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Complexation of Aluminum with N-Substituted 3-Hydroxy-4-pyridinones[1]

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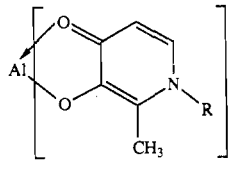
A series of 3-hydroxy-2-methyl-4-pyridinones and their complexes with aluminum(III) have been characterized by potentiometric (glass electrode) titration. The equilibria have been examined at 25.0 ± 0.1 °C and at ionic strengths of μ = 0.15 and 0.6 M (NaCl). The pyridinones have a variety of substituents at the ring nitrogen atom (H, CH_3, C_2H_5, and n-C_6H_{13}), and the pyridinonate anions are characterized by two stepwise protonation constants of $\sim 10^{9.8}$ and $\sim 10^{3.7}$. These ligands form AlL_n complexes (n = 1–3) of high stability; the overall stability constants β_3 for the 3:1 complexes are all $>10^{30}$. At ligand to metal ratios ≥1, the ligands prevent Al(III) hydrolysis at millimolar concentrations, even under slightly basic conditions, and the effective formation constants (β_{3eff}) of the various ligands for Al^{3+} at physiological pH are 10^{24}–10^{25}. The binding of these ligands to Al^{3+} is considerably enhanced (10 orders of magnitude) in comparison to that of their pyrone congeners. Two examples of the practical application of these data are discussed: (1) confirmation of Al^{3+} speciation (particularly hydrolysis behavior) as deduced from ^{27}Al NMR spectra and (2) simulation of comparative metal binding in a simple blood plasma model.

Biological metal ion chelation has now assumed a central role in the study of coordination chemistry. In particular, thermodynamic data allow an unprecedented predictive capacity, which can be used in ligand design for the specific chelation of various metal ions.[3] In this contribution, the thermodynamic characterization of an aluminum–ligand system is discussed, and some of the predictive capability of these data, when applied to a simple blood plasma model, is demonstrated.

As part of projects[4–8] in both our laboratories to detail the coordination chemistry (especially in water) of various high-valent metal ions including aluminum and silicon, a solution study of the chelation of Al^{3+} with N-substituted 3-hydroxy-2-methyl-4-pyridinones has been undertaken. This work has been prompted by the involvement of Al and Si in neurological and osteological disorders and by the increasing mobilization of Al(III) and Si(IV) into groundwaters as a result of acid precipitation in both our countries.

Previous work with 3-hydroxy-4-pyrones[6–8] uncovered an unusual combination of properties in tris(maltolato)aluminum(III),[6] which have led to its use[9] in the study of aluminum neurotoxicity: water solubility, hydrolytic stability, and lipophilicity. These properties prompted the synthesis and characterization of complexes of their nitrogen-containing congeners the 3-hydroxy-2-methyl-4-pyridinones with several of the group 13 (IIIA) metal ions.[5,8] The interesting solid-state properties of these compounds have been discussed,[5,8] and their solution characterization is now reported.



R = H, Al(mpp)$_3$
R = CH_3, Al(dpp)$_3$
R = C_2H_5, Al(mepp)$_3$
R = C_6H_{13}, Al(mhpp)$_3$

The solution characterization of Al/mimosine chelates has been reported;[10] the amino acid mimosine is a 3-hydroxy-4-pyridinone with R = alanine. An overall formation constant β_3 for AlL_3 of 1.5×10^{29} was found. Herein the solution characterization of the series of Al complexes with the 3-hydroxy-4-pyridinones shown above is reported. The ligands are 3-hydroxy-2-methyl-4(1*H*)-pyridinone (Hmpp); 3-hydroxy-1,2-dimethyl-4-pyridinone (Hdpp), 3-hydroxy-2-methyl-1-ethyl-4-pyridinone (Hmepp), and 3-hydroxy-2-methyl-1-hexyl-4-pyridinone (Hmhpp).

Some applications of these data to answer questions of metal ion chelation are discussed. The hydrolysis of Al(dpp)$_3$ is compared with that deduced from ^{27}Al NMR spectra, and it is also shown how thermodynamic results can be used to infer Al speciation in a simple computer model of blood plasma. The computer model also allows direct comparisons of ligand affinities for Al^{3+} regardless of differing denticities.

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Experimental Section

Chemicals and Analysis. All ligands were prepared by published methods[11–13] and were twice recrystallized or sublimed prior to use. The ligand content of the different stock solutions was determined potentiometrically and was found to agree within 0.2% of the value expected from weighing. The preparation and standardization of other solutions are fully described elsewhere.[14,15]

Temperature and Ionic Media. The studies were carried out at 25.0 ± 0.1 °C in ionic media consisting of 0.15 and 0.6 M NaCl. This temperature is not physiological, but it does allow comparison of the results with those for many other ligands.[16] The two ionic strengths correspond to simplified physiological and seawater conditions, respectively, and enable us to evaluate parameters for the medium dependence of the different formation constants.

Potentiometric Measurements. Equilibrium measurements were performed as potentiometric titrations, with procedures being the same as described earlier.[14,15]

Protonation and deprotonation reactions of the ligands were studied in separate experiments within the range $2 \le -\log [H^+] \le 10$. The three component titrations were performed at constant ratios of total ligand (C) to total aluminum ion (B) concentration. In the Hmpp and Hdpp systems (0.6 M NaCl) the C:B ratios 1, 2, 3, and 5 ($2 \le -\log [H^+] < 8$) were studied. From these experiments it was concluded that the complexation can be described by the stepwise formation of a series of $AlL_n^{(3-n)+}$ complexes (n = 1–3). Effects due to the possible formation of mixed Al^{3+}–OH^-–L^- species were found to be negligible at these ratios. On the basis of these findings, the total ligand to metal ratio was kept at just greater than 3 in the other systems studied.

Data Treatment. The interpretation of the experimental data was started with the plotting of $\bar{n}$ vs $-\log [L^-]$ curves. The quantity $\bar{n}$ is the average number of L^- coordinated per Al^{3+}.[17] Coincident $\bar{n}$ curves are formed if predominantly mononuclear AlL_n complexes are formed; this was found (for Al–Hdpp, see Figure 1), with a limiting value of $\bar{n}$ equal to 3. This shows the formation of a series of simple binary complexes AlL_n (n = 1–3).

(1) Equilibrium and Structural Studies of Silicon(IV) and Aluminum(III) in Aqueous Solution. 18. The previous paper in this series is ref 4.
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Table I. Logarithms of Stepwise Protonation Constants (log K_n) and Aluminum–Ligand Stability Constants (log β_n) for the Ligands Employed in This Study at 25 °C and at Ionic Strengths of μ = 0,[a] 0.15, and 0.6 M (NaCl)[b]

constant	μ, M	Hmpp	Hdpp	Hmepp	Hmhpp
log K_1	0	10.10	10.16		
	0.15	9.80 (1)	9.86 (3)	9.81 (2)	9.92 (2)
	0.6	9.58 (1)	9.64 (1)		
log K_2	0	3.62	3.69		
	0.15	3.65 (1)	3.70 (1)	3.64 (2)	3.59 (1)
	0.6	3.74 (1)	3.73 (1)		
log β_1	0	12.31	12.72		
	0.15	11.87 (3)	11.91 (2)	11.75 (4)	11.51 (1)
	0.6	11.43 (2)	11.57 (2)		
log β_2	0	23.97	24.26		
	0.15	22.54 (3)	22.83 (2)	22.52 (5)	22.49 (1)
	0.6	21.73 (2)	22.01 (2)		
log β_3	0	33.98	34.09		
	0.15	32.05 (3)	32.25 (5)	32.17 (6)	31.71 (3)
	0.6	30.41 (5)	30.90 (5)		

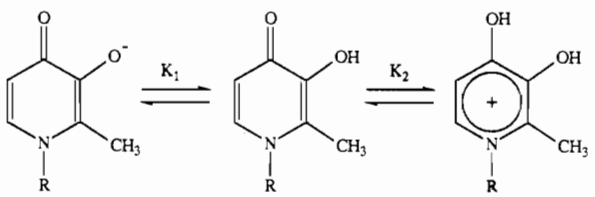
[a] Calculated a_i, b_i(Hmpp), and b_i(Hdpp) values as follows. HL: −1.02, 0.1, 0.1. H_2L^+: 0, 0.2, 0.1. AlL^{2+}: −3.07, 0.1, 0.3. AlL_2^+: −5.11, 0.0, 0.0. AlL_3: −6.13, −1.5, −0.8. [b] Numbers in parentheses represent standard deviations between successive runs (0.15 M data) or three standard deviations calculated according to Sillén[38] (0.6 M data).

The calculation of the overall formation constants defined according to the equilibrium $Al^{3+} + nL^- = AlL_n^{(3-n)+}$, β_n, as well as the proton association constants ($mH^+ + L^- = H_mL^{(m-1)+}$ (m = 1, 2)) was performed with the least-squares computer programs PKAS,[18] BEST,[19] and LETAGROPVRID[20] (version ETTIR[21]).

In the calculations, a hydrolysis model consisting of the species $[Al(OH)_n]^{(3-n)+}$ (n = 1–4), $[Al_2(OH)_2]^{4+}$, and $[Al_3(OH)_4]^{5+}$ with formation constants according to ref 22 and 23 (0.6 M NaCl) and ref 24 (0.15 M NaCl) was applied. In addition, the constant[22] for $[Al_{13}O_4(OH)_{24}]^{7+}$ was included in the treatment of the 0.6 M NaCl data.

Results and Discussion

The 3-hydroxy-2-methyl-4-pyridinones are amphoteric. The two stepwise protonation constants (K_1 and K_2) are given in Table I. Comparison with the analogous values for the 3-hydroxy-4-pyrones shows that the pyrones are stronger acids.[7,16,25,26] Maltol has a hydroxyl log K_1 of 8.38, while that for kojic acid is 7.61.[7] The pyridinones have analogous log K_1 values of about 9.8. In all the hydroxypyrones and hydroxypyridinones there is an additional protonation constant (log K_2) of about −1 in the former[25] and 3.6 or 3.7 in the latter. This difference is most likely an effect of the ring nitrogen atom, which is better able to delocalize positive charge into the ring than a ring oxygen, thereby stabilizing a dihydroxypyridinium cation in acidic solution.



According to Baes and Mesmer,[27] the equation

$$\log \beta_i = \log \beta_i^0 + a_i I^{1/2}/(1 + I^{1/2}) + b_i I$$

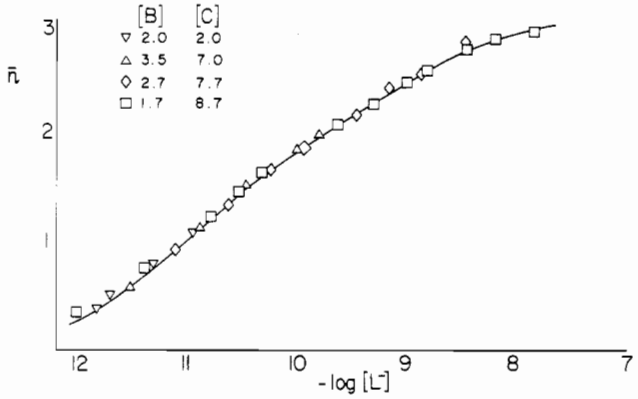


Figure 1. Part of the experimental data for the Al^{3+}–Hdpp system (0.6 M NaCl, 25 °C) plotted as $\bar{n}$ vs −log [L^-]. $\bar{n}$ is the average number of ligands coordinated per Al^{3+}, [B] is the total Al concentration, and [C] is the total ligand concentration (both in mM). The curve was calculated by using the appropriate formation constants from Table I.

suffices for describing the medium dependence of numerous hydrolytic equilibria. Here $a_i = (\Delta Z^2)S$, where ΔZ^2 is the square of the charge on each species summed over the formation reaction. S denotes the Debye–Hückel limiting slope (0.511 $kg^{1/2}/mol^{1/2}$ at 25 °C), and b_i is regarded as an adjustable parameter that reflects the sum of interaction coefficients for the interaction between cations and anions in the equilibrium solution. In the present study, β_i^0 and b_i were evaluated in the Hmpp and Hdpp systems by using data from 0.15 and 0.6 M NaCl media. The results of these calculations are also presented in Table I. The medium dependence of the protonation constants is, as expected,[28] small. The variations in the log β_n values become greater mainly due to the change in a_i with increasing n (see Table I).

The $\bar{n}$ plots (one of which is shown in Figure 1) demonstrated that mixed Al–ligand–hydroxo complexes were a negligible factor within the concentration ranges studied. As evinced by the results displayed in Table I, the Al complexes of the N-substituted 3-hydroxy-4-pyridinones are very stable. Overall formation constants (β) are given; the expected differences between the two media (0.15 and 0.6 M NaCl) are observed, and these have been treated as described above to give the results at zero ionic strength (log K_n^0, log β_n^0). It is obvious from the results in Table I that the Al-binding efficacy of the ligands is not seriously affected by the N-substituent. Effective overall formation constants[29] at pH 7.4 have been calculated for the 0.15 M data, and these reiterate this fact (log β_{3eff} = 24.2 for $Al(mhpp)_3$, 24.9 for the rest).

The great stability of five-membered oxygen-containing metallacycles incorporating group 13 metal ions has been previously documented.[16,30] The functionalizable ring N in the hydroxypyridinones allows a number of properties to be varied (water solubility, lipophilicity, hydrolytic stability) without affecting the thermodynamic binding constants. The N–H and N–CH_3 derivatives ($Al(mpp)_3$ and $Al(dpp)_3$) are water soluble (>1 mM) but not lipophilic, while the N-hexylated complex ($Al(mhpp)_3$) is much less water soluble but highly lipophilic.[5,12]

The increased thermodynamic stability of the aluminum pyridinonates compared with that of the aluminum pyronates[7] must be a result of the poorer ability of the nitrogen-containing ring to delocalize negative charge in the formation of the complex. The N-containing heterocycle is badly equipped (relative to the O-containing hydroxypyrone) to delocalize negative charge, so the hydroxyl oxygen is harder (i.e. more polarized $C(\delta^+)$–$O(\delta^-)$) than in the hydroxypyrones. Comparison of the Ga–O(hydroxyl) distances in $Ga(dpp)_3$ (1.967 (3) Å)[5] and the tris(catecholato)-

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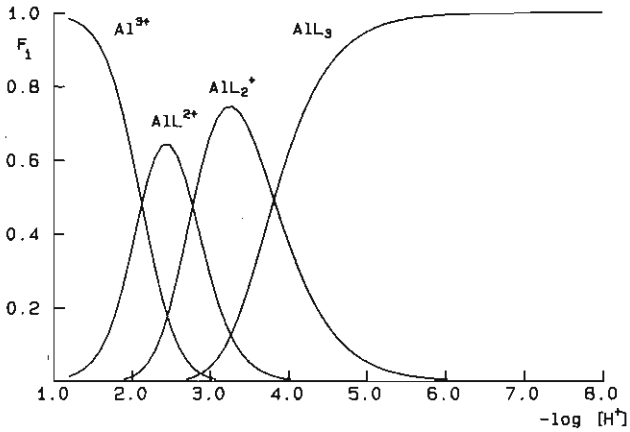

Figure 2. Equilibrium speciation diagram calculated for 1 mM Al^{3+} and 4 mM Hdpp (25 °C, μ = 0.6 M(NaCl)). F_i is the fraction of total Al in solution.

gallate trianion (average 1.986 (6) Å)[31] shows the strength of this electrostatic interaction.

A representative equilibrium speciation diagram calculated for 4 mM Hdpp and 1 mM Al^{3+} (μ = 0.6 M (NaCl)) is shown in Figure 2. It demonstrates that the tris complex $Al(dpp)_3$ becomes dominant at a pH of 4.5. This complex is stable to hydrolysis to pH 9; this result is characteristic of all of the complexes regardless of ligand or medium. This agrees with hydrolysis experiments previously reported,[5] which were monitored by using ^{27}Al NMR spectroscopy. Using the same concentrations of Al and Hdpp as in the NMR experiment and the results of Table I, it is possible to confirm the ^{27}Al NMR spectral results in a qualitative and quantitative fashion, and this is shown in Figure 3. The appropriate chemical shifts for the five relevant species are given in the caption. The potentiometric titrations are performed in a more limited pH range (pH ≤ 8) than the NMR studies; however, the agreement between the two different methods is striking.

Figure 4 presents a plot that can be used to compare metal-binding affinities of various ligands, regardless of denticities. By use of formation constants taken from the literature for Al complexes of citrate[4] and transferrin,[32] ligands are compared with Hdpp under the physiologically relevant conditions 1 μM Al^{3+}, 100 μM citrate, and 50 μM vacant sites of transferrin at pH 7.4 and 25 °C as a simple model of blood plasma. Figure 4 shows that Hdpp is more efficient (lower [C] required) at complexing 100% of Al in this model than is edta[16] (which is hexadentate and tetraprotic), maltol[7] (bidentate and monoprotic), or catechol[33] (bidentate and diprotic). It should be noted that Fe has not been included in the model and temperature or ionic strength changes have not been taken into account. These factors should not affect the result unduly, however. It is emphasized that the model's predictive powers are limited in an absolute sense but are very powerful in a comparative sense.

One challenge for future work is to determine what fraction of the highly increased thermodynamic binding (hydroxypyridinones vs hydroxypyrones) is from entropic contributions and what is from enthalpic contributions. This is being approached via variable-temperature potentiometric studies.

The 3-hydroxy-4-pyridinoate anions have a high affinity for the smaller trivalent metal ions. This can be concluded from the work presented here from biodistribution experiments[34] with $^{67}Ga(dpp)_3$, which demonstrate that the complex does not give up ^{67}Ga to transferrin under conditions of excess ligand, and from the observations of Kontoghiorghes and co-workers that dpp^- is

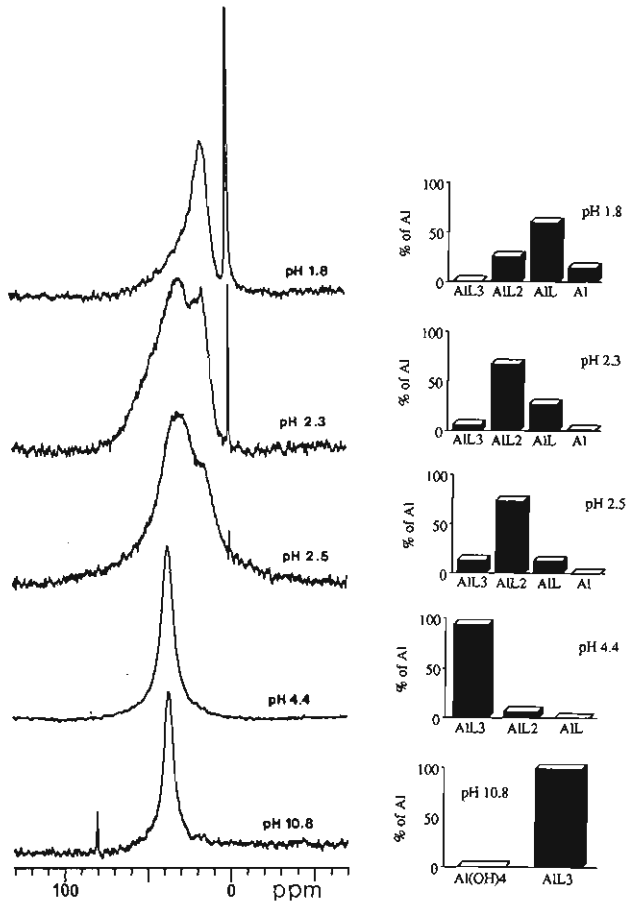

Figure 3. Left: observed ^{27}Al NMR spectra as a function of pH for 0.035 M $Al(dpp)_3$. Chemical shifts (ppm): 80, $[Al(OH)_4]^-$; 36, $[Al(dpp)_3]$; 26, $[Al(dpp)_2(H_2O)_2]^+$; 14, $[Al(dpp)(H_2O)_4]^{2+}$; 0, $[Al(H_2O)_6]^{3+}$. Right: Al speciation calculated for 0.035 M $Al(dpp)_3$ by using the data at 25 °C and μ = 0.15 M (NaCl), where L = dpp.

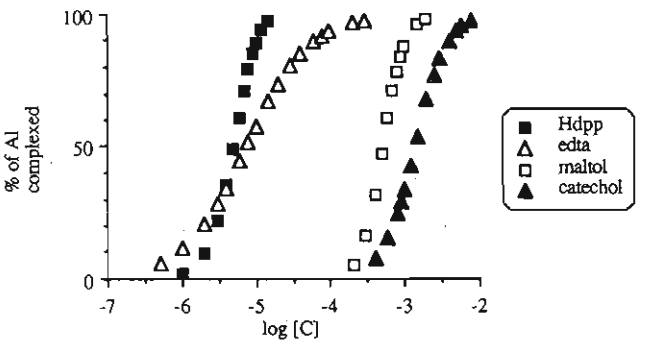

Figure 4. Plot of Al^{3+} complexation (%) vs log of the total ligand concentration ([C]) for several ligands at the conditions 1 μM Al^{3+}, pH 7.4, 25 °C, 100 μM citrate, and 50 μM empty transferrin-binding sites.

capable of removing Fe^{3+} from transferrins[35,36] and ferritin.[37]

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Registry No. Hmpp, 17184-19-9; Hdpp, 30652-11-0; Hmepp, 30652-12-1; Hmhpp, 30652-18-7.

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