Aluminium Carboxylates in Aqueous Solutions. Part 3.[1] Synthesis and Solution State of $[Al_2(cit)_2(H_2O)_6]$, $[Al_2(tart)_3(H_2O)_4]$ and $[Al(gluc)(OH)_2]$ (H_3cit = citric acid, H_2tart = tartaric acid, Hgluc = gluconic acid)

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The complexes $[Al_2(cit)_2(H_2O)_6]$ and $[Al_2(tart)_3(H_2O)_4]$ (H_3cit = citric acid, H_2tart = tartaric acid) have been prepared by controlled addition of the relevant α-hydroxycarboxylic acids to $Al(OH)_3$ while $[Al(gluc)(OH)_2]$ (Hgluc = gluconic acid) was obtained by stoichiometric addition of potassium gluconate to a solution of $[Al(H_2O)_6]^{3+}$. The solution state of these complexes was investigated by means of combined IR and ^1H NMR spectroscopies in D_2O, at room temperature. In all cases, solutions were analysed at autogenous (2.5–4.0) and at physiological pH values, with the aim of checking the *agreement* between the solution state as *predicted* from available thermodynamic data and the *real, toxicologically relevant,* state stemming from spectroscopic observations. The Al^{III}–citrate system is found to behave according to the thermodynamic expectations down to millimolar metal concentrations. On the contrary, the tartrate and gluconate systems do not agree with thermodynamic predictions, albeit differently, at 0.1 and 0.3 mol dm^{-3} analytical concentrations.

In Part 2 of this series [1] we elucidated the solution state of Al^{III} in the presence of lactate at physiological pH values. Aluminium lactate, $Al(lact)_3$, is a chemical widely employed in toxicological experimentation [2] both *in vivo* and *in vitro*. The primary reason for its wide use is that it gives rise to metastable solutions at pH 7.5, down to millimolar analytical concentrations. Under these conditions, metastable aqua–hydroxo complexes including $[Al(OH)_3(H_2O)_3]$ appear to be the predominant species so that they turn out to be the actual form of Al^{III} when administered to animals or to cell cultures in toxicological work based on $Al(lact)_3$.

Chemicals referred to as aluminium citrate, tartrate and gluconate have also been employed in experimental pathology investigations [3] and their actual molecular form (speciation of Al^{III}) at pH 7.5 is of major toxicological relevance.[2] Particularly interesting is the solution state of aluminium gluconate. It has been found that neutral solutions of aluminium gluconate (ill defined in terms of commercial source and synthetic origin [3c]), after intravenous injection to rats, shows exceptional bioavailability of Al^{III}, indeed much more so than aqueous aluminium lactate. Most remarkable is also a toxicological result obtained with neutral solutions of Al^{III} in the presence of tartrate which were reported to cause neurofibrillary tangles, after subcutaneous administration to rabbits, with intraneural accumulation of aluminium in the hyppocampus, without any evident neurologic effect.[3b] Moreover, neutral solutions of aluminium citrate have been recently found to be unable to produce biological effects *in vitro*.[4–6]

The expected metal speciation in aqueous α-hydroxycarboxylate solutions can be accurately predicted on the basis of literature data (see below) only up to pH 4–5. In neutral solutions, potentiometric measurements are extremely difficult (if even possible) owing to the intrinsic inertness of ligand release-exchange reactions in the co-ordination sphere of Al^{III}.[7] Therefore, the expected speciation profile at pH 7.5, based on thermodynamic predictions, will necessarily be an estimate.

A paramount example of this circumstance is illustrated for $Al(lact)_3$ in ref. 1, in which, although the expected non-existence of Al^{III}-co-ordinated lactate is confirmed by IR analysis and ^1H and ^{13}C NMR spectroscopy, the thermodynamically based expectation of quantitative precipitation of $Al(OH)_3$ at pH 7.5 is in fact belied by the kinetically controlled formation of very metastable soluble aqua–hydroxo species. On the contrary, the dominance of α-hydroxycarboxylate chelate complexes of the ligand glycolate (expected to exhibit hydrolytical stability comparable to that of the lactate analogues [1]) has recently been observed in the range pH 7–8 by means of ^{27}Al NMR spectroscopy.[8]

We report here the synthesis and IR characterization of the species $[Al_2(cit)_2(H_2O)_6]$ **1**, $[Al_2(tart)_3(H_2O)_4]$ **2** and $[Al(gluc)(OH)_2]$ **3** [H_3cit = citric acid (2-hydroxypropane-1,2,3-tricarboxylic acid), H_2tart = tartaric acid, Hgluc = gluconic acid]. The results of a combined IR–^1H NMR investigation on the solution state of these species in D_2O at room temperature is also described.

Experimental

Infrared spectra were recorded with a Perkin-Elmer 580 B spectrophotometer equipped with a Perkin-Elmer 3600 data station. NMR data were obtained with a Bruker AC 200 FT spectrometer. Spectra were recorded in D_2O. Proton chemical shifts are referenced to sodium 3-(trimethylsilyl)propanoate (internal reference).

Syntheses.—$[Al_2(cit)_2(H_2O)_6]$. A 0.2 mol dm^{-3} solution (50 cm^3) of $AlCl_3 \cdot 12H_2O$ (99%, Aldrich) was treated gradually with 20% aqueous ammonia up to pH 9.9, under stirring. Aluminium

Table 1 Analytical data on commercial (K & K) samples of aluminium lactate, citrate and tartrate

Compound	Analysis[a] (%) C	H	Al
Aluminium lactate	36.50 (36.70)	5.20 (5.10)	9.3 (9.3)
Aluminium citrate	16.85,[b]	2.30,[b]	3.7,[b] 4.1[c]
	19.95[c] (33.30)	2.75[c] (2.30)	(12.50)
Aluminium tartrate	23.50,[b]	3.90,	7.1,[b]
	24.70[c] (28.90)	4.00[c] (2.40)	7.7[c] (10.80)

[a] Required values for $Al(lact)_3$, Al(cit) and $Al_2(tart)_3$ given in parentheses. [b] As received. [c] After filtration and liophilization.

hydroxide was separated upon centrifugation, resuspended in water (50 cm^3) and after washing, centrifuged. This operation was repeated four times and then the $Al(OH)_3$ was resuspended in an aqueous solution (100 cm^3) of citric acid (99.8%, Baker analysed reagent) (1.87 g, 9.7 mmol). No visual change was observed. The suspension was then heated at 90 °C for 24 h to give a slightly turbid solution, which was filtered through a millipore membrane (0.22 μm). The resulting solution was rotary evaporated at 40 °C to a final volume of 5–7 cm^3. The product was obtained by liophilization (2.54 g, 95% yield) (Found: C, 26.50; H, 4.20; Al, 9.4. Calc. for $C_{12}H_{22}Al_2O_{20}$: C, 26.65; H, 4.10; Al, 10.0%).

$[Al_2(tart)_3(H_2O)_4]$. The procedure employed was identical to that described above. Aluminium hydroxide (10 mmol) was treated with L-(+)tartaric acid (99.5%, Prolabo) (2.23 g, 14.8 mmol) and 2.55 g of product was obtained (85% yield) (Found: C, 25.95; H, 3.95; Al, 9.4. Calc. for $C_{12}H_{20}Al_2O_{22}$: C, 25.25; H, 3.55; Al, 9.45%).

$[Al(gluc)(OH)_2]$. The procedure was adapted from a recipe reported in the patent literature.[9] Potassium gluconate (98%, Merck) (4.4 g, 18.8 mmol) was dissolved in water (20 cm^3), previously acidified with concentrated HCl (37%) (1.5 cm^3). After addition of aluminium trispropan-2-olate (98%, Merck) (3.8 g, 18.6 mmol), the solution was heated at 60 °C for 3 h. After cooling to room temperature, **3** was obtained as a white powder after gradual addition of acetone (20 cm^3). After filtration, the crude product was redissolved in water and reprecipitated with ethanol (4.21 g, 93% yield) (Found: C, 27.05; H, 4.90; Al, 10.7. Calc. for $C_6H_{13}AlO_9$: C, 28.15; H, 5.10; Al, 10.55%).

Results

Evaluation of Commercial Aluminium Lactate, 'Aluminium Citrate' and 'Aluminium Tartrate'.—The commercial (K & K) products were analysed for C, H and Al and the relevant data are collected in Table 1.

The complex $Al(lact)_3$ appears to be a well defined and pure chemical. 'Aluminium citrate' and 'aluminium tartrate' however do not meet purity requisites. 'Aluminium citrate' is a white amorphous powder, which gives rise to turbid solutions, in the 1×10^{-3}–1.0 mol dm^{-3} analytical concentration range. Filtration, followed by liophilization, leads to water soluble materials, but again giving elemental analyses (Table 1) which we could not rationalize. 'Aluminium tartrate' is a white material in which an amorphous component is intimately mixed with a microcrystalline one. The behaviour of this material is similar to that of 'aluminium citrate' but, in this case, filtration followed by liophilization gives analytical results not far from those expected for $[Al_2(tart)_3(H_2O)_4]$.

In spite of the very poor analytical quality of commercial 'aluminium citrate' and of the poor quality of 'aluminium tartrate', the IR spectra of the materials do contain features which resemble those of the properly prepared and characterized samples of $[Al_2(citr)_2(H_2O)_6]$ and of $[Al_2(tart)_3(H_2O)_4]$ described here. Therefore, they are likely to be mixtures of authentic α-hydroxycarboxylate complexes and, possibly, $Al(OH)_3$.

Synthesis and IR Characterization of $[Al_2(cit)_2(H_2O)_6]$ **1**, $[Al_2(tart)_3(H_2O)_4]$ **2** *and* $[Al(gluc)(OH)_2]$ **3**.—Complexes **1** and **2** were obtained upon addition of the stoichiometric amount of the relevant acid to a hot suspension of freshly prepared $Al(OH)_3$. Both **1** and **2** are very soluble complexes and their formation is indicated by the gradual complete solubilization of $Al(OH)_3$. Careful operations make it possible to obtain directly analytically pure products, simply upon solvent removal under vacuum.

The complex $[Al_2(cit)_2(H_2O)_6]$ is obtained as a microcrystalline powder, the IR spectrum of which exhibits two strong ν(CO) bands at 1627 and 1398 cm^{-1} [$\Delta\tilde{\nu}$(CO) = 229 cm^{-1}]. A very intense composite O–H band is seen in the range 2500–3700 cm^{-1}. A simple comparison of the IR spectrum of **1** with those of $Al(OH)_3$ and citric acid reveals that the crude sample is not appreciably contaminated by the reagents. The $\Delta\tilde{\nu}$(CO) value strongly suggests[10] that the ligand co-ordination is ester-like (forming a hydroxyl–carboxylate chelate) just as is the case for $Al(lact)_3$.[11] The analytical and spectral data are in accord with a structure in which two tricarboxylate citrate ligands are joined to two $\{Al(H_2O)\}$ units. It is pertinent to mention here that a trinuclear anionic citrate complex, $[Al_3(H_{-1}cit)_3(OH)(H_2O)]^{4-}$, has been recently isolated and fully characterized including by X-ray single-crystal analysis.[12]

The complex $[Al_2(tart)_3(H_2O)_4]$ was also obtained as a white microcrystalline powder and its IR spectrum displays ν(CO) bands at 1680 and 1385 cm^{-1} [$\Delta\tilde{\nu}$(CO) = 305 cm^{-1}], again in agreement with an ester-like bonding mode as observed in $Al(lact)_3$. A very strong and composite ν(OH) band dominates the spectrum in the range 2700–3700 cm^{-1}. The analytical and spectral data point to a dimeric structure in which one dicarboxylate tetradentate ligand is attached to two $\{Al(tart)(H_2O)\}$ units in which tartrate is tridentate.

The complex $[Al(gluc)(OH)_2]$ was obtained by means of a less straightforward procedure and is precipitated as a microcrystalline powder, upon addition of acetone or ethanol. The IR spectrum of **3** exhibits ν(CO) bands at 1650 and 1390 cm^{-1} [$\Delta\tilde{\nu}$(CO) = 260 cm^{-1}]. Both ν(CO) and $\Delta\tilde{\nu}$(CO) values are close to those observed for $Al(lact)_3$ (1613, 1403, 210 cm^{-1}) thus suggesting a quite similar ligating mode. Chemical intuition, elemental analysis and the IR spectrum for **3** suggest a structure in which the $\{Al(OH)_2\}$ unit is connected to the ligand *via* the carboxylic ester-like function and by the α, γ and ε hydroxy groups.

The Solution State of Complexes **1**–**3** *at Autogenous (Acidic) pH and at* pH 7.5.—The solution state of Al^{III} in the presence of citrate has been a matter of debate.[13,14] The data utilized for obtaining Fig. 1 have been taken from ref. 13, which reports potentiometric work performed under ordinary (*i.e.* acidic) and difficult conditions (see below), *i.e.* in almost neutral solutions. The main prediction based on Fig. 1 is the dominance at pH 7.5 of the species $[Al_3(H_{-1}cit)_3(OH)]^{4-}$ down to *ca.* 10^{-4} mol dm^{-3} analytical concentration.

The IR spectrum of a 0.1 mol dm^{-3} solution of **1** in D_2O at autogenous (*ca.* 4) and neutral (7.5) pH values furnish interesting observations. At pH 4.0 no free carboxylate function is observed [$\tilde{\nu}$(CO) = 1590 cm^{-1}] and the major ν(CO) band (1620 cm^{-1}), evidently due to ester-like co-ordinated $-C(O)O^-$ functions [$\Delta\tilde{\nu}$(CO) = 210 cm^{-1}], is accompanied by distinct shoulders, of which that at *ca.* 1710 cm^{-1} is attributable to unco-ordinated C(O)OH groups.

In neutral solutions [Fig. 2(*b*)], the above mentioned shoulders disappear and the major ν(CO) band appears as a doublet at $\tilde{\nu}$(CO) = 1620 [Al-co-ordinated $-C(O)O^-$] and 1590 cm^{-1} [unco-ordinated $-C(O)O^-$]. The IR data at pH 7.5 strongly suggest the predominance of species in which both Al^{III}-co-ordinated and free carboxylate functions are simultaneously present within the metal co-ordination sphere.

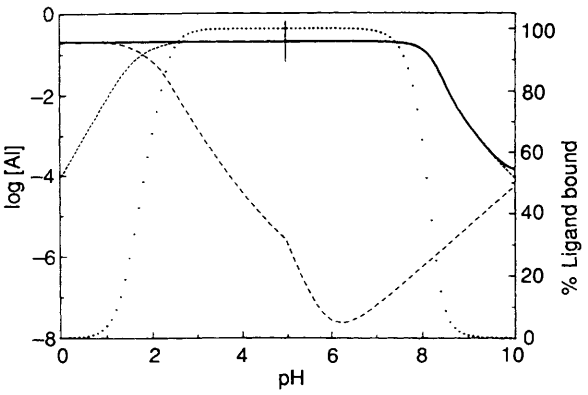

Fig. 1 Distribution diagram for a 0.1 mol dm^{-3} solution of $[Al_2(cit)_2(H_2O)_6]$; $log[Al^{III}]_{tot}$ (——), $log[Al^{III}]_{inorg}$ {sum of $[Al(H_2O)_6^{3+}]$, $[Al(OH)^{2+}]$, $[Al(OH)_2^{+}]$, $[Al(OH)_3]$, $[Al(OH)_4^{-}]$, $[Al_3(OH)_4^{5+}]$ and $[Al_{13}(OH)_{32}^{7+}]$} (— — —), $log[Al^{III}]_{org}$ {sum of $[(Al(Hcit)^{+}]$, $[Al(cit)]$, $[Al(cit)_2^{3-}]$, $[Al_3(OH)(H_{-1}cit)_3^{4-}]$, $[Al(H_{-1}cit)^{-}]$, $[Al(OH)(H_{-1}cit)^{2-}]$ and $[Al_3(OH)_4(H_{-1}cit)_3^{7-}]$} (— · — ·) and fraction of bound ligand (· · · ·)

The ^1H NMR spectrum of a 0.1 mol dm^{-3} solution of **1** in D_2O at pH 4 is remarkably complex but it can be viewed as due to the partial merging of two AB multiplets, centred[15] at δ = 3.00, 2.83 (AB_1) (J = 16.0 Hz) and 2.85, 2.72 (J = 17.8 Hz) (AB_2) respectively. The pattern given by a 0.1 mol dm^{-3} solution of free citrate is in accord with the presence of two diastereotopic[16] CH_2 groups giving rise to an AB pseudo-quartet (δ 2.567 and 2.537, J = 15.2 Hz). At pH 7.5, the spectrum of **1** appears to be related to that observed at pH 4.0 and multiplets AB_1 and AB_2 are now centred at δ 2.46, 2.61 (J = 17.0 Hz) and 2.51, 2.63 (J = 14.8 Hz) respectively. Moreover, a weak third AB_3 multiplet is now observed[15] at δ 2.61 and 2.79 (J = 24.4 Hz). This complex pattern suggests the predominance at pH 7.5 of either a single aluminium(III)–citrate complex, in which two electronically different citrate ligands are present (see IR data) or of two major, structurally different, aluminium(III) complexes. This second possibility is in accord with data based on ^{13}C NMR measurements performed on *in situ* generated aluminium(III)–citrate complexes in slightly acidic solutions.[17] It is worth pointing out that, at 10^{-3} mol dm^{-3} analytical concentration and pH 7.5, the solution of **1** displays a ^1H NMR spectrum remarkably similar to that just described for a 0.1 mol dm^{-3} solution (unchanged δ values, with the pseudo-quartet AB_3 quantitatively dominant with respect to the AB_1 and AB_2 multiplets). In terms of metal speciation at this biologically significant aluminium concentration,[7] it has to be underlined that no *free* citrate ligand is observed.

The solution state of Al^{III} in the presence of tartrate as a function of pH has been investigated by several authors both potentiometrically[14] and spectrometrically.[18] The distribution diagram (Fig. 3) is worked out from ref. 14(*a*) and it clearly shows that at pH 7.5, even at 0.2 mol dm^{-3} metal analytical concentration, practically all tartrate previously co-ordinated up to pH *ca.* 6 is expected to be unco-ordinated and extensive precipitation of $Al(OH)_3$ is foreseen. Lower analytical concentrations will make the stability window of tartrate complexes consequently narrower. The diagram of Fig. 3 refers to an initial tartrate:Al^{III} ratio of 1.5:1. As in all species identified in ref. 14(*b*) the corresponding ratio is 1:1, some 65% of the ligand is predicted to be unbound even in the range of maximal stability of the complexed forms (pH 2–6).

Complex **2** dissolves readily in water and 0.1 mol dm^{-3} solutions are found to be quite stable both at autogenous (*ca.* 2.0) and neutral (*ca.* 7.5) pH values. The IR spectrum at autogenous pH is depicted in Fig. 2(*c*). The strong $\nu(CO)_{asym}$ band (1670 cm^{-1}) displays two evident shoulders at 1720 and *ca.* 1600 cm^{-1}. The 1670 cm^{-1} band is again attributable to an ester-

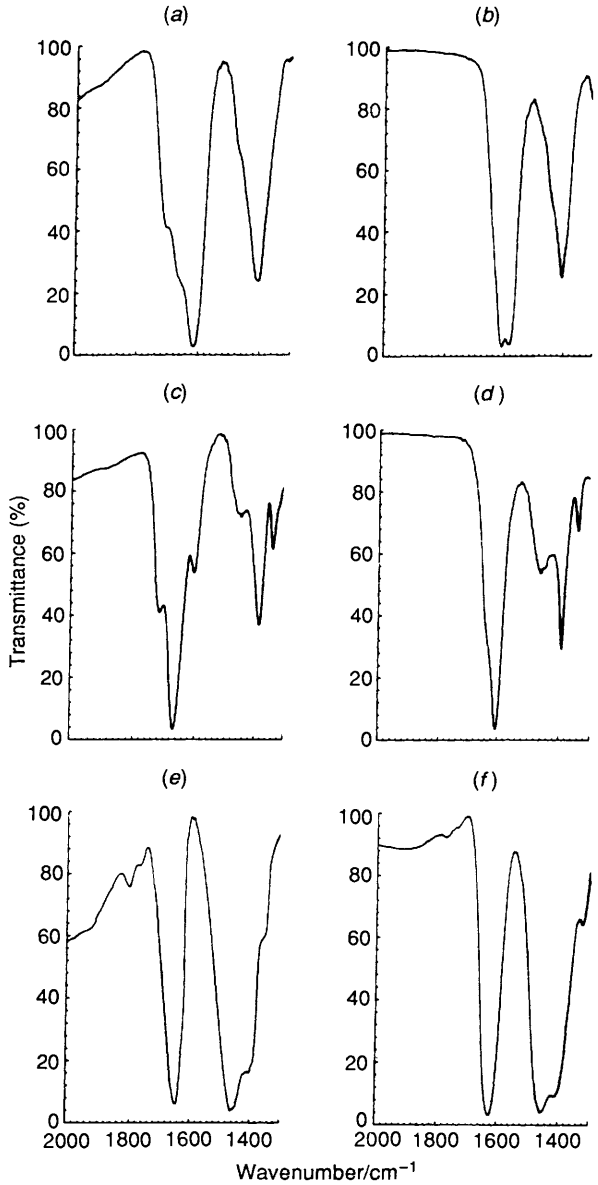

Fig. 2 IR spectra of 0.1 mol dm^{-3} solutions of $[Al_2(cit)_2(H_2O)_6]$ [(*a*), (*b*)], $[Al_2(tart)_3(H_2O)_4]$ [(*c*), (*d*)] and $[Al(gluc)(OH)_2]$ [(*e*), (*f*)] in D_2O at autogenous [(*a*), (*c*), (*e*)] and neutral pH values [(*b*), (*d*), (*f*)] at room temperature. Cell path length = 0.01 cm

like Al^{III}–carboxylate ligating mode [$\Delta\tilde{\nu}(CO)$ = 285 cm^{-1}], the weaker one at 1720 cm^{-1} to free carboxylic functions and that at *ca.* 1600 cm^{-1} to free carboxylate groups. This pattern agrees with the dominance at autogenous pH of an α-hydroxycarboxylate complex, possibly $[Al_2(H_{-1}tart)_2]$, according to ref. 14(*b*).

At pH 7.5 the former absorption at *ca.* 1600 cm^{-1} appears as a well defined band, while the previous peak at 1670 cm^{-1} appears now as a weak shoulder of this major band. This pattern reveals that most of the tartrate is no longer co-ordinated at pH 7.5 and only a small fraction (shoulder at *ca.* 1640 cm^{-1}) of the α-hydroxycarboxylate appears to be co-ordinated to the metal, possibly as $[Al_2(H_{-2}tart)_2]^{2-}$ [ref. 14(*b*)]. The major piece of information obtained from the IR data is the substantial release of tartrate ligand from the metal co-ordination sphere at pH 7.5, in agreement with the prediction from Fig. 3; this release is however *not* accompanied by any concomitant precipitation of $Al(OH)_3$, just as observed in the case of $Al(lact)_3$.[1]

The ^1H NMR data of this solution provides complementary information. Free tartrate exhibits a peak at δ 4.320 due to the two equivalent methylene groups. At pH 2.5 two distinct sharp

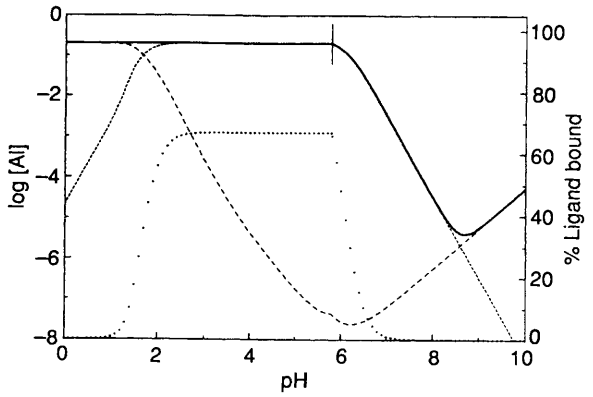

Fig. 3 Distribution diagram for a 0.1 mol dm^{-3} solution of $[Al_2(tart)_3(H_2O)_4]$; $log[Al^{III}]_{tot}$ (——), $log[Al^{III}]_{inorg}$ {sum of $[Al(H_2O)_6^{3+}]$, $[Al(OH)^{2+}]$, $[Al(OH)_2^{+}]$, $[Al(OH)_3]$, $[Al(OH)_4^{-}]$, $[Al_3(OH)_4^{5+}]$ and $[Al_{13}(OH)_{32}^{7+}]$} (— — —), $log[Al^{III}]_{org}$ {sum of $[Al(tart)^{+}]$, $[Al_2(H_{-1}tart)(tart)^{+}]$, $[Al_2(H_{-1}tart)_2]$, $[Al_2(H_{-1}tart)(H_{-2}tart^{-})]$ and $[Al_2(H_{-2}tart)_2^{2-}]$} (— — —), and fraction of bound ligand (· · · ·)

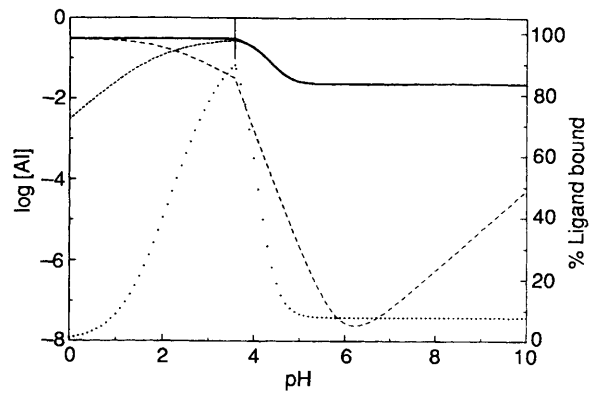

Fig. 4 Distribution diagram for a 0.3 mol dm^{-3} solution of $[Al(gluc)(OH)_2]$; $log[Al^{III}]_{tot}$ (——), $log[Al^{III}]_{inorg}$ {sum of $[Al(H_2O)_6^{3+}]$, $[Al(OH)^{2+}]$, $[Al(OH)_2^{+}]$, $[Al(OH)_3]$, $[Al(OH)_4^{-}]$, $[Al_3(OH)_4^{5+}]$ and $[Al_{13}(OH)_{32}^{7+}]$} (— — —), $log[Al^{III}]_{org}$ {sum of $[Al(gluc)^{2+}]$, $[Al(H_{-1}gluc)^{+}]$ and $[Al(H_{-3}gluc)^{-}]$} (— — —), and fraction of bound ligand (· · · ·)

peaks at δ 4.788 and 4.698 are detected, which might correspond to two different, not mutually exchanging, tartrate complexes. At pH 7.5, these two peaks disappear completely from the spectrum and a sharp singlet at δ 4.388 (free tartrate) is now flanked by an array of minor peaks in the range δ 4.0–4.5 Although this pattern is certainly unclear, it can be concluded that a significant percentage of tartrate is no longer co-ordinated to Al^{III}. In this connection it is of note that a multinuclear magnetic resonance study of the co-ordination of Al^{III} with tartrate[18] has supported the existence of *in situ* prepared α-hydroxyl–carboxylate chelate species at pH *ca.* 8.

Complex **3** gives rise to stable 0.3 mol dm^{-3} solutions in D_2O at pH 4.0. The solution state of Al^{III} in the presence of gluconate was investigated potentiometrically by Motekaitis and Martell[14a] up to pH 5 and a distribution diagram worked out from their data is depicted in Fig. 4. At pH higher than 5, precipitation of $Al(OH)_3$ was observed (they did not start from an Al^{III}–gluconate species, but instead prepared Al^{III} species *in situ* upon mixing Al^{III} and gluconate).

In our study, 0.3 mol dm^{-3} solutions of **3** appear to be stable for months, after adjustment of the pH from the autogenous value (4) to 7.5.

In contrast with our findings, Fig. 4 reveals that the thermodynamic prediction (data worked out from ref. 13) forecasts extensive decomposition of $[Al(H_{-3}gluc)(H_2O)]^{-}$ at pH 7.5 to give mainly solid $Al(OH)_3$. Apparently kinetic restrictions are particularly effective in this case and no precipitation is observed. The IR spectra [Fig. 2(*e*)] of 0.3 mol dm^{-3} solutions of **3** (pH 4.0) exhibit a strong fairly symmetric $\nu(CO)_{asym}$ band at 1670 cm^{-1} due to metal-co-ordinated gluconate with a $\Delta\tilde{\nu}(CO) = 230$ cm^{-1} [*cf.* 265 cm^{-1} for $Al(lact)_3$[1]], changing to 1635 cm^{-1} upon neutralization [Fig. 2(*f*)]. Most remarkably, this band turns out to be quite distinct from the $\nu(CO)_{asym}$ band of the unco-ordinated ligand [$\tilde{\nu}(CO) = 1597$ cm^{-1}]. Infrared data reveal therefore the dominance of a metastable Al^{III}–gluconate complex at pH 7.5 without any detectable release of gluconate.

The ^1H NMR spectrum of a 0.3 mol dm^{-3} solution at pH 4 displays a complex pattern [Fig. 5(*b*)] with two multiplets at δ 4.38 and 4.17 and a complex multiplet centred at δ *ca.* 3.78. After adjustment to pH 7.5, the spectrum [Fig. 5(*c*)] exhibits substantial changes; in particular, a doublet at δ 4.13 and a rather broad singlet at δ 4.03 replace the two multiplets seen at pH 4.0 at δ 4.38 and 4.17. Moreover, although the complex multiplet is still centred at δ 3.77, its detailed structure appears quite changed. The ^1H NMR spectrum of free gluconate at pH *ca.* 7.5 is depicted in Fig. 5(*a*) and it can be appreciated that the overall pattern turns out to be somewhat similar to those seen for solutions of **3** at pH 7.5. The major difference is the apparent better resolution observed for free gluconate in the range δ 4.0–4.5. It is apparent that the one-dimensional NMR analysis is unable to provide a reliable answer on the solution state of this system at pH 7.5. In fact, if we admit that, in line with the strong IR evidence, the gluconate is metal-co-ordinated in a fashion similar to that seen for solid $Al(lact)_3$,[10] *i.e.* with involvement only of the C(O)(O$^-$)–CH(OH)– portion of the ion, it can be safely predicted that the individual resonances of the C^{3-6}-bound hydrogen atoms will be hardly distinguishable from those of unco-ordinated gluconate. The only ^1H-affected resonance would be therefore that at C^2.

Discussion

A summary of the characteristics of the solution state of Al^{III} after dissolution of $Al(lact)_3$, $[Al_2(cit)_2(H_2O)_6]$, $[Al_2(tart)_3(H_2O)_4]$ and $[Al(gluc)(OH)_2]$ in water and neutralization at pH 7.5 is given in Table 2.

In contrast with the behaviour of $[Al_2(cit)_2(H_2O)_6]$, for which the predicted metal speciation in neutral solutions is substantially confirmed by spectroscopic data down to millimolar concentration levels, $Al(lact)_3$,[1] $[Al_2(tart)_3(H_2O)_4]$ and $[Al(gluc)(OH)_2]$ give rise to metastable solutions, after adjustment to pH 7.5. From these solutions the expected precipitation of $Al(OH)_3$ is delayed for several months, at least for analytical concentrations higher than *ca.* 1×10^{-3} mol dm^{-3}. In the case of $Al(lact)_3$ the major metastable (down to millimolar concentrations) species do not contain Al^{III}-co-ordinated lactate. In the case of $[Al(gluc)(OH)_2]$, the dominating metastable species does contain metal-co-ordinated gluconate, as clearly shown by IR spectroscopy and also indicated by NMR analysis.

Neutral solutions of $[Al_2(tart)_3(H_2O)_4]$ appear particularly complex and they are likely to contain both metastable aqua–hydroxo species and minor amounts of tartrate-containing complexes. Inspection of Fig. 3 reveals that this latter observation is in agreement with the thermodynamic predictions obtained from the relevant distribution diagram.

The behaviour of complex **3** is perhaps the most interesting in that both the visual observation and the spectral data contrast with thermodynamic expectations which predicts both full ligand dissociation and precipitation of $Al(OH)_3$ (Fig. 4). It is possible that the lack of ligand release is a consequence of a particular kinetic reluctance of the multidentate gluconate ligand to leave the metal co-ordination sphere.

This work has revealed two clear examples of disagreement between expectations based on distribution diagrams (normally obtained from measurements carried out at acidic pH values)

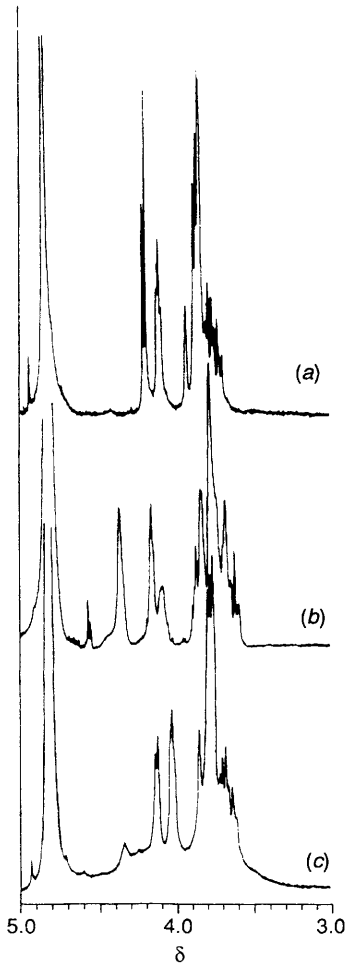

Fig. 5 Room-temperature 200 MHz ^1H NMR spectra of (*a*) free gluconate at pH *ca.* 7.5; (*b*) complex **3** at autogenous pH (4); and (*c*) complex **3** at pH 7.5 in D_2O

and the visual and spectrometric observations, at pH 7.5 [no precipitation of $Al(OH)_3$ for **2** and full retention of the co-ordinated ligand for **3**]. Moreover, this work and previous papers in this series have shed considerable light on the solid-state structure and the solution state at physiological pH values of four synthetic aluminium toxins, for which a massive toxicological documentation is available in the literature. Actually, the majority of these references do refer to aluminium α-hydroxycarboxylate complexes prepared *in situ* and some are likely to refer to solutions in which the metal speciation has been in fact ill defined. In view of the strong relevance of metal speciation in directing the biological effect of Al^{III},[2] the complete definition of the solution state of the metal in the presence of citrate, tartrate and gluconate will be of service to aluminium toxicologists. The availability of chemically well defined samples of $[Al_2(cit)_2(H_2O)_6]$, $[Al_2(tart)_3(H_2O)_4]$ and $[Al(gluc)(OH)_2]$ should be also appreciated for a better control of dose-response conditions in experimental aluminium pathology. We expect that two-dimensional ^1H NMR as well as further exploitation of IR spectroscopy will be useful for further clarification of the citrate and gluconate systems down to millimolar concentrations. In this connection, work is in progress in these laboratories.

Table 2 The solution state of various aluminium(III) α-hydroxycarboxylates at pH 7.5

Complex	Major species	Remarks
$Al(lact)_3$	Aqua and hydroxo complex(es)	Metastable down to a concentration of 1×10^{-3} mol dm^{-3}. Most of the ligand is unco-ordinated
$[Al_2(cit)_2(H_2O)_6]$	Aqua(?)–citrate complex(es)	IR evidence of both co-ordinated (mainly) and unco-ordinated carboxylate groups (0.1 mol dm^{-3}). No NMR evidence of free ligand down to a concentration of 1×10^{-3} mol dm^{-3}
$[Al_2(tart)_3(H_2O)_4]$	Aqua and hydroxo complex(es)	Metastable at 0.1 mol dm^{-3}. Most of the ligand is unco-ordinated
$[Al(gluc)(OH)_2]$	Aqua–, hydroxo–gluconate complex(es)	Metastable at 0.3 mol dm^{-3}. Only co-ordinated ligand is observed

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