Preparation of 2- and 4-substituted 3-hydroxy-5-methylfurans and the aluminum and gallium complexes of 3-hydroxy-5-methyl-2-(*N*-methylformamido)furan[1]

T.G. Lutz, D.J. Clevette, H.R. Hoveyda, and V. Karunaratne
Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada

A. Nordin and S. Sjöberg[2]
Department of Inorganic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

and

M. Winter and C. Orvig[2]
Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada

Received October 8, 1993

T.G. Lutz, D.J. Clevette, H.R. Hoveyda, V. Karunaratne, A. Nordin, S. Sjöberg, M. Winter, and C. Orvig. Can. J. Chem. **72**, 1362 (1994).

In model studies designed to study the synthesis of potentially hexadentate chelates based on the linkage of three furan rings to a triamine via amide linkages, new 2- and 4-substituted 3-hydroxy-5-methylfurans have been prepared. Particularly, 3-hydroxy-5-methyl-(*N*-methylformamido)furan (Hahm) and its Al and Ga complexes ($M(ahm)_3$) have been prepared and thoroughly characterized by a variety of techniques, in the solid state and in solution. Solution equilibrium studies (μ = 0.6 M NaCl, 25°C) uncovered a complicated set of equilibria in the Al^{3+}/Hahm system; the solution potentiometric data were best explained by the presence of mixed ligand (HL = Hahm, L^- = ahm^-) hydroxo species $[Al_3(OH)_4L_3]^{2+}$ and $[Al(OH)_2L_2]^-$, in addition to the expected $[AlL_n]^{(3-n)+}$ (n = 1, 2, 3) species. Further solution studies at HL:M ratios of 3:1 (μ = 0.15 M NaCl, 25°C) showed that Hahm is a relatively weak complexing agent for both Al and Ga, forming tris-ligand species with overall formation constants of $10^{19.5}$ and $10^{20.6}$, respectively.

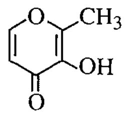
T.G. Lutz, D.J. Clevette, H.R. Hoveyda, V. Karunaratne, A. Nordin, S. Sjöberg, M. Winter et C. Orvig. Can. J. Chem. **72**, 1362 (1994).

Dans le cadre de travaux orientés vers l'étude de la synthèse de chélates hexacoordinés potentiels basés sur la liaison de trois noyaux furaniques à une triamine par le biais de liaisons amides, on a synthétisé de nouveaux 3-hydroxy-5-méthylfuranes substitués en positions 2 et 4. On a préparé en particulier le 3-hydroxy-5-méthyl-2-(*N*-méthylformamido)furane (Hahm) ainsi que ses complexes avec de l'aluminium et du gallium ($M(ahm)_3$) et on les a caractérisés à fond par diverses techniques, tant à l'état solide qu'en solution. Les études d'équilibre en solution (μ = 0,6 M NaCl, 25°C) ont permis de mettre en évidence l'existence d'un ensemble d'équilibres compliqués dans le système Al^{3+}/Hahm; pour bien expliquer les données potentiométriques en solution, on doit suggérer l'existence d'espèces hydroxo $[Al_3(OH)_4L_3]^{3+}$ et $[Al(OH)_2L_2]^-$ à coordinats mixtes (HL = Hahm, L^- = ahm^-), en plus des espèces $[AlL_n]^{(3-n)+}$ (n = 1, 2 et 3) attendues. Des études ultérieures en solution, à des rapports HL:M des 3:1 (μ = 0,15 M NaCl, 25°C) montrent que le Hahm est un agent complexant relativement faible tant pour l'aluminium que pour le gallium, formant des espèces tricoordinées avec des constantes de formation globales respectives de $10^{19,5}$ et $10^{20,6}$.

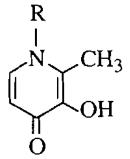
[Traduit par la Rédaction]

Introduction

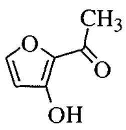
A number of low molecular weight complexes of aluminum, gallium, and indium have been prepared and investigated in these laboratories in recent years; their properties have recommended them for *in vivo* examination (2, 3). These complexes are tris(bidentate ligand)metal(III) species, and incorporate as ligands various pyrones (e.g. maltol, **1**) (4, 5), *N*-substituted-3-hydroxy-4-pyridinones (**2**) (6–8) and isomaltol (**3**) (9). The properties of interest are hydrolytic stability, water solubility, neutral charge, and lipophilicity, all occurring simultaneously. Some of these ligands had very high affinities for the group IIIA (or 13) ions (8) and certain of the complexes formed unusual solid state hydrogen bonding arrays (6, 7).



1



2



3

In efforts to extend the coexistence of these four properties into hexadentate analogs of these binding moieties, we have undertaken model studies involving the preparation of some new ligands for the group 13 ions. The hydrolytic instability (10) of aluminum, gallium, and indium is an important factor in the aqueous chemistry of their trivalent ions and must be compensated for in the design of their chelates.

Initial model studies designed to study the synthesis of potentially hexadentate chelates were based on the functionalization of maltol (**1**) with triamines to form hexadentate tris(3-hydroxy-4-pyridinone) analogs of **2** similar to the bis(pyridinones) already reported (11); however, in both the bis and tris cases the 1 position of the maltol ring (where R—N is substituted for O) is far removed from the α-hydroxyketone chelating moiety and the resulting ligands form polymeric complexes by bridging metal ions. The ketone carbonyl of isomaltol (**3**) does not undergo Schiff base condensation with amines to form imines, rather isomaltol undergoes a ring opening, dehydration, and ring closing sequence of reactions to produce *N*-substituted-3-hydroxy-2-methyl-4-pyridinones (**2**) (12). The failure to form imines with isomaltol initiated a search for a ligand that had a

---

[1] Equilibrium and structural studies of silicon(IV) and aluminum(III) in aqueous solution. 32. The previous paper in this series is ref. 1.

[2] Authors to whom correspondence should be addressed.

bulkier substituent at the 5 position to inhibit the ring opening reaction. An attractive candidate was found, 2-ethoxycarbonyl-3-hydroxy-5-methylfuran (Hehm, see Scheme 1), which not only had a methyl group at the 5 position, but also had an ester group at the 2 position, allowing for a route to modify the ligand by the formation of various amides. Little work has been done on such highly substituted furans, especially those containing a butanedionyl moiety, but a short communication by Takei et al. described the synthesis of furan derivatives (including the desired Hehm) by reacting diketene with various sulfur ylides in benzene (13).

The possibility of linking three isomaltol analogs together to a tripodal backbone such as tris(2-aminoethyl)amine (tren) via the replacement of the 2-acyl group with an amide linkage was envisaged. We report herein on model studies toward the objective of linking three furan rings to a triamine via amide linkages; new 2- and 4-substituted 3-hydroxy-5-methylfurans have been prepared, and their chemistry has been studied both in the presence and absence of the group 13 ions. 3-Hydroxy-5-methyl-2-(*N*-methylformamido)furan (Hahm) and its Al and Ga complexes ($\mathrm{M(ahm)_3}$) have been prepared and thoroughly characterized by a variety of techniques in the solid state and in solution.

Experimental

Materials and methods

These were mostly as previously described (4, 6, 8, 9). Dimethylsulfide (Aldrich), ethyl bromoacetate (Aldrich), methylamine (40% in $\mathrm{H_2O}$ — Fisher), and $\mathrm{Al(NO_3)_3{\cdot}9H_2O}$ (Mallinckrodt) were used as supplied. Ga ingots (Alfa) were dissolved in concentrated HCl; this solution was standarized and used as the starting material for the synthesis of Ga complexes. Diketene and benzene were freshly distilled before use. Carbethoxymethyldimethylsulfonium bromide was synthesized according to the method of Payne (14).

NMR spectra are reported δ downfield from TMS (^{13}C, ^{1}H, APT, SINEPT) and were recorded on Bruker AC-200E, Varian XL 300, and Varian XL 400 spectrometers. IR spectra were recorded as KBr disks with a PE 783 spectrophotometer and are referenced to polystyrene film. Mass spectra were obtained with either a Kratos MS 50 (electron-impact ionization, EI) or an AE MS-9 (fast-atom-bombardment ionization, FAB) instrument. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Analyses for C, H, N were performed by Mr. Peter Borda in this department.

Ethyl (dimethylsulfuranylidene)acetate (EDSA)

This was prepared from dimethylsulfide and ethyl bromoacetate via carbethoxymethyldimethylsulfonium bromide according to Payne (14), with some modification. The carbethoxymethyldimethylsulfonium bromide solution was stirred vigorously using an overhead stirrer, and was cooled for 15 min in an ice bath. After the additions of the saturated $\mathrm{K_2CO_3}$ and 12.5 M NaOH solutions, the ice bath was removed and the mixture was left to stir for an additional 25 min. The light yellow ylide was stored at 5°C under $\mathrm{N_2}$.

2-Ethoxycarbonyl-3-hydroxy-5-methylfuran (Hehm) (13)

EDSA (12 g, 75 mmol) was stirred in 40 mL of benzene. To this, freshly distilled diketene (4.8 g, 57 mmol) was added, and the mixture was refluxed for 15 h. Most of the benzene was removed by rotary evaporation; the remaining solution was cooled and a precipitate formed. The precipitate was removed by filtration and recrystallized from methanol to give 6.9 g (75%) of an off-white crystalline product (mp 50–51°C). It was soluble in methanol, ethanol, chloroform, ether, ethyl acetate, benzene, and water. Anal. calcd. for $\mathrm{C_8H_{10}O_4}$: C 56.47, H 5.92; found: C 56.40, H 5.80. ^{1}H NMR ($\mathrm{CDCl_3}$): 7.6 (br, OH), 5.9 (q, *J* = 1 Hz, 1H, ring H), 4.3 (q, *J* = 6 Hz, 2H, $\mathrm{CH_2}$), 2.25 (s, 3H, ring $\mathrm{CH_3}$), 1.35 (t, *J* = 6 Hz, 3H, $\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$): 160.4 (*C*=O), 156.2 (*C*C=O), 155.9 (*C*$\mathrm{CH_3}$), 124.4 (*C*OH), 100.9 (*C*H), 59.7 (*C*$\mathrm{H_2CH_3}$), 13.6 (C*C*$\mathrm{H_3}$), 13.5 ($\mathrm{CH_2}$*C*$\mathrm{H_3}$). EIMS *m/z*: 170 ($\mathrm{M^+}$), 142, 124. IR ($\mathrm{cm^{-1}}$): 3240 (br); 1670, 1630, 1555 ($\nu_{\mathrm{C=O}}$, $\nu_{\mathrm{C=C}}$, mixed); 1260, 1180, 1080.

4-(1′,3′-Butanedionyl)-2-ethoxycarbonyl-3-hydroxy-5-methylfuran (Hehbm)

A preparation similar to that for Hehm using a 2:1 ratio of diketene to EDSA afforded a pale yellow solid. Anal. calcd. for $\mathrm{C_{12}H_{14}O_6}$: C 56.69, H 5.55; found: C 56.59, H 5.80. ^{1}H NMR ($\mathrm{CDCl_3}$): 8.45 (s, ~1H, OH), 6.23 (s, 1H, ring H), 4.41 (q, *J* = 6 Hz, 2H, ethyl $\mathrm{CH_2}$), 2.67 (s, 3H, acetyl $\mathrm{CH_3}$), 2.19 (s, 3H, ring methyl), 1.43 (t, *J* = 6 Hz, 3H, ethyl $\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$): 191.4 ($\mathrm{CH_3}$*C*O), 179.4 (exocyclic *C*OH), 160.8 (ring *C*C=O), 160.5 (ring *C*=O), 153.6 (*C*$\mathrm{CH_3}$), 124.7 (ring *C*OH), 111.1 (ring *C*=$\mathrm{CCH_3}$), 99.1 (methine C), 60.7 (*C*$\mathrm{H_2CH_3}$), 24.7 (CO*C*$\mathrm{H_3}$), 15.4 (C*C*$\mathrm{H_3}$), 14.1 ($\mathrm{CH_2}$*C*$\mathrm{H_3}$). EIMS: *m/z*: 254 ($\mathrm{M^+}$), 239, 197, 166, 151, 124. IR ($\mathrm{cm^{-1}}$): 3320 (br); 1680, 1630 ($\nu_{\mathrm{C=O}}$, $\nu_{\mathrm{C=C}}$, mixed).

3-Hydroxy-5-methyl-2-(N-methylformamido)furan (Hahm)

Hehm (4.67 g, 27 mmol) was dissolved in 110 mL ethanol and methylamine (40% in $\mathrm{H_2O}$) (2.12 g, 27 mmol) was added. The resulting solution was refluxed for 20 h. The volume was then reduced by rotary evaporation to give 3.3 g (77%) of an off-white powder which was recrystallized from ethanol. It was soluble in methanol, ethanol, chloroform, water, and benzene. Anal. calcd. for $\mathrm{C_7H_9NO_3}$: C 54.20, H 5.85, N 9.03; found: C 53.94, H 5.82, N 8.79. ^{1}H NMR ($\mathrm{CD_3OD}$): 5.94 (q, *J* = 1 Hz, 1H, ring H), 3.47 (s, 3H, amide $\mathrm{CH_3}$), 2.27 (d, *J* = 1 Hz, 3H, ring methyl). EIMS: *m/z*: 155 ($\mathrm{M^+}$), 140, 126. IR ($\mathrm{cm^{-1}}$): 3390 (s, ν_{NH}); 3400–2800 (br, ν_{OH}); 1665, 1610, 1575, 1485, 1445 (amide bands, $\nu_{\mathrm{C=O}}$, $\nu_{\mathrm{C=C}}$, all mixed).

$\mathrm{Al(ahm)_3{\cdot}3H_2O}$

Hahm (0.475 g, 3.1 mmol) was dissolved in 40 mL $\mathrm{H_2O}$ and the pH was raised to 9 (2 M NaOH). $\mathrm{AlCl_3{\cdot}6H_2O}$ (0.246 g, 1.0 mmol) was then added and the pH was adjusted to 7.3. A white precipitate formed (0.36 g, 72%) which was recrystallized from methanol. $\mathrm{Al(ahm)_3}$ was soluble in methanol, acetone, and water (3.1 mM). Anal. calcd. for $\mathrm{C_{21}H_{24}AlN_3O_9{\cdot}3H_2O}$: C 46.16, H 5.53, N 7.72; found: C 45.94, H 5.27, N 7.66. ^{1}H NMR ($\mathrm{CD_3OD}$): 6.11 (s, 1H, ring H), 3.56 (s, 3H, amide $\mathrm{CH_3}$), 2.28 (s, 3H, ring methyl). FABMS *m/z*: 824 ($\mathrm{M_2L_5^+}$); 490 ($\mathrm{HML_3^+}$); 355 ($\mathrm{ML_2^+}$). IR ($\mathrm{cm^{-1}}$): 3700–2800 (br, ν_{NH}, ν_{OH}); 1645, 1590, 1530, 1475, 1450 (amide bands, $\nu_{\mathrm{C=O}}$, $\nu_{\mathrm{C=C}}$, all mixed).

$\mathrm{Ga(ahm)_3}$

Hahm (0.528 g, 3.4 mmol) was dissolved in 60 mL $\mathrm{H_2O}$ and the pH was raised to 9. A solution of 0.445 M $\mathrm{GaCl_3}$ in excess HCl (2.5 mL, 1.1 mmol) was added. Adjustment of the pH to 7.0 with 2 M NaOH resulted in an off-white powder (0.45 g, 75%) which was recrystallized from pyridine. It was soluble in pyridine, methanol, water (1.6 mM), and slightly soluble in acetone. Anal. calcd. for $\mathrm{C_{21}H_{24}GaN_3O_9}$: C 47.39, H 4.55, N 7.93; found: C 47.15, H 4.70; N 7.99. ^{1}H NMR (pyridine-d_5): 6.38 (s, 1H, ring H), 3.03 (s, 3H, amide $\mathrm{CH_3}$), 1.86 (s, 3H, ring methyl). FABMS *m/z*: 532 ($\mathrm{HML_3^+}$); 377 ($\mathrm{ML_2^+}$). IR ($\mathrm{cm^{-1}}$): 3700–2500 (br, ν_{NH}, ν_{OH}); 1630, 1580, 1530, 1470, 1440 (amide bands, $\nu_{\mathrm{C=O}}$, $\nu_{\mathrm{C=C}}$, all mixed).

Potentiometric equilibrium measurements

Potentiometric measurements (at $\mu = 0.6$ or 0.15 M NaCl for the Al/Hahm system; at $\mu = 0.15$ M NaCl for the Ga/Hahm system) of the ligand in the absence, and presence, of metal ions were performed as described previously (9, 15). The temperature was maintained at 25.0 ± 0.1°C throughout. Stock solutions of Hahm were prepared by dissolving it in slightly acidified solutions ($-\log[\mathrm{H^+}] \approx 2.5$, $\mu = 0.6$ or 0.15 M NaCl). The total ligand concentration was determined potentiometrically using the Gran extrapolation method (16). The titrated amount was found to be within ± 0.2% of the value expected from weighing. Stock solutions of NaCl, $\mathrm{AlCl_3}$, and dilute HCl were prepared and standarized as described previously (15). Metal containing solutions were also prepared from appropriate dilution of atomic absorption standard solutions of Al or Ga (Sigma or Aldrich). The exact amount of excess acid present in the metal ion solutions was determined by a Gran's plot (17). The reproducibility and reversibility of Al/Hahm equilibria (μ = 0.6 M NaCl) were tested by performing both forward titrations (increasing $-\log[H^+]$ by coulometrically generated OH^-) and backward titrations (decreasing $-\log[H^+]$ by the addition of H^+).

The deprotonation of Hahm in 0.6 M NaCl was studied in separate experiments within the range $2.5 \le -\log[H^+] \le 9$. The three component titrations (μ = 0.6 M NaCl) were performed at constant ratios of the total concentrations of Hahm (B) and Al (C). The B/C ratios 1, 2, 3, 6, and 8 were studied with $0.001 \le B \le 0.008$ M and $0.001 \le C \le 0.007$ M. The upper $-\log[H^+]$ limits in these titrations were set by the appearance of sluggish equilibria, probably due to the formation of polynuclear hydrolysis products, viz. $[Al_{13}O_4(OH)_{24}]^{7+}$, at low B/C ratios; and $-\log[H^+] \ge 4$. At B/C high ratios with $-\log[H^+] \ge 7$ the formation of a precipitate was frequently observed.

A limited number of potentiometric titrations in μ = 0.15 M NaCl were then undertaken at 3:1 HL:M ratios to compare the overall formation constants of the 3:1 Hahm complexes with aluminum and gallium. For the determination of the formation constants, titrations were done with $B \sim 0.002$ M in the range $2 \le -\log[H^+] \le 4$ because the formation of mixed hydroxo species can be neglected in this range.

Data treatment

The equilibria can be divided into three groups:

(*i*) the binary Hahm equilibrium:

$$[1] \quad HL \rightleftharpoons H^+ + L^- \qquad \beta_{-110}$$

(*ii*) the hydrolytic equilibria for the metal ions:

$$[2] \quad pH^+ + rM^{3+} \rightleftharpoons [H_pM_r]^{(p+3r)+} \qquad \beta_{p0r}$$

incorporating the hydrolysis species for Al: $[Al(OH)_n]^{(3-n)+}$ (n = 1, 2, 3, 4), $[Al_3(OH)_4]^{5+}$, and $[Al_{13}O_4(OH)_{24}]^{7+}$ with appropriate formation constants (18–20)

(*iii*) three component equilibria of the general form:

$$[3] \quad pH^+ + q\text{Hahm} + rM^{3+} \rightleftharpoons [H_p(\text{Hahm})_qM_r]^{(p+3r)+} \qquad \beta_{pqr}$$

In the evaluation of the experimental μ = 0.6 M data, the least-squares computer program LETAGROPVRID (21) (version ETITR (22)) was used. Triplets of pqr, and corresponding equilibrium constants that best fit the experimental data were determined by minimizing the error squares sum $U = \Sigma(H_{calc} - H_{exp})^2$. The LETAGROP calculations also give standard deviations $\sigma(H)$ and $3\sigma(\log \beta_{pqr})$ defined according to Sillén (23, 24). Here H denotes the total proton concentration calculated over the zero level H_2O, HL, and Al^{3+}.

The analysis of the μ = 0.6 M experimental data was started by calculating Z values for each point in a titration using the relation

$$[4] \quad Z = ([H^+] - H - k_w[H^+]^{-1})/B$$

This is the average number of OH^- reacted per B. The experiments thus provide sets of data Z vs. $-\log[H^+]$ which are presented in Fig. 1; the Al complexation clearly starts at low $-\log[H^+] < 2$. Furthermore, at B/C ratios of 1, Z clearly exceeds 1. This is direct evidence that hydroxo and/or mixed ligand hydroxo-complexes of Al were formed. To discover whether specified ranges existed where the formation of binary Al^{3+}/L^- complexes prevail, $\bar{n}$ vs. $-\log[L^-]$ (L^- = ahm^-) curves were plotted (Fig. 2). The quantity $\bar{n}$ is the average number of L^- coordinated per Al^{3+} (25). Coincident $\bar{n}$ curves are obtained if predominantly mononuclear AlL_n complexes are formed. A limited curve with $\bar{n} \le 2.5$ was found; however, deviations from this curve are clearly seen at C/B ratios 1 and 2, as well as at high ratios with $\bar{n} > 2.5$. Data from the "mononuclear wall" were used to evaluate the stability of the different $Al(ahm)_n$ species (n = 1, 2, 3). The results of this calculation are presented in Table 1.

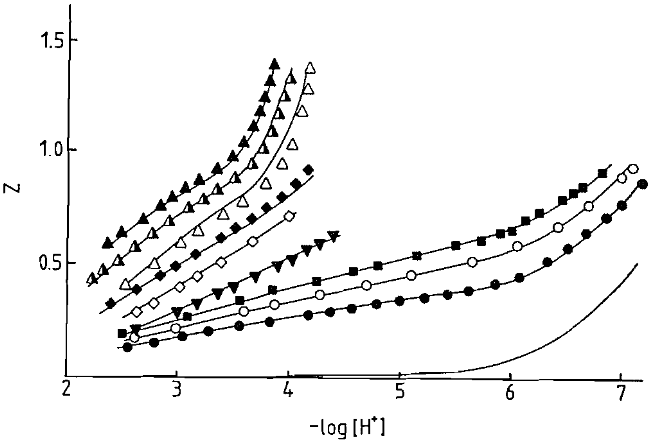


FIG. 1. A part of the experimental data (25°C, μ = 0.6 M NaCl) plotted as curves of Z vs. $-\log[H^+]$. The full curves were calculated using the set of proposed constants in Table 1. The bottom curve represents the ligand in the absence of Al^{3+}. The different symbols denote starting concentrations B, C: ▲ 7.29, 7.00; ◭ 3.79, 3.75; △ 1.89, 1.88; ◆ 4.67, 2.30; ◇ 2.35, 1.18; ▼ 5.04, 1.67; ■ 5.76, 1.15; ○ 6.32, 1.05; ● 7.28, 0.91.

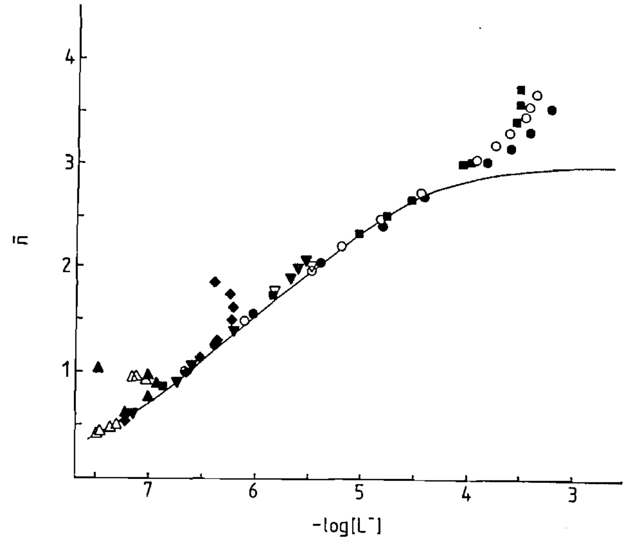


FIG. 2. Experimental data (25°C, μ = 0.6 M NaCl) plotted as curves of $\bar{n}$ vs. $-\log[L^-]$ (L^- = ahm^-). The symbols are the same as in Fig. 1. The full curve was calculated using $\log \beta_{-n,n,1}$ values (n = 1, 2, 3) from Table 1.

In the search for composition (pqr) and stability (β_{pqr}) of any additional complexes (necessary to explain the deviations from the mononuclear $\bar{n}$ curve), pqr analysis using the LETAGROPVRID program was undertaken. The principle behind this method is that complexes of different pqr compositions are tested successively, one by one, and the complex that gives the lowest error square sum is considered to give the best fit. If there are still systematic deviations between calculated and experimental values of H, additional complexes must be included and combinations of two or more pqr sets must be tested. In this work, two data sets were defined; one with $B/C \ge 3$ (set 1) and one with B/C = 1 and 2 (set 2). The result of the analysis on set 1 is presented in Fig. 3, and shows that the lowest value in U was obtained for the complex $[H_{-4}(HL)_2Al]^-$; $\log \beta_{-421} = -12.08$ (5) and $\sigma(H)$ = 0.05 mM indicate a good fit to experimental data, and no systematic deviations were

TABLE 1. Binary and ternary complexes in the H^+–Hahm–Al^{3+} system determined potentiometrically at 25°C, μ = 0.6 M NaCl[a]

No. of titr./ No. points	p	q	r	Tentative structure	log β_{pqr}	Reference
3/98	−1	1	0	L^-	−7.090 (2)	This work
	−1	0	1	$[Al(OH)]^{2+}$	−5.52	18
	−2	0	1	$[Al(OH)_2]^+$	−11.3	20
	−3	0	1	$Al(OH)_3$	−17.3	20
	−4	0	1	$[Al(OH)_4]^-$	−23.46	19
	−4	0	3	$[Al_3(OH)_4]^{5+}$	−13.57	18
	−32	0	13	$[Al_{13}O_4(OH)_{24}]^{7+}$	−109.2	18
14/552	−1	1	1	$[AlL]^{2+}$	0.19 (1)	This work
	−2	2	1	$[AlL_2]^+$	−0.76 (2)	This work
	−3	3	1	AlL_3	−3.02 (3)	This work
	−7	3	3	$[Al_3(OH)_4L_3]^{2+}$	−10.43 (5)	This work
	−4	2	1	$[Al(OH)_2L_2]^-$	−12.08 (5)	This work

[a] The formation constants are defined according to the reaction: $p\text{H}^+ + q\text{HL} + r\text{M}^3 \rightleftharpoons [\text{H}_p\text{M}_r]^{(p+3r)+}$ where HL = Hahm. Numbers in parentheses represent errors corresponding to 3σ(log β_{pqr}).

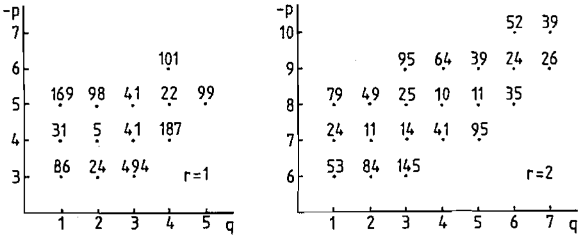


FIG. 3. Results of the *pqr* analysis on data with *B/C* > 3. The figure gives $U_H(p, r)_q$ assuming one ternary complex.

observed. Similar calculations were performed on set 2. The high Z values ($Z \leq 1.5$) that were observed with − log [H^+] ≈ 4, indicate the formation of ternary hydroxo species; furthermore, the high buffer capacity of the system in this range also implied that polynuclear Al complexes were likely. The *pqr* search clearly showed that polynuclear complexes were formed, the best fit being obtained with p,q,r −7,3,3. No attempts were made to include additional complexes as the remaining residuals were too small to justify this ($\sigma(H)$ = 0.07 mM). The results of the final calculation where the different formation constants were refined on the whole data set are given in Table 1. In order to visualize the amounts of different species, the program SOLGASWATER (26) was used and calculated distribution diagrams are presented in Fig. 4.

In the μ = 0.15 NaCl HL:M 3:1 studies, the computations allowed for the presence of hydrolytic species of Al and Ga with formation constants for these various metal species taken from ref. 10. The stability constants for the main species ML^{2+}, ML_2^+, and ML_3 were determined by using the Fortran computer program BEST (27). Because of the presence of mixed hydroxo/ligand/aluminum complexes noted from the μ = 0.6 M data, these 3:1 results are noted in the results and discussion section only for comparison between the two metal ions.

Results and discussion

Hehm

The yield of Hehm was improved significantly by increasing the ratio of EDSA to diketene to 1.3:1 from 1:1 (13) and by refluxing for 6 h (Scheme 1). Any impurities in the starting materials or benzene solvent resulted in a red oil, shown by thin layer chromatography to consist of at least eight products. Hexanes extraction of the oil gave rise to Hehm and another product (Hehbm) that was separable from Hehm by fractional crystallization. For this reason, both the benzene and the diketene were distilled before use, and the EDSA was checked for impurities by ^{1}H NMR. Using pure starting materials in the appropriate stoichiometry resulted in a 75% yield of Hehm, which was then recrystallized from ethanol.

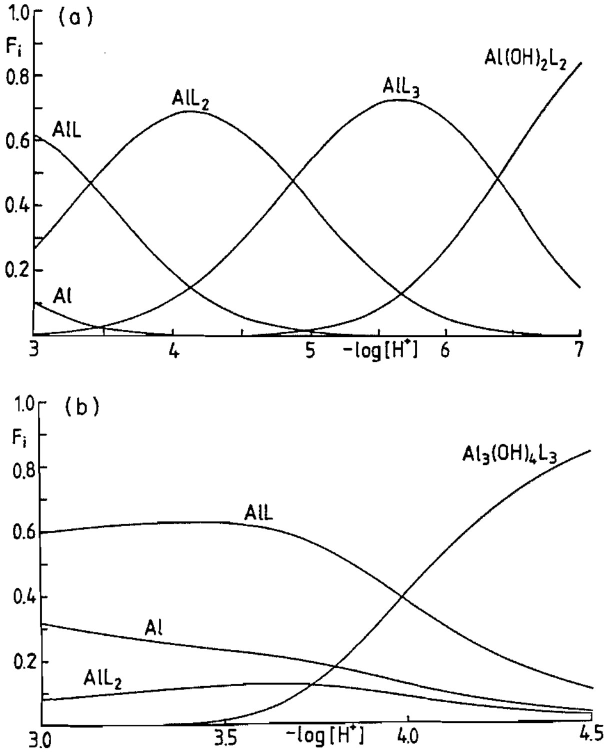
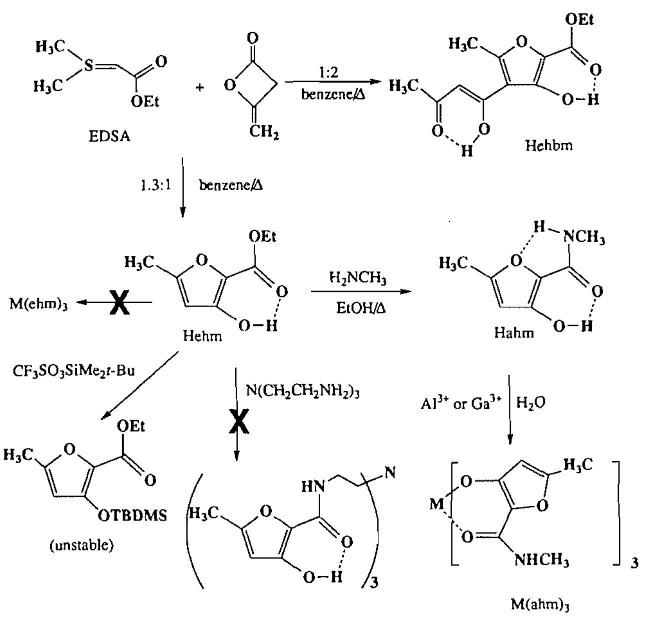


FIG. 4. Distribution diagrams F_i vs. −log [H^+], where F_i is defined as the ratio between Al^{3+} in a species and total Al^{3+}. The total ligand and Al^{3+} concentrations (mM): (*a*) 5 and 1, respectively, and (*b*) 5 and 5, respectively.

A short communication characterized Hehm only by elemental analysis and mp (13). In our work, the IR spectrum of Hehm showed a broad OH stretch at 3240 cm^{-1} indicative of a hydrogen bonded, rather than a free, OH group. Hehm also has two strong bands occurring at 1670 and 1630 cm^{-1} corresponding to C=O and C=C stretches, respectively (28). The C=O stretch occurs at a lower energy than in saturated esters due to exten-



SCHEME 1

sive conjugation and hydrogen bonding with the hydroxyl hydrogen, analogous to that seen with isomaltol (9). There are three bands in the C—O stretch region at 1260, 1180, and 1080 cm^{-1}, but it is not possible to assign any one band due to ring vibrations and C—H bending modes occurring in the same region. The ^{1}H NMR spectrum showed the presence of an ethyl group with chemical shifts diagnostic of esters. The long range coupling between the ring methyl hydrogens and the adjacent ring hydrogen is also consistent with the Hehm structure. A broad OH peak was also seen further downfield at δ 8.45 in CDCl$_3$. The EI mass spectrum of Hehm showed a parent peak at *m/z* 170, a peak at *m/z* 142 from loss of ethanol, and a base peak at *m/z* 124 from fragmentation typical of β-hydroxy esters by means of the McLafferty rearrangement (29).

Functionalization of Hehm

Hehm did react with methylamine to form the amide Hahm, but did not react completely with triamines such as tren to form potentially hexadentate chelating ligands (Scheme 1). With tren (dioxane, 24 h, 65°C) there was evidence that two of the three amines had reacted to form a difunctionalized compound with the third arm unreacted. There was, however, ample evidence that Hehm would not lend itself to a variety of transformations. Its reaction with di(isobutyl)aluminumhydride gave starting material; even functionalization of the 3-OH was elusive as reactions with benzyl chloride, or KH/benzyl bromide, yielded no reaction. The only successful reaction, the protection of the 3-hydroxy group as a *t*-butyldimethylsilyl ether, worked satisfactorily (Scheme 1); however, the protected compound underwent basic hydrolysis (NaOH/THF) to yield the starting material. A considerable number of attempts were made to make Hehm analogs in which the ester functionality was more active in order to complete the target hexadentate molecule; these were all unsuccessful.

Metal complexes of Hehm

Metal complexes of Hehm were prepared by a 3:1 stoichiometric addition of ligand to metal in a 3:2 water:ethanol solution due to the low water solubility of Hehm. The pH was initially raised to 9, and upon slow addition of the metal salt, the pH dropped to ~ 2. The pH was then raised again to 6.5 with 2 M NaOH resulting in an off-white precipitate. ^{1}H NMR, IR and MS evidence was found for the Al and Ga complexes M(ehm)$_3$, but isolation of analytically pure samples was impossible, and the spectra always contained features attributable to Hehm. Hehm reversibly hydrolyzes under the acidic synthetic conditions, so that as the pH was increased from 2 to 7, only low yields of the complexes were found. The isolated products usually contained ~ 20% Hehm. Any attempts to purify the complexes resulted in decomposition to starting materials. The IR spectra showed the expected bathochromic shifts in $\nu_{C=O}$, but there was also a peak at 1670 cm^{-1} from Hehm. The DCI (negative ion detection) mass spectrum of the gallium complex of Hehm showed two parent ion peaks corresponding to [ML$_3$ − H]$^-$ at *m/z* 575 and 577 (^{69}Ga, ^{71}Ga). The base peaks were *m/z* 547 and 549 ([M(ehm)$_3$ − CH$_2$CH$_3$]$^-$) suggesting that a gallium complex incorporating one hydrolyzed Hehm ligand may be formed.

Hehbm

If the reaction of EDSA and diketene was carried out using an excess of diketene, rather than an excess of EDSA, the side product in the synthesis of Hehm became the predominant product (Scheme 1). This product (Hehbm-4-(1′,3′-butanedionyl)-2-ethoxycarbonyl-3-hydroxy-5-methylfuran) was characterized by IR, NMR, MS, and elemental analyses. If two equivalents of diketene react instead of one, the extra diketene unit is attached at the 4 position of the ring. Hehbm has potential as a ligand in its own right, and has not been reported in the literature. The mass spectrum of Hehbm showed a parent peak at *m/z* 254, loss of a methyl group (*m/z* 239), loss of CH$_3$CO and a methyl (*m/z* 197), and loss of ethanol from the 197 peak (*m/z* 151). The base peak at *m/z* 124 is from the loss of CO from the *m/z* 151 fragment peak. The ^{1}H NMR spectrum in deuterated chloroform confirmed the structure shown (Scheme 1) by comparison with the spectrum of Hehm. There was no long range coupling between the methine hydrogen and the furan ring methyl hydrogens (as seen in Hehm), thus providing evidence that the methine hydrogen is not directly attached to the C-4 ring carbon. Only one peak due to the OH hydrogen on the side chain at the 4-position is seen at 8.45 ppm, suggesting that strong hydrogen bonding is occurring in the enol form in solution. Further evidence to support this structure was found in the ^{13}C NMR spectrum (CDCl$_3$). An attached proton test (APT) showed twelve carbons present, three of which were methyl, one methylene, one methine, and six quaternary. The extra C$_4$ unit attached to the 4-position of the ring showed ^{13}C NMR chemical shifts of 179.4, 99.1, 191.4, and 24.7 ppm, analogous to a similar β-diketone compound (30).

The positions of the various ring substituents were confirmed by using the NMR technique SINEPT. Irradiation of the methine hydrogen on the side chain on the ring 4-position resulted in the enhancement of ^{13}C signals at 99.1 ppm (one bond coupling), 191.4 and 179.4 ppm (two bond coupling), and at 111.1 ppm (three bond coupling). No enhancement was seen at the methyl carbon on the C$_4$ side chain. The pulse sequence requires a known $^3J_{CH}$ value for three bond coupling (in this case 4 Hz), or an approximation if not known, such that enhancement of the ^{13}C signal will be selective to coupled carbons that are three bonds away. However, some enhancement breakthrough can occur at carbons that are coupled through only one or two bonds if the coupling constants through one and/or two bonds are multiples of the chosen $^3J_{CH}$ value; the ^{13}C enhancements at 99.1, 191.4, and 179.4 ppm are all due to breakthrough. The lack of enhancement expected at the methyl carbon on the C_4 side chain and at the ring 4 carbon may be because the time involved in the refocussing sequence is longer than the hydrogen relaxation time, a factor commonly found when trying to enhance carbon signals through three bonds. This results in the hydrogens relaxing to their normal Boltzmann distribution of populations before the ^{13}C spectrum is acquired. However, the enhancement breakthroughs as well as the expected enhancement, confirm the presence of the predicted side chain, which is bonded to the 4-position of the ring. Irradiation of the methyl at the 5 position resulted in enhancement of the carbon signals at 160.8, 15.4 ppm, as well as 191.4, 99.1, and 24.7 ppm. The 15.4 and 160.8 ppm enhancements occur through two and three bond couplings, respectively. The other three enhancements are actually due to the irradiation of the methyl group on the C_4 side chain, also showing enhancements due to one (24.7 ppm), two (191.4 ppm), and three (99.1 ppm) bond coupling. Simultaneous irradiation of both methyl groups was seen because the irradiation was not selective enough to distinguish between the two methyl groups. This SINEPT experiment shows that the ring 5-methyl is bonded to a carbon having a chemical shift of 160.8 ppm, and therefore must be bonded to the carbon next to the ring oxygen. This experiment also reinforces the structure of the C_4 side chain. Due to the presence of two metal binding sites on Hehbm, its use as a ligand was not pursued in this work but should be of interest.

Hahm

Hahm (3-hydroxy-5-methyl-2-(*N*-methylformamido)furan) is a new potentially bidentate amide ligand which has not been previously reported, to our knowledge. Hahm was prepared in high yield by refluxing overnight equimolar quantities of Hehm and methylamine (40% in H_2O) in ethanol. Reactions of isomaltol (**3**) with methylamine, or other primary amines, resulted in 6-membered-ring pyridinone insertion products (**2**) obviating the formation of furan-based Schiff base chelating agents (31); however, the fact that Hehm contains a bulkier methyl group at the 5 position on Hehm rather than a hydrogen, favored the formation of an amide, and no pyridinones were detected. Two intramolecular hydrogen bonds probably provide a very stable structure for Hahm (Scheme 1). In the solid state, Hahm is a stable off-white powder; however, in water, it undergoes a slow decomposition which is time-, concentration-, and pH-dependent. Unusual aqueous solution behavior was first observed during the potentiometric titrations; as a result compound preparation (*vide infra*) and solution studies in water were undertaken with freshly prepared solutions.

The infrared spectrum of Hahm, in the solid form, showed an N—H stretch at 3390 cm^{-1}, suggesting that a conjugate structure predisposed to chelation may be formed (Scheme 1). The O—H stretching vibration results, due to hydrogen bonding, in a broad band centered around 3100 cm^{-1}. Due to solubility limitations in non-protic solvents, solution studies to investigate the hydrogen bonding in Hahm, although desirable, were not undertaken. A band characteristic of all amides is the strongly absorbing $\nu_{C=O}$ (amide I band) which occurs at 1665 cm^{-1} in Hahm. There is considerable mixing of the C=O and the C=C vibrations such that the bands at 1665 and 1610 cm^{-1} are most likely combination bands, being primarily due to $\nu_{C=O}$ and $\nu_{C=C}$, respectively. The broad band at 1575 cm^{-1} (amide II band) is a combination band primarily due to a δ_{NH} coupled to a ν_{CN}. The C—N stretch (amide III band) region occurs between 1305 and 1220 cm^{-1}, but because of the presence of many other bands in this region, a definite assignment was not possible.

The ^1H NMR spectra of Hahm were obtained in D_2O, CD_3OD, and DMSO-d_6. In all solvents, the spectra of the ring substituents were consistent with the proposed structure (three peaks in a 3:3:1 ratio). A small long range coupling (1 Hz) between the ring hydrogen at the 4-position and the methyl group at the 5-position was also observed. The EI mass spectrum of Hahm showed the parent peak at *m/z* 155; loss of a methyl group resulted in a peak at *m/z* 140 and loss of N—CH_3 gave rise to a peak at *m/z* 126.

Hahm complexes

Synthesis of the metal complexes of Hahm in high yield were carried out in water, but required that the pH be raised to 9 initially due to the lower water solubility of Hahm. The nitrate salt of the desired metal was then added to a freshly prepared Hahm solution, giving a 3:1 Hahm-to-metal ratio; the pH was readjusted to ~7. The aluminum and gallium complexes were obtained in 72 and 75% yields, respectively.

Upon coordination to the metal, the N—H and O—H stretches in the IR spectrum broadened to cover the ~3500 to 2800 cm^{-1} region, with maximum absorbance at 3400 cm^{-1}. Notably, the carbonyl stretch shifted 20 to 40 cm^{-1} lower in the complexes, consistent with complexation, and there was one very strong amide band at 1530 cm^{-1}, with weaker shoulder bands at higher wavenumbers. The two bands at 1610 and 1575 cm^{-1} in the spectrum of Hahm shifted into one overlapped band at 1530 cm^{-1}.

The ^1H NMR spectra of the Hahm complexes were consistent with the formulations; they showed that the environment at the 5-methyl was scarcely affected by chelation to the metal and the 1 Hz coupling constant between the ring 4-hydrogen and 5-methyl group, which was small for the ligand, was unresolvable for the metal complexes. The ring hydrogen and the amide methyl underwent significant shifts, since they are closer to the binding site. $Ga(ahm)_3$ decomposed in methanol, showing a broad shoulder or additional peaks from the free ligand. A spectrum consistent with the proposed structure was obtained in pyridine-d_5. In an effort to detect the amide hydrogen, DMSO-d_6 was used, but both the aluminum and gallium complexes decomposed becoming solvolyzed in this solvent.

The metal complexes decomposed under electron impact ionization conditions, so their mass spectra were obtained by fast atom bombardment ionization. Peaks from HML_3^+, ML_2^+, and ML^+ were present for both complexes. For the aluminum complex, the base peak was that from ML_2^+, while a weak $M_2L_5^+$ peak was observed at *m/z* 824, typical of neutral tris(bidentate) chelate complexes (4). The mass spectrum of the gallium complex showed many peaks due to the matrix (thioglycerol), but the most intense metal–ligand fragment was ML_2^+. Peaks due to HML_3^+ and $M_2L_5^+$ were observed with the appropriate isotopic ratios, the former being more intense.

Stability constants for $M(ahm)_3$

Solution potentiometry at $\mu = 0.6$ M demonstrated that Hahm is a weak acid ($K_a = 10^{-7.09}$) and that the ahm$^-$ anion is not an outstanding binding group for aluminum (Table 1). The ahm$^-$

anion, however, may have potential as the metal binding component of higher dentate chelating agents. Table 1 lists the formation constants β_{pqr} at μ = 0.6 M as defined in the experimental section. The speciation was characterized by a series of $AlL_n^{(3-n)+}$ complexes (n = 1, 2, 3). These had the following stepwise constants: log K_1 = 7.28, log K_2 = 6.14, log K_3 = 4.83 as calculated from the data in Table 1 and defined by:

$$[5] \quad K_n = \frac{[ML_n^{\{3-n\}+}]}{[ML_{n-1}^{\{4-n\}+}][L^-]}$$

(for an overall stability constant for the $Al(ahm)_3$ complex of $10^{18.25}$). The formation constants are less than those for the group 13 M^{3+} complexes of the 2,4-pentanedionato (acac) anion where log K_1 is ~ 8.7, log K_2 ~ 7.8, and log K_3 ~ 6.5 (32).

In neutral solutions with excess ligand ($B/C > 3$), a deprotonation of the AlL_3 complex was observed with elimination of the ligand. Whether the resulting –4,2,1 complex was a mixed hydroxo complex, $[Al(OH)_2L_2]^-$, or a species where the amide N is deprotonated cannot be predicted from the pH measurements; however, it seems reasonable to assume this species to be a mixed hydroxo complex. Similar anions have been found in other Al^{3+} systems with ligands forming complexes of high and intermediate stability, such as polycarboxylates like oxalate (33) and citrate (20), polyphenols like gallate (15), catecholate (34), and 1,2-dihydroxynaphthalene-4-sulfonate (35), as well as aromatic *o*-carboxylic phenols like salicylate (36). All these complexes are formed in neutral or slightly alkaline solutions and can be regarded as precursors to the $[Al(OH)_4]^-$ ion. In acidic solutions ($-\log [H^+] \approx 4$) with $B/C < 3$ a cationic trinuclear complex is formed (cf. Fig. 4*b*). A possible structure of this complex is $[Al_3(OH)_4L_3]^{2+}$, consistent with the connection between the binary hydrolysis (cf. $[Al_3(OH)_4]^{5+}$) and mixed ligand/hydroxo complexes formed. Mixed complexes of this type have been reported in several Al^{3+} systems and seem to be formed more as a rule than as an exception (37).

For purposes of rough comparison, the pK_a of Hahm and the logarithms of the overall formation constants for the 3:1 aluminum and gallium complexes were determined from the 0.15 M data to be 7.15, 19.5, and 20.5, respectively. Determination of the protonation constant of Hahm actually showed two inflection points, one corresponding to the deprotonation of the hydroxyl proton, and one that might be due to the deprotonation of the amide nitrogen ($-\log K \approx 12.4$); however, the ionic strength was no longer constant at $-\log [H^+] > 12$. Although the overall values are higher than those of isomaltol (9), at millimolar concentration, the predominant species was still due to undesirable hydrolysis, at pH greater than 7 for gallium and at pH greater than 8.5 for aluminum. The onset of hydrolysis was delayed until a higher pH compared to isomaltol, but still occurred to a significant extent. At higher ratios of Hahm:M, the ligand easily competes with hydrolysis, such that the ML_3 species predominate in the intermediate pH regime.

Concluding remarks

The synthesis of Hehm can be carried out cleanly and in high yield if the starting materials are pure and an excess of EDSA is used. A close analogue of Hehm, Hehbm, was formed as an impurity if the ratio was inappropriate and as a major product if a 1:1 ratio of EDSA:diketene was used. Attempts to prepare potentially hexadentate ligands based on the amidation of Hehm failed and Hehm did not undergo reactions typical of an ester; however, Hahm was produced in high yield from Hehm and methylamine. Aluminum and gallium complexes of Hahm have been prepared and thoroughly characterized; they have higher formation constants than their isomaltol analogs, likely as a result of the amide carbonyl being a harder donor by resonance than a ketone carbonyl. The Al system has been shown by extensive potentiometric study to contain mixed ahm⁻/hydroxo $[Al(OH)_2L_2]^-$ and $[Al_3(OH)_4L_3]^{2+}$ complexes, in addition to the simple $AlL_n^{(3-n)+}$ species (n = 1, 2, 3).

Acknowledgements

Acknowledgement is made to the British Columbia Health Research Foundation, NSERC of Canada, the U.S. Public Health Service (CA 48964), and the Swedish Natural Science Research Council for support of this work, to Drs. Ray Andersen and Nick Burlinson for most helpful discussions, and to Dr. Lars-Olaf Öhman for assistance.

1. I. Fattahpour Sedeh, S. Sjöberg, and L.-O. Öhman. J. Inorg. Biochem. **50**, 119 (1993).
2. D.J. Clevette, D.M. Lyster, W.O. Nelson, T. Rihela, G.A. Webb, and C. Orvig. Inorg. Chem. **29**, 667 (1990).
3. Z. Zhang, D.M. Lyster, G.A. Webb, and C. Orvig. Nucl. Med. Biol. **19**, 327 (1992).
4. M.M. Finnegan, T.G. Lutz, W.O. Nelson, A. Smith, and C. Orvig. Inorg. Chem. **26**, 2171(1987).
5. T. Hedlund and L.-O. Öhman. Acta Chem. Scand. **A42**, 702 (1988).
6. W.O. Nelson, T.B. Karpishin, S.J. Rettig, and C. Orvig. Inorg. Chem. **27**, 1045 (1988); W.O. Nelson, S.J. Rettig, and C. Orvig. Inorg. Chem. **28**, 3153 (1989).
7. C.A. Matsuba, W.O. Nelson, S.J. Rettig, and C. Orvig. Inorg. Chem. **27**, 3935 (1988).
8. D.J. Clevette, W.O. Nelson, A. Nordin, C. Orvig, and S. Sjöberg. Inorg. Chem. **28**, 2079 (1989).
9. T.G. Lutz, D.J. Clevette, S.J. Rettig, and C. Orvig. Inorg. Chem. **28**, 715 (1989).
10. C.F. Baes, Jr. and R.E. Mesmer. The hydrolysis of cations. 2nd. ed. Wiley, New York. 1976.
11. W.O. Nelson, T.B. Karpishin, S.J. Rettig, and C. Orvig. Can. J. Chem. **66**, 123 (1988).
12. R.L.N. Harris. Aust. J. Chem. **29**, 1329 (1976); Th. Severin and A. Loidl. Z. Lebensm. Unters.-Forsch. **161**, 119 (1976).
13. H. Takei, M. Higo, K. Saito, and T. Mukaiyama. Bull. Chem. Soc. Jpn. **41**, 1738 (1968).
14. G.B. Payne. J. Org. Chem. **32**, 3351 (1967).
15. L.-O. Öhman and S. Sjöberg. Acta Chem. Scand. Ser. A, **A35**, 201 (1981).
16. G. Gran. Acta Chem. Scand. **4**, 559 (1950).
17. G. Gran. The Analyst, **77**, 661 (1952); Anal. Chim. Acta, **206**, 111 (1988).
18. L.-O. Öhman and W. Forsling. Acta Chem. Scand. Ser. A, **A35**, 795 (1981).
19. L.-O. Öhman, S. Sjöberg, and N. Ingri. Acta Chem. Scand. Ser. A **A37**, 561 (1983).
20. L.-O. Öhman. Inorg. Chem. **27**, 2565 (1988).
21. N. Ingri and L.G. Sillén. Ark. Kemi, **23**, 97 (1964).
22. N. Arnek, L.G. Sillén, and O. Wahlberg. Ark. Kemi, **31**, 353 (1969); P. Brauner, L.G. Sillén, and R. Whiteker. Ark. Kemi, **31**, 365 (1969).
23. L.G. Sillén. Acta Chem. Scand. **16**, 159 (1962).
24. L.G. Sillén and B. Warnqvist. Ark. Kemi, **31**, 341 (1969).
25. H. Rossotti. The study of ionic equilibria. Longman, London. 1978. p. 76.
26. G. Eriksson. Anal. Chim. Acta, **112**, 375 (1979).
27. R.J. Motekaitis and A.E. Martell. Can. J. Chem. **60**, 2403 (1982).

28. L.J. Bellamy. Infrared spectra of complex molecules. Vol. 2. Chapman and Hall, New York. 1980. p. 210.
29. R. Grigg, M.V. Sargent, D.H. Williams, and J.A. Knight. Tetrahedron, **21**, 3441 (1965).
30. R.J. Andersen, M.J. Le Blanc, and F.W. Sum. J. Org. Chem. **45**, 1169 (1980).
31. T.G. Lutz. M.Sc. thesis, University of British Columbia, Vancouver, BC. 1988.
32. A.E. Martell and R.M. Smith. Critical stability constants. Vol. 3. Plenum, New York. 1977. p. 246.
33. L.-O. Öhman and S. Sjöberg. J. Chem. Soc. Dalton Trans. 2665 (1985).
34. L.-O. Öhman and S. Sjöberg. Polyhedron, **2**, 1329 (1983).
35. L.-O. Öhman, S. Sjöberg, and N. Ingri. Acta Chem. Scand. Ser. A, **A37**, 561 (1983).
36. L.-O. Öhman and S. Sjöberg. Acta Chem. Scand., Ser. A, **A37**, 875 (1983).
37. L.-O. Öhman and S. Sjöberg. *In* Metal speciation: theory, analysis and application. *Edited by* J.R. Kramer, H.E. Allen. Lewis Publishers, Chelsea, MI. 1988. p. 1.