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Group 13 and Lanthanide Complexes with Mixed *O*,*S* Anionic Ligands Derived from Maltol

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Four mixed *O*,*S* binding ligand precursors derived from maltol (3-hydroxy-2-methyl-4-pyrone) have been chelated to gallium(III), indium(III), and lanthanide(III) ions to yield a series of metal complexes. The four ligand precursors include two pyranthiones, 3-hydroxy-2-methyl-4-pyranthione, commonly known as thiomaltol (Htma), and 2-ethyl-3-hydroxy-4-pyranthione, commonly known as ethylthiomaltol (Hetma), and two pyridinethiones, 3-hydroxy-2-methyl-4(H)-pyridinethione (Hmppt) and 3-hydroxy-1,2-dimethyl-4-pyridinethione (Hdppt). Dimeric forms of the pyridinethiones, Hmppt dimer and Hdppt dimer, were also isolated and characterized. Complete characterization of the monomeric organic compounds is reported including acidity constants and crystal structures of Htma, Hetma, and Hdppt dimer. Reacting the four monomeric ligand precursors with Ga^{3+} and In^{3+} ions yielded new tris(bidentate ligand) complexes. X-ray-quality crystals of the fac isomer of $Ga(tma)_3$ were also obtained. New complexes with a range of lanthanides (Ln^{3+}) were also synthesized with the two pyranthiones, Htma and Hetma. The synthesis reactions yielded complexes of the type $LnL_3 \cdot xH_2O$ and $LnL_2(OH) \cdot xH_2O$, as indicated by elemental analysis and spectroscopic evidence such as mass spectral data and IR and NMR spectra.

Introduction

Many gallium(III), indium(III), and lanthanide(III) complexes are widely used as pharmaceutical agents for their diagnostic or therapeutic (chemotherapeutic and radiotherapeutic) properties.[1−4] Whereas the distinctive magnetic properties of lanthanide(III) ions (Gd^{3+}, Ho^{3+}, Eu^{3+}) are used for MRI (magnetic resonance imaging),[3,5] emissions from the radioactive isotopes of Ga, In, and Ln can be utilized for SPECT (single photon emission computed tomography)[1] and PET (positron emission tomography).[6] These imaging techniques have been successfully used to diagnose cancer, infection, thrombosis, and kidney and liver abnormalities, as well as many other cardiac and neurological disorders.[1]

The radioactive isotopes of group 13 metal ions are becoming indispensable in nuclear medicine and are currently a primary driving force for the development of the coordination chemistry of these elements. Group 13 and lanthanide complexes have shown numerous biochemical responses in vivo (vide infra). It has been postulated that biological effects are seen because these metal ions have chemical and physical properties (e.g., ionic radii) similar to those of metal ions found naturally in biological systems, elements such as Fe^{3+}, Ca^{2+}, and Na^{+}. A major requirement for coordination complexes to be used as radiopharmaceuticals is in vivo thermodynamic stability: the metal−ligand binding should be stable enough to resist hydrolysis of the metal ion and competition from endogenous biomolecules that can behave as ligands, such as the plasma protein transferrin. Because of their myriad of potential biological applications, our group has studied the coordination chemistry of group 13 and lanthanide metal ions extensively over the years.[7−11] Two classes of bidentate *O*,*O* (pro)ligands that have been studied

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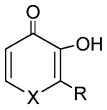
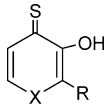
extensively in our group are 3-hydroxy-4-pyrones and 3-hydroxy-4-pyridinones.[7,12−15] The synthesis, solution studies, and biodistribution of group 13 complexes with 3-hydroxy-4-pyrone and 3-hydroxy-2-methyl-4-pyridinone derivatives (Hma,[12] Hmpp,[16,17] and Hdpp[16,17]) were reported previously by our group. For the pyridinone ligands, it was found that the resulting complexes were stable to hydrolysis and the overall formation constants were much higher than those of Ga-transferrin, a commonly used radiopharmaceutical for SPECT (log $\beta_3 \approx 36$[17] vs log $K_1 \approx 20$[18] for Ga-transferrin). The efficacies of the ^{67}Ga-labeled complexes were evaluated in vitro and in vivo and were compared to that for ^{67}Ga-citrate.[19] It was found that these complexes were stable in vivo (in rabbits and dogs) and accumulated in the heart.[19] At present, Ga(ma)$_3$ is being revisited and evaluated as an orally active agent for the treatment of several cancers.[20] Lanthanide complexes with Hma and Hdpp have also been reported by a few research groups.[21−23]



R = CH_3,	X = O,	Hma
R = C_2H_5,	X = O,	Hema
R = CH_3,	X = NH,	Hmpp
R = CH_3,	X = NCH_3,	Hdpp

The chemical and physical properties of elements, however, vary down a group and across a period. Therefore, for this study, ligands for Ga, In, and Ln metal ions were designed keeping in mind the general trend in the chemical properties of these metal ions (vide infra). For the group 13 metal ions, hardness (i.e., affinity for hard donors such as O and N) decreases down the group (e.g., Ga^{3+} is harder than In^{3+}), whereas hardness increases with decreasing ionic size across the series for the lanthanides (e.g., Lu^{3+} is harder than La^{3+}). Considering similar conditions, several researchers have synthesized numerous Ga(III) and In(III) complexes with bidentate and multidentate sulfur-containing ligands and tested the radio-labeled complexes for in vivo stability and biodistribution as imaging agents.[24,25] Despite the fact that lanthanides are considered to be hard metal ions, some lanthanide complexes with sulfur-containing ligands have been evaluated for potential in radiotherapy. ^{166}Holmium (which undergoes β^- decay to ^{166}Er) was chelated to *N,N*′-ethylenedi-L-cysteine (EC, a N_2S_2 donor set); the ^{166}Ho-labeled complex showed the desired rapid renal clearance when used for post-angioplasty intravascular radiotherapy (IVRT),[26] thus promoting the application of other such complexes in the future.



R = CH_3,	X = O,	Htma
R = C_2H_5,	X = O,	Hetma
R = CH_3,	X = NH,	Hmppt
R = CH_3,	X = NCH_3,	Hdppt

Herein, four compounds, two pyranthiones, Htma and Hetma, and two pyridinethiones, Hmppt and Hdppt, are reported as potential monoanionic bidentate mixed hard−soft donors with an *O,S* binding moiety. For all four thio compounds, the ligands bind through a deprotonated hydroxyl oxygen, O^- and a neutral thiocarbonyl group, C═S. Because O^- is considered to be a hard donor, it was expected to bind strongly to the harder metal ions (e.g., Ga^{3+}, Lu^{3+}), whereas binding to the softer S (from C═S) should be favored by the softer metal ions (e.g., In^{3+}, La^{3+}). Thiomaltol, one of the ligands studied in this work, is the thio analogue of maltol, an approved food additive in the U.K., U.S., and Canada. The coordination chemistry of the maltolato ligand has been explored thoroughly with vanadium,[8] group 13,[12] lanthanide, and many other metal ions.[27−29] Comparing the well-documented work on maltolato and other similar (pro)-ligands (ethylmaltol and 3-hydroxy-4-pyridinones) with that on the thio analogues should provide insight concerning the differences in chemical and biological properties of the resultant metal complexes. The thiomaltolato anion has been chelated previously to various metal ions (Cu, Hg, Ni, Fe, Mo, In, V, Pb, Sn, Cd, Co) to explore the coordination and extraction ability of this ligand.[30−33] Recently, there seems to be renewed interest in this compound as a ligand because of its trans-influencing ability.[31] A series of pyridinethiones was also patented recently for therapeutic antioxidant properties[34] and effectiveness against carcinoma.[35] When coordinated to M^{3+} ions in a 1:3 ratio (M^{3+}/L^-), the resulting complexes with these ligands are expected to be low in molecular weight (∼500−640), neutral and six coordinate with an O_3S_3 coordination sphere, all properties important

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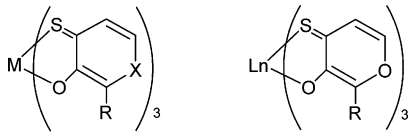
for demonstrating higher thermodynamic stability in vivo. The five-membered chelate ring that forms as a result of the coordination of O^- and S to the metal ion should also add to the stability of the complex.

This work describes in detail the synthesis and characterization (including the acidity constants) of thiomaltol; its close analogue, ethylthiomaltol (thio analogue of another approved food additive, ethylmaltol); and two 3-hydroxy-4-pyridinethiones, Hmppt and Hdppt.



ML_3, M = Ga^{3+}, In^{3+} $\quad$ LnL_3

R = CH_3, X = O, L^- = tma^-
R = C_2H_5, X = O, L^- = $etma^-$
R = CH_3, X = NH, L^- = $mppt^-$
R = CH_3, X = NCH_3, L^- = $dppt^-$

The coordination chemistry of these ligand precursors with group 13 metal ions gallium and indium has also been explored in detail and compared to that of their oxygen analogues. Some new lanthanide (Ln = La, Pr, Nd, Sm, Gd, Ho, Yb, and Lu) complexes with the two pyranthiones, Htma and Hetma, are also reported. It was expected that the bidentate mixed *O,S* donor ligands would favor both types of metal ions (hard and soft) and might be an ideal choice for synthesizing strong metal complexes down the group (group 13) or across the (lanthanide) series. Furthermore, the influence of O to S substitution on the binding strength of these diverse trivalent metal ions can be examined. Another unique feature of these ligands is the covalent coordinate bond to the thiocarbonyl group (C═S); most of the other sulfur-containing ligands tested as imaging agents were chelated through a deprotonated thiol, S^-. It is noteworthy that the sulfur atom in a thiolate group has a tendency to bridge metal centers and form polymeric species.[36] With a thiocarbonyl binding moiety (instead of a thiolate group), isolation of the desirable monomeric species is more probable. Furthermore, it was of interest to examine the difference in binding properties when chelating a neutral C═S moiety instead of the anionic S^-.

Experimental Section

Materials and Methods. All chemicals [P_2S_5, NaCl, NaOH, 40% aqueous $MeNH_2$, NH_4OH, HCl, DTT (dithiothreitol), $Ga(NO_3)_3 \cdot 9H_2O$, $Ga(ClO_4)_3 \cdot 6H_2O$, $In(NO_3)_3 \cdot 3H_2O$, $In(ClO_4)_3 \cdot 6H_2O$, $Ln(ClO_4)_3 \cdot 6H_2O$, NaOH, NEt_3] were obtained from Sigma-Aldrich or Fisher Scientific and were used as received without further purification. Maltol and ethylmaltol were obtained from Pfizer or Cultor Food Science, potassium biphthalate (KHP) from Anachemia, and silica gel 230−400 mesh from Silicycle. All solvents were reagent-grade and were obtained from Fisher Scientific. Water was deionized (Barnstead D8902 and D8904 Cartridges) and distilled (Hytrex II GX50-9-7/8 and GX100-9-7/8 filter cartridges) before use. All synthetic reactions were carried out in degassed solvents under Ar. Yields are reported for the analytically pure compounds and were calculated on the basis of the respective metal starting material for the metal complexes.

Instrumentation. Infrared spectra were recorded as KBr disks in the range of 4000−500 cm^{-1} on a Galaxy Series 5000 FTIR spectrometer and were standardized to polystyrene. Mass spectra were obtained with a Kratos MS 50 (electron-impact ionization mass spectrometry, EIMS), a Kratos Concept II H32Q (Cs^+ liquid secondary ion mass spectrometry, LSIMS), or a Micromass LCT or Bruker Esquire Ion Trap (electrospray ionization mass spectrometry, ESIMS) spectrometer. Mr. Peter Borda or Mr. Minaz Lakha in the UBC chemistry department performed the elemental analyses for C, H, N, and S. ^1H and $^{13}C\{^1H\}$ NMR spectra, respectively, were recorded on Bruker AC-200E (200, 50.2 MHz) or Bruker AV300 (300, 75.5 MHz) NMR spectrometer with δ referenced to the deuterated solvent. For the 2D HMQC and HMBC NMR experiments, a Bruker AV400 spectrometer at 400 MHz was used. Melting points were measured using a Gallenkamp melting point apparatus and are corrected. UV−visible spectra were recorded using a Hewlett-Packard 8543 diode array spectrophotometer.

Synthesis of the Ligand Precursors. Please refer to the Supporting Information for detailed characterization of the organic compounds.

(i) Thiomaltol, 3-Hydroxy-2-methyl-4-pyranthione, Htma. Phosphorus pentasulfide (P_2S_5, 8.94 g, 0.04 mol) was added slowly to a solution of maltol (25.38 g, 0.202 mol) in 1,4-dioxane (200 mL) at 45 °C. The resulting solution was heated with stirring for 3 h, cooled to room temperature, and clarified by filtration. The filtrant was washed with 10 mL of 1,4-dioxane. The filtrate was added to water (500 mL), and a yellow crystalline product instantly precipitated. The water/dioxane mixture (including the precipitate) was placed in the refrigerator (4 °C, 2 h) to maximize precipitation of the product, which was filtered out to yield the pure yellow crystalline product (13.30 g, 0.094 mol, 46% yield) that had a pungent smell. Slow evaporation of a hexane solution of Htma gave X-ray-quality crystals. Anal. Calcd (found) for $C_6H_6O_2S$: C, 50.69 (50.58); H, 4.25 (4.27); S, 22.55 (22.74).

(ii) Ethylthiomaltol, 2-Ethyl-3-hydroxy-4-pyranthione, Hetma. Ethylthiomaltol was prepared in a manner similar to that used for thiomaltol. P_2S_5 (3.69 g, 0.017 mol) was added slowly to a solution of ethylmaltol (11.63 g, 0.083 mol) in 1,4-dioxane (25 mL) at 45 °C. The resulting solution was heated with stirring overnight, cooled to room temperature, and clarified by filtration. The filtrate was washed with 10 mL of 1,4-dioxane and the filtrant (solvent) was evaporated to yield a brown viscous oily layer. Column purification (silica gel, 230−400 mesh, 7:3 ethyl acetate/hexane solvent) of the reaction mixture yielded a viscous brown oil (7.23 g, 0.046 mol, 56% yield) that had a distinct smell. Placing the brown oil in a flask on dry ice and slowly warming the flask to room temperature gave yellow X-ray-quality crystals of Hetma. It was noted that the compound decomposes in air (on melting) after a few days; hence, it was always stored under Ar or vacuum. Anal. Calcd (found) for $C_7H_8O_2S$: C, 53.83 (53.78); H, 5.16 (5.24); S, 20.53 (20.60).

(iii) 3-Hydroxy-2-methyl-4(H)-pyridinethione, Hmppt. Thiomaltol (3.54 g, 0.025 mol) was dissolved in degassed water (330 mL) at 78 °C. As the solution was slowly cooled to 34 °C, degassed ethanol (150 mL) was added to redissolve the thiomaltol that precipitated as the temperature was decreased. At this point, concentrated NH_4OH (8.4 mL, 0.126 mol) was added dropwise to the solution. After the solution (pH ≈ 9) had been stirred for 36 h at 34 °C, it was concentrated in vacuo and cooled at 4 °C overnight.

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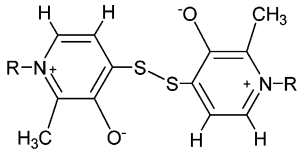
Pale brown needles of the pure product were collected by filtering the solution (1.51 g, 43%). Anal. Calcd (found) for C_6H_7NOS: C, 51.04 (50.85); H, 5.00 (4.95); N, 9.92 (9.72); S, 22.71 (22.66).

(iv) 3-Hydroxy-1,2-dimethyl-4-pyridinethione, Hdppt. To a solution of thiomaltol (1.97 g, 0.014 mol) in degassed water (150 mL) at 78 °C was added 40% methylamine (11.9 mL, 0.14 mol), dropwise, over a period of 2 h. The resulting deep red solution was heated for 12 h. Concentration in vacuo and cooling at 4 °C overnight gave 1.49 g of a mixture of mostly Hdppt and some Hdppt dimer. Column purification (silica gel, 230−400 mesh, 3:1 ethyl acetate/methanol solvent) of this mixture yielded pale yellowish-brown fine needles of the pure compound (1.00 g, 47%). Anal. Calcd (found) for C_7H_9NOS: C, 54.17 (54.25); H, 5.84 (5.70); N, 9.02 (9.02); S, 20.66 (20.60).



R = H, 4,4'-dithiobis(2-methylpyridinium-3-oxide), Hmppt-dimer
R = CH_3, 4,4'-dithiobis(1,2-dimethylpyridinium-3-oxide), Hdppt-dimer

(v) 4,4′-Dithiobis(2-methylpyridinium-3-oxide), Hmppt Dimer. The synthesis of Hmppt dimer was done in a fashion analogous to that for Hmppt except that the temperature was maintained at 78 °C for the duration of the reaction (36 h) and no ethanol was added to the reaction mixture. To verify the disulfide bond in the dimer, an NMR experiment was done with a reducing agent, dithiothreitol (DTT). DTT (0.011 g, 0.071 mmol) was added to a solution of Hmppt dimer (0.0047 g, 0.017 mmol) in DMSO-d_6. The ^{1}H NMR spectrum of the solution was taken before and after addition of DTT to monitor the reduction. Hmppt dimer was immediately reduced to its monomeric form, Hmppt. Anal. Calcd (found) for $C_{12}H_{12}N_2O_2S_2\cdot 2H_2O$: C, 45.56 (45.68); H, 5.10 (5.10); N, 8.85 (8.97).

4,4′-Dithiobis(1,2-dimethylpyridinium-3-oxide), Hdppt Dimer. A small amount of Hdppt dimer always formed with Hdppt and was isolated by column purification as described for Hdppt. To verify the disulfide bond in the dimer, an NMR experiment was done with dithiothreitol (DTT). DTT (0.01 g, 0.065 mmol) was added to a solution of Hdppt dimer (0.0049 g, 0.016 mmol) in DMSO-d_6. The ^{1}H NMR spectrum of the solution was taken before and after addition of DTT to monitor the reduction. Hdppt dimer was immediately reduced to its monomeric form, Hdppt. Anal. Calcd (found) for $C_{14}H_{16}N_2O_2S_2\cdot 2H_2O$: C, 48.82 (49.11); H, 5.85 (5.94); N, 8.13 (8.23).

Synthesis of the Gallium(III) and Indium(III) Complexes. (i) Tris(thiomaltolato)gallium(III), Ga(tma)$_3$. $Ga(NO_3)_3\cdot 9H_2O$ (0.0564 g, 0.135 mmol) was added to a solution of Htma (0.116 g, 0.82 mmol) in 10 mL of degassed water under Ar at 75 °C. As the pH of the solution was raised slowly (over 10 min) with 1 M NaOH (0.4 mL, 0.4 mmol) to ∼7.5, a yellow solid precipitated from the solution. The resulting reaction mixture was refluxed for 3 h and then cooled to room temperature. A yellow precipitate was collected by vacuum filtration, washed twice with 5 mL of cold water, and dried overnight in vacuo to yield 0.06 g, 90%. Anal. Calcd (found) for $C_{18}H_{15}GaO_6S_3$: C, 43.83 (43.50); H, 3.07 (2.91). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (1H, d, ^2J = 4.64 Hz, OCH), 7.45 [1H, d, ^2J = 4.65 Hz, HCC(S)], 2.41 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 175.73 (*C*═S), 155.41 (*C*−O−Ga), 150.88 (*C*−CH_3), 147.52 (O*C*H), 120.45 [H*C*C(S)], 15.94 (*C*H_3). MS (+ESIMS): *m*/*z* 532 ([$KGaL_3$]$^+$), 494 ([$HGaL_3$]$^+$), 352 ([GaL_2]$^+$). IR (cm^{-1}, ±4 cm^{-1}): 1578, 1499 (ring vibrations), 820 (ν_{C-O-C}), 664 (ν_{Ga-O}).

(ii) Tris(thiomaltolato)indium(III), In(tma)$_3$. In(tma)$_3$ was synthesized according to the same method as employed for Ga(tma)$_3$, except that the molar ratio of In^{3+} to L^- was 1:3 instead of 1:6, using $In(NO_3)_3\cdot 3H_2O$ (0.66 g, 1.86 mmol) and Htma (0.7925 g, 5.58 mmol) to yield 0.69 g, 69%. Anal. Calcd (found) for $C_{18}H_{15}InO_6S_3$: C, 40.16 (40.36); H, 2.81 (2.79); S, 17.87 (17.90). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (1H, d, ^2J = 4.26 Hz, OCH), 7.56 [1H, d, ^2J = 4.23 Hz, HCC(S)], 2.48 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 173.70 (*C*═S), 156.84 (*C*−O−In), 153.66 (*C*−CH_3), 146.60 (O*C*H), 122.01 [H*C*C(S)], 16.33 (*C*H_3). MS (+ESIMS): *m*/*z* 538 ([InL_3]$^+$), 397 ([InL_2]$^+$). IR (cm^{-1}, ±4 cm^{-1}): 1570, 1482 (ring vibrations), 822 (ν_{C-O-C}), 658 (ν_{In-O}).

(iii) Tris(ethylthiomaltolato)gallium(III), Ga(etma)$_3$. $Ga(NO_3)_3\cdot 9H_2O$ (0.0441 g, 0.106 mmol) was added to a solution of Hetma (0.0988 g, 0.63 mmol) in 10 mL of degassed water and 5 mL of MeOH under Ar at 70 °C. As the pH of the solution was raised slowly (over 10 min) with 1 M NaOH (0.2 mL, 0.2 mmol) to ∼7.5, a yellow solid precipitated from the solution. The resulting reaction mixture was refluxed for 3 h and then cooled to room temperature. A yellow precipitate was collected by vacuum filtration, washed twice with 5 mL of cold water, and dried overnight in vacuo to yield 0.05 g, 90%. Anal. Calcd (found) for $C_{21}H_{21}GaO_6S_3$: C, 47.12 (47.31); H, 3.95 (3.94). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (1H, d, ^2J = 4.63 Hz, OCH), 7.46 [1H, d, ^2J = 4.62 Hz, HCC(S)], 2.79 (2H, q, ^2J = 7.51 Hz, CH_2), 1.11 (3H, t, ^2J = 7.51 Hz, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 176.26 (*C*═S), 154.97 (*C*−O−Ga), 154.80 (*C*−C_2H_5), 147.54 (O*C*H), 120.43 [H*C*C(S)], 22.67 (*C*H_2), 10.35 (*C*H_3). MS (+ESIMS): *m*/*z* 558 ([$NaGaL_3$]$^+$), 380 ([GaL_2]$^+$). IR (cm^{-1}, ±4 cm^{-1}): 1572, 1497 (ring vibrations), 822 (ν_{C-O-C}), 662 (ν_{Ga-O}).

(iv) Tris(ethylthiomaltolato)indium(III), In(etma)$_3$. In(etma)$_3$ was synthesized according to the same method as employed for Ga(etma)$_3$, except that the molar ratio of In^{3+} to L^- was 1:3 instead of 1:6, using $In(NO_3)_3\cdot 3H_2O$ (0.167 g, 0.47 mmol) and Hetma (0.2208 g, 1.42 mmol) to yield 0.17 g, 61%. Anal. Calcd (found) for $C_{21}H_{21}InO_6S_3\cdot 0.5H_2O$: C, 42.79 (42.53); H, 3.76 (3.47); S, 16.32 (16.69). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (1H, d, ^2J = 4.62 Hz, OCH), 7.57 [1H, d, ^2J = 4.62 Hz, HCC(S)], 2.86 (2H, q, ^2J = 7.50 Hz, CH_2), 1.13 (3H, t, ^2J = 7.50 Hz, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 174.15 (*C*═S), 157.43 (*C*−C_2H_5), 156.40 (*C*−O−In), 146.64 (O*C*H), 122.01 [H*C*C(S)], 22.93 (*C*H_2), 10.22 (*C*H_3). MS (+ESIMS): *m*/*z* 1005 ([In_2L_5]$^+$), 603 ([$NaInL_3$]$^+$), 425 ([InL_2]$^+$), 270 ([InL]$^+$). IR (cm^{-1}, ±4 cm^{-1}): 1573, 1487 (ring vibrations), 824 (ν_{C-O-C}), 657 (ν_{In-O}).

Note: Metal perchlorate salts should be handled with care.

(v) Tris(2-methyl-3-oxy-4-pyridinethionato)gallium(III), Ga(mppt)$_3$. $Ga(ClO_4)_3\cdot 6H_2O$ (0.0755 g, 0.16 mmol) was added to a solution of Hmppt (0.0693 g, 0.49 mmol) in 10 mL of dry, degassed MeCN under Ar at room temperature. As the pH of the solution was raised slowly (over 10 min) with NEt_3 (0.075 mL, 0.54 mmol), a beige solid precipitated from the solution. The resulting reaction mixture was stirred for 3 h and then vacuum filtered. The beige product was washed twice with 5 mL of cold MeCN and dried overnight in vacuo to yield 0.054 g, 68%. Anal. Calcd (found) for $C_{18}H_{18}GaN_3O_3S_3\cdot 2H_2O$: C, 41.08 (41.22); H, 4.21 (4.30); N, 7.98 (7.56). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (1H, br, OCH), 7.39 [1H, br, HCC(S)], 2.38 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 121.92 (H*C*C(S)], 15.83 (*C*H_3) (see Results and Discussion for explanation of the other ^{13}C signals). MS (+ESIMS): *m*/*z* 529 ([$KGaL_3$]$^+$), 350 ([GaL_2]$^+$), 210 ([GaL]$^+$).

IR (cm^{-1}, ± 4 cm^{-1}): 2919 (ν_{N-H}), 1590, 1458, 1316, 1228 (ring and C−N−C vibrations), 607 (ν_{Ga-O}).

(vi) Tris(2-methyl-3-oxy-4-pyridinethionato)indium(III), In(mppt)$_3$. In(mppt)$_3$ was synthesized according to the same method as employed for Ga(mppt)$_3$ using $In(ClO_4)_3 \cdot 6H_2O$ (0.077 g, 0.14 mmol) and Hmppt (0.0586 g, 0.42 mmol) to yield 0.036 g, 50%. Anal. Calcd (found) for $C_{21}H_{21}InN_3O_3S_3 \cdot 3H_2O$: C, 36.68 (36.63); H, 4.10 (3.92); N, 7.13 (6.99). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.35 (1H, br, OCH), 7.23 (1H, br, HCC(S)), 2.25 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 159.75 (*C*−O−In), 158.99 (*C*═S), 130.75 (*C*−CH_3), 123.50 (N−*C*H), 121.23 [H*C*C(S)], 15.27 (*C*H$_3$). MS (+ESIMS): *m*/*z* 558 ([$NaInL_3$]$^+$), 536 ([$HInL_3$]$^+$), 395 ([InL_2]$^+$). IR (cm^{-1}, ± 4 cm^{-1}): 2911 (ν_{N-H}), 1581, 1454, 1314, 1225 (ring and C−N−C vibrations), 594 (ν_{In-O}).

(vii) Tris(1,2-dimethyl-3-oxy-4-pyridinethionato)gallium(III), Ga(dppt)$_3$. Ga(dppt)$_3$ was synthesized according to the same method as employed for Ga(mppt)$_3$ using $Ga(ClO_4)_3 \cdot 6H_2O$ (0.0484 g, 0.102 mmol) and Hdppt (0.0493 g, 0.32 mmol) to yield 0.032 g, 60%. Anal. Calcd (found) for $C_{21}H_{24}GaN_3O_3S_3$: C, 47.38 (47.57); H, 4.54 (4.32); N, 7.89 (8.29). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36 (1H, d, ^2J = 6.54 Hz, OCH), 7.09 [1H, d, ^2J = 6.54 Hz, HCC(S)], 3.81 (3H, s, N−CH_3), 2.36 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 159.92 (*C*═S), 158.94 (*C*−O−Ga), 131.08 (*C*−CH_3), 127.43 (N−*C*H), 120.98 [H*C*C(S)], 43.28 (N−*C*H$_3$), 13.20 (*C*H$_3$). MS (+ESIMS): *m*/*z* 378 ([GaL_2]$^+$), 224 ([GaL]$^+$). IR (cm^{-1}, ± 4 cm^{-1}): 1584, 1294 (ring and C−N−C vibrations), 529 (ν_{Ga-O}).

(viii) Tris(1,2-dimethyl-3-oxy-4-pyridinethionato)indium(III), In(dppt)$_3$. In(dppt)$_3$ was synthesized according to the same method as employed for Ga(mppt)$_3$ using $In(ClO_4)_3 \cdot 6H_2O$ (0.0454 g, 0.082 mmol) and Hdppt (0.0383 g, 0.25 mmol) to yield 0.030 g, 64%. Anal. Calcd (found) for $C_{21}H_{24}InN_3O_3S_3$: C, 43.68 (43.28); H, 4.19 (4.16); N, 7.28 (7.39). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.37 (1H, d, ^2J = 6.47 Hz, OCH), 7.21 [1H, d, ^2J = 6.32 Hz, HCC(S)], 3.84 (3H, s, N−CH_3), 2.41 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 160.15 (*C*−O−In), 157.13 (*C*═S), 133.42 (*C*−CH_3), 126.47 (N−*C*H), 122.76 [H*C*C(S)], 43.59 (N−*C*H$_3$), 13.36 (*C*H$_3$). MS (+ESIMS): *m*/*z* 1000 ([In_2L_5]$^+$), 600 ([$NaInL_3$]$^+$), 423 ([InL_2]$^+$), 270 ([HInL]$^+$). IR (cm^{-1}, ± 4 cm^{-1}): 1584, 1310 (ring and C−N−C vibrations), 521 (ν_{In-O}).

General Procedure for the Synthesis of the Ln(III)-Pyranthione Complexes. (See Results and Discussion and Supporting Information for the detailed characterization of all of the Ln(III) complexes.)

(i) Tris(thiomaltolato)lanthanum(III), La(tma)$_3$. $La(ClO_4)_3 \cdot 6H_2O$ (0.0655 g, 0.13 mmol) was added to a solution of Htma (0.112 g, 0.79 mmol) in 10 mL of EtOH under Ar at room temperature. As the pH of the solution was raised slowly (over 20 min) with 6 M NaOH (0.06 mL, 0.36 mmol), a yellow solid precipitated from the solution. The resulting reaction mixture was stirred for 3 h and then vacuum filtered to collect the product. The yellow precipitate was washed with 5 mL of cold EtOH and dried overnight in vacuo to yield 0.065 g, 83%. IR (cm^{-1}, ± 4 cm^{-1}): 1586, 1503, 824 (ring vibrations and ν_{C-O-C}), 658 (ν_{La-O}).

(ii) Hydroxobis(thiomaltolato)praseodymium(III), Pr(tma)$_2$(OH). $Pr(ClO_4)_3 \cdot 6H_2O$ (0.135 mL of 50% w/w solution, 0.12 mmol) was added to a solution of Htma (0.1017 g, 0.72 mmol) in 10 mL of EtOH under Ar at room temperature. As the pH of the solution was raised slowly (over 20 min) with 6 M NaOH (0.1 mL, 0.6 mmol), a yellow solid precipitated from the solution. The resulting reaction mixture was stirred for 3 h and then vacuum filtered to collect the product. The yellow precipitate was washed with 5 mL of cold EtOH and dried overnight in vacuo to yield 0.060 g, 53%. IR (cm^{-1}, ± 4 cm^{-1}): 1580, 1497, 824 (ring vibrations and ν_{C-O-C}), 662 (ν_{Pr-O}).

Potentiometric Equilibrium Measurements. Potentiometric measurements were carried out with an automatic titration system consisting of a Metrohm 713 pH meter equipped with a Metrohm 6.0123.100 pH glass electrode, a Metrohm 6.0726.100 silver chloride reference electrode, a model 665 Metrohm Dosimat autoburet, and water-jacketed 50-mL titration vessels maintained at 25.0 ± 0.1 °C with a Julabo UC circulating bath. Both the pH meter and the autoburet were controlled by an IBM-compatible PC so that the titrations were automated. The titrations were controlled by a locally written Qbasic program. Ar, passed through water and 2 M NaOH (to exclude CO_2), was bubbled through the solutions during the titrations.

All solutions were prepared with freshly boiled, deionized, distilled water that was purged with Ar while being boiled and cooled to ensure removal of CO_2. The electrodes were calibrated before each titration by titrating a known amount of aqueous HCl with a known amount of NaOH. A plot of current (mV, calculated) vs pH gave a working slope and intercept so that the pH could be read as $-\log [H^+]$ directly. The ionic strength (I) of the titration solution was kept constant with 0.16 M NaCl. The value of pK_w used at I = 0.16 M NaCl and T = 25 °C was 13.76.[37] The NaOH solution was standardized potentiometrically with potassium biphthalate.

Acidity constants for the compounds were determined by titrating 50 mL of aqueous 3.0 mM HCl (I = 0.16 M NaCl, T = 25 °C) in the presence of 0.5−0.7 mM solution of the desired compound (HL) under Ar with ∼1−1.5 mL of ∼0.1 M NaOH. The constants were calculated using the data within the range $\sim 2.5 \leq$ pH ≤ 10.5 on an IBM-compatible computer containing a Pentium II processor using a curve-fit procedure (a Newton−Gauss nonlinear least-squares program). The final values for the acidity constants for all compounds were obtained from the average of 10 independent titrations.

X-ray Crystallographic Analyses. The X-ray crystal structures were determined by mounting the crystals on a glass fiber. The measurements were made on a Rigaku/ADSC CCD area detector with graphite-monochromated Mo Kα radiation. All data were processed and corrected for Lorentz and polarization effects and absorption using the d*TREK program[38] or the multiscan technique (SADABS).[39] The structures were solved by direct methods[40] and expanded using Fourier techniques.[41] Final refinements were carried out using teXsan.[42]

ORTEP diagrams from the X-ray structures of Htma and Hetma, plus Hdppt dimer are shown in Figures S1 and 1, respectively. For Ga(tma)$_3$, the material crystallized as the fac isomer. For complete details of the X-ray crystallographic analyses, please refer to the Supporting Information.

(37) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*, VCH: New York, 1988; p 4.
(38) *d*TREK: Area Detector Software*, version 7.11; Molecular Structure Corporation: The Woodlands, TX, 2001.
(39) *SADABS*: *Bruker Nonius Area Detector Scaling and Absorption Correction*, version 2.05; Bruker AXS Inc.: Madison, WI.
(40) SIR97: Altomare, A.; Burla, M. C.; Cammali, G.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, A. *J. Appl. Crystallogr.* **1999**, *32*, 115.
(41) DIRDIF94: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *The DIRDIF-94 Program System*; Technical Report of the Crystallography Laboratory; University of Nijmegen: Nijmegen, The Netherlands, 1994.
(42) *TeXsan: Crystal Structure Analysis Package*; Molecular Structure Corporation: The Woodlands, TX, 1985 and 1992.

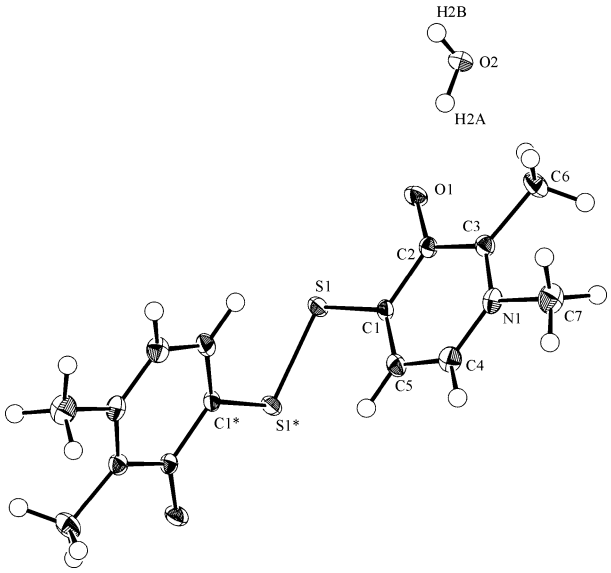
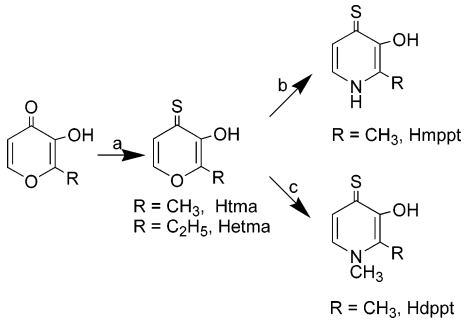


Figure 1. ORTEP diagram of Hdppt dimer (50% thermal ellipsoids).

Scheme 1. Synthesis of the Compounds[a]



[a] Conditions: (a) excess P_2S_5, dioxane, 45 °C; (b) excess NH_4OH, H_2O/EtOH, 34 °C, 36 h; (c) excess 40% $MeNH_2$, H_2O, 75 °C, 12 h.

Results and Discussion

The pyranthiones thiomaltol (Htma) and ethylthiomaltol (Hetma) were prepared by reacting maltol/ethylmaltol with P_2S_5 in a 1:2 ratio followed by recrystallization with hexanes and column purification to obtain pure Htma and Hetma, respectively. The syntheses were based on the work of Blazevic et al.,[43] but some of the conditions were modified significantly (temperature; reaction time; volume of the solvents; ratio of reagents, i.e., maltol/ethylmaltol to P_2S_5; and recrystallization solvent) to improve the yields (Scheme 1). While this work was ongoing, Cohen and co-workers[31] described the synthesis of Htma using P_2S_5 in combination with hexamethyldisiloxane (HMDO) based on the work by Curphey.[44] Although Cohen et al.'s procedure reports[31] a higher overall yield (70% vs 46% in this work) for Htma, the synthesis described here is simple, faster (one-step), and less expensive. There is a CAS registry number (84642−58−0) for ethylthiomaltol (Hetma); however, this is the first reported synthesis for this compound, to our knowledge.

The pyridinethiones Hdppt and Hmppt were prepared by doing a ring-conversion reaction with Htma (Scheme 1), in a fashion analogous to the synthesis of their oxygen analogues (pyridinones) synthesized in our laboratory previously.[45] The ring oxygen in Htma was replaced with N−H or N−CH_3 by reacting Htma with aqueous NH_4OH or $MeNH_2$ to obtain Hmppt or Hdppt, respectively. For the N−H pyridinethione, if the reaction mixture was left refluxing at the higher temperature (80 °C), the major product obtained was Hmppt dimer. For Hdppt, a small amount of dimer always formed with the monomer despite varying temperature and solvents. A different route to synthesize Hdppt by reacting the pyridinone with Lawesson's reagent to convert the carbonyl group to the thiocarbonyl group was reported recently.[34] This synthesis, however, includes many byproducts, requires multiple purification steps, and gives a low yield (20%). The procedure reported herein is much simpler. The reaction is a one-step process, followed by simple column purification, and gives the product in a higher yield (> 47%).

All of the organic compounds were characterized completely by EA, EIMS, mp, and IR and NMR spectroscopies (see Supporting Information for complete details). The most significant (expected) change in the IR spectrum is the appearance of $\nu_{C=S}$ and disappearance of $\nu_{C=O}$. Because of substitution with a heavier atom (sulfur), $\nu_{C=S}$ appears at a lower value (∼1176−1196 cm^{-1}) as compared to $\nu_{C=O}$ (∼1650 cm^{-1}). This is in agreement with various other reports for $\nu_{C=S}$ in pyranthiones and pyridinethiones.[46] The $\nu_{C=O}/\nu_{C=S}$ ratio for maltol to thiomaltol was found to be ∼1.40, in agreement with other similar studies for a conjugated system.[47,48] For the pyridinethiones, $\nu_{C=S}$ was the most intense peak in the spectrum and was also confirmed by its absence in the IR spectra of the pyridinethione dimers.

The most diagnostic features of the ^1H NMR spectra in all four monomeric thio compounds were the expected AB split doublets for the ring hydrogens ($J_{a,b} \approx 4-5$ Hz for pyranthiones, $J_{a,b} \approx 6.4-6.6$ Hz for pyridinethiones), a singlet for the methyl hydrogens on C-1 (or ethyl hydrogens for Hetma), and a sharp singlet for the hydroxyl hydrogen. As compared to those in their oxygen analogues, the ring hydrogen peaks in pyranthiones and pyridinethiones shift downfield (Table S1). The ring hydrogen next to C═S, H_b, shows the most significant downfield shift ($\Delta\delta \approx 1-1.2$ ppm). The lack of intramolecular hydrogen bonding (due to the replacement of C═S for C═O) is evident from the upfield shift of the hydroxyl peak with respect to that in their oxygen analogues ($\Delta\delta \approx 0.6$ ppm). With respect to their synthetic precursor, Htma, the ring hydrogens in the pyridinethiones shift upfield. This was expected because of the positive

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Table 1. Acidity Constants for the Thio Compounds and Their Oxygen Analogues (I = 0.16 M NaCl, T = 25 °C, [HL][a]= 0.5−0.7 mM)

compd	pK_{a1}	pK_{a1} of corresponding oxygen analogues
Htma	8.12 ± 0.02	8.67 ± 0.03[b]
Hetma	8.16 ± 0.03	8.72 ± 0.03[b]
Hmppt	8.93 ± 0.02	9.80 ± 0.01[c]
Hdppt	9.44 ± 0.01	9.86 ± 0.03[c]

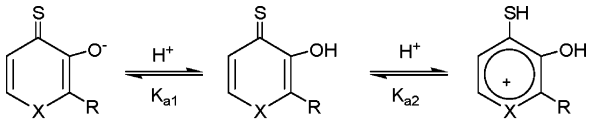
[a] HL: general abbreviation for protonated ligand precursor; [b] Reference 49. [c] Reference 50 (I = 0.15 M NaCl).

inductive effect resulting from the substitution of the ring oxygen atom with the less electronegative nitrogen (Table S1).

The molecular structures of the dimeric form of pyridinethiones were verified by ^{1}H NMR spectroscopy. Dithiothreitol (DTT), a well-known reagent for reducing disulfide bonds, was used to confirm the presence of a disulfide bond. ^{1}H NMR spectra were taken before and after addition of DTT. As expected, the representative peaks for the dimer disappeared from the 1H NMR spectrum, and peaks for the monomer appeared almost immediately, indicating complete reduction of the disulfide bond (and hence verifying its existence).

^{13}C NMR spectra for all of the compounds were also recorded, and peaks were assigned by running 2D-HMQC and/or HMBC NMR experiments (Figure S2).

In addition to the usual methods of characterization, acidity constants (OH hydrogen) were also determined for all of the monomeric organic compounds. All of the organic monomeric compounds (and their oxygen analogues) synthesized in this project are amphoteric in nature. Potentiometric titrations were done to determine the acidity constants (K_{a1}) for the hydroxyl hydrogen of the compounds. Table 1 lists the pK_{a1} values for all four monomeric organic compounds and their oxygen analogues.



R = C_2H_5 for Hetma, CH_3 otherwise
X = O, pyranthiones
X = NH or NCH_3, pyridinethiones

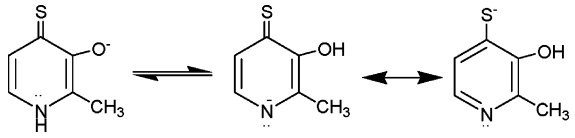
In comparison to their oxygen analogues, the pyranthiones and pyridinethiones were found to be more acidic (Table 1).[49,50] The slightly lower (more acidic) pK_a values were expected because of the less electronegative sulfur. Furthermore, the polarizable nature of sulfur increases the delocalization of the negative charge of the deprotonated hydroxyl oxygen. This makes the conjugate bases of the thio compounds more stable. Another contributing factor to the higher acidity is the decrease in hydrogen bonding between the thiocarbonyl sulfur and OH hydrogen as compared to that between the carbonyl oxygen and OH hydrogen.

Table 2. Selected Bond Lengths (Å) and Angles (deg) in Hdppt Dimer

Bond Lengths (Å)			
S(1)−S(1*)	2.0472(7)	C(1)−C(2)	1.424(2)
S(1)−C(1)	1.763(1)	C(1)−C(5)	1.383(2)
O(1)−C(2)	1.278(2)	C(2)−C(3)	1.427(2)
N(1)−C(3)	1.362(2)	C(4)−C(5)	1.377(2)
N(1)−C(4)	1.351(2)	C(3)−C(6)	1.489(2)
N(1)−C(7)	1.482(2)		

Bond Angles (deg)			
S(1)−S(1*)−C(1)	104.22(5)	N(1)−C(4)−C(5)	119.9(1)
S(1)−C(1)−C(2)	112.1(1)	O(1)−C(2)−C(1)	120.8(1)
S(1)−C(1)−C(5)	126.0(1)	O(1)−C(2)−C(3)	123.4(1)
C(3)−N(1)−C(4)	123.0(1)	C(2)−C(1)−C(5)	121.9(1)
C(3)−N(1)−C(7)	119.4(1)	C(1)−C(2)−C(3)	115.8(1)
C(4)−N(1)−C(7)	117.5(1)	C(1)−C(5)−C(4)	119.4(1)
N(1)−C(3)−C(2)	119.9(1)	C(2)−C(3)−C(6)	120.0(1)
N(1)−C(3)−C(6)	120.1(1)		

For Hmppt, tautomerism must be considered in determining its pK_{a1} value. Deprotonated Hmppt (mppt$^-$) can have two tautomeric forms. An attempt was made to determine two separate deprotonation constants but the results showed that the OH and NH hydrogens are exchangeable and have the same pK_a value (i.e., pK_{a1}).



Comparing pyranthiones with pyridinethiones, it was found that the pK_{a1} values for the pyranthiones are smaller. The pyranthiones are more acidic because of the higher stabilities of their conjugate bases. Because of its higher electronegativity, the ring oxygen delocalizes (and hence, stabilizes) the negative charge of the deprotonated hydroxyl oxygen better than does the N−R group. Consequently, the pyridinethiones are more basic.

X-ray-quality crystals for Htma were obtained by slow evaporation from its hexane solution (Figure S1). While this work was ongoing, the structure of Htma was published by Cohen and co-workers.[31] Although the synthesis and recrystallization methods are different, the crystallographic data for Htma found in this work are identical to those reported by Cohen and co-workers (Tables S2−S4). X-ray-quality crystals for Hetma were also obtained by cooling the brown oil form of the compound in dry ice and then warming it slowly to room temperature (Figure S1). As compared to maltol (C═O, bond length ≈ 1.25 Å),[51] the C═S bond lengths in Htma and Hetma were found to be longer (∼1.675 and 1.681 Å, Table S3), as expected. The C(1)−C(6) distance in Htma (1.481 Å) is almost exactly the same as that in maltol (1.482 Å), indicating that the methyl group is the least affected by the thio substitution.

X-ray-quality crystals for Hdppt dimer were obtained by slow evaporation of its solution in ethyl acetate (Figure 1 and Table S5). The C−S bond length (1.763 Å, see Table 2) in Hdppt dimer is longer than that in Htma (1.675 Å)

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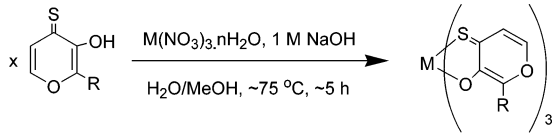
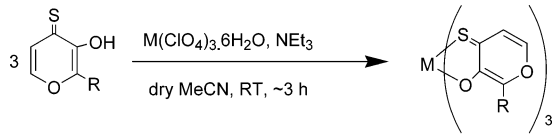
Scheme 2. Syntheses of Tris(pyranthionato)Ga(III) and In(III) Complexes



R = CH_3	M = Ga	$Ga(tma)_3$	x = 6
R = CH_3	M = In	$In(tma)_3$	x = 3
R = C_2H_5	M = Ga	$Ga(etma)_3$	x = 6
R = C_2H_5	M = In	$In(etma)_3$	x = 3

Scheme 3. Syntheses of Tris(pyridinethionato)Ga(III) and In(III) Complexes



R = H	M = Ga	$Ga(mppt)_3$
R = H	M = In	$In(mppt)_3$
R = CH_3	M = Ga	$Ga(dppt)_3$
R = CH_3	M = In	$In(dppt)_3$

indicating a C−S single bond (Table S6 and S7). The S−S distance (2.047 Å) is typical of disulfide bonds and is representative of an S−S bond with electron-withdrawing groups attached.[52] The C−C distances in the ring, ranging from 1.377 to 1.427 Å, are also longer, indicating more delocalization, but the C−CH_3 distance is still similar to those in Htma and Hma [C(3)−C(6) = 1.489 Å].

Four neutral gallium(III) complexes [$Ga(tma)_3$, $Ga(etma)_3$, $Ga(mppt)_3$, and $Ga(dppt)_3$] and indium(III) complexes [$In(tma)_3$, $In(etma)_3$, $In(mppt)_3$, and $In(dppt)_3$] were synthesized by adding the metal salt to a solution of the ligand precursor and adjusting the pH to ∼7−8 to deprotonate the ligand precursor with aqueous 1 M NaOH or NEt_3 (Schemes 2 and 3). For the pyranthiones Htma and Hetma, metal nitrate salts were used, and the reactions were carried out in aqueous solutions. Although the indium(III) complexes could be obtained by reacting the indium salt and the ligand precursor in a 1:3 ratio, an excess of ligand precursor was required for the gallium(III) complexes (1:6). This can be explained by the slightly softer (HSAB) nature of indium(III) and, hence, the slightly higher affinity of indium(III) for sulfur as compared to that of gallium(III). All of the complexes were obtained in moderate to high yields (∼60−90%).

For the pyridinethiones Hmppt and Hdppt, the reactions were carried out in dry, degassed acetonitrile, and NEt_3 replaced NaOH as the base (Scheme 3). These conditions were required to avoid pyridinethione dimerization, which occurs in the presence of a strong base (such as OH^-) and molecular oxygen in aqueous solutions. Because metal nitrate salts dissolve sparingly in MeCN, metal perchlorate salts were used for these reactions. Unlike the Ga(III)-pyranthione complexes, only the stoichiometric 1:3 ratio of metal salt to ligand precursor was required to obtain the pure, neutral tris(ligand) complexes with Ga(III), as well as with In(III). This implies that the deprotonated pyridinethiones are better ligands than are the pyranthiones and is consistent with the pK_a values of the ligand precursors because the conjugate bases of Hmppt and Hdppt are more stable than are those of Htma and Hetma. This also contributed to the reasonable yields of these complexes (∼50−68%) even though a weaker base (NEt_3) was used.

All eight complexes precipitated from the respective reaction mixtures and were collected by vacuum filtration, washed with cold water (or cold acetonitrile), and dried overnight in vacuo. All of the Ga(III) and In(III) complexes with the pyranthiones were yellow solids, whereas the Ga(III)/In(III)-pyridinethione complexes were beige. Attempts at recrystallizing the complexes (in hot solvents) resulted in loss of product because of decomposition. Washing the precipitated solid thoroughly with cold solvents to remove excess (or unreacted) ligand or other side products and drying the solid overnight in vacuo yielded pure products with expected analytical results.

All of the group 13 metal complexes were found to be air-stable. All of the complexes were characterized by elemental analysis; positive ion electrospray ionization (ESI) or liquid secondary ion (LSI) mass spectrometry; and IR and ^1H, ^{13}C and 2D (HMBC) NMR spectroscopies (where possible), all of which gave the expected patterns. Potentiometric titrations were attempted to determine the stepwise formation constants for the pyranthionato group 13 complexes. Because of precipitation at very low pH for the In(III) complexes and no complexation of the Ga(III) ions with the ligands at the low concentrations used, no data were obtained.

Elemental analyses of all of the complexes correlated well with the calculated values. With the exception of $In(etma)_3$, $Ga(mppt)_3$, and $In(mppt)_3$, which are hydrates, all other Ga(III) and In(III) complexes were found to be ML_3 species. For the NH pyridinethione complexes, the formation of hydrates is similar to that also found for the vanadium complexes with this ligand and probably portrays the increased hydrogen-bonding ability of the N−H hydrogen in this ligand.[53]

Positive ion detection mode mass spectrometry was used to analyze all of the complexes, and diagnostic mass spectra were obtained with the expected isotopic patterns. As expected and reported[12] for other ML_3 species, the most intense peak for all of the group 13 complexes corresponded to $[ML_2]^+$, generated by the gas-phase loss of one ligand. Other major peaks in the spectra of the Ga(III) and In(III) complexes were the protonated parent ion peak $[HML_3]^+$ or its sodium or potassium adduct ($[NaML_3]^+$ or $[KML_3]^+$). For most of the ML_3 complexes (group 13 and Ln), a peak corresponding to $[M_2L_5]^+$ was also detected, as is usually seen for tris(bidentate ligand) trivalent metal ion, based on the corresponding oxygen analogues.[12,16]

Overall, the IR spectra of all of the ML_3 complexes are almost superimposable, indicating similar structures in the solid state. For the Ga(III) and In(III) complexes, the pyranthione vibrations undergo a larger shift (∼40−50 cm^{-1})

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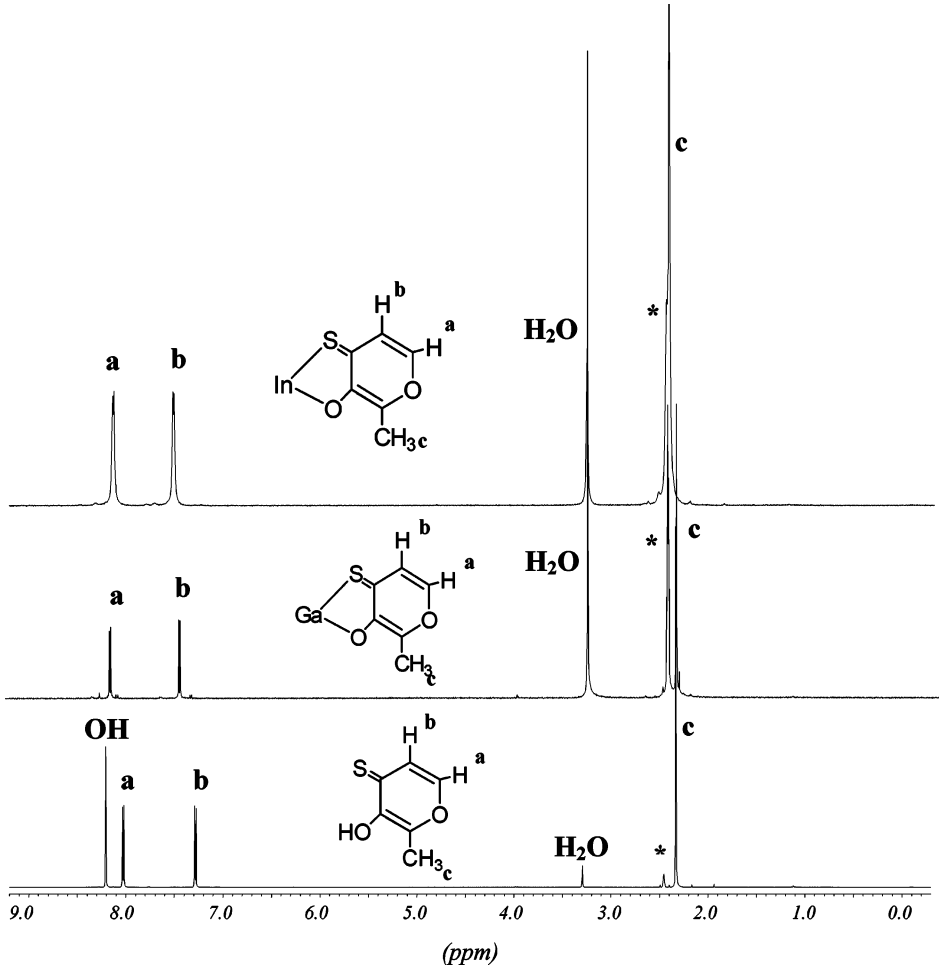

Figure 2. ^{1}H NMR spectra of In(tma)$_3$, Ga(tma)$_3$ and Htma (300 MHz, DMSO-d_6, room temperature, * represents the solvent peak).

than do the pyridinethione peaks, which shift by only ~10−23 cm^{-1} to lower energies. This bathochromic shift was also observed for the oxygen analogues.[12] The absence of ν_{NO_3} (~1384 cm^{-1}) or ν_{ClO_4} (~1007 cm^{-1}) in the IR spectra indicated the absence of any corresponding counterions in the complexes. The appearance of a new peak around ~521−664 cm^{-1} for M−O stretches [where M = Ga(III) or In-(III)] confirmed the complexation of the ligand to the respective metal ions. Compared to the oxygen analogues, these complexes had lower ν_{M-O} stretching frequencies, as expected.

To study the solution structures of these complexes, ^{1}H, ^{13}C, and 2D-HMBC NMR spectra were obtained for all of the group 13 metal complexes. For the group 13 metal complexes with tma$^-$ and etma$^-$, both ring hydrogens shifted downfield (Figure 2). This was expected because binding to the electropositive metal ion pulls electron density away from these hydrogens. A similar shift was also seen for the ring hydrogens in the Al(III) and Ga(III) complexes with the corresponding oxygen analogue, the maltolato ligand.[12] A larger downfield shift was detected for H_b (0.11−0.23 for H_b, 0.07−0.10 for H_a) because it is closer to the coordinating C═S group. The greater shift for H_b in the In(III) complexes (~0.22 ppm for InL_3 vs ~0.10 ppm for GaL_3) confirms the stronger binding of the softer sulfur donor to the softer In(III) ion as compared to that to Ga(III) metal ion.

With the pyridinethiones, the involvement of the nitrogen atom in the ring current affected H_a more than H_b (H_a $\Delta\delta \approx$ 0.15−0.30 ppm, H_b $\Delta\delta \approx$ 0.06−0.19 ppm) as H_a is closer to the nitrogen atom. The ring hydrogens for the group 13 metal complexes with mppt$^-$ and dppt$^-$ shift upfield [except for Ga(mppt)$_3$]. For the corresponding oxygen analogues, an upfield shift was observed for H_a (H_a $\Delta\delta \approx$ 0.10 ppm), but H_b shifted slightly downfield. The contrast with the thio ligands could be attributed to the presence of the more polarizable and less electronegative sulfur, which pulls less electron density toward itself as compared to the oxygen atom in C═O. Comparing the mppt$^-$ complexes with those of dppt$^-$, it was noted that a greater shift is observed for the N−CH$_3$ (dppt$^-$) complexes.

The anomalous behavior of Ga(mppt)$_3$ can be explained by the more electropositive Ga(III) [as compared to In(III)] deshielding the ring hydrogens more strongly than those for In(mppt)$_3$. Because the signals for the ring hydrogens are broad for both Ga(III) and In(III) complexes, the chemical shift could be an average value for rapidly interconverting geometric (fac and mer) isomers. This could also explain the small change in δ ($\Delta\delta \approx$ 0.01−0.10 ppm). A similar (small) change was also observed with Ga(dpp)$_3$, the oxygen analogue of Ga(dppt)$_3$.[16]

The ^{13}C NMR spectra were very useful in predicting the molecular structures of the complexes in solution. The most

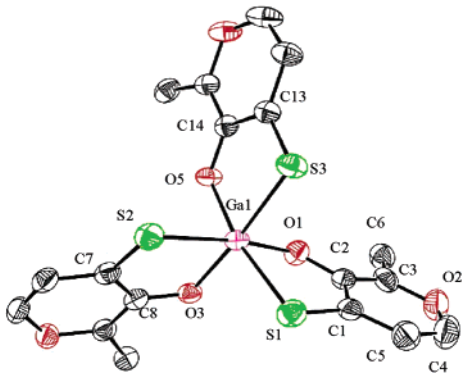

Figure 3. ORTEP diagrams of *fac*-Ga(tma)$_3$ (50% thermal ellipsoids).

significant shifts were observed for the C═S ($\Delta\delta \approx 10$ ppm) and C−O−M ($\Delta\delta \approx 5-7$ ppm) peaks for all group 13 complexes. 2D-HMBC NMR spectra (Figure S3) were obtained to distinguish between *C*−O−M and *C*−CH$_3$ as both are quaternary carbon atoms and these two peaks appear very close together in the ^{13}C NMR spectra of most of these complexes.

An X-ray crystal structure for Ga(tma)$_3$ was obtained (Figure 3). Yellow chip crystals of Ga(tma)$_3$ suitable for X-ray diffraction were grown by mixing warm solutions of tris(acetylacetonato)gallium(III), Ga(acac)$_3$, in EtOH and Htma in THF (Ga^{3+}/Htma in a 1:3 ratio) followed by slow evaporation of the resulting solution. The material crystallizes as the fac isomer with both enantiomers, Δ and Λ, in the asymmetric unit (Tables S8−S10). Other group 13 complexes with similar ligands have been found to crystallize out as fac[54] or mer isomers.[36] For the Al(III) complex of the corresponding oxygen analogue (maltol), Al(ma)$_3$, only the mer isomer was isolated.[55] On the other hand, the pyridinone complexes with Al(III) and Ga(III) were isolated as the fac isomers.[16] In both enantiomers of Ga(tma)$_3$, the three thiomaltolato ligands are arranged in an octahedral arrangement, with two sulfur atoms and two oxygen atoms in a cis arrangement in the equatorial plane and one sulfur and one oxygen atom along the perpendicular axis. Table 3 lists selected bond lengths and bond angles for *fac*-Ga(tma)$_3$. The Ga−O [1.95(2) Å] and Ga−S [avg 2.46(1) Å] distances for the fac isomer of Ga(tma)$_3$ are shorter than are those for the mer isomer of an In(III) complex with a similar coordination sphere [*mer*-In(O$_3$S$_3$), In−O =2.20(4) Å, In−S = 2.53(2) Å for tris(1-oxopyridine-2-thionato)indium(III), In(PT)$_3$].[36] The longer bonds in In(PT)$_3$ are an outcome of increased electron density in the system due to the ring nitrogen (instead of oxygen). Compared to the structure of its oxygen analogue, Al(ma)$_3$, the M−O (hydroxyl oxygen) bond length in Ga(tma)$_3$ is slightly longer [1.888(2) Å][55] than that in Al(ma)$_3$ [1.874(2) Å], suggesting a slightly weaker M−O bond.

A range of lanthanide complexes was synthesized by reacting the respective metal perchlorate salts with the two pyranthiones, Htma and Hetma, in ethanol at room temperature (Scheme 4). All of the Ln(III) complexes with both pyranthiones were yellow solids, but the Ln(etma)$_3$ complexes had a shiny texture and were obtained in moderate to high yields (53−95%, Table S11). Several attempts to recrystallize the precipitated solids resulted in decomposition of the product and hydrolysis of the Ln(III) ions.

The elemental analyses of the lanthanide complexes gave the empirical formula LnL$_3$·*x*H$_2$O or LnL$_2$(OH)·*x*H$_2$O (see Table 4). The formation of two different species with similar ligands can be explained by the extremely sensitive nature of the Ln(III) ions toward the pH of a solution and the ability to hydrolyze easily with increasing pH.[56] Although it is difficult to predict the exact structure of the complex without a crystal structure, these formulas and the two different species are consistent with the Ln complexes reported previously with the oxygen analogue of thiomaltol (maltol)[21,22] and other bidentate O,S donor ligands with Ln such as ethylthioacetate,[57] acetoanilide,[58,59] and thiohydroxamic

Table 3. Selected Bond Lengths (Å) and Bond Angles for *fac*-Ga(tma)$_3$

Bond Lengths (Å)			
C(1)−S(1)	1.684(4)	O(1)−Ga(1)	1.941(3)
C(7)−S(2)	1.693(4)	O(3)−Ga(1)	1.963(2)
C(13)−S(3)	1.699(4)	O(5)−Ga(1)	1.959(2)
C(2)−O(1)	1.322(4)	S(1)−Ga(1)	2.4822(11)
C(8)−O(3)	1.293(4)	S(2)−Ga(1)	2.4610(11)
C(14)−O(5)	1.318(4)	S(3)−Ga(1)	2.4594(11)
Bond Angles (deg)			
S(3)−Ga(1)−S(2)	92.00(4)	O(5)−Ga(1)−S(1)	168.78(8)
S(3)−Ga(1)−S(1)	85.27(4)	O(3)−Ga(1)−S(3)	175.10(8)
S(2)−Ga(1)−S(1)	93.13(4)	O(3)−Ga(1)−S(2)	83.60(8)
O(1)−Ga(1)−S(3)	95.28(9)	O(3)−Ga(1)−S(1)	97.09(8)
O(1)−Ga(1)−S(2)	172.14(9)	O(1)−Ga(1)−O(5)	92.16(11)
O(1)−Ga(1)−S(1)	84.56(8)	O(1)−Ga(1)−O(3)	89.22(11)
O(5)−Ga(1)−S(3)	84.34(8)	O(5)−Ga(1)−O(3)	93.59(10)
O(5)−Ga(1)−S(2)	91.47(8)		

Scheme 4. Syntheses of Tris(pyranthionato)Ln(III) Complexes

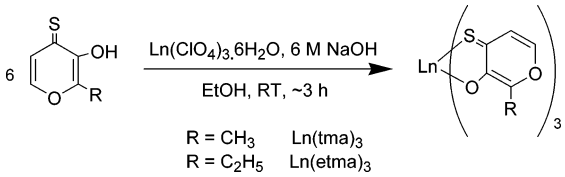

Table 4. Elemental Analyses of the Ln(III) Complexes of tma$^-$ and etma$^-$

complex	C% Calcd (found)	H% Calcd (found)
La(tma)$_3$·2H$_2$O	36.13 (36.03)	3.20 (2.96)
La(etma)$_3$·H$_2$O	40.52 (40.26)	3.72 (3.40)
Pr(tma)$_2$(OH)·H$_2$O	31.45 (31.31)	2.86 (2.88)
Pr(etma)$_3$·0.5H$_2$O	40.98 (40.89)	3.60 (3.66)
Nd(tma)$_2$(OH)·H$_2$O	31.23 (31.05)	2.84 (2.81)
Nd(etma)$_3$·2H$_2$O	39.05 (38.91)	3.90 (3.58)
Sm(tma)$_3$	37.67 (37.47)	2.63 (2.96)
Sm(etma)$_3$·0.5H$_2$O	39.23 (39.33)	3.76 (3.46)
Gd(tma)$_2$(OH)·H$_2$O	30.37 (30.10)	2.76 (2.74)
Gd(etma)$_3$·2.5H$_2$O	37.77 (37.75)	3.92 (3.49)
Ho(tma)$_3$·1.5H$_2$O	35.13 (35.16)	2.95 (3.08)
Ho(etma)$_3$·2H$_2$O	37.84 (38.07)	3.78 (3.48)
Lu(tma)$_3$	36.12 (36.24)	2.53 (2.91)
Lu(etma)$_2$(OH)·H$_2$O	32.88 (32.84)	3.15 (3.07)

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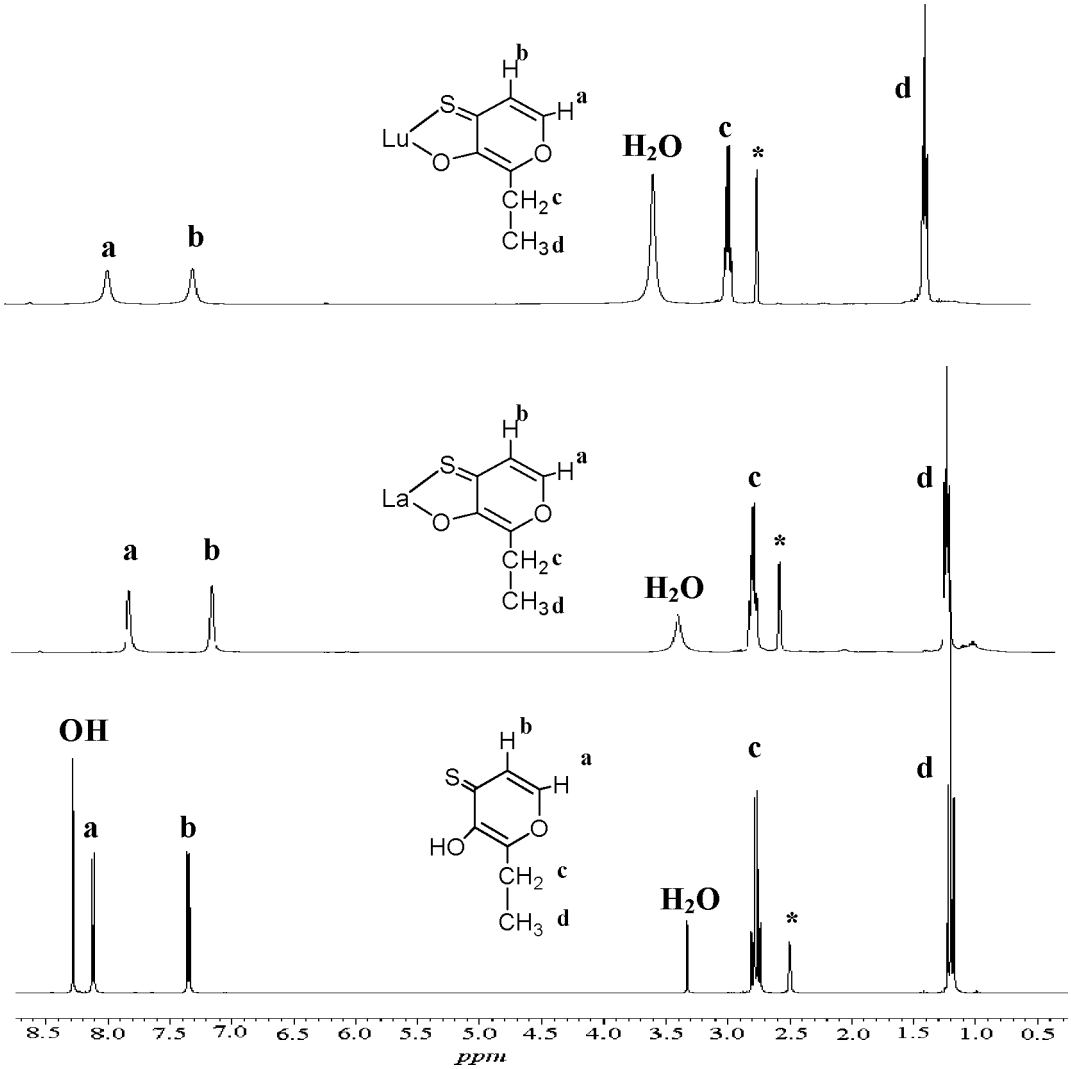
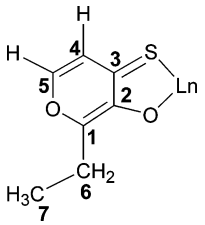


Figure 4. ^{1}H NMR spectra of Lu(etma)$_2$(OH), La(etma)$_3$ and Hetma (400 MHz, DMSO-d_6, room temperature, * represents the solvent peak).

acids.[60] Characteristic data from the mass and IR spectra for the Ln complexes are given in Table S11 and Figure S4. As seen in Figure S4, all of the Ln-ethylthiomaltolato complexes are almost superimposable with identical shifts in the frequencies with respect to the free ligands (~40−50 cm^{-1}).

^{1}H, ^{13}C, and 2D-HMBC NMR spectra were also obtained for the diamagnetic lanthanide complexes La(tma)$_3$, Lu(tma)$_3$, La(etma)$_3$, and Lu(etma)$_2$(OH)·H$_2$O. Figure 4 shows the relative shift in the ^{1}H NMR signals for the La(III) and Lu(III) metal complexes with respect to the free ligand precursor (also see Table S12). Lack of free ligand precursor peaks and observed shifts in both C−H hydrogens conclusively indicate binding of the ligand to the Ln(III) ions. For the lanthanide complexes, the relative chemical shifts in the ^{13}C NMR spectra (with respect to the free ligand) are not as prominent as for the group 13 complexes but still show that the ligands are bound to the Ln(III) ion (Table 5). This was also confirmed by obtaining 2D-HMBC NMR spectra. The

Table 5. ^{13}C NMR Chemical Shift (δ) Data in ppm for the All of the Ln(III) Complexes (400 MHz, DMSO-d_6, Room Temperature)



compd	C-1	C-2	C-3	C-4	C-5	C-6[a]	C-7
Htma	146.31	150.09	185.45	124.31	148.51	14.81	−
La(tma)$_3$	146.64	163.27	186.62	123.11	144.10	14.92	−
Lu(tma)$_3$[a]	147.62	161.52	185.28	122.76	144.90	15.04	−
Hetma	150.07	149.44	185.73	124.30	148.66	21.78	10.49
La(etma)$_3$[a]	150.94	162.79	186.91	123.01	144.10	21.80	10.92
Lu(etma)$_2$(OH)[a]	151.53	161.41	185.65	122.56	144.55	21.86	10.96

[a] C-6 is CH$_3$ group for Htma and Ln-tma.

C═S peak shifts by only ~0.3−1.2 ppm, a behavior that has been observed in other ketonic oxygen-[61] and sulfur-bound group 13 and Ln complexes.[62] The broadening and

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the small chemical shift of the peaks in the ^{13}C NMR spectra of the Ln(III) metal complexes could also be indicative of monodentate (from O^-) freely rotating ligands in a strongly coordinating solvent such as DMSO. Because Ln(III) ions have a lower affinity for sulfur (than the group 13 metal ions), the S−Ln covalent coordinate bond might be getting replaced by DMSO−Ln. The NMR spectra for the La(III) and Lu(III) complexes are comparable, indicating that the ligands bind in a similar manner with metal ions at either end of the lanthanide series.

Conclusions

Four new mixed *O,S* ligand precursors, Htma, Hetma, Hmppt, and Hdppt, were synthesized successfully in good yields; various characterization techniques, including X-ray crystallographic analysis, were used to verify the structures in solid state and in solution. The characterization data were comparable to those for their respective oxygen analogues, and the shifts (in IR and NMR spectra) were reasonable on the basis of replacing C═O with C═S.

New Ga(III) and In(III) complexes with two pyranthiones (Htma and Hetma) and two pyridinethiones (Hmppt and Hdppt) were successfully synthesized and characterized. The characterization indicates that In(III) binds to these thio ligands better than does Ga(III) and, hence, forms more stable complexes with these ligands. Successful complexation and similar characterization of these thio ligands with Ga(III) and In(III) ions suggests that these thio compounds with mixed *O,S* donors are good ligands for these metal ions. It would be interesting to further evaluate the in vivo stability of these complexes for comparison to that of the corresponding oxygen analogues so that their potential as diagnostic or therapeutic pharmaceutical agents can be tested in the future.

Preliminary results are also presented for the synthesis of a range of Ln(III)-pyranthione complexes across the series. Some complexes were isolated only as $LnL_2(OH)$ complexes rather than the expected LnL_3 species, demonstrating that the coordination chemistry of these thio ligands with Ln(III) metal ions is very sensitive to pH.

Acknowledgment. The authors thank the Natural Sciences and Engineering Research Council (NSERC) and the Canadian Institutes of Health Research (CIHR) for financial support. Dr. Bin Song is thanked for his help with the potentiometric titrations.

Supporting Information Available: Complete characterization data for the thiomaltol derivatives including a table of NMR data; crystallographic data and complete bond lengths and angles for the four X-ray structures; yields and mass spectrometry data for the lanthanide complexes, as well as NMR data for the La and Lu derivatives; ORTEP diagrams for Htma and Hetma; 2-D NMR data for Hetma and $Ga(etma)_3$; and IR data for Hetma and $etma^-$ lanthanide complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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