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Preliminary communication

A selective synthesis of 2,4-di-*C*-(hydroxymethyl)-3-pentulose in the formose reaction*

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The "formose reaction" is the generic name for the base-catalyzed condensation of formaldehyde to give monosaccharides[2]. "Formose" is a general term for the product, a complex mixture of sugars and alditols[3]. The formose reaction has long been of interest in connection with the microbial utilization of formose[4] and the prebiotic synthesis of carbohydrates[5]. Formose, however, has not yet proved useful, because of its complexity. 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. Recently, a modified formose reaction, in which the catalyst is changed at the end of the induction period, was found to afford selectively three sugar alcohols, namely 2-*C*-(hydroxymethyl)-glycerol, 2,4-di-*C*-(hydroxymethyl)pentitol, and a mixture of three diastereoisomers of 3-*C*-(hydroxymethyl)pentitol[6,7].

Our studies on the formose reaction[8,9] have shown that reactions in non-aqueous solvents, methanol especially, depress the Cannizzaro reaction and raise the yield of sugars[10–12]. Continued investigations of the reaction in non-aqueous solvents have shown *a branched ketose to be formed with high selectivity* when the reaction is catalyzed by barium chloride–potassium hydroxide.

In a typical experiment, the reaction was conducted with 2.5M methanolic formaldehyde in the presence of barium chloride (0.01M) at 60° under nitrogen, with immediate adjustment of the pH of the mixture to 12.0 with potassium hydroxide pellets. At convenient intervals, ~5 mL aliquots were withdrawn into a 20-mL flask and immediately cooled in a Dry Ice–acetone bath to ~0°, at which temperature the reaction is essentially arrested. These aliquots were analyzed for formaldehyde by the method of Bricker *et al.*[13], except that the optical density was measured at 579 nm. After 70% completion of the reaction (20–25 min), the yield of sugar reached a constant value, although the formaldehyde was further consumed. After 20 min, some aliquots were analyzed for total sugar[14] (50%)

*Formose reactions: Part 10. For Part 9, see ref. 1.

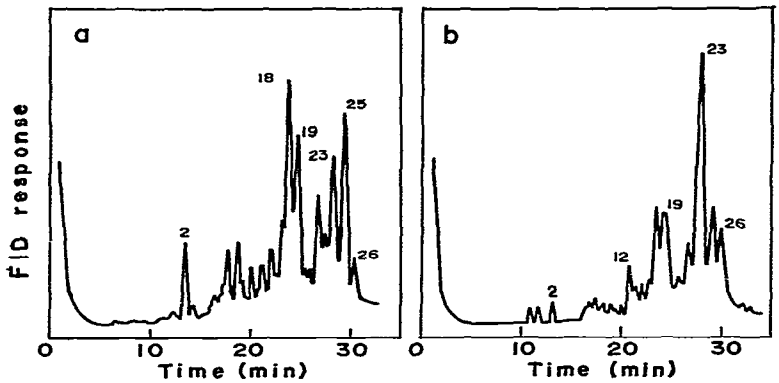


Fig. 1. The g.l.c. patterns of per(trimethylsilyl)ated products obtained from (*a*) a conventional calcium oxide-catalyzed formose reaction in methanol starting from [HCHO] = 1.0M and [CaO] = 0.15M at 60°, and (*b*) the selective formose reaction in methanol starting from [HCHO] = 2.5M and [$BaCl_2$] = 0.01M at 60° and by adjusting the apparent pH of the mixture to 12.0 from start to finish.

and product distribution was determined by g.l.c. of per(trimethylsilyl)ated products. The g.l.c. pattern (Fig. 1b) dramatically indicates the selective formation of a product corresponding to the peak number 23 (yield, 33% by g.l.c.).

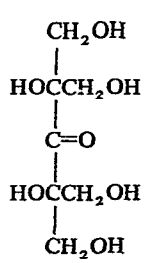
The product corresponding to g.l.c. peak no. 23 was isolated by chromatography on cellulose powder (Whatman CF-11) with wet 1-butanol as eluent. The product (**1**) was obtained as a colorless syrup.

The ^{13}C-n.m.r. spectrum of **1** showed four equivalent CH_2 groups, two equivalent tertiary carbon atoms, and a carbonyl carbon atom. The ^{13}C-n.m.r. chemical shifts (p.p.m. from external tetramethylsilane), multiplicities (based on an off-resonance spectrum) and relative integrated intensities (determined by use of an n.O.e.-suppressed, gated-decoupling technique) were (for a solution in D_2O): 65.34 (t, 4), 86.71 (s, 2), and 215.7 (s, 1). The chemical-ionization mass spectrum (isobutane) showed *m/e* 211 (quasi-M^+, intensity 20), 193 (100), 175 (30), and 163 (45). The i.r. spectrum showed a carbonyl group by an intense band at 1700–1710 cm^{-1}. The ^{1}H-n.m.r. spectrum (D_2O; internal standard, sodium 4,4-dimethyl-4-silapentane-1-sulfonate) showed geminal, non-equivalent CH_2 protons at δ 3.71 (4H, d, $J_{H,H}$ 12 Hz) and 4.01 (4H, d, $J_{H,H}$ 12 Hz).

Reduction of **1** with sodium borohydride gave 2,4-di-*C*-(hydroxymethyl)pentitol as white crystals, m.p. 117°; this value and the i.r. spectrum were in fair agreement with data for an authentic sample[7].

The results led us to assign the structural constitution 2,4-di-*C*-(hydroxymethyl)-3-pentulose (**1**), for the product of peak 23.

1



Formation of this branched ketose (**1**) may be rationalized by a conventional mechanism[15] involving cumulative aldol condensation of formaldehyde. The selective formation of such aldoses or ketoses as **1** in the formose reaction is significant. To the best of our knowledge, no one has obtained particular sugars or sugar alcohols selectively in the formose reaction, except for our previously reported selective formation of sugar alcohols [2-*C*-(hydroxymethyl)glycerol and pentaerythritol] in a photochemical formose reaction[16], and 2,4-di-*C*-(hydroxymethyl)pentitol and 3-*C*-(hydroxymethyl)pentitol in a modified formose reaction[7]. Recently, although glucose was not isolated, Likholobov *et al.*[17] reported that, at 18% conversion and 98°, the formose reaction has a 75.4 wt.-percent selectivity for glucose, and no branched species were identified.

At this stage of our knowledge, the selective formation of **1** is difficult to explain; efforts are underway to elucidate a mechanism for this selectivity.

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