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Complexation of aluminium(III) with 3-hydroxy-2(1*H*)-pyridinone. Solution state study and crystal structure of tris(3-hydroxy-2(1*H*)-pyridinonato)aluminium(III)

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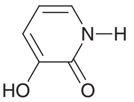
The formation of complexes between aluminium(III) and 3-hydroxy-2(1*H*)-pyridinone (HL) in aqueous 0.6 *m* (Na)Cl at 25 °C has been investigated by means of potentiometric titrations. The following complex stability constants have been evaluated ($pK_a = 8.590 \pm 0.008$): $\log \beta_{AlL} = 8.59 \pm 0.01$, $\log \beta_{AlL_2} = 16.34 \pm 0.03$, $\log \beta_{AlL_3} = 23.11 \pm 0.05$, $\log \beta_{AlL_3H_{-1}} = 13.85 \pm 0.04$. The qualitative and quantitative results obtained have been confirmed in part by UV spectrophotometry and ^{1}H NMR spectroscopy. Some potentiometric titrations were executed at 37 °C as well, and the following stability constants were obtained ($pK_a = 8.452 \pm 0.004$): $\log \beta_{AlL} = 8.19 \pm 0.02$, $\log \beta_{AlL_2} = 16.03 \pm 0.04$, $\log \beta_{AlL_3} = 21.77 \pm 0.08$, and $\log \beta_{AlL_3H_{-1}} = 13.0 \pm 0.2$. Crystals of the complex AlL_3 were obtained and analysed by X-ray diffraction. The neutral species is an octahedral six-co-ordinate complex with the ligand chelating in a bidentate fashion through the pyridinone oxygen and the deprotonated hydroxylic group.

Introduction

Over the last 20–30 years the mainstay of aluminium (and iron) chelation therapy has been Desferal (desferrioxamine mesylate).[1] Despite its good prognosis the general use of Desferal is restricted because of its several drawbacks and toxic side effects.[1,2] For this reason, a number of chelators have been tested *in vitro* and in animals for the replacement of Desferal with a more suitable chelating drug;[1–4] these studies necessarily have to be accompanied by accurate chemical investigations, in order to determine the thermodynamic and kinetic properties of likely compounds of the metal under physiological conditions.

Hydroxypyridinones have been extensively tested, and sometimes also used, as alternatives to Desferal.[1,2] For some compounds of this class, especially for 1,2-dialkyl-3-hydroxy-4(1*H*)-pyridinones, much thermodynamic data for aluminium complexes in aqueous solutions have been collected,[5,6] whereas for other ligands, like 3-hydroxy-2(1*H*)-pyridinones, which are not used to the same extent as the 3-hydroxy-4(1*H*)-pyridinones,[1,7] these studies are less systematic.[7]

In the present study the stability constants for aluminium complexes of 3-hydroxy-2(1*H*)-pyridinone, hereafter named HL, have been determined. The thermodynamic properties of its aluminium complexes in aqueous solutions have not yet been examined. The study has been conducted at 25 °C, in order to allow the direct comparison with thermodynamic data for other hydroxypyridinones evaluated at this temperature, and at 37 °C to investigate how the stability constants vary with temperature under physiological conditions. The results obtained from potentiometric measurements at 25 °C have been checked using two independent techniques, UV spectrophotometry and NMR spectroscopy; in the case of the complex AlL_3, solid-state data (elemental analysis and X-ray diffraction) were also obtained.



HL

Experimental

Apparatus, reagents and measurement methods were similar to those reported previously,[8] and the following summary indicates where details differ.

Apparatus

Potentiometric measurements were performed with a Radiometer ABU93 Triburette apparatus equipped with 1, 5 and 10 mL burettes and with two independent potentiometric channels. The UV spectra were recorded with a Perkin-Elmer Lambda 5 instrument and ^{1}H NMR spectra with Bruker 200 AC and AM 400 spectrometers.

Reagents

All analyte concentrations were expressed in the molality scale (mol kg^{-1} of water). For the potentiometric titrations, standard solutions of HCl (*ca.* 0.1 *m*), $AlCl_3$ (*ca.* 0.05 *m*), NaOH (*ca.* 0.1 *m*) and ligand were used; 3-hydroxy-2(1*H*)-pyridinone (Acros, nominal purity 98%) was used as received to prepare a 0.009 *m* (+0.01 *m* HCl) working solution. Solutions for UV and ^{1}H NMR measurements were prepared by dissolving in water (H_2O and D_2O, respectively) the correct amounts of the ligand and/or $AlCl_3$.

Potentiometric measurements

The measurements were carried out in a 200 mL water-jacketed cell, and duplicate potentiometric measurements obtained by using an Ag–AgCl–3 M KCl reference electrode (BDH 309/1030/06) and two different glass electrodes (Radiometer pHG201 and BDH 309/1015/02); titrations were executed at 25.00 ± 0.05 and at 37.00 ± 0.05 °C in aqueous 0.6 *m* (Na)Cl.

Titrations of the ligand in the absence of Al^{III} were performed to determine its acid–base properties and to check its exact titre. Ligand concentrations ranged from 1.90×10^{-4} to 2.21×10^{-3} *m*; the pH range was from 2.5 to 11.

In the titrations in the presence of both ligand and Al^{III}, concentrations ranged from 2.82×10^{-4} to 2.78×10^{-3} *m* for the ligand and from 1.68×10^{-4} to 1.29×10^{-3} *m* for the metal; the ligand : metal ratio varied from 8 : 1 to 1 : 2; the pH range was from 2.5 to 11. The potentiometric study of aqueous solutions containing aluminium and HL has been partially complicated by the low water solubility of the neutral AlL_3 complex, which precipitates at $pH \approx 4.5$–6.5, depending on the initial aluminium and ligand concentrations, and redissolves at $pH > 9$. To avoid the presence of solid, titrations had to be stopped at acidic or slightly acidic pH values; otherwise they had to be performed at a concentration of aluminium lower than the solubility of AlL_3 (*ca.* 2×10^{-4} *m*).

The ligand protonation constants and the metal–ligand complex stability constants were calculated using the computer program PITMAP.[9] The values of the formation constants of aluminium hydroxo-complexes at 25 °C and in 0.6 M NaCl have been taken from the literature[10] and were held constant during data optimisation.

UV measurements

Spectra were collected at various pH values at 25 °C for solutions containing aluminium (*ca.* 10^{-2} *m*), ligand (*ca.* 10^{-3} *m*) and 0.6 *m* (Na)Cl; the concentrations of Al^{III} and ligand and the pH interval were chosen so that only two absorbing species, AlL and HL (charges omitted), were present in solution at significant concentrations, as predicted from the equilibrium constants previously obtained from potentiometric data; under these conditions only the equilibrium (1) needs to be

$$HL + Al \rightleftharpoons AlL + H \qquad K = [AlL][H]/[HL][Al] \quad (1)$$

considered. The absorbance difference between AlL and HL is sufficiently large in the wavelength range 200–325 nm to allow the value of *K* to be determined by fitting the experimental points (absorbances *vs.* pH at a given wavelength) by the theoretical equation obtained by combining the above mass-law expression with the mass balance equations for the metal and the ligand; the only unknown parameters of the equation are the equilibrium constant *K* and the absorption coefficients of HL and AlL.

^{1}H NMR measurements

Spectra were obtained for D_2O solutions containing the ligand alone (10^{-2} *m*) and for these also containing aluminium (3×10^{-3} *m*) at various pH values at 25 °C. Only the spectrum at the neutral pH value was obtained with a 400 MHz instrument (instead of 200 MHz) in order to allow the detection of the species AlL_3; in this case, after the addition of the ligand and the metal and the adjustment of the pH value, a brown precipitate was formed; the NMR spectrum of this solution was collected after filtration and a subsequent small addition of D_2O in order to prevent further precipitation during the measurement. In all cases the pH readings were corrected by adding 0.41 pH units[11] to allow for isotopic and solvent effects caused by the substitution of normal water (calibration environment) with heavy water (measurement environment).

Preparation of solid AlL_3

The compound HL (3 mmol), 3 mmol of KOH (Fluka) and 1 mmol of $Al(NO_3)_3 \cdot 9H_2O$ (Prolabo) were dissolved in 50 mL of water at 60 °C ($pH \approx 4$) under moderate stirring. The hazel-brown powder obtained from the solution was washed with water and dried under vacuum (269 mg, 75%). Elemental analysis (expected value): C, 48.52 (50.43%); H, 3.58 (3.39%); N, 11.59 (11.76%). From this raw material useful crystals for XRD analysis could not be obtained.

The crystallisation of AlL_3 was therefore performed in a different way. Compound HL (3 mmol) and 1 mmol of $AlCl_3 \cdot 6H_2O$ were dissolved in 50 mL water at room temperature; this acidic solution ($pH \approx 2$) was brought to $pH \approx 10$ using NaOH. The slow neutralisation of this clear, brown solution by atmospheric CO_2 (about one month, room temperature) gave the complex in the form of brown crystals. No elemental analysis could be done on these crystals due to their small quantity.

Table 1 Acidic properties of HL in aqueous 0.6 *m* NaCl at 25 and 37 °C; $\Delta G^\circ = -49.03 \pm 0.05$ kJ mol^{-1}, $\Delta H^\circ = -20 \pm 2$ kJ mol^{-1}, $\Delta S^\circ = 97 \pm 6$ J mol^{-1} at 25 °C

25 °C		37 °C	
pK_a	*n*	pK_a	*n*
8.590 ± 0.008	22	8.452 ± 0.004	24

[a] *n* is the number of titrations from which the data were obtained; the reported uncertainty is the standard deviation of the mean calculated from the *n* results.

Crystal analysis

Crystal data were collected on a Rigaku/MSC Raxis II imaging plate system (Mo-Kα, $\lambda = 0.71073$ Å) on a single crystal of *ca.* $0.3 \times 0.3 \times 0.3$ mm in size. Some experimental details are reported in Table 4.

CCDC reference number 186/1514.

See http://www.rsc.org/suppdata/dt/1999/2427/ for crystallographic files in .cif format.

Results and discussion

Potentiometric results

As a check of the accuracy of the whole experimental system the pK_w value for water in 0.6 *m* (Na)Cl was computed from HCl + NaOH titrations at 25 °C. The value obtained from seven experiments (p$K_w = 13.714 \pm 0.002$) compares well with the literature value[12] in 0.6 M NaCl at 25 °C (13.727 ± 0.001). A value for pK_w has also been obtained at 37 °C from twelve experiments (13.352 ± 0.002), which is in a good agreement with the calculated value, 13.355, obtained from tabulated values of pK_w and ΔH^0 at 25 °C[13] by applying the van't Hoff equation.

The pK_a values of free HL at the two investigated temperatures are given in Table 1, together with other thermodynamic parameters; the deprotonation occurs at the phenolic oxygen.[14] Reasonable similar pK_a values are reported in the literature [8.694 ± 0.007 in 0.1 M KCl at 25 °C,[14] 9.00 ± 0.01 at 20 °C (ionic strength not specified),[15] 8.66 ± 0.01 at 25 °C and ionic strength 0.1 M[16]]. The deprotonation of the oxy-group, *i.e.* of the species H_2L^+, has occasionally been detected (pK_a about 0.1–0.2[14,15]); the deprotonation of the species L^- at the pyridinic nitrogen, which has a significant amidic character, is not measurable in water[14] (p$K_a > 13$).

In the present study of metal–ligand complexes, the interpretation of potentiometric data was started by plotting $\bar{n}_{L,M}$ *vs.* $-\log[L]$ curves. If predominantly mononuclear AlL_n complexes are formed in solution the quantity $\bar{n}_{L,M}$ is the average number of L co-ordinated per Al^{3+},[17] and the $\bar{n}_{L,M}$ curves are coincident. This was found in the present case (Fig. 1), with a limiting value of $\bar{n}_{L,M}$ larger than 2, even if, at low $\bar{n}_{L,M}$ values, some small differences of the curves could support the existence of other, protonated or polynuclear, species. It was noticed that these differences are not correlated to modifications either of aluminium and ligand concentration or of their ratio, *i.e.* they seem to be only due to experimental uncertainties. In any case, the experimental low-pH data were carefully reanalysed, see later. The complete computer treatment of experimental titration data gives the stoichiometries and stability constants of the aluminium–ligand complexes reported in Table 2.

The logarithmic distribution diagram of most important aluminium species at concentrations typical for the potentiometric measurements is in Fig. 2 (25 °C).

The main aluminium complexes in solution are AlL, AlL_2 and AlL_3. An estimate of the solubility product of AlL_3 was evaluated from the pAl and pL values obtained from the distribution diagram at the pH value corresponding to the observed start of AlL_3 precipitation: pK_s (AlL_3) = 26.58 ± 0.07 (mean of 5 values, 25 °C). At an initial aluminium concentration about 2×10^{-4} *m* or lower and at ligand : metal ratio ⩾ 3 : 1 alkaline pH values could be reached without the occurrence of AlL_3 or $Al(OH)_3$ precipitation. Under these conditions another species could be detected in solution, AlL_3H_{-1}, which is the deprotonation product of AlL_3 at the pyridinic nitrogen, with a pK_a of 9.26 at 25 °C ($\log \beta_{1,3,0} - \log \beta_{1,3,-1}$); this value is reasonable, because for this species there can be a significant resonance formula which delocalises the positive charge from the nitrogen to the *ortho*-oxygen. In fact, the pK_a of AlL_3 is a compromise of the value typical of a pyridinic proton ($pK_a \approx 5$) and that of an amidic proton ($pK_a > 13$). Other possible deprotonation products, like $AlLH_{-1}$, AlL_2H_{-1}, AlL_3H_{-2} and AlL_3H_{-3}, could not be detected: in the first two cases the attachment of another ligand to the metal centre is favoured, whereas formation of last two species is likely to occur only at more alkaline pH values, where however only $Al(OH)_4$ was found to exist.

A careful investigation of the experimental low-pH data was also executed, in order to verify whether the observed small differences in the starting parts of the $\bar{n}_{L,M}$ curves were due to the presence of polynuclear or deprotonated species. No complexes except AlL could be detected.

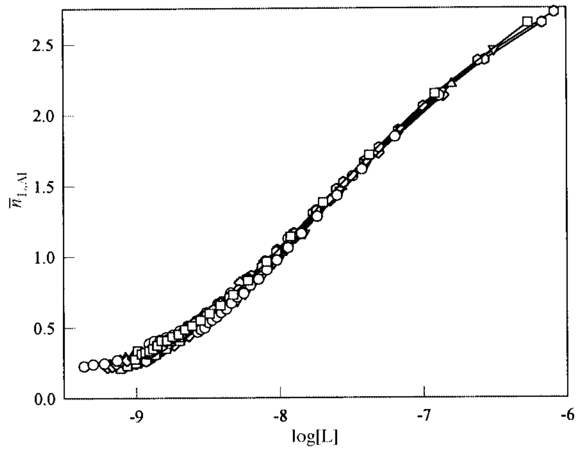


Fig. 1 Experimental data from the Al^{III}–HL system (25 °C) plotted as $\bar{n}_{L,M}$ *vs.* log [L] curves at various ligand and metal concentrations.

The increase of the temperature (from 25 to 37 °C) causes a decrease of the stability constants of all complexes. The $\Delta H°$ and $\Delta S°$ values could be obtained from the Van't Hoff equation; they are however very imprecise (and not reported in Table 2), because of the small difference between the two investigated temperatures.

UV results

The UV spectra for solutions containing known concentrations of aluminium and ligand at various pH values are given in Fig. 3, and the value obtained for log *K* (reaction (1), see Experimental section) was: 0.00 ± 0.05. This value has to be compared with the potentiometric one at 25 °C [0.00 ± 0.02, obtained by combining pK_a (Table 1) with $\log \beta_{1,1,0}$ (Table 2)]; the excellent agreement suggests the absence of any bias in the results.

^1H NMR results

The ^1H NMR spectra of D_2O solutions containing aluminium and ligand, at various pH values at 25 °C, are reported in Fig. 4. In addition to the strong signals of the "free" ligand at δ 7.1–7.2 and 6.4–6.55, at pH 2.5 and 2.9 two new groups of peaks at δ 6.95–7.1 and at 6.7–6.85 are observed. These signals (labelled with "1" and "2" respectively) can be attributed to the pyridinic protons of two (and probably not more than two) complexes, which should be AlL and AlL_2 according to the potentiometric data. There are two reasons to attribute peaks "1" to AlL and peaks "2" to AlL_2. (1) In the spectrum at pH 2.9 signal "2" becomes more intense with respect to signal "1", as predicted

Table 2 Results of potentiometric study of complex formation between Al^{3+} and HL in aqueous 0.6 *m* NaCl at 25 and 37 °C (reactions: $m\,Al^{3+} + lL^- + hH^+ \rightleftharpoons Al_mL_lH_h^{3m-l+h}$

	25 °C		37 °C	
m,l,h	log β	*n*	log β	*n*
1,1,0	8.59 ± 0.01	26	8.19 ± 0.02	9
1,2,0	16.34 ± 0.03	24	16.03 ± 0.04	10
1,3,0	23.11 ± 0.05	20	21.77 ± 0.08	4
1,3,−1	13.85 ± 0.04	6	13.0 ± 0.2	6

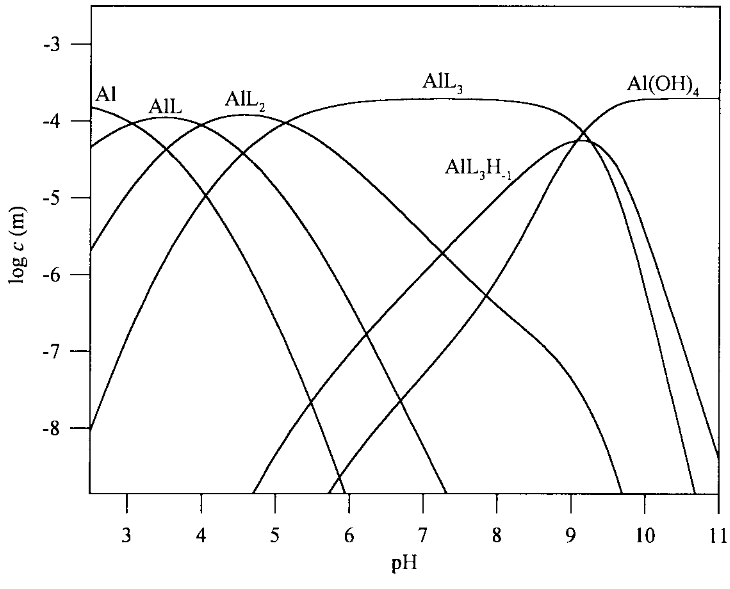


Fig. 2 Logarithmic distribution diagram of most important aluminium species in the presence of HL (aqueous 0.6 *m* NaCl, *T* = 25 °C, $[Al]_0 = 2 \times 10^{-4}$ *m*, $[HL]_0 = 10^{-3}$ *m*; pK_s of amorphous $Al(OH)_3$ = −10.8, pK_s of AlL_3 = 26.58).

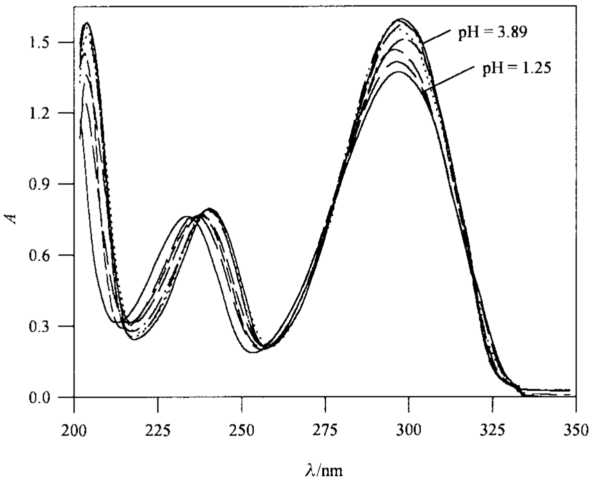


Fig. 3 The UV spectra for solutions containing aluminium and HL (aqueous 0.6 *m* NaCl, 25 °C, $[Al]_0 = 9.95 \times 10^{-3}$ *m*, $[HL]_0 = 1.80 \times 10^{-3}$ *m*, pH 1.25, 1.64, 2.00, 2.36, 2.77, 3.11, 3.50 and 3.89); cell length = 0.1 cm. Calculations were performed at $\lambda = 206$, 227, 247, 268.5, 300 and 323 nm.

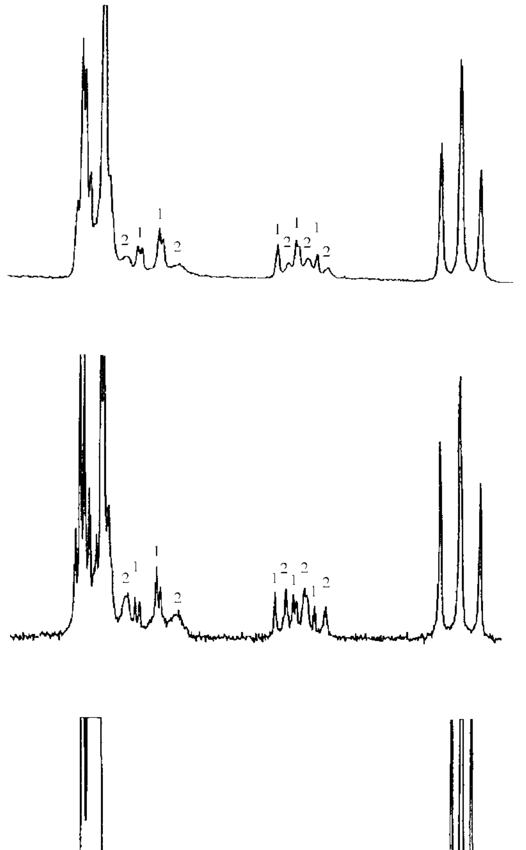


Fig. 4 The ^1H NMR spectra in D_2O, 0.6 *m* NaCl at 25 °C of a solution containing aluminium and HL ($[Al]_0 = 3 \times 10^{-3}$ *m*, $[HL]_0 = 10^{-2}$ *m*, pH 2.5, 2.9 and 6.8 from top to bottom).

Table 3 Percentages of "free" and complexed ligand

pH	From NMR data		From potentiometric results	
2.5	"Free" ligand	73.7	HL	71.3
	Complexed ligand	26.3	AlL + 2AlL$_2$	28.7
2.9	"Free" ligand	66.7	HL	62.1
	Complexed ligand	33.3	AlL + 2AlL$_2$	37.9

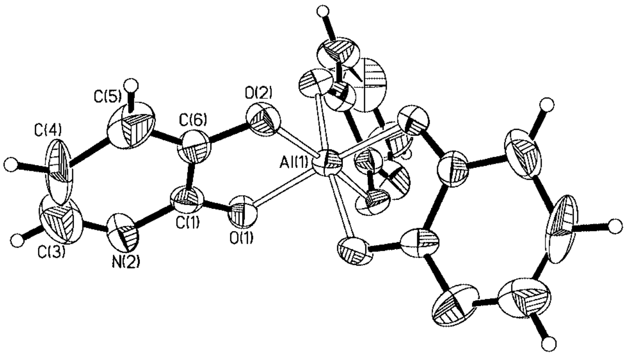


Fig. 5 Crystal structure of AlL_3.

by potentiometric results. (2) The peaks labelled with "1" are narrow, whereas those labelled with "2" are broader; this fact is likely to be caused by the presence of isomers (for AlL there is only one isomer, whereas for AlL_2 there can be up to 8 isomers simultaneously present in solution), which are identical in potentiometric titrations, but can be (and in fact they are) different in the NMR analysis. It is also probable that these isomers interchange ligand molecules with slower rates than before, because the peaks of the "free" ligand at pH 2.9 are slightly broader than the corresponding ones at pH 2.5.

The integration of the signals gives the relative amount of "free" and complexed ligand; the values obtained are reported in Table 3 together with the corresponding values calculated from the potentiometric results. The agreement between the two sets of data is reasonably good; the differences can be attributed to isotopic and solvent effects introduced by using D_2O instead of H_2O.

The analysis of the spectrum at pH 6.8 suggests the presence of only one complex, the signal pattern of which is different from those of AlL and AlL_2. According to the potentiometric data this complex should be AlL_3.

Crystal structure analysis

The structure of the complex AlL_3 is shown in Fig. 5. Bond distances and interbond angles are reported in Table 5.

Initial refinement with Al(1), O(1) and O(2) anisotropic, and the six atoms of the ring as isotropic carbons, resulted in a lower thermal parameter for atom N(2) than for C(5) ($U = 0.0424$ and 0.0581 Å^3). Atoms C(1) and C(6) have very similar thermal parameters, as do C(3) and C(4). Accordingly, the nitrogen atom in the ring is identified as N(2). An attempt to refine N(2) and C(5) as partially disordered nitrogen and carbon atoms found no significant evidence for disorder. This is entirely consistent with O(1) being the ketonic oxygen of the parent ligand, with C–O and O–Al distances of 1.285(6) and 1.915(3) Å, respectively, and O(2) being derived from the hydroxyl oxygen, with C–O and O–Al distances of 1.317(6) and 1.899(3) Å, respectively. The six ring atoms were then refined anisotropically. It should be noted that the partial ketonic character of the C(1)–O(1) bond was also suggested by comparing the pK_a values of AlL_3, HL and pyridinic protons (see potentiometric results). Although the acentric space group chosen, *R*3*c*, is racemic, with alternate molecules of opposite handedness in each stack (parallel to the *c* axis), it is a polar space group, and here it is to the polarity of the structure to which the Flack asymmetry parameter refers. With only one aluminium atom as a "heavy" atom in the molecule, it was likely

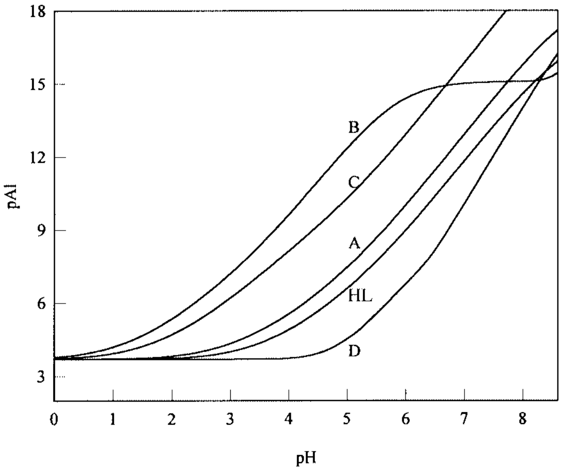


Fig. 6 Aluminium complexation strength, reported as pAl *vs.* pH, of HL and other similar ligands at 25 °C (A = 3-hydroxy-*N*-methyl-2-pyridinone in 0.1 M KCl,[7] B = 1-hydroxy-2-pyridinone in 0.1 M KCl,[20] C = 3-hydroxy-2-methyl-4(1*H*)-pyridinone in 0.6 M NaCl,[6] D = catechol in 0.6 M NaCl[21]).

that this structure would prove to be a borderline case as to whether the polarity could be determined reliably. This was indeed the case; the final value for χ, $-0.44(0.51)$, differs from $+1$ by just under 3σ. Inverting the structure inevitably results in a value for χ greater than unity. While the polarity of the structure has not quite been established, that chosen is much the more likely. The possible presence of twinning was investigated using the appropriate TWIN and BASF command lines in SHELXTL.[18] From an initial value of 0.5, BASF refined to zero, suggesting that no twinning was present. The model was further tested with reference to the structure of the analogous iron complex reported by Scarrow *et al.*,[16] in which they assumed complete disorder of the ligands, selecting the space group *R*3*c*. The present structure was therefore tested in that space group, but the thermal parameters for some of the atoms became unreasonable. Therefore, in contrast to Scarrow *et al.*, we believe that our aluminium complex crystallises in *R*3*c*, with no detectable disorder in the ligand.

Conclusion

The ligand HL forms very stable complexes with aluminium, and can inhibit the formation of hydroxo-complexes of the metal and the precipitation of $Al(OH)_3$ even at neutral and alkaline pH values. Its high affinity towards aluminium is due to the significant acidity of the phenolic group and to the high partial negative charge of the chelating oxygens (almost 1). The speciation is relatively simple because only AlL_n complexes ($n = 1$, 2 or 3) and a deprotonation product of AlL_3 are formed in aqueous solution.

Data obtained at 37 °C show a slight reduction of complex stability constants with respect to corresponding values at 25 °C; the enthalpic and entropic properties of the complexes cannot however be evaluated from our data, because the temperature interval examined is too narrow.

The accuracy of the formation constant values obtained from potentiometric data at 25 °C is substantiated by the agreement with the result obtained from UV spectrophotometry regarding AlL and, in some degree, from ^{1}H NMR spectroscopy regarding AlL and AlL_2; this agreement indirectly confirms the whole speciation model.

The crystal structure of tris(3-hydroxy-2(1*H*)-pyridinonato)-aluminium(III) (AlL_3) is in agreement with the solution state findings; AlL_3 crystallises in space group *R*3*c*, with no detectable disorder in the ligand.

Table 4 Crystal data for AlL_3

Empirical formula	$C_{15}H_{12}AlN_3O_6$		
Formula weight	357.26		
T/K	296 ± 2	*V*/Å^3	2397.7 ± 0.7
		Z	6
Crystal system	Rhombohedral	Independent reflections	705
Space group	*R*3*c*	R_{int}	0.0474
a,*b*/Å	9.6840 ± 0.0014	Final *R*1, *wR*2 [$I > 2\sigma(I)$]	0.0468, 0.1098
c/Å	29.523 ± 0.006	(all data)	0.0434, 0.1211

Table 5 Bond distances (Å) and angles (°) in AlL_3

Al(1)–O(2^1)	1.899(3)	Al(1)–O(2)	1.899(3)
Al(1)–O(2^2)	1.899(3)	Al(1)–O(1^1)	1.915(3)
Al(1)–O(1)	1.915(3)	Al(1)–O(1^2)	1.915(3)
O(1)–C(1)	1.285(6)	O(2)–C(6)	1.317(6)
C(1)–N(2)	1.362(6)	C(1)–C(6)	1.412(5)
N(2)–C(3)	1.295(9)	C(3)–C(4)	1.294(11)
C(4)–C(5)	1.538(10)	C(5)–C(6)	1.355(6)
C(3)–H(3)	0.93	C(4)–H(4)	0.93
C(5)–H(5)	0.93		
O(2^1)–Al(1)–O(2)	91.40(15)	O(2^1)–Al(1)–O(2^1)	91.40(15)
O(2)–Al(1)–O(2^2)	91.40(15)	O(2^1)–Al(1)–O(1^1)	84.08(9)
O(2)–Al(1)–O(1^1)	170.47(11)	O(2^2)–Al(1)–O(1^1)	97.08(10)
O(2^1)–Al(1)–O(1)	97.08(10)	O(2)–Al(1)–O(1)	84.08(9)
O(2^2)–Al(1)–O(1)	170.47(10)	O(1^1)–Al(1)–O(1)	88.14(14)
O(2^1)–Al(1)–O(1^2)	170.47(11)	O(2)–Al(1)–O(1^2)	97.09(10)
O(2^2)–Al(1)–O(1^1)	84.08(9)	O(1^1)–Al(1)–O(1^2)	88.14(14)
O(1)–Al(1)–O(1^2)	88.14(14)	C(1)–O(1)–Al(1)	111.1(3)
C(6)–O(2)–Al(1)	112.6(3)	O(1)–C(1)–N(2)	120.5(4)
O(1)–C(1)–C(6)	118.0(4)	N(2)–C(1)–C(6)	121.4(5)
C(3)–N(2)–C(1)	121.3(5)	C(4)–C(3)–N(2)	121.1(6)
C(3)–C(4)–C(5)	122.8(5)	C(6)–C(5)–C(4)	113.0(5)
O(2)–C(6)–C(5)	125.8(5)	O(2)–C(6)–C(1)	114.1(4)
C(5)–C(6)–C(1)	120.1(5)	C(4)–C(3)–H(3)	119.5(4)
N(2)–C(3)–H(3)	119.5(3)	C(3)–C(4)–H(4)	118.6(4)
C(5)–C(4)–H(4)	118.6(3)	C(6)–C(5)–H(5)	123.5
C(4)–C(5)–H(5)	123.5(3)		

Symmetry transformations used to generate equivalent atoms: 1 $-x + y + 1, -x + 1, z$; 2 $-y + 1, x - y, z$.

As a final comment, a comparison between the complexation strength of HL and other hydroxypyridinones can be made. The relative affinities of the different ligands have been compared by means of pAl plots[19] ($pAl = -\log[Al^{3+}]$) *vs.* pH at a given ligand and metal concentration (Fig. 6): the greater the value of pAl, the more stable are the corresponding aluminium complexes. Strictly speaking, pAl values reported in Fig. 6 cannot be directly compared, because corresponding thermodynamic data were obtained at different ionic strengths; however, differences introduced by changing an ionic medium are usually small and, for our present purpose, negligible. The pAl curves suggest that HL forms weaker complexes than do the other hydroxypyridinones. 1-Hydroxy-2-pyridinone is a stronger aluminium chelator because of the greater acidity of the phenolic group. For 3-hydroxy-*N*-methyl-2-pyridinone and for 3-hydroxy-2-methyl-4(1*H*)-pyridinone the higher complexation strength arises from the greater stabilisation of a positive charge on the pyridinic nitrogen, due to the methyl group (inductive stabilising effect) and to the larger distance from the positive metal centre (minor inductive destabilising effect) respectively.[16] Therefore a higher negative charge on the chelating oxygens is allowed, for both ligands.

In the case of 3-hydroxy-2-methyl-4(1*H*)-pyridinone, this "chemical" result verifies medical tests, which showed that derivatives of 3-hydroxy-4(1*H*)-pyridinones can be better therapeutic agents against aluminium overload than other hydroxypyridinones.

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