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Lipophilic Coordination Compounds: Aluminum, Gallium, and Indium Complexes of 1-Aryl-3-hydroxy-2-methyl-4-pyridinones

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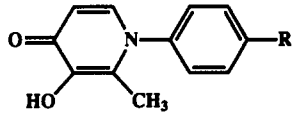
Received June 19, 1990

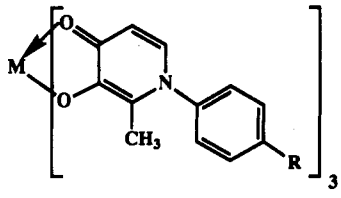
A series of 1-aryl-3-hydroxy-2-methyl-4-pyridinones and tris(1-aryl-3-hydroxy-2-methyl-4-pyridinonato)aluminum(III), -gallium(III), and -indium(III) complexes have been prepared and completely characterized. The pyridinones have a variety of aryl substituents at the ring nitrogen atom (phenyl, *p*-tolyl, *p*-methoxyphenyl, *p*-nitrophenyl). The complexes have been studied by a number of techniques including *n*-octanol/water partitioning, potentiometry, and single-crystal X-ray diffraction. The uncomplexed ligands have log (*n*-octanol/water partition coefficients) (log *p*) greater than 1, except for the *p*-nitrophenyl case; the log *p* values are significantly higher in the complexes (>2, except for the *p*-nitrophenyl cases). The complexes of 3-hydroxy-2-methyl-1-phenyl-4-pyridinone with aluminum(III), gallium(III), and indium(III) have been characterized by potentiometric (glass electrode) titration. The equilibria have been examined at 25.0 ± 0.1 °C (and 37.0 ± 0.1 °C for Al) at an ionic strength of μ = 0.15. This ligand forms ML_n complexes (n = 1–3) of high stability; at 25 °C the overall stability constants β_3 for the 3:1 complexes are $10^{30.7}$ ($M = Al^{3+}$), $10^{36.3}$ (Ga^{3+}), and $10^{31.1}$ (In^{3+}). At ligand to metal ratios ≥ 1, the ligands prevent M(III) hydrolysis at millimolar concentrations, even under slightly basic conditions, and the effective formation constants (β_{3eff}) for the metal ions at physiological pH are $10^{24.7}$ ($M = Al^{3+}$), $10^{30.3}$ (Ga^{3+}), and $10^{25.1}$ (In^{3+}). Crystals of the $ML_3 \cdot 5.5H_2O$ complexes $C_{39}H_{36}MN_3O_6 \cdot 5.5H_2O$ (where M is Al or Ga, respectively, and L is the anion of 3-hydroxy-2-methyl-1-*p*-tolyl-4-pyridinone) are isomorphous and isostructural, crystallizing in the trigonal space group $P\bar{3}1c$ with Z = 4, a = 16.2990 (8), 16.2817 (8) Å, and c = 16.784 (2), 16.948 (2) Å. The structure of the Al complex was solved by direct methods, and the structure of the Ga complex was solved by starting with the coordinates for Al complex. The two structures were refined by full-matrix least-squares procedures to R = 0.040 and 0.036 for 1593 and 1665 reflections with $I \geq 3\sigma(I)$, respectively. They form *fac* geometries incorporating hydrogen-bonding water molecules that bridge the metal chelating ligand oxygen atoms. These water molecules are all that remain of the exoclathrate array that is formed with smaller N substituents.

Introduction

As part of a continuing project to study the coordination chemistry of aluminum, gallium, and indium complexes, we have been exploring tris(ligand) complexes of these metal ions with certain bidentate monobasic ligands. From our work with the 3-hydroxy-4-pyrones and 3-hydroxy-4-pyridinones, we determined that the tris(ligand)metal complexes have a unique combination of properties: water solubility, hydrolytic stability, and lipophilicity.[1-7] Because of their great mobility in vivo, the complexes have presented interesting opportunities for the study of these metals in the etiology and diagnosis of disease.[7,8] The ^{67}Ga biodistribution studies[7] showed that, at appropriate concentrations, the 1-alkyl-3-hydroxy-2-methyl-4-pyridinones could redirect ^{67}Ga from transferrin, the main scavenger for trivalent metal ions in the body;[9] however, rapid renal excretion of the ^{67}Ga–ligand complexes in mice and rabbits was observed. This result indicates that the 1-alkyl-3-hydroxy-4-pyridinones have significant enough thermodynamic stability to compete with transferrin at appropriate concentration but that their lipophilicity is lower than ideal. Therefore, we found it necessary to develop new ligands that have higher lipophilicity while maintaining the thermodynamic properties. Lipophilicity in this class of ligands can be altered by changing the substituents on the ring nitrogen atom without altering the formation constants for the metal ions; aryl substituents potentially fit the criteria.



R = H Hppp
CH_3 Hptp
OCH_3 Hpap
NO_2 Hpnp



M = Al, Ga, In
R = H, CH_3, OCH_3, NO_2

Aryl substituents at the ring nitrogen are also of interest to our continuing solid-state study of the exoclathrate matrix. This array incorporates extensive hydrogen bonding through water molecules between tris(3-hydroxy-4-pyridinonato)metal(III) complexes and hexagonal water channels; we have found it in complexes where the metal ion is Al^{3+}, Ga^{3+}, and In^{3+} and the N substituent is CH_3 or C_2H_5.[3,4,6]

A number of *N*-aryl-3-hydroxy-4-pyridinones are known.[10-12] They are reported to be suitable extractants from aqueous solution for many metal ions (e.g. gallium(III),[13] iron(III),[14,15] vanadium(V),[16] etc.). The advantage of these pyridinones is that a number of aromatically functionalized pyridinones of considerable, but variable, lipophilicity can be easily obtained by the insertion of substituted anilines into maltol (a commercially available 3-hydroxy-4-pyrone).

In this report, we present the synthesis, characterization, and X-ray crystallography of a series of 1-aryl-3-hydroxy-2-methyl-4-pyridinones, where aryl is phenyl, *p*-tolyl, *p*-methoxyphenyl, or *p*-nitrophenyl, and their metal complexes with aluminum(III), gallium(III), and indium(III).

Experimental Section

Materials and Methods. All chemicals were reagent grade and were

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0020-1669/91/1330-0509$02.50/0

used as received unless specified: $Al(NO_3)_3 \cdot 9H_2O$ (Mallinckrodt), $Ga(NO_3)_3 \cdot 9H_2O$ and $In(NO_3)_3 \cdot 5H_2O$ (Alfa), maltol (3-hydroxy-2-methyl-4-pyrone, Sigma), aniline (Fisher), *p*-toluidine and *p*-anisidine (Eastman Organic Chemicals), and *p*-nitroaniline (MCB). Benzyl-protected maltol (3-(benzyloxy)-2-methyl-4-pyrone) was prepared according to the method of Harris.[17] Water was deionized (Barnstead D8902 and D8904 cartridges) and distilled (Corning MP-1 Megapure still). The ligands were prepared as described below. As many of the synthetic procedures were similar, only representative preparations are given.

Proton NMR spectra of compounds were recorded in $CDCl_3$ or DMSO-d_6 with a Varian XL-300 or a Bruker AC-200E 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. Infrared spectra were recorded as KBr pellets in the range 4000–200 cm^{-1} with a Perkin-Elmer PE 783 spectrophotometer and were referenced to polystyrene film. Ultraviolet spectra were recorded in the range of 400–200 nm with a Shimadzu UV-2100 spectrophotometer. Octanol/water partition coefficients (p) were determined spectrophotometrically for the water-soluble compounds from the ca. 280–290-nm (for ligands) or 300-nm (for metal complexes) band at 25 °C by an established method.[18] Analyses for C, H, and N were performed by Mr. P. Borda of this department. Potentiometric equilibrium measurements were done as previously described.[5,7]

^{27}Al NMR Spectroscopy. Spectra were recorded at 25 °C with the Varian XL-300 spectrometer operating at 78.16 MHz and accumulating 3500 transients with a pulse width of 15 μs and a spectral window of 37 kHz. 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. The background correction was done for each spectrum by subtracting a spectrum run under identical conditions with the solvent.[2]

3-Hydroxy-2-methyl-1-phenyl-4-pyridinone, Hppp. Maltol (4.03 g, 32.2 mmol) and aniline (6.35 g, 68.2 mmol) were suspended in 100 mL of dilute HCl solution (3 mL of concentrated HCl in 100 mL of water). This mixture was refluxed for 72 h and then cooled to room temperature. A light yellow solid was collected by filtration. It was recrystallized from hot methanol (after being decolorized with activated charcoal for 30 min), yielding an off-white solid (3.52 g, 55% yield), mp 222 °C. Anal. Calcd (found) for $C_{12}H_{11}NO_2$: C, 71.63 (71.66); H, 5.51 (5.56); N, 6.96 (6.96). Mass spectrum (EI): m/e 201 (molecular ion M^+). Infrared spectrum (cm^{-1}, KBr disk): 3200, 1630, 1575, 1530, 1490, 1455, 1390 (w), 1320, 1300, 1240 (br), 1210, 1180, 1100 (w), 830.

3-Hydroxy-2-methyl-1-(*p*-tolyl)-4-pyridinone, Hptp. A suspension of maltol (4.00 g, 31.8 mmol) and *p*-toluidine (6.95 g, 65.0 mmol) in 100 mL of dilute acidic solution was refluxed for 72 h and yielded 3.56 g of recrystallized product (52% yield), mp 253 °C. Anal. Calcd (found) for $C_{13}H_{13}NO_2$: C, 72.54 (72.70); H, 6.09 (6.10); N, 6.51 (6.52). Mass spectrum (EI): m/e 215 (M^+), 199 ($M^+ - CH_3$). Infrared spectrum (cm^{-1}, KBr disk): 3180, 1630, 1580, 1535, 1515, 1500, 1400, 1380, 1310, 1285, 1250 (br), 1210, 1190, 1100 (w), 1040, 830, 820.

3-Hydroxy-1-(*p*-methoxyphenyl)-2-methyl-4-pyridinone, Hpap. Maltol (4.02 g, 31.9 mmol) and *p*-anisidine (7.93 g, 64.4 mmol) gave 4.27 g of the product (58% yield), mp 249 °C. Anal. Calcd (found) for $C_{13}H_{13}NO_3$: C, 67.52 (67.51); H, 5.67 (5.71); N, 6.06 (6.13). Mass spectrum (EI): m/e 231 (M^+), 215 ($M^+ - CH_4$), 199 ($M^+ - OCH_3$). Infrared spectrum (cm^{-1}, KBr disk): 3180, 1630, 1578, 1530 (w), 1510, 1465, 1400 (w), 1380 (w), 1320 (w), 1300, 1250, 1205, 1170, 1105 (w), 1040, 845, 825.

3-Hydroxy-2-methyl-1-(*p*-nitrophenyl)-4-pyridinone, Hpnp. 3-(Benzyloxy)-2-methyl-4-pyrone (5.14 g, 23.8 mmol) and *p*-nitroaniline (5.00 g, 36.2 mmol) were suspended in 120 mL of 5:1 dilute HCl/methanol. This suspension was refluxed for 73 h. An oily layer was separated from the aqueous layer while hot and was discarded. The aqueous layer was cooled to yield a yellow solid, which was collected by filtration and washed with diethyl ether. The resulting bright yellow solid was dissolved in hot acidified water and recrystallized by adding 8 N NaOH solution dropwise to raise the pH of the solution to 7. The final product yield was 1.62 g (28%), mp 293–295 °C. Anal. Calcd (found) for $C_{12}H_{10}N_2O_4$: C, 58.54 (58.36); H, 4.09 (4.07); N, 11.38 (11.36). Mass spectrum (EI): m/e 246 (M^+), 245 ($M^+ - H$), 199 ($M^+ - NO_2 - H$). Infrared spectrum (cm^{-1}, KBr disk): 3200, 1635, 1590, 1530, 1515, 1495, 1405 (w), 1350, 1310, 1260 (br), 1210, 1105, 1040, 860, 840 (br).

Tris(3-hydroxy-2-methyl-1-phenyl-4-pyridinonato)aluminum(III) Sesquihydrate, $Al(ppp)_3 \cdot 1.5H_2O$. $Al(NO_3)_3 \cdot 9H_2O$ (0.232 g, 0.617 mmol) and Hppp (0.400 g, 1.99 mmol) were dissolved in 40 mL of water with heating. The pH of this solution was raised to 9.5 with 2 N NaOH, and a white solid precipitated. This was collected by filtration while hot and recrystallized from hot MeOH to yield 0.367 g (91%) of product. Anal. Calcd (found) for $C_{36}H_{33}AlN_3O_{7.5}$: C, 66.05 (65.79); H, 5.08 (5.16); N, 6.42 (6.33). Mass spectrum (EI): m/e 627 (ML_3^+), 427 (ML_2^+), 228 (HML^+), 200 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1605, 1590, 1540, 1510, 1470, 760 (m, sh), 650, 475 (br). ^{27}Al NMR ($CDCl_3$): 37 ppm ($W_{1/2}$ = 1270 Hz).

Tris(3-hydroxy-2-methyl-1-phenyl-4-pyridinonato)gallium(III) Dihydrate, $Ga(ppp)_3 \cdot 2H_2O$. The preparation was as for $Al(ppp)_3$. Hppp (0.834 g, 4.15 mmol) and $Ga(NO_3)_3 \cdot 9H_2O$ (0.601 g, 1.44 mmol) yielded 0.846 g (83%) of the complex. Anal. Calcd (found) for $C_{36}H_{34}GaN_3O_8$: C, 61.21 (61.17); H, 4.85 (4.89); N, 5.95 (6.02). Mass spectrum (FAB): m/e 670 and 672 (3:2, HML_3^+), 469 and 471 (3:2, ML_2^+), 270 (HML^+), 200 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1600, 1590, 1550, 1515, 1470, 765, 650, 400 (m, br).

Tris(3-hydroxy-2-methyl-1-phenyl-4-pyridinonato)indium(III) Hydrate, $In(ppp)_3 \cdot H_2O$. The preparation was as for $Al(ppp)_3$. $In(NO_3)_3 \cdot 5H_2O$ (0.267 g, 0.683 mmol) and Hppp (0.427 g, 2.12 mmol) were used. Crystallization from hot methanol yielded 0.480 g (95%) of the product. Anal. Calcd (found) for $C_{36}H_{32}InN_3O_7$: C, 58.95 (59.16); H, 4.40 (4.41); N, 5.73 (5.65). Mass spectrum (EI): m/e 715 (ML_3^+), 515 (ML_2^+), 315 (ML^+), 200 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1605, 1590, 1540, 1510, 1470, 765, 390 (m, b).

Tris(3-hydroxy-2-methyl-1-(*p*-tolyl)-4-pyridinonato)aluminum(III)–5.5-Water, $Al(ptp)_3 \cdot 5.5H_2O$. A suspension of Hptp (0.598 g, 2.78 mmol) in 50 mL of water was heated to boiling, and 6 N HCl (2 mL) was added to dissolve the Hptp. $Al(NO_3)_3 \cdot 9H_2O$ (0.332 g, 0.886 mmol) was dissolved in this solution, and the pH was raised to 9.85 with 2 N NaOH. The reaction mixture was cooled to room temprature, and a white solid was obtained. This was recrystallized in hot ethanol to yield 0.624 g (92%) of the product. Crystals suitable for X-ray analysis were obtained from acetone/2-propanol by slow evaporation. Anal. Calcd (found) for $C_{39}H_{47}AlN_3O_{11.5}$: C, 60.93 (61.04); H, 6.16 (6.11); N, 5.47 (5.50). Mass spectrum (EI): m/e 669 (ML_3^+), 455 (ML_2^+), 242 (HML^+), 214 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1600, 1550, 1520, 1510, 1475, 740, 690, 470 (br). ^{27}Al NMR ($CDCl_3$): 38 ppm ($W_{1/2}$ = 1355 Hz).

Tris(3-hydroxy-2-methyl-1-(*p*-tolyl)-4-pyridinonato)gallium(III) Hydrate, $Ga(ptp)_3 \cdot H_2O$. To a suspension of Hptp (1.015 g, 4.71 mmol) in 90 mL of distilled water/methanol (2:1) was added 2 mL of 6 N HCl solution. $Ga(NO_3)_3 \cdot 9H_2O$ (0.612 g, 1.46 mmol) was then added. The solution was heated to ~60 °C, and a white solid was precipited by raising the pH of the solution to 7 with 2 N NaOH solution. This precipitate was extracted with CH_2Cl_2 (4 × 25 mL) when the solution was cool. The aqueous layer was separated from the organic layer and discarded. Evaporation of CH_2Cl_2 yielded a light pink solid, which was recrystallized from hot ethanol to give 0.950 g (89%) of product. Anal. Calcd (found) for $C_{39}H_{38}GaN_3O_7$: C, 64.13 (63.93); H, 5.24 (5.20); N, 5.75 (5.65). Mass spectrum (EI): m/e 497 and 499 (3:2, ML_2^+), 283 and 285 (3:2, ML^+), 214 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1600, 1550, 1520, 1505, 1470, 740, 685, 320 (m, br). Crystals suitable for X-ray analysis were obtained from acetone/2-propanol by slow evaporation, and these analyzed for $Ga(ptp)_3 \cdot 5.5H_2O$. Anal. Calcd (found) for $C_{39}H_{47}GaN_3O_{11.5}$: C, 57.72 (57.80); H, 5.84 (5.80); N, 5.18 (5.16).

Tris(3-hydroxy-2-methyl-1-(*p*-tolyl)-4-pyridinonato)indium(III) Sesquihydrate, $In(ptp)_3 \cdot 1.5H_2O$. The preparation was as for $Ga(ptp)_3$. Hptp (1.077 g, 5.01 mmol) and $In(NO_3)_3 \cdot 5H_2O$ (0.632 g, 1.62 mmol) yielded 1.120 g of product (90%). Anal. Calcd (found) for $C_{39}H_{37}InN_3O_{7.5}$: C, 59.70 (59.67); H, 5.01 (4.91); N, 5.36 (5.28). Mass spectrum (EI): m/e 757 (ML_3^+), 543 (ML_2^+), 329 (ML^+), 214 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1590, 1540, 1515, 1500, 1465, 740, 680, 300 (m, br).

Tris(3-hydroxy-1-(*p*-methoxyphenyl)-2-methyl-4-pyridinonato)aluminum(III) Hydrate, $Al(pap)_3 \cdot H_2O$. Hpap (0.993 g, 4.30 mmol) was dissolved in 40 mL of hot distilled water, and $Al(NO_3)_3 \cdot 9H_2O$ (0.504 g, 1.34 mmol) was added. The pH was raised slowly to 7 with 8 N NaOH. A white solid was obtained after cooling to room temperature; this was then extracted with CH_2Cl_2 (4 × 20 mL). The aqueous layer was separated and discarded. The CH_2Cl_2 was removed under reduced pressure to yield a pinkish solid. The product was collected by filtration, washed with diethyl ether, and dried in vacuo, producing 0.671 g (68%). Anal. Calcd (found) for $C_{39}H_{38}AlN_3O_{10}$: C, 63.67 (63.81); H, 5.21 (5.32); N, 5.71 (5.58). Mass spectrum (EI): m/e 717 (ML_3^+), 487 (ML_2^+), 231 (HL^+). Infrared spectrum (cm^{-1}, KBr disk): 1610, 1600, 1560, 1520, 1470, 740, 690 (m), 490. ^{27}Al NMR ($CDCl_3$): 37 ppm ($W_{1/2}$ = 1743 Hz).

Tris(3-hydroxy-1-(*p*-methoxyphenyl)-2-methyl-4-pyridinonato)gallium(III) Hydrate, $Ga(pap)_3 \cdot H_2O$. The synthetic procedure was as for $Al(pap)_3$. Hpap (0.504 g, 2.18 mmol) and $Ga(NO_3)_3 \cdot 9H_2O$ (0.292 g, 0.698 mmol) yielded 0.456 g (84%) of the complex. Anal. Calcd (found) for $C_{39}H_{38}GaN_3O_{10}$: C, 60.17 (60.08); H, 4.92 (4.92); N, 5.40 (5.38). Mass spectrum (FAB): m/e 760 and 762 (3:2, HML_3^+), 529 and 531 (3:2, ML_2^+), 299 and 301 (3:2 ML^+), 232 (H_2L^+). Infrared spectrum

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Table I. Crystallographic Data for the $M(ptp)_3$ Complexes

	$Al(ptp)_3 \cdot 5.5H_2O$	$Ga(ptp)_3 \cdot 5.5H_2O$
formula	$C_{39}H_{36}AlN_3O_6 \cdot 5.5H_2O$	$C_{39}H_{36}GaN_3O_6 \cdot 5.5H_2O$
fw	768.79	811.53
cryst system	trigonal	trigonal
space group	$P\bar{3}1c$	$P\bar{3}1c$
a, Å	16.2990 (8)	16.2817 (8)
c, Å	16.784 (2)	16.948 (2)
V, Å^3	3861.6 (6)	3890.9 (6)
Z	4	4
ρ_{calc}, g/cm^3	1.322	1.385
T, °C	21	21
radiation	Cu	Cu
λ, Å	1.541 78	1.541 78
μ(Cu Kα), cm^{-1}	9.77	14.77
transm factors	0.89–1.00	0.88–1.00
$R(F_o)$	0.040	0.036
$R_w(F_o)$	0.054	0.048

(cm^{-1}, KBr disk): 1610, 1590, 1550, 1520, 1470, 735 (m), 685 (m).

Tris(3-hydroxy-1-(*p*-methoxyphenyl)-2-methyl-4-pyridinonato)indium(III) Dihydrate, $In(pap)_3 \cdot 2H_2O$. The procedure was as for $Al(pap)_3$. Hpap (0.993 g, 4.30 mmol) and $In(NO_3)_3 \cdot 5H_2O$ (0.539 g, 1.39 mmol) gave 1.04 g (90%) of product. Anal. Calcd (found) for $C_{39}H_{40}InN_3O_{11}$: C, 55.66 (56.00); H, 4.79 (4.58); N, 4.99 (4.97). Mass spectrum (EI): m/e 805 (ML_3^+), 575 (ML_2^+), 345 (ML^+), 230 (L^+). Infrared spectrum (cm^{-1}, KBr disk): 1610, 1595, 1540, 1510, 1470, 735 (m), 680 (m).

Tris(3-hydroxy-2-methyl-1-(*p*-nitrophenyl)-4-pyridinonato)aluminum(III) Dihydrate, $Al(pnp)_3 \cdot 2H_2O$. The preparation was as for $Al(pap)_3$. Hpnp (0.503 g, 2.04 mmol) and $Al(NO_3)_3 \cdot 9H_2O$ (0.251 g, 0.670 mmol) yieldcd 0.522 g (98%) of product. Anal. Calcd (found) for $C_{36}H_{31}AlN_6O_{14}$: C, 54.14 (54.14); H, 3.91 (3.91); N, 10.52 (10.51). Mass spectrum (FAB): m/e 763 (HML_3^+), 517 (ML_2^+), 273 (HML^+). Infrared spectrum (cm^{-1}, KBr disk): 1605, 1595, 1550, 1525, 1475, 855, 720 (m), 665 (w), 590 (w, br). ^{27}Al NMR ($CDCl_3$): 38 ppm ($W_{1/2}$ = 1368 Hz).

Tris(3-hydroxy-2-methyl-1-(*p*-nitrophenyl)-4-pyridinonato)gallium(III)–2.5-Water, $Ga(pnp)_3 \cdot 2.5H_2O$. The procedure was as for $Al(pap)_3$. Hpnp (0.916 g, 3.72 mmol) and $Ga(NO_3)_3 \cdot 9H_2O$ (0.501 g, 1.20 mmol) gave 0.616 g of product (60%). Anal. Calcd (found) for $C_{36}H_{32}GaN_6O_{14.5}$: C, 50.85 (50.85); H, 3.79 (3.70); N, 9.88 (9.85). Mass spectrum (FAB): m/e 805 and 807 (3:2, ML_3^+), 559 and 561 (3:2 $ML_2^+ - H$). Infrared spectrum (cm^{-1}, KBr disk): 1605, 1590, 1550, 1525, 1470, 865, 715 (m), 655 (w), 550 (w, br).

Tris(3-hydroxy-2-methyl-1-(*p*-nitrophenyl)-4-pyridinonato)indium(III) Hemihydrate, $In(pnp)_3 \cdot 0.5H_2O$. The procedure was as for $Al(pap)_3$. Hpnp (0.517 g, 2.10 mmol) and $In(NO_3)_3 \cdot 5H_2O$ (0.265 g, 0.677 mmol) gave 0.229 g of product (40%). Anal. Calcd (found) for $C_{36}H_{28}InN_6O_{12.5}$: C, 50.31 (50.04); H, 3.28 (3.35); N, 9.78 (9.78). Mass spectrum (FAB): m/e 851 (HML_3^+), 605 (ML_2^+), 360 (ML^+). Infrared spectrum (cm^{-1}, KBr disk): 1610 (m), 1590, 1540, 1505, 1470, 860, 715 (m), 655 (w), 550 (w, br).

X-ray Crystallographic Analyses. Crystallographic data for $M(ptp)_3 \cdot 5.5H_2O$ (where M = Al and Ga) appear in Table I. The final unit cell parameters were obtained by least-squares refinements on the setting angles for 25 reflections with 2θ = 59.3–76.6° for M = Al and 59.3–76.7° for M = Ga. The intensities of three standard reflections, measured every 150 reflections throughout the data collections, remained essentially constant in each case. The data were processed[19] and corrected for Lorentz and polarization effects and for absorption (empirical, based on azimuthal scans for four reflections).

The structure of the aluminum complex was solved by direct methods, the coordinates of the non-hydrogen atoms of the $Al(ptp)_3$ moiety being determined from an E map and those of the water oxygen atoms from subsequent difference Fourier syntheses. The structure analysis of the Ga complex was initiated with the coordinates of the Al complex. The $M(ptp)_3$ molecules have crystallographically imposed C_3 symmetry (Figure 1). The water molecules are disordered in two regions, 2-fold at one site (O(3)) and 3-fold (O(4)) at the other. The total occupancy of the disordered water sites was constrained to be 5.5 per $M(ptp)_3$ complex molecule in accordance with microanalytical data obtained from the same batches of crystals as those used for data collection (vide supra). The individual site occupancy factors for the disordered water oxygen atoms could not be refined along with the thermal parameters due to high correlation coefficients between these parameters but were adjusted to give nearly equal equivalent isotropic thermal parameters for each site. All non-hydrogen atoms (with the exception of one low-occupancy water oxygen atom in the Ga complex) were refined with anisotropic thermal parameters. Hydrogen atoms of the ptp ligands were fixed in idealized positions (d_{C-H} = 0.98 Å, $B_H = 1.2B_{bonded\ atom}$), and some water hydrogen atoms were placed in difference map positions and not refined. Difference Fourier maps showed 1:1 2-fold disordering of the methyl hydrogen atoms associated with C(1) and C(13) in both the complexes. This rotational disordering was included in the model and is apparent in Figure 1. Corrections for secondary extinction were applied, the final values of the extinction coefficient being 5.25×10^{-7} and 4.38×10^{-7} for the Al and Ga complexes, respectively. Neutral-atom scattering factors and anomalous dispersion corrections for the non-hydrogen atoms were taken from ref 20. Final atomic coordinates and equivalent isotropic thermal parameters [$B_{eq} = {}^4/_3\sum_i\sum_j\beta_{ij}(\mathbf{a}_i \cdot \mathbf{a}_j)$], bond lengths, bond angles, and possible hydrogen-bond distances appear in Tables II–V, respectively. Hydrogen atom parameters, anisotropic thermal parameters, torsion angles, intermolecular contacts, least-squares planes, and measured and calculated structure factor amplitudes are included as supplementary material (see paragraph at the end of paper).

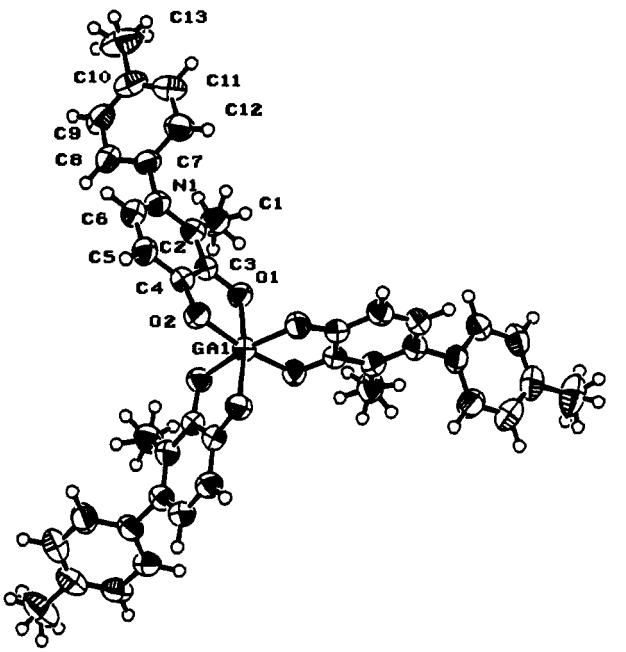

Figure 1. Perspective view of the $Ga(ptp)_3$ molecule. 50% probability thermal ellipsoids are shown for the non-hydrogen atoms. Labeled non-hydrogen atoms comprise the asymmetric unit.

Results and Discussion

A series of 1-aryl-3-hydroxy-2-methyl-4-pyridinones have been prepared in ~50% yield from acidic aqueous solution by the direct reaction of the appropriate para-substituted aniline with maltol. The reaction of maltol with *p*-nitroaniline lead to no isolable product so the hydroxy-protected maltol was used.[21] The acidic conditions required for the preparations obviated the one-pot synthesis[22] of the metal complexes, and the aluminum, gallium, and indium compounds had to be separately synthesized (in high yield) from aqueous solutions at neutral pH. Analyses for C, H, and N in each complex were consistent with the formulations of tris(ligand)metal species; however, the compounds were very hygroscopic, forming reproducibly analyzable hydrates. Analytical results corresponding to the anhydrous ML_3 formulations could not be obtained even by drying at 85 °C in vacuo for 24 h with subsequent storage and analysis under nitrogen atmosphere. The complexes are all nonvolatile, charring and decomposing above

(19) TEXSAN/TEXRAY structure analysis package, which includes versions of the following: DIRDIF, direct methods for difference structures, by P. T. Beurskens; ORFLS, full-matrix least squares, ORFFE, function and errors, by W. R. Busing, K. O. Martin, and H. A. Levy, and ORTEP II, illustrations, by C. K. Johnson.

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Table II. Final Atomic Coordinates (Fractional) and B_{eq} (Å^2)

atom	x	y	z	B_{eq}	occ
		Al(ptp)$_3$·5.5H$_2$O			
Al(1)	1/3	2/3	0.48195 (7)	3.79 (3)	1/3
O(1)	0.2850 (1)	0.5574 (1)	0.54634 (9)	4.18 (6)	
O(2)	0.3807 (1)	0.6024 (1)	0.41693 (9)	4.27 (6)	
O(3A)	0.4572 (3)	0.8360 (4)	0.8232 (3)	13.4 (3)	0.816
O(3B)	0.35 (1)	0.710 (5)	0.7942 (7)	14 (3)	0.163
O(4A)	0.4156 (6)	−0.4156	1/4	13.0 (1)	0.264
O(4B)	0.351 (2)	0.556 (2)	0.247 (1)	13 (1)	0.281
O(4C)	0.4422 (9)	0.4314 (9)	0.2322 (6)	13.2 (6)	0.317
N(1)	0.3345 (1)	0.3657 (1)	0.5344 (1)	4.48 (8)	
C(1)	0.2507 (2)	0.3967 (2)	0.6440 (2)	5.7 (1)	
C(2)	0.2994 (2)	0.4206 (2)	0.5652 (1)	4.13 (9)	
C(3)	0.3159 (2)	0.5001 (2)	0.5235 (1)	3.80 (8)	
C(4)	0.3693 (2)	0.5258 (2)	0.4520 (1)	3.80 (8)	
C(5)	0.4068 (2)	0.4698 (2)	0.4257 (1)	4.5 (1)	
C(6)	0.3871 (2)	0.3908 (2)	0.4673 (2)	4.8 (1)	
C(7)	0.3091 (2)	0.2755 (2)	0.5710 (1)	4.7 (1)	
C(8)	0.3766 (2)	0.2630 (2)	0.6086 (2)	5.3 (1)	
C(9)	0.3497 (2)	0.1761 (2)	0.6443 (2)	5.9 (1)	
C(10)	0.2568 (3)	0.1031 (2)	0.6429 (2)	5.9 (1)	
C(11)	0.1910 (2)	0.1179 (2)	0.6042 (2)	6.4 (1)	
C(12)	0.2165 (2)	0.2035 (2)	0.5676 (2)	5.6 (1)	
C(13)	0.2282 (3)	0.0102 (2)	0.6827 (2)	8.4 (2)	
		Ga(ptp)$_3$·5.5H$_2$O			
Ga(1)	1/3	2/3	0.48079 (3)	3.95 (2)	1/3
O(1)	0.2835 (1)	0.5527 (1)	0.5469 (1)	4.51 (8)	
O(2)	0.3811 (1)	0.5978 (1)	0.4149 (1)	4.36 (7)	
O(3A)	0.4581 (4)	0.8353 (4)	0.8237 (3)	12.5 (3)	0.758
O(3B)	0.367 (2)	0.712 (1)	0.804 (1)	12.4 (7)	0.180
O(4A)	0.4174 (5)	−0.4174	1/4	13.2 (1)	0.315
O(4B)	0.350 (2)	0.563 (2)	0.251 (2)	12 (1)	0.255
O(4C)	0.4581 (9)	0.4455 (9)	0.2375 (8)	12.8 (7)	0.330
N(1)	0.3362 (2)	0.3631 (2)	0.5348 (1)	4.60 (9)	
C(1)	0.2517 (3)	0.3950 (2)	0.6426 (2)	6.0 (1)	
C(2)	0.3009 (2)	0.4184 (2)	0.5643 (2)	4.5 (1)	
C(3)	0.3164 (2)	0.4973 (2)	0.5228 (2)	3.9 (1)	
C(4)	0.3694 (2)	0.5224 (2)	0.4517 (2)	4.0 (1)	
C(5)	0.4067 (2)	0.4664 (2)	0.4262 (2)	4.7 (1)	
C(6)	0.3883 (2)	0.3876 (2)	0.4678 (2)	5.0 (1)	
C(7)	0.3106 (2)	0.2732 (2)	0.5717 (2)	4.8 (1)	
C(8)	0.3783 (2)	0.2616 (2)	0.6095 (2)	5.3 (1)	
C(9)	0.3510 (3)	0.1748 (3)	0.6457 (2)	6.1 (2)	
C(10)	0.2585 (3)	0.1020 (2)	0.6437 (2)	6.1 (2)	
C(11)	0.1928 (3)	0.1158 (2)	0.6044 (2)	6.6 (2)	
C(12)	0.2174 (2)	0.2009 (2)	0.5680 (2)	5.9 (1)	
C(13)	0.2310 (4)	0.0088 (3)	0.6840 (3)	8.9 (2)	

Table III. Bond Lengths (Å) with Estimated Standard Deviations for M(ptp)$_3$·5.5H$_2$O

	M = Ga	M = Al
M(1)–O(1)	1.962 (2)	1.886 (2)
M(1)–O(2)	1.996 (2)	1.922 (2)
O(1)–C(3)	1.323 (3)	1.321 (3)
O(2)–C(4)	1.302 (3)	1.306 (3)
N(1)–C(2)	1.382 (3)	1.381 (3)
N(1)–C(6)	1.352 (4)	1.350 (3)
N(1)–C(7)	1.448 (3)	1.450 (3)
C(1)–C(2)	1.498 (4)	1.491 (3)
C(2)–C(3)	1.372 (4)	1.374 (3)
C(3)–C(4)	1.419 (4)	1.418 (3)
C(4)–C(5)	1.394 (4)	1.399 (3)
C(5)–C(6)	1.359 (4)	1.355 (3)
C(7)–C(8)	1.367 (4)	1.369 (4)
C(7)–C(12)	1.380 (4)	1.374 (4)
C(8)–C(9)	1.394 (4)	1.392 (4)
C(9)–C(10)	1.374 (5)	1.381 (4)
C(10)–C(11)	1.372 (5)	1.374 (4)
C(10)–C(13)	1.512 (5)	1.500 (4)
C(11)–C(12)	1.380 (5)	1.386 (4)

260 °C. Except for M(ppp)$_3$ compounds, which are marginally soluble, the complexes are not soluble in water at neutral pH, but they are highly lipophilic.

The mass spectra of the complexes showed the expected HML_3^+, ML_2^+, and HML^+ fragmentation pattern when recorded in the FAB mode[2] or the ML_3^+, ML_2^+, ML^+, and L^+ fragmentation in EI mode. The four-band infrared spectral pattern (1610–1400 cm^{-1}), characteristic of pyrones and pyridinones,[21,23] was preserved in the complexes with a general bathochromic shift and a possible reordering upon complexation. These four bands are collectively assigned $\nu_{c=o}$ and ν_{ring}, since resolving these two highly mixed modes is extremely difficult. All the hydrated complexes showed broad water O–H stretches in the region 3500–3400 cm^{-1}. Below 800 cm^{-1} some new bands appeared, and these were tentatively assigned as ν_{M-O} although there may be coupling to ring deformation modes in this frequency range.

^{27}Al NMR chemical shifts were consistent with those observed previously for 3-hydroxy-4-pyridinone complexes of Al, and the line widths at half-height ($W_{1/2}$ = 1270–1743 Hz) were consistent with the increased size of the ligands from those that we have previously reported.[3,6] Because of the low aqueous solubilities of the compounds, ^{27}Al NMR spectra were recorded in $CDCl_3$. As the ^{27}Al nucleus is quadrupolar ($I = 5/2$), the quadrupole moment interacts with electric field gradients (at the nucleus) that couple the nucleus with molecular motions, and an efficient relaxation mechanism results.[24] The broad line widths have their origin in

Table IV. Bond Angles (deg) for M(ptp)$_3$·5.5H$_2$O[a]

	M = Ga	M = Al
O(1)–M(1)–O(1)′	90.65 (8)	90.42 (7)
O(1)–M(1)–O(2)	83.15 (7)	84.41 (6)
O(1)–M(1)–O(2)′	95.04 (8)	94.67 (6)
O(1)–M(1)–O(2)″	171.62 (8)	172.77 (6)
O(2)–M(1)–O(2)′	91.76 (8)	90.95 (7)
M(1)–O(1)–C(3)	110.6 (2)	112.0 (1)
M(1)–O(2)–C(4)	110.3 (2)	111.2 (1)
C(2)–N(1)–C(6)	121.0 (2)	121.5 (2)
C(2)–N(1)–C(7)	119.9 (2)	119.9 (2)
C(6)–N(1)–C(7)	118.8 (2)	118.4 (2)
N(1)–C(2)–C(1)	119.9 (3)	120.1 (2)
N(1)–C(2)–C(3)	118.9 (3)	118.1 (2)
C(1)–C(2)–C(3)	121.1 (3)	121.7 (2)
O(1)–C(3)–C(2)	122.2 (2)	123.7 (2)
O(1)–C(3)–C(4)	117.4 (2)	115.5 (2)
C(2)–C(3)–C(4)	120.4 (2)	120.7 (2)
O(2)–C(4)–C(3)	117.4 (2)	115.9 (2)
O(2)–C(4)–C(5)	124.2 (3)	125.5 (2)
C(3)–C(4)–C(5)	118.4 (2)	118.5 (2)
C(4)–C(5)–C(6)	119.6 (3)	119.1 (2)
N(1)–C(6)–C(5)	121.6 (3)	121.9 (2)
N(1)–C(7)–C(8)	119.8 (3)	120.3 (2)
N(1)–C(7)–C(12)	118.7 (3)	118.9 (2)
C(8)–C(7)–C(12)	121.5 (3)	120.8 (2)
C(7)–C(8)–C(9)	118.4 (3)	118.9 (3)
C(8)–C(9)–C(10)	121.4 (3)	121.4 (3)
C(9)–C(10)–C(11)	118.5 (3)	118.2 (3)
C(9)–C(10)–C(13)	120.1 (4)	121.1 (3)
C(11)–C(10)–C(13)	121.4 (4)	120.7 (3)
C(10)–C(11)–C(12)	121.6 (3)	121.3 (3)
C(7)–C(12)–C(11)	118.6 (3)	119.4 (3)

[a] Here and elsewhere in this paper, primed and double-primed atoms have coordinates related to those in Table II by the symmetry operations $y - x$, $1 - x$, z and $1 - y$, $1 + x - y$, z, respectively.

Table V. Possible Hydrogen Bonds (Å) in M(ptp)$_3$·5.5H$_2$O (M = Al, Ga)

	M = Al	M = Ga	sym operation (second O atom)
O(1)···O(3A)	2.876 (4)	2.872 (5)	$1 - y$, $1 - x$, $3/2 - z$
O(1)···O(3B)	2.93 (4)	2.96 (2)	x, $1 + x - y$, $3/2 - z$
O(1)···O(3B)	3.08 (6)	2.84 (2)	$1 - y$, $1 - x$, $3/2 - z$
O(2)···O(4B)	2.90 (2)	2.94 (3)	$1 - y$, $1 - x$, $1/2 - z$
O(2)···O(4A)	2.902 (4)	2.893 (4)	x, $1 + y$, z
O(2)···O(4B)	2.93 (2)	2.84 (3)	x, y, z
O(3A)···O(4C)	2.68 (1)	2.60 (1)	$1 - x$, $1 - x + y$, $1/2 + z$
O(3A)···O(4C)	2.89 (1)	2.78 (1)	y, $1 - x + y$, $1 - z$

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(24) Akitt, J. W. *Prog. NMR Spectrosc.* **1989**, *21*, 1.

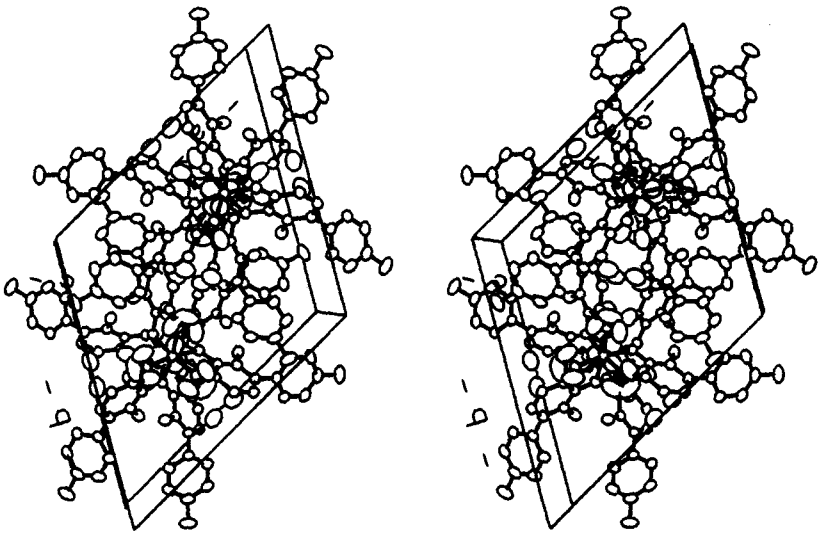

Figure 2. Stereoview along *c* of the unit cell of $Ga(ptp)_3 \cdot 5.5H_2O$.

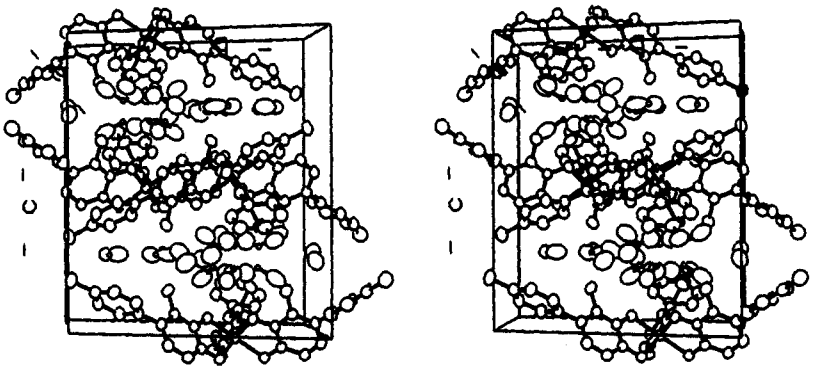

Figure 3. Stereoview along *a* of the unit cell of $Ga(ptp)_3 \cdot 5.5H_2O$.

this fast magnetic relaxation. The relaxation mechanism is modulated by the rate of tumbling of the molecule in solution: the more slowly the molecule tumbles, the larger is the line width.[25] The chemical shifts were 37 or 38 ppm, typical of the tris(3-hydroxy-4-pyridinonato)aluminum(III) chromophore,[3,6] and the line widths of these *N*-arylpyridinone complexes were wider than those of *N*-alkylpyridinone complexes (400–900 Hz). As expected, the $W_{1/2}$ values increased with the steric bulk of the para-substituted aryl substituent: $H < CH_3 \approx NO_2 < OCH_3$.

The ultraviolet spectral data and *n*-octanol/water partition coefficients (log *p*) are shown in Table VI. In the free ligands (except Hpnp, which is complicated by the nitro group), E (ethylinic) and B (benzenoid) bands[26] originating from $\pi-\pi^*$ transitions were observed at ~220 and 289 nm, respectively. There was, in addition, a third shoulder in each case. The complexation of the ligands with the metal ions resulted in bathochromic shifts of all three absorptions. Partition coefficients were determined from the lower energy band in each case. With the method used, we could only determine a lower limit for the indium complexes because their solubility in water at neutral pH was so low. The high partition coefficients (log *p*) confirmed that the desired lipophilicity had been introduced into the complexes. This should increase their lipid solubility and membrane permeability.

Proton NMR data for the compounds are listed in Table VII. The doublet of ring proton doublets, H_cH_d, characteristic of the hydroxypyrone[2] and *N*-alkylhydroxypyridinone[3,4,6] complexes was seen in the $M(ppp)_3$ and $M(pnp)_3$ complexes, with a coupling constant in each case of 6–8 Hz. In the $M(ptp)_3$ and $M(pap)_3$ spectra, the H_d doublets appeared in the envelope of phenyl protons. For Hpnp and its complexes with aluminum, gallium, and indium, two sets of doublets with different coupling constants were observed: one doublet arose from the H_cH_d protons on the pyridinone ring (coupling constants of 6–8 Hz) and the other from the two equivalent pairs of protons H_eH_f on the phenyl ring (coupling constants of 8–9 Hz).

The crystal structures of the $M(ptp)_3 \cdot 5.5H_2O$ complexes were solved and found to be isostructural. The complexes crystallize as the *fac* isomers (Figure 1). The intraligand distances and angles (Tables III and IV) are consistent with the previously solved aluminum and gallium tris(3-hydroxy-4-pyridinonate) structures.[3,6] The distances and angles in the five-membered chelate rings are also very close in value to those for the structurally characterized complexes of Al^{3+} or Ga^{3+} with the three different ligands (N-CH_3, N-C_2H_5, N-$C_6H_4CH_3$).

The new feature in the ptp complex structures is the absence of the exoclathrate structure that we,[3,4,6] and others,[27] have seen in tris(N-substituted-3-hydroxy-2-methyl-4-pyridinonato)metal(III) complexes with small substituents at the ring nitrogen. The gross structural features of the exoclathrate lattice are ice-I_h hexagonal water channels (in the corners of the unit cell), which comprise homodromic circles of water molecules, various O···H hydrogen-bond donor types, the use of every hydrogen-bonding donor in the unit cell as such, the hydrogen bonding by water molecules of all the chelating O atoms, and the type IA donor–acceptor interactions throughout the structure. In the $M(ptp)_3 \cdot 5.5H_2O$ structures the hexagonal channels and the chains of water molecules that hydrogen bonded the channels to the ML_3 units are absent but the hydrogen-bonding interactions between water molecules and the metal-chelating O atoms remain (Table V).

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(26) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; pp 305–331.
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Table VI. Ultraviolet Spectral Data[a,b] and Partition Coefficients[c]

compd	λ, nm (ε, M^{-1} cm^{-1})	log *p*
Hppp	289 (19 200), 221 (19 400 sh), 206 (28 500)	1.12
$Al(ppp)_3$	307 (34 300), 232 (79 500), 208 (53 200)	2.10
$Ga(ppp)_3$	308 (32 700), 233 (79 400), 207 (54 000)	2.13
$In(ppp)_3$	309 (34 700), 234 (75 600), 208 (52 600)	>3
Hptp	289 (19 400), 220 (18 600 sh), 205 (27 000)	1.72
$Al(ptp)_3$	306 (34 300), 232 (85 200), 209 (62 500)	2.65
$Ga(ptp)_3$	307 (35 400), 233 (76 300), 209 (56 300)	>3
$In(ptp)_3$	308 (33 900), 235 (82 900), 211 (62 700)	>3
Hpap	289 (20 100), 219 (22 000), 205 (28 200)	1.27
$Al(pap)_3$	306 (34 500), 229 (79 000), 207 (53 600)	2.46
$Ga(pap)_3$	307 (33 400), 230 (77 500), 205 (53 900)	2.55
In(pap)	308 (35 900), 229 (82 400)	>3
Hpnp	310 (sh), 284 (13 700), 260 (sh), 215 (sh)	0.76
$Al(pnp)_3$	345 (sh), 297 (29 000), 255 (41 600), 227 (72 900)	1.46
$Ga(pnp)_3$	345 (sh), 298 (32 900), 255 (48 000), 227 (85 600)	1.49
$In(pnp)_3$	345 (sh), 298 (30 000, sh), 253 (43 600), 225 (75 700)	>3

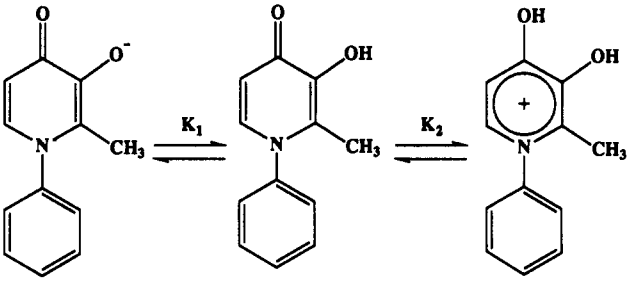
[a] In MeOH. [b] sh = shoulder. [c] In *n*-octanol/water; determined only for water-soluble compounds.

The complete picture is accessible by examination of the two stereoviews in concert (Figures 2 and 3). Comparison of the unit cell stereoview along *c* (Figure 2) with those for the exoclathrate compounds shows that the *p*-tolyl substituents are too sterically demanding to allow the necessary space near the corners of the unit cell for the hexagonal channels. The water molecules that hydrogen bond to the chelating O atoms are clearly seen in this view between neighboring $Ga(ptp)_3$ units down the *c* axis. The 2-fold-disordered lattice waters are also clearly seen in the center of the unit cell and in each face. The replacement of $N-CH_3$ or $N-C_2H_5$ with $N-C_6H_4CH_3$ on the pyridinone ring causes the disappearance of the exoclathrate structure but does not completely remove all the hydrogen-bonding interactions despite the greatly increased lipophilicity of the ligand.

The protonation constants of, and formation constants of the metal ion complexes with, ppp^- are listed in Table VIII. The protonation equilibria for the amphoteric[5] ligand are described by eqs 1 and 2, where $L^- = ppp^-$. The Hppp constants at 25 °C

$$H^+ + L^- \rightleftharpoons HL \qquad K_1 = \frac{[HL]}{[H^+][L^-]} \tag{1}$$

$$H^+ + HL \rightleftharpoons H_2L^+ \qquad K_2 = \frac{[H_2L^+]}{[H^+][HL]} \tag{2}$$



are lower than those that we have reported[5] for the *N*-alkyl-3-hydroxy-4-pyridinones ($\log K_1$ = 9.4 vs 9.8, $\log K_2$ = 3.0 vs 3.7) consistent with the electron-withdrawing effect of the phenyl ring substituent versus electron donation of the alkyl groups. The metal–ligand equilibria are adequately described by eqs 3–5.

$$M^{3+} + L^- \rightleftharpoons ML^{2+} \quad \beta_1 \tag{3}$$

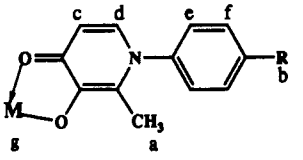
$$M^{3+} + 2L^- \rightleftharpoons ML_2^+ \quad \beta_2 \tag{4}$$

$$M^{3+} + 3L^- \rightleftharpoons ML_3 \quad \beta_3 \tag{5}$$

$$\beta_n = \frac{[ML_n^{(3-n)+}]}{[M^{3+}][L^-]^n}$$

Hppp was found to have a very high affinity for the group 13 (IIIA) trivalent metal ions, particularly for Ga^{3+}. This is evinced

Table VII. ^1H NMR Spectral Data[a,b] for



M	R	a	b	c	d + e + f	g
H	H	2.11 (s, 3 H)	*b*	6.48 (d, 1 H, *J* = 7.6 Hz)	7.2–7.6 (m, 6 H)	5.76 (s, 1 H)
Al	H	2.18 (s, 9 H)	*b*	6.67 (d, 3 H, *J* = 7.2 Hz)	7.18 (d, 3 H, *J* = 7.2 Hz) 7.2–7.5 (m, 15 H)	
Ga	H	2.19 (s, 9 H)	*b*	6.72 (d, 3 H, *J* = 7.2 Hz)	7.17 (d, 3 H, *J* = 7.2 Hz) 7.2–7.6 (m, 15 H)	
In	H	2.19 (s, 9 H)	*b*	6.72 (d, 3 H, *J* = 7.2 Hz)	7.15 (d, 3 H, *J* = 7.2 Hz) 7.2–7.6 (m, 15 H)	
H	CH_3	2.11 (s, 3 H)	2.45 (s, 3 H)	6.46 (d, 1 H, *J* = 7.2 Hz)	7.1–7.4 (m, 5 H)	5.23 (s, 1 H)
Al	CH_3	2.18 (s, 9 H)	2.43 (s, 9 H)	6.66 (d, 3 H, *J* = 6.9 Hz)	7.0–7.4 (m, 15 H)	
Ga	CH_3	2.19 (s, 9 H)	2.43 (s, 9 H)	6.70 (d, 3 H, *J* = 6.9 Hz)	7.1–7.4 (m, 15 H)	
In	CH_3	2.23 (s, 9 H)	2.44 (s, 9 H)	6.73 (d, 3 H, *J* = 6.9 Hz)	7.0–7.4 (m, 15 H)	
H	OCH_3	2.11 (s, 3 H)	3.90 (s, 3 H)	6.45 (d, 1 H, *J* = 7.8 Hz)	6.9–7.3 (m, 5 H)	5.66 (s, 1 H)
Al	OCH_3	2.13 (s, 9 H)	3.84 (s, 9 H)	6.61 (d, 3 H, *J* = 6.8 Hz)	6.8–7.3 (m, 15 H)	
Ga	OCH_3	2.15 (s, 9 H)	3.83 (s, 9 H)	6.64 (d, 3 H, *J* = 6.8 Hz)	6.9–7.3 (m, 15 H)	
In	OCH_3	2.17 (s, 9 H)	3.84 (s, 9 H)	6.67 (d, 3 H, *J* = 6.9 Hz)	6.9–7.3 (m, 15 H)	
H[c]	NO_2	1.99 (s, 3 H)		6.25 (d, 1 H, *J* = 7.4 Hz)	7.61 (d, 1 H, *J* = 7.4 Hz) 7.79 (d, 2 H, *J* = 8.9 Hz) 8.38 (d, 2 H, *J* = 8.9 Hz)	3.6 (br)
Al[c]	NO_2	2.01 (s, 9 H)		6.49 (d, 3 H, *J* = 6.7 Hz)	7.63 (d, 3 H, *J* = 6.7 Hz) 7.85 (d, 6 H, *J* = 8.6 Hz) 8.41 (d, 6 H, *J* = 8.6 Hz)	
Ga[c]	NO_2	2.04 (s, 9 H)		6.53 (d, 3 H, *J* = 6.8 Hz)	7.63 (d, 3 H, *J* = 6.8 Hz) 7.85 (d, 6 H, *J* = 8.7 Hz) 8.41 (d, 6 H, *J* = 8.7 Hz)	
In[c]	NO_2	2.08 (s, 9 H)		6.58 (d, 3 H, *J* = 6.9 Hz)	7.63 (d, 3 H, *J* = 6.9 Hz) 7.83 (d, 6 H, *J* = 8.8 Hz) 8.42 (d, 6 H, *J* = 8.8 Hz)	

[a] $CDCl_3$. [b] Protons b in $M(ppp)_3$ are listed with d + e + f. [c] DMSO-d_6.

Table VIII. log Protonation Contants (K_1, K_2), Metal-Ligand Stability Constants (β_n), and Effective Stability Constants (β_{3eff}, pH 7.4) for the Equilibrium Reactions of Al, Ga, and In with Hppp at 25 and 37 °C in 0.15 M NaCl[a,b]

constant	metal	25 °C	37 °C
log K_1		9.40 (1)	9.61 (1)
log K_2		3.03 (1)	3.18 (1)
log β_1	Al	11.36 (3)	11.86 (10)
	Ga	17.5 (2)[c]	
	In	13.34 (1)	
log β_2	Al	21.78 (8)	23.13 (21)
	Ga	28.8 (2)[c]	
	In	22.66 (2)	
log β_3	Al	30.74 (11)	32.44 (23)
	Ga	36.3 (2)[c]	
	In	31.12 (3)	
log β_{3eff}	Al	24.74 (14)	25.81 (26)
	Ga	30.3 (2)[c]	
	In	25.12 (6)	

[a] Ga constants are reported for solutions containing ~0.2 M NaCl (see ref 7). [b] Numbers in parentheses represent standard deviations between successive runs. [c] Estimated by LFER.

by the high overall (β_3) and conditional ($\log \beta_{3eff} = \log \beta_3 - 3(\log K_2 - pH)$[28]) formation constants for $Ga(ppp)_3$ in Table VIII. The overall constant is lower than we found[7] for the Ga complexes of *N*-alkylated pyridinones ($\log \beta_3 = 36$ vs ~38); however, the lower K_2 value for this ligand means that the conditional stability constant at pH 7.4 is only slightly smaller than that for the *N*-alkylated ligands ($\log \beta_{3eff} = 30.3$ vs ~30.8). The same holds true for the Al and In complexes of ppp^-. The overall stability constants are lower than we found for Al[5] or In[7] with the *N*-alkylated pyridinones, but the conditional stability constants are only very slightly smaller for ppp^- (for Al $\log \beta_{3eff} = 24.7$ vs 24.9; for In $\log \beta_{3eff} = 25.1$ vs 25.6). Clearly, changes in the substituent on the ring nitrogen of the pyridinone ring make minor alterations in the overall formation constants ($\log \beta_3$), and these variations may be attributed to the changes in the pK_as of the ligands. The effective overall formation constant at pH 7.4 ($\log \beta_{3eff}$) demonstrates this thermodynamic indifference when β_3 is normalized to blood plasma conditions (pH 7.4 and 0.15 M NaCl). The predominance of the ML_3 species at physiological pH was demonstrated in the $\log \beta_{3eff}$ values in Table VIII.

The consistently high $\log \beta_{3eff}$ values for the tris(N-substituted-3-hydroxy-2-methyl-4-pyridinonato)gallium(III) complexes led us previously to study in detail the in vivo biodistribution of these compounds with $^{67}Ga^{3+}$.[7] The *N*-alkyl ligands were excreted quickly via the urinary pathway. We have prepared the compounds described herein in order to increase the lipophilicity and alter the biodistribution.

Acknowledgment is made to the British Columbia Health Care Research Foundation, the NSERC of Canada, and the U.S. Public Health Service (CA 48964) for operating grants, to the NSERC for a University Research Fellowship (C.O.), and to the UBC for a University Graduate Fellowship (Z.Z.). We are particularly indebted to Prof. David Clevette for help with the potentiometric measurements and to Prof. James Trotter for discussions and the use of his crystallographic facilities.

Supplementary Material Available: Complete crystallographic data (Table SI), hydrogen atom parameters (Tables SII and SIII), anisotropic thermal parameters (Tables SIV and SV), intramolecular bond distances involving hydrogen atoms (Tables SVI and SVII), intramolecular bond angles involving hydrogen atoms (Tables SVIII and SIX), torsion angles (Tables SX and SXI), intermolecular contacts (Tables SXII and SXIII), and least-squares planes (Tables SXIV and SXV) (24 pages); measured and calculated structure factor amplitudes (Tables SXVI and SXVII) (38 pages). Ordering information is given on any current masthead page.

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Contribution from the Departments of Chemistry and Physiological Sciences, University of Florida, Gainesville, Florida 32611

Platinum(II)-Thiolate Cluster Formation in Heptaplatinum Metallothionein

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Received March 20, 1990

The binding of platinum(II) to metallothionein (MT) has been studied by spectrophotometric titrations of rat liver apometallothionein-1 (apoMT) with platinum(II) complexes at pH 7.4-7.5. A red shift of ~6000 cm^{-1} in the intense absorption maximum in the electronic spectra of the partially platinated apoMT adducts is observed upon the binding of ≥3 molar equiv of platinum(II). This shift is similar to red shifts of the lowest energy LMCT transitions observed for $[X_2Pt(\mu\text{-}X)_2PtX_2]^{2-}$ ions (X = Br, I) relative to the corresponding PtX_4^{2-} ions and can be attributed to a lowering in energy of $M\sigma^* \leftarrow L\pi$ transitions from the terminal thiolates due to the presence of bridging thiolates. The partially platinated apoMT solutions (0-7 molar equiv of bound platinum(II) ions) were also assayed for free thiolate contents by using 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB). The DTNB studies showed that platinum equivalents 1-3 block 4 ± 1 cysteines/platinum and that equivalents 5-7 block a total of 3 ± 1 cysteines (an average of 1 cysteine/Pt). These experiments suggest that the platinum(II)-thiolate clusters in Pt_7MT form via the initial production of approximately three $Pt(cysteine)_4^{2-}$ centers followed by formation of μ-thiolato bridges.

Metallothionein (MT)[1-5] is a low molecular weight cytosolic protein with an unusually high cysteine content (20 cys in the mammalian proteins) that chelates a diversity of metal ions in vivo and in vitro. Native MT contains primarily Cd(II) and Zn(II) in two metal-thiolate clusters, and in vitro reconstitutions of the metal-free form of the protein (apoMT) to generate Cd_7MT and Zn_7MT have been widely studied by spectroscopic techniques.[6] Adducts of MT with a variety of other metal ions have also been studied by spectroscopic means, including Co(II),[7-9] Ni(II),[7] Fe(II),[10] and Hg(II) adducts.[11]

Available evidence strongly suggests that MT is a major in vivo binding site for metabolites of *cis*-diamminedichloroplatinum(II)

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