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IONISATION OF METHYL GLYCOFURANOSIDES IN AQUEOUS ALKALI METAL HYDROXIDES

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ABSTRACT

Equilibrium constants for the ionisation of several methyl glycofuranosides have been determined spectrophotometrically in aqueous alkali metal hydroxides, using aromatic nitrogen bases as indicators for the equilibrium concentration of the hydroxide ion. The results obtained have been compared to the retention of the same compounds on a strong anion-exchange resin. The effects of the glycon configuration on the acidity of methyl glycofuranosides are discussed.

INTRODUCTION

Carbohydrates and their derivatives are weak polybasic acids, the first acidity constants[1] of which fall in the range of 10^{-14}–10^{-12} mol.dm^{-3}. Although there have been several investigations on the ionisation of free sugars[2–7] and acyclic polyhydric alcohols[2,4,8–11], the data on the acidity of glycosides are quite limited. Michaelis reported[2] that the acidity constants of methyl α- and β-D-glucopyranosides are 1.97 and 2.64 $\times$ 10^{-14} mol.dm^{-3}, respectively. The longer retention time of the β anomer on a strongly basic ion-exchange resin lends further support for the suggested order of acidity[12]. Examination of the relative reactivities of various hydroxyl groups with alkylating agents has revealed HO-2 to be the most acidic in glycopyranosides[13–16]. This is expected because of the proximity of HO-2 to the electronegative glycosidic and endocyclic oxygen atoms. In methyl β-D-glucopyranoside, the dipole moments of these oxygen atoms reinforce each other, making HO-2 exceptionally acidic, whereas they are partially cancelled in the α anomer and ionisation is facilitated to a lesser extent[12].

The only data on the ionisation of carbohydrate derivatives containing five-membered rings are the acidity constants reported for the nucleosides adenosine[5,17,18], guanosine[19], inosine[19], and xanthosine[19]. The β-D-ribofuranosyl groups of these compounds exhibit pK_a values ranging from 12.0 to 12.4 at 298.2 K. Presumably, HO-2 is the most acidic hydroxyl-group.

A knowledge of the acidities of the hydroxyl groups in glycosides is of importance for several reasons. Firstly, oxyanions can act as intramolecular nucleophilic catalysts in numerous reactions of carbohydrate derivatives, particularly in alkaline

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degradations[20]. Secondly, carbohydrates form reasonably stable complexes with several metal ions in aqueous solution[21], and ionisation of the hydroxyl groups may affect the structures and stabilities of these complexes. Thirdly, basic ion-exchange resins can be utilised in preparative separations of glycosides and related compounds[22]. An understanding of the factors that affect the ionisation of the hydroxyl groups is essential in developing the chromatographic methods.

The aim of the present study was to elucidate the relationships between the acidity and configuration of glycofuranosides. Attention has been paid to the possibility that interactions with the cation of the alkali metal hydroxide employed may affect the apparent acidity of the compounds investigated.

EXPERIMENTAL

Materials. — Methyl β-D-lyxofuranoside was prepared according to the method of Angyal *et al.*[23]. The preparations of the other methyl glycofuranosides have been described[24–26]. Benzimidazole and 2-methylbenzimidazole were purchased from Fluka AG, and recrystallised from water prior to use. The inorganic salts employed were of analytical grade.

Apparatus and procedure — The spectrophotometric measurements were performed on a Cary 17D spectrophotometer. The temperature of the cell compartment was adjusted to 298.2 ±0.1 K with water circulating from a thermostated bath.

The acidity constants of methyl glycofuranosides were determined as follows. The u.v. spectra of the indicators benzimidazole and 2-methylbenzimidazole were recorded for solutions containing known amounts of the appropriate glycoside (0.1–0.3M) and alkali metal hydroxide (0.1 or 0.2M); the indicator concentration employed was 150μM. The equilibrium concentrations of the hydroxide ion were obtained by comparing the absorbances at suitable wavelengths with those observed at various hydroxide-ion concentrations in the absence of the glycoside. The wavelengths used were 275, 282, and 283 nm for benzimidazole, and 275, 283, and 285 nm for 2-methylbenzimidazole. The results obtained at different wavelengths were equal, within the limits of experimental error. The equilibrium constant, K, for the reaction of the glycoside with the hydroxide ion was calculated by using Eq. *1*, where $[HO^-]_{eq}$ is the equilibrium concentration of the hydroxide ion, and $[MOH]_{tot}$ and $[S]_{tot}$ are the total concentrations of the alkali metal hydroxide and glycofuranoside, respectively. Multiplication of the equilibrium constant with the ionic product of water under the experimental conditions yields the acidity constants of the glycosides.

$$K = \frac{[S^-]}{[SH][HO^-]_{eq}} = \frac{[MOH]_{tot} - [HO^-]_{eq}}{\{[S]_{tot} - ([MOH]_{tot} - [HO^-]_{eq})\}[HO^-]_{eq}} \qquad (1)$$

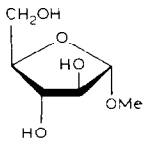
The reliability of the method described above was checked with D-mannitol,

D-glucitol, and *myo*-inositol, the acidity constants of which are given in the literature.

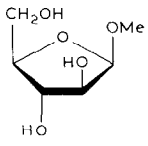
The retention of methyl glycofuranosides on a strongly basic ion-exchange resin was studied by elution with distilled water through a thermostated column (298.2 K; 1 × 35 cm) filled with Dowex 1-X2 (HO^-) resin (200–400 mesh). The flow rate was adjusted to 10 $cm^3.h^{-1}$ with a peristaltic pump. The appearance of the glycoside was determined by hydrolysing aliquots (0.5 cm^3) of the collected fractions (4 cm^3) in 0.1M hydrochloric acid and measuring the amount of the released reducing-sugar by the method of Sumner[27].

RESULTS AND DISCUSSION

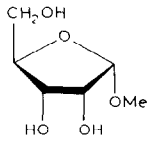
Table I records the acidity constants for the isomeric methyl glycofuranosides studied, namely, anomeric arabinosides (**1α,β**), ribosides (**2α,β**), xylosides (**3α,β**), and lyxosides (**4α,β**). The acidity constants of a few polyhydric alcohols, used as reference materials, are also included. The latter values are in a reasonably good agreement with those reported[2,4,8,11], when the differences in temperature and ionic strength are taken into account. Accordingly, the spectrophotometric procedure employed seems reliable.



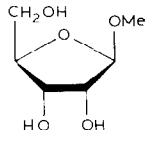
1α



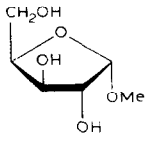
1β



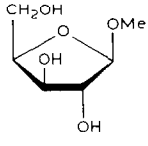
2α



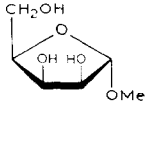
2β



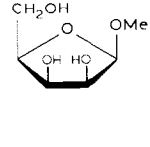
3α



3β



4α



4β

As seen from the data in Table I, the acidity constants measured in aqueous lithium, sodium, and potassium hydroxides do not markedly deviate from each other; possibly, the acidities observed in potassium hydroxide are slightly lower. Complexing of anionic glycosides with various alkali metal ions appears to be too weak to cause marked effects on the ionisation equilibria of the hydroxyl groups. Alternatively, the interactions with all the cations are of comparable strength. The slightly decreased acidities in potassium hydroxide may reflect weaker interaction with potassium ion, which has the lowest charge density among the cations considered.

TABLE I

ACIDITY CONSTANTS FOR SOME POLYHYDRIC ALCOHOLS AND METHYL GLYCOFURANOSIDES IN AQUEOUS SOLUTION AT 298.2 K[a]

Compound	$-\log(K_a\ mol\ dm^{-3})$			
	[b]	[c]	[d]	[e]
D-Mannitol[f]		13.12		13.00
D-Glucitol[g]		13.08		13.02
myo-Inositol[h]		13.44		13.40
Methyl α-D-arabinofuranoside (**1α**)	12.82	12.74	12.88	12.76
Methyl β-D-arabinofuranoside (**1β**)	13.17	13.20	13.23	13.20
Methyl α-D-ribofuranoside (**2α**)	13.15	13.23	13.31	13.08
Methyl β-D-ribofuranoside (**2β**)	12.89	12.84	12.94	12.68
Methyl α-D-xylofuranoside (**3α**)	13.45	13.47	13.59	13.30
Methyl β-D-xylofuranoside(**3β**)	12.95	12.91	13.03	12.87
Methyl α-D-lyxofuranoside (**4α**)	12.43	12.60	12.66	12.51
Methyl β-D-lyxofuranoside (**4β**)		13.18		

[a]The values for the ionic product of water at various ionic strengths were taken from ref. 29. [b]In 0.1M lithium hydroxide, using benzimidazole as indicator. [c]In 0.1M sodium hydroxide, using benzimidazole as indicator. [d]In 0.1M potassium hydroxide, using benzimidazole as indicator. [e]In 0.2M sodium hydroxide, using 2-methylbenzimidazole as indicator. [f]13.07 ± 0.08 in 3M sodium chloride[11]. [g]13.56 ± 0.08 in 3M sodium chloride[11]. [h]13.78 ± 0.08 in 3M sodium chloride[11].

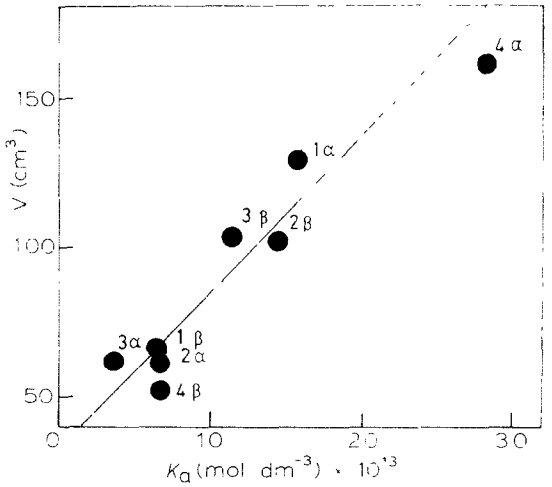


Fig. 1. The relationship between the retention volumes for methyl glycofuranosides on a strongly basic anion-exchange resin and the acidity constants of the same compounds. For the enumeration of the compounds, see Table I.

In Fig. 1, the retention of various methyl glycofuranosides on a strongly basic ion-exchange resin has been compared with the respective acidity constants. The linear dependence obtained, although rather rough, lends support to the suggested acidity order.

The acidities of methyl glycofuranosides fall in two groups, with the *trans*-1,2-glycosides (**1α**, **2β**, **3β**, and **4α**) exhibiting acidity constants 2–4 times greater than their *cis* counterparts. This regularity strongly suggests that the most acidic hydroxyl group in glycofuranosides is HO-2, as expected on the basis of inductive effects. A possible explanation for the acidity difference is that given by Eliel *et al.*[28]. The 2-oxyanion is more strongly solvated than the neutral hydroxyl group, and a neighboring *cis*-methoxyl group impedes solvation more efficiently than a *trans* group. Therefore, in each pair, the anomer having the *cis*-1,2-configuration is the weaker acid.

Another factor that possibly affects the ionisation of glycofuranosides is the hydrogen bonding of the ionised HO-2 with the other hydroxyl groups in the molecule. Of the *trans*-1,2-glycosides, the most acidic is the α-lyxoside (**4α**), which has both HO-3 and $HOCH_2$-4 on the same side of the plane of the glycon ring as the ionisable HO-2. In contrast, the β-xyloside (**3β**), which has no hydroxyl substituents in the proximity of HO-2, is the least acidic of the *trans*-1,2-glycofuranosides. The α-arabinoside (**1α**) and β-riboside (**2β**), having one group capable of hydrogen bonding with the 2-oxyanion, constitute the intermediary group. With *cis*-1,2-glycofuranosides, the situation is comparable, although the differences are of the order of experimental errors.

Comparison of the data in Table I with those reported in the literature reveals that glycofuranosides are somewhat more acidic than glycopyranosides[2], but less acidic than nucleosides[18,19]. The latter finding is expected, because the electron-withdrawing nature of the aromatic base in nucleosides is greater than that of the methoxyl group in methyl glycofuranosides.

In summary, two factors appear to influence the acidity of methyl glycofuranosides, namely, the steric orientation of HO-2 with respect to the glycosidic oxygen atom, and the possibility of intramolecular hydrogen bonding of the 2-oxyanion. Of these two factors, the former seems to be more important.

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