

Formose Reactions. XI. Gas Chromatographic Analysis of Formose Synthesized under Various Reaction Conditions

by

Yoshihiro SHIGEMASA*, Toshinori SHIMA*, Rumi KAKIYA*, Eiichi WAKI*, and Ruka NAKASHIMA*

(Received June, 30, 1979)

The product distribution was divided into four types and investigated under various reaction conditions by gas chromatography of trimethyl silylated (TMS) derivatives. The effects of cocatalyst, calcium salts, solvents, the concentration of formaldehyde and dissolved calcium ions, and the pH of the reaction mixture, were discussed. The ratio of $[Ca]/[HCHO]$ was found to be a very important factor in order to decide whether the product distribution was simple or complex.

1 Introduction

For more than 100 years, there have been many reports concerning the effectiveness of various kinds of bases as catalyst and of enediol compounds, such as glyceraldehyde, fructose, glucose etc. as cocatalyst for the formose reaction, competitions among the formose reaction, Cannizzaro reaction, and cross-Cannizzaro reaction, the effects of various alcohols, the product analyses, and the mechanism in the reaction. But none of these could have succeeded in synthesizing formose selectively, separating the products, and identifying them except our recent reports on the selective formation of 2-C-hydroxymethyl glycerol and pentaerythritol in a photochemical formose reaction¹⁾ and of 2-C-hydroxymethyl glycerol, 2,4-C-dihydroxymethyl pentitol, and probably a mixture of three diastereomers of 3-C-hydroxymethyl pentitol in a modified formose reaction using the oxidation-reduction potential (ORP) method.^{2,3)} 2,4-C-Dihydroxymethyl pentulose, furthermore, has been found to form under such reaction conditions as $[HCHO]=2.5$ M, $[BaCl_2]=0.01$ M, solvent = methanol, temp. = 60°C, and pH = 12.0 (adjusted by KOH).⁴⁾

Thus, in this survey we intend to research other types of selectivity under various reaction conditions by using the gas chromatography of trimethylsilyl (TMS) derivatives of products.

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

2 Experimental

Materials. A formaldehyde solution and CaO were prepared and stored by the same methods as those described previously.^{5,6} Ion exchange resins used as catalyst were commercial Amberlite IR 120(Ca) and Amberlite IRC 50 (Ca). Calcium polyacrylates which have various polymerization degrees were prepared as follows: Acrylic acid in benzene or dioxan was polymerized in the presence of given amounts of benzoyl peroxide as an initiator and n-lauryl mercaptan as a chain transfer reagent. The molecular weight of polyacrylic acid was determined by measuring the viscosity of its dioxan solution at 30°C.⁷ All other reagents were of reagent grade.

Procedure. The procedure and apparatus used in the present experiments, the methods for determining the formaldehyde consumption and the sugar yield, and the manner of measuring the ORP were essentially the same as those described previously.^{2,5,6,8,9} However, three major procedures were adopted as follow.

Procedure A: In the presence or absence of enediol compounds, such as glycolaldehyde, fructose, glucose, etc., the formose reaction was carried out by adding Ca(OH)₂ or CaO to a formaldehyde solution pre-heated at 60±1°C.

Procedure B: This procedure was virtually the same as Procedure A except that the reaction was started by adding calcium salts, such as CaCl₂, Ca(HCOO)₂, etc., and adjusting the reaction mixture to a given pH with KOH, instead of adding Ca(OH)₂ or CaO. In this case, the effects of adding salts, e.g. KCl, HCOOK, and chelate reagents, such as EDTA, were also studied.

Procedure C: The reaction was started in same manner as Procedure A. When the ORP of the reaction mixture showed minimum, KOH or HCOOH was added to adjust the reaction mixture to a given pH.

Gas Chromatography. An aliquot (1 or 2 ml) of the neutralized reaction mixture was evaporated to dryness in vacuo at 40°C by the repeated addition and concentration of water in order to remove as much formaldehyde as possible. Through this operation the pH of the mixture must be carefully controlled to 6.0-8.0, or else some of the products would change. The residue was trimethylsilylated in the usual manner¹⁰ and extracted with chloroform and the chloroform extract was submitted to GLC on a Shimadzu GC-5A chromatograph equipped with a hydrogen-flame ionization detector under the following conditions: coiled glass column of 3 m by 3 mm o.d.; adsorber, 5% silicon gum SE-30 on 60-80 mesh Chromosorb-W; nitrogen flow rate, 60 ml/min; temperature, 100-250°C, rising at the rate of 4°C/min.

The yield of products were given measuring peak area as glc-% or by comparing the peak area with that of α -bromonaphthalen as an internal standard.

The GLC patterns of products under the various reaction conditions were classified into four types which are shown in Fig. 1. The gas chromatogram of type 1 was

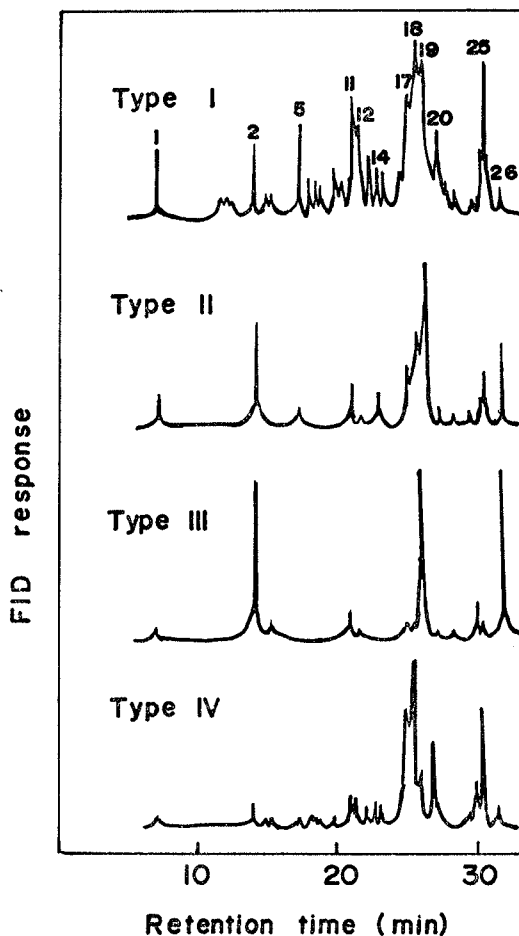


Fig. 1. GLC patterns of TMS derivatives of products.

Type I: $[\text{HCHO}] = 1.0 \text{ M}$, $[\text{CaCl}_2] = 0.15 \text{ M}$, $\text{pH} = 11.0$ (adjusted by conc. KOH), $\text{temp.} = 60^\circ\text{C}$;
 Type II: $[\text{HCHO}] = 1.0 \text{ M}$, $[\text{CaCl}_2] = 0.03 \text{ M}$, $\text{pH} = 11.0$, $\text{temp.} = 60^\circ\text{C}$;
 Type III: The reaction was started with 1.0 M aqueous formaldehyde solution in the presence of $\text{Ca}(\text{OH})_2$ (0.1 M) at 60°C . The progress of the reaction was followed by the ORP measurement. At T_{min} , the dissolved calcium ions were precipitated as calcium oxalate by adding 0.1 M of oxalic acid. Then the reaction was initiated again by adding 0.1 M of magnesium hydroxide and adjusting immediately the pH to 12.0 with conc. KOH aqueous solution.
 Type IV: $[\text{HCHO}] = 1.0 \text{ M}$, $[\text{CaO}] = 0.15 \text{ M}$, solvent; $\text{H}_2\text{O} : \text{CH}_3\text{OH} = 4:1$, $\text{temp.} = 60^\circ\text{C}$.

very complex and not selective. The usual reaction conditions could give this type and the representative reaction conditions were as follow: $[\text{HCHO}] = 1.0 \text{ M}$, $[\text{CaCl}_2] = 0.15 \text{ M}$, the pH of the reaction mixture was kept to 11.0 by KOH , $\text{temp.} = 60^\circ\text{C}$. Type II was intermediate between type I and type III and the representative reaction conditions were of $[\text{HCHO}] = 1.0 \text{ M}$, $[\text{CaCl}_2] = 0.03 \text{ M}$, $\text{pH} = 11.0$, and $\text{temp.} =$

60°C. Type III has been already reported as a selective formose reaction and the products corresponding to GLC peaks 1, 2, 19, and 26 were isolated by mainly using ion exchange resin column chromatography and identified as glycerin, 2-C-hydroxymethyl glycerin, 3-C-hydroxymethyl pentitol, and 2,4-dihydroxymethyl pentitol, respectively.²⁾ The typical procedure was as follows: The reaction was started with 1.0 M aqueous formaldehyde solution in the presence of calcium hydroxide (0.1 M) at 60°C. The progress of the reaction was followed by the ORP measurement. At T_{\min} which was the time of the beginning of the formose-forming step, the dissolved calcium ions were precipitated as calcium oxalate by adding 0.1 M of oxalic acid. Then the reaction was initiated again by adding 0.1 M of magnesium hydroxide and adjusting immediately the pH to 12.0 with a conc. KOH aqueous solution. In type IV, the products which had relatively long retention time were major, whereas sugar alcohols, such as glycerin, (GLC peak 1), 2-C-hydroxymethyl glycerin (GLC peak 2), 3-C-hydroxymethyl pentitol (peak 19), 2,4-C-dihydroxymethyl pentitol, and so on, were minor compounds. The representative reaction conditions were of $[HCHO]=1.0$ M, $[CaO]=0.15$ M, solvent; $H_2O:CH_3OH=4:1$, temp. = 60°C, and the pH of the reaction mixture was kept to the initial pH^* (apparent pH) of 11.8.

3 Results and Discussion

As already reported,²⁾ in the course of kinetic studies of the $Ca(OH)_2$ -catalyzed formose reaction, which usually gives a complex mixture of more than 30 sugar products, a selective formose reaction was observed, giving 3 kinds of branched sugar alcohols. 2-C-Hydroxymethyl glycerol, 2,4-C-dihydroxymethyl pentitol, and probably a diastomeric mixture of 3-C-hydroxymethyl pentitol, when the major part of the dissolved calcium ions were removed as sparingly soluble salts or chelate complexes at the end of the induction period. However, there is one question, and this is: is it essential or not for a selective formose reaction that the dissolved calcium ions be removed? So, it was very interesting for us to study how the concentration of HCHO and the dissolved calcium ions $[Ca]$ influenced the distribution of the product. The results are shown in Table 1. The relationships among T_{\min} , T_{\max} , the sugar yield, $[Ca]$, and $[HCHO]$ are in fair agreement with the results which were obtained by using $Ca(HCOO)_2$ instead of $CaCl_2$.³⁾ Concerning the distribution of products, with a decrease of $[Ca]$ and an increase of formaldehyde concentration, the type of GLC varied from type I to II and so we could appreciate that the selectivity of the reaction was affected by not only $[Ca]$ but also the formaldehyde concentration.

In the case of using paraformaldehyde as such, not dissolved in water previously, or an aqueous formaldehyde which was irradiated internally with a 450-W high

Table 1. Effects of [HCHO] and [Ca]^{a)}

[CaCl ₂] (M)	[HCHO] (M)	T _{min} (min)	T _{max} (min)	Sugar yield (%)	Type of GLC ^{b)}
0.15	1.0	14.0	16.0	55.2	I
0.05	1.0	65.5	74.5	36.0	I
0.03	1.0	163	178	28.9	II
0.15	2.0	20.0	22.0	—	I
0.15	5.0	63.0	66.5	—	II

a) Reaction conditions: pH=11.0 (adjusted by KOH), temp.=60°C, total volume=200 ml.

b) See Fig. 1.

pressure mercury lamp in a Pyrex tube for 5 h, either product type was 1. Furthermore, under the reaction condition, such as [HCHO] = 1.0 M, [Ca(OH)₂] = 0.1-0.3 M, and procedure A, it was also type 1.

Table 2. Effects of various calcium complexes^{a)}

Chelating agent (M)	T _{max} (min)	Sugar yield (%)	Type of GLC ^{b)}
(CH ₃) ₂ N(CH ₂) ₂ N(CH ₃) ₂ (0.6)	13.5	43.4	I
N(CH ₂ COOH) ₃ (0.075)	21.0	36.8	I
N(CH ₂ COOH) ₃ (0.11)	95.5	39.5	II
N(CH ₂ COOH) ₃ (0.127)	130	—	II
N(CH ₂ COOH) ₃ (0.13)	213	24.9	III
EDTA (0.05)	26	46.4	II
EDTA (0.11)	154	23.0	III
D-Fructose (0.063)	—	26.8	II
D-Fructose (0.003)	—	45.5	II
Redukton (0.013)	—	40.0	II
Redukton (0.001)	—	52.0	II

a) Reaction conditions: [HCHO]=1.0 M, [CaCl₂]=0.15 M, temp.=60°C, pH=11.0 (adjusted by KOH), total volume=200 ml.

b) See Fig. 1.

Table 2 shows the effects of calcium complexes on the distribution of products. Proper addition of chelating agents which form a stable complex with calcium ions, such as nitrilotriacetic acid (NTA), EDTA, etc., gave a selective formose reaction. Fujino et al.¹¹⁾ pointed out the relationship between activities and the ease of Ca-complex formation with enediol compounds, and that the complex could catalyze the formose reaction. When cocatalysts, such as fructose, redukton, etc., were not added under the reaction conditions in Table 2, the formose reaction did not or was not able to proceed. The product distribution became a little simpler, but it was

scarcely influenced by this kind of cocatalyst. From Table 1 and 2, it can be easily estimated that the ratio of effective or free calcium ion concentration and formaldehyde concentration might be an important factor for giving a selective formose reaction. This relationship between selectivity and the ratio will be reported elsewhere.

The effects of various cations and anions on the formose reaction are summarized in Table 3. The sugar yield and T_{\max} were affected by salts, but the type of products could not be varied except CH_3COOK , Amberlite IRC 50 (Ca), and calcium

Table 3. Effects of various salts on the formose reaction^{a)}

Source of calcium ions (M)	Salts (M)	pH ^{b)}	T_{\max} (min)	Sugar yield (%)	Type of GLC ^{c)}	
CaCl_2	0.15 KCl	0.3	11.0	18.5	53.1	I
CaCl_2	0.15 KCl	0.6	11.0	29.0	57.5	I
CaCl_2	0.15 KCl	6.0	11.0	22.5	37.5	I
$\text{Ca}(\text{HCOO})_2$	0.15 HCOOK	0.6	11.0	43.5	44.2	I
$\text{Ca}(\text{HCOO})_2$	0.15 HCOOK	2.0	11.0	105	41.6	I
$\text{Ca}(\text{HCOO})_2$	0.15 HCOOK	3.0	11.0	168	25.8	I
$\text{Ca}(\text{HCOO})_2$	0.15 KCl	1.0	11.0	35.0	57.7	I
CaCl_2	0.15 KBr	0.6	11.0	37.0	34.8	I
CaCl_2	0.15 CH_3COOK	1.5	11.0	183	40.7	II
CaBr_2	0.15 HCOOK	1.0	11.0	35.0		I
CaBr_2	0.15 HCOOK	3.0	11.0	56.5		I
$\text{Ca}(\text{OH})_2$	0.1		11.0	26.5	54.1	I
CaO	0.15		11.0	16.0	36.9	I
CaCl_2	0.15		11.0	16.0	55.2	I
CaBr_2	0.14		11.0	21.0	42.6	I
$\text{Ca}(\text{HCOO})_2$	0.15		11.0	20.0	45.0	I
$\text{Ca}(\text{CH}_3\text{COO})_2$	0.15		11.0	31.0	50.4	I
$\text{Ca}(\text{C}_2\text{H}_5\text{COO})_2$	0.15		11.0	23.5	45.0	I
IR 120 (Ca)	0.15		10.5			
IR 120 (Ca)	0.15		11.0	37.5	42.0	I
IR 120 (Ca)	0.15		12.0	14.5	30.0	I
IRC 50 (Ca)	0.15		11.0			
IRC 50 (Ca)	0.15		11.5	51.5	24.8	II
IRC 50 (Ca)	0.15		12.0	44.5	35.0	I
Ca polyacrylate ^{d)}	0.15		11.0	183	47.6	III
Ca polyacrylate ^{e)}	0.15		12.0	66.0	21.8	I

a) $[\text{HCHO}] = 1.0 \text{ M}$, temp. = 60°C , total volume = 200 ml.

b) The pH of the reaction mixture was adjusted by conc. KOH.

c) See Fig. 1.

d) Polymerization degree was 5000.

e) Polymerization degree was 4040.

polyacrylate. This could be considered as follow. Owing to their low dissociation constants, the concentration of effective calcium ion species decreased, so the ratio of $[Ca]/[HCHO]$ became suitable for a selective formose reaction. It seems reasonable to assume the same conception for explaining Table 4, although polymer effects due to the high polymerization degree could not be neglected.

Table 4. Effects of the polymerization degree^{a)}

Polymerization degree	[Ca] (M)	T _{max} (min)	Sugar yield (%)	Type of GLC ^{b)}
5000	5.3×10^{-3}	183	47.6	III
4040	6.0×10^{-3}	91.5	32.1	II
1800	11.3×10^{-3}	90.5	41.5	II
910	11.6×10^{-3}	74.5	44.2	II

a) $[HCHO]=1.0$ M, $[calcium\ polyacrylate]=0.3$ M, $temp.=60^{\circ}C$, $pH=11.0$ (adjusted by KOH), total volume=200 ml.

b) See Fig. 1.

Lowering the pH of the reaction mixture at the end of the induction period (T_{min}), the type of GLC became simpler. On the other hand, when the pH was kept constant from start to finish, it was very complex in spite of the pH value (Table 5).

Table 5. Effects of pH of the reaction mixture^{a)}

$[Ca(HCOO)_2]$ (M)	$pH_i^{b)}$	$pH_{min}^{c)}$	Sugar yield (%)	Type of GLC ^{d)}
0.1	11.5	11.5	48.0	I
0.1	11.0	11.0	50.0	I
0.3	10.5	10.5	46.5	I
0.55	10.5	10.5	52.5	I
0.15	11.0	12.0	32.1	I
0.15	11.0	11.0	45.0	I
0.15	11.0	10.5	47.8	II
0.15	11.0	10.0	44.0	III

a) $[HCHO]=1.0$ M, $temp.=60^{\circ}C$, total volume=200 ml.

b) pH_i means initial pH and the pH was adjusted by KOH.

c) pH_{min} means the pH of the reaction mixture which shows minimum ORP, and the pH was adjusted by KOH or HCOOH.

d) See Fig. 1.

Although methanol gave the type of GLC iv, the products distributions were essentially complex (Table 6). In the presence of water, the sugar yield had a max-

Table 6. Solvent effects on the product distribution^{a)}

Solvent (v/v)	Sugar yield (%)	Type of GLC ^{b)}
H ₂ O	36.9	I
CH ₃ OH/H ₂ O 1/4	64.3	I
CH ₃ OH/H ₂ O 7/3	54.2	I
CH ₃ OH	28.2	iv
Dioxane/H ₂ O 1/3	55.7	I
Dioxane/H ₂ O 1/1	48.4	I
Dioxane/H ₂ O 7/3	25.9	I
Methyl cellosolve/H ₂ O 1/1	47.5	I
Methyl cellosolve/H ₂ O 3/1	56.5	I

a) [HCHO]=1.0 M, [CaO]=0.15 M, temp.=60°C, total volume=200 ml.

The pH of the reaction mixture was kept to the initial one.

b) See Fig. 1.

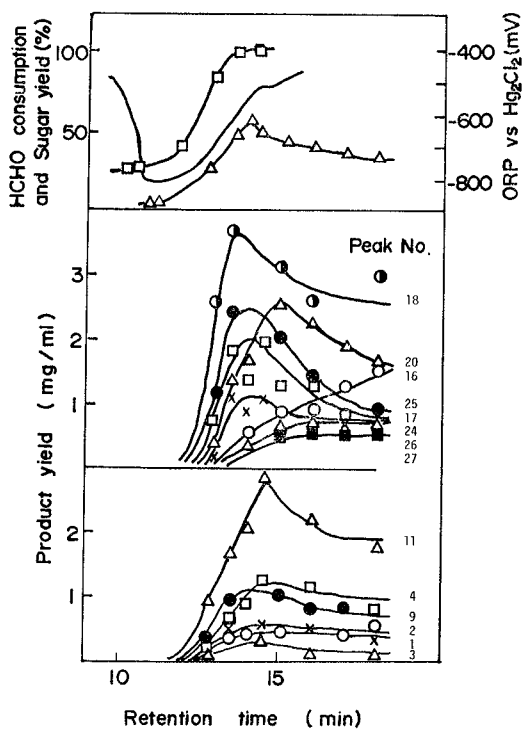


Fig. 2. Time courses of ORP, formaldehyde consumption, the sugar yield, and the amounts of products.

[HCHO]=2.0 M, [Ca(OH)₂]=0.22 M, total volume=880 ml. □, HCHO consumption; △, Sugar yield; Peak No., see Fig. 1.

imum value at a proper content of H₂O, but this type of GLC was complicated and was not influenced by any kind of solvent and the H₂O content. In methanol solvent, furthermore, when the reactions were carried out under the pH* of 8.5-10.3, the product distribution was type iv, but the rate of the reaction increased with an increase of pH.

Time courses of ORP, formaldehyde consumption, the sugar yield, and the amounts of products are shown in Fig. 2. When a commercial formaline was used, T_{max} was 11.5 min, the sugar yield was 53%, and the product distribution was the same as that obtained from paraformaldehyde. The behavior of peak 4, 11, 17, 18, 20, and 25 was very similar to that of the sugar yield. From these results it can be estimated that these peaks might be sugars which could be measured by the phenol-sulfuric acid method and could possess a reduction group.

References

- 1) Y. Shigemasa, Y. Matsuda, C. Sakazawa, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **50**, 222 (1977).
- 2) Y. Shigemasa, O. Nagae, C. Sakazawa, R. Nakashima, and T. Matsuura, *J. Am. Chem. Soc.*, **100**, 1309 (1978).
- 3) Y. Shigemasa, M. Kawahara, C. Sakazawa, R. Nakashima, and T. Matsuura, *J. Catal.*, in press.
- 4) Y. Shigemasa, S. Akagi, and R. Nakashima, *Carbohydr. Res.*, in press.
- 5) Y. Shigemasa, T. Fujitani, C. Sakazawa, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **50**, 1527 (1977).
- 6) Y. Shigemasa, Y. Matsuda, C. Sakazawa, R. Nakashima, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **52**, 1091 (1979).
- 7) J. Brandrup and E. H. Immergut "Polymer Handbook" Interscience, New York (1965), p. iv-21.
- 8) Y. Shigemasa, M. Shima, C. Sakazawa, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **50**, 2138 (1977).
- 9) Y. Shigemasa, M. Shima, C. Sakazawa, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **48**, 2099 (1975).
- 10) C. C. Sweely, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).
- 11) S. Fujino, J. Kobayashi, I. Higuchi, *Nippon Kagaku Kaishi*, **1972**, 2292.