

KINETIC STUDIES ON THE REACTION OF AMINES WITH ALDEHYDES

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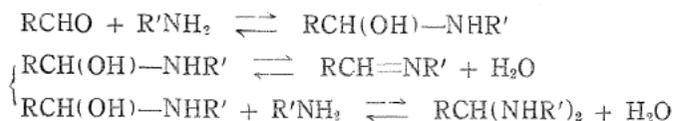
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Introduction

The carbonyl carbon atom, in general, has strongly electrophilic character owing to the following resonance structure: $\text{>C=O} \leftrightarrow \text{>C}^+ - \text{O}^-$. Thus, carbonyl compounds may be attacked at the carbonyl carbon atom by nucleophiles such as amines, alcohols, cyanide ion, sulfite ion and water¹⁾.

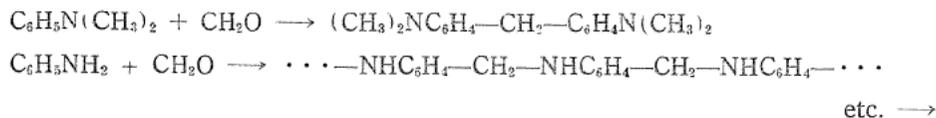
Among the most carbonyl compounds, aldehydes are relatively reactive, compared with ketones, since the former suffers less electron-release and less steric effect by alkyl groups than the latter.

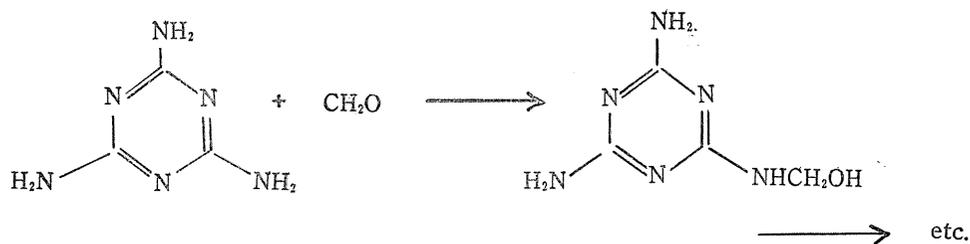
The reactions of primary amines with aldehydes involve the initial attack of the electron-rich nitrogen atom in amines on the electron-deficient carbonyl carbon atom. The reactions may be divided into two main steps; the first one is the addition of amines to carbonyl group to form α -aminoalcohols and the second involves either an intramolecular dehydration of the resulting α -aminoalcohols to form the products with C=N bond or an intermolecular dehydration between the α -aminoalcohols and another amine molecule to give the products having alkylidene bridge.



The first class of products involves Schiff bases, semicarbazones, oximes, hydrazones and so on. The second class involves urea resin, urea fertilizers, melamine resin, hexamines, and so on. Generally most intermediary α -aminoalcohols are difficult to isolate because of their low stability except for mono-hydroxymethylated urea and amide and α -hydroxyethylated urea.

One of the authors has studied on the kinetics and mechanism of the condensation of formaldehyde with dimethylaniline^{2a)}, aniline^{2b)} and melamine^{2c)} as shown in the following equations.

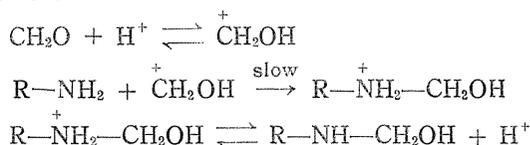




The former two reactions are acid-catalyzed, and the rate increases with increasing acidity at the lower acidity, but after a definite pH, it decreases with increasing acidity.

On the other hand, the condensation of melamine with formaldehyde is subject to both acid and base catalysis, suggesting the reaction between free base and protonated formaldehyde in acidic media, the reaction between free base and free formaldehyde in neutral media, and the reaction between the conjugate base of amine and free formaldehyde in basic media. The difference may be due to the difference in basicities of aniline and melamine^{2c)}.

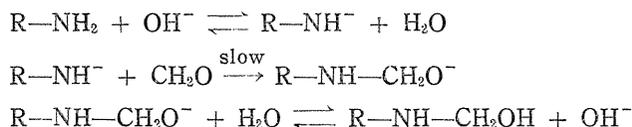
At pH 3.0 to 3.8



At pH 5.0 to 6.0



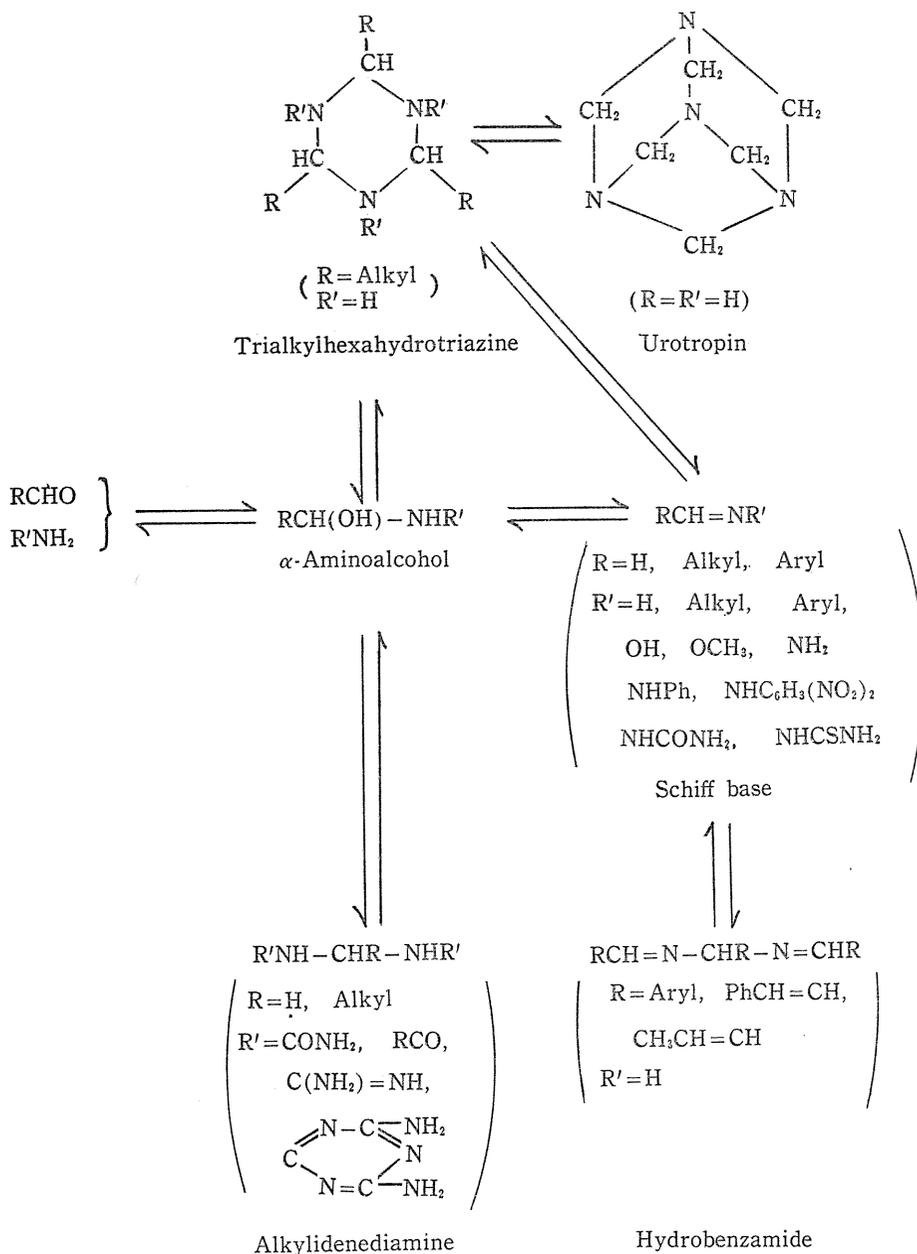
At pH 10.0 to 10.6



Most of these reactions are not only of industrial importance but also involve some important problems in physical organic chemistry, such as failure of linear free energy relationships, change in rate-determining step, and general acid and base catalysis. Similarly as stated above, reactive species may be free aldehyde molecule and free amine base, conjugate acid of aldehyde, or conjugate base of amine in these reactions. In general, carbonyl compounds may be activated by acids, while weakly basic amines may be converted to their reactive conjugate bases by strong bases, hence the reaction between carbonyl compounds and weakly basic amines is subject to both acid and base catalysis. On the other hand, the reaction of amines having stronger basicity is subject to acid catalysis alone, and further, the reaction between highly reactive aldehydes and strong bases is subject to neither base catalysis nor acid catalysis¹⁾.

Electron-withdrawing substituents in aldehydes may decrease the electron density on carbonyl group, resulting in an increase in rate, and electron-releasing

substituents in amines may increase the electron density on nitrogen atom, resulting in an increase in rate. However, simple Hammett's or Taft's rule has scarcely been observed for the formation of semicarbazones and oximes. These phenomena may be explained by the lack of resonance between benzene ring and carbonyl group at the transition state, or by the change in the rate-determining step between addition of amines to aldehydes and dehydration of the resulting α -aminoalcohols¹.



In the present report the kinetic studies of the condensation of ammonia (a stronger base) or urea (a weaker base) with various aldehydes are described. The studies involve a maximum in rate-pH profile (§1), acid and base catalysis (§2, 3, 5 and 6), the Taft's equation and hydration of aldehydes (§2, 3, 5 and 6). Further, the failure of the Hammett's equation and the change in the rate-determining step (§4), and the mechanisms derived from these data on the reactions are discussed.

In summary, the present study together with the other references including in this laboratory suggest for the reaction of amines with aldehydes the following scheme.

1. Kinetics of the Reaction of Formaldehyde with Ammonia

1-1. Summary

The kinetics of the reaction of formaldehyde with ammonia to form hexamethylenetetramine has been investigated in dilute aqueous solutions at 20°C in the pH range between 6.3 and 11.9. The reaction was first-order with respect to ammonia and second-order with respect to formaldehyde. The rate increased sharply with the increasing pH to a maximum between 9 and 10, and then it decreased gradually. These results may be explained by a mechanism involving a rate-determining attack of methylolamine on free formaldehyde to form dimethylolamine through cyclotrimethylenetriamine and 1,5-endomethylene-1,3,5,7-tetrazacyclooctane.

1-2. Introduction

It is well known that formaldehyde reacts with ammonia to form hexamethylenetetramine or hexamine (VI) in a good yield. Although kinetic studies have been reported^{3~4)}, no decisive evidence has been presented about the dependency of the rate on the concentration of each reactant. Richmond, Myers and Wright⁵⁾ suggested a mechanism not on the basis of the kinetics but on that of the isolated derivatives of intermediates.

In the present section are described the results of the kinetic study of the reaction of formaldehyde with ammonia, especially the relation between the pH of the solution and the rate, which implies a probable mechanism of the reaction.

1-3. Experimental

Materials.—The ammonia and formaldehyde used were of G.R. grade. Small amounts of formic acid and methanol in the formaldehyde had no effect on the rate.

Buffer solutions were prepared from 0.4 M monopotassium phosphate and 0.2 M borax solutions for pH 6-9 and from 0.2 M borax solution and 0.1 N sodium hydroxide solutions for pH 9.8-12. No Cannizzaro reaction of formaldehyde using this buffer solution with a pH of 11 was observed.

Rate Measurements.—A solution of 0.1 M aqueous formaldehyde (50 ml.) and a solution of 0.05 M aqueous ammonia (50 ml.), maintained previously at 20°C, were mixed in a flask and thermostated at $20 \pm 0.1^\circ\text{C}$. At known intervals of time, an aliquot (5 ml.) was pipetted out into an ice-cooled Nessler solution⁶⁾⁷⁾

(6.5 ml.) containing mercuric chloride (3 g) and potassium iodide (40 g) in distilled water (100 ml.). An aqueous solution of 0.1 N iodine (10 ml.) and then 2 N aqueous sodium hydroxide (5 ml.) were added to the solution, and it was kept standing for 30 min. at 0–5°C. The solution was then acidified with 2 N hydrochloric acid (10 ml.), the excess iodine being titrated with 0.1 N sodium thiosulfate. The amount of unreacted formaldehyde was determined by a blank test. A crystalline precipitate of hexamine (84%), (m.p. 295°C) was obtained at the end of these rate measurements.

Methylolamines and Related Intermediates.—0.1 M aqueous formaldehyde (50 ml.) and 0.05 M aqueous ammonia (50 ml.) were mixed in a flask and thermostated at 20°C. After 15–20 min. the reaction mixture was added to 0.1 M aqueous acetic acid (100 ml.) which had been previously cooled with ice-water. Two aliquots (10 ml. or 20 ml. each) were immediately pipetted out; one was employed to determine the concentration of formaldehyde by Nessler reagent iodometry, and the other, to determine that of ammonia by titrating excess acetic acid with 0.1 N sodium hydroxide using phenolphthalein. The solution was kept standing at 20°C for one hour to complete the decomposition, as above. Then the concentrations of ammonia and formaldehyde was again determined; they indicated the composition of the unstable intermediates *i.e.*, it was found to be composed of $\text{NH}_3 : \text{CH}_2\text{O} = 1 : 2$.

Methylenedibenzamide and Tribenzoylcyclotrimethylenetriamine.—Aqueous formaldehyde (0.1 mol.) was added to aqueous ammonia (0.2 mol.) cooled by ice for over a 10 min. period. The solution was treated with benzoyl chloride (0.13 mol.) as described by Richmond⁹. Methylenedibenzamide (2.14 g, 8.4%) (m.p. 223°C) was obtained. The freezing point method, using dimethyl sulfoxide as a solvent, gave a molecular weight of 227; calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{N}_2$: 254. IR spectrum: ν cm^{-1} 3370 (-NH-); 1640, 1535, 1290 (*s*-amide). A trace of tribenzoylcyclotrimethylenetriamine was obtained.

On the other hand, aqueous ammonia (0.1 mol.), was added to a cold solution of formaldehyde (0.2 mol.) and then the solution was treated with benzoyl chloride. The chloroform extract gave tribenzoylcyclotrimethylenetriamine (1.88 g, 7.1%) (m.p. 219–220°C). IR spectrum: ν cm^{-1} 1655 (*t*-amide) (Found: C, 72.3; H, 5.26; N, 10.9, Calcd. for $\text{C}_{24}\text{H}_{21}\text{O}_3\text{N}_3$: C, 72.2; H, 5.26; N, 10.5%). Furthermore, methylenedibenzamide (0.324 g, 2.6%) was obtained from the ethanolic extract.

The change in pH was measured by a Hitachi M4 pH meter during the reaction. The ultraviolet absorption spectra were measured by a Shimadzu SV 50 A spectrophotometer in the ranges of 210–300 $\text{m}\mu$ and 190–210 $\text{m}\mu$ by nitrogen purging.

1-4. Results and Discussion

Rate Equation.—The stoichiometric equation for the formation of hexamine from formaldehyde and ammonia has been expressed as



Although the analysis of ammonia and formaldehyde in the reaction mixture indicated that the molar ratio of consumed ammonia vs. formaldehyde was 2 : 3

throughout the reaction, the consumption of formaldehyde estimated by analysis is due not only to the formed hexamine but also to some intermediates, because the consumed formaldehyde may exist as some intermediates besides hexamine. If the reaction mixture was acidified with dilute acetic acid before analysis, the analytical value of formaldehyde became higher. Since hexamine did not decompose under these conditions, the higher value may be due to the decomposition of the intermediates to formaldehyde and ammonia. In alkaline solutions held at 0–5°C for the analysis of formaldehyde, however, the decomposition of the intermediate was slow and negligible. The presence of methanol did not affect this analysis.

The rate of the consumption of formaldehyde, v , may be expressed as the third-order equation:

$$v = \frac{dx}{dt} = k \left(a - \frac{2}{3}x \right) \cdot (f - x)^2 \quad (2)$$

where a and f are the initial concentrations (M) of ammonia and formaldehyde, respectively, x is the concentration of consumed formaldehyde after t seconds, and k , the third-order rate constant. If $a = (2/3)f$, Eq. 2 gives:

$$k = \frac{3}{2} \frac{1}{2t} \left\{ \frac{1}{(f-x)^2} - \frac{1}{f^2} \right\}$$

If $a \neq (2/3)f$,

$$k = \frac{3}{2t} \cdot \frac{2.303}{((3/2)a - f)^2} \log \frac{(3/2)a(f-x)}{f((3/2)a - x)} + \frac{1}{(3/2)a - f} \frac{x}{f(f-x)} \quad (3)$$

The values of k , as calculated by Eq. 3 from the data in an unbuffered solution up to 70% conversion, are shown in Table 1. Although the change in the pH of the solution was small, even in these unbuffered solutions, and although the effect of the pH on the rate was very small within the 10.2–10.5 pH range, most of our experiments were made on buffered solutions. The kinetics except at pH 9–10 follow the above rate equation with a precision similar to that of the example in Table 1. The rate constant at pH 9–10 tended to decrease slightly as the reaction proceeded. The rapid titration of ammonia with hydrochloric acid,

TABLE 1. Typical Rate Data for the Reaction of Formaldehyde with Ammonia in Unbuffered Solution at 20°C Initial conc.: formaldehyde, 0.0532 M; ammonia, 0.0264 M. Change of pH: 10.5–10.2

Time (sec.)	$f-x$ (M)	Conversion (%)	k (M ⁻² sec. ⁻¹)
310	0.0443	22.6	0.535
610	0.0384	37.5	0.579
910	0.0340	48.5	0.633
1145	0.0320	53.1	0.615
1815	0.0291	61.0	0.552
2700	0.0254	70.4	0.584
			Av. 0.584 ± 0.016

using rosolic acid as an indicator to estimate the unreacted ammonia alone, also gave the same third-order constants. While these k values show a good constancy, those value obtained by means of the other third-order or the second-order equations do not. Consequently, it may be concluded that the reaction is first-order with ammonia and second-order with formaldehyde.

The Variation of the Rate with the pH of the Solution.—The rate constants with the varying of pH the solution are shown in Fig. 1 (curve A). The rate increased sharply with an increasing pH to a maximum at pH 9–10 and decreased. An analogous relation has been reported for the reaction of amine or phenol with carbonyl compounds⁹. No appreciable acid catalysis was detected, at least in these alkaline solutions. The maximum is not due to general acid catalysis, but to preliminary equilibria of ammonia and formaldehyde (Eqs. 4 and 6). No appreciable salt effect was observed with the run at pH 7.9. These results suggest the following mechanism, involving an attack of ammonia on free formaldehyde, at least under these conditions:

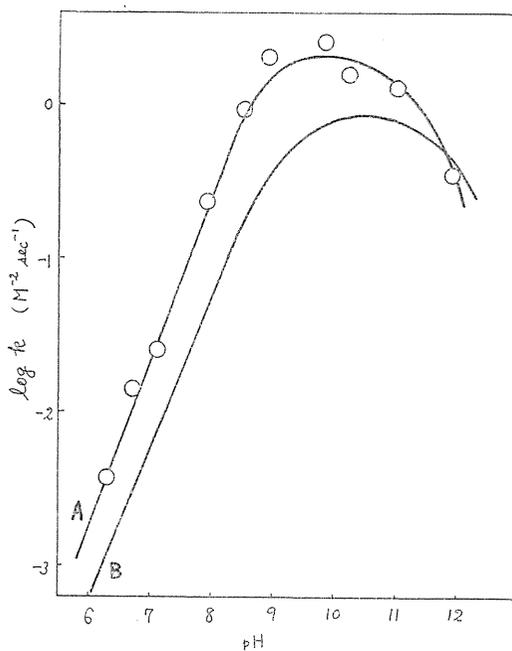
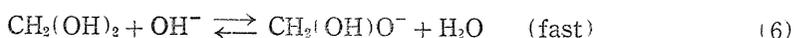
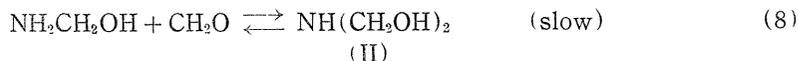


FIG. 1. Plots of logarithm of the observed rate constants (A) and calculated values of $[1/\{1+(K_b/K_w)[H^+]\}][1/\{1+(K_s/[H^+])\}]$ (B) against pH for the reaction of formaldehyde with ammonia.



(I)



The mechanism requires that the rate of the consumption of formaldehyde should be expressed as;

$$v = k_s[\text{NH}_2\text{CH}_2\text{OH}][\text{CH}_2\text{O}] = k_s K_7[\text{NH}_3][\text{CH}_2\text{O}]^2$$

Here, k and K are the rate and equilibrium constants of the subscripted steps, respectively. The estimation of formaldehyde by Nessler reagent iodometry^{6,7)} gives only the concentration of the unreacted formaldehyde, but not those from methylolamine and other formaldehyde derivatives. The experiments were carried out in a dilute aqueous solution; hence,

$$\begin{aligned} a - (2/3)x &= [\text{NH}_3] + [\text{NH}_4^+] = [\text{NH}_3] \left\{ 1 + \frac{K_4[\text{H}_2\text{O}][\text{H}^+]}{K_w} \right\} \\ f - x &= [\text{CH}_2\text{O}] + [\text{CH}_2(\text{OH})_2] + [\text{CH}_2(\text{OH})\text{O}^-] \\ &= [\text{CH}_2\text{O}] \left(1 + K_5[\text{H}_2\text{O}] + \frac{K_5 K_6 K_w}{[\text{H}^+]} \right) \end{aligned}$$

Hence,

$$v = k_s K_7 \frac{1}{1 + (K_4[\text{H}_2\text{O}][\text{H}^+]/K_w)} \left\{ \frac{1}{1 + K_5[\text{H}_2\text{O}] + (K_5 K_6 K_w / [\text{H}^+])} \right\}^2 \times \left(a - \frac{2}{3}x \right) (f - x)^2 \quad (9)$$

Here, K_w is the ionic product of water. At 20°C, $K_4[\text{H}_2\text{O}] = K_b^0 = 1.75 \times 10^{-5}$, $K_5[\text{H}_2\text{O}] = K_f^{(0)} = 10^4$, $K_5 K_w / [\text{H}_2\text{O}] = K_s^{(1)} = 1.62 \times 10^{-13}$, and $K_w = 0.681 \times 10^{-14}$.

Therefore, comparing Eq. 9 with Eq. 2,

$$k = \frac{k_s K_7}{K_f^2} \frac{1}{1 + [\text{H}^+](K_b/K_w)} \left\{ \frac{1}{1 + (K_s/[\text{H}^+])} \right\}^2 \quad (10)$$

or

$$\log k = \log \frac{k_s K_7}{K_f^2} + \log \frac{1}{1 + [\text{H}^+](K_b/K_w)} \left\{ \frac{1}{1 + (K_s/[\text{H}^+])} \right\}^2 \quad (11)$$

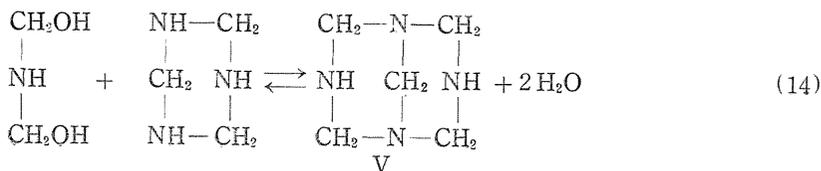
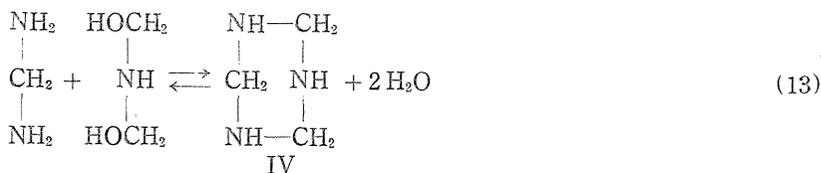
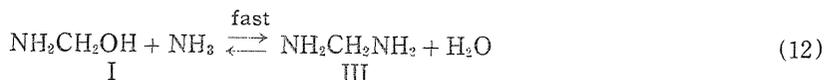
The differentiation of Eq. 10 with respect to $[\text{H}^+]$ gives the pH value of the maximum rate, where the values of K_b , K_w and K_s were corrected for the ionic strength of 0.35 by means of the Debye-Hückel limiting law.

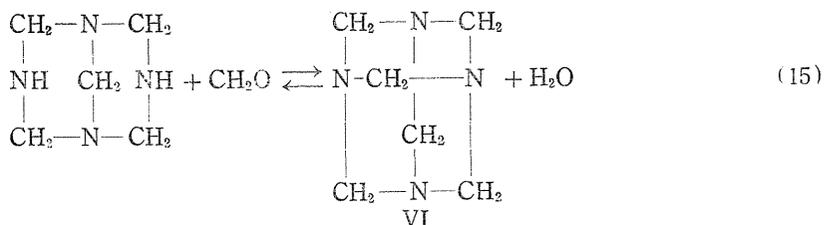
$$[\text{H}^+] = \frac{2 K_w K_s}{K_b} = 2.27 \times 10^{-11} \text{ or pH} = 10.64$$

The plots of the calculated values of $\log [1/\{1 + [\text{H}^+](K_b/K_w)\}] \cdot [1/(1 + K_s/[\text{H}^+])]^2$ and the observed value of $\log k$ against pH are shown in Fig. 1. The observed values show a little deviation from the calculated ones in acidic solutions. In alkaline solutions (pH 10), the observed rate deviates more from the calculated ones.

The difference in height of $0.80 \text{ M}^{-2}\text{sec}^{-1}$ in both linear parts with the slope of ca. 1.0 gives the value of $\log(k_3K_7/K_f^2)$, which leads to 8.8×10^6 for the value of k_3K_7 . However, most of formaldehyde is hydrated *i.e.*, the concentration of free formaldehyde is very small^{10,12}; hence, the concentration of I is negligible except at the initial stages of reaction. Although step 8 is also reversible, the rate of the reverse reaction may be almost negligible at a higher pH.

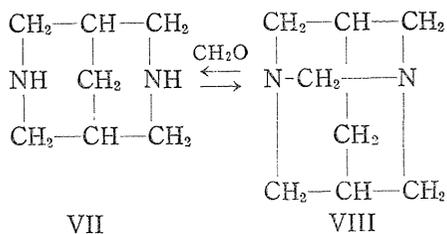
The reaction product, hexamine, did not appreciably decompose in dilute aqueous acetic acid, at least in an hour's time, but there were intermediates which decomposed completely to ammonia and formaldehyde in 30 min. under similar conditions. The concentrations of ammonia and formaldehyde produced from the intermediates were observed to be 0.0030 M and 0.0060 M at 15.5 min., 0.0044 and 0.0088 (30 min.), 0.0045 and 0.0094 (60 min.), respectively. Therefore, the molar composition ratio of formaldehyde and ammonia in intermediates should be 2.0, although Bose⁹ suggested the value of 1.0 for this ratio. The unstable intermediates may include mono-, di-, and trimethylolamine and other cyclic compounds. Dimethylolamine II rather than N-methylolmethylenimine $\text{CH}_2=\text{N}-\text{CH}_2\text{OH}$ may be present, since the reaction mixture had no absorption maximum in range of 210–240 $\text{m}\mu$ corresponding to a $\text{C}=\text{N}$ bond¹³, only a maximum at 191–210 $\text{m}\mu$ (by nitrogen purging), which suggests the presence of amines. Di- and triethanolamine also had absorption maxima in this region. Another probable intermediate, methylenediamine III, the existence of which has been suggested by Richmond *et al.*⁵, should be more stable than dimethylolamine II and would not decompose, because N–C–N bonds in hexamine VI and 1,3-diaza-adamantane VIII are stable in aqueous acetic and mineral acids¹⁴, respectively, and methylenediamine sulfate is isolable in a strongly acidic solution⁵. Nitroso or benzoyl derivatives of cyclo-trimethylenetriamine IV and 1,5-endomethylene-1,3,5,7-tetrazacyclooctane V have been obtained from the reaction mixture^{2a,5}. When formaldehyde was added to an excess of ammonia and then to benzoyl chloride, methylenedibenzamide (8.4%) was obtained exclusively. On the other hand, both tribenzoylcyclo-trimethylenetriamine (7.1%) and methylenedibenzamide (2.6%) were obtained when ammonia was added to an excess of formaldehyde. These facts seem to suggest that the formation of III is faster than that of IV, and that a large ratio of CH_2O vs. NH_3 is favorable for the formation of IV. The following scheme may explain the facts described above.



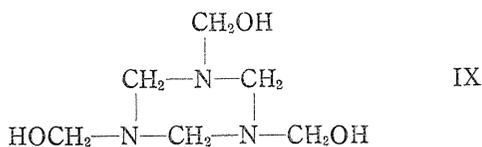


We followed the reaction by estimating the remaining formaldehyde alone; thus, steps 13, 14 and 15 may not be very fast. Therefore, it is not surprising that the derivatives of IV and V were isolated as stable intermediates.

Analogous reactions to steps 13 and 14 have been observed in the reaction between dimethylnitramide and methylenediamine sulfate to form 1,5-endo-methylene-3,7-dinitro-1,3,5,7-tetrazacyclooctane⁵⁾. In support of step 15, it has been known that bispidines VII with a structure similar to V react readily with formaldehyde to form 1,3-diaza-adamantane VIII¹⁴⁾; for example,



Another mechanism^{3 d) 5)}, by which hexamine is formed through trimethylol-cyclotrimethylenetriamine IX, requires that all three methylol groups should be in cis-configuration¹⁵⁾. Moreover, the reaction of the trimethylols with ammonia would be more difficult, since 1-aza-adamantane has been prepared, not directly by the reaction of cis-1,3,5-tris-methylolcyclohexane with ammonia, but by that of its bromoderivative or methanesulfonate and ammonia in a low yield^{14) 16)}.



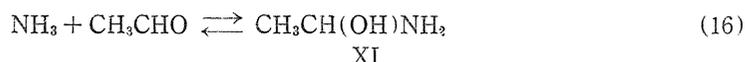
2. Kinetics of the Condensation of Acetaldehyde with Ammonia

2-1. Summary

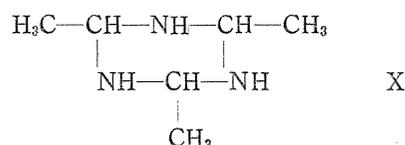
The reaction of acetaldehyde and ammonia to form α -aminoethanol in water and aqueous *t*-butanolic solutions at 5°C has been studied kinetically by means of spectrophotometry. The reaction is reversible, the rate being expressed as: $v = k_1[\text{CH}_3\text{CHO}][\text{NH}_3]$ for the forward reaction and $v = k_{-1}[\text{CH}_3\text{CHOHNH}_2]$ for the reverse reaction. The observed forward rate increase only slightly with increasing pH of the solution, while the reverse reaction is subject to acid catalysis over the pH range 9.4-11.1. The forward rate increases with increasing content of *t*-butanol in the aqueous solvent. A probable mechanism is suggested and discussed.

2-2. Introduction

The product of the reaction of ammonia with formaldehyde is hexamine, the reaction mechanism being rather complex as reported previously^{3-5,17}. On the other hand, reactions with other aliphatic aldehydes result in the formation of α -aminoalcohols or hexahydrotriazine compounds. The reaction of ammonia with acetaldehyde generally yields crystalline triethylhexahydrotriazine trihydrate (X)^{18,19} via α -aminoethanol (XI), but in aqueous solution the triethylhexahydrotriazine may dissociate α -aminoethanol. Since no kinetic studies have been reported on the reaction, the reaction has been studied kinetically in dilute solutions by estimating the concentration of acetaldehyde by means of spectrophotometry to elucidate the probable mechanism of the condensation (16).



XI



2-3. Experimental

Materials.—Ammonia used was of G.R. grade. Commercial acetaldehyde of C.P. grade was redistilled five times (b.p. 22–23°C). It gave UV absorption spectrum with a single maximum at 278 m μ . Commercial acetic acid and t-butanol were redistilled, and had no absorption at wave-length over 265 m μ .

The Reaction Products Criterion.—A crystalline product, m.p. 92–93°C¹⁸ (in a sealed tube), was obtained in 74% yield by the condensation of conc. NH₄OH aq. (0.6 mole) with aqueous acetaldehyde (0.29 mole) at room temp. The product was composed of equimolar ammonia and acetaldehyde, having the characteristic IR spectra²⁰ of OH and NH: $\nu_{\text{Max}}^{\text{Nujol}}$, cm⁻¹ 3440 (-OH), 3330 (-NH-)²¹, 1510 (-NH-)²¹, but no absorption maximum corresponding to C=N (1690–1640) or NH₂ (1650–1590) band was observed. The product had little absorption at wave-length over 250 m μ . The product was hexahydrotriazine trihydrate but the determination of the molecular weight by means of depression of freezing point of a dimethyl sulphoxide solution gave the values of 62.1 and 62.7 which agree with that of α -aminoethanol (61.1). Hence it should exist as α -aminoethanol at least in this solvent.

Typical Procedure for Kinetic Study.—The rates were measured by following the decrease of the carbonyl peak at 278 m μ with a Shimadzu SV 50 A spectrophotometer. 0.2 M ammonia (50 ml.) containing an appropriate amount of acetic acid and 0.2 M acetaldehyde (50 ml.) were mixed in a flask and thermostated at 5°C. Aliquots (about 4 ml.) were pipetted out and introduced into cells at regular intervals of time, and the extinctions at 278 m μ were determined spectrophotometrically.

The forward and reverse rate constants were calculated by means of the following equations derived from Eq. 16.

$$k_1 = \frac{1}{t} \cdot \frac{2.303 x_e}{ab - x_e^2} \log \frac{(ab - xx_e)x_e}{(x_e - x)ab} \quad (17)$$

$$k_{-1} = \frac{1}{K} k_1 = \frac{(a - x_e)(b - x_e)}{x_e} k_1 \quad (18)$$

Here, k_1 and k_{-1} are the apparent rate constants for the forward and reverse reactions, respectively, a the initial concentration of ammonia and b that of acetaldehyde, x the concentration of consumed acetaldehyde at time t and x_e that at the equilibrium, and K is the equilibrium constant of step 15. Since the reaction was fast, the values of k_1 were calculated from the slopes of plots of $\log \{x - (ab/x_e)/(x - x_e)\}$ vs. t .

2-4. Results and Discussion

The condensation of acetaldehyde with ammonia yields triethylhexahydrotriazine trihydrate (X) which is reported in the literature^{18,19}. The IR spectrum shows absorption maxima at wave numbers 3330 and 1510 cm^{-1} corresponding to $-\text{NH}-$, but no maximum corresponding to NH_2 . The depression of freezing point in which dimethyl sulphoxide was used as the solvent indicates that the product exists mainly as monomeric α -amino-ethanol in this ionizing solvent. Hence it is probable that the product exists also mainly in the form of aminoalcohol in dilute aqueous solution, where the molecular weight cannot be determined because of the easy dissociation of the product to aldehyde and ammonia.

The kinetic data satisfies the mechanism involving Eq. 16. The observed rate data are shown in Table 2.

TABLE 2. Observed Equilibrium and Rate Constants of the Reaction of Acetaldehyde with Ammonia in Aqueous Solutions Containing Acetic Acid at 5°C. Init. concn.: ammonia, 0.1 M; acetaldehyde, 0.1 M

$\text{CH}_3\text{CO}_2\text{H}$ (M)	pH	K^{a} (M^{-1})	K'^{b} (M^{-1})	$k_1 \times 10^2$ ($\text{M}^{-1}\text{sec.}^{-1}$)	$k_{-1} \times 10^4$ (sec.^{-1})
0.00	11.1	88.0	88.0	1.68±0.03	1.19
.01	10.35	61.6	87.3	1.47±0.01	2.39
.02	10.0	45.2	99.5	1.52±0.02	3.37
.03	9.8	27.8	85.7	1.38±0.01	4.97
.04	9.6	17.4	75.8	1.41±0.02	8.10
.05	9.4	11.9	76.6	1.18±0.01	9.93
Av. 85.5					

a) Apparent equilibrium constant

b) Equilibrium constant calculated from the equation

$$K' = \frac{x_e}{(a - c - x_e)(b - x_e)}, \text{ where } c \text{ is the concentration of added acetic acid.}$$

The apparent equilibrium constant K for equilibrium 16 varies, while the constant K' is constant (Table 2), where K' values are calculated by assuming that added acetic acid deactivates equimolar ammonia. On the other hand, the equilibrium between the reactants and triethylhexahydrotriazine (X) is unlikely because the calculated equilibrium constant varies. Probably the product exists as α -aminoethanol in dilute aqueous solutions. Although the formation of imine has been observed in some amine-carbonyl reactions^{22,23}, the concentration of $\text{NH}=\text{CHCH}_3$ must be low here, since the solution has no indication of absorption maximum at near 230 $\text{m}\mu$ corresponding to $\text{C}=\text{N}$ bond^{13,22} and also the imine with little conjugation should be less stable than Schiff's base with effective conjugation.

The apparent rate constants for the forward reaction decrease very slightly with increasing acidity, whereas the constants for the reverse reaction increase sharply with increasing pH of the solution. These results suggest that both reactions are subject to acid catalysis.

Assuming that the reactive species are free ammonia and acetaldehyde, the forward rate v_f is expressed as:

$$v_f = k_f[\text{NH}_3][\text{CH}_3\text{CHO}] = k_f \cdot \frac{1}{1 + (K_{20}[\text{H}_2\text{O}]/[\text{OH}^-])} \cdot \frac{1}{1 + K_{21}[\text{H}_2\text{O}]} \times (a - x)(b - x) \quad (19)$$

Here, k_f is the true rate constant for step 16, a and b are the initial stoichiometric concentrations of ammonia and acetaldehyde, respectively, and K 's are the equilibrium constants of the subscripted steps.



Hence, the apparent rate constant for the forward reaction is expressed as:

$$k_1 = k_f \cdot \frac{1}{1 + (K_{20}[\text{H}_2\text{O}][\text{H}^+]/K_w)} \cdot \frac{1}{1 + K_{21}[\text{H}_2\text{O}]} \quad (22)$$

i.e., k_1 should be reversely proportional to the value of $\{1 + (K_{20}[\text{H}_2\text{O}][\text{H}^+]/K_w)\}$. Assuming that $K_{20}[\text{H}_2\text{O}]$ is 1.36×10^{-5} ²⁴, $K_{21}[\text{H}_2\text{O}]$ is 1.785 ²⁵ and K_w is 0.185×10^{-14} ²⁶ at 5°C, the calculated values of k_f from k_1 by Eq. 22 decreases with decreasing acidity of the solution (Table 3). Since acetic acid is converted almost completely to acetate ion in this pH range, k_f is expressed as:

$$k_f = k_{fw} + k_{fH}[\text{H}^+] \quad (23)$$

Here, k_{fw} and k_{fH} are the catalytic constants for water and oxonium ion, respectively. The values of k_{fw} and k_{fH} were calculated to be $4.5 \times 10^{-2} \text{M}^{-1} \text{sec}^{-1}$ and $2.6 \times 10^8 \text{M}^{-2} \text{sec}^{-1}$, respectively. Similarly, the rate constant for the reverse reaction may be expressed as:

$$k_{-1} = k_{rw} + k_{rH}[\text{H}^+] \quad (24)$$

The values of k_{fw} and k_{rH} were calculated by the least square method to be $1.7 \times 10^{-3} \text{sec}^{-1}$ and $2.2 \times 10^6 \text{M}^{-1} \text{sec}^{-1}$, respectively.

It was observed that the conversion or equilibrium concentration of the product increases with a decrease in ionizing power of solvent by the addition of *t*-butanol to the aqueous solution. This fact may be due to an increase in the rate constants of forward reaction but not to the decrease in the reverse rate. The plot of $\log k_1$ vs. reciprocal of dielectric constant²⁷, $1/D$, is an approximate straight line. The phenomenon may be ascribed to a decrease in the degree of hydration of acetaldehyde (K_{21}) and ionization of ammonia (K_{20}) at initial stages, *i.e.*, to an increase in the relative concentration of reactive species or free acetaldehyde and free ammonia.

The apparent energy and entropy of activation, and the heat of reaction for the forward reaction were calculated to be $6.5 \text{ kcal mole}^{-1}$, -8.7 e.u. , and $-19.0 \text{ kcal mole}^{-1}$, respectively from the following average values of $k_1 \times 10^2 \text{M}^{-1} \text{sec}^{-1}$: 5°C, 1.34; 10°C, 1.64; 15°C, 2.00; K_M^{-1} : 5°C, 85.5; 10°C, 45.9.

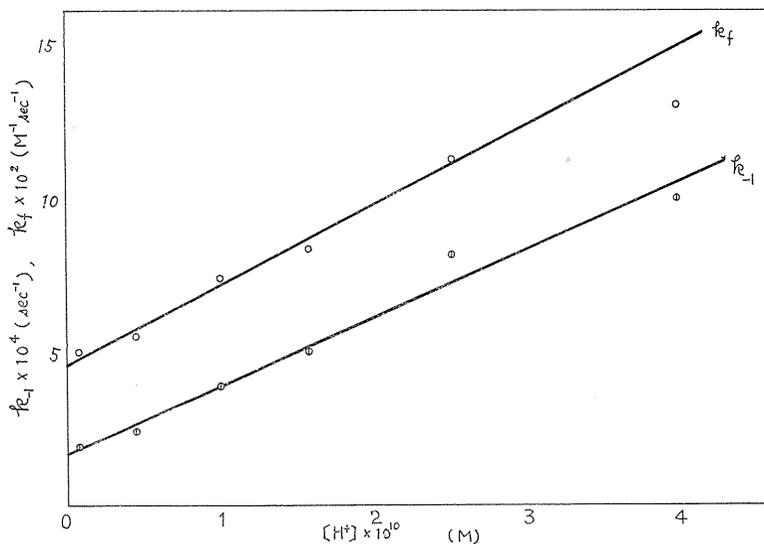


FIG. 2. Plots of the rate constant vs. $[H^+]$ for the reaction of acetaldehyde with ammonia and the reverse one at 5° .

○: forward ⊙: reverse.

TABLE 3. The Values of k_f Calculated from k_1 and Eq. 22

pH	$k_f \times 10^2$ ($M^{-1} \text{sec}^{-1}$)
9.4	12.96
9.6	11.20
9.8	8.30
10.0	7.35
10.35	5.46
11.1	4.96

The deviation of the Arrhenius plot from the straight line at higher temperature is probably due to the aldol condensation of acetaldehyde. At 5°C the aldol condensation of acetaldehyde is negligible at pH below 11, but at pH above 11 it becomes appreciable, which was confirmed in a buffer solution of acetaldehyde in the absence of ammonia.

These results suggest a probable mechanism involving a simultaneous attack of ammonia and acid (HA) on acetaldehyde analogous to that in the reaction of aromatic aldehyde and

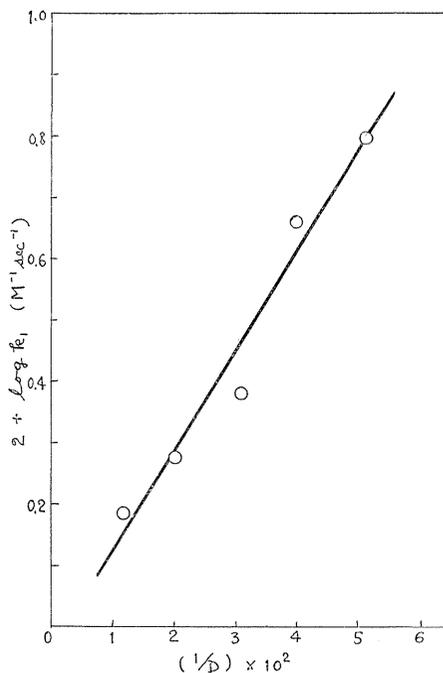
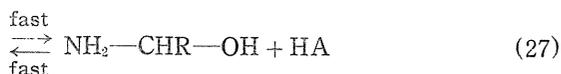
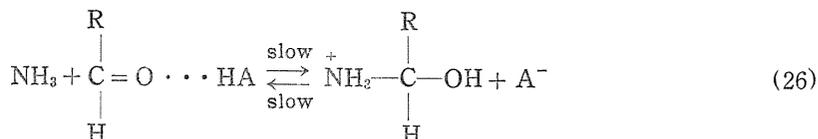
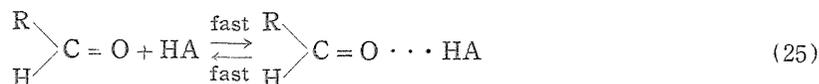


FIG. 3. Plot of $\log k_1$ vs. $1/D$ for the reaction of ammonia with acetaldehyde in various mixtures of t-butanol-water containing 0.02 M acetic acid at 5° .

semicarbazide in acidic media²⁸).



It has been suggested that the rate-determining step for the butylamine-sulphonic acid-catalysed reaction of benzaldehydes with anilines in benzene is the attack of aniline on protonated aldehyde²⁹).

3. Kinetics of the Condensation of Some Aliphatic Aldehydes with Ammonia

3-1. Summary

The rate and equilibrium constants of the reaction of some aliphatic aldehydes with ammonia have been measured in aqueous solutions at 20°C by means of spectrophotometry. The rate equations are $v = k_f$ [unhydrated aldehyde]·[free ammonia] for the forward reaction and $v = k_r$ [α -aminoalcohol] for the reverse. The reaction was subject to acid catalysis. Electron-releasing groups in aldehydes tended to decrease the rate of the forward reaction with Taft's ρ^* of 2.29, while the same groups increased the rate of the reverse reaction with ρ^* of -6.29 (decomposition of α -aminoalcohols). These results agree with the expectation from suggested reaction mechanism involving a simultaneous attack of ammonia and acid on acetaldehyde.

3-2. Introduction

It has been known that the simple Hammett's or Taft's rule is not applicable in most cases for the formation and the hydrolysis of various Schiff's bases³⁰⁻⁴². Some investigators explained these facts by the lack of resonance between carbonyl and aromatic ring at the transition state³¹, but some others by the shift of the rate-determining step from the formation to the dehydration of intermediary α -aminoalcohols^{30,34}).

In the present section are summarized the data on the kinetic study of analogous reactions of aliphatic aldehydes with ammonia to α -aminoalcohols⁴², Eq. 16 in an aqueous solution to obtain information concerning the substituent effect.



There is no kinetic study of this kind of reaction. The rates of the reactions were determined by the spectrophotometric estimation of remaining aldehydes.

3-3. Experimental

Materials.—Ammonia used was of G.R. grade. Commercial acetaldehyde, pro-

pionaldehyde and *n*-butyraldehyde of C.P. grade were purified by repeated distillations. Acetaldehyde, b.p. 22–23°C; propionaldehyde b.p. 48.0–48.5°C; *n*-butyraldehyde, b.p. 74–75°C. Isovaleraldehyde was prepared by the chromic acid oxidation⁴³⁾ of isoamylalcohol. b.p. 91–93°C.

The Reaction Product Criterion.—The product of the reaction of acetaldehyde with ammonia was acetaldehyde ammonia, m.p. 92–93°C⁴²⁾. Similarly, the condensation of other aliphatic aldehydes with ammonia give unstable aldehyde ammonia. For example, a crystalline product, *n*-butyraldehyde ammonia, m.p. 25.5–26°C⁴⁴⁾, was obtained in 63% yield by the condensation of conc. NH₄OH with *n*-butyraldehyde at 0°C. This material was very soluble in water and unstable at room temp. It decomposed or polymerized to yellow viscous liquid.

Kinetic Procedure.—The rate of the reaction in aqueous solution was determined spectrophotometrically at 20°C according to our previous report⁴²⁾, *i.e.*, the decrease of the carbonyl peak at 278 m μ (acetaldehyde), 280 m μ (propionaldehyde), 283 m μ (*n*-butyraldehyde), or 288 m μ (isovaleraldehyde) was followed by a Shimadzu SV 50 A spectrophotometer. Sodium chloride was added to the reaction mixture to keep the ionic strength constant ($\mu=0.5$). For the reaction of isovaleraldehyde, a mixture of 40% dioxane and 60% water was used as a solvent because of the poor solubility of isovaleraldehyde in water. The rate constant was calculated by means of Eqs. 17 and 18, as reported previously⁴²⁾.

3-4. Results and Discussion

The observed rate and equilibrium constants for the present reactions are summarized in Table 4. As stated previously for acetaldehyde⁴²⁾, the corrected equilibrium constant K' remains constant for propionaldehyde and *n*-butyraldehyde. These facts suggest that there is an analogous equilibrium 16 between the reactants and α -aminoalcohols. The apparent rate constants (k_1) for the forward reaction do not vary with acidity, whereas the constants (k_{-1}) for the reverse reaction increase sharply with increasing acidity of the solution.

As reported previously⁴²⁾, the reaction of acetaldehyde with ammonia to form α -aminoethanol is second-order for the forward reaction and first-order for the reverse reaction and both reactions are acid-catalyzed. Also, the apparent rate constant k_1 for the forward reaction is expressed as:

$$k_1 = k_f \cdot \frac{1}{1 + (K_{20}[\text{H}_2\text{O}][\text{H}^+]/K_w)} \cdot \frac{1}{1 + K_{21}[\text{H}_2\text{O}]} \quad (22)$$

Here, k_f is the true rate constant for step 16, and the K 's are the equilibrium constants of the subscripted steps²⁴⁾²⁵⁾⁴⁵⁾⁴⁶⁾⁴²⁾. The calculated values of k_f using Eq. 22 increase with increasing acidity. Hence the rate constant k_f is expressed as:

$$k_f = k_{fw} + k_{fH}[\text{H}^+] \quad (23)$$

Similarly, k_{-1} is expressed as:

$$k_{-1} = k_{rw} + k_{rH}[\text{H}^+] \quad (24)$$

The catalytic constants calculated by means of the least square method for the

TABLE 4. Observed Equilibrium and Rate Constants of the Reaction of Some Aliphatic Aldehydes with Ammonia in Aqueous Solutions Containing Sodium Chloride (Ionic Strength 0.5) at 20°C

Acetaldehyde, initial conc. 0.0582 M

Initial conc. NH ₃ (M)	Added CH ₃ CO ₂ H (M)	pH	Corrected equilibrium constant <i>K'</i> , (M ⁻¹)	Apparent rate constant	
				forward <i>k</i> ₁ × 10 ² (M ⁻¹ sec. ⁻¹)	reverse <i>k</i> ₋₁ × 10 ³ (sec. ⁻¹)
0.190	0.063	9.735	43.3	2.93	1.20
0.190	0.084	9.535	43.7	2.87	1.52
0.190	0.105	9.35	48.5	2.95	2.05
0.190	0.126	9.145	50.6	2.90	3.07
0.190	0.147	8.93	(73.5)	3.01	4.71
			Av. 46.5	Av. 2.93	

Propionaldehyde, initial conc. 0.0728 M

0.203	0.021	10.42	11.45	2.07	2.07
0.203	0.042	10.10	10.55	2.16	2.76
0.203	0.063	9.90	10.64	2.13	3.13
0.203	0.084	9.70	10.26	2.28	4.31
0.203	0.105	9.51	10.31	1.94	4.79
0.203	0.126	9.33	10.06	1.78	6.04
			Av. 10.54	Av. 2.06	

n-Butyraldehyde, initial conc. 0.0530 M

0.203	0.021	10.37	7.13	2.05	3.26
0.203	0.042	10.08	7.68	2.21	3.79
0.298	0.021	10.57	7.79	2.05	2.92
0.298	0.042	10.30	7.93	2.20	3.30
0.298	0.063	10.10	7.45	2.21	3.88
0.298	0.084	10.00	8.16	2.51	4.35
0.298	0.105	9.85	8.27	2.49	4.81
0.298	0.126	9.70	8.58	2.56	5.51
			Av. 7.87	Av. 2.28	

Isovaleraldehyde^{a)}, initial conc. 0.0269 M

0.393	0.011	10.72	2.16	0.471	2.24
0.393	0.022	10.54	2.07	0.611	3.12
0.393	0.043	10.30	2.11	0.646	3.46
0.393	0.065	10.14	2.02	0.729	4.36
0.393	0.087	10.06	2.03	0.823	5.68
			Av. 2.06		

a) The reaction was carried out in 40 vol% dioxane—60 vol% water containing NaCl (ionic strength 0.25) at 20°C.

forward and reverse reactions are listed in Table 5. For the reaction of isovaleraldehyde with ammonia in 40% dioxane aqueous solution, the apparent rate constant for the forward reaction increases with increasing acidity. The acid-catalytic constants increase by changing the solvent from water to 40 vol% dioxane.

Since reactive species are supposed to be unhydrated aldehyde and free base

TABLE 5. The Catalytic Constants for the Forward and Reverse Reactions at 20°C

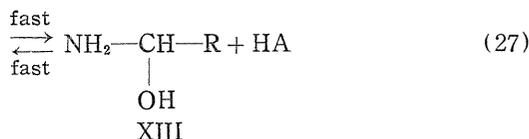
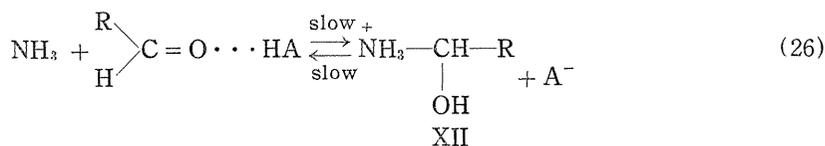
Aldehyde R in RCHO	$k_{rw} \times 10^2$ (M ⁻¹ sec. ⁻¹)	$k_{rH} + 10^{-8}$ (M ⁻² sec. ⁻¹)	$k_{rw} + 10^4$ (sec. ⁻¹)	$k_{rH} \times 10^{-6}$ (M ⁻¹ sec. ⁻¹)
CH ₃	4.81	1.54	4.91	3.58
C ₂ H ₅	3.56	1.26	20.3	8.94
<i>n</i> -C ₃ H ₇	2.49	1.31	26.0	15.2
<i>i</i> -C ₄ H ₉ ^{a)}	0.38	5.03	14.6	44.7

a) The values in 40 vol% dioxane—60 vol% water containing sodium chloride of ionic strength 0.25.

of ammonia as stated previously⁴²), it is necessary to see the extent of hydration of aldehydes (Eq. 21) and of acid catalysis for the comparison of their forward reaction rates. The values of the apparent rate constants, k_1 , hold approximate constancy with varying acidity of the solution (Table 4). Therefore, the extent of hydration of aldehyde only need be considered. Molar fraction of unhydrated aldehyde, f , is expressed as $1/(1+K_{21}[H_2O])$ which can be determined by the measurement of K_{21} . The value of k_1/f may be used to compare the rates of forward reactions.

As the susceptibility to oxonium ion catalysis is not uniform as has been suggested³⁷), the value of k_{rw} may be used to compare the rates of reverse reactions. Further, if the equilibrium constant, K_0 , is defined as $(k_1/f)/k_{rw}$, the constant may be considered to represent the stability of α -aminoalcohols independent of the acidity and of the hydration of aldehydes as shown in Table 6.

The rate with isobutyraldehyde could not be determined, because the reaction rate was too fast and the conversion to the α -aminoalcohol was too low as expected from the data in Table 6. The plot of the Taft's equation gave a positive ρ^* value for the forward rate (2.29) and a negative ρ^* value for the reverse rate (-6.29). These results suggest a mechanism⁴²):



The positive ρ^* value for the forward reaction shows that an electron-releasing group R in the aldehyde deactivates the electrophilicity of the carbonyl group, resulting in a decrease of the rate of the nucleophilic attack of ammonia on the carbonyl group.

The negative high ρ^* value for the reverse reaction is probably caused by overlapping of favorable effects of alkyl group on the protonation of α -aminoalcohol XIII (equilibrium) and on the cleavage of C—N⁺ bond of the conjugate acid XII (rate), which means that an electron-releasing group may increase the

TABLE 6. The Relative Rate and Equilibrium Constants for the Reaction of Aliphatic Aldehyde with Ammonia at 20°C

Aldehyde R in RCHO	f	$(k_1/f) \times 10^2$ (M ⁻¹ sec. ⁻¹)	$k_{rw} \times 10^4$ (sec. ⁻¹)	$K_0^{b)}$ (M ⁻¹)
CH ₃	0.541	5.42	4.91	110
C ₂ H ₅	0.562	3.67	20.3	18.1
<i>n</i> -C ₃ H ₇	0.774	2.95	26.0	11.4
<i>i</i> -C ₄ H ₉	—	—	24.3 ^{a)}	—

a) The value in pure water calculated by neglecting the solvent effect.

b) The relative equilibrium constant independent of the acidity and of the hydration of aldehydes.

basicity of α -aminoalcohol XII, resulting in an increase of the concentration of protonated α -aminoalcohol XII, and that the same group may stabilize the carbonyl group or carbonium ion produced by the C—N⁺ fission. Such negative high ρ^* values have been observed for the hydrolysis of formals in water (-8.345)⁴⁷⁾, ketals and acetals in 50% aqueous dioxane (-3.660)⁴⁸⁾ via the analogous mechanism (cleavage of C—O⁺ bond) and for the dissociation of trimethyl boron addition compounds with primary amines⁴⁹⁾ (-7.26).

On the contrary, if the rate-determining step were the dehydration of α -aminoalcohol to aldimine, as in the semicarbazone formation of aromatic aldehydes³⁴⁾, a very small or positive ρ^* value for the rate of the reverse reaction should be obtained. For an electron-releasing group should increase the dehydration rate of aminoalcohol XIV by electron donation to leaving oxygen atom ($\rho = -1.74$ for the semicarbazone formation)^{34);50)}, but it should decrease the equilibrium concentration of α -aminoalcohol XIV ($\rho = 1.81$ for the equilibria of the formation of α -aminoalcohols)³⁴⁾, which results in an increase or a small decrease in the overall

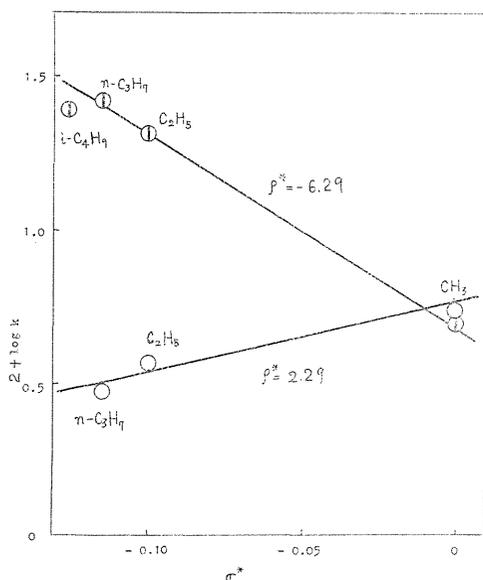
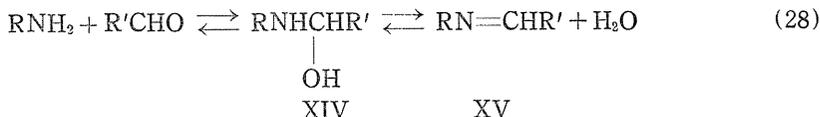


FIG. 4. Plots of $\log(k_1/f)$, \odot , and $\log k_{rw}$, $\textcircled{1}$, for the reaction of aliphatic aldehydes with ammonia vs. Taft's sigma constants.

forward rate. Conversely, for the reverse reaction, the same group should retard the hydration rate of aldimine ($\rho=1.26$ for OH^- attack, 1.71 for H_2O attack on the conjugate acid of aldimine XV)³⁸⁾, but should increase the equilibrium concentration of the conjugate acid of the aldimine XV, resulting in a decrease or a small increase in the overall reverse rate.



These expectations were not observed in the present reactions, hence it is rational that the dehydration of α -aminoalcohol is not rate-determining.

4. Kinetics of the Reaction of Aromatic Aldehydes with Ammonia

4-1. Summary

The kinetics of the reaction of aromatic aldehydes with ammonia to form hydrobenzamides have been studied spectrophotometrically in methanol at 30°C. The reaction is first order with respect to aldehyde and first order with ammonia. The effect of water, potassium hydroxide, and temperature on the rate has been studied. The application of Hammett's law to the rates gives a positive ρ -value for the reaction of aldehydes with electron-releasing substituents and a negative ρ -value with electron-withdrawing substituents. Induction periods were observed in the formation of hydrobenzamides with electron-withdrawing substituents. These results suggest a probable mechanism involving α -aminobenzyl alcohol and benzylidenimine, etc.

4-2. Introduction

The reaction of benzaldehydes with ammonia gives hydrobenzamides, $\text{ArCH}=\text{NCH}(\text{Ar})\text{N}=\text{CHAr}$. Dobler has observed the rate of the reaction by means of acidimetry to be second order⁵¹⁾. He observed no systematic substituent effect. The analogous condensation of aromatic aldehydes with *n*-butylamine³³⁾, semicarbazide³¹⁾³⁴⁾, or anilines²⁹⁾⁵²⁾ has been studied, Hammett's rule not being applicable for the benzylidenimine or semicarbazone formation. Some investigators have reported that the reaction of benzaldehyde with ammonia also produces benzylidenimine⁵³⁾⁵⁴⁾, $\text{NH}=\text{CHPh}$; α, α' -dioxydibenzylamine⁵⁵⁾, $\text{NH}(\text{CH}(\text{OH})\text{Ph})_2$; and 2, 4, 6-triphenyl-1, 3, 5-hexahydrotriazine⁵⁶⁾, $(-\text{NH}-\text{CHPh}-)_3$. The present section describes the data on the kinetic investigation of the reaction involving the effect of basicity of the solution, the effect of substituents, and a probable mechanism derived from the results. Since acidimetry gave no accurate rates of reaction, we employed spectrophotometry.

4-3. Experimental

Materials.—Commercial benzaldehyde, b.p. 78.8°C (26 mm.), and *p*-anisaldehyde, b.p. 159.0°C (44 mm.), were purified by vacuum distillation under nitrogen. *p*-Chlorobenzaldehyde, m.p. 46.5–47.5°C, and *p*-cyanobenzaldehyde, m.p. 101–102°C, were prepared by the chromic acid oxidation of *p*-chlorotoluene and *p*-tolunitrile⁵⁷⁾, respectively. Commercial methanol was purified by distillations and used as the solvent. Aqueous ammonia was of guaranteed reagent grade. Methanolic am-

monia free of water was prepared by passing ammonia gas, dried with sodium hydroxide, into methanol dried by boiling with magnesium.

Products.—Hydrobenzamides were prepared by the reaction of concentrated aqueous ammonia and aldehydes in methanol, the resulting precipitates being recrystallized from methanolic ammonia: hydrobenzamide, m.p. 100–101°C (lit.⁵⁸) m.p. 102°C); hydroanisamide, m.p. 128.5–130.5°C (lit.⁵⁹) m.p. 130°C); 4, 4', 4''-trichlorohydrobenzamide, m.p. 87–90°C; 4, 4', 4''-tricyanohydrobenzamide, m.p. 130–132°C. The infrared spectra⁶⁰ showed the C=N band at 1632–1636 cm⁻¹.

Anal. Calcd. for C₂₁H₁₅Cl₃N₂: C, 62.78; H, 3.76; N, 6.97. Found: C, 62.73; H, 3.87; N, 6.87.

Anal. Calcd. for C₂₄H₁₅N₅: C, 77.20; H, 4.05; N, 18.76. Found: C, 77.62; H, 4.10; N, 18.18.

Rate Measurements.—For the determination of the concentrations of benzaldehyde and hydrobenzamide, two wave length of benzaldehyde at 245 m μ (absorption max.) and 270 m μ (absorption min.) were selected. Their concentrations were determined by ultraviolet spectrophotometry for binary mixtures⁶¹. The values of the molar extinction coefficient were determined experimentally: for benzaldehyde, ϵ_{\max} 1.319 $\times 10^4$ (lit.⁶²) 1.32 $\times 10^4$, ϵ_{\min} 1.098 $\times 10^3$; for hydrobenzamide, ϵ_{\max} 2.800 $\times 10^4$, ϵ_{\min} 1.016 $\times 10^4$. The absorption of the product, hydrobenzamide, could be determined by converting the remaining benzaldehyde into acetal with a drop of sulfuric acid in methanol. The spectrum of hydrobenzamide (λ_{\max} 251 m μ) showed a bathochromic shift (λ_{\max} 281 m μ) by addition of sulfuric acid. A methanolic solution of hydrobenzamide was stable at room temperature. Since the decomposition of hydrobenzamide was negligible within a minute after the addition of sulfuric acid, the absorbances were measured at just 1 min. after the addition. Then the rate of the formation of hydrobenzamide was measurable. The rate constants by both methods were identical within experimental error with unsubstituted benzaldehyde. The rates with other substituted benzaldehydes were estimated by the latter method. Absorption maxima of substituted hydrobenzamides were as follows: *p*-MeO, 320; *p*-Cl, 295; and *p*-CN, 270 m μ . The rate constants, k_2 , with *p*-chloro- and *p*-cyanobenzaldehyde were calculated by eliminating their induction periods, which were obtained by the extrapolation of plots of the concentration of formed hydrobenzamides vs. time to zero concentration.

The typical experiment for the rate measurements was as follows: 0.450 M benzaldehyde (25 ml.) in methanol and 0.976 M methanolic ammonia (25 ml.) which had previously attained thermal equilibrium were mixed in a 100 ml. thermostated flask kept at 30.0 \pm 0.1°C. Aliquots were periodically withdrawn and diluted with methanol by a factor of 1.6 $\times 10^3$. Then their absorbances at 245 and 270 m μ were determined by Shimadzu automatic spectrophotometer SV 50 A at room temperature. Infrared spectra were measured by Shimadzu spectrophotometer IR-27 B.

4-4. Results and Discussion

Rate Law.—The reaction was found to be second order and satisfied the rate equation that follows.

$$v = \frac{dx}{dt} = k_2 \left(a - \frac{2}{3}x \right) (b - x) \quad (29)$$

or

$$k_2 = \frac{1}{t} \frac{2.303}{a - (2/3)b} \left(\log \frac{a - (2/3)x}{b - x} - \log \frac{a}{b} \right) \quad (30)$$

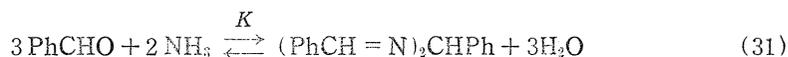
Here, a and b are the initial concentrations of ammonia and benzaldehyde, respectively, x the concentration of consumed benzaldehyde at time t , and k_2 the apparent second-order rate constant. Typical rate data are shown in Table 7. The rate constant tended to decrease very slightly with increasing initial molar ratio of ammonia vs. benzaldehyde. As the reaction proceeds, the molar ratio with an excess of ammonia increases and hence the rate constants decrease very slightly at the end of the reaction. If the reactants are converted completely to the product, x moles of consumed benzaldehyde should yield $x/3$ moles of hydrobenzamide according to the following stoichiometric equation (31).

TABLE 7. Typical Rate Data for the Reaction of Benzaldehyde and Ammonia at 30°C. $[\text{NH}_3]_0 = 0.488 \text{ M}$; $[\text{PhCHO}]_0 = 0.225 \text{ M}$

Time (sec.)	$[\text{PhCHO}]$ (M)	Conversion (%)	$k_2 \times 10^4$, ($\text{M}^{-1}\text{sec.}^{-1}$)
0	0.225	0	
610	0.211	6.2	2.16
1225	0.196	12.8	2.34
1810	0.187	17.0	2.15
2710	0.170	24.4	2.19
3610	0.154	31.6	2.29
5400	0.128	43.1	2.31
7200	0.112	50.3	2.19
			Av. 2.23 ± 0.02

However, consumed benzaldehyde was not quantitatively converted to hydrobenzamide, as shown in Fig. 5, which suggested that a very small but constant amount of benzaldehyde existed as some intermediates during the reaction. The difference in the curves of Fig. 5 is more than the experimental error on the basis of several experiments. The difference is more obvious at a very early stage of the reaction. This effect was so small with benzaldehyde that the rate constant obtained by the estimation of the product ($1.91 \times 10^{-4} \text{ M}^{-1}\text{sec.}^{-1}$) and that of the reactant ($1.83 \times 10^{-4} \text{ M}^{-1}\text{sec.}^{-1}$) agreed. However, an induction period was observed with benzaldehydes having electron-withdrawing substituents, as will be stated later.

The Effect of Addition of Water or Alkali.—The addition of water retarded the apparent rate and the rate equation deviates from Eq. 29. Conversions at 120 min. were as follows (added water in vol. % and conversion in %): 5, 47.5; 10, 43.6; 15, 37.8; 20, 35.2. These facts may be due to the predomination of the decomposition of the product or the reverse reaction of Eq. 31.



Observed equilibrium constants K in the presence of various amounts of water

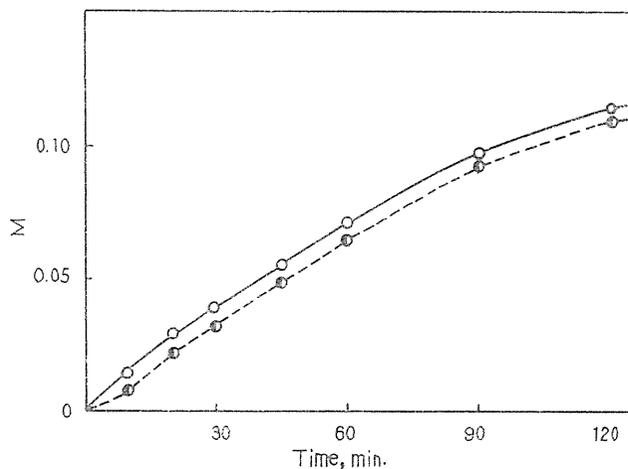


FIG. 5. The comparison of the consumption of benzaldehyde and the formation of hydrobenzamide, $[\text{NH}_3]_0 = 0.488 \text{ M}$, $[\text{PhCHO}]_0 = 0.255 \text{ M}$, at 30°C : O, benzaldehyde consumed; ●, benzaldehyde converted to hydrobenzamide.

TABLE 8. Effects of Water Added at 30°C

$[\text{NH}_3]_0$ (M)	$[\text{PhCHO}]_0$ (M)	$[\text{H}_2\text{O}]$ (vol.%)	$k_2 \times 10^4$ ($\text{M}^{-1}\text{sec.}^{-1}$)	$K \times 10^{-5}$ (M^{-1})
0.494	0.215	5	2.11	1.37
0.494	0.219	10		1.37
0.490	0.224	15		1.24
0.490	0.227	20		2.62 ^{a)}
				1.21 ^{b)}
				Av. 1.30

a) Hydrobenzamide was precipitated.

b) The calculated value of K by eliminating the amount of precipitate.

held constancy (Table 8).

$$K = \frac{[(\text{PhCH}=\text{N})_2\text{CHPh}][\text{H}_2\text{O}]^3}{[\text{PhCHO}]^3[\text{NH}_3]^2} \quad (32)$$

In the presence of 20 vol.% of water, hydrobenzamide corresponding to 54% of consumed benzaldehyde was precipitated, hence the observed equilibrium constant became higher, while the equilibrium constant calculated by eliminating the amount of precipitate of hydrobenzamide agreed with other values.

It is well known that Schiff's base formation is subject to acid catalysis. The data in Table 9 show that an increase of concentration of alkali results in retardation of the formation of hydrobenzamide, hence increase in the concentration of intermediates (amino alcohols) and deviation from the above kinetic equation; *i.e.*, the order of the reaction became more than 2. These results may be caused by the suppression of acid catalysis for the dehydration of amino alcohols with added alkali.

TABLE 9. Effect of Potassium Hydroxide at 30°C

$[\text{NH}_3]_0$ (M)	$[\text{PhCHO}]_0$ (M)	$[\text{KOH}]$ (M)	$k_2 \times 10^4$ ($\text{M}^{-1}\text{sec}^{-1}$)	Time (min.)	Conversion (%)
0.251	0.142	0	2.46	240	60
0.250	0.149	0.152	1.52	240	33
0.252	0.139	0.247	0.94	240	26.7
0.232	0.123	0.280	—	240	23.2

Energy and Entropy of Activation.—The apparent energy and entropy of activation were calculated to be 9.73 kcal. mole⁻¹ and -40.3 e.u., respectively, by means of the Arrhenius equation from the rate data: $k_2 \times 10^4$ 1. mole⁻¹sec.⁻¹, 0.690 at 10°C, 2.23 at 30°C, 5.13 at 50°C. These values can be expected in the analogous reaction, *i.e.*, the reaction of *p*-dimethylaminobenzaldehyde with ammonia (10.9 kcal. mole⁻¹ -43.7 e.u.)⁵³, *p*-chlorobenzaldehyde with *n*-butylamine (7.0 kcal. mole⁻¹, -41.3 e.u.)³³, or *p*-nitrobenzaldehyde with *n*-butylamine (8.0 kcal. mole⁻¹, -33.7 e.u.)³³. These resemblances in energies and entropies of activation suggest that the analogous imine formation and transition state are involved. If the rate-determining step is the addition of ammonia to aldehyde, such a large negative value for entropy of activation is conceivable, since reactions in which the total number of molecules decreases⁵³ or the reactions involving a strongly polar transition state⁶⁴ produced from neutral molecules may be remarkably negative.

Effect of Substituents in Aldehydes on the Rate.—A simple Hammett's rule was not applicable to the reaction as shown in Fig. 6. The Hammett's plot for the reaction of benzaldehydes with ammonia in methanol gave a positive ρ -value (+1.1) for the reaction of aldehydes with electron-releasing groups and a negative ρ -value (-0.65) with electron-withdrawing groups. Analogous relationships have been

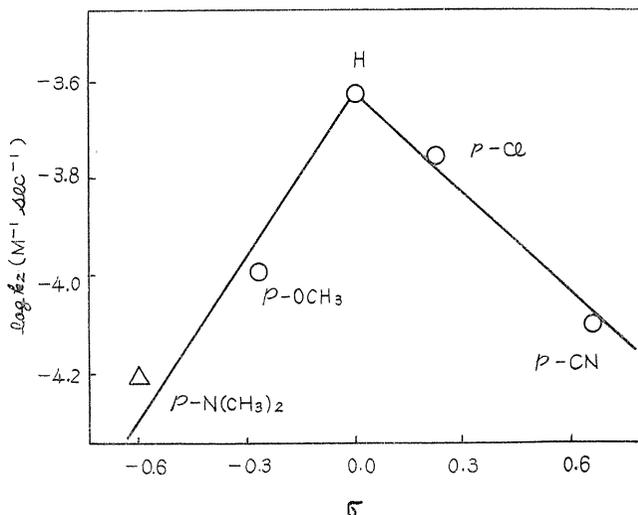


FIG. 6. Hammett's plot for the reaction of aromatic aldehydes with ammonia: Δ , the value was calculated from the data of McLeod and Crowell⁵³,

observed previously for the reaction of aromatic aldehydes with semicarbazide in 75% ethanol³¹⁾ and with *n*-butylamine in methanol³³⁾. The reaction was followed by the estimation of the rate of the formation of the products. No induction period was observed with an electron-releasing group (OCH₃), whereas an induction period was observed with electron-withdrawing groups (CN, Cl) as has been reported in the formation of oximes and semicarbazones³⁵⁾ of aromatic aldehydes.

A 0.8 M *p*-chlorobenzaldehyde solution and a 0.8 M methanolic ammonia solution were mixed at 30°C, and the absorption corresponding to carbonyl group (250–260 m μ) was measured. The absorption of the aldehyde at 255 m μ decreased at the start of reaction, and after an interval the absorption of hydrobenzamide at 259 m μ increased, until it became stronger than that at the start. The same phenomenon was also confirmed by means of infrared spectrum. The carbonyl absorption of *p*-cyanobenzaldehyde at 1702 cm⁻¹ decreased at room temperature to 91% of the initial absorbance after 5 min., 86% after 14 min., 80% after 20 min., and 61% after 94 min. The absorption at 1635 cm⁻¹ corresponding to C=N did not appear within 20 min., whereas the absorption was appreciable after 94 min. On the contrary, the absorption of unsubstituted hydrobenzamide at 1634 cm⁻¹ increased with decreasing absorption at 1697 cm⁻¹ in the reaction of benzaldehyde which had no induction period. The second-order rate constant (1.90×10^{-4} l. mole⁻¹sec.⁻¹) of the consumption of *p*-cyanobenzaldehyde calculated from the absorption at 1702 cm⁻¹ was ca. twice as large as that of benzaldehyde (0.83×10^{-4} l. mole⁻¹sec.⁻¹) from 1697 cm⁻¹ within 20% conversion under the same conditions. As shown in Fig. 6, the rate constant for the formation of hydrobenzamide was higher than that of 4,4',4''-tricyanohydrobenzamide. These facts show that electron-withdrawing groups accelerate the rate of the consumption of aldehyde but retard the rate of the formation of the hydrobenzamide, and suggest that the rate-determining step shifts from addition to dehydration as suggested by Jencks in the formation of oximes and semicarbazones³⁴⁾.

The Reaction Mechanisms.—The results in the reaction of benzaldehydes with ammonia in methanol are summarized (1–7) and suggest Scheme.

(1) The over-all reaction is reversible, and the addition of water makes the reverse reaction appreciable.

(2) Since the reaction is second order, the rate-determining step may be the addition of ammonia with aldehyde or the dehydration of the resulting α -amino-benzyl alcohol.

(3) The rate of the formation of hydrobenzamide decreases slightly with increasing molar ratio of the initial concentration of ammonia vs. that of benzaldehyde.

(4) The addition of potassium hydroxide retards the rate of the reaction and the amount of intermediate may increase with increasing time.

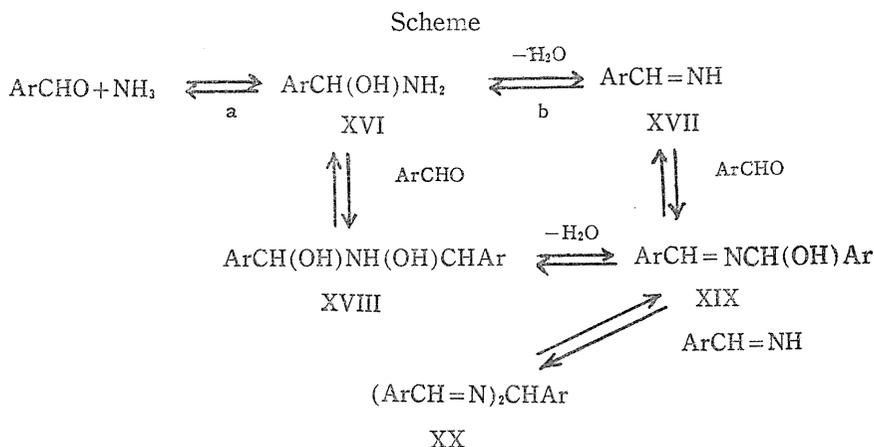
(5) A positive Hammett's ρ -value was obtained with electron-releasing *p*-substituents in benzaldehyde and a negative ρ -value with the electron-withdrawing substituents.

(6) An induction period was observed in the formation of hydrobenzamides with electron-withdrawing substituents.

(7) The rate of the consumption is faster with *p*-cyanobenzaldehyde than

with benzaldehyde, while the rate of the formation of hydrobenzamides from *p*-cyanobenzaldehyde is slower than that from benzaldehyde.

The steps leading to benzylideneimine (XVII) have been reported in very dilute solution⁵³). As stated above, the rate-determining step may be the formation of α -aminobenzyl alcohol XVI (step a) or the dehydration to XVII (step b). The formation of hydrobenzamide XX from XVII should be fast, since the rate is second order. The dehydration (b) may be rate-determining in weakly basic media as reported by Jencks and others^{35),65),66)}.



The mechanism explains the facts that a constant amount of intermediates exists (Fig. 5), that the rate of the formation of hydrobenzamide decreases on addition of alkali by retarding acid-catalyzed dehydration, and that electron-withdrawing substituents increase the rate of the consumption of the reactants and reduce the rate of the formation of the products because of the elongation of induction period. However, in the reaction of benzaldehydes with electron-releasing groups the rate-determining step may be the addition (a) because of its positive ρ -value and the absence of induction period. When the initial concentration of benzaldehyde was higher than that of ammonia, the reaction of XVI with benzaldehyde yielding α, α' -dioxidibenzylamine XVIII isolated by Francis⁵⁵⁾ became appreciable and caused a little increase in the rate constant. There was no evidence for the formation of 2, 4, 6-triphenyl-1, 3, 5-hexahydrotriazine⁵⁶⁾ under these conditions. Although the formation of hydrobenzamide from XVII or XVIII seems to be fast, these steps are still obscure with the present data.

5. Kinetics of the Condensation of Urea with Acetaldehyde

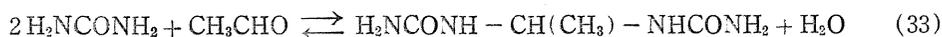
5-1. Summary

The reaction of urea and acetaldehyde in molar ratio of over 3 : 1 gives ethylidenediurea as main product. The rate of reaction in aqueous solutions has been measured by means of spectrophotometric estimation of remaining acetaldehyde. The rate is expressed as $v = k[\text{H}_2\text{NCONH}_2][\text{CH}_3\text{CHO}]$. The reaction is reversible and the forward reaction is catalyzed by both general acid and general base. The

Brönsted catalysis law is applicable to the general acid catalysis of the forward reaction. The reverse reaction, the decomposition of ethylidenediurea is general acid catalyzed in acidic buffered solutions. A probable mechanism is suggested for the forward reaction involving a rate-determining reaction of urea and acetaldehyde to form ethylolurea, as is a mechanism for the reverse reaction involving a preliminary rapid decomposition of ethylidenediurea to ethylolurea.

5-2. Introduction

There have been a number of kinetic studies on the condensation of formaldehyde with amides^{67,68} involving urea. Most of the studies are concerned with the formation of methylolamides, and it is known that their rates are expressed as $v = k[\text{HCHO}][\text{RCONH}_2]$. However, the reaction of other aldehydes with amides have been scarcely studied. It is known that the reaction of urea with acetaldehyde gives various products with varying ratios of urea vs. acetaldehyde⁶⁹. It was confirmed that the reaction of more than 3 moles of urea with 1 mole of acetaldehyde gave ethylidenediurea. The present section deals with the kinetic results obtained on the condensation of urea with acetaldehyde to form ethylidenediurea.



5-3. Experimental

Materials.—Commercial reagent grade acetaldehyde dried over Drierite was purified by rectification, b.p. 20.2°C. Commercial reagent grade urea was purified by recrystallization from methanol, m.p. 132.5°C. Ion-exchanged pure water was used as the solvent.

The Reaction Products.—Ethylidenediurea was prepared by the reaction of 1 mole of acetaldehyde and more than 3 moles of urea in an aqueous solution at room temperature. The resulting solution was evaporated under reduced pressure at 40°C and, after being washed with methanol, gave crystals, m.p. 182–183°C (lit.⁷⁰ m.p. 181°C).

Anal. Calcd. for $\text{C}_4\text{H}_{10}\text{N}_4\text{O}_2$: mol. wt., 146. Found: mol. wt., 150 (cryoscopic method in aqueous solution).

The decomposition of the product (0.292 g.) by heating with 0.2285 N aqueous sulfuric acid (20 ml.) and 0.4 N hydroxylamine hydrochloride (10 ml.) for 2.5 hr. at 60–80°C gave acetaldehyde oxime which was estimated by titration with 0.1069 N sodium hydroxide (60.78 ml.); *i.e.*, 2.0×10^{-3} mole of the sample gave 1.93×10^{-3} mole of acetaldehyde. The infrared spectra of this compound showed no OH peak at 3700–3500 and 1200–1000 cm^{-1} .

Rate Measurements.—The concentration of acetaldehyde was measured by its absorbance at 277 μ (absorption maximum), where urea, ethylolurea, and ethylidenediurea have no appreciable absorption. The molar extinction coefficient of acetaldehyde in water was as follows: 6.67 at 12.0°C; 8.02 at 24.2°C; and 9.05 at 36.3°C. Except in phosphate buffer ($\mu = 0.8$) all runs were carried out at the same ionic strength ($\mu = 0.2$) by adding sodium chloride. The hydroxide-ion catalysis was measured in a borate buffer where no appreciable catalytic effect of the buffer

was observed.

A typical experiment for the rate measurements was as follows: 0.150 M acetaldehyde (25 ml.) in a buffered aqueous solution and 3.00 M urea (25 ml.) in the same buffered solution which had previously come to thermal equilibrium were mixed in a flask and immediately introduced to a glass-stoppered quartz cell thermostated at $24.2 \pm 0.2^\circ\text{C}$ in a Hitachi spectrophotometer, type EPU 2 A. The absorbance at $277 \text{ m}\mu$ was measured at known intervals of time and the concentration of acetaldehyde was calculated.

The decomposition of ethylenediurea was carried out in a chloroacetate buffer ($\mu=0.2$) at 24.2°C , the resulting acetaldehyde being determined spectrophotometrically.

5-4. Results and Discussion

The Order of the Reaction Rate.—Pseudo-first-order rate constants were calculated by measuring acetaldehyde in kinetic experiments, where a 10-20-fold excess of urea to acetaldehyde was used. As shown in Fig. 7, the plot of the pseudo-first-order rate constant vs. initial concentration of urea was a straight line passing through the origin. Therefore, the rate is expressed as $v = k[\text{H}_2\text{NCONH}_2] \cdot [\text{CH}_3\text{CHO}]$.

Hydronium Ion and Hydroxide Ion Catalysis.—The reaction seems to be catalyzed by H_3O^+ and OH^- ions as in the case of formaldehyde^{67,4) 68)}. A linear relationship (Fig. 8) was observed between the $\log k$ and $\log[\text{H}_3\text{O}^+]$ or $\log[\text{OH}^-]$ at pH of 2.9-4.2 or 8.2-9.6, respectively. The plot gives two straight lines with unit slope, and $\log k$ has a minimum at pH ca. 6.8, which indicates both hydronium ion and hydroxide ion catalysis.

In unbuffered solutions the rate constants can be expressed as

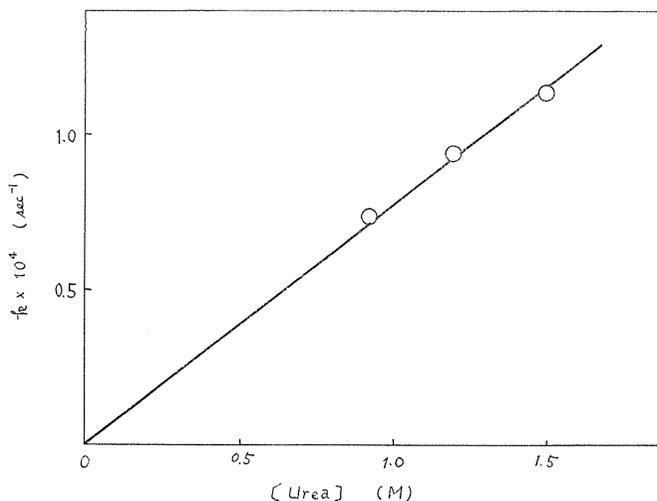


FIG. 7. Plot of the pseudo-first-order rate constant vs. the initial concentration of urea for the condensation of urea with acetaldehyde at 24.2°C .

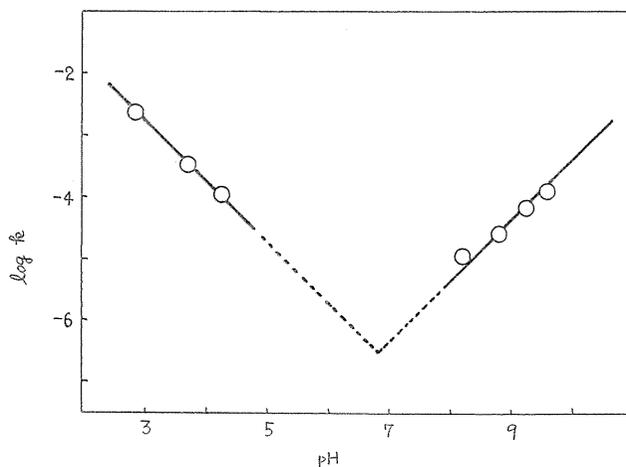


FIG. 8. The relationships between the logarithm of the second-order rate constant and pH for the condensation of urea with acetaldehyde at 24.2° and ionic strength of 0.2.

$$k = k'[\text{H}_2\text{O}] + k''[\text{H}_3\text{O}^+] + k'''[\text{OH}^-] \quad (34)$$

The catalytic constants, k'' and k''' , can be evaluated from Fig. 8.

$$k = k'[\text{H}_2\text{O}] + 1.3 [\text{H}_3\text{O}^+] + 1.4 [\text{OH}^-] \quad (35)$$

A similar relationship has been reported for the condensation of urea with formaldehyde⁶⁷.

$$k = (5.6 \times 10^{-5}) + (1.4 \times 10^{-1}[\text{H}_3\text{O}^+]) + 1.7[\text{OH}^-]$$

Catalysis in Buffered Solutions.—A series of experiments were carried out in various acetate buffer concentrations with constant pH to examine the possibility of general acid and general base catalysis. The plot of second-order constant vs. concentration of acetate buffer shows straight parallel lines corresponding to their pH values (see Fig. 9). This fact indicates that the reaction is subject to general acid catalysis with acetic acid, but not to general base catalysis with acetate ion. The slope of line gives the specific acid catalytic constant for acetic acid as $2.50 \times 10^{-3} \text{ M}^{-2} \text{ sec.}^{-1}$. Similar results were obtained with formate, chloroacetate, methoxyacetate, and pivalate buffers. The catalytic constants k_A satisfy the Brønsted catalysis law (Fig. 10), where K_A is the acidity constant of the corresponding acid and G_A and α are constants.

$$\log k_A = \log G_A + \alpha \log K_A \quad (36)$$

Fig. 10 gives $\alpha = 0.46$ and $G_A = 0.41$

On the other hand, the result with phosphate buffers shows the general acid and general base catalysis (see Fig. 11). The phenomenon is explicable by the

stronger basicity of monophosphate ion (secondary dissociation constant of phosphoric acid is 6.023×10^{-8} at 25°C) compared with the acetate ion (the dissociation constant for acetic acid is 1.75×10^{-5}). The similar phenomenon was observed with the urea-formaldehyde reaction⁶⁸).

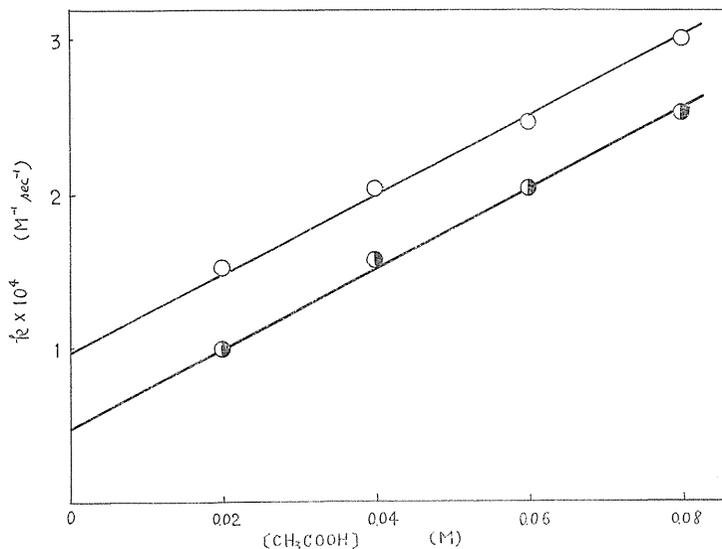


FIG. 9. The illustration of the general acid catalysis for the condensation of urea with acetaldehyde in acetate buffers at 24.2° and ionic strength of 0.2. $\gamma = [\text{CH}_3\text{COO}^-]/[\text{CH}_3\text{COOH}]$: \circ , $\gamma = 0.5$; \ominus , $\gamma = 1$.

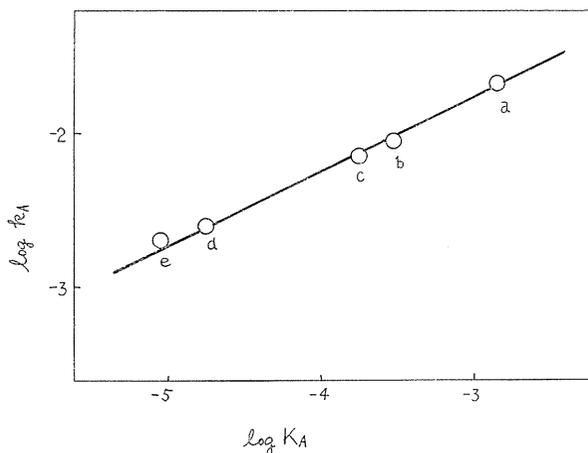


FIG. 10. Application of Brønsted catalysis law, $\log k_A = \log G_A + \alpha \log K_A$, to the condensation of urea with acetaldehyde at 24.2° and ionic strength of 0.2: a, chloroacetic acid; b, methoxyacetic acid; d, acetic acid; e, pivalic acid. $\alpha = 0.46$, $G_A = 4.1 \times 10^{-1}$.

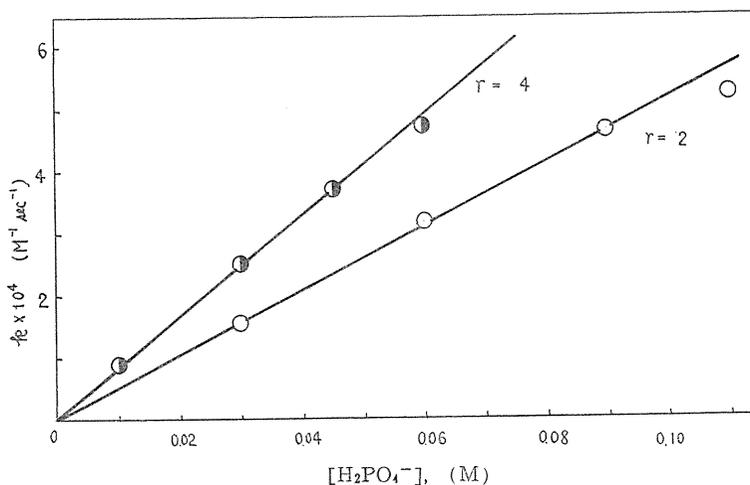
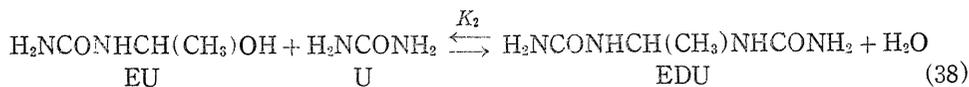


FIG. 11. The illustration of general base catalysis for the condensation of urea with acetaldehyde in phosphate buffers at 24.2° and ionic strength of 0.2. $r = [\text{HPO}_4^{2-}]/[\text{H}_2\text{PO}_4^-]$: ○, $r=2$; ●, $r=4$.

The activation energy for the reaction was 9.97 kcal. mole⁻¹ in water.

Equilibrium Constants.—The calculation of the overall equilibrium constant gave unsatisfactory results, which suggested an intermediary formation of ethylolurea. Therefore, the equilibrium constants were calculated using following abbreviations to represent participants⁽⁷¹⁾.



$$[\text{A}] = [\text{A}_0] - [\text{EU}] - [\text{EDU}] \quad (39)$$

$$K_1 = \frac{[\text{EU}]}{([\text{A}_0] - [\text{EU}] - [\text{EDU}])([\text{U}_0] - [\text{EU}] - 2[\text{EDU}])} \quad (40)$$

$$K_2 = \frac{[\text{EDU}]}{[\text{EU}]([\text{U}_0] - [\text{EU}] - 2[\text{EDU}])} \quad (41)$$

$$K_2 = \frac{(1 - K_1[\text{A}])\{K_1[\text{A}]([\text{A}_0] - [\text{A}] - [\text{U}_0]) + ([\text{A}_0] - [\text{A}])\}}{K_1[\text{A}](2[\text{A}_0] - 2[\text{A}] - [\text{U}_0])^2} \quad (42)$$

Here, subscript 0 means the initial concentration. The introduction of the values of [EU] and [EDU] from Eqs. 39 and 40 into Eq. 41 leads to Eq. 42. The binary equation including unknown K_1 and K_2 and measurable A_0 , A, and U_0 can be solved and the calculated values are listed in Table 10. The constancy of K_1 is satisfactory, while the constancy of K_2 is considerably poorer, because the value of K_2 is sensitive to the small variation in K_1 . The value of K_1 , 2.05 M⁻¹ at 24.2°C is smaller than the corresponding value of 25.7 M⁻¹ at 25°C for the reaction of formaldehyde and urea⁽⁶⁷⁾ and that of 22.3 M⁻¹ at 25°C for the reaction of formal-

TABLE 10. The Equilibrium Constants for the Condensation of Urea with Acetaldehyde in Water^{a)}

[A ₀], (M)	[U ₀], (M)	[A], (M)	K ₁ , (M ⁻¹)	K ₂ , M(- ¹)	[U ₀]/[A ₀]
0.1008	0.4506	0.0497	Standard		4.5
0.1008	0.7496	0.0332	2.02	0.803	7.0
0.1008	0.9001	0.0286	2.15	0.564	9.0
0.1008	1.2009	0.0195	1.93	0.925	12.0
0.1008	1.4990	0.0148	2.01	0.804	15.0
0.0873	1.5020	0.0142	2.10	0.540	17.1 ^{b)}
0.0605	1.2009	0.0116	2.08	0.701	19.9 ^{c)}
			Av. 2.05	0.723	

a) At 24.2°C, b) pH 4.9, c) pH 4.4

dehyde and benzamide⁶⁸⁾, which means a less favorable tendency for the acetaldehyde condensation.

The Decomposition of Ethylidenediurea in Acidic Buffered Solutions.—The decomposition of ethylidenediurea was kinetically studied in a chloroacetate buffer at pH 3.0. The following facts suggest that ethylidenediurea forms ethylolurea in a rapid equilibrium (Eq. 38) and the decomposition of ethylolurea to urea and acetaldehyde is rate-determining (reverse of step 37). (1) The rate of formation of acetaldehyde is of simple first order with ethylidenediurea as shown in Table 11. (2) If the decomposition of ethylidenediurea (the reverse step of Eq. 38) were rate-determining, the rate should not be affected by the addition of urea. As shown in Fig. 12, the apparent rate falls with increasing concentration of added urea, which implies the shift of equilibrium 38 to the right side by the addition of urea. (3) The decomposition of ethylidenediurea as well as the formation of ethylolurea is general acid catalyzed. In spite of this, the decomposition of methylenediurea to methylolurea which corresponds to the reverse of step 38 has been known to be not general acid catalyzed, but specific oxonium ion catalyzed^{67d)}. In analogy, it is probable that the reverse of step 37 is rate-determining and general acid catalyzed.

The value of K_2 (0.72 M^{-1}) in Table 10 implies that most of the ethylidenediurea is converted immediately to ethylolurea which decomposes slowly to urea

TABLE 11. The Decomposition of Ethylidenediurea in Chloroacetate Buffer^{a)}

[EDU ₀], (M)	$k \times 10^3$, (sec. ⁻¹)
0.1500	1.23
0.1250	1.33
0.1000	1.41
0.0750	1.37
0.0500	1.47
Av. 1.37	

a) pH 3.0, at 24.2°C, $\mu=0.2$

$$K_1 = \frac{2.30 \times 10^{-3}}{1.37 \times 10^{-3}} = 1.68 \text{ M}^{-1}$$

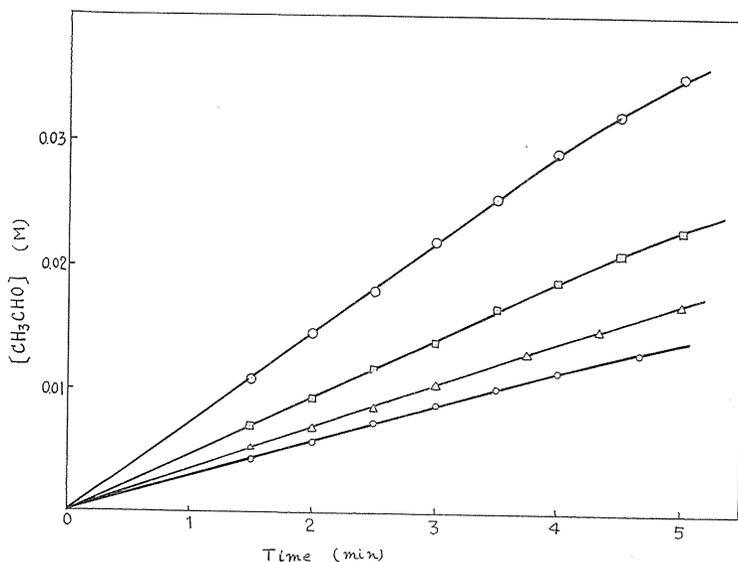
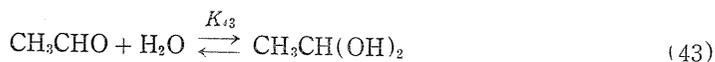


FIG. 12. The decomposition of ethylidenediurea in chloroacetate buffers (pH 3) with initial concentration of ethylidenediurea of 0.1000 M: ●, $[U_0]=0$; □, $[U_0]=0.250$ M; △, $[U_0]=0.500$ M; ○, $[U_0]=0.750$ M.

and acetaldehyde and that the formation of ethylidenediurea needs a large excess of urea. The value of K_1 (1.68 M^{-1}) obtained from the ratio of the rate constants of the forward and the reverse reactions agrees in order with the value (2.05 M^{-1}) that was measured directly.

Reaction Mechanism.—As stated above, the formation of ethylolurea from urea and acetaldehyde is rate-determining because of the observed second-order kinetics.

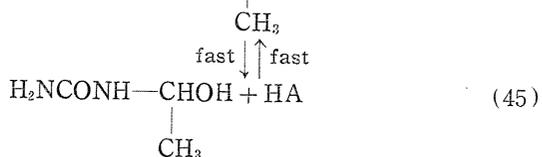
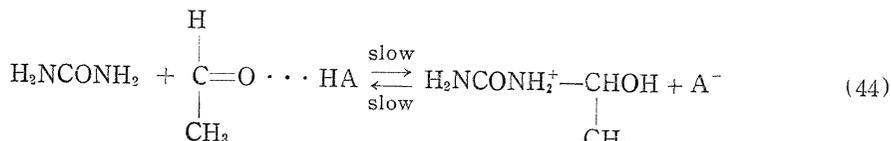
In a dilute aqueous solution about half of the amount of acetaldehyde is hydrated, since $K_{13}[\text{H}_2\text{O}]=1.02^{72}$.

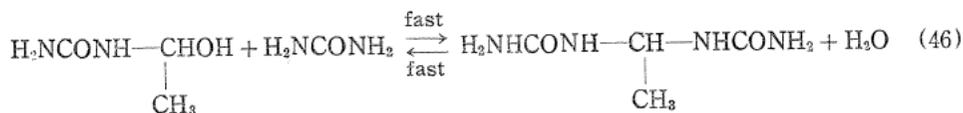


Hydrated acetaldehyde is inactive as in the case of formaldehyde^{67,68}.

The observed general acid catalysis may be explained by a mechanism involving a simultaneous attack of urea and acid (HA) on acetaldehyde, which is analogous to amide-formaldehyde^{67,68}) and ammonia-aldehyde^{42,73}) reactions.

Similarly, the following mechanism may be suggested for the base catalysis.





However, the possibility of the specific oxonium ion and the specific hydroxide ion catalysis is not ruled out on the basis of the present data.

6. Kinetics of the Condensation of urea with some Aliphatic Aldehydes

6-1. Summary

The rate and equilibrium constants of the condensation of urea with some aliphatic aldehydes to form alkylidenediureas have been measured spectrophotometrically in aqueous solutions at 24.2°C. The rate is always expressed as: $v = k[\text{H}_2\text{NCONH}_2][\text{free RCHO}]$. Electron-releasing groups in aldehydes tend to decrease the rate of forward reaction with Taft's ρ^* value of +3.5. The reaction is reversible and is subject to both general acid and general base catalysis. The Brønsted catalysis law, $k_A = G_A K_A^\alpha$, is applicable to the general acid catalysis, and the α values in the equation are 0.38 for propionaldehyde, 0.43 for *n*-butyraldehyde, and 0.45 for isobutyraldehyde. These results agree with the expectation from the suggested reaction mechanism involving the rate-determining attack of urea on free aldehyde molecule.

6-2. Introduction

There have been many kinetic studies on the condensation of formaldehyde with amines^{2-4,17,67,68} involving amides, but the reports on the reaction of other aliphatic aldehydes are few. The authors have previously reported the kinetic studies on the reaction of some aliphatic aldehydes with ammonia^{42,73} and of acetaldehyde with excess urea to form ethylidenediurea⁷⁴. The present section deals with the kinetic results obtained on the condensation of urea with some aliphatic aldehydes to form alkylidenediureas by means of spectrophotometric estimation of remaining aldehyde.



6-3. Experimental

Materials.—Commercial reagent grade aldehydes were purified by rectification, propionaldehyde, b.p. 48.8°C; butyraldehyde, b.p. 74.2°C; isobutyraldehyde, b.p. 65.5°C. Commercial reagent grade urea was purified by recrystallization from methanol m.p. 132.5°C. Ion exchanged water was used as the solvent. Acetic, formic, and chloroacetic acids were of commercial reagent grade. Methoxyacetic acid was prepared from chloroacetic acid⁷⁵, b.p. 84.5°C/5 mm and pivalic acid was prepared by the Grignard reaction of *t*-butyl chloride⁷⁶, b.p. 165–167°C.

Products.—Alkylidenediureas were prepared by the reaction of one mole of aldehydes and ten moles of urea in an aqueous solution at room temperature. The resulting precipitates were filtered and recrystallized from water.

Propylidenediurea, m.p. 191–192°C (dec.); *butylidenediurea*, m.p. 186–187°C (dec.); *isobutylidenediurea*, m.p. 221–222°C (dec.).

Infrared spectra of these compounds showed no OH peak. These are new compounds.

Propylidenediurea (Found: C, 37.23; H, 7.17; N, 34.98. $C_5H_{12}N_4O_2$ requires: C, 37.49; H, 7.55; N, 34.98%). Butylidenediurea (Found (normal): C, 43.60; H, 8.23; N, 30.06. (iso); C, 41.03; H, 7.89; N, 32.28. $C_6H_{14}N_4O_2$ requires: C, 41.37; H, 8.10; N, 32.17%).

The deviation with *n*-butylidenediurea is probably due to the contamination of aldehyde-urea (1:1) condensate. The product (1 m mole) was found to be hydrolyzed with H_2SO_4 aq. giving *n*-butyraldehyde (1.08 m mole) (hydroxylamine method), which suggests that it is the condensate of urea: aldehyde=2:1.

Kinetic Procedure.—As stated previously for acetaldehyde⁷⁴, the rate of reaction of urea with some aliphatic aldehydes in aqueous solutions at 24.2°C was determined by measuring unreacted aldehyde spectrophotometrically, *i.e.*, the decrease of the carbonyl peak. The molar extinction coefficient of aldehydes in water at 24.2°C was as follows: 10.6 at 280 $m\mu$ (propionaldehyde); 13.4 at 283 $m\mu$ (butyraldehyde); 14.6 at 284 $m\mu$, and 20.8 at 295 $m\mu$ in *n*-hexane (isobutyraldehyde).

Rates were measured as pseudo-first-order reaction in 10–25 fold moles of urea to one mole of acetaldehyde. Isobutylidenediurea precipitated at the end of reaction under kinetic conditions. Except in phosphate buffer (μ , 0.8) all runs were carried out at the same ionic strength (μ , 0.2) by adding NaCl.

A typical experiment for the rate measurement was as follows: 0.147 M propionaldehyde (25 ml.) in a buffered solution and 2.80 M urea (25 ml.) in the same buffered solution, which had previously attained to the thermal equilibrium, were mixed in a flask and immediately introduced to a glass-stoppered quartz cell thermostated at $24.2 \pm 0.2^\circ C$ in a Hitachi spectrophotometer type EPU-2 A. The absorbance at absorption maximum of aldehyde was measured at known intervals of time. Typical rate data are shown in Table 12.

The rate may be expressed as the rate equation for the reversible reaction:

$$v = k_1[A] - k_{-1}[UAU]$$

TABLE 12. Typical Rate Data for the Reaction of Propionaldehyde, with Urea in Acetate Buffered Solution at 24.2°C and Ionic Strength of 0.2. Initial conc.: propionaldehyde, 0.0734 M; urea, 1.474 M

Time (sec.)	$E_{278}^{(a)}$	$[C_2H_5CHO]^{(b)}$ (M)	$k \times 10^{(c)}$ (sec. ⁻¹)
0	0.776	0.0734	
600	0.692	0.0653	1.33
900	0.651	0.0614	1.35
1260	0.605	0.0570	1.36
1680	0.555	0.0523	1.37
2100	0.510	0.0481	1.37
2640	0.456	0.0430	1.37
3120	0.416	0.0392	1.36
			Av. 1.36

a) Extinction at 278 $m\mu$

b) Concentration of residual propionaldehyde

c) Pseudo-first-order rate constant

Hence, the observed rate constant k is equal to $(k'_1 + k_1)$. However, the reverse reaction should be neglected at early stages of the reaction, since a large excess of urea is used. In fact, the plot of the observed rate constant vs. the concentration of urea does pass the origin (Fig. 13), which suggests that the observed rate constant k is equal to pseudo-first-order rate constant k'_1 and hence to k_1 [urea].

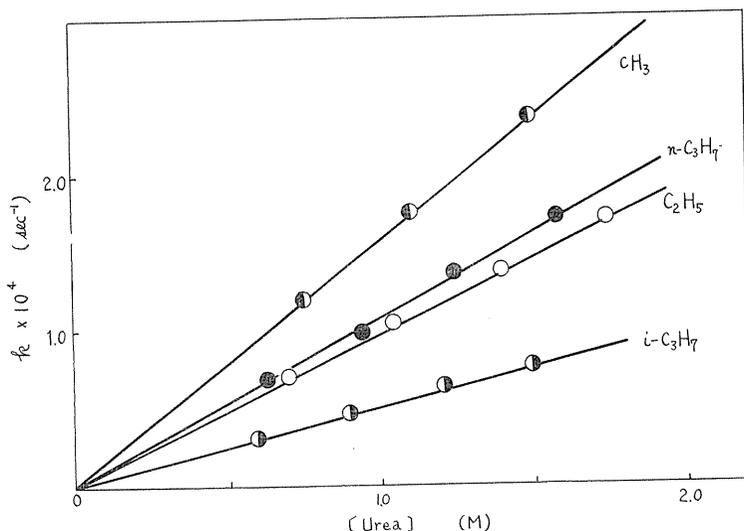
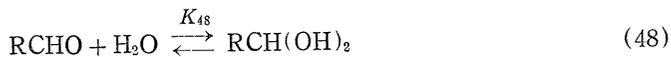


FIG. 13. Plot of the pseudo-first-order rate constant vs. the initial concentration of urea for the condensation of urea with aliphatic aldehydes, RCHO, at 24.2°C and ionic strength of 0.2 in the same acetate buffer solution.

6-4. Results and Discussion

Rate Law.—Pseudo-first-order rate constants were calculated by measuring aldehyde in acetate buffered solutions at 24.2°C, where a 10–25 fold excess of urea to acetaldehyde was used. As shown in Fig. 13, the plot of pseudo-first-order constant of each aldehyde vs. initial concentration of urea was a straight line passing through the origin. Therefore, the rate is expressed as: $v = k$ [urea] [RCHO]. Second-order rate constants were determined from the slope of those lines. The observed second-order constants did not satisfactorily fit to the Taft's equation. Since reactive species are supposed to be unhydrated aldehyde and urea as stated previously⁽⁴²⁾⁽⁷³⁾⁽⁷⁴⁾, it seems to be necessary to see the extent of hydration of aldehyde in Eq. 48.



Molar fraction of unhydrated aldehyde, f , is expressed as $1/(1 + K_{48}[\text{H}_2\text{O}])$ which can be determined by the measurement of K_{48} ⁽⁴⁶⁾. The k_2/f (the rate constant with free aldehyde) was used for the purpose of comparing the rates of the forward reaction. These values are summarised in Table 13. The plot of $\log k$ vs. Taft's σ^* value gave a positive ρ^* value (+3.5). The positive ρ^* value means

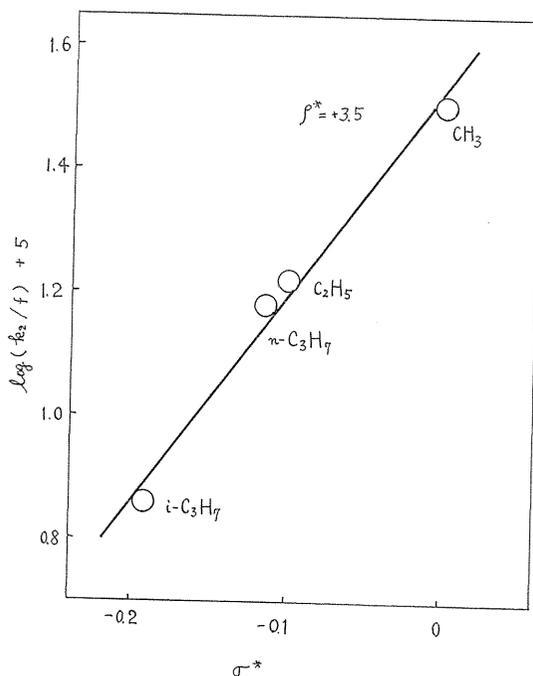


FIG. 14. Plot of $\log(k_2/f)$ vs. Taft's sigma constant for the condensation of aliphatic aldehydes with urea in an acetate buffer at 24.2°C and ionic strength of 0.2.

TABLE 13. The Relative Rate Constants for the Reaction of Aliphatic Aldehydes, RCHO, with Urea in an Acetate Buffered Solution at 24.2°C and Ionic Strength of 0.2

R	Rate const. $k_2 \times 10^4$ ($\text{M}^{-1}\text{sec.}^{-1}$)	Equil. const. K_2 , (M^{-1})	Mol. frac. of free aldehyde	$(k_2/f) \times 10^4$ ($\text{M}^{-1}\text{sec.}^{-1}$)
CH_3	1.58	1.02	0.496	3.19
C_2H_5	0.990	0.680	0.595	1.66
$n\text{-C}_3\text{H}_7$	1.09	0.388	0.720	1.51
$i\text{-C}_3\text{H}_7$	0.505	0.425	0.703	0.720

that an electron-releasing group in aldehyde decreases the electrophilicity of the carbonyl group, resulting in a slow reaction with urea.

Catalysis in Buffered Solutions.—As observed in the reaction of acetaldehyde with urea reported previously⁽¹⁴⁾, the reaction of aliphatic aldehydes with urea seems to be subject to both general acid and general base catalysis. The plots of second-order constant for propionaldehyde vs. concentration of acetate buffer with constant pH values show straight parallel lines corresponding to their pH values. The fact indicates that the reaction is subject to general acid catalysis with acetic acid, but not to general base catalysis with acetate ion. The slope of line gives specific acid catalytic constant for acetic acid to be $2.78 \times 10^{-3} \text{ M}^{-2} \text{ sec.}^{-1}$. The similar results were obtained with butyraldehyde and isobutyralde-

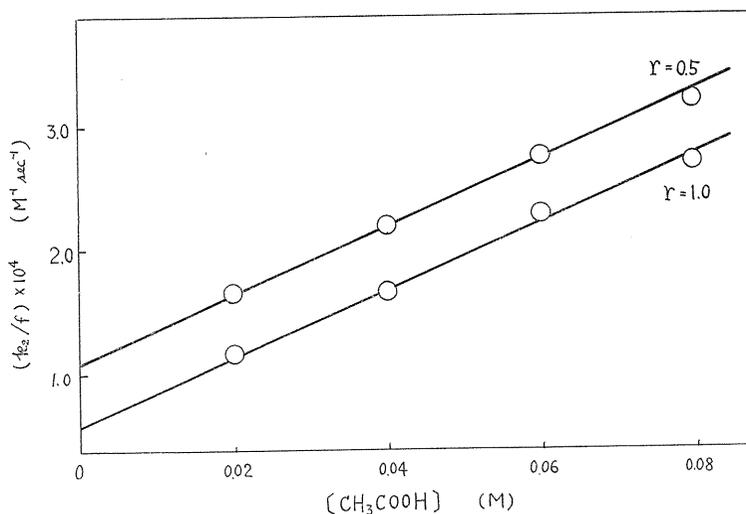


FIG. 15. The illustration of the acid catalysis for the condensation of urea with acetaldehyde in acetate buffers at 24.2°C and ionic strength of 0.2, where r is $[\text{CH}_3\text{COO}^-]/[\text{CH}_3\text{COOH}]$.

hyde, and with formate, chloroacetate, methoxyacetate and pivalate buffers on these aldehydes. The catalytic constants with each aldehyde satisfy the Brönsted catalysis law (Fig. 16), where K_A is the acidity constant of the corresponding acid and G_A and α are constants.

$$\log k_A = \log G_A + \alpha \log K_A \quad (49)$$

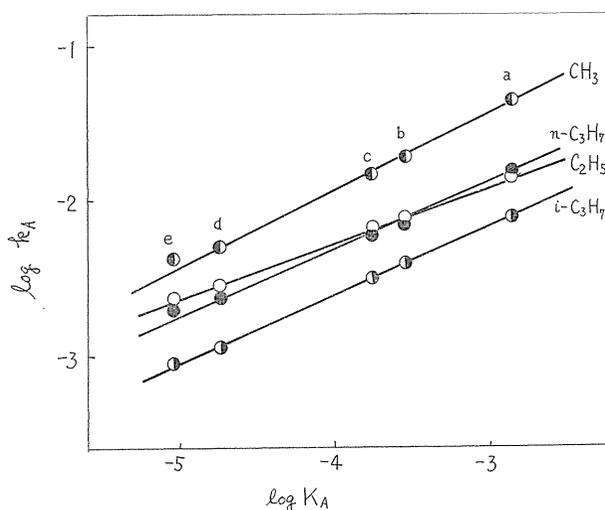


FIG. 16. The application of Brönsted catalysis law $\log k_A = \log G_A + \alpha \log K_A$ to the condensation of urea with aliphatic aldehydes at 24.2°C and ionic strength of 0.2. a: Chloroacetic acid, b: Methoxyacetic acid, c: Formic acid, d: Acetic acid, e: Pivalic acid.

TABLE 14. The G_A and α Values in the Brønsted Equation, $k_A = G_A K_A^\alpha$, for the Condensation of Urea with Aliphatic Aldehydes, RCHO, at 24.2°C

R	α	G_A
CH ₃	0.46	0.79
C ₂ H ₅	0.38	0.17
<i>n</i> -C ₃ H ₇	0.43	0.26
<i>i</i> -C ₃ H ₇	0.45	0.15

The values of G_A and α are summarized in Table 14.

The similarity of the α values for aldehyde indicates the similar catalytic abilities of a given acid for various aliphatic aldehydes in these reactions. On the other hand, the result with phosphate buffers shows both general acid and general base catalysis. Fig. 17 shows the results obtained with propionaldehyde. The similar phenomenon was observed with *n*- and isobutyraldehyde. The phenomenon is explicable by the stronger basicity of monophosphate ion compared with acetate ion. Catalytic constants calculated from the slope of line are summarized in Table 15.

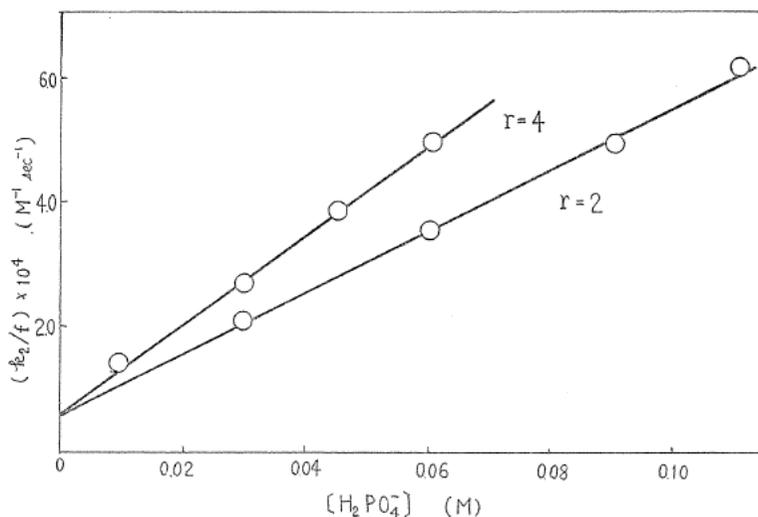
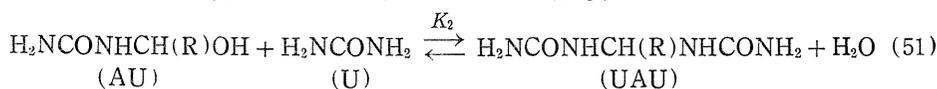
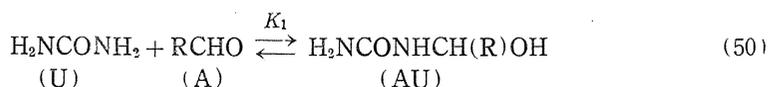


FIG. 17. The illustration of both general acid and base catalysis for the condensation of urea with propionaldehyde in phosphate buffers at 24.2°C and ionic strength of 0.8, where r is $[\text{HPO}_4^{--}]/[\text{H}_2\text{PO}_4^-]$.

TABLE 15. The Catalytic Constants, $\text{M}^{-2}\text{sec}^{-1}$, of H_2PO_4^- and HPO_4^{--} for the Condensation of Urea with Aliphatic Aldehydes in Phosphate Buffers at 24.2°C and Ionic Strength of 0.8,

Aldehyde Cat. const.	CH ₃ CHO	C ₂ H ₅ CHO	<i>n</i> -C ₃ H ₇ CHO	<i>i</i> -C ₃ H ₇ CHO
$k_{\text{H}_2\text{PO}_4^-}$	4.33×10^{-3}	3.10×10^{-3}	2.19×10^{-3}	8.25×10^{-4}
$k_{\text{HPO}_4^{--}}$	3.25×10^{-3}	1.14×10^{-3}	8.40×10^{-4}	3.44×10^{-4}

Equilibrium Constants.—The calculation of overall equilibrium constant gave unsatisfactory results (K in Table 16), which suggests an intermediary formation of alkylolurea. Therefore, the equilibrium constants were calculated using following abbreviations, reported previously in the condensation of acetaldehyde with urea forming ethylidenediurea⁷⁴). Similar treatment has been reported in the condensation of formaldehyde with urea forming dimethylolurea⁷¹).



$$[\text{A}] = [\text{A}_0] - [\text{AU}] - [\text{UAU}] \quad (52)$$

$$[\text{U}] = [\text{U}_0] - [\text{AU}] - 2[\text{UAU}] \quad (53)$$

$$K_1 = \frac{[\text{AU}]}{([\text{U}_0] - [\text{AU}] - 2[\text{UAU}])([\text{A}_0] - [\text{AU}] - [\text{UAU}])} \quad (54)$$

$$K_2 = \frac{[\text{UAU}]}{[\text{AU}]([\text{U}_0] - [\text{AU}] - 2[\text{UAU}])} \quad (55)$$

Here, subscript 0 means the initial concentration. The introduction of the values of $[\text{AU}]$ and $[\text{UAU}]$ from Eqs. 52 and 54 into Eq. 55 leads to

$$K_2 = \frac{(1 - K_1[\text{A}])\{K_1[\text{A}]([\text{A}_0] - [\text{A}] - [\text{U}_0]) + ([\text{A}_0] - [\text{A}])\}}{K_1[\text{A}](2[\text{A}_0] - 2[\text{A}] - [\text{U}_0])^2} \quad (56)$$

TABLE 16. The Equilibrium Constants for the Condensation of Urea with Propionaldehyde in Acetate Buffer at 24.2°C

$[\text{P}_0]^{\text{a)}}$ (M)	$[\text{U}_0]^{\text{b)}}$ (M)	$[\text{U}_0]/[\text{P}_0]$	$[\text{P}]^{\text{c)}}$ (M)	$K^{\text{d)}}$ (M ⁻²)	$K_1^{\text{e)}}$ (M ⁻¹)	$K_2^{\text{f)}}$ (M ⁻¹)
0.0628	0.2162	3.4	0.0442	13.14		
0.0628	0.6583	10.5	0.0209	6.07	1.62	1.82
0.0628	0.8701	13.9	0.0156	5.03	1.65	1.63
0.0628	1.0897	17.4	0.0124	4.15	1.74	1.30
0.0628	1.2998	20.7	0.0099	3.74	1.59	1.46
				Av.	1.65	1.55

a) Initial concentration of propionaldehyde

b) Initial concentration of urea

c) Concentration of propionaldehyde in the equilibrium mixture

d) Over-all equilibrium constants in Eq. 47

e) Equilibrium constant in Eq. 50

f) Equilibrium constant in Eq. 51

Binary equation including unknown K_1 and K_2 and measurable A_0 , A , and U_0 can be solved and the calculated values with propionaldehyde are listed in Table 16. Similar calculation is applied to butyraldehyde and isobutyraldehyde-urea condensations. The application of these equilibrium constants to the Taft's equation (Fig. 18) shows a positive ρ^* value for the first equilibrium K_1 (+0.93) and a

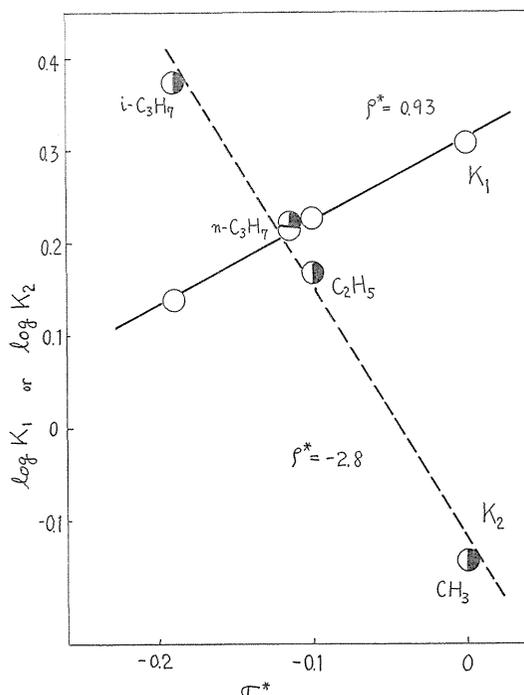


FIG. 18. Plot of $\log K_1$ and $\log K_2$ vs. Taft's sigma for the condensation of aliphatic aldehydes with urea in an acetate buffer at 24.2°C and ionic strength of 0.2.

negative ρ^* value for the second equilibrium K_2 (-2.8). The positive ρ^* value for K_1 shows that an electron-releasing group in aldehyde reduces the electrophilicity of the carbonyl group resulting in an unfavorable equilibrium. Similar tendency has been observed in the equilibrium constants of the reaction of some aliphatic aldehydes with ammonia to form α -aminoalcohols⁷³. On the other hand, the fact that the Taft's treatment for the equilibrium constant K_2 gives a larger negative ρ^* value means that equilibrium 51 is shifted to the right side with electron-releasing groups; electron-releasing groups in aldehyde lower the stability of the intermediary alkylolurea, $\text{H}_2\text{NCONHCH(R)OH}$, and facilitate its condensation with urea. This consideration suggests the following mechanism with the rate-determining step 57 on the assumption that the reaction 51 is subject to specific oxonium ion catalysis similar to the reaction of formaldehyde⁷⁴.

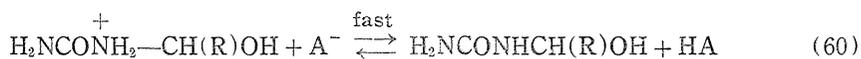
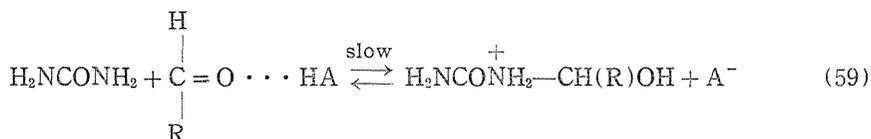


An electron-releasing group accelerates the forward reaction (k_{57}) of the step 57 and retards the reverse reaction (k_{-57}), hence equilibrium constants K_{57} should have a rather large negative ρ^* value, which is consistent with the observation. In contrast, the equilibrium constant K_{58} should give a larger positive ρ^* value

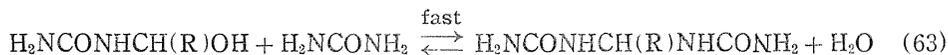
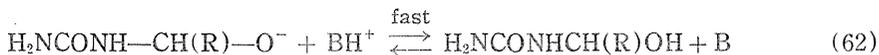
because an electron-releasing group retards the forward reaction (k_{58}) and accelerates the reverse one (k_{-58}). Therefore, the contribution of alkyl group to step 57 is more significant than that to step 58.

Reaction Mechanism.—As stated above, the formation of alkylolureas from urea and unhydrated aldehydes is rate-determining because of the observed second-order kinetics and of both general acid and general base catalysis.

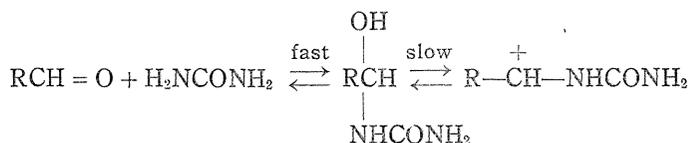
The observed general acid catalysis may be explained by a mechanism suggested previously⁽⁶⁸⁾⁽⁷⁰⁾⁽⁷¹⁾.



Similarly, the following mechanism may be suggested for the base catalysis.

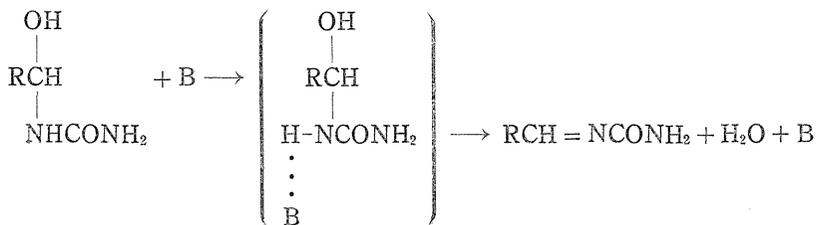


The following mechanism also agrees with the second-order kinetics.



However, the observed general base catalysis could not be explained by this mechanism.

The following mechanism, similar to that postulated by Anderson and Jencks⁽³⁴⁾ for the semicarbazone formation, also agrees with the second-order kinetics.



However, the mechanism does not seem to be applicable to the present reaction. Since it is known that the reaction of urea with methylolurea is not subject to the base catalysis but only to the specific oxonium ion catalysis⁶⁷, it is less probable that the reaction of urea with ethylolurea is subject to general base catalysis because of the lower acidity of hydrogen atom on nitrogen of C-N-C compared with methylolurea.

Acknowledgement

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