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A SELECTIVE SYNTHESIS OF 3-C-(HYDROXYMETHYL)PENTOFURANOSE IN THE FORMOSE REACTION[1)]

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A selective formose reaction was found to occur giving 3-C-(hydroxymethyl)-pentofuranose with high selectivity, when the major part of the dissolved calcium ions were removed as sparingly soluble salts at the end of the induction period, followed by the addition of $Pb_2O(OH)_2$ and by adjusting the pH to 10.0 with aqueous KOH, succesively.

In a series of our studies[3-6)] on the formose reaction, the oxidation-reduction potential (ORP) of the reaction mixture has been measured as an indication of the reaction process. The reaction catalyzed by only calcium hydroxide in aqueous media, which gives rise to a product mixture of 30 or more very complex components (Fig. 1a), proceeds via three distinct steps: (1) the induction period during which a small amount of formaldehyde condensation products of C_2 and C_3 would be formed; (2) the formose-forming step at which formose formation occurs rapidly and the yield of formose sugars reaches a maximum when the ORP shows a maximum and the reaction mixture shows yellow coloration (the so-called yellowing point[7)]); (3) the third step includes the decomposition of the formed formose sugars under the reaction conditions.

At the end of the induction period, at which ORP shows a minimum, the equivalent amount of oxalic acid to the catalyst, $Ca(OH)_2$, and another metal hydroxide, for example $Mg(OH)_2$, were successively added, then the reaction was immediately restarted by adjusting the mixture to a given pH with conc. KOH. The selective formose reaction was found to occur giving three branched sugar alcohols, 2-C-(hydroxymethyl)glycerol, 2,4-di-C-(hydroxymethyl)pentitol, and probably a diastereomeric mixture of 3-C-(hydroxymethyl)pentitol.[5,6)] On the other hand, it has been already reported that addition of $Pb_2O(OH)_2$ instead of $Mg(OH)_2$ resulted in a different selective reaction giving peak 18 product as the major one (Fig. 1b).[5,6)]

In a typical run, the reaction was started with 1.0 M aqueous formaldehyde solution in the presence of $Ca(OH)_2$ (0.1 M) at 60°C. The progress of the reaction was followed by the ORP measurement. At T_{min} (the time when the induction period is terminated) an equivalent amount of oxalic acid (0.1 M) was added to precipitate the dissolved calcium ions as oxalates, followed by addition of $Pb_2O(OH)_2$ (0.1 M) and adjusting the pH to 10.0 with an aqueous KOH, the formose reaction was restarted. At T_{max} (the time when the sugar yield becomes maximum), the reaction was stopped by

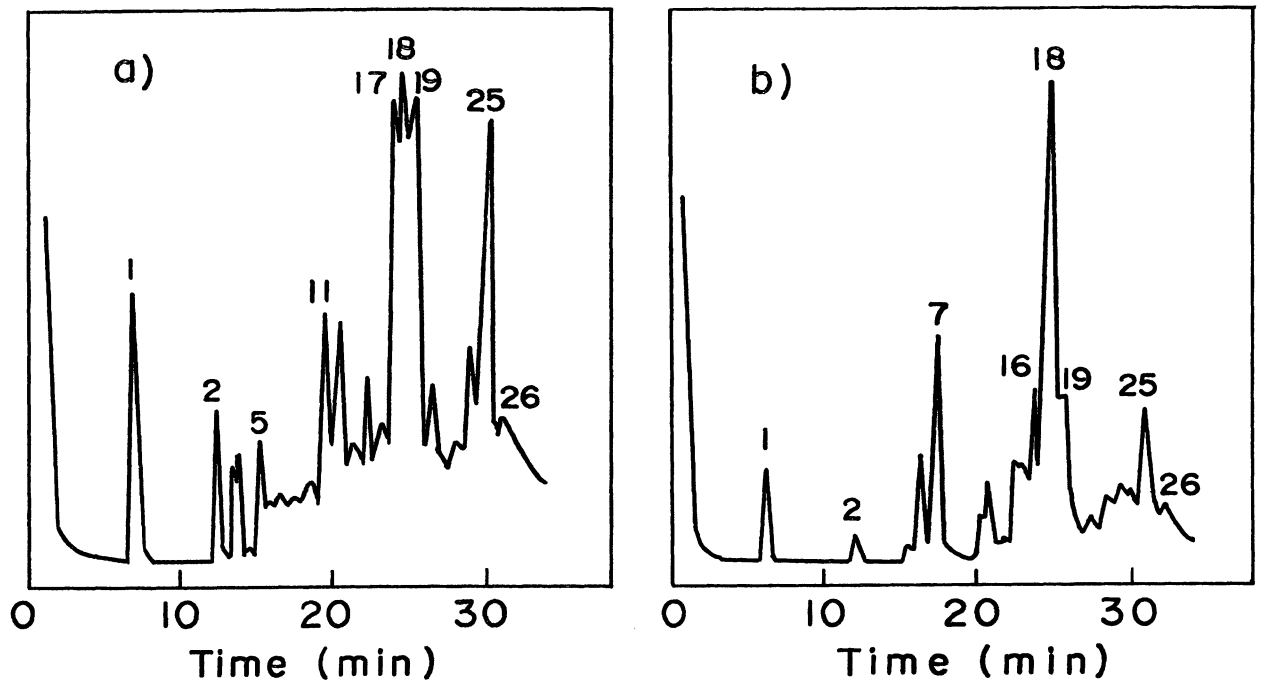
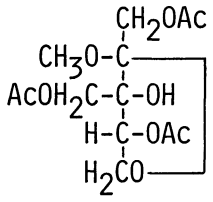


Fig. 1 The glc patterns of trimethylsilylated products from: (a) The usual calcium hydroxide-catalyzed formose reaction starting from [HCHO]=2.0 M and $[Ca(OH)_2]$= 0.22 M at 60°C,[3,4] and (b) the selective formose reaction starting from [HCHO]=1.0 M and $[Ca(OH)_2]$=0.1 M at 60°C followed by removing calcium ions with the addition of oxalic acid at the end of the induction period, by the addition of $Pb_2O(OH)_2$ (0.1 M), and by adjusting the pH to 10.0 with aqueous KOH, successively.

acidifying the mixture, which was then analyzed for total sugar (64% as glucose based on starting formaldehyde)[8] and the product distribution was determined by glc of trimethylsilylated products. Quite importantly, the glc pattern shown in Fig. 1b indicates the selective formation of a product corresponding to peak 18.

A colorless sirup (2.6 g) of products was methylated in methanol by sulfuric acid catalysis,[9] followed by acetylation of the methyl ether of the formose with acetic anhydride in pyridine.[9] The acetylated product corresponding to glc peak 18 (product 1) was isolated by chromatography on silica gel with methanol-benzene (5:95 v/v). (1.4 g) The product 1 was obtained in a crystalline form, mp. 96°C.[10] Its ^{13}C-nmr spectrum[11] showed a methoxy carbon, three equivalent CH_3s, three CH_2s, a CH, two tertiary carbons and three carbonyl carbons. Its chemical ionization mass spectrum using ammonia as reagent gas (CI(NH_3) mass spectrum) showed a quasi-molecular ion ($M+NH_4^+$) at m/z 338, which precisely indicated the molecular weight (320), besides, a predominant ion was observed at m/z 289 (oxionium-type ion; $M+NH_4^+-CH_3OH-NH_3$). In the CI(ND_3) mass spectrum of the product 1, an ammonium adduct ion ($M+NH_4^+$) observed at m/z 338 in CI(NH_3) mass spectrum was shifted to m/z 343. This latter ion corresponds to $d_1M+ND_4^+$, which shows the presence of one active hydrogen in the molecule. Above results and ^1H-nmr spectrum of the product 1[12] led us to assign structure 1 (methyl 1,4,6-tri-O-acetyl-3-C{hydroxymethyl)pentofuranoside) for the product 1.

Deacetylation of the product 1 with barium hydroxide[13] gave product 2 as a colorless sirup. Its ^{13}C-nmr spectrum[14] showed a methoxy carbon, three CH_2s, a CH, and two tertiary carbons. Its CI(NH_3) mass spectrum exhibited characteristic ions at m/z 212 ($M+NH_4^+$), 180 ($M+NH_4^+-CH_3OH$, base peak), 163 ($180-NH_3^+$). Shift of the ion at m/Z 212 in the CI(NH_3) mass spectrum to m/z 220 in the CI(ND_3) mass spectrum indicated that four active hydrogens of hydroxy group were present in the product 2. The results led us to assign structure 2 (methyl 3-C-(hydroxymethyl)pentofuranoside) for the product 2.



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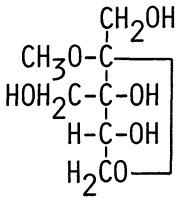

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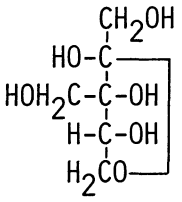

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Demethylation of the product 2 with 4% aqueous hydrochloric acid gave product 3 as a colorless sirup, which trimethylsilyl derivative showed the same retention time as the product corresponding to peak 18. Its CI(NH_3) mass spectrum showed an ammonium adduct ion at m/z 198, which shifted to m/z 207 in the CI(ND_3) mass spectrum. These results demonstrated that the molecular weight of the product 3 was 180 and five active hydrogens were involved in the molecule.

Reduction of the product corresponding to peak 18 with sodium borohydride gave a product as a colorless sirup. The glc retention time of its trimethylsilylate was the same as that of 3-C-(hydroxymethyl)pentitol.

Based on the above results, we propose structure 3 (3-C-(hydroxymethyl)pentofuranose) for peak 18 product.

The selective formation of such aldoses or ketoses as 3 in the formose reaction is significant. Likholobov et al.[15] also reported that the formose reaction has a 75.4 wt% selectivity for glucose at 18% conversion, and no branched species were identified. However, they could not isolate glucose from the reaction mixture. To the best of our knowledge, no one has succeeded to isolate and identify the formose components from the reaction mixture, except for our previously reported sugar alcohols[5,6,16,17] and ketose[18]: 2-C-(hydroxymethyl)glycerol, pentaerythritol, 2,4-di-C-(hydroxymethyl)pentitol, 3-C-(hydroxymethyl)pentitol, and 2,4-di-C-(hydroxymethyl)-3-pentulose.

At the moment there is no reasonable explanation for the occurrence of the present selective formose formation. We are undertaking toward mechanistic elucidation of the selective formose reaction and a search of other types of selectivity.

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10) Satisfactory microanalytical data for $C_{13}H_{20}O_9$ were obtained for this compound.
11) ^{13}C-nmr ($CDCl_3$) (chemical shifts given in parts per million from Me_4Si and the multiplicities based on an off-resonance spectrum and number of carbon are given in parenthesis): 20.1(q, 3), 48.4(q, 1), 57.9(t, 1), 66.2(t, 1), 68.8(t,1), 75.3(d, 1), 79.3(s, 1), 106.6(s, 1), 169.3(s, 1), 169.6(s, 1), 170.5(s, 1).
12) ^1H-nmr (C_6D_6; internal standard, Me_4Si): δ 1.58, 1.64, and 1.65(3s, 9H, $-COCH_3$), 3.03(s, 3H, $-OCH_3$), 3.28(br. s, 1H, -OH), 3.70(m, 1H, CH_aH-), 4.10(m, 1H, $-CH_bH$-), 4.65(m, 4H, $-CH_2O$-), 5.51(m, 1H, $-\dot{C}H_x$), $J_{Ha,Hb}$=9.0 Hz, J_{HaHx}=6.0 Hz, $J_{Hb,Hx}$=7.5 Hz.
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14) ^{13}C-nmr (D_2O) (see note 11): 49.4(q, 1), 57.1(t, 1), 63.2(t, 1), 71.1(t, 1), 72.9(d, 1), 82.4(s, 1), 110.1(s, 1).
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