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Carbohydrate Research 325 (2000) 16–29

CARBOHYDRATE
RESEARCH

Sulfuric acid-catalyzed acetolysis of anomeric methyl 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosides: kinetics and mechanism

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Received 10 May 1999; revised 25 October 1999; accepted 22 November 1999

Abstract

The kinetics of the acetolysis and accompanying anomerization of methyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-mannopyranosides at different concentrations of sulfuric acid in acetic anhydride–acetic acid mixtures were studied. The progress of the reactions was followed by gas chromatography, and the rate constants of the partial reactions were calculated on the basis of the time-dependent product distribution obtained. The mechanisms of the reactions involved are discussed. The involvement of unstable ionic intermediates is taken into account in the evaluation of the kinetic results, and simplified and extended models are used in the mathematical treatment of the results. A fourth-order Runge–Kutta algorithm is used to calculate rate constants. Acetolysis was found to be faster for mannosides than for glucosides relative to their anomerization. The β-mannopyranoside prefers endocyclic CO-bond rupture, while in the α anomer the endocyclic and exocyclic cleavages are comparatively rapid. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Acetolysis; Anomerization; Mannopyranosides; Kinetics

1. Introduction

Acetolysis is one of the degradation methods used to elucidate the structure of oligo- and polysaccharides [1–5]. The specificity of this approach is clearly seen in the fragmentation of polysaccharides containing (1 → 6) linkages, which are extremely labile to acetolysis but relatively resistant to acid hydrolysis [6–9]. Thus, a detailed understanding of the influence of the sugar configuration on the kinetics and mechanism of acetolysis appears desirable, as it is of fundamental importance for the chemical manipulation of carbohydrates [10]. The identity of the ionic intermediates involved in acetolysis (cyclic versus acyclic oxocarbenium ion) is particularly relevant.

The most commonly used medium for acetolysis is a mixture of acetic anhydride and acetic acid containing a catalytic amount of sulfuric acid. In such solutions, the sugars are released from polysaccharides as an anomeric mixture of peracetates. Similarly, methyl glycopyranoside peracetates have been shown to yield anomeric mixtures of fully acetylated glycopyranoses, while glycofuranosides are

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PII: S0008-6215(99)00308-0

converted under the same conditions to either acyclic aldehyde acetates or to furanoid acetates [11]. We have shown previously [12] that the acetolysis of ethyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosides is accompanied by rather rapid anomerization. Together with the time-dependent product distributions, this observation suggests that acetolysis proceeds by one of two parallel routes. Either a cyclic glucopyranosyl oxocarbenium ion is formed and subsequently trapped by acetic acid to yield an anomeric mixture of glucose penta-acetate, or an acyclic 2,3,4,5,6-penta-*O*-acetyl-1-*O*-ethyl-D-glucitol-1-*C*-ylium ion is generated and converted via the diastereoisomeric acyclic ethyl acetals of per-*O*-acetyl-*aldehydo*-D-glucose and traces of anomeric D-glucofuranose peracetates. The recyclization of the intermediate oxocarbenium ion is fast, compared with its reaction with an external nucleophile, i.e., acetic acid.

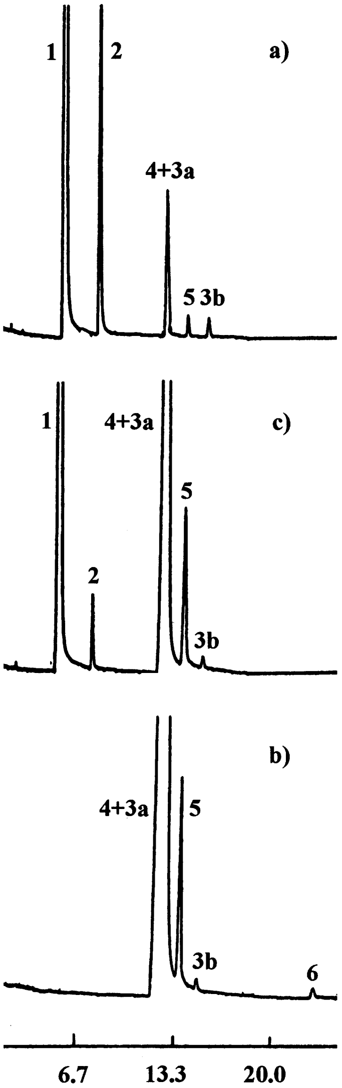


Fig. 1. Gas chromatograms of the product mixtures after (a) 5 min, and (c) 24 h acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside **2**, and (b) 1 h acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**, in a 1:1 acetic anhydride–acetic acid mixture, containing 1% sulfuric acid, at 25 °C. For the structures of the compounds, see Scheme 3.

We now report on a similar kinetic analysis of the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-mannopyranosides with an extended model of the reaction set that includes ionic species.

2. Results and discussion

The acetolysis reactions of the anomeric methyl mannopyranoside tetra-acetates (**1** and **2**) were carried out in a 1:1 acetic anhydride–acetic acid mixture at three different concentrations of sulfuric acid (0.25, 0.5 and 1%), followed by neutralization with sodium acetate, and analyzed by gas chromatography (GC). Both mixtures were observed to contain seven components, which were identified by spiking with authentic samples: mannosides **1** and **2**, the anomeric D-mannopyranose penta-acetates **4** and **5**, equimolar diastereoisomeric (1*R*,1*S*)-1,2,3,4,-5,6-hexa-*O*-acetyl-D-mannose methyl hemiacetals **3***R* and **3***S* (further labelled as **3** in the text or **3a** and **3b** in Fig. 1 and Scheme 3) and *aldehydo*-D-mannose-hepta-acetate **6** (Fig. 1). Tables 1 and 2 present the time-dependent product distributions of **1**–**6** for the acetolysis of anomeric methyl per-*O*-acetyl-D-mannopyranosides. The plots of the time-dependent distributions of **1**–**6** obtained by quantitative GC with either **1** or **2** as starting material are illustrated in Figs. 2 and 3 (only for a 0.25% sulfuric acid content). A similar seven-component mixture was obtained elsewhere from **1** in an acetic anhydride–boron trifluoride medium [17].

As can be seen from Figs. 2 and 3, the acetolysis of **1** and **2** is always accompanied by mutual anomerization. As the α-D-mannopyranoside is thermodynamically much

Table 1
Time-dependent product distribution for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1** in a 1:1 acetic acid–acetic anhydride mixture containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C [a]

Time (h)	Concentration of the catalyst																	
	0.25% Compounds (%)						0.5% Compounds (%)						1% Compounds (%)					
	1	**2**	**3** [b]	**4**	**5**	**6**	**1**	**2**	**3** [b]	**4**	**5**	**6**	**1**	**2**	**3** [b]	**4**	**5**	**6**
0	100	0	0	0	0	0	100	0	0	0	0	0	100	0	0	0	0	0
0.0833	97.65	0.67		1.47	0.21		96.17	1.03		2.54	0.26		90.65	1.73		6.80	0.82	
0.1667	96.12	1.13		2.34	0.41		95.21	1.17		3.12	0.50		84.93	1.98		11.63	1.46	
0.3333	94.22	1.50		3.67	0.61		91.64	1.33		6.06	0.97		78.79	1.88	0.06	17.31	1.96	
0.5	92.93	1.64		4.82	0.61		87.40	1.79	0.07	9.35	1.39		73.48	1.83	0.16	22.49	2.04	
1	87.45	2.09	0.08	8.97	1.41		78.94	2.20	0.08	16.01	2.77		52.59	1.36	0.17	41.61	4.27	
2	80.16	2.08	0.12	15.56	2.08		64.01	1.82	0.17	31.25	2.75		27.04	0.68	0.39	66.10	5.79	
3	74.09	1.80	0.13	21.44	2.54		49.82	1.13	0.22	44.53	4.30		13.74	0.66	0.39	78.17	7.04	
6	56.00	1.47	0.17	38.02	4.34		26.76	0.75	0.36	66.13	6.00		2.63	0.25	0.51	89.88	6.73	
12	30.76	0.80	0.33	62.13	5.98		6.31	0.21	0.42	86.54	6.47	0.05			0.30	92.61	6.66	0.43
24	8.07	0.22	0.35	83.40	7.87	0.09	0.62		0.39	92.39	6.52	0.08			0.28	93.09	6.18	0.45
48	0.58		0.29	91.73	7.19	0.21			0.38	92.55	6.79	0.28			0.36	92.79	6.19	0.66

[a] For the structures of the compounds, see Scheme 3.

[b] **3** is the sum of **3***R*+**3***S*.

Table 2

Time-dependent product distribution for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside **2** in a mixture of 1:1 acetic acid–acetic anhydride containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C [a]

Time (h)	Concentration of the catalyst																	
	0.25% Compounds (%)						0.5% Compounds (%)						1% Compounds (%)					
	1	**2**	**3** [b]	**4**	**5**	**6**	**1**	**2**	**3** [b]	**4**	**5**	**6**	**1**	**2**	**3** [b]	**4**	**5**	**6**
0	0	100	0	0	0	0	0	100	0	0	0	0	0	100	0	0	0	0
0.0833	27.27	71.64	0.22	0.87			50.76	47.78	0.15	1.12	0.19		75.84	18.68	0.50	4.37	0.61	
0.1667	44.59	53.80	0.25	1.11	0.25		65.36	32.26	0.28	1.76	0.34		80.82	10.10	0.56	7.49	1.03	
0.3333	55.77	41.96	0.26	1.79	0.22		76.42	18.99	0.32	3.83	0.44		79.76	3.46	0.56	14.62	1.60	
0.5	67.76	29.00	0.34	2.54	0.36		81.25	11.15	0.42	6.26	0.92		79.39	3.33	0.63	14.89	1.76	
1	82.69	9.48	0.42	6.45	0.96		78.33	2.57	0.50	16.50	2.10		54.48	2.12	0.67	38.76	3.97	
2	81.76	3.09	0.48	13.01	1.66		67.09	1.60	0.63	27.34	3.34		27.04	0.78	0.76	65.57	5.85	
3	75.43	2.08	0.53	19.58	2.38		51.64	1.13	0.87	42.09	4.27		16.00	0.49	0.90	76.53	6.08	
6	59.43	1.56	0.66	34.27	4.08		27.90	0.80	0.93	65.34	5.03		1.90	0.26	0.91	89.84	6.83	0.26
12	33.72	1.01	0.74	58.59	5.76	0.18	8.00	0.27	0.94	84.17	6.42	0.20	0.54	0.14	0.71	90.96	6.73	0.92
24	10.09	0.41	0.85	81.02	7.32	0.31	0.87	0.13	0.93	91.18	6.63	0.26		0.09	0.53	91.87	6.50	1.01
48	1.96		0.75	90.29	6.58	0.42			0.54	92.28	6.70	0.48		0.08	0.35	91.83	6.52	1.22

[a] For the structures of the compounds, see Scheme 3.

[b] **3** is the sum of **3***R*+**3***S*.

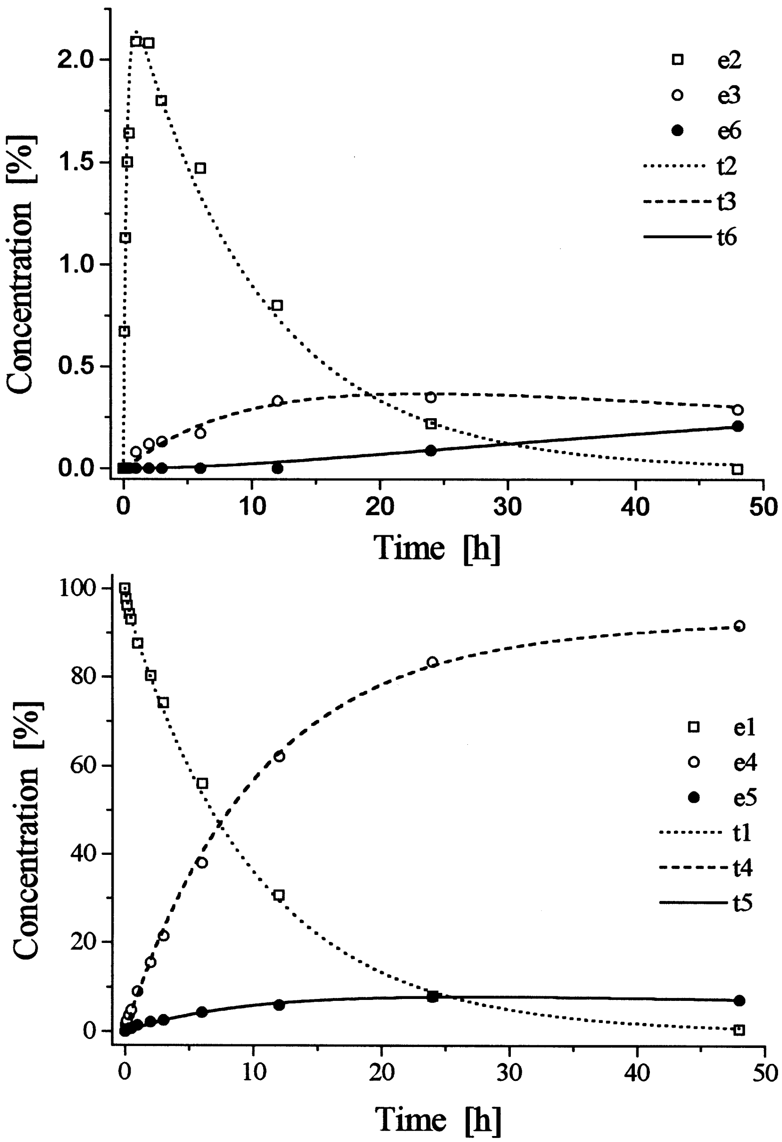


Fig. 2. Time-dependent product distributions for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**, in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25% sulfuric acid, at 25 °C. For the structures of the compounds, see Scheme 3; e1–e6 correspond to experimental points, t1–t6 correspond to theoretical curves. Upper curves concern the product distributions appearing in the mixture at low concentration.

more stable than its β anomer [13], this anomerization is more readily detectable when the less stable β anomer **2** is used as starting material. But as the anomerization is actually faster than the acetolysis, an equilibrium mixture of **1** and **2** containing 97.6 and 2.4% of the α and β anomer, respectively, is produced. The same equilibrium mixture is also obtained on using the α anomer **1** as the starting material.

A preliminary, simplified approach to the reactions taking place during acetolysis of **1** and **2** is shown in Scheme 1. This depicts the smallest amount of reactions needed to describe the kinetics of the two anomers. The least-squares method was employed for the conversion ratios (ca. 0–60%), while the first-order rate constants for the anomerization and acetolysis of **1** and **2** were calculated as in Ref. [12]. The rate constants obtained for the partial reactions involved are listed in Table 3. At this step of evaluation, the following conclusions may be drawn for **2** as substrate: (i) anomerization of methyl 2,3,4,6-tetra-*O*-

acetyl-α-D-mannopyranoside **1** to its β anomer proceeds about four times as fast, and that of the β anomer to the α anomer about 40 times as fast, as the acetolysis of the anomeric mixture **1** and **2** to anomeric mannose penta-acetates **4** and **5**, or acyclic acetyl methyl acetals **3***R* and **3***S*; (ii) formation of the anomeric mixture of mannose penta-acetates **4** and **5** is about 30 times as fast as that of acetyl methyl acetals **3***R* and **3***S*; (iii) acetolysis of the acetyl methyl acetals yields only the acyclic hepta-acetate **6**; (iv) the first-order rate constants for the partial reactions increase with catalyst concentration; these relations are obvious for anomers **1** and **2**, and even more for the β anomer; (v) acetolysis is faster for mannosides than for glucosides, relative to their anomerization [12].

As discussed previously [12], the anomerization of ethyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosides proceeds by the formation of cyclic 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylium **7** and acyclic 2,3,4,5,6-penta-*O*-acetyl-1-*O*-methyl-D-glucitol-1-*C*-ylium **8** ions.

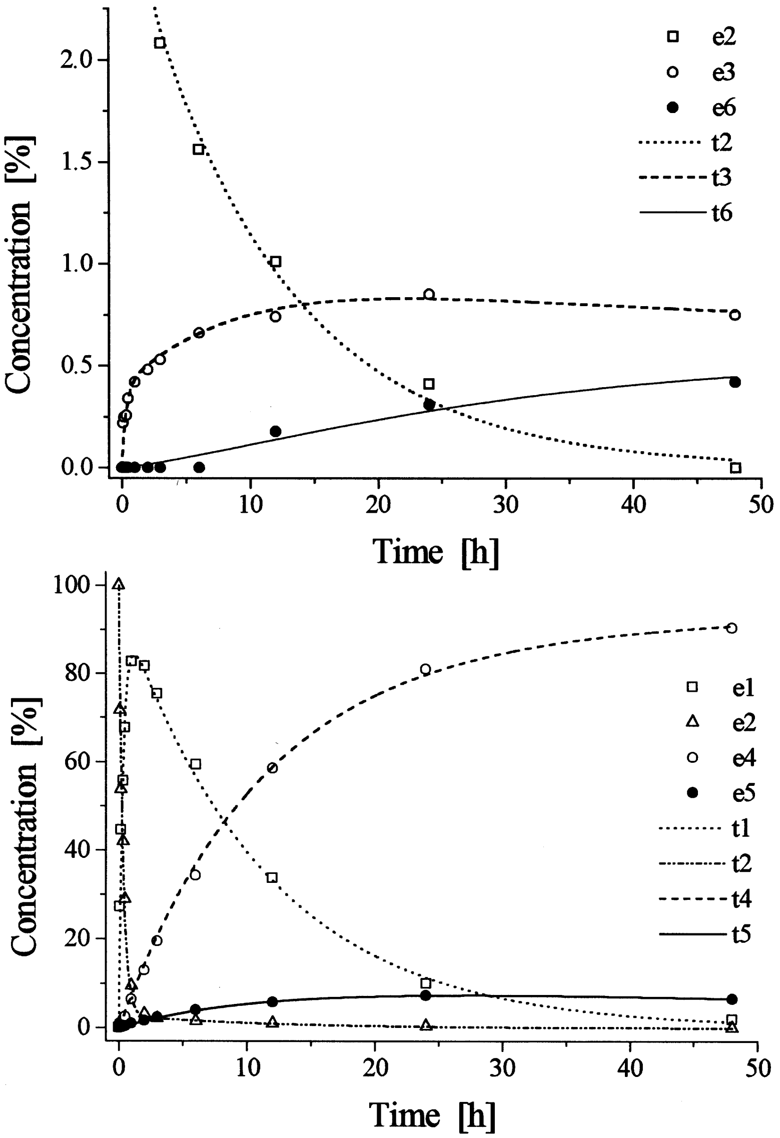
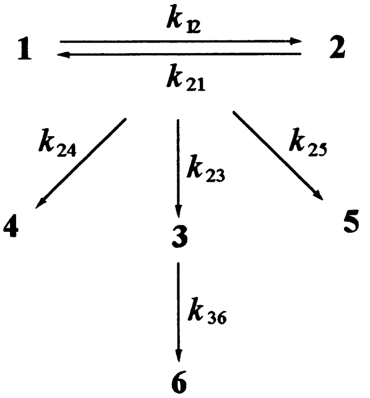
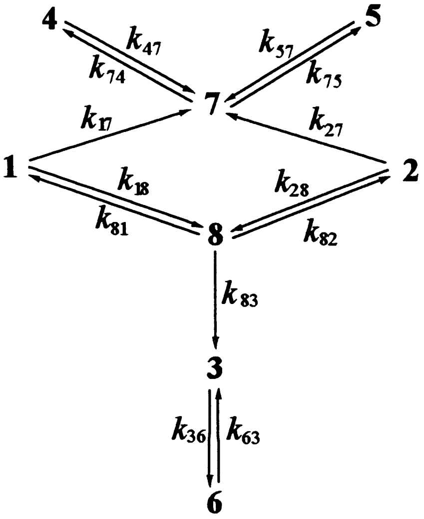


Fig. 3. Time-dependent product distributions for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside **2**, in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25% sulfuric acid, at 25 °C. For the structures of the compounds, see Scheme 3; e1–e6 correspond to experimental points, t1–t6 correspond to theoretical curves. Upper curves concern the product distributions appearing in the mixture at low concentration.



Scheme 1.



Scheme 2.

Therefore, a more extensive model of the kinetics and mechanism must be employed, which includes the ion formation (Scheme 2). As in the simplified approach, compounds **1** and **2** are quite readily interconvertible through the acyclic ion **8**, but acetolysis takes place via a different ionic intermediate. Both **1** and **2** were observed to yield 1,2,3,4,6-penta-*O*-acetyl-α- and -β-D-mannopyranose in a constant 7:1 concentration ratio. It is especially worthwhile recording that this ratio remains unchanged during the acetolysis of **2**, in spite of the fact that **2** simultaneously undergoes anomerization to **1**. Thus, it appears reasonable to assume that the acetolysis of **1** and **2** proceeds via a common intermediate, i.e., the cyclic mannosyl oxocarbenium ion (**7** in Scheme 2), which is produced when the acetylium ion of the 1-methoxy group is split off in the form of a methyl acetate molecule. As **1** and **2** both produce **4** and **5** in the same 7:1 ratio, the oxocarbenium ion of **7** appears to be generated before the attack of acetic acid on the anomeric carbon (Scheme 2).

The kinetics of the above processes, which involve the formation of cyclic and acyclic ions, can be described by a set of first-order differential equations (Eqs. (1)–(8)), where k_{ij} are the pseudo-first-order rate constants indicated in Scheme 2, and x_i denotes the time-dependent molar fractions of compounds **1**, **2**, **3**, **4**, **5** and **6**, and intermediates **7** and **8**. The values k_{ij} were determined by a fourth-order Runge–Kutta algorithm [18] to give the best

Table 3
First-order rate constants for the partial reactions involved in the acid-catalyzed acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α- (**1**) and -β-D-mannopyranoside (**2**) in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C [a]

Rate constant 10^6 k (s^{-1})	Acetolysis of **1**			Rate constant 10^6 k (s^{-1})	Acetolysis of **2**		
	Concentration of the catalyst				Concentration of the catalyst		
	0.25%	0.5%	1%		0.25%	0.5%	1%
k_{12}	25 ± 30	40 ± 50	110 ± 200	k_{12}	60 ± 40	250 ± 150	600 ± 350
k_{21}	1100 ± 100	1450 ± 300	5300 ± 900	k_{21}	930 ± 100	2300 ± 300	6000 ± 600
k_{13}	0.17 ± 0.05	0.28 ± 0.1	0.92 ± 0.4	k_{23}	2.0 ± 0.8	3.0 ± 1.2	5.0 ± 2.5
k_{14}	24 ± 0.5	56 ± 1	180 ± 5	k_{24}	20.6 ± 0.5	48.7 ± 0.7	152.7 ± 4.5
k_{15}	3.4 ± 0.7	8 ± 1	16 ± 2	k_{25}	3.0 ± 0.5	6.0 ± 0.5	15 ± 2
k_{36}	0.05 ± 0.07	0.06 ± 0.08	1.2 ± 1.7	k_{36}	0.7 ± 0.6	0.4 ± 0.5	0.7 ± 1.0

[a] For the rate constants, see Scheme 1.

least-squares fit between the calculated and experimental values of x_i. The results obtained are set out in Table 4, and show good agreement between the calculated and experimental time-dependent distributions of compounds **1**, **2**, **3**, **4**, **5** and **6** (see also Figs. 2 and 3).

$$\frac{dx_1}{dt} = k_{81}x_8 - k_{18}x_1 - k_{17}x_1 \tag{1}$$

$$\frac{dx_2}{dt} = k_{82}x_8 - k_{28}x_2 - k_{27}x_2 \tag{2}$$

$$\frac{dx_3}{dt} = k_{83}x_8 - k_{36}x_3 + k_{63}x_6 \tag{3}$$

$$\frac{dx_4}{dt} = k_{74}x_7 - k_{47}x_4 \tag{4}$$

$$\frac{dx_5}{dt} = k_{75}x_7 - k_{57}x_5 \tag{5}$$

$$\frac{dx_6}{dt} = k_{36}x_3 - k_{63}x_6 \tag{6}$$

$$\frac{dx_7}{dt} = k_{17}x_1 + k_{27}x_2 + k_{47}x_4 + k_{57}x_5 - k_{74}x_7 - k_{75}x_7 \tag{7}$$

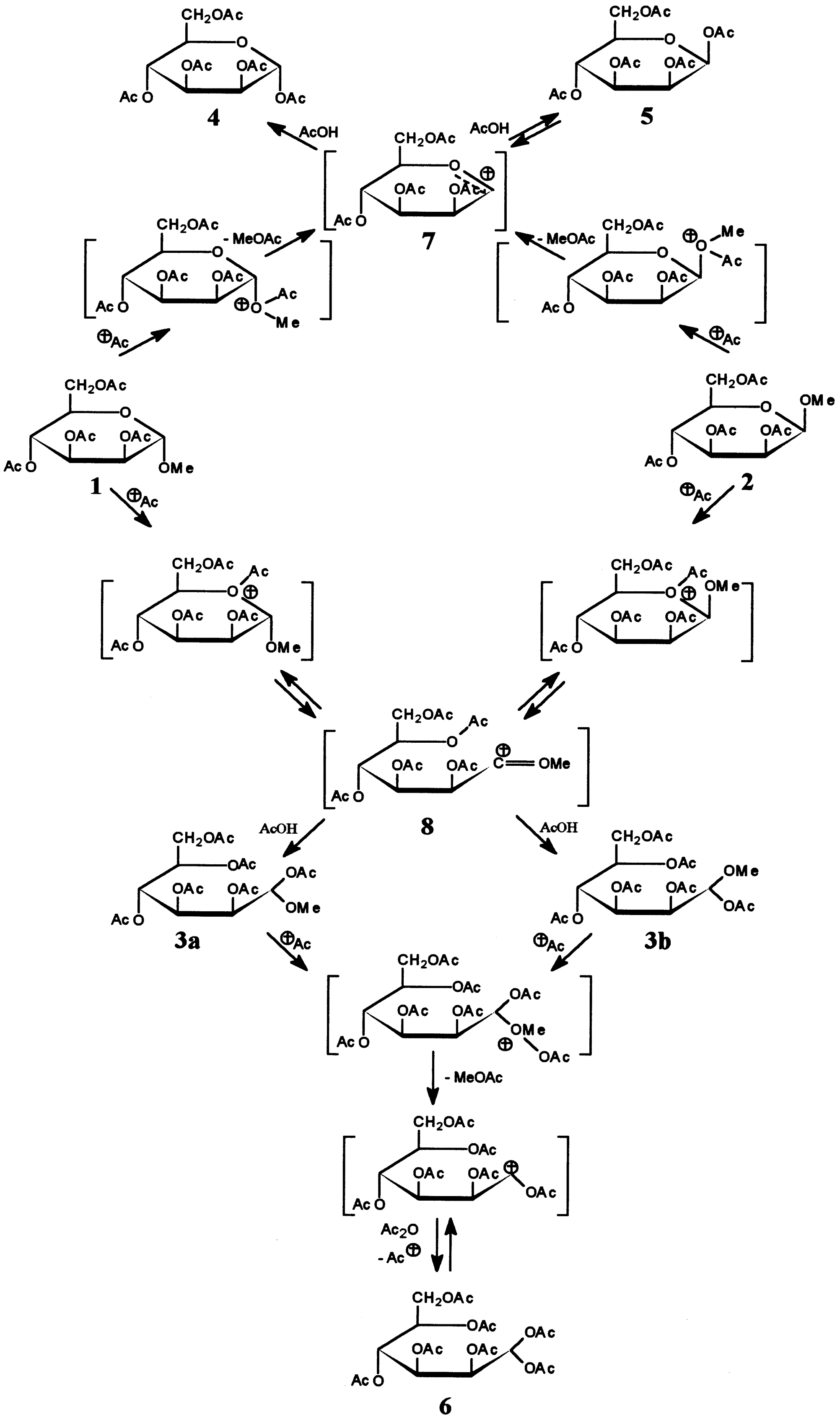
$$\frac{dx_8}{dt} = k_{18}x_1 + k_{28}x_2 - k_{81}x_8 - k_{82}x_8 - k_{83}x_8 \tag{8}$$

The rate constants listed in Table 4 allow the following inferences to be made: (i) Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside **2** forms the cyclic mannopyranosyl oxocarbenium ion **7** (Scheme 3) slightly faster than its anomer **1** (cf. k_{27} and k_{17}); in other words, the β anomer undergoes acetolysis faster than its counterpart does. The anomeric distribution of per-*O*-acetyl mannopyranoses is due to thermodynamic factors. (ii) The ring opening of the two substrates proceeds in a similar fashion, though much more distinctly: β anomer **2** forms the acyclic oxocarbenium ion **8** (Scheme 3) 30 times faster than the α anomer (cf. k_{28} and k_{18}). Accordingly, the β anomer prefers endocyclic CO-bond rupture, while in the α anomer the endocyclic and exocyclic cleavages are comparatively rapid. (iii) Acetic-acid attack on the mannopyranosyl oxocarbenium ion **7** from the α face is ten times faster than from the β face (cf. k_{74} and k_{75}). The equilibrium mixture of anomeric D-mannopyranose penta-acetates contains 92%

Table 4
First-order rate constants for the partial reactions involved in the acid-catalysed acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α- (**1**) and -β-D-mannopyranoside (**2**) in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C [a]

Rate constant 10^6 k (s^{-1})	Acetolysis of **1** Concentration of the catalyst			Acetolysis of **2** Concentration of the catalyst		
	0.25%	0.5%	1%	0.25%	0.5%	1%
k_{18}	48 ± 3	111 ± 5	417 ± 10	47 ± 3	113 ± 5	417 ± 10
k_{81}	26,700 ± 300	23,100 ± 600	15,600 ± 1000	27,200 ± 800	25,600 ± 300	19,200 ± 400
k_{28}	1800 ± 100	3470 ± 500	11,700 ± 700	1600 ± 100	3670 ± 400	11,700 ± 700
k_{82}	26,400 ± 500	19,400 ± 2000	13,900 ± 2000	27,500 ± 1000	24,400 ± 1000	20,500 ± 2000
k_{74}	27,500 ± 1000	3,2000 ± 1500	33,600 ± 2000	27,000 ± 1000	28,000 ± 2000	27,000 ± 2000
k_{47}	0	0	0	0	0	0
k_{75}	2940 ± 80	2920 ± 100	2860 ± 150	2960 ± 100	2500 ± 150	2180 ± 200
k_{57}	2.2 ± 0.5	1.4 ± 0.7	1.6 ± 0.9	3.0 ± 0.5	1.7 ± 0.7	0.8 ± 1
k_{17}	26 ± 1	56 ± 2	146 ± 5	25 ± 1	54 ± 2	142 ± 5
k_{27}	81 ± 2	306 ± 50	1580 ± 100	25 ± 2	81 ± 15	306 ± 100
k_{83}	82 ± 2	78 ± 3	51 ± 5	119 ± 8	109 ± 3	83 ± 5
k_{36}	3.8 ± 0.5	4 ± 1	16 ± 3	6 ± 2	5 ± 2	19 ± 3
k_{63}	0.0 ± 0.5	0 ± 1	0.6 ± 2	7 ± 5	5 ± 2	4 ± 2
$\Sigma_{i=1}^{6} \Delta_i^2$ (%)	1.7	3.5	4.4	1.3	1.8	1.5

[a] For the rate constants, see Scheme 2.



Scheme 3.

of the α anomer **4** and 8% of the β anomer **5**. The acyclic 2,3,4,5,6-penta-*O*-acetyl-1-*O*-methyl-D-mannitol-1-C-ylium ion **8** is cyclized to methyl α and β mannosides (**1** and **2**) (cf. k_{81} and k_{82}). In contrast to ring opening, reclosure is not accelerated by increasing the concentration of sulfuric acid. (iv) The attack of acetic acid on the acyclic oxocarbenium ion **8**, giving diastereoisomeric (1*R*,1*S*)-1,2,3,4,5,6-hexa-*O*-acetyl-D-mannose methyl hemiacetals (**3***R*, **3***S*), is more than 200 times slower than the cyclization of **8** (cf. $k_{83,}$ k_{81} and k_{82}). The rate of this reaction is also independent of the sulfuric acid concentration. (v) The subsequent acetolysis of **3***R* and **3***S* to 1,1,2,3,4,5,6-hepta-*O*-acetyl-*aldehydo*-D-mannose **6** is acid catalyzed and is slower than the formation of **3***R* and **3***S* from **8** (cf. k_{36} and k_{83}). In accordance with the above, we suggest that the mechanism of the acetolysis of methyl per-*O*-acetyl mannosides is as in Scheme 3, which takes into account not only all the stable products (**1**–**6**) but also the ionic intermediates **7** and **8**.

The acid-catalyzed acetolysis of anomeric methyl 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosides **1** and **2** is quite similar to that described previously [12] for anomeric ethyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosides. The acetolysis of all the glycosides mentioned is accompanied by a markedly faster anomerization of the starting material. This anomerization is faster with mannosides than with glucosides: the conversion of *cis*-1,2-mannoside (β) to its more stable trans counterpart (α) is four times as fast as the corresponding isomerization (α → β) of glucosides. The acetolysis rates differ even more strikingly: the anomeric mixture of mannosides **1** and **2** is converted to anomeric penta-acetates up to 30 times as fast as the anomeric glucosides. Both glycosides produce 1,1,2,3,4,5,6-hepta-*O*-acetyl-*aldehydo*-hexose only as a minor side product.

The acetolysis of glycosides has been studied by several research teams since the late 1940s, and alternative mechanisms via either cyclic or acyclic intermediates [10,19–23] have been suggested for the acetolysis and/or accompanying anomerization. The present kinetic study indicates that acetolysis and anomerization depend on the respective attack of the acetylium ion (CH_3CO^+) on the glycosidic or heterocyclic oxygen, as was suggested earlier. These results and those reported recently for ethyl glucoside tetra-acetates corroborate the early suggestion of Lindberg [20,21] that anomerization takes place via an acyclic intermediate. In fact, acyclic glycosyl oxocarbenium ions are formed more readily than cyclic glycopyranosyl oxocarbenium ions, the relative rates of these two reactions being markedly dependent on the sugar moiety configuration. It should, however, be noted that acetolysis, i.e., the cleavage of the glycosidic bond, does not take place via the acyclic oxocarbenium ion, but by the formation of a cyclic oxocarbenium ion. Obviously, very rapid recyclization keeps the concentration of the acyclic ion at such a low level that acetolysis via this intermediate cannot compete with that via the cyclic oxocarbenium ion.

Calculation of the rate constants.—The reactions involved in the kinetics of the acetolysis reactions are summarized in Scheme 2. The rates of these reactions are described by a set of first-order differential equations (Eqs. (1)–(8)). The rate constants k_{ij} were determined by the solution for the set that gives the best least-squares fit between the calculated and experimental values of x_i. If all the constants k_{ij} are known, Eqs. (1)–(8) can be solved by numerical integration. The values of k_{ij} were initially guessed, and the fourth-order Runge–Kutta algorithm [18] was applied to solve the equation system. The values of k_{ij} were then optimized to give the best fit. For the best fit of the experimental and theoretical values, the relative differences δ_i, Eq. (9), and the mean-squared relative difference Δ_i^2, Eq. (10), were used, where x_{eij} and x_{tij} are the respective experimental and theoretical values for the *i*th compound and *j*th point in time.

$$\delta_i = \sum_{j=1}^{12} (x_{eij} - x_{tij}) / \sum_{j=1}^{12} x_{eij} \qquad (9)$$

$$\Delta_i^2 = \sum_{j=1}^{12} (x_{eij} - x_{tij})^2 / \sum_{j=1}^{12} x_{eij}^2 \qquad (10)$$

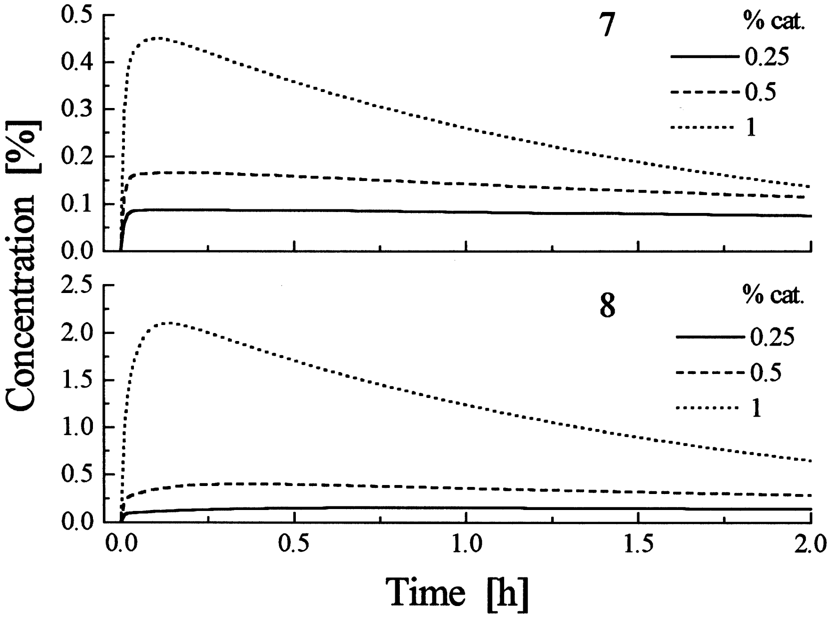


Fig. 4. Theoretical time-dependent ion intermediate **7** (above) and **8** (below) distributions for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**, in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C. For the structures of the ion intermediates, see Scheme 3.

The final step involves minimizing the squared value Δ_i^2, not only for each product of the reaction mixture but also for the total sum of all observable compounds ($i = 1, 2, 3, \ldots 6$, Eq. (11)).

$$TSum = \sum_{i=1}^{6} \Delta_i^2 \qquad (11)$$

The total sum *TSum* was $< 5\%$ for all the products studied (see Table 4), where Δ_6^2 contains about 70% of *TSum*.

The theoretical concentrations of ion intermediates (**7** and **8**) of the acetolysis for different catalyst concentrations and different reaction times are presented in Figs. 4 and 5. For a 0.25% catalyst concentration, intermediates **7** and **8** exist during the whole time of acetolysis of anomers **1** and **2**. For higher catalyst concentrations, the intermediate concentrations increase. The relation between the concentrations of intermediates and the catalyst concentration in the case of methyl per-*O*-acetyl-β-D-mannopyranoside is more distinct, and the concentrations of the former achieve a maximum in shorter times.

3. Experimental

General procedures.—The purity of the compounds prepared, **1**, **2**, **4**, **5**, **3*R***, **3*S*** and **6**, was assessed by GC on a 60 m Rtx-225 capillary column (Restec Co., USA) under isothermal conditions (215 °C) using flame-ionization detection. The intermediates and products of acetolysis were identified by co-injection with authentic samples. The AcOH and Ac_2O used in the experiments were distilled prior to use. ^1H and ^{13}C NMR spectra were recorded using a 400 MHz spectrometer (Varian-Mercury, USA). The specific rotations were measured using a Jasco J-20 spectropolarimeter (Japan).

*Methyl 2,3,4,6-tetra-*O*-acetyl-α-* (**1**) *and -β-D-mannopyranoside* (**2**).—A mixture of methyl mannosides was obtained by refluxing D-mannose in MeOH in the presence of a strong cation-exchange resin [24]. The products were separated on a 50 × 2.7 cm ion-exchange column (Dowex 1 × 8, 200–400 mesh, OH^- form). The products obtained were identified, following silylation, by GC. Methyl α- and -β-D-mannopyranosides were acetylated with a 1:1 Ac_2O–pyridine mixture, 1.5 h, 90 °C, in order to obtain **1** and **2**, respectively.

1,2,3,4,6-Penta-O-*acetyl*-α-D- (**4**) *and* -β-D-*mannopyranose* (**5**).—Compounds **4** and **5** were prepared as described by Hudson and Dale [15].

*[(1*R*)- and (1*S*)-]-1,2,3,4,5,6-Hexa*-O-*acetyl*-D-*mannose methyl hemiacetals* 3R *and* 3S.—The procedure of Keith et al. [14] to obtain acetal ester from dimethyl acetal was adapted for the synthesis of compounds **3***R* and **3***S*. 2,3,4,5,6-Penta-*O*-acetyl-D-mannose dimethyl acetal (4.34 g, 9.95 mmol) was treated with Ac_2O (12.6 mL) in the presence of Dowex 50W-X4 (1 g, 100–200 mesh, H^+ form). The mixture was kept at 65 °C for 1.5 h, after which time the resin was filtered off and the soln concentrated to an oil, under reduced pressure. The crude, yellow syrup was purified with a mixture of diethyl ether and *n*-hexane. The oily product was separated from the solvents and stored under diminished pressure at 60 °C until constant weight to yield 3.37 g (73%). $[\alpha]_D^{25} + 0.4°$ (c 1, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 5.77 (d) and 5.63 (d) H-1, 5.20 (dd) and 5.11 (dd) H-2, 5.48 (dd) and 5.60 (dd) H-3, 5.41 (dd) 5.53 (dd) H-4, 5.06 (m) H-5, 4.22 (m) and 4.03 (m), H-6, 3.41 and 3.40 (2 s, 6 H, 1*R*,1*S* CH_3O–HC-1-$OCOCH_3$), 2.12 and 2.10 (2 s, 6 H, 1*R*,1*S* CH_3OCO–HC-1-OCH_3), 2.09–2.04 (10 s, 30 H, (1*R*,1*S*) × 5 × CH_3CO); ^{13}C NMR: δ 170.2–169.1 (12 peaks, C=O), 95.8 and 94.6 C-1, 68.1 and 68.0 C-2, 67.2 and 67.3 C-3, 67.3 and 67.4 C-4, 67.7, 67.5 C-5, 61.7, 61.7 C-6; 57.6, 57.4 (C–OCH_3), 20.8–20.6 (12 peaks CH_3C=O). Anal. Calcd for $C_{19}H_{28}O_{13}$: C, 49.14; H, 6.03. Found: C, 49.00; H, 6.02.

1,1,2,3,4,5,6-Hepta-O-*acetyl*-aldehydo-D-*mannose* (**6**).—This compound was prepared according to Lerner's procedure for obtaining the hepta-acetate of D-galactose [16]. 2,3,4,5,6-Penta-*O*-acetyl-D-mannose diethyl dithioacetal [25] (2.0 g, 4.03 mmol) was stored with an acetylating mixture (45.8 mL) of 4:40:1.8 acetic anhydride–acetic acid–sulfuric acid, for 72 h at room temperature (rt). The reaction mixture was poured onto crushed ice and mixed for 1 h. The product was extracted several times with $CHCl_3$ and this $CHCl_3$ soln was rinsed alternately with water, a satd soln of $NaHCO_3$, and water, then finally dried over anhyd Na_2SO_4. The solvent was evaporated, and the residue dissolved in EtOH and

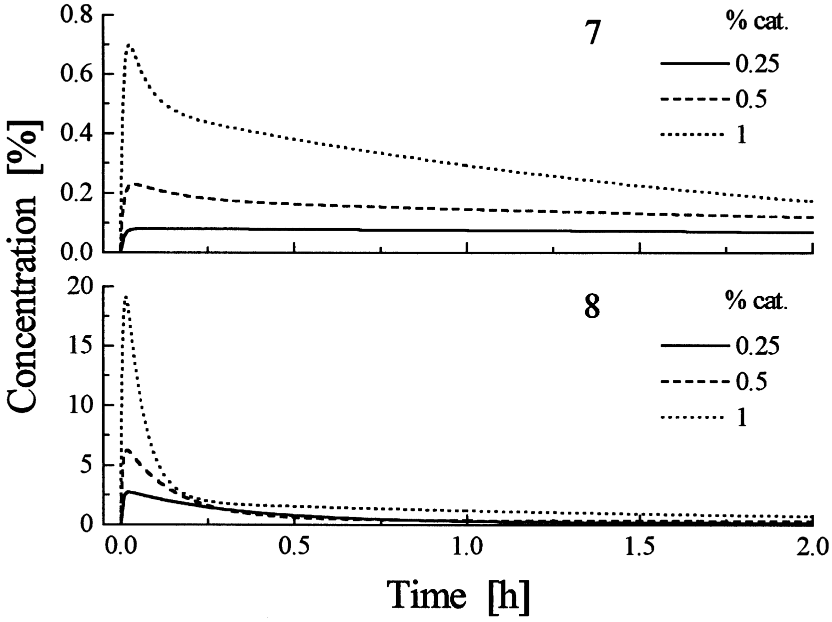


Fig. 5. Theoretical time-dependent ion intermediate **7** (above) and **8** (below) distributions for the acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside **2**, in a 1:1 acetic anhydride–acetic acid mixture, containing 0.25, 0.5, and 1% sulfuric acid, at 25 °C. For the structures of the ion intermediates, see Scheme 3.

refluxed with charcoal. The suspension was filtered and the supernatant concentrated to a small volume and left at rt. The product was recrystallized from a diethyl ether–*n*-hexane mixture to yield 0.88 g of **6** (44.4%) as a solid; mp 116–118 °C. $[\alpha]_D^{25} + 1.5°$ (*c* 1, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 6.78 (d) H-1, 5.25 (dd) H-2, 5.51 (dd) H-3, 5.44 (dd) H-4, 5.05 (o) H-5, 4.21 (q) and 4.04 (q) H-6, 2.13 and 2.12 (2 s, 6 H, CH_3OCO–HC-1-$OCOCH_3$), 2.10–2.01 (5 s, 15 H, 5 × CH_3CO); ^{13}C NMR: δ 170.1–167.9 (six peaks C=O), 85.9 C-1, 67.0 C-2, 66.7 C-3, 67.0 C-4, 67.6 C-5, 61.7 C-6; 20.8–20.5 (six peaks CH_3C=O). Anal. Calcd for $C_{20}H_{28}O_{14}$: C, 48.78; H, 5.69. Found: C, 48.91; H, 5.69.

Kinetic measurements.—Acetolysis was carried out in sealed tubes immersed in a water bath thermostatted at 25 °C. The tubes, each containing 1 mL of 28 M soln of the starting material in a 1:1 AcOH–Ac_2O mixture containing 1, 0.5 or 0.25% H_2SO_4, were removed at suitable intervals. An aliquot of 0.1 mL was withdrawn, neutralized with a satd soln of NaOAc in AcOH, and centrifuged. The peaks of the chromatograms were assigned by spiking with standard samples.

To determine the molar response factors for the seven compounds in the reaction mixtures, a standard mixture of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**, 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose **5**, the mixture of diastereoisomers [(1*R*)- and (1*S*)-]-1,2,3,4,5,6-hexa-*O*-acetyl-D-mannose methyl hemiacetals **3***R* and **3***S*, and 1,1,2,3,4,5,6-hepta-*O*-acetyl-*aldehydo*-D-mannose **6** dissolved in CH_2Cl_2 was injected into the gas chromatograph. The peak areas are expressed relative to the peak area of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**, which was used as an internal standard. The relative molar response factors for the compounds under consideration were: methyl 2,3,4,6-tetra-*O*-acetyl-α-**1** and -β-D-mannopyranoside **2**, 1.00; 1,2,3,4,6-penta-*O*-acetyl-α-D- **4** and -β-D-mannopyranose **5**, 1.26; [(1*R*)- and (1*S*)-]-1,2,3,4,5,6-hexa-*O*-acetyl-D-mannose methyl hemiacetals **3***R* and **3***S*, 1.69; 1,1,2,3,4,5,6-hepta-*O*-acetyl-*aldehydo*-D-mannose **6**, 1.65.

The molar percentages of the reaction mixture were obtained from the ratios of the experimental data and molar response factor.

One of the two GC peaks of the diastereoisomeric [(1*R*)- and (1*S*)-]-1,2,3,4,5,6-hexa-*O*-acetyl-D-mannose methyl hemiacetals **3***R* and **3***S*, corresponding to compound **3a** in Fig. 1, was overlapped by a large signal of 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose **4**. Assuming both hemiacetals to have equal areas, the total area of acetals was calculated by multiplying the area of **3b** by two. In turn, the area of per-*O*-acetylated α-D-mannopyranose was calculated by subtracting the area of **3b** from that of **4** + **3a**.

Acknowledgements

Financial support from the Polish State Committee for Scientific Research (grant DS/8200-4-0085 of the University of Gdańsk) is gratefully acknowledged.

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