Complexation of Aluminium(III), Gallium(III) and Indium(III) Ions with D-Gluconic and Lactobionic Acids. A Potentiometric and Nuclear Magnetic Resonance Spectroscopic Study†

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The interaction of the trivalent metal ions aluminium(III), gallium(III) and indium(III) with D-gluconic and lactobionic (4-*O*-β-D-galactopyranosylgluconic) acids has been studied by means of potentiometry and NMR spectroscopy. Potentiometric measurements gave the stoichiometry, species distribution and equilibrium constants of the complexes in aqueous solution at 20.0 °C and $I = 0.10$ mol dm^{-3} ($NaNO_3$). The ^{13}C NMR spectroscopic studies revealed line-broadening effects upon complexation, which selectively affected those carbons involved in the complex formation. This enabled the co-ordination sites at both acids to be elucidated. It seems that whereas aluminium(III) prefers to displace the OH protons from the sugar acids even in alkaline media, gallium(III) and indium(III) are able to form hydroxo complexes on increasing the pH.

The objective of this study was to determine both the stability constants and the likely structures of complexes of Group III trivalent metal ions, namely aluminium(III), gallium(III) and indium(III), with D-gluconic and lactobionic (4-*O*-β-D-galactopyranosylgluconic) acids. These metal complexes are of potential interest in several medical applications, such as the treatment of aluminium intoxication,[1] and the use of Ga^{3+} and In^{3+} as radiopharmaceuticals. The latter metal ions can be employed as the radioisotopes ^{67}Ga, ^{68}Ga, ^{111}In and ^{113}In in standard imaging techniques for the diagnosis and location of tumours and for the imaging of cancerous tissue.[2–4] Complexes of ^{68}Ga, which is a positron emitter, can be used for positron emission tomography imaging. These three metal ions may be considered to be strong type A acceptors (hard acids)[5] and one would expect very high affinity for bases which provide negative oxygen donors as do those considered here.

In order to understand the transport of aluminium(III), gallium(III) and indium(III) *in vivo*, it is necessary to obtain quantitative equilibrium data on their complexes, so that their conversion into active species in biological systems can be predicted. This was obtained by potentiometric methods and processed by the FORTRAN computer program BEST[6a] which provides the stability constants of the complexes. Since potentiometry does not yield microscopic information concerning the metal co-ordination sites this was obtained by means of NMR spectroscopy.

Since iron(III) ion is a competitor for binding to the oxygen-donor sequestering agents, the complexes under investigation are compared with those formed by Fe^{III}, studied previously.[7]

Experimental

Reagents.—Lactobionic acid and the sodium salt of D-gluconic acid were obtained from Sigma and their purities confirmed by elemental analysis, ^{13}C NMR and potentiometric titrations.

A 0.020 mol dm^{-3} stock solution of Al^{III} was prepared by dissolving $Al(NO_3)_3 \cdot 9H_2O$ (AR) in 0.05 mol dm^{-3} nitric acid solution. Standard solutions of about 0.20 mol dm^{-3} $Ga(NO_3)_3$ and $In(NO_3)_3$ were prepared by dissolving weighed samples of 99.9% pure gallium and indium metals in concentrated HNO_3. The metal concentrations were checked by titrations with previously standardized ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (H_4edta) solution in the presence of appropriate indicators.[8] The exact amount of excess of HNO_3 in the aluminium(III), gallium(III) and indium(III) solutions was determined by Gran's method.[9] Solutions of carbonate-free NaOH and HNO_3 were standardized against potassium hydrogenphthalate and sodium carbonate, respectively.

Potentiometric Equipment and Measurements.—Potentiometric measurements were carried out with the procedures described in detail elsewhere.[7] Briefly, measurements were made under a nitrogen atmosphere at 20.0 ± 0.1 °C and the ionic strength was adjusted to 0.10 mol dm^{-3} with $NaNO_3$.

Prior to each experiment, the Corning Research 125 pH meter used was fitted with glass and calomel reference electrodes and calibrated to read pH directly with freshly prepared solutions of standard acid (HNO_3), standard base (NaOH) and standard acetic acid. Thus the term pH in this paper is defined as $-\log[H^+]$. The concentrations of the experimental solution [(1 or 2) × 10^{-3} mol dm^{-3}] were low enough so that they did not significantly contribute to the ionic strength of the medium. These concentrations are typical of those found in biological media. In addition to measuring the 1:1 metal–gluconic acid systems, the 1:2 ratio was also investigated but in neither case was there any indication of the formation of 1:2 complexes.

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Equilibrium pH values were determined at every incremental addition of NaOH or HNO_3 to the experimental solutions. These increments were sufficiently small so as to provide a ratio of experimental points per a value of higher than 10:1 (a = moles of base per mol of gluconic acid). For each system eight or more replicate measurements were performed. Reversibility of the reactions was suggested by the fact that the direct and inverse titration data were coincident, within the investigated range.

Calculation of Equilibrium Constants.—Protonation constants of D-gluconic acid and lactobionic acid were calculated in previous works.[7,10] Since all the complexes studied were not fully formed at low pH, their stability constants could be determined by direct potentiometric titration, with the aid of the BEST program.[6a] For the determination of species distributions the program SPE was used.[6b]

NMR Spectroscopy.—All spectra were acquired on a Bruker AC-200 E pulsed Fourier-transform instrument with a 4.3 T Supercon magnet, at a carbon-13 resonance frequency of 50.1 MHz. The samples were in the range 0.2–0.4 mol dm^{-3} gluconic acid solution in distilled deionized water mixed with 10% D_2O to provide the deuterium lock. The metal ions were introduced as appropriate aliquots to give concentrations between 0.02 and 0.2 mol dm^{-3}. Adjustments of the pH were made by adding either 1 or 2 mol dm^{-3} NaOH. In the indium(III) systems, where hydroxide precipitation is detected in alkaline media, the solutions were kept at an acid pH (4.7). Since in the aluminium(III) systems the hydroxide precipitates beyond pH 5 but dissolves at high pH, the spectra were recorded at both pH 4.7 and 10. In the gallium(III) systems the spectra were also acquired at both acid and alkaline pH.

Results and Discussion

Potentiometric Measurements.—All hydrolysis constants of the cations investigated were calculated from the data of Baes and Mesmer.[11]

Aluminium(III) systems. The titration curve for aluminium and D-gluconic acid (HL) in 1:1 ratio was fitted by considering $[AlH_{-1}L]^+$ and $[AlH_{-3}L]^-$ as the major components before precipitation was detected (pH ≈ 5). The negative stoichiometric coefficient for H represents the non-carboxylic protons displaced upon complex formation. In the present work it was not necessary to introduce $[AlL]^{2+}$ or the intermediate $[AlH_{-2}L]$ species because their concentrations were found to be unimportant. The overall aluminium hydrolysis constants used in the computations were: log $K_{MH_{-1}}$ = −5.41, log $K_{MH_{-2}}$ = −9.98, log $K_{MH_{-3}}$ = −15.69, log $K_{MH_{-4}}$ = −23.45, log $K_{M_2H_{-2}}$ = −7.70 and log $K_{M_3H_{-4}}$ = −13.69.[11a] The large polymeric species $[Al_{13}O_4(OH)_{24}]^{7+}$ was not considered because its rate of formation is very slow, and its equilibrium is not achieved under our experimental conditions.[11a] Also, the concentrations of both mono- and lower poly-nuclear hydrolytic aluminium species were found to be considerably smaller than those involving gluconate as ligand. The log K_w value used throughout this work was −13.78.[11b] All these values correspond to 25 °C and I = 0.10 mol dm^{-3}.

The equilibrium constants for the aluminium(III)–D-gluconic acid complexes are listed in Table 1. These constants were previously reported by Motekaitis and Martell,[12] and our values are in agreement, with due account of the different media. In the standard titration experiments, equilibration times allowed between the addition of each base increment were large (at pH > 5). This fact and the observation that the concentration of free aluminium(III) ion is sufficient to precipitate $Al(OH)_3$ were indicative that a second phase was present before it became visible. In the back-titrations a slow drift in the solution pH was also observed in the alkaline zone upon addition of aliquots of acid and hydroxide precipitation was visible between pH 5 and 7. Therefore, the data corresponding to pH > 5 were not employed in equilibrium computations. However, the dissolution of the precipitate at high pH suggests additional reactions that could involve $[Al(OH)]_4^-$ complex formation.

In addition to the potentiometric evaluation, spectroscopic studies were performed in order to obtain microscopic structural information on the species of interest and will be discussed below.

In the 1:1 aluminium(III)–lactobionic acid (HL) solution only the $[AlH_{-3}L]^-$ complex was detected prior to hydroxide precipitation. Since the pH values in the alkaline region were also unstable this zone was not quantitatively investigated. The binding constant of the $[AlH_{-3}L]^-$ complex (Table 1) indicates that this species is less stable than the D-gluconic acid analogue. The NMR data may suggest, however, than an additional complex $[AlH_{-4}L]^{2-}$ is formed in alkaline media (see below).

Gallium(III) systems. The experimental data from potentiometric titrations in both D-gluconic and lactobionic acid 1:1 systems may be described by considering equilibria (1)–(3)

Table 1 Deprotonation constants of D-gluconic and lactobionic acids and equilibrium constants for some of their trivalent metal-ion complexes at I = 0.10 mol dm^{-3} ($NaNO_3$) and 20.0 °C[a]

		Ligand (HL)	
Quotient	Metal ion	D-Gluconic acid	Lactobionic acid
$[H][L]/[HL]$		−3.40[b]	−3.53[b]
$[H][MH_{-1}L]/[L][M]$			
	Fe^{III}[b]	2.43	2.03
	Al^{III}	−0.84 (0.02)	
		−0.89[c]	
$[H]^2[MH_{-2}L]/[L][M]$			
	Fe^{III}[b]	−0.80	−1.86
	Ga^{III}	−2.83 (0.03)	−3.02 (0.05)
$[H]^3[MH_{-3}L]/[L][M]$			
	Fe^{III}[b]	−5.18	−11.79
	Al^{III}	−10.70 (0.02)	−11.98 (0.03)
		−10.18[c]	
	Ga^{III}	−8.94 (0.03)	−8.95 (0.05)
	In^{III}	−9.21 (0.02)	−9.53 (0.04)
$[H]^4[MH_{-4}L]/[L][M]$			
	Ga^{III}	−16.45 (0.03)	−16.40 (0.05)

[a] Charges are omitted. [b] Ref. 7. [c] Ref. 12 (25 °C, I = 0.10 mol dm^{-3}).

$$Ga^{3+} + L^- \rightleftharpoons [GaH_{-2}L] + 2H^+ \quad (1)$$

$$[GaH_{-2}L] \rightleftharpoons [GaH_{-3}L]^- + H^+ \quad (2)$$

$$[GaH_{-3}L]^- \rightleftharpoons [GaH_{-4}L]^{2-} + H^+ \quad (3)$$

where L^- represents either D-gluconate or lactobionate anion.

The complexes $[Ga(OH)]^{2+}$ and $[Ga(OH)_2]^+$ were included in the refinement using the log hydrolysis constants at $I = 0.1$ mol dm^{-3} (-3.05 and -6.6 respectively).[11c] Other hydrolysis products do not appear to be significant in the evaluated pH range (2.5–11). A typical potentiometric profile corresponding to the 1 : 1 gallium–gluconate system is presented in Fig. 1, along with the calculated pH values.

Although above pH 3.3 the free metal-ion concentration is of the order of that required to satisfy the solubility product of its hydroxide, the solution is stable yet supersaturated with respect to the insoluble component. This fact has been observed in other complex systems of gallium(III).[13] Therefore, and according to the suggestion of Martell,[6c] the data were considered as corresponding to equilibrium and the binding constants were determined and are listed in Table 1. As with other investigated systems the sugar complexes formed at low pH co-exist with the hydrolytic forms of gallium (Fig. 2), but in the studied alkaline zone the complex $[Ga(OH)]_4^-$ was not potentiometrically

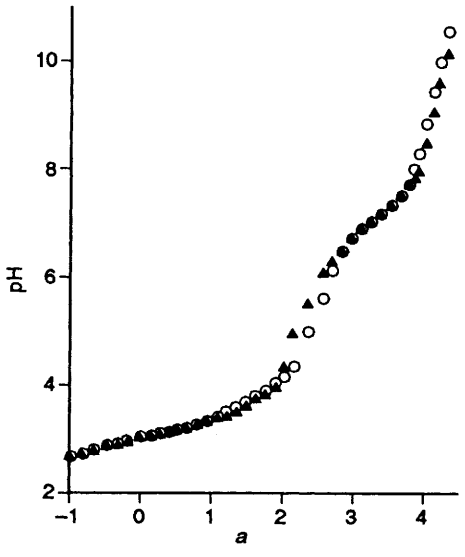

Fig. 1 Comparison of experimental (○) and calculated (▲) pH values *versus a* (moles of base per mol of gluconic acid) in the case of the 1 : 1 gallium(III)–D-gluconate system. $c_M = c_L = 1.56 \times 10^{-3}$ mol dm^{-3}, $I = 0.10$ mol dm^{-3} ($NaNO_3$), 20.0 °C

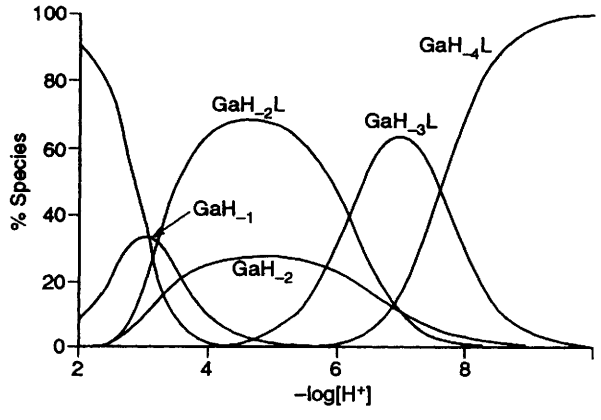

Fig. 2 Species distribution plot of the gallium(III)–D-gluconic acid system. Conditions as in Fig. 1

detected. To determine whether the upper pH buffer region is the result of continuing chelate hydrolysis or the complex is breaking apart with further hydrolysis of the metal ion, spectroscopic methods can be employed. In this case, the similarity between the ^{13}C NMR spectra of the gallium(III)–D-gluconic acid solution at low and high pH seems to indicate that the affinity of the sugar for the metal ion is enough to resist metal hydrolysis. This method also helped us to decide which of the hydroxyl groups was involved in the metal co-ordination.

Indium(III) *systems.* The equilibrium potentiometric profiles of both indium(III)–D-gluconic acid and –lactobionic acid 1 : 1 systems indicated that three non-carboxylic protons were released from the complexes. Beyond pH 5–6 a white precipitate of $In(OH)_3$ was detected in both systems and measurements of useful potentiometric data for stability constant computations were not possible. The solid phase did not dissolve even at high pH. In the soluble regions the stoichiometry of the complex found was $[InH_{-3}L]^-$ and the corresponding equilibrium values are shown in Table 1. The hydrolysis constants used were: log $K_{MH_{-1}} = -4.30$, log $K_{MH_{-2}} = -8.33$ and log $K_{MH_{-3}} = -12.93$.[11d]

As in the above cases, additional spectroscopic measurements to correlate stability with binding sites were performed.

^{13}C *NMR Measurements.—Ligands.* We have previously analysed and assigned the solution (D_2O) ^{13}C NMR spectrum of lactobionic acid in media where the carboxylate group is already ionized (*i.e.* pH 8).[7] This assignment remains valid at both pH values at which we have studied its complexation with Al^{III}, Ga^{III} and In^{III}.

Corresponding data for D-gluconic acid are also available from the literature.[14,15] However, since the ^{13}C NMR spectrum of D-gluconic acid displays several carbon resonances within a relatively restricted range of chemical shifts, we decided to carry out a thorough analysis using two-dimensional techniques, as was the case with lactobionic acid. Fig. 3 shows the one-dimensional ^1H NMR slices obtained from the corresponding correlated ^1H–^{13}C two-dimensional NMR spectrum at pH 4.7. These ^1H NMR slices retain the *J*-coupled ^1H multiplets and are therefore highly useful for carbon assignments. It may be noted that the ^1H–^{13}C two-dimensional correlated spectrum does not give directly this information from ^1H and ^{13}C chemical shifts, since all the protons in D-gluconic acid appear in a small range of chemical shifts (*ca.* 0.5 ppm). As seen in Fig. 3, the multiplicities observed for H^2, H^4 and $H^{6,6'}$ are consistent with the ^{13}C literature assignments and with a gluconate anion having the carbon skeleton in an all-*trans* conformation: d(J = 4.1), dd(J = 4.1 and 7.5 Hz) and the AB portions of an ABC

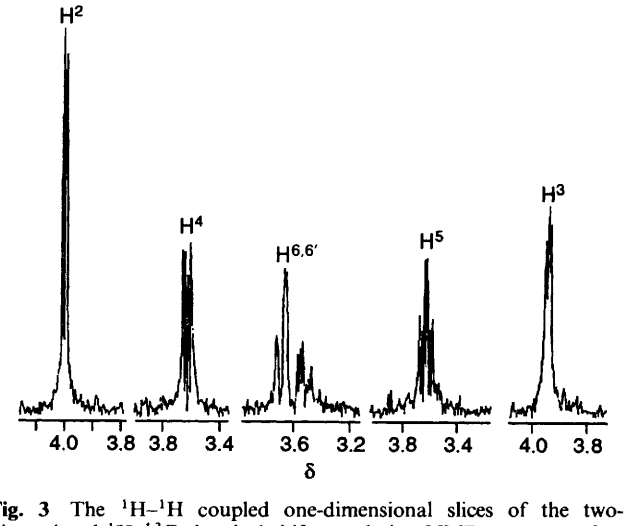

Fig. 3 The ^1H–^1H coupled one-dimensional slices of the two-dimensional ^1H–^{13}C chemical shift correlation NMR spectrum of D-gluconic acid in water at pH 4.7

spectrum respectively. However, the reported assignments[14] for carbons C^3 and C^5 have to be reversed according to the present results. Carbon C^3 correlates with a ^1H NMR projection (Fig. 3) which is a triplet having $J = 3.9$ Hz, consistent with coupling to H^2 and H^4, in both cases with dihedral angles of *ca.* 60°. On the other hand, C^5 correlates with a ^1H slice which appears as a doublet of triplets ($J = 7.7$ and 3.3 Hz), consistent wth H^5 being coupled to H^4 and to H^6 (in both cases with a dihedral angle of 180°) and also to $H^{6'}$ (dihedral angle of *ca.* 60°).

This unambiguous analysis of the carbon chemical shifts of both gluconic acids studied in the media in which their complexing behaviour has been probed is essential for the correct assignment of the carbon resonances which are affected by the presence of metal ions. It should be noted that the presently applied method (*i.e.* the projection of ^1H–^1H coupled one-dimensional slices from the ^1H–^{13}C chemical shift correlated NMR spectrum) has been shown to be highly useful for the correct assignment of carbon resonances both for lactobionic and D-gluconic acid, but may suffer from poor resolution in the ^1H frequency dimension for other compounds. It is somewhat ironic that the great disadvantage of carbohydrates for ^1H NMR spectra (many proton resonances within a restricted chemical shift range combined with the appearance of the water resonance) makes it possible to register the well resolved spectra shown in Fig. 3.

Aluminium(III). It should first be noted that the total concentrations of metal and gluconic acid used to obtain the ^{13}C NMR spectra described below are considerably higher than those used in the potentiometric study, due to the poor sensitivity of NMR towards the ^{13}C nucleus. Corresponding studies in the mmol dm^{-3} range are prohibitive. The main concern when the concentration is increased is the possible formation of polynuclear aluminium(III)–sugar acid species. However, this would lead to the observation of multiple signals for each sugar acid carbon, since the complexes will possess several non-equivalent carbon atoms, corresponding to each carbon in the constitutive sugar moieties. In all cases, non-broadened signals were detected as singlets. Calculation of the species distribution both at low and high concentration (typical for the potentiometric and NMR solutions respectively) revealed a similar pattern, *i.e.* the presence of polynuclear Al_mH_{-n} species in negligibly low concentrations.

Upon addition of aluminium(III) ion to a D_2O solution of D-gluconic acid significant changes are observed. At pH 4.7 all carbon signals are broadened [Fig. 4(*a*)]. However, the signals ascribed to C^1, C^2, C^3 and C^4 suffer both broadening and chemical shift displacement from the values observed for gluconate itself, and are significantly more affected than those corresponding to C^5 and C^6. The values of $\Delta\delta = \delta(\text{complex}) - \delta(\text{ligand})$ amount to *ca.* 5 ppm for C^1 when the molar ratio aluminium(III):gluconic acid is 1:1. The $\Delta\delta$ values observed are positive or negative depending on the affected carbon (Table 2) and are directly proportional to the relative concentration of aluminium(III) added. This is understandable if it is assumed that the observed chemical shifts are a weighted average of those corresponding to the complexes and unbound gluconic acid in equilibrium.

The ^{13}C line broadening for certain carbons could in principle be due to the presence of small amounts of paramagnetic iron(III) in the aluminium(III) solution. Iron(III) complexes of gluconate in equilibrium with aluminium(III) complexes could contribute to the broadening. However, determination of the iron(III) content in the NMR aluminium solutions by atomic absorption spectroscopy revealed that the former ion was present in less than 1/40 000 with respect to aluminium(III), a concentration which is too low to produce observable chemical shift or width changes, as compared with those observed when gluconate was treated with known amounts of iron(III) ion.

Instead we ascribe the observed ^{13}C line broadening to the presence of chemical exchange between bound and free gluconate anion. Fig. 4(*a*) shows the spectrum corresponding to a solution where aluminium(III) and gluconate were dissolved in a 1:2 molar ratio at pH 4.7. The potentiometric results at this pH revealed the presence of two complexes $[AlH_{-1}L]^+$ and $[AlH_{-3}L]^-$, the former being predominant. Since four ^{13}C NMR signals are affected by both shift and line broadening in this case (C^1, C^2, C^3 and C^4), we are in fact observing the average result of the presence of both of these complexes in equilibrium. Calculation of the relative concentrations of all species in this medium shows that gluconate anion and $[AlH_{-1}L]^+$ are in approximately equimolar amounts (even after inclusion of polynuclear aluminium hydrolytic species). Therefore, carbons C^1 and C^2 may be said to correspond to an effective two-site exchange system with approximately equal site populations. In Fig. 4(*b*), on the other hand, a spectrum is shown for a mixture of aluminium(III) and gluconate at pH 10. None of the ^{13}C lines exhibits broadening, although the signals corresponding to C^{1-4} suffer significant chemical shift changes from those of the complex. The unequal concentrations of free and bound gluconic acid selected for the spectrum of Fig. 4(*b*) allowed us to assign the carbon resonances, since two separate sets of ^{13}C lines are observed, one belonging to gluconate itself and another (with lower intensity) due to the gluconate bound to aluminium(III). This means that the spectrum is in the slow-exchange regime on the NMR time-scale, consistent with the drift in pH which was detected during the potentiometric measurements. This also excludes the possibility that the broadening observed at acidic pH is due to the presence of paramagnetic impurities. Furthermore, the chemical shifts registered for the complex in this case are consistent with the population averages observed at pH 4.7 (see Table 2), since the exchange-broadened lines of Fig. 4(*a*) lie approximately midway between the extremes shown in Fig. 4(*b*). If W is the width at half-height of lines which are above the coalescence point and $\Delta\nu$ is the difference in frequency between the ^{13}C signals at two equally populated chemical sites [$\Delta\nu$ can be

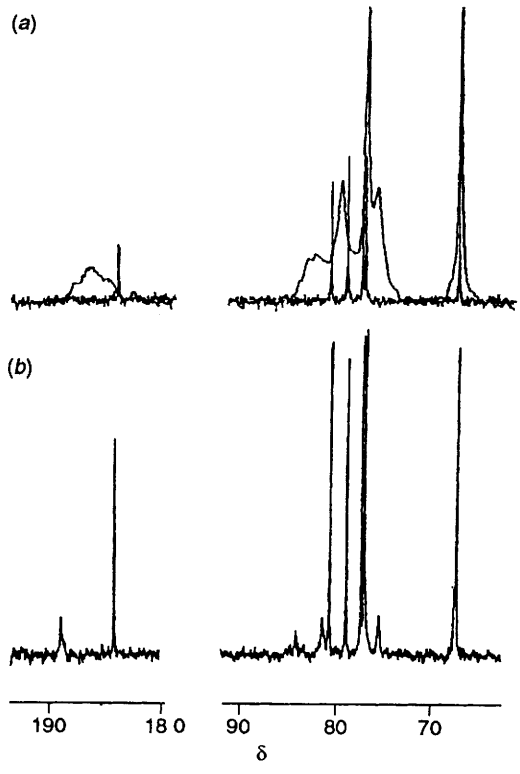

Fig. 4 (*a*) Superimposed ^{13}C NMR spectra of water solutions containing D-gluconic acid alone and a mixture of 0.1 mol dm^3 aluminium(III) and 0.2 mol dm^{-3} D-gluconic acid. In both cases the pH was 4.7. (*b*) The ^{13}C NMR spectrum of a water solution containing 0.04 mol dm^{-3} aluminium(III) and 0.4 mol dm^{-3} D-gluconic acid at pH 10

Table 2 Carbon-13 NMR chemical shifts for the metal complexes with D-gluconic acid in water solution at different pH [a]

Carbon	D-Gluconic acid [b]	Al^{III}		Ga^{III}		In^{III}
		pH 4.7 [c]	10 [d]	4.7 [e]	10 [f]	4.7 [e]
1	184.5	(187.3)	189.3	(185.7)	(185.9)	(184.9)
2	80.1	(82.0)	83.1	(80.6)	(80.8)	(80.0)
3	77.0	(76.4)	75.7	(76.7)	(76.8)	(77.0)
4	78.6	(79.5)	80.8	(79.2)	(79.3)	(78.6)
5	77.3	77.3	77.0	77.3	77.3	77.3
6	68.7	69.0	68.9	68.9	68.9	68.7

[a] Values in parentheses are for broad signals. [b] This work, pH 4.7. [c] Metal:gluconic acid molar ratio 1:2; $c_M = 0.1$, $c_L = 0.2$ mol dm^{-3}. [d] Metal:gluconic acid ratio 1:10; $c_M = 0.04$, $c_L = 0.4$ mol dm^{-3}. In this case no broadening was detected, but significant chemical shift changes were observed for C^{1-4}. [e] Metal:gluconic acid molar ratio 1:2; $c_M = 0.14$, $c_L = 0.28$ mol dm^{-3}. [f] Metal:gluconic acid molar ratio 1:5; $c_M = 0.08$, $c_L = 0.4$ mol dm^{-3}.

obtained from Fig. 4(*b*)], the pseudo-first-order rate constant is given by equation (4).

$$k = (\pi\Delta\nu/2)[(\Delta\nu/W)^2 - (W/\Delta\nu)^2 + 2]^{\frac{1}{2}} \qquad (4)$$

Applying equation (4) to the exchange-broadened ^{13}C NMR lines assigned to C^1 and C^2 appearing in Fig. 4(*a*), the values of $k = 420$ and 390 s^{-1} respectively are obtained. Their similarity lends support to the idea that the observed broadening is indeed due to exchange phenomena. Equation (4) can only be applied to the signals of C^1 and C^2 which were found (see above) to belong to an equally populated two-site exchange problem. Those for C^3 and C^4 correspond to an unequally populated system, since they are only affected in the minor complex $[AlH_{-3}L]^-$ at acid pH. One could anticipate that these latter lines would suffer a correspondingly smaller broadening, as is indeed observed [Fig. 4(*a*)]. Therefore, the changes in the ^{13}C NMR spectrum of gluconate upon complexation strongly suggest that the sites involved in the most deprotonated aluminium(III)–gluconate complex ($[AlH_{-3}L]^-$) are C^{1-4} at both pH 4.7 and 10, and that the line broadening observed in the resonances of these carbons at pH 4.7 is due to chemical exchange between bound and free gluconate.

In the case of lactobionic acid, the exchange broadening observed upon addition of small amounts of aluminium(III) ion at pH 4.7 allows one to establish that the affected carbons in the $[AlH_{-3}L]^-$ complex are C^{1-4} and C^6. In this case no significant changes were observed in the chemical shifts of the affected carbons. Since C^4 does not bear a hydroxyl group in this case, its interaction with aluminium(III) might take place through the oxygen lone pair of electrons. Indeed, the use of molecular models reveals that in a complex of lactobionic acid with aluminium(III) in which the OH groups at C^{1-3} and C^6 participate, the oxygen bonded to C^4 is forced to lie spatially close to the metal centre. At pH 10, on the other hand, the affected carbons are C^{1-3}, C^5 and C^6. This would indicate that the oxygen bonded to C^5 participates through its lone pair of electrons in the $[AlH_{-3}L]^-$ complex, where now C^4 is far from the metal centre, and is therefore not affected in its linewidth. A further possibility is that $[AlH_{-4}L]^{2-}$ is formed (where the fourth non-carboxylic proton is lost from C^5–OH), although the highly alkaline region was not studied potentiometrically (see above).

The overall results are in agreement with the potentiometric measurements in the investigated range, which show that three non-carboxylic protons are released from the ligands, despite the different concentrations used in the two methods. This suggests that at high concentrations a similar speciation pattern is obtained as compared to diluted solutions. As has been previously shown during an investigation of several hydroxy carboxylic acids as ligands, aluminium(III) does not have a tendency to form hydroxochelates as the pH is increased, but is able to displace protons from the OH groups of the ligand.[12] This behaviour has also been observed in the present work. In the case of lactobionic acid as ligand, in which not only the possibility of binding to C^4–O is blocked but marked steric restrictions occur, aluminium(III) ion preferred to displace the proton from the OH at C^6 instead of that from a co-ordinated water molecule.

Aluminium gluconate and other related gluconates have been isolated in the crystalline state and their detailed structures will be studied shortly.[16] It would be interesting to study whether the '1,2,3,4' chelation is retained upon crystallization.

Gallium(III). The ^{13}C NMR spectra recorded for gallium(III) complexes of gluconate consist of single, averaged resonances at both pH values studied. Changes in chemical shifts are observed in certain resonances (Table 2), although they are smaller than with aluminium(III). This may be ascribed to the smaller ionic radius of Al^{3+} (0.50 Å) as compared to Ga^{3+} (0.62 Å): the former should be able to induce larger electronic changes in the bonded oxygens, which are transferred to the corresponding carbons.[17] Selective ^{13}C signal broadening was also observed in the presence of gallium(III) ion and thus on this basis the metal binding sites may be assigned. The carbons involved in the complex formation are C^{1-4}, suggesting the formation of five-membered chelate rings. It seems that ligands that form this type of ring bind gallium(III) much more effectively.[17] As shown in Fig. 2, the $[GaH_{-3}L]^-$ species begins to be detected at an acid pH, although its maximum concentration is observed in alkaline media. In the latter region the $[GaH_{-4}L]^{2-}$ complex is also detected. This means that in going to alkaline pH, gallium(III) ion binds to an extra OH from a co-ordinated water molecule. This conclusion is reached since at both pH 4.7 and 10, NMR spectroscopy suggests the participation of three hydroxyl groups from the sugar moiety, implying that the fourth proton displaced in forming $[GaH_{-4}L]^{2-}$ comes from water and not from gluconate, and that the complex can be represented as shown in Fig. 5. This result is not surprising since gallium(III) has a very strong tendency to form hydroxo complexes.[19]

When the ligand is lactobionic acid the affected carbons are also C^{1-4}, the latter involving the interaction with the oxygen lone pair of electrons. Again the stoichiometries for the most deprotonated complexes are $[GaH_{-3}L]^-$ and $[GaH_{-4}L]^{2-}$, meaning that one and two OH respectively from water bind to gallium(III).

Indium(III). The complexes of indium(III) with both D-gluconic and lactobionic acids were only studied by ^{13}C NMR spectroscopy at acid pH since $In(OH)_3$ precipitates in alkaline media. Potentiometric data indicate that only the $[MH_{-3}L]^-$ complex is present with both gluconic acids and that the stabilities are similar to those of the analogously constituted gallium(III) complexes. According to the NMR results, the carbons involved in forming the complexes are C^{1-4} in both cases. Lactobionic acid lacks a hydroxyl group at the C^4

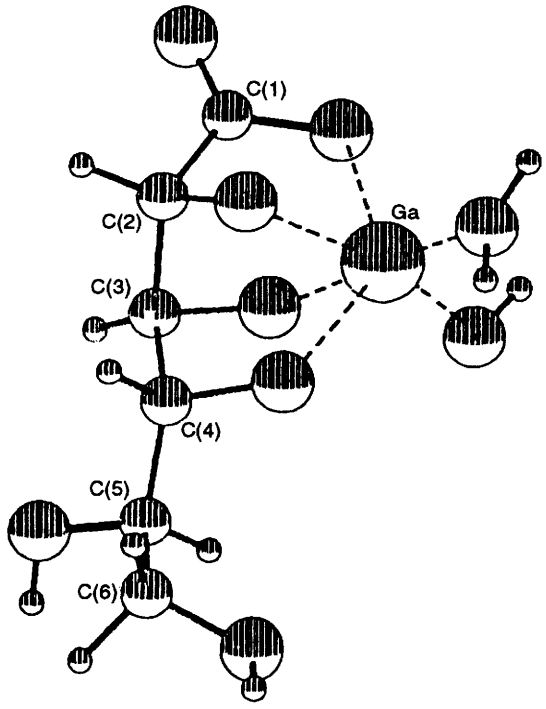

Fig. 5 Proposed structure for the $[GaH_{-4}L]^{2-}$ complex

position, implying that the fourth proton is removed from a co-ordinated water molecule, and that the oxygen at C^4 interacts with indium(III) through its lone pair of electrons. The indium(III) ion and its complexes have a lower hydrolytic tendency compared to gallium(III). However, indium(III) shows a similar tendency to form a hydroxo complex when the ligand is lactobionic acid, instead of replacing the blocked C^4–O position by another hydroxyl group of the sugar moiety. In comparison, iron(III) and aluminium(III) ions, with their smaller ionic radii, prefer binding to all possible OH groups of the ligand.

Conclusion

The stoichiometries of the complexes formed between the two sugars with trivalent metal ions of group III were similar to those found in the corresponding iron(III) systems. However, they are not as stable as the analogous iron(III) chelates, and a competition with the hydrolytic forms of the metals was verified at different pH. The larger iron(III) affinity relative to those of the other trivalent metal ions may be attributed to the greater covalent character of its bonds.[20]

Lactobionic acid forms metal chelates through co-ordination to its D-gluconic acid portion. As in the iron(III) system, the interaction of the presently studied hard metal ions with the disaccharide is lower, owing to the increased rigidity of the latter, with respect to D-gluconic acid.

It was found that gallium(III) and indium(III) have a significant tendency towards the displacement of protons from the hydroxyl groups of sugar acids. In contrast to aluminium, these metal ions also form hydroxo complexes due to the ionization of bonded water molecules. The determination of the equilibrium constants and the characterization of the gallium(III)– and indium(III)–sugar acid complexes represent the first examples for this type of chelate. The results obtained provide a reference for chemical procedures used to prepare effective chelating agents for these metals with appropriate donor groups.

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