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Note

Interactions of sodium, calcium, and lanthanum ions with methyl glycofuranosides in methanol

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Calcium ions have been shown[1] to complex in neutral, aqueous solution with some furanoid methyl glycosides, and the stabilities of the complexes depend decisively on the configuration of the glycon ring. In agreement with the suggestion of Angyal *et al.*[2–6], three vicinal oxygen atoms in an all-*cis* arrangement, such as HO-2, HO-3, and the glycosidic oxygen atom in an α-D-ribofuranoside, constitute the most suitable site for co-ordination. However, complex formation with methyl α-D-lyxofuranoside, having HO-2 and HO-3 *cis* to the hydroxymethyl group but *trans* to the glycosidic oxygen atom, appears to occur almost as readily. With other spatial arrangements, only weak interactions have been observed. We now report that the steric requirements for complex formation with metal ions are somewhat altered on going from calcium ion to ions of alkali and rare-earth metals having approximately the same ionic radius.

Table I records the effects of sodium, calcium, and lanthanum ions on the rate of the acid-catalysed methanolysis of some methyl glycofuranosides. For example, addition of calcium chloride to the acidic reaction mixture retards the solvolysis of the α-D-riboside and α-D-lyxoside considerably, but exerts only a slight effect on the rate for the other glycosides. As suggested previously[1], these differences in salt effects probably reflect the differences in the complex-forming abilities of the substrates. It is generally accepted[7] that the acid-catalysed hydrolysis of methyl glycofuranosides proceeds by rapid, initial protonation of the substrate, and presumably this also applies for solvolysis in methanol. Complexing of the substrate with a metal ion prevents its protonation and hence decreases the solvolysis rate. Since α-D-ribo- and α-D-lyxo-furanosides form rather stable Ca^{2+} complexes[1], the greatest retardation of methanolysis is to be expected for these glycosides.

If it is assumed that a proton and a metal ion are not simultaneously attached to the same substrate molecule, the solvolysis of methyl glycofuranosides can be depicted by Eq. *1*.

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TABLE I

FIRST-ORDER RATE CONSTANTS AT 298.2 K FOR THE SOLVOLYSIS OF SOME METHYL GLYCOFURANOSIDES IN 0.10 MOL.DM^{-3} METHANOLIC HYDROGEN CHLORIDE CONTAINING SODIUM, CALCIUM, OR LANTHANUM CHLORIDE

Methyl glycofuranoside	MCl_z	$[MCl_z]$ *(mol.dm^{-3})*	k*(obs.)* *($10^{-4}.s^{-1}$)*
α-D-Ribofuranoside	—	—	4.35 ±0.10
	NaCl	0.12	2.42 0.05
	$CaCl_2$	0.060	0.518 0.013
	$LaCl_3$	0.015	1.11 0.05
		0.030	0.590 0.019
		0.045	0.390 0.007
		0.060	0.277 0.009
β-D-Ribofuranoside	—	—	1.60 ±0.03
	NaCl	0.12	1.47 0.03
	$CaCl_2$	0.060	1.11 0.03
	$LaCl_3$	0.030	1.27 0.03
		0.060	0.929 0.025
		0.12	0.779 0.015
		0.15	0.694 0.019
α-D-Lyxofuranoside	—	—	1.50 ±0.02
	NaCl	0.12	1.32 0.02
	$CaCl_2$	0.060	0.372 0.006
	$LaCl_3$	0.015	0.235 0.007
		0.030	0.132 0.004
		0.045	0.0798 0.0012
		0.060	0.0664 0.0009
α-D-Xylofuranoside	—	—	7.88 ±0.15
	NaCl	0.12	7.06 0.10
	$CaCl_2$	0.060	6.13 0.25
	$LaCl_3$	0.015	3.44 0.05
		0.030	2.24 0.08
		0.045	1.48 0.02
		0.060	1.26 0.02
β-D-Xylofuranoside	—	—	7.74 ±0.18
	NaCl	0.12	6.70 0.10
	$CaCl_2$	0.060	6.37 0.14
	$LaCl_3$	0.030	3.85 0.11
		0.060	2.25 0.05
		0.12	1.48 0.05

$$SM^{z+} \underset{+M^{z+}}{\overset{-M^{z+}}{\rightleftharpoons}} S \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} SH^+ \rightarrow P \qquad (1)$$

Consequently, the rate law of Eq. *2* is obeyed. The expressions (*3*) and (*4*)

$$d[P]/dt = k[SH^+] \qquad (2)$$

for the formation constants of the protonated and complexed forms of the substrate,

together with the approximation presented in Eq. *5*, enable $[SH^+]$ to be formulated as a function of $[M^{z+}]$, $[H^+]$, and [S(tot.)], as described by Eq. *6*. Substitution of

$$K(SH^+) = [SH^+]/([S][H^+]) \tag{3}$$

$$K(SM^{z+}) = [SM^{z+}]/([S][M^{z+}]) \tag{4}$$

$$[S(tot.)] = [SM^{z+}] + [S] + [SH^+] \sim [SM^{z+}] + [S] \tag{5}$$

$$[SH^+] = \frac{K(SH^+) \times [H^+][S(tot.)]}{K(SM^{z+}) \times [M^{z+}] + 1} \tag{6}$$

in Equation *2* indicates that first-order kinetics are followed, the observed rate constant being of the form of Eq. *7*. In a fixed concentration of hydrogen ion, the product $k \times K(SH^+) \times [H^+]$ is equal to the first order rate constant, $k(H^+)$, obtained in the absence of metal ions. Consequently, Eq. *7* can be transformed into Eq. *8*.

$$k(\text{obs.}) = \frac{k \times K(SH^+) \times [H^+]}{K(SM^{z+}) \times [M^{z+}] + 1} \tag{7}$$

$$\frac{k(H^+)}{k(\text{obs.})} = K(SM^{z+}) \times [M^{z+}] + 1 \tag{8}$$

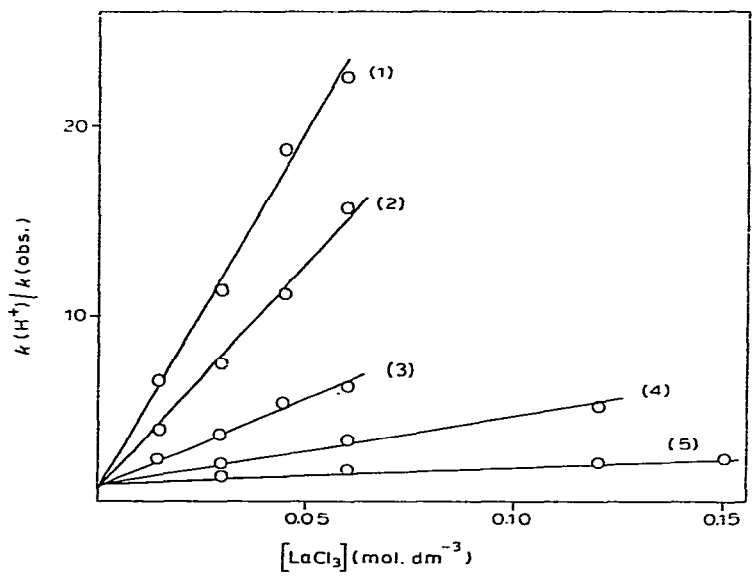

Fig. 1. The effect of lanthanum chloride on the rate of the acid-catalysed solvolysis of some methyl glycofuranosides in methanol at 298.2 K. The observed rate constant, k(obs.), stands for the first-order rate constant obtained at a given salt concentration, and $k(H^+)$ denotes the first-order rate constant in the same conditions in the absence of lanthanum chloride. Notation: (1) α-D-lyxo-, (2) α-D-ribo-, (3) α-D-xylo-, (4) β-D-xylo-, and (5) β-D-ribo-furanoside.

TABLE II

KINETICALLY DETERMINED FORMATION CONSTANTS, $K(SM^{z+})^a$, FOR COMPLEXES OF SOME METHYL GLYCOFURANOSIDES WITH SODIUM, CALCIUM, AND LANTHANUM IONS IN METHANOL AT 298.2 K

Methyl glycofuranoside	$K(SNa^+)$ ($dm^3.mol^{-1}$)	$K(SCa^{2+})$ ($dm^3.mol^{-1}$)	$K(SLa^{3+})$ ($dm^3.mol^{-1}$)
α-D-Ribofuranoside	7	120 (1.2)[b]	240
β-D-Ribofuranoside	<1	<10 (0.3)	<10
α-D-Lyxofuranoside	<1	50 (0.9)	370
α-D-Xylofuranoside	<1	<10 (0.1)	90
β-D-Xylofuranoside	<1	<10 (—)	40

[a]Formation of a 1:1 complex assumed. [b]The values in parantheses refer to aqueous solutions[1].

It should be noted that $k(H^+)$ and k(obs.) refer here to the same concentration of hydrogen ion. In the determinations of k(obs.), the total substrate concentration was low compared to the equilibrium concentration of the uncomplexed metal ion, and the latter value can therefore be approximated by the total concentration of the metal ion.

In Fig. 1, the kinetic data measured in the presence of lanthanum ion have been presented in terms of Equation *8*. With each compound, a fairly good, linear plot was obtained. The formation constants, $K(SLa^{3+})$, calculated from the slopes of these lines are listed in Table II, which also includes the formation constants for the complexes with sodium and calcium ions. However, the latter values are based on measurements at one salt concentration only.

The preceding method for determining the formation constants for metal ion–glycoside complexes relies on the assumption that common salt effects on $k(H^+)$ and $K(SM^{z+})$ can be neglected. The linearities of the plots of $k(H^+)/k$(obs.) *vs.* $[M^{z+}]$ and the fact that Ca^{2+} ion does not markedly affect the solvolysis of anomeric xylofuranosides, with which it interacts only weakly, support this assumption.

The kinetically determined equilibrium constants, $K(SCa^{2+})$, for the complexing of methyl glycofuranosides with calcium ion in methanol correlate reasonably well with the values measured in aqueous solution[1], being about a hundred-times greater than the latter. Accordingly, the α-D-riboside is the most efficient complexing agent, followed by the α-D-lyxoside. The other glycosides investigated exhibit barely noticeable interactions with calcium ion. As expected, La^{3+}, being of approximately the same size as Ca^{2+}, forms somewhat more stable complexes than Ca^{2+}. However, the α-D-lyxoside, having HO-2 and HO-3 *cis* to the hydroxymethyl group at C-4, is now complexed more strongly than the α-D-riboside, which has HO-2, HO-3, and the glycosidic oxygen atom in an all-*cis* arrangement. This change in the order of complexing-abilities of different glycofuranosides may reflect the greater attraction of the lanthanum ion, because of its greater charge, to the oxygen atoms of the ligand. For this reason, it has a greater ability to change the conformation of the glycosides

suitable for complex formation. It should also be noted that lanthanum ion tends to form complexes having greater co-ordination numbers than those of calcium[8]. Besides the α-D-riboside and α-D-lyxoside, anomeric xylofuranosides appear to interact with lanthanum ion, but the structure of the possible complexes cannot be deduced on the basis of the available data.

The α-D-ribofuranoside also interacts with Na^+, as can be seen from the decreased solvolysis rate of this compound in the presence of sodium chloride. None of the other glycofuranosides investigated, including the α-D-lyxoside, responded in this manner. These findings receive some support from the chromatographic behaviour of aqueous solutions of methyl glycofuranosides on a cation-exchange resin in the Na^+ form. The α-D-lyxoside and the anomeric xylosides were eluted in 480 ± 5 cm^3 of distilled water, whereas the α-D-riboside showed a marked retention, the elution volume being 560 cm^3. Most probably the co-ordination of sodium ions occurs at the triangle of oxygen atoms formed by HO-3, HO-2, and MeO-1 in methyl α-D-ribofuranoside. However, it is not clear why complexing with the α-lyxoside does not occur, although calcium and lanthanum ions, being of the same size as Na^+, interact strongly with this compound.

In summary, the solvolysis of methyl glycofuranosides in acidic methanol is markedly affected by the presence of ions of alkali, alkaline earth or rare earth metals, the rate-retarding effect increasing in this order. The reason for these inhibitory effects is the complexing of metal ions with the glycon ring of the substrates. The steric arrangement of the oxygen-containing groups constituting the optimal coordination site appears to vary on going from sodium ion to calcium and lanthanum ions, which all have about the same ionic radius.

EXPERIMENTAL

Methyl glycofuranosides tritiated at the methyl group were prepared by treating the furanoside-rich syrups obtained by Fischer glycosidation[9] with small volumes of boiling, methanolic hydrogen chloride containing ~200 μCi of tritiated methanol (NEN). The isolation of the furanoid anomers was performed as previously described[10–12]. The physical constants and the ^1H-n.m.r. data of the furanoside products agreed well with those previously reported[10–12].

Hydrated lanthanum chloride was converted into its tetramethanolate by treatment with methanolic 2,2-dimethoxypropane[13]. Sodium and calcium chlorides were commercial reagents of analytical grade and they were dried at 200° before use. Methanolic solutions of hydrogen chloride were prepared by passing hydrogen chloride through conc. sulphuric acid into methanol dried previously with methylmagnesium iodide. After dissolution of the salts, the acid concentrations were checked by titrations with standard base.

Methanolyses of methyl glycofuranosides were performed in stoppered bottles immersed in a bath thermostated at 298.2 K. Reactions were started by adding the substrate as a methanol solution in the pre-thermostated reaction solution. The initial

substrate concentration was of the order of 2×10^{-3} mol.dm^{-3}. Aliquots of 2 cm^3 were withdrawn at appropriate intervals and transferred to bottles containing methanolic sodium methoxide (to neutralise the catalytic acid). Most of the methanol was removed by distillation and its content of tritiated methanol was measured by scintillation counting in a toluene-based scintillation liquid. The rate constants for the methanolysis reactions were calculated from the integrated first-order rate-law.

Ion-exchange chromatography on Dowex-50W X8 (Na^+) resin (mesh 200–400) was performed as described earlier[1].

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