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KINETICS AND MECHANISM OF THE ACID-CATALYSED BUTANOLYSIS OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE

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ABSTRACT

The sulfuric acid-catalysed reaction of 1,6-anhydro-β-D-glucopyranose in 1-butanol at 80° gave butyl α- and β-D-glucopyranoside as the sole products. The initial kinetic α/β ratio was 1.5, and the final α/β ratio upon equilibration was 2.7. The four pseudo-first-order reaction rate constants involved have been determined. Conformational studies showed that the reaction probably proceeds *via* a $^1C_4$–$B_{0,3}$ interconversion of 1,6-anhydro-β-D-glucopyranose and a $^4H_3$-like oxycarbonium species.

INTRODUCTION

Long-chain alkyl α-D-glucopyranosides are of interest because of their surface-active[1] and liquid-crystalline[2] properties. In this respect, we have described the acid-catalysed alcoholysis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[3] and the direct acetalation of D-glucose[4] with $\geq C_8$ fatty alcohols. Upon liberation of acetone and water, respectively, a mixture of alkyl D-glucosides was formed, from which the α-D-pyranoside isomer could be isolated by direct crystallisation. As the rate of formation of this thermodynamically more favourable isomer appeared to be relatively low, subsequent equilibration of the alkyl D-pyranoside mixture was required in order to obtain a maximum yield of the α-D-pyranoside isomer. Therefore, it was decided to study the possibly selective kinetic formation of alkyl α-D-glucopyranosides by acid-catalysed alcoholysis of 1,6-anhydro-β-D-glucopyranose (**1**), available from starch[5,6] or cellulose[6,7] thermolysis.

The alcoholysis of **1** has been little studied. Although the hydrogen chloride-catalysed methanolysis of **1** was supposed to yield initially methyl β-D-glucopyranoside[8], later reports on the acid-catalysed alcoholysis of **1** and its derivatives gave no further mechanistic information[9–13]. On the other hand, the Lewis acid-catalysed polymerisation of derivatives of **1** has been intensively studied[14,15]. Highly

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stereoregular (1→6)-α-D-glucopyranan was obtained by the phosphorus pentafluoride-catalysed reaction of the 2,3,4-tri-*O*-methyl derivative of **1** in dichloromethane at −78°. The concurrent formation of β linkages under less stringent conditions has been attributed to premature chair inversion of a cationic $^1C_4$ transition-state complex[14,15]. We now present a kinetic and mechanistic study of the sulfuric acid-catalysed conversion of **1** in 1-butanol as a model alcoholysis reaction. For comparison, the behaviour of butyl β-D-glucopyranoside (**2β**) under the same reaction conditions was also studied.

RESULTS

Figs. 1 and 2 show the course of the homogeneous reaction of 1,6-anhydro-β-D-glucopyranose (**1**) and butyl β-D-glucopyranoside (**2β**), respectively, catalysed by sulfuric acid in 1-butanol at 80°. A clean mixture of **2α** and **2β** was obtained, accounting for the total molar balance according to h.p.l.c. (in the presence of traces of water, however, formation of a few % of butyl D-glucofuranoside occurred.) The reaction from either **1** or **2β** finally yielded an equilibrium mixture of 73% of **2α** and 27% of **2β**.

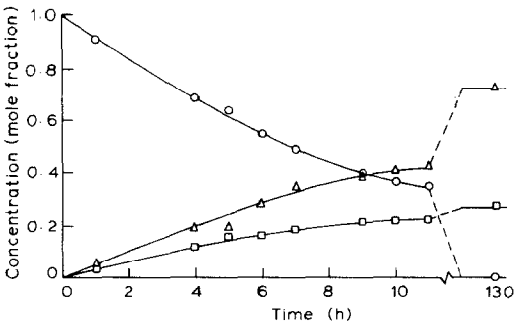


Fig. 1. Acid-catalysed conversion of **1** (○) into an equilibrium mixture of **2α** (△) and **2β** (□) (50mM **1**, 5mM sulfuric acid, 1-butanol, 80°).

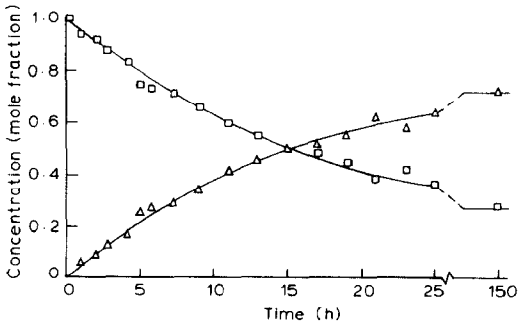
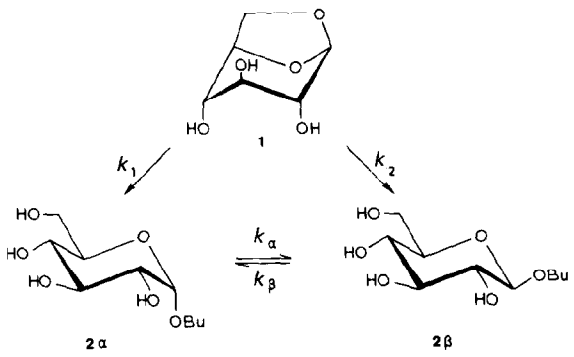


Fig. 2. Acid-catalysed conversion of **2β** (□) into an equilibrium mixture with **2α** (△) (50mM **2β**, 5mM sulfuric acid, 1-butanol, 80°).



The pseudo-first-order reaction rate constants k_1, k_2, k_α, and k_β have been determined in the following way. In the isomerisation of **2β**, its rate of conversion is given by

$$-\frac{d[\mathbf{2\beta}]}{dt} = k_\beta[\mathbf{2\beta}] - k_\alpha[\mathbf{2\alpha}], \tag{1}$$

or, in the integrated form, by $y = (k_\alpha + k_\beta)t$, with

$$y = -\ln\{(k_\alpha/k_\beta + 1)[\mathbf{2\beta}] - k_\alpha/k_\beta\}. \tag{2}$$

The kinetic data yield $(k_\alpha + k_\beta) = (21.5 \pm 1.0) \times 10^{-6}\ s^{-1}$, from which k_α and k_β may be obtained using $[\mathbf{2\beta}]/[\mathbf{2\alpha}] = k_\alpha/k_\beta = 0.37$ (Table I).

The rate of conversion of **1** is given by

$$-\frac{d[\mathbf{1}]}{dt} = (k_1 + k_2)[\mathbf{1}], \tag{3}$$

or, in the integrated form, by

$$\ln[\mathbf{1}] = -(k_1 + k_2)t. \tag{4}$$

From the experimental data, an overall rate constant $(k_1 + k_2) = (27.5 \pm 1.0) \times 10^{-6}\ s^{-1}$ is obtained.

The rate of formation of **2β** during the butanolysis of **1** is given by

$$\frac{d[\mathbf{2\beta}]}{dt} = k_2[\mathbf{1}] + k_\alpha[\mathbf{2\alpha}] - k_\beta[\mathbf{2\beta}], \tag{5}$$

which can be integrated to $z = (k_2 - k_\alpha)x$, with

$$z = [2\beta] - \frac{k_\alpha}{k_\alpha + k_\beta}\{1 - \exp[-(k_\alpha + k_\beta)t]\}, \text{ and} \quad (6)$$

$$x = \frac{\exp[-(k_1 + k_2)t] - \exp[-(k_\alpha + k_\beta)t]}{k_\alpha + k_\beta - (k_1 + k_2)}. \quad (7)$$

The experimental data give $(k_2 - k_\alpha) = (5.1 \pm 0.3) \times 10^{-6}\ s^{-1}$, from which k_1 and k_2 are obtained using $(k_1 + k_2)$ and k_α (Table I).

DISCUSSION

The mechanism of the acid-catalysed anomerisation of butyl D-glucopyranosides in 1-butanol should be comparable to that of the methyl homologues in methanol. It has been shown that, in tetradeuteriomethanol, methyl β-D-glucopyranoside is not converted into its α anomer but into trideuteriomethyl α-D-glucopyranoside (>80%) and its β anomer (<20%) in the initial stage of the reaction[16]. Therefore, following protonation of the exocyclic oxygen atom and loss of methanol, the formation of an intermediate D-glucopyranosyl oxycarbonium ion (**3**) has been proposed[16]. A study of the solvolysis of D-glucopyranosyl derivatives in mixtures of ethanol and 2,2,2-trifluoroethanol revealed that the transition state for α- or β-D-glucoside formation contained the leaving group[17]. The preferred conformation of this transition state will be probably a $^4H_3$-like half-chair (*cf.* Scheme 1), solvated at the α- and β-face of C-1 by an alcohol.

Such a transition state together with a low rate of exchange with bulk solvent molecules results in a clean S_N2 reaction. Where there is a high rate of exchange, an S_N1 reaction will be observed. Previous studies[16–18] indicate that the rates of exchange and reaction are of the same order of magnitude.

In the butanolysis of **1**, the leaving group cannot diffuse into the bulk solvent. Apparently, the bond between O-6 and C-1 is selectively broken, since pyranosides rather than septanosides are formed. Upon protonation of O-6 and bond cleavage, the $^1C_4$ conformation of **1** will be converted into an oxycarbonium ion (**3**) with a $^3H_4$-like half-chair conformation (Scheme 1). This conformation will be energetically rather unfavourable because of the four pseudo-axial substituents.

TABLE I

PSEUDO-FIRST-ORDER REACTION RATE CONSTANTS FOR THE BUTANOLYSIS OF **1**, **2α**, AND **2β**[a]

Rate constant	$10^{-6}\ s^{-1}$
k_1	16.5 ±1.1
k_2	11.0 ±0.4
k_α	5.8 ±0.5
k_β	15.7 ±0.6

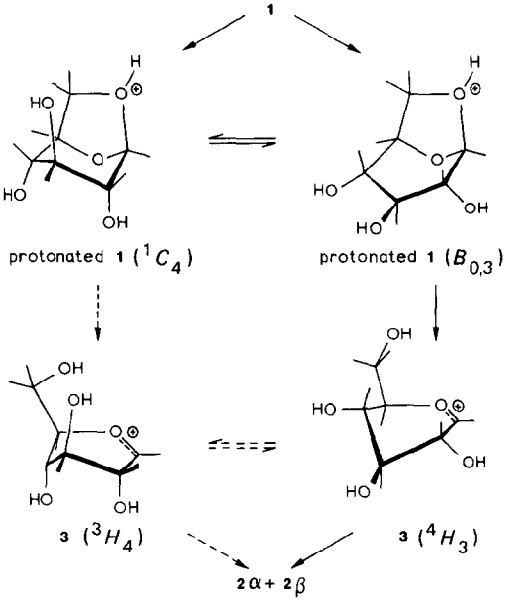
[a]Reaction conditions: 50mM substrate and 5mM H_2SO_4 in 1-butanol at 80.0°.

Alternatively, the $^4H_3$ conformation of the oxycarbonium species **3** is formed from the $B_{0,3}$ conformation of **1**. The $^4H_3$ conformation lacks pseudo-axial interactions and is energetically a more favourable reaction intermediate than the $^3H_4$ conformation.

In order to ascertain the most probable reaction pathway, the free enthalpies of the different reacting species have been estimated. The 3-amino-3-deoxy derivative of **1** exists in solution as a mixture of the $^1C_4$ and $B_{0,3}$ conformations[19]. Although the $B_{0,3}$ conformation of **1** has not been observed in n.m.r. experiments[20], MM-2 calculations suggest that the two conformations of **1** have similar energies[21]. On the other hand, the $^4H_3$ conformation of **3** is estimated to be 10 kJ/mol more favourable than its $^3H_4$ conformation, using the method of Angyal[22]. Therefore, the reaction is thought to take place predominantly *via* the $B_{0,3}$ conformation of **1**, as depicted in energetic terms in Fig. 3.

The ratio of attack by 1-butanol from the α- and β-side of **3** will be determined by steric and electronic factors, which are understood insufficiently at present for a useful prediction[23]. A high selectivity to α-D-glucosides from the $^4H_3$ conformation of **3**, however, cannot be expected, in accordance with the experimental ratio of $k_1/k_2 = 1.5$.

The initial **2α/2β** ratio (1.5) from **1** is somewhat higher than that (~1) found starting from D-glucose, but, if a maximal yield of **2α** is desired, subsequent (slow) anomerisation to the thermodynamic ratio of **2α** and **2β** (2.7) is still required.



Scheme 1. Possible mechanisms for the acid-catalysed butanolysis of **1** into **2α** and **2β**.

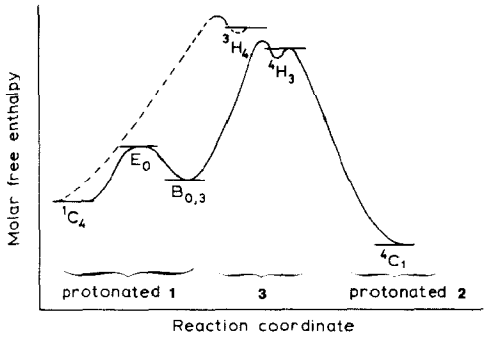


Fig. 3. Schematic representation of the relative free enthalpies for the possible pathways in the butanolysis of **1**, assuming that the intermediate oxycarbonium ions **3** closely resemble the transition states of the reaction.

EXPERIMENTAL

Reaction procedure. — 1,6-Anhydro-β-D-glucopyranose[5] (m.p. 178–182°) and butyl β-D-glucopyranoside[24] (m.p. 62°) were >99% pure according to h.p.l.c. Tubes were filled with a freshly prepared solution (~2 mL) of **1** or **2β** (50.0mM) and anhydrous[25] sulfuric acid (5.0mM) in 1-butanol at 0°. The tubes were sealed and heated in a water bath at 80.0°. At regular intervals, a tube was removed and cooled to 0°. After opening, a portion (1.00 mL) of the contents was pipetted-off and neutralised with sodium hydrogencarbonate (1.00 mL, 10mM). D-Mannitol was added as internal standard for h.p.l.c. analysis, and 1-butanol was removed *in vacuo* at 50°.

H.p.l.c. analysis. — H.p.l.c. was performed on a M6000A system equipped with a R401 refractive index detector (Waters Assoc.). An Aminex HPX 87C column (300 × 7 mm, Bio-Rad) at 60° was eluted with water at 0.6 mL/min[26]. Retention times (min): 14.6, **2β**; 17.8, **2α**; 21.3, D-mannitol; 25.3, **1**. The response factor of **2α** was assumed to be identical to that of **2β**. Each sample was analysed in duplicate. Concentrations are expressed in mole fractions.

Linear regression. — The data sets were fitted to the straight line $y = p.x$ using the method of least squares, with calculation of the 95% confidence interval of the thus estimated value of p[27].

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