

## Studies on Intermediates Involved in the Syntheses of Pentaerythritol and Related Alcohols. II.\* Kinetics of the Base Catalyzed Aldol Condensation Reactions of Formaldehyde with Its Nearest Homologs

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The aldol condensation reactions of formaldehyde with acetaldehyde, propionaldehyde, butyraldehyde, and isobutyraldehyde, respectively, have been studied kinetically. In each case the rate of disappearance of the enolizable aldehyde has been followed by means of vapour phase chromatography. Various factors affecting the observed rates of reaction are discussed.

The rates and mechanisms of the aldol condensation reactions of formaldehyde (I) with acetaldehyde (II), propionaldehyde (III), butyraldehyde (IV), and isobutyraldehyde (V), respectively, are of considerable interest since these reactions constitute the first steps in the industrially important syntheses of the polyalcohols pentaerythritol, trimethylolethane, trimethylolpropane, and neopentylglycol. These syntheses generally can be described as series of crossed aldol condensations with I resulting in replacement of all  $\alpha$ -hydrogens by hydroxymethyl groups. Final irreversible crossed Cannizzaro reactions then convert the fully hydroxymethyl-substituted aldehydes to the alcoholic end products. The aldol condensations of the starting materials in each of these reaction series do not seem to have been studied kinetically with the exception of the reaction of I with II. One reason for the lack of published data may be that, since the Cannizzaro reactions are generally believed to be rate determining for the overall reactions, it may have been thought of less interest to determine the rates of the faster aldol condensations preceding the Cannizzaro reactions. Furthermore, the industrial reaction mixtures are rather complex and it is no easy task to determine the different reacting species therein. However, the rates of the first condensation steps may influence the extent to which side reactions occur under various reaction conditions and thus be of great importance.

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The reaction between II and I has been studied by Bell and McTigue,<sup>1</sup> by McTigue and coworkers,<sup>2</sup> and by Ogata *et al.*<sup>3</sup> Bell and McTigue determined the rate of reaction of II with I in the presence of basic catalysts primarily in order to obtain the rate constant for the ionization of II and to elucidate the mechanism of the aldol condensation of II. Since these authors used a dilatometric method without knowledge of the volume change of the reaction in  $M^{-1}$ , they did not obtain proper reaction rate constants, and therefore their results cannot be used to calculate rates of reaction in pentaerythritol synthesis mixtures. They showed, however, that the aldol condensation of II is subject to general base catalysis and that the condensation with I is of zero order with respect to I in the concentration range studied (1.6–4.8 M).

McTigue, Kirsanovs and Tankey<sup>2</sup> found that the reaction of II with I is of first order with respect to II (0.05–0.20 M) and to hydroxide ion ( $3 \times 10^{-4}$ – $6 \times 10^{-3}$  M as measured with a glass electrode) and of zero order with respect to I (0.45–3.5 M) within the concentration ranges specified.

Ogata, Kawasaki and Yokoi<sup>3</sup> attempted to determine proper reaction rate constants under various reaction conditions. They used rather concentrated acetaldehyde solutions as was the case with McTigue *et al.* In these solutions several other reactions, *e.g.* acetaldol formation, occur simultaneously and therefore affect the measured rate of reaction. The rate of total aldehyde disappearance was followed by means of the sodium sulphite procedure. The rate of disappearance of II due to reaction with I was then calculated based on the following assumptions:

(a) The total aldehyde concentration, as determined, equalled the sum of II, I, 3-hydroxypropionaldehyde, and 3-hydroxybutyraldehyde.

(b) No other reaction products occurred, at least at an early stage of the reaction.

(c) The rate of formation of 3-hydroxybutyraldehyde in the presence of I was the same as in separate experiments with II only.

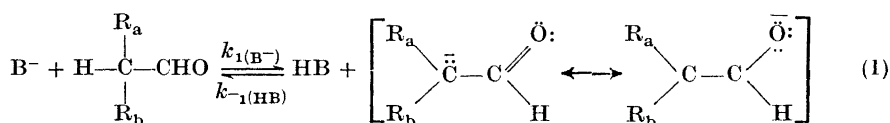
The correction due to the formation of 3-hydroxybutyraldehyde was considerable.

The aim of this work has been to determine the rates of reaction of the aldehydes II, III, IV, and V, respectively, with formaldehyde under conditions similar to those used in industrial polyalcohol syntheses. Therefore, no attempts have been made to use buffer solutions in order to keep the hydroxide ion concentration at a predetermined value or to correct the observed rate constants for changes in this concentration due to the presence of various acidic species such as the aldehyde hydrates. Such corrections necessarily must be based on present incomplete knowledge of the acidities of the various molecular species in the reaction mixtures and are therefore uncertain. The apparent rate constants given in this work on the other hand are based only on knowledge of the amount of catalyst initially added. For an industrial reaction mixture the corresponding value of the catalyst concentration is easily determined by titration. It is thought that the constants given are of more practical use in their uncorrected form and that the rates which can be deduced from eqn. 7 will be correct to within  $\pm 5\%$ .

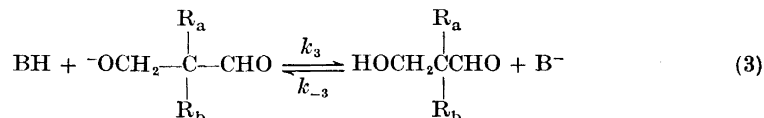
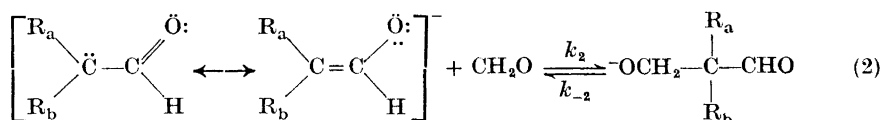
In order to obtain reliable results based on as few assumptions as possible, it was thought necessary to determine directly the rate of disappearance of

the enolizable aldehyde under different reaction conditions, so chosen as to minimize self-condensation reactions. To this end, gas chromatographic methods have been worked out making possible the determination of small amounts of II, III, IV, and V, respectively, in reaction mixtures with water, formaldehyde, and condensation products present.

According to the commonly accepted view, the reactions studied take place in three steps, all of which are reversible:<sup>4</sup>



- II:  $R_a = R_b = H$   
 III:  $R_a = H, R_b = CH_3$   
 IV:  $R_a = H, R_b = CH_2CH_3$   
 V:  $R_a = R_b = CH_3$



The experimental evidence accumulated during this work indicates that, under the conditions used, the reactions go more or less to completion. This follows from the fact that the rate of disappearance of the enolizable aldehyde in each case followed the first order rate law at least to 95 % completion of the reaction, *i.e.* as far as the reactions could be followed quantitatively. Since the third reaction step and its reversal are fast reactions in aqueous solutions, one can therefore deduce the following generalized rate expression (where [E] denotes the concentration of the enolizable aldehyde) making the usual steady-state approximation:

$$\frac{d[E]}{dt} = - \frac{k_2(k_{1(OH^-)}[OH^-] + \sum_{B^-} k_{1(B^-)}[B^-])[E][CH_2O]}{k_{-1(H_2O)}[H_2O] + \sum_{HB} k_{-1(HB)}[HB] + k_2[CH_2O]} \quad (4)$$

This expression reduces to two limiting cases:

(1) At high  $[CH_2O]$  we obtain

$$\frac{d[E]}{dt} = - (k_{1(OH^-)}[OH^-] + \sum_{B^-} k_{1(B^-)}[B^-])[E] \quad (5)$$

In this case the rate of ionization of the enolizable aldehyde is rate determining and the reaction exhibits general base catalysis and is furthermore of zero order with respect to I.

(2) At low  $\text{CH}_2\text{O}$  we obtain

$$\frac{d[\text{E}]}{dt} = - \frac{k_{1(\text{OH}^-)}k_2[\text{E}][\text{OH}^-][\text{CH}_2\text{O}]}{k_{-1(\text{H}_2\text{O})}[\text{H}_2\text{O}]} \quad (6)$$

Here the condensation step is rate determining and the reaction is of first order with respect to I and exhibits specific hydroxide ion catalysis.

In both cases the reactions are expected to be of first order with respect to  $[\text{E}]$  and, as already mentioned, this was indeed found in all the cases studied (Fig. 1).

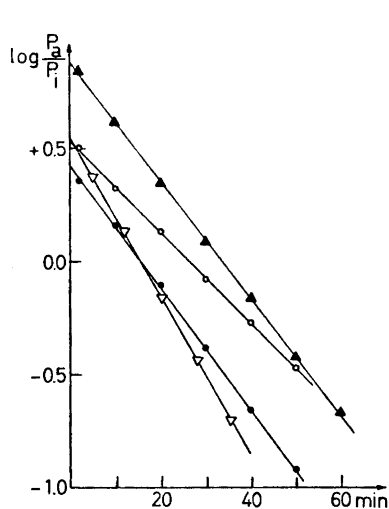


Fig. 1. Pseudo first-order disappearance of the enolizable aldehyde in 0.50 M  $\text{CH}_2\text{O}$ .  $P_a/P_i$ : Peak area of signal from enolizable aldehyde relative to that of internal standard.  $\circ$ : Acetaldehyde with nominal conc. of  $\text{NaOH} = 0.05$  M;  $\blacktriangle$ : Propionaldehyde, nom. conc. of  $\text{NaOH} = 0.01$  M;  $\nabla$ : Butyraldehyde, nom. conc. of  $\text{NaOH} = 0.015$  M;  $\bullet$ : Isobutyraldehyde, nom. conc. of  $\text{NaOH} = 0.02$  M.

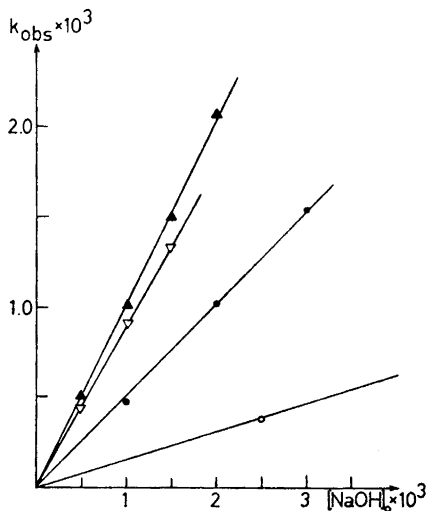


Fig. 2.  $k_{\text{obs}} \times 10^3 \text{ sec}^{-1}$  in 0.50 M  $\text{CH}_2\text{O}$  as a function of the amount of sodium hydroxide initially added.  $\circ$ : Acetaldehyde;  $\blacktriangle$ : Propionaldehyde;  $\nabla$ : Butyraldehyde;  $\bullet$ : Isobutyraldehyde. Further experimental points from acetaldehyde runs with higher  $\text{NaOH}$ -concentrations fall on the same line as the one given in the figure.

As seen from Table 1, the dependence of the rates of reaction on the total amount of I present in the reaction mixtures was more complicated. The rate constants given here and in Table 3 refer to the rate expression

$$\frac{d[\text{E}]}{dt} = -k'[\text{E}][\text{NaOH}]_{\text{added}} \quad (7)$$

where  $k'[\text{NaOH}]_{\text{added}}$  is equal to  $k_{\text{obs}}$  for the first order disappearance of E.

The Arrhenius activation energies calculated from these data for the reactions in 0.50 M  $\text{CH}_2\text{O}$  are 19.7, 15.1, 15.4, and 15.1 kcal  $\text{mol}^{-1}$  for II, III, IV, and V, respectively.

Table 1. ( $k_{\text{obs}}/[\text{NaOH}]) \times 10^2 \text{ M}^{-1} \text{ sec}^{-1}$  for the disappearance of the enolizable aldehyde at different temperatures and concentrations of formaldehyde.

T°C	20.0										30.0	40.0
$[\text{CH}_2\text{O}]_{\text{total}}, \text{M}$	0.10	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	0.50	0.50	
Reacting aldehyde												
$\text{CH}_3\text{CHO}$ (II)	0.91	1.42	1.56	1.48	1.36	1.12	0.95	0.70	0.55	4.91	13.5	
$\text{CH}_3\text{CH}_2\text{CHO}$ (III)	10.0	10.7	10.2	9.77	9.30	8.30	7.65	6.20	5.28	23.6	52.5	
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$ (IV)	7.51	8.96	8.94	8.58	8.06	7.11	6.19	4.88	4.02	21.3	48.2	
$(\text{CH}_3)_2\text{CHCHO}$ (V)	5.48	5.40	5.12	4.86	4.49	4.01	3.66	3.00	2.71	12.5	27.3	

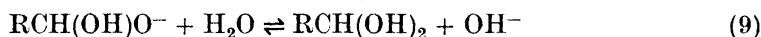
When studied at constant total formaldehyde concentration (0.50 M), the rates of all of the reactions studied were found to be directly proportional to the amount of sodium hydroxide added initially (Fig. 2).

At low concentrations of I the reaction rates should be proportional to this concentration. The reaction of IV with I was the only reaction studied at lower concentrations of I than 0.10 M. From experiments performed with concentrations of I from 0.02 M up to 0.10 M, one could deduce an approximately linear (actually slightly convex upwards) function describing the dependence of the observed rate of disappearance of IV on the concentration of I. In these runs, the concentrations of IV were significant compared with the concentrations of I. Therefore, the rates of butyraldol formation were appreciable compared with the rates of reaction of IV with I, and this caused the pseudo first-order plots to deviate from linearity. Even if the results of these experiments are therefore of a more qualitative nature, they indicate that, at low concentrations of I, the rate determining step is the attack of the enolate ion on a free molecule of I (eqn. 2).

At higher concentrations of I, the rates of anion formation (eqn. 1) could be expected to become rate determining and the orders of the reactions in I therefore to decrease to zero. Actually rate maxima were observed at concentrations of I in the range 0.2–0.5 M for the reactions of II, III, and IV with I whereas for V a continuous decrease in rate was observed at increasing concentrations of I from 0.10 to 4.0 M.

The decreases in rates cannot be explained by decreasing concentrations of free monomeric I or of the other aldehydes due to increasing formation of hydrates or oligomers. At a total formaldehyde concentration of 4.0 M, methylene glycol still accounts for more than 60 % of the total amount of formaldehyde present, and the dimeric hydrate is next in importance.<sup>5</sup> The concentration of free monomeric formaldehyde in equilibrium with the methylene glycol thus continues to increase throughout the concentration range studied.<sup>6</sup>

The dependence of the rates of reaction on the total formaldehyde concentration therefore reflects a gradual shift in rate determining step from eqn. 2 to eqn. 1 and a simultaneous decrease in basicity of the medium. As already pointed out by Bell and McTigue,<sup>1</sup> the various hydrated aldehyde species in the reaction mixtures act as weak acids and thus reduce the hydroxide ion concentrations according to the following equations:



These equilibria and the consequential decreases in hydroxide ion concentrations cause the observed rate decreases at increased concentrations of I. It was found from pH-measurements in preneutralized formaldehyde solutions of different concentrations and with sodium hydroxide added to a nominal value of 0.02 M, that the actual hydroxide ion concentrations were far lower than in 0.02 M NaOH (Table 2).

Table 2. Observed and calculated <sup>a</sup> pH-values for nominally 0.02 M NaOH-solutions in the presence of various amounts of formaldehyde at 25°C.

[CH <sub>2</sub> O] <sub>total</sub> , M	0.10	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00
pH <sub>exp</sub>	11.86	11.71	11.46	11.30	11.15	10.93	10.79	10.52	10.36
pH <sub>calc</sub>	12.08	11.91	11.72	11.59	11.48	11.34	11.23	11.07	10.95

<sup>a</sup> Values calculated from the pK<sub>a</sub>-value of 13.27 for CH<sub>2</sub>(OH)<sub>2</sub> given by Bell and Onwood.<sup>7</sup>

The pH-values experimentally determined differ considerably from the calculated values. Although the experimental errors involved in the accurate measurement of hydroxide ion concentrations in this pH-region are considerable, the experimentally determined pH-values at least reflect the general trend. There is agreement between the calculated and the experimentally determined values in that there is about a tenfold decrease in hydroxide ion concentration going from 0.50 M to 4.00 M solutions of I. The corresponding decreases in rates observed (Table 1) are smaller. This finding can be explained by general base catalysis in the concentration range where the formation of the enolate anion (eqn. 1) is partly or wholly rate determining.

The slopes at the beginning of the curves, showing the dependence of the observed rates of reaction on the formaldehyde concentration (*cf.* Table 1), reflect in part the acidities of the enolizable aldehydes and in part the reactivity of their corresponding enolate ions towards formaldehyde (*cf.* eqn. 6). The enolate ions can be expected to be more reactive the more alkyl substituents they have since these substituents will increase the electron densities at the α-carbons. The experimental results seem to justify the conclusion that the order of reactivities in this region is II < III ≈ IV < V which follows the order of increasing numbers of alkyl substituents. This also implies that steric effects play a minor role in this reaction series.

In the region where the formation of the enolate ion, that is the kinetic acidity of the aldehyde, is rate determining, the influence of alkyl substituents is obviously more complex since the order of reactivity found here is II < V < IV ≤ III. One would expect the electron-releasing alkyl substituents to decrease the acidities of the aldehydes and thus give the reactivity order V < IV ≤ III < II, but acetaldehyde is anomalous here and also in that its

activation energy is distinctly higher than for the other aldehydes. The explanation must be that acetaldehyde is more stabilized by solvation and its carbonyl group is more extensively hydrated than those of the other aldehydes.<sup>8</sup> Determination of the temperature dependence of the rate of reaction of II with I at both higher (2.0 M I) and lower (0.10 M I) concentrations of formaldehyde showed that the activation energy increases with the formaldehyde concentration, reflecting the shift in rate determining step (Table 3).

Table 3. ( $k_{\text{obs}}/[\text{NaOH}] \times 10^2 \text{ M}^{-1} \text{ sec}^{-1}$ ) for the disappearance of acetaldehyde at different temperatures and concentrations of formaldehyde.

[CH <sub>2</sub> O] <sub>total</sub> , M	Temperature, °C			Activation energy kcal/mol
	20.0	30.0	40.0	
0.10	0.91	2.58	6.52	18.0
0.50	1.56	4.95	13.5	19.7
2.00	0.95	3.43	9.80	21.3

The overall enthalpies of activation are, of course, easily obtainable from the Arrhenius activation energies by subtracting the value of  $RT$  (appr. 0.6 kcal mol<sup>-1</sup>), but it does not seem justified to give values for the entropies of activation based on the rate constants presented since these are only pseudo second-order constants.

### EXPERIMENTAL

The formaldehyde used was of the DM-42 grade from Perstorp AB. This grade is a solution of 42.0 ± 0.5 % of I, 0.3–0.5 % of methanol, and 0.015–0.020 % of acid (calculated as formic acid) in water (all percentages by weight). Acetaldehyde and butyraldehyde were of *puriss.* quality from Fluka AG and were used without further purification. Propionaldehyde and isobutyraldehyde were of *purum* quality and were distilled before use. Fischer certified reagent 1-propanol and dimethoxymethane distilled under nitrogen were used as internal standards. Sodium hydroxide stock solutions were freshly prepared each week from Merck Titrisol ampoules and freshly boiled water.

The reactions were carried out in volumetric flasks immersed in a thermostatted bath of type Lauda, controllable to within ±0.05°C. Vapour phase chromatography was performed using a Varian 1740 gas chromatograph with FI-detector and equipped with an electronic integrator of type Varian 480. pH-Measurements were made with a Metrohm Potentiograph E 336 equipped with a glass electrode of type EA 121 UX. The following stock solutions were prepared: Formaldehyde, 10.0 M and 1.00 M; neutralized to pH 7.0. Acetaldehyde and propionaldehyde, 0.01 M. Butyraldehyde and isobutyraldehyde, 0.10 M. 1-Propanol, 0.08 % by weight in water. Dimethoxymethane, 0.025 % and 0.4 % by weight in water. Sodium hydroxide, 0.100 M, 0.200 M, and 0.500 M.

*General procedure.* The proper amounts of formaldehyde, of the second aldehyde and of internal standard solution were pipetted into a 100 ml volumetric flask and diluted to about 80 ml. The flask was thermostatted at the desired temperature for about half an hour. Then the proper amount of sodium hydroxide solution was added, the reaction mixture diluted to the mark and thoroughly mixed by shaking and the flask again immersed in the bath. At different times after the start of the reaction, as measured after addition of about half of the amount of sodium hydroxide, 5 ml samples of the reaction mixture were pipetted into 10 ml septum capped serum flasks. To these flasks the proper amounts of 0.5 M sulphuric acid required to make the samples slightly acid

had been added in advance. The flasks were then immediately sealed and the contents analyzed by VPC within an hour. In all cases studied, it was ascertained that no losses of volatile aldehydes occurred in experiments performed in the above-mentioned way, but without sodium hydroxide added. It was also shown that the rate of disappearance due to self-aldol condensation in experiments performed without addition of formaldehyde was at most 3 % of the observed rate of aldehyde disappearance in the presence of formaldehyde (the value 3 % applies to the runs with the highest formaldehyde concentrations where the rates were relatively low) and in most cases not higher than 1 % of these rates. Furthermore, the decreases in hydroxide ion concentrations caused by the presence of acidic formaldehyde hydrates also affect the rates of the self-aldol condensations in these solutions. Therefore these rates may safely be neglected when compared with the rates of the condensations with formaldehyde.

*Gas chromatographic data.* Acetaldehyde: At the start of the experimental runs, the reaction mixtures were 0.001 M in II and about 0.0013 % in dimethoxymethane, which was used as internal standard. The catalyst concentration ranged from 0.025 to 0.100 M. The following chromatographic conditions were used: Column of stainless steel, 2 m  $\times$  0.22 cm (i.d.), stationary phase 20 % Ethofat 60/25 on Gas Chrom 100/120 mesh, injection temperature 130°, column temperature 80° and detector temperature 140°, carrier gas 20 ml/min of N<sub>2</sub>, attenuation 10<sup>-11</sup> on the chromatograph and 1 on the integrator and injected volume 2.0  $\mu$ l.

Propionaldehyde: Initial concentrations of III, 0.001 M, and of dimethoxymethane about 0.0013 % by weight. Catalyst concentration varied from 0.005 to 0.020 M. Column of stainless steel 1 m  $\times$  0.22 cm. Stationary phase Porapak Q 100/120 mesh. Injection temperature 150°, column temperature 115° and detector temperature 150°. Carrier gas 30 ml/min of N<sub>2</sub>, attenuation 10<sup>-11</sup> on the chromatograph and 1 on the integrator (in the runs with the highest formaldehyde concentrations peak height measurements were used instead of integration because of tailing of formaldehyde). Injected volume 2.0  $\mu$ l.

Butyraldehyde: Initial concentrations of IV, 0.005 M, and of 1-propanol 0.016 % by weight (internal standard). Catalyst concentration range 0.005 to 0.015 M. The column was the same as for III. Injection temperature 155°, column temperature 135° and detector temperature 150°. Carrier gas 30 ml/min of N<sub>2</sub>, attenuation 2  $\times$  10<sup>-10</sup> on the chromatograph and 1 on the integrator. Injected volume 2.0  $\mu$ l.

Isobutyraldehyde: Initial concentrations of V, 0.005 M, and of dimethoxymethane 0.013 % by weight. Catalyst concentration range 0.010 to 0.030 M. The column was the same as for III. Injection temperature 155°, column temperature 150° and detector temperature 150°, attenuation 4  $\times$  10<sup>-11</sup> on the chromatograph and 1 on the integrator. Injected volume 2.0  $\mu$ l.

All runs were performed at least twice and the reproducibility was generally within  $\pm$  3 % of the mean value.

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