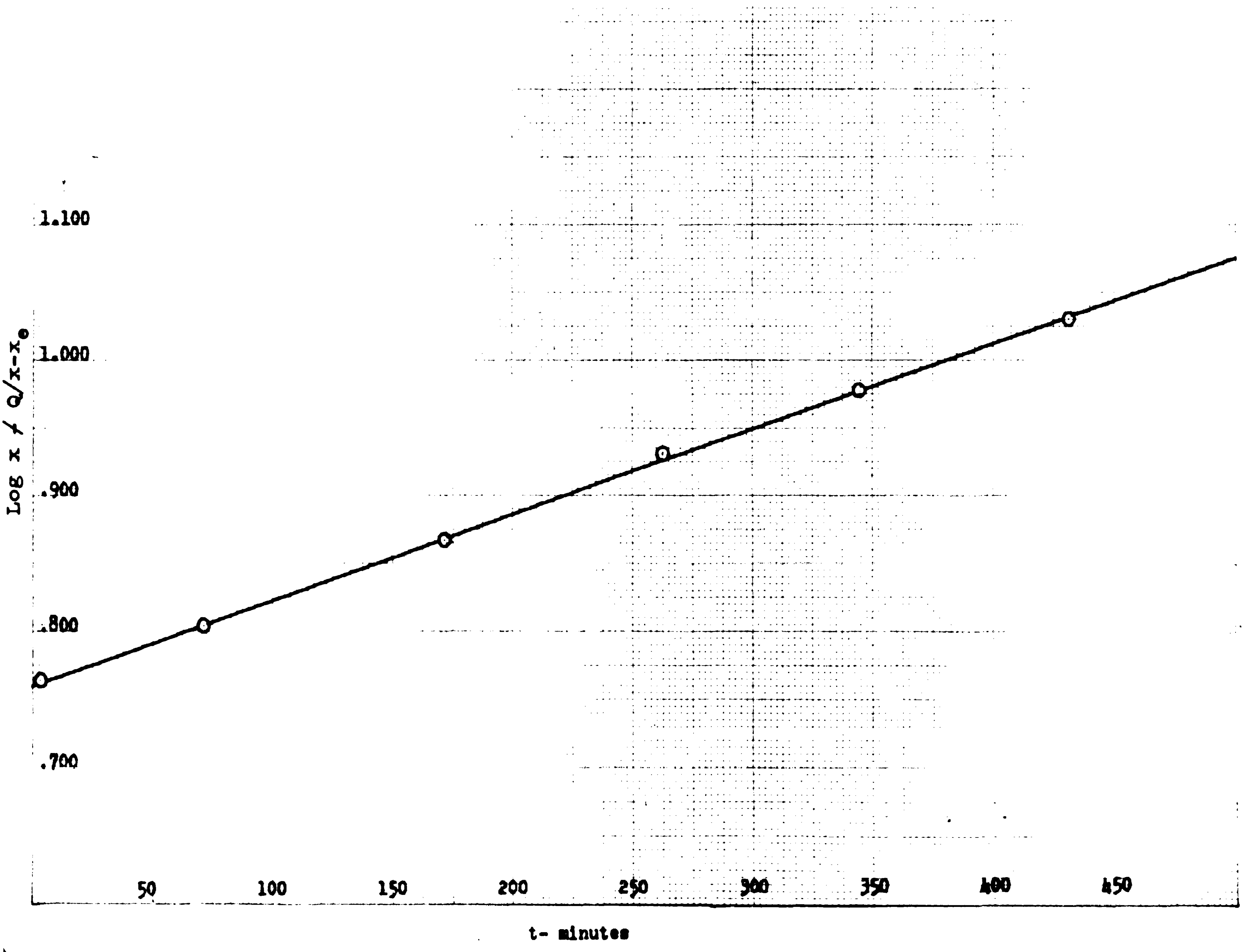


FIGURE 3

Experiment 35

Table 3*

Experiment #1 Solvent: water

Initial HCN = 0.1082N
Initial propionaldehyde= 0.0663N
Equilibrium conc. of HCN= 0.0412N

Sample	a-x (mol/l)	b-x (mol/l)	log a-x/b-x	t (min.)
1	0.0864	0.0445	0.288	7.28
2	0.0758	0.0339	0.350	13.63
3	0.0686	0.0267	0.410	19.73
4	0.0636	0.0217	0.467	26.28
5	0.0593	0.0174	0.533	33.17
6	0.0547	0.0128	0.631	40.70

Slope = 0.00988 min.$^{-1}$
k = 0.542 min.$^{-1}$ (mol/liter)$^{-1}$

Experiment #2 Solvent: water

Initial HCN = 0.1069
Initial propionaldehyde = 0.0692
Equilibrium conc. of HCN = 0.0376

1	0.0896	0.0519	0.238	5.50
2	0.0788	0.0411	0.284	11.22
3	0.0683	0.0306	0.350	20.50
4	0.0617	0.0240	0.411	27.63
5	0.0574	0.0197	0.465	34.58
6	0.0540	0.0163	0.521	43.38

Slope = 0.00800
k = 0.487

Experiment #3 Solvent:water

Initial HCN = 0.1057
Initial propionaldehyde = 0.0693
Equilibrium conc. of HCN = 0.0364

1	0.0920	0.0556	0.220	6.00
2	0.0802	0.0438	0.263	11.00
3	0.0738	0.0374	0.296	17.00
4	0.0693	0.0329	0.325	22.95
5	0.0628	0.0264	0.378	30.05
6	0.0588	0.0224	0.420	37.15

Slope = 0.00640
k = 0.404

* Units are the same throughout Tables 3 to 20 as shown in Experiment #1.

Table 4

Propionaldehyde
Buffer composition: 0.0341N HOAc, 0.0342N NaOAc
u = 0.0342

Experiment #4

Equilibrium concentration of HCN = 0.0306

Sample	a-x	b-x	log a-x/b-x	t
1	0.0680	0.0374	0.260	5.22
2	0.0555	0.0249	0.348	10.67
3	0.0467	0.0161	0.462	18.18
4	0.0417	0.0111	0.575	24.15

Slope = 0.01616
k = 1.22

Experiment #5

Equilibrium concentration of HCN = 0.0392

1	0.0732	0.0340	0.333	3.65
2	0.0659	0.0267	0.392	6.93
3	0.0582	0.0190	0.486	11.13
4	0.0540	0.0148	0.562	14.57
5	0.0507	0.0115	0.644	18.50

Slope = 0.02095
k = 1.23

Table 4 (continued)

Experiment #6

Equilibrium concentration of HCN = 0.0277

Sample	a-x	b-x	log a-x/b-x	t
1	0.0704	0.0427	0.217	3.20
2	0.0607	0.0330	0.265	6.25
3	0.0557	0.0280	0.299	8.83
4	0.0516	0.0239	0.334	11.17
5	0.0472	0.0195	0.384	14.30
6	0.0436	0.0159	0.438	18.57

Slope = 0.01468
k = 1.22

Experiment #7*

Initial concentration of HCN = 0.0883
Initial concentration of propion. = 0.1189

1	0.0888	0.0582	0.183	2.82
2	0.0783	0.0477	0.215	4.75
3	0.0664	0.0358	0.268	7.95
4	0.0580	0.0274	0.326	11.25
5	0.0527	0.0221	0.377	14.97
6	0.0484	0.0178	0.434	18.97

Slope = 0.01657
k = 1.25

average k = 1.23 ± .02

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* For this experiment the designations of a and b are reversed relative to HCN and propionaldehyde.

Table 5

Propionaldehyde
Buffer composition: 0.0234N HOAc, 0.0234N NaOAc
u = 0.0234

Experiment #8

Equilibrium concentration of HCN = 0.0438

Sample	a-x	b-x	log a-x/b-x	t
1	0.0904	0.0466	0.288	3.18
2	0.0792	0.0354	0.350	6.20
3	0.0706	0.0268	0.421	9.22
4	0.0638	0.0200	0.504	12.73
5	0.0592	0.0154	0.585	16.25
6	0.0542	0.0104	0.717	21.40

Slope = 0.02360
k = 1.24

Experiment #9

Equilibrium concentration of HCN = 0.0446

1	0.0899	0.0453	0.298	3.33
2	0.0789	0.0343	0.362	6.17
3	0.0703	0.0257	0.437	9.13
4	0.0640	0.0194	0.518	12.88
5	0.0583	0.0137	0.629	17.48

Slope = 0.02342
k = 1.22

average k = 1.23 ± .01

Table 6

Propionaldehyde
Buffer composition: 0.0234N HOAc, 0.0234N NaOAc
u = 0.0900

Experiment #10

Equilibrium concentration of HCN = 0.0408

Sample	a-x	b-x	log a-x/b-x	t
1	0.0901	0.0493	0.262	3.20
2	0.0792	0.0384	0.314	5.75
3	0.0704	0.0296	0.376	8.77
4	0.0569	0.0161	0.548	16.18

Slope = 0.02202
k = 1.24

Experiment #11

Equilibrium concentration of HCN = 0.0402

1	0.0890	0.0488	0.261	3.42
2	0.0773	0.0371	0.319	6.22
3	0.0692	0.0290	0.378	8.47
4	0.0629	0.0227	0.442	11.40
5	0.0587	0.0185	0.501	14.33
6	0.0558	0.0156	0.554	17.05

Slope = 0.02193
k = 1.25

average k = 1.24 ± .01

Table 7

Propionaldehyde
Buffer composition: 0.0234N HOAc, 0.0234N NaOAc
u = 0.2000

Experiment #12

Equilibrium concentration of HCN = 0.0346

Sample	a-x	b-x	log a-x/b-x	t
1	0.0917	0.0571	0.206	2.72
2	0.0784	0.0438	0.253	5.13
3	0.0699	0.0353	0.297	7.65
4	0.0625	0.0279	0.350	10.17
5	0.0581	0.0235	0.393	12.63
6	0.0536	0.0190	0.450	15.43

Slope = 0.01912
k = 1.27

Experiment #13

Equilibrium concentration of HCN = 0.0358

1	0.0887	0.0529	0.224	3.00
2	0.0776	0.0418	0.269	5.28
3	0.0695	0.0337	0.314	7.83
4	0.0631	0.0273	0.364	10.52
5	0.0575	0.0217	0.423	13.02

Slope = 0.01920
k = 1.23

average k = 1.25 ± .02

Table 8

Propionaldehyde
Buffer composition: 0.1010N HOAc, 0.0509N HOAc
u = 0.0509

Experiment #14

Equilibrium concentration of HCN = 0.0424

Sample	a-x	b-x	log a-x/b-x	t
1	0.0990	0.0566	0.243	2.78
2	0.0906	0.0482	0.274	5.33
3	0.0830	0.0406	0.311	8.17
4	0.0706	0.0282	0.399	15.23
5	0.0653	0.0229	0.455	19.80

Slope = 0.01243
k = 0.676

Experiment #15

Equilibrium concentration of HCN = 0.0386

1	0.0947	0.0561	0.227	3.23
2	0.0870	0.0484	0.255	5.78
3	0.0789	0.0403	0.293	8.90
4	0.0730	0.0344	0.326	11.87
5	0.0683	0.0297	0.362	15.48
6	0.0621	0.0235	0.422	20.45

Slope = 0.01140
k = 0.679

Experiment #16

Equilibrium concentration of HCN = 0.0351

1	0.0944	0.0593	0.202	2.92
2	0.0863	0.0512	0.227	5.58
3	0.0775	0.0424	0.262	8.57
4	0.0712	0.0361	0.295	12.02
5	0.0658	0.0307	0.331	15.42
6	0.0605	0.0254	0.377	20.70

Slope = 0.01032
k = 0.677

average k = 0.677 ± .002

Table 9

Propionaldehyde
Buffer composition: 0.0202N HOAc, 0.0102N NaOAc
u = 0.0102

Experiment #17

Equilibrium concentration of HCN = 0.0365

Sample	a-x	b-x	log a-x/b-x	t
1	0.0910	0.0545	0.223	3.63
2	0.0834	0.0469	0.250	6.48
3	0.0768	0.0403	0.280	9.27
4	0.0695	0.0330	0.323	13.23
5	0.0650	0.0285	0.358	17.12

Slope = 0.01008
k = 0.633

Experiment #18

Equilibrium concentration of HCN = 0.0310

1	0.0899	0.0589	0.184	3.32
2	0.0822	0.0512	0.206	5.75
3	0.0772	0.0462	0.223	8.38
4	0.0705	0.0395	0.252	11.52
5	0.0641	0.0331	0.287	15.78
6	0.0577	0.0267	0.335	21.28

Slope = 0.00840
k = 0.624

average k = 0.628 ± .005

Table 10

Propionaldehyde
Buffer composition: 0.0202N HOAc, 0.0102N NaOAc
u = 0.0509

Experiment #19

Equilibrium concentration of HCN = 0.0362

Sample	a-x	b-x	log a-x/b-x	t
1	0.0734	0.0372	0.295	2.75
2	0.0687	0.0325	0.325	5.62
3	0.0645	0.0283	0.358	9.15
4	0.0600	0.0238	0.402	13.18
5	0.0559	0.0197	0.453	17.75
6	0.0526	0.0164	0.506	22.22

Slope = 0.01028
k = 0.654

Experiment #20

Equilibrium concentration of HCN = 0.0350

1	0.0747	0.0397	0.275	2.73
2	0.0700	0.0350	0.301	5.28
3	0.0655	0.0305	0.332	8.47
4	0.0609	0.0259	0.371	12.48
5	0.0570	0.0220	0.413	16.50
6	0.0536	0.0186	0.460	21.00

Slope = 0.00996
k = 0.656

average k = 0.655 ± .001

Table 11

Propionaldehyde
Buffer composition: 0.1595N HOAc, 0.0506N NaOAc
u = 0.0506

Experiment #21

Equilibrium concentration of HCN = 0.0432

Sample	a-x	b-x	log a-x/b-x	t
1	0.0916	0.0484	0.277	2.78
2	0.0868	0.0436	0.299	5.55
3	0.0809	0.0377	0.332	9.28
4	0.0729	0.0297	0.390	17.32
5	0.0671	0.0239	0.448	24.47

Slope = 0.00792
k = 0.422

Experiment # 22

Equilibrium concentration of HCN = 0.0405

1	0.0901	0.0496	0.259	3.33
2	0.0853	0.0448	0.280	6.32
3	0.0781	0.0376	0.317	10.82
4	0.0721	0.0316	0.358	16.42
5	0.0666	0.0261	0.407	23.43

Slope = 0.00752
k = 0.427

average k = 0.425 ± .003

Table 12

Propionaldehyde
Buffer composition: 0.0319N HOAc, 0.0101N NaOAc
u = 0.0101

Experiment #23

Equilibrium concentration of HCN: 0.0444

Sample	a-x	b-x	log a-x/b-x	t
1	0.0893	0.0449	0.299	3.45
2	0.0834	0.0390	0.330	6.88
3	0.0788	0.0344	0.360	10.77
4	0.0733	0.0289	0.404	15.67
5	0.0705	0.0261	0.432	20.65
6	0.0678	0.0234	0.462	24.73

Slope = 0.00756
k = 0.392

Experiment #24

Equilibrium concentration of HCN = 0.0410

1	0.0894	0.0484	0.266	3.10
2	0.0833	0.0423	0.294	6.37
3	0.0780	0.0370	0.324	11.00
4	0.0726	0.0316	0.361	16.38
5	0.0674	0.0264	0.407	23.12

Slope = 0.00692
k = 0.389

average k = 0.390 ± .002

Table 13

Propionaldehyde
Buffer composition: 0.0319N HOAc, 0.0101N NaOAc
u = 0.0506

Experiment #25

Equilibrium concentration of HCN = 0.0469

Sample	a-x	b-x	log a-x/b-x	t
1	0.0876	0.0407	0.333	2.88
2	0.0830	0.0361	0.362	5.97
3	0.0795	0.0326	0.387	10.17
4	0.0738	0.0269	0.438	15.37
5	0.0687	0.0218	0.499	22.38

Slope = 0.00824
k = 0.405

Experiment #26

Equilibrium concentration of HCN = 0.0396

1	0.0842	0.0446	0.276	2.67
2	0.0759	0.0363	0.320	9.00
3	0.0710	0.0314	0.354	13.75
4	0.0673	0.0277	0.386	18.60
5	0.0630	0.0234	0.430	24.52

Slope = 0.00696
k = 0.405

Experiment #27

Equilibrium concentration of HCN = 0.0449

1	0.0847	0.0398	0.328	3.00
2	0.0805	0.0356	0.354	5.85
3	0.0756	0.0307	0.391	10.12
4	0.0708	0.0259	0.437	16.13
5	0.0663	0.0214	0.491	23.07

Slope = 0.00792
k = 0.406

average k = 0.405 ± .001

Table 14

Propionaldehyde
Buffer composition: 0.02006N HOAc, 0.0509N NaOAc
u = 0.0509

Experiment #28

Equilibrium concentration of HCN = 0.0416

Sample	a-x	b-x	log a-x/b-x	t
1	0.0831	0.0415	0.302	3.17
2	0.0798	0.0382	0.320	6.45
3	0.0747	0.0331	0.353	12.02
4	0.0680	0.0264	0.411	21.13
5	0.0635	0.0219	0.462	30.40

Slope = 0.00600
k = 0.332

Experiment #29

Equilibrium concentration of HCN = 0.0392

1	0.0847	0.0455	0.270	2.60
2	0.0801	0.0409	0.292	6.63
3	0.0743	0.0351	0.326	12.13
4	0.0679	0.0287	0.374	20.30
5	0.0627	0.0236	0.425	30.25

Slope = 0.00573
k = 0.337

average k = 0.335 ± .003

Table 15

Propionaldehyde
Buffer composition: 0.0401N HOAc, 0.0102N NaOAc
u = 0.0102

Experiment #30

Equilibrium concentration of HCN = 0.0403

Sample	a-x	b-x	log a-x/b-x	t
1	0.0814	0.0411	0.297	2.73
2	0.0780	0.0377	0.316	7.25
3	0.0728	0.0325	0.350	13.08
4	0.0691	0.0288	0.380	19.12
5	0.0614	0.0211	0.464	34.18

Slope = 0.00534
k = 0.305

Experiment #31

Equilibrium concentration of HCN = 0.0431

1	0.0819	0.0388	0.324	2.98
2	0.0777	0.0346	0.351	7.37
3	0.0732	0.0301	0.386	13.93
4	0.0698	0.0267	0.417	19.28
5	0.0630	0.0199	0.500	34.38

Slope = 0.00568
k = 0.304

average k = 0.305 ± .001

Table 16

Propionaldehyde
Buffer composition: 0.0401N HOAc, 0.0102N NaOAc
u = 0.0509

Experiment #32

Equilibrium concentration of HCN = 0.0413

Sample	a-x	b-x	log a-x/b-x	t
1	0.0792	0.0379	0.320	2.83
2	0.0763	0.0350	0.338	7.08
3	0.0729	0.0316	0.363	12.13
4	0.0683	0.0270	0.403	18.10
5	0.0650	0.0237	0.438	24.63
6	0.0620	0.0207	0.476	31.12

Slope = 0.00568
k = 0.316

Experiment #33

Equilibrium concentration of HCN = 0.0464

1	0.0740	0.0276	0.427	7.27
2	0.0711	0.0247	0.458	13.20
3	0.0683	0.0219	0.494	18.15
4	0.0653	0.0189	0.538	24.25
5	0.0629	0.0165	0.581	31.37

Slope = 0.00643
k = 0.319

average k = 0.317 ± .002

Table 17

Acetone
Buffer composition: 0.0441N HOAc, 0.0496N NaOAc
u = 0.0496

Experiment #34

Initial HCN = 0.0775
Initial acetone = 0.1086
Equilibrium concentration of HCN = 0.0392
$Q = c + x_e + 1/K$

Sample	x	$x+Q/x-x_e$	log $x+Q/x-x_e$	t
1	0.0777	0.2199/0.0385	0.757	4.27
2	0.0738	0.2160/0.0346	0.795	65.43
3	0.0699	0.2121/0.0307	0.839	139.33
4	0.0651	0.2073/0.0259	0.903	236.62
5	0.0620	0.2042/0.0228	0.952	340.65
6	0.0585	0.2007/0.0193	1.017	433.75

Slope = 0.000600
k_1 = 0.00762

Experiment #35

Initial HCN = 0.0758
Initial acetone = 0.1164
Equilibrium concentration of HCN = 0.0366

1	0.0748	0.2241/0.0382	0.768	4.37
2	0.0710	0.2203/0.0344	0.806	73.23
3	0.0655	0.2148/0.0289	0.871	172.52
4	0.0610	0.2103/0.0244	0.935	265.38
5	0.0584	0.2077/0.0218	0.979	346.70
6	0.0557	0.2050/0.0191	1.031	434.37

Slope = 0.000624
k_1 = 0.00778

Experiment #36

Initial HCN = 0.0758
Initial acetone = 0.1052
Equilibrium concentration of HCN = 0.0387

1	0.0750	0.2141/0.0363	0.771	4.48
2	0.0710	0.2101/0.0323	0.813	67.38
3	0.0662	0.2053/0.0275	0.873	159.05
4	0.0625	0.2016/0.0238	0.928	276.73
5	0.0587	0.1978/0.0200	0.995	372.37
6	0.0555	0.1946/0.0168	1.063	481.40

Slope = 0.000604
k_1 = 0.00782

average k_1 = 0.00774 ± .00012

Table 18

Acetone
Buffer composition: 0.0110N HOAc, 0.0124N NaOAc
u = 0.0496

Experiment #37

Initial HCN = 0.0753
Initial acetone = 0.1101
Equilibrium concentration of HCN = 0.0375*

Sample	x	$x+Q/x-x_e$	log $x+Q/x-x_e$	t
1	0.0747	0.2187/0.0372	0.769	4.45
2	0.0698	0.2138/0.0323	0.821	73.35
3	0.0648	0.2088/0.0281	0.871	165.43
4	0.0619	0.2059/0.0244	0.926	249.13
5	0.0586	0.2026/0.0211	0.982	356.73

Slope = 0.000604
k_1 = 0.00766

Experiment #38

Initial HCN = 0.0730
Initial acetone = 0.1088
Equilibrium concentration of HCN = 0.0363

1	0.0717	0.2151/0.0354	0.784	4.37
2	0.0674	0.2108/0.0311	0.831	88.38
3	0.0623	0.2057/0.0260	0.898	190.15
4	0.0585	0.2019/0.0222	0.958	289.32
5	0.0556	0.1990/0.0193	1.013	385.50

Slope = 0.000608
k_1 = 0.00779

average k_1 = 0.00772 ± .00007

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* In this run the experimental value for x_e was obviously in error. The value used is based upon a value of K obtained by averaging three previous results for K which were in close agreement.

Table 19

Acetaldehyde
Buffer composition: 0.1372N HOAc, 0.0503N NaOAc
u = 0.0503

Experiment #39

Equilibrium concentration of HCN = 0.0273

<u>Sample</u>	<u>a-x</u>	<u>b-x</u>	<u>log a-x/b-x</u>	<u>t</u>
1	0.0657	0.0384	0.233	3.28
2	0.0619	0.0346	0.253	11.12
3	0.0569	0.0296	0.284	24.43
4	0.0515	0.0242	0.328	40.35
5	0.0463	0.0190	0.387	67.22

Slope = 0.002491

k = 0.210

Experiment #40

Equilibrium concentration of HCN = 0.0339

1	0.0664	0.0325	0.310	3.32
2	0.0630	0.0291	0.335	11.13
3	0.0585	0.0246	0.376	23.25
4	0.0553	0.0214	0.412	35.35
5	0.0490	0.0151	0.511	67.35

Slope = 0.003142

k = 0.214

average k = 0.212 ± .002

Table 20

Acetaldehyde
Buffer composition: 0.0275N HOAc, 0.0101N NaOAc
$u = 0.0503$

Experiment #41

Equilibrium concentration of HCN = 0.0321

Sample	a-x	b-x	log a-x/b-x	t
1	0.0656	0.0335	0.292	3.27
2	0.0609	0.0288	0.325	14.33
3	0.0559	0.0238	0.371	30.23
4	0.0524	0.0203	0.412	49.30
5	0.0476	0.0155	0.487	72.35
6	0.0442	0.0121	0.563	97.27

Slope = 0.002893
k = 0.207

Experiment #42

Equilibrium concentration of HCN = 0.0327

1	0.0662	0.0335	0.296	3.28
2	0.0620	0.0293	0.326	12.25
3	0.0579	0.0252	0.361	24.20
4	0.0539	0.0212	0.405	39.27
5	0.0496	0.0169	0.467	59.30

Slope = 0.003000
k = 0.211

average k = 0.209 ± .002

INTERPRETATION OF RESULTS

In order to maintain a proper perspective as to the significance of the results obtained, it is necessary to consider the precision of the data and the probable margin of error in the rate constants. From an inspection of the values of the rate constants for duplicate runs, it would appear as though they are reproducible to 1%.

It is difficult to evaluate the combined error involved from all the particular operations of the experimental procedure, such as volumetric technique, weighing, timing and temperature control. Individually they should be reliable to one part in a thousand. However, one series of experiments is useful in indicating the probable overall error. When HCN solution was placed in the reaction flask and successive samples withdrawn and analyzed, the average deviation of the KSCN titer was ± 0.03 ml. The procedure followed approximated that used in the rate measurements.

The velocity constants were evaluated graphically from the slope of the best straight line that could be drawn through the points plotted. It was found, on analysis of several plots, that the average deviation of the points from the straight line drawn generally corresponded to an average deviation of ± 0.03 ml of KSCN. Due to these deviations from a straight line, there was usually a slight uncertainty in the slope of the line drawn. This uncertainty corresponded to a maximum flexibility of about 2% in the value of the rate constant. The method of least squares seemed to offer no advantage in the determination of the slope. This was adjudged because the method of least squares gives equal weight to all deviations and this procedure would not be justified. A certain deviation in the latter part of the run corresponds to a much smaller deviation in the early part in terms of the same error in ml of KSCN. An alternative would be to use the method of least squares and apply a weighting factor to all the deviations. This, however, would be too arbitrary since the implicit errors in the experimental procedure are not known with certainty.

It is concluded that the rate constants are reproducible within 1 to 2%.

At first several attempts were made to obtain reproducible results in unbuffered water solution but, despite all efforts made to exclude impurities, this could not be accomplished. The data of Table 3 illustrate the wide variations in k which were obtained in water. Although each run yielded a linear second order plot, the evaluated constants differed from each other. This behavior is fairly characteristic of acid-base catalyzed reactions in water. In an attempt to obtain reproducible results, acetate buffers were used for the reaction media and these proved to be successful. The data of Table 4, Experiments 4,5,6,7, illustrate the consistency of k values obtained in four runs using different initial concentrations of HCN and aldehyde. This consistency is also evidence for the correctness of the second order formulation. Thus it is necessary to establish a definite acidity to obtain reproducible results.

On the basis of the values obtained in the buffered solutions and the magnitude of those obtained in water, it seems probable that the chief difficulty encountered in water is the presence of very small but varying amounts of propionic acid which has a profound effect on the reaction rate. Assuming that it would be possible to eliminate completely any oxidation of aldehyde, it is doubtful that one could then obtain reproducible results. The reaction rate is so sensitive to pH that even traces of acid-base impurities would exert an unfavorable influence. Moreover, the study of the reaction in theoretically pure water would offer little advantage. It would not represent an uncatalyzed reaction, but rather a reaction controlled by the pH obtained from the dissociation of HCN. The reaction would occur in a medium of constantly changing pH and the kinetics would be expected to follow a 3/2 order law, first order relative to aldehyde and 1/2 order relative to HCN. This will become clearer after a discussion of the results.

The influence of ionic strength on the propionaldehyde reaction is illustrated by Table 21. In this and subsequent tables, A denotes the concentration of HOAc and B denotes the concentration of NaOAc. It is apparent from the data of Table 21 that the ionic strength influence is very small and amounts from about 2 to 4% for the range studied. Thus an acceptable mechanism must not predict either an appreciable primary or secondary salt effect.

Table 21

Influence of Ionic Strength

HOAc	NaOAc	A/B	u	k
0.0234	0.0234	1.00	0.0234	1.23
0.0234	0.0234	1.00	0.0900	1.24
0.0234	0.0234	1.00	0.2000	1.25
0.0202	0.0102	1.98	0.0102	0.628
0.0202	0.0102	1.98	0.0509	0.655
0.0319	0.0101	3.15	0.0101	0.390
0.0319	0.0101	3.15	0.0506	0.405
0.0401	0.0102	3.94	0.0102	0.305
0.0401	0.0102	3.94	0.0509	0.317

The next point to be considered is the evidence relative to generalized catalysis. The reactions of acetone and acetaldehyde will be examined first because the results are clearer. In Table 22 are summarized the pertinent data for these reactions.

Table 22

Effect of Buffer Composition at Constant pH

Acetone

	HOAc	NaOAc	A/B	u	k
(A)	0.0441	0.0496	0.889	0.0496	0.00774
(B)	0.0110	0.0124	0.889	0.0496	0.00772

Acetaldehyde

	HOAc	NaOAc	A/B	u	k
(A)	0.1372	0.0503	2.73	0.0503	0.212
(B)	0.0275	0.0101	2.73	0.0503	0.209

In all the experiments designed to test for generalized catalysis, the ratio of A/B is the same for series (A) and (B). The buffer for series (B) was prepared by quantitative dilution of the buffer used in series (A). The constancy of ionic strength in (A) and (B) suppresses any salt effects. Since the values of k for series (A) and (B) are constant, within the probable error, it is evident that no generalized catalysis is detectable in the reactions of acetone and acetaldehyde.

The propionaldehyde reaction was studied more extensively and the results are presented in Table 23.

Table 23

Effect of Buffer Composition at Constant pH

Propionaldehyde

	HOAc	NaOAc	A/B	u	k
(A)	0.1010	0.0509	1.98	0.0509	0.677
(B)	0.0202	0.0102	1.98	0.0509	0.655
(A)	0.1595	0.0506	3.15	0.0506	0.425
(B)	0.0319	0.0101	3.15	0.0506	0.405
(A)	0.2006	0.0509	3.94	0.0509	0.335
(B)	0.0401	0.0102	3.94	0.0509	0.317

As already indicated, the ionic strength effect is very small. Therefore the slight differences in the various ionic strengths cited in Table 23 are of little import and it may safely be approximated that the ionic strength is the same in all these experiments.

In comparing each series (A) with series (B), it appears as though the value of k varies in a manner which suggests the presence of generalized catalysis. Even when the ratio of HOAc to NaOAc is constant, and hence, the pH is constant, the rate decreases with decreasing buffer composition. The effect is relatively small and amounts to 4 to 6%, depending on the ratio involved.

The extent of generalized catalysis in various reactions has been found to vary within considerable limits. It is therefore conceivable that for some reactions it may amount to only a few percent. The difficulty then arises of demonstrating that the effect is clearly outside of the experimental error. For the cyanohydrin reaction this would be particularly important because the definite presence of generalized catalysis would have a profound implication on the reaction mechanism.

On consideration of the reproducibility of k values, it appears as though the effect observed is greater than the experimental error. However, the greatest source of error in the accuracy of the rate measurements may undoubtedly be ascribed to oxidation of the aldehyde, and unfortunately, such oxidation, even in relatively small amounts, would exert the same effect on the rate constant as generalized catalysis would.

Consider, for instance, the buffer compositions associated with the k values, 0.677 and 0.655. The initial concentrations of propionaldehyde for these experiments were about 0.06N and 0.04N respectively. If there were truly no generalized catalysis, then k should be inversely proportional to the ratio of HOAc to NaOAc. For the purpose of this analysis, the dissociation constant of propionic acid may be considered to be practically the same as that of acetic acid. If we assume about 2% oxidation of the aldehyde, this would effectively increase the acid concentration of (A) by 0.0012 and of (B) by 0.0008. In the case of (B), this would mean a 4% increase in the ratio of HOAc to NaOAc and consequently a 4% decrease in the value of k from its true value at the supposed buffer composition. In the case of (A), the increase in acid would cause only a 1% decrease in the value of k. Thus a 2% oxidation could account for the values 0.677 and 0.655, within experimental error. By similar considerations, it would be necessary to assume about 3.5% oxidation to account for the values 0.425 and 0.405 and to assume about 5% oxidation to account for the values 0.335 and 0.317. It remains to consider the validity of the oxidation hypothesis as an explanation of the variations in k.

From the above analysis it is apparent that differing amounts of oxidation (2 to 5%) must be assumed to explain the deviations observed. This, however, is subject to criticism. The reproducibility of rate constants for a given medium would require that the amount of oxidation be fairly constant. Since all the experiments listed in Table 23 involved the same procedure, one would expect the constancy to be manifested throughout. 5% oxidation can explain the last set of k values; yet 5% oxidation in the first set would cause k to vary from 0.677 to 0.625 instead of 0.655. The best indication of the extent of oxidation would be experimental evidence. As previously stated, the propionaldehyde reaction goes to completion. One would therefore expect that, in experiments with HCN in excess, the amount of HCN which disappears at equilibrium should correspond to the amount of propionaldehyde initially present. If oxidation of the aldehyde occurred, this would not be so. Table 24 contains a summary of the data from the most reliable experiments performed illustrating this particular point.

Table 24

Propionaldehyde by Weight and by Analysis

	Initial HCN	Equil. HCN	Δ HCN	Initial Propion.
(1)	0.1082	0.0412	0.0670	0.0663
(2)	0.1069	0.0376	0.0693	0.0692
(3)	0.1057	0.0364	0.0693	0.0693
(4)	0.0950	0.0306	0.0644	0.0654
(5)	0.0893	0.0277	0.0616	0.0615

The initial propionaldehyde concentration was determined by weight. Δ HCN represents the amount of HCN which has reacted and, therefore, should also represent the initial amount of aldehyde in the solution in the absence of oxidation. Oxidation, however, would diminish the amount of aldehyde present in the solution and would result in a smaller value of HCN compared to the initial concentration of aldehyde by weight. In Table 24 only (4) indicates such an effect, to the extent of 1.5%. The average result of the five determinations indicates no significant amount of oxidation, certainly not enough to account for the variations of k in Table 23.

According to equation (30), the Lapworth mechanism predicts that the value of k should not vary at a constant ionic strength and a constant buffer ratio. Similarly, according to equation (36), the mechanism involving the specific OH ion catalyzed addition of undissociated HCN predicts the same effect. However, the latter mechanism could readily be expanded to include the generalized base catalysis of HCN addition. This would be compatible with the variation of k with buffer composition. Thus a definite manifestation of generalized catalysis would enable differentiation between these two possible mechanisms whose kinetics would otherwise be indistinquishable.

In the case of acetone and acetaldehyde, it is clear that generalized catalysis is not detectable. In the case of propionaldehyde, the results are difficult to interpret with certainty. The effects seem to lie just outside the range of experimental error, but there is always a danger in these circumstances in attempting to attach a definite significance to such results. Unfortunately, therefore, the conclusions on the propionaldehyde reaction can not be very definite. There is an indication of generalized catalysis beyond the probable margin of error, but the effect is not unequivocally demonstrated.

The fact that the acetone and acetaldehyde reactions do not indicate generalized catalysis does not preclude the possibility that the propionaldehyde reaction might. The variations of the extent of generalized catalysis in a series of similar substrates has already been discussed in the theory section. There is no definite principle from which any generalizations may be drawn.

It is of interest to compare the rate constants of the acetaldehyde and propionaldehyde reactions in a medium of the same composition. The value of the rate constant for acetaldehyde in a buffer of 0.1372N HOAc and 0.0503N NaOAc is 0.212. The value for propionaldehyde in such a buffer may be obtained by interpolation of the data in Table 23. For the series (A), in which the NaOAc concentration is 0.05N, the values of k are very closely proportional to the ratio of NaOAc to HOAc. The value of k for propionaldehyde in a buffer of 0.1372N HOAc and 0.0503N NaOAc would, by interpolation, be 0.494 within a probable accuracy of about 2%. The possible significance of these results will be discussed in detail in the next section.

In connection with the rate measurements which were conducted, information has been obtained relative to the equilibrium constants of the three reactions studied.

No value for the equilibrium constant of the propionaldehyde reaction in dilute aqueous solution has been previously reported. However, Jones[12] investigated the equilibrium of acetaldehyde cyanohydrin formation in dilute aqueous solution at 25°C. He reported the equilibrium constant for the formation of acetaldehyde cyanohydrin to be 139.2.

The results of the present investigation have shown that both the acetaldehyde and propionaldehyde reactions go to completion, within the limits of detection of the method of analysis used. The sensitivity of the method is such that the reaction must proceed at least 99.99% to completion. This means that the equilibrium constant for acetaldehyde and propionaldehyde cyanohydrin formation is about 10^9 or greater. This value is at variance with that reported by Jones by a factor of 10^7 or greater. On examining the experiments performed by Jones, it may be observed that the HCN was in excess of aldehyde in every case. If he had performed one experiment with acetaldehyde in excess, it would have been apparent that the reaction goes to completion. Jones does not furnish any details of the experimental procedure he used, but it is probable that his greatest sources of error were the volatility and ease of oxidation of acetaldehyde. The consistency of his results is remarkable considering their inaccuracy, but this might be attributable to a systematic error.

Values of the equilibrium constant for the acetone reaction in dilute aqueous solution at 25°C have been reported by Jones[12] and by Stewart and co-workers[17,18]. Their values for acetone cyanohydrin formation are, respectively, 12.56 and 15.38. Experiments 34, 35, 36 and 38 of the present investigation yield the following values for the equilibrium constant: 13.90, 13.87, 14.08, and 14.02, respectively. The average result with a mean deviation of less than 1% is 13.97. Thus three different investigations have produced three different values for the equilibrium constant, although each of the values is the result of several apparently consistent determinations. The work of Jones is probably not too accurate, as already indicated by the unreliable results he obtained for the acetaldehyde reaction. In the case of the acetone reaction, even his calculation of the mean value of the equilibrium constant is incorrect. Based on the experimental data he reports, the mean value of K for formation of cyanohydrin is 11.55 instead of 12.56. Moreover, the average deviation of the individual equilibrium constant values is 21%. On the other hand, the work of Stewart and co-workers appears to be very reliable. The difference between our value of 13.97 and their value of 15.38 is equivalent to a difference of 3 to 4% in the determination of the equilibrium concentration of HCN. This discrepancy, though relatively small, is difficult to explain. The fact that our results were obtained in buffer solutions, whereas those of Stewart and co-workers were obtained in unbuffered solution should have no bearing on this discrepancy. In both studies the pH was sufficiently low as to have caused no detectable shift in the equilibrium.

DISCUSSION

In the discussion of various mechanisms for the cyanohydrin reaction which will follow, the apparent generalized catalytic effect in the propionaldehyde reaction will be ignored because of its uncertainty. Therefore, the kinetics of the reaction are considered to be in accord with equation (30). Let us now examine the kinetics of the following mechanisms:

$$>C{=}O + H^+ + CN^- \rightleftharpoons\ >C(OH)CN \qquad (37)$$

$$>C{=}O + H^+ \overset{\text{slow}}{\rightleftharpoons} \overset{+}{C}OH + CN^- \overset{\text{fast}}{\rightleftharpoons}\ >C(OH)CN \qquad (38)$$

$$>C{=}O + H^+ \overset{\text{fast}}{\rightleftharpoons}\ >\overset{+}{C}OH + CN^- \overset{\text{slow}}{\rightleftharpoons}\ >C(OH)CN \qquad (39)$$

$$>C{=}O + \overset{-}{CN} \overset{\text{slow}}{\rightleftharpoons}\ >C(CN)\overset{-}{O} + H^+ \overset{\text{fast}}{\rightleftharpoons}\ >C(OH)CN \qquad (40)$$

$$>C{=}O + \overset{-}{CN} \overset{\text{fast}}{\rightleftharpoons}\ >C(CN)\overset{-}{O} + H^+ \overset{\text{slow}}{\rightleftharpoons}\ >C(OH)CN \qquad (41)$$

$$>C{=}O + \overset{-}{CN} \overset{\text{slow}}{\rightleftharpoons}\ >C(CN)\overset{-}{O} + H_2O \overset{\text{fast}}{\rightleftharpoons}\ >C(OH)CN + OH^- \qquad (42)$$

$$>C{=}O + \overset{-}{CN} \overset{\text{fast}}{\rightleftharpoons}\ >C(CN)\overset{-}{O} + H_2O \overset{\text{slow}}{\rightleftharpoons}\ >C(OH)CN + OH^- \qquad (43)$$

$$>C{=}O + \overset{-}{CN} + H_2O \rightleftharpoons\ >C(OH)CN + OH^- \qquad (44)$$

(37), (39) and (41) are rejected because they predict that k should be independent of pH. (38) is rejected because it predicts that the rate should be independent of HCN concentration. (40), (42), (43) and (44) all lead to the correct kinetics.

The preceding mechanisms were various modifications involving cyanide ion as the reactive species. Now let us consider some possibilities involving undissociated HCN as suggested in equation (31).

$$\rangle C{=}O + HCN + OH^- \rightleftharpoons \rangle C(OH)CN + OH^- \tag{45}$$

$$\rangle C{=}O + OH^- \overset{\text{fast}}{\rightleftharpoons} \rangle C(OH)O^- + HCN \overset{\text{slow}}{\rightleftharpoons} \rangle C(OH)CN + OH^- \tag{46}$$

$$\rangle C{=}O + OH^- \overset{\text{slow}}{\rightleftharpoons} \text{enol} \;........\; \xrightarrow{\text{fast}} \text{products} \tag{47}$$

$$\rangle C{=}O + OH^- \overset{\text{fast}}{\rightleftharpoons} \text{enol} \;........\; \xrightarrow{\text{slow}} \text{products} \tag{48}$$

$$\rangle C{=}O + HCN \overset{\text{fast}}{\rightleftharpoons} \underset{\text{(complex)}}{\rangle CO...HCN} + OH^- \overset{\text{slow}}{\rightleftharpoons} \rangle C(OH)CN + OH^- \tag{49}$$

(45), (46) and (49) all lead to the correct kinetics. (47) is rejected because it predicts that the rate should be independent of HCN concentration. (48) is rejected because it is known that enolization is not a fast reaction. The fact that cyanohydrin formation does not depend on enolization may be confirmed by comparing the rate constant of acetone cyanohydrin formation with the rate constant of the hydroxyl catalyzed acetone enolization given by Dawson and Spivey[31].

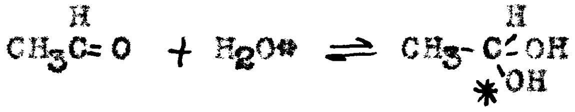
It is difficult to decide which of the possible mechanisms considered above are the more probable. All of the mechanisms which lead to the correct kinetics expression are capable of explaining equally well the effects of acids and bases on the rate of cyanohydrin formation observed by Lapworth. In terms of existing theory on the attack of nucleophilic reagents on carbonyl carbon, one would prefer a possibility involving cyanide ion rather than HCN as the reactive species. However, strictly on the basis of kinetics, one can not exclude the possibility that the reaction proceeds by the base catalyzed addition of HCN either partly or entirely. As will be discussed later, other carbonyl addition reactions which have been studied quantitatively are characterized by similar ambiguities. In these latter reactions, the results obtained can not be used to exclude basic catalysis.

Whether cyanide ion and/or HCN is the reactive species, (44) and (45) represent interesting possibilities because of the recent speculation by Swain[32] that carbonyl addition reactions may generally proceed by termolecular mechanisms. If one accepts the interpretation that semicarbazone, oxime and phenylhydrazone formation are generalized acid-catalyzed reactions, then (44) provides an interesting contrast in terms of Swain's termolecular explanation of acid-base catalysis in aqueous solution. (44) would be an illustration of the case in which H_2O, functioning as an acid to enhance the electronic shift of the carbonyl linkage, is so much more reactive than other acids that the rate is determined almost entirely by acid catalysis of the solvent molecules. An explanation of this sort would provide a common basis for the cyanohydrin reaction and the semicarbazone, oxime and phenylhydrazone reactions. This could be the answer to the quest for a generalized interpretation of carbonyl addition reactions. However, the fact that the presence of basic catalysis in all of these reactions has not been excluded prohibits the unqualified acceptance of the aforementioned explanation. It may be that basic catalysis would not impose any serious modifications on the termolecular mechanism. Whether or not basic catalysis is operative, the ambiguities are such that the results do not justify a preference of a termolecular mechanism over the various bimolecular mechanisms.

(46) is of interest because of the suggestion by Watson[3] that the function of the catalyst in carbonyl reactions may be the activation of the carbonyl group by the formation of a complex between the catalyst and the substrate. Thus the mechanisms represented by (40), (44), (45) and (46) each have a basis in some theory of carbonyl reactivity and, solely on the basis of the kinetics, it is not possible to decide among them.

The calculation of the rate constants of cyanohydrin formation has been based on the tacit assumption that the total aldehyde content of the reaction solutions exists in a free and reactive form. This assumption may require certain modifications, particularly with reference to the influence of hydration on the aldehydes. It will become apparent that hydration has a significant bearing on cyanohydrin kinetics and, possibly, on the mechanism.

In the case of formaldehyde, the evidence that the aldehyde exists almost entirely in a hydrated form in dilute aqueous solution is overwhelming[33]. Homfray[34], from refractive index measurements, calculated that approximately 50% of acetaldehyde is present in the glycol form in aqueous solution. Schou[35], from measurements of ultraviolet absorption bands, estimates 26% of acetaldehyde is present in the glycol form in aqueous solution. Herbert and Lauder[36] have investigated the oxygen exchange between water and acetaldehyde. Their results show that a rapid interchange of oxygen takes place, equilibrium being reached in about twenty hours at room temperature. The exchange reaction, which goes about halfway to equilibrium in two hours, may be written:



$$CH_3\overset{H}{C}=O + H_2O^{*} \rightleftharpoons CH_3-\overset{H}{C}\begin{smallmatrix}\diagup OH\\ \diagdown {}^{*}OH\end{smallmatrix} \qquad (50)$$

Cohn and Urey[37] have investigated the oxygen exchange between water and acetone and acetaldehyde. They found, in the case of acetone, that no exchange occurred in 24 hours at 25°C but that partial exchange occurred in 24 hours at 100°C. In the case of acetaldehyde, complete exchange took place in 24 hours at 25°C. Unfortunately, it was necessary to conduct the exchange studies in solutions of about 80% carbonyl-20% water. Therefore, the results are not strictly valid for dilute aqueous solutions. It seems probable, however, that in dilute aqueous solution the extent of hydration and the rate of hydration will be more pronounced. It is difficult to estimate whether acetone would be hydrated to any extent under such conditions.

Propionaldehyde hydration has been studied much less completely, although undoubtedly it also forms a hydrate in dilute aqueous solution at 25°C. Herold and Wolf[38] have investigated the absorption spectra of solutions of various aldehydes in water and in several alcohols. In water their results indicate the formation of a hydrate for acetaldehyde, propionaldehyde and butyraldehyde. The study of various alcohols with different aldehydes indicated that the larger the side chain of the aldehyde, the slower the reaction and the greater the proportion of free aldehyde at equilibrium. If this effect is also applicable to water solutions, one would expect the extent of hydration to be less for propionaldehyde than for acetaldehyde.

The influence of hydration on cyanohydrin kinetics will depend on a number of factors. It will depend on whether or not the hydration reaction comes to rapid equilibrium, and it will depend on whether free and/or hydrated aldehyde may react to form cyanohydrin. If there is instantaneous equilibrium, then the "true" rate constant of cyanohydrin formation will be a function of the equilibrium constant of the hydration reaction. If there is not a rapid equilibrium, then it will be a function of the rate of formation of the hydrate and of the mechanism of hydration. The possible modifications to cyanohydrin kinetics which may be written taking into account the hydration reaction are many, but they will not be considered here because of the lack of definite information about the kinetics and mechanism of the hydration reaction itself in dilute aqueous solution. One possibility, however, will be examined to illustrate what might be the "true" rate constant of cyanohydrin formation.

Let us assume that the hydration equilibrium is instantaneous and that the reactive species in the formation of cyanohydrin is free aldehyde. Let AO# represent free aldehyde, $A(OH)_2$ represent hydrated aldehyde and AO represent AO# + $A(OH)_2$, total aldehyde. The equilibrium constant K for hydration equation (50), considering the water concentration constant, may be written

$$K = x/a-x \tag{51}$$

where a is the concentration of total aldehyde at any time, x is the concentration of $A(OH)_2$ and a-x is the concentration of AO#.

Rearranging (51)

$$x = Ka/K+1 \tag{52}$$

$$a-x = \frac{1}{1+K}\,a \tag{53}$$

a-x/a is the fraction of total aldehyde, AO, which is present at any time as free aldehyde. Thus

$$C_{AO\#}/C_{AO} = a-x/a = 1/1+K \tag{54}$$

The rate equation in terms of free aldehyde is

$$\frac{dx}{dt} = k\ C_{AO\#}C_{HCN} \tag{55}$$

where k is the true rate constant based on the reactive species AO*. Substituting equation (54),

$$\frac{dx}{dt} = k \frac{1}{1+K} C_{AO} C_{HCN} \qquad (56)$$

$$\frac{dx}{dt} = k' \ C_{AO} \ C_{HCN} \qquad (57)$$

where

$$k' = k \frac{1}{1+K} \qquad (58)$$

Equation (58) relates the observed rate constant k' based on total aldehyde with the true rate constant k, in a fixed medium.

In the previous section the rate constants for acetaldehyde and propionaldehyde cyanohydrin formation in the same medium were shown to be 0.212 and 0.494 respectively. Therefore, one would ordinarily say that propionaldehyde is more reactive than acetaldehyde. On the basis of the inductive effect, the reverse order of reactivity would have been expected. It is possible, of course, that a hyperconjugative effect is operative here which supersedes the inductive effect and which would be in accord with the apparent reactivities. The real interest in this discussion, however, attaches to whether or not the observed rate constants may truly be accepted as an index of the relative reactivities of the two compounds. If the condition of instantaneous hydration equilibrium which was assumed in the above derivation is correct, then it is immediately apparent from equation (58) that this is not so. If, for instance, the equilibrium constant of acetaldehyde hydration was sufficiently larger than that of propionaldehyde, acetaldehyde would be more reactive in cyanohydrin formation than propionaldehyde, even though the observed rate constants do not indicate this. Whether the hydration equilibrium is rapid or not, the observed rate constants will be a function either of the equilibrium constant or the rate constant of hydration. Thus a valid comparison of reactivity may not be made solely on the basis of the observed rate constants of cyanohydrin formation. This same conclusion may be applied to other carbonyl reactions in water and possibly, in alcoholic solution where the compounds may exhibit significant amounts of solvation.

It is concluded that the kinetics of the cyanohydrin reaction in aqueous solution may be explained by several mechanisms, some of which involve significant differences. The rate measurements do not permit a distinction between the various possibilities. The study of benzaldehyde cyanohydrin formation in 50% alcoholic acetate buffers by Albers and Hamann[16] indicated that the rate was a function of the pH. Although their investigation was less comprehensive than the present study, it seems probable that the kinetics in the solvent medium used by them is very similar to that in water.

Möller[14] interpreted her results on benzaldehyde cyanohydrin kinetics in a nonpolar solvent to indicate that a termolecular mechanism is operative. The results have been presented on pages 7 to 9. This work is of interest because of the possibility that the kinetics in nonpolar solvents might be free of some of the ambiguities which appear in aqueous solution and might, therefore, offer some clues as to the course of the reaction in water. Unfortunately, when the interpretation of the observed kinetics is examined, this does not appear to be the case.

It was observed that the rate constant k is a function of the ratio of initial concentrations of base and HCN. According to the mechanism proposed in order to explain this effect, one would expect that, since the ratio of base:HCN concentration is changing continuously during the course of a particular run, the value of k would also change continuously during that run. This was not found to be so. Moreover, the mechanism suggested does not predict the order of reaction kinetics observed. It predicts first order kinetics instead of the third order law observed. The reader is referred to reference (14) for further details.

Thus the third order kinetics are not explainable by the mechanism proposed. The assumption that the base interacts with HCN completely to form simple monovalent ions seems unlikely. Comprehensive investigations of the conductances of salts in nonpolar solvents have indicated the attendance of many complicating factors such as ion-pairing, association, ionic dissociation and molecular complexing. Giauque and Ruehrwein[39] investigated the thermodynamics of gaseous HCN. Their results indicate that HCN is associated in the gas phase in aggregates ranging from a dimer to a heptamer. It therefore seems very probable that HCN is associated to some extent in nonpolar solvents. Until more information is available on the various equilibria which prevail in a nonpolar solution of HCN and base, it seems futile to attempt any explanation of the benzaldehyde kinetics.

It may be that the kinetics of the benzaldehyde reaction was fortuitously third order. Stewart and Fontana[18] investigated the relative rates of acetone cyanohydrin dissociation in a variety of nonpolar solvents. Fontana[19] states that the kinetic data do not fit any simple rate law. The time-concentration data were not reported and it is not possible to see whether or not the equation used by Möller would be applicable. However their equilibrium data in the nonpolar solvents are not in accord with a third order formulation of the kinetics of acetone cyanohydrin formation. It may be that the kinetics of cyanohydrin formation in nonpolar solvents is subject to even more complications than the kinetics in aqueous solution.

Another approach to the problem of selecting a likely candidate from among the ambiguous cyanohydrin mechanisms is an examination of the kinetics and mechanism of other carbonyl addition reactions. The study of semicarbazone formation[5] is probably the most comprehensive investigation of a carbonyl addition reaction. The results are interpreted to indicate generalized acid catalysis and to indicate that the reaction involves carbonyl compound, free semicarbazide and the acid catalyst as the reactive species. However this interpretation is subject to some doubt. The agreement of k_A values for acetone in Table VI of reference (5) was taken to establish that the reaction involves the species suggested. If, however, it is assumed that the reactive species are carbonyl compound and semicarbazide acid ion subject to basic catalysis, then the k_A (or k_B in this case) values calculated on this basis agree just as well as those calculated on the basis of generalized acid catalysis. This would be expected from the equilibrium,

$$RNH_2 + HOAc \rightleftharpoons RNH_3^+ + OAc^-$$

Another point of doubt about the validity of the k_A values in Table VI derives from the results presented in Table V for furfural. In this case, extrapolation of a plot of k_2 vs. buffer composition to zero concentration indicates that, if it is generalized acid catalysis only, there is a contribution toward the value k_2, at the given pH, of 9.0 by H_3O^+ and/or H_2O catalysis. For the first composition in Table V this means that catalysis due to acids other than HOAc accounts for 40% of the rate constant. In the case of acetone, the data of Table VI ~~does~~ not consider at all catalysis by any acid other than HOAc. No justification for doing this was mentioned. It is difficult to say what the relative amounts of catalysis by undissociated acid should be for acetone on the basis of the results for furfural. According to the findings of Bell and Lidwell discussed on page 20 of this thesis, it even seems possible that acetone, being a less reactive compound, might show a larger proportion of catalysis by acids other than HOAc than furfural. Obviously experimental investigation is necessary. The absence of such investigation renders uncertain the interpretation which may be made on the data of Table VI.

The investigators report that they could find no clear evidence of basic catalysis. They found that the rate constant of cyclohexanone semicarbazone formation in 1N NaOH solution was less than one-twentieth of that in a buffer solution of pH 7. They conclude that basic catalysis, if present, must be exceedingly small. However, it must be pointed out that the rate constants which were involved in the above comparison are based on the total amount of semicarbazide present, whether in the free base or acid form. If there is any basic catalysis, the reactive species must be the acid form of semicarbazide in order to conform to the rate equation observed. Therefore, the rate constants must be referred to semicarbazide present in the acid form if they are to express basic catalysis in the reaction. This may be done by dividing the observed rate constants (actually the portion of the rate constants due to the base catalyzed reaction) by the fraction of semicarbazide present in the acid form. When an attempt is made to correct the observed rate constants in this manner, it is apparent that nothing can be said about the extent of basic catalysis on the basis of the experimental results presented.

In connection with the formulation of a mechanism for semicarbazone formation, it has been suggested[6] that the absence of a kinetic salt effect demonstrates that the rate-controlling step can not be one between ions. A similar deduction for other reactions, on the basis of salt effects, has appeared in the literature. Let us, however, consider the mechanism proposed by Hammett[40] for semicarbazone formation. If step VIII, which involves two ions, is the rate determining step, then the rate equation written according to the Bronsted theory is in agreement with the experimental rate equation and, moreover, predicts no salt effects. The presence or absence of a salt effect in any reaction can not be used as an unqualified criterion of reaction mechanism. Each case should be examined individually.

Oxime and phenylhydrazone formation have been studied in water-alcohol mixtures and the results interpreted to indicate generalized acid catalysis[6]. The same analysis as was given the semicarbazone reaction may be applied and, within the limitations of the experimental data, leads to similar conclusions. The conclusion seems to be that in all of these reactions, as in cyanohydrin formation, no definite deductions may be made as to the mechanism or even the reactive species by a study of the kinetics. Other carbonyl reactions seem to be of little value as a guide to the nature of cyanohydrin formation.

A more complete understanding of the cyanohydrin reaction must remain the object of further researches.

ANALYTICAL APPLICATIONS

The fact that acetaldehyde and propionaldehyde react quantitatively with HCN and the information obtained about the conditions which govern the equilibrium and the rate of these reactions suggested that certain analytical applications could be successfully devised.

First of all, by the addition of an excess of aldehyde to a solution containing halides and cyanide, it should be possible to quantitatively remove the cyanide by formation of the cyanohydrin and then determine the remaining halide by the Volhard method. This would enable one to analyze qualitatively and quantitatively for halides in the presence of cyanide. Secondly, it should be possible to reverse the procedure and analyze quantitatively for acetaldehyde or propionaldehyde. This would be done by the addition of a sample of aldehyde solution to an excess of standard cyanide solution and an analysis of the unreacted cyanide at equilibrium.

Procedures of this sort have long been reported involving the use of formaldehyde, even though the formaldehyde cyanohydrin reaction has not been extensively studied. The various modifications of those procedures are summarized by Kolthoff and Stenger[41]. Certain preliminary experiments have been performed to verify the proposed applications for propionaldehyde and acetaldehyde.

Using the rate constants of propionaldehyde and acetaldehyde, it can be shown, with equation (9), that in a solution of about pH 6.5 or greater, the reaction of the aldehydes and HCN proceeds at least 99.9% to equilibrium in less than five minutes. This was calculated assuming concentrations of about the order of those usually employed. At the pH of NaCN solutions, the reaction is almost instantaneous. However, at this pH the equilibrium would be shifted and the reaction might not be quantitative. In order to obtain information about the state of equilibrium, the following procedure was used:

An approximately 0.2N solution of NaCN was prepared. To 10 ml of this solution was added 25 ml of 0.12N aldehyde solution (an excess). The solution was then acidified with 6 ml of 6N HNO_3 and 0.1N $AgNO_3$ added. With acetaldehyde and propionaldehyde, a precipitate was formed indicating that these reactions are incomplete at the pH of NaCN. With formaldehyde, on the other hand, no precipitate was formed, indicating complete reaction at the pH of NaCN. Then the procedure was modified for propionaldehyde and acetaldehyde. After the addition of the aldehyde solution, 6 drops of bromcresol purple indicator (pH range 5.2-6.8) was added. This solution was slowly titrated with 0.1N HNO_3 (titration conducted over 10-15 minute interval) until the indicator changed color to a definite yellow. The amount of 0.1N HNO_3 was recorded. Then to a similar solution, without indicator, was added the same amount of 0.1N HNO_3, to the nearest 0.1 ml or so, in the same time interval. 6 ml of

6N HNO_3 was introduced and finally 25 ml of 0.1000N $AgNO_3$ added. No precipitate was observed. On filtration and titration of the filtrate with 0.1000N KSCN, the titration value corresponded exactly to that obtained when 25 ml of the $AgNO_3$ was directly titrated with KSCN. Thus at the pH of this indicator the reactions of acetaldehyde and propionaldehyde are complete, since the same result was obtained for both. The solutions of acetaldehyde and propionaldehyde were prepared using purified aldehydes.

This provided the necessary information about the state of equilibrium under the conditions investigated. The 0.1N HNO_3 is added slowly to allow sufficient time for equilibrium to be attained at the pH of the indicator. A separate sample was used to determine the amount of 0.1N HNO_3 required because the indicator color interferes with the color change of the Volhard titration. Propionaldehyde was then used to test the procedure for the determination of chloride in the presence of cyanide as follows:

A 0.1000N NaCl solution was prepared by weighing out the necessary amount of purified NaCl and diluting to volume in a volumetric flask. 10 ml of this solution was placed in an Ehrlenmeyer flask and 10 ml of approximately 0.2N NaCN was added. Then 1.5 ml of technical grade propionaldehyde (calculated to be an excess) was added. 6 drops of bromcresol indicator was introduced and the solution was slowly titrated with 0.1N HNO_3 to the color change. The same amount of 0.1N HNO_3 was added to a sample similarly treated except for the elimination of the indicator. 6 ml of 6N HNO_3 was added, followed by 25 ml of 0.1000N $AgNO_3$. The precipitate which formed was filtered and thoroughly washed with several portions of water. The filtrate was titrated with KSCN in the usual way. The original NaCl solution was also analyzed by the Volhard method. All AgCl precipitates were handled in the absence of sunlight. Each determination was run in triplicate and the average results were as follows:

<u>NaCl Concentration</u>

0.1000N by weight
0.0999N by analysis in absence of cyanide
0.1000N by analysis in presence of cyanide

It is thus obvious that the procedure used is suitable for the quantitative determination of chloride in the presence of cyanide. It is undoubtedly suitable for other halides as well. From a practical standpoint, the use of formaldehyde is much to be preferred. The fact that formaldehyde reacts quantitatively at the pH of NaCN simplifies the procedure because it is not necessary to adjust the pH of the solution to the acid side.

However, the above results are of interest in providing a method for the quantitative determination of acetaldehyde and propionaldehyde. The data of Table 24 furnish an indication of the accuracy obtainable in such analyses. Although the experiments cited in Table 24 were performed using HCN solutions, there is no reason why NaCN solutions could not be used instead. The use of NaCN would be preferred because of the smaller HCN losses and because of the rapidity of the reaction in basic solution. No specific experiments were performed to validate a procedure using NaCN, but from all the results so far obtained, a suitable procedure is readily suggested. One would prepare a standard solution of NaCN, add a sample of aldehyde solution to an excess of the NaCN, adjust the pH using bromcresol purple as described above, and then analyze for unreacted cyanide. The analysis of cyanide has already been described. In this procedure, the factor limiting the accuracy of the aldehyde determination would probably be the margin of accuracy of the cyanide analyses. If suitable precautions were taken to minimize losses of HCN, the analysis should be accurate to a few tenths of a percent or better.

SUMMARY

(1) The kinetics of acetaldehyde, propionaldehyde and acetone cyanohydrin formation has been studied in dilute aqueous solution at 25°C. The propionaldehyde reaction was investigated in water and in acetate buffers of various pH's, buffer compositions and ionic strengths. The acetaldehyde and acetone reactions were investigated in acetate buffers at a fixed pH and ionic strength, but varying buffer composition.

(2) Reproducible rate constants could not be obtained in unbuffered solution, but were obtained in acetate buffers. All of the reactions followed a second order rate law.

(3) The influence of ionic strength was found to be very small. The kinetic salt effect amounted to about 2 to 4% for the range of concentrations studied.

(4) In the acetone and acetaldehyde reactions, no generalized catalysis was detectable. In the case of propionaldehyde, a small effect amounting to a few percent was observed which could be interpreted as evidence of generalized catalysis. However, the effect is not sufficiently greater than the experimental error to justify any definite conclusions.

(5) At the pH of acetate buffers, acetaldehyde and propionaldehyde react quantitatively with HCN. In a similar pH region, the reaction of acetone with HCN is incomplete and the equilibrium constant has been found to be 13.97.

(6) In a solution of 0.1372N HOAc and 0.0503N NaOAc, the observed rate constants of acetaldehyde and propionaldehyde are 0.212 and 0.494 respectively. The significance of these values as an index of reactivity has been discussed taking into consideration the hydration reactions of these aldehydes.

(7) Various mechanisms for the cyanohydrin reaction have been examined and it is concluded that several different mechanisms are compatible with the kinetics observed. At least three of these have a basis in some theory of carbonyl reactivity.

(8) Analytical applications of the cyanohydrin reaction are discussed. A procedure is suggested for the quantitative determination of acetaldehyde and propionaldehyde.

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ABSTRACT

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Title of thesis: The Kinetics and Mechanism of the Cyanohydrin Reaction in Aqueous Solution
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The kinetics of acetaldehyde, propionaldehyde and acetone cyanohydrin formation have been studied in dilute aqueous solution at 25°C. Measurements were conducted in acetate buffers under various conditions to ascertain the influence of ionic strength, pH and buffer composition on the rate constants. The progress of the reaction was followed by withdrawal of samples and determination of the unreacted cyanide from time to time.

It was found that the reaction of carbonyl compound with HCN proceeded mole for mole. The reaction followed a second order law, first order relative to HCN and first order relative to the carbonyl compound. The kinetic salt effect is very small and amounts to only a few percent for the range of ionic strength studied. It was found that acetaldehyde and propionaldehyde react quantitatively with HCN. The acetone reaction is incomplete and the equilibrium constant for cyanohydrin formation was found to be 13.97. These results for acetone and acetaldehyde are not in agreement with the results reported by other investigators.

In the case of acetone and acetaldehyde, no generalized

catalysis was detectable. The propionaldehyde reaction, however, exhibited an effect ranging from 4 to 6% which could be interpreted as generalized catalysis. Although the rate constants were reproducible to within 1 or 2%, it is doubtful whether the effect observed is sufficiently greater than the experimental error to permit a definite significance to be attached to the results. Therefore, the possibility of generalized catalysis was ignored in the consideration of reaction mechanisms.

The currently accepted Lapworth mechanism for cyanohydrin formation was found to be in accord with the kinetics observed. However, this mechanism is not uniquely indicated by the kinetics. Several other mechanisms lead to the same rate equation as the Lapworth mechanism and the kinetics is therefore ambiguous. The other possibilities which have a basis in some theory of carbonyl reactivity are discussed.

Thus the study of the kinetics of the cyanohydrin reaction in aqueous solution provides no clear definition of the reactive species or of the manner in which the reactive species interact. The kinetics of cyanohydrin formation in other solvents and the kinetics of other carbonyl addition reactions have been considered in an attempt to obtain some information which might serve as a basis for selecting preferentially one of the possible cyanohydrin mechanisms. However, these latter investigations appear to be subject to complications which obscure their own mechanisms and they are, accordingly, of little value as a guide to cyanohydrin formation.

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