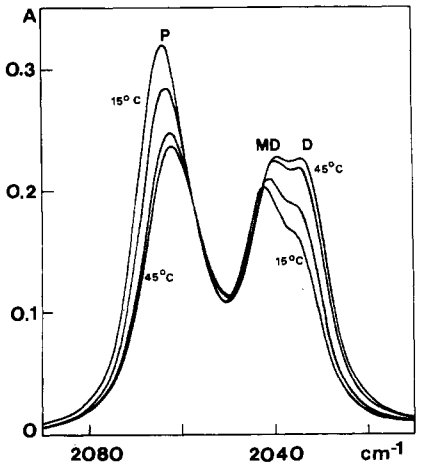

Figure 3. Infrared spectra of a LiCl (0.053 M)–LiSCN (0.036 M) solution in THF (33%) + benzene at temperatures of 15, 25, 35, and 45 °C. Cell thickness = 56 μm.

indicate that the dimerization enthalpy of LiCl in THF is about 1 kcal/mol, which is in agreement with a stability of Li_2Cl_2 greater than that of $(LiNCS)_2$. From these results it can be concluded that the bonding is the same in pure and in mixed dimers and that lithium halide and thiocyanate aggregates are quite similar.

Mixed Tetramers. The investigation of mixed aggregates has also been performed in ethers. These solvents belong to the solvent class that has been called DT (dimer–tetramer). The equilibrium constant of the tetramerization reaction $2(LiNCS)_2 = (LiNCS)_4$ is strongly dependent on the steric hindrance of the alkyl residues R and R′ of the solvent ROR′.[11b,13] When both R and R′ are unbranched (Et_2O, Bu_2O) or when R′ is a methyl group (*t*-Bu-MeO) the tetramerization constant is very low (~0.1 M^{-1}). Lithium chloride is insoluble in ethers while lithium bromide is moderately soluble. It is completely tetramerized in Et_2O.[4] The tetramers Li_4Br_4 and $(LiNCS)_4$ have the same cubane-like structure.[9,13] Lithium iodide, as well as lithium perchlorate,[19] is highly soluble in ethers and probably less aggregated than LiBr.

LiBr–LiSCN solutions have been investigated in the five above ethers. In all cases a new band is observed at 2003 ± 1 cm^{-1}. This value is very close to the mean ν(CN) frequency in $(LiNCS)_4$:

$$\nu(CN) = \frac{1}{4}\nu(A_1) + \frac{3}{4}\nu(T_2) = \frac{1}{4}2022 + \frac{3}{4}1993 = 2000\ cm^{-1} \quad (4)$$

Hence in both cases the SCN groups are bonded in the same manner (μ_3). Job's method has been applied to LiBr–LiSCN solutions in Et_2O (Figure 2). Both LiSCN and LiBr are in well-defined states of aggregation: $(LiNCS)_2$ and Li_4Br_4. The maximum of Job's plot is located at the composition 3LiBr, LiSCN. Consequently, in the concentration range that has been used only two tetramers are found in equilibrium: Li_4Br_4 and Li_4Br_3NCS. This behavior is consistent with a decrease in the stability of aggregates from Li_4Br_4 to $(LiNCS)_4$. Finally LiI–LiSCN solutions have been investigated in ethers. In Et_2O we did not find any new absorption band, but one or two such bands were found between 2001 and 2006 cm^{-1} in Bu_2O, *s*-BuEtO, and *i*-PrPrO. These frequencies are in agreement with a μ_3 bonding of SCN, and they are attributed to mixed tetramers $Li_4I_p(NCS)_{4-p}$. The finding of these species in the most associating ethers only is in agreement with a weak aggregation of LiI.

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Neutral Water-Soluble Post-Transition-Metal Chelate Complexes of Medical Interest: Aluminum and Gallium Tris(3-hydroxy-4-pyronates)

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A series of tris(3-hydroxy-4-pyronato)aluminum(III) and -gallium(III) complexes have been prepared with the pyrones pyromeconic acid (Hpa), maltol (Hma), kojic acid (Hka), and chlorokojic acid (Hck). They have been characterized by their IR, UV, ^1H and ^{27}Al NMR, and fast atom bombardment (FAB) mass spectra. The complexes of Hma and Hka are water-soluble (2–60 mM) but retain their neutral charge in water according to conductivity measurements. Variable-pH ^{27}Al NMR spectra demonstrate that $Al(ma)_3$ and $Al(ka)_3$ are stable to hydrolysis in pH 4.5–8 solutions while *n*-octanol/water partition coefficients show that the most water-soluble complexes—$Al(ma)_3$ (60 mM) and $Ga(ma)_3$ (31 mM)—are also the most lipophilic. Preliminary toxicity studies show that $Al(ma)_3$ is extremely neurotoxic.

Introduction

Active investigations, in the past 30 years, of the role that metal ions play in biological processes[1] have been supplemented more recently by studies directed toward the use of metal complexes for medical applications, both therapeutic and diagnostic.[2] In this manner, the bioinorganic chemistry of rarer metals such as technetium, platinum, and plutonium is gradually being integrated with that of the commonly occurring metals such as iron, copper, and zinc to afford a cohesive overview of the varied biological and medical roles that may be played by all the elements in the periodic table. A new, directed approach to the coordination chemistry of many metals results where the basic chemistry is explored with ligands that may either direct the metal in vivo or impart certain desired properties to the resulting complex for subsequent in vivo study.

As recently as 1974, aluminum was regarded as a generally benign element,[3] however, a considerable body of evidence[4-10] has

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accumulated in the last 20 years linking Al with neurological dysfunctions (e.g. Alzheimer's disease,[4,5] dialysis encephalopathy,[6] amyotrophic lateral sclerosis[7]) and bone disorders (e.g. osteoporosis,[8] osteomalacia[9]). In Alzheimer's disease, for instance, intracellular sites of Al accumulation are the neurofibrillary tangles in the nuclei of the brain cells, and the senile plaques, where it is found in the form of aluminosilicates.[10] The general agreement concerning aluminum's involvement in the pathogenesis of Alzheimer's disease does not extend to its role therein or to the mechanism by which it is delivered to the nuclei of brain cells. Simple coordination chemistry of aluminum that might be pertinent to its role in disease states or to any in vivo system is almost nonexistent.

A similar situation is found for aluminum's group 13 congener gallium. The discovery, in the 1960s, by Edwards and Hayes[11] that ^{67}Ga administered as the citrate localized in soft tumor tissue engendered considerable clinical research in the area. The citrate is now widely used in oncological nuclear medicine for tumor detection;[12] however, the mechanism of uptake of ^{67}Ga by tumor cells remains to be clarified.[13] A surge of activity in chemical studies of gallium might have been expected, but it never transpired despite the fact that Ga has not one but two isotopes that lend themselves well to the detection methods of nuclear medicine: ^{67}Ga ($t_{1/2}$ = 78.1 h; γ = 93.3, 185, 300 keV; accelerator product) and ^{68}Ga ($t_{1/2}$ = 68.3 min; γ = 511 keV from β^+ annihilation; generator product). Despite the easy availability of these nuclei, they have been limited to the detection of soft tissue tumors[12,13] and inflammatory lesions.[14,15] The known chemistry relative to radiopharmaceutical development has remained a limited field.[16-18]

The extensive complicated hydrolysis chemistries of aluminum[19] and gallium[20] have limited most quantitative studies of solution reactions of these elements to acidic media,[21] thereby leaving undeveloped the study of aluminum and gallium chelate complexes in aqueous solution, especially at neutral pH. If coordination chemistry of these two elements is to be relevant to their roles in disease states and diagnosis, respectively, then pH 7.4 is the regime of most interest.

We have recently reported an unusual aluminum complex ($Al(ma)_3$) that is stable to hydrolysis and quite soluble in aqueous solution at physiological pH.[22] The chelate complex is also of neutral charge, with the result that it is extremely neurotoxic,[23] presumably crossing brain cell walls with considerable facility and delivering the neurotoxic agent Al^{3+} to some as yet unidentified receptor.

The combination (for Al) of water solubility and neutral charge and the varied biological roles that may be played by Al and Ga have prompted us to conduct a more thorough study of the complexes formed by Al and Ga with several 3-hydroxy-4-pyrones: 3-hydroxy-4*H*-pyran-4-one (pyromeconic acid, Hpa), 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol, Hma), 5-hydroxy-2-(hydroxy-methyl)-4*H*-pyran-4-one (kojic acid, Hka), and 5-hydroxy-2-(chloromethyl)-4*H*-pyran-4-one (chlorokojic acid, Hck).

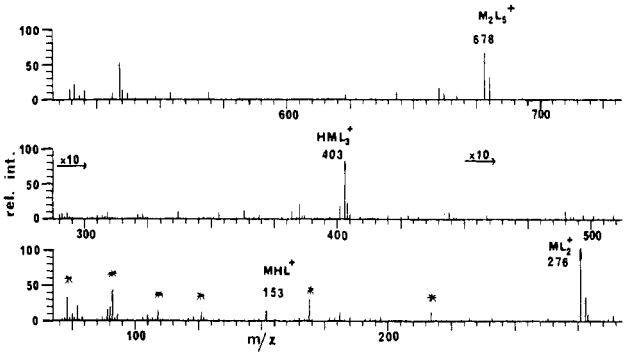
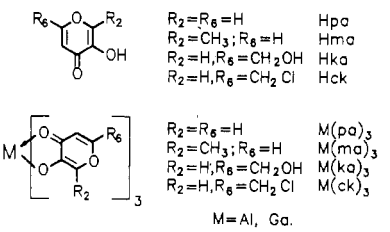


Figure 1. FAB mass spectrum of $Al(ma)_3$. Asterisked (*) peaks are due to the thioglycerol matrix.



Thermodynamic data for the complexation of Al^{3+} with Hka[24] and Hma[25] indicate very high overall formation constants (log β_3 = 19.5 and 21.8, respectively), suggesting that very stable complexes are formed. Complete characterization of these complexes is offered herein along with studies to determine which of them might be of interest for in vivo examination.

Experimental Section

Materials and Methods. All chemicals were reagent grade and were used as received unless specified: Ga ingots (Alfa), $Ga(NO_3)_3 \cdot 9H_2O$ (Alfa), $AlCl_3 \cdot 6H_2O$ (BDH), $Al(NO_3)_3 \cdot 9H_2O$ (Mallinckrodt), 8-hydroxyquinoline (BDH), kojic acid (Sigma), and maltol (Sigma or Aldrich). Pyromeconic acid was a gift of Professor J. H. Looker of the Univeristy of Nebraska (Lincoln, NE), and chlorokojic acid was prepared by the reaction of distilled thionyl chloride with kojic acid according to the method of Yabuta.[26] Water was deionized (Barnstead D8902 and D8904 cartridges) and distilled (Corning MP-1 Megapure still). A 1.37 M solution of $GaCl_3$ in HCl was prepared by dissolving Ga ingots (9.5610 g) in 70 mL of HCl with heating over 4 days and with periodic additions of HCl. This solution was cooled, diluted to 100 mL, and standardized by EDTA titration.

Conductivity studies in distilled water employed a Yellow Springs 3403 cell and a Serfass Model 15B1 conductivity bridge. Infrared spectra were recorded as KBr pellets in the range 4000–200 cm^{-1} with a Perkin-Elmer PE783 spectrophotometer and referenced to polystyrene film. Proton NMR spectra were recorded in D_2O, CD_3OD, or $CDCl_3$ with a Bruker WP-80 or a Varian XL-300 spectrometer. Mass spectra were obtained with either a Kratos MS50 (electron impact ionization, EI) or an AEI MS 9 (fast atom bombardment ionization, FAB) instrument. Ultraviolet spectra were recorded in the range 360–235 nm with a Perkin-Elmer Coleman 124 spectrophotometer. Octanol/water partition coefficients were determined spectrophotometrically for the water-soluble compounds from the ca. 300-nm band at room temperature by an established method.[27] Analyses for C, H, and Cl were performed by P.

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Borda of this department. Al and Ga were determined gravimetrically with 8-hydroxyquinoline.[28]

^{27}Al NMR. Spectra were recorded at 25 °C with the XL-300 operating at 78.16 MHz and accumulating 3500 transients with a pulse width of 15 μs, a spectral window of 50 KHz, and acquisition times of 0.05–0.20 s (usually 0.12 s). The spectra in Figure 1 were processed with a line-broadening function of 2 Hz. All spectra were referenced to 0.20 M $Al(ClO_4)_3$ in 0.10 M $HClO_4$ with D_2O added as a lock signal, and downfield chemical shifts are positive. For dilute samples it was necessary to correct each spectrum for Al in the probe head by subtracting a spectrum run under identical conditions with a tube of water.[29,30]

Tris(pyromeconato)aluminum(III), Al(pa)$_3$. To pyromeconic acid (1.000 g, 8.9 mmol) in 30 mL of water was added $Al(NO_3)_3 \cdot 9H_2O$ (1.100 g, 2.9 mmol) in 10 mL of water. The pH was adjusted to 5.2 with 2.0 N NaOH, and a white solid precipitated. It was recrystallized from hot water to yield 0.941 g (84%) of product, mp 300 °C dec. Anal. Calcd (found) for $C_{15}H_9AlO_9$: C, 50.02 (49.84); H, 2.52 (2.50); Al, 7.49 (7.38). Solubility: 2.8 mM in water, insoluble in other solvents. The resistance of a 1.0 mM aqueous solution was 190 kΩ. ^{27}Al NMR (H_2O): 39 ppm ($W_{1/2}$ = 410 Hz).

Tris(pyromeconato)gallium(III) Hemihydrate, Ga(pa)$_3$·0.5H$_2$O. To pyromeconic acid (0.691 g, 6.16 mmol) in 25 mL of water was added 1.37 M $GaCl_3$ (1.38 mL, 1.89 mmol). After pH adjustment to 5.2, a beige solid was removed by filtration. It was recrystallized from $CHCl_3$ to yield 0.724 g (95%) of product, mp 260 °C dec. Anal. Calcd (found) for $C_{15}H_{10}GaO_{9.5}$: C, 43.73 (43.49); H, 2.45 (2.26); Ga, 16.92 (17.11). Solubility: <1 mM in water (very slight); soluble in $CHCl_3$; insoluble in other solvents.

Tris(maltolato)aluminum(III), Al(ma)$_3$. With constant stirring, maltol (3.866 g, 30.7 mmol) and $Al(NO_3)_3 \cdot 9H_2O$ (3.812 g, 10.2 mmol) were added to 40 mL of deionized distilled water. The resulting yellow suspension was acidic (pH 2). The pH was adjusted to 8.3, and a pale yellow solution resulted. When the mixture was heated to 65 °C, a precipitate appeared and the yield was increased upon continued heating and reduction of volume. The resulting solid was filtered, washed with acetone, and dried overnight in vacuo. The yield of off-white plates was 3.53 g (86%). Recrystallization from methanol/ether via liquid diffusion[31] afforded off-white blocks suitable for X-ray structural analysis;[22] mp 240 °C dec. Anal. Calcd (found) for $C_{18}H_{15}AlO_9$: C, 53.74 (53.50); H, 3.76 (3.76); Al, 6.71 (6.50). Solubility: 60 mM, in water; soluble in acetonitrile, methanol, and ethanol. The resistance of a 1.0 mM aqueous solution was 300 kΩ. ^{27}Al NMR (H_2O): 39 ppm ($W_{1/2}$ = 900 Hz).

Tris(maltolato)gallium(III), Ga(ma)$_3$. The preparation was as for Al(ma)$_3$ with maltol (2.592 g, 20.55 mmol) and 1.37 M $GaCl_3$ (5.00 mL, 6.85 mmol). The yield of white microcrystalline powder was 2.75 g (90%). Recrystallization from methanol/ether gave white blocks or needles, mp 220 °C dec. Anal. Calcd (found) for $C_{18}H_{15}GaO_9$: C, 48.58 (48.32); H, 3.40 (3.45); Ga, 15.67 (15.70). Solubility: 31 mM in water; soluble in methanol and ethanol. The resistance of a 1.0 mM aqueous solution was 110 kΩ.

Tris(kojato)aluminum(III) Dihydrate, Al(ka)$_3$·2H$_2$O. The preparation was analogous to that for Al(ma)$_3$ with kojic acid (1.623 g, 11.4 mmol) and $Al(NO_3)_3 \cdot 9H_2O$ (1.428 g, 3.8 mmol); volume reduction to 15 mL by heating (75 °C) at pH 8 produced a yellow solid (1.24 g, 67%) and a brown filtrate, which was discarded. Recrystallization from methanol/ether gave a pale yellow microcrystalline solid, mp 235 °C dec. Anal. Calcd (found) for $C_{18}H_{19}AlO_{14}$: C, 44.46 (44.67); H, 3.94 (3.93); Al, 5.55 (5.78). Solubility: 5.5 mM in water; slightly soluble in methanol and ethanol. The resistance of a 1.0 mM aqueous solution was 220 kΩ. ^{27}Al NMR (H_2O): 40 ppm ($W_{1/2}$ = 950 Hz).

Tris(kojato)gallium(III), Ga(ka)$_3$. A preparation analogous to that for Ga(ma)$_3$ with kojic acid (2.133 g, 15.0 mmol) and 1.37 M $GaCl_3$ (3.65 mL, 5.0 mmol) yielded 2.246 g (91%) of an off-white microcrystalline compound. Recrystallization was from methanol/ether; mp 240 °C dec. Anal. Calcd (found) for $C_{18}H_{15}GaO_{12}$: C, 43.85 (43.75); H, 3.07 (3.29); Ga, 14.14 (14.23). Solubility: 2.0 mM in water; slightly soluble in methanol and ethanol. The resistance of a 1.0 mM solution was 230 kΩ.

Tris(chlorokojato)aluminum(III), Al(ck)$_3$. In 50 mL of water were dissolved chlorokojic acid (2.564 g, 16.0 mmol) and $AlCl_3 \cdot 6H_2O$ (0.966 g, 4.0 mmol). The pH was adjusted to 8.8, and an off-white solid precipitated. This was removed by filtration, washed with acetone, and recrystallized from chloroform/petroleum ether to yield 1.564 g (78%) of a white microcrystalline solid, mp 310 °C dec. Anal. Calcd (found) for $C_{18}H_{12}AlCl_3O_9$: C, 42.76 (43.00); H, 2.39 (2.28); Cl, 21.03 (20.78). Solubility: soluble in $CHCl_3$. ^{27}Al NMR ($CHCl_3$): 41 ppm ($W_{1/2}$ = 650 Hz).

Tris(chlorokojato)gallium(III), Ga(ck)$_3$. Chlorokojic acid (1.528 g, 9.52 mmol) was dissolved in 40 mL of 1:1 water/ethanol, and 1.37 M $GaCl_3$ (1.64 mL, 2.25 mmol) was added. The pH was adjusted to 8.7, and an off-white solid precipitated and was removed by filtration. The product was extracted in a Soxhlet apparatus with 300 mL of $CHCl_3$ overnight. The $CHCl_3$ solution was reduced in volume to 50 mL, and when petroleum ether was added and the mixture was cooled (−20 °C), a white solid appeared. This was removed by filtration and washed with ethanol to yield 1.178 g (95%) of product, mp 270 °C dec. Anal. Calcd (found) for $C_{18}H_{12}Cl_3GaO_9$: C, 39.43 (39.45); H, 2.21 (2.20); Cl, 19.40 (18.79). Solubility: sluggishly soluble in $CHCl_3$ and CH_2Cl_2.

Table I. Ultraviolet Spectral Data[a] and Partition Coefficients[b]

complex	λ_{max}, nm (ε, M^{-1} cm^{-1})	p
Al(pa)$_3$	296 (13 500)	0.076
	252 (8800)	
Ga(pa)$_3$[c]	313 (17 400)	
	247 (6800)	
Al(ma)$_3$	305 (18 800)	0.67
	250 (8900)	
Ga(ma)$_3$	305 (20 130)	0.51
	250 (9030)	
Al(ka)$_3$	296 (13 300)	0.088
	254 (14 900)	
Ga(ka)$_3$	297 (14 000)	0.080
	253 (13 920)	
Al(ck)$_3$[c]	323 (15 000)	
	265 (12 000, sh)	
Ga(ck)$_3$[c]	311 (14 800)	
	254 (12 000, sh)	

[a] In water saturated with *n*-octanol, except where noted; sh = shoulder. [b] In *n*-octanol/water; determined only for water-soluble compounds. [c] In $CHCl_3$.

Results and Discussion

The Al and Ga chelate complexes of several 3-hydroxy-4-pyrones can be readily prepared from aqueous solutions of the metal salts and several equivalents of ligand by raising of the pH to 5–9 and suitable workup. The yields are high, depending on the water solubility of the complex and the respective ligand. Analyses for three elements (of C, H, M, X) in each complex were consistent with the formation of tris(ligand)metal formulations; however, the compounds were in general quite hygroscopic, forming analyzable hemi-, mono-, and dihydrates. Correct analytical results were obtained only after drying at 80 °C in vacuo overnight followed by storage and analysis (C, H, or X) under a nitrogen atmosphere. The compounds are all nonvolatile, charring and decomposing above 200 °C. Significantly, several of the compounds are water-soluble (greater than 1 mM: Al(pa)$_3$, M(ma)$_3$, M(ka)$_3$) at neutral pH (6–8). In general, the Al compounds are at least twice as water-soluble as those of Ga, and the solubility is a function of the ring substituents, decreasing in the order CH_3 (M(ma)$_3$) > CH_2OH (M(ka)$_3$) > H (M(pa)$_3$) > CH_2Cl (M(ck)$_3$). Neither Al(ck)$_3$ nor Ga(ck)$_3$ is water-soluble, while Ga(pa)$_3$ is very sparingly soluble. As a result, solution characterization of these three complexes was carried out in $CHCl_3$ or CH_2Cl_2. The conductivity (resistance) measurements clearly indicate that all the water-soluble complexes remain uncharged at millimolar concentration in aqueous solution. Measured resistances of the five water-soluble complexes at 1 mM (100–300 kΩ) correspond to molar conductivities[32] Λ_M = 3–10 cm^2 Ω^{-1} M^{-1} while the measured resistance of purified water was about 400 kΩ and that of 1 mM KCl was 9.0 kΩ (Λ_M = 124 cm^2 Ω^{-1} M^{-1}).

The fairly unusual combination of neutral charge and water solubility suggested a study of *n*-octanol/water partition coefficients (p) as a very rough model of the lipid solubility and brain capillary permeability[33] of the complexes. The latter parameter

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Table II. FAB Mass Spectral Data (m/e)

peak	$Al(pa)_3$	$Ga(pa)_3$	$Al(ma)_3$	$Ga(ma)_3$	$Al(ka)_3$	$Ga(ka)_3$	$Al(ck)_3$	$Ga(ck)_3$
ML_2^+	249	291, 293	277	321, 319	309	351, 353	345, 347, 349	389[a]
HML_3^+	361	403, 405	403	447, 445	451	493, 495	505, 507, 509	549[a]
$M_2L_5^+$	609	693, 695, 697	679	763, 765, 767	759	843, 845, 847	851[a]	937[a]

[a] Broad envelope of peaks due to ^{69}Ga, ^{71}Ga and/or ^{35}Cl, ^{37}Cl. The most intense peak is listed.

is of interest if the complexes are to be of use in medical studies of the mobilization of metals into and out of mammalian brain. In Table I the ultraviolet spectral data for all the complexes is reported along with *n*-octanol/water partition coefficients. The $\pi \rightarrow \pi^*$ transition characteristic of each ligand is split into its two components (α- and p-bands)[34] upon coordination to the metal in the anionic form. Partition coefficients were determined from the lower energy band in each case and are highest for the two maltol complexes (also the most water soluble). The coefficients are high enough (about 0.1 or greater) to suggest the use of these complexes in studies of brain Al or Ga.[35] The highest p (for the maltol complexes) suggests that $Al(ma)_3$ might be of neurological interest (vide infra).

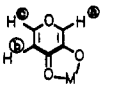
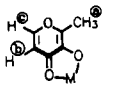
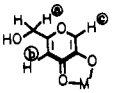
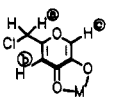
The mass spectra (Table II, Figure 1) were diagnostic of the complex formulations. In all cases, loss of one ligand from a ML_3 unit to give ML_2^+ (m/e 276 for $Al(ma)_3$) as the base peak was observed, as well as cationization by proton attachment to form HML_3^+ ($(M + 1)^+ - 403$) as a lower intensity parent peak—characteristic in FABMS.[36] The observation of $M_2L_5^+$ (m/e 678) peaks of very low intensity (ca. 1% of ML_2^+) was general in the compound series and occurred through the cationization of the molecular unit by attachment of a ML_2^+ unit (eq 1). Cationi-

$$ML_3 + ML_2^+ \rightarrow M_2L_5^+ \quad (1)$$

zation of molecular species by the attachment of H^+, Na^+, K^+, or tetraalkylammonium cations is well-known[37] in field desorption mass spectrometry (FDMS); however, the cationization reaction in eq 1, although more unusual, will surely prove to be quite general for FAB mass spectra of neutral chelate complexes. Simulations verified peak intensities in the peak envelopes (due to Ga and Cl) for $Ga(ck)_2^+$ and $HGa(ck)_3^+$, but for $Ga_2(ck)_5^+$ the intensities were too low for accurate measure and comparison.

Proton NMR chemical shifts (Table III) are consistent with coordination of the ligands to the metals in each case but allow little deduction as to the arrangement of the ligands about the metal because only one environment is observed for each proton. For three unsymmetric bidentate ligands situated around a central metal, the optical isomers Λ and Δ[38] and the geometrical isomers *fac* and *mer*[39] can exist. Assuming the former are rapidly interconverting, evidence for the latter may be sought in variable-temperature NMR studies. Some broadening of the peaks in $Al(ma)_3$ is observed at low temperature (−70 °C, CD_3OD, 300 MHz) but not enough to suggest the formation of new sets of resonances. The conclusion may be reached that at room temperature either (a) there is rapid interconversion of *fac* and *mer* that starts to be resolvable at −70 °C in CD_3OD or (b) the three different ligand environments in the *mer* arrangement are rapidly interconverting and that this interconversion is slowed at −70 °C. Distinguishing between these possibilities is a nontrivial matter, although the solid-state structure of $Al(ma)_3$ is known to be *mer*.[22] Both Al and Ga are considered to undergo very rapid isomerization and inversion in solution.[40]

Table III. ^1H NMR Data[a]

		M = H	M = Al	M = Ga
	H^a	8.14	8.50	8.00[b]
	H^b	6.58	7.00	6.70[b]
	H^c	8.09	8.26	7.90[b]
	J_{bc}	5.6	5.3	5.3[b]
	H^a	2.36	2.48	2.49
	H^b	6.47	6.85	6.86
	H^c	7.95	8.32	8.27
	J_{bc}	5.8	5.3	5.1
	H^a	4.50	4.63	4.67
	H^b	6.55	6.93	7.00
	H^c	8.06	8.12	8.23
	H^a	4.37[b]	4.43[b]	4.41[b]
	H^b	6.58[b]	6.83[b]	6.84[b]
	H^c	7.88[b]	7.96[b]	8.01[b]

[a] In D_2O except where noted; chemical shifts are in ppm downfield from Me_4Si and are singlets, or doublets where a coupling constant J_{bc} is indicated. [b] In $CHCl_3$.

Despite being quadrupolar ($I = {}^5/_2$), the ^{27}Al nucleus is a useful NMR probe because of its high natural abundance (100%) and sensitivity (0.206 relative to protons).[41] This has allowed acquisition of ^{27}Al spectra for the Al complexes; chemical shifts and line widths at half-height ($W_{1/2}$) are listed in the Experimental Section. The quadrupole moment ($Q = 0.149 \times 10^{-28}$ m^2) interacts with electric field gradients (at the nucleus) that couple the nucleus with molecular motions, and an efficient relaxation mechanism results. The broad line widths have their origin in this fast magnetic relaxation. The chemical shifts are all about 40 ppm, and the line widths are similar, except $W_{1/2}$ is significantly lower for $Al(pa)_3$. Chemical shifts of −40 to +20 ppm are often quoted[41] for hexacoordinate Al nuclei while AlO_6 species usually appear very close to 0 ppm ($[Al(H_2O)_6]^{3+}$ being the standard). The documented exceptions are the octahedral tris(hydroxamato) complexes and the alumichrome trihydroxamate peptides, which are observed at 36–42 ppm.[42] Both tris(3-hydroxy-4-pyronato)aluminum and tris(hydroxamato)aluminum complexes will not be subject to a rigorously octahedral field, the chemical shift reflecting this deviation. The line width also reflects this deviation, being subject to numerous parameters including temperature, solvent viscosity, exchange processes, and molecular symmetry and weight. The lower $W_{1/2}$ for $Al(pa)_3$ (410 vs. 900, 950 Hz) originates in either a higher molecular pseudosymmetry of the complex resulting from a lack of ring substituents on the ligand or a *fac* arrangement of ligands as in the crystallographically characterized $Fe(pa)_3$.[43] The latter is most likely as we have recently observed the ^{27}Al spectrum of a crystallographically characterized *fac* aluminum tripyridinone complex with a shift of 39 ppm and a line width of 580 Hz.[44]

Variable-pH ^{27}Al NMR has been used to study the formation of various Al complexes as a function of pH.[42,45-49] Figure 2 shows

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Table IV. Characteristic Infrared Absorptions (cm^{-1})[a]

assignt[b]	Hpa	$Al(pa)_3$	$Ga(pa)_3$	Hma	$Al(ma)_3$	$Ga(ma)_3$	Hka	$Al(ka)_3$	$Ga(ka)_3$	Hck	$Al(ck)_3$	$Ga(ck)_3$
$\nu_{O-H}(CH_2OH)$							3275	3340	3320			
ν_{O-H}(ring)	3140			3260			3180			3240		
ν_{C-H}(ring)	3110 m	3080 m	3080 m	3060 m	3080 m	3070 m	3100 m	3090 m	3090 m	3110 m	3080 m	3050 m
$\nu_{C-H}(CH_3)$				2920 m	2915 m	2920 m						
$\nu_{C=O}$	1655	1560	1550	1650	1570	1570	1655	1570	1565	1655	1575	1572
	1620	1608	1601	1620	1610	1610	1610	1615	1615	1625	1601	1615
$\nu_{C=C}$	1565	1520	1510	1558	1515	1505	1577	1520	1515	1585	1523	1517
	1457	1465	1455	1457	1465	1460	1467	1472	1470	1455	1470	1470
σ_{C-H}[c]	1107	1123	1123	1028	1040	1040	1070	1080	1080			
σ_{C-H}[d]	1001	1010	1010	920	920	925	940	950	945	955	955	960
	870	870	870	850	850	850	860	870	870	885	890	890
ν_{C-Cl}										745 m	745 m	742 m
		455	328		464	360		475	365 m		453	308
ν_{M-O}		433 m	291		445	270 m		410 m	290 m		425 m	290
		375 m	262 m?		410 m	230 m		400 m	240 m?		?	240 m?

[a] All strong or very strong (except m = moderate) intensity. [b] ν = vibration; σ = bending deformation. [c] In plane. [d] Out of plane.

spectra of $Al(ma)_3$ over the pH range 1.7–11. The observation of several peaks at acidic pHs illustrates that the various Al species are exchanging more slowly than their respective chemical shift differences. The spectrum of $Al(ma)_3$ at pH 7 is that whose parameters are listed in the Experimental Section. As the pH is lowered, three new peaks appear at 26, 13, and 0 ppm. The sharp line at 0 ppm is the standard $[Al(H_2O)_6]^{3+}$ formed from the complete hydrolysis of $Al(ma)_3$. The partial protonation of maltolate ligands in the coordination sphere of Al and their displacement by H_2O result in the formation of $[Al(ma)_2(H_2O)_2]^+$ (26 ppm) and $[Al(ma)(H_2O)_4]^{2+}$ (13 ppm) as the pH is lowered. This is verified by the relative intensities of the peaks as the pH is reduced. Spectra for tris(ligand)aluminum hydrolysis experiments have been observed for acetohydroxamate,[42] oxalate,[45] lactate,[47] and a variety of hydroxy carboxylate[47-49] ligands, although only with acetohydroxamate[42] have both the mixed-ligand species and both of the binary complexes been resolved. When the pH is raised, $Al(ma)_3$ undergoes basic hydrolysis as ligands are replaced by OH^-, forming, ultimately, aluminate ($[Al(OH)_4]^-$, 80 ppm, $W_{1/2} \cong 60$ Hz). In the basic hydrolysis of the lactate, mixed-hydroxo–lactato complexes were ascribed to a broad 60 ppm peak at pH 10.[46] There is no evidence for a similar species in this work, although a shoulder (33 ppm) and a very small peak (19 ppm) do appear at pH 11. These do not increase in intensity as the pH is raised to 12, where >90% of the Al occurs as $[Al(OH)_4]^-$. The window of stability to hydrolysis is therefore from about pH 4 to 9 at this concentration (0.05 M). Variable-pH spectra at lower concentration (0.004 M) for $Al(ma)_3$ and the less soluble $Al(ka)_3$ were quite similar, displaying a somewhat narrower window of hydrolytic stability (pH 4.5–8). Below this concentration, the amount of Al in the probe renders spectra almost meaningless, especially in the limit of several broad lines. This window of stability does suggest, however, that $Al(ma)_3$ and $Al(ka)_3$ are sufficiently hydrolytically stable for biological studies and should survive the variations of in vivo pHs, except the acidic conditions in the stomach. Attempts to use ^{71}Ga NMR in a similar study of $Ga(ma)_3$ were unsuccessful as the only observable peaks were $[Ga(H_2O)_6]^{3+}$ (0 ppm, $W_{1/2}$ = 250 Hz) and $[Ga(OH)_4]^-$ (190 ppm, $W_{1/2}$ = 600 Hz). The peak due to the complex was too broad (presumably several kilohertz) to be seen.

The four-band infrared pattern between 1660 and 1450 cm^{-1}, which is characteristic of the γ-pyrones,[50] is preserved in all the complexes although the energy ordering is changed upon coordination (Table IV). $\nu_{C=O}$[51] undergoes the largest bathochromic shift (75–105 cm^{-1}) upon coordination, as might be expected, while

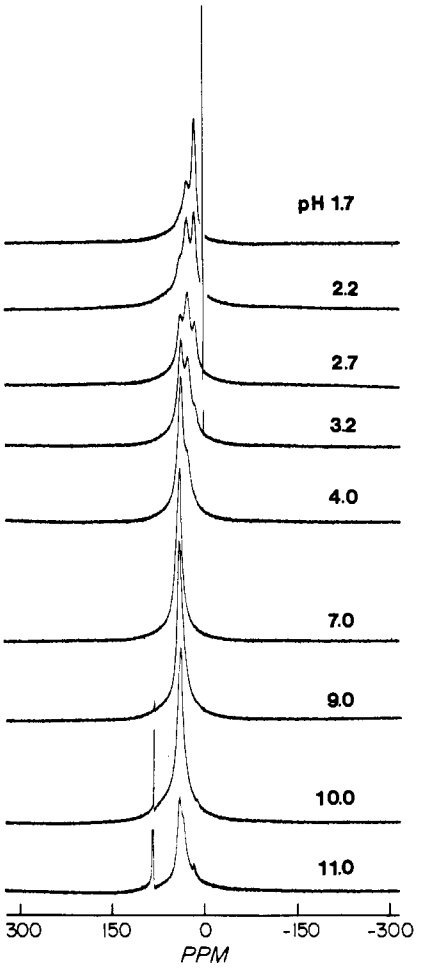

Figure 2. Variable-pH ^{27}Al NMR spectra of $Al(ma)_3$ (0.05 M).

the ring modes scarcely shift (Figure 3). The other stretches are assignable as three of the ring modes known to occur in pyrones, mostly of $\nu_{C=C}$ character (although there is considerable mixing of $\nu_{C=O}$ and $\nu_{C=C}$,[50] and are labeled as such. The different relative intensities as a function of absorption frequency (e.g. $\nu_{C=O}$ in Figure 3 for Hma and its complexes) have been noted previously in spectra of pyrones and pyridinones.[50] Assignments in the 1400–600-cm^{-1} region of ν_{C-O} and O—H deformations proved impossible, owing to the plethora of ring modes, C—H deformations, and cyclic ether modes. In the lower frequency region, the assignment of several ν_{M-O} bands is possible by comparing the spectra of both the Al and Ga complexes with that of the free ligand (Figure 3), although these may be coupled to chelate ring O—M—O motions or ring deformation modes and hence are quite tentative.

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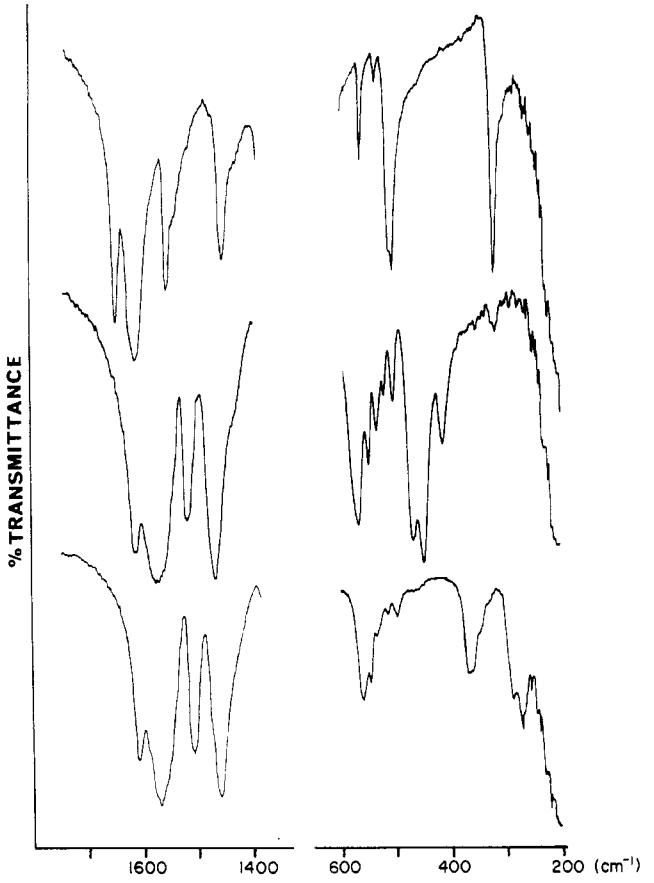

Figure 3. Infrared spectra (KBr pellets) of the 1700–1400- and 600–200-cm^{-1} regions of (from top to bottom) Hma, $Al(ma)_3$, and $Ga(ma)_3$.

Preliminary X-ray structural data on $Ga(ma)_3$ were very similar to those of $Al(ma)_3$[22] (space group *Pbca*, identical systematic absences, slightly larger cell dimensions), and solution of the structure was not pursued. The solid-state structure of $Al(ma)_3$ is *mer*,[22] and the X-ray structural data on $Ga(ma)_3$ indicate that $Ga(ma)_3$ is isomorphous. All the evidence presented herein is consistent with a common structure for all the complexes—*mer*, except possibly for the $M(pa)_3$ complexes. Although thermodynamic data were available for $Al(ka)_3$[24] and $Al(ma)_3$,[25] and there was even one obscure report of the isolation of $Al(ka)_3$ in 1949,[52] these most interesting compounds have eluded systematic investigation until now. Structural study is the most difficult because crystal growth is a very real problem—over 100 attempts each were made via a variety of methods before usable crystals of $Al(ma)_3$ and $Ga(ma)_3$ were obtained through a liquid diffusion method[31] that has proven useful in a number of difficult cases.

The compounds $Al(ma)_3$ and $Al(ka)_3$ are both highly neurotoxic.[23] When administered intracranially (13 μmol) in rabbits, they proved much more neurotoxic than aluminum lactate, an agent commonly used to induce a typical aluminum encephalopathy over a 21-day period. For $Al(ma)_3$, the neurotoxicity is 20 times that for aluminum lactate; i.e., only $^1/_{20}$ of the dose must be administered to induce a lethal encephalopathy and to have the same final amount of Al in the brain. The neurotoxicity of $Al(ma)_3$ is greater than that of $Al(ka)_3$. Considering the water solubility of $Al(ma)_3$ (0.06 M) and the *n*-octanol/water partition coefficient (0.67), it may be concluded that the neutral, soluble complex crosses brain cell walls more easily than the soluble charged aluminum lactate or the soluble, but less lipid extractable, $Al(ka)_3$. For $Al(ma)_3$ and $Ga(ma)_3$ a variety of brain-related in vivo experiments are planned because they fit the criteria of neutral charge, some lipid solubility, and molecular weight below 500, cited as necessary for significant passage of the blood–brain barrier.[33] Neutral complexes of low enough molecular weight (estimated upper limit of 657[33]) can cross cell membranes via a passive diffusion mechanism (e.g. Pt complexes[53]) whereas a carrier-mediated mechanism is necessary for charged molecules.[54]

Maltol is a natural product, easily obtained by the alkaline hydrolysis of streptomycin[55] and commonly used as a flavoring additive in breads, cakes, malted beverages, and chocolate milk. This may be of some concern since dietary citric acid has recently been discovered to enhance the absorption of aluminum in antacids in humans[56] and the administration of aluminum citrate increased brain concentrations of aluminum in rats.[57] The coadministration of toxic metals and good ligands for them may be a situation to avoid.

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