Formose Reactions. XIII. Various Factors Affecting the Formose Reaction in Methanol

by

Yoshihiro SHIGEMASA*, Tamotsu SHIBATA*, Eiichi WAKI*, and Ruka NAKASHIMA*

* Department of Industrial Chemistry, Faculty of Engineering, Tottori University, Tottori 680

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At the initial formaldehyde concentration of 0.55–2 M, the sugar yield reaches to maximum when 70–80% of formaldehyde is consumed. When the concentration of calcium ion ([Ca]) is fixed, T_{70} (the time when 70 % of formaldelyde is consumed) has a minimum at [HCHO] / [Ca] ratio of *ca.* 6. The formaldehyde consumption rate increases with an increase in the formaldehyde concentration and has a constant value above 1.0M of the concentration. The formose reaction which was carried out in the absence of calcium ion with the addition of reductone as cocatalyst or catalyzed by sodium hydroxide was found to give rise to peak 11 with high selectivity which has not been yet isolated and identified. Even at same pH* 13.0, furthermore, the formose reaction catalyzed by sodium hydroxide gave higher sugar yield and shorter T_{80} than that by potassium hydroxide.

1 Introduction

In a series of our studies on the formose reaction, [1,2] the reaction can occur in methanol even at a low [CaO]/[HCHO] ratio (0.05), at which the reaction does not take place in an aqueous solution and, contrary to the formose reaction in an aqueous solution, the sugar yield in methanol becomes higher with an increase in the formaldehyde concentration. The rates of the sugar degradation and the formaldehyde consumption increase with an increase in the pH. Competitions among the Cannizzaro reaction, the sugar formation, and the sugar decomposition are important factors affecting the sugar yield.

The distribution of products is different from that in an aqueous solution, but both of them are very complex and essentially nonselective. Continued investigations of the formose reaction in non-aqueous solvents have shown a branched ketose, 2,4-di-C-hydroxymethyl-3-pentulose, to be formed with high selectivity when the reaction is catalyzed by barium chloride-potassium hydroxide.[3]

The purpose of this paper is to explore various factors affecting the sugar yield, the formaldehyde consumption, and the product distribution of the formose reaction in methanol. Particular attention is placed on the following factors : the formaldehyde concentration, the calcium ion concentration (in this paper calcium chloride-potassium hydroxide was used as catalyst instead of calcium oxide), the fructose concentration, and the pH of the reaction mixture.

2 Experimental

The apparatus and the experimental procedure were virtually the same as those described previously.[4,5] The preparation of trimethylsilylated (TMS) derivatives of products and its gas-chromatography were carried out in the same manner as described in the previous paper.[6]

The methanolic formaldehyde solution was prepared from paraformaldehyde (Merck Co.).[4] Other reagents used were of an analytical grade.

3 Results and Discussion

The Formose Reaction Catalyzed by Calcium Chloride-Potassium Hydroxide. In an aqueous solution, we have already reported that the formose reaction homogeneously-catalyzed by calcium chloride-potassium hydroxide at pH 10.5–12.0 was found to proceed as effectively as that heterogeneously-catalyzed by calcium hydroxide.[5] The gas-chromatogram of TMS derivatives of products synthesized with calcium chloride-potassium hydroxide in methanol is quite similar to that obtained by calcium oxide (Fig. 1). Hence, it is easily supposed that the catalysis of calcium chloride-potassium hydroxide would also virtually the same in methanol as that of calcium oxide.

Figure 2 shows the effect of the concentration of calcium ion ([Ca]) on the sugar yield and T_{70}. Here, T_{70} is the time when the formaldehyde consumption reaches 70% as described later. With increasing [Ca], T_{70} decreases and the sugar yield increases to *ca.* 60% (based on the used formaldehyde). At any [Ca] studied in this paper, furthermore, the product distribution was quite similar to that in Fig. 1.

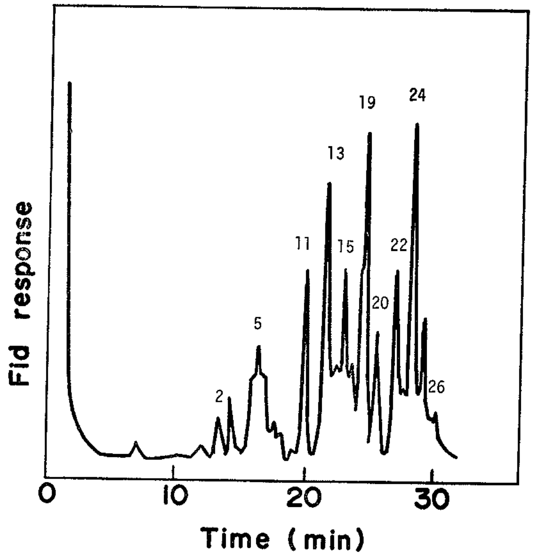

Fig. 1 **Gas chromatogram of TMS derivatives of products.**
[HCHO]=1.0M, [Frucose]=1.39×10^{-2} M, Solvent=Methanol, pH*=13.0 (adjusted by KOH pellet), Temp.=60°C, Under N_2 , Total volume=200ml.

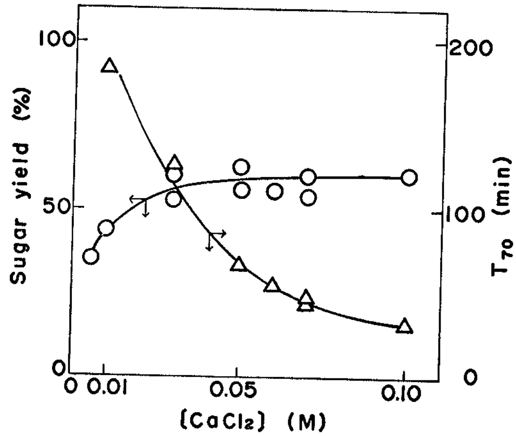

Fig. 2 Effect of $CaCl_2$ concentration on the sugar yield and T_{70}.
[HCHO]=1.0M, Solvent=Methanol, pH* = 10.0 (adjusted by KOH), Temp.= 60° C, Total volume=200ml.

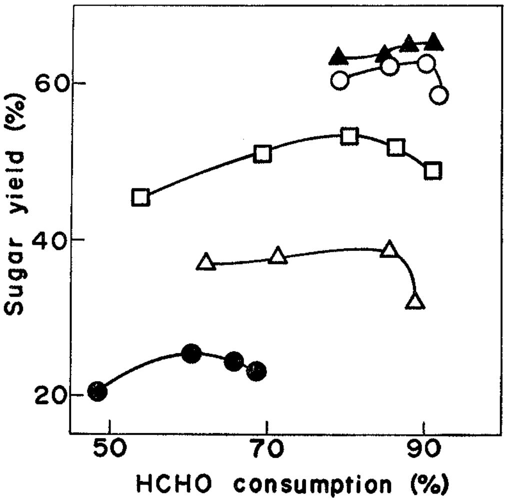

Fig. 3 Relationship between formaldehyde consumption and sugar yield.
Solvent=Methanol, pH* =10.0 (adjusted by KOH), Temp.=60° C, Total volume =200ml, [$CaCl_2$]=0.05M, [HCHO] : ●, 0.1M ; △, 0.25M ; □, 0.5M ; ○, 1.0M ; ▲, 2.0M.

Effect of the Formaldehyde Concentration. Figure 3 shows the relationship between the formaldehyde consumption and the sugar yield at various formaldehyde concentrations. The maximum sugar yield increases with an increase in the formaldehyde concentration. This result has already observed in the previous paper.1) Maximum sugar yields are obtained at the formaldehyde consumption of 70–80% except the formaldehyde concentration of 0.1 M. Therefore, in this paper the abbreviation T_{70} or T_{80} has been used for the time when the formaldehyde consumption reaches 70–80% and the sugar yield goes up to maximum. The sugar yield, furthermore, decreases with a decrease in the residual formaldehyde concentration. This suggests that the decomposition of products would be suppressed in the presence of formaldehyde, although it might be considered that this decrease is mainly attributable to the difference between the sugar decomposition rate and the sugar forming rate : even if the decomposition rate is not changed, the sugar forming rate decreases with a decrease in the formaldehyde concentration as mentioned later.

As shown in Fig. 4, when the concentration of calcium ion ([Ca]) is fixed, T_{70} has a minimum at [HCHO]/[Ca] ratio of *ca.* 6. When the reaction is catalyzed by calcium oxide, the plot of T_{max} vs. the formaldehyde concentration gives a similar curve, but the ratio of [HCHO]/[Ca] which gives a minimum to T_{70} is not constant.1) This difference might be ascribed in part to the pH of the reaction mixture which changes during the reaction catalyzed by calcium oxide.

Furthermore, the formaldehyde consumption rate increases with an increase in the

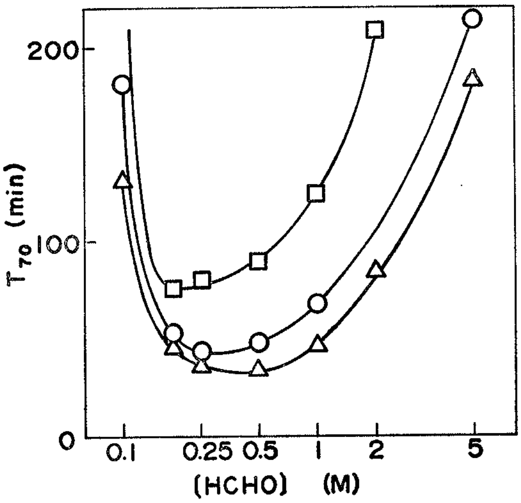

Fig. 4 Effect of formaldehyde concentration on T_{70}.
Solvent=Methanol, pH* =10.0 (adjusted by KOH), Temp.=60° C, Total volume =200ml, $[CaCl_2]$: □, 0.03 M ; ○, 0.05 M ; △, 0.07M.

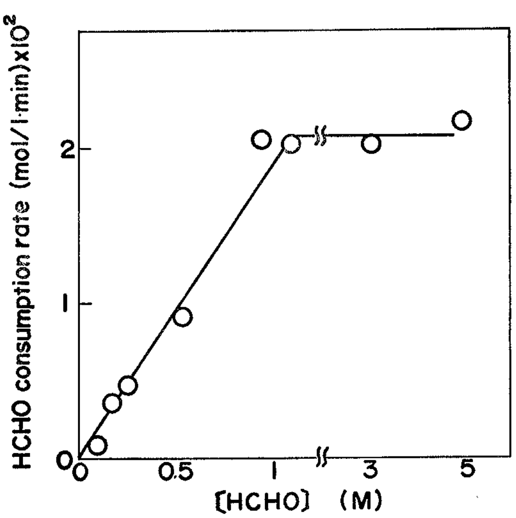

Fig. 5 Effect of formaldehyde concentration on HCHO consumption rate.
$[CaCl_2]$=0.05M, Solvent =Methanol, pH* =10.0 (adjusted by KOH), Temp.=60° C, Total volume=200ml.

formaldehyde concentration and has a constant value above 1.0M of the concentration (Fig. 5). Hence, T_{70} becomes longer as the formaldehyde concentration is higher than a certain concentration.

Effect of Fructose. At various pHs, the effect of the fructose concentration on the sugar yield and T_i was examined. Here, T_i is the time when the oxidation-reduction potential shows a minimum and from this point the sugar-forming step begins.[1] The results are shown in Fig. 6. At constant pH, the sugar yield is not affected by the fructose concentration. Above the fructose concentration of 6.5×10^{-4} M, T_i is not also affected. Similar results were obtained in the formaldehyde consumption curve as shown in Fig. 7.

On the other hand, T_i and the sugar yield decrease with an increase in the pH of the reaction mixture. These phenomena are in fair agreement with those[1] obtained in the formose reaction which was carried out in the absence of fructose.

The Formose Reaction in the Absence of Calcium Ion. Figure 8 shows the gas chromatogram of TMS derivatives of products which were synthesized in the absence of calcium ion in methanol. Under similar reaction conditions in an aqueous solution, 2-C-hydroxymethyl glycerol (peak 2), 3-C-hydroxymethyl pentitol (peak 19), and 2,4-di-C-hydroxymethyl pentitol (peak 26)[7] were found to be formed with high selectivity. However, in methanol, peak 11 becomes a main product instead of peak 19. The product of peak 11 has not been yet isolated and identified.

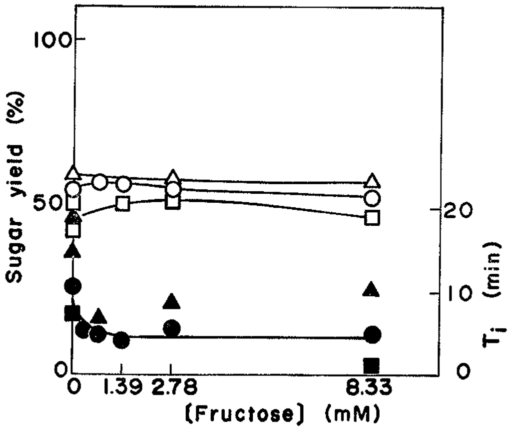

Fig. 6 Effect of fructose concentration on the sugar yield and T_i .
〔HCHO〕=1.0M, 〔$CaCl_2$〕= 0.05M, Solvent =Methanol, Temp.=60° C, Total volume =200ml.

pH*	T_i	Sugar yield
9.5	▲	△
10·0	●	○
10.5	■	□

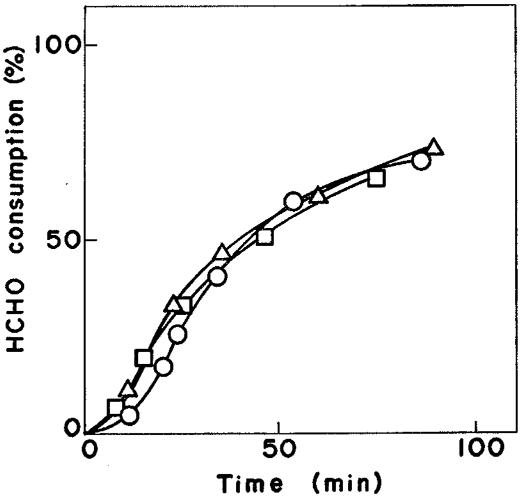

Fig. 7 Effect of fructose concentration on HCHO consumption.
〔HCHO〕=1.0M, 〔$CaCl_2$〕 = 0.05M, Solvent = Methanol, pH* = 10.0 (adjusted by KOH), Temp.=60° C,Total volume=200ml, 〔Fructose〕 : ○, 0M ; △, 2.78×10^{-3}M ; □, 8.33×10^{-3}M.

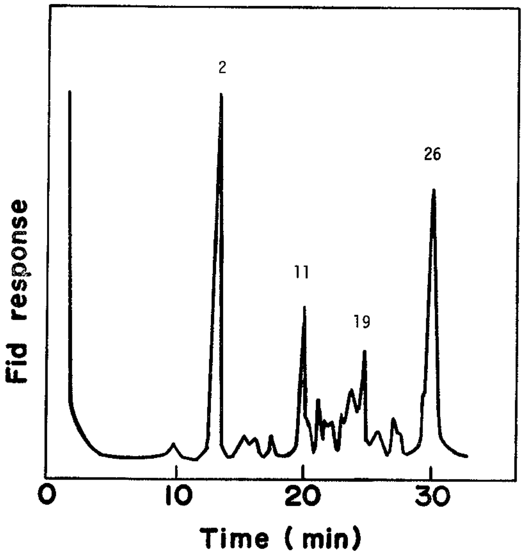

Fig. 8 Gas chromatogram of TMS derivatives.
〔HCHO〕=1.0M, 〔Fructose〕=1.39×10^{-2}M, Solvent= Methanol, pH* = 13.0 (adjusted by KOH),Temp.=60° C, Total volume = 200ml.

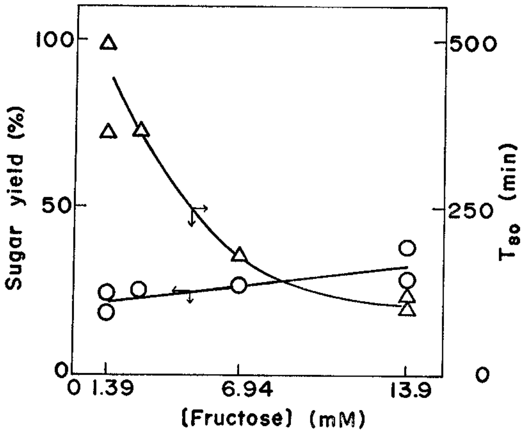

Fig. 9 Effect of fructose concentration on the sugar yield and T_{80}.
〔HCHO〕=1.0M, Solvent=Methanol, pH* =13.0 (adjusted by KOH), Temp.=60° C, Total volume=200ml.

As shown in Fig. 9, effects of the fructose concentration on T_{80} and the sugar yield are more clear compared to those in the presence of calcium ion ; T_{80} decreases and the sugar yield slightly increases with an increase in the fructose concentration. In these cases, however, the product distribution was not varied by the fructose concentration and the gas-chromatogram was similar to that shown in Fig. 8.

Effect of pH. Effects of the pH of the reaction mixture on the formose reaction were examined and the results are summarized in Table 1. With an increase in the pH, T_{80} decreases, the sugar yield slightly increases, peak 2 and 26 both decrease, but quite importantly peak 11 increases to 24.4 glc-%. In case of no addition of fructose, formaldehyde was scarcely consumed for 7 h even at pH* 13.0 and 13. 5. Here, the pH* is used for the apparent pH in methanol which was measured by electrodes adjusted with aqueous buffers.

Table 1 Effect of the pH of the reaction mixture[a)]

pH*	T_{80} (min)	Sugar yield (%)	Products (glc-%) 2-HG	11	3-HP	22	2,4-DHP
12.0	$(27)^{b)}_{350}$	9.8	—	—	—	—	—
12.5	194	27.1	19.9	13.7	c)	c)	23.7
13.0	119	27.5	20.8	9.3	9.5	1.6	18.1
13.5	73	38.5	9.8	24.4	11.1	6.5	8.3

a) [HCHO] = 1.0M, [Fructose] = 1.39×10^{-2} M, Solvent = Methanol, pH was adjusted by KOH, Temp. = 60°C, Total volume = 200ml.

b) The number in parentheses is the HCHO consumption (%) at the time (min) shown by the subscript.

c) Glc-% was below 1%.

As described above, furthermore, the sugar yield in methanol does not increase so remarkably as the reaction time, (T_{70} or T_{80}), becomes shorter, compared to the results[4)] obtained from the formose reaction which is carried out in an aqueous solution. These results suggest that the Cannizzaro reaction of formaldehyde scarcely proceeds in methanol.

The Formose Reaction with Various Cocatalysts. The actions of enediol compounds have been already reported[8)] : the addition of enediol compounds such as dioxyacetone, glucose, fructose, benzoin *etc.*, causes the induction period in the formose reaction to decrease. As shown in Table 2, glucose, xylose, and fructose give rise to similar T_{80}, sugar yield, and product distribution to each other ; in case of reductone, T_{80} is longer and peak 11 is formed as a main product ; in the presence of benzoin, the formose reaction cannot proceed, although benzoin was mentioned to be useful as cocatalyst.[8)] We have already reported that benzoin behaved as substrate in the formose reaction in an aqueous solution and gave rise to 1,2-diphenyl glycerol as a final product.[9)]

Table 2 Effect of various cocatalysts[a)]

Cocatalyst	T_{80} (min)	Sugar yield (%)	Products (glc-%)				
			2-HG	11	3-HP	22	2,4-DHP
Glucose	130	33.8	35.8	10.2	5.1	2.8	23.2
Xylose	118	31.7	22.1	15.5	1.3	4.0	26.5
Fructose	119	27.5	20.8	9.3	9.5	1.6	18.1
Benzoin	$(2)^{b)}_{183}$	—	—	—	—	—	—
Reductone	211	29.2	22.7	23.0	4.6	2.1	13.2

a) [HCHO] = 1.0M, [Cocatalyst] = 1.39×10^{-2} M, pH* = 13.0 (adjusted by KOH), Solvent = Methanol, Temp. = 60°C, Total volume = 200ml.

b) The number in parentheses is the HCHO consumption (%) at the time (min) shown by the subscript.

Table 3 Formose reactions catalyzed by various catalysts[a)]

Catalyst (M)	pH*	Fructose (mM)	T_{80} (min)	Sugar yield (%)	Products (glc-%)				
					2-HG	11	3-HP	23	2,4-DHP
—	13.0	13.9	120	27.5	20.8	9.3	9.5	c)	18.1
$CaCl_2$, 0.05	10.0	0	140	56.3	2.3	4.6	12.3	11.3	2.0
$Mg(OH)_2$, 0.3	13.0	13.9	131	28.9	31.1	16.9	3.4	1.4	20.9
Amberlite IR120(Ca), 0.15	11.0	0	310	40.7	2.8	10.2	14.4	5.3	3.2
$Ba(OH)_2$, 0.05	b)	0	13	62.3	c)	1.4	13.4	4.8	23.5
NaOH	13.0[d)]	13.9	20	52.0	4.1	23.5	5.7	4.1	21.3

a) [HCHO] = 1.0M, Solvent = Methanol, pH was adjusted by KOH, Temp. = 60°C, Total volume = 200ml.

b) pH was not controlled. c) Glc-% was below 1%.

d) pH was adjusted by NaOH.

Formose Reaction Catalyzed by Various Catalysts. As shown in Table 3, peak 11 which was not yet identified was found to be formed with high selectivity (23.5 glc-%) by sodium hydroxide. Furthermore, even at same pH* 13.0 the formose reaction catalyzed by sodium hydroxide gave higher sugar yield and shorter T_{80} than that by potassium hydroxide. Quite importantly, it was proved that barium hydroxide is an excellent catalyst for the formose reaction in methanol, because it does not need a cocatalyst ; T_{80} is short ; formose is produced in a good sugar yield. In addition, we have already reported that the formose reaction catalyzed by barium chloride-potassium hydroxide in methanol gives rise to 2,4-di-C-hydroxymethyl-3-pentulose with high selectivity.[3)]

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