Formose Reactions. III. Evaluation of Various Factors Affecting the Formose Reaction

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By an analytical method using oxidation-reduction potential measurements of the formose reaction, which were previously shown to be useful for separately analyzing the induction and the formose-forming steps, the influence of various factors on each step and on the sugar yield were examined. It was found for the batch-system formose reaction that the rate of both steps and the sugar yield are affected by the concentration of formaldehyde, the amount of calcium hydroxide, and also by the ratio of the two. The dissolved calcium ion is believed to be an essential catalyst for either the induction or the formose-forming step, with the hydroxy anion playing significant role as the catalyst for the latter step. The optimum conditions necessary for obtaining the sugars in high yields are discussed.

Since Butlerow[1] found in 1861 that various saccharides are formed from an aqueous formaldehyde solution in the presence of $Ca(OH)_2$, many investigations concerning the formose reaction have been undertaken concerning many aspects,[2] such as the catalytic effect of organic and inorganic bases,[3–5] the function of a co-catalyst having enediol-forming ability,[6] and analytical techniques for the products.[7] The formose reaction is considered to proceed *via* the following two steps.[2] The first step is an induction period involving most probably formaldehyde condensation forming glycolaldehyde, and this induction period can be reduced by the addition of substances capable of forming an enediol, *e.g.*, various monosaccharides and benzoins.[8] In the subsequent step, rapid aldol condensation, a Cannizzaro reaction, and a cross-Cannizzaro reaction take place simultaneously resulting in formaldehyde condensation to saccharides. Some other reactions such as the interconversion of intermediates (the Lobry de Bruyn-Alberda van Eckenstein rearrangement) and the decomposition of various products also accompany the above reactions.

There are two important unsolved problems concerning the formose reaction which has rather complex features. One is to provide a convenient method for separately analyzing the induction step and the formose-forming step, and the other is to separately examine the roles of the dissolved and undissolved amounts of the $Ca(OH)_2$ catalyst. Although many approaches have been made to understanding the mechanism of the formose reaction and a number of workers have proposed the mechanism of $Ca(OH)_2$ catalytic action,[4,9,10] there are still ambiguities to be clarified with respect to these two points. Weiss *et al.* have reported important aspects of the kinetics of the formose reaction using a continuously stirred tank reactor (CSTR) which was desinged to maintain the reaction in steady-state conditions. They observed inevitable instabilities caused by varying the formaldehyde concentration, the calcium hydroxide concentration,** or the reaction pH.[9,11,12] However, as far as their method is concerned, no discussion of the induction-step mechanism is possible because they allowed the reaction to start by adding an endiol initiator, in which case the formose-forming step occurred instantly without any induction period.

In an approach to the investigation of the formose reaction, the measurement of the oxidation-reduction potential (ORP) during the $Ca(OH)_2$-catalyzed reaction in the batch system has proven useful for the separate analysis of each reaction step.[13,14] This showed that whenever the formose reaction occurs, the ORP curve invariably shows a minimum at the beginning of the formose-forming step and a maximum near the end point of the reaction (the so-called yellowing point[5,15]), at which the highest sugar yield is usually obtained. In a continuation of this study using the ORP method, this paper reports detailed examinations of various factors affecting the induction step, the sugar-forming step, and the sugar yield. Particular attention is placed on the following factors; the formaldehyde concentration, the $Ca(OH)_2$ quantity and particle size, the dissolved $Ca(OH)_2$, and the initial pH.

Experimental

A formaldehyde solution was prepared as follows: 200 g of paraformaldehyde (Merck) was suspended in 400 ml of distilled water, refluxed for 4 h, and filtered through a sintered glass disk. The filtrate containing *ca.* 30 wt-% of formaldehyde was stored in a brown bottle at the dark and was used for experiments within a few days, in order that no substances accelerating the formose reaction be produced. Commercial grade $Ca(OH)_2$ was used as a catalyst and the ground powder was passed through a 200 mesh sieve. When other $Ca(OH)_2$ particle sizes were required, the $Ca(OH)_2$ was prepared by a method similar to that described by Huttig and Arbes[16] and fractionated into the desired sizes by sieving.

The formose reaction was started without adding any initiator but by adding $Ca(OH)_2$ to a formaldehyde solution pre-heated to 60 ± 1 °C. The procedure and apparatus used in the present experiments, the methods for determining the formaldehyde consumption and sugar yield, and the manner of measuring the ORP were essentially the same as those

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** The term "concentration," which was used by Weiss *et al.* for $Ca(OH)_2$, is not relevant, because their reaction system (CSTR) was not initially homogeneous, but can accurately be called heterogeneous, in view of the coexistence of dissolved and undissolved calcium hydroxide in the system.

described in a previous paper.[14] The dissolved calcium ion concentration was determined by the EDTA method with an NN-reagent as the indicator.[17]

The sugar composition of the formose product for several runs was determined by GLC after trimethylsilylation.[18] The chromatographic patterns obtained were virtually identical in all cases.

Results and Discussion

Throughout the present paper, the following terms are adopted: [HCHO] is the formaldehyde concentration, $[Ca(OH)_2]$ the quantity of calcium hydroxide added as catalyst, T_{min} the length of the induction period, which is the time from the start of the formose reaction to the ORP minimum,[14] T_{max} the time from the start to the ORP maximum,[14] and $T_{max}-T_{min}$ the length of the formose-forming period. T_{min} and $T_{max}-T_{min}$ can be used for evaluating the rate of each step.

Effects of [HCHO] and $[Ca(OH)_2]$. As has been observed by Weiss *et al.*, the formose reaction is sensitive to [HCHO] and $[Ca(OH)_2]$. In the present work, this sensitivity to concentration is shown to occur in both the induction and formose-forming steps and to affect the sugar yield.

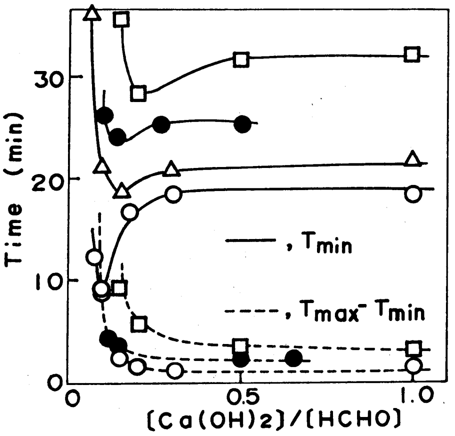

Fig. 1. Effect of $[Ca(OH)_2]$ on T_{min} and $T_{max}-T_{min}$. [HCHO]: □, 0.1 M; ●, 0.5 M; △, 1.0 M; ○, 2.2 M; $Ca(OH)_2$: 200 mesh.

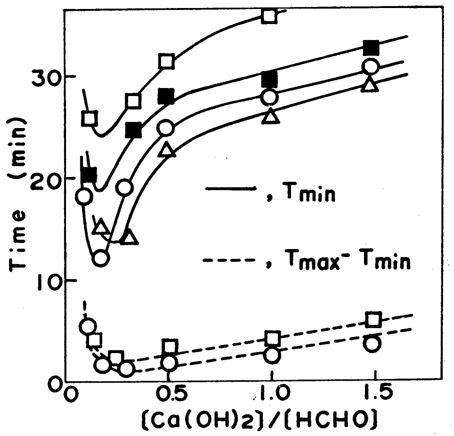

Fig. 2. Effect of [HCHO] on T_{min} and $T_{max}-T_{min}$. $Ca(OH)_2$: 200 mesh; □, 0.05 M; ■, 0.13 M; ○, 0.25 M; △, 0.33 M.

The Effect on the Induction Period: These are shown in Figs. 1 and 2. Figure 1 shows that, for increased $[Ca(OH)_2]$ at constant [HCHO], T_{min} decreases, passes through a minimum and then at about $[Ca(OH)_2]/[HCHO]=0.1-0.2$ becomes constant. Similar behavior is observed for decreased [HCHO] at constant $[Ca(OH)_2]$, however, T_{min} tends to be prolonged (Fig. 2). In both cases, the formose reaction did not occur when the $[Ca(OH)_2]/[HCHO]$ ratio was set to less than 0.05. As is seen in Table 1, which shows the effects of $[Ca(OH)_2]/[HCHO]$ on the initial pH, the $Ca(OH)_2$ solubility and the amount of HCHO adsorbed on solid $Ca(OH)_2$, the pH decreases at lower $[Ca(OH)_2]/[HCHO]$ ratios; for example, it is as low as 10.5 at $[Ca(OH)_2]/[HCHO]=0.05$. It is known that the formose reaction does not occur such a low pH value.[9]

TABLE 1. THE EFFECTS OF [HCHO] AND $[Ca(OH)_2]$ ON pH AND $Ca(OH)_2$ SOLUBILITY AT 60 °C

[HCHO] (M)	$[Ca(OH)_2]$ (M)	$[Ca(OH)_2]/[HCHO]$	pH	Dissolved $Ca(OH)_2$	HCHO adsorbed on solid $Ca(OH)_2$ (mg/ml)
1.90	0.60	0.32	11.3	0.11	10.9
1.90	0.40	0.21	11.2	0.12	6.8
1.90	0.20	0.11	11.0	0.12	3.3
1.90	0.16	0.08	11.0	0.12	1.4
1.53	0.30	0.20	11.4	0.09	1.0
2.99	0.30	0.10	11.0	0.14	4.2
5.94	0.30	0.05	10.5	0.21	8.4

In spite of the fact that Weiss *et al.* have observed in their CSTR experiments that the reaction does not occur when the $[Ca(OH)_2]/[HCHO]$ ratio is more than 2, it was demonstrated that the reaction did occur for the appearance of the ORP minimum and maximum even at $[Ca(OH)_2]/[HCHO]=5$. Furthermore, experiments at extremely low or high [HCHO] showed that such conditions are not appropriate for the formose reaction. Thus, when the [HCHO] is set to less than 0.01 M, neither did the ORP minimum appear nor did the reaction occur even for an extension of the reaction time up to 90 min. At high [HCHO] (*ca.* 10 M), the reaction occurred whenever an adequate amount of $Ca(OH)_2$ was used. However, because of a highly exothermic reaction, the mixture became too viscous to control properly.

The Effect on the Formose Forming Step. These effects were examined at constant [HCHO] and $[Ca(OH)_2]$ and are shown as dotted curves in Figs. 1 and 2, respectively. At constant [HCHO], $T_{max}-T_{min}$ is sharply reduced with increased $[Ca(OH)_2]$ in the range of $[Ca(OH)_2]/[HCHO]$ ratios between 0.1 and 0.3, and remains constant at higher ratios. For constant $[Ca(OH)_2]$, it also decreases with decreasing [HCHO] for lower $[Ca(OH)_2]/[HCHO]$ ratios but increases with decreasing [HCHO] for higher ratios.

In comparison with the effects on the induction period (Figs. 1 and 2), the kinetics for the formose-forming step apparently differ from those for the induction step. However, when a comparison is made in the region of $[\mathrm{Ca(OH)_2}]/[\mathrm{HCHO}]$ ratios greater than 0.3, for both steps the rate increases with increasing [HCHO] at constant $[\mathrm{Ca(OH)_2}]$ (Fig. 2), but the rate remains unchanged with increasing $[\mathrm{Ca(OH)_2}]$ at constant [HCHO] (Fig. 1). These results suggest that, under certain conditions ($[\mathrm{Ca(OH)_2}]/[\mathrm{HCHO}]\geq 0.3$), the reactions for both the induction and formose-forming steps are of zeroth order for $\mathrm{Ca(OH)_2}$ and probably of first order for formaldehyde. This is contrary to the concept of Weiss and Lapierre12) that, at intermediate conversion levels, the formose reaction is of first order for $\mathrm{Ca(OH)_2}$ and of zeroth order for the organics. Although there are some difficulties in accounting for the discrepancy between their and the present results, it is reasonable to assume that this is due to a difference between the CSTR kinetics and those of the present study.

The Effect on Sugar Yield: As shown in Figs. 3 and 4, the sugar yield is considerably altered by varying the [HCHO] and $[\mathrm{Ca(OH)_2}]$. In summarizing the results, it can generally be said that the sugar yield increases with a decrease in either the [HCHO] or $[\mathrm{Ca(OH)_2}]$. This may be partly explained in terms of the Cannizzaro reaction for formaldehyde. The consumption of formaldehyde in the induction period is known to be largely caused by the Cannizzaro reaction,14) the rate of which is expressed by $-\mathrm{d}[\mathrm{HCHO}]/\mathrm{d}t=k[\mathrm{OH^-}]^{1-2}[\mathrm{HCHO}]^{1-2}$.2,19—21) Therefore, a higher [HCHO] or $[\mathrm{Ca(OH)_2}]$ is not recommended for obtaining sugar products in a high yield. As discussed below, a higher $[\mathrm{Ca(OH)_2}]$ also causes facile decomposition of the sugars formed.

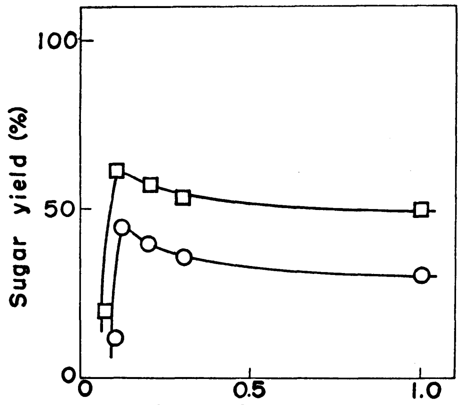

Fig. 3. Effect of $[\mathrm{Ca(OH)_2}]$ on the sugar yield.
[HCHO]: □, 1.0 M; ○, 2.2 M; $\mathrm{Ca(OH)_2}$: 200 mesh. The sugar yield is based on the used formaldehyde.

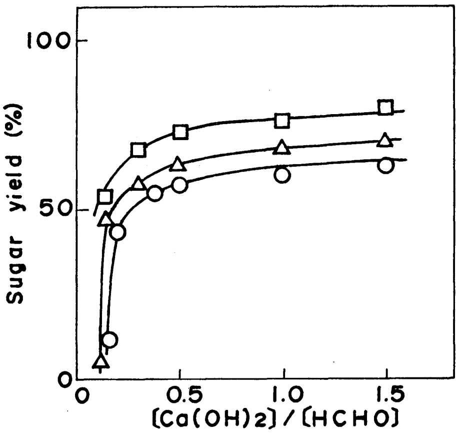

Fig. 4. Effect of [HCHO] on the sugar yield.
$\mathrm{Ca(OH)_2}$: 200 mesh; □, 0.13 M; △, 0.25 M; ○, 0.33 M. The sugar yield is based on the used formaldehyde.

Effect of $Ca(OH)_2$ Particle Size. As a probe of the catalytic action of $\mathrm{Ca(OH)_2}$, which exists in several forms, *e.g.*, dissolved, undissolved, or free and bound to organic materials, the influence of $\mathrm{Ca(OH)_2}$ particle size was examined. The results are shown in Table 2. For a constant $[\mathrm{Ca(OH)_2}]$ (0.22 or 0.33 M), an increase in particle size led to an increase of both T_{min} and $T_{\mathrm{max}}-T_{\mathrm{min}}$.

Since, in general, the particle size of a solid is inversely proportional to the specific surface area, the increase in the $\mathrm{Ca(OH)_2}$ particle size causes a lowering of the dissolved rate. Thus, as shown in Table 3 (Runs 2, 5, and 6), the dissolved calcium ions at the beginning (T_{S}) decrease with increasing $\mathrm{Ca(OH)_2}$ particle size. The delay in the induction period caused by the increase in $\mathrm{Ca(OH)_2}$ size suggests that the dissolved calcium species plays an important role in the catalysis of this step. Conversely, undissolved $\mathrm{Ca(OH)_2}$ may not be an essential catalyst but may play the role of either continuously supplying the dissolved calcium species or maintaining the pH range required for the induction period.

The delay effect on the rate of the formose-forming step for the larger $\mathrm{Ca(OH)_2}$ particles can also be explained in terms of the slow dissolution rate. The particle size did not have any appreciable influence on the sugar yield, even when the formose reaction proceed-

TABLE 2. THE INFLUENCE OF $\mathrm{Ca(OH)_2}$ PARTICLE-SIZE ON THE FORMOSE REACTIONa)

$[\mathrm{Ca(OH)_2}]$ (M)	Particle size (mesh)	T_{min} (min)	T_{max} (min)	$T_{\mathrm{max}}-T_{\mathrm{min}}$ (min)	Sugar yield at T_{max} (%)	Sugar yield 3 min after T_{max}
0.22	200	12.5	23.0	10.5	39.6b)	48.4b)
0.22	60—100	19.0	unknown	—	3.8c)	—
0.22	20—30	unknown	unknown	—	0.6c)	—
0.33	200	13.2	15.3	2.1	48.5	16.4
0.33	60—100	15.2	18.7	3.5	48.0	24.3
0.33	20—30	38.6	47.5	8.9	49.1	31.3

a) [HCHO]; 2.2M. b) T_{max} was somewhat obscure. c) Sugar yield at 30 min.

TABLE 3. THE EFFECTS OF INITIAL CONDITIONS ON THE FORMOSE REACTION[a]

Run No.	[HCHO] (M)	[Ca$(OH)_2$] (M)	T_{min} (min)	T_{max} (min)	pH at			HCHO consumption (%) at		Dissolved Ca^{2+} (mM) at			Sugar yield (%) at	
					T_s	T_{min}	T_{max}	T_{min}	T_{max}	T_s	T_{min}	T_{max}	T_{max}	T_3[f]
1	2.0	0.16	—[d]	—[d]	11.0	$(10.6)_{10}$[e]	$(10.2)_{30}$	$(18)_{10}$	$(25)_{30}$	110	$(140)_{30}$		—	—
2	2.0	0.22	14.6	18.5	11.2	10.9	9.8	30	98	116	182	196	48.4	40.4
3	2.0	0.60	16.8	20.5	11.3	11.1	10.9	34	98	112	262	425	36.5	14.6
4	2.0	1.00	17.0	18.5	11.4	11.1	10.9	28	98	108	220	368	33.0	7.5
5[b]	2.0	0.22	22.0	—[d]	11.1	10.7	$(9.1)_{30}$	34	$(55)_{30}$	89	192	$(205)_{30}$	$(15.0)_{30}$	
6[c]	2.0	0.22	—[d]	—[d]	11.2	$(11.1)_{10}$	$(10.8)_{30}$	$(14)_{30}$	$(33)_{30}$	30	$(175)_{30}$		—	—
7	0.5	0.25	19.4	21.6	11.2	11.5	11.5	23	99	35	53	195	58.7	27.0
8	1.3	0.25	15.0	17.0	11.4	11.2	11.0	25	98	72	133	210	48.7	18.8
9	2.5	0.25	11.8	—[d]	11.1	10.8	$(9.0)_{30}$	26	$(85)_{30}$	121	212	$(220)_{30}$	$(23.1)_{30}$	
10	5.0	0.25	—[d]	—[d]	10.8	$(10.3)_{10}$	$(9.5)_{30}$	$(13)_{10}$	$(18)_{30}$	150	$(232)_{30}$		—	—
11	1.0	0.10	21.0	28.8	11.3[g]	11.0	10.2	28	98	53	80	85	52.4	48.6
12	1.0	0.10	33.7	37.7	11.5[g]	11.2	10.9	42	99	32	69	86	50.5	15.8
13	1.0	0.10	41.5	44.2	11.7[g]	11.3	11.3	42	99	16	50	86	46.7	12.9
14	1.0	0.10	—[d]	—[d]	12.0[g]	$(11.9)_{30}$	$(11.6)_{60}$	$(41)_{30}$	$(52)_{60}$	9	$(14)_{30}$	$(19)_{60}$	—	—

a) Reaction temp, 60 °C; Ca$(OH)_2$, 200 mesh. b) Ca$(OH)_2$, 60—100 mesh. c) Ca$(OH)_2$, 20—35 mesh. d) The minimum ORP and/or maximum ORP were obscure. e) In cases when T_{min} and T_{max} were obscure, the measurement were performed for reaction times of 10 and 30 min respectively, the results of which are shown in parenthesis with a subscript number. f) T_3=3 min after T_{max}. g) The pH was adjusted with concd KOH.

ed slowly (see Table 2, for a 0.33 M [Ca$(OH)_2$]). However, the decomposition of sugar products after T_{max} was found to be suppressed with increased Ca$(OH)_2$ size, although the $T_{max}-T_{min}$ was prolonged. This may also be due to the slow dissolution rate of Ca$(OH)_2$ which is considered to accelerate the decomposition of sugar in dissolved form.

Effects of the pH and the Dissolved Calcium Ions. The above results led us to the preliminary conclusion that the pH and the dissolved calcium species may be important factors in the formose reaction, in addition to the effect of the [HCHO] and [Ca$(OH)_2$]. The importance of the pH effect has already been pointed out.[9,22,23] Weiss and John have shown that the consumption rate of formaldehyde using CSTR is highly pH-dependent at constant [HCHO] and [Ca$(OH)_2$]: for example, the highest rate is observed for a pH of *ca.* 11.0 for 1.3 M [HCHO] and 0.45 M [Ca$(OH)_2$] and for a pH of *ca.* 11.5 for 1.3 M [HCHO] and 0.35 M [Ca$(OH)_2$].[9]

In order to gain more insight into the nature of the formose reaction, the effects of the initial conditions were examined while measuring the initial pH and dissolved calcium ion and the T_{min} and T_{max} points, as well as the formaldehyde consumption and the sugar yield. The results are summarized in Table 3. The most typical standard conditions that give good sugar yields are Runs 2, 8, and 11, which will be compared with other Runs in the following discussion.

The Effect of [Ca$(OH)_2$] (Runs 1—4). At the same [HCHO] and Ca$(OH)_2$ particle size, the initial pH (at T_S) increases with increasing [Ca$(OH)_2$], in accord with the results shown in Table 1, however, the initial concentration of the dissolved calcium ion is virtually independent of the [Ca$(OH)_2$] which has a significant effect on the yield and the sugar decomposition rate.

The Effect of the Ca$(OH)_2$ Particle Size (Runs 2, 5, and 6). Delayed effects similar to those described above were observed for T_{min} and $T_{max}-T_{min}$ (Table 2). It should be noted that the initial concentration of the dissolved calcium ion decreases significantly with increased particle size despite the fact that the initial pH is practically the same in all cases.

The Effect of [HCHO] (Runs 7—10). For the same [Ca$(OH)_2$] and Ca$(OH)_2$ particle size, the initial pH showed a tendency to decrease with increasing [HCHO], while the initial dissolved calcium ion increased.

The Effect of the Initial pH (Runs 11—14). For constant [HCHO] and [Ca$(OH)_2$], the effect of the initial pH was examined, as adjusted to the desired value by the addition of potassium hydroxide. For increased pH, the initial concentration of dissolved calcium ions decreased and, in proportion to this decrease, T_{min} increased while $T_{max}-T_{min}$ decreased.

Other Significant Observations. T_{min} is increased with decreasing initial concentration of the dissolved calcium ion. Also, $T_{max}-T_{min}$ is prolonged with decreasing pH at T_{min}. A lowering of the pH was observed throughout the induction and formose-forming steps; this was more significant in the latter step. The pH lowering near the end of the formose-forming step has previously been reported.[5,6] This may be largely due to the facile complex formation between sugars and Ca$(OH)_2$.[5,9] In fact, when an aqueous Ca$(OH)_2$ solution was titrated with a solution of several sugars, an appreciable fall in the pH was observed, as is shown in Fig. 5. However, for titration with 0.1 M glucose, the pH of a Ca$(OH)_2$ solution showed no tendency to decrease. It should be noted that the formation of organic acids by the Cannizzaro reaction may also contribute to the pH lowering either in the induction or the formose-forming step, and it has been shown that the rate of organic-acid formation in the induction period is similar to that for the formose-

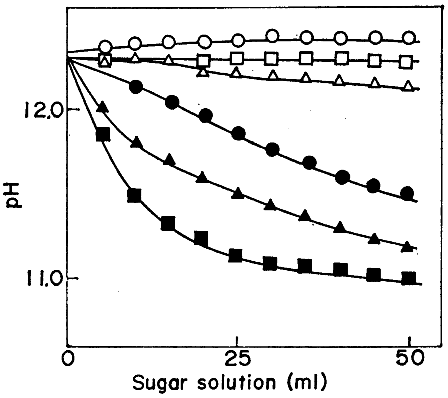

Fig. 5. pH change of 0.1 M $Ca(OH)_2$ solution (50 ml) by titration with an aqueous sugar solution. Temp, 26°C; Sugar solution: □, Blank; ○, 0.1 M glucose; △, 0.1 M xylose; ●, 1.0 M glucose; ▲, 1.0 M xylose; ■, 1.0 M fructose.

forming step.[3,14]

Conclusion. From these observations, one can draw the following conclusions. First, the formose reaction does not occur for low $[Ca(OH)_2]/[HCHO]$ ratios (<0.05). Under such conditions, the induction step is not initiated because of the low pH (<10.5). Second, the dissolved calcium ion may act as an active catalyst in the induction step when the pH is maintained at the appropriate range (approximately 10.8—11.7) and when the $[Ca(OH)_2]/[HCHO]$ ratio is not extremely low (<0.1). The undissolved $Ca(OH)_2$ may not play a significant role in the catalysis during the induction period, but may serve as a supplier of dissolved calcium ions, which are consumed by the Cannizzaro reaction for formaldehyde, and for maintaining the neccessary pH. Third, the dissolved calcium ion is considered to be essential for catalyzing the formose-forming step. However, due to the fact that the rate of this step is accelerated with increasing initial pH (T_{min}), it is suggested that the OH^- ion plays a significant role in the catalysis of the formose-forming step.

There are some discrepancies between the results of Weiss *et al.*[9,11,12] and those presented here regarding the kinetic behavior of the formose reaction. However, the above conclusions are not inconsistent with those of Weiss *et al.* such as the suggestion that $CaOH^+$ might be the true catalyst in the overall formose reaction, in view of the pH dependence and the sensitivities to the $[Ca(OH)_2]$ and $[HCHO]$. More details on the nature of the catalyst will be reported in a subsequent paper.

Finally, the present investigation provides the following guide-lines for obtaining high sugar yield in batch-reaction systems. The amount of formaldehyde consumed by the Cannizzaro reaction must be minimized. This may be done at low formaldehyde concentrations ($[HCHO]<1$ M), at relatively low pH values, such as *ca.* 11.2 (Table 3, Runs 7 and 11) and at high $[Ca(OH)_2]/[HCHO]$ ratios with low $[Ca(OH)_2]$ (Fig. 4). In order to prevent sugar decomposition, it is strongly recommended to stop the reaction exactly at T_{max} and to set the pH as low as possible. For example, under the conditions described here, when the $[Ca(OH)_2]/[HCHO]$ ratio was set in the range from 0.11 to 0.15, the sugar yields were 45 and 58% at 2.2 and 1.0 M $[HCHO]$, respectively (Fig. 3). When the $[Ca(OH)_2]/[HCHO]$ ratio was set to 1.5, the sugar yields were 60 and 77% at 0.33 and 0.13 M $[Ca(OH)_2]$, respectively (Fig. 4). However, when the $[HCHO]$ was less than 0.01 M for any $[Ca(OH)_2]/[HCHO]$ ratio, the formose reaction could not occur.

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