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A MODIFICATION OF THE MECHANISM OF FORMATION OF METHYL GALACTOSIDES BY THE FISCHER REACTION INCLUDING A COMPUTER SIMULATION*

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ABSTRACT

The Fischer reaction of D-galactose and methanol, catalyzed by a strongly acidic ion-exchange resin, to form the four methyl galactosides has been run at two temperatures under conditions that allow a computer simulation of the mechanism. The reaction was followed by gas-liquid chromatography of the trimethylsilyl ethers. The data obtained differs appreciably from that described in a previous paper [*J. Org. Chem.*, 38 (1973) 3272–3277)] owing to an error in peak assignment in that paper. The mechanism previously proposed, however, has required only a slight modification to explain the new data. A possible set of rate constants, equilibrium constants, and *apparent* activation energies which fit the experimental data have been obtained.

INTRODUCTION

In a preceeding paper[2] we proposed a mechanism for the formation of the four methyl D-galactosides from D-galactose by the Fischer method using an ion-exchange resin as catalyst. That work was undertaken principally for use of the reaction as a means of preparing the four methyl galactosides. A relatively large quantity of D-galactose (50 g) was used and complete solution did not occur until 20–30 min into the reaction. For this reason, the reaction was not easily simulated by computer to test the proposed reaction scheme. In the present work, the amount of D-galactose used (3 g) was completely dissolved in the 250 mL of methanol either before the start (65° reaction) or within the first minute or two (53° reaction) of the reaction. Since the previous paper[2] was published, it has been shown that peak number 5 referred in that paper and also in the present paper is not methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**) but rather trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**7**) at the start of the reaction and

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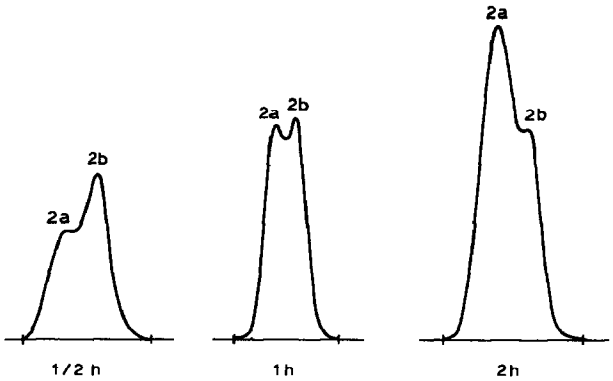
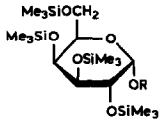


Fig. 1. G.l.c. patterns of peak number 2 of the silylated reaction mixture at three time intervals chromatographed at 174° on a 3.2 mm × 16 m OD-1 column.

2,3,4,5,6-penta-*O*-(trimethylsilyl)-*aldehydo*-D-galactose dimethyl acetal (**8**) later on. Since both of these compounds are present in only minor quantities (2% maximum total), they need not be included in the reaction scheme or composition calculations. It has also been found that peak No. 2, in this and the previous paper[2], which was thought to contain *only* 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**1**), actually also contains methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**) and trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-β-D-galactofuranoside (**7**). The second of these additional compounds occurs to the extent of only 8–10% in the reaction mixture, before addition of the ion-exchange resin, and would be expected to disappear very rapidly after the reaction starts. It, also, may therefore be neglected in the reaction scheme. A partial resolution of methyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**1**) from methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**) was possible with a longer chromatographic column, a lower temperature, and when they are present in not too widely divergent quantities, as shown in Fig. 1. Their respective percentages in the reaction mixture may therefore be calculated. Although the mechanism proposed previously was derived by use of incorrect data for the proportion of methyl α-D-galactofuranoside present, it appears that (with a small modification) this mechanism still predicts the experimental compositions, as demonstrated by a computer simulation. It also accounts for the difference observed in the behavior of D-galactose and L-fucose (6-deoxy-L-galactose), as well as the large difference in the initial (5 min) ratio of α- to β-galactofuranoside at 53° (8:5) as compared to that at 65° (16:25).

RESULTS AND DISCUSSION

Peak identification. — The equipment and chromatographic conditions used in this work are the same as those used in the previous investigation[2], and the two methyl galactopyranosides, and α- and β-D-galactopyranose were identified by the



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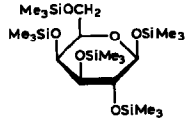
2 R = SiMe3



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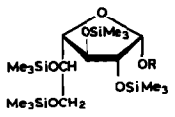
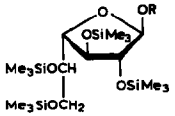
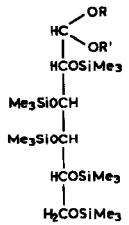


4 R = Me
5 R = SiMe3



6 R = Me
7 R = SiMe3



8 R = R' = Me
9 R = Me, R' = SiMe3

retention times of authentic samples of their per-*O*-(trimethylsilyl) derivatives. Compounds producing three new peaks have now been observed in the reaction mixture *before* addition of the ion-exchange resin catalyst. Acree *et al.*[3] separated the per-*O*-(trimethylsilyl) derivatives of the four tautomers of D-galactose by vapor-phase chromatography using an ethylcyanosilicone (XF-1150) as the stationary phase. They obtained peaks for the per-*O*-(trimethylsilyl) derivatives of β-D-galactofuranose (11 min), α-D-galactopyranose (14.5 min), α-D-galactofuranose (17.5 min), and β-D-galactopyranose (20.5 min). The pattern of these retention times agrees with that obtained with our OV-1 column (Fig. 2) of 41, 49, 54, and 58 min, respectively, where the peak at 49 min corresponds to trimethylsilyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**2**) and that at 58 min to trimethylsilyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-β-D-galactopyranoside (**3**); thus, the peak at 41 min corresponds to trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-β-D-galactofuranoside (**7**) and that at 54 min (peak No. 5) to trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**5**). These assignments are also supported by the observation that α-D-galactofuranose was found in appreciably smaller amount than β-D-galactofuranose in water solutions of D-galactose[4], and a similar distribution would be expected for a methanol solution. The third new peak having a retention time of 79 min, was observed *before* addition of the ion-exchange resin and up to 10–15 min thereafter. The compound corresponding to this peak has not yet been identified, but its retention time, small proportion (2–3%), and short life (10–15 min) are in keeping with the assumption that it is 2,3,4,5,6-penta-*O*-(trimethylsilyl)-*aldehydo*-D-galactose methyl trimethylsilyl acetal (**9**). Two new peaks were observed after addition of the resin catalyst, and one peak (No. 5), observed previously, has been reassigned (see Fig. 3). An authentic sample of *aldehydo*-D-galactose dimethyl acetal was trimethylsilylated and found to produce a peak (No. 5) having a retention time of 54 min identical with that of trimethylsilyl

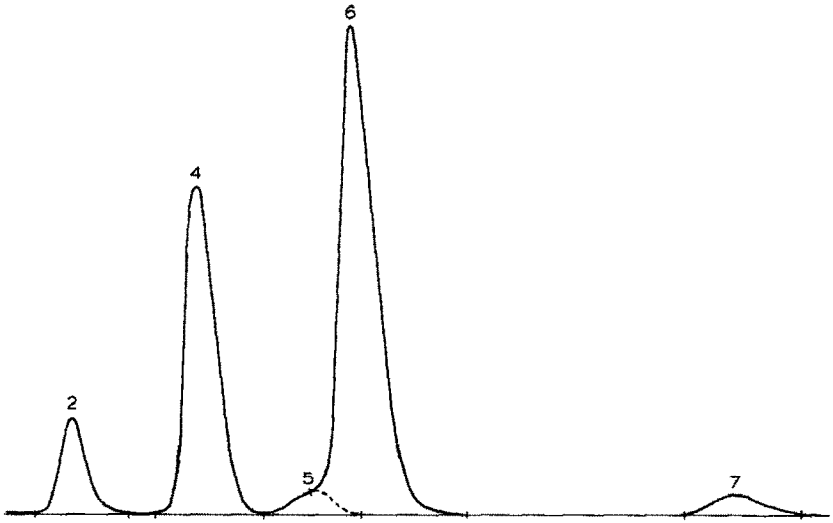


Fig. 2. G.l.c. pattern of the equilibrium mixture of D-galactose in boiling methanol after per-*O*-(trimethylsilyl)ation, chromatographed at 190° on a 3.2 mm × 8 m copper OV-1 column. Peak numbers and retention times: (2) β-furanose (**7**, 41 min), (4), α-pyranose (**2**, 49 min), (5), α-furanose (**5**, 54 min), (6) β-pyranose (**3**, 58 min), and (7) *aldehydo* methyl hemiacetal? (**9**, 79 min).

2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**6**). This peak was incorrectly assigned to methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**) in the previous paper[2]. Also, peak No. 2 has now been partially resolved into methyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**1**) and a second component which is believed to be trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**5**). The assignment of methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-

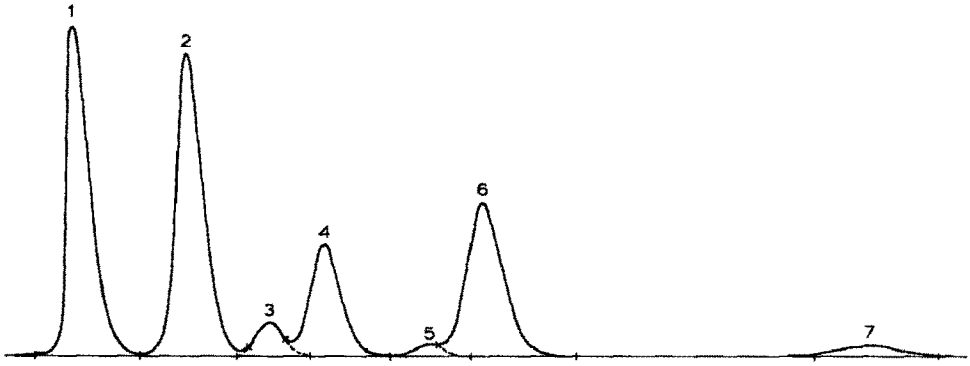


Fig. 3. G.l.c. pattern of the per-*O*-(trimethylsilyl)ated products of the Fischer reaction, 3 min after addition of the ion-exchanged resin to a boiling methanol solution of D-galactose, chromatographed under the conditions described in the legend to Fig. 2. Retention time (min), and molar proportion in percent: (1) β-furanoside (35, 28); (2) β-furanose, α-pyranoside, and α-furanoside (41, 30); (3) β-pyranoside (46, 3); (4) α-pyranose (49, 12); (5) α-furanose and *aldehydo* dimethyl acetal (54, 2); (6) β-pyranose (58, 23%); and (7) *aldehydo* methyl hemiacetal? (79, 2).

α-D-galactofuranoside (**1**) to this peak (17%, from Table I) and methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-β-D-galactofuranoside (**6**) to peak No. 1 (56%, from Table I) was deduced from the observation that the specific rotation of the 65° reaction mixture at about 1 h is negative, in keeping with the specific rotations for methyl α-D-galactofuranoside (17%) of +104°, for methyl β-D-galactofuranoside (56%) of −113°, for methyl α-D-galactopyranoside (17%) of +192°, and for methyl β-D-galactopyranoside (8%) of 0°. An unidentified compound having a retention time of 49 min, the same as that of trimethylsilyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**2**) appeared in the 53° reaction from 24–48 h to an extent of ~1% and in the 65° reaction from 2–48 h increasing from ~1% to 3%. This is neglected in Tables I and II.

Estimation of the composition of peak No. 2 (Fig. 2). — This peak was found to consist of methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**) and methyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**1**) which are not resolved by the 8-m column at 190°. A partial resolution of the 0.5-, 1-, and 2-h samples was obtained on a 16-m column at 174°, as shown in Fig. 1 for the 65° reaction mixture. In this figure, peak No. 2a represents methyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**1**), which is increasing with time, and peak No. 2b, methyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**4**), which is decreasing. The fraction of pyranoside **1** in the peak is approximately equal to the height of peak No. 2a divided by the height of peak No. 2a, plus the height of peak No. 2b. These data (asterisk) are shown in Table (III). The other data in this column were obtained by interpolation from a smooth curve starting at 0 for 0 time and passing through the points with asterisk and by extrapolation beyond the last point with asterisk. The molar proportions of α-D-pyranoside **1** and α-D-furanoside **4**, were obtained by applying these proportions to the total content determined for peak No. 2 by chromatography at 190° on an 8-m column. The 53°-reaction data were treated similarly.

Modification of the reaction scheme. — Because of the appreciably different data for methyl galactoside formation, as compared with that presented in the previous paper[2], the new reaction scheme was expected to be quite different. However, the same scheme (see Scheme 1, reactions **1–5**) with two modifications seems to predict the experimental data very well. The two modifications are the introduction of the interconversion of α-D-galactopyranose (**11**) and methyl β-D-galactopyranoside (**10**), and also the interconversion of α-D-galactopyranose (**11**) and methyl α-D-galactofuranoside (**12**) (see Scheme 1). The latter interconversion presumably would take place *via* β-D-galactofuranose, according to reaction (**2**) (Scheme 1). This would be expected to lead *initially* to a larger proportion of methyl α- than β-D-galactofuranoside (**12** and **15**, respectively). This is true for the reaction at 53° (23% of α *vs.* 14% of β), but not for the reaction at 65° (32% of α *vs.* 50% of β). This suggests that there is a secondary pathway of higher activation energy (*i.e.*, *via* the bicyclic intermediate, **14**, requiring 155 kJ/mol) to methyl β-D-galactofuranoside (**15**), which becomes the preponderant compound at the higher temper-

TABLE I

MOLAR PROPORTIONS[a] DURING THE FISCHER REACTION OF D-GALACTOSE WITH METHANOL AT 65°[b]

Time of reaction (h)	*Galactopyranose*		*Methyl furanoside*		*Methyl pyranoside*	
	α	β	α	β	α	β
0[c]	32	56				
1/12	4(3)	6(6)	32(32)	50(50)	4(4)	4(5)
1/6	1(1)	1(2)	25(26)	61(60)	7(7)	5(4)
1/4	1(1)	1(1)	20(22)	64(63)	9(9)	5(4)
1/2	1(1)	1(1)	19(20)	61(62)	12(12)	6(4)
1	1(1)	1(1)	17(18)	56(57)	17(17)	8(6)
2[d]	1(0)	1(1)	16(15)	46(48)	26(26)	10(10)
4[d]	1(0)	1(1)	13(11)	35(37)	35(37)	15(14)
8[d]	1(0)	1(0)	8(8)	23(24)	48(49)	19(19)
12[d]	1(0)	1(0)	5(5)	19(19)	54(55)	20(21)
24[d]	1(0)	1(0)	3(4)	17(16)	57(58)	21(22)
48[d]	1(0)	1(0)	2(4)	17(16)	58(58)	21(22)

[a]Relative to 100. [b]Computer-calculated values in parentheses. [c]Not shown: α-D-galactofuranose (2%), β-D-galactofuranose (8%), and *aldehydo*-D-galactose methyl hemiacetal (2%). [d]Not included, an unidentified product (1,1,2,3,3, and 3%, respectively).

TABLE II

MOLAR PROPORTIONS[a] DURING THE FISCHER REACTION OF D-GALACTOSE WITH METHANOL AT 53°[b]

Time of reaction (h)	*Galactopyranose*		*Methyl furanoside*		*Methyl pyranoside*	
	α	β	α	β	α	β
0[c]	32	53				
1/12	21(22)	39(39)	23(22)	14(15)	2(0)	1(2)
1/6	13(13)	24(24)	31(31)	27(27)	3(2)	2(3)
1/4	9(9)	17(16)	32(32)	35(36)	4(3)	3(4)
1/2	2(3)	5(5)	29(30)	54(53)	6(6)	4(3)
1	1(1)	1(2)	21(22)	64(63)	8(9)	5(3)
2	1(1)	1(2)	17(18)	64(63)	11(12)	6(4)
4	1(1)	1(1)	16(17)	59(58)	16(17)	7(6)
8	1(0)	1(1)	14(14)	51(50)	23(25)	10(10)
12	1(0)	1(1)	13(12)	42(42)	31(33)	12(12)
24[d]	1(0)	1(0)	8(8)	28(29)	46(46)	16(17)
48[d]	1(0)	1(0)	3(5)	18(19)	58(56)	19(20)

[a]Relative to 100. [b]Computer-calculated values in parentheses. [c]Not shown: α-D-galactofuranose (2%), β-D-galactofuranose (10%), and *aldehydo*-D-galactose methyl hemiacetal (2,3%). [d]Not included, an unidentified product (1%).

ature. Further evidence for the bicyclic intermediate **14** is the observation that L-fucose[1] (6-deoxy-L-galactose) behaves similarly to D-galactose in the initial α- to β-furanoside and α- to β-pyranoside equilibriums, but differs markedly in the initial furanoside-to-pyranoside equilibrium ratio (1.3:1 for L-fucose *vs.* 10:1 for D-

TABLE III

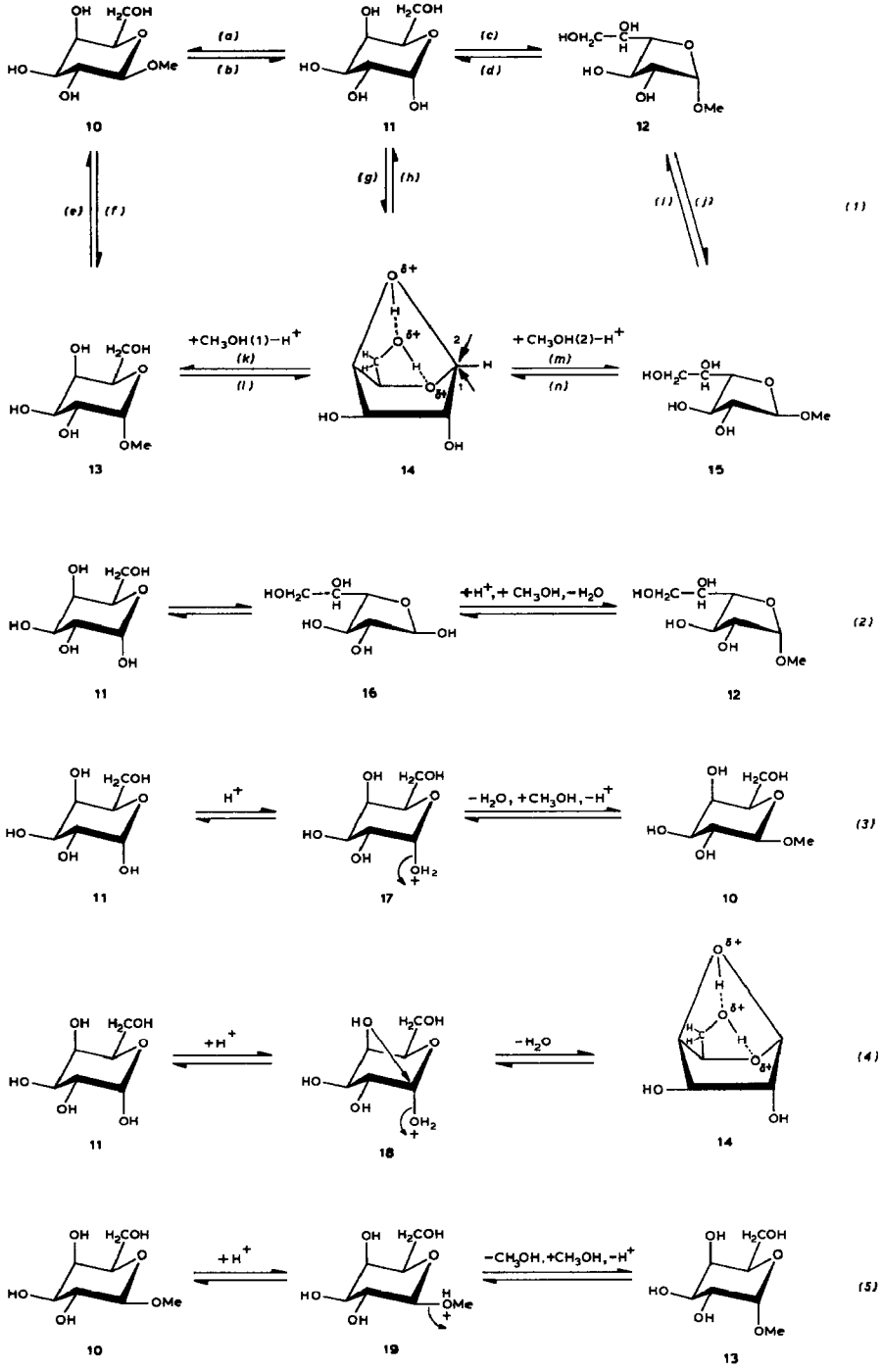
MOLAR PROPORTIONS OF α-D-PYRANOSIDE **1** AND α-D-FURANOSIDE FOR PEAK NO. 2[a]

Time of reaction (h)	*Reaction at*							
	53°				*65°*			
	Proportion of **1**[b]	*Peak No. 2*			*Proportion of* **1**[b]	*Peak No. 2*		
		Total	**1**	**4**		*Total*	**1**	**4**
1/12	0.06	25	2	23	0.13	36	4	32
1/6	0.08	34	3	31	0.23	32	7	25
1/4	0.10	36	4	32	0.28	29	9	20
1/2	0.18	35	6	29	0.39*	31	12	19
1	0.26*	29	8	21	0.49*	34	17	17
2	0.35*	28	11	17	0.60*	42	26	16
4	0.48*	32	16	16	0.73	48	35	13
8	0.60*	37	23	14	0.83	56	48	8
12	0.68	44	31	13	0.88	59	54	5
24	0.86	54	46	8	0.95	60	57	3
48	0.95	61	58	3	0.97	60	58	2

[a]Peak No. 2 of Fig. 2, see Fig. 1. [b]Relative to 100. Asterisk indicates values obtained by calculation from chromatographic double peaks.

galactose). The only difference being the presence of OH-6 in D-galactose, its presence is not expected to alter reactivity at C-1 appreciably, but would be expected to disperse the positive charge so as to stabilize a bicyclic intermediate and, thus, favor the conversion into furanosides rather than pyranosides. Although the positive charges on the two ring oxygen atoms of the bicyclic intermediate **14** would be expected to be about the same, it appears likely that the attacking nucleophile, methanol, would be oriented more toward the three positively charged oxygen atoms and, therefore, reaction (*h*) in (1) would be favored, to give preponderantly the β-furanoside rather than the α-pyranoside in the case of D-galactose. A more complicated mechanism could be written for this reaction which would include direct interconversions between β-D-galactopyranose and methyl α-D-galactopyranoside, and between α-D-galactofuranose and methyl β-D-galactofuranoside, but the mechanism proposed here appears to be the simplest one, capable of explaining all the experimental data.

Computer-generated composition data for the reaction. — The molar proportions calculated by computer (data in parentheses in Tables I and II) for the reaction *1* (Scheme 1) are in good agreement with the experimental data, the sum of the squares of the deviations being 66 for both the reaction at 53° (Table I) and the reaction at 65° (Table II). The rate constants generating these data, the equilibrium constants, and apparent activation energies calculated from them are listed in Table IV. These constants are probably not a unique set but are included merely to show that it is possible to construct a set of constants which will enable the



Scheme 1. Reaction scheme for Fischer glycosidation of D-galactose.

reaction scheme to be fitted to the experimental data. As the activation energies are calculated from the constants, they, also, are not true activation energies. Furthermore, increasing the temperature from 53 to 65° would increase the rate of diffusion of the various forms into and out of the ion-exchange resin, resulting in calculated activation energies larger than the true ones.

Comparison of the behavior of four hexoses. — Contrary to the conclusion of the previous paper[2], the present work shows that D-galactose is no different in the Fischer reaction from other hexoses investigated, all of which initially form furanosides that are later converted into pyranosides. A comparison of initial (1/12–1/8 h) ratios of furanosides to pyranosides, α- to β-furanoside, and α- to β-pyranoside at 65° is shown in Table V for four hexoses. As may be seen, the data for D-galatose differ appreciably from those previously[2] presented. The initial ratios of α- to β-furanoside and α- to β-pyranoside do not differ significantly from those of D-glucose and L-fucose. The larger ratios of α- to β-furanoside and α- to β-pyranoside for D-mannose have been explained before[2]. Possibly, the most interesting result of the present work is the large initial ratio of furanosides to pyranosides for D-galactose (10) as compared to L-fucose (1.3). This has been explained earlier in this work and in a previous paper[1]. The very large ratio of furanosides to pyranosides for D-glucose (10) has also been explained earlier[2]. It is probably due to the greater tendency of its bicyclic intermediate to protonate on the pyranoid ring oxygen, which would disperse positive charge to OH-6, rather than on the furanoid ring oxygen with no dispersal of charge. The pyranoid ring would then be cleaved to form a furanose monocarboxonium cation which would react with methanol to form methyl furanosides. In contrast to D-glucose, L-fucose has no

TABLE IV

RATE CONSTANTS, EQUILIBRIUM CONSTANTS, AND APPARENT ACTIVATION ENERGIES FOR MECHANISM *I*[a]

Reaction	*Rate constant (h^{-1}) at*		*Equilibrium constant at*		*Activation energy (kJ/mol)*
	53°	*65°*	*53°*	*65°*	
(a)	1.40×10^{0}	6.70×10^{0}	7.14×10^{1}	7.69×10^{1}	121
(b)	1.96×10^{-2}	8.71×10^{-2}			
(c)	8.50×10^{0}	4.00×10^{1}	1.43×10^{1}	1.54×10^{1}	121
(d)	5.95×10^{-1}	2.60×10^{0}			
(e)	1.50×10^{0}	3.60×10^{0}	3.57×10^{-1}	3.85×10^{-1}	67
(f)	4.20×10^{0}	9.36×10^{0}			
(g)	6.40×10^{0}	4.50×10^{1}	1.25×10^{-1}	1.25×10^{-1}	155
(h)	5.12×10^{1}	3.60×10^{2}			
(i)	6.00×10^{-1}	2.50×10^{0}	2.86×10^{-1}	3.08×10^{-1}	109
(j)	2.10×10^{0}	8.13×10^{0}			
(k)	1.50×10^{1}	5.00×10^{1}	1.60×10^{3}	1.60×10^{3}	96
(l)	9.38×10^{-3}	3.13×10^{-2}			
(m)	7.00×10^{2}	1.50×10^{3}	4.00×10^{2}	4.00×10^{2}	63
(n)	1.75×10^{0}	3.75×10^{0}			

[a]Scheme 1.

TABLE V

EQUILIBRIA OF VARIOUS FORMS OF FOUR HEXOSES

Hexose	*Ratio of furanosides to pyranosides*	*Ratio of α- to β-furanoside*	*Ratio of α- to β-pyranoside*	*Ref.*
D-Glucose	10	0.7	0.7	2
D-Mannose	4	1.9	3.5	5
L-Fucose	1.3	0.8	0.9	1
D-Galactose	10	0.6	1.0	This work

OH-6 to stabilize protonation on the pyranoid ring oxygen of its bicyclic intermediate, so protonation on both ring oxygen atoms occurs, resulting in an almost equal (1.3) ratio of furanosides to pyranosides.

EXPERIMENTAL

Materials. — D-Galactose (CP) was obtained from Pfanstiehl Lab. Inc. (Waukegan, IL) and pyridine from Reilly Tar and Chemical Corp. (Indianapolis IN), and was dried over NaOH. Methanol was reagent grade and the strongly acidic ion-exchange resin Dowex 50W-X8 (50–100 mesh) equilibrated with methanol as described previously[5]. Chlorotrimethylsilane and hexamethyldisilazane were obtained from Pierce Chemical Co. (Rockford, IL).

Formation of methyl D-galactosides. — Fischer glycosidation was carried out by dissolving D-galactose (3.00 g) in methanol (250 mL) in a 500-mL, 3-neck flask fitted with a condenser and a stirrer with a Teflon paddle at 500-r.p.m. constant-speed. A reflux temperature of 65° or a thermostatically controlled temperature of 53.0 ±0.2° was used. After an initial heating period of ~1 h, a sample (5-mL) was pipetted out and mixed with pyridine (5 mL). Ion-exchange resin (25.0 g) was added and a timer started. At various times, samples (10 mL) were pipetted out without stopping the stirrer. In each sample, the resin was allowed to settle and a part (5 mL) of the supernatant liquid was quickly pipetted out and mixed with pyridine (5 mL). Aliquots (2 mL) of these mixtures (containing ~12 mg of D-galactose) were evaporated *in vacuo* several times at 50° after addition of pyridine to remove methanol. The trimethylsilyl ethers were formed by addition of pyridine (1 mL), hexamethyldisilazane (0.2 mL), and chlorotrimethylsilane (0.1 mL) according to the method of Sweeley *et al.*[6].

Chromatography of the trimethylsilyl ether derivatives. — A Hewlett–Packard Model 5750 gas chromatograph equipped with a flame-ionization detector and a 3.2 mm × 8 m copper column containing 9% OV-1 on 80–100 mesh Chromosorb W-HP was used. The oven temperature was 190°, except for experiments to resolve peak No. 2 (Fig. 1), where it was 174° with a 3.2 mm × 16 m column. Prepurified N_2 at 3.5 kg/cm^2 pressure and 20 mL/min flow-rate was used as a carrier gas. Sample

injections varied from 0.5 to 6 μL, and electrometer attenuations from ~400 to 16 000. Chart speed was 31.75 cm/h and peak areas were determined with a planimeter in the manner illustraed by the construction lines in Figs. 2 and 3. As stated in a previous paper[2], detector constants determined for available trimethylsilyl ethers of monosaccharides and methyl glycosides have been found to be essentially the same and are assumed to be the same for all ten trimethylsilyl ethers chromatographed in this work.

Enhancement of α-D-galactofuranose and aldehydo-D-*galactose methyl hemiacetal in the methanol solution.* — A solution of D-galactose (5 g) in methanol (150 mL) was boiled under reflux for 3 h and filtered hot to recover 2.69 g of D-galactose. The filtrate was cooled in an ice bath and allowed to evaporate to a volume of 50 mL under a stream of air (13–14°). Two crops of crystals were filtered off and dried in a dessicator (1.41 g). The filtrate was evaporated *in vacuo* to dryness at 50° and again after addition of ~10 mL of pyridine (final wt. 0.74 g). This was per-*O*-(trimethylsilyl)ated with pyridine (30 mL), hexamethyldisilazane (6 mL), and chlorotrimethylsilane (3 mL). A sample (5 μL) of this solution was chromatographed at 190° on a 3.2 mm × 16 m OD-1 column. Five peaks were obtained: trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-β-D-galactofuranoside (**7**, 1%, 44 min); trimethylsilyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-α-D-galactopyranoside (**2**, 12%, 53 min); trimethylsilyl 2,3,5,6-tetra-*O*-(trimethylsilyl)-α-D-galactofuranoside (**5**, 31%, 62 min); trimethylsilyl 2,3,4,6-tetra-*O*-(trimethylsilyl)-β-D-galactopyranoside (**3**, 44%, 74 min); and 2,3,4,5,6-penta-*O*-(trimethylsilyl)-*aldehydo*-D-galactose methyl trimethylsilyl acetal (**9**, 12%, 101 min). The trimethylsilylated mixture was evaporated *in vacuo* at 50° for ~1 h, dry hexane (15 mL) added, and the precipitate centrifuged. Part of the supernatant solution (5 μL) was again chromatographed to produce the same peaks as before but with a level baseline: **7**, 1%, 46 min; **2**, 13%, 55 min; **5**, 32%, 65 min; **3**, 42%, 78 min; and **9**, 12%, 104 min.

Computer simulation of the reaction. — Computer simulation was carried out by use of the Midas Program[7] for "Solution of coupled differential equations". This is a relatively short but efficient program which uses a fifth order Runge–Kutta–Merson type algorithm. Four parameters were input into the program: initial time (0 h), final time (48 h), time increment (0.001 h), and error limit (0.0001). Also input were six derivatives (initial slopes of the reactions at 53 and 65°, respectively): α-pyranose (**11**) (−0.22, −0.56), α-furanoside (**12**) (0.26, 0.48), β-furanoside (**15**) (0.28, 0.98), α-pyranoside (**13**) (0.04, 0.08), β-pyranoside (**10**) (0.02, 0.08), and bicyclic intermediate (**14**) (0.01, 0.01); the total concentration of D-galactose (0.067 m/L); the ratio of concentration of α- to β-pyranose (0.56, 0.64); eleven time intervals; and 66 experimental molar proportions of the six detectable components. Finally, five equilibrium constants [α-furanoside (**12**) to β-pyranoside (**10**), 0.20; β-furanoside (**15**) to α-pyranose (**11**), 50; β-furanoside (**15**) to α-pyranoside (**13**), 0.25; β-furanoside (**15**) to bicyclic intermediate (**14**), 400; and α-pyranoside (**13**) to β-pyranoside (**10**), 2.8 at 53, 2.6 at 65°] and seven rate constants (*a*, *c*, *e*, *g*, *i*, *k*, and *m*; two are dependent and were calculated from the others) were input

and adjusted until the sum of the squares of the deviations of the calculated molar proportions from the experimental data was minimal (66 for both reactions at 53 and 65°).

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