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One-step Synthesis of Straight-chain Carbohydrates from Formaldehyde and Syngas

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Straight-chain carbohydrates such as trioses, tetroses, pentoses, and hexoses are readily obtained in good yields by a reaction of formaldehyde with syngas in the presence of RhCl(CO)$(PPh_3)_2$ and tertiary amine. A selective synthesis of trioses or tetroses is also described.

The formose reaction, which is the only known method for synthesizing carbohydrates and their analogues in one step, has recently attracted increasing attention because of its potential importance to the production of polyols and bio-utilizable carbohydrates.1) However, the formose reaction gives a mixture of manifold products containing large quantities of branched-chain isomers.1) Although the selective syntheses of dihydroxyacetone2) and some branched-chain carbohydrates3) have been reported, the methods for obtaining straight-chain carbohydrates other than trioses have scarcely been investigated.4) We have found that straight-chain carbohydrates are formed under certain conditions in the hydroformylation of formaldehyde to glycol aldehyde.5) This carbohydrate formation reaction is superior to the formose reaction as regards of the raw materials, because these carbohydrates are formed from syngas and formaldehyde. Herein, our results concerning the selective synthesis of straight-chain carbohydrates are described.

The experimental procedure is as follows: Paraformaldehyde(622 mg, $CH_2O = 20$ mmol),6) RhCl(CO)$(PPh_3)_2$(69 mg, 0.1 mmol), and a pyridine solution(10 ml) containing tertiary amine were placed in a 54 ml stainless steel autoclave, which was charged with syngas($H_2/CO = 2$). The mixture was heated with vigorous stirring. After cooling and depressurizing, certain amounts of n-BuOH and 2-hydroxymethyl-2-methyl-1,3-propanediol were dissolved in the reaction mixture, which was directly analyzed by GC on a Chromosorb-101 column. The yields of methanol, glycol aldehyde, and ethylene glycol were determined on the basis of the peak area of n-BuOH. Since a direct trimethylsilylation of the mixture was unsuited to the GC analysis for the carbohydrates because of the poor reproducibility, we employed an improved Kim's method,7) in which the carbohydrates were reduced with $NaBH_4$, followed by acetylation with acetic anhydride, and analyzed by GC on a OV-17 column using 2-acetoxymethyl-2-methylpropane-1,3-diacetate formed in situ as a standard.8) The gas chromatograms of a typical reaction mixture(I) and authentic samples(II) are shown in Fig. 1. Each isomer of the authentic samples was similar in retention time and almost equal in GC-sensitivity. Therefore, on the basis of the peak areas of gcp 1, gcp 3-4, gcp 5-7, and gcp 8 in I, the yields of straight-chain trioses (C_3), tetroses (C_4), pentoses (C_5), and hexoses (C_6) were estimated, respectively. The many small peaks which appeared in I are considered to be assigned to branched-chain compounds.

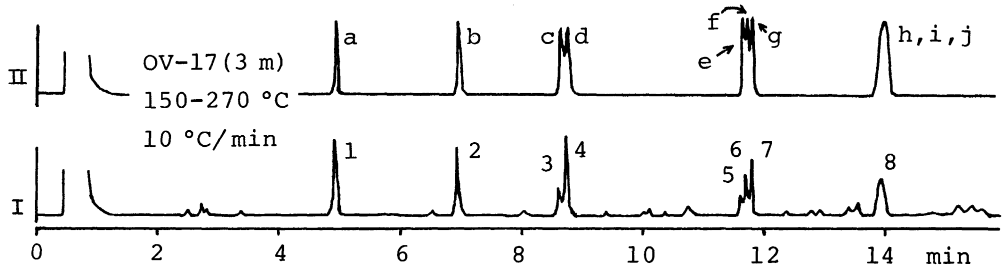

Fig. 1. Gas chromatograms of a typical reaction mixture(I) and authentic samples(II; acetates of glycerol(a), 2-hydroxymethyl-2-methyl-1,3-propanediol(b), erythritol(c), DL-threitol(d), D-adonitol(e), arabitol(f), xylitol(g), dulcitol(h), D-sorbitol (i), and D-mannitol(j)).

The results are shown in Table 1. As the carbohydrates were hardly formed in the absence of $RhCl(CO)(PPh_3)_2$ at 120 °C for 0.5 h, the formose reaction catalyzed by triethylamine is considered negligible under these conditions. The concentration and basicity of amines had a strong effect on the total carbohydrate yield ($\sum_{n=3}^{6} C_n$). When the reactions were carried out either in the presence of weak amines such as 1-methylimidazole and N,N-dimethylbenzylamine or under the low concentrations of triethylamine, the total carbohydrate yields were poor and the large amounts of glycol aldehyde were detected. On the other hand, the reaction in the presence of a strong base, 1-azabicyclo[2.2.2]octane(quinuclidine), gave low yields of both the carbohydrates and glycol aldehyde. In this case, many GC peaks of supposed branched-chain carbohydrates were found. Consequently, these results suggest that the carbohydrate formation reaction is due to an amine-catalyzed condensation of glycol aldehyde which is formed by the rhodium-catalyzed hydroformylation of formaldehyde(Eq. 1).$^{5)}$ The absorbed amounts of syngas indicated that further hydroformylation of glycol aldehyde to give carbohydrates did not occur. Therefore, the yields of products were calculated from Eqs. 1—6.

Table 1. Catalytic Synthesis of Straight-chain Carbohydrates from CH_2O and Syngas

Co-catalyst	Total	Product yield/%						$\sum_{n=3}^{6} C_n$/%
Amine/mol dm^{-3}	yield/% a)	MeOH	C_2 b)	C_3	C_4	C_5	C_6	
Triethylamine (0.04)	97	7	53	14	16	6	1	37
Triethylamine (0.1)	98	9	34	20	25	8	2	55
Triethylamine (0.2)	94	9	18	21	27	14	5	67
Triethylamine (0.2) c)	87	10	9	16	28	17	7	68
Triethylamine (0.2) d)	79	15	5	17	20	16	6	59
Triethylamine (0.4)	89	11	9	18	22	20	9	69
Quinuclidine (0.2)	64	10	3	8	15	18	10	51
N,N-Dimethylbenzylamine(0.2)	99	9	61	12	13	3	1	28
1-Methylimidazole (0.2)	88	5	75	5	2	1	0	8

The reactions were carried out at 120 °C for 0.5 h under 120 atm($H_2/CO = 2$). a) MeOH + $\sum_{n=2}^{6} C_n$. b) Total of $HOCH_2CHO$ and $HOCH_2CH_2OH$. c) For 1 h. d) At 140 °C.

$$CH_2O + CO + H_2 \longrightarrow HOCH_2CHO \quad (1) \qquad CH_2O + H_2 \longrightarrow CH_3OH \quad (2)$$

$$2\,CH_2O + CO + H_2 \longrightarrow C_3H_6O_3 \quad (3) \qquad 2\,CH_2O + 2\,CO + 2\,H_2 \longrightarrow C_4H_8O_4 \quad (4)$$

$$3\,CH_2O + 2\,CO + 2\,H_2 \longrightarrow C_5H_{10}O_5 \quad (5) \qquad 3\,CH_2O + 3\,CO + 3\,H_2 \longrightarrow C_6H_{12}O_6 \quad (6)$$

As this is a consecutive reaction, the yields of C_5 and C_6 increased with reaction time. An elevated reaction temperature caused an increase in the yields of C_5 and C_6, but the amounts of methanol and supposed branched-chain carbohydrates increased. Under favorable conditions, the total yield of the straight-chain carbohydrates was about 70%. The amount of branched-chain carbohydrates was estimated to be small, considering the material balance.

The syngas pressure had an effect on the selectivity for the respective carbohydrates. The C_3-selectivity was relatively high under a low pressure of syngas, though the total yield of carbohydrates was poor. This fact can be explained by the interpretation that the slow hydroformylation of formaldehyde caused the C_3-formation reaction(Eq. 3) to be dominant. The C_4-selectivity was conversely improved under a high pressure condition. On the basis of these facts, the selective synthesis of tetroses was examined under such conditions as to complete the hydroformylation(Eq. 1) in advance of the condensation reactions. The C_4-selectivity and the total carbohydrate yield were considerably improved at 100 °C for 2 h even in the presence of triethylamine. The use of a weak base, N,N-dimethylbenzylamine, further improved the selectivity. Under our best conditions (at 100 °C for 1 h and then 130 °C for 1 h), 66% of the C_4-selectivity was attained. The C_3-selectivity was studied in the presence of triethylamine and 3-ethylbenzothiazolium bromide. The yield of C_3 increased with increasing amounts of the thiazolium salt, and the other carbohydrates greatly decreased. On addition of 0.15 mol dm^{-3} of the salt, the C_3-selectivity went up to 87%.

Table 2. Selective Syntheses of Straight-chain Trioses(C_3) and Tetroses(C_4)

Amine and	Pressure	Total	Product yield/%						$\sum_{n=3}^{6} C_n$	Selectivity/%	
additive	atm	yield/%$^{a)}$	MeOH	$C_2$$^{b)}$	C_3	C_4	C_5	C_6		$C_3$$^{c)}$	$C_4$$^{d)}$
NEt_3	30	69	18	14	21	10	5	1	37	57	27
NEt_3	60	93	16	20	26	17	11	3	57	46	30
NEt_3	120	94	9	18	21	27	14	5	67	31	40
NEt_3 $^{e)}$	120	95	7	15	12	37	16	8	73	16	51
$PhCH_2N(CH_3)_2$ $^{f)}$	120	92	4	26	6	41	7	8	62	10	66
$NEt_3 - C_9H_{10}NSBr$$^{g)}$	120	86	0	22	31	19	11	3	64	48	30
$NEt_3 - C_9H_{10}NSBr$$^{h)}$	60	53	0	1	40	7	4	1	52	77	13
$NEt_3 - C_9H_{10}NSBr$$^{i)}$	120	48	0	1	41	4	2	0	47	87	9

The reactions were carried out in the presence of amine(0.2 mol dm^{-3}) at 120 °C for 0.5 h. a) MeOH + $\sum_{n=2}^{6} C_n$. b) Total of $HOCH_2CHO$ and $HOCH_2CH_2OH$. c) $C_3/\sum_{n=3}^{6} C_n$. d) $C_4/\sum_{n=3}^{6} C_n$. e) At 100 °C for 2 h. f) At 100 °C for 1 h and then at 130 °C for 1 h. g) 3-Ethylbenzothiazolium bromide(0.05 mol dm^{-3}) was used. h) 0.1 mol dm^{-3}. i) 0.15 mol dm^{-3}.

Since the thiazolium salt is known as a good catalyst for selective cross-acyloin condensation,[9)] at least this C_3-formation reaction is probably due to the acyloin condensation.

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