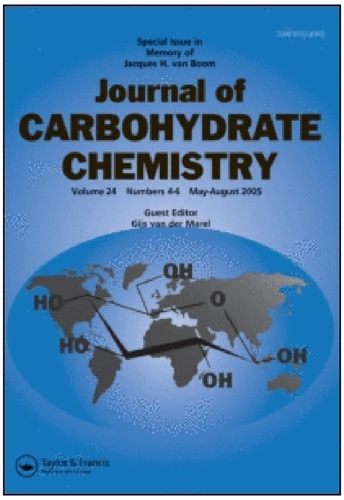

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FORMOSE REACTIONS. XXXII. SYNTHESIS OF DL-2-*C*-HYDROXYMETHYL-3-PENTULOSE FROM FORMALDEHYDE IN *N,N*-DIMETHYLFORMAMIDE-WATER MIXED SOLVENT (II)

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ABSTRACT

The carbon number of the main product and the total yield of products increased with an increase in the amount of triethylamine (TEA). Furthermore, the decrease of DL-2-*C*-hydroxymethyl-3-pentulose (2-H-3-P) was speeded up by increasing the TEA concentration and 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) increased smoothly along with the progress of the reaction. In the low formaldehyde (HCHO) concentration range (ca. 0.5 M), dihydroxyacetone (DHA) and DL-*glycero*-tetrulose were main products. 2-H-3-P and 2,4-BH-3-P increased with an increase in the formaldehyde concentration. Dihydroxyacetone, DL-*glycero*-tetrulose, 2-H-3-P and 2,4-BH-3-P were favorably obtained from a formose reaction by choosing a suitable [thiamine·HCl]/[HCHO] ratio. Under the reaction conditions reported in this paper, thiamine decomposed rapidly and lost its catalytic ability.

INTRODUCTION

In the preceding papers,[1-3] the formose reactions in *N,N*-dimethylformamide (DMF)-H_2O mixed solvent catalyzed by triethylamine (TEA) and thiamine HCl were found to give rise to DL-*glycero*-tetrulose or DL-2-hydroxymethyl-3-pentulose (2-H-3-P) favorably. They were isolated from the formose and their spectral data were discussed. At 1.0 M of formaldehyde concentration, the distribution of products could be controlled by changing the H_2O/DMF ratio of the solvent. Namely, 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) (30 %), 2-H-3-P (30 %), DL-*glycero*-tetrulose (25 %), and DHA (75 %) were favorably formed at an H_2O/DMF ratio of 50/50, 30/70, 13/87, and 0/100 mL/mL, respectively. Above 90/10 mL/mL of the H_2O/DMF ratio, 2,4-bis(hydroxymethyl)pentitol (2,4-BHP) was a main product, which was formed by cross-Cannizzaro reaction of 2,4-BH-3-P and formaldehyde. It was suggested that the addition reaction of formaldehyde to ketoses proceeded more smoothly in higher basicity of the reaction mixture.

In this paper, the authors wish to describe how the product distribution (especially DL-*glycero*-tetrulose and 2-H-3-P), the formaldehyde consumption, and the yield of organic acids are affected by the reaction conditions, such as the base concentration, the amount of thiamine·HCl, and the formaldehyde concentration. They were also investigated during the course of the formose reaction starting with various reaction conditions.

RESULTS AND DISCUSSION

Effect of Triethylamine Concentration. Reactions were carried out under various TEA concentrations keeping the H_2O/DMF ratio at 20/80 mL/mL and the total volume of the reaction mixture at 100 mL. The results are shown in Figs. 1 and 2. At 1/2 v/v of the H_2O/DMF ratio and below 50 mL of TEA, the reaction mixture was homogeneous and only about 40% of the formaldehyde was consumed.[4] In the reaction conditions studied here (Fig. 1), the reaction mixtures were homogeneous and the HCHO consumption reached to 60 % in 40 min regardless of the amount of TEA (15-100 mmol), after which formaldehyde was not consumed any more. It is estimated that under these reaction conditions thiamine·HCl would decompose rapidly and lose its catalytic ability.[5] The total yield (mg/mL) of products, which was measured by the internal standard [trimethylolethane, $CH_3C(CH_2OH)_3$] method as described in the preceding paper,[1] increased with an increase in the amount of TEA and above 30 mmol of TEA it was ca. 34 mg/mL. In the case of 1 M of HCHO (Fig. 3),

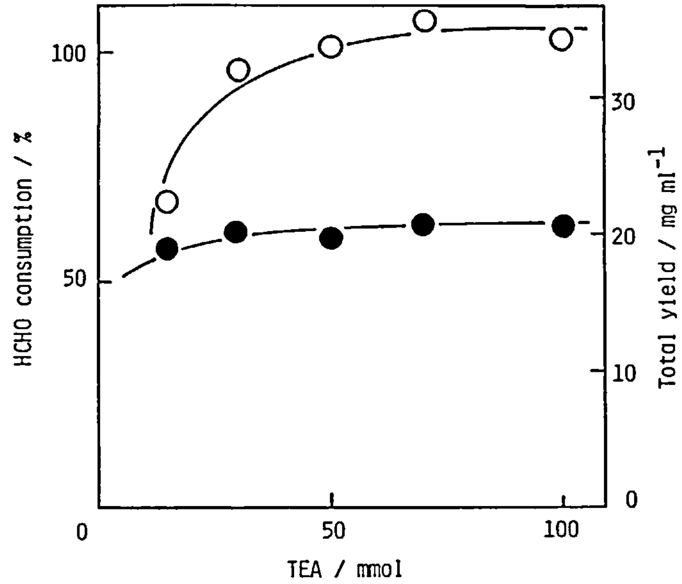


Fig. 1. Effect of the TEA concentration on the HCHO consumption and the total yield. HCHO=300 mmol; thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C; 180 min.
●, HCHO consumption; ○, total yield.

on the other hand, T_{90}, which was the reaction time when the formaldehyde consumption reached to 90 %, shortened with an increase in the amount of TEA and was ca. 40 min above 30 mmol of TEA. These total yields were ca. 16 mg/mL (Fig. 3). In this case, below 50 mmol of TEA, 2-H-3-P increased with increasing the amount of TEA, then 2-H-3-P became a main product (ca. 20 %) above 50 mmol of TEA.

As shown in Fig. 2, DL-*glycero*-tetrulose and 3-pentulose,[6] which would be a precursor of 2-H-3-P and DL-3-*C*-hydroxymethyl-2-pentulose[7] (3-H-2-P), decreased with an increase in the amount of TEA. The yield of 2-H-3-P was maximum (30 %) at ca. 25 mmol of TEA and above 50 mmol of TEA, 2,4-BH-3-P was a main product. From these results, it would be concluded that the addition reaction of formaldehyde to ketoses proceeded more smoothly in more basic reaction mixtures.

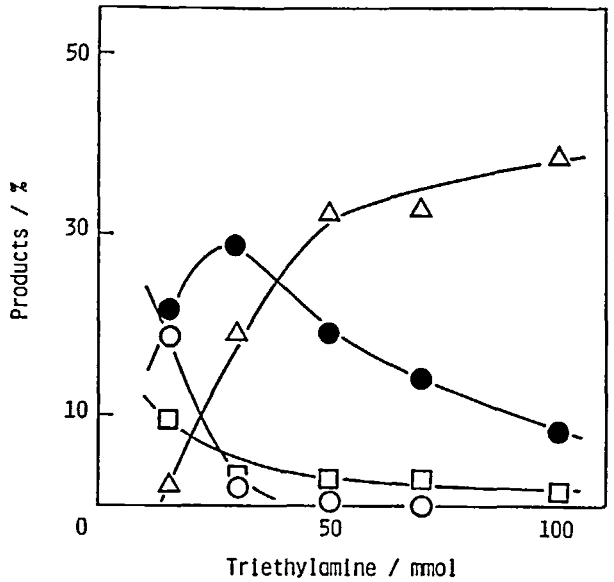


Fig. 2. Effect of the TEA concentration on the product distribution at the maximum total yield.
HCHO=300 mmol; thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C.
□, DL-*glycero*-Tetrulose; ○, 3-pentulose; ●, 2-H-3-P; △, 2,4-BH-3-P.

Time-courses of the yield of 2-H-3-P at various TEA concentrations in the solvent of H_2O/DMF=1/5 v/v were investigated under the same reaction conditions as those in Fig. 2 and the results are shown in Fig. 4. The reaction time, when the maximum yield of 2-H-3-P was obtained, shortened with an increase in the TEA concentration. The decrease of 2-H-3-P was accelerated by increasing the TEA concentration. 2,4-BH-3P, furthermore, increased smoothly as the reaction progressed and the increase in the amount of TEA made the formation rate of 2,4-BH-3-P faster. Hence, it could be concluded that the formation of 2-H-3-P and 2,4-BH-3-P, which were obtained from the successive addition of formaldehyde to DHA as shown in Scheme 1, was catalyzed by TEA.

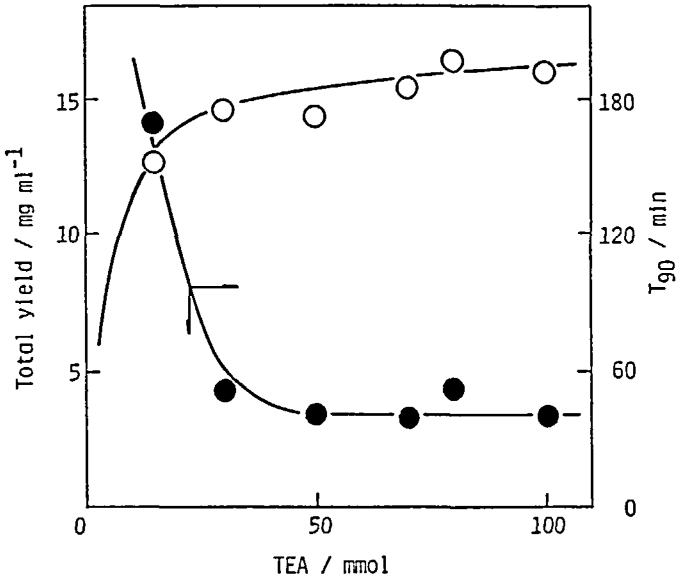


Fig. 3. Effect of the TEA concentration on T_{90} and the total yield. HCHO=100 mmol; thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C.
●, T_{90}; ○, total yield.

Fig. 5 shows time-courses of the yield of 2-H-3-P at various TEA concentrations in the solvent of H_2O/DMF=1/2 v/v. Above 180 mmol of TEA, 2-H-3-P decreased smoothly as the reaction progressed and 2,4-BH-3-P increased with decreasing the amount of 2-H-3-P. At 18 mmol of TEA, 2-H-3-P increased with increasing the reaction time. As described previously,[4] in a range of the TEA concentration from 360 to 1080 mmol, the distribution of 2,4-BH-3-P at 180 min of the reaction time, was constant (ca. 30-40 %), but the formaldehyde consumption and the yeild of 2,4-BH-3-P increased with an increase in the amount of TEA. Above 180 mmol of TEA, furthermore, the amount of formic acid formed was constant (ca. 2 mg/mL). These results would suggest that the addition reaction of formaldehyde is strongly affected by the basicity of the reaction mixture and demands a larger amount of TEA than the Cannizzaro reaction does.

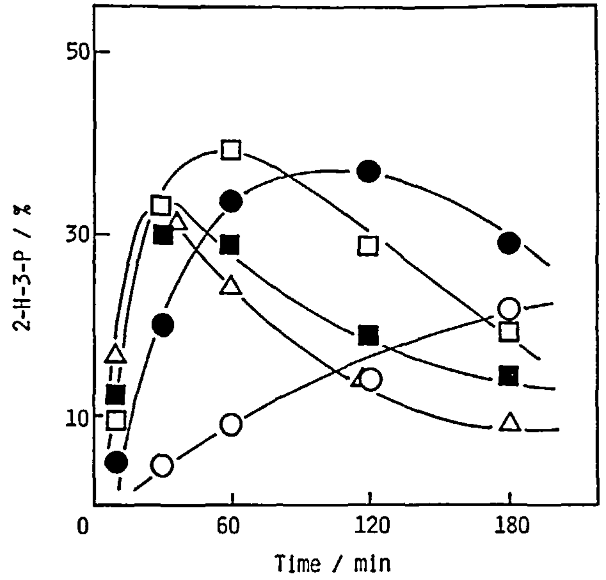


Fig. 4. Time-courses of the yield of 2-H-3-P at various TEA concentrations in DMF solvent containing 20 vol% water. HCHO=300 mmol; thiamine·HCl=5 mmol; total volume, 100 mL; 75 °C. TEA/mmol: ○ , 15; ● , 30; □ , 50; ■ , 70; △, 100.

Effect of Formaldehyde Concentration. Reactions were carried out under various HCHO concentrations keeping the H_2O/DMF ratio of the solvent at 20/80 mL/mL and the total volume of the reaction mixture at 100 mL. Fig. 6, in which the total yield is given by the summation of total products as measured by gas chromatography, shows the effect of the HCHO concentration on the distribution of products. In the low HCHO concentration range (ca. 50 mmol), dihydroxyacetone (DHA) and DL-*glycero*-tetrulose were main products. 2-H-3-P and 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) increased with an increase in the formaldehyde concentration. These results would suggest that 2-H-3-P and 2,4-BH-3-P were formed by the successive addition of formaldehyde to DHA (Scheme 1), as described in the preceding paper.[1]

Effects of the HCHO concentration on the formaldehyde consumption and the total yield are shown in Fig. 7. With an increase in the amount

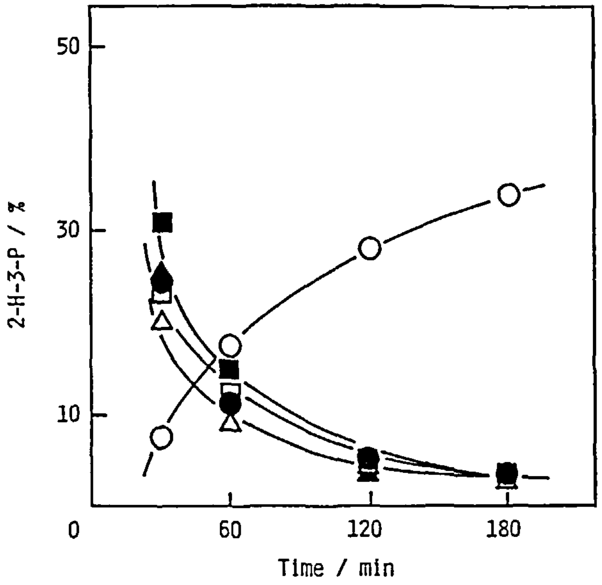
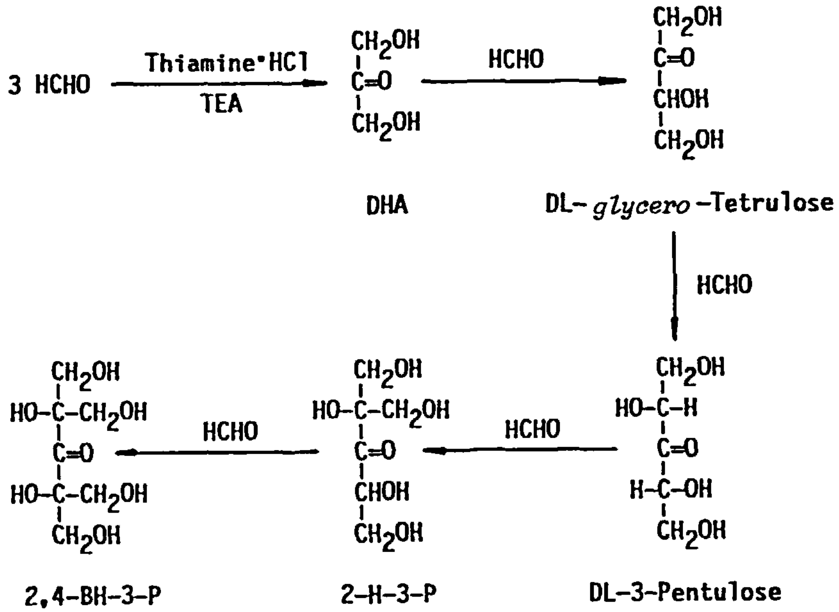


Fig. 5. Time-courses of the yield of 2-H-3-P at various TEA concentrations in DMF solvent containing 33 vol% water. HCHO=180 mmol; thiamine·HCl=5 mmol; total volume, 180 mL; 75 °C. TEA/mmol: ○, 18; ●, 180; △, 360; ▲, 650; □, 870; ■, 1080.



Scheme 1. A pathway for the formation of formose.

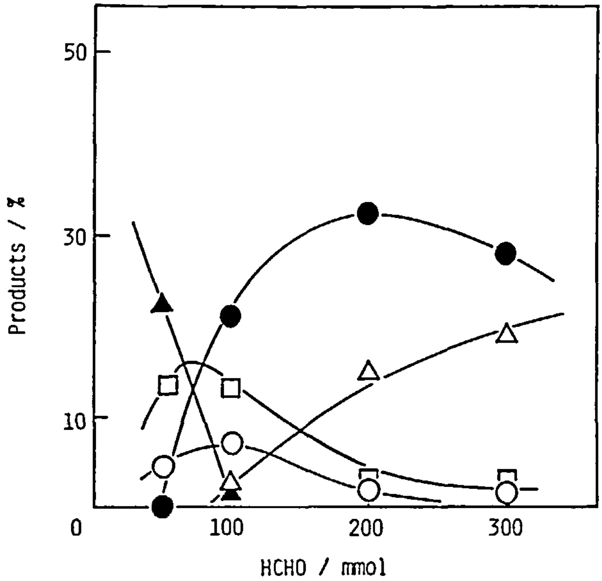


Fig. 6. Effect of the HCHO concentration on the distribution of products at the maximum total yield.
Thiamine·HCl=5 mmol; TEA=30 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75°C.
▲, DHA; □, DL-*glycero*-tetrulose; ○, 3-pentulose;
●, 2-H-3-P; △, 2,4-BH-3-P.

of formaldehyde added, the HCHO consumption (%) decreased, however the amount of consumed formaldehyde and the total yield increased.

Under the reaction conditions studied here, the reaction mixtures were homogeneous and the HCHO consumption reached a constant value (50-100 %) in 40-60 min regardless of the amount of HCHO (50-300 mmol). After that formaldehyde was not consumed any more, as previously reported.[4] It is concluded that under these reaction conditions thiamine·HCl would decompose rapidly and lose its catalytic ability, since the C-2 position of the thiazolium ring is substituted with a polyhydric alcohol group and thiazolium salt changes to thiazole.[5]

Effect of Thiamine·HCl Concentration. The formose was scarcely formed in DMF by inorganic bases such as $Ca(OH)_2$, $Ba(OH)_2$, etc.[10] The formose reaction in DMF was effectively catalyzed by thiazolium

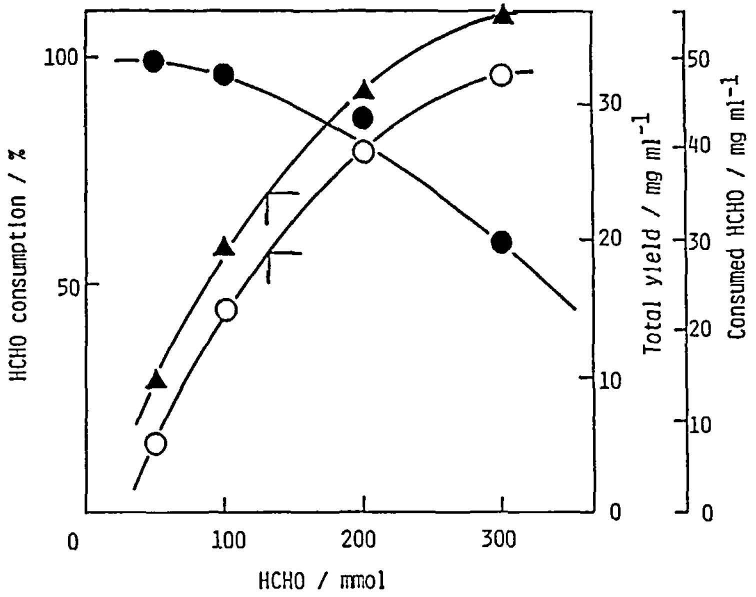


Fig. 7. Effect of the HCHO concentration on the HCHO consumption and the total yield.
Thiamine·HCl=5 mmol; TEA=30 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C; 180 min.
●, HCHO consumption; ○, total yield; ▲, HCHO consumed.

salts.[3,5,8-10] Figs. 8 and 9 show the effects of the thiamine·HCl concentration on the distribution of products at 100 and 300 mmol of formaldehyde, respectively. As shown in Fig. 8, products of lower carbon number, such as DHA, DL-*glycero*-tetrulose, and 3-pentulose increased with an increase in the thiamine·HCl concentration. On the other hand, 2-H-3-P showed the maximum percentage (35%) at ca. 3 mmol of thiamine·HCl and 2,4-BH-3-P decreased by increasing the thiamine·HCl concentration. Because the larger amount of thiamine·HCl caused relatively rapid consumption of formaldehyde to yield DHA as a main product, it appears that only a little amount of formaldehyde is necessary for increasing the carbon number of products. The selective formation of 2-H-3-P is strongly influenced by the rate of the addition reaction of formaldehyde to 2-H-3-P.

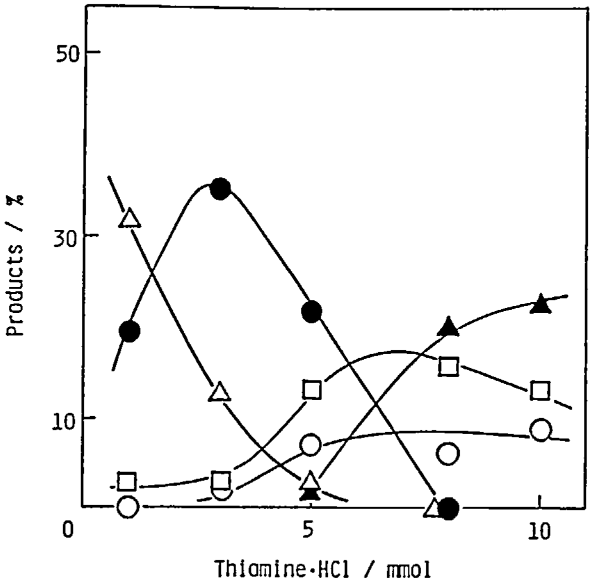


Fig. 8. Effect of the thiamine·HCl concentration on the distribution of products at the maximum total yield.
HCHO=100 mmol; TEA=30 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C.
▲, DHA; □, DL-*glycero*-tetrulose; ○, 3-pentulose;
●, 2-H-3-P; △, 2,4-BH-3-P.

With an increase in the thiamine·HCl concentration, formaldehyde was consumed more smoothly and T_{90} shortened. For example, at 3 mmol of thiamine·HCl the formaldehyde consumption of 120 min was 71% and at 5 mmol of thiamine·HCl T_{90} was 60 min. In these cases, regardless of the concentration of thiamine·HCl, formaldehyde was also smoothly consumed for the first 30 min and scarcely, or very slowly, after 60 min because of the rapid decomposition of thiamine·HCl, as described previously.[4] At 300 mmol (3 M) of formaldehyde (Fig. 9), 2-H-3-P formed favorably (ca. 30%) in a range of the amount of thiamine·HCl from 5 to 8 mmol and even at 10 mmol of thiamine·HCl, DHA, DL-*glycero*-tetrulose, and 3-pentulose were minor products. In particular the presence of DHA was negligible. As described above, 2,4-BH-3-P decreased with increasing the amount of thiamine·HCl and at 10 mmol of thiamine·HCl it was below

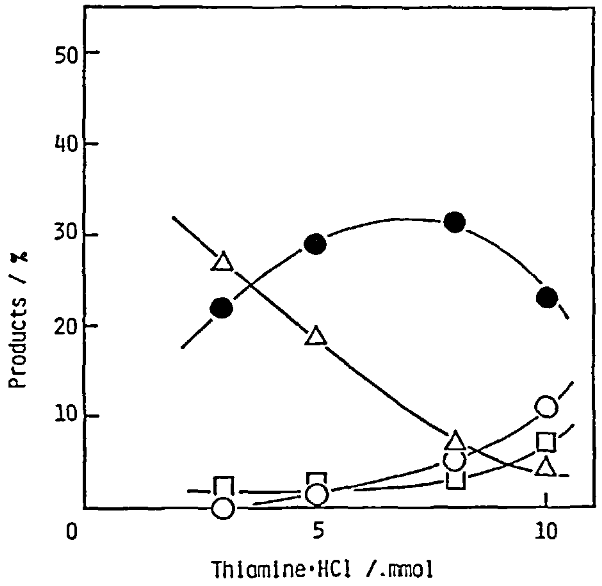


Fig. 9. Effect of the thiamine·HCl concentration on the distribution of products at the maximum total yield.
HCHO=300 mmol; TEA=30 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; 75 °C; 180 min.
□ , DL-*glycero*-Tetrulose; ○, 3-pentulose; ● , 2-H-3-P;
△ , 2,4-BH-3-P.

3%. In the case of 100 mmol of formaldehyde (Fig. 8), 2,4-BH-3-P formed below 3% at 5 mmol of thiamine·HCl. With an increase in the thiamine·HCl concentration, formaldehyde was consumed more smoothly and the formaldehyde consumption of 120 min at 8 mmol of the thiamine·HCl concentration was 83%.

These results indicate that the [thiamine]/[HCHO] ratio is an important factor affecting the formation of 2-H-3-P. With increasing the thiamine·HCl concentration, the formation rate of 2-H-3-P increases and most of formaldehyde is consumed because of an increase in the reaction rate of formaldehyde with the synthetic intermediates such as dihydroxyacetone (DHA), DL-*glycero*-tetrulose, and 3-pentulose. Consequently, 2,4-BH-3-P cannot form by the addition of formaldehyde to 2-H-3-P, owing to a deficiency of formaldehyde.

EXPERIMENTAL

General Procedures. The reaction and analyses were carried out in a similar manner as described in the preceding paper.[1] The amount of formic acid and organic acids in the formose mixture was determined by a Shimadzu Isotachophoresis. In this paper, we mainly investigated the formose reaction conditions in the solvent H_2O/DMF ratio of 20/80 mL/mL (DMF solvent containing 20 vol% water), because, at the ratio of 30/70 mL/mL, the HCHO consumption and the total yield were low (80 % and 15 mg/mL, respectively) in spite of the high percentage (30 %) of 2-H-3-P.[1]

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