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The Gallium(III) and Indium(III) Complexes of Tris(2-mercaptobenzyl)amine and Tris(2-hydroxybenzyl)amine

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Tris(2-mercaptobenzyl)amine, S_3N, and tris(2-hydroxybenzyl)amine, O_3N, were investigated with In^{3+} and Ga^{3+} in solution and in the solid state to help interpret the contrasting in vivo behavior of their complexes as diagnostic imaging probes. To this end the protonation and metal binding constants were determined and their similarities and differences with those of analogous ligands, including the O_3N analogue, are discussed. Seven new crystal structures of Ga(III) and In(III) complexes are also reported: [Ga(S_3N)], [Ga(S_3N)(1-Me-imid)], [In(S_3N)(1-Me-imid)], [In(S_3N)(DMF)], [Ga(O_3N)(1-Me-imid)], [Ga(O_3N)(DMF)], and [In(O_3N')(1-Me-imid)$_2$], where O_3N' is the tris(2-hydroxy-3,5-dimethylbenzyl)amine homologue of O_3N. The structure of [Ga(S_3N)] is 4-coordinate, that of [In(O_3N')(1-Me-imid)$_2$] is 6-coordinate, and the remaining structures are 5-coordinate.

Introduction

Broadly speaking Ga(III) and In(III) have similar solution coordination properties yet, depending on the type of compound, show significant differences in coordination requirements. Thus a detailed study of the interactions of both metal ions with ligands containing thiolate groups is warranted, because their properties may vary widely. There are many chelating agents for which In(III) stability constants are considerably higher than the corresponding Ga(III) stability constants.[1] This category is exemplified by EDTA (ethylenedinitrilotetraacetic acid) and other similar aminopolycarboxylic acids such as CDTA (*trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid), EEDTA (oxybis(ethylenenitrilo)tetraacetic acid), TEDTA (thiobis(ethylenenitrilo)tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), NTA (nitrilotriacetic acid), and cyclic compounds such as DOTA (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*′′,*N*′′′-tetraacetic acid), TETA (1,4,8,11-tetraazacyclotetradecane-*N*,*N*′,*N*′′′,*N*′′′-tetraacetic acid), and TRITA (1,4,7,10-tetraazacyclotridecane-*N*,*N*′,*N*′′,*N*′′′-tetraacetic acid). On the other hand, there are many chelating agents whose stability constants with In(III) and Ga(III) are comparable in size. Among these are certain 8-hydoxyquinoline derivatives, bipyridyls, catechols, phosphonic monoesters and 2,3-dimercaptopropionylglycine. There is also a group of ligands where the In^{3+} stability constants are substantially lower when compared to the Ga^{3+} constants. This group is represented by DFO (desferriferrioxamine), HBED (*N*,*N*′-bis(*o*-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid), PLED (*N*,*N*′-bis(pyridoxyl)-*N*,*N*′-ethylenediaminediacetic acid), EHPG (1,2-ethylenebis(o-hydroxyphenylglycine) and EC (N,N′-ethylenebiscysteine), as well as cysteine itself. The thiolate and dithiolate ligands included in each of the above types of ligands have widely divergent relative stabilities in their corresponding Ga(III) and In(III) chelates. The remaining ligands contain only N and O coordinating groups and cannot be used to predict relative stabilities of Ga(III) and In(III) complexes with thiolate donors.

Recently, research in our laboratory has dealt with a number of promising new ligands for diagnostic imaging with Ga(III) and In(III) isotopes: *N*,*N*′-bis(2-mercaptoethyl)ethylenediamine-*N*,*N*′-diacetic acid,[2,3] mercaptoethylamines,[4] *N*,*N*′-ethylene-di-L-cysteine,[5,6] 1,4,7-tris(2-mercaptoethyl)-1,4,7-triazacyclononane,[7] and various ligands containing aminoethanethiol groups.[8−11] All of the ligands described showed considerable promise for further investigation and led us to the concept that much of the in vivo results could be understood in terms of stability constants and net overall charge of the complexes. However the tripodal S_3N type of ligand, **1**, is not yet represented in the stability constant literature (Chart 1).

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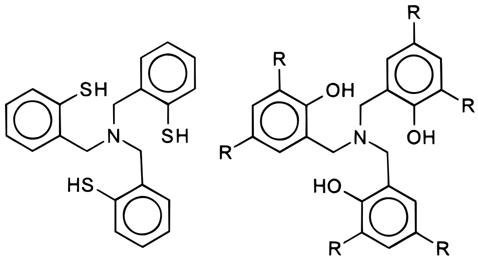
Chart 1



1 S_3N **2** O_3N (R = H)
O_3N' (R = Me)

Since neutral and low molecular weight complexes appeared to be particularly desirable for membrane penetration, the work of this paper is a study of a tripodal, tetracoordinating ligand **1** first prepared for spectroscopic and structural studies.[12,13] Initial reports are that the Ga^{3+} complex of S_3N crosses the blood−brain barrier and also localizes in the heart. These characteristics make it unique among the Ga(III) complexes described so far.[14] The present paper describes the equilibrium determinations of the protonation constants of this ligand, the stability constants of the Ga(III) and In(III) chelates, and analogous determinations of **2**, O_3N, with SH donor groups of **1** replaced by OH groups.

Seven crystal structures are described: the Ga(III) complex, GaS_3N of tris(*o*-mercaptobenzyl)amine, the *N*-methylimidazole adducts of the Ga(III) and In(III) complexes of tris(*o*-mercaptobenzyl)amine, the DMF adduct of the In(III) complex of tris(*o*-mercaptobenzyl)amine, the 1-methylimidazole adduct of the Ga(III) complex of tris(*o*-hydroxybenzyl)amine, and the 1-methylimidazole adduct of the In(III) complex of tris(2-hydroxy-3,5-dimethylbenzyl)amine. The nature of the adducts formed indicated the difference in properties of the Ga(III) and In(III) complex of these two ligands. The Ga(III) complex of the tris(2-mercaptobenzyl)amine has the lowest tendency to react with an adduct to expand its coordination sphere. This tendency to remain tetrahedral is perhaps related to the ability of the complex to pass through the blood−brain barrier.

Experimental Section

Materials and Solutions. CO_2-free "Dilute-it" ampules of KOH were obtained from J. T. Baker Inc., and absolute ethanol (200 proof) was obtained from McCormick Distilling Co., Inc. The KOH solutions were prepared in 70% ethanol−30% doubly distilled water (v/v) and standardized by titration against potassium hydrogen phthalate with phenolphthalein indicator. The extent of carbonate accumulation ($\leq$2%) was checked periodically by titration of standard HCl solution. Reagent grade Ga metal was dissolved quantitatively in a minimal amount of concentrated HCl and evaporated to near dryness. Doubly distilled water was added and the solution was re-evaporated several times to remove much of the excess HCl present. The actual concentration of the excess acid was analyzed by the determination of total acid by ion exchange. In^{3+} solution was prepared from crystalline $InCl_3$ with a known concentration of HCl acid, and the In^{3+} concentration was determined by ion-exchange and titration for total acid.[15]

Ligands. The ligands S_3N and O_3N were prepared[12,13] as the hydrochlorides and were further assayed by FAB^+ mass spectrometry, elemental analysis, and potentiometric titration. S_3N FAB^+ (thioglycerol) has three major peaks: 384 (parent), 260 (parent − mercaptobenzyl), and 123 (*o*-mercaptobenzyl). The ligand O_3N (thioglycerol/TFA/MeOH) also has only three peaks: 336 (parent), 230 (parent − *o*-hydroxybenzyl), and 108 (*o*-hydroxybenzyl). The S_3N, as a solid colorless powder, is stable in air but its solutions are extremely sensitive to oxygen. Special precautions were employed to avoid this air oxidation. O_3N on the other hand possesses normal inertness to air and was easier to handle. The proton stoichiometry of both neutral ligands is H_3L.

Potentiometric Instrumentation. A Corning 150 digital pH meter was used for potentiometric titrations. A Metrohm 10 mL capacity piston buret was used for precise delivery of standard 0.1 M KOH (70% ethanol v/v). The experimental solution was contained in a 75 mL jacketed glass cell thermostated at 25.00 ± 0.05 °C by a circulating constant-temperature water bath, and equipped with Ar gas protection, separate blue glass and calomel reference extension electrodes, and a magnetic stirring assembly.

Samples for UV−vis spectroscopy were studied with a Perkin-Elmer 553 fast scan UV−vis spectrophotometer connected to a Heath Co. Model SR-255 A/B strip chart recorder. The spectrophotometer was equipped with matched 1.000 ± 0.001 cm quartz cells obtained from Wilmad Glass Co. The cells were mounted in a thermostated holder connected to a VWR constant-temperature bath set at 25.00 ± 0.05 °C.

Potentiometric Determinations. All pH calibrations were performed with standard dilute acid in mixed solvent in order to measure hydrogen ion concentration directly. The ionic strength was adjusted to 0.100 M with KCl. p[H] is defined as $-\log[H^+]$, and pM is $-\log[M^{n+}]$. Ligand and metal−ligand complexes in aqueous and 70% ethanol-30% water (v/v) systems were performed in the manner described by Martell and Motekaitis.[16] Titration cell solutions were purged of CO_2 and O_2 gases with a purified argon gas stream for at least 4 h prior to the commencement of a titration. Standard base (0.1 M) was introduced into the cell through the tip of the Metrohm piston buret drawn to a fine capillary and submerged below the meniscus. The concentrations of the experimental solutions were approximately 2×10^{-3} M. Experimental runs were carried out by adding increments of standard base to a solution containing free ligand plus other components. The range of accurate p[H] measurements was considered to be 2−12.

The pK_w for the mixed solvent system, defined in terms of $-\log([H^+][OH^-])$ at the ionic strength employed, was found to be 14.78 ± 0.04, based on several titrations, by calculating the value of pK_w necessary to bring the titration points in the alkaline range of a solution of standard dilute acid titrated with standard base in line with those in the acid range.

Ligand Solutions. The volume of each test solution was 48.04 mL (35.00 mL of ethanol + 15.00 mL of aqueous components), made up of appropriate volumes of 1.00 M KCl, standard metal solution and doubly distilled water, and absolute ethanol to achieve a 70/30 (v/v) ethanol/water system. The solid ligand hydrochloride was weighed separately and added to the prepurged solution to avoid oxidation. Some 60−80 incremental data points were collected in each titration. Three or more titrations with 0.1 M standard KOH (70% v/v ethanol) were performed for each ligand, excluding the practice titrations to achieve fully anaerobic procedures.

Metal−Ligand Solutions. Metal−ligand experimental solutions are similar to the above except that an appropriate aliquot of standard In^{3+} or Ga^{3+} was added with a equivalent reduction of volume of added water. The deprotonation constant of the $Fe^{3+}-O_3N-OH$ chelate was obtained by back-titration with 0.100 M HCl of a solution prepared by sonication of a basic ferric hydroxide/ligand mixture. The stability constant of $Fe^{3+}-O_3N$ was calculated from spectrophotometric measurement of 1:1 EDTA competition as a function of pH.

Spectrophotometric Determination of the High pK_a's of O_3N. Spectral determinations were made for 1.0×10^{-4} M solutions of O_3N

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as a function of calculated pH by following the absorbance of the 305 nm peak which increases with the proportion of deprotonated phenols.

Calculations. Equilibrium constants from direct titrations as well as the protonation constants were calculated from potentiometric data with the program BEST.[16] The spectrophotometric data were treated with BASIC programs written specifically for the given mass/absorbance conservation equations. The pK_w was maintained fixed during all refinements and the estimated errors are based on averages of at least three determinations unless stated otherwise.

Species distribution diagrams were computed from the measured equilibrium constants with SPE and plotted with SPEPLOT. Titration curves were plotted with LSQFIT, an in-house program.

Preparation of Gallium(III) and Indium(III) Compounds. [GaN(CH_2-*o*-C_6H_4S)$_3$][Ga(S_3N)]. Tris (mercaptobenzyl)amine hydrochloride[13] (0.55 g 1.3 mmol) and lithium wire (0.036 g, 5.2 mmol) were reacted in 20 mL of methanol. A saturated acetonitrile solution containing 0.72 g (1.3 mmol) of [Ph_4P][$GaCl_4$][17] was added. The solution mixture immediately produced a fine precipitate. The reaction mixture was stirred for an additional half hour and cooled at −20 °C for 12 h. A 65% yield (0.38 g, 0.85 mmol) of white powder was isolated by filtration and dried in a vacuum. The compound was recrystallized from DMF/H_2O. ^1H NMR ($CDCl_3$): 3.42 ppm (d, 3H, -C**H**$_2$), 4.63 ppm (d, 3H, -C**H**$_2$), 7.16−7.30 ppm (9H, **Ar**), 7.52 ppm (d, 3H, **Ar**).

[GaN(CH_2-*o*-C_6H_4S)$_3$(1-methylimidazole)], [Ga(S_3N)(1-Me-imid)]. 1.0 mmol of **9** was dissolved with a sufficient quantity of methylene chloride, to which 16 drops (ca. 10 mmol) of 1-methylimidazole was added. The solution slowly evaporated at room temperature during a 2 day period, producing colorless rod-shaped crystals.

Alternatively, 0.55 g 1.0 mmol of [Ph_4P][$GaCl_4$] was added to a solution of 1.1 mmol of the fully deprotonated ligand in methanol. A 1.0 mL volume of 1-methylimidazole (ca. 13 mmol) was introduced to the reaction slurry. The mixture was stirred for 15 min producing an off-white crystalline product (0.37 g, 70% yield). ^1H NMR ($CDCl_3$): 3.49 ppm (d, 3H, -C**H**$_2$), 3.67 ppm (s, 6H, -C**H**$_3$), 4.56 (d, 3H, -C**H**$_2$), 6.87 ppm (s, 2H, -**H** (1-Me-imid)), 7.04 ppm (s, 2H, -**H** (1-Me-imid)), 7.10−7.24 ppm (9H, **Ar** (S_3N)), 7.47 ppm (3H, **Ar** (S_3N)), 7.49 ppm (2H, -**H** (1-Me-imid)).

[InN(CH_2-*o*-C_6H_4S)$_3$ (DMF)], [In(S_3N)(DMF)]. A methanol solution containing 1.2 mmol of the trilithium salt of the ligand was produced as previously described. $InCl_3$ (0.25 g, 1.1 mmol) was added and the reaction mixture was stirred for half an hour. The solvent was removed in vacuo. The white residue was redissolved in 5 mL of DMF, which was layered with distilled water and cooled at −20 °C. Off-white crystalline needles (0.49 g) separated from the solution in 76% yield. ^1H NMR ($CDCl_3$): 2.91 ppm (6H, -C**H**$_3$), 2.98 ppm (6H, -C**H**$_3$, DMF), 3.18 ppm (3H, -C**H**$_2$), 7.12−7.15 ppm (6H, **Ar** (S_3N)), 7.58 ppm (d, 3H, **Ar** (S_3N)), 8.05 ppm (s, 3H, **Ar** (S_3N)).

[InN(CH_2-*o*-C_6H_4S)$_3$(1-methylimidazole)], [In(S_3N)(1-Me-imid)]. The trilithiated tris benzylthiolato amine was generated by the solution of the hydrochloride salt of the ligand (0.46 g, 1.1 mmol) in the presence of Li wire (0.031 g, 4.5 mmol) in methanol. $InCl_3$ (0.23 g, 1.0 mmol) in 10 mL of methanol was added. The cloudy reaction mixture was stirred for several minutes preceding the addition of an excess of 1-methylimidazole (1.0 mL, ca. 13 mmol). A copious white precipitate formed. The solid (0.46 g; 70% yield) was filtered, washed with methanol, and dried. ^1H NMR ($CDCl_3$): 3.13 ppm (d, 3H, -C**H**$_2$), 3.68 ppm (s, 6H, -C**H**$_3$), 4.57 (d, 3H, -C**H**$_2$), 6.88 ppm (s, 2H, -**H** (1-Me-imid)), 7.03−7.18 ppm (9H, **Ar** (S_3N)), (2H, -**H** (1-Me-imid)), 7.54 ppm (d, 3H, **Ar** (S_3N)), 7.49 ppm (2H, -**H** (1-Me-imid)), 7.69 ppm (s, 2H, -**H** (1-Me-imid)).

[In(S_3N)(1,10-phen)]. An 1.6 mmol amount of the trilithiated tristhiolato amine was generated as previously described. In a separate flask a slurry of [$InCl_3$(1,10-phen)] was generated *in situ*[18] by mixing equimolar methanolic solutions of $InCl_3$ (0.29 g, 1.3 mmol) and 1,10-phen (0.24 g, 1.3 mmol). Upon addition of the thiolate to the metal slurry, a pale yellow powdery solid formed. The reactants were stirred for an additional hour; [In(S_3N)(1,10-phen)] was harvested by filtration (0.72 g, 82% yield). ^1H NMR (DMSO-d_6): 3.20 ppm (1H, -C**H**$_2$), 3.44 ppm (d, 2H, -C**H**$_2$), 4.08 ppm (1H, -C**H**$_2$), 4.20 ppm (d, 2H, -C**H**$_2$), 7.10−7.40 ppm (12H, **Ar** (S_3N)), 8.12 ppm (m, 2H, (**1,10-phen**)), 8.26 ppm (s, 2H, (**1,10-phen**)), 8.93 ppm (d, 2H, (**1,10-phen**)), 9.25 ppm (d, 2H, (**1,10-phen**)). FABMS (*m*-nitrobenzyl alcohol): M^+, 675 (M^+ + 1 at 676) *m/z*; In(S_3N)$^+$, 495 (+1 at 496) *m/z*.

[GaN(CH_2-*o*-C_6H_4O)$_3$)(1-Me-imid)], [Ga(O_3N)(1-Me-imid)]. A solution of [Ph_4P][$GaCl_4$] (0.21 g, 0.40 mmol) in 20 mL acetonitrile was cannulated into a solution which contains of tris(2-hydroxybenzyl)amine[13] (0.17 g, 0.50 mmol) and of lithium wire (0.011 g, 1.5 mmol) in 10 mL of methanol. The mixture was stirred for 2 h, and 5 equiv of 1-methylimidazole was added. Solvent was removed, and 15 mL of methanol was added. After 1 day at −20 °C, white solid precipitated in 45% yield, which was recrystallized from THF/hexane. ^1H NMR ($CDCl_3$): 3.70−3.95 ppm (s(br), 6H, C**H**$_2$), 3.84 ppm (s, 3H, C**H**$_3$ (1-Me-imid)), 6.65 ppm (t, 3H, 5-**H**), 6.76 ppm (d, 3H, 3-**H**), 6.95 ppm (d, 3H, 6-**H**), 7.00 ppm (s, 1H, C**H**(1-Me-imid)), 7.14 ppm (t, 3H, 4-**H**), 7.63 ppm (s, 1H, C**H**(1-Me-imid)), 8.30 ppm (s, 1H, C**H**(1-Me-imid)).

[GaN(CH_2-*o*-C_6H_4S)$_3$)(DMF)], [Ga(O_3N)(DMF)]. A solution of [Ph_4P][$GaCl_4$] (0.21 g, 0.40 mmol) in 10 mL acetonitrile was cannulated to a trilithium salt of the tris(2-hydroxybenzyl)amine (0.50 mmol) solution in 20 mL methanol. White solid precipitated upon stirring for 1 h. This precipitate was filtered and recrystallized from DMF/2-propanol. ^1H NMR (DMSO-d_6): 2.71 ppm (s, 3H, C**H**$_3$(DMF)), 2.87 ppm (s, 3H, C**H**$_3$(DMF)), 3.60 ppm (s, 6H, C**H**$_2$), 6.63 ppm (t, 3H, 5-**H**), 6.68 ppm (d, 3H, 3-**H**), 7.00 ppm (d, 3H, 6-**H**), 7.11 ppm (t, 3H, 4-**H**), 7.93 ppm (s, 1H, −C**H**O).

[In(O_3N')(1-Me-imid)$_2$]. $InCl_3$ (0.089 g, 0.40 mmol) was dissolved in methanol and cannulated into a solution of the trilithium salt of tris-(2-hydroxy-3,5-dimethylbenzyl)amine[13] (0.50 mmol) in methanol, resulting in a clear colorless solution. Excess of 1-methylimidazole was added to the solution and white solid precipitate formed after stirring for 4 h. The compound was recrystallized from THF/hexane. ^1H NMR ($CDCl_3$): 2.11 ppm (s, 9H, C**H**$_3$), 2.15 ppm (s, 9H, C**H**$_3$), 3.82 ppm (s, 3H, C**H**$_3$(1-Me-imid)), 6.59 ppm (s, 3H, 6-**H**), 6.80 ppm (s, 3H, 4-**H**), 7.01 ppm (s, 1H, C**H**(1-Me-imid)), 7.28 ppm (s, 1H, C**H**(1-Me-imid)), 7.92 ppm (s, 1H, C**H**(1-Me-imid)).

X-ray Crystallography. Unit cell determination and data collection were performed at room temperature on a CAD4 X-ray diffractometer using standard techniques. A conventional unit cell determination was made from 25 reflections, which were randomly observed at low 2θ. Refined cell parameters were obtained by centering on 25 high-angle reflections ($20 < 2\theta < 22$). Structure solution and refinement were performed using texsan software (Molecular Structure Corporation). Hydrogen atoms were calculated and were included in the structure factor calculations but were not refined. Parameters associated with unit cell determination, data collection and structure refinement are included in Tables 1 and 2. Tables of atomic coordinates are included in the Supporting Information.

Colorless diamond-shaped crystals of [Ga(S_3N)] were obtained from DMF/H_2O. Crystals of [Ga(S_3N)(1-Me-imid)] were obtained by the slow evaporation of a dilute methylene chloride solution of Ga(S_3N) in the presence of excess 1-methylimidazole. An attempt to recrystallize [In(S_3N)(1,10-phen)] in DMF/H_2O produced colorless needles of [In(S_3N)(DMF)]·DMF. [In(S_3N)(DMF)]·DMF crystallized in the acentric monoclinic space group, *Cc*. The structure was completed by a least-squares refinement which converged with a residual $R = 0.037$, $R_w = 0.038$. The crystal structure solution was confirmed for the proper enantiomer by applying the coordinates for the opposite enantiomer which raised the R values to $R = 0.040$ and $R_w = 0.041$. Colorless crystals of [In(S_3N)(1-Me-imid)] of approximate parallelepiped morphology were grown from a solvent mixture of DMF layered with distilled water that was left standing at room temperature for 3 days. Colorless crystals of [Ga(O_3N)(1-Me-imid)] were grown from THF/hexane solution. Colorless crystals of [Ga(O_3N)(DMF)] were grown from DMF/2-propanol solution. Crystals of [In(O_3N')(1-Me-imid)$_2$](THF)$_{0.5}$] were grown from THF/hexane solution. One molecule of THF was located and refined at 50% occupancy. The final R and R_w values obtained were 0.068 and 0.073, respectively. This relatively high R(R_w) value is due to the disorder of solvent (THF) molecule.

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Table 1. Crystallographic Data for X-ray Diffraction Studies of Ga and in [$M(S_3N)$] Compounds

	[$Ga(S_3N)$]	[$Ga(S_3N)$(1-Me-imid)]	[$In(S_3N)$(DMF)]·DMF	[$In(S_3N)$(1-Me-imid)]
empirical formula	$GaS_3ON_2C_{24}H_{25}$	$GaS_3N_3C_{25}H_{24}$	$InS_3O_2N_3C_{27}H_{32}$	$InS_3N_3C_{25}H_{24}$
fw	523.37	532.32	641.57	577.48
a (Å)	10.448(1)	14.844(2)	21.197(3)	8.445(3)
b (Å)	14.3817(8)	10.813(6)	9.889(3)	21.973(3)
c (Å)	15.677(2)	15.194(2)	15.116(3)	13.864(2)
α (deg)	90	90	90	90
β (deg)	92.310(6)	95.213(6)	116.16(1)	104.683(3)
γ (deg)	90	90	90	90
V Å^3	2353.7(4)	2429(1)	2844(1)	2488.4(8)
Z	4	4	4	4
space group	$P2_1/c$	$P2_1/a$	Cc	$P2_1/n$
temp	ambient	ambient	ambient	ambient
radiation (graphite monochromator)	Mo Kα ($\lambda = 0.710\ 73$ Å)	Mo Kα	Mo Kα	Mo Kα
linear abs coeff (cm^{-1})	14.38	14.09	10.79	12.19
scan mode	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$
2θ range (deg)	$0 < 2\theta < 50$	$0 < 2\theta < 50$	$0 < 2\theta < 50$	$0 < 2\theta < 50$
no. of unique reflcns with $\|F_o\|^2 > 3\sigma\|F_o\|^2$	1186	2264	2129	2390
final no. of variables	280	289	318	289
$R^a = \sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$	0.026	0.029	0.037	0.030
$R_w = [\sum w(\|F_o\| - \|F_c\|)^2/\sum wF_o^2]^{1/2}$	0.033	0.038	0.038	0.039
std error in observation of unit wt	1.83	2.01	3.64	1.70

[a] Quantity minimized ($\sum w(|F_o| - |F_c|)^2$); weight $w = 1/(\sigma^2(F_o) + 0.0016F_o^2)$.

Table 2. Crystallographic Data for X-ray Diffraction Studies of Ga and in [$M(O_3N)$] Compounds

	[$Ga(O_3N)$(1-Me-imid)]	$Ga(O_3N)$(DMF)]	$In(O_3N')(1\text{-Me-imid})_2$
empirical formula	$GaC_{25}H_{24}O_3N_3$	$GaC_{24}H_{25}O_4N_2$	$InC_{37.5}H_{42}O_3$
fw	484.22	463.19	815.59
a (Å)	14.783(2)	14.778(4)	28.109(2)
b (Å)	9.4164(9)	9.384(4)	28.109(2)
c (Å)	17.093(3)	16.688(6)	20.013(3)
α (deg)	90	90	90
β (deg)	110.841(6)	107.91(2)	90
γ (deg)	90	90	90
V (Å^3)	2223(1)	2197(3)	15812(4)
Z	4	4	16
space group	$P2_1/c$	$P2_1/c$	I_1/a
temp	ambient	ambient	ambient
radiation (graphite monochromator)	Mo Kα	Mo Kα	Mo Kα
linear abs coeff (cm^{-1})	12.618	12.745	6.236
scan mode	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$
2θ range, deg	$0 < 2\theta < 50$	$0 < 2\theta < 50$	$0 < 2\theta < 50$
unique reflcns with $\|F_o\|^2 > 3\sigma\|F_o\|^2$	2091	1886	2097
final no. of variables	289	280	417
$R^a = \sum[\|F_o\| - \|F_c\|]/\sum\|F_o\|$	0.038	0.036	0.068
$R_w = [\sum w(\|F_o\| - \|F_c\|)^2/\sum wF_o^2]^{1/2}$	0.039	0.037	0.073
std error in observation of unit wt	1.298	1.276	2.219

[a] Quantity minimized ($\sum w(|F_o| - |F_c|)^2$); weight $w = 1/(\sigma^2(F_o) + 0.0016F_o^2)$.

Results and Discussion

Protonation Constants of S_3N. Tris(2-mercaptobenzyl)amine S_3N is found to be alcohol soluble but water insoluble. After some testing it was determined that a 70% ethanol/water (v/v) solvent system would be suitable for potentiometry of this compound. This is a dependable, convenient, solvent system for the determination of stability constants where water presents solubility problems.[19] In addition, this ligand proved to be extremely air sensitive when in solution as evidenced by an immediate clouding of the solution when exposed to air. Presumably high molecular weight disulfide polymers which are formed possess reduced solubility. Purified argon gas atmosphere was satisfactory for carrying out these titrations. Figure 1 shows the potentiometric equilibrium curve for S_3N·HCl (top curve) as a function of pH and indicates an initial unusually low pK_a for the protonated nitrogen, followed by three strongly overlapping pK_a's attributable to the aromatic mercapto groups.

The potentiometrically determined log protonation constants of S_3N valid at 25.0 °C and $\mu = 0.100$(KCl), are listed in Table 3. The spacing of the values of thiolate protonations is remarkably narrow indicating independence of successive protonation steps. The total 1.67 log unit spread in S_3N S-protonations is reminiscent of the 1.71 spread observed in TREN (tris(2-aminoethyl)amine) where the amino groups are also quite independent. The absolute magnitude of the thio protonation constants is reasonable in that phenylmercaptan has a pK_a of 6.46.

The unexpectedly low protonation constant for the trigonal N is indeed uncommon and the stability constant literature contains only indirect hints of effects of aromatic mercapto groups on adjacent groups. For example ethylamine has a log protonation constant of 10.64. A β-hydroxy group lowers the protonation constant to 9.40. A β-mercapto group on the other hand lowers the intrinsic pK_a more than 2 log units down to

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(19) Madsen, S. L.; Welch, M. J.; Motekaitis, R. J.; Martell, A. E. *Nucl. Med. Biol.* **1992**, *19*, 431.

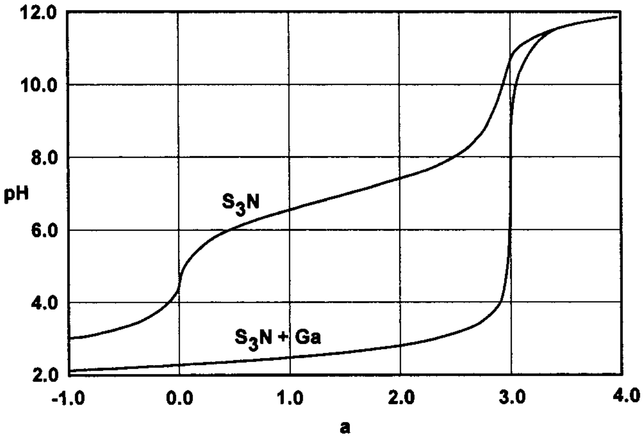

Figure 1. Potentiometric equilibrium curves for S_3N alone (top) and 1:1 Ga^{3+}/S_3N at 25.0 °C and $\mu = 0.100$(KCl) in 70% (v/v) ethanol/water. $T_{S_3N} = 2.0 \times 10^{-3}$ M, $T_{Ga^{3+}} = 2.0 \times 10^{-3}$ M, a = moles KOH (0.10 M, 70% (v/v) ethanol/water)/mole of S_3N, and pH = $-\log [H^+]$. H_3L is the neutral ligand.

Table 3. Protonation Constants of S_3N (25 °C, $\mu = 0.100$(KCl), 70% v/v Ethanol)

$L^{3-} + H^+ \rightleftharpoons HL^{2-}$	$\log K_1 = 7.88(3)$
$HL^{2-} + H^+ \rightleftharpoons H_2L^-$	$\log K_2 = 6.90(2)$
$H_2L^- + H^+ \rightleftharpoons H_3L$	$\log K_3 = 6.21(1)$
$H_3L + H^+ \rightleftharpoons H_4L^+$	$\log K_4 = 2.53(1)$
	$\log \beta_4 = 23.52$

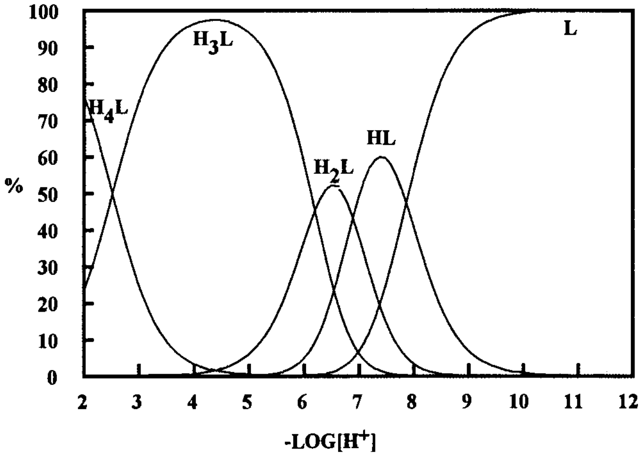

Figure 2. Species distribution of S_3N as a function of pH. $T_{S_3N} = 2.0 \times 10^{-3}$ M and pH = $-\log [H^+]$ at 25.0 °C and $\mu = 0.100$(KCl) in 70% (v/v) ethanol/water. H_3L is the neutral ligand.

8.23. Attached benzyl and *o*-hydroxybenzyl groups are known to lower the basicities of the aliphatic amino groups by 1−2 log units also. The three mercaptobenzyl groups on the tripodal of S_3N act in concert to significantly lower the basicity of the amino nitrogen.

Figure 2 shows these relationships, namely, between pH 3 and 6 the dominant species is the neutral ligand H_3L, followed by overlapping conversions to H_2L^-, HL^{2-}, and L^{3-} by pH 8.

In^{3+} and Ga^{3+} Interactions with S_3N in Solution. In the presence of either In^{3+} or Ga^{3+}, both metal chelate formation potentiometric p[H] curves are similar and structureless and terminate at $a = 3$ with a steep potential jump into the alkaline region. Figure 1 (bottom curve) shows the 1:1 Ga^{3+}/S_3N potentiometric equilibrium curve. While not visually apparent, the mathematical analysis of the titration points associated with each metal ion reveals that in addition to the normal ML species a monoprotonated MLH^+ complex also forms concomitantly.

Table 4. Stability Constants of S_3N (25 °C, $\mu = 0.100$(KCl), 70% v/v Ethanol)

$Ga^{3+} + L^{3-} \rightleftharpoons GaL$	$\log K_{ML} = 20.5(1)$
$GaL + H^+ \rightleftharpoons GaHL^+$	$\log K^{H}_{MHL} = 2.0(1)$
$In^{3+} + L^{3-} \rightleftharpoons InL$	$\log K_{ML} = 21.2(1)$
$InL + H^+ \rightleftharpoons InHL^+$	$\log K^{H}_{MHL} = 1.8(1)$

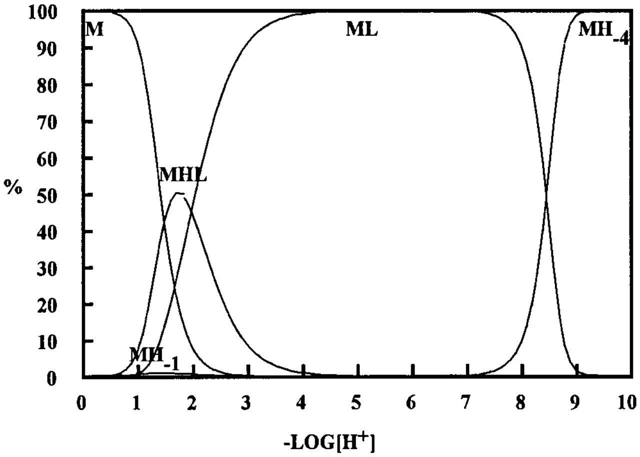

Figure 3. Species distribution of 1:1 Ga^{3+}/S_3N as a function of pH. $T_{S_3N} = T_{Ga^{3+}} = 2.0 \times 10^{-3}$ M and pH = $-\log [H^+]$ at 25.0 °C and $\mu = 0.100$(KCl) in 70% (v/v) ethanol/water; M = Ga^{3+}, L = S_3N^{3-}. H_3L is the neutral ligand, and MH_{-1}, MH_{-3}, and MH_{-4} represent $Ga(OH)^{2+}$, $Ga(OH)_3$, and $Ga(OH)^-_4$, respectively.

The final stability constants obtained are listed in Table 4 together with the defining equations.

To appreciate the magnitudes of the stability constants it may be useful to compare the In^{3+} stability constants (Ga^{3+} constant unavailable) with those of the bidentate ligands 2-aminoethylmercaptan and 2-hydroxyethylmercaptan. From the stability constant of the latter it appears that the intrinsic $\log K_{ML}$ for a mercapto group with In^{3+} is ~9.1 and from the former it can be concluded that the chelating amino group would contribute about 4 log units more to the stability constant. Because S_3N contains three mercapto groups and one amino, it appears that the predicted formation constant should be higher than 27 log units. However both the tripodal arrangement of coordinating groups in S_3N around the large In^{3+} ion, together with larger chelate rings, are apparently responsible for the somewhat lower than predicted stability constant.

It is unusual that the Ga^{3+} stability constant with S_3N is smaller than that of In^{3+} based on observations of aromatic phenol type ligands such as HBEP or HBED but not unusual when compared to TACN trithiolate results of Ma et al.[7] Also Ga^{3+} superiority would be predicted on the basis of Hancock's "chelate ring size" argument,[20] namely, that complexes with smaller ions should be more stable with larger chelating rings, a conclusion based on the examination of many N and O ligands. Sulfur ligands were not included. Besides ionic radii arguments, there are other factors such as bond strength increase resulting from a more favorable overlap of In^{3+} orbitals to sulfur compared those of Ga^{3+}.

Nevertheless, in each case the stability of the neutral complex is sufficiently large to prevent precipitation of $M(OH)_3$ up to and beyond pH 8. A species distribution diagram (Figure 3) shows that between pH 4 and 8 a single, neutral gallium (or indium)-containing species exists in 100% yield. Included in this speciation diagram is a solubility product for $Ga(OH)_3$

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[20] Hancock, R. D.; Martell, A. E. *Metal Ions in Aqueous Solution*; Plenum: New York, 1997.

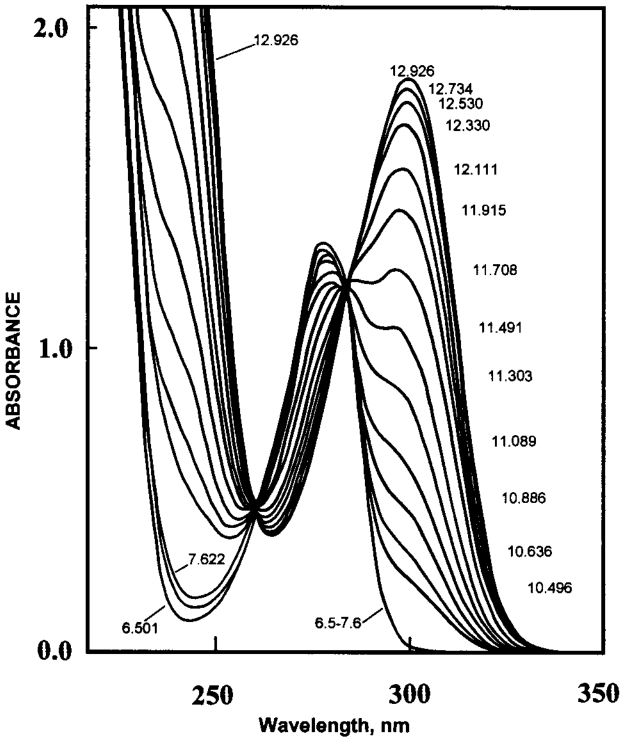

Figure 4. UV spectra of O_3N as a function of pH at 25.0 °C and $\mu = 0.100$(KCl) in 70%(v/v) ethanol/water 1.9×10^{-4} M; pH = $-\log [H^+]$.

which apparently is exceeded at pH > 8. The exact K_{sp} for $Ga(OH)_3$ is known only in pure water.

Because the solution coordination chemistry with S_3N for both Ga^{3+} and In^{3+} is so similar, any in vivo differences in biodistributions must be explained by other factors, such as kinetic, structural and mechanistic properties, rather than on differences in stability constants.[22]

In this regard it is interesting to compare the pM values ($-\log[M^{3+}]$) for both gallium and indium with 100% excess ligand at pH 7.4 with the pM value of In in the presence of 100% excess transferrin.[23] The pM value of Ga S_3N is 19.7 while that for In S_3N is 20.4, reflecting the differences in the stability constants. The literature[23] transferrin value for In is 19.6. Thus pM values also provide little clue as to the efficacy of Ga vs In S_3N.

Protonation Constants of O_3N. The protonation reactions of O_3N are parallel to those of S_3N except that O_3N is much more basic and the protonation constants are orders of magnitude higher. When the species distribution diagrams of both S_3N and O_3N are overlaid and shifted ~5 log units, each corresponding protonation peak of S_3N overlaps the O_3N peak of the same degree of protonation. Because of this large increase in overall basicity, the phenolic pK_a's of O_3N were determined by spectrophotometric measurements, rather than by direct titration alone, as the potentiometric measurements are insensitive to extremely weak acids with pK_a's of 12 or higher.

Figure 4 shows the UV spectra for O_3N as a function pH. The absorbance at 305 nm represents the deprotonated phenolic groups. This series of absorbance data was subjected to a computation for the three highest protonation constants with the use of least-squares procedures to find K_1, K_2, K_3, ϵ_1, and ϵ_2, such that the sum of the squares of the differences of calculated and observed absorbances is minimized while the mass balance (eq 1) and total optical absorbance (eq 2) equations are employed. The ϵ_0 and ϵ_3 were determined in separate experiments and thus were fixed during the refinements.

Table 5. Protonation Constants of O_3N (25 °C, $\mu = 0.100$(KCl), 70% v/v Ethanol)

$L^{3-} + H^+ \rightleftharpoons HL^{2-}$	$\log K_1 = 13.0(1)$
$HL^{2-} + H^+ \rightleftharpoons H_2L^-$	$\log K_2 = 11.92(2)$
$H_2L^- + H^+ \rightleftharpoons H_3L$	$\log K_3 = 11.00(1)$
$H_3L + H^+ \rightleftharpoons H_4L^+$	$\log K_3 = 7.01(1)$
	$\log \beta_4 = 42.94$

$$T_L = [L]\{1 + K_1[H^+] + K_1K_2[H^+]^2 + K_1K_2K_3[H^+]^3\} \quad (1)$$

$$A = [L]\{\epsilon_0 + \epsilon_1K_1[H^+] + \epsilon_2K_1K_2[H^+]^2 + \epsilon_3K_1K_2K_3[H^+]^3\} \quad (2)$$

The results of this combined effort are shown in Table 5.

It is interesting that the log K_i's ($i = 1-3$) of O_3N show a slightly higher spread, 2.0 relative to 1.67 for S_3N; a higher average magnitude relative to phenol, 11.97 vs 9.77; a much higher magnitude for average phenolic pK_a's, 11.97 compared to the benzylmercaptans of S_3N of 6.99; and a considerably higher tripodal N pK_a, 7.01 vs 2.53 for the thiolate analogue. No doubt the superior hydrogen bonding characteristics of the O atoms present serve to prevent proton dissociation reactions relative to the more facile dissociations of the S_3N molecule. Such an increase in the basicity of the *o*-hydroxybenzyl group finds precedent for example in monophenolic compounds such as *N*-(*o*-hydroxybenzyl)iminodiacetic acid ($\log K_1 = 11.8$) and diphenolic compounds such as HBED, wherein the highest phenolic protonation constant is 12.5. Thus with three *o*-hydroxybenzyl groups substituted on a single amino nitrogen, the combined effects would put pK_1 in the vicinity of 13.0 log units.

Confirmation of this high value may be made by plotting the potentiometrically measurable values of the log protonation constants of O_3N vs those of S_3N. The least-squares fit line has a slope of 1.11, intercept −3.77, correlation coefficient $r = 0.9996$, and the extrapolated log $K_1(O_3N)$ is 12.95. This agrees very well with the spectrophotometric result.

In^{3+}, Ga^{3+}, and Fe^{3+} Interactions with O_3N in Solution. The higher basicity of O_3N precludes the determination of the stability constants of O_3N chelates of trivalent metal ions (other than the stronger binding Ga^{3+}) by direct potentiometric titration. Indium(III) hydroxide, $In(OH)_3$ has a very small solubility product, and direct titration results in the total precipitation of In^{3+} ions from solution before any complex can form. The fact that precipitation takes place near pH 4 in the presence of O_3N is an indication that complexation at this pH is very weak.

However, success was achieved with Ga^{3+} since its stability constant was high enough for this type of determination. Figure 5 reveals that the window of stability relative to $Ga(OH)_3$ precipitation is optiminal. Thus near complete formation of MHL^+ takes place up to pH 3 and even though formally the K_{sp} for $Ga(OH)_3$ has been slightly exceeded, the conversion of MHL^+ to ML is also potentiometrically observed. (It is not uncommon to work with slightly supersaturated solutions with respect to the hydroxide.) At higher pH values there is eventual conversion of chelated Ga^{3+} to gallate ion $Ga(OH)^-{}_4$.

The fact that In^{3+} does not form a complex below pH 4 where In^{3+} precipitates as the hydroxide, indicates that its stability constant is lower than that of Ga^{3+}, because the solubilities of

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(21) Cutler, C. S.; Reichert, D. E.; Anderson, C. J.; Giron, M. C.; Motekaitis, R. J.; Quarless, D. A.; Jones, L. A.; Lewis, J. S.; Koch, S. A.; Martell, A. E.; Welch, M. J. *J. Labeled Compds Radiopharm.* **1997**, *40*, 504.

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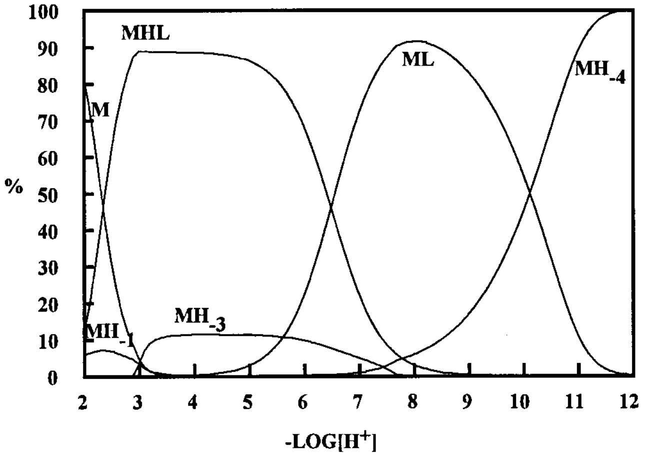

Figure 5. Species distribution of 1:1 Ga^{3+}/O_3N as a function of pH taking $K_{sp}(Ga(OH)_3)$ into account. $T_{O_3N} = T_{Ga^{3+}} = 2.0 \times 10^{-3}$ M and pH = −log [H^+] at 25.0 °C and $\mu = 0.100$(KCl) in 70% (v/v) ethanol/water; M = Ga^{3+}, L = O_3N^{3-}.

Table 6. Stability Constants of O_3N (25 °C, $\mu = 0.100$(KCl), 70% v/v Ethanol)

$Ga^{3+} + L^{3-} \rightleftharpoons GaL$	$\log K_{ML} = 32.32(2)$
$GaL + H^+ \rightleftharpoons GaHL^+$	$\log K^{H}_{MHL} = 6.50(2)$
$Fe^{3+} + L^{3-} \rightleftharpoons FeL$	$\log K_{ML} = 37.(1)$
$FeL + H^+ \rightleftharpoons FeHL^+$	$\log K^{H}_{MHL} = 7.40(1)$

the hydrioxides are similar This is not unusual as comparisons of Ga^{3+} vs In^{3+} stabilities for phenolic ligands such as HBED, EHPG and catechols always show a stronger preference for Ga^{3+} by up to 6 or more orders of magnitude. Thus it is not surprising that the formation of $In(OH)_3$ prevented direct potentiometric determination.

Iron(III) was studied to shed some light on the initial lack of success with In^{3+}. With Fe^{3+} a variation of the precipitation problem was encountered in that near pH 2 all the Fe^{3+} precipitated as the hydroxide. However after the pH was raised further the suspension slowly dissolved through prolonged sonication. A back-titration with standard dilute mineral acid was then possible, to observe the protonation reaction ML + $H^+ \rightleftharpoons MHL^+$. The stability constant was eventually estimated spectrophotometrically by competition with EDTA. Thus initially, the Fe^{3+} ion is kept in solution as an EDTA chelate, wherein near pH 9 the FeEDTA complex exchanged its chelated Fe^{3+} with O_3N. The final values of the constants determined for O_3N together with the corresponding equations, are listed in Table 6. While the magnitude of the Fe^{3+} constant is very large, its effect is counterbalanced by the extremely high protonation constants of the ligand and the very low K_{sp} of ferric hydroxide.

Synthesis and Structures of Ga and Indium S_3N Complexes. Synthesis of Ga and In complexes was achieved by the reactions of the trilithium salt of Li_3S_3N with $[Ph_4P][GaCl_4]$[17] or $InCl_3$ in MeOH solution. Recrystallization of the products of the reactions from DMF/H_2O gave the four-coordinate complex [Ga(S_3N)] and the five-coordinate DMF adduct, [In(S_3N)(DMF)]. [Ga(S_3N)] crystallizes with a molecule of DMF; however the O of the DMF is more than 6 Å from the Ga center. For both Ga and In, five-coordinate [M(S_3N)(1-methylimidazole)] adducts were isolated when 4 equiv of 1-methylimidazole was added to the original reaction mixtures or by reaction of isolated [Ga(S_3N)] with 1-methylimidazole.

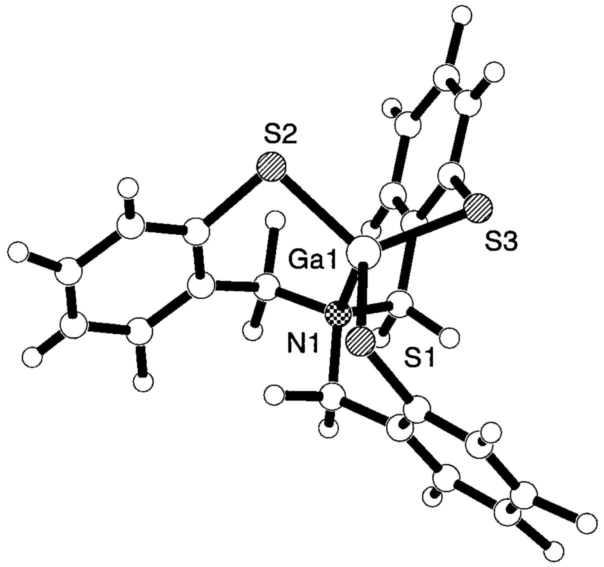

Figure 6. Structural diagram of [Ga(S_3N)].

Table 7. Comparison of Metrical Parameters of Ga and in [M(S_3N)] Compounds

bonds (Å), angles (deg)	[Ga(S_3N)]	[Ga(S_3N) (1-Me-imid)]	[In(S_3N) (1-Me-imid)]	[In(S_3N) (DMF)]
M−S1	2.232(2)	2.274(1)	2.445(2)	2.401(3)
M−S2	2.225(2)	2.268(1)	2.453(2)	2.425(3)
M−S3	2.233(2)	2.274(1)	2.439(2)	2.431(4)
M−N	2.045(4)	2.202(3)	2.386(6)	2.335(9)
M−L		2.226(3)	2.312(6)	2.35(1)
S1−M−S2	116.25(7)	123.74(4)	119.36(8)	123.5(1)
S1−M−S3	115.02(7)	116.10(4)	121.34(9)	117.1(1)
S2−M−S3	115.21(7)	117.67(4)	119.17(8)	118.7(1)
N−M−L		177.2(1)	179.1(2)	178.4(4)
N−M−S(av)	102.4(2)	95.3(3)	91.2(5)	92.9(4)
L−M−S(av)		84.8(21)	88.8(7)	87.1(16)
M−(S_3 plane)[a]	0.47	0.21	0.05	0.12
M−S−C(av)	95.5(7)	109.2(2)	104.7(15)	102.6(18)

[a] Positive numbers indicate a displacement from the S_3 plane toward the amine N.

[Ga(S_3N)] (Figure 6, Table 7) has a distorted tetrahedral coordination with average S−Ga−S angles of 115.5(7)° and average N−Ga−S angles of 102.4(2)°. The gallium is displaced from the plane defined by the three S donors by 0.47 Å toward the amine nitrogen atom. The average Ga−S distance (2.230(4) Å) in [Ga(S_3N)] is shorter than the Ga−S distance in $Et_4N[Ga(SPh)_4]$ (2.26(1) Å) and $Et_4N[Ga(SEt)_4]$ (2.264(1) Å).[17] A similar trend has been observed for the Zn−S distances in the structures of $[Zn(SR)_4]^{2-}$ and $[Zn(SR)_3(1\text{-Me-imid})]^{1-}$ complexes.[23] As expected, the Ga−S (2.234(5) Å) and Ga−N (2.053(6) Å) distances in the four-coordinate [Ga(S_3N)] are shorter than the corresponding distances in the six-coordinate amine thiolate complex [Ga(1,4,7-tris(2-thiolatoethyl)-1,4,7-triazacyclononane)] (Ga−S 2.34(1), Ga−N 2.21(1) Å)[24] and 2-thiopyridine complex $[Ga(SC_5H_4N)_3]$ (Ga−S 2.420(3), Ga−N 2.071(9) Å).[25] The Ga−S distances in [Ga(S_3N)] are longer than those in the 3-coordinate compound, Ga(S-2,4,6-*t*-$Bu_3C_6H_2)_3$ (Ga−S_{av} 2.205(6) Å).[26] [Ga(S_3N)] has a chiral C_3 conformation with both enantiomorphs present in the centric unit cell. As a result the N−CH_2−Ph protons are diastereotopic with one set of benzyl protons almost parallel to the Ga−N bond (the Ga−N−C−H torsion angles = 170−176°) and the second set of protons has Ga−N−C−H torsion angles of 65−

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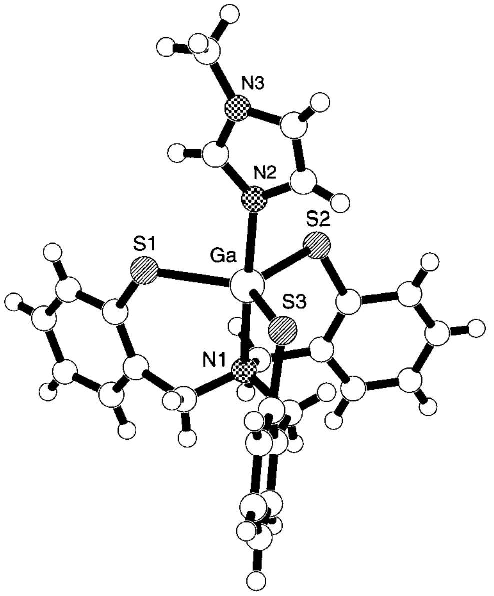

Figure 7. Structural diagram of [Ga(S_3N)(1-Me-imid)].

70°. The C_3 structure is preserved in solution as the benzyl protons have distinct resonances at 3.42 and 4.63 ppm, (^2J = 13 Hz). At elevated temperatures, the two resonances coalesce (~50 °C) and emerge as a single resonance. Racemization of the enantiomorphs is achieved by inversion of the six-membered chelate rings which results in the exchange of the benzyl protons. The C_3 arrangement of the M(S_3N) ligand is preserved in all the structures of the M(S_3N)L reported in this paper.

[Ga(S_3N)(1-Me-imid)] (Figure 7, Table 7) is isomorphous with the previously reported [Fe(S_3N)(1-Me-imid)] complex.[12] The Ga compound has slightly shorter M−S bond distance and a slightly longer M−N (imidazole) distance than the iron analogue. A Ga^{3+} complex with a bisaminoethanethiol (S_2N_2) tetradentate ligand also forms a five-coordinate compound.[27]

The increase in the coordination number from four in [Ga(S_3N)] to five in [Ga(S_3N)(1-Me-imid)] is associated (i) with the movement of the Ga toward the S_3 plane from 0.47 to 0.21 Å, (ii) an increase in the Ga−S distance from 2.230(4) to 2.272(3) Å and the Ga−N(amine) distance from 2.045(4) to 2.202(3) Å, (iii) a decrease in the N−Ga−S angles from 102.4(2) to 95.3(3)°, and (iv) an increase in the Ga−S−C bond angles for 95.5(7) to 109.2(2)°. There is a more pronounced twist in the S_3N ligand in [Ga(S_3N)(1-Me-imid)] with the trigonal GaS_3 and NC_3 units making S−Ga−N−C torsion angles of −26° for [Ga(S_3N)(1-Me-imid)] versus −4° for [Ga(S_3N)].

The structural parameters of [Ga(S_3N)(1-Me-imid)] give some insight into the instability of [Ga(S_3N)(DMF)] with respect to the four-coordinate [Ga(S_3N)] complex. The Ga is displaced 0.21 Å out of the plane defined by the three sulfur atoms away from the monodentate imidazole ligand. The acute S−Ga−N (imidazole) angles (84.8(21)°) and obtuse S−Ga−N(amine) angles (95.3(3)°) reflect the displacement of the Ga toward the amine nitrogen. In the absence of a strong donor ligand, the geometric constraints of the chelating ligands in combination with the relatively small size of the Ga^{3+} cation disfavors the increase in the coordination number from 4 to 5.

In contrast, the structure of [In(S_3N)(1-Me-imid)] ((Figure 8, Table 7) the indium is displaced only by 0.05 Å from the S_3 plane and the S−In−N (imidazole) angles (88.8(7)°) and S−In−N(amine) angles (91.2(5)°) are much closer to 90°. For the larger In^{3+} cation, weaker donors such as EtOH and DMF also produce five-coordinate adducts (Figure 9, Table 7). With a weaker donor ligand, DMF, the indium atom has a greater displacement from the S_3 plane toward the amine N and a decrease in S−In−O angles. There is also a significant shortening of the In−N (amine) distance in the DMF adduct compared to the 1-Me-imid adduct. The In−S bonds are also shorter in the DMF adduct than in the 1-Me-imid adduct. The trends in the metrical parameters suggest that the weaker DMF adduct is a structural intermediate between the stronger imidazole adduct and the hypothetical four-coordinate [In(S_3N)] complexes.

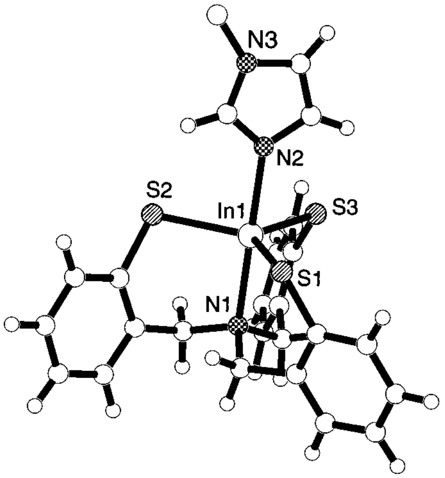

Figure 8. Structural diagram of [In(S_3N)(1-Me-imid)].

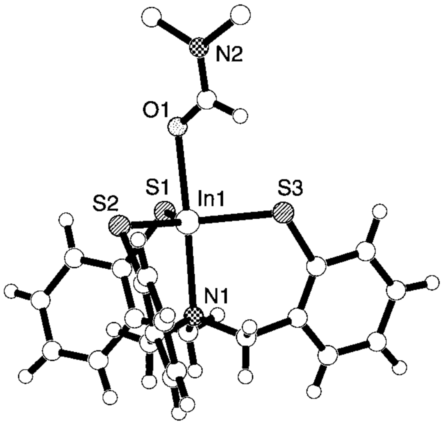

Figure 9. Structural diagram of [In(S_3N)(DMF)].

^{1}HMR and mass spectra evidence indicated that a six-coordinate In(S_3N)(phen) compound could be prepared. However attempts to grow crystals of this compound resulted in the displacement of the phen ligand to give five-coordinate In(S_3N)L where L = DMF, DMSO, or EtOH. Literature examples of indium trithiolate compounds include the three-coordinate compound, In(S-2,4,6-*t*-$Bu_3C_6H_2$)$_3$ (In−S_{av} 2.398(7) Å),[28] the tetrahedral compound [In(S-2,4,6-CF_3-C_6H_2)$_3$(Et_2O)] (In−S_{av} 2.418(7) Å),[29] the trigonal bipyramidal compound, In(SPh)$_3$-py$_2$, which has In−S (2.458(8) Å) and In−N (2.39(1) Å)[30] and the octahedral compound, [In(1,4,7-tris(2-thiolatoethyl)-1,4,7-triazacyclononane)] (In−S 2.51(1) Å, In−N 2.40(1) Å).[31]

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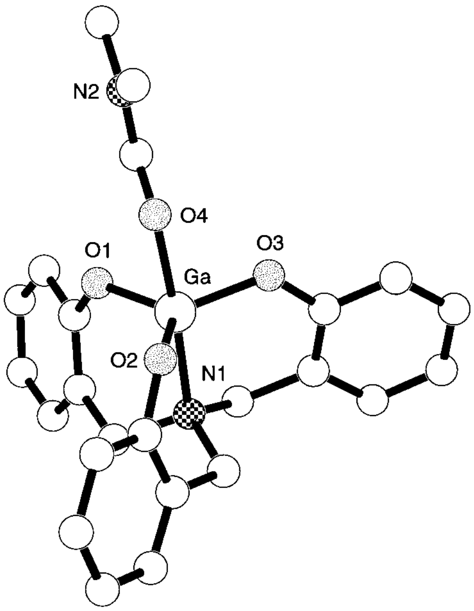

Figure 10. Structural diagram of [Ga(O_3N)(DMF)].

Table 8. Selected Distances (Å) and Angles (deg) for [Ga(O_3N)L

bonds (Å), angles (deg)	[Ga(O_3N)(1-Me-imid)]	[Ga(O_3N)(DMF)]
M−O1	1.862(3)	1.859(4)
M−O2	1.855(3)	1.843(4)
M−O3	1.839(3)	1.834(4)
M−N	2.121(4)	2.118(4)
M−L	2.018(4)	2.010(4)
O1−M−O2	125.2(2)	123.7(2)
O1−M−O3	117.6(1)	115.3(2)
O2−M−O3	116.9(2)	119.9(2)
N−M−L	175.4(2)	176.4(2)
N−M−O(av)	92.0(11)	93.4(13)
L−M−O(av)	88.2(28)	86.6(20)
M−(O_3 plane)[a]	0.06	0.11
M−O−C(av)	130.3(11)	128.9(8)

[a] Positive numbers indicate a displacement from the O_3 plane toward the amine N.

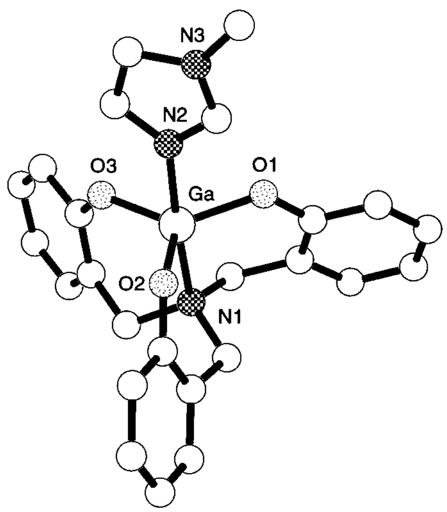

Figure 11. Structural diagram of [Ga(O_3N)(1-Me-imid)].

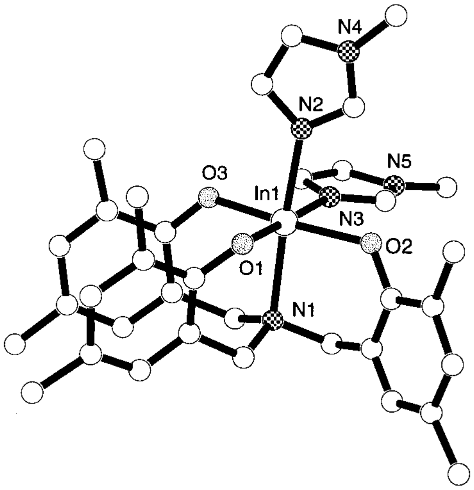

Figure 12. Structural diagram of [In(O_3N')(1-Me-imid)$_2$].

Table 9. Selected Distances (Å) and Angles (deg) for In(O_3N')(1-Me-imid)$_2$

In1−O1	2.08(1)	In1−N1	2.29(1)
In1−O2	2.08(1)	In1−N2	2.24(2)
In1−O3	2.04(1)	In1−N3	2.32(2)
O1−In1−O2	97.0(5)	O3−In1−N1	92.5(5)
O1−In1−O3	96.0(5)	O3−In1−N2	92.3(7)
O1−In1−N1	86.8(5)	O3−In1−N3	83.5(6)
O1−In1−N2	91.2(5)	N1−In1−N2	174.9(7)
O1−In1−N3	179.0(6)	N1−In1−N3	94.1(6)
O2−In1−O3	167.0(5)	N2−In1−N3	87.9(5)
O2−In1−N1	87.7(6)	In1−O1−C3	119(1)
O2−In1−N2	87.9(7)	In1−O2−C12	125(1)
O2−In1−N3	83.5(6)	In1−O3−C21	126(1)

Synthesis and Structures of Ga and In (O_3N) Complexes. Under conditions that the four-coordinate [Ga(S_3N)] complexes was isolated, the five-coordinate complex, [Ga(O_3N)(DMF)] is obtained (Figure 10, Table 8). The addition of 1-methylimidazole gives the five-coordinate [Ga(O_3N)(1-Me-imid)] (Figure 11, Table 8). For indium, five-coordinate [In(O_3N)L compounds could not be isolated. Attempts to prepare the imidazole adduct resulted in the synthesis of a bis(1-Me-imid) adduct, [In(O_3N')(1-Me-imid)$_2$] (Figure 12, Table 9). [Ga(O_3N)(DMF)] and [Ga(O_3N)(1-Me-imid)] are isomorphous. The five non-hydrogen atoms of the DMF molecules occupy the position of five of the six non-hydrogen atoms of the 1-methylimidazole. The Ga(O_3N)L compounds have trigonal bipyramidal structures similar to those of the five-coordinate Ga and In complexes with the S_3N ligand. The Ga atoms are displaced from the plane of the three O atoms of the phenolate ligands toward the amine N. As a result, the O−Ga−N(amine) angles are greater than 90° and the O−Ga−L angles are less than 90°. The displacement is less in the stronger 1-Me-imid adduct. The Ga−N(amine) and Ga−N(imidazole) distances are 0.08 and 0.20 Å longer in the [Ga(O_3N)(1-Me-imid)] than in the [Ga(S_3N)(1-Me-imid)]. A series of square pyramidal Ga complexes with salen type ligands have been structural characterized, their basal Ga−O(Ph) distances (1.87−1.92 Å) are longer than the equatorial Ga−O distances (1.85(1) Å) in the Ga(O_3N)L complexes.[32] Still longer Ga−O distances are found in octahedral complexes of gallium with polydentate amine phenolate ligands.[33]

The structure of [In(O_3N')(1-Me-imid)$_2$] demonstrates the ability of the O_3N series of ligands to support an octahedral coordination in the case of the larger In^{3+} cation. The structure can be envisioned to have been formed by the addition of the second 1-Me-imid to the trigonal O_3 plane of a trigonal

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bipyramidal [In(O_3N)(1-Me-imid)]. The largest deviations for octahedral geometry come in the tetragonal GaO_3N plane. The trans phenolate oxygens make O−In−N angles of 83.5(6)° with the second imidazole and an O−In−O angle of 167.0(5)°. The In−O (2.07(2) Å) and In−N (2.28(4) Å) distances are comparable to the metrical parameters observed in other octahedral indium complexes with amine phenolate polydentate ligands.[33e,34,35]

To summarize, it can be seen that the novel tetradentate amine thiolate S_3N ligand and amine phenolate O_3N ligands can support a variety of different coordination numbers and geometries as a function of the size of the metal ion and the donor strength of added ligands. The tetrahedral [Ga(S_3N)] complex will increase its coordination number in the presence of a 1-methylimidazole but not for weaker ligands such as water and DMF. The larger indium cation gives five-coordinate complexes even with weaker donor ligands. The O_3N ligands favor five-coordination for Ga^{3+} and octahedral complexes for the In^{3+}. The synthetic studies suggest that aqueous solution of [Ga(S_3N)] will be four-coordinate while [In(S_3N)] will be five-coordinate with a bound H_2O molecule. In complexes with the O_3N ligand, both gallium and indium can be expected to bind H_2O molecules to become, respectively, five- and six-coordinate. In the series of complexes, the [Ga(S_3N] complex is unique in that it does not bind H_2O.

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Supporting Information Available: Tables of atomic coordinates, thermal parameters, and bond distances and angles (40 pages). Ordering information is given on any current masthead page.

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