[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Mannich Reaction Mechanisms

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A modified method for following the course of the Mannich reaction is described which makes it possible to analyze for formaldehyde in the presence of aldehydes or ketones. Kinetic data on the reaction between cyclohexanone, dimethylamine, and formaldehyde are presented, and mechanisms consistent with the data are proposed. Different mechanisms are indicated for acidic and basic media. Complex combinations of mechanisms appear to take place at intermediate *p*H values.

The base-catalyzed reaction appears to involve the reaction of a carbanion (derived from the active hydrogen compound) with the aminomethylol by an S_N2 mechanism. The rate increases at higher *p*H values.

The reaction in acid media appears to involve the reaction of a carbonium ion (derived from the aminomethylol) with the active hydrogen compound. The rate is slower than for the reaction in basic media and is independent of *p*H at low *p*H values.

The Mannich reaction[2] involves the combination of an aldehyde, usually formaldehyde, with ammonia or a primary or secondary amine, and with a compound containing an activated hydrogen. The reaction may be illustrated by the following equation:

$$R_2NH + HCHO + R'H \longrightarrow R_2N—CH_2—R' + H_2O$$

The active hydrogen compound, R'H, is most frequently a ketone, an acid, or an ester, although recently work has been done with nitroalkanes.[3–7]

The mechanism of this reaction has been the subject of considerable discussion. Bodendorf and Koralewski[8] concluded from their experiments that neither the condensation of the formaldehyde with the amine nor with the active hydrogen compound to yield the corresponding methylols showed the true course of the reaction. Lieberman and Wagner[9] presented an attractive mechanism involving the formation of a carbonium ion, $R_2NCH_2^+$ from the amine and formaldehyde and also the formation of a carbanion, $R':^-$, by the removal of a proton from the active hydrogen compound. The final, essentially irreversible step was the combination of the carbonium ion and carbanion to yield the Mannich base.

Alexander and Underhill[10] carried out a kinetic study on the Mannich reaction involving dimethylamine, formaldehyde, and ethylmalonic acid in acid solution. Their experiments showed third-order kinetics with no primary salt effect. This contradicts the mechanism of Lieberman and Wagner, which postulated the final and rate-controlling step as the reaction between the two ions which should show a primary salt effect. The mechanism presented in their paper was only postulated for acidic media. The most significant objection to their conclusion is that they ignore the fact that the amine is largely present in the salt form and this alters the prediction of specific hydronium ion dependence, as will be shown later.

RESULTS AND DISCUSSION

In view of the conflicting evidence in the prior literature, it was decided that an investigation should be made into the mechanism of the Mannich reaction, particularly in basic medium. A kinetic study was carried out after the development of an improved method for following the variation in the concentration of formaldehyde in the presence of compounds such as aldehydes and ketones which interfere with the usual analytical procedures. Using equivalent quantities of dimethylamine and formaldehyde and the active hydrogen compound, cyclohexanone, the progress of the reaction was followed by the variation in the concentration of the formaldehyde that was not combined to form the Mannich base. The procedure involved analysis for the formaldehyde which might be combined in the form of methylols of the amine or the active hydrogen compound, as well as the unreacted formaldehyde.

No primary salt effect could be demonstrated. As seen in Table I, there is no appreciable change in the rate constant when the ionic strength was varied from zero to 0.09. Above this concentration there is a slight increase with increasing ionic strength. This is to be expected when the solvation of potassium chloride is taken into account. This is in agreement with the findings of Alexander and Underhill[10] and would eliminate the mechanism of Lieberman and Wagner as such; but if their mechanism were modified to take into account the probable effect of changing the *p*H of the solution,

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[2] F. F. Blicke, *Org. Reactions*, Wiley, New York, 1942, 1, 303.

[3] M. Senkus, *J. Am. Chem. Soc.*, **68**, 10 (1946).

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[7] R. A. Smiley, *J. Org. Chem.*, **23**, 1115 (1958).

[8] K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

[9] S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

[10] E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949).

TABLE I

EFFECT OF VARIATION OF IONIC STRENGTH UPON THE THIRD-ORDER RATE CONSTANT

Run	pH	M HCHO	T.	g. KCl	k, M^{-2} min.$^{-1}$	Ionic Strength
74	10.6	0.096	26	0.0000	0.329	0.00
82	10.6	0.093	25	0.1865	0.329	0.01
85	10.6	0.093	25	0.1867	0.278	0.01
83	10.6	0.093	25	0.7452	0.329	0.04
86	10.6	0.093	25	0.7458	0.316	0.04
84	10.6	0.093	25	1.6781	0.329	0.09
87	10.6	0.093	25	1.6762	0.316	0.09
79	10.6	0.096	25	2.9851	0.500	0.16
80	10.6	0.096	25	4.6595	0.500	0.25
81	10.6	0.096	25	9.1349	0.615	0.49

a reasonable mechanism fitting the data can be postulated.

Increasing the concentration of the hydronium ion would certainly reduce the concentration of the carbanion formed by the removal of a proton from the active hydrogen compound. If this concentration were reduced to negligible proportions, the course of the reaction would have to be through some other intermediate. On the other hand, as the *p*H of the solution was increased, the concentration of the carbanion would be increased and the concentration of the carbonium ion (formed by the removal of the hydroxyl group from the aminomethylol) would be reduced. If the carbonium ion concentration were reduced to a negligible value, the reaction would have to proceed through some other intermediate.

TABLE II

EFFECT OF VARIATION IN *p*H AND TEMPERATURE UPON THE THIRD-ORDER RATE CONSTANT

Run	*p*H	*M* HCHO	T.°	k, M^{-2} min.$^{-1}$
103	10.6	0.1046	6.5	0.0223
100	1.15	0.1046	25	0.0005
94	3.23	0.1046	25	0.0005
96	5.05	0.1046	25	0.0005
97	5.92	0.1046	25	0.0005
98	6.90	0.1046	25	0.0027
102	8.21	0.1046	25	complex
90	9.75	0.1046	25	0.240
91	10.06	0.1046	25	0.260
89	10.23	0.1046	25	0.290
93	11.00	0.1046	25	0.290
108	1.02	0.1046	50	0.0033
110	2.13	0.1046	50	0.0033
112	3.20	0.1046	50	0.0033
114	4.19	0.1046	50	0.0030
116	5.02	0.1046	50	0.0050
117	6.07	0.1046	50	complex
118	7.05	0.1046	50	complex
122	8.00	0.1046	50	complex
124	8.90	0.1046	50	0.735
104	10.60	0.1046	50	3.19
109	1.10	0.1046	70	0.0050
111	2.09	0.1046	70	0.0050
113	3.18	0.1046	70	0.0180
94	3.23	0.1046	70	0.0193
95	4.15	0.1046	70	complex
96	5.05	0.1046	70	complex
97	5.92	0.1046	70	complex
119	8.00	0.1046	70	complex
120	8.55	0.1046	70	8.03
107	10.60	0.1046	70	17.95

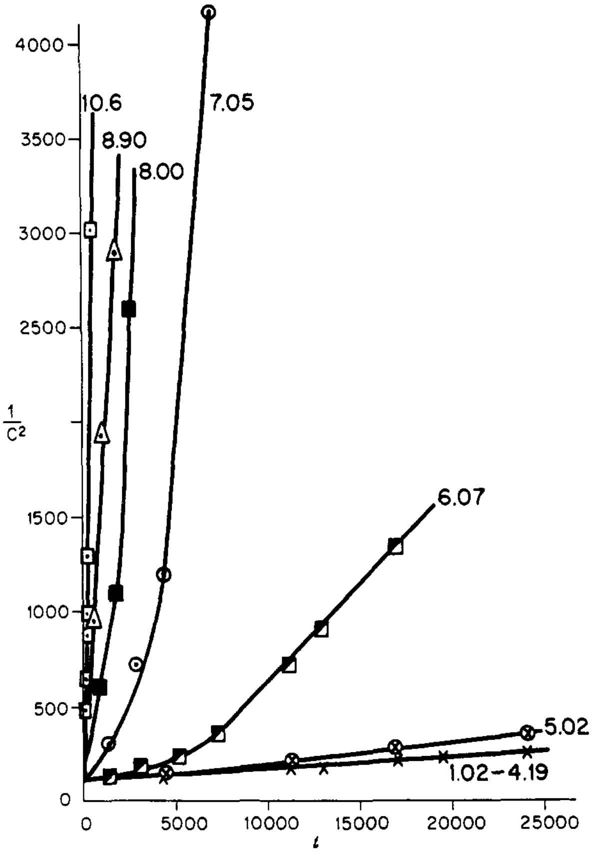


Fig. 1. Third-order plot of the utilization of formaldehyde in the Mannich Reaction

$\frac{1}{C^2}$ *vs.* t at various *p*H levels
C = mole/l.
t = min.

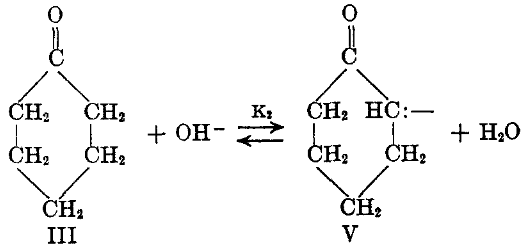
Runs were made at various *p*H values from 1 to 11 and at temperatures from 6.5° to 70°. If the reaction were to follow third-order kinetics, a plot of $1/C^2$ *vs.* time should give a straight line, where C is the concentration of each of the three reactants remaining at any time t. Fig. 1 is a plot of the reciprocal of the square of the concentration (the reactants were added in equivalent quantities to the solution) *vs.* time in minutes for various *p*H values at 50°. Similar curves for data obtained at 25° and 70° can be plotted. From these plots the overall rate constants for the reaction were determined, when the data gave straight lines. If the plot were not a straight line, the rate constant was recorded as complex. In this manner the rate constants in Tables I and II were determined. Other duplicating runs were made which are not included, but check these data.

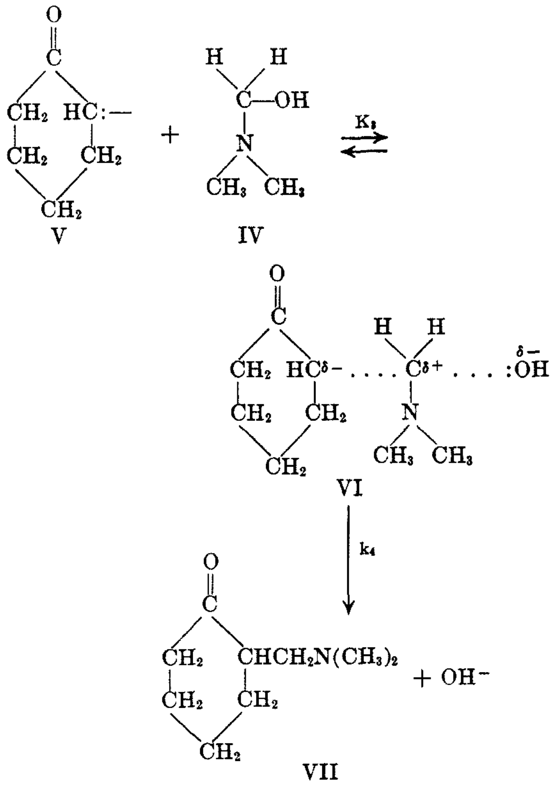
In Fig. 1 it can be seen that the plots for *p*H values in the range 1 to 5 are reasonably straight lines and that the rate constant is approximately the same in each case. The plot for pH 6 no longer is a straight line and the rate is much faster. Each succeeding increase in pH increases the rate. With the pH approximately 9, the plot once more becomes a straight line. The rate increases with increasing pH until pH 10.6 is reached. Apparently there is a change of mechanism as the pH changes from acid to base.

From Table II it can be seen that the rate constant is quite temperature dependent. The rate constant at pH values from 1 to 6 at 25° was indistinguishable from one pH value to the next. Above this the rate increases, becomes complex—in that the plot of $1/C^2$ *vs.* time is no longer a straight line—and then follows third-order kinetics with gradually increasing rate constants at higher pH values approaching a constant value above a pH of 10. At 50° the reaction becomes complex at a lower pH than at 25° and at even a lower pH at 70°.

A mechanism which is consistent with the data for the basic medium follows:

$$\underset{\text{I}}{(CH_3)_2NH} + \underset{\text{II}}{HCHO} \xrightleftharpoons{K_1} \underset{\text{IV}}{(CH_3)_2NCH_2OH} \qquad (1)$$


(2)


(3)

Dimethylamine (I) combines with formaldehyde (II) to set up an equilibrium with the dimethylaminomethylol (IV). Cyclohexanone (III) reacts with hydroxide ion to set up an equilibrium with the carbanion (V) and water. Intermediates (IV) and (V) react by an S_N2 mechanism to form an equilibrium concentration of the activated complex, or transition state (VI), which decomposes by a relatively irreversible rate-controlling step to yield the Mannich base (VII).

The rate equation is:

$$\text{Rate} = \frac{dx}{dt} = k_4(\text{VI}) \qquad (4)$$

$$= k_4K_3(\text{IV})(\text{V}) \qquad (5)$$

$$= k_4K_3K_2K_1(\text{I})(\text{II})(\text{III})(OH^-) \qquad (6)$$

$$= k\,[(CH_3)_2NH]\,[HCHO]\,[C_6H_{10}O]\,[OH^-] \qquad (7)$$

which predicts that at any given pH at which this mechanism predominates, the reaction should exhibit third-order kinetics and that with increasing pH the rate should increase. This is borne out by the increase in the rate, Fig. 1, with increasing pH, and above pH 9 third-order kinetics are observed at 50°.

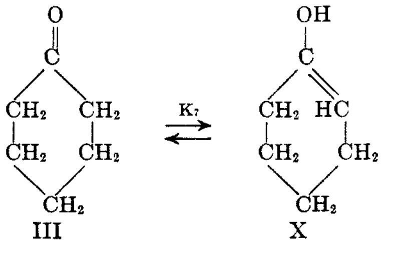
The deviation from third-order kinetics for the reaction in the region between pH 5 and pH 9, while third-order kinetics are followed above and below these values, suggests that the mechanisms are different in acidic and basic media and that both mechanisms are involved in varying degrees at the intermediate pH values.

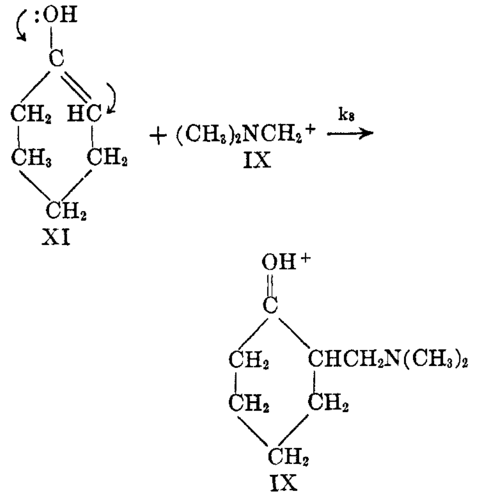
A mechanism for acid solution follows which fits our data and that of Alexander and Underhill. It is a modification of the mechanism which they considered and rejected on the basis that it predicted specific hydronium ion catalysis. The proposed mechanism differs in that the amine is recognized as being present in equilibrium with the salt form in acid media.

$$\underset{\text{VIII}}{(CH_3)_2NH_2^+} + A^- \xrightleftharpoons{K_5} \underset{\text{I}}{(CH_3)_2NH} + HA \qquad (8)$$

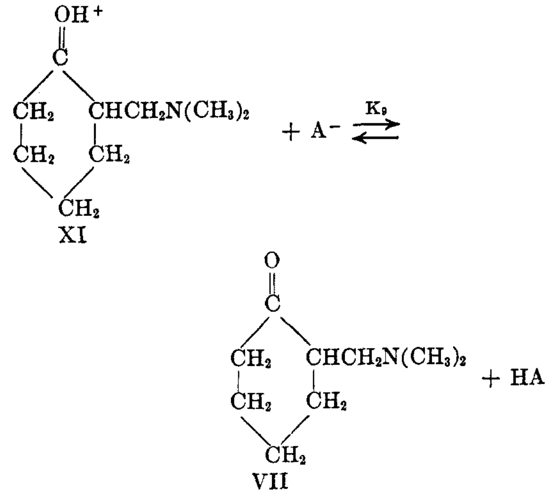
$$\underset{\text{I}}{(CH_3)_2NH} + \underset{\text{II}}{HCHO} \xrightleftharpoons{K_1} \underset{\text{IV}}{(CH_3)_2NCH_2OH} \qquad (9)$$

$$\underset{\text{IV}}{(CH_3)_2NCH_2OH} + HA \xrightleftharpoons{K_6} \underset{\text{IX}}{(CH_3)_2NCH_2^+} + H_2O + A^- \qquad (10)$$


(11)



(12)



(13)

From the above equations, with equation (12) essentially irreversible and rate-determining:

$$\text{Rate} = \frac{dx}{dt} = k_8K_7K_6K_1K_5\,[(CH_3)_2NH_2^+]\,[HCHO] \times [C_6H_{10}O] \quad (14)$$

$$= k\,[(CH_3)_2NH_2^+]\,[HCHO]\,[C_6H_{10}O] \quad (15)$$

An S_E2 mechanisn at the α-carbon atom of cyclohexanone analogous to the $S_N{}^2$ mechanism shown for the reaction in basic medium can be formulated as an alternative to equations (11), (12) and (13).

The rate equation for this modification is identical with equation (15). Thus, either route predicts that in acid medium the rate is independent of the acid concentration which is what was observed at sufficiently low *p*H values. In the case of Alexander and Underhill where an acid was employed as the active hydrogen compound, if the reactive form is the acid, as shown in their equations, then another term would have to be introduced into the rate equation to account for the equilibrium between the acid form and the ionic form—at *p*H 4 the compound exists about 90% as the monoanion—and this would make the rate equation once again dependent upon the concentration of the hydronium ion.

Lieberman and Wagner[9] reported that in general the methylenebisamines could be substituted for the amine plus formaldehyde in the Mannich reaction. In their mechanism, as mentioned earlier, the carbonium ion, $R_2NCH_2^+$, was used. They postulated that it was formed either by the removal of the hydroxyl group from the aminomethylol, or through the formation of the methylenebisamine and the subsequent decomposition to the carbonium ion. As both routes involve equilibrium reactions, it is not possible to distinguish between them for both yield third-order kinetics. The formation of the methylol is used in our mechanism because it is the shorter, simpler route.

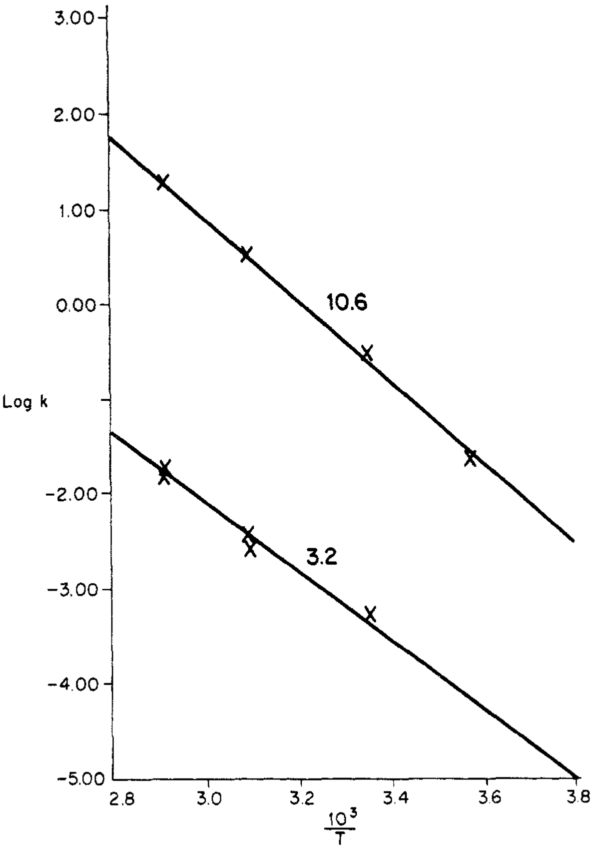


Fig. 2. Plot of the Arrhenius Equation

$\log k$ *vs.* $\frac{1}{T}$

at *p*H = 10.6 and
*p*H = 3.2

$k = \frac{\text{liter}^2}{\text{mol.}^2\text{-min.}}$

T = °K

A plot of log K *vs.* 1/T, at two *p*H values, was prepared, Fig. 2, based on the Arrhenius equation:[11]

$$\frac{d\,ln\,k}{dT} = \frac{\Delta E^*}{RT^2}$$

$$\log k = \frac{-\Delta E^*}{2.303RT} + C$$

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[11] C. F. Prutton and S. H. Maron, *Fundamental Principles of Physical Chemistry*, Revised Edition, Macmillan, New York, 1951, 634–635.

where k is the rate constant, ΔE^* is the energy of activation, T is the absolute temperature and C is the constant of integration. From the slope of the plot of log k vs 1/T, ΔE^*, a composite energy of activation, can be determined from the following equation:

$$\text{slope} = \frac{-\Delta E^*}{2.303R} = \frac{-\Delta E^*}{4.58}$$

As can be seen in Fig. 2, the points fall quite close to a straight line. The best straight line was determined by a modification of the method of least squares.

Although the plot gives an energy of activation which is a composite value for the several equilibria involved as well as the rate-determining step, and is therefore of little value in itself, the observation that the points do fall closely on a straight line is significant. Theory demands that such a composite energy of activation should produce a straight-line plot and the observation that they do is an indication that the data are valid.

EXPERIMENTAL

Equimolar quantities of dimethylamine and formaldehyde were used in all of the experiments. The quantity of the active hydrogen compound used was determined by the number of α-carbons which had hydrogens attached. In the case of cyclohexanone, with two equally reactive α-carbons, 0.5 mole of the ketone was used to each mole of formaldehyde.

Reaction of cyclohexanone, formaldehyde, and dimethylamine. All solutions were approximately 0.1*M* in dimethylamine and formaldehyde. A weighed sample of cyclohexanone was transferred to a 250 ml. volumetric flask followed by addition of buffer and amine with dilution to approximately 180 ml., and finally the formaldehyde was added. The solution was then made up to 250 ml., shaken and placed in the constant-temperature bath. In the case of the low temperature run, 6.5°, the solutions were cooled to reaction temperature before the final addition of the formaldehyde and dilution to 250 ml. The same procedure was used in the runs at 50° and 70° for basic solutions. The rate of reaction in acid solution was so slow that the error introduced by mixing first and then placing in the baths was negligible.

The cyclohexanone was weighed on an analytical balance (to ±0.0001 g.) in a beaker and rinsed into the volumetric flask. The approximately 1.2*N* dimethylamine, 0.5*M* formaldehyde and the buffer solutions were pipetted in. The buffer solutions used were made from hydrochloric acid, potassium chloride, potassium dihydrogen orthophosphate, boric acid, and sodium hydroxide as recommended by Diehl and Smith[12] with the modification that an equivalent quantity of hydrochloric acid was added to each solution below *p*H 9 to equal the dimethylamine added, in addition to the buffer recommended. The *p*H of the solution was taken with a *p*H meter, at room temperature, both at the start of the run and toward the end. There was little or no variation in *p*H during the runs.

Determination of Formaldehyde. Duplicate samples were taken from the volumetric flask at given time intervals. These samples were pipetted immediately into 50 ml. Nessler's Reagent as prepared by Alexander and Underhill.[10] These solutions were shaken intermittently for a minimum of 5 min., following which a solution containing 35 ml. 2*N* acetic acid and 50 ml. acetone was added. This solution was shaken for a minimum of 15 min.—a greater length of time made the filtration easier—then filtered. The mercury precipitate was rinsed with water to eliminate acetone from the filter paper. When the run had gone to or beyond 70% conversion, it was necessary to rinse with acetone first to remove any Mannich base in the precipitate and then with water. The precipitate and filter paper were returned to the flask into which the 5 ml. samples had originally been pipetted, 25 ml. 0.1*N* iodine solution was pipetted in, followed by approximately 25 ml. water. The mixture was shaken intermittently for 30 to 60 min., and the excess iodine was titrated with 0.1*N* sodium thiosulfate. This procedure permitted analysis for the formaldehyde that was combined with the ketomethylol or the aminomethylol as well as that which was present as free formaldehyde.[10] The modification of the procedure of Alexander and Underhill was made necessary by the interference of cyclohexanone and other carbonyl compounds with the determination. The essential feature of the modification is the filtration which separates the mercury from the carbonyl compounds prior to the reaction with iodine. This procedure has been tested with other ketones and some aldehydes, and appears to be a satisfactory method of analysis for formaldehyde, although in the case of aldehydes the presence of other aldehyde groups must be taken into account in the calculations.

Runs were made at various ionic strengths, at various *p*H values, and various temperatures in order to determine the effects of these variants on the rate of the reaction. Typical results are recorded in Tables I and II. Many additional check runs were made which confirm the results as reported here.

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[12] H. Diehl and G. F. Smith, *Quantitative Analysis,* Wiley, New York, 1952, 455.