JOURNAL OF CATALYSIS 69, 58–68 (1981)

# Formose Reactions

## XVI. Some Factors Affecting the Selective Formation of 2,4-Di-C-(hydroxymethyl)-3-pentulose[1]

YOSHIHIRO SHIGEMASA, SHIN-ICHI AKAGI, EIICHI WAKI, AND RUKA NAKASHIMA

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

Received September 30, 1980; revised November 21, 1980

The formose reaction catalyzed by $BaCl_2$–KOH in methanol was found to give 2,4-di-C-(hydroxymethyl)-3-pentulose (2,4-DH-3-P) with high selectivity. The yield of 2,4-DH-3-P increased with a decrease in the amount of barium ion, however, at less than 0.001 *M* of barium ion, the formose reaction was no longer allowed to proceed. The rate of the formaldehyde consumption decreased with a decrease in the pH of the reaction mixture. The yield of 2,4-DH-3-P was largely dependent on pH. 2,4-DH-3-P was obtained in higher yield by adjusting the initial pH* of the reaction mixture to 12.0–13.0 than that obtained by the continuous adjustment of the pH* to 13.0 during the reaction. The conversion rate of 2,4-DH-3-P into 2,4-di-C-(hydroxymethyl)-pentitol (2,4-DHP) was much slower in methanol than that in aqueous media and decreased with decreases in the pH of the reaction mixture and the formaldehyde concentration. A conventional mechanism for the formation of this branched ketose (2,4-DH-3-P) was suggested, which involved a cumulative aldol condensation of formaldehyde.

## INTRODUCTION

In the presence of base, aqueous formaldehyde forms a complex mixture of sugars and sugar alcohols. This formose reaction has long been of interest in connection with the microbial utilization (*2–4*) of formose and the prebiotic synthesis of carbohydrates (*5*). Formose, however, has not yet been useful, because of the complexity of the reaction mechanism and the product. For the utilization of formose, it is necessary to produce a desired sugar in high yield and, therefore, improvement of selectivity in the formose reaction is very important. To the best of our knowledge at the present stage, there have been a few reports (*1, 5–13*) concerning the selectivity in the formose reaction, but it has been very rare that products are isolated from the reaction mixture in spite of numerous attempts.

We have thus attempted to investigate selective syntheses in the formose reaction (*1, 6–10*) and succeeded in separating the products from reaction mixtures: 2-C-(hydroxymethyl)glycerol (2-HG), 3-C-(hydroxymethyl)pentitol (3-HP), 2,4-di-C-(hydroxymethyl)pentitol (2,4-DHP), 2,4-di-C-(hydroxymethyl)-3-pentulose (2,4-DH-3-P), pentaerythritol (PE), and 3-C-(hydroxymethyl)pentofuranose (3-HPF).

On the other hand, the Cannizzaro reaction (*14–16*) and the cross-Cannizzaro reaction (*17*) of formaldehyde easily proceed in aqueous medium simultaneously and competitively with the formose reaction to produce methanol and higher polyols as well as formate. Hence, the Cannizzaro reaction decreases the yield of formose formed by the condensation of formaldehyde. Our studies on the formose reaction (*18, 19*) have shown that the reaction in nonaqueous solvents, methanol especially, depresses the Cannizzaro reaction and raises the yield of sugars.

The formose reaction catalyzed by bar-

---

[1] Part XV: Yoshihiro Shigemasa, Toshio Hamada, Mikio Hirabayashi, Eiichi Waki, Ruka Nakashima, Ken-ichi Harada, Naohito Takeda, and Makoto Suzuki, manuscript in preparation.

0021-9517/81/050058-11$02.00/0

ium chloride–potassium hydroxide in methanol, furthermore, has been found to give 2,4-DH-3-P with high selectivity (*10*). The selective formation of 2,4-DH-3-P in the formose reaction is of important significance. In this investigation, we dealt with the various factors affecting the formation of 2,4-DH-3-P. Particular attention is placed on the following factors: the formaldehyde concentration, the barium concentration, the pH of the reaction mixture, and the solvent effect. We, furthermore, attempted to elucidate a mechanism concerning the selective formose reaction and to search for the selective formation of other products as well.

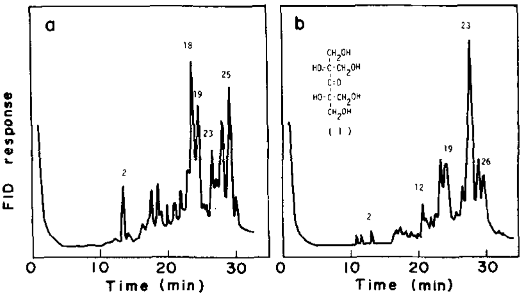


FIG. 1. The gas chromatograms of TMS derivatives of the products obtained from (a) a conventional calcium oxide-catalyzed formose reaction in methanol starting from [HCHO] = 1.0 *M* and [CaO] = 0.15 *M* at 60°C, and (b) the selective formose reaction in methanol starting from [HCHO] = 2.5 *M* and [$BaCl_2$] = 0.01 *M* at 60°C and by adjusting the apparent pH of the mixture to 12.0 from start to finish.

## EXPERIMENTAL

*General.* The apparatus and materials were virtually the same as those described previously (*10, 18*). The oxidation–reduction potential (ORP), pH, the formaldehyde consumption, and the sugar yield were measured by the methods described in the previous papers (*19–21*). The apparent pH (pH*) in methanol was measured by electrodes adjusted with aqueous buffers. Aliquots taken from the reaction mixture at convenient intervals were instantly cooled in an acetone-bath (−60°C) to ca. 0°C to stop the reaction and were then immediately analyzed. The product distribution was investigated by gas–liquid chromatography of trimethylsilylated (TMS) derivatives of products (*22*). glc analysis was virtually the same as described previously (*8, 9*). Typical gas chromatograms of TMS derivatives obtained from the calcium oxide-catalyzed formose reaction starting from [HCHO] = 1.0 *M* and [CaO] = 0.15 *M* in methanol at 60°C (Fig. 1a) and the selective formose reaction starting from [HCHO] = 2.5 *M* and [$BaCl_2$] = 0.01 *M* in methanol by adjusting the pH* of the reaction mixture to 12.0 (Fig. 1b), are shown in Fig. 1.

Melting points were obtained by packing capillaries and were uncorrected. The IR and CIMS were recorded with a Hitachi EPI-G2 grating spectrometer and Shimadzu LKB 9000A mass spectrometer, respectively. $^1H$ and $^{13}C$ NMR spectra were taken on a Varian T-60A and JEOL FX-100 spectrometer, respectively, and chemical shifts were given by ppm from TMS as an internal or external standard.

*Procedure.* In a typical experiment, the reaction was conducted with 2.5 *M* methanolic formaldehyde in the presence of barium chloride (0.01 *M*) at 60°C under nitrogen, with immediate adjustment of the pH of the mixture to pH* 12.0 with potassium hydroxide pellets. After 20–25 min, the reaction mixture was immediately cooled in acetone bath (−60°C) to ca. 0°C, at which temperature the reaction is essentially arrested. After 70% completion of the reaction (20–25 min), the yield of sugar (ca. 50% as glucose based on phenol-sulfuric acid method (*23*)) reached a constant value, although the formaldehyde was further consumed. The glc pattern shown in Fig. 1b indicated the selective formation of a product (**I**) corresponding to the peak number 23 (33 glc%).

Figure 2 shows a typical time-course of the formose reaction catalyzed by barium chloride–potassium hydroxide in methanol with respect to the formaldehyde consump-

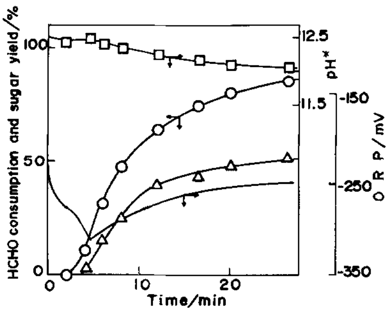


FIG. 2. Typical potentiometric and products analyses of the formose reaction in methanol. [HCHO] = 2.0 *M*; [$BaCl_2$] = 0.01 *M*; [KOH] = 0.22 *M*; temperature, 60°C; total volume, 200 ml; under $N_2$. ○, HCHO consumption; △, sugar yield; □, pH* (apparent pH in methanol); ——, ORP.

tion, the sugar yield, the oxidation–reduction potential (ORP), and the pH* (apparent pH in methanol) of the reaction mixture. As shown in this figure, minimum ORP is able to be observed resulting in distinguishing between the induction period and the sugar-formation step. In aqueous solution, maximum ORP and the yellowing point are observable at the end of the formose-forming step where the sugar yield becomes maximum (*20*, *24*), whereas, in the formose reaction catalyzed by barium chloride–potassium hydroxide in methanol, the yellowing point does not correspond to the end of this step and any convenient method, e.g., maximum ORP, to determine the progress of the reaction could not be found. In this report, the reaction time ($T_{70}$) at which the formaldehyde consumption in ca. 70% and after which formaldehyde is consumed slowly and the sugar yield reaches a constant value, is employed as an indication of reactivity.

*Separation and identification of the product* (**I**). The reaction mixture (200 ml) was repeatedly treated with 200 ml of IR-120($H^+$) and IR-45($OH^-$) until a neutral solution was obtained. The neutral solution was concentrated *in vacuo* at 40°C to a pale yellow syrup (9.1 g). The obtained syrup was chromatographed on a cellulose powder (whatman CF-11) column (115 × 2.4 cm) with wet 1-butanol as eluent. The product (**I**) corresponding to glc peak 23 was obtained as a colorless syrup (purity, over 97 glc%; yield, 12.3 wt%). The $^{13}C$ NMR chemical shifts (ppm from external tetramethylsilane), multiplicities (based on an off-resonance spectrum), and relative integrated intensities (determined by using NOE-suppressed and gated-decoupling technique) (in $D_2O$) are 65.3(t, 4), 86.7(s, 2), and 215.7(s, 1). These data suggest that the product (**I**) has four equivalent $CH_2$ groups, two equivalent tertiary alcohol carbon atoms, and a carbonyl carbon atom. ir (KBr): 3400–3300, 2940, 2870, 1710–1700, 1465, 1400, and 1160–1000 $cm^{-1}$. The intense absorption band at 1710–1700 $cm^{-1}$ was assigned to carbonyl stretching vibration. The chemical ionization mass spectrum (CIMS(isobutane)) showed *m*/*z* 211 (quasi-molecular ion, (M + $C_4H_{10}$); intensity, 20), 193(100), 175(30), and 163(45). The $^1H$ NMR spectrum ($D_2O$; internal standard, sodium 4,4-dimethyl-4-silapentane-1-sulfonate) of (**I**) showed geminal, nonequivalent $CH_2$ protons at δ 3.71(4H, d, $J_{HH}$ = 12 Hz) and 4.01(4H, d, $J_{HH}$ = 12 Hz).

These results led us to assign the structure constitution 2,4-di-C-(hydroxymethyl)-3-pentulose (**I**) for the product of glc peak 23. This structure is also supported by the results from derivatives of product (**I**) as described later.

*Derivatives of product* (**I**). Trimethylsilylation (*22*): The colorless syrup (**I**) (10–15 mg) carefully dryed up *in vacuo* at room temperature was dissolved into 1 ml of anhydrous pyridine (kept over NaOH pellets) and allowed to stand for 30 min, followed by addition of 0.2 ml of hexamethyldisilazane (HMDS) and 0.1 ml of trimethylchlorosilane (TMS). Immediately the mixture was shaken vigorously for about 30 sec and then allowed to stand for 90–100 min at room temperature. The reaction mixture was diluted with chloroform (6 ml) and washed with three or four 5-ml portions of water. The chloroform layer from which water was removed physically was concentrated *in vacuo*, giving ca. 30 mg of trimethylsilyl derivatives as a syrup.

ir (KBr): 2950, 2870, 1710–1700, 1250, 1150–1080, 900–820, and 750 cm$^{-1}$. The intense absorption band at 1700 cm$^{-1}$ was also assigned to carbonyl group stretching vibration. $^1$H NMR ($CDCl_3$): 0–0.13 ($-Si(CH_3)_3$, 54H, *m*), 3.7–3.8 ($-CH_2-$, 8H, *m*).

Acetylation (*25*): The product (**I**) (100–200 mg) was treated with 1 ml of dry pyridine (kept over NaOH pellets) and 1 ml of acetic anhydride for 4–5 days at room temperature or at 2–3°C. Then the mixture was poured into ca. 100 ml of precooled water and extracted with five 40-ml portions of chloroform. The chloroform layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*, giving 180–350 mg of a white residue. Recrystallization from hot chloroform gave 100–200 mg of white crystals: yield, 56.6%; mp, 104–105°C; ir (KBr): 3500–3400, 1730–1710, 1370, 1240–1220, and 1050 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 2.18(15H, s), 3.80(1H, s, D exchangeable), 4.35(4H, s), 4.70(4H, s); $^{13}$C NMR ($CDCl_3$): 20.07(q, $-CH_3$), 61.69, 66.03(t, $-CH_2-$), 81.18, 84.40(s, $-\overset{|}{\underset{|}{C}}-$), 169.68, 170.48(s, $-CO-CH_3$), and 201.96(s, $>C{=}O$); CIMS($NH_3$): *m/z* 438 (($M + NH_4^+$), 100); CIMS($ND_3$), *m/z* 443 (($M + d_1 + ND_4^+$), 100).

The ir spectrum showed that some of hydroxyl groups would not be acetylated (3500–3400 cm$^{-1}$). The $^1$H NMR spectrum of the acetate in chloroform-d also shows a hydroxyl group of which proton is exchangeable with deuterium. In the CI($ND_3$) mass spectrum of the acetate, an ammonium adduct ion ($M + NH_4^+$) observed at *m/z* 438 in CI($NH_3$) mass spectrum is shifted to *m/z* 443. This latter ion corresponds to ($d_1M + ND_4^+$), which shows the presence of one active hydrogen in the molecule. These results led us to conclude that this acetate is pentaacetate and its molecular weight is 420. This molecular weight supports that the molecular weight of (**I**) is 210.

Deacetylation with barium methoxide in methanol: The acetate of the product (**I**) (20–100 mg) was dissolved in 2–4 ml of dry methanol and ca. 0.25 *N* barium methoxide solution (50 ml of dry methanol containing 2.0 g of barium metal refluxed for 6 hr and then diluted with methanol) was added to the acetate solution until acetates completely disappeared on tlc (developing solvent: benzene : chloroform : methanol = 3 : 3 : 2). The reaction mixture was then filtered through a sintered glass disk. The filtrate was concentrated to one-tenth of its original volume. The concentrate was put on the top of Sephadex LH-20 columns (1.6 × 16 cm) and eluated with methanol (100 ml). The eluate was concentrated to a syrup (20–40 mg) under reduced pressure, which gave same spectra of ir (KBr), $^1$H NMR ($D_2O$), and $^{13}$C($D_2O$), and CIMS ($NH_3$) : *m/z* 228(($M + NH_4^+$), 35), 210(100) as those of the product (**I**).

Reduction of product (**I**) (*24*): The product (**I**) (50 mg) was dissolved in 0.5 ml of water and treated with 1 ml of 0.22 *M* sodium borohydride for 1 hr at room temperature. After the sodium ion was removed by stirring with a slight excess of Amberlite IR-120B($H^+$), the filtrate was concentrated *in vacuo* in dryness by the repeated addition and concentration of methanol in order to remove the boric acid as its volatile methyl ester. The residue was dissolved in methanol (1 ml) and diluted with acetone (ca. 0.5 ml) to separate 2,4-di-*C*-(hydroxymethyl)pentitol as white crystals (yield, 70%: mp, 117°C) which were identical with an authentic sample (*7, 9*) (ir, mp, and the retention time in gas–liquid chromatography). These results also led us to assign the structure constitution 2,4-di-*C*-(hydroxymethyl)-3-pentulose (**I**), for the product of glc peak 23.

## RESULTS AND DISCUSSION

### *Effects of Barium Hydroxide Concentration*

In a series of our studies (*10, 18, 19*) on the formose reaction in methanol, many

TABLE 1

Effect of $Ba(OH)_2 \cdot 8H_2O$ Concentration[a]

| [HCHO] (*M*) | $[Ba(OH)_2 \cdot 8H_2O]$ (mol/liter) | pH* | | $T_{80}$ (min) | Sugar yield (%) | Products (glc%)[c] | | |
|---|---|---|---|---|---|---|---|---|
| | | $T_s$ | $T_{80}$ | | | 18 | 3-HP | 2,4-DH-3-P |
| 2.0 | 0.01 | 11.6 | 10.4 | $(40)_{18}$[b] | 23.5 | 10.3 | 10.3 | 15.8 |
| 2.0 | 0.06 | 12.2 | 11.1 | 9 | 55.1 | 13.9 | 8.0 | 16.5 |
| 2.0 | 0.1 | 12.2 | 11.0 | 3 | 60.3 | 21.4 | 5.5 | 9.5 |
| 2.0 | 0.2 | 12.1 | 11.5 | 1 | 67.4 | 22.7 | 7.0 | 12.6 |
| 2.0 | 0.3 | 12.2 | 11.8 | 1 | 54.6 | 22.7 | 6.3 | 8.0 |
| 2.5 | 0.01 | 11.4 | 9.5 | $(37)_{56}$[b] | 23.5 | 6.7 | 14.8 | 18.3 |
| 2.5 | 0.03 | 12.2 | 10.1 | 27 | 48.5 | 6.2 | 11.0 | 17.5 |
| 2.5 | 0.06 | 12.3 | 10.9 | 9 | 49.1 | 14.8 | 8.6 | 14.6 |
| 4.1 | 0.03 | 11.8 | 10.1 | $(60)_{22}$[b] | 46.2 | 5.1 | 15.6 | 22.4 |
| 4.4 | 0.06 | 11.9 | 10.4 | 12 | 60.7 | 11.0 | 10.1 | 17.9 |
| 4.0 | 0.3 | 12.1 | 11.0 | 1 | 59.4 | 20.3 | 4.9 | 16.1 |

[a] Solvent, $CH_3OH$; total volume, 200 ml; temp., 60°C; under $N_2$.

[b] Parentheses and subscripts stand for the HCHO consumption (%) and the reaction time (min), respectively.

[c] 3-HP, 3-C-(hydroxymethyl)pentitol; 2,4-DH-3-P, 2,4-di-C-(hydroxymethyl)-3-pentulose.

bases have been investigated to find out the effective catalyst for this reaction. Among them, the formose reaction catalyzed by barium hydroxide was found to proceed more rapidly than other examined catalysts and to give a significant product distribution at which glc peak 23 (2,4-DH-3-P) was formed with high yield.

At first the effects of barium hydroxide concentration in the formose reaction were examined and the results are summarized in Table 1. At any formaldehyde concentrations, with an increase in the barium hydroxide concentration, the yield of 2,4-DH-3-P decreases, glc peak 18 increases, and $T_{80}$ (the time at which the formaldehyde consumption is 80%) is shortened, although the sugar yield is little affected by the concentration of barium hydroxide.

### *Effects of Addition of Potassium Chloride*

As reported previously (*10*), the formose reaction catalyzed by $BaCl_2$–KOH by controlling the pH of the reaction mixture by potassium hydroxide pellets was found to give 2,4-DH-3-P with higher selectivity (ca. 30 glc%) than those in Table 1. In order to examine the effect of potassium ion, the formose reaction was carried out in the presence of barium hydroxide by varying the amount of potassium chloride. As Table 2 shows, the addition of potassium chloride would raise the yield of 2,4-DH-3-P a little.

### *Effect of pH Adjuster*

The formose reaction with continuous adjustment of the pH* of the reaction mixture to 12.0 with sodium hydroxide pellets proceeded more rapidly with less yield of 2,4-DH-3-P than the reaction with continuous pH adjustment with potassium hydroxide (Table 3). These results would be contributable to the large amount of sodium hydroxide compared to the amount of potassium hydroxide for maintaining the pH* of the reaction mixture to 12.0. When both concentration of sodium hydroxide and potassium hydroxide were equimolar, the reaction time ($T_{70}$), the sugar yield, and the product distribution were quite similar to each other, though the pH of the mixture with the adjustment by potassium hydroxide pellets was higher than that by sodium hydroxide pellets (Table 3). Both time-courses of the product, the sugar yield, the formaldehyde consumption, and the pH of the reaction mixture in the formose reactions catalyzed by $BaCl_2$–KOH and $BaCl_2$–

TABLE 2

Effect of KCl Addition[a]

| $[Ba(OH)_2 \cdot 8H_2O]$ (mol/liter) | [KCl] (*M*) | pH* |  | $T_{80}$ (min) | Sugar yield (%) | Products (glc%) |  |  |
|---|---|---|---|---|---|---|---|---|
|  |  | $T_s$ | $T_{80}$ |  |  | 18 | 3-HP | 2,4-DH-3-P |
| 0.03 | 0 | 12.2 | 10.1 | 27 | 48.5 | 6.2 | 11.0 | 17.5 |
| 0.03 | 0.005 | 11.9 | 10.6 | 20 | 42.7 | 9.7 | 9.9 | 20.7 |
| 0.03 | 0.01 | 11.9 | 10.7 | 18 | 44.3 | 12.9 | 8.5 | 20.4 |
| 0.03 | 0.05 | 11.9 | 10.5 | 22 | 44.0 | 11.2 | 10.3 | 22.0 |
| 0.03 | 0.2 | 11.9 | 10.3 | 19 | 55.3 | 13.2 | 9.4 | 23.4 |

[a] [HCHO] = 2.5 *M*; solvent, $CH_3OH$; pH, not adjusted; temp., 60°C.

NaOH ([Base] = 0.2 *M*) show no significant difference (Fig. 2). Furthermore, the formose reaction catalyzed by $BaCl_2$–KOH (or NaOH) (Table 3) was found to give 2,4-DH-3-P with high selectivity than the reaction catalyzed by $Ba(OH)_2 \cdot 8H_2O$–KCl (Table 2). In this case, however, there were a little difference, that is, the pH of the reaction mixture of the former was higher (pH* changed 12.3 to 12.0) than the latter (pH* changed 11.9 to 10.3) or the former pH* was adjusted to 12.0 during the reaction.

### *Effect of the Amount of $BaCl_2$*

Table 4 shows the effect of the barium chloride amount on the formose reaction which was carried out at [HCHO] = 2 *M* in methanol with the continuous adjustment of the pH of the reaction mixture to pH* 12.0 by potassium hydroxide pellets during the reaction. The reaction time ($T_{70}$) was decreased with an increase in the barium concentration. The sugar yield was almost independent of the amount of barium chloride over 0.007 *M*. The yield of 2,4-DH-3-P increases with a decrease in the amount of barium chloride and is above 35 glc% at $[BaCl_2]$ = 0.01 *M*. At less than 0.001 *M* of barium chloride, however, the formose reaction itself was no longer allowed to proceed. Although the formose reaction catalyzed by barium chloride–potassium hydroxide gives the selective formation of 2,4-DH-3-P, the high concentration of barium chloride is not suitable for the high selective formation of 2,4-DH-3-P. On the other hand, increasing amount of barium chloride tends to increase the formation of

TABLE 3

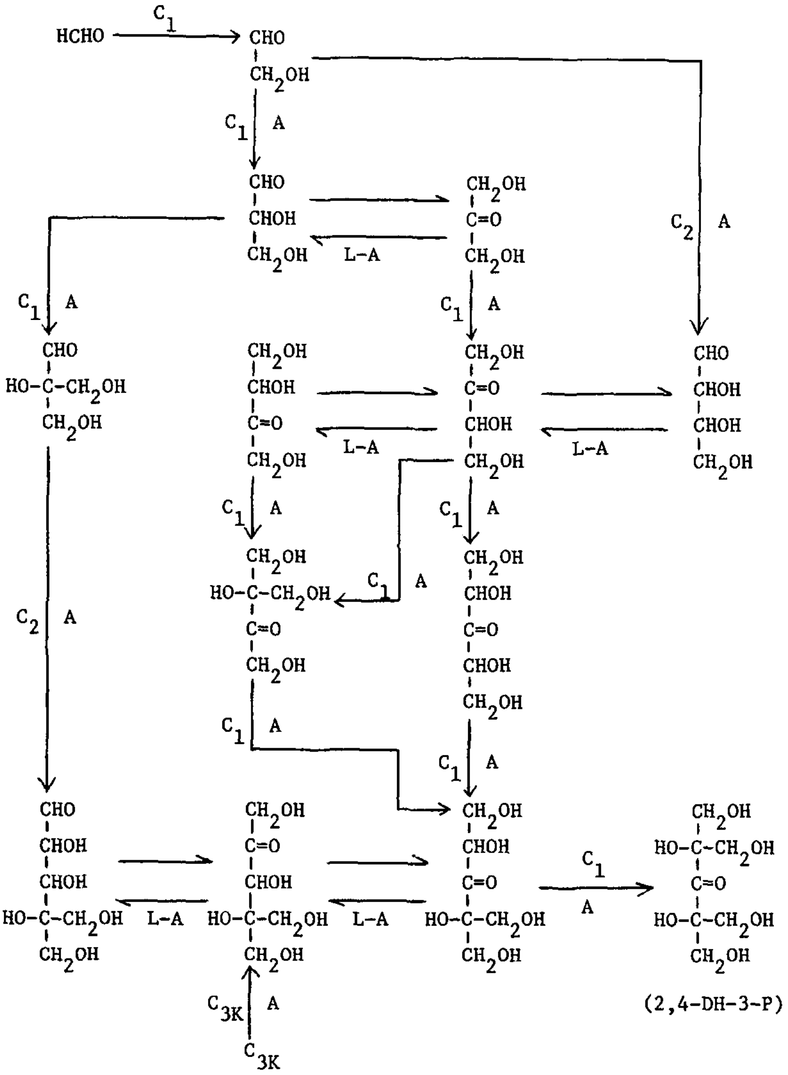
Effect of Means of pH Adjustment[a]

| Base (*M*) | $T_{70}$ (min) | Sugar yield (%) | Products (glc%)[c] |  |  |  |
|---|---|---|---|---|---|---|
|  |  |  | 18 | 3-HP | 2,4-DH-3-P | 2,4-DHP |
| KOH |  |  |  |  |  |  |
| 0.2 | 16 | 50.0 | 7.9 | 8.5 | 33.0 | 3.7 |
| KOH[b] | 24 | 42.9 | 7.2 | 7.8 | 34.7 | 6.9 |
| NaOH |  |  |  |  |  |  |
| 0.2 | 15 | 50.0 | 9.9 | 6.3 | 33.7 | 5.3 |
| NaOH[b] | 13 | 47.0 | 11.4 | 7.2 | 20.1 | 4.4 |

[a] [HCHO] = 2.0 *M*; $[BaCl_2]$ = 0.01 *M*; solvent, $CH_3OH$; total volume, 200 ml; temp., 60°C.

[b] The pH of the reaction mixture was adjusted to pH*, 12.0, during the reaction by KOH or NaOH pellets.

[c] 2,4-DHP, 2,4-di-C-(hydroxymethyl)pentitol.



$C_1$: HCHO; $C_2$: Glycolaldehyde; $C_{3K}$: Dihydroxyacetone;

A : Aldol Condensation; L-A: Lobry de Bruyn-Alberda von Eckenstein rearrangement.

SCHEME 1. Possible pathways for 2,4-di-C-(hydroxymethyl)-3-pentulose.

the product of glc peak 18. Efforts are under way to identify the product of glc peak 18. It might be guessed that peak 18 would be one of intermediates of 2,4-DH-3-P (Scheme 1). Furthermore, in spite of this high pH* of 12.0 and the low concentration of barium ion, the formation of 2-HG and 2,4-DHP was small (below 5%), although in aqueous medium they were found to form with high selectivity (*6, 7, 9*). $T_{70}$, the sugar yield, and the product distribution, were little affected by using $Ba(OH)_2 \cdot 8H_2O$ instead of $BaCl_2$. It would be estimated that 2,4-DH-3-P might be formed with high selectivity in the presence of barium and potassium ions by maintaining the pH of the reaction mixture above certain value (pH* 12.0).

TABLE 4

Effect of $BaCl_2$ Concentration[a]

| $[BaCl_2]$ (*M*) | $T_{70}$ (min) | Sugar yield (%) | Products (glc%) | | |
|---|---|---|---|---|---|
| | | | 18 | 3-HP | 2,4-DH-3-P |
| 0.003 | $(10)_{210}$[b] | 6.2 | — | — | — |
| 0.005 | $(51)_{35}$[b] | 31.9 | 6.0 | 7.6 | 37.7 |
| 0.007 | 39 | 55.9 | 7.3 | 7.7 | 35.0 |
| 0.007[c] | 31 | 48.0 | 7.4 | 7.9 | 39.7 |
| 0.01 | 24 | 42.9 | 7.2 | 7.8 | 34.7 |
| 0.01[c] | 23 | 46.9 | 7.9 | 10.1 | 30.9 |
| 0.03 | 12 | 53.0 | 11.2 | 10.0 | 22.0 |
| 0.05 | 12 | 50.5 | 14.9 | 7.4 | 25.0 |
| 0.1 | 6 | 50.3 | 15.3 | 7.3 | 20.7 |
| 0.2 | 7 | 50.0 | 17.1 | 6.2 | 20.8 |

[a] [HCHO] = 2.0 *M*, pH* 12.0 (adjusted by KOH pellets); solvent, $CH_3OH$; total volume, 200 ml; temp., 60°C.

[b] Parentheses and subscript stand for the HCHO consumption (%) and the reaction time (min), respectively.

[c] $Ba(OH)_2 \cdot 8H_2O$ was used instead of $BaCl_2$.

### *Effect of pH*

Table 5 shows the effects of the concentration of potassium hydroxide on the formose reaction, in which the reaction was carried out by the addition of the prescribed amount of potassium hydroxide pellets to the reaction mixture and measuring the pH* of the mixture during the reaction. With an increase in the concentration of potassium hydroxide, 2,4-DH-3-P and 2,4-DHP increase, $T_{70}$ decreases, and the sugar yield becomes constant above 0.2 *M* of potassium hydroxide. Using sodium hydroxide instead of potassium hydroxide, the results were in fair agreement with those in Table 5, although the pH of the reaction mixture was lower than that of potassium hydroxide as described above. In order to examine the effect of pH on the formose reaction, the reaction was conducted with immediate adjustment of the pH of the mixture to a prescribed pH with potassium hydroxide solution and/or pellets during the reaction.

As shown in Table 6, the rate of the formaldehyde consumption decreased with a decrease in the pH of the reaction mixture and at pH*s of 11.0 and 10.5, the formaldehyde consumptions of 60 min and 105 min of the reaction time were 53 and 49%, respectively. The yield of 2,4-DH-3-P was largely dependent on pH. In the pH* range 10.5–13.0, the formation of 2,4-DH-3-P increased with increasing pH. However, in the case of [KOH] = 0.7 *M* (higher than pH* of 13.0), the yield of 2,4-DH-3-P (33.8 glc%) was lower than that (46.0 glc%) at [KOH] = 0.5 *M*. On the other hand, the yield of 2,4-DH-3-P, obtained from the formose reaction starting with the initial adjustment of the pH of the reaction mixture to pH* 12.8–13.0, is higher than that obtained from the reaction of the continuous adjustment to pH* 13.0 (Tables 5 and 6). These results suggest that higher pH (pH* 13.0) of the reaction mixture would cause the rapid degradation of 2,4-DH-3-P and its conversion into other products.

In order to study the selective formation

TABLE 5

Effect on KOH Concentration[a]

| [KOH] (*M*) | pH* | | $T_{70}$ (min) | Sugar yield (%) | Products (glc%) | | | |
|---|---|---|---|---|---|---|---|---|
| | $T_s$ | $T_{70}$ | | | 18 | 3-HP | 2,4-DH-3-P | 2,4-DHP |
| 0.05 | 11.8 | 11.4 | $(55)_{25}$[b] | 29.8 | 8.5 | 9.0 | 20.5 | 2.2 |
| 0.1 | 12.1 | 11.6 | 22 | 39.5 | 7.2 | 8.5 | 24.2 | 3.9 |
| 0.2 | 12.4 | 11.9 | 16 | 52.7 | 7.9 | 8.5 | 30.7 | 3.7 |
| 0.5 | 12.8 | 12.6 | 14 | 45.0 | 6.1 | 7.2 | 46.0 | 10.2 |
| 0.53 | 13.0 | 12.9 | 13 | 48.0 | 5.6 | 6.6 | 44.5 | 9.9 |
| 0.7 | 13.1 | 13.2 | 5.5 | 47.0 | 8.0 | 7.1 | 33.8 | 6.4 |

[a] [HCHO] = 2.0 *M*; $[BaCl_2]$ = 0.01 *M*; solvent, $CH_3OH$; total volume, 200 ml; temp., 60°C.

[b] Parentheses and subscript stand for the HCHO consumption (%) and the reaction time (min), respectively.

TABLE 6

Effect of pH[a]

| pH* | $T_{70}$ (min) | Sugar yield (%) | Products (glc%) | | | |
|---|---|---|---|---|---|---|
| | | | 18 | 3-HP | 2,4-DH-3-P | 2,4-DHP |
| 10.5 | $(48.5)_{105}$[b] | 29.8 | 9.1 | 10.3 | 26.3 | 4.6 |
| 11.0 | $(53.0)_{60}$[b] | 32.1 | 12.3 | 9.6 | 23.1 | 3.0 |
| 12.0 | 24 | 42.9 | 7.2 | 7.8 | 34.7 | 4.0 |
| 13.0 | 10 | 53.1 | 6.4 | 6.2 | 35.8 | 13.3 |

[a] [HCHO] = 2.0 *M*; [$BaCl_2$] = 0.01 *M*; solvent, $CH_3OH$; total volume, 200 ml; temp., 60°C; the pH of the reaction mixture was adjusted by KOH pellets.

[b] Parentheses and subscripts stand for the HCHO consumption (%) and the reaction time (min), respectively.

of 2,4-DH-3-P, the reaction of 2,4-DH-3-P with formaldehyde under various conditions was carried out at 60°C for 1 hr. The results are summarized in Table 7 in which $pH_s$ and $pH_{60}$ stand for the pH of the reaction mixture at the reaction time of initial and 60 min, respectively. When the reactions of 2,4-DH-3-P with formaldehyde were carried out at $pH_s$ of 12.0 and 13.0 in methanol, the recoveries of 2,4-DH-3-P were 95.7 and 22.0%, respectively. This results suggest that 2,4-DH-3-P would be stable at pH* 12.0 in methanol, whereas, at pH* 13.0, it would be liable to degradate. The conversion of 2,4-DH-3-P into 2,4-DHP, furthermore, would tend to occur with an increase in the pH of the reaction mixture (Tables 5, 6, and 7). On the other hand, in aqueous media 2,4-DH-3-P was more easily converted into 2,4-DHP than in methanol (Table 7). In addition, the reduction of 2,4-DH-3-P with sodium borohydride was found to give 2,4-DHP in good yield (70%) as noted previously (*10*). These results led us to assume the reduction of 2,4-DH-3-P with formaldehyde in the presence of base would proceed more rapidly in aqueous media than in methanol. From the above results, it would also be supposed that, above pH* 13.0, the reduction of 2,4-DH-3-P to 2,4-DHP and the degradation of 2,4-DH-3-P might easily proceed, although 2,4-DH-3-P might form more selectively and rapidly at pH* 13.0 than at lower pH*.

TABLE 7

Reaction of 2,4-Di-C-(hydroxymethyl)-3-pentulose with Formaldehyde[a]

| 2,4-DH-3-P[b] (mg) | HCHO (mg) | pH | | Solvent | Products (glc%)[c] | | | |
|---|---|---|---|---|---|---|---|---|
| | | $pH_s$ | $pH_{60}$ | | 2-HG | 2,4-DH-3-P | 2,4-DHP | Others |
| 9 | 3 | 12.0 | 7.2 | $CH_3OH$ | 2.7 | 75.8 | — | 21.5 |
| 9 | 3 | 13.0 | 12.8 | $CH_3OH$ | 6.2 | 17.4 | 5.9 | 70.5 |
| 9 | 12 | 13.0 | 12.8 | $CH_3OH$ | 6.5 | 31.4 | 11.3 | 50.8 |
| 42 | 89 | 13.0 | 11.5 | $CH_3OH$ | 5.7 | 41.5 | 25.7 | 27.1 |
| 9 | 3 | 12.0 | 8.5 | $H_2O$ | 5.5 | 38.3 | 17.1 | 39.1 |
| 12 | 16 | 12.0 | 6.8 | $H_2O$ | 2.8 | 35.6 | 36.7 | 24.9 |
| 17 | 24 | 12.0 | 12.0 | $H_2O$ | 6.2 | 18.7 | 50.2 | 24.9 |

[a] Solvent, 1 ml; temp., 60°C; reaction time, 60 min; the pH of the reaction mixture was adjusted by KOH solution.

[b] 79.2 glc%.

[c] 2-HG, 2-G-(hydroxymethyl)glycerol.

*Effect of Formaldehyde Concentration*

The reaction was carried out in the formaldehyde concentration, 0.25 to 4 $M$, at the barium chloride concentration of 0.01 $M$. At the formaldehyde concentration, 1.0–2.0 $M$, the reaction time ($T_{70}$) was minimum (24–25 min) and the sugar yield was maximum (48–50%) (Table 8). These features are similar to those obtained in the formose reaction catalyzed by calcium oxide in methanol (*18*). In the low formaldehyde concentration of 0.25–0.5 $M$, the product of glc peak 18 was formed above 20 glc%, however, the yield of 2,4-DH-3-P increased with increasing formaldehyde concentration. At the formaldehyde concentration of 2.5 $M$, the yield of 2,4-DH-3-P was ca. 36 glc%, whereas, at the formaldehyde concentration of 4 $M$, it became lower (20 glc%) and 2,4-DHP, instead of 2,4-DH-3-P, formed in good yield, 28 glc%. As described previously, the yield of 2,4-DH-3-P decreased with an increase in the barium chloride concentration. The results led us to speculate that the ratio, [HCHO]/[Ba], would be an important factor affecting the formation of 2,4-DH-3-P, as the selective formation of 2-HG, 3-Hp, and 2,4-DHP observed in the formose reaction catalyzed by calcium chloride–potassium hydroxide in aqueous solution (*27*).

## SUMMARY

From these observations, one can draw the following conclusions. The selective formation of 2,4-di-C-(hydroxymethyl)-3-pentulose (2,3-DH-3-P) increases with an increase of the condensation rate of formaldehyde to 2,4-DH-3-P, and with decreases of the conversion rate of 2,4-DH-3-P into 2,4-DHP and the degradation rate. First, the condensation rate of formaldehyde to 2,4-DH-3-P increases with increasing pH of the reaction mixture and formaldehyde concentration and with decreasing barium concentration. Second, the conversion rate of 2,4-DH-3-P into 2,4-DHP is much slower in methanol than that in aqueous media and decreases with decreases in the pH of the reaction mixture and the formaldehyde concentration. Third, the degradation rate would decrease with increasing formaldehyde concentration and decreasing pH of the reaction mixture.

For example, suitable reaction conditions for the formation of 2,4-DH-3-P are as follows: The formose reaction in methanol, starting with [HCHO] = 2.5 $M$, [BaCl$_2$] = 0.01 $M$, temperature = 60°C, and pH* 13.0 (the pH of the reaction mixture is adjusted by KOH pellets and not controlled during the reaction), gives 2,4-DH-3-P in 20.4 wt% yield.

Formation of this branched ketose (2,4-DH-3-P) may be rationalized by a conventional mechanism involving cumulative aldol condensation of formaldehyde as shown in Scheme 1. The selective forma-

TABLE 8

Effect of HCHO Concentration[a]

| [HCHO] ($M$) | $T_{70}$ (min) | Sugar yield (%) | $d$[HCHO]/$dt$ ($M$/min) | Products (glc%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 2-HG | 18 | 3-HP | 2,4-DH-3-P | 2,4-DHP |
| 0.1 | $(0)_{310}$ | — | — | — | — | — | — | — |
| 0.25 | 53 | 44.6 | $1.16 \times 10^{-2}$ | — | 20.4 | 5.7 | 8.7 | 2.2 |
| 0.5 | 49 | 46.7 | $1.66 \times 10^{-2}$ | — | 22.3 | 7.5 | 12.3 | 1.7 |
| 1.0 | 25 | 47.4 | $1.04 \times 10^{-1}$ | 0.7 | 7.0 | 6.0 | 18.6 | 7.3 |
| 2.0 | 24 | 42.9 | $1.00 \times 10^{-1}$ | 1.5 | 7.2 | 7.8 | 34.7 | 6.9 |
| 2.5 | 30 | 45.1 | $1.00 \times 10^{-1}$ | 2.1 | 5.7 | 9.2 | 36.3 | 6.7 |
| 4.0 | 33 | 37.0 | $0.71 \times 10^{-1}$ | 10.1 | 1.3 | 9.0 | 20.0 | 28.1 |

[a] [BaCl$_2$] = 0.01 $M$; pH* 12.0 (adjusted by KOH); solvent, CH$_3$OH; total volume, 200 ml; temp., 60°C.

tion of 2,4-DH-3-P would mainly contribute to the inhibition of the reduction of 2,4-DH-3-P with formaldehyde to 2,4-DHP by using methanol as solvent, although the reaction was carried out at high pH (pH* 12.0) of the reaction mixture.

## REFERENCES

1. Shigesmasa, Y., Hamada, T., Hirabayashi, M., Waki, E., Nakashima, R., Harada, K., Takeda, N., and Suzuki, M., manuscript in preparation.
2. Mizuno, T., Kawai, K., Muramatsu, K., and Banba, K., *Nippon Nogei Kagaku Kaishi* **46,** 73 (1972).
3. Mizuno, T., *Kagaku no Ryoiki* **26,** 58 (1973).
4. Weiss, A. H., Krylov, O. V., Sakharov, M. M., and Ghorochovatskii, V. B., *J. Food Process Preserv.* **2,** 63 (1978).
5. Gable, N. W., and Ponnamperuma, *Nature* **216,** 453 (1967).
6. Shigemasa, Y., Sakazawa, C., Nakashima, R., and Matsuura, T., *Origin of Life* 211 (1978).
7. Shigemasa, Y., Nagae, O., Nakashima, R., Sakazawa, C., and Matsuura, T., *J. Amer. Chem. Soc.* **100,** 1309 (1978).
8. Shigemasa, Y., Matsuda, Y., Sakazawa, C., and Matsuura, T., *Bull. Chem. Soc. Japan* **50,** 222 (1977).
9. Shigemasa, Y., Kawahara, M., Sakazawa, C., Nakashima, R., and Matsuura, T., *J. Catal.* **62,** 107 (1980).
10. Shigemasa, Y., Akagi, S., Nakashima, R., and Saito, S., *Carbohyd. Res.* **80,** Cl (1980).
11. Weiss, A. H., Translated from *Kinet. Katal.* **18,** 539 (1977).
12. Likholobov, V. A., Weiss, A. H., and Sakharov, M. M., *React. Kinet. Catal. Lett.* **8,** 155 (1978).
13. Matsumoto, T., Komiyama, M., and Inoue, S., *Chem. Lett.* 1980, 839.
14. Pfeil, E., and Schroth, G., *Chem. Ber.* **85,** 293 (1952).
15. Pfeil, E., and Ruckert, H., *Justus Liebigs Ann. Chem.* **641,** 121 (1961).
16. Mayer, R., and Juschke, L., *Justus Liebigs Ann. Chem.* **635,** 145 (1960).
17. Tambawala, H., and Weiss, A. H ., *J. Catal.* **26,** 388 (1972).
18. Shigemasa, Y., Matsuda, Y., Sakazawa, C., Nakashima, R., and Matsuura, T., *Bull. Chem. Soc. Japan* **52,** 1091 (1979).
19. Shigemasa, Y., Taji, T., Sakazawa, C., Nakashima, R., and Matsuura, T., *J. Catal.* **58,** 296 (1979).
20. Shigemasa, Y., Fujitani, T., Sakazawa, C., and Matsuura, T., *Bull. Chem. Soc. Japan* **50,** 1527 (1977).
21. Shigemasa, Y., Shimao, M., Sakazawa, C., and Matsuura, T., *Bull. Chem. Soc. Japan* **50,** 2138 (1977).
22. Sweely, C. C., Bentley, R., Makita, M., and Wells, W. W., *J. Amer. Chem. Soc.* **85,** 2497 (1963).
23. Dubois, M., Gilles, K. A., Hamilton, J. K., Rebers, P. A., and Smith, F., *Anal. Chem.* **28,** 350 (1956).
24. Shigemasa, Y., Shimao, M., Sakazawa, C., and Matsuura, T., *Bull. Chem. Soc. Japan* **48,** 2099 (1975).
25. Behrend, R., and Roth, P., *Ann.* **331,** 359 (1904); Hudoson, C. S., and Dale, J. K., *J. Amer. Chem. Soc.* **37,** 1264 (1915).
26. Whistler, R. L., and Wolfrom, M. L., *Methods Carbohyd. Chem.* **II,** 65 (1963).
27. Shigemasa, Y., Taji, T., Waki, E., and Nakashima, R., *Bull. Chem. Soc. Japan,* in press.