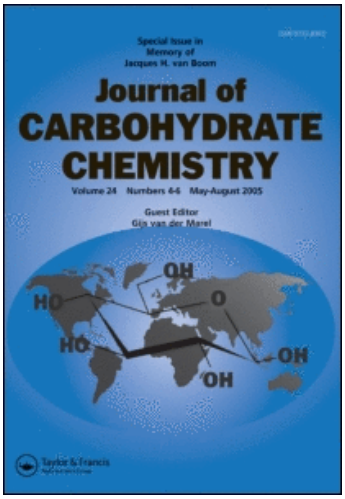

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Communication

A SELECTIVE SYNTHESIS OF 3,3-DI-C-(HYDROXYMETHYL)-3-DEOXY-FURANORONO-1,4-LACTONE IN THE FORMOSE REACTION+

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The formose reaction, by which a complex mixture of sugars and sugar alcohols (the so-called formose) are produced by the base-catalyzed condensation of formaldehyde, has received much attention in connection with the prebiotic synthesis of carbohydrates[2] and the microbial utilization of formose.[3-5] Formose, however, has not been useful yet, because of the complexity of this product mixture (Fig. 1a). Therefore, it seemed desirable to make the reaction more selective.

+Formose Reactions. Part 18. For Part 17, see ref. 1.

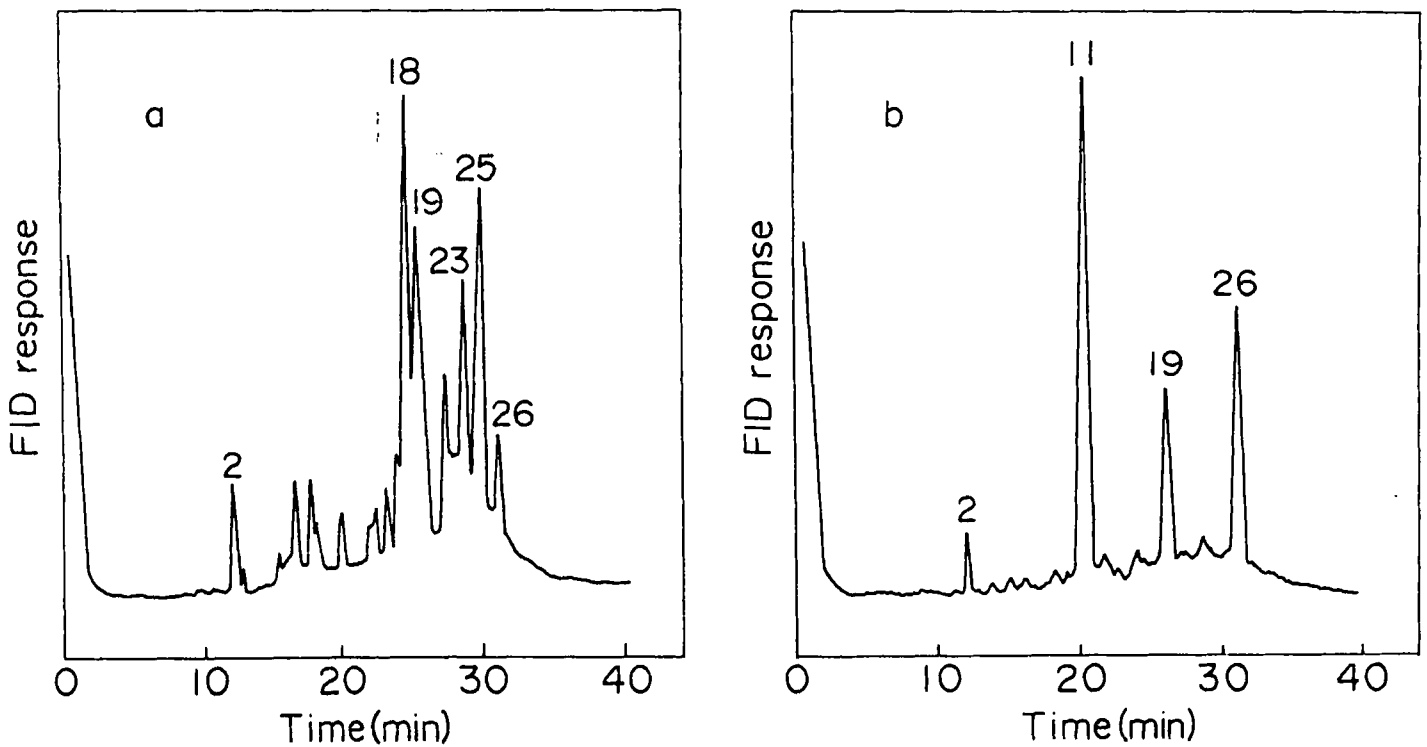


FIG. 1. The glc patterns of pertrimethylsilylated products obtained from (a) a conventional calcium oxide-catalyzed formose reaction in methanol starting from [HCHO]=1.0 M and [CaO]=0.15 M at 60°C, and (b) selective formose reaction in methanol starting from [HCHO]=1.0 M, [NaOH]= 1.0 M and [D-fructose]=1.39×10^{-2} M at 65°C.

After several attempts to gain insight into the formose reaction and to make it selective, we have succeeded in isolating products from several reaction mixtures and have identified them as follows: 2-C-(hydroxymethyl)glycerol,[6-10] 3,-C-(hydroxymethyl) pentitol,[6,7,9,10] 2,4-di-C-(hydroxymethyl)pentitol,[6,7,9,10] 2,4-di-C-(hydroxymethyl)pentulose,[11,12] pentaerythritol,[8] and 3-C-(hydroxymethyl)pentofuranose.[13] Herein, we wish to report an aspect of the formose reaction in a non-aqueous solvent, the sodium hydroxide catalyzed reaction in methanol, which is shown to produce a branched lactone as the major product. In a typical experiment, the reaction was started with 1.0 M methanolic formaldehyde in the presence of sodium hydroxide (1.0 M) and D-fructose (1.39×10^{-2} M) at 65 °C under nitrogen. At ca. 90% consumption of formaldehyde (15-20 min), the reaction was stopped by acidifying the reaction mixture to pH 6-7 with 9N methanolic HCl. Sugar yield (35% as glucose) was determined by the phenol-sulfuric acid method.[14] The formose was pertrimethylsilylated and analyzed by gas-liquid chromatography. The gas chromatogram shown in Fig. 1b indicates the somewhat selective formation of the product corresponding to peak number 11 (33 glc%).

The product corresponding to peak 11 was isolated by chromatography on charcoal with water as the eluent. The product (1) was obtained as colorless crystals (mp. 161 °C). The ^{13}C-NMR spectrum (CD_3OD; internal standard, Me_4Si) showed three CH_2 carbons (61.94 t, 62.23 t, 70,52 t), a CH carbon (70.27 d), a quarternary carbon atom (50.97 s) and a carbonyl carbon atom (179.45 s). The ^{1}H NMR spectrum of the compound ($(CD_3)_2SO$; internal standard, Me_4Si) showed four equivalent CH_2 protons at δ 3.44 (s, 4H), CH_2 protons at δ 4.15 (2H, J=9 Hz) and a CH proton at δ 4.36 (s,1H). The chemical ionization spectrum, using isobutane as a reagent gas, showed an M+1 ion at m/z 163 (base peak), consistent with the molecular formula of $C_6H_{10}O_5$. The chemical ionization mass spectrum using ammonia as a reagent gas showed characteristic ions at m/z 180 ($M+NH_4^+$, base peak), and 150 ($M+NH_4^+$ - HCHO). The shift of the ion at m/z 180 in the $CI(NH_3)$ mass spectrum to m/z 187 ($d_3M+ND_4^+$) in the $CI(ND_3)$ mass spectrum indi-

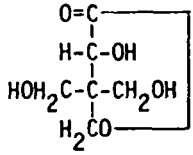
cated that three active hydrogens of hydroxy group were present in the product (1). The IR spectrum of 1 contained a strong as follows: 2-C-(hydroxymethyl)glycerol,[6-10] 3,-C-(hydroxymethyl) pentitol,[6,7,9,10] 2,4-di-C-(hydroxymethyl)pentitol,[6,7,9,10] 2,4-di-C-(hydroxymethyl)pentulose,[11,12] pentaerythritol,[8] and 3-C-(hydroxymethyl)pentofuranose.[13] Herein, we wish to report an aspect of the formose reaction in a non-aqueous solvent, the sodium hydroxide catalyzed reaction in methanol, which is shown to produce a branched lactone as the major product.

In a typical experiment, the reaction was started with 1.0 M methanolic formaldehyde in the presence of sodium hydroxide (1.0 M) and D-fructose (1.39×10^{-2} M) at 65 °C under nitrogen. At ca. 90% consumption of formaldehyde (15-20 min), the reaction was stopped by acidifying the reaction mixture to pH 6-7 with 9N methanolic HCl. The formose was pertrimethylsilylated and analyzed for total sugar[14] (35%) by gas-liquid chromatography. The gas chromatogram shown in Fig. 1b indicates the somewhat selective formation of the product corresponding to peak number 11 (33 glc%).

The product corresponding to peak 11 was isolated by chromatography on charcoal with water as the eluent. The product (1) was obtained as colorless crystals (mp. 161 °C). The ^{13}C-NMR spectrum (CD_3OD; internal standard, Me_4Si) showed three CH_2 carbons (61.94 t, 62.23 t, 70.52 t), a CH carbon (70.27 d), a quarternary carbon atom (50.97 s) and a carbonyl carbon atom (179.45 s). The ^{1}H NMR spectrum of the compound ($(CD_3)_2SO$; internal standard, Me_4Si) showed four equivalent CH_2 protons at δ 3.44 (s, 4H), CH_2 protons at δ 4.15 (2H, J=9 Hz) and a CH proton at δ 4.36 (s,1H). The chemical ionization spectrum, using isobutane as a reagent gas, showed an M+1 ion at m/z 163 (base peak), consistent with a molecular formula of $C_6H_{10}O_5$. The chemical ionization mass spectrum using ammonia as a reagent gas showed characteristic ions at m/z 180 ($M+NH_4^+$, base peak), and 150 ($M+NH_4^+$ - HCHO). The shift of the ion at m/z 180 in the CI(NH_3) mass spectrum to m/z 187 ($d_3M+ND_4^+$) in the CI(ND_3) mass spectrum indi-

cated that three active hydrogens of hydroxy group were present in the product (1). The IR spectrum of 1 contained a strong band at 1770 cm^{-1} indicative of a γ-lactone.

The above results led us to assign the product corresponding to peak 11 as 3,3-di-C-(hydroxymethyl)-3-deoxy-furanorono-1,4-lactone 1.



1

At present, we have not explained why 1 is formed with such selectivity under the reaction conditions employed. However, the formation of 1 is of interest from the standpoint of the prebiotic syntheses of deoxy sugars. We are now undertaking studies on the mechanistic elucidation for the selective formation of 1.

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