Formose Reactions. XII. Formose Reaction in the Presence of Benzoin

by

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Effects of various co-catalysts on the formose reaction and its product distribution were studied. Benzoin was found to give a simple gas chromatogram of trimethyl silylated (TMS) derivatives of products. The main product was separated and assigned to 1,2-diphenyl glycerol. The scheme of the formation of 1,2 diphenyl glycerol in the formose reaction in the presence of benzoin was also proposed.

1. Introduction

Formose is composed of over thirty products which are obtained by condensation of formaldehyde in the presence of a base. As monosaccharides are obtained in a high yield by this simple procedure, formose has been noted as a solution for the food problem in the future, furthermore, the reaction has drawn the interest of researchers who think that it may provide an explanation for the primordial origin of monosaccharides.

Since Butlerow[1] found the reaction in 1861 and the product mixture, $C_6H_{12}O_6$, was termed formose by Loew,[2] many investigations have been carried out. However, formose has not yet been utilized in spite of such efforts. The important factors involved in solving the problem are the selectivity of products and the isolation of the desired product.

Recently, we[3,4] have reported that 2-C-hydroxymethyl glycerin, 3-C-hydroxymethyl pentitol, and 2,4-C-dihydroxymethyl pentitol could be synthesized selectively by using the ORP method,[5,6] which is very effective in finding out the formose reaction step.

It is already known that the formose reaction consists of three steps, namely, the induction period, the sugar-formation step, and the sugar-decomposition period, and the induction period is shortened by the addition of enediol compounds, such as glyceraldehyde, glucose, acetoin etc.[7]

However, there are few papers which have described the effect of enediol comp-

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ound on the products distribution. In this paper, we wish to report about the product of the formose reaction, which is carried out in the presence of enediol compounds, especially, benzoin and acetoin.

2. Experimental

Materials. A formaldehyde solution was prepared as follows : 200g 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 in a dark place, and was used for experiments within a few days, in order that no substances accelerating the formose reaction could be produced.

Phenacyl alcohol was prepared by refluxing 4 g of phenacyl bromide and 4 g of $BaCO_3$ in 50 ml of distilled water and recrystalization from ethanol.[8] Reductone was prepared from glucose according to the general procedure.[9] Chromotropic acid used for the determination of formaldehyde was of an extra pure reagent. Monosaccharides, ascorbic acid, benzoin, acetoin, and other reagents were of an analytical grade.

Procedure. The apparatus and the experimental procedures were virtually the same as those described previously.[6] The reaction mixture was kept to pH 12.0 during the reaction by adding a saturated KOH solution. The formaldehyde consumption, the sugar yield, and the oxidation-reduction potential (ORP) of the reaction mixture were measured by the methods described in the previous papers.[6]

The preparation of trimethyl silylated (TMS) derivatives of products and its gas chromatography were carried out in the same manner as described previously.[10]

Quantitative estimation of products was made by measuring the areas under the peaks given by the separated components[11] and using pentaerythritol as an internal standard. This measurement could be accomplished by tracing the peaks onto paper of uniform density from which they were cut and weighed.

Separation and Identification of Products. Formaldehyde (5.7g), benzoin (2.12 g), and $CaCl_2$ (0.11 g) in 200 ml of water were added to the reactor and the formose reaction was started by adjusting immediately the pH of the reaction mixture to 12.0 with an aqueous KOH at 60°C. Then, at the yellowing point, the reaction was stopped by slightly acidifying the reaction mixture with 9N-HCl. The GLC pattern of Fig. 1 thus obtained indicates a very selective formation of products corresponding to peaks 22 and 23 (above 90%). At first, unreacted benzoin (0.08 g), which was suspended in the reaction mixture, was recovered by filtering in a sintered glass disk. The aqueous mixture was extracted with fifteen 50 ml portions of benzene. The eluate was dried with anhydrous sodium sulfate and concentrated in

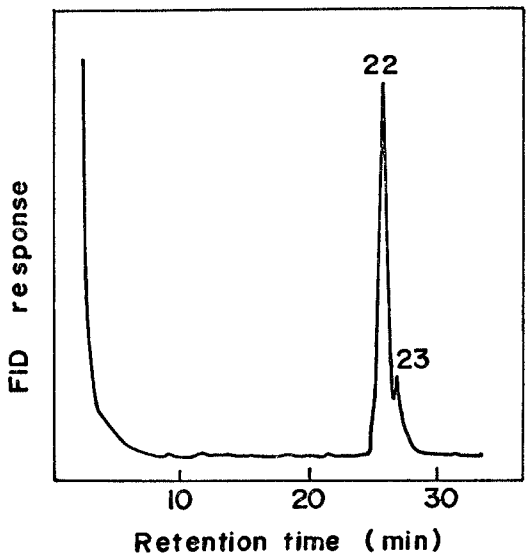
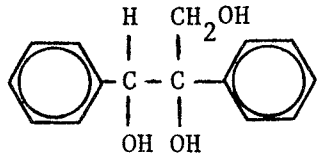


Fig. 1. Gas chromatogram of TMS derivatives of products.

[HCHO] = 1.0 M, [$CaCl_2$] = 0.005 M, [Benzoin] = 0.01 M, pH = 12.0 (adjusted by KOH), temp. = 60°C, total volume = 200 ml.

vacuo to give 1.95 g of a product corresponding to peaks 22 and 23 as a yellow sirup (83.1% based on the starting benzoin). 0.86 g of the yellow sirup could be purified by distillation (4mm-Hg, 200°C) using a "Kugelrohr" distillation oven, and amounted to 0.84 g.

IR (KBr) : 3400 (OH stretch), 3050 (CH stretch ; aromatics), 2890 (CH stretch ; branched hydrocarbons), 2000-1667, 1600, 1480, 1060, and 710 cm^{-1} ; NMR δ ($CDCl_3$) : 7.12 (10H, m), 4.68 (1H, s, CH), 3.91 (1H, d, geminal nonequivalent a, b type CH_2), and 3.52 (1H, d, geminal nonequivalent a,b type CH_2), J_{HH} =18 Hz, $J/_{\Delta\nu}$ = 0.5 ; MS : acetate derivative (yellow syrup), m/e (relative intensity), 311 ($M-CH_3COO$, 3), 180 (84), and 138 (100) ; UV : λ_{max}, 214 nm (solvent, MeOH).



(1)

Structure (1) [1,2-diphenyl glycerol] was assigned for the product of peaks 22 and 23, based on the above data. Furthermore, this product was identical with an authentic sample by the comparison of the NMR and IR spectra.

Synthesis of 1, 2-diphenyl glycerol. 1,2-Diphenyl glycerol was synthesized in order to ascertain that 1,2-diphenyl glycerol corresponded with a product of GLC peaks 22 and 23 in the formose reaction.

5.82 g of benzoin, 2.7 ml of 37% aqueous formaldehyde, and 10.5 ml of triethyl amine were refluxed in 7.6 ml of ethanol for 3 h, diluted with water (50 ml), and then extracted with four 50 ml portions of benzene.[12] The benzene extract was dried (Na_2SO_4), and concentrated in vacuo, giving a white residue, Recrystallization from ethanol gave 6.57 g of α-methylol benzoin, white crystal : yield, 98.9% mp, 85°C ; IR (KBr) : 3500, 3360, 3050, 2890, 1660, 1600, 1480, 1070 and 710 cm^{-1} ; NMR δ ($CDCl_3$) : 7.3 (10H, m), 4.46 (1H, d, J_{HH} = 18 Hz, $J/_{\Delta\nu}$= 0.2, geminal nonequivalent

a, b type CH_2), 3.40 (1H, d, J_{HH} = 18 Hz, J/Δ_ν = 0.2, geminal nonequivalent a, b type CH_2), 4.00 (1H, br. s, OH, disappeared by D_2O), 3.30 (1H, s, OH, disappeared by D_2O).

1.82 g of α-methylol benzoin and 0.85 g of $NaBH_4$ was allowed to stand for 8 h in 30 ml of ethanol at room temperature, then diluted with water (100 ml). The reaction mixture was passed through the 40 ml cation exchange resin Amberlite IR 120 (H) column and extracted with twelve 50 ml portions of benzene. The benzene extract was dried with anhydrous sodium sulfate and concentrated in vacuo, giving 1.2 g of a yellow syrup, 1,2-diphenyl glycerol : yield, 61.4% ; IR, NMR, and the retention time of 1,2-diphenyl glycerol TMS derivatives agreed those of the product of the formose reaction corresponding to the GLC peaks of 22 and 23.

IR and NMR spectra of commercial benzoin are as follows. IR (KBr) : 3400, 3050, 2930, 1660, 1600, 1480, 1070, and 710 cm^{-1} ; NMR δ ($CDCl_3$) : 7.18 (10H, s) and 6.10 (1H, s, CH).

Quantitative analysis of benzoin, α-methylol benzoin, and 1,2-diphenyl glycerol.

An aliquot of the reaction mixture which contained about 100 mg of benzoin, α-methylol benzoin, and 1,2-diphenyl glycerol was neutralized with 9N HCl, extracted with five 10 ml portions of $CHCl_3$, and concentrated in vacuo to a pale yellow sirup. ^{1}H NMR spectrum of the sirup was taken on a Varian T-60A spectrometer. The relative amounts of these three compounds were calculated by measuring the peaks of 5.90, 4.46d, and 3.91d ppm corresponding to benzoin, α-methylol benzoin, and 1,2-diphenyl glycerol, respectively. Table 1 shows the results in which these authentic samples were determined by this method. On the other hand, the GLC

Table 1. Quantitative analysis of products by NMR

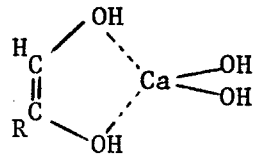
Benzoin (mg)	α-methylol benzoin (mg)	1,2-diphenyl glycerol (mg)	Integral ratio in ^{1}H NMR[a)]		
			Benzoin	α-methylol benzoin	1,2-diphenyl g ycerol
—	15	30	—	16	28
—	25	25	—	17	15
—	30	15	—	17	8
25	—	25	28	—	21

a) Integrating the peaks of 5.90, 4,46d, and 3.91d ppm corresponding to benzoin, α-methylol benzoin, and 1,2-diphenyl glycerol, respectively.

analysis using pentaerythritol as an internal standard gave only qualitative data, but it could not be applied to these compounds quantitatively (Table 3).

3. Results and Discussion

Effect of Various Cocatalysts on the Product Distribution. It is reported that cocatalysts which have an enediol structure, such as fructose, glucose, and xylose, shorten the induction period in the formose reaction.[7] Fujino *et al*[13] proposed that the complex (2) of enediol compound and alkaline earth metal is effective on the formose reaction and the catalytic activity of the complex (2) depends upon the kind of alkaline earth metal or of enediol compound.



(2)

However, no relationship between the cocatalyst and the product distribution has been discussed. Table 2 shows the effects of various cocatalysts on the product

Table 2. Effects of cocatalysts[a]

Cocatalyst	T_{max} (min)	Sugar yield (%)	Products (glc-%) 2	13	14	18	19	22	23	26
Fructose	27.0	32.5	10	2	b)	2	23	b)	2	31
Ascorbic acid	53.0	25.0	10	2	2	2	28	b)	2	39
Glucose	25.0	31.0	8	2	2	2	23	2	4	27
Xylose	31.5	36.0	10	b)	b)	b)	21	2	2	40
Phenacyl alcohol	23.5	37.0	4	b)	b)	5	23	2	6	39
Triose reductone	32.0	29.0	10	2	b)	2	23	2	3	31
Acetoin	192	7.0	2	10	37	9	3	2	5	8
Benzoin	143	10.0	b)	b)	b)	b)	b)	50	36	b)

a) Reaction conditions : [HCHO] = 1.0M, [$CaCl_2$] = 0.005 M, [Cocatalyst] = 0.01 M, pH = 12.0 (adjusted by KOH), Temp. = 60°C, Total volume=200 ml.
b) Glc-% was below 1%.

distribution. The addition of monosaccharides, triose reductone, ascorbic acid, and phenacyl alcohol was found to give a selective formose reaction which is similar to those described in a previous paper[3),4)] and of which the main products are 2-C-hydroxymethyl glycerol, 3-C-hydroxymethyl pentitol corresponding to the GLC peaks of 2, 19, and 26, respectively.

The addition of benzoin, however, resulted in a different selective reaction giving the peaks of 22 and 23 (about 90 glc-%). In the case of acetoin, a GlC peak of 14 was a main procuct and amounted to 36 glc-%. Benzoin and acetoin are supposed

to have different effects on the formose reaction compared with monosaccharides. On the other hand, in the absence of cocatalysts no formose reaction could proceed under the reaction conditions described in Table 2.

The Formose Reaction in the Presence of Benzoin. It is worth noting that the addition of benzoin resulted in a selective formation of products corresponding to the GLC peaks of 22 and 23. The effects of the concentration of benzoin was investigated (Table 3). The results qualitatively show that increasing the concentration of benzoin tended to increase the GLC peaks of 22 and 23. The products corresponding to the GLC peaks of 22 and 23 were extracted with benzene, purified by distillation, and identified as 1,2-diphenyl glycerol. Perhaps, they might be diastereomers of 1,2-diphenyl glycerol.

Table 3. Effects of the benzoin concentration[a)]

[HCHO] (M)	[Benzoin] (M)	T_{max} (min)	Sugar yield (%)	Products[b)] (glc-%) 22	23
1.0	0.01	94.0	11.0	61(3.6)	28(1.6)
1.0	0.05	84.0	13.0	78(9.7)	15(1.9)
1.0	0.1	82.0	15.0	80(16.2)	11(2.2)

2) Reaction conditions : [$CaCl_2$] = 0.005M, pH = 12.0 (adjusted by KOH), Temp. = 60°C, Total volume = 200 ml.

b) Parentheses indicate the product concentration (mg/ml), which was determined in gas chromatogram of TMS derivatives by pentaerythritol as an internal standard.

In order to know this reaction pathway, the timecourse of products was measured. The reaction was carried out in a higher concentration of benzoin because, under such reaction condition, intermediates such as α-methylol benzoin would be secured easily. In these cases, the total amount of the products which were extracted with chloroform was nearly equivalent to the initial amount of benzoin. In Table 4, it seems reasonable to assume that α-methylol benzoin would be an intermediate of 1,2-diphenyl glycerol.

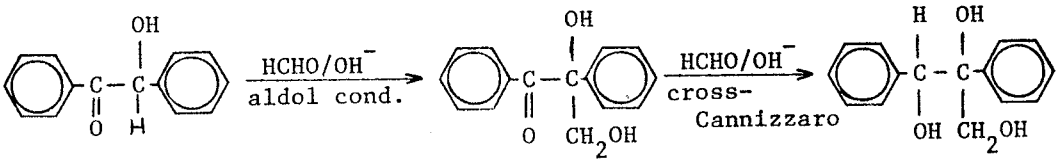
Table 4. Time course of the products[a)]

Reaction time (min)	HCHO consumption (%)	Benzoin	α-methylol benzoin	1,2-diphenyl glycerol[b)]
10	40.0	46.5	0	2
30	62.0	43	6	6
115	95.0	41	7	16

a) Reaction conditions : [HCHO] = 1.0 M, [Benzoin] =0.5 M, [$CaCl_2$] = 0.005 M, pH=12.0 (adjusted by KOH), Temp. = 60°C, Total volume = 200 ml.

b) The ratios were calculated by integrating the peaks of 5.90, 4.46d, and 3.91d ppm

The above results led us to propose the reaction mechanisms of the formose reaction in the presence of benzoin as follow : At first, the methylollation of benzoin with formaldehyde proceeds selectively to form α-methylol benzoin, followed by a cross-Cannizzaro reaction of α-methylol benzoin with formaldehyde to yield, finally, 1,2-diphenyl glycerol. Of course, the Cannizzaro reaction of formaldehyde takes place simultaneously with the above reactions.



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