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Preferred Bonding Motif for Indium Aminoethanethiolate Complexes: Structural Characterization of $(Me_2NCH_2CH_2S)_2InX/SR$ (X = Cl, I; R = 4-MeC_6H_4, 4-$MeOC_6H_4$)

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The metathesis reaction of $InCl_3$ with $Me_2NCH_2CH_2SNa$ or the redox reaction of indium metal with elemental iodine and the disulfide $(Me_2NCH_2CH_2S)_2$ yield the indium bis(thiolate) complexes $(Me_2NCH_2CH_2S)_2InX$ [X = Cl (**3**) and I (**4**)], respectively. Compounds **3** and **4** may be further reacted with the appropriate sodium thiolate salts to afford the heteroleptic tris(thiolate) complexes $(Me_2NCH_2CH_2S)_2InSR$ [R = 4-MeC_6H_4 (**5**), 4-$MeOC_6H_4$ (**6**), and Pr (**7**)]. Reaction of 2,6-$Me_2C_6H_3SNa$ with **4** affords $(Me_2NCH_2CH_2S)_2InS$(2,6-$Me_2C_6H_3$) (**8**), while no reaction is observed with **3**, suggesting a greater reactivity for **4**. All isolated compounds were characterized by elemental analysis, melting point, and Fourier transform IR and ^1H and $^{13}C\{^1H\}$ NMR spectroscopies. X-ray crystallographic analyses of **3**–**6** show a bicyclic arrangement and a distorted trigonal-bipyramidal geometry for In in all cases. The two sulfur and one halogen (**3** and **4**) or three sulfur (**5** and **6**) atoms occupy equatorial positions, while the nitrogen atoms of the chelating (dimethylamino)ethanethiolate ligands occupy the axial positions. The metric parameters of the $(Me_2NCH_2CH_2S)_2In$ framework were found to change minimally upon variation of the X/SR ligand, while the solubility of the corresponding compounds in organic solvents varied greatly. ^1H NMR studies in D_2O showed that **6** and **7** react slowly with an excess of the tripeptide L-glutathione and that the rate of reaction is affected by the pendant thiolate ligand –SR.

Introduction

In recent years, indium-111 has been found to be a very useful radionuclide for incorporation in radiopharmaceuticals for diagnostic imaging.[1] The isotope was first used in the labeling of white blood cells, which are then used to help diagnose inflammation and to determine the success of organ transplants. More recently, the focus has been on the preparation of bioconjugates, in which the metal is bound to a peptide or monoclonal antibody (MAb) via a tethered chelating ligand, usually *N*,*N*′,*N*′′,*N*′′′-diethylenetriaminepentaacetic acid. Despite the useful decay properties of the radioisotope, indium compounds are often unstable in vivo, and retention in the liver is common because of reactions with sulfur-containing proteins.[2,3] Further, indium complexes are often found to be unstable in the presence of intercellular blood proteins, such as the iron transport protein transferrin.[4] As a result, ligand design for indium radiopharmaceuticals is an important area of research, with the preparation of kinetically inert and metabolically stable complexes being crucial for the control of in vivo distribution.

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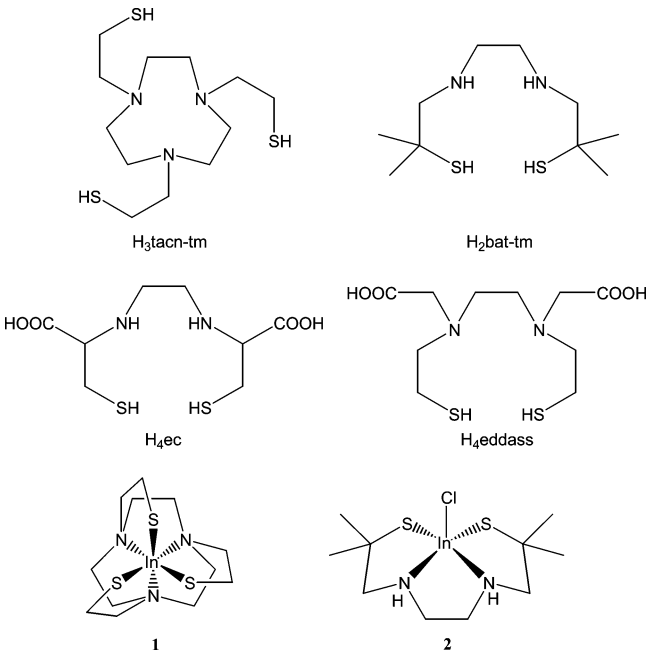
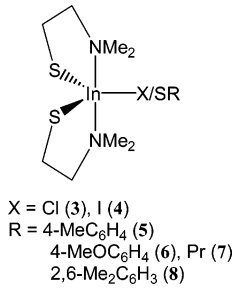
Chart 1



Several previous studies aimed at identifying kinetically stable indium complexes have focused on tethered aminoethanethiolate ligands, such as 1,4,7-tris(2-mercaptoethyl)-1,4,7-triazacyclononane (H_3tacn-tm) and tetramethylbis(aminoethanethiol) (H_2bat-tm), ethylenedi-L-cysteine (H_4ec), and *N*,*N*′-bis(2-mercaptoethyl)ethylenediamine-*N*,*N*′-diacetic acid (H_4eddass) (Chart 1). The thiolate sulfur atoms of these ligands bind to In^{3+} with high stability constants, while the amine nitrogen atoms form strong dative bonds and fill coordination sites at the metal.[3,5−9] Interestingly, the majority of this work focuses on potentiometric solution studies of protonation and metal complex stability constants, while few indium complexes have been isolated and definitively characterized. Structural studies are limited to the complexes (tacn-tm)In (**1**)[7] and (bat-tm)InX [X = Cl (**2**), NCS, $O_2CC_6H_5$].[9] The six-coordinate InS_3N_3 core of **1**, which features three tethered aminoethanethiolate groups in the ligand, exhibits a very distorted facial octahedral geometry at indium. Here, the nonlinear trans S−In−N bond angles (153−156°) are a result of the acute N−In−N (73.8−74.5°) and N−In−S (79.8−81.6°) bond angles. Compound **2** shows indium chelated by the two tethered aminoethanethiolate groups of the $(bat\text{-}tm)^{2-}$ ligand, the two sulfur and two nitrogen atoms of which provide the basal atoms for the distorted square-pyramidal bonding environment at indium.

Chart 2



The N−In−N [75.1(5)°] and N−In−S [79.8−82.1(3)°] bond angles are similar to those in **1**. Deviations from ideal geometry in these structures are a result of the restrictions imposed by the ligand framework, which result in less stable complexes.[5] Interestingly, complexes of the untethered aminoethanethiolate ligand have been studied in solution[8a] but not in the solid state, and no examples have been structurally characterized.

To study the preferred coordination geometries of indium with the untethered aminoethanethiolate ligand, we have prepared the bis[(dimethylamino)ethanethiolato]indium halide complexes $(Me_2NCH_2CH_2S)_2InX$ [X = Cl (**3**) and I (**4**); Chart 2]. Further, compounds **3** and **4** were used as intermediates in the preparation of the novel heteroleptic tris(thiolate) complexes $(Me_2NCH_2CH_2S)_2InSR$ [R = 4-MeC_6H_4 (**5**), 4-$MeOC_6H_4$ (**6**), Pr (**7**), and 2,6-$Me_2C_6H_3$ (**8**); Chart 2]. Synthetic details and spectroscopic, structural, solubility, and stability data are reported herein.

Results and Discussion

Syntheses. Metathesis or ligand-exchange reactions of $InCl_3$ and NaSR are an established synthetic route in preparing $(RS)_3In$.[10] We employed this approach in the reaction of 2 equiv of sodium 2-(dimethylamino)ethanethiolate with a refluxing methanol solution of indium(III) chloride. After 3 h, the resulting reaction mixture was filtered and slowly concentrated at 23 °C to yield **3** as a white powder (method A). Interestingly, the analogous reaction involving 3 equiv of the sodium thiolate ligand also resulted in the precipitation of the bis(thiolate) chloride complex **3** as colorless crystals. This suggests that the 2:1 bicyclic product is more kinetically favorable than the 3:1 complex and that five-coordinate, trigonal-bipyramidal geometries are favored (vide infra). Our inability to isolate the 3:1 complex via this reaction route is interesting given the previously reported preparation of the tris(thiolate) complex $(pmq)_3In$ (Hpmq = 2-phenyl-8-mercaptoquinoline), which exhibits a five-coordinate bonding environment at indium.[11,12] Further, the preparation of **3** in air suggests significant hydrolytic stability. This observation is in accordance with previous potentiometric studies of the aminoethanethiolate/In^{3+} system in

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aqueous solution, in which the presence of 2:1 complexes and the absence of 3:1 complexes were noted.[8a] The preparation of **3** under an inert atmosphere in toluene was adopted in an attempt to obtain higher yields and minimize the formation of hydrolysis products (method B). Here, ^{1}H NMR analysis of the reaction mixture shows that **3** is formed in near-quantitative yield. Solvent removal yielded crude **3**·4NaCl, which could be used without purification for further metathesis reactions.

The presence of a chloride ligand on indium in **3** suggested the potential for further reaction to afford heteroleptic tris(thiolate) species. This was achieved through reaction with a stoichiometric amount of the corresponding sodium aryl- and alkythiolate salts in toluene to give **5**−**7**. Product yields were determined to be near-quantitative by ^{1}H NMR analysis of the reaction mixtures. However, crystalline yields were moderate (30−49%).

Interestingly, ^{1}H NMR analysis of the reaction mixture of **3** with the bulky thiolate ligand NaS-2,6-$Me_2C_6H_3$ showed minimal formation (∼20%) of the desired tris(thiolate) product. Therefore, **4** was prepared in order to exploit the expected greater lability of the In−I versus In−Cl bond in **3**. Unlike the metathesis reaction utilized for the preparation of **3**, compound **4** was prepared as an analytically pure powder in moderate yield through the redox reaction of indium metal, diiodine, and (dimethylamino)ethane disulfide. A similar reaction was reported previously by Tuck et al. to prepare $(PhS)_2InI$;[13] however, the synthetic route was not found to be general.[14] The analogous stoichiometric reaction of **4** and 2,6-$Me_2C_6H_3SNa$ afforded the corresponding heteroleptic tris(thiolate) **8**. Further, ^{1}H NMR analysis of the reaction mixture showed the reaction to proceed near quantitatively. Compounds **5**−**7** may also be prepared from **4**, thus suggesting that the metathesis reaction of **4** and a sodium thiolate salt is a general reaction route to the formation of $(Me_2NCH_2CH_2S)_2InSR$ (R = aryl, alkyl) species.

It should be noted that these are, to the best of our knowledge, the first heteroleptic indium tris(thiolate) compounds reported, and their syntheses represent a new reaction route to these types of compounds. Further, attempts to prepare **5** though a one-pot 2:2:1 redox reaction of elemental indium with $(Me_2NCH_2CH_2S)_2$ and $(4\text{-}MeC_6H_4S)_2$ were unsuccessful. The addition of catalytic amounts of diiodine had no effect on the result. This is interesting considering the formation of **4** and $(4\text{-}MeC_6H_4S)_3In$[15] via similar redox reactions.

Solution NMR Studies. Compounds **3**−**8** were characterized by both ^{1}H and ^{13}C{^{1}H} NMR spectroscopy using methanol-d_4 as the solvent. The ^{1}H NMR spectra of all tris(thiolate) compounds (**5**−**7**) show slight changes for the $Me_2NCH_2CH_2S$ resonances in comparison to **3**. Methylene peaks were found to shift upfield by δ 0.04−0.16 in **5**−**7**, while shifts in the methyl resonances were negligible. When the ^{1}H NMR spectrum of **4** is compared to that of **8**, the methylene peaks shifted upfield by δ 0.18 and 0.11, while the methyl peak shifted by δ 0.16.

Although the changes in the (dimethylamino)ethanethiolate ligand ^{1}H NMR resonances were useful in determining product formation, comparisons of the spectra of the sodium thiolate reactants and corresponding tris(thiolate) products (**5**−**8**) proved to be more unambiguous. Aryl peaks in **5**, **6**, and **8** were found to shift downfield by δ 0.18−0.32, while methyl peaks shifted downfield by δ 0.06−0.24. For the propanethiolate analogue (**7**), downfield shifts of δ 0.30 and 0.09 (methylene) and δ 0.07 (methyl) were observed. This downfield trend is as expected upon incorporation of the anion ligand into a neutral complex.

X-ray Structural Analysis. Crystals suitable for X-ray crystallographic analysis were isolated from the reaction mixtures by slow evaporation (**3** and **4**) or by solvent diffusion of a hexane overlayer (**5** and **6**). Crystallographic data are given in Table 1. Selected bond distances and angles are given in Table 2.

The structures of **3**−**6** (Figures 1−4) all show a similar bicyclic $(Me_2NCH_2CH_2S)_2In$ arrangement, with indium in a five-coordinate, distorted trigonal-bipyramidal geometry. The two axial positions are occupied by the nitrogen atoms of the chelating (dimethylamino)ethanethiolate ligands, while the sulfur atoms occupy two equatorial positions. The third equatorial position is occupied by a halogen atom [i.e., Cl (**3**) or I (**4**)] or a sulfur atom of a monodentate thiolate ligand [i.e., 4-MeC_6H_4S (**5**) or 4-$MeOC_6H_4S$ (**6**)]. Bond length and angle parameters for the bicyclic $(Me_2NCH_2CH_2S)_2In$ fragment vary only slightly and are most significantly different for the chloride analogue (**3**).

The differences in In1−Cl1, In1−I1, and In1−S3 bond distances are mainly a result of the varying covalent radii of chlorine (0.99 Å), iodine (1.33 Å), and sulfur (1.03 Å), respectively.[16] However, observation of the bond distances of the dative axial In−N bonds for **3**−**6** shows a smaller average value for **3**, which is accompanied by slightly lower calculated bond valency for the In1−Cl1 bond in **3** (0.67) versus the In1−I1 bond in **4** (0.72) and In1−S3 bonds in **5** and **6** (0.70 and 0.72, respectively).[17] This may be a result of the higher polarity of the In−Cl bond in **3**, which produces a greater positive charge on the indium center. It is also worth noting that in **5** and **6** the In1−S3 bond distances involving the monodentate thiolate ligands (SR) are significantly longer than the In1−S1 and In1−S2 bond distances involving the chelating aminothiolate ligands.

Distortions from the ideal trigonal-bipyramidal geometry are partially a result of the small (<90°) bite angle of the aminoethanethiolate ligands [S−In−N 81.63(8)−83.3(2)°], resulting in N_{ax}−In−N_{ax} bond angles of 166.5(2)−173.7-

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Table 1. Crystallographic Data for **3**−**6**

	3	**4**	**5**	**6**
formula	$C_8H_{20}Cl_1In_1N_2S_2$	$C_8H_{20}I_1In_1N_2S_2$	$C_{15}H_{27}In_1N_2S_3$	$C_{15}H_{27}In_1N_2OS_3$
fw	358.65	450.10	446.39	462.39
cryst syst	monoclinic	monoclinic	triclinic	orthorhombic
space group	$P2_1/n$ (No. 14)	$P2_1/c$ (No. 14)	$P\bar{1}$ (No. 2)	$Pc2_1n$ (No. 33)
a (Å)	10.5150(2)	10.8640(3)	7.4499(3)	7.1598(1)
b (Å)	9.6190(2)	9.6860(3)	10.2419(5)	8.7840(1)
c (Å)	13.6770(3)	17.2470(3)	13.1509(6)	31.3428(3)
α (deg)	90	90	92.147(3)	90
β (deg)	94.1160(8)	126.348(1)	104.192(3)	90
γ (deg)	90	90	95.171(3)	90
V (Å^3)	1379.78(5)	1461.76(7)	967.00(8)	1971.30(4)
Z	4	4	2	8
F(000)	720	864	456	1888
ρ_{calcd} (Mg/m^3)	1.727	2.045	1.533	1.558
μ (mm^{-1})	2.179	3.986	1.542	1.519
T (K)	173(2)	173(2)	173(2)	173(2)
λ (Å)	0.710 73	0.710 73	0.710 73	0.710 73
R1[a]	0.0390	0.0304	0.0517	0.0359
wR2[b]	0.0966	0.0703	0.1230	0.0885

[a] $R1 = [\sum||F_o| - |F_c||]/\sum|F_o|$ for $F_o^2 > 2\sigma(F_o^2)$. [b] $wR2 = \{[\sum w(F_o^2 - F_c^2)^2]/[\sum w(F_o^4)]\}^{1/2}$ for all data.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **3**−**6**[a]

	3	**4**	**5**	**6**
In1−N1	2.343(7)	2.390(3)	2.400(4)	2.380(3)
In1−N2	2.364(8)	2.384(3)	2.377(4)	2.409(3)
In1−S1	2.437(2)	2.4436(8)	2.446(1)	2.444(1)
In1−S2	2.440(2)	2.4412(8)	2.440(1)	2.4449(9)
In1−S3			2.476(1)	2.471(1)
In1−Cl1	2.424(2)			
In1−I1		2.7602(3)		
N1−In1−N2	173.7(3)	169.56(9)	166.5(2)	168.8(1)
S1−In1−S2	128.68(9)	130.84(3)	130.28(5)	129.89(4)
S1−In1−X	117.6(1)	111.54(2)	120.21(4)	105.90(4)
S2−In1−X	113.59(9)	117.50(2)	109.46(5)	124.20(4)
S1−In1−N1	83.3(2)	82.23(7)	82.3(1)	82.89(9)
S2−In1−N1	96.0(2)	91.09(7)	90.9(1)	92.48(9)
X−In1−N1	94.8(2)	93.95(6)	96.2(1)	95.68(8)
S1−In1−N2	92.3(2)	94.86(7)	92.9(1)	93.52(8)
S2−In1−N2	83.2(2)	83.21(7)	82.6(1)	81.63(8)
X−In1−N2	91.2(2)	96.44(7)	97.1(1)	95.53(8)

[a] X = Cl1 (**3**), I1 (**4**), and S3 (**5** and **6**).

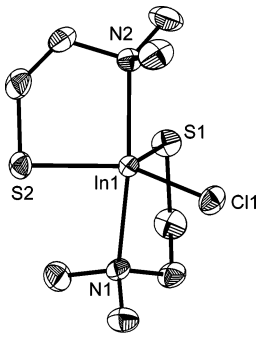

Figure 1. X-ray structure of **3** (30% probability ellipsoids). Hydrogen atoms are removed for clarity.

(3)°. The majority of equatorial bond angles deviate significantly from the idealized 120° [111.54(2)−130.84(3)°], with the largest in each compound (S1−In−S2) involving the sulfur atoms of the aminoethanethiolate ligands. Despite this, the sum of the equatorial bond angles is approximately 360° for all compounds. InN_2S_2Cl and InN_2S_3 bonding environments similar to those reported herein have been observed for the previously reported compounds $(imq)_2InCl$ (Himq = 2-isopropyl-8-mercaptoquinoline) and $(pmq)_3In$ (Hpmq = 2-phenyl-8-mercaptoquinoline), respectively.[11,18] However, distortions from the ideal trigonal-bipyramidal geometry are much greater than those in **3**−**6**, presumably as a result of the rigid ligand backbones.

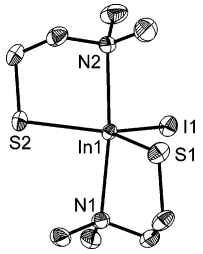

Figure 2. X-ray structure of **4** (30% probability ellipsoids). Hydrogen atoms are removed for clarity.

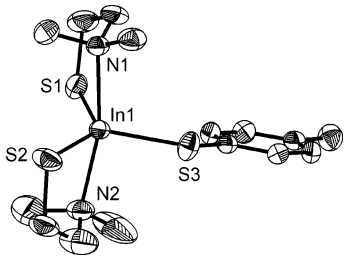

Figure 3. X-ray structure of **5** (30% probability ellipsoids). Hydrogen atoms are removed for clarity.

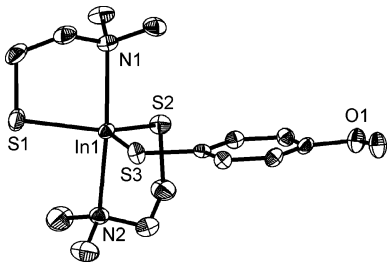

Figure 4. X-ray structure of **6** (30% probability ellipsoids). Hydrogen atoms are removed for clarity.

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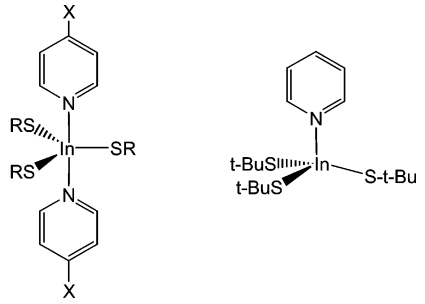
Chart 3



9, R = Ph, X = H
10, R = Et, X = NMe_2

11

To determine whether the trigonal-bipyramidal geometry is the preferred bonding environment for five-coordinate InS_3N_2 complexes, it is useful to examine those in which the amine and thiolate groups are untethered. Structurally characterized examples include the tris(thiolato)indium−pyridine adducts $(PhS)_3In(py)_2$ (**9**) and $(i\text{-}PrS)_3In(dmap)_2$ (**10**) [py = pyridine, dmap = 4-(dimethylamino)pyridine; Chart 3], which are prepared from the reaction of indium tris(thiolate) with excess amine.[19] Both five-coordinate systems show a distorted trigonal-bipyramidal bonding environment for indium, with the sulfur atoms occupying the equatorial positions and the nitrogen atoms occupying the axial positions. Further, the 1:1 adduct $(t\text{-}BuS)_3In(py)$ (**11**; Chart 3) shows a four-coordinate, distorted trigonal-pyramidal geometry at indium, with the pyridine nitrogen in the apical position. Indium is 0.43 Å out of the plane generated by the three basal sulfur atoms [$\sum$(S−In−S) ∼351°]. Interestingly, no analogous tris(amine) adducts have been reported in the literature. The structures of compounds **9**−**11**, as well as **3**−**6**, may be rationalized in terms of a simple valence bond description, in which the amine nitrogen atoms form dative bonds with the empty p orbital of the covalently bound indium tris(thiolate) center.

Solubility Data. Qualitative observations demonstrate that substituting the chlorine atom in **3** with various thiolate ligands results in significant changes in solubility. When 50 mg of product was added to 1 mL of solvent, **3** and **5**−**7** were found to be completely soluble in methanol. However, **5**−**7** were also found to be soluble in toluene, while compound **7** was the only compound completely soluble in hexanes. This demonstrates that the solubility of the $(Me_2NCH_2CH_2S)_2InSR$ complex in organic media may be tuned with the appropriate choice of alkyl- or arylthiolate ligand. None of these neutral compounds were found to be soluble in water, however, and preparation of ionic complexes may be required for solubility in aqueous media.

Stability Studies. Although compounds **5**−**8** were prepared with the exclusion of moisture, all compounds are stable in air for a period of days. Further, ^{1}H NMR analysis shows that no hydrolysis products are formed on attempting to dissolve each compound in D_2O.

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The stability of indium compounds in the presence of sulfur-containing proteins in vivo is an important factor in determining the potential utility of indium compounds as medicinal agents. Therefore, we have studied the reactivity of our novel indium tris(thiolate) compounds with the biomolecule L-glutathione, which contains potentially reactive thiol functionality. In these experiments, compound **6** or **7** was added to 4 equiv of L-glutathione in D_2O. The degree of decomposition was determined by monitoring the formation of 4-MeC_6H_4SH (**6**) or PrSH (**7**) by ^{1}H NMR at regular time intervals. Both compounds were found to be quite stable over a 24-h period under these conditions, with approximately 4% of **6** and 13% of **7** undergoing reaction. The differing degrees of reactivity, however, demonstrate the possible influence of a pendant aryl- versus alkylthiolate group on the in vivo stability of similar InS_3N_2 complexes involving tethered aminoethanethiolate ligands.

Conclusions

The bicyclic indium bis(thiolate) compounds **3** and **4** were prepared from metathesis and redox reaction routes, respectively. Further reaction with the appropriate sodium thiolate salts yields the heteroleptic tris(thiolate) complexes **5**−**8**. Although the reaction route is general in these cases, the use of the more reactive indium iodide compound (**4**) is required for the preparation of **8**, which involves a sterically bulky thiolate ligand. Compounds **3**−**8** were spectroscopically characterized, while X-ray crystallographic data were also obtained for **3**−**6**. All compounds were found to have distorted trigonal-bipyramidal geometries at indium, with similar bond lengths and bond angles in the bicyclic framework. Through the addition of a third thiolate ligand, it was shown that the solubility of the resulting product in organic solvents could be varied, while none of the compounds were found to be soluble in water. ^{1}H NMR studies of the stability of **6** and **7** against excess L-glutathione in D_2O show both compounds to be quite stable under these conditions. This work suggests that tethered aminoethanethiolate ligands that yield trigonal-bipyramidal InS_3N_2 bonding motifs are desirable candidates for the preparation of indium complexes with high in vivo stability.

Experimental Section

General Considerations. Solution ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at 23 °C on a JEOL GMX 270-MHz spectrometer (270.2 and 67.9 MHz, respectively) or a Varian MERCURYplus 200-MHz spectrometer (200.0 and 50.3 MHz, respectively), and chemical shifts are calibrated to the residual solvent signal. Fourier transform (FT) IR spectra were recorded as Nujol mulls on a Mattson Genesis II FT-IR spectrometer in the range of 4000−400 cm^{-1}. Melting points were measured on an Electrothermal MEL-TEMP melting point apparatus and are uncorrected. Elemental analyses were performed by Chemisar Laboratories Inc., Guelph, Ontario, Canada.

Synthetic Procedures. 2-(Dimethylamino)ethanethiol hydrochloride (95%), indium(III) chloride, sodium metal, 4-methylbenzenethiol (98%), 4-methoxybenzenethiol (97%), 1-propanethiol (99%), 2,6-dimethylbenzenethiol (95%), indium powder (99.99%), and L-glutathione (98%) were used as received from Aldrich.

Hydrogen peroxide (30% solution in water) and sodium hydroxide (97%) were used as received from ACP. Diiodine (99.8%) was used as received from B and A. Reactions were carried out under an atmosphere of N_2 gas, using standard Schlenk techniques unless otherwise specified. Solvents were dried using an MBraun SPS column solvent purification system.

The sodium salts NaSR (R = 4-MeC_6H_4, 4-$MeOC_6H_4$, Pr, and 2,6-$Me_2C_6H_3$) were prepared by the addition of the appropriate HSR thiol ligand (0.50 g) to a stoichiometric amount of sodium metal in methanol (10 mL). After the solvent was refluxed for 2 h, it was removed in vacuo to yield the sodium thiolates as white powders. These were used without further purification. ^{1}H NMR data (methanol-d_4): R = 4-MeC_6H_4, δ 2.15 (s, 3H, SC_6H_4*Me*), 6.73 (d, $^3J_{H-H}$ = 8 Hz, 2H, SC_6*H*$_4$Me), 7.23 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_4$Me); R = 4-$MeOC_6H_4$, δ 3.67 (s, 3H, SC_6H_4O*Me*), 6.53 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_4$OMe), 7.24 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_4$-OMe); R = Pr, δ 0.93 (t, $^3J_{H-H}$ = 7 Hz, 3H, SCH_2CH_2C*H*$_3$), 1.54 (m, $^3J_{H-H}$ = 8 Hz, 2H, SCH_2C*H*$_2CH_3$), 2.43 (t, $^3J_{H-H}$ = 7 Hz, 2H, SC*H*$_2CH_2CH_3$); R = 2,6-$Me_2C_6H_3$, δ 2.40 (s, 6H, SC_6H_3*Me*$_2$), 6.58 (t, $^3J_{H-H}$ = 7 Hz, 1H, SC_6*H*$_3Me_2$), 6.84 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_3Me_2$).

$(Me_2NCH_2CH_2S)_2$ was prepared in air using the following procedure. NaOH (16.94 g, 0.4237 mol) was added to a solution of 2-(dimethylamino)ethanethiol hydrochloride (10.00 g, 0.07059 mol) in water (40 mL). After the addition of H_2O_2 (30% in water; 5.34 g, 0.0470 mol), the solution was stirred overnight. The product was extracted from the solution three times with diethyl ether (3 × 40 mL). The ether was then removed by rotary evaporation to give a pale-yellow oil. The product was distilled under vacuum to yield $(Me_2NCH_2CH_2S)_2$ as a colorless oil (5.02 g, 0.0241 mol, 68%).

Preparation of $(Me_2NCH_2CH_2S)_2InCl$ (3). Method A. In air, sodium hydroxide (0.22 g, 5.6 mmol) was added to a solution of 2-(dimethylamino)ethanethiol hydrochloride (0.40 g, 2.8 mmol) in methanol (10 mL) to form a cloudy white solution. After 1 h, the mixture was added dropwise to a refluxing slurry of $InCl_3$ (0.21 g, 0.94 mmol) in methanol (10 mL). After 3 h, the reaction mixture was filtered to remove a white powder and the solvent allowed to evaporate slowly at 23 °C. After 2 days, colorless crystals of **3** were collected (0.19 g, 0.53 mmol, 57%). FT-IR (cm^{-1}): 538w, 665m, 767s, 892m, 950s, 995s, 1031s, 1103w, 1124m, 1168m, 1224m, 1247m, 1299s. ^{1}H NMR (methanol-d_4): δ 2.33 (s, 12H, SC_2H_4N*Me*$_2$), 2.65 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$) 2.81 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$). ^{13}C{^{1}H} NMR (methanol-d_4): δ 22.59 (SCH_2CH_2N*Me*$_2$), 43.88 ($SCH_2CH_2NMe_2$), 60.17 ($SCH_2CH_2NMe_2$). Mp: 241 °C. Anal. Calcd for [$(Me_2NCH_2CH_2S)_2InCl$]: C, 26.79; H, 5.63; N, 7.81. Found: C, 26.81; H, 5.64; N, 7.67.

Method B. Under an atmosphere of N_2 gas, 2-(dimethylamino)-ethanethiol hydrochloride (0.50 g, 3.5 mmol) and sodium metal (0.16 g, 7.0 mmol) were combined in methanol (10 mL). After the solution was refluxed for 1 h, it was added dropwise to a refluxing solution of $InCl_3$ (0.39 g, 1.8 mmol) in methanol (10 mL). After 3 h, the solvent was removed in vacuo to yield a white powder (0.51 g). This material (**3**·4NaCl) was used without further purification. ^{1}H NMR (methanol-d_4): δ 2.31 (s, 12H, SC_2H_4N*Me*$_2$), 2.63 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$) 2.81 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$).

Preparation of $(Me_2NCH_2CH_2S)_2InI$ (4). $(Me_2NCH_2CH_2S)_2$ (1.00 g, 4.81 mmol), In powder (0.55 g, 4.8 mmol), and I_2 (0.61 g, 2.4 mmol) were combined in a vessel with toluene (10 mL) to produce an orange solution. The solution was then refluxed for 7 h and filtered. The solvent was then removed in vacuo to obtain **4** as a pale-yellow powder (1.20 g, 2.67 mmol, 56%). Alternatively, colorless crystals of **4** were obtained by allowing the reaction mixture to sit 1 h at 23 °C. ^{1}H NMR (methanol-d_4): δ 2.36 (s, 12H, SCH_2CH_2N*Me*$_2$), 2.64 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$), 2.88 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$). ^{13}C{^{1}H} NMR (methanol-d_4): δ 22.99 (SCH_2CH_2N*Me*$_2$), 44.11 ($SCH_2CH_2NMe_2$), 59.27 ($SCH_2CH_2NMe_2$). FT-IR (cm^{-1}): 534vs, 798vs, 866w, 1018s, 1091s, 1261m. Mp: 201 °C. Anal. Calcd: C, 21.35; H, 4.47; N, 5.89. Found: C, 21.77; H, 4.83; N, 5.89.

Preparation of $(Me_2NCH_2CH_2S)_2In(SC_6H_4$-4-Me) (5). A solution of **3** (0.41 g, 0.68 mmol) and 4-MeC_6H_4SNa (0.10 g, 0.68 mmol) in toluene (15 mL) was brought to reflux. After 2 h, the reaction was cooled to 23 °C, a white precipitate was removed by filtration, and the resulting solution was concentrated in vacuo to 1.5 mL. This concentrated solution was then layered with hexane (1.5 mL) and kept at −15 °C. After 2 days, the reaction mixture was filtered to yield colorless crystals of **5** (0.091 g, 0.20 mmol, 30%). ^{1}H NMR (methanol-d_4): δ 2.24 (s, 3H, SC_6H_4*Me*), 2.30 (s, 12H, SCH_2CH_2N*Me*$_2$), 2.48 (t, $^3J_{H-H}$ = 5 Hz, 4H, SC_2*H*$_4$NMe$_2$), 2.73 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$), 6.95 (d, $^3J_{H-H}$ = 8 Hz, 2H, SC_6*H*$_4$Me), 7.48 (d, $^3J_{H-H}$ = 8 Hz, 2H, SC_6*H*$_4$Me). ^{13}C{^{1}H} NMR (methanol-d_4): δ 19.53 (SC_6H_4*Me*), 22.79 (SCH_2CH_2N*Me*$_2$), 44.04 ($SCH_2CH_2NMe_2$), 60.60 ($SCH_2CH_2NMe_2$), 128.76 (SC_6H_4-Me), 133.19 (SC_6H_4Me), 133.67 (SC_6H_4Me), 134.22 (SC_6H_4Me). FT-IR (cm^{-1}): 625w, 666w, 816s, 889m, 951w, 1032s, 1084s, 1163m, 1261m, 1298s. Mp: 142 °C. Anal. Calcd: C, 40.36; H, 6.10; N, 6.28. Found: C, 40.13; H, 6.10; N, 6.66.

Preparation of $(Me_2NCH_2CH_2S)_2In(SC_6H_4$-4-OMe) (6). A solution of **3** (0.40 g, 0.68 mmol) and 4-$MeOC_6H_4SNa$ (0.11 g, 0.68 mmol) in toluene (15 mL) was brought to reflux. After 2 h, the reaction was cooled to 23 °C, a white precipitate was removed by filtration, and the resulting solution was concentrated in vacuo to 1.5 mL. This concentrated solution was then layered with hexane (1.5 mL) and stored at −15°C for 2 days. The reaction mixture was filtered to yield colorless crystals of **6** (0.16 g, 0.34 mmol, 49%). ^{1}H NMR (methanol-d_4): δ 2.30 (s, 12H, SC_2H_4N*Me*$_2$), 2.47 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$), 2.72 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$), 3.73 (s, 3H, SC_6H_4O*Me*), 6.74 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_4$OMe), 7.50 (d, $^3J_{H-H}$ = 7 Hz, 2H, SC_6*H*$_4$OMe). ^{13}C-{^{1}H} NMR (methanol-d_4): δ 22.76 (SCH_2CH_2N*Me*$_2$), 44.02 (SCH_2-CH_2NMe_2), 54.45 (SC_6H_4O*Me*), 60.32 ($SCH_2CH_2NMe_2$), 113.76 ($SC_6H_4OCH_3$), 128.01 ($SC_6H_4OCH_3$), 134.42 ($SC_6H_4OCH_3$), 157.45 ($SC_6H_4OCH_3$). FT-IR (cm^{-1}): 623m, 665w, 831s, 890w, 950m, 997w, 1034s, 1090m, 1180m, 1236s, 1275s, 1593w. Mp: 108 °C. Anal. Calcd: C, 38.96; H, 5.89; N, 6.06. Found: C, 39.29; H, 5.91; N, 6.26.

Preparation of $(Me_2NCH_2CH_2S)_2In(SPr)$ (7). A solution of **3** (0.41 g, 0.68 mmol) and PrSNa (0.067 g, 0.68 mmol) in toluene (10 mL) was brought to reflux. After 2 h, the reaction mixture was cooled to 23 °C, a white precipitate was removed by filtration, and the resulting solution was concentrated in vacuo to 1 mL. The solution was then layered with pentane (2 mL) and stored at −15 °C for 1 day. The reaction mixture was filtered to yield colorless crystals of **7** (0.11 g, 0.29 mmol, 42%). ^{1}H NMR (methanol-d_4): δ 1.00 (t, $^3J_{H-H}$ = 7 Hz, 3H, SCH_2CH_2C*H*$_3$), 1.65 (m, $^3J_{H-H}$ = 7 Hz, 2H, SCH_2C*H*$_2CH_3$), 2.34 (s, 12H, SCH_2CH_2N*Me*$_2$), 2.59 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$), 2.73 (t, $^3J_{H-H}$ = 7 Hz, 2H, SC*H*$_2$-CH_2CH_3), 2.77 (t, $^3J_{H-H}$ = 6 Hz, 4H, SC_2*H*$_4$NMe$_2$). ^{13}C{^{1}H} NMR (methanol-d_4): δ 12.55 ($SCH_2CH_2CH_3$), 22.75 (SC_2H_4N*Me*$_2$), 28.06 ($SC_2H_4CH_3$), 29.29 ($SC_2H_4CH_3$), 43.86 ($SCH_2CH_2NMe_2$), 60.53 ($SCH_2CH_2NMe_2$). FT-IR (cm^{-1}): 596m, 671w, 764m, 800s, 890m, 953m, 1034s, 1099m, 1259s, 1296s. Mp: 67 °C. Anal. Calcd: C, 33.17; H, 6.83; N, 7.03. Found: C, 33.53; H, 7.04; N, 7.25.

Preparation of $(Me_2NCH_2CH_2S)_2In(S$-2,6-$Me_2C_6H_3)$ (8). A solution of **4** (0.26 g, 0.58 mmol) and 2,6-$Me_2C_6H_3SNa$ (0.093 g, 0.58 mmol) in toluene (10 mL) was brought to reflux. After 2 h,

the reaction mixture was cooled to 23 °C, a pale-yellow precipitate was removed by filtration, and the resulting solution was concentrated in vacuo to 1.5 mL. The solution was then layered with hexane (3 mL) and stored at −15 °C. After 1 day, the reaction mixture was filtered to yield pale-yellow crystals of **8** (0.13 g, 0.29 mmol, 49%). ^{1}H NMR (methanol-d_4): δ 2.15 (s, 12H, $SCH_2CH_2NMe_2$), 2.46 (t, $^3J_{H-H} = 6$ Hz, 4H, $SC_2H_4NMe_2$), 2.64 (s, 6H, S-2,6-$Me_2C_6H_3$), 2.77 (t, $^3J_{H-H} = 6$ Hz, 4H, $SC_2H_4NMe_2$), 6.90 (t, $^3J_{H-H} = 7$ Hz, 1H, S-2,6-$Me_2C_6H_3$), 7.02 (d, $^3J_{H-H} = 7$ Hz, 2H, S-2,6-$Me_2C_6H_3$). ^{13}C{^{1}H} NMR (methanol-d_4): δ 22.88 ($SCH_2CH_2NMe_2$), 23.33 (S-2,6-$Me_2C_6H_3$), 43.84 ($SCH_2CH_2NMe_2$), 60.43 ($SCH_2CH_2NMe_2$), 124.70 (S-2,6-$Me_2C_6H_3$), 127.29 (S-2,6-$Me_2C_6H_3$), 136.35 (S-2,6-$Me_2C_6H_3$), 142.04 (S-2,6-$Me_2C_6H_3$). FT-IR (cm^{-1}): 584m, 764m, 802s, 891w, 939w, 1030s, 1093m, 1261m, 1296w. Mp: 63 °C. Anal. Calcd: C, 41.73; H, 6.36; N, 6.11. Found: C, 42.09; H, 6.06; N, 5.86.

X-ray Structural Analysis. Crystals of **3**−**6** were isolated from the reaction mixtures as indicated above. Single crystals of each compound were coated with Paratone-N oil, mounted using a CryoLoop (Hampton Research), and frozen in the cold stream of the goniometer. Data were measured on a Nonius Kappa CCD 4-Circle Kappa FR540C diffractometer using monochromated Mo Kα radiation ($\lambda = 0.710\ 73$ Å) at −90 and −100 °C, respectively. Data were collected using φ and/or ω scans.[20] Data reduction was performed with *HKL DENZO* and *SCALEPACK* software, which corrects for beam inhomogeneity, possible crystal decay, and Lorentz and polarization effects. A multiscan absorption correction was applied (*SCALEPACK*).[21] Transmission coefficients were calculated using *SHELXL97-2*.[22] The structures were solved by direct methods (*SIR-97* for **3** and **4**; *SHELXS-97* for **5** and **6**)[22] and refined by full-matrix least squares on F^2 (*SHELXL97-2*).[23] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at geometrically idealized positions (C−H bond distances 0.95 and 0.99 Å) and were not refined. The isotropic thermal parameters of the hydrogen atoms were fixed at 1.2 times that of the preceding carbon atom.

The crystal data for **5** showed signs of twinning: (a) For all of the "most disagreeable" reflections, F_o was much greater than F_c. (b) K = Mean[F_o^2]/Mean[F_c^2] is systematically high for the reflections with low intensity. (c) There was a high value for wR2 (0.2138) before twin refinement. Using the program *ROTAX* (program in *WinGX*),[24] the structure was tested for possible twin laws. It was determined that twinning occurred around the [0 1 0] reciprocal lattice direction. The program *WinGX* was used to prepare an HKLF5 reflection file for further refinement in *SHELXL-97*.[23] The refinement of the structure was successful, indicating the correct twin assignment.

The structure for **6** was solved in a noncentrosymmetric space group $Pc2_1n$. Attempts to solve the structure in the centrosymmetric space group *Pnma* led to no solution. The refined absolute structure parameter [0.43(3)] was neither unity nor nil and was used in the scale parameter in the racemic twin refinement.

Stability Studies. Compound **6** or **7** (0.01 g) and 4 mol equiv of L-glutathione were added to an NMR tube with D_2O (1 mL), and the mixture was shaken. A ^{1}H NMR spectrum was obtained after 15 min and at regular intervals for 24 h. Percent decomposition was monitored by comparing integration values of the reprotonated HSR thiol ligand resonances [for **6**, δ 6.78 (d, 2H, HSC_6H_4OMe), 7.28 (d, 2H, HSC_6H_4OMe); for **7**, δ 0.84 (t, 3H, $HSCH_2CH_2CH_3$)] against l-glutathione [δ 4.46 (t, 1H)].

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Supporting Information Available: X-ray crystallographic data for **3**−**6** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for all structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, under CCDC 611816 (**3**), 611817 (**4**), 611818 (**5**), and 611819 (**6**). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44-1223-336033; e-mail deposit@ccdc.cam.ac.uk; web site http://www.ccdc.cam.ac.uk).

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