Aluminium Carboxylates in Aqueous Solutions. Part 2.[1] Metal Speciation in the Al^{III}–Lactate–OH^-–H_2O System

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The tris(hydroxyl–carboxyl) chelated complex $Al(lact)_3$ (lact = lactate) dissolves in water to give stable acidic (pH *ca.* 3) solutions, in which free and metal-co-ordinated lactate ligands are detected by IR spectra in D_2O. Proton NMR spectra (90 MHz) reveal that ligand exchange between metal-bonded and free lactate ligands occurs, also at +4 °C. The separate resonances due to metal-bonded and free lactate are clearly detected at 400 MHz. When the pH of an $Al(lact)_3$ solution (analytical concentration 0.1 mol dm^{-3}) is adjusted to 7.5 with NaOD the resulting ^1H and ^{13}C NMR spectra are very similar to those exhibited by a 0.3 mol dm^{-3} Na(lact) solution. The IR spectrum of the 0.1 mol dm^{-3} aluminium(III) solution displays two major bands at 1585 and 1420 cm^{-1} due to the unco-ordinated lactate ligands. A 0.1 mol dm^{-3} neutralised solution is (meta)stable for months and the whole of the data at pH 7.5 can be interpreted in terms of the release of most of the lactate from the co-ordination sphere of Al^{III}, with concomitant formation of metastable species including possibly $[Al(OH)_3(H_2O)_3]$.

The toxicity of Al^{III} to aquatic biocenoses and to humans can be considered well established by numerous ecotoxicological[2] and clinical observations[3,4] and by extensive toxicological data both *in vivo* and *in vitro*.[5]

Pathological conditions have very often been induced experimentally by utilising aluminium(III) carboxylates, such as lactate, tartrate, citrate, *etc.*[6] Theoretical calculations based on known formation constants of the relevant carboxylate complexes lead to the expectation that such complexes should not exist as predominant species in solutions at physiological pH values, owing to the precipitation of $Al(OH)_3$. An example of this situation is offered by aluminium lactate, which has been used for many years in *in vivo* and *in vitro* toxicological work.[5] The basic reason for the popularity of aluminium lactate is due the fact that relatively concentrated (more than *ca.* 5×10^{-2} mol dm^{-3}) aqueous solutions of this chemical do not produce aluminium hydroxide when neutralised to physiological pH values. As it will be seen, precipitation takes place spontaneously only after months.

The aqueous solution chemistry of $Al(lact)_3$ (Hlact = lactic acid) has been investigated in recent years both by potentiometric techniques[7,8] and by ^{27}Al NMR spectrometry.[9] Marklund *et al.*[8] determined the stability constants of the species $[Al(lact)]^{2+}$, $[Al(lact)_2]^+$, $Al(lact)_3$, and $[Al(lact)(H_{-1}lact)]$ or $[Al(lact)_2(OH)]$, from measurements at pH < *ca.* 5; their data lead to the conclusions, that (*i*) the dominant species at autogenous pH are $[Al(lact)_2]^+$ and $[Al(lact)(H_{-1}lact)]$ and (*ii*) the trilactate species $Al(lact)_3$ is not expected to exist in appreciable concentrations at neutrality. On the contrary the authors of ref. 9 proposed the predominance of the complex $[Al(lact)_2(OH)(H_2O)]$ at pH 3–4 and of $Al(lact)_3$ at pH 7.5.

We have recently reported[1] an X-ray investigation on solid $Al(lact)_3$, which is found to exhibit a monomeric, relatively uncomplicated molecular structure with typical metal-to-ligand covalent bonds. In the present paper we report an investigation of the state of $Al(lact)_3$ in aqueous (D_2O) solutions at acidic and neutral pH values, based on ^1H and ^{13}C NMR and IR spectrophotometry.

Experimental

Chemicals.—Aluminium D-lactate (99%, Fluka), sodium D-lactate (98%, Fluka), deuterium oxide (98% in D, Aldrich), sodium deuteroxide solution (40%) in deuterium oxide (99% in D, Aldrich), D-lactic acid (99%, Prolabo), sodium 3-(trimethylsilyl)propionate (99% in D, Aldrich) and $KAl(SO_4)_2$ (99.5%, Carlo Erba).

Apparatus and Procedures.—Infrared spectra were obtained with a Perkin-Elmer 580 B spectrometer equipped with a Perkin-Elmer 3600 data station. Solid-phase spectra of $Al(lact)_3$ and Na(lact) were obtained from KBr pellets; CaF_2 cells (pathlength 0.01 cm) were used for solutions. The pH of the examined solutions were adjusted with standardised NaOD. Infrared spectra were recorded within *ca.* 30–60 min after pH adjustment; NMR analyses were carried out on the same solutions with a JEOL FX90Q and a Bruker AM400 NMR spectrometer. The solubility of $Al(lact)_3$ in water was determined by analysing a saturated solution for Al^{III} (quinolin-8-olate spectrophotometric method). The stability of aqueous solutions of $Al(lact)_3$ was estimated from the time required for the onset of a visually detectable turbidity due to $Al(OH)_3$ precipitation.

Results

Solubility and Apparent Stability of Aluminium Lactate in Water.—The solubility of $Al(lact)_3$ in water at 25 °C is 0.70 ± 0.01 mol dm^{-3}; the pH of the saturated solution is 2.9. A 0.4 mol dm^{-3} solution, neutralised to pH *ca.* 7, is stable (*i.e.* it appears clear to visual inspection) for months at room temperature. Solutions obtained by serial dilution of this solution down to 0.005 mol dm^{-3} are stable for approximately 2 weeks. On the other hand, solutions neutralised after dilution are stable for shorter periods, *i.e.* again about 2 weeks for 0.2 and 0.1 mol dm^{-3}, but about 1 week for 0.05 and 0.02 mol dm^{-3}, and less than 24 h for more dilute solutions.

Infrared Spectra in D_2O.—The spectrum of $Al(lact)_3$ (0.1 mol dm^{-3}) at autogenous pH in D_2O is depicted in Fig. 2 [$Al(lact)_3$ concentrations here and elsewhere in the text refer to the analytical concentrations of the metal complex]. In the spectral range 2000–1300 cm^{-1} two major bands can be observed at 1660

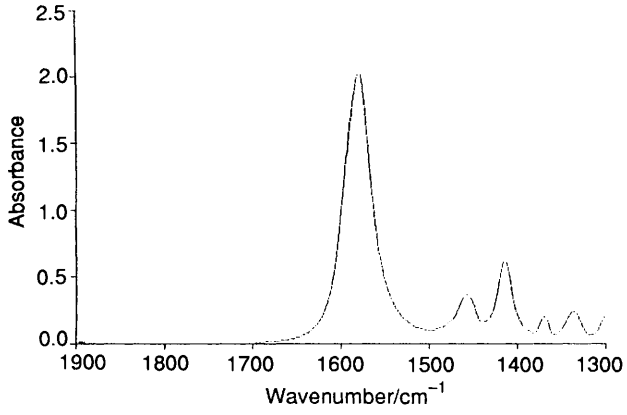

Fig. 1 Infrared spectrum of Na(lact) (0.3 mol dm^{-3} in D_2O, cell path = 0.01 cm), pH *ca.* 12

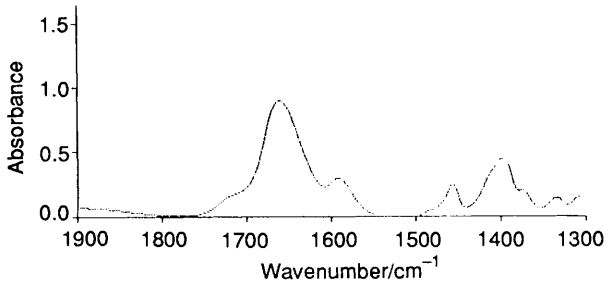

Fig. 2 Infrared spectrum of Al(lact)$_3$ (0.1 mol dm^{-3} in D_2O, cell path = 0.01 cm), pH 3.6 (autogenous)

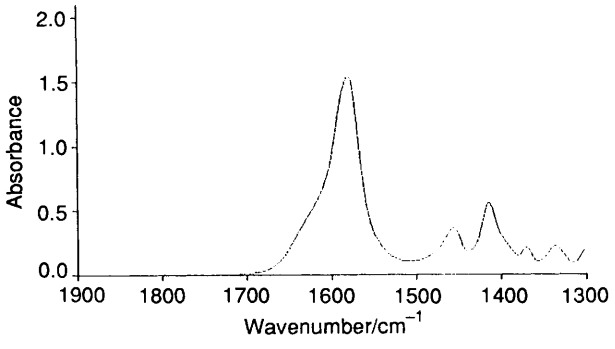

Fig. 3 Infrared spectrum of Al(lact)$_3$. Conditions as in Fig. 2 except pH adjusted to 7.5

and 1400 cm^{-1}. On the basis of the solid-state spectrum,[1] such bands are attributed to ν_{asym}(CO) and ν_{sym}(CO) respectively and they are interpreted[10] as due to the presence of chelate metallorganic rings, in which both the carboxylate and the hydroxyl donating sites are co-ordinated. The absorption at 1585 cm^{-1} is attributed to ν_{asym}(CO) of unco-ordinated lactate, as indicated by comparison with the spectrum of a 0.3 mol dm^{-3} solution of Na(lact) in D_2O (Fig. 1), while the shoulder at *ca.* 1725 cm^{-1} is due to lactic acid.

A rough quantitative estimate of the areas of individual peaks indicates that *ca.* 0.5 mol of lactate is released per mol of Al(lact)$_3$ (calculations based on data from ref. 8 predict the presence of *ca.* 0.7 mol of ligand per metal atom).

Upon gradual addition of NaOD solution, the pattern in Fig. 2 gradually changes to that in Fig. 3. Under these conditions, the band at 1585 cm^{-1} attributed to free lactate now dominates in the explored region and also the weaker ν_{sym}(CO) band due to free lactate at 1420 cm^{-1} becomes evident. The residual shoulder at *ca.* 1650 cm^{-1} can be interpreted as being due to about 0.5 mol of bound lactate per mol of aluminium.

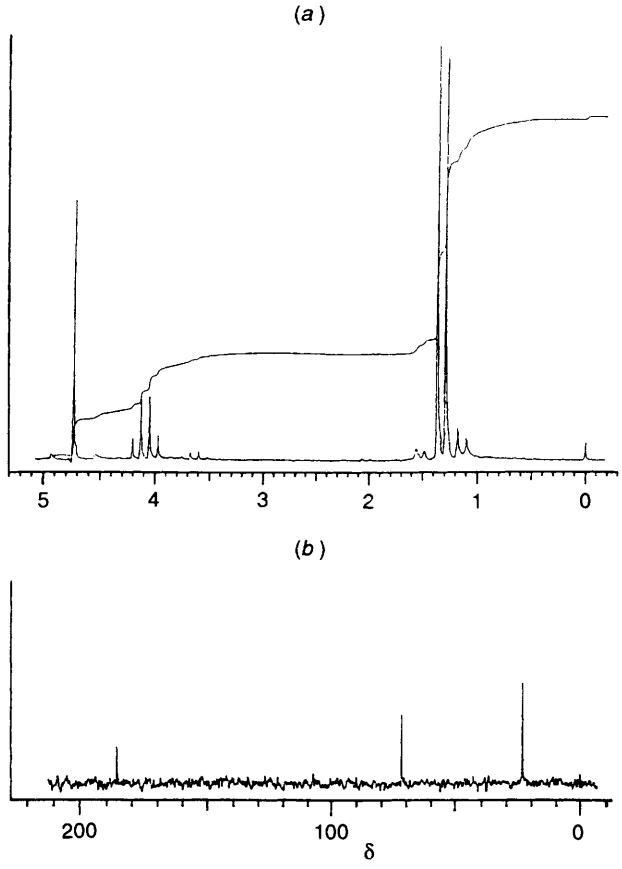

Fig. 4 Proton (*a*) and ^{13}C (*b*) NMR spectra of Na(lact) (0.3 mol dm^{-3}, pH 8, 27 °C)

NMR Spectra in D_2O.—Solutions of Al(lact)$_3$ and Na(lact) with concentrations identical to those employed for the IR analysis were investigated by ^1H and ^{13}C NMR spectrometry. The chemical shift data are collected in Table 1. The ^1H and ^{13}C NMR spectra (Fig. 4) of Na(lact) (pH 8.0, autogenous) are consistent with a structure of the ligand where the carboxylic group is fully deprotonated and with literature data[11] (the sharp peak at δ 4.77 ± 0.01 observed in all ^1H spectra is due to the quantitative formation of HDO resulting from rapid exchange of the lactate hydroxylic proton with the solvent).

Although the ^1H and ^{13}C NMR spectra of Al(lact)$_3$ at autogenous pH (3.6) (Fig. 5) are reminiscent of those of Na(lact), quite appreciable differences can be observed. In the ^1H spectrum the quartet due to the tertiary hydrogen atom appears as a broad singlet and the doublet due to CH_3 appears slightly broadened and shifted to lower fields (from δ 1.32 to 1.42) (the CH_3 resonance in lactic acid[11] falls at δ 1.5). A temperature increase to 50 °C produces a modest sharpening effect on this last resonance, whereas a temperature decrease to 5 °C modifies the spectrum as illustrated in Fig. 6. Particularly remarkable is the absorption due to CH_3, which appears as a pair of doublets in which two individual components accidentally overlap. The temperature effect is reversible.

The 400 MHz ^1H NMR spectrum of a 0.1 mol dm^{-3} solution of Al(lact)$_3$ at pH 3.6 at 4 °C makes it possible to separate the pair of merged doublets due to the CH_3 group (data in Table 1) of the free (δ 1.352) and Al^{III}-co-ordinated lactate ligand. The co-ordinated carboxylate appears as a major doublet at δ 1.395 and as a minor one at 1.450. In these spectra the methine group gives rise to a resolved quartet (δ 4.24) (free lactate) and to two partially overlapping broad singlets (δ *ca.* 4.53 and *ca.* 4.46) (Al^{III}-bound lactate). The ratio of the area of the unresolved band to that of the quartet is *ca.* 2:1. The presence of at least

Table 1 NMR data[a] for $Al(lact)_3$ and Na(lact) solutions

				$^1H(\delta)$		$^{13}C(\delta)$		
v/MHz	Compound	pH	T/°C	>CH	CH_3	CO_2	>CH	CH_3
90	Na(lact)	8.0	27	4.11 (q) (J = 7.0)	1.32 (d) (J = 7.0)	185.4	71.2	23.0
	$Al(lact)_3$	3.6	27	4.45 (s) (J = 7.0)	1.42 (d) (J = 7.1)	182.5	71.8	21.6
	$Al(lact)_3$	7.5	27	4.14 (q) (J = 7.0)	1.33 (d) (J = 7.0)	185.5	71.3	22.9
400	Na(lact)	8.0	4	4.116 (q)	1.331 (d)	—	—	—
	Na(lact)	3.5	4	4.273 (q)	1.375 (d)	—	—	—
	$Al(lact)_3$	3.6	4	4.243 (q)	1.352 (d)	—	—	—
				≈4.46[b]	1.395 (d)	—	—	—
				≈4.53[b]	1.450 (d)	—	—	—

[a] Internal standard for ^1H and ^{13}C: $Na(O_2CCH_2CH_2SiMe_3)$; J values in Hz. [b] Signals partially merged.

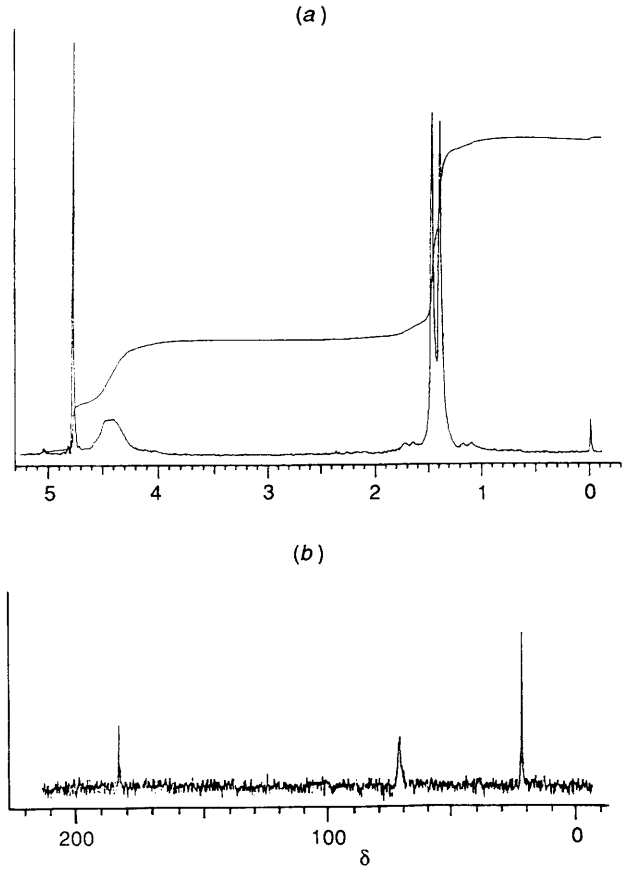

Fig. 5 Proton (*a*) and ^{13}C (*b*) NMR spectra of $Al(lact)_3$ (0.1 mol dm^{-3}, pH 3.6, 27 °C)

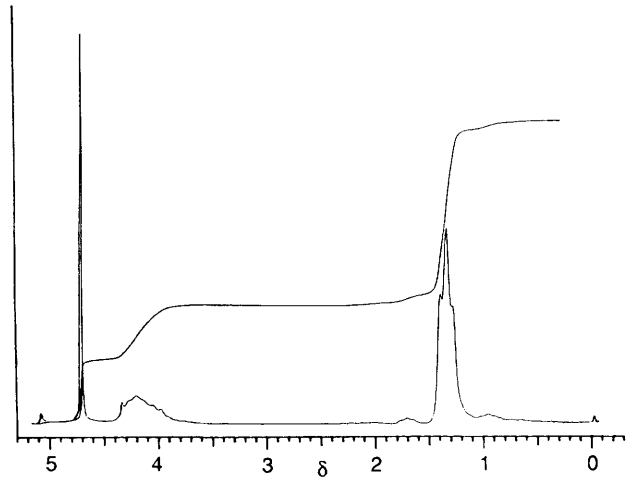

Fig. 6 Proton NMR spectrum of $Al(lact)_3$ (0.1 mol dm^{-3}, pH 3.6, 5 °C)

two lactate complexes is in agreement with the observation of two ^{27}Al NMR signals reported in ref. 9.

In neutralised $Al(lact)_3$ solution (Fig. 7), both ^1H and ^{13}C NMR spectra appear virtually identical to those of aqueous Na(lact), the only difference being in the less sharp appearance of the bands in the ^1H spectrum.

Discussion

The solution state of $Al(lact)_3$, as a function of pH, as predicted on thermodynamic grounds[8] is illustrated in Fig. 8. The contrast between the observed 'stability' of the aqueous solutions of $Al(lact)_3$ at pH 7.5 [*i.e.* lack of precipitation of $Al(OH)_3$] and the expected instability of the complex $Al(lact)_3$ at this pH value (see Fig. 8) can be explained both by (*i*) the existence, at neutrality, of other, yet unknown, co-ordination compounds under equilibrium conditions, and (*ii*) the survival of unstable species due to the occurrence of very effective kinetic factors. The latter kind of behaviour is not unexpected for aluminium(III) complexes under non-acidic conditions.[6]

The IR spectrum of $Al(lact)_3$ at pH 3.6 clearly shows the coexistence of free and metal-co-ordinated lactate, in agreement with the prediction based on the potentiometric results reported in ref. 8. Proton NMR data are also consistent with this solution state, if a rapid exchange between free and metal-co-ordinated lactate occurs. This interpretation is supported by the low-temperature spectrum at 90 MHz (Fig. 6) and is fully confirmed at 400 MHz.

The occurrence of ligand exchange explains also the broad singlet due to the CH group. Both the change of magnetic environment and the recurrent exposure of the methine carbon atom to the quadrupole field of ^{27}Al are expected to produce the observed broadening effect. This broad singlet appears partially resolved at 4 °C at 400 MHz in the quartet due to the free ligand and in the broad singlet attributable to the metal-co-ordinated carboxylate.

The assumption of ligand exchange at pH 3.6 is in agreement with the rapid attainment of complexation equilibria observed in potentiometric measurements.[8]

As to the molecular nature of the predominant species at pH 3.6, the observation of two different signals attributable to metal-co-ordinated ligand, coupled with the observed ratio of *ca.* 2:1 between bound and free lactate, is in accord with the presence of a mixture of $[Al(lact)_2(H_2O)_2]^+$ and $[Al(lact)_2(OH)(H_2O)]$ or/and $[Al(lact)(H_{-1}lact)(H_2O)_2]$ with possibly a smaller amount of $Al(lact)_3$. These species are those predicted to be present at pH *ca.* 3.5 (Fig. 8).

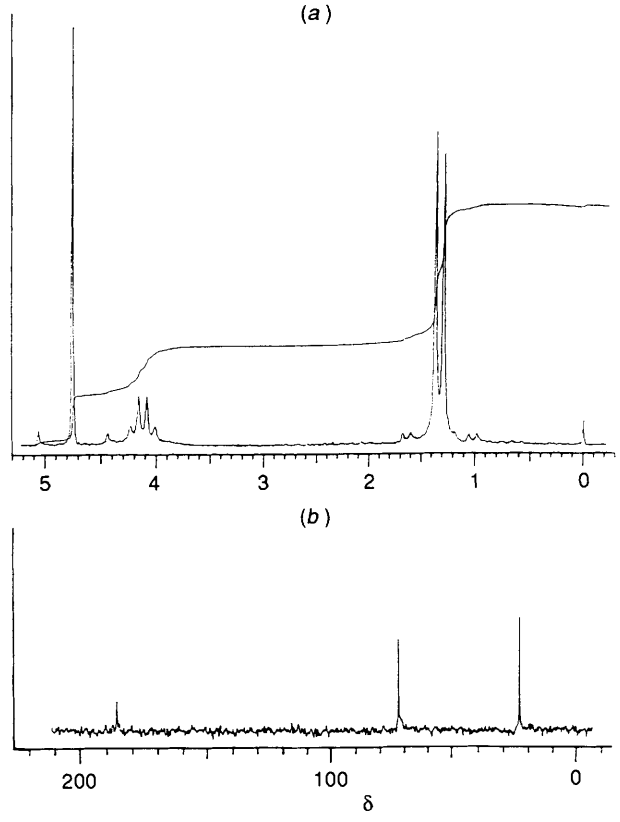

Fig. 7 Proton (*a*) and ^{13}C (*b*) NMR spectra of neutralised $Al(lact)_3$ (0.1 mol dm^{-3}, pH 7.5, 27 °C)

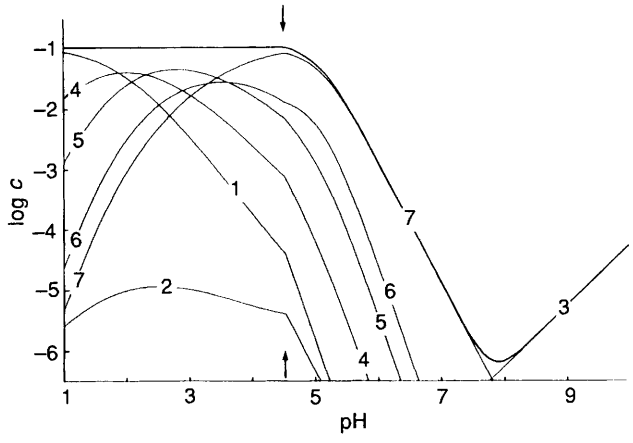

Fig. 8 Solution state of $Al(lact)_3$ in water as predicted from thermodynamic data.[8,12] The data refer to a constant ionic medium of 0.6 mol dm^{-3} NaCl at 25°C, and can be applied in the present context as a reasonable approximation. Species: 1, $[Al(H_2O)_6]^{3+}$; 2, $[Al(OH)(H_2O)_5]^{2+}$; 3, $[Al(OH)_4]^-$; 4, $[Al(lact)(H_2O)_4]^{2+}$; 5, $[Al(lact)_2(H_2O)_2]^+$; 6, $Al(lact)_3$; 7, $[Al(lact)(H_{-1}lact)(H_2O)_2]$ or $[Al(lact)_2(OH)(H_2O)]$. The vertical arrows mark the beginning of precipitation (pH *ca.* 4.5)

The potentiometric data from ref. 8 and literature thermodynamic data for aluminium hydrolysis (see, for example, Table 1 in ref. 12 and refs. therein) lead to the expectation that the only stable aluminium species at pH 7.5 is solid $Al(OH)_3$. The apparent stability of the solutions may be the consequence either of the presence of stable lactate complexes (not detectable from potentiometric data at pH < *ca.* 5) or to the presence of metastable aluminium co-ordination compounds. This second possibility is evidently supported by the slow precipitation of aluminium hydroxide. As to the nature of these species, the IR data reveal that most of the ligand is not co-ordinated, as only the presence of the shoulder at *ca.* 1650 cm^{-1} (Fig. 4) suggests that an appreciable fraction of the ligand may be still present in the metal co-ordination sphere. However, the presence of co-ordinated lactate is not supported by both ^1H and ^{13}C NMR spectra of solutions of sodium lactate and of aluminium lactate at pH 7.5, which are substantially identical. On the basis of the arguments above, the difference in sharpness cannot be explained in terms of ligand exchange.

These conclusions are in substantial disagreement with the interpretation of ^{27}Al NMR spectra proposed in ref. 9 [*i.e.* the prevalence of $Al(lact)_3$ in neutral solutions].

The structure of the metastable aluminium complex prevailing at pH 7.5 is still an open question which cannot be answered on the basis of the present data and it may well be that more than one such species is present in solution. It is certain that most of the lactate ligand is not co-ordinated and, in this case less than 1 mol of lactate is likely to be present on average in the aluminium co-ordination sphere. The aquahydroxo species dominating the metal solution state cannot be the same as those which are formed during neutralisation of Al^{3+} in the absence of lactate. If this were the case, the neutralisation of 'Al^{3+}' in the presence of lactate would also lead to $Al(OH)_3$. In the Al^{III}–lactate–water–OH^- system, gradual substitution of the co-ordinated ligand by OH^- occurs at pH values at which the aquahydroxo polymeric species, precursors[13] of $Al(OH)_3$, evidently do not form and the aluminium species thus formed may be metastable for long times. The simplest metastable monomeric aluminium complex to be considered is $[Al(OH)_3(H_2O)_3]$. However, the presence at pH 7.5 of an appreciable amount of metal-bound lactate (estimated from IR spectra) and the incomplete identity of the ^1H NMR spectra of solutions containing free lactate and $Al(lact)_3$ suggest also the presence of more complex oligomeric species, in which the ligand still plays a role in solubilization of Al^{III}. The high metastability of these complexes would be in agreement with the obvious absence of acid catalysis at pH 7.5.

The major toxicological implication of our analysis of the solution state of aluminium lactate is that the administration of aqueous solutions of aluminium lactate to biological systems at physiological pH is in fact the administration of Al^{III} mainly co-ordinated to water and hydroxo ligands and not to carboxylate ones. Although the administered species is metastable towards the formation of $Al(OH)_3$, such an event may not occur during the course of any given biological experiment.

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