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Note

Carbohydrate adducts with alkaline-earth metal ions. Interaction of β-D-glucurono-1,4-lactone with Mg(II) and Ca(II) cations in aqueous and non-aqueous solutions

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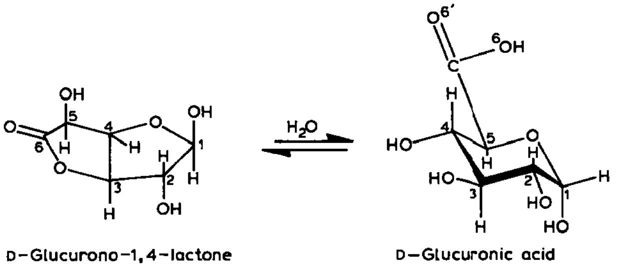
D-Glucurono-1,4-lactone has considerable biological importance. In animal and human bodies[2] it is converted into vitamin C and it has been demonstrated[3] to have an antihypnotic effect against sodium 5,5-diethylbarbiturate. The crystal structure of this sugar derivative has been reported[4], and it is readily converted into D-glucuronic acid in aqueous solution (see Scheme 1).



Scheme 1

In previous reports[5,6], it was demonstrated how $AgNO_3$ binds to D-glucuronic acid and to D-glucono-1,5-lactone in aqueous solution, whereas the $AgClO_4$ and CH_3CO_2Ag compounds facilitate hydrolysis of the lactone and ionization of the acid in H_2O solution. The interaction of alkaline-earth metal ions with D-glucuronic acid in aqueous solution and solid complexes has been studied, and the effects of binding of these metal ions on the sugar anomeric changes have been reported[7,8]. In the present work are described the interaction of β-D-glucurono-1,4-lactone with Mg(II) and Ca(II) ions, both in ethanolic and aqueous solutions, and the isolation of several complexes formed in these solutions, and characterization using F.t.-i.r.

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and ^{1}H-n.m.r. spectroscopy, X-ray powder diffraction, and molar-conductivity measurements, not hitherto reported.

EXPERIMENTAL

Materials and methods. — β-D-Glucurono-1,4-lactone was purchased from Aldrich Chemical Company and used as supplied. Other chemicals were reagent grade, and were used without purification.

Synthesis of the alkaline-earth metal–D-glucurono-1,4-lactone adducts. — The alkaline-earth metal–sugar adducts were prepared by addition of the hydrated metal halide salt (1 mmol) in absolute ethanol (20 mL) to a hot solution of D-glucurono-1,4-lactone (1 mmol) in absolute ethanol (20 mL). The solution was then cooled to room temperature, and kept for one week, with slow evaporation. After colorless crystals had been deposited, these were filtered off, washed several times with absolute ethanol, and dried over $CaCl_2$. The analytical results given in Table I show the composition of M(D-glucurono-1,4-lactone)$X_2 \cdot 4\ H_2O$, where M = Mg(II) or Ca(II), and X = Cl^- or Br^-. When the reaction is carried out in H_2O solution, in the presence of these metal cations, the solid compounds isolated show the composition of M(D-glucuronate)$_2 \cdot 4\ H_2O$, where M = Mg(II) or Ca(II) ions; the synthesis and characterization of metal D-glucuronates of these types had previously been reported[7,8]. The alkaline earth metal–D-glucurono-1,4-lactone adducts are very hygroscopic and should be kept in a desiccator. The adducts are very soluble in water, and slightly in hot ethanol and Me_2SO, but not soluble in other common organic solvents.

Physical measurements. — The F.t.-i.r. spectra were recorded with a DIGILAB FTS 15/C Fourier-transform infrared interferometer equipped with a high-sensitivity HgCdTe detector and a KBr beam-splitter. The spectra were recorded for KBr pellets, with a spectral resolution of 2 to 4 cm^{-1}. The X-ray

TABLE I

ELEMENTAL ANALYSES FOR THE ALKALINE-EARTH METAL–D-GLUCURONO-1,4-LACTONE ADDUCTS

Adducts		*M*[a] *(%)*	*C* *(%)*	*H* *(%)*	*X*[b] *(%)*
Mg(D-glucurono-1,4-lactone)$Cl_2 \cdot 4\ H_2O$	Found	6.90	20.35	4.76	19.95
	Calc.	7.12	20.96	4.66	20.65
Mg(D-glucurono-1,4-lactone)$Br_2 \cdot 4\ H_2O$		5.30	16.25	3.65	36.40
		5.65	16.65	3.70	36.90
Ca(D-glucurono-1,4-lactone)$Cl_2 \cdot 4\ H_2O$		10.85	19.60	4.70	19.35
		11.14	20.00	4.46	19.77
Ca(D-glucurono-1,4-lactone)$Br_2 \cdot 4\ H_2O$		8.55	15.90	3.70	35.20
		8.92	16.08	3.58	35.71

[a]M = alkaline-earth metal. [b]X = Br or Cl.

powder diagrams were taken, for comparative purposes, with a powder camera (Philips–Debye–Scherrer) with Cu*K*α radiation. Conductance measurements were conducted at room temperature in H_2O solution (mM) with a conductivity meter, type CDM2e (Radiometer, Copenhagen). The ^{1}H-n.m.r. spectra were recorded with a Varian XL-200 instrument for solutions in MeSO-d_6 containing Me_4Si as reference.

RESULTS AND DISCUSSION

F.t.-i.r. spectra. — The F.t.-i.r. spectra of the free β-D-glucurono-1,4-lactone and its alkaline-earth metal adducts were studied in the region of 3700–500 cm^{-1}; the results of the spectral analysis are described.

Lactone OH-stretching vibrations and binding modes. — X-Ray structural analysis showed[4] that, in the crystal structure of β-D-glucurono-1,4-lactone, the free sugar molecules are associated by a simple system of intermolecular hydrogen-bonding. Based on the intermolecular O···O distances of the H-bonding structure of the free lactone, given in Table II, O-1–H is a hydrogen-bond donor to the O-6 carbonyl group, and a hydrogen-bond acceptor from O-2–H. The O-2–H group participates as a donor to the O-1–H only, and O-5–H is not involved in a hydrogen-bonding network[4].

The three strong absorption bands observed at ~3500–3300 cm^{-1} in the i.r. spectrum of the free lactone could be assigned to the strongly H-bonded O-1–H

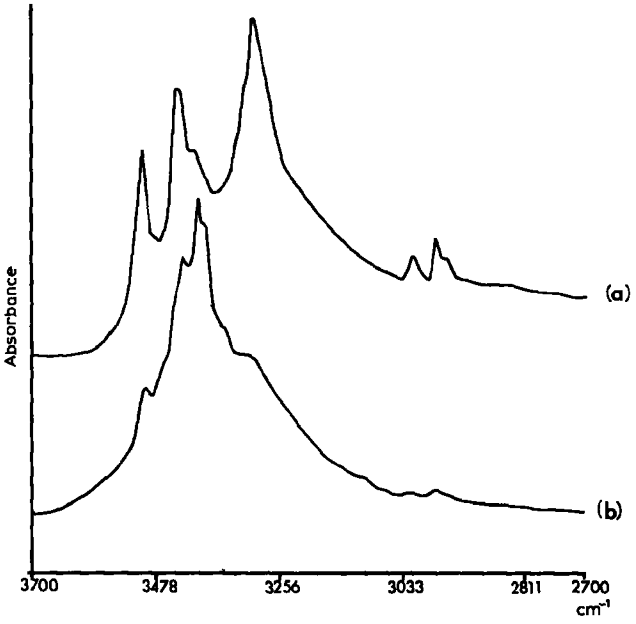

Fig. 1. F.t.-i.r. spectra of β-D-glucurono-1,4-lactone and one of its alkaline-earth metal adducts in the region of 3700–2700 cm^{-1} for (a, β-D-glucurono-1,4-lactone; b, Mg (D-glucurono-1,4-lactone)$Cl_2 \cdot 4$ H_2O).

TABLE II

F.t.-i.r. ABSORPTION BANDS[a] (cm^{-1}) FOR β-D-GLUCURONO-1,4-LACTONE AND ITS ALKALINE-EARTH METAL ADDUCTS IN THE REGION OF 3700–500 cm^{-1} WITH POSSIBLE ASSIGNMENTS

β-D-Glucurono-1,4-lactone	*Mg(D-Glucurono-1,4-lactone)$Cl_2 \cdot 4\,H_2O$*	*Mg(D-Glucurono-1,4-lactone)$Br_2 \cdot 4\,H_2O$*	*Ca(D-Glucurono-1,4-lactone)$Cl_2 \cdot 4\,H_2O$*	*Ca(D-Glucurono-1,4-lactone)$Br_2 \cdot 4\,H_2O$*	*Assignments*[5–8,11,12]
3504 vs	3490 s	3485 s	3485 s	3475 s	ν O-5–H
3433 vs	3432 s	3430 s	3425 s	3423 s	ν O-2–H···O-1–H
	3406 vs	3410 vs	3400 vs	3405 vs	O···O = 2.839 Å
3399 sh	3398 s	3394 s	3390 s	3393 vs	νH_2O
	3358 s	3355 s	3352 vs	3350 vs	ν O-1–H···O-6
3297 bs	3265 s	3260 vs	3255 vs	3250 s	O···O = 2.730 Å
3010 m	3010 m	3008 m	3005 m	3010 w	ν C–H of C-1
2980 m	2975 m	2970 m	2875 m	2977 m	ν C–H of C-2
2960 sh	2965 w	2960 w	2965 w	2960 w	ν C–H of C-3
2895 w	—	—	—	—	ν C–H of C-4
2840 vw	—	—	—	—	ν C–H of C-5
	1788 s	1785 sh	1780 s	1778 s	ν C-6=O
1757 bs	1758 vs	1760 s	1759 sh	1758 vs	
—	1639 s	1640 mb	1640 bs	1642 s	δH_2O
—	—	—	—	1632 sh	
1430 m	1435 m	1433 m	1435 m	1435 w	δ(COH) + δ(CCH)
1400 m	1405 m	1403 w	1405 m	1400 m	δ(COH) + δ(CCH)
1352 s	1353 s	1355 vs	1355 s	1352 vs	δ(COH) + δ(CCH)
1300 sh	1303 sh	1305 sh	1302 sh	1305 sh	δ(OCH) + δ(CCH)
1269 s	1271 m	1273 m	1269 m	1268 m	δ(COH) + δ(CCH)
	1245 sh	1250 sh	1250 sh	1249 sh	

1187 s	1193 s	1190 s	1192 vs	1192 vs	δ(COH) + δ(CCH)
	1179 sh	1180 sh	1182 sh	1180 sh	
1128 s	1131 s	1131 s	1130 vs	1129 vs	ν(CO) + ν(CC)
1078 s	1070 w	1110 m	1110 m	1111 m	ν(CC) + ν(CO)
	1058 s	1056 m	1076 s	1078 s	
1042 bs	1040 vs	1043 vs	1040 vs	1040 vs	ν(CO) + δ(CCO)
1001 s	1000 s	1000 s	1018 s	1018 s	ν(CO) + ν(CC)
	—	—	1001 s	1001 s	ν(CO) + δ(COC)
937 s	978 m	—	970 m	968 m	ν(CO) + δ(OCO)
	948 sh	946 sh	—	—	
903 m	933 m	936 m	935 s	936 s	
	906 m	906 m			
			905 m	906 m	ν (CO) + δ (CCH)
843 m	846 m	845 m	845 m	847 m	
803 m	809 w	807 w	810 w	809 w	ν(CO) + ν(CC)
	794 w	793 w	790 w	795 w	
768 s	771 m	770 s	767 m	769 s	δ(CH)
712 m	713 w	714 m	750 m	751 m	δ(CH)
	701 w	700 sh	710 m	711 m	
680 sh	682 sh	—	690 vw	690 w	τ(CO) + δ(CCO)
	665 w	666 vw	665 w	666 w	
631 m	632 m	633 m	635 m	636 m	δ(CCO) + δ(OCO)
571 m	576 w	577 m	575 s	574 s	δ(CCO) + δ(OCO)
550 sh	545 vw	543 vw	542 m	540 s	δ(OCO) + δ(CCO)

[a] Key: b, broad; m, medium; s, strong; sh, shoulder; v, very; w, weak; δ, bending; ν, stretching; τ, internal rotation.

(3297 cm^{-1}), to O-2–H (3433 cm^{-1}), and to the unperturbed O-5–H (3504 cm^{-1}) stretching frequencies (see Fig. 1 and Table II). A shoulder absorption band at ~3400 cm^{-1} in the spectrum of the free sugar could be related to the H_2O stretching vibration (the water absorbed by the sugar during the i.r. measurement).

The OH-stretching vibrations of the free lactone exhibited splitting and shifted towards lower frequencies, upon alkaline-earth metal–adduct formation (see Fig. 1 and Table 2). The spectral changes observed are due to participation of the sugar OH groups in metal–ligand bondings.

The C–H stretching vibrations of the free lactone appeared as several absorption bands in the region of 3000–2800 cm^{-1} in the spectrum of the free sugar, and showed no major alterations on sugar-complex formation (see Fig. 1 and Table II).

H_2O binding. — Due to overlapping of the water OH stretching vibration with those of the lactone OH stretchings in the region of 3500–3200 cm^{-1}, it is rather difficult to draw, with certainly, any conclusion as to nature of metal–H_2O bonding. However, a strong absorption band at ~1640 cm^{-1} in the spectra of the alkaline-earth metal–lactone adducts that is absent from the spectrum of the free sugar is assigned to the bending mode of the bonded H_2O molecules (see Fig. 2 and Table II).

Lactone carbonyl stretching vibrations, and metal ion coordination. — A strong, broad absorption band at 1757 cm^{-1} in the free lactone spectrum, which is assigned to the sugar C-6=O group[6], shifted towards higher frequency, and split into two components, in the spectra of the Mg(II)– and Ca(II)–D-glucurono-1,4-lactone adducts (see Fig. 2 and Table II). The spectral changes observed are due to participation of the lactone carbonyl group in metal–sugar bonding. Similar spectral changes were observed for the carbonyl stretching vibrations in the i.r. spectra of the Ag(D-glucono-1,5-lactone)$NO_3 \cdot H_2O$ adduct, where it was suggested[6] that the silver ion coordination might be through the carbonyl oxygen atom.

In the i.r. spectra of the M(D-glucuronate)$_2 \cdot 4\ H_2O$ salts (isolated from aqeous solution), the carbonyl stretching vibration of the free lactone exhibited major splitting and shifted towards lower frequencies (see Fig. 2). The two strong, broad absorption bands observed at ~1600 and 1450 cm^{-1} in the spectra of these metal–sugar salts, are assigned to the antisymmetric and symmetric OCO^- stretching vibrations of the D-glucuronate anion[7]. The changes observed in the spectra of these alkaline-earth metal ion salts are indicative of lactone hydrolysis, and the binding of these metal cations through the negatively charged OCO^- group, and possibly O-5 of the ring system. A similar binding mode was observed in the crystal structure of the known Ca(D-glucuronate)Br$\cdot 3\ H_2O$, where one of the sugar anions was chelated to the calcium ion through O-6 of the carboxyl group and the sugar-ring O-5 atom[9]. It should be noted that the chelation of the sugar carboxyl group to a calcium ion through both OCO^- oxygen atoms, or to one of the carboxyl oxygen-atoms in concert with other sugar donor atoms in the α-position, has been observed in the crystal structures of several calcium–sugar complexes[10].

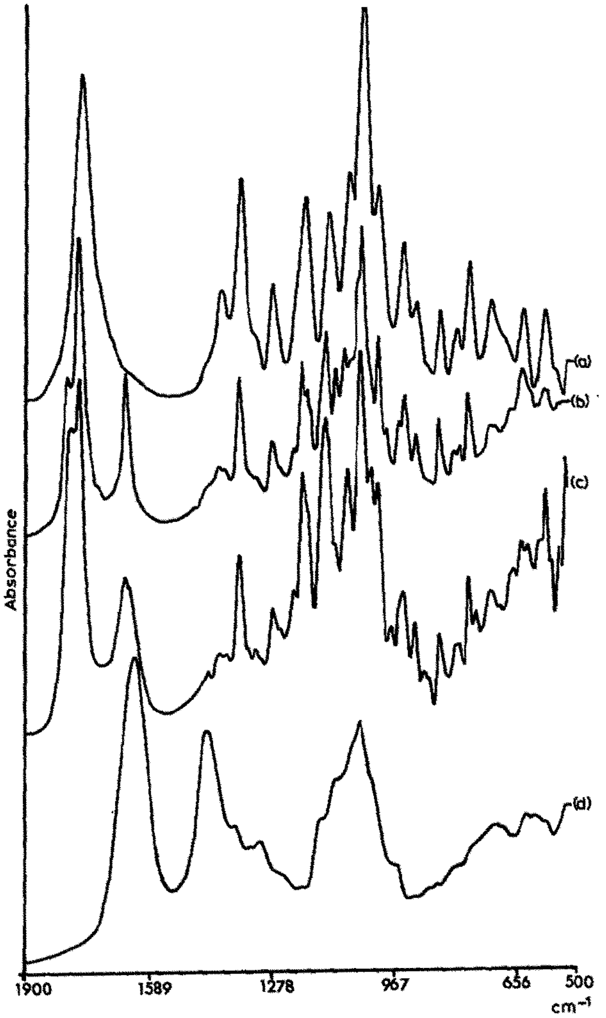

Fig. 2. F.t.-i.r. spectra of β-D-glucurono-1,4-lactone and its alkaline-earth metal compounds in the region of 1900–500 cm^{-1} for (a, β-D-glucurono-1,4-lactone; b, Mg (D-glucurono-1,4-lactone)$Cl_2 \cdot 4\ H_2O$; c, Ca(D-glucurono-1,4-lactone)$Br_2 \cdot 4\ H_2O$; d, Mg(D-glucuronate)$_2 \cdot 4\ H_2O$.

It is worth mentioning that the solution spectra of the alkaline-earth metal–D-glucurono-1,4-lactone adducts recorded (in ethanol) in the region of 1800–1400 cm^{-1} showed marked similarities to those of the corresponding solid adducts (for the carbonyl group), which is indicative of sugar–metal coordination through the lactone form, in ethanolic solution. On the other hand, the i.r. spectra of these metal–sugar adducts obtained in aqueous solution (D_2O) in the region of 1800–1400 cm^{-1} were quite similar to those of the corresponding solid salts[7,8], which is indicative of sugar hydrolysis and acid ionization in aqueous solution.

Sugar-ring vibrational frequencies, and metal–ion binding. — The strongly coupled sugar ring COH and CCH bending modes[11,12] appeared as several medium-intensity bands in the region of 1450-1100 cm^{-1} in the spectrum of the free lactone, and exhibited major changes in intensity and shifted towards higher frequencies upon sugar-adduct formation (see Fig. 2 and Table II). The shifts of the COH bending towards higher frequencies, together with the shifts of the sugar OH stretching vibrations (3500–3200 cm^{-1} towards lower frequencies are related to sugar OH-group participation in metal–ligand bonding. The lactone ring C–O stretching vibrations appeared as several strong absorption bands in the region of 1100–900 cm^{-1}, and shifted towards higher frequencies on sugar complexation (see Fig. 2 and Table II). The shifts of the C–O stretching vibrations towards higher frequencies are due to the non-participation of the ring C–O groups in metal-adduct formation. It should be added that the participation of the sugar ring C–O group in metal–ligand bonding caused a shift of the C–O stretching vibrations towards lower frequencies[7,8].

^{1}H-N.m.r. spectra. — The chemical shifts of the anomeric protons (H-1) of the free lactone in D_2O solution (α-H 5.56 p.p.m. and β-H 5.45 p.p.m.) showed marked similarities to those of D-glucuronic acid with preponderance of the β anomer. The spectra of the Mg(II)– and Ca(II)–D-glucurono-1,4-lactone adducts also exhibited similarities to those of the alkaline-earth metal–D-glucuronate complexes in D_2O solution, with preponderance of the α anomer, as previously reported[8]. The observed similarities are indicative of lactone hydrolysis and metal–sugar binding through the acid anion in aqueous solution, consistent with the i.r. results, already discussed. On the other hand, the β-anomeric configuration of the free D-glucurono-1,4-lactone is preponderant in Me_2SO solution, with the α-OH and β-OH chemical shifts appearing at 6.50 and 6.30 p.p.m., respectively. In the Mg(II) and Ca(II) halide adducts, the sugar moiety has the α-anomeric configuration, with the β-OH chemical shift appearing at ~6.55 p.p.m. The observed downfield shift of the anomeric OH chemical shift in Me_2SO solution is indicative of possible participation of the lactone O-1–H and O-2–H groups in metal–sugar bondings. It is worth mentioning that, in the crystal structure of Ca(α-D-glucuronate)Br·3 H_2O, one of the D-glucuronate anions is bonded to the Ca(II) ion *via* the O-1–H and O-2–H groups[9].

Molar conductivity and X-ray powder diffraction. — The high molar conductivities (150–200 $\Omega^{-1}.cm^2.mol^{-1}$ observed for the alkaline-earth metal–D-glucurono-1,4-lactone adducts in aqueous solution are indicative of considerable dissociation and the absence of direct metal–halide binding in these metal–sugar complexes. The results are consistent with the X-ray structural information reported[9] for Ca(D-glucuronate)Br·3 H_2O and other calcium–sugar adducts[13,14], which showed no direct metal–halide interaction.

The X-ray powder patterns of the magnesium and calcium halide adducts of the lactone were similar, as in the case of their i.r. spectra. The similarities observed are indicative of similar binding arrangements of the sugar moieties in these metal–sugar adducts. Therefore, in the M(D-glucurono-1,4-lactone)X_2·4 H_2O (M =

magnesium or calcium ion, and X = Cl^- or Br^-), each metal ion could be bonded to two lactone molecules *via* O-1–H, O-2–H of the first sugar and O-6, O-5–H (five-membered ring chelation) of the second, and to four H_2O molecules for the Ca(II) ion and two H_2O for the Mg(II) ion, resulting in an eight-coordination around the Ca(II) ion, and six-coordination for the Mg(II) ion. On the other hand, each alkaline-earth metal cation in the M(D-glucuronate)$_2\cdot$4 H_2O salts would be coordinated to two sugar anions through negatively charged carboxyl O-6 and the ring O-5 atoms (five-membered ring chelation) and to two or four H_2O molecules, forming a six-coordination geometry around the magnesium ion and an eight-coordination for the calcium ion, as reported earlier[7,8].

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