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ISOMER DISTRIBUTION DURING METHYL FUCOSIDE FORMATION BY THE FISCHER METHOD. FURTHER SUPPORT FOR THE PREVIOUSLY PROPOSED REACTION MECHANISM*

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ABSTRACT

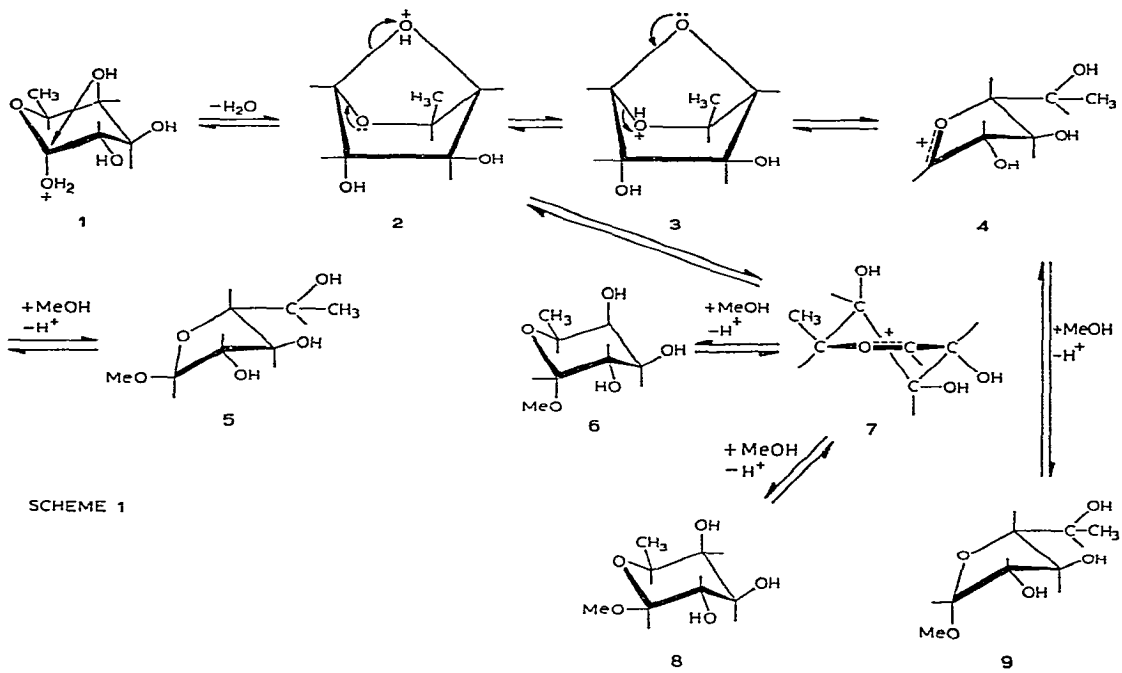
The formation of the four methyl L-fucosides by the Fischer reaction in boiling methanol, with a strongly acidic ion-exchange resin as catalyst, was followed by gas-liquid chromatography of their trimethylsilyl ethers. The initial rapid formation of all four methyl fucosides differs markedly and predictably from the behavior of D-galactose, which is enantiomeric with L-fucose except for the presence of the hydroxyl group at C-6 in the latter. It also differs somewhat from the behavior of L-arabinose, which is enantiomeric except for the absence of the methyl group at C-5. The initial boiling methanol solution may contain 5% of an L-fucofuranose, in addition to 38% of α-L-fucopyranose and 57% of β-L-fucopyranose. The final equilibrium mixture contains ~6% of methyl α-L-fucofuranoside, 13% of β-L-fucofuranoside, 54% of methyl α-L-fucopyranoside, and 27% of methyl β-L-fucopyranoside.

INTRODUCTION

In the previous paper of this series[1], the unusual behavior of D-galactose, when subjected to the Fischer reaction, suggested a bicyclic intermediate. D-Galactose is the only naturally occurring sugar in which the proposed bicyclic intermediate would be expected to be stabilized by double hydrogen-bonding between the hydroxyl group at C-6 and the two ring oxygen atoms. Attack of methanol upon this intermediate should produce initially the β-D-furanoside and α-D-pyranoside, experimentally observed in the case of D-galactose, instead of the two furanosides observed in all other cases so far investigated. No other sugars that have the structure of galactose necessary to form a doubly hydrogen-bonded bicyclic intermediate, *i.e.* opposite configurations of OH-4 and OH-5 plus a hydroxyl group at C-6, are readily available. Consequently, we investigated the behavior of L-fucose, a sugar enantiomeric in configuration with D-galactose but lacking the crucial hydroxyl group at C-6, necessary for stabilization of the bicyclic intermediate by internal hydrogen-bonding.

*This paper is number VII in a series utilizing chromatographic adsorption in the study of carbohydrate reaction mechanisms. For paper number VI, see Ref. 1.

L-Fucose, therefore, is not expected to yield initially one furanoside and one pyranoside, as in the case of D-galactose, but rather two furanosides or possibly both furanosides and both pyranosides. The previously proposed mechanism[1], as applied to the Fischer reaction of L-fucose, is shown in Scheme 1. Protonated α-L-fucopyranose (**1**) loses water to produce the bicyclic cation **2**, protonated on the ring oxygen atom at C-4, which is in equilibrium with the bicyclic cation 3, protonated on the ring oxygen atom at C-5. SN1 ring-opening of **2** yields the pyranose monocyclic carboxonium cation **7**, which, upon attack by methanol from either side of the ring followed by loss of a proton, produces methyl α-L-fucopyranoside (**6**) or methyl β-L-fucopyranoside (**8**). SN1 ring-opening of 3, on the other hand, yields the furanose monocyclic carboxonium cation **4**, which leads to methyl α-L-fucofuranoside (**9**) and methyl β-L-fucofuranoside (**5**).



SCHEME 1

DISCUSSION

Since no adsorbent material (g.l.c.) that completely resolves the six major components of the reaction mixtures was available, an OV-1 column that resolved all but two of the components, and an OV-17 column that resolved those two components were employed. The chromatograms on the OV-1 column and on the OV-17 column given by the per(trimethylsilyl)ated sample after a 5-min Fischer reaction are reported in Figs. 1 and 2, respectively. Peaks 4 of the OV-1 column and 2 of the OV-17 column were identified as those given by per-*O*-(trimethylsilyl)-α-L-fucose by comparison with

an authentic sample. Peaks 5 of the OV-1 column and 4 of the OV-17 column were identified as those given by per-*O*-(trimethylsilyl)-β-L-fucose by comparison with the chromatogram given by the per(trimethylsilyl)ated sample, taken at zero time, containing α- and β-L-fucose. Peak 2 of both columns was identified as that given by methyl 2,3,4-tri-*O*-(trimethylsilyl)-α-L-fucopyranoside by comparison with an authentic sample. Peak 3 of both columns was identified as that given by methyl 2,3,4-tri-*O*-(trimethylsilyl)-β-L-fucopyranoside by comparison with a silylated crystalline fraction, obtained from the final reaction mixture, that gave Peaks 2 and 3 on both columns and, before silylation, showed a specific rotation corresponding to that of a mixture of α- and β-pyranoside. Consideration of the ratios of the various peak areas in both chromatograms indicates that Peak 1 produced by both columns corresponds to one of the L-fucofuranosides and Peak 3 produced by the OV-1 column and Peak 2 by the OV-17 column correspond to the other L-fucofuranoside. In order to distinguish between the two furanosides, the sample of the 60-min reaction was examined, as it showed no unreacted L-fucose. The experimental $[M]_D$ was calculated as $(-6.77° \times 25.00 \times 164 \times 241) \times (4.34 \times 4 \times 45.6)^{-1} = -8400°$. If the first

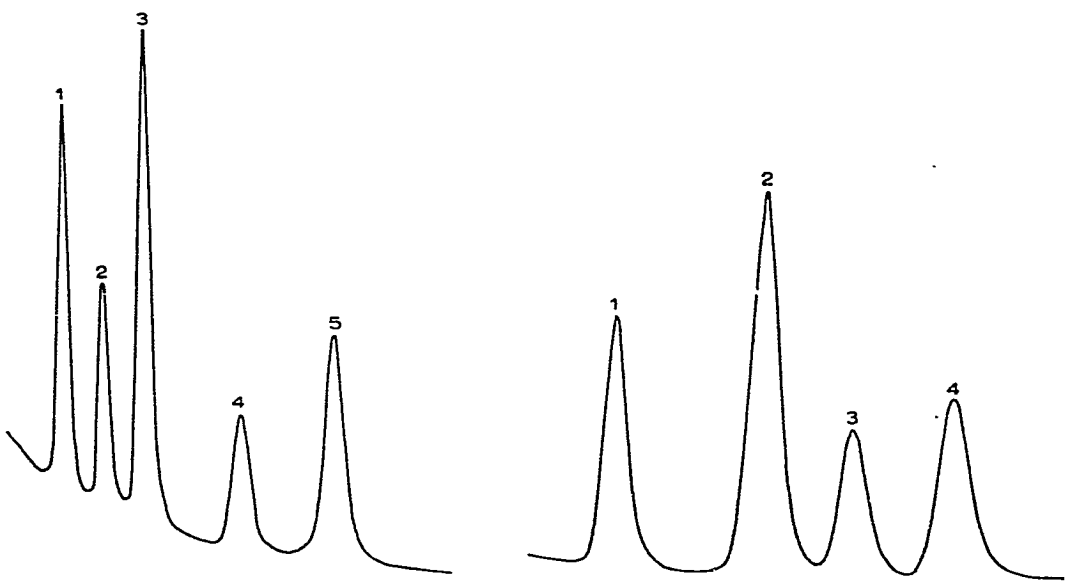


Fig. 1. G.l.c. pattern of the per(trimethylsilyl)ated Fischer-reaction products of treatment of L-fucose for 5 min, chromatographed at 180° and 3.5 kg/cm² on a 3.2 mm × 8 m copper column packed with 9% OV-1 on 80–100 mesh Chromosorb W-HP (Analabs, Inc., North Haven, Conn. 06473). Peak order and retention times (in min): 1, β-furanoside (18); 2, α-pyranoside (20); 3, α-furanoside, β-pyranoside, and γ-L-fucose (22); 4, α-L-fucose (26); and 5, β-L-fucose (31).

Fig. 2. G.l.c. pattern of the per(trimethylsilyl)ated Fischer-reaction products of treatment of L-fucose for 5 min, chromatographed at 180° and 3.5 kg/cm² on a 3.2 mm × 15 m stainless-steel column packed with 4.8% OV-17 on 80–100 mesh Anakron H (Analabs, Inc., North Haven, Conn. 06473). Peak order and retention times (in min): 1, β-furanoside and γ-L-fucose (37); 2, α-L-fucose, α-furanoside, and α-pyranoside (44); 3, β-pyranoside (48); and 4, β-L-fucose (53).

peak is assumed to be α-L-fucofuranoside, $[M]_D$ calculated from the ratios of each area to the sum of the areas, and from the values of the specific rotations taken from the literature[2] is $178[0.30(-108°)+0.36(-191°)+0.12(+112°)+0.22(+10.5°)] = -15{,}200°$. On the other hand, if the first peak is assumed to be β-L-fucofuranoside, the calculation gives $[M]_D$: $178[(0.30(+112°)+0.36(-191°)+0.12(-108°)+0.22(+10.5°)] = -8200°$. This figure is in good agreement, considering the experimental accuracy of the figures involved, with the calculated value of −8400°. The first peak on both columns is, therefore, identified as that corresponding to methyl 2,3,5-tri-*O*-(trimethylsilyl)-β-L-fucofuranoside and Peak 3 on the OV-1 column and Peak 2 on the OV-17 column as that corresponding to methyl 2,3,5-tri-*O*-(trimethylsilyl)-α-L-fucofuranoside.

The sample taken from the reaction at zero-time, after boiling α-L-fucose in methanol for 30 min but before introduction of the ion-exchange resin, showed a third peak in both columns, in addition to the two expected for per-*O*-(trimethylsilyl)-α- and per-*O*-(trimethylsilyl)-β-L-fucose. The retention time of this peak, which accounts for 5% of the total peak area, corresponds to the retention time of Peak 3 [methyl 2,3,5-tri-*O*-(trimethylsilyl)-α-L-fucofuranoside + methyl 2,3,4-tri-*O*-(trimethylsilyl)-β-L-fucopyranoside] on the OV-1 column and to the retention time of Peak 1 [methyl 2,3,5-tri-*O*-(trimethylsilyl)-β-L-fucofuranoside] on the OV-17 column. It cannot, therefore, have been produced by silylation of any of the four methyl L-fucosides, possibly formed prematurely by the presence of a trace of acid in the methanol used. The chromatogram on the OV-17 column of the per(trimethylsilyl)ated sample of α-L-fucose used in the reaction indicated 97.3% of α-L-fucose, 2.0% of β-L-fucose, and 0.7% of a peak having a retention time of 37 min, which corresponds to the unknown peak in the sample of zero reaction-time. It is suggested that this peak is produced by either per-*O*-(trimethylsilyl)-α- or per-*O*-(trimethylsilyl)-β-L-fucofuranose (γ-fucose in Table I). Further work is under way to verify this assumption.

RESULTS

Table I shows the variation with time of the molar proportion of each component in the Fischer reaction of L-fucose. These molar proportions were calculated from the relative peak areas given in Table II, assuming that the detector responses for the various compounds were approximately the same, as was found to be the case in the Fischer reactions[1] of D-glucose and D-galactose. It appears that both L-fucofuranosides and both L-fucopyranosides are formed simultaneously in the first stages of the reaction, in contrast to the initial formation of the β-furanoside and α-pyranoside in the case of D-galactose. This observation supports the mechanism proposed previously[1]. It might be expected that furanosides would form faster than pyranosides, as in the case of L-arabinose[3], since the basicity[1] and protonation of the oxygen atom at C-5 (3) should be greater than that of the oxygen atom at C-4 (2). However, since an ion-exhange resin is the source of protons, it is possible that the

methyl group at C-5 in the L-fucose bicyclic intermediate may sterically hinder protonation of the oxygen atom at C-5 to a greater extent than do the hydrogen atoms at C-5 in the corresponding L-arabinose bicyclic intermediate. Study of a model of the pyranose monocyclic carboxonium cation (7) indicates that an approximately equal blocking of an attack by methanol on the anomeric carbon would be expected

TABLE I

RELATIVE PROPORTIONS OF PRODUCTS OF THE REACTION OF L-FUCOSE[a]

Reaction time (min)	*L-Fucose*			*Furanosides*		*Pyranosides*	
	α	*β*	*γ*	*α*	*β*	*α*	*β*
0[b]	38	57	5				
1	29	44	5	7	6	4	5
5	11	22	2	16	21	13	15
10	4	6		20	30	19	21
15	2	2		18	34	23	21
30	1	1		14	35	27	22
60				12	30	36	22
120				10	25	43	22
240				8	18	49	25
480				7	14	54	25
720				6	13	54	27
1440				6	13	54	27

[a]In mol %. [b]After reflux for 30 min, but before addition of ion-exchange resin.

TABLE II

RELATIVE PEAK AREAS OF GAS-LIQUID CHROMATOGRAMS[a]

Reaction time (min)	*Peak number of column OV-1*					*Peak number of column OV-17*			
	1	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*
0[b]			5	38	57	5	38		57
1	6	4	17	29	44	11	40	5	44
5	21	13	33	11	22	23	41	15	21
10	31	19	41	4	5	30	42	21	7
15	34	23	39	2	2	34	42	21	3
30	35	27	36	1	1	35	42	22	1
60	30	36	34			30	48	22	
120	25	43	32			25	52	23	
240	18	49	33			18	57	25	
480	13	54	33			15	60	25	
720	13	54	33			13	60	27	
1440	13	54	33			13	60	27	

[a]Of the per(trimethylsilyl)ated sample, reported in %. [b]After reflux for 30 min, but before addition of ion-exchange resin.

from both sides of the ring, and would lead to the initial formation of α- and β-pyranoside at about equal rates. The same is true of the furanose monocyclic carboxonium cation (4), which would lead to approximately equal initial rates of formation of α- and β-furanoside, as was found experimentally.

EXPERIMENTAL

General. — L-Fucose was obtained from Nutritional Biochemicals Corporation (Cleveland, Ohio 44128) and showed $[\alpha]_D^{29} = -75.1°$ (*c* 2.0, water). Methyl α-L-fucopyranoside was crystallized from the final Fischer-reaction mixture and showed $[\alpha]_D^{25} = -192°$ (*c* 2.0, water). The polarimeter used for the measurements of optical activity was a Hilger and Watts standard instrument with a glass scale graduated in 0.01° divisions. Other materials were as specified in the previous paper in this series[1].

Formation of methyl L-fucosides. — Glycoside formation from L-fucose according to the procedure of Fischer was effected as described previously[1,3]. Complete solution of L-fucose (45.6 g) in boiling methanol (195 g) took place within 30 min before addition of Dowex-50W ion-exchange resin (H^+, 25 g, previously equilibrated with methanol). Equilibrium was reached in 12 h. The per(trimethylsilyl) ethers were prepared as previously described[1]. The optical rotations were determined on 5-ml samples, having the weights specified, after evaporation *in vacuo* and dilution to 25.00 ml with water at 20°. The following polarimeter readings were observed with a 4-dm tube, at 25–26°, with a sodium light: 0 min, −9.64°, 4.32 g; 5 min, −5.74°, 4.31 g; 10 min, −4.15°, 4.34 g; 15 min, −3.45°, 4.32 g; 30 min, −4.02°, 4.32 g; 60 min, −6.76°, 4.34 g; 120 min, −9.14°, 4.31 g; 240 min, −12.61°, 4.34 g; 480 min, −14.30°, 4.35 g; 720 min, −14.95°, 4.36 g.

Chromatography of the trimethylsilyl ether derivatives. — The chromatographic conditions and columns were as described previously[1], and all areas were determined with a planimeter. The volume of sample injected varied from 1–2 μl, and the electrometer had an attenuation of about 4×10^3. Table II gives the relative areas, expressed in %, under Peaks 1–5 for the OV-1 column (Fig. 1) and under Peaks 1–4 for the OV-17 column (Fig. 2).

REFERENCES

1 R. H. PATER, R. A. COELHO, AND D. F. MOWERY, JR., *J. Org. Chem.*, 38 (1973) 3272–3277.
2 J. G. GARDINER AND E. PERCIVAL, *J. Chem. Soc.*, (1958) 1414–1418.
3 D. F. MOWERY, JR., *J. Org. Chem.*, 26 (1961) 3484–3486.