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KINETICS OF THE CONDENSATION OF UREA WITH SOME ALIPHATIC ALDEHYDES[1]

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Abstract—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°. The rate is always expressed as: $v = k[H_2NCONH_2]$[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 acid and base catalysis. The Brönsted catalysis law, $k_A = G_A K_A{}^{\alpha}$, is applicable to the 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.

THERE have been many kinetic studies on the condensation of formaldehyde with amines[2,3] involving amides, but the reports on the reaction of other aliphatic aldehydes are few, the kinetic studies being confined to the reaction of some aliphatic aldehydes with ammonia[4] and of acetaldehyde with excess urea to form ethylidenediurea.[5] The present paper deals with the kinetics of the condensation of urea with some aliphatic aldehydes to form alkylidenediureas by means of spectrophotometric estimation of residual aldehyde.

$$RCHO + 2NH_2CONH_2 \rightleftharpoons NH_2CONHCH(R)NHCONH_2 + H_2O \qquad (1)$$

RESULTS AND DISCUSSION

Rate law. Pseudo-first-order rate constants were calculated by measuring aldehyde in acetate buffered solutions at 24·2°, where a 10–25 fold excess of urea to acetaldehyde was used. As shown in Fig. 1, 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: $v = k[H_2NCONH_2][RCHO]$. Second-order rate constants were determined from the slope of these 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,[4,5] it is necessary to determine the extent of hydration of aldehyde in Eq. 2.

$$RCHO + H_2O \overset{K_2}{\rightleftharpoons} RCH(OH)_2 \qquad (2)$$

Molar fraction of unhydrated aldehyde, f, is expressed as $1/(1 + K_2[H_2O])$ which can

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[1] Contribution No. 75.

[2] For example, J. Ugelstad and J. de Jonge, *Rec. Trav. Chim.* **76**, 919 (1957).

[3] Y. Ogata and A. Kawasaki, *Bull. Chem. Soc. Japan* **37**, 514 (1964).

[4] Y. Ogata and A. Kawasaki, *Tetrahedron* **20**, 855, 1573 (1964).

[5] Y. Ogata, A. Kawasaki and N. Okumura, *J. Org. Chem.* **30**, 1636 (1965).

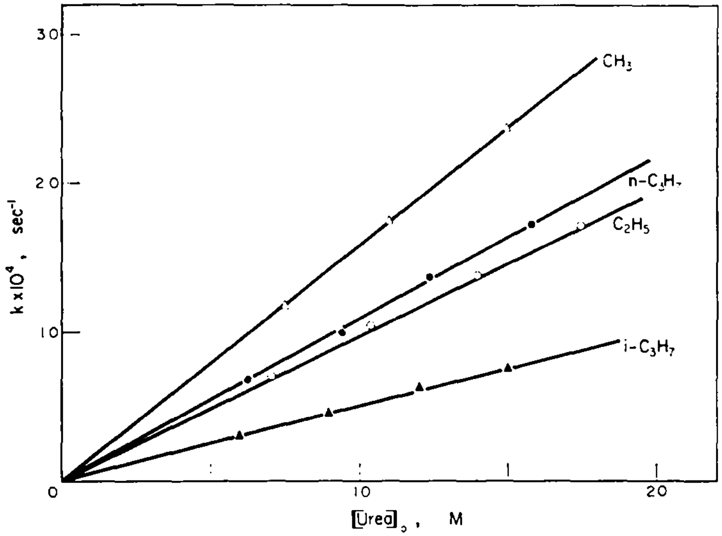

FIG. 1. Plot of the pseudo first-order rate constants for various aldehydes *vs.* the initial concentration of urea in the same acetate buffer solution at 24·2° and ionic strength of 0·2.

TABLE 1. THE RELATIVE RATE CONSTANTS FOR THE REACTION OF ALIPHATIC ALDEHYDES, RCHO, WITH UREA IN AN ACETATE-BUFFERED SOLUTION AT 24·2° AND IONIC STRENGTH OF 0·2

R	Rate const. k_2, M^{-1} sec^{-1}	Equil. const. K_2	Mol. frac. of free aldehyde, f	k_2/f M^{-1} sec^{-1}
CH_3	$1·58 \times 10^{-4}$	1·02	0·496	$3·19 \times 10^{-4}$
C_2H_5	$0·990 \times 10^{-4}$	0·680	0·595	$1·66 \times 10^{-4}$
n-C_3H_7	$1·09 \times 10^{-4}$	0·388	0·720	$1·51 \times 10^{-4}$
i-C_3H_7	$0·505 \times 10^{-4}$	0·425	0·703	$0·720 \times 10^{-4}$

be determined by the measurement[6] of K_2. 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 summarized in Table 1. The plot of log k *vs.* Taft's σ^* value gave a positive ρ^* value (+3·5). The positive ρ^* value means 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,[5] the reaction of aliphatic aldehydes with urea is subject to both acid and 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 acid catalysis with acetic acid, but not to base catalysis with acetate ion. The slope of line gives specific acid catalytic constant for acetic acid to be $2·78 \times 10^{-3}$ M^{-2} sec^{-1}. Similar results were

[6] The equilibrium constants (K_2) were determined spectrophotometrically according to R. Bieber and G. Trümpler, *Helv. Chim. Acta* **30**, 1860 (1947).

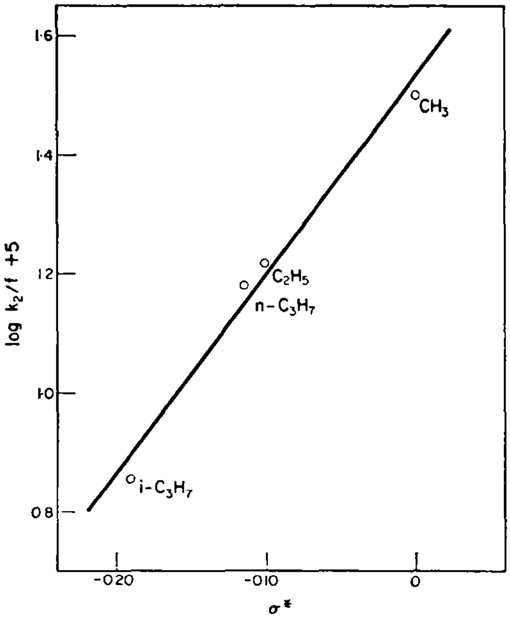

FIG. 2. Plot of log (k_2/f) vs. Taft's sigma constant for the condensation of aliphatic aldehydes with urea in an acetate buffer at 24·2° and ionic strength of 0·2.

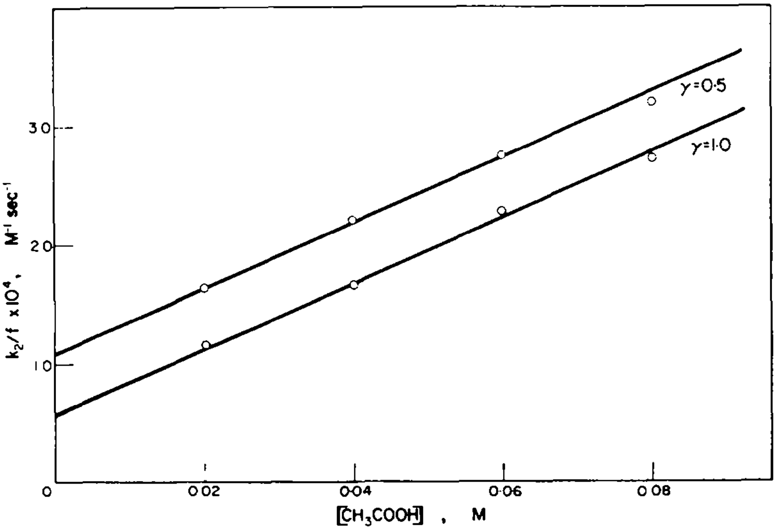

FIG. 3. The illustration of the acid catalysis for the condensation of urea with acetaldehyde in acetate buffers at 24·2° and ionic strength of 0·2, where r is $[CH_3COO^-]/[CH_3COOH]$.

obtained with butyraldehyde and isobutyraldehyde, and with formate, chloroacetate, methoxyacetate and pivalate buffers on these aldehydes. The catalytic constants with each aldehyde satisfy the Brönsted catalysis law (Fig. 4), where K_A is the acidity constant of the corresponding acid and G_A and α are constants.

$$\log k_A = \log G_A + \alpha \log K_A \tag{3}$$

The values of G_A and α are summarized in Table 2. The similarity of the α values for aldehydes indicates equivalent catalytic activity of a given acid for various aliphatic aldehydes in these reactions. On the other hand, the result with phosphate buffers shows both acid and base catalysis. Fig. 5 shows the results obtained with propionaldehyde. A similar phenomenon was observed with n- and isobutyraldehyde, explicable by the stronger basicity of the monophosphate ion as compared with the acetate ion. Catalytic constants calculated from the slope of line are summarized in Table 3.

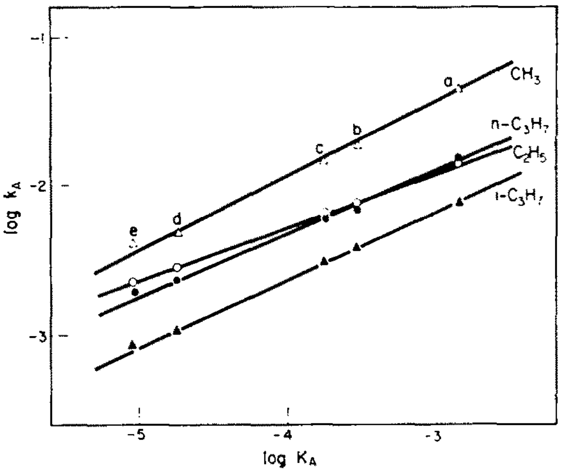

FIG. 4. The application of Brönsted catalysis law $\log k_A = \log G_A + \alpha \log K_A$ to the condensation of urea with aliphatic aldehydes at 24·2° and ionic strength of 0·2.
a: Chloroacetic acid b: Methoxyacetic acid c: Formic acid
d: Acetic acid e: Pivalic acid

TABLE 2. THE α AND G_A VALUES IN THE BRÖNSTED EQUATION, $k_A = G_A K_A^{\alpha}$, FOR THE CONDENSATION OF UREA WITH ALIPHATIC ALDEHYDES, RCHO, AT 24·2°.

R	α	G_A
CH_3	0·46	0·79
C_2H_5	0·38	0·17
n-C_3H_7	0·43	0·26
i-C_3H_7	0·45	0·15

Equilibrium constants. The calculation of the overall equilibrium constant gave unsatisfactory results (K_1 in Table 4), which suggests an intermediary formation of

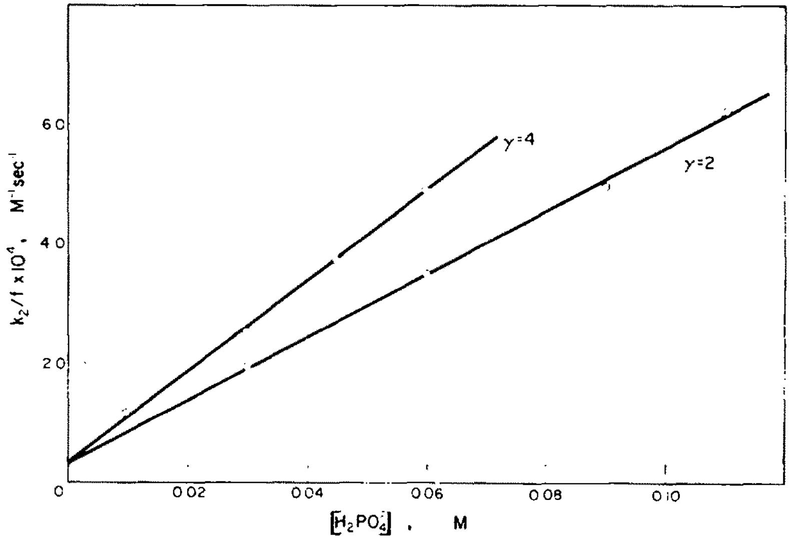

FIG. 5. The illustration of both acid and base catalysis for the condensation of urea with propionaldehyde in phosphate buffers at 24·2° and ionic strength of 0·8, $r = [HPO_4^{2-}]/[H_2PO_4^-]$.

alkylolurea. Therefore, the equilibrium constants were calculated using following abbreviations.[7]

$$\underset{(U)}{H_2NCONH_2} + \underset{(A)}{RCHO} \overset{K_4}{\rightleftharpoons} \underset{(AU)}{H_2NCONH(R)OH} \tag{4}$$

$$\underset{(AU)}{H_2NCONHCH(R)OH} + \underset{(U)}{H_2NCONH_2} \overset{K_5}{\rightleftharpoons} \underset{(UAU)}{H_2NCONHCH(R)NHCONH_2} + H_2O \tag{5}$$

$$[A] = [A_o] - [AU] - [UAU] \tag{6}$$

$$[U] = [U_o] - [AU] - 2[UAU] \tag{7}$$

$$K_4 = \frac{[AU]}{([U_o] - [AU] - 2[UAU])([A_o] - [AU] - [UAU])} \tag{8}$$

$$K_5 = \frac{[UAU]}{[AU]\,([U_o] - [AU] - 2[UAU])} \tag{9}$$

TABLE 3. THE CATALYTIC CONSTANTS, M^{-2} sec^{-1}, OF $H_2PO_4^-$ AND HPO_4^{2-} FOR THE CONDENSATION OF UREA WITH ALIPHATIC ALDEHYDES IN PHOSPHATE BUFFERS AT 24·2° AND IONIC STRENGTH OF 0·8

Aldehyde Cat. const.	CH_3CHO[a]	C_2H_5CHO	n-C_3H_7CHO	i-C_3H_7CHO
$k_{H_2PO_4^-}$	$4·33 \times 10^{-3}$	$3·10 \times 10^{-3}$	$2·19 \times 10^{-3}$	$8·25 \times 10^{-4}$
$k_{HPO_4^{--}}$	$3·25 \times 10^{-3}$	$1·14 \times 10^{-3}$	$8·40 \times 10^{-4}$	$3·44 \times 10^{-4}$

[a] Data calculated, see Ref. 3.

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[7] Similar treatment has been reported in the condensation of formaldehyde with urea forming dimethylolurea. H. Sobue and K. Murakami, *Kobunshi Kagaku* 9, 454 (1952). This treatment is also applied to the condensation of acetaldehyde with urea forming ethylidenediurea as reported previously.[5]

Here, subscript *o* means the initial concentration. The introduction of the values of [AU] and [UAU] from Eqs. 6 and 8 into Eq. 9 leads to:

$$K_5 = \frac{(1 - K_4[\mathrm{A}])\{K_4[\mathrm{A}]([\mathrm{A}_o] - [\mathrm{A}] - [\mathrm{U}_o]) + ([\mathrm{A}_o] - [\mathrm{A}])\}}{K_4[\mathrm{A}](2[\mathrm{A}_o] - 2[\mathrm{A}] - [\mathrm{U}_o])^2} \tag{10}$$

The binary equation including unknown K_4 and K_5 and measurable A_o, A, and U_o can be solved and the calculated values with propionaldehyde are listed in Table 4. A similar calculation is applied to butyraldehyde and isobutyraldehyde–urea condensations. The application of these equilibrium constants to the Taft's equation (Fig. 6) shows a positive ρ^* value for the first equilibrium $K_4(+0{\cdot}93)$ and a negative ρ^* value for the second equilibrium $K_5(-2{\cdot}8)$. The positive ρ^* value for K_4 shows that an electron-releasing group in aldehyde reduces the electrophilicity of the carbonyl group resulting in an unfavorable equilibrium. A similar tendency has been observed in the equilibrium constants of the reaction of some aliphatic aldehydes with ammonia to form α-aminoalcohols.[4] On the other hand, the fact that the Taft's treatment for the constant equilibrium K_5 gives a larger negative ρ^* value means that equilibrium 5 is shifted to the right with electron-releasing groups; electron-releasing groups in aldehyde lower the stability of the intermediary alkylolurea, $H_2NCONHCH(R)OH$, and facilitate its condensation with urea. This consideration suggests the following mechanism with the rate-determining step 11 on the assumption that the reaction 5 is subject to specific oxonium ion catalysis similar to the reaction of formaldehyde.[8]

TABLE 4. THE EQUILIBRIUM CONSTANTS FOR THE CONDENSATION OF UREA WITH PROPIONALDEHYDE IN ACETATE BUFFER AT 24·2°

Init. concn. of EtCHO (P_o), M	Init. concn. of Urea (U_o), M	Equil. concn. of EtCHO, M	U_o/P_o	K_1, M^{-2}	K_4, M^{-1}	K_5, M^{-1}
0·0628	0·2162	0·0442	3·4	13·14	standard	
0·0628	0·6583	0·0209	10·5	6·07	1·62	1·82
0·0628	0·8701	0·0156	13·9	5·03	1·65	1·63
0·0628	1·0897	0·0124	17·4	4·15	1·74	1·30
0.0628	1·2998	0·0099	20·7	3·74	1·59	1·46
					Av. 1·65	1·55

$$H_2NCONHCH(R)OH + H^+ \underset{}{\overset{\text{slow}}{\rightleftarrows}} H_2NCONH\overset{+}{C}HR + H_2O \tag{11}$$

$$H_2NCONH\overset{+}{C}HR + H_2NCONH_2 \overset{\text{fast}}{\rightleftarrows} H_2NCONHCH(R)NHCONH_2 + H^+ \tag{12}$$

An electron-releasing group accelerates the forward reaction (k_{11}) of the step 11 and retards the reverse reaction (k_{-11}), hence equilibrium constant K_{11} should have a rather large negative ρ^* value, which is consistent with the observation. In contrast, the equilibrium constant K_{12} should give a larger positive ρ^* value because an electron-releasing group retards the forward reaction (k_{12}) and accelerates the reverse one (k_{-12}).

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[8] J. I. de Jong and J. de Jonge, *Rec. Trav. Chim.* 72, 202 (1953).

Therefore, the contribution of alkyl group to step 11 is more significant than that to step 12.

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 acid and base catalysis.

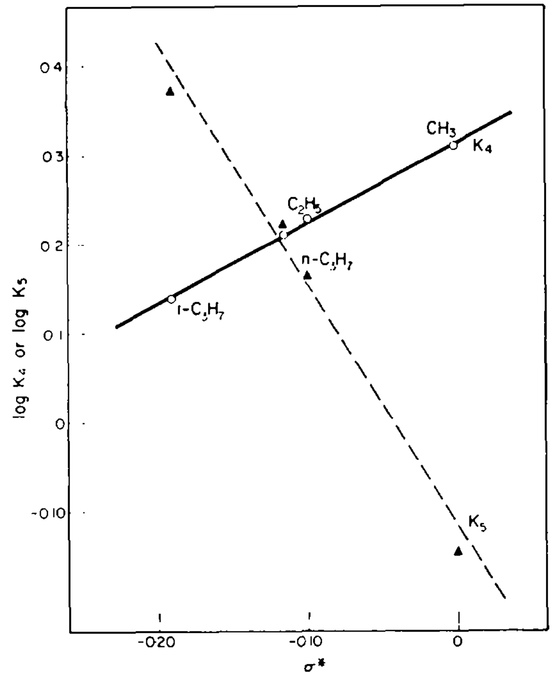
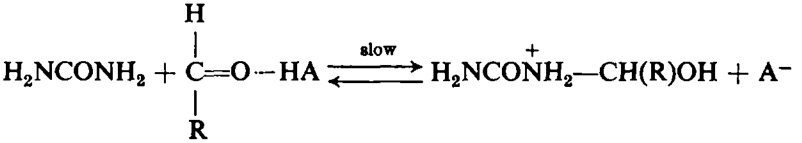


FIG. 6. Plots of the equilibrium constants K_4 and K_5 *vs*. Taft's sigma constants for the condensation of urea with aliphatic aldehydes at 24·2°.

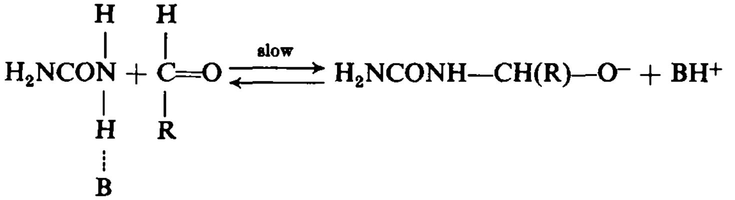
The observed acid catalysis may be explained by a mechanism suggested previously.[2,4,5]



$$\mathrm{H_2NCONH_2} + \underset{\substack{|\\ \mathrm{R}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{C}}}\!=\!\mathrm{O}\cdots\mathrm{HA} \xrightleftharpoons{\text{slow}} \mathrm{H_2NCO\overset{+}{N}H_2{-}CH(R)OH} + \mathrm{A^-} \tag{14}$$

$$\mathrm{H_2NCO\overset{+}{N}H_2{-}CH(R)OH} + \mathrm{A^-} \xrightleftharpoons{\text{fast}} \mathrm{H_2NCONHCH(R)OH} + \mathrm{HA} \tag{15}$$

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

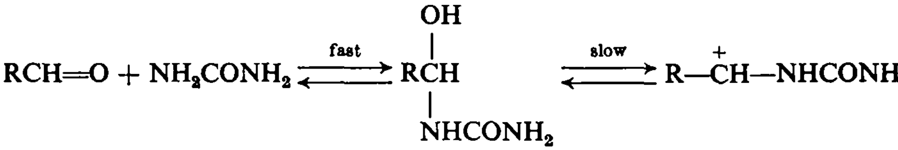


$$\mathrm{H_2NCO}\underset{\substack{|\\ \mathrm{H}\\ \vdots\\ \mathrm{B}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{N}}} + \underset{\substack{|\\ \mathrm{R}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{C}}}\!=\!\mathrm{O} \xrightleftharpoons{\text{slow}} \mathrm{H_2NCONH{-}CH(R){-}O^-} + \mathrm{BH^+} \tag{16}$$

$$\mathrm{H_2NCONH{-}CH(R)O^-} + \mathrm{BH^+} \xrightleftharpoons{\text{fast}} \mathrm{H_2NCONHCH(R)OH} + \mathrm{B} \tag{17}$$

$$\mathrm{H_2NCONHCH(R)OH} + \mathrm{H_2NCONH_2} \xrightleftharpoons{\text{fast}} \mathrm{H_2NCONHCH(R)NHCONH_2} + \mathrm{H_2O} \tag{18}$$

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



$$RCH{=}O + NH_2CONH_2 \xrightleftharpoons{\text{fast}} \begin{matrix} OH \\ | \\ RCH \\ | \\ NHCONH_2 \end{matrix} \xrightleftharpoons{\text{slow}} R{-}\overset{+}{C}H{-}NHCONH_2$$

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

TABLE 5. TYPICAL RATE DATA FOR THE REACTION OF PROPIONALDEHYDE WITH UREA IN ACETATE BUFFERED SOLUTION AT 24·2° AND IONIC STRENGTH OF 0·2. INITIAL CONCENTRATIONS: PROPIONALDEHYDE, 0·0734 M; UREA, 1·474 M

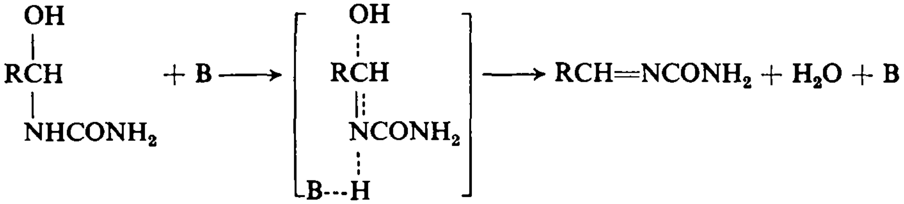
Time sec	E_{278}[a]	$[C_2H_5CHO]$[b] M	$k^c \times 10^4$ sec^{-1}
0	0·776	0·0734	—
600	0·692	0·0653	1·33
900	0·651	0·0614	1·35
1260	0·605	0·0570	1·36
1680	0·555	0·0523	1·37
2100	0·510	0·0481	1·37
2640	0·456	0·0430	1·37
3120	0·416	0·0392	1·36
		Av	1·36

[a] Extinction at 278 mμ

[b] Concentration of residual propionaldehyde

[c] Pseudo-first-order rate constant

The following mechanism, similar to that postulated by Anderson and Jenks for the semicarbazone formation,[9] also agrees with the second-order kinetics.



$$\begin{matrix} OH \\ | \\ RCH \\ | \\ NHCONH_2 \end{matrix} + B \longrightarrow \left[\begin{matrix} OH \\ \vdots \\ RCH \\ \|\!\vdots \\ NCONH_2 \\ \vdots \\ B\cdots H \end{matrix}\right] \longrightarrow RCH{=}NCONH_2 + H_2O + B$$

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 catalysis,[8] it is less probable that the reaction of urea with ethylolurea is subject to base catalysis because of the lower acididity of hydrogen atom on nitrogen of C—N—C compared with methylolurea.

EXPERIMENTAL

Materials. Commercial reagent grade aldehydes were purified by rectification, propionaldehyde, b.p. 48·8°; butyraldehyde, b.p. 74·2°; isobutyraldehyde, b.p. 65·5°. Commercial reagent grade urea was purified by recrystallization from MeOH m.p. 132·5°. Ion-exchanged water was used as the solvent. Acetic, formic, and chloroacetic acids were of commercial reagent grade. Methoxyacetic acid was prepared from chloroacetic acid,[10] b.p. 84·5°/5 mm and pivalic acid was prepared by the Grignard reaction of t-butyl chloride,[11] b.p. 165–167°.

Products. Alkylidenediureas were prepared by the reaction of 1 mole aldehyde and 10 moles

[9] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.* **82**, 1773 (1960).

[10] R. C. Fuson and B. H. Wojcik, *Organic Syntheses* Coll. Vol. II, p. 260 (1945).

[11] S. V. Puntambeker and E. A. Zollinger, *Organic Syntheses* Coll. Vol. I, p. 524 (1941).

urea in an aqueous solution at room temp. The resulting precipitates were filtered off and recrystallized from water.

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

IR spectra of these compounds showed no OH peak. 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 mmole) was hydrolysed with H_2SO_4aq giving n-butyraldehyde (1·08 mmole) (hydroxylamine method), which suggests that it is the condensate of urea:aldehyde = 2:1.

Kinetic procedure. As stated previously for acetaldehyde,[5] the rate of reaction of urea with some aliphatic aldehydes in aqueous solutions at 24·2° 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° was as follows: 10·6 at 280 mμ (propionaldehyde); 13·4 at 283 mμ (butyraldehyde); 14·6 at 284 mμ, and 20·8 at 295 mμ in n-hexane (isobutyraldehyde).

Rates were measured as pseudo-first-order reaction in 10–25 moles urea to 1 mole 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: 0·147M propionaldehyde (25 ml) in a buffered solution and 2·80M 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 ± 0·2° in a Hitachi spectrophotometer type EPU-2A. The absorbance at absorption maximum of aldehyde was measured at known intervals of time. Typical rate data are shown in Table 5.

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

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

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. 1), which suggests that the observed rate constant k is equal to pseudo-first order rate constant k_1' and hence to k_1 [urea].

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