The atomic heats of solution of potassium, rubidium and cesium have been measured over a fairly wide range of concentrations and found to be zero.

The atomic heats of solution of metallic lithium, calcium, barium and strontium have been measured over a range of concentrations and have been found to have a negative heat of dilution.

Schenectady, N. Y. Received September 29, 1938

[Contribution from the Chemical Laboratory of the University of California]

The Kinetics and Mechanism of α-Aminoisobutyronitrile Formation

By T. D. Stewart and Choh-hao Li

Introduction

The α-amino nitriles are generally obtained by the reaction of equimolecular proportions of an alkali cyanide and an amine salt with an aldehyde or ketone in aqueous or aqueous alcoholic solution,[1] or by the reaction between equimolecular proportions of a cyanohydrin and an amine.[2] The main reaction is

$$R_2C(OH)CH + R_2NH \rightleftharpoons R_2C(NR_2)CN + H_2O \quad (1)$$

This equation implies that the oxygen is removed from the cyanohydrin and is replaced by the amino group directly; but in view of the following argument this path is extremely unlikely.

When a cyanohydrin is placed in an alkaline medium, such as a solution of an amine, the following equilibria are rapidly established

$$R_2C(OH)CN \rightleftharpoons R_2CO + HCN \quad (2)$$

$$HCN + R_2NH \rightleftharpoons R_2NH_2CN \rightleftharpoons R_2NH_2^+ + CN^- \quad (3)$$

The rapid appearance of cyanide ion demonstrates an apparent high reactivity of the carbon–cyanide bond in the cyanohydrin and shows the improbability of the hydroxyl group being dissociated or exchanged in alkaline solution. Ultee[3] showed that this reactivity was not a property of the cyanohydrin as such, because in acidic medium prussic acid was not formed.

The mechanism[4] of the dissociation in alkali can be expressed

$$R_2C(CN)OH + OH^- \rightleftharpoons R_2C(CN)O^- + H_2O \quad (4)$$

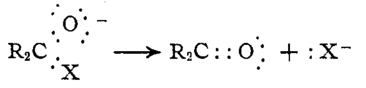
$$R_2C(CN)O^- \rightleftharpoons R_2CO + CN^- \quad (5)$$

in which both reactions are rapid and reversible. Equations (4) and (5) are of particular interest inasmuch as a similar effect of alkali has been noted in other cases, namely, aldehyde bisulfite and formocholine dissociations.

$$C_6H_5CH(SO_3)OH^- \xrightleftharpoons{-OH^-} C_6H_5CH(SO_3)O^- \longrightarrow C_6H_5CH\dot{O} + SO_3^= + H_2O \quad (6)$$

$$(CH_3)_3\overset{+}{N}CH_2OH \xrightleftharpoons{-H^+} CH_3)_3\overset{+}{N}CH_2O^- \longrightarrow (CH_3)_3N + CH_2O \quad (7)$$

In each case[5] the rate of appearance of cyanide ion, sulfite ion or trimethylamine, respectively, is proportional to the hydroxide ion concentration which in turn governs the concentration of the intermediate ion. In each case the intermediate takes the form



$$R_2C\begin{matrix}:\ddot{O}:^-\\ \vdots\\ X\end{matrix} \longrightarrow R_2C::\ddot{O}: + :X^- \quad (8)$$

in which the electron pair bonding the radical X is replaced by an unshared electron pair of the charged oxygen; the dissociation is therefore a substitution reaction and not an ionization in the ordinary sense, and as such would be a relatively rapid reaction.[6] The alkaline catalysis of sugar mutarotation as well as alkaline catalysis of diacetone alcohol dissociation[7] may be represented similarly. It is clear that in an acidic medium the concentration of the intermediate ion would be reduced and hence the rate of dissociation inhibited; in alkali neither the cyanohydrin as such nor the intermediate ion could be expected to dissociate hydroxyl or react to replace it by the amine group.

A clue as to the path by which the oxygen (Eq. 1) is removed is given by the known reactions of the α-amino alcohols and their ethers. Lapworth and his co-workers[8] have pointed out

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[1] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1931, Vol. XI, p. 4.

[2] Zelinski and Stadnikoff, *Ber.*, **39**, 1722 (1906).

[3] A. J. Ultee, *Rec. trav. chim.*, **28**, 248 (1909).

[4] A. Lapworth, *J. Chem. Soc.*, **85**, 1206 (1904).

[5] (a) T. D. Stewart and L. H. Donnally, This Journal, **54**, 2333 (1932); (b) T. D. Stewart and H. P. Kung, *ibid.*, **55**, 4813 (1933).

[6] A. R. Olson, *J. Chem. Phys.*, **1**, 418 (1933).

[7] F. H. Westheimer and H. Cohen, This Journal, **60**, 90 (1938).

[8] (a) W. Cocker, A. Lapworth and A. Walton, *J. Chem. Soc.*, **111**, 449 (1930). (b) T. D. Stewart and W. E. Bradley, This Journal, **54**, 4172 (1932).

the capacity of the hydroxyl and alkoxyl groups in these substances to dissociate

$$R_2C(NR_2)OH + H^+ \rightleftarrows R_2C{=}N^+R_2 + H_2O \quad (9)$$

The reaction conforms to the generalized intramolecular substitution reaction presented in Equation 8, and, unlike the cyanohydrin case, both the oxygen and nitrogen systems are susceptible to dissociation. It is evident that in the α-amino alcohols a means is to be found by which the oxygen of a ketone may be removed readily. We may therefore superimpose upon the system represented in Equations 2 and 3 the further reactions

$$R_2C{=}O + R_2NH \rightleftarrows R_2C(OH)NR_2 \quad (10)$$

$$R_2C(OH)NR_2 + HCN \rightleftarrows R_2C(CN)NR_2 + H_2O \quad (11)$$

$$R_2C(OH)NR_2 + R_2C(OH)CN \rightleftarrows R_2C(CN)NR_2 + R_2C(OH)_2 \quad (12)$$

showing how the hydroxyl of the cyanohydrin is formally replaced by the amine group. Evidence favoring this viewpoint is presented below.

Experimental Results

The Rate Law in Acetone as a Solvent.—The rate of the reaction

$$(CH_3)_2C(OH)CN + (C_2H_5)_2NH \longrightarrow (CH_3)_2C(CN)N(C_2H_5)_2 + H_2O$$

was determined to be proportional to the concentration of each of the reactants in acetone solution. Tables I and II present typical data; *a* and *b* represent the concentration of acetonecyanohydrin and diethylamine, respectively, and k'' is the specific reaction rate constant as normally calculated for a second order reaction. In Table II the rate constant was calculated for each interval of time and shows no trend up to 65% of the total reaction, showing that the equilibrium lies far to the right in this solvent.

TABLE I

RATE OF REACTION USING DIFFERENT INITIAL CONCENTRATIONS AT 25°

a g. mole/l.	*b* g. mole/l.	Time sec. × 10^{-3}	% of *b* reacted	$k'' \times 10^5$ g. mole/l./sec.
0.1277	0.1277	86.4	11.95	1.225
.2554	.1277	43.2	11.80	1.174
.1277	.2554	43.2	6.05	1.211
.0487	.4756	22.2	1.25	1.233

TABLE II

RATE OF REACTION BETWEEN DIETHYLAMINE AND ACETONECYANOHYDRIN AT 25°; $a = b = 0.1277$

Time sec. × 10^{-3}	Per cent. reacted	$k'' \times 10^5$ g. mole/l./sec.
0.0	0.0	
86.4	11.95	1.225
175.2	21.62	1.276
262.8	29.20	1.218
376.8	37.38	1.266
585.0	48.26	1.248
1196.4	65.40	1.225
	Av.	1.243

Catalysis by Tertiary Amines.—When triethylamine or tri-*n*-propylamine is added to the reacting mixture of acetonecyanohydrin and diethylamine in acetone, the rate of the reaction is increased in proportion to the concentration of tertiary amine present, as shown in Fig. 1. If k''_t is the over-all bimolecular specific reaction rate constant we may write

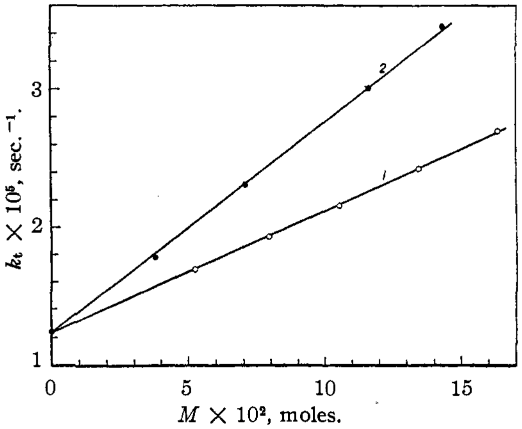

Fig. 1.—The catalytic effect of tertiary amines: 1, tri-*n*-propylamine; 2, triethylamine.

$$k'' = k'' + mk''_c$$

where *m* is the molarity of the tertiary amine, k''_c the specific reaction rate constant of the catalyzed reaction, and k'' that of the uncatalyzed reaction. The rate law becomes

$$\text{Rate} = k''(a)\,(b) + k''_c(a)\,(b)\,(m)$$

as an expression of two independent rate determining steps. The data are summarized in Table III.

TABLE III

CATALYTIC EFFECT OF TERTIARY AMINES AT 25°

Triethylamine $k'' = 1.539 \times 10^{-4}$		Tri-*n*-propylamine $k''_c = 8.890 \times 10^{-5}$	
100*m*	$k''_t. \times 10^5$	100*m*	$k''_t \times 10^5$
0.000	1.240	0.000	1.240
3.799	1.783	5.245	1.690
7.078	2.355	7.940	1.930
11.620	3.037	10.560	2.162
14.300	3.457	13.430	2.428
		16.360	2.698

Catalysis by Alcohols.—Figure 2 and Table IV show the change in specific reaction rate when varying portions of ethanol are added to the ace-

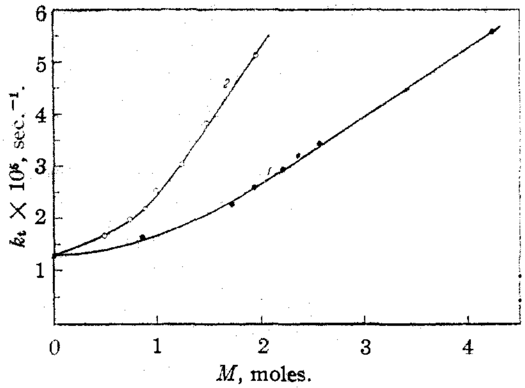

Fig. 2.—The catalytic effect of alcohols: 1, ethanol: 2, methanol.

tone solution. No correction was necessary for initial dissociation of the cyanohydrin (Eqs. 2 and 3) for the calculation of the rate constant, since the dissociation was negligible due to the high acetone concentration. In these solvents equilibrium is reached when the reaction has proceeded about 60%, so that for each solvent the equilibrium was determined and used in the calculation of the rate constant. Table V presents typical data in which k_t has been calculated, using the equation

$$dx/dt = k_t(a - x)(b - x) - k_2x^2$$

where k_t and k_2 are specific velocity constants of the forward and reverse reactions, respectively.

TABLE IV

CATALYTIC EFFECT OF ETHANOL AT 25°

Molality of ethanol	$k_t \times 10^5$
0.000	1.240
.855	1.618
1.352	1.948
1.712	2.260
1.931	2.588
2.205	2.942
2.372	3.207
2.570	3.450
4.240	5.579

TABLE V

TYPICAL KINETIC DATA IN ETHANOL-ACETONE MIXTURE AT 25°

Molality of ethanol: 4.240; equilibrium constant, K, 1.872; $a = 0.0925$ M; $b = 0.925$ M.

Time (sec. $\times 10^{-3}$)	X ($M \times 10^3$)	$k_t \times 10^6$ (g. mole/l./sec.)
00.0	0.00	
12.9	6.08	5.44
31.5	13.62	5.45
45.0	18.69	5.58
85.8	29.38	5.42
118.2	37.10	5.79
167.1	44.08	5.82
212.1	48.25	5.58

Methanol also shows the same effect on the rate as ethanol as shown numerically in Table VI and graphically in Fig. 2 (curve II). Addition of t-butyl alcohol does not affect the rate up to 3 M alcohol; dioxane up to 2 M has no effect upon the reaction rate in acetone.

TABLE VI

CATALYTIC EFFECT OF METHANOL AT 25°

Molality of methanol	$k_t \times 10^5$
0.000	1.240
.491	1.657
.734	1.972
.884	2.170
.983	2.525
1.225	3.003
1.475	3.820
1.950	5.115

The Rate Law in Alcohol. Catalysis by Acetone.—It is found in alcohol containing up to 1.4 M acetone that the rate constant calculated from the bimolecular rate law decreases as the initial concentration of the reactants increases. The rate of the reaction is actually independent of acetonecyanohydrin and at constant acetone concentration is proportional to the concentration of diethylamine as shown in Figs. 3 and 4. Since the acetone concentration is high,[9] the dissociation of cyanohydrin is small and may be considered to be constant over the small portion of the total reaction studied. The data are shown graphically in Figs. 3 and 4 where the logarithm of the diethylamine concentration is plotted against the time. The velocity constants, summarized in Table VII, were evaluated by multi-

TABLE VII

INITIAL CONCENTRATIONS AND REACTION RATES IN ALCOHOL SOLUTION. RATE DATA PLOTTED IN FIGS. 3, 4 AND 5

Run	a(Cyanohydrin) m./l.	b(Diethylamine) m./l.	c(Acetone) m./l.	$k_t' \times 10^6$
E_7	0.1058	0.1058	0.4160	3.38
E_{22}	.1062	.2124	.4170	....
E_{13}	.2155	.2155	.440	....
E_5	.1033	.1033	.1541	....
E_6	.2106	.2106	.1551	1.44
E_9	.2166	.2166	.1710	....
E_{17}	.2157	.2157	.6910	....
E_{23}	.1050	.1050	.6793	5.12
E_{18}	.2159	.1079	.6920	....
E_{19}	.2166	.2166	1.3680	9.67
E_{24}	.1059	.1059	1.3545	....
E_{16}	.2147	.2147	0.073(x.)	0.928
E_{20}	.2160	.1080	1.3500	....

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(9) In Expt. E16 no acetone was added; that present was due to dissociation of the cyanohydrin. The initial reaction rate only was calculated, as the acetone concentration was not constant in this case.

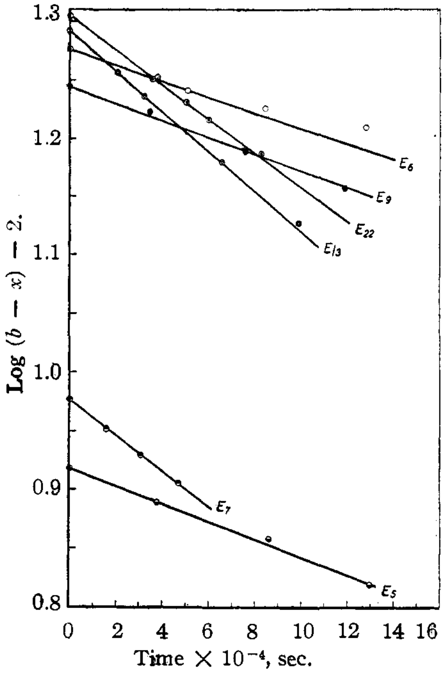


Fig. 3.—The reaction rate in ethanol.

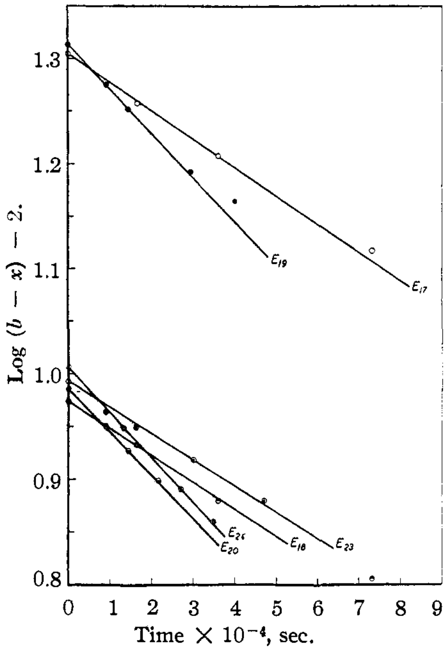


Fig. 4.—The reaction rate in ethanol.

plying the negative slopes of the straight lines by 2.303. In Fig. 5 the acetone concentration is plotted against the unimolecular rate constants of Table VII. The result indicates a reaction rate proportional to the acetone concentration.

Discussion of Results

Empirical rate laws have been obtained in solutions using acetone as solvent with varying amounts of alcohol present, and in solutions using alcohol as solvent with varying acetone content. For the first series the rate law found is

$$d(P)/dt = k''(\text{amine})(\text{cyanohydrin}) \qquad (A)$$

where P is the product of the reaction.

In ethanol as solvent a different rate law has been found

$$d(P)/dt = k'(\text{acetone})(\text{amine}) \qquad (B)$$

It is improbable that these rate laws should involve two fundamentally different mechanisms, and an attempt will be made to derive them from a simple mechanism.

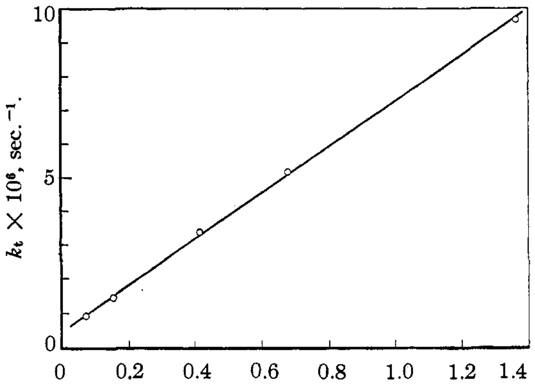


Fig. 5.—Effect of acetone concentration upon the specific reaction rate in alcohol.

The Reaction Mechanism.—Assume the existence of the reaction

$$R_2C{=}O + R_2NH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R_2C(OH)NR_2 \qquad (13)$$

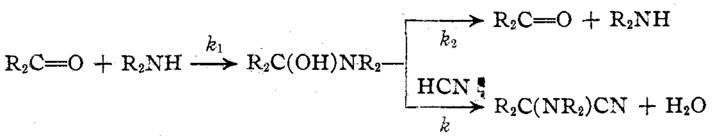
where k_1 is the specific rate of amino alcohol formation and k_2 its specific dissociation rate. We also assume that the mechanism of aminonitrile formation may be expressed

$$d(P)/dt = k(\text{amino alcohol})(\text{HCN}) \qquad (C)$$

The concentration of the hydrocyanic acid is determined by the equilibrium

$$R_2C(OH)CN \rightleftharpoons R_2C{=}O + HCN \qquad (14)$$

From these considerations the empirical rate laws above (Eqs. A and B) may be derived upon the additional assumptions that in acetone as a solvent the equilibrium between the amino alcohol, acetone and amine (Eq. 13) is maintained as the reaction proceeds, whereas in alcohol as a solvent the amino alcohol is no longer at its equilibrium concentration but a low steady state value. This value is determined largely by the acetone concentration. A low acetone concentration permits a higher hydrocyanic acid concentration (Eq. 14) and thereby decreases the probability that any amino alcohol formed will dissociate into its original constituents.



$$R_2C{=}O + R_2NH \xrightarrow{k_1} R_2C(OH)NR_2 \begin{cases} \xrightarrow{k_2} R_2C{=}O + R_2NH \\ \xrightarrow[k]{HCN} R_2C(NR_2)CN + H_2O \end{cases}$$

The rates of appearance and disappearance of amino alcohol may be expressed

$$d(\text{amino alcohol})/dt = k_1(\text{acetone})(\text{amine})$$
$$-d(\text{amino alcohol})/dt = k_2(\text{amino alcohol}) + k(\text{amino alcohol})(\text{HCN})$$

When the steady state is established, these rates are equal and

$$(\text{amino alcohol}) = \frac{k_1(\text{acetone})\ (\text{amine})}{k(\text{HCN}) + k_2}$$

Therefore

$$d(P)/dt = \frac{k_1(\text{acetone})\ (\text{amine})\ (\text{HCN})}{k(\text{HCN}) + k_2} \qquad (D)$$

If k_2 is small and negligible in comparison with the factor k(HCN), Equation (D) becomes

$$d(P)/dt = k'(\text{acetone})(\text{amine}) \qquad (B)$$

which is the empirically determined rate law, and implies that the major rate determining step is the rate of amino alcohol formation.

In acetone as the solvent, where the amino alcohol is maintained at or near its equilibrium concentration[10]

$$(\text{amino alcohol}) = k_1/k_2(\text{acetone})(\text{amine})$$

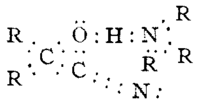
and from Equations C and 14

$$d(P)/dt = kk_1k_2(\text{acetone})(\text{amine})(\text{HCN}) \qquad (E)$$
$$= k''(\text{amine})(\text{cyanohydrin}) \qquad (A)$$

It is thus possible to use a single reaction mechanism (Eq. C) involving amino alcohol and hydrocyanic acid over the whole range of mixed solvents, and yet account in a simple way for the observed change in the rate law from an apparent bimolecular form in pure acetone, to a pseudomonomolecular law in alcohol as a solvent.

The Catalytic Effect of Tertiary Amines and Alcohols.—The factor described as (HCN) in the rate determining steps (Eq. C) was evaluated from Eq. 14 as the ratio: (cyanohydrin)/(acetone). An equally valid evaluation would be the ratio: (amine cyanide salt)/(amine). Actually, hydrocyanic acid is present not only as such, but in various solvated forms; the cyanohydrin itself as well as a tertiary amine salt could be considered as belonging to the solvated hydrocyanic acid species of molecule, and as such enter the rate law. Each such variation of hydrocyanic acid would contribute to the total reaction rate in a specific and characteristic way. From the slopes of the curves in Figs. 1 and 2 the catalytic constants in acetone for the alcohols and amines appear in the order: ethanol, 4.0; methanol, 8.0; tri-*n*-propylamine, 89; and triethylamine, 154.

It is striking that there is no evidence of the secondary amine (one of the reactants) taking the place of the tertiary amine (a catalyst) and thereby entering the rate law to the second power. A ten-fold excess of diethylamine was used to test this, and any adequate hypothesis of this catalytic action should consider it. It is obvious that as bases, the tertiary and secondary amines are nearly equivalent, but in one respect their complexes with acetone cyanohydrin are very different.



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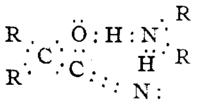

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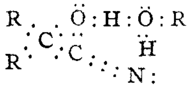

III

Formulas II and III present chelated complexes between the cyanohydrin and secondary amine and alcohol. In these cases, the presence of the protons from the secondary amine and alcohol, respectively, offers opportunity for completion of a ring structure through hydrogen bond formation between the cyanide group and the nitrogen or oxygen atoms. The corresponding tertiary amine structure is not chelated, and, as discussed in the Introduction, its formation would increase the reactivity of the cyanide residue and thereby increase the availability of cyanide for replacement of the hydroxyl group of the amino alcohol (Eqs. 11 and 12). Chelation in II would both stabilize the complex, and in case of rupture of the carbon–cyanide bond, effectively reduce the activity of the cyanide ion by its association with the amine residue. The alcohol complex, on the other hand,

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[10] The fact that pure acetone and diethylamine react only slightly to form the amino alcohol is indicated by the properties of their binary solution. Results of this study will appear in a separate communication.

is intermediate in its reactivity; as a chelated structure it might be reasonably stable and less reactive than the tertiary amine derivative; as an oxonium rather than an ammonium derivative it would offer a source of hydrocyanic acid far more reactive than the secondary amine complex. It is interesting that *t*-butyl alcohol and dioxane do not participate in this catalysis, a result which clearly indicates that these substances are no better proton acceptors than acetone, and very much poorer than the primary alcohols.[11]

The Reaction in Alcohol.—The pseudo first order reaction found in alcohol as a solvent is well supported. Doubling cyanohydrin concentration produces very little difference in the rate of the reaction, as measured by the slopes of the curves in Figs. 3 and 4. On the other hand, doubling the amine concentration doubles the actual rate but not the specific rate. Moreover, tertiary amines do not catalyze the reaction in alcohol, that is, under conditions where the rate determining step is primarily amino alcohol formation. Since the reaction probably comes to an equilibrium at close to 60% completion in alcohol, the measurements have been carried to but 25% in any one experiment. In Fig. 3, Curve E_{22}, there is evidence of a slower reaction than would be predicted from Curves E_7 and E_{13}, and this may be ascribed to the fact that amine is in excess in this experiment, with consequent increase in the steady state value of the amino alcohol concentration. The fact that in Fig. 5 where the specific reaction rate constant is plotted against the acetone concentration, the straight line does not pass through the origin, indicates that the steady state value of the amino alcohol concentration is not zero, but decreases relatively with decreasing acetone concentration. At any one acetone concentration k_2 is small compared to k_2 (HCN) as discussed above, and no interference arises with the apparent first order law. The accuracy of the data does not warrant an attempt to calculate specific values for k_1, k_2 and k_3 which would be required for a complete analysis.

Experimental

Materials.—The preparation of acetonecyanohydrin has been described already.[11] All amines were fractionated after standing over fused potassium hydroxide for at least one week. The fractions used distilled as follows: $(C_2H_5)_2NH$, 55.46° (corr.); $(C_2H_5)_3N$, 89.23° (corr.); and $(CH_3CH_2CH_2)_3N$, 156.47° (corr.). Acetone was refluxed for several days with solid potassium permanganate, distilled, dried over calcium chloride and fractionated in a 1-meter column of the Podbielniak type. The central fraction had a constant boiling point of 56.20° (corr.). Alcohols were treated as previously described.[11]

Experimental Procedure.—The diethylamine was dissolved in the dried solvent, pure acetone or acetone–alcohol mixtures. in known concentrations, and added to weighed portions of cyanohydrin in a thermostat. Aliquot parts of this solution were transferred at known time intervals to known volumes of 0.020 *M* silver nitrate in 0.20 *M* nitric acid solution and the mixture allowed to stand for an hour to complete the precipitation of silver cyanide. The latter was then filtered off, washed with water, and the filtrate titrated with standard thiocyanate using ferric alum as indicator. Accuracy in the end-point depends upon having an appreciable excess of silver nitrate in the filtrate and thorough removal of the precipitated silver cyanide.

The above analytical method for the determination of the amount of aminonitrile formed depends upon several factors. In the presence of appreciable acetone the cyanohydrin does not dissociate hydrocyanic acid. even in the presence of amines. In the solvents low in acetone allowance was made for such dissociation. Neither does the cyanohydrin lose cyanide ion to acidified silver nitrate. The rate at which aminonitrile loses cyanide ion depends upon the acidity. When the excess nitric acid is 0.05 *M*. half of a given amount of aminonitrile reacts in three minutes; when the excess acid is 0.13 *M* the half-life is about six and one-half minutes: no appreciable reaction occurs in 1 *M* nitric acid. It is important that no local concentration of alkali exist during the mixing of the alkaline reaction mixture and the acidified silver nitrate. To avoid this, vigorous stirring is employed and a concentration of acid greater than the concentration of amine is required.

Summary

The specific reaction rates of the reaction

$$(CH_3)_2C(CN)OH + (C_2H_5)_2NH \longrightarrow (CH_3)_2C(CN)N(C_2H_5)_2 + H_2O$$

have been measured in acetone and in alcohol as solvents, and the corresponding rate laws deduced. The two rate laws are, for the alcohol and acetone solvents, respectively

$$d(P)/dt = k'(\text{acetone})(\text{amine})$$
$$d(P)/dt = k''(\text{amine})(\text{cyanohydrin})$$

These have been shown to be related through a common reaction mechanism, and this in turn has been discussed from the general standpoint of the reactions of carbonyl systems.

BERKELEY, CALIF. RECEIVED JULY 22, 1938

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[11] C. H. Li and T. D. Stewart, THIS JOURNAL, 59, 2596 (1937).