The Kinetics of the Reaction of Formaldehyde with Ammonia

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It is well known that formaldehyde reacts with ammonia to form hexamethylenetetramine or hexamine (VI) in a good yield.[1] Although kinetic studies have been reported,[2-4] no decisive evidence has been presented about the dependency of the rate on the concentration of each reactant. Richmond, Myers and Wright[5] suggested a mechanism not on the basis of the kinetics but on that of the isolated derivatives of intermediates.

The present report summarizes the results of our 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.

Results and Discussion

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

$$4NH_3 + 6CH_2O \rightarrow N_4(CH_2)_6 + 6H_2O \quad (1)$$

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

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[1] P. Duden and M. Scharf, *Ann.*, **288**, 218 (1895).

[2] M. L. Boyd and C. A. Winkler, *Can. J. Research*, **25B**, 387 (1947); J. R. Polley, C. A. Winkler and R. V. V. Nicholls, ibid., **25B**, 525 (1947).

[3] E. Baur and W. Rüetschi, *Helv. Chim. Acta*, **24**, 754 (1941).

[4] S. Bose, *J. Ind. Chem. Soc.*, **34**, 663 (1957).

[5] H. H. Richmond, G. S. Myers and G. F. Wright, *J. Am. Chem. Soc.*, **70**, 3659 (1949).

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 intermediates 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:

$$v=\frac{\mathrm{d}x}{\mathrm{d}t}=k\left(a-\frac{2}{3}x\right)(f-x)^2 \tag{2}$$

where a and f are the initial concentrations (mol. l^{-1}) 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 $a\neq 2/3\ f$,

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

The values of k, as calculated by Eq. 3 from the data in an unbuffered solution up to 70% conversion, are shown in Table I. 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 I. The rate constant at pH 9~10 tended to decrease slightly as the reaction proceeded. The rapid titration of ammonia with hydrochloric acid, 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 values 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.

TABLE I. TYPICAL RATE DATA FOR THE REACTION OF FORMALDEHYDE WITH AMMONIA IN UNBUFFERED SOLUTION AT 20°C

Initial concn.: ammonia, 0.0264 M;
formaldehyde; 0.0532 M
Change of pH: 10.5~10.2

Time sec.	Concn. of unreacted formaldehyde 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±0.051

The Variation of the Rate with the pH of the Solution.—The rate constants with the varying pH of the solution are listed in Table II. The rate increased sharply with an increasing pH to a maximum at pH 9~10, and then it decreased gradually. An analogous relation has

TABLE II. THE VARIATION OF RATE CONSTANTS WITH pH OF THE SOLUTION AT 20°C

pH	Buffer concn., M		Initial concn., M		$k\times10^2$, $M^{-2}\,sec^{-1}$
	KH_2PO_4	$Na_2B_4O_7$	Ammonia	Formaldehyde	
6.3	0.351	0.025	0.0265	0.0549	3.81
6.7	0.315	0.022	0.1050	0.0551	14.0
7.1	0.249	0.075	0.0530	0.0525	25.1
7.9	0.178	0.102	0.0265	0.0525	234
7.9[a]	0.178	0.102	0.0265	0.0525	213
8.5	0.034	0.020	0.0265	0.0523	916
8.9	0.070	0.165	0.0265	0.0525	2040
	NaOH	$Na_2B_4O_7$			
9.8	0.097	0.122	0.0265	0.0265	2520
10.2	0.243[b]	0.075	0.0265	0.0265	1560
11.0	0.136	0.072	0.0530	0.0530	1280
11.9	0.147	0.066	0.0530	0.0530	348

a) 0.28 M KCl was added.
b) Na_2CO_3 was used instead of NaOH.

been reported for the reaction of amine or phenol with carbonyl compounds.6) 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 ammonia2) on free formaldehyde, at least under these conditions:

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^- \quad \text{(fast)} \tag{4}$$

$$CH_2O + H_2O \rightleftharpoons CH_2(OH)_2 \quad \text{(fast)} \tag{5}$$

$$CH_2(OH)_2 + OH^- \rightleftharpoons CH_2(OH)O^- + H_2O \quad \text{(fast)} \tag{6}$$

$$NH_3 + CH_2O \rightleftharpoons \underset{\text{(I)}}{NH_2CH_2OH} \quad \text{(fast)} \tag{7}$$

$$NH_2CH_2OH + CH_2O \rightleftharpoons \underset{\text{(II)}}{NH(CH_2OH)_2} \quad \text{(slow)} \tag{8}$$

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

$$\begin{aligned} v &= k_8[NH_2CH_2OH][CH_2O] \\ &= k_8K_7[NH_3][CH_2O]^2 \end{aligned}$$

Here, k and K are the rate and equilibrium constants of the subscripted steps respectively. The estimation of formaldehyde by Nessler reagent iodometry7,8) 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,

$$\begin{aligned} a-(2/3)x &= [NH_3]+[NH_4{}^+] \\ &= [NH_3]\left\{1+\frac{K_4[H_2O]\,[H^+]}{K_w}\right\} \\ f-x &= [CH_2O]+[CH_2(OH)_2] \\ &\quad +[CH_2(OH)O^-] \\ &= [CH_2O]\left(1+K_5[H_2O]+\frac{K_5K_6K_w}{[H^+]}\right) \end{aligned}$$

Hence,

$$v = k_8K_7\frac{1}{1+(K_4[H_2O]\,[H^+]/K_w)} \times\left[\frac{1}{1+K_5[H_2O]+(K_5K_6K_w/[H^+])}\right]^2$$

$$\times\left(a-\frac{2}{3}x\right)(f-x)^2 \tag{9}$$

Here, K_w is the ionic product of water. At 20°C, $K_4[H_2O]=K_b{}^{9)}=1.75\times10^{-5}$, $K_5[H_2O]=K_f{}^{10)}=10^4$, $K_6K_w/[H_2O]=K_s{}^{11)}=1.62\times10^{-13}$, and $K_w=0.681\times10^{-14}$.

Therefore, comparing Eq. 9 with Eq. 2,

$$k=\frac{k_8K_7}{K_f{}^2}\frac{1}{1+[H^+]\,(K_b/K_w)}\left[\frac{1}{1+(K_s/[H^+])}\right]^2 \tag{10}$$

or

$$\log k=\log\frac{k_8K_7}{K_f{}^2}+\log\frac{1}{1+[H^+]\,(K_b/K_w)} \times\left[\frac{1}{1+(K_s/[H^+])}\right]^2 \tag{11}$$

The differentiation of Eq. 10 with respect to $[H^+]$ 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.

$$[H^+]=\sqrt{\frac{2K_wK_s}{K_b}}=2.27\times10^{-11} \text{ or } pH=10.64$$

The plots of the calculated values of $\log[1/\{1+[H^+]\,(K_b/K_w)\}]\,[1/(1+K_s/[H^+])]^2$ 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.12)

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 $\log(k_8K_7/K_f{}^2)$, which leads to 6.3×10^8 for the value of k_8K_7. However, most of formaldehyde is hydrated—i. e., the concentration of free formaldehyde is very small; 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

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6) J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2893 (1932); E. H. Cordes and W. P. Jencks, ibid., **84**, 832 (1962); T. Minami and T. Ando, *J. Chem. Soc. Japan, Ind. Chem. Sec.* (*Kogyo Kagaku Zassi*), **60**, 1078 (1957).

7) J. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publ. Corp., New York, N. Y. (1953), p. 387.

8) S. Bose, *J. Ind. Chem. Soc.*, **34**, 497 (1957).

9) T. S. Moore and T. F. Winmill, *J. Chem. Soc.*, **101**, 1635 (1912).

10) R. Bieber and G. Trümpler, *Helv. Chim. Acta*, **30**, 1860 (1947).

11) M. Wadano, C. Trogus and K. Hess, *Ber.*, **67**, 174, 191 (1934).

12) This fact may be due to the change of the rate-determining step to the following step:

$$NH(CH_2OH)_2 + H^+ \overset{\text{(slow)}}{\rightleftharpoons} HOCH_2NHCH_2{}^+ + H_2O$$

The dependence of the rate constant on the acidity at pH 9~10 seems to support this assumption, but there is little further evidence.

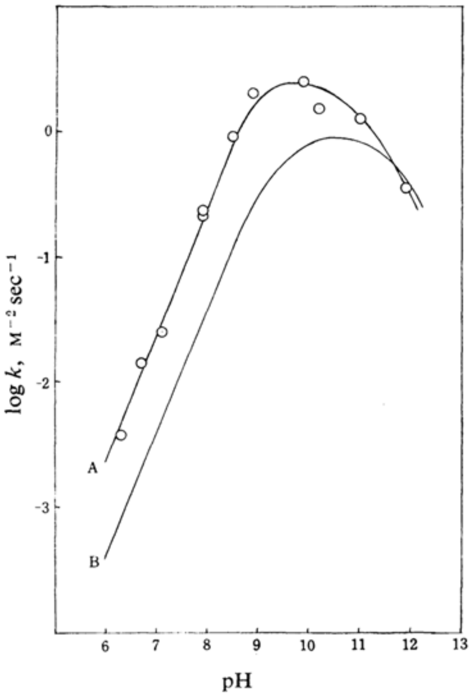


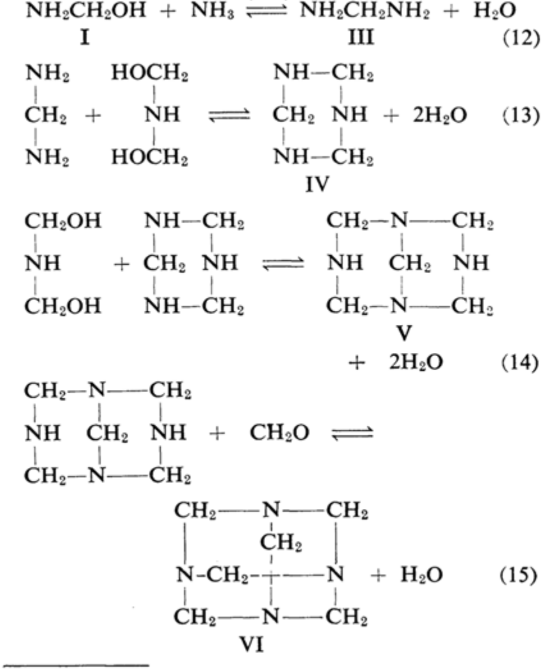
Fig. 1. Plots of logarithm of the observed rate constants (A) and calculated values of $[1/\{1+(K_b/K_w)[H^+]\}][1/\{1+(K_s/[H^+])\}]$ (B) against pH for the reaction of formaldehyde with ammonia.

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 Bose[4] 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 $CH_2=N-CH_2OH$ may be present, since the reaction mixture had no absorption maximum in the range of 210~240 mμ corresponding to a C=N bond,[13] only a maximum at 191~210 mμ (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 acids,[14] respectively, and methylenediamine sulfate is isolable in a strongly acidic solution.[5] Nitroso or benzoyl derivatives of cyclotrimethylenetriamine IV and 1, 5-endomethylene-1, 3, 5, 7-tetrazacyclooöctane V have been obtained from the reaction mixture.[1,5] 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 tribenzoylcyclotrimethylenetriamine (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.

TABLE III. THE MOLAR RATIO OF FORMALDEHYDE VS. AMMONIA PRODUCED FROM UNSTABLE INTERMEDIATE USING 0.0265 M FORMALDEHYDE AT 23°C AFTER 1 hr.

Run	Increase in concn., M		Molar ratio
	Ammonia	Formaldehyde	
1[a]	0.0044	0.0090	2.0
2	0.0019	0.0044	2.3
3	0.0029	0.0054	1.9
4	0.0014	0.0023	1.7
5	0.0018	0.0041	2.3
			Av. 2.0

a) 0.0530 M formaldehyde was used.


$$\underset{\text{I}}{NH_2CH_2OH} + NH_3 \xrightleftharpoons{\text{(fast)}} \underset{\text{III}}{NH_2CH_2NH_2} + H_2O \qquad (12)$$

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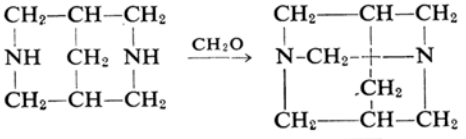
[13] R. P. Linstead and M. Whalley, *J. Chem. Soc.*, **1955**, 3530; G. E. Ficken and R. P. Linstead, ibid., **1955**, 3525; A. Maccoll, *Quart. Revs.*, **1**, 28 (1947).

[14] H. Stetter, *Angew. Chem.*, **74**, 361 (1962).

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 dimethylolnitramide and methylenediamine sulfate to form 1, 5-endomethylene-3, 7-dinitro-1, 3, 5, 7-tetrazacyclooctane.[5] 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 VIII;[14] for example,



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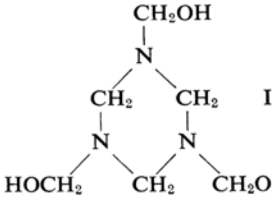
Another mechanism,[3,5] by which hexamine is formed through trimethylolcyclotrimethylenetriamine IX, requires that all three methylol groups should be in cis-configuration.[15] Moreover, the reaction of the trimethylols with



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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]

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 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 fomaldehyde (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±0.1°C. At known intervals of time, an aliquot (5 ml.) was pipetted out into an ice-cooled Nessler solution[7,8] (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 (decomp.)) was obtained at the end of these rate measurements.

Intermediates.—*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 $NH_3 : CH_2O = 1 : 2$.

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 Richmond.[5] Methylenedibenzamide (2.14 g., 8.4%) (m. p. 223°C) was obtained. The freezing point method, using dimethylsulfoxide as a solvent, gave a molecular weight of 227; calcd. for $C_{15}H_{14}O_2N_2$: 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 spectum: ν cm^{-1} 1655 (*t*-amide) (Found: C, 72.3; H, 5.26; N, 10.9. Calcd. for $C_{24}H_{21}O_3N_3$: C, 72.2; H, 5.26; N, 10.5%.). Futhermore, methylenedibenzamide (0.324 g., 2.6%) was obtained from the ethanolic extract.

The change in pH measured by a Hitachi M4 pH meter during the reaction is shown in Table IV. The ultraviolet absorption spectra were measured by a Shimadzu SV50A spectrophotometer in the ranges of 210~300 mμ and 190~210 mμ by nitrogen purging.

Summary

The kinetics of the reaction of formaldehyde with ammonia to form hexamethylenetetramine

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15) H. Stetter, ibid., **66**, 217 (1954).

16) M. S. Newman and H. S. Lowric, *J. Am. Chem. Soc.*, **48**, 861 (1951).

TABLE IV. THE VARIATION OF pH IN UNBUFFERED SOLUTION AT 23°C
Initial concn.: Ammonia, 0.0265 M (with pH of 10.94)
Formaldehyde, 0.0530 M

Reaction time, min.	0	3	7	10	15	25	35	55	80	285
pH	10.57	10.47	10.40	10.36	10.32	10.26	10.17	10.03	9.88	9.64

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, followed by the formation of hexamine through cyclotrimethylenetriamine and 1, 5-endomethylene-1, 3, 5, 7-tetrazacycloöctane.

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