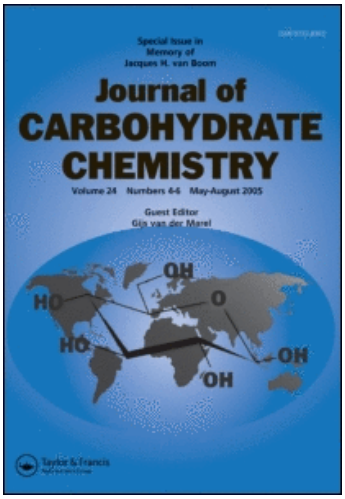

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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David Rolf[a]; John A. Bennek[a]; Gary R. Gray[a]
[a] Department of Chemistry, University of Minnesota, S.E. Minneapolis, Minnesota

To cite this Article Rolf, David , Bennek, John A. and Gray, Gary R.(1983) 'Reductive Cleavage of Glycosides, Stereochemistry of Trapping of Cyclic Oxonium Ions', Journal of Carbohydrate Chemistry, 2: 4, 373 — 383
To link to this Article: DOI: 10.1080/07328308308057884
URL: http://dx.doi.org/10.1080/07328308308057884

J. CARBOHYDRATE CHEMISTRY, 2(4), 373-383 (1983)

REDUCTIVE CLEAVAGE OF GLYCOSIDES. STEREOCHEMISTRY OF TRAPPING OF CYCLIC OXONIUM IONS

David Rolf, John A. Bennek and Gary R. Gray*

Department of Chemistry
University of Minnesota
207 Pleasant Street S.E.
Minneapolis, Minnesota 55455

Received August 1, 1983

ABSTRACT

Reductive cleavage of the glycosidic carbon-oxygen bonds of methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (1), methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside (2), permethylated cellulose (6) and permethylated cyclohexaamylose (7) was carried out in the presence of deuteriotriethylsilane, and the configuration of deuterium in the 1-deuterio-1,5-anhydro-D-glucitol derivatives (4, 5 and 9, 10) that were produced was established by ^{1}H- and ^{2}H-NMR spectroscopy. All reductions were carried out with boron trifluoride etherate as the catalyst as originally reported [D. Rolf and G. R. Gray, J. Am. Chem. Soc., 104, 3539 (1982)], as well as with trimethylsilyl trifluoromethanesulfonate which we now report efficiently catalyzes the regiospecific reductive cleavage of glycosides. Spectroscopic studies revealed that the configuration of deuterium in the products was independent of the configuration of the starting glycoside. The predominant (∿95%) axial configuration observed leads us to propose that free oxonium ions (3 and 8) are formed as intermediates in these reductions.

INTRODUCTION

We have recently shown that reductive cleavage of the glycosidic carbon-oxygen bond can be accomplished by ionic

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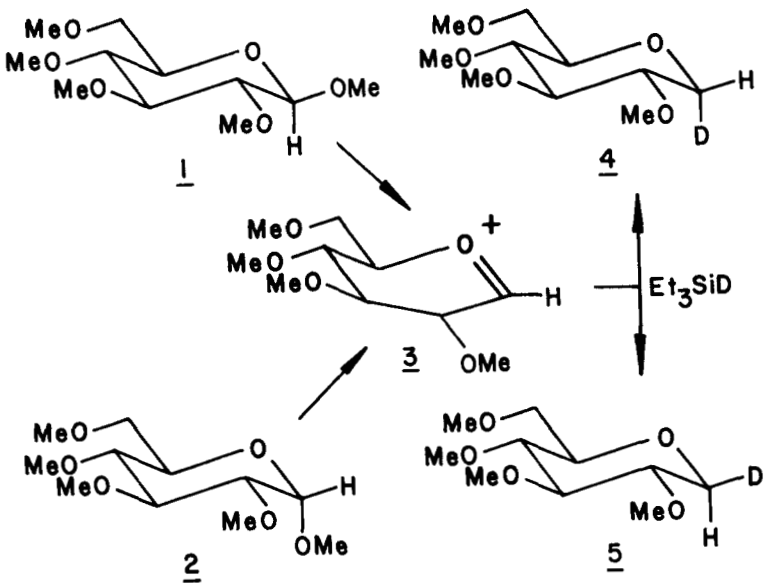
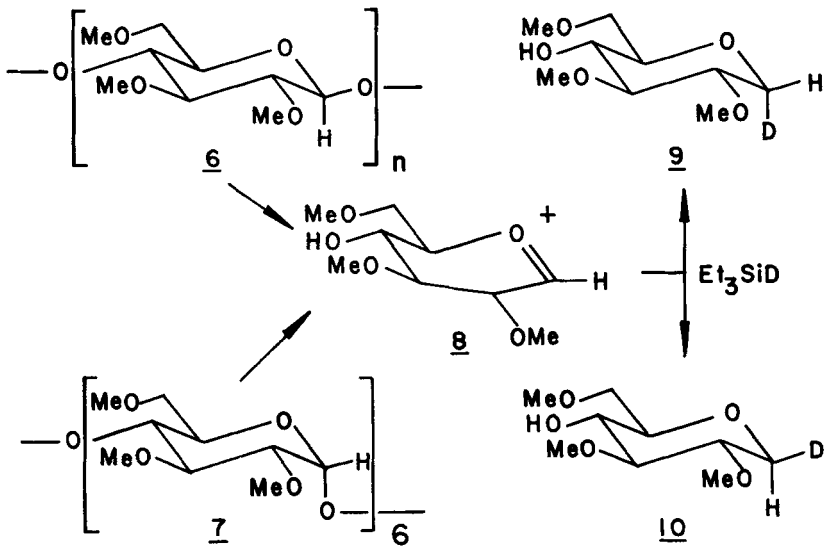
hydrogenation, employing triethylsilane as the reducing agent and boron trifluoride etherate as the acid.[1] Studies employing several model glycosides demonstrated that the reaction had potential synthetic utility, as a means to prepare anhydroalditols, as well as analytical utility, as a general method for polysaccharide structure determination. In both of these applications, the salient feature of the ionic hydrogenation reaction is the regiospecific cleavage of the glycosidic carbon-oxygen bond; i.e., for the model glycosides examined, cleavage of the other acetal oxygen bond (anomeric carbon-ring oxygen) was not observed. Aldopyranosides were thus cleaved to produce 1,5-anhydroalditols and aldofuranosides were cleaved to produce 1,4-anhydroalditols.

From these results it can be inferred that ionic hydrogen-



Scheme I

ation of glycosides proceeds exclusively via *cyclic* oxonium ions, as exemplified by structure 3 (Scheme 1). If free oxonium ions were indeed formed in these reduction reactions, the stereospecificity of reduction would be independent of the configuration of the starting glycoside. If, however, reduction was proceeding through intermediates formed prior to heterolytic cleavage of the glycosidic carbon-oxygen bond, some degree of stereospecificity with regard to the glycoside might be observed in the reduction. In order to investigate these possibilities, the model glycosides 1 and 2 were reduced with deuteriotriethylsilane, and the configuration of deuterium in the products (4 and 5) was established. These studies were also performed using fully methylated cellulose (6) and cyclohexaamylose (7) (Scheme 2), and the results were compared. The reductions were performed



Scheme 2

using boron trifluoride etherate as catalyst as previously reported,[1] as well as with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst which we now report also effects regiospecific cleavage of glycosides.

RESULTS AND DISCUSSION

Deuteriotriethylsilane reductions were carried out with either $BF_3 \cdot Et_2O$ as the catalyst as previously described or with TMSOTf as the catalyst[2] under comparable conditions (overnight at room temperature), and the products were analyzed by combined gas-liquid chromatography/mass spectrometry (Table 1). With TMSOTf as the catalyst, both 1 and 2 were quantitatively reduced

TABLE 1

Yields of Products Obtained in the Reductive Cleavage of Model Glucosides with Deuteriotriethylsilane

Compound	Catalyst[a]	Product	Yield,%
1	TMSOTf	4 + 5	100
1	$BF_3 \cdot Et_2O$	4 + 5	68[b]
2	TMSOTf	4 + 5	100
2	$BF_3 \cdot Et_2O$	4 + 5	76[b]
6	TMSOTf	9 + 10	94[c]
6	$BF_3 \cdot Et_2O$[d]	9 + 10	trace
7	TMSOTf	9 + 10	92[c]
7	$BF_3 \cdot Et_2O$[d]	9 + 10	93[c]

a. Reactions were carried out with 5 equiv. of Et_3SiD and 5 equiv. of catalyst per equivalent of acetal, except where noted.
b. Incomplete reactions; starting material and isomerized starting material were also present.
c. One other product was formed that was found by GC–MS analysis to be isomeric with the expected 1,5-anhydroalditol.
d. Reactions were carried out with 10 equiv. of Et_3SiD and 10 equiv. of catalyst per equivalent of acetal.

to give a mixture of the expected 1,5-anhydroalditols (4 + 5), but under the same conditions, incomplete reactions were observed with $BF_3 \cdot Et_2O$ as the catalyst. Longer reaction times or higher ratios of catalyst were found to effect the quantitative conversion of 1 and 2 to the expected 1-deuterio-1,5-anhydroalditols (4, 5), however. Permethylated cellulose (6) and permethylated cyclohexaamylose (7) were also reduced to the expected 1-deuterio-1,5-anhydroalditol derivative (9 + 10) in excellent yields in the presence of TMSOTf. Interestingly, $BF_3 \cdot Et_2O$ was an effective catalyst for the reductive depolymerization of permethylated cyclohexaamylose (7) but not for permethylated cellulose (6). A variety of reaction conditions employing $BF_3 \cdot Et_2O$ as the catalyst failed to produce good yields of the desired anhydroalditol from permethylated cellulose.

The stereochemistry of deuterium transfer in these reductive cleavage reactions was obtained through a comparison of the deuterated products and the respective non-deuterated authentic 1,5-anhydro-D-glucitol derivatives by ^1H NMR spectroscopy. In addition, the deuterated derivatives were examined by ^2H NMR spectroscopy in order to accurately quantify the percent of axial and equatorial deuterium substitution. All spectra were obtained on chromatographically (GLC) pure samples. In the case of reactions that were incomplete or where another product was observed, the desired 1,5-anhydro-D-glucitol derivative was isolated in pure form by preparative GLC.

In the spectrum of authentic 2,3,4,6-tetra-O-methyl-1,5-anhydro-D-glucitol, the H-1e resonance is observed at δ4.05 as a doublet of doublets ($J_{H\text{-}1e,1a}$ = 11.1 Hz and $J_{H\text{-}1e,2a}$ = 5.2 Hz), well separated from the other resonances, but the H-1a resonance occurs in a complex region of the spectrum and cannot be integrated. In the ^1H NMR spectrum of the product (4 + 5) obtained from the reductive cleavage of either 1 or 2 in the presence of Et_3SiD, the H-1e resonance of 4 is observed at δ4.04 as a doublet

TABLE 2

Percent of Products with Equatorial and Axial Deuterium Substitution Obtained in the Reductive Cleavage of Compounds 1, 2, 6 and 7 with Deuteriotriethylsilane[a]

Compound	Catalyst	Product	
		Axial (%)	Equatorial (%)
1	TMSOTf	4 (96)	5 (4)
1	$BF_3 \cdot Et_2O$	4 (95)	5 (5)
2	TMSOTf	4 (98)	5 (2)
2	$BF_3 \cdot Et_2O$	4 (93)	5 (7)
6	TMSOTf	9 (94)	10 (6)
7	TMSOTf	9 (96)	10 (4)
7	$BF_3 \cdot Et_2O$	9 (93)	10 (7)

a. Values were obtained by integration of ^2H NMR spectra, and are accurate ± 1%.

($J_{H\text{-}1e,2a}$ = 5.2 Hz), as expected. The inability to integrate the H-1a resonance of 5, however, prevents accurate quantification of the two isomers. The percentages of the two isomers (4 and 5) present in the mixture are readily established by ^2H NMR spectroscopy, however. In the 46.06 MHz ^2H NMR spectrum of the 4 + 5 mixture, the equatorial deuterium of 5 is observed at δ4.05 as a broad singlet, whereas the axial deuterium of 4 is observed as a broad singlet at δ3.10. Integration of these resonances provides the percentages of 4 and 5 present in the various reaction mixtures (Table 2).

A similar analysis of the ^2H NMR spectra of the 4-O-acetyl derivatives of the 9, 10 mixture reveals the percentages of equatorial and axial deuterium substitution (Table 2). For the acetyl derivative of 9, the axial deuterium resonance was observed at δ3.20, whereas the equatorial deuterium resonance of the acetyl derivative of 10 was observed at δ4.15. The 9, 10

mixture could also be satisfactorily analyzed by ^{1}H NMR spectroscopy. In this case, both the H-4 resonance of the 4-O-acetyl derivative (δ4.82, t, J = 9.2 Hz) and the H-1e resonance of 9 (δ4.09, d, J = 5.2 Hz) were well separated from each other and from the other resonances and could be readily integrated. Integration of the H-1e resonance relative to the H-4 resonance provided values within 1% agreement with those obtained by ^{2}H NMR spectroscopy (Table 2).

The results of these studies (Table 2) clearly establish that the stereochemistry of the reduction is independent of the configuration of the starting glycoside. If free oxonium ions (3 or 8) are indeed formed as intermediates in these reactions, then the stereospecificity observed in the reduction is that expected based on the work of Deslongchamps, et al.;[3] i.e., "hydride transfer will take place with minimum energy only when the intermediate oxonium ion can develop an electron pair which will become antiperiplanar to the newly formed C-H bond in the final product." Preference for axial attack from the sterically more hindered face has also been observed by Lewis, et al.[4] in the addition of carbon nucleophiles to cyclic pyran oxonium ions.

EXPERIMENTAL

General. Nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer. ^{1}H Spectra were recorded at 300 MHz with $CDCl_3$ as solvent and are referenced to internal tetramethylsilane. ^{2}H Spectra were recorded at 46.06 MHz with $CHCl_3$ as solvent and are referenced to internal $CDCl_3$ at δ7.25. Proton decoupled ^{13}C spectra were recorded at 75.46 MHz with $CDCl_3$ as solvent and are referenced to internal tetramethylsilane. Combined GLC/MS was carried out on a Finnigan 4000 mass spectrometer equipped with a VG Multispec data system. Chromatography (GLC) was carried out on a 3.2 mm x 244 cm column of SP2401 on 100/120 Supelcoport. Preparative GLC was carried out on a 6.4 mm x 244 cm column of OV225. Deuteriotriethylsilane was

prepared from triethylsilyl chloride and lithium aluminum deuteride using the procedure described by Sommer, et al.[5] Trimethylsilyl trifluoromethanesulfonate (Aldrich) was stored in 0.5 mL portions in glass ampules under argon.

Model Compounds. Methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (1),[6] methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside (2),[6] permethylated cellulose (6), permethylated cyclohexaamylose (7),[7] and 1,5-anhydro-2,3,4,6-tetra-O-methyl-D-glucitol[8] were prepared by Hakomori methylation[9,10] of methyl β-D-glucopyranoside, methyl α-D-glucopyranoside, cellulose, cyclohexaamylose and 1,5-anhydro-D-glucitol,[11] respectively. 1,5-Anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-glucitol was prepared as previously reported.[1] Monosaccharide derivatives were isolated in chromatographically (GLC) pure form and had optical rotations, melting points (where appropriate), and ^{1}H- and ^{13}C NMR spectra in agreement with those reported. Permethylated cyclohexaamylose likewise had a melting point,[7] optical rotation,[7] ^{1}H NMR spectrum[12] and ^{13}C NMR spectrum[13] in agreement with those reported. The infrared spectrum of permethylated cellulose contained no hydroxyl absorption.

Reductive Cleavage with $BF_3 \cdot Et_2O$ as Catalyst. Approximately 50 mg of the permethylated glycoside was added to a dry 5 mL round-bottomed flask equipped with a stir bar, and 5 equiv. each of Et_3SiD and $BF_3 \cdot Et_2O$ per equivalent of acetal were sequentially added. Dry CH_2Cl_2 was added to a total volume of 1.0 mL, and the reaction was stoppered and allowed to stir overnight at room temperature. Reactions employing 1 and 2 as starting materials were quenched with saturated aqueous $NaHCO_3$, then extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over anhyd. Na_2SO_4 and evaporated to dryness under vacuum. The reaction employing 7 as a starting material was quenched with CH_3OH (30 mL) and deionized by passage through

a column (0.5 x 7 cm) of 20-50 mesh AG501-X8 analytical grade mixed bed resin. Methanol and CH_2Cl_2 were removed by evaporation under vacuum, and the product was acetylated with acetic anhydride in pyridine in the usual fashion.

Reductive Cleavage with TMSOTf as Catalyst. Approximately 20-30 mg of the dry permethylated glycoside was added to a dry Wheaton V vial containing a small stir bar and fitted with an open-top screw cap containing a Teflon liner. Dry CH_2Cl_2 (0.5 mL) and 5 equiv. each of Et_3SiD and TMSOTf (per equiv. of acetal) were added sequentially, and the reaction was capped and allowed to stir overnight at room temperature. The reaction was quenched by adding to 30 mL of CH_3OH, and was then deionized by passage through a column (0.5 x 7 cm) of 20-50 mesh AG501-X8 analytical grade mixed bed resin. Methanol and CH_2Cl_2 were removed by evaporation under vacuum. The products derived from permethylated cellulose and permethylated cyclohexaamylose were subsequentially acetylated with acetic anhydride in pyridine in the usual fashion.

1,5-Anhydro-1-deuterio-2,3,4,6-tetra-O-methyl-D-glucitol (4, 5). A mixture of 4 and 5 was prepared from 1 and 2 by reduction with Et_3SiD in the presence of either $BF_3{\cdot}Et_2O$ or TMSOTf as described above. ^1H NMR ($CDCl_3$): δ3.08-3.19 (complex, 3H, H-2,3,4), 3.21 (ddd, J = 2.10, 4.58, 9.77 Hz, 1H, H-5), 3.52 (dd, J = 4.58, 10.38 Hz, 1H, H-6), 3.60 (dd, J = 2.10, 10.38, 1H, H-6), 3.40, 3.47 3.53, 3.64 (four s, 12H, methoxyl), 4.04 (d, J = 5.24 Hz, ∿1H, H-1e); ^{13}C NMR ($CDCl_3$)(^1H decoupled): δ58.7, 59.2, 60.4, 60.6 (methoxyl), 67.3 (t, J = 21.5 Hz, C-1), 71.7, 79.0, 79.6, 79.9, 87.9 (C-2, 3, 4, 5, 6); ^2H NMR ($CHCl_3$); δ3.1 (broad s, ^2H-1a of 4),4.05 (broad s, ^2H-1e of 5).

1,5-Anhydro-4-O-acetyl-1-deuterio-2,3,6-tri-O-methyl-D-glucitol (4-O-acetyl 9 and 10). A mixture of 4-O-acetyl-9 and 4-O-acetyl-10 was prepared from 6 by reduction with Et_3SiD in the presence of either $BF_3{\cdot}Et_2O$ or TMSOTf and from 7 by reduction with

Et_3SiD in the presence of TMSOTf. The major product of these reactions was separated from an isomeric impurity (4-7%) by preparative GLC. ^1H NMR ($CDCl_3$): δ2.10 (s, 3H, acetoxy), 3.24 (t, J = 9.00 Hz, 1H, H-3), 3.28-3.46 (complex, 4H, H-2,5,6), 3.35, 3.48, 3.53 (three s, 9H, methoxyl), 4.09 (d, J = 5.22 Hz, ∿1H, H-1e), 4.81 (t, J = 9.28 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ21.0 (acetoxy C-2), 58.9, 59.4, 60.3 (methoxyl), 67.4 (t, J = 21.8 Hz, C-1), 70.8, 72.3, 77.8, 79.4, 85.1 (C-2,3,4,5,6), 169.8 (acetoxy C-1); ^2H NMR ($CHCl_3$): δ3.2 (broad s, ^2H-1a of 4-O-acetyl-9), 4.15 (broad s, ^2H-1e of 4-O-acetyl-10).

ACKNOWLEDGMENT

This investigation was supported by Grant CA15325, awarded by the National Cancer Institute, Department of Health, Education and Welfare.

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