A MECHANISM FOR THE ANOMERIZATION OF ACETYLATED ALKYL GLYCOPYRANOSIDES[1]

By R. U. Lemieux[2] and W. P. Shyluk

ABSTRACT

Unequivocal evidence that the anomerization of acetylated alkyl glycopyranosides can proceed by way of an intramolecular mechanism was obtained through the observation that a racemic mixture of methyl β-glucopyranoside tetraacetate with the D-isomer labelled in the methoxyl group with carbon-14 is anomerized both by titanium tetrachloride and boron trifluoride without transfer of radioactive methoxyl groups to the L-isomer. It is submitted that these intramolecular anomerizations are best rationalized as the result of an unsuccessful attempt by the environment to bring about glycosidic cleavage and proceed by way of an ion-pair intermediate in which the anion is derived from the aglycon group.

INTRODUCTION

In 1928, Pacsu reported that methyl β-D-glucopyranoside tetraacetate was transformed to the α-anomer by refluxing a solution of the substance in chloroform containing either stannic chloride (20) or titanium tetrachloride (21). Titanium tetrachloride was the more effective catalyst and the method has found wide application for the preparation of alkyl glycosides anomeric to the form obtained by the Koenigs–Knorr reaction with stable 1,2-*cis*-*O*-acetylglycosyl halides (11, 14, 21, 22, 24). In 1944, Lindberg (10) showed that the *O*-acetylated ethyl β-glycopyranosides of D-glucose and cellobiose are rearranged to the α-anomer by heating a solution in benzene with hydrogen bromide and mercuric bromide. In 1948, Lindberg (11) reported the anomerization of a number of *O*-acetylated alkyl β-D-glucopyranosides in chloroform solution with boron trifluoride as catalyst. Recently, Reeves and Mazzeno (25) have used titanium tetrachloride to anomerize a variety of β-D-glucopyranoside tetrabenzoates.

In 1944, Montgomery *et al.* (17) found that a solution of methyl α-D-arabinopyranoside triacetate in a mixture of 4% sulphuric acid in 7 : 3 acetic anhydride – acetic acid changed in rotation from −19° to −114° in one minute and declined to an equilibrium value of −25° at the end of 20 min. When the experiment was interrupted at the rotation peak of −114°, a 14% yield of methyl β-D-arabinopyranoside triacetate was obtained. In more recent years, Lindberg has studied the polarimetric rates for the reactions of a variety of β-D-glucosides (12, 13, 14), β-D-galactosides (1), and β-D-xylosides (2) in 10 : 3 mixtures of acetic anhydride – acetic acid with sulphuric acid as catalyst. In most cases there was a rapid increase in rotation followed by a decrease to a constant value. The reaction products at maximum rotation gave ethyl, isopropyl, and tertiary butyl α-D-glucopyranoside tetraacetates in 60, 70, and

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[2]*Present address: Department of Chemistry, University of Ottawa, Ottawa, Ontario.*

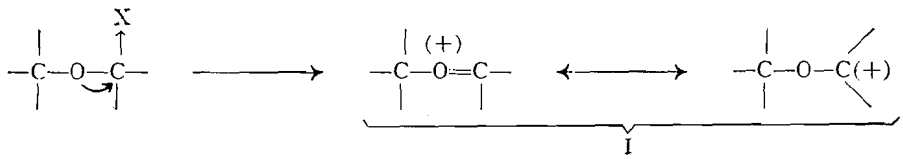
30% yields, respectively (12), and ethyl α-D-galactopyranoside tetraacetate in 55% yield (1). Thus, it was apparent that the initial rapid rise in rotation was related to the formation of the α-anomer. It is to be noted that Lemieux *et al.* (9) have shown that these polarimetric rates are complex expressions which are not susceptible to simple interpretation. For example, it was found (9) that although the change in rotation on the acetolysis of methyl β-D-glucopyranoside tetraacetate did not clearly pass through a maximum, the α-glucoside content did pass through a maximum in 60% yield. Montgomery *et al.* (18) have observed that methyl α-D-glucopyranoside tetraacetate was formed when the β-anomer was treated with an excess of phenol which contained either zinc chloride or *p*-toluenesulphonic acid.

It was apparent that the anomerization of acetylated alkyl glycosides proceeds by way of an intramolecular mechanism since the only attractive alternative mode of reaction was by way of intermediate carbonium ions and this was unlikely because of the presence in the environment of a large excess of nucleophilic substances when the reaction takes place under conditions for acetolysis or phenolysis. Lindberg (12) concluded that the reactions are intramolecular on the basis that he was able to isolate isopropyl α-D-glucopyranoside tetraacetate and ethyl α-D-cellobioside heptaacetate in 66 and 75% yields, respectively, on isomerizing a mixture of isopropyl β-D-glucopyranoside tetraacetate and ethyl β-D-cellobioside heptaacetate using titanium tetrachloride in chloroform. However, considering the rather low yields obtained, this evidence was not compelling in the absence of information on the relative rates for the anomerization of the two β-glycosides since it was possible that one of the anomerizations was substantially finished before the other was well under way. Unequivocal evidence appeared desirable since Lemieux and Brice (6) have found that stannic chloride rapidly dissociates β-D-glucopyranose pentaacetate to acetate and carbonium ions during the process of bringing about anomerization. Obviously, a similar situation could be anticipated for the interaction of the related acetylated glycosides and titanium tetrachloride. We have now obtained unequivocal evidence that acetylated methyl glucopyranosides are not dissociated under conditions for anomerization and that the anomerization must therefore proceed by way of an intramolecular mechanism. This was accomplished by anomerizing a racemic mixture of methyl β-glucopyranoside tetraacetate with the methoxyl group of the D-isomer labelled with carbon-14. Both boron trifluoride and titanium tetrachloride were used as catalysts. Analysis of the products by the method of isotopic dilution showed in both cases that all the radioactivity was in the methyl α-D-glucopyranoside tetraacetate portion.

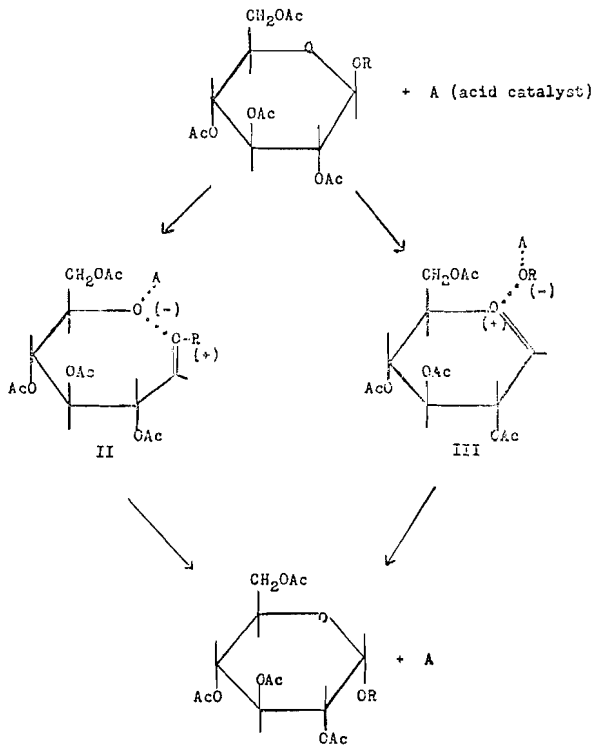
Lindberg (12) has proposed that the anomerizations proceed by way of a ring-opening–ring-closing mechanism. The ring-opening stage was considered to lead either to a carbonium ion or a dipolar ion depending on whether or not the acid catalyst was positively charged. As was indicated above, such a mechanism is unlikely in view of the ability of the anomerization to proceed under conditions for acetolysis or phenolysis. The present authors believe that a more plausible mechanism can be postulated based on the recent discovery

by Winstein and associates (27, 28) of ion-pair intermediates in a wide variety of rearrangements.

The great ease with which an electronegative substituent (X) can be replaced from the α-carbon of an ether has long been recognized and has been attributed to the participation of the ether oxygen in the dissociation of the carbon to X bond which results in the formation of a resonance stabilized carbonium ion (I). Several investigators (4, 6, 12, 19, 23) have suggested the

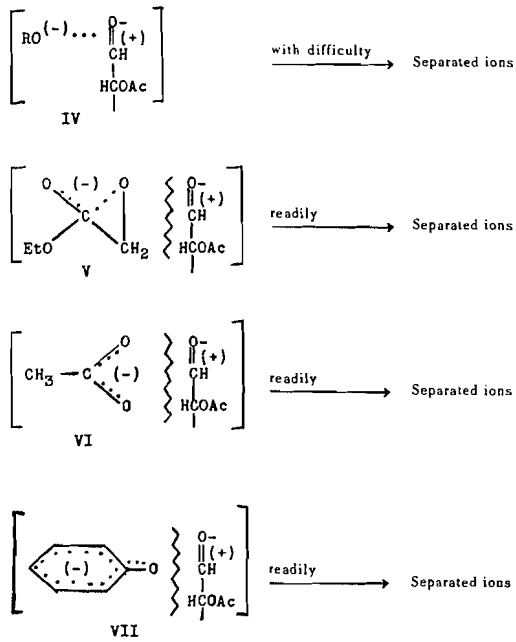


occurrence of an intermediate carbonium ion of this type in replacements at the anomeric center of sugar derivatives. On this basis and the fact that, as pointed out by Winstein and Schreiber (28), the ion-pair phenomenon can in principle be present in all processes which involve neighboring group participation, the anomerization of glycosides can be envisaged to proceed by way of either one of the two possible ion-pair intermediates represented by the formulas II and III. The postulation of the ion-pair (II) would be a refinement of the mechanism proposed by Lindberg (12). However, the present authors submit that the available evidence favors the ion-pair III. First of all, it is noteworthy that Hickinbottom (5) has shown 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride to undergo anomerization as well as glucoside formation when dissolved in methanol. There can be no doubt that in this case the C1 to chlorine bond was the bond to be disrupted and the occurrence of anomerization in the presence of methanol precludes the presence of a solvated carbonium ion intermediate. Therefore, an ion-pair of the type depicted by structure III was most probably an intermediate for the reaction. Secondly, evidence for an intermediate of type III is provided by the effect of changes in the aglycon on the behavior of the compound under conditions for anomerization. The isotopic dilution analysis for methyl α-D-glucopyranoside tetraacetate in the product from the anomerization of the β-anomer which is described in the experimental portion of this paper shows that when titanium tetrachloride was used as catalyst, the yield of α-anomer was 76%. Reynolds (26) found that carboethoxymethyl β-D-glucopyranoside tetraacetate is not anomerized when treated with titanium tetrachloride in chloroform but instead is converted to tetra-*O*-acetyl-α-D-glucopyranosyl chloride in high yield (75%). Pacsu (21) has shown that β-D-glucopyranose pentaacetate is converted to the latter compound by titanium tetrachloride. Lemieux and Brice (6) have shown that the first reaction product is tetra-*O*-acetyl-β-D-glucopyranosyl chloride. Unsuccessful attempts to anomerize phenyl β-D-glucopyranoside tetraacetate are mentioned in the literature (15, 18). However, no experimental details were reported. We have found that phenyl β-D-glucopyranoside tetraacetate is



much more resistant to change by titanium tetrachloride than is methyl β-D-glucopyranoside tetraacetate and has little, if any, tendency for anomerization. Thus, while the conversion of methyl β-D-glucopyranoside tetraacetate to the α-anomer using an equimolar amount of titanium tetrachloride in boiling chloroform was complete within one hour, the much more drastic conditions of a threefold greater amount of titanium tetrachloride and six hour reaction time did not change more than 52% of phenyl β-D-glucopyranoside tetraacetate. When the product from the latter reaction was treated with silver acetate in acetic acid, little silver chloride was formed. This product, 60% yield by weight, specific rotation −5.9° in chloroform, was found by chromatography to comprise at least 81% starting material and 8% α-D-glucopyranose pentaacetate. Therefore, little, if any, phenyl α-D-glucopyranoside tetraacetate was formed. This result was not due to an unexpectedly high reactivity of the latter compound since under the same conditions for anomerization this substance was recovered in 95% yield. Reeves and Mazzeno (25) have recently shown that *O*-nitrophenyl β-D-glucopyranoside tetrabenzoate is more prone to glycosidic cleavage than to anomerization by titanium tetrachloride by finding that the substance was converted to tetra-*O*-benzoyl-α-D-glucopyranosyl chloride in 44% yield. Lemieux *et al.* (7) have recently shown that the anomerization of β-D-glucopyranose pentaacetate in a 0.5 *M* solution of sulphuric acid in 1 : 1 acetic acid – acetic anhydride mixture at 25°C. proceeds only to a very small extent by way of an intramolecular mechanism. On the other hand,

Lemieux *et al.* (9) have shown that under the same conditions methyl β-D-glucopyranoside tetraacetate passes into the α-form approximately four times



more rapidly than it is cleaved to form β-D-glucopyranose pentaacetate. These experimental facts appear to be best rationalized by assuming that both anomerization and glycosidic cleavage result from an attack by the acid catalyst at the aglycon group. When the aglycon group is derived from an anion such as alkylate ion (IV) where charge localization is high, a large proportion of the interactions can reasonably be expected to lead to a fairly stable ion-pair of structure III which can collapse to the α-glycoside instead of leading to separated ions. On the other hand, it is reasonable that ion separation leading to glycosidic cleavage should be extensive when the anion of the ion-pair can dissipate the negative charge through resonance as in the case for the carboethoxymethylate (V), acetate (VI), and phenolate (VII) ions.

EXPERIMENTAL

Methyl β-D-Glucopyranoside Tetraacetate

The substance was prepared labelled with carbon-14 in the methoxyl group by the procedure of Lemieux and Shyluk (8). β-D-Glucopyranose pentaacetate (1.77 mM.) was added to 9 ml. of dry benzene which contained 1.8 mM. of stannic chloride and 1.77 mM. of radioactive methanol. The solution was kept at 40°C. for one hour and the reaction product was isolated in the usual way (8). The substance was pure, m.p. 104.5–105°C., after three crystallizations from methanol and when counted as barium carbonate at infinite thickness possessed a radioactivity of 98,000 counts per minute.

Methyl β-L-Glucopyranoside Tetraacetate

L-Glucose, 1 gm., was converted to sirupy tetra-*O*-acetyl-L-glucopyranosyl bromide by the procedure of Bárczai-Martos and Kőrösy (3). The sirup was reacted with dry methanol, 30 ml., in presence of silver carbonate, 2 gm., at room temperature for 10 hr. The product was isolated in the usual manner and crystallized from 3 ml. of methanol to yield 1.06 gm. of crude methyl β-L-glucopyranoside tetraacetate, m.p. 103–104.5°C. The substance was pure after three recrystallizations from methanol, m.p. 104.8–105.2°C., $[\alpha]_D^{25}+19.3$ (*c*, 1 in chloroform).

Methyl α-L-Glucopyranoside Tetraacetate

Methyl β-L-glucopyranoside tetraacetate, 700 gm., was dissolved in 45 ml. of pure chloroform and the solution was saturated with dry boron trifluoride (11). The reaction mixture was allowed to stand at room temperature for 24 hr. and was then poured into saturated aqueous sodium bicarbonate solution and the product was isolated in the usual way. The substance, 350 mgm., was pure after three recrystallizations from ethanol, m.p. 102–102.5°C., $[\alpha]_D^{25}-130.5$ (*c*, 1 in chloroform).

Anomerization Catalyzed by Boron Trifluoride

Methyl β-D-glucopyranoside tetraacetate labelled in the methoxyl group with carbon-14, 11.04 mgm., 98,000 c.p.m., and non-radioactive methyl β-L-glucopyranoside tetraacetate, 9.98 mgm., were dissolved in 2 ml. of pure chloroform and the solution was saturated with boron trifluoride. After 24 hr. at room temperature, the reaction product was isolated in the usual manner (11). A sample of the sirupy product, 8.3 mgm., was mixed with 101 mgm. of pure methyl α-D-glucopyranoside tetraacetate for crystallization from ethanol. After six recrystallizations from ethanol, the substance melted at 101.5–102.5°C. and possessed a radioactivity of 3560 c.p.m. when counted as barium carbonate at infinite thickness. The radioactivity was unchanged, within experimental error, by further recrystallization. The radioactivity expected on the basis of an intramolecular mechanism and quantitative yield was 3860 c.p.m. The product of the anomerization, 7.8 mgm., was mixed with 99.5 mgm. of pure methyl α-L-glucopyranoside tetraacetate for crystallization from ethanol. After seven recrystallizations the melting point was 102–102.5°C. and the radioactivity was insignificant, 6 c.p.m.

Anomerization Catalyzed by Titanium Tetrachloride

Methyl β-D-glucopyranoside tetraacetate labelled in the methoxyl group with carbon-14, 10.9 mgm., 98,000 c.p.m., was dissolved in 0.3 ml. of pure chloroform which contained an equal amount of non-radioactive L-isomer. The solution was mixed with 0.3 mgm. of 0.2 *M* titanium tetrachloride in chloroform and the container was sealed for heating at 61°C. for five hours. The product was isolated in the usual way (21) and dissolved in 50 ml. of chloroform. The resulting solution was divided into two equal portions which were evaporated to yield two samples of dry sirupy product each weighing 11 mgm. One sample was diluted with 86.8 mgm. of non-radioactive methyl α-D-glucopyrano-

side tetraacetate for crystallization as described above in the anomerization using boron trifluoride. After seven recrystallizations, the material, m.p. 102–103°C., possessed a radioactivity of 4420 c.p.m. The radioactivity expected on the basis of an intramolecular mechanism and quantitative yield was 5840 c.p.m. The other sample of reaction product was mixed with 85.9 mgm. of methyl α-L-glucopyranoside tetraacetate and the mixture was recrystallized six times from ethanol to yield material, m.p. 101.5–102.5°C., which possessed insignificant radioactivity, 16 c.p.m.

Rate of Anomerization Catalyzed by Titanium Tetrachloride

At zero time, equal amounts, 0.6 ml., of 0.2 *M* solutions of methyl β-D-glucopyranoside tetraacetate and titanium tetrachloride in pure chloroform were mixed in glass tubes which were immediately sealed and placed in a water bath controlled at 61°C. After each of the various reaction times, a tube was placed in about 50 ml. of saturated aqueous bicarbonate solution contained in a stainless steel beaker and smashed with a heavy steel rod. The product was isolated by extraction with chloroform in the usual manner. The rotations of the product, measured in chloroform, were as follows: after 30 min. reaction time, +90°; 60 min., 112°; 90 min., 111°; 120 min., 113°.

Attempt to Anomerize Phenyl β-D-Glucopyranoside Tetraacetate

Dry phenyl β-D-glucopyranoside (8) tetraacetate, 424 mgm. (1 mM.) was added to a solution of 3 mM. of titanium tetrachloride in 10 ml. of pure chloroform and the mixture was refluxed for three hours. The brown colored solution was added to ice-water mixture and the resulting mixture was extracted four times with chloroform. The chloroform extracts were washed once with sodium bicarbonate solution, then with water, dried, and evaporated to a sirup which possessed a strong odor of phenol. The product was dissolved in 10 ml. of dry acetic acid which contained silver acetate (1 mM.) and the mixture was shaken at 60°C. for one hour. There appeared to be little reaction. The silver salts were removed by filtration and the filtrate was added to water before extraction with chloroform. The washed and dried chloroform extract was evaporated to a crystalline residue, 252 mgm. yield (60% by weight), $[\alpha]_D$ −5.9° in chloroform. Chromatography on Magnesol–Celite (5 : 1) according to the procedure of McNeely *et al.* (16) afforded 204 mgm. of essentially pure starting material, m.p. 123–125°C. and 20 mgm. of α-D-glucopyranose pentaacetate which was identified by mixed melting point, infrared spectra, and rotation.

When phenyl α-D-glucopyranoside tetraacetate (18), 424 mgm., was treated under the above conditions, the material was recovered in essentially pure condition, m.p. 110–112°C., $[\alpha]_D$ +161° in chloroform in 95% yield.

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