

## Formose Reactions. Part 3.<sup>1</sup> Selective Formose Reaction Catalyzed by Organic Bases

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In the formose reaction catalyzed by an organic base such as diethylaminoethanol, a compound with a potential 1,2-oxy-oxo-structure, an acceleration effect was observed on the main reaction and a suppression effect on the Cannizzaro side-reaction. Organic bases with high basicity not only showed high catalytic activity but also enabled a selective formose reaction to occur, giving 2-C-(hydroxymethyl)glycerol as the main product. A mechanism to account for the formation of 2-C-(hydroxymethyl)glycerol is proposed.

THE formose reaction, in which formaldehyde in the presence of base gives a mixture of carbohydrates and their analogues (so-called formoses), was first reported by Butlerow in 1861,<sup>2</sup> and has been studied intermittently since then. This reaction is of much interest in connection with (1) possible large-scale manufacture of edible carbohydrates from a simple starting material,<sup>3</sup> (2) the establishment of metabolic-cycle systems of carbon resources in sustained space flights,<sup>4</sup> and (3) the prebiotic synthesis of carbohydrates and substances related to nucleic acids, as a fundamental process in the generation of life.<sup>5,6</sup> Although a number of inorganic catalysts have been examined for the formose reaction (*e.g.* alkaline earth and alkali-metal hydroxides), few investigations have been concerned with organic catalysts.<sup>1,7-10</sup>

Formaldehyde not only undergoes the formose reaction but also takes part in the Cannizzaro reaction (the side-reaction) which proceeds simultaneously and competitively to produce methanol as well as formic acid. Furthermore, the formose reaction catalyzed by calcium hydroxide gives a complex mixture of *ca.* 30 products<sup>11,12</sup> some of which have toxic properties for humans.<sup>13</sup> Although derivatives of the products have recently been examined by g.l.c. and combined g.l.c.-mass spectrometry,<sup>14-16</sup> the isolation of products has been successful only for some branched-chain polyols, polyhydroxyaldehydes, and polyhydroxyketones.<sup>10,17,18</sup>

In order to further the practical development of the formose reaction to obtain specific products in high yield we have examined the use of various organic bases as catalysts.

### RESULTS AND DISCUSSION

**Effect of Additive on the Formose Reaction.**—With an organic base as catalyst, very little reaction had occurred after 20 h at 100 °C. Although consumption of formaldehyde was observed, the quantity of methanol formed suggested that it was mainly as a result of the Cannizzaro reaction. The fact that the addition of monosaccharide greatly enhanced the formose reaction with inorganic base as catalyst<sup>19-21</sup> led us to examine the effect of adding D-fructose to the reaction system using diethylaminoethanol as catalyst. As shown in Figure 1,

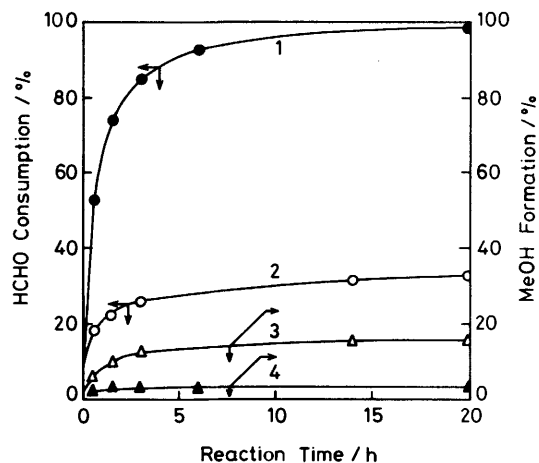


FIGURE 1 Formose reaction catalyzed by diethylaminoethanol. Effect of addition of D-fructose. Runs 1 and 4, [D-fructose] = 0.056M; runs 2 and 3, without D-fructose; [HCHO]<sub>0</sub> = 1.5M, [catalyst] = 0.23M, 100 °C

the addition of D-fructose considerably increased the consumption of formaldehyde and caused some suppression of the Cannizzaro reaction.

Figure 2 shows the change in pH of the reaction mixture catalyzed by diethylaminoethanol, both in the

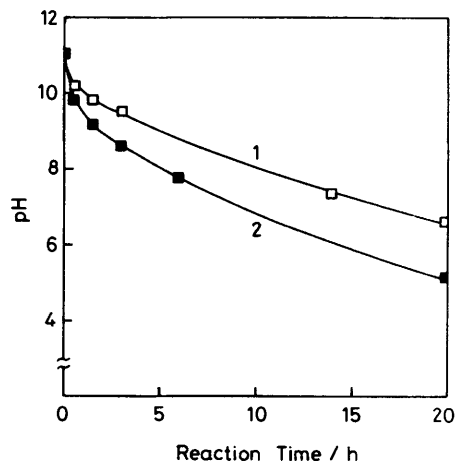


FIGURE 2 Formose reaction catalyzed by diethylaminoethanol. pH Change in reaction system. Run 1, without D-fructose; run 2, [D-fructose] = 0.056M; [HCHO]<sub>0</sub> = 1.5M, [catalyst] = 0.23M, 100 °C

presence and the absence of D-fructose. The extent of pH drop in the presence of D-fructose is larger than in its absence. This seems to conflict with the result above where the addition of D-fructose exhibited a suppression effect on the methanol and formic acid producing Cannizzaro reaction. (A cross-Cannizzaro reaction, for example, between formaldehyde and polyhydroxy-aldehydes, producing polyols and formic acid, would account for the pH drop.)

Table 1 shows the effect of adding various organic

TABLE 1

Formose reaction catalyzed by diethylaminoethanol.  
Effect of addition of various organic compounds <sup>a</sup>

Run	Additive	HCHO Consumption (%)		MeOH Formation (%)	
		1.5 h	20 h	1.5 h	20 h
1	None	24	37	9	14
2	D-Fructose	82	97	2	2
3	D-Glucose	72	96	2	3
4	D-Mannose	58	81	3	4
5	D-Galactose	64	94	3	2
6	L-Sorbose	82	98	0	0
7	D-Ribose	67	86	3	4
8	D-Xylose	64	84	2	3
9	D-Arabinose	57	77	3	4
10	Dihydroxyacetone	55	86	3	4
11	Maltose	83	100	1	1
12	Lactose	82	100	2	2
13	Methyl $\alpha$ -D-glucoside	23	35	8	14
14	L-Rhamnose	39	58	7	7
15	2-Deoxy-D-ribose	33	36	4	11
16	Sucrose	24	31	9	16
17	$\alpha$ -Cyclodextrin <sup>b</sup>	30	28	8	18
18	Ethyleneglycol	19	38	10	19
19	Glycerol	23	29	7	19
20	Acetylacetone	30	37	5	13
21	Acetoin	25	36	8	16

<sup>a</sup> [HCHO]<sub>0</sub> = 1.5M, [catalyst] = 0.23M, [additive] = 0.056M, 100 °C. <sup>b</sup> [C<sub>8</sub>H<sub>10</sub>O<sub>6</sub>] = 0.056M.

compounds on the consumption of formaldehyde and the formation of methanol in the reaction catalyzed by diethylaminoethanol. The formose reaction was greatly enhanced and the Cannizzaro reaction suppressed by the addition of D-fructose, D-glucose, D-mannose, D-galactose, L-sorbose, D-ribose, D-xylose, D-arabinose, dihydroxyacetone, maltose, or lactose. On the other hand, such an effect was not observed on the addition of methyl  $\alpha$ -

D-glucoside, 2-deoxy-D-ribose, sucrose, or  $\alpha$ -cyclodextrin, or of a polyol such as ethyleneglycol or glycerol, or of an organic compound such as acetylacetone or acetoin. The above results suggest that, by the addition of a compound with potential 1,2-oxy-oxo-structure, the consumption of formaldehyde is greatly increased and the Cannizzaro reaction is suppressed.

*Catalysis by Organic Bases.*—Table 2 shows the initial pH of the reaction system in relation to the consumption of formaldehyde and the formation of methanol in the reactions catalyzed by various organic bases. In most cases very little formose reaction took place in the absence of D-fructose. In the case of aminoethanol or polyethyleneimine [a polymer with a branched-chain structure and primary, secondary, and tertiary (mol ratio, 1 : 2 : 1) amino-groups], the extent of formaldehyde consumption was large and that of methanol formation small even in the absence of D-fructose. This is probably due to Schiff-base formation between formaldehyde and the primary amino-group of these compounds. The comparison being limited to systems with D-fructose present, the catalysts are classified into three types according to their catalytic activity for the formose reaction: diethylaminoethanol, quinuclidine, 3-quinuclidinol, 1,4-diazabicyclo[2.2.2]octane, and potassium lactylhydroxamate are high; ethylaminoethanol is medium; imidazole and pyridine are low. The catalytic activity was strongly dependent on the initial pH of the reaction system, compounds with higher basicity showing higher activity for the formose reaction.

On the other hand, in the reaction catalyzed by potassium hydroxide, in the presence of D-fructose, the initial pH of the reaction system was as high as 14 and dropped rapidly, reading 8 after reacting for an hour. The extent of formaldehyde consumption was ca. 50%, but this was due mainly to the Cannizzaro reaction; the extent of the formose reaction was small, judging by the amount of methanol formed.

The results above suggest that the high catalytic activity of very basic organic bases for the formose reaction is caused, at least partly, by the maintenance of a moderate pH range in the system during the reaction so that aldol condensation (the main reaction of the

TABLE 2

Formose reaction catalyzed by various organic bases <sup>a</sup>

Run	Catalyst	HCHO Consumption (%)		MeOH Formation (%)		pH <sup>c</sup>
		With D-Fructose	Without	With D-Fructose	Without	
1	Diethylaminoethanol	97	28	2	15	11.0
2	Quinuclidine	88	29	2	19	11.1
3	3-Quinuclidinol	98	43	1	23	10.8
4	1,4-Diazabicyclo[2.2.2]octane	94	22	3	18	10.9
5	Potassium lactylhydroxamate	88	27	0	3	d
6	Ethylaminoethanol	40	17	2	8	9.8
7	Aminoethanol	60	46	1	2	d
8	Polyethyleneimine <sup>b</sup>	57	40	0	1	d
9	Imidazole	20	1	0	0	9.3
10	Pyridine	11	3	1	1	8.7

<sup>a</sup> [HCHO]<sub>0</sub> = 2.0M, [catalyst] = 0.23M, [D-fructose] = 0.056M, 100 °C, 20 h. <sup>b</sup> [Ethyleneimine unit] = 0.23M. <sup>c</sup> In the presence of D-fructose. <sup>d</sup> Not measured.

formose reaction) takes place, but not the Cannizzaro reaction which requires higher pH ranges.

*Characterization of Formose.*—Three formose reactions, catalyzed by typical organic bases and in the presence of D-fructose, were allowed to proceed for 20 h. Ion exchange chromatography gave products from which trimethylsilyl derivatives were obtained; the g.l.c. patterns of these derivatives are shown in Figure 3. As can

tion period), production of glycolaldehyde from two molecules of formaldehyde by acyloin condensation; (ii) second stage, rapid production of various carbohydrates from glycolaldehyde and formaldehyde by aldol condensation and Lobry de Bruyn-Alberda van Eckenstein rearrangement (interconversion between aldose and ketose via an ene-diol intermediate); and (iii) third stage, rearrangement and degradation of the products to their

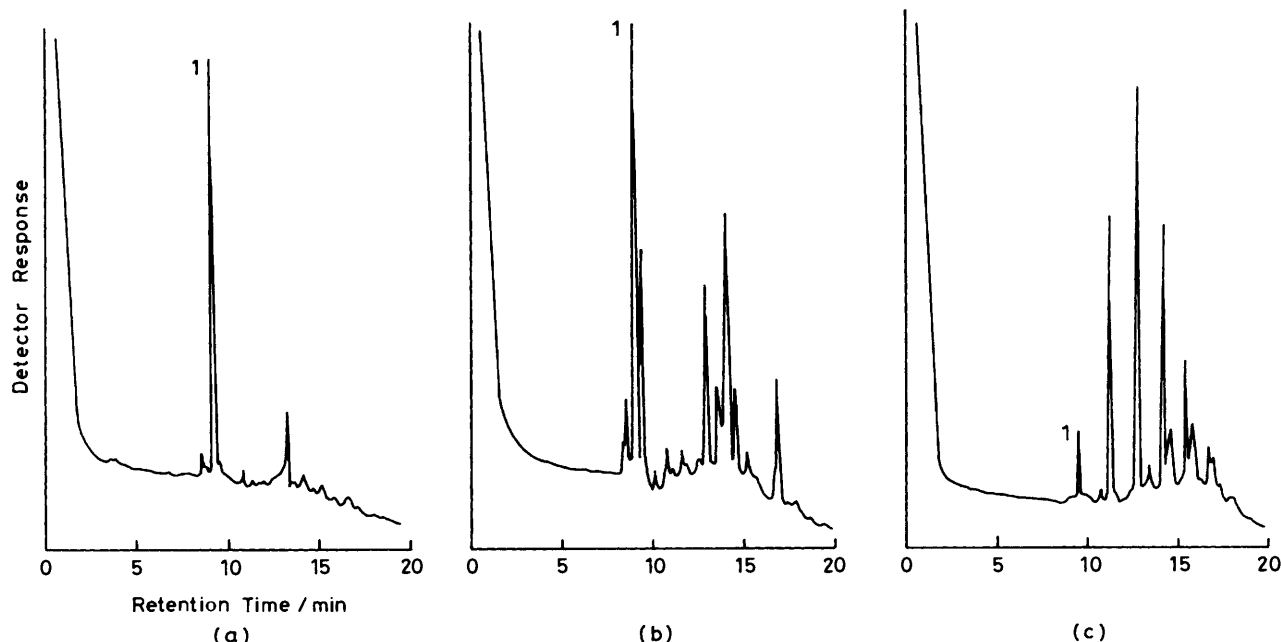


FIGURE 3 The g.l.c. patterns of trimethylsilyl derivatives of products obtained using (a) diethylaminoethanol, (b) ethylaminoethanol, and (c) imidazole as the catalyst.  $[HCHO]_0 = 2.0M$ ,  $[catalyst] = 0.23M$ ,  $[D-fructose] = 0.056M$ ,  $100^\circ C$ , 20 h; ion exchange chromatography on columns of Amberlite IR-120B(H) and IRA-402(OH)

be seen from Figure 3, the g.l.c. pattern of trimethylsilyl derivatives from products of the formose reaction catalyzed by diethylaminoethanol (high catalytic activity) was dramatically simple, and those of the derivatives from quinuclidine, 3-quinuclidinol, and 1,4-diazabicyclo-[2.2.0]octane-catalyzed reactions were similar. These catalysts not only showed high catalytic activity but also enabled a selective formose reaction to occur. On the other hand the g.l.c. patterns of trimethylsilyl derivatives of products obtained with ethylaminoethanol (medium catalytic activity) and imidazole (low activity) were very complicated making these catalysts undesirable with respect to the selectivity as well as the catalytic activity for the formose reaction. The yield of the products, in a syrup form, obtained from the diethylaminoethanol-catalyzed reaction was 20–30% with respect to the consumption of formaldehyde and D-fructose. The product corresponding to peak 1 in Figure 3 was isolated by g.l.c. and identified as the trimethylsilyl derivative of 2-C-(hydroxymethyl)glycerol by the  $^1H$  and  $^{13}C$  n.m.r. spectra and GC-MS measurements.<sup>10</sup>

*Proposed Mechanism.*—It has been generally accepted that the reaction catalyzed by calcium hydroxide consists of three stages as follows: (i) first stage (induc-analogues by cross-Cannizzaro reaction (redox reaction

between polyhydroxyaldehyde or polyhydroxyketone and formaldehyde producing polyol and formic acid), retroacyloin condensation, and other, unknown reactions. It has been suggested that the catalytically active species in the induction period is a complex formed from  $[CaOH]^+$ , water, and formaldehyde. In the second stage, a complex formed from  $[CaOH]^+$  or calcium hydroxide and a 1,2-oxy-oxo-compound (e.g. polyhydroxyaldehyde) has been considered as the active species, based on the fact that the induction period was shortened by the addition of 1,2-oxy-oxo-compound.<sup>19–22</sup>

On the other hand, the formation of such a complex is not possible in the reaction catalyzed by organic base, and the mechanism must be different from that of the calcium hydroxide-catalyzed reaction. A reaction mechanism involving the self-condensation of formaldehyde to glycolaldehyde<sup>8</sup> is not considered to be predominant, taking into account the following results: (i) in the formose reaction with an organic base as catalyst, very little reaction took place in the absence of an additive (e.g. D-fructose), under the conditions examined; and (ii) 2-C-(hydroxymethyl)glycerol was formed gradually as the D-fructose disappeared.

Figure 4 shows a proposed mechanism for the reaction



using a very basic organic catalyst (*e.g.* diethylaminoethanol) in the presence of D-fructose which accounts for the formation of 2-C-(hydroxymethyl)glycerol as the main product. Intermediate (1) is formed by aldol condensation between D-fructose and three molecules of formaldehyde. It then undergoes retroacyloin condensation to produce intermediates (2) and (3). Compound (2) produces 2-C-(hydroxymethyl)glycerol and formic acid by cross-Cannizzaro reaction with formaldehyde. Intermediates (4), (5), (6), and (7) are derived successively from compounds (3), (4), (5), and (6) respectively, by a series of reactions as described above; eight molecules of formaldehyde are consumed to produce two molecules of 2-C-(hydroxymethyl)glycerol, and two molecules of formic acid. The ketone (7) undergoes further aldol condensation with four molecules of formaldehyde to produce the intermediate (8) from which compound (2) is formed with the reproduction of the initial compound (7). Further reaction proceeds by recycling compound (7).

It is considered that all the additives which exhibit an acceleration effect on the formose reaction have potential 1,2-oxy-oxo-structures and can undergo aldol condensation, retroacyloin condensation, and cross-Cannizzaro reactions following the proposed mechanism described above. On the other hand, the additives which do not show such an effect are either unable to undergo even aldol condensation, because of lack of active hydrogen in the molecules (as for methyl  $\alpha$ -D-glycoside), or can undergo aldol condensation but not retroacyloin condensation (as for acetoin).

#### EXPERIMENTAL

Aqueous formaldehyde solutions were prepared as follows: commercial paraformaldehyde (30 g) was suspended in distilled water (500 ml), refluxed for several hours and filtered through a sintered-glass disk under nitrogen. The amount of formaldehyde in the filtrate was determined by sodium sulphite titration.<sup>23</sup>

*N,N*-Diethylaminoethanol, *N*-ethylaminoethanol, and pyridine were distilled over calcium hydride and stored under nitrogen. Imidazole and quinuclidine were purified by recrystallization from light petroleum and diethyl ether, respectively. 1,4-Diazabicyclo[2.2.2]octane was purified by sublimation *in vacuo*. Potassium lactylhydroxamate was synthesized from hydroxylamine, ethyl lactate, and potassium hydroxide.<sup>24</sup>

**Formose Reaction.**—A 50-ml flask fitted with a three-way cock, which had been flushed with dry nitrogen, was charged successively with an additive [*e.g.* D-fructose (2.78 mmol)], aqueous formaldehyde solution (50 ml; 75 mmol), and catalyst (11.3 mmol). The reaction was started by immersing the flask in an oil-bath adjusted to the required temperature; it was quenched at intervals by immersion in solid CO<sub>2</sub>-ethanol and aliquots were taken from the reaction mixture with a syringe and neutralized with a given volume of 1*N*-hydrochloric acid. The consumption of formaldehyde and the formation of methanol (a product of the Cannizzaro reaction) were determined by g.l.c., using a Yanaco model G-80 chromatograph equipped with a thermal conductivity detector, under the following conditions: stainless steel

column of 3m × 3mm o.d.; adsorber, TSR-1; helium flow-rate, 17.5 ml min<sup>-1</sup>; column temperature, 120 °C. The pH of the aliquot was also measured with a Horiba F-7SS pH meter.

**Characterization of Formose.**—On completion of the reaction, an aliquot (5 ml) of the reaction mixture was neutralized with 1*N*-hydrochloric acid and passed successively through columns of Amberlite IR-120B(H) (30 ml) and Amberlite IRA-402(OH) (30 ml) which were washed with distilled water (*ca.* 1 500 ml) at a constant flow-rate (2 ml min<sup>-1</sup>). Water was then removed from the effluent at 50 °C under reduced pressure to give a syrupy mixture of products (formose). The syrup was trimethylsilylated in the usual way<sup>25</sup> and the resulting mixture of trimethylsilyl derivatives extracted with chloroform. The extract was subjected to g.l.c. on an Ohkura model-103 chromatograph equipped with a thermal-conductivity detector under the following conditions: stainless steel column of 3m × 3mm o.d.; adsorber, 5% silicone gum GE SE-30 on 60–80 mesh CE 545; helium flow-rate, 17.5 ml min<sup>-1</sup>; column temperature, 150–300 °C, rising at a rate of 10 °C min<sup>-1</sup>.

2-C-(Hydroxymethyl)glycerol, a major product of the reaction, was identified by the <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra and GC-MS measurements.<sup>10</sup> The <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra and GC-MS measurements were taken on a JEOL JNM-PS-100, a JEOL JNM-PFT-100, and a Hitachi M-52 GC-MS spectrometer, respectively.

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