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Mechanism of the reductive cleavage reaction of permethylated methyl D-glycopyranosides

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Abstract

The mechanism of the reductive cleavage reaction of permethylated methyl D-glycopyranosides was investigated by measuring the rate of reaction. Glycosides employed were of α-Glc, β-Glc, α-Man, α-Gal, and β-Gal. Seven silanes were used to explore the reactivities of the reducing agents as well as to examine the stereoelectronic effects of the agents. Trimethylsilyl trifluoromethanesulfonate was employed as catalyst. In general, the rates of β anomers were about twice as fast as those of the α anomers. The rates of anomerization were about five to ten times lower than those of reduction. A cyclic oxonium ion has been proposed as a sole intermediate for the reductive cleavage of the α-glycoside linkage, but the attack of the reducing agent on both cyclic and acyclic forms as well as on the substrate–Lewis acid complex seems to be involved for the β anomer.

Keywords: Reductive cleavage of glycoside linkages; Anomerization; Cyclic oxonium ion; Acyclic oxonium ion

1. Introduction

The reductive cleavage method is one of the important tools in determining the structure of polysaccharides [1]. Various aspects of the method have been studied extensively [2–13]. So far, the investigation has concentrated mostly on the variation of polysaccharides and catalysts while triethylsilane and dichloromethane are employed as the reducing agent and solvent, respectively.

The method consists of exhaustive methylation of the free OH groups in a polysaccharide, reductively cleaving all glycosidic linkages with Et_3SiH in the presence of Lewis acid catalyst, acylating the free OH group generated by the cleavage, and identifying the partially methylated and acylated 1,5- or 1,4-anhydroalditol products present in the final reaction mixture. Any knowledge related to the mechanism of the reductive cleavage step should therefore be very useful for understanding the nature of the reaction, and providing better reaction conditions that could make the method more applicable to various types of substrates.

Although a mechanistic aspect of the reaction was not investigated in depth, a cyclic oxonium ion was suggested to be formed during the course of the reaction, based on the stereochemistry of the 1-monodeuterio-1,5-anhydroglucitol produced upon reduction with Et_3SiD [2]. The stereochemistry of the deuterio-1,5-anhydroalditol products seems to support this rationale, because the predominant ($>90\%$) axial configuration of the deuterium atom in the products could arise from

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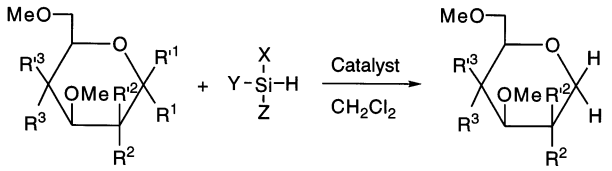
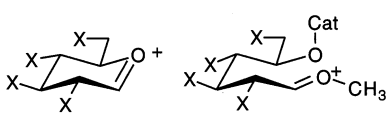


1-3 4 5-7

	R^1	R'^1	R^2	R'^2	R^3	R'^3
1α (α-Glc)	OMe	H	OMe	H	OMe	H
1β (β-Glc)	H	OMe	OMe	H	OMe	H
2α (α-Glc)	OMe	H	H	OMe	OMe	H
3α (α-Glc)	OMe	H	OMe	H	H	OMe
3β (β-Glc)	H	OMe	OMe	H	H	OMe
5 (anhydro-Glc)	H	H	OMe	H	OMe	H
6 (anhydro-Man)	H	H	H	OMe	OMe	H
7 (anhydro-Gal)	H	H	OMe	H	H	OMe
	X		Y		Z	
4a	C_2H_5		C_2H_5		C_2H_5	
4b	C_2H_5O		C_2H_5O		C_2H_5O	
4c	*i*-C_3H_7		*i*-C_3H_7		*i*-C_3H_7	
4d	C_6H_5		C_6H_5		C_6H_5	
4e	t-C_4H_9		CH_3		CH_3	
4f	C_6H_5		CH_3		CH_3	
4g	C_6H_5		C_6H_5		H	

Scheme 1.

the cyclic oxonium intermediate. A cyclic oxonium ion has also been proposed as an intermediate for the anomerization of permethylated methyl D-glycosides, along with an acyclic oxonium ion [14,15]. It has also been suggested that a similar cyclic oxonium ion is involved in the process of transglycosylation and acetolysis [16].



Cyclic oxonium ion Acyclic oxonium ion

We report here the results of our studies on the rates of reaction for the reductive cleavage of several permethylated methyl D-glycopyranosides (Scheme 1).

2. Results and discussion

The reductive cleavage of methyl glycosides has some analogy with the hydrolysis reaction of acetals or ketals [17]. Needless to say, glycosides are acetals and formation of an oxonium ion in the course of both reactions may imply mechanistic similarities. An A-2 mechanism has been suggested for hydrolysis of methyl (or phenyl) D-glycopyranosides [18]. According to this mechanism for the hydrolysis of D-glucopyranosides, it is apparent that the pyranoside ring does not open during the course of reaction. It is also important to point out that attack by a water molecule on the oxonium ion takes place in the rate-determining step. However, this step is a fast one in the hydrolysis of other acetals in general.

Kaczmarek et al. studied the acetolysis of ethyl 2,3,4,6-tetra-*O*-acetyl-α and -β-D-glucopyranosides in 1:1 (v/v) acetic anhydride–acetic acid containing 1% of sulfuric acid [16]. They concluded that anomerization of the α to β anomer proceeds 30 times, and anomerization of the β to α anomer 300 times, as fast as the acetolysis of the substrate to form the anomeric glucose pentaacetates. Based on kinetic analysis, they ruled out the involvement of a cyclic oxonium ion intermediate for the process of anomerization, and instead proposed an acyclic oxonium ion to be responsible for anomerization. On the other hand, the former intermediate is the key intermediate for acetolysis, which is an intermolecular process.

It is reasonable to assume that an oxonium ion, either cyclic or acyclic, may be involved in the course of reductive cleavage because the reducing agent itself is anionic by nature. However, the most critical problem to be solved is whether the rate-determining step is the formation of an oxonium ion from the substrate or the reduction of the ion by a silane. This means that the factors which may influence the observed rates should be: (1) the structural characteristics of the substrates, especially the configuration of the anomeric carbons; (2) the nature of the reducing agents; and (3) the nature of the catalysts.

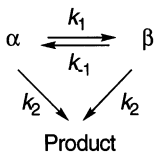
The rate of disappearance of the substrate should be the sum of the rate of the anomerization and that of formation of the product. Anomerization is known to be a reversible process and the calculation of k_2 would be complicated if the product is formed from both of the oxonium intermediates.

Table 1
The mole percent of substrate (**1α**), its anomer (**1β**) and 1,5-anhydroglucitol (**5**) present in the reaction mixture of **1α**, triethylsilane, and $Me_3SiOSO_2CF_3$ in CH_2Cl_2 after 0.5, 1, and 24 h, as determined by GLC

	0.5 h			1 h				24 h		
Silane	**1α**	**1β**	**5**	**1α**	**1β**	**5**	**α/β**	**1α**	**1β**	**5**
4a	71.3	2.6	26.1	57.0	2.0	41.0	28.5	1.2	2.2	96.6
4b	96.7	1.4	1.9	93.6	2.2	4.2	42.5	34.4	2.2	63.4
4c	75.7	3.8	20.5	62.0	5.2	32.8	11.9	9.8	1.8	88.4
4d	86.9	4.6	8.5	76.8	5.2	18.0	14.8	26.5	3.9	69.6
4e	72.3	2.3	25.4	54.8	3.3	41.9	16.6	0.0	0.0	100.0
4f	80.8	1.6	17.6	75.5	1.7	22.8	44.4	41.7	1.4	56.9
4g	63.2	1.6	35.2	43.6	1.5	54.9	29.1	3.8	1.0	95.2

Table 2
The mole percent of substrate (**1β**), its anomer (**1α**) and 1,5-anhydroglucitol (**5**) present in the reaction mixture of **1β**, triethylsilane, and $Me_3SiOSO_2CF_3$ in CH_2Cl_2 after 0.5, 1, and 24 h, as determined by GLC

	0.5 h			1 h				24 h		
Silane	**1α**	**1β**	**5**	**1α**	**1β**	**5**	**α/β**	**1α**	**1β**	**5**
4a	9.8	46.8	43.4	12.4	28.1	59.5	0.44	1.4	0.1	98.5
4b	23.8	73.6	2.6	37.1	57.6	5.3	0.64	11.8	2.9	85.2
4c	18.1	40.1	41.8	23.0	24.0	53.0	0.96	0.5	0.2	99.3
4d	27.0	38.0	35.0	27.0	27.6	45.4	1.00	16.0	3.2	80.7
4e	16.0	23.5	60.5	14.1	10.7	75.2	1.32	0.0	0.1	100
4f	6.0	63.0	31.0	5.6	62.0	32.4	0.09	6.9	7.2	85.9
4g	21.2	44.5	34.3	27.2	27.8	43.0	0.98	7.3	0.0	92.7



Our investigation of the rate of anomerization of permethylated methyl D-glycosides indicates that the rate of anomerization of β to α is about four times faster than that of α to β for methyl D-glucopyranosides [14]. Furthermore, the former process seems to take place via an acyclic oxonium ion, whereas the latter favors a cyclic oxonium ion [15]. In the presence of a reducing agent both ions may compete with reduction and anomerization. The cyclic oxonium ion, if formed, should compete with methoxytrimethylsilane and the reducing agent. Since the reducing agent is used at a five or ten times molar excess, it is probable that the rate of reduction is much higher than that of anomerization.

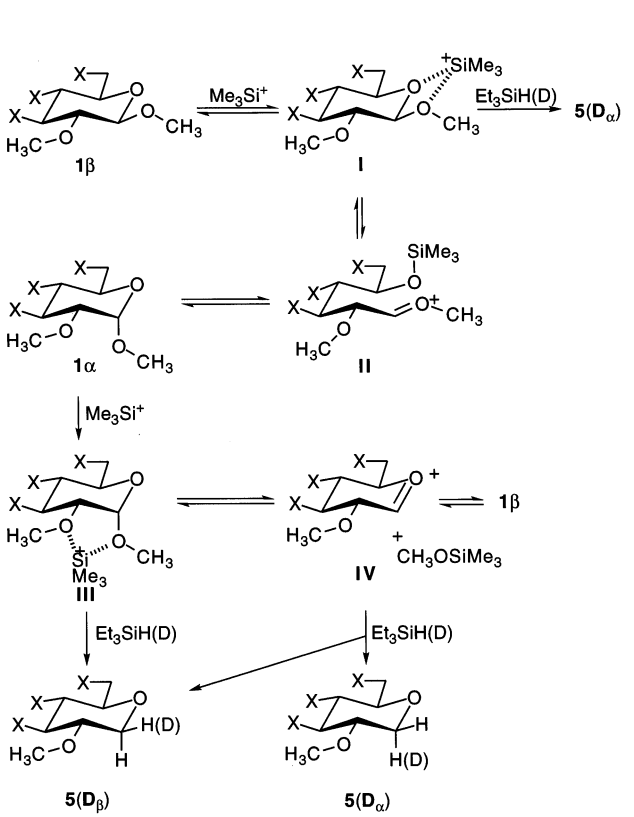
Tables 1 and 2 show clearly that both anomerization and reduction are much slower for the α anomer than those of the β anomer. Furthermore, the reduction takes place at a far greater rate than the anomerization, regardless of the reducing agent. These results are consistent with the process proceeding via a cyclic oxonium ion intermediate. The silane, which is present in five-fold excess, should be a better nucleophile than methoxytrimethylsilane. Consequently, the rate of formation of the product is much greater than that of anomerization.

On the other hand, the β substrate forms a substantial amount of α anomer, in addition to **5**, in 1 h. It seems to favor the acyclic oxonium pathway because the intermediate can readily recyclize intramolecularly to the α anomer. Then the question remains as to whether the cyclic oxonium ion is the sole intermediate for reduction of both α and β anomers. This may be true if a weak reducing agent, such as triethoxysilane (**4b**) is employed, which gives only 2.6 and 5.3% of **5** in 0.5 and 1 h, respectively (Table 2). However, it

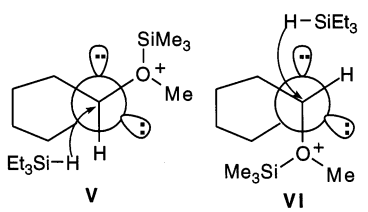
should be pointed out that the rate of formation of the product from the β anomer is about twice as high as that from the α anomer. If the cyclic oxonium ion is the sole intermediate, the rates should be very similar for both the α and β anomers.

Our observation can be explained by suggesting two reaction pathways, as shown in Scheme 2. In the case of the β anomer, the reduction may take place without the formation of the cyclic oxonium ion. The trimethylsilyl cation derived from $Me_3SiOSO_2CF_3$ may coordinate to both O-5 and O-1 atoms of the β anomer to form a complex such as **I**. This kind of coordination is plausible if one looks at the spatial arrangement of the lone-pair orbitals in the two oxygen atoms. Then the complex **I** may be directly attacked by a silane to form an anhydroalditol product **5** and methoxytrimethylsilane, or the ring may open to form an acyclic oxonium ion **II**. The direct attack may be considered as an S_N2 process, which can be illustrated as **V**. This may be the reason that the α-deuterio-1,5-anhydroglucitol **5D**$_\alpha$ formed almost exclusively when Et_3SiD was used for the reductive cleavage of **1β** [2]. Also, this is why the reduction takes place much faster than the anomerization. The acyclic oxonium ion **II** may undergo mostly intramolecular recyclization to form the α anomer.

On the other hand, in the case of the α anomer, the complexation to O-1 and O-2 is plausible (such as **III**) and the resulting *anti* arrangement of the lone-pair orbital in the O-5 and 1-C–O bond may readily lead to formation of a cyclic oxonium ion (**IV**). Once it is formed, a silane can readily attack from the axial direction to produce the alditol **5** (and **5D**$_\alpha$ when Et_3SiD is used). An S_N2 type of reaction of **III** with Et_3SiD should give **5D**$_\beta$ as the major product, and this was not observed. For such a displacement to occur, a silane has to approach from the direction parallel to the one of the lone-pair orbitals of the ring oxygen atom, as shown in **VI**. This seems unfavorable because of the repulsive nature of the interaction between the lone-pair electrons and the partially negatively charged hydrogen of the reducing agent.



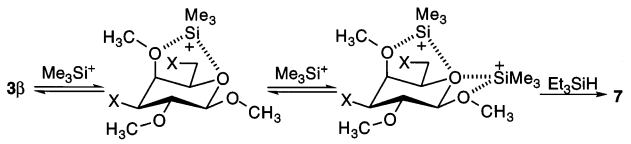
Scheme 2.



When the substrate was mixed with $Me_3SiOSO_2CF_3$ in the absence of the reducing agent, rapid equilibrium was reached within 1 h [15]. The α/β ratio was approximately four for permethylated methyl D-glucopyranoside and five for the galactopyranoside, regardless of the anomeric configuration of the starting material. The presence of a silane significantly decreases the rate of anomerization of **1α** to **1β**, as shown in Table 1. This is not surprising because the cyclic oxonium ion intermediate **IV** should react with the silane (which should be present in at least five-fold excess) at a higher rate than recombination with methoxytrimethylsilane to form **1β**. The anomerization of **1β** to **1α** is also retarded by the presence of a silane, the ratio of α/β ranging from 0.09 to 1.32. However, the retar-

Table 3
Rates of formation of 1,5-anhydroalditol by reductive cleavage of permethylated methyl D-glycopyranosides with triethylsilane and $Me_3SiOSO_2CF_3$ (1:5:5 by molar equiv) at 25 °C

Glycoside	k (min^{-1})
1α	$9.6\ (\pm 0.5)\times 10^{-3}$
1β	$3.7\ (\pm 0.5)\times 10^{-2}$
2α	$6.0\ (\pm 0.5)\times 10^{-3}$
3α	$2.2\ (\pm 0.5)\times 10^{-2}$
3β	$1.2\ (\pm 0.5)\times 10^{-1}$



Scheme 3.

dation is much less significant than with the case of **1α** to **1β**.

tert-Butyldimethylsilane (**4e**) seems to be the most effective among the reducing agents employed in the present investigation. This may be an indication that the silane itself, not the free hydride ion, approaches the anomeric carbon in the rate-determining step. The stereoelectronic factor seems to play an important role. Triethoxysilane (**4b**), triphenylsilane (**4d**), and dimethylphenylsilane (**4f**) are less effective than the trialkylsilanes **1a**, **1c**, and **1e**. Diphenylsilane (**4g**) seems to be as effective as triethylsilane (**4a**) in spite of the presence of two phenyl groups. The presence of two hydrogen atoms may increase the reducing power of **4g**.

The rates of the formation of the 1,5-anhydroalditols (**5**–**7**) are listed in Table 3. The highest rate is observed with the β-galactoside (**3β**) and the α-mannoside shows the lowest rate among the five glycosides examined. The rate enhancement in **3β** may be due to the complexation of Me_3Si^+ with the oxygen atom at C-4 and the ring oxygen atom, as shown in Scheme 3. Such complexation may increase the partial charge at C-1, which should be more susceptible to the attack by a silane.

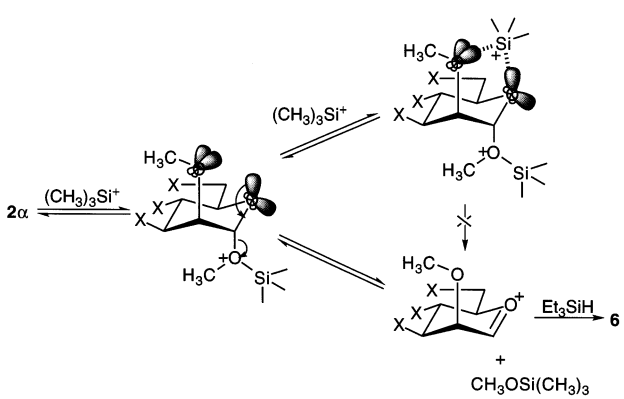
A similar kind of complex formation is also possible with the α-mannoside (**2α**). Once the complex is formed, the lone-pair orbital of the ring oxygen atom, which should be used for complexation with Me_3Si^+ and the oxygen atom of 2-C–OCH_3, is no longer available to push out the α-methoxy group at C-1 to form a cyclic oxonium ion (Scheme 4). This may be the reason for the lowest rate of the reductive cleavage of **2α**.

We also examined the effect of the molar ratio of the substrate, triethylsilane, and $Me_3SiOSO_2CF_3$, and have listed the results in Table 4. Surprisingly, the rate does not vary much as might be expected due to the ratio changes. The highest rate was observed when the ratio was 1:5:10. This may constitute additional evidence that the formation of the cyclic oxonium ion is rate determining in the case of the α anomer.

Table 4
Rates of formation of 1,5-anhydroglucitol by reductive cleavage of permethylated methyl α-D-glucopyranoside (**1α**) under different ratios of substrate, triethylsilane, and catalyst at 25 °C

Ratio [a]	k (s^{-1})
1:5:5	$9.0\ (\pm 0.5)\times 10^{-3}$
1:10:20	$1.0\ (\pm 0.5)\times 10^{-2}$
1:10:5	$9.3\ (\pm 0.5)\times 10^{-3}$
1:10:2	$7.4\ (\pm 0.5)\times 10^{-3}$
1:10:1	$7.5\ (\pm 0.5)\times 10^{-3}$
1:20:10	$8.8\ (\pm 0.5)\times 10^{-3}$
1:5:10	$1.6\ (\pm 0.5)\times 10^{-2}$
1:2:10	$1.4\ (\pm 0.5)\times 10^{-2}$
1:1:10	$2.8\ (\pm 0.5)\times 10^{-3}$

[a] **1α**:Et_3SiH:$Me_3SiOSO_2CF_3$.



Scheme 4.

3. Experimental

Starting materials.—Methyl α- and β-D-glucopyranosides, methyl α-D-mannopyranoside, and methyl α- and β-D-galactopyranosides were all commercial products. Permethylated methyl D-glycopyranosides (**1α**, **1β**, **2α**, **3α**, **3β**) were prepared as described previously [19]. Triethylsilane, $(C_2H_5)_3SiH$ (**4a**), triethoxysilane, $(C_2H_5O)_3SiH$ (**4b**), triisopropylsilane, $(i\text{-}C_3H_7)_3SiH$ (**4c**), triphenylsilane, $(C_2H_5)_3SiH$ (**4d**), *tert*-butyldimethylsilane, $t\text{-}C_4H_9(CH_3)_2SiH$ (**4e**), dimethylphenylsilane, $C_6H_5(CH_3)_2SiH$ (**4f**), and diphenylsilane $(C_6H_5)_2SiH_2$ (**4g**) were commercial products and were used without purification. Trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$) was also a commercial product and was distilled prior to use. CH_2Cl_2 was dried over CaH_2 and distilled prior to use.

Analytical methods.—^1H NMR spectra were recorded on a Varian 500 VXR-FT NMR spectrometer in CD_2Cl_2 containing Me_4Si as the internal standard. A Hewlett–Packard 5890 Plus gas–liquid chromatograph equipped with a capillary column (HP-5, 25 m, 0.53 μm × 1.0 mm) and a flame-ionization detector was used for analysis. The column was held at 120 °C for 2 min after injection then programmed to 250 °C at 6 °C/min. Nitrogen was used as the carrier gas at a flow rate of 1 mL/min.

Measurement of rates

Method A (use of GLC). A stock soln of permethylated methyl D-glycopyranoside (1.8×10^{-1} M) in CH_2Cl_2 was prepared. The reaction mixture was prepared by mixing the soln (2.6 mL) with a silane (10 equiv), $Me_3SiOSO_2CF_3$ (0.84 mL, 10 equiv) and docosane (47 mg). The mixture was divided into 12 V vials (0.2 mL each) and stirred at room temperature. At the predetermined time interval, the reaction was quenched by adding a soln (0.5 mL) of satd $NaHCO_3$. The organic layer was carefully separated with a syringe and stored in a freezer (−10 °C) prior to conducting the GLC. The mole percentages of each component present after 30 min, 1 h, and 24 h are listed in Tables 1 and 2 for **1α** and **1β**, respectively.

Method B (use of NMR). Stock solutions of a mixture of a glycoside and a reducing agent were prepared in a 1 mL volumetric flask by dissolving 36.5 mg of the substrate and appropriate amount of Et_3SiH in CD_2Cl_2 so that the concentrations of substrate and reducing agent were about 0.146 and 0.730 M, respectively. A soln of $Me_3SiOSO_2CF_3$ was prepared by dissolving 0.200 mL in CD_2Cl_2 in a 2 mL volumetric flask so that the concentration was 0.517 M. The soln of glycoside (0.2 mL) was taken with a gas-tight syringe (0.25 mL) and placed in an NMR tube (5 mm diameter) and the soln of $Me_3SiOSO_2CF_3$ (0.29 mL) was introduced by a gas-tight syringe (0.50 mL). The molar ratio of the glycoside, the silane, and Me_3SiOTf was 1:5:5. ^1H NMR spectra of the soln were obtained at predetermined intervals using a kinetics program. The spectra were retrieved and the peaks corresponding to H-1 at around δ 4.2 for β, δ 4.8 for α, δ 4.0 for the product, and CH_2Cl_2 at around δ 5.2 were integrated. The pseudo-first-order rate constants (k_{obs}) were calculated from the slope of a plot of time versus $\ln[(A_0 - A_\infty)/(A_t - A_\infty)]$ for a period of 1 h [20] and the results are listed in Table 3. '*A*' values were calculated from the ratio of the integrations of the anomeric proton and CH_2Cl_2 that was present in the solvent. The value of A_0 was the one obtained from the first spectrum of each run and the value of A_∞ was the one at which the concentration of the product reached a maximum. The first spectrum was usually obtained within 2 min and the progress of the reaction during the period was less than 1 and 3% for the α and β anomers, respectively.

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