Solvolysis of Methyl D-Xylothiapyranosides and 2,3,4-Tri-*O*-acetyl-α-D-xylothiapyranosyl Bromide[1]

ROY L. WHISTLER AND T. VAN ES

Department of Biochemistry, Purdue University, Lafayette, Indiana

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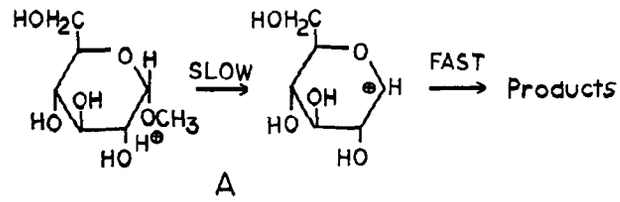
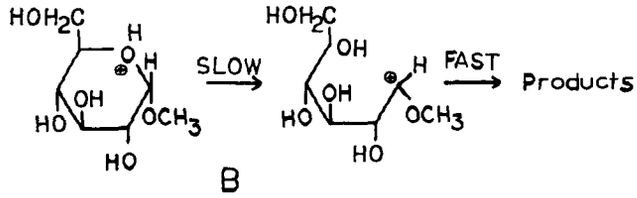
Rates of hydrolysis of methyl α- and β-D-xylopyranosides and methanolysis of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromides are compared with those of the corresponding anomers from 5-thiol-D-xylose. The faster hydrolysis of the sulfur-containing glycosides and slower methanolysis of the sulfur-containing glycosyl bromides support the existence of intermediate glycosyl carbonium ions.

Use of labeled water, H_2O^{18}, in the acid-catalyzed hydrolysis of methyl glycosides has shown[2] that cleavage takes place at the glucosyl–oxygen bond. The reaction involves a rapid reversible protonation to a

$$ROCH_3 + H_2O^{18} \longrightarrow RO^{18}H + HOCH_3$$

conjugate acid, which undergoes slow, unimolecular dissociation. Two mechanisms are conceivable, differing in the manner of protonation and cleavage. In one, a proton combines with the glycosidic oxygen, and in the other proton attachment is to the ring oxygen.





Support for the first mechanism has been given by Rhind-Tutt[3] and by others[4] who have examined the analogous methanolysis of phenyl tetra-*O*-methyl-α-D-glucopyranoside and found that this glycoside gave a ratio of anomers similar to that obtained in the methanolysis of tetra-*O*-methyl-α-D-glucopyranosyl chloride. Since methanolysis of the chloride probably involves a carbonium ion at C-1, it seems likely that methanolysis of the glycoside also involves this carbonium ion. Overend and co-workers[3b,5] have explained the slow hydrolysis of 1-thioglycosides on the basis of the mechanism involving initial protonation of the glycosidic sulfur, since the low basicity of sulfur would cause a low concentration of the conjugate acid. Although these workers reported no actual rates for the D-xylosides the data obtained in the present work (Table I) shows that methyl 1-thio-β-D-xylopyranoside hydrolyzes at approximately half the rate for methyl β-D-xylopyranoside. It also is found that methyl

TABLE I

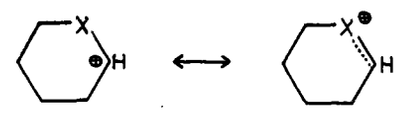
	Rate of acid-catalyzed hydrolysis in $sec.^{-1} \times 10^{-5}$
Methyl α-D-xylopyranoside	3.45[a]
Methyl β-D-xylopyranoside	6.90[a]
Methyl α-D-xylothiapyranoside	35.0
Methyl β-D-xylothiapyranoside	100
Methyl 1-thio-β-D-xylopyranoside	3.50

[a] Determined by Isbell and Frush.[14]

α-D-xylothiapyranoside hydrolyzes approximately ten times faster than the α-D-xylopyranoside while the β-D-thia sugar hydrolyzes approximately fourteen times faster than the oxygen analogs. The data support the view that hydrolysis proceeds by mechanism A.

The high rate of hydrolysis of a D-xylothiapyranoside may be explained by the high concentration of its conjugate acid, due to the inductive effect of the sulfur-releasing electrons to the exocyclic oxygen. On the other hand, the ring oxygen of normal D-xylopyranosides probably undergoes competitive protonation with the exocyclic oxygen, thus decreasing the amount of conjugate acid effective in the hydrolysis. These two effects could overcome the rate promoting effect due to greater resonance stabilization of carbonium ions on D-xylopyranosyl rings containing oxygen.

Solvolysis of 2,3,4-tri-*O*-acetyl α-D-xylopyranosyl bromide in methanol is forty times faster than that of 2,3,4-tri-*O*-acetyl-α-D-xylothiapyranosyl bromide. The solvolysis of such glycosyl halides probably proceeds by an SN1 mechanism.[6,7] High reactivity of the halogen is typical of that displayed by α-halogeno ethers.[8] It is known[9] that chloromethyl ethers are more reactive than chloromethyl sulfides. In fact chloromethyl ethyl ether hydrolyzes some 1600 times faster than chloromethyl ethyl sulfide in an aqueous dioxane. Furthermore, 2,3-dichlorotetrahydropyran methanolyzes much faster than 2,3-dichlorothiacyclohexane. These observations are similar to those obtained from examination of the thia- and oxoglycosyl halides. Differences in the rate of solvolysis may be ascribed, in each instance, to the more effective resonance stabilization of the carbonium ion by oxygen compared to sulfur.



X is oxygen or sulfur

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Experimental

D-Xylosides.—Methyl D-xylopyranosides were made by standard methods[10] and methyl α-D-xylothiapyranoside was prepared as previously described.[11]

2,3,4-Tri-*O*-acetyl-α-D-xylothiapyranosyl Bromide.—1,2,3,4-Tetra-*O*-acetyl-D-xylothiapyranose[12] (5.0 g.) was dissolved at 0° in 50 ml. of a 30% solution of hydrobromic acid in glacial acetic acid. After warming to room temperature the mixture darkened slightly in 1 hr. At this point 50 ml. of ethanol-free chloroform was added and the reaction was poured into a mixture of ice and water. The chloroform layer was separated and the aqueous phase washed twice with fresh 25-ml. portions of chloroform. The combined chloroform extracts were washed rapidly with sodium bicarbonate solution and dried over calcium chloride and a small amount of anhydrous sodium bicarbonate. The solution was removed and evaporated to a sirup which was taken up in petroleum ether (b.p. 66–68°). Crystals formed on cooling, m.p. 115°; $[\alpha]^{25}D$ +245 (*c* 1.75 in methanol); yield, 4.5 g. (85%).

Anal. Calcd. for $C_{11}H_{15}BrO_6S$: S, 9.02. Found: S, 8.92.

Methyl 2,3,4-Tri-*O*-acetyl-β-D-xylothiapyranoside.—Five grams of the previous bromide was stirred with 100 ml. of anhydrous methanol and 25 g. of silver carbonate for 48 hr. The reaction mixture was filtered through Celite and concentrated to a sirup which crystallized upon addition of petroleum ether; yield, 3.0 g. (70%). Recrystallization from ethyl acetate–petroleum ether gave 2.0 g. of crystals, m.p. 122°; $[\alpha]^{25}D$ −70.6 (*c* 0.99 in methanol).

Anal. Calcd. for $C_{12}H_{18}O_7S$: S, 10.46; OCH_3, 10.12. Found: S, 10.41; OCH_3, 10.11.

Methyl β-D-Xylothiapyranoside.—The prior acetate (3.0 g.) was dissolved in 20 ml. of anhydrous methanol, and 1.0 ml. of 2 *N* sodium methoxide in methanol was added. After 16 hr. the solution was treated with 1 g. of cation-exchange resin Amberlite 120 (H), filtered, and concentrated. The residue crystallized from ethyl acetate, m.p. 162°; $[\alpha]^{25}D$ −66.3 (*c* 1.03 in water); yield, 1.3 g. (74%).

Anal. Calcd. for $C_6H_{12}O_4S$: S, 17.77; OCH_3, 17.22. Found: S, 17.51; OCH_3, 17.08.

Methyl 1-thio-β-D-xylopyranoside and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide were made by the method of Zinner, Koine, and Nimz.[13]

Solvolysis.—Rates of acid-catalyzed hydrolysis of methyl D-xylopyranosides and the sulfur analogs were determined by the method of Isbell and Frush.[14] Hydrolyses were conducted in 0.50 *N* hydrochloric acid solution at 75° and were followed polarimetrically (Table I).

Methanolysis of 0.05 *M* solutions of the acetobromosugars were conducted at 0.05 *M* sugar concentrations and followed polarimetrically at 23°. The rate for 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide was 178 sec.$^{-1}$ × 10^{-5} and that for 2,3,4-tri-*O*-acetyl-α-D-xylothiapyranosyl bromide was 4.36 sec.$^{-1}$ × 10^{-5}.

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Directive Influences in the Preparation of Purine Nucleosides[1]

JOHN A. MONTGOMERY AND H. JEANETTE THOMAS

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham 5, Alabama

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A study of some of the directive influences in the preparation of purine nucleosides by the conventional coupling reaction of acyl glycosyl halides with the chloromercuri salts of purines has led to the successful preparation of some new 7-D-pentofuranosylpurines.

The classical method for the synthesis of a glycosyl derivative of a purine or pyrimidine is the coupling of a poly-*O*-acyl glycosyl halide with the heavy metal salt of the purine or pyrimidine. This reaction leads to nucleosides "with a *C*-1–*C*-2-*trans* configuration in the sugar moiety regardless of the original configuration of *C*-1–*C*-2."[2] Applied to the reaction of heavy metal salss of purines with tri-*O*-acyl-D-ribofuranosyl halides, this rule predicts that the resulting purine ribonucleosides will have the β-configuration at the glycosyl center. Although the chemical basis for this stereochemical control of the formation of the glycosyl center was not understood at the time, Todd and co-workers fortuitously applied this reaction to the synthesis of adenosine (9-β-D-ribofuranosyladenine).[3] It was equally fortuitous that the condensation of tri-*O*-acetyl-D-ribofuranosyl chloride with 2,8-dichloroadenine led to the formation of the 9- rather than the 7-isomer.[4] Otherwise, the synthesis of the purine nucleosides that occur in the nucleic acids might have been delayed by the difficulties that have so far prevented the synthesis of the nucleoside known to occur in pseudo vitamin B_{12}. Although final proof is still lacking, this nucleoside is almost surely 7-α-D-ribofuranosyladenine.[6] At least one unsuccessful attempt to synthesize this nucleoside has been recorded.[7] Two problems must be solved for this synthesis to be accomplished. First, a method for producing the α-ribonucleoside must be devised and, second, a method for directing the entering sugar to *N*-7 rather than *N*-9 must be developed.

Since methods that can probably be applied to the production of the α-configuration of D-ribofuranose at *N*-7 have been described,[8,9] an investigation of the effect of certain substituents in the pyrimidine moiety of the purine ring on the position (*N*-7 or *N*-9) of alkylation or sugar coupling in the imidazole ring was undertaken.[10] The point of attack by various sugars

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