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COMPLEXING OF GLYCOFURANOSIDES WITH CALCIUM ION, AND ITS EFFECT ON THEIR ACID-CATALYSED SOLVOLYSIS

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ABSTRACT

Stability constants for the calcium-ion complexes of several methyl aldofuranosides have been determined in aqueous solution by using a potentiostatic technique with an electrode that is selective for calcium ions. The results obtained have been verified by examining the chromatographic behaviour of the compounds on a strong cation-exchange resin in the Ca^{2+} form. The rate constants for the acid-catalyzed hydrolysis and methanolysis of a few 4-chlorophenyl aldofuranosides having different complexing abilities have been determined at various concentrations of calcium chloride. The dependences of the observed salt effects on the complexing ability of the substrate are discussed.

INTRODUCTION

Carbohydrates and polyols have long been known to complex with metal ions in neutral, aqueous solution[1,2]. Some monosaccharides, for example, form reasonably stable complexes[3–7] with several metal cations, including Pb^{2+}, La^{3+}, and alkaline-earth metal cations, except Be^{2+} and Mg^{2+}. Angyal *et al.*[3–5,8,9] suggested, on the basis of n.m.r. data, that the steric arrangement required for complexing of six-membered rings consists of three vicinal hydroxyl-groups in an *ax–eq–ax* sequence. The experimental data concerning five-membered rings are limited. The most suitable co-ordination site appears to be a vicinal *cis–cis* triol, the complexing ability of which is only slightly less than that of the *ax–eq–ax* arrangement on a six-membered ring[3–5,7–9]. In each case, the complex between a monosaccharide and a metal ion is probably[3–9] of the 1 : 1 type with a stability constant $< 10\ dm^3.mol^{-1}$. Besides free monosaccharides, it has been suggested[3–5,8] that the corresponding methyl glycosides form complexes, but no stability constants for these compounds have been reported. In order to further the understanding of the configurational factors that affect complex formation between metal ions and carbohydrate derivatives having a five-membered ring, and to elucidate the effects that this kind of complexing can exert on the solvolytic decomposition of glycofuranosides, the stability constants for the calcium complexes of seven methyl aldofuranosides were determined. We now report on this study. On the basis of the results obtained, three compounds having markedly differ-

ent complexing-ability were chosen and the effect of the concentration of calcium ion on the rates for the acid-catalysed hydrolysis and methanolysis of the corresponding phenyl derivatives was measured.

EXPERIMENTAL

Determination of the stability constants. — A modified potentiostatic technique[10] with an electrode sensitive for calcium ions was applied for the determination of the stability constants of the Ca^{2+}–carbohydrate complexes. The titration procedure was as follows. To a thermostated vessel containing an Orion 93-20 calcium-ion electrode and a Metrohm EA 404 calomel reference-electrode were added distilled water (4 cm^3), 3M aqueous KCl (0.125 cm^3), and 0.1M aqueous $CaCl_2$ (0.125 cm^3). The mixture was kept under nitrogen, and agitated with a magnetic stirrer. After the meter readings had settled, a known amount of carbohydrate was added; there was a drop in the potential if complexing with calcium ion occurred. In contrast, addition of non-complexing carbohydrate material caused, as would be expected[11], a slight increase in the meter reading. After complete dissolution of the ligand, which usually took place within 1–2 min, 0.1M $CaCl_2$ was added from an Agla micrometer syringe until the potential reached its initial value, corrected with respect to the effect of the non-complexing material.

The stability constants were calculated from equation *1*, where [S], [S · Ca^{2+}], and [Ca^{2+}] are the concentrations for the carbohydrate, carbohydrate–Ca^{2+} complex, and free calcium ion, respectively.

$$K = [S \cdot Ca^{2+}]/[S][Ca^{2+}] \qquad (1)$$

To test the procedure described above, the apparent stability constant for the complex between D-ribose and calcium ion was determined. D-Xylose was used as the non-complexing material. The potential changes and the stability constants at various concentrations of sugar are collected in Table I. Within the limits of experimental

TABLE I

THE EFFECTS OF D-RIBOSE AND D-XYLOSE ON THE READINGS OF A CALCIUM-ION SELECTIVE ELECTRODE[a], AND THE APPARENT STABILITY CONSTANTS FOR THE Ca^{2+}–RIBOSE COMPLEX AT 298.2 K

[S] (M)	D-*Xylose* *ΔE/mV*	D-*Ribose* *ΔE/mV*	*K* ($dm^3.mol^{-1}$)
0.1	+0.4	−1.2	1.6
0.2	+0.7	−2.4	1.6
0.3	+1.0	−3.5	1.5
0.4	+1.3	−4.7	1.5
0.5	+1.5	−5.8	1.5

[a] 2.95mM calcium chloride.

error, all of the stability constants obtained are equal and in good agreement with the value of 1.6 $dm^3.mol^{-1}$ determined by e.m.f. measurements[7].

Ion-exchange chromatography. — The investigated glycosides (0.5 mmol) were eluted with carbon dioxide-free water through a column (3.4 × 40 cm) filled with Dowex-50W X8 resin (200–400 mesh) in the Ca^{2+} form. The elution rate was kept constant (3 cm^3/min) with a peristaltic pump. The appearance of the glycoside was determined by hydrolysing 0.1-cm^3 aliquots of the collected fractions (6 cm^3) in M HCl and measuring the released reducing sugar by the method of Sumner[12].

Kinetic measurements. — The kinetic measurements were performed as described earlier[13]. The acid concentrations of the reaction solutions were checked by titration with standard base.

Preparation of materials. — The preparation and identification of the methyl and 4-chlorophenyl glycosides investigated were described earlier[13,14]. Otherwise, commercial reagents of analytical grade were employed.

RESULTS AND DISCUSSION

The stability constants obtained by a modified potentiostatic titration for the calcium-ion complexes of methyl aldofuranosides in water at 298.2 K are collected in Table II. Of the glycosides studied, only methyl α-D-ribo- and α-D-lyxo-furanosides complexed considerably, the stability constants being of the order of 1 $dm^3.mol^{-1}$. The β-riboside and α-xyloside exhibit much lower complexing-abilities, while the β-xyloside and anomeric arabinosides show no tendency for complex formation with calcium ion. To verify these findings, the retention of methyl aldofuranosides on a strong cation-exchange resin loaded with calcium ions was examined. As seen in Fig. 1, an approximately linear correlation exists between the elution volumes and the potentiometrically determined, stability constants. Those methyl glycosides suggested

TABLE II

STABILITY CONSTANTS FOR THE COMPLEXES[a] BETWEEN CALCIUM ION AND METHYL ALDOFURANOSIDES IN WATER AT 298.2 K

Compound	[*S*] (M)	*K* ($dm^3.mol^{-1}$)
Methyl α-D-ribofuranoside	0.16	1.2
	0.29	1.1
	0.41	1.4
Methyl β-D-ribofuranoside	0.42	0.3
Methyl α-D-lyxofuranoside	0.42	0.9
Methyl α-D-xylofuranoside	0.41	0.1
Methyl β-D-xylofuranoside	0.44	—
Methyl α-D-arabinofuranoside	0.35	—
Methyl β-D-arabinofuranoside	0.37	—

[a]A 1:1 complex is assumed.

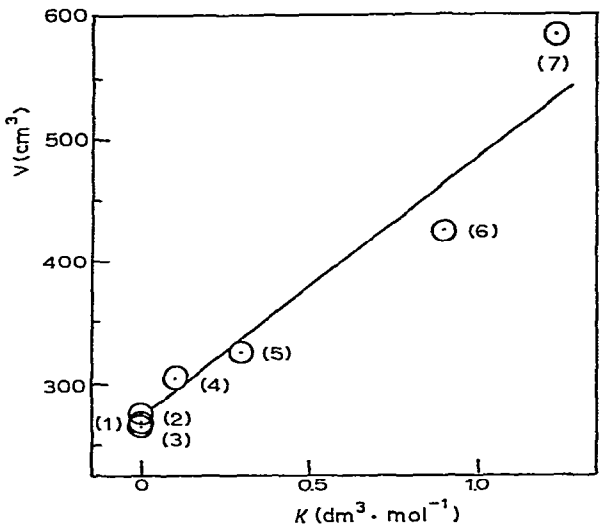

Fig. 1. The relationship between the retention volumes for methyl aldofuranosides on a strong cation-exchange resin in the Ca^{2+} form, and the potentiometrically determined stability-constants for the calcium-ion complexes of the same compounds: (1) α-D-arabinoside, (2) β-D-arabinoside, (3) β-D-xyloside, (4) α-D-xyloside, (5) β-D-riboside, (6) α-D-lyxoside, and (7) α-D-riboside.

above to be non-complexing are eluted in ~270 cm^3. This is also the case with D-xylose, which interacts only weakly, if at all, with metal ions. The α-xyloside, β-riboside, and α-lyxoside exhibited, in this order, increasing retardations, and the elution volume of the α-riboside approached the value of 600 cm^3 measured with free D-ribose, for which an apparent stability constant of 1.6 $dm^3.mol^{-1}$ has been reported[7]. Accordingly, the chromatographic behaviour of methyl aldofuranosides fully corroborates the conclusions based on the results of potentiostatic titrations.

The relatively strong complexing of methyl α-D-ribofuranoside with calcium ion is expected, since the glycosidic oxygen atom, HO-2, and HO-3 in this compound form an all-*cis* arrangement suitable for co-ordination. Thus, for the calcium-ion complex of α-D-ribofuranose, values of 4.4 $dm^3.mol^{-1}$ (Ref. 7) and 5 $dm^3.mol^{-1}$ (Ref. 4) have been calculated for the stability constant, on the basis of the effect that calcium ions exert on the equilibrium composition of D-ribose. In contrast, the complexing of methyl α-D-lyxofuranoside to a significant extent is unexpected. In this compound, the glycosidic oxygen atom is *trans* to the other oxygen-containing substituents, and is thus unable to participate in the complex formation. Probably, HO-2 and HO-3 together with the hydroxymethyl group constitute the site for co-ordination with calcium ion. In a suitable conformation of the five-membered ring, these oxygen atoms can form an equilateral triangle, being at a distance of ~3 Å from each other. The weak interactions of methyl β-D-ribo- and α-D-xylofuranosides with calcium ion are difficult to explain. Either only two oxygen substituents are involved in the complexation, or the ring oxygen affords the third point for co-ordination.

TABLE III

FIRST-ORDER RATE CONSTANTS FOR THE ACID-CATALYSED METHANOLYSIS OF 4-CHLOROPHENYL α-D-RIBO-, β-D-RIBO-, AND β-D-XYLO-FURANOSIDES AT VARIOUS CONCENTRATIONS OF CALCIUM CHLORIDE AT 322.5 K

$[Ca^{2+}]$ (M)	k^a (10^{-3} s^{-1})		
	α-D-*Ribofuranoside*	β-D-*Ribofuranoside*	β-D-*Xylofuranoside*
0	22.6 ±0.2	1.445 ±0.019	4.04 ±0.04
0.25	13.59 ±0.14	1.019 ±0.012	4.50 ±0.07
0.50	10.82 ±0.06	0.944 ±0.008	5.16 ±0.03
0.75	9.43 ±0.11	0.722 ±0.007	5.55 ±0.03
1.0	7.15 ±0.09	0.695 ±0.008	5.99 ±0.08

[a]In 96mM methanolic hydrogen chloride.

Table III records the first-order rate constants for the acid-catalysed methanolysis of 4-chlorophenyl α-D-ribo-, β-D-ribo-, and β-D-xylo-furanosides at various concentrations of calcium chloride. The rate constants for the methanolysis of the β-xyloside increase slightly with increasing concentration of salt (Fig. 2). In contrast, the methanolysis of 4-chlorophenyl α-D-ribofuranoside is considerably retarded by addition of calcium chloride to the reaction mixture. The β anomer behaves similarly, but the retardations in rate are somewhat smaller than with the α-riboside. This kind of change in salt effects can be accounted for by the different complexing abilities of the substrates with calcium ion. As indicated above, the stabilities of the calcium-ion complexes of methyl α-D-ribo-, β-D-ribo-, and β-D-xylo-furanosides decrease in

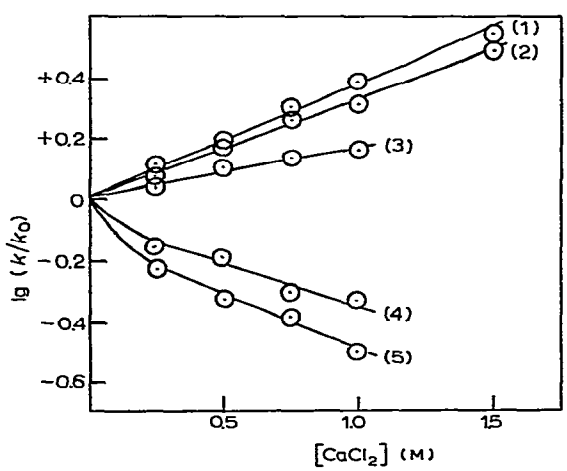

Fig. 2. The effect of calcium chloride concentration on the relative rate constants, k/k_0, for the acid-catalysed hydrolysis and methanolysis of some 4-chlorophenyl aldofuranosides: (1) hydrolysis of β-D-xyloside, (2) hydrolysis of α-D-riboside, (3) methanolysis of β-D-xyloside, (4) methanolysis of β-D-riboside, and (5) methanolysis of α-D-riboside.

TABLE IV

FIRST-ORDER RATE CONSTANTS FOR THE ACID-CATALYSED HYDROLYSIS OF 4-CHLOROPHENYL α-D-RIBO- AND β-D-XYLO-FURANOSIDES AT VARIOUS CONCENTRATIONS OF CALCIUM CHLORIDE AT 343.2 K

$[Ca^{2+}]$ (M)	k^a (10^{-3} s^{-1})	
	α-D-Ribofuranoside	*β-D-Xylofuranoside*
0	3.74 ±0.05	0.926 ±0.008
0.25	4.44 ±0.06	1.214 ±0.008
0.50	5.68 ±0.05	1.481 ±0.018
0.75	6.93 ±0.02	1.901 ±0.013
1.0	7.80 ±0.05	2.31 ±0.02
1.5	11.52 ±0.15	3.30 ±0.03

[a]In 0.10M aqueous hydrogen chloride.

this order in aqueous solution. The same stability order probably holds when the corresponding 4-chlorophenyl derivatives in methanol are concerned, although the complexing is, no doubt, much stronger in methanolic than in aqueous solution[2]. The acid-catalysed hydrolysis of aryl aldofuranosides has been shown to involve a rapid, initial protonation of the glycosidic oxygen atom followed by rate-limiting rupture of the glycosyl–oxygen bond to form a cyclic oxocarbonium ion[13]. Methanolysis probably proceeds analogously. Accordingly, complexing of the substrate with calcium ion may retard the decomposition markedly. The positive charge of a complexed metal ion would tend to oppose both the protonation of the substrate and the development of a partial charge on the anomeric carbon. In addition, the conformational changes that occur during the passage from the initial state to the transition state may also be retarded. On this basis, it is easy to understand that the methanolysis of the relatively strongly complexing α-riboside is considerably retarded by an increasing concentration of calcium ions, whereas the β-xyloside, which interacts weakly if at all with calcium ion, shows a positive salt effect.

Table IV summarises the rate constants obtained for the hydrolysis of 4-chlorophenyl α-D-ribo- and β-D-xylo-furanosides in aqueous hydrogen chloride at various concentrations of calcium chloride. Both reactions are accelerated as the salt concentration increases (Fig. 2), and no marked difference in the rate enhancements can be detected on going to 1.5M calcium chloride. Accordingly, the interactions in aqueous solution between calcium ion and the substrates investigated seem to be too weak to affect the kinetics of the hydrolysis reactions.

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