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Transglucosidation of methyl and ethyl D-glucopyranosides by alcoholysis

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Abstract

The transglucosidations of methyl 4-*O*-methyl-α- and -β-D-glucopyranoside in ethanolic camphor-10-sulfonic acid, and of ethyl 4-*O*-methyl-α- and -β-D-glucopyranoside in methanolic camphor-10-sulfonic acid, have been studied. Samples were removed at intervals and the proportions of the glucosides determined by GC of their acetates. The results show that the anomer with the inverted configuration predominates in the initially formed product ($\approx 59-70\%$). This indicates that all the studied reactions proceed via the same mechanism, involving exocyclic C–O cleavage and formation of a glucopyranosylium ion, but that the eliminated alcohol exerts some steric hindrance, which favors the approach of the other alcohol from the opposite side. © 2002 Published by Elsevier Science Ltd.

Keywords: Transglucosylation; Kinetics; Mechanistic studies

1. Introduction

Acid-catalyzed hydrolysis and anomerization of glycopyranosides are extensively studied reactions.[1,2] Investigating these reactions is an important goal of chemistry. Any attempt to change enzymatic transformations or to mimic enzymes with a synthetic catalyst requires an understanding of the reaction pathways involved.

The theory of stereoelectronic effects predicts that α anomers should proceed via an exocyclic pathway, whereas β anomers should proceed via an endocyclic pathway.[3] The ratio between endocyclic and exocyclic cleavage of cis-fused decalin pyranoside acetals was recently studied by Anslyn's research group.[4] They found that a quantifiable percentage of endocyclic cleavage was found for β-pyranosides, whereas α-pyranosides showed exclusively exocyclic cleavage. However, the general acceptance of exocyclic cleavage, even for β-anomers, has led to postulations of conformational changes of the pyranosidic ring, and thereby promote an exocyclic pathway, to match the theory of stereoelectronic control.[5–8] The theory of least motion predicts that both anomers should utilize an exocyclic mechanism.[9,10] We now report studies on the transglucosidation of methyl glucopyranosides in ethanolic camphor-10-sulfonic acid (CSA) and of ethyl glucopyranosides in methanolic CSA, with the aim to determine the α/β ratio for the initially formed products.

2. Results and discussion

The methyl and ethyl glucopyranosides used were methylated in the 4-position in order to exclude formation of furanosides. The methyl 4-*O*-methyl-α- and -β-D-glucopyranosides[11] and the ethyl 4-*O*-methyl-β-D-glucopyranoside[12] are known substances. The ethyl 4-*O*-methyl-α-D-glucopyranoside was prepared by ethanolysis of methyl 4-*O*-methyl-α-D-glucopyranoside followed by chromatography. The methyl 4-*O*-methyl-

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α- and -β-D-glucopyranosides were treated with 1 M ethanolic CSA at 50.0 ± 0.1 °C, samples were removed at intervals, neutralized, acetylated, and the components analyzed by GC. The ethyl 4-*O*-methyl-α- and -β-D-glucopyranosides were treated with 1 M methanolic CSA at 50.0 ± 0.1 °C, and the components analyzed as above. From these results, the ratio of the initially formed glucosides could be determined, as exemplified for the transglucosidation of methyl 4-*O*-methyl-α-D-glucopyranoside (Scheme 1). In this scheme, α-Me stands for the methyl 4-*O*-methyl-α-D-glucopyranoside, etc.

The k_1 and $(k_3 + k_4)$ represent the rate constants for the initial formation of α-Et and that for the equilibration of the initially formed product, respectively.

The analytical solutions of the differential equation system (gained from Scheme 1)

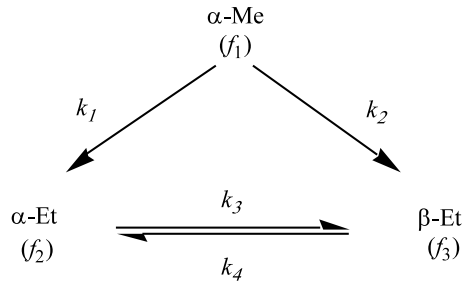
$$df_1/dt = -(k_1 + k_2)f_1 \quad (1)$$

$$df_2/dt = k_1 f_1 - k_3 f_2 + k_4 f_3 \quad (2)$$

$$df_3/dt = k_2 f_1 + k_3 f_2 - k_4 f_3 \quad (3)$$

may be written in the form

$$f_1(t) = f_1(0)\exp[-(k_1 + k_2)t] \quad (4)$$



Scheme 1. Transglucosidation of methyl 4-*O*-methyl-α-D-glucopyranoside in ethanolic CSA.

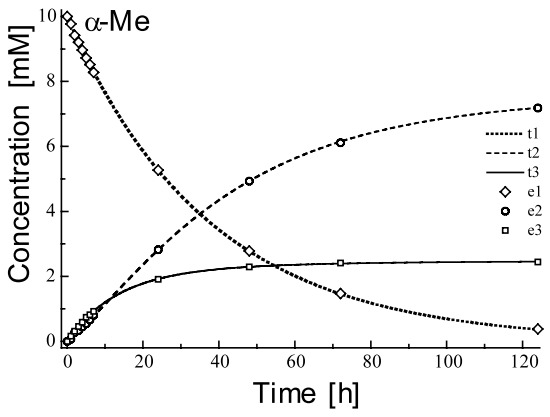


Fig. 1. Transglucosidation of methyl 4-*O*-methyl-α-D-glucopyranoside in ethanolic CSA. e_1–e_3 correspond to experimental points and t_1–t_3 correspond to theoretical curves

$$f_2(t) = f_1(0)\{A_1 - A_2\exp[-(k_1 + k_2)t] - A_3\exp[-(k_3 + k_4)t]\} \quad (5)$$

$$f_3(t) = f_1(0)\{1 - A_1 - (1 - A_2)\exp[-(k_1 + k_2)t] + A_3\exp[-(k_3 + k_4)t]\} \quad (6)$$

where

$$A_1 = \frac{k_4}{k_3 + k_4}, \qquad A_2 = \frac{k_1 - k_4}{k_1 + k_2 - k_3 - k_4},$$

$$A_3 = A_1 - A_2 \quad (7)$$

$$f_1(t) + f_2(t) + f_3(t) = f_1(0) \quad (8)$$

Based on Eqs. (4)–(6), all unknown rate constants can be obtained by fitting of a theoretical function to respective experimental data. Thus, $k_1 + k_2$ is obtainable by means of Eq. (4). To estimate k_1 and k_2 separately, the short-time expansions

$$f_2(t) = f_1(0)\{k_1 t - [k_1(k_1 + k_2 + k_3) - k_2 k_4]t^2/2 + \ldots\} \quad (9)$$

$$f_3(t) = f_1(0)\{k_2 t - [k_2(k_1 + k_2 + k_3) - k_1 k_3]t^2/2 + \ldots\} \quad (10)$$

can be used and then applied to each a parabolic fit, e.g., $f = a + bt + ct^2$, where a, b and c are the free parameters which will be known after calculations. Then $k_1 = b$ is obtained from Eq. (9), and $k_2 = b$ from Eq. (10), $k_3 + k_4$ and k_4/k_3 ($= f_{2eq}/f_{3eq}$) from Eqs. (5) and (6). In this paper, the total estimation has also been performed. Eqs. (4)–(6), are simultaneously fitted to the experimental data. The total correlation factor, defined as $R = (R_1 + R_2 + R_3)/3$, has been used as a control parameter. R_1, R_2 and R_3 are the partial correlation factors between each pair of experimental and theoretical values. When R approaches maximum (ideally $R = 1$), we assume that the best fit has been obtained.[13]

From these equations and the observed values for α-Me, α-Et, β-Et, the rate constants for the initial formed α-Et and β-Et and the rate constants for the equilibration of ethyl glucosides can be calculated (Figs. 1–4). The experimental results for the alcoholysis of methyl or ethyl 4-*O*-methyl-α- and -β-D-glucopyranosides are given in Tables 1–4.

The rate constants and the ratios of α- and β-forms initially formed and present at equilibrium are given in Table 5.

As evident from Table 5, there is some predominance of the anomer with the inverted anomeric configuration, independent of whether the transglucosidation starts from the α- or the β-glucoside. This strongly indicates that the transglucosidation of both the α- and the β-glucosides proceeds via the same mechanism namely via exocyclic C–O cleavage and formation of a glucopyranosylium ion. The eliminated alcohol (MeOH or EtOH) exerts some steric hindrance, which favors

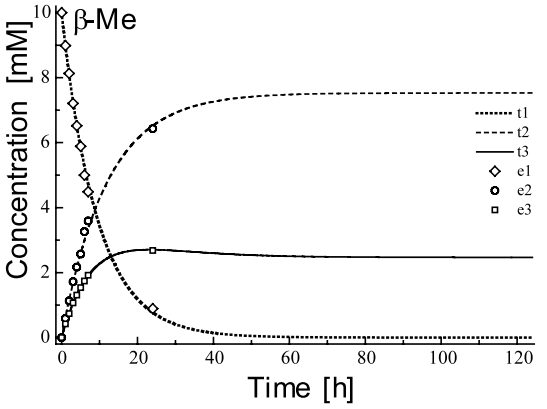


Fig. 2. Transglucosidation of methyl 4-*O*-methyl-β-D-glucopyranoside in ethanolic CSA. e_1–e_3 correspond to experimental points and t_1–t_3 correspond to theoretical curves.

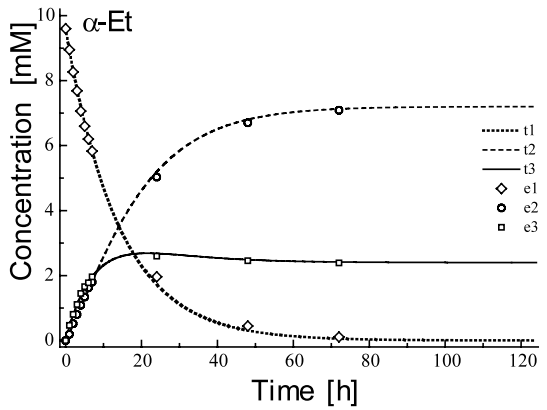


Fig. 3. Transglucosidation of ethyl 4-*O*-methyl-α-D-glucopyranoside in methanolic CSA. e_1–e_3 correspond to experimental points and t_1–t_3 correspond to theoretical curves

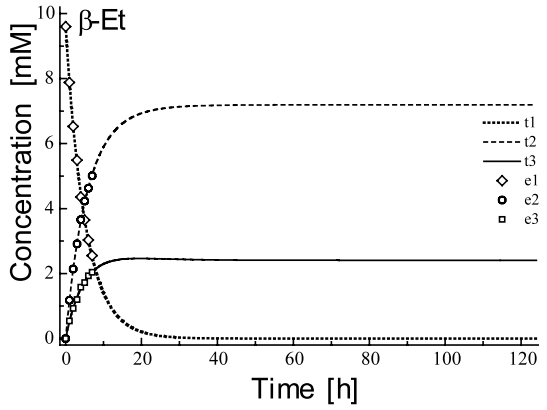


Fig. 4. Transglucosidation of ethyl 4-*O*-methyl-β-D-glucopyranoside in methanolic CSA. e_1–e_3 correspond to experimental points and t_1–t_3 correspond to theoretical curves.

the approach of the other alcohol from the opposite side, as indicated in Scheme 2 for the transglucosidation of methyl 4-*O*-methyl-α-D-glucopyranoside. It seems probable that the transglycosidation of other alkyl pyranosides, the related Fischer synthesis of glycopyranosides, and the acid hydrolysis of α- and β-glycopyranosides, also proceed via glycopyranosylium ions.

Table 1
Ethanolysis of methyl 4-*O*-methyl-α-D-*gluco*-pyranoside in 1 M ethanolic CSA at 50.0 ± 0.1 °C

Time (s)	α-Me (mM)	α-Et (mM)	β-Et (mM)
3600	9.77	0.066	0.16
7200	9.42	0.27	0.31
10,800	9.21	0.33	0.46
14,400	8.97	0.44	0.59
18,000	8.72	0.54	0.74
21,600	8.52	0.66	0.82
25,200	8.28	0.80	0.92
86,400	5.27	2.82	1.91
172,800	2.78	4.93	2.29
259,200	1.47	6.11	2.41
446,400	0.38	7.18	2.44

Table 2
Ethanolysis of methyl 4-*O*-methyl-β-D-*gluco*-pyranoside in 1 M ethanolic CSA at 50.0 ± 0.1 °C

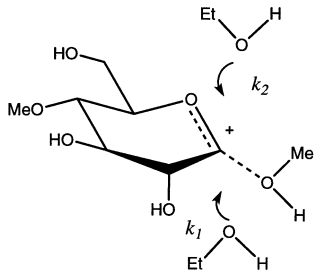
Time (s)	β-Me (mM)	α-Et (mM)	β-Et (mM)
3600	8.99	0.59	0.42
7200	8.13	1.13	0.74
10,800	7.21	1.72	1.07
14,400	6.52	2.17	1.31
18,000	5.89	2.57	1.54
21,600	5.00	3.26	1.74
25,200	4.49	3.60	1.92
86,400	0.89	6.43	2.68

Table 3
Methanolysis of ethyl 4-*O*-methyl-α-D-*gluco*-pyranoside in 1 M ethanolic CSA at 50.0 ± 0.1 °C

Time (s)	α-Et (mM)	α-Me (mM)	β-Me (mM)
3600	8.95	0.19	0.47
7200	8.27	0.52	0.81
10,800	7.69	0.80	1.11
14,400	7.06	1.09	1.45
18,000	6.60	1.34	1.66
21,600	6.20	1.62	1.78
25,200	5.83	1.80	1.96
86,400	1.96	5.03	2.60
172,800	0.45	6.70	2.46
259,200	0.11	7.09	2.39

Table 4
Methanolysis of ethyl 4-*O*-methyl-β-D-*gluco*-pyranoside in 1 M ethanolic CSA at 50.0 ± 0.1 °C

Time (s)	β-Et (mM)	α-Me (mM)	β-Me (mM)
3600	7.88	1.18	0.54
7200	6.53	2.14	0.93
10,800	5.49	2.91	1.20
14,400	4.36	3.66	1.58
18,000	3.65	4.23	1.72
21,600	3.03	4.63	1.93
25,200	2.55	5.01	2.04



Scheme 2. Transglucosidation of methyl 4-*O*-methyl-β-D-glucopyranoside in ethanolic CSA.

3. Experimental

General methods.—Methanol was distilled over Mg/I_2 and kept over 3 Å molecular sieves. Ethanol (99.5%) was dried over 3 Å molecular sieves (powder). CSA was recrystallized from EtOAc and dried under reduced pressure over phosphorus pentoxide. The acidic solutions were titrated with aq 0.5 M NaOH before and after the kinetic run, and no change was observed. Kinetic runs were performed in Supelco screw cap vials with PTFE/Neoprene septa. Glassware was dried for 10 h at 110 °C and cooled in a desiccator. Concentrations were performed under reduced pressure below 40 °C. TLC was performed on 0.25 mm precoated silica-gel plates (E. Merck, Silica-Gel $60F_{254}$) and detection by spraying the plates with 8% aq H_2SO_4 solution, followed by heating at 250 °C. For column chromatography Silica-Gel K 60 (E. Merck, 0.040–0.063 mm) was used. ^{13}C NMR spectra were recorded on a JEOL JNM-GSX 270 instrument and chemical shifts were measured relative to acetone (δ 31.0 ppm, CH_3) as internal standard. FAB-MS, in the negative mode, was performed on a JEOL SX 102 instrument, using a triethanolamine matrix. Optical rotations were determined with on a Perkin–Elmer 241 polarimeter. Kinetic runs were performed in a Heto Birkeröd 08 C 623 water thermostat. GC was conducted on a HP 5890 instrument with a flame-ionization detector and hydrogen as the carrier gas. In order to get baseline separation, a HP-5 column fused-silica capillary column was used for the methanolysis experiments, and a BD-225 fused-silica capillary column for the ethanolysis experiments.

*Ethyl 4-*O*-methyl α-*D*-glucopyranoside* (**1**).—Methyl 4-*O*-methyl-α-D-glucopyranoside[11] (0.916 g, 4.40 mmol) was dissolved in 40 mL 1 M ethanolic hydrogen chloride, and the solution was boiled under reflux for 10 h. After standard work-up, the two anomers was separated by column chromatography (19:1 toluene–EtOAC) and the α anomer was crystallized form $CHCl_3$ in 28% yield. Mp 130–131 °C. $[\alpha]_D^{25}$ +157° (*c* 0.52, water). FAB-MS. Anal. Calcd for [M − 1]: 221.1025. Found: 221.1019. ^{13}C NMR (D_2O) δ 98.5 (C-1), 80.0 (C-4), 73.6 (C-3), 72.0 (C-2), 71.3 (C-5), 64.6 (CH_2CH_3), 61.0 (C-6), 60.7 (CH_3), 14. 8 (CH_2CH_3).

Kinetic runs.—All glucosides were dissolved in 1 mL of water and freeze-dried. The methyl glucosides (10 mg, 52 μmol) or ethyl glucosides (10 mg, 48 μmol) were dissolved in anhyd 1 M methanolic or 1 M ethanolic CSA (5 mL). The solutions were transferred to the reaction vial and the atmosphere was exchanged for argon. The vial was then placed in the thermostat (50.0 ± 0.1 °C). Aliquots (100 μL) were withdrawn with a syringe at suitable intervals and neutralized with DOWEX 1X4-200 resin (OH^-). The solutions were concentrated, acetylated, and analyzed by GC. The components were identified by comparison with authentic substances. The relative amounts of the components were estimated from the areas under the peaks and corrected by response factors.[14]

Table 5
Rate constants (s^{-1}) and β/α ratios for the initial transglucosidation reaction and for the equilibration of initially formed product, on ethanolysis of methyl 4-*O*-methyl-α- and -β-D-glucopyranoside and on methanolysis of ethyl 4-*O*-methyl-α- and -β-D-glucopyranoside

Starting material	k_1 (10^5 s^{-1})	k_2 (10^5 s^{-1})	k_2/k_1	Inversion (%) [a]	k_3 (10^5 s^{-1})	K_4 (10^5 s^{-1})	k_4/k_3	*R*
α-Me	0.27 ± 0.01	0.48 ± 0.01	1.76	64	0.55 ± 0.01	1.67 ± 0.01	3.1	0.9999
β-Me	1.77 ± 0.04	1.19 ± 0.05	0.67	60	0.58 ± 0.04	1.79 ± 0.06	3.1	0.9987
α-Et	0.66 ± 0.05	1.32 ± 0.05	2.0	67	0.85 ± 0.07	2.54 ± 0.07	3.0	0.9992
β-Et	3.68 ± 0.08	1.66 ± 0.08	0.45	69	0.84 ± 0.07	2.52 ± 0.07	3.0	0.9995

[a] Inversion (%) of configuration during the initial reaction.

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