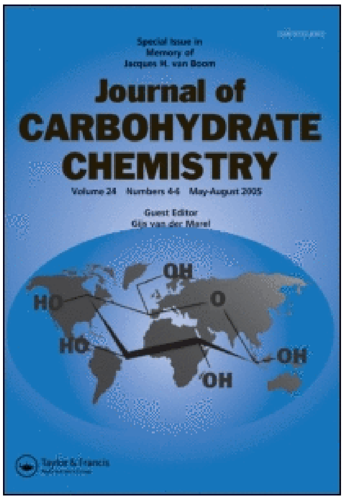

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First Synthesis of DL-2-*C*-Hydroxymethyl-3-Pentulose in the Formose Reaction

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COMMUNICATION

FIRST SYNTHESIS OF DL-2-C-HYDROXYMETHYL-3-PENTULOSE IN THE FORMOSE REACTION*

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The formose reactions[2] in N,N-dimethylformamide (DMF) catalyzed by 2-(dimethylamino)ethanol and thiamine hydrochloride, have been found to give rise to dihydroxyacetone and DL-glycero-tetrulose selectively at 1.1 M and 3.0 M of formaldehyde concentration, respectively. In our consecutive study on the formose reaction in DMF, it has been fortunately found that the distribution of products is able to be controlled by the amount of water added to the reaction mixture. We describe herein the first example of the favored formation of DL-2-C-hydroxymethyl-3-pentulose (GP-19[1]) in the formose reaction using DMF-H_2O solvent, and it's isolation and structure elucidation.

In a typical experiment, the reaction was performed with N,N-dimethylformamide (138 mL), H_2O (17 mL), and 3.0 M formaldehyde (17.1 g)

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*Formose reactions. Part 26. For Part 25, see ref. 1.

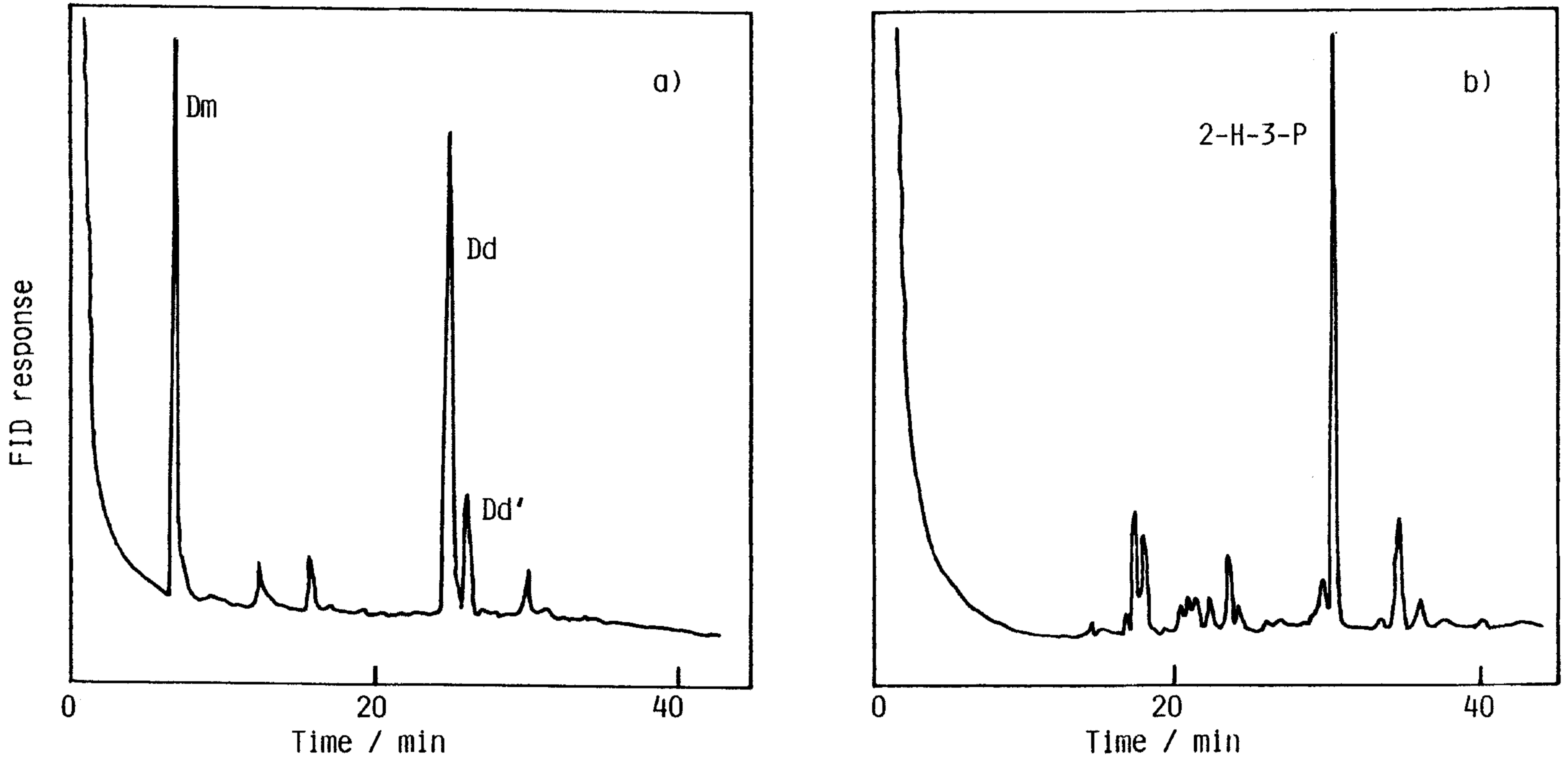
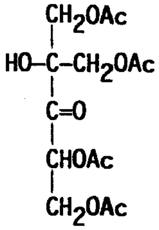


Fig. 1. GLC patterns of pertrimethylsilylated products obtained from selective formose reactions in: (a) N,N-dimethylformamide in the presence of 1.1 M formaldehyde, 28 mM thiamine hydrochloride, and 0.11 M 2-(dimethylamino)ethanol at 60°C, (b) 138 mL N,N-dimethylformamide and 17 mL water in the presence of 3.0 M formaldehyde, 50 mM thiamine hydrochloride, and 0.3 M triethylamine at 75°C.
Dm, Dd, and Dd': monomer and diastereomeric dimers of dihydroxyacetone;
2-H-3-P: 2-hydroxymethyl-3-pentulose.

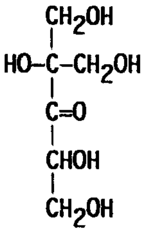
in the presence of 1M triethylamine (25 mL) and 50 mM thiamine hydrochloride (3.0 g) at 75°C under nitrogen. At various time-intervals, aliquots (5 mL) were transferred into a 10-mL flask and the reaction was quenched immediately by acidification with 9M hydrochloric acid. These aliquots were analyzed for formaldehyde by the method of Bricker and Johnson,[3] except that the absorbance was measured at 579 nm. The product distribution as pertrimethylsilylated products was determined by GLC, the pattern of which (Fig. 1b) clearly indicated the favored formation of a product corresponding to peak number 19^1 (GP-19^1) (30% by GLC).

After 1 h, the reaction mixture was neutralized and concentrated to ca. 50 mL under reduced pressure (25-30°C /1 mmHg), then the concentrate was passed through a column of active carbon with water as eluent. Concentration of the filtrate gave a pale-yellow syrup (14.2 g, contained GP-19^1 28% by GLC). GP-19^1 (1.3 g, a colorless syrup) was isolated by repeating chromatography on cellulose powder with wet n-butanol as eluent; ν_{max} 3300-3400 (O-H) and 1710 (C=O) cm^{-1}; ^1H NMR(D_2O; int. standard, sodium2,2-dimethyl-2-silapentane-5-sulfonate): δ 3.61(d, 2H, J=11.7 Hz, -C(OH)(HCHOH)(HCH-OH)), 3.83(d, 1H, J=11.7 Hz, -C(OH)-(HCHOH)(HCHOH)), 3.83(dd, 1H, J=5.4 and 12.2 Hz, -HC(OH)(**H**CHOH)), 3.85(d, 1H, J=11.7 Hz, -C(OH)(HCHOH)(HC**H**OH)), 4.00(dd, 1H, J=3.4 and 12.2 Hz, -HC(OH)(HC**H**OH)), and 4.86(dd, 1H, J=3.4 and 5.4 Hz, O=C-C**H**(OH)-); ^{13}C-n.m.r.(D_2O, int. standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate): δ 64.9(t), 66.4(t), 67.4(t), 78.5(d), 86.8(s), and 217.4(s), corresponding to 3 CH_2, a CH, and a quarternary C groups, and a carbonyl C atom. After acetylation with acetic anhydride in pyridine, the acetylated product **1** was isolated by thin layer chromatography on silica gel with methanol-benzene (1:10 v/v) at R_f=0.26. The product **1** was obtained as a colorless syrup; ν_{max} 3400-3450 (O-H), 2920, and 1740 (C=O) cm^{-1}; ^1H NMR($CDCl_3$; int. standard, Me_4Si): δ 2.09, 2.10, 2.13, and 2.16 (each peak: s, 3H, -C=OCH_3), 3.95(s, 1H, -OH), 4.25 and 4.27(d, 1H, J=11.7 Hz, -C(OH)(HC**H**-OAc)(HCH-OAc) and -C(OH)(HCH-OAc) (HC**H**-OAc)), 4,38 and 4.40(d, 1H, J=11.7 Hz, -C(OH)(**H**CH-OAc)(HCH-OAc) and -C(OH)(HCH-OAc)(**H**CH-OAc)), 4.42(dd, 1H, J=5.9 and 12.2 Hz, -HC(OAc)-**H**CH-OAc), 4.65(dd, 1H, J=2.9 and 12.2 Hz, -HC(OAc)-HC**H**-OAc), and 5.82(dd, 1H, J=2.9 and 5.9 Hz, -**H**C(OAc)-HCH-OAc); ^{13}C NMR($CDCl_3$; int. standard, Me_4Si): δ 20.4(q), 20.6(2q), 20.7(q), 61.7(t), 65.9(t), 66.7(t), 74.3(d), 77.2(s), 170.0(s), 170.6(s), 170.9(s), 171.6(s), and 203.9(s) corresponding to 4 O=C-CH_3, 3 **C**H_2, a **C**H, a quaternary **C**, and 4 O=**C**-CH_3 groups and a carbonyl C atom; m.s.(70 eV); m/z 349(MH^+, 3), 331(MH^+-H_2O, 31), 217(44), 173(76),131(86), 61(100). Thus, the structure of the product **1** was established as **D**L-1,4,5,6-tetra-*O*-acetyl-2-*C*-hydroxymethyl-3-pentulose. GC-MS of pertrimethylsilylated derivative of GP-19[1] (70 eV); m/z 540(M^+, 2), 525(M^+-CH_3, 4), 435(M^+-CH_3-Me_3SiOH, 31), 309(97), 308(92), 218(92), 156(97), 73(24).



$$\begin{array}{c} CH_2OAc \\ | \\ HO-C-CH_2OAc \\ | \\ C=O \\ | \\ CHOAc \\ | \\ CH_2OAc \end{array}$$

1



$$\begin{array}{c} CH_2OH \\ | \\ HO-C-CH_2OH \\ | \\ C=O \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

2

These results indicate that the product corresponding to peak number 19[1] (GP-19[1]) is **D**L-2-hydroxymethyl-3-pentulose (2-H-3-P)(**2**).

On the basis of the formation of 2-H-3-P it is suggested that 3-pentulose would be a precursor of 2-H-3-P and should be formed selectively in the formose reaction under suitable reaction conditions. We have got the experimental results supporting the formation of 3-pentulose in the formose reaction catalyzed by thiamine hydrochloride and $Pb_2O(OH)_2$ in dimethylsulfoxide and have tried to isolate 3-pentulose from the formose. We are now undertaking studies on the mechanistic elucidation for the favored formation of 2-H-3-P. It has become apparent that 2-H-3-P would be a precursor of 2,4-bis(hydroxymethyl)-3-pentulose and 2,4-bis(hydroxymethyl)pentitol which are formed selectively and isolated from the formose.[4]

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