

# Tripodal Iminophenolate Ligand Complexes of Gallium(III), Indium(III), and Thallium(III)

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The polydentate tripodal Schiff base ligand **H<sub>3</sub>L** has been prepared by treating a methanolic solution of tris(aminoethyl)-amine and 5-bromosalicylaldehyde. This ligand, and its complexes with group-13 metal ions (Ga<sup>III</sup>, In<sup>III</sup>, and Tl<sup>III</sup>) have been characterized by elemental analysis, NMR spectroscopy, FAB<sup>+</sup>-MS, and X-ray diffraction analysis. The ligand, not preorganized in the solid state, acts as a hexadentate N<sub>3</sub>O<sub>3</sub> ligand in all cases to form octahedral structures, the

apical nitrogen not being involved in the chelation even for the [Tl(L)] complex. NMR studies reveal that the intact and rigid structures of the complexes are maintained in solution. For the [Tl(L)] complex, long-range thallium isotope effect on the chemical shift ( $\delta_{\text{H}}$  and  $\delta_{\text{C}}$ ) and on the coupling constants ( $J_{\text{Tl-H}}$  and  $J_{\text{Tl-C}}$ ) has been observed, confirming a strong and stable bond between Tl<sup>III</sup> and **H<sub>3</sub>L**.

## Introduction

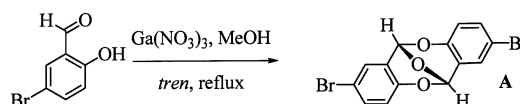
Single photon emission computed tomography (SPECT) imaging with <sup>99m</sup>Tc radionuclide is the most widely used method for routine diagnostic in nuclear medicine. If technetium-99m holds the foremost rank, this is due to its favorable nuclear characteristics (half-life 6.02 h,  $\gamma$  140 keV), availability, and low cost. But when the pharmacokinetics of the radiopharmaceuticals are not well matched with the physical half-life of <sup>99m</sup>Tc, the preferred radionuclides for imaging are <sup>111</sup>In (half-life 67.4 h) or <sup>67</sup>Ga (half-life 78.1 h). Despite the great potential of the group-13 metal radionuclides in diagnostics, there are still few ligands devoted to the complexation of such radioactive ions. The most popular one, especially for In<sup>III</sup> is diethylenetriaminetetraacetic acid (DTPA)<sup>[1]</sup> and its derivatives, in which one carboxylate group is often engaged to link the chelate moiety and the receptor-binding motif. However, the decreased denticity of such DTPA derivatives lower the stability of the formed complexes.<sup>[2]</sup> Thus, studying other chelation systems for the group-13 metal ions constitutes an important strategy for enhanced labelling efficiency of molecules of biological interest like peptides and monoclonal antibodies. Our laboratory is involved in the search and the synthesis of new radiopharmaceuticals for diagnostic or therapeutic applications. This led us to investigate the coordination chemistry of Ga, In, and to a lesser extent Tl (which have fewer biomedical applications). It might be worthwhile considering that, like [DTPA–In], numerous indium- or gallium-based radiopharmaceuticals are not fully chemically characterized. It is, however, of prime interest to determine the actual structure that is essential for obtaining a satisfactory com-

prehension of the properties of the complexes. Since group-13 (M<sup>III</sup>) metal ions are usually hexacoordinated, we have investigated the chelating pattern of the tripodal imine ligand **H<sub>3</sub>L**, derived from triethylenetriamine (*tren*) and 5-bromosalicylaldehyde. Complexes of lanthanides and imine ligands derived from *tren* and salicylaldehyde<sup>[3,4]</sup> or aromatic ketones have already been described by Orvig et al.<sup>[5,6]</sup> These complexes were very unstable to moisture, and this property was attributed to the imine function, presumably hydrolyzed in water with the assistance of the acidic Ln<sup>III</sup> ion. This observation led the author to study the complexation of lanthanides<sup>[7]</sup> and some group-13 metal ions (Al, Ga, and In)<sup>[8]</sup> with the saturated **H<sub>3</sub>L**, where the imine double –N=CH– bond has been reduced to the much more stable amine –NH–CH<sub>2</sub>– bond. The capability of the imine **H<sub>3</sub>L** ligand to chelate Ga, In, or Tl has not been previously reported. This situation could be due to the reluctance of chemists to work with the so-called acid-sensitive imine-derived ligands. We report here the synthesis and the spectroscopic and structural characterizations of the whole post-transition group-13 metal complexes with **H<sub>3</sub>L**.

## Results and Discussion

### Preparation

The one-pot complexation of M<sup>III</sup> ions is not an effective method. Indeed, mixing a methanolic solution of *tren* and 5-bromosalicylaldehyde followed by the appropriate metal salt, results in the formation of a crystalline product, which was identified as the bicyclic acetal **A** shown in Scheme 1.

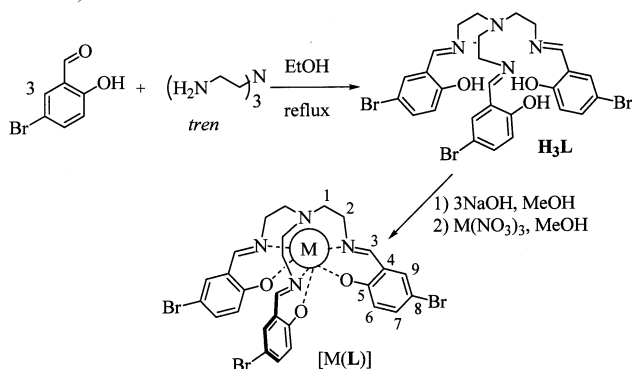


Scheme 1. Self-acetalization of 5-bromosalicylaldehyde

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The recovery of this product is very likely due to the high Lewis acidity of the tricationic oxidation state of the group-13 metal ions, which are able to catalyze the self condensation of the bromosalicylaldehyde. The strong acidic character of  $M^{III}$  is also confirmed by the formation of the nitrate salt of *tren*, also recovered under these conditions. Curiously, the more expected dimethoxyacetal, resulting from the reaction of the solvent (MeOH) and the aldehyde, is not isolated. This fact could be explained by a competition between the two reactions of acetalization that are chemically in equilibrium; but since **A** is less soluble in methanol than the dimethoxyacetal, the precipitation of the former shifts the equilibrium to its formation.

We can infer these observations to the lack of stability of the imine functions of the ligand in strongly acidic solutions. In other respects it is preferable to purify the ligand **H<sub>3</sub>L** before complexation, otherwise poorer purity of the chelates results. Thus, a two-step synthesis was preferred. As depicted in Scheme 2, the tripodal **H<sub>3</sub>L** ligand was synthesized according to Liu et al.<sup>[7]</sup> and purified by recrystallization in ethanol. It is of prime necessity to neutralize the acidic phenol functions of the ligand with a methanolic solution of NaOH (3 equiv.) prior to the introduction of a methanolic solution of the selected  $M^{III}$  salts in order to isolate the desired complexes. By this way, the result is a high recovery of the chelates (the yields ranging from 75 to 95%).



Scheme 2. Preparation scheme of **H<sub>3</sub>L** ligand and **[M(L)]** complexes where  $M = Ga^{III}, In^{III}$  or  $Tl^{III}$

The complexes are air-stable under neutral conditions both in the solid state and in solution in MeOH,  $CHCl_3$ , or DMSO, allowing their NMR characterization {exception **[In(L)]**, scarcely soluble}. These results point out that once isolated, the imine complexes are not subject to hydrolysis as was written by Orvig et al.<sup>[7]</sup> Thus, the experimental preparation process is the key point for hydrolysis to occur. It happens only at low pH values if the acidity released during the complexation is not neutralized with a base. Our results are in accordance with those of Costes et al.,<sup>[9]</sup> and Kocian et al.<sup>[10]</sup> In this latter case, triethylamine proves to be too weak to allow the recovering of imine-phenol  $Gd^{III}$  complexes, only a strong base like hydroxide or methoxide ion permits the preparation of the desired chelates.

All our complexes gave satisfactory elemental analyses. The  $FAB^+$  mass spectra obtained in a 3-nitrobenzyl alcohol

matrix show the molecular ion peaks at  $[M + H]^+$  (100% intensity) and the IR data show a characteristic strong band near  $1625\text{ cm}^{-1}$  that confirms the presence of the imine function. Furthermore, no band was detected in the range  $3500\text{--}3000\text{ cm}^{-1}$ , indicating the complete deprotonation of the phenol groups by NaOH and the absence of the N–H bond. This later remark also strongly supports the stability of the imine function in the complexes. Indeed, as a possible event, hydrolysis of the imine should result in the formation of such an N–H bond. All these data are consistent with the proposed formulation  $[M(L)]^0$ . Slow concentration of diluted methanolic solution gave crystalline material suitable for X-ray crystallographic study.

### Crystallographic Studies

An ORTEP drawing of **H<sub>3</sub>L** is illustrated in Figure 1 and details of the structure determination are collected in Table 1.

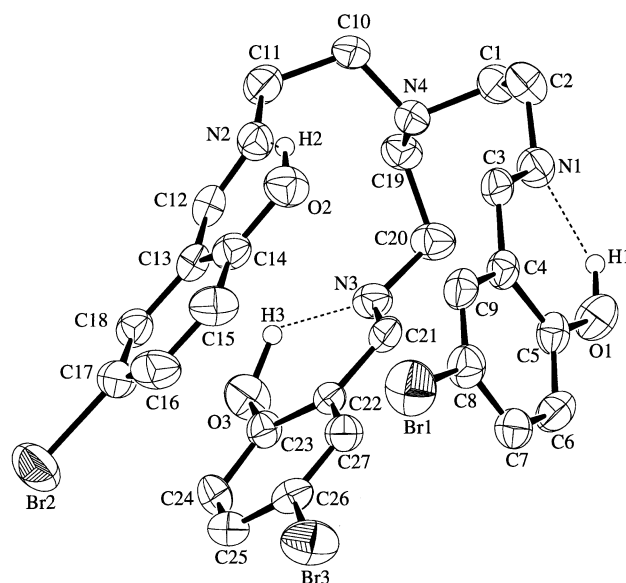


Figure 1. Structural representation of **H<sub>3</sub>L**; hydrogen atoms are omitted for clarity

There are two **H<sub>3</sub>L** molecules in each triclinic unit cell. All the interatomic distances and bond angles for the organic part are in the range of those given by Allen et al.<sup>[15]</sup> There is a strong hydrogen bond connecting the hydroxy hydrogen atoms and the imine nitrogen atoms ( $O1-H1\cdots N1$  1.89 Å,  $O2-H2\cdots N2$  1.67 Å,  $O3-H3\cdots N3$  1.79 Å) thus forming an almost planar six-membered ring. No interstrand bonds are detected, and contrary to what it is observed for other tripodal ligands,<sup>[16,17]</sup> there is no preorganization of **H<sub>3</sub>L** in the solid state. The formation of a three-dimensional cavity with a specific spatial arrangement of the donor atoms is only achieved in the presence of the metal ions.

An ORTEP drawing of **[Ga(L)]** is illustrated in Figure 2. All the complexes are neutral with a triply deprotonated  $N_3O_3$  imine phenol ligand completely encapsulating the  $M^{III}$  ions. The  $In^{III}$  and  $Tl^{III}$  compounds are isostructural.

Table 1. Summary of crystallographic data and structure refinement for  $\text{H}_3\text{L}$ ,  $[\text{Ga}(\text{L})]$ ,  $[\text{In}(\text{L})]$ , and  $[\text{Tl}(\text{L})]$ 

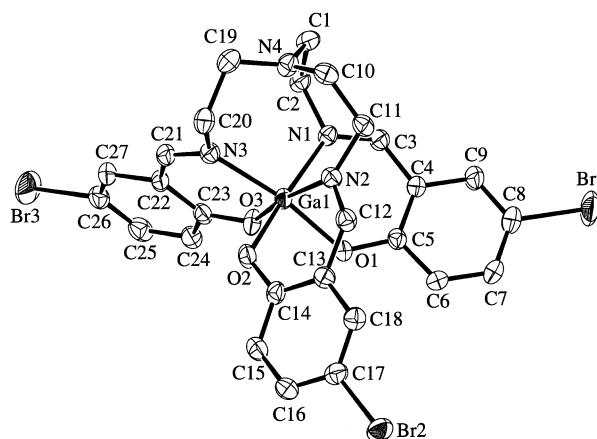
Compound	$\text{H}_3\text{L}$	$[\text{Ga}(\text{L})]$	$[\text{In}(\text{L})]$	$[\text{Tl}(\text{L})]$
Empirical formula	$\text{C}_{27}\text{H}_{27}\text{Br}_3\text{N}_4\text{O}_3$	$\text{C}_{27}\text{H}_{24}\text{Br}_3\text{GaN}_4\text{O}_3 \cdot \text{CH}_3\text{OH}$	$\text{C}_{27}\text{H}_{24}\text{Br}_3\text{InN}_4\text{O}_3$	$\text{C}_{27}\text{H}_{24}\text{Br}_3\text{N}_4\text{O}_3\text{Tl}$
Molecular mass	695.25	793.99	807.04	896.59
$F(000)$	692	784	784	848
Color/habit	pale yellow/triclinic prism	pale yellow/triclinic prism	pale yellow/triclinic prism	pale yellow/triclinic prism
Crystal size [mm]	$0.24 \times 0.22 \times 0.21$	$0.18 \times 0.16 \times 0.16$	$0.22 \times 0.20 \times 0.19$	$0.17 \times 0.16 \times 0.16$
$a$ [Å]	9.957(1)	9.632(3)	10.366(1)	10.437(1)
$b$ [Å]	11.970(1)	11.766(4)	11.852(4)	11.808(1)
$c$ [Å]	13.347(1)	13.240(2)	12.899(4)	12.844(1)
$\alpha$ [°]	89.36(1)	101.67(2)	114.15(3)	113.69(1)
$\beta$ [°]	77.21(1)	101.41(2)	95.62(2)	95.75(1)
$\gamma$ [°]	67.19(1)	89.12(2)	102.18(3)	100.89(1)
$V$ [Å <sup>3</sup> ], $Z$	1425.0(3), 2	1440.0(7), 2	1383.0(9), 2	1395.8(3), 2
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
$d_{\text{calcd.}}$ [g/cm <sup>3</sup> ]	1.620	1.831	1.938	2.133
Wavelength [Å]	0.5608 (Ag- $K_{\alpha}$ )	0.7107 (Mo- $K_{\alpha}$ )	0.7107 (Mo- $K_{\alpha}$ )	0.5608 (Ag- $K_{\alpha}$ )
$\mu$ [cm <sup>-1</sup> ]	22.96	51.72	52.37	54.80
Diffractometer	Enraf–Nonius Kappa CCD	Enraf–Nonius Cad-4	Enraf–Nonius Cad-4	Enraf–Nonius Kappa CCD
Scan type	$\phi$	$\phi$	$\omega$	$\omega$
$2\theta$ max [°]	36.3	59.9	60.0	51.5
No. of reflections				
measured/unique	7381/3925	8563/8323	8387/8040	14978/7964
with $F_o > n\sigma(F_o)$	2669 ( $n = 2$ )	4674 ( $n = 2$ )	5375 ( $n = 2$ )	6410 ( $n = 3$ )
Decay (%), correction	—	4.04, applied	0.22, none	—
Data reduction software	DENZO <sup>[a]</sup>	TEXSAN <sup>[b]</sup>	TEXSAN <sup>[b]</sup>	DENZO <sup>[a]</sup>
No. of variables	334	433	415	415
Structure solution software	TEXSAN <sup>[b]</sup>	TEXSAN <sup>[b]</sup>	TEXSAN <sup>[b]</sup>	TEXSAN <sup>[b]</sup>
Refinement ( $F$ )	full-matrix	full-matrix	full-matrix	full-matrix
H (from difference Fourier)	not refined	refined with riding model	refined with riding model	refined with riding model
Weighting scheme	$w = [\sigma^2(F_o) + p^2/4 F_o ^2]^{-1}$	$w = [\sigma^2(F_o) + p^2/4 F_o ^2]^{-1}$	$w = [\sigma^2(F_o) + p^2/4 F_o ^2]^{-1}$	$w = [\sigma^2(F_o) + p^2/4 F_o ^2]^{-1}$
Fudge factor ( $p$ )	0	0.021	0.020	0
Extinction correction	none	none	none	none
Absorption correction	none	$\psi$ scan <sup>[c]</sup>	$\psi$ scan <sup>[c]</sup>	multiscan <sup>[d]</sup>
$T_{\text{max}}/T_{\text{min}}$		0.999/0.835	0.999/0.822	0.999/0.880
Max. resid. dens. [e <sup>-</sup> /Å <sup>3</sup> ]	−0.51/0.47	−0.67/1.00	−1.30/1.25	−1.29/1.22
Goodness of fit	1.514	1.881	1.955	1.286
Max shift/error	0.02	0.02	0.02	0.02
$R/R_w$	0.049/0.039	0.048/0.041	0.044/0.039	0.029/0.037

[a] Ref.<sup>[11]</sup> — [b] Ref.<sup>[12]</sup> — [c] Ref.<sup>[13]</sup> — [d] Ref.<sup>[14]</sup>

In the three complexes, the cations have an octahedral environment where the ligand occupies all six coordination sites around the metal ion by bonding through the lone pairs of the three imino nitrogen atoms and the three deprotonated phenolic oxygen atoms, leading to a three-fold axis passing through the metal ion and the tertiary amine function.

Despite the larger size of  $\text{In}^{\text{III}}$  and  $\text{Tl}^{\text{III}}$ , the coordination of all seven donor atoms is not observed. Indeed, the apical nitrogen atom of the *tren* part, being in all cases at much longer distances from the metal center [Tl: 2.759(3) Å; In: 2.828(3) Å; and Ga: 3.342(3) Å] does not participate in the chelation of group-13 metal ions. Each  $\text{N}_3$  and  $\text{O}_3$  donor set coordinates to the  $\text{M}^{\text{III}}$  ions in a facial way to form a distorted octahedral geometry as shown in Table 2.

The  $\text{TlO}_3\text{N}_3$  and  $\text{InO}_3\text{N}_3$  octahedra are more distorted than the  $\text{GaO}_3\text{N}_3$  one. For  $[\text{Tl}(\text{L})]$ , the distortion of the coordination sphere is most evident in the compression of  $\text{O}–\text{Tl}–\text{O}$  (average 85.76°) and expansion in the  $\text{N}–\text{Tl}–\text{O}$  angles (average 106.77°) from 90°. As a result, the three

Figure 2. Structural representation of  $[\text{Ga}(\text{L})]$ ; hydrogen atoms are omitted for clarity

*trans*- $\text{O}–\text{Tl}–\text{N}$  angles have an average value of 163.08°. If one considers the angles, those of the  $\text{GaO}_3\text{N}_3$  octahedron are closer to regular values.

Table 2. Main bond angles [°] in the GaO<sub>3</sub>N<sub>3</sub>, InO<sub>3</sub>N<sub>3</sub> and TlO<sub>3</sub>N<sub>3</sub> entities; standard deviations are given in parentheses

[Ga(L)]		[In(L)]		[Tl(L)]	
O1–Ga1–O2	89.4(1)	O1–In1–O2	86.97(9)	O1–Tl1–O2	85.72(9)
O1–Ga1–O3	85.3(1)	O1–In1–O3	90.01(9)	O1–Tl1–O3	88.73(9)
O2–Ga1–O3	96.4(1)	O2–In1–O3	84.84(9)	O2–Tl1–O3	82.84(8)
O1–Ga1–N1	89.1(1)	O1–In1–N1	82.59(9)	O1–Tl1–N1	81.17(9)
O1–Ga1–N2	85.7(1)	O1–In1–N2	84.27(9)	O1–Tl1–N2	85.04(9)
O1–Ga1–N3	171.1(1)	O1–In1–N3	167.2(1)	O1–Tl1–N3	164.3(1)
O2–Ga1–N1	174.8(1)	O2–In1–N1	165.73(9)	O2–Tl1–N1	163.92(9)
O2–Ga1–N2	86.4(1)	O2–In1–N2	81.13(9)	O2–Tl1–N2	78.83(9)
O2–Ga1–N3	83.9(1)	O2–In1–N3	82.9(1)	O2–Tl1–N3	82.70(9)
O3–Ga1–N1	88.5(1)	O3–In1–N1	85.5(1)	O3–Tl1–N1	87.59(9)
O3–Ga1–N2	170.6(1)	O3–In1–N2	165.09(9)	O3–Tl1–N2	161.01(9)
O3–Ga1–N3	89.6(1)	O3–In1–N3	81.35(9)	O3–Tl1–N3	79.33(9)
N1–Ga1–N2	88.5(1)	N1–In1–N2	107.3(1)	N1–Tl1–N2	109.1(1)
N1–Ga1–N3	98.1(1)	N1–In1–N3	105.9(1)	N1–Tl1–N3	108.2(1)
N2–Ga1–N3	99.7(1)	N2–In1–N3	101.78(9)	N2–Tl1–N3	103.01(9)

The coordination behavior of **H<sub>3</sub>L** is not dependent on the size of the coordinated metal ion. This ligand presents a roughly invariable coordination cavity. Indeed, the three metal ions (Ga<sup>III</sup>, In<sup>III</sup>, and Tl<sup>III</sup>) are bonded in a similar way by an N<sub>3</sub>O<sub>3</sub> donor set, which leads us to consider that **H<sub>3</sub>L** is well tailored for six-coordinated neutral group-13 and lanthanide metal ion complexes. This cavity seems to fit to these three metal ions, with no significant strain on the coordinated ligand framework, contrary to the tripodal N<sub>4</sub>O<sub>3</sub> amine phenol ligand where the coordination mode is metal-dependent: for large lanthanide ions, homodinuclear dimers are formed, while cationic mononuclear complexes are obtained with Al<sup>III</sup> and Ga<sup>III</sup>.<sup>[7,18]</sup> Selected bond lengths and angles are listed in Table 3 for the three complexes.

Table 3. Main interatomic distances [Å] for [Ga(L)], [In(L)], and [Tl(L)]

[Ga(L)]		[In(L)]		[Tl(L)]	
Ga1–O1	1.932(2)	In1–O1	2.125(2)	Tl1–O1	2.235(2)
Ga1–O2	1.922(2)	In1–O2	2.131(2)	Tl1–O2	2.243(2)
Ga1–O3	1.931(2)	In1–O3	2.148(2)	Tl1–O3	2.252(2)
Ga1–N1	2.077(3)	In1–N1	2.245(3)	Tl1–N1	2.295(3)
Ga1–N2	2.190(3)	In1–N2	2.271(3)	Tl1–N2	2.343(3)
Ga1–N3	2.090(3)	In1–N3	2.280(3)	Tl1–N3	2.328(3)

Comparison of the bond lengths shows that M<sup>III</sup>–N and M<sup>III</sup>–O increase on going from Ga<sup>III</sup> to Tl<sup>III</sup>. This trend is consistent with the larger ionic radius of the Tl<sup>III</sup> ion in an octahedral environment. Ga–O and Ga–N, In–O and In–N distances are very similar to those found in other tripodal amine phenol N<sub>4</sub>O<sub>3</sub> and N<sub>3</sub>O<sub>3</sub> complexes<sup>[18,19]</sup> and imine phenol N<sub>3</sub>O<sub>3</sub> complexes.<sup>[20]</sup>

It has been postulated that complex stability is closely related to the size of the chelate rings, and to the size of metal ion.<sup>[21]</sup> As chelate ring size increases from five to six, stability of metal complexes generally decreases. The larger the coordinated metal ion, the greater the destabilization in the metal complex as the chelate ring size increases from five to six. However, despite this general trend, we have

been able to synthesize and characterize the three [M(L)] complexes.

### NMR Studies

<sup>1</sup>H NMR spectra of the ligand **H<sub>3</sub>L** and the three complexes are shown in Figure 3. The <sup>1</sup>H NMR spectrum of the ligand in CDCl<sub>3</sub> at 400 MHz is relatively simple, with three aromatic proton signals at δ = 6.49, δ = 6.83, and δ = 7.32. The imine proton resonates at δ = 7.80 and the two methylene groups giving an AA'XX' splitting pattern at δ = 2.83 and δ = 3.55. The proton signals were assigned using homonuclear 2D techniques (COSY) and are consistent with literature results.<sup>[7,17]</sup>

<sup>1</sup>H and <sup>13</sup>C NMR spectra of the Ga<sup>III</sup> and In<sup>III</sup> complexes were recorded in CDCl<sub>3</sub> while the Tl<sup>III</sup> complex was recorded in [D<sub>6</sub>]DMSO. However, they both show similar features. Only one set of <sup>1</sup>H NMR resonance signals proved that the three chelating arms of the ligand remained chemically equivalent upon coordination. This is in contrast with amine phenol Al, Ga, and In complexes described by Orvig et al.,<sup>[8]</sup> in which the Ga atom is coordinated by an N<sub>4</sub>O<sub>2</sub> donor set from the N<sub>4</sub>O<sub>3</sub> amine phenol ligand, with one of the three phenolate oxygen atoms remaining noncoordinating and protonated.

For the [Ga(L)] complex, the ethylenic hydrogen atoms form an AA'BB' spin system consisting of a distinct resonance corresponding to each of the four hydrogen atoms. This is a pattern already described for similar systems<sup>[22,23]</sup> and small heterocyclic ring structures,<sup>[24]</sup> whereby the ethylenic hydrogen atoms are locked in an axial/equatorial-type conformation.

From the crystallographic data, the angles and dihedral angles between the four different protons are available. The schematic Newman representation depicted in Figure 3 is drawn from these values. The angles between H<sub>A</sub> and H<sub>A'</sub>, H<sub>A</sub> and H<sub>B</sub>, and H<sub>B</sub> and H<sub>B'</sub> are 70°, –61°, and 169°, respectively. According to the literature,<sup>[25]</sup> the coupling constants  $J_{BB'}$  =  $J_{trans}$  lie in the range of 10 to 13 Hz, while the geminal coupling constants  $J_{AB}$  and  $J_{A'B'}$  or  $J_{gem}$  have aver-



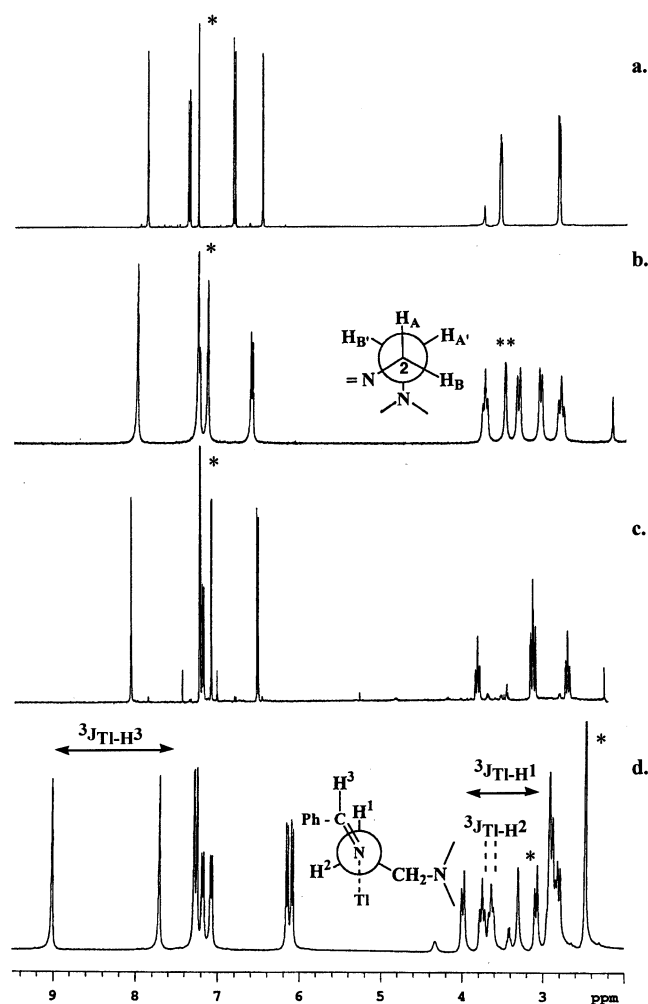


Figure 3.  $^1\text{H}$  NMR spectra of a:  $\text{H}_3\text{L}$ , b:  $[\text{Ga}(\text{L})]$ , c:  $[\text{In}(\text{L})]$ , in  $\text{CDCl}_3$  and d:  $[\text{Tl}(\text{L})]$  in DMSO; the asterisks (\*) represent residual solvent peaks and methanol (\*\*)

age values of  $-10$  to  $-16$  Hz. Moreover, if we take into account the model of Karplus, the  $J_{AA'}$  and  $J_{BA'}$  values must be very small or equal to zero. Finally, considering all of these data, the AA'BB' part of the spectrum can be simulated and compared to the experimental spectrum. Using an iteration method, one can obtain a simulated spectrum for the [Ga(L)] complex superimposed on the experimental one, for the values of  $J_{BB'}$ ,  $J_{AB}$ , and  $J_{A'B'}$  equal to 13.3 Hz,  $-11.3$  Hz, and  $-13.2$  Hz, respectively. Similarly, the  $J_{A'B}$ ,  $J_{AB'}$  and  $J_{AA'}$  values are 0.2 Hz, 0.1 Hz, and 0.2 Hz, respectively. In this case, the two protons  $H_A$  and  $H_{A'}$  appear as two doublets at  $\delta = 3.05$  and  $\delta = 3.32$ , respectively, while the two protons  $H_B$  and  $H_{B'}$  appear as two pseudo triplets at  $\delta = 3.73$  and  $\delta = 2.80$ , respectively. The same analysis has been ruled out for the [In(L)] complex, and the experimental spectrum could be simulated. The only difference to note with [Ga(L)] is the overlap of the two doublets of protons A and A' giving rise to another pseudo triplet with an intensity of two. These observations clearly demonstrate that the rigid structures of the complexes are consistent with the determined structures by X-ray diffraction.

The  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum consist for the  $[\text{Ga}(\text{L})]$  complex of nine resonances. The complete assignment was made with the aid of 2D homonuclear (COSY) and heteronuclear (HMQC and HMBC) experiments. The aromatic carbon signals all appear in the range of  $\delta = 105\text{--}168$ . The ethylenic carbon signals appear at  $\delta = 57\text{--}61$ , while the imine carbon signal lies at  $\delta = 170$ . The analysis of this spectrum also supports the structure of the complex shown in Figure 2 in which the metal ion is bound to the  $\text{N}_3\text{O}_3$  core in a facial arrangement. The solubility of the  $[\text{In}(\text{L})]$  complex was so poor in most of the common NMR solvents that recording the  $^{13}\text{C}$  spectrum was excluded.

The [Ti(L)] complex has also been studied in solution in [D<sub>6</sub>]DMSO. The <sup>1</sup>H NMR spectrum characterizing the complex is reported in Figure 3, and is very similar to the two previous complexes [Ga(L)] and [In(L)]. All three arms are equivalent as a result of the symmetric binding of the ligand to the metal center. Indeed, the observation of the relative simplicity of the <sup>1</sup>H and <sup>13</sup>C spectra implies that a C<sub>3</sub> symmetry axis is present for [M(L)] in solution. <sup>205,203</sup>Tl—<sup>1</sup>H couplings are noticeable for most of the protons of the complex. The largest coupling constant (<sup>3</sup>J<sub>Tl-H<sub>3</sub></sub> = 523 Hz) is observed for the imine proton. A value of 709 Hz has also recently been given for a macrobicyclic complex of Tl<sup>III</sup>.<sup>[26]</sup> Aromatic protons also show small coupling constants with Tl<sup>III</sup> ranging from 13 to 41 Hz for <sup>4</sup>J and <sup>5</sup>J. The ethylenic protons H<sup>1</sup> and H<sup>2</sup> of the complex also form a part of an AA'BB' spin system, but are split by the presence of the Tl<sup>III</sup> ion. Assuming that a Karplus-like relationship<sup>[27,28]</sup> is also valid for this kind of vicinal coupling between Tl and the protons, the larger value of <sup>3</sup>J<sub>Tl-H</sub> is indicative of a *trans* position between H<sup>1</sup> and Tl, while the smaller one (<sup>3</sup>J<sub>Tl-H<sub>2</sub></sub> = 45 Hz) is interpreted as resulting from a torsional angle smaller than 90°, where a minimum in the Karplus function is expected. These considerations are supported by the crystallographic data. Indeed, in the solid state, the dihedral angle values between Tl and H<sup>1</sup>, and Tl and H<sup>2</sup> are −171° and 62°, respectively. Moreover, the dihedral angle value between the imine proton (H<sup>3</sup>) and Tl is −167°, which explains the large value of this coupling. The <sup>3</sup>J<sub>Tl-H</sub> can thus be seen as a stereochemically sensitive parameter, as described for [Tl—EDTA] complexes.<sup>[29]</sup> Once formed, the neutral complex is stable, and even in DMSO, a good coordinating solvent, the spectroscopic behavior of [Ti(L)] is in complete agreement with the solid-state data. The stability in DMSO of such complexes has also been noted for tripodal Ln complexes derived from 3-methoxysalicylaldehyde, only if deprotonation of the ligands is made with a strong base prior to the addition of Ln<sup>III</sup> ions.<sup>[30]</sup>

In order to examine the fluxionality of the complexes in organic solvents ( $\text{CDCl}_3$  and  $[\text{D}_6]\text{DMSO}$ ), the variable-temperature (298–355 K)  $^1\text{H}$  NMR spectra were recorded for  $[\text{Ga}(\text{L})]$  and  $[\text{Tl}(\text{L})]$ , since all the complexes have very similar structures, the behavior of the In species must be very similar. No significant changes in the spectral parameters were noticed, except for minor shifts probably caused by

the thermal vibrations of the coordinated ligand framework. This clearly shows that all the complexes remain unchanged in solution in this temperature range. Therefore, the intact and rigid structure of these complexes in solution is demonstrated.

Finally, a specificity interesting to notice is that natural thallium consists of two spin 1/2 isotopes,  $^{203}\text{Tl}$  and  $^{205}\text{Tl}$  present in the relative abundance of 0.295 and 0.705, respectively. Spin-spin coupling constants between Tl and  $^1\text{H}$ , and Tl and  $^{13}\text{C}$  are thus observable. Moreover, one can observe a  $^{205/203}\text{Tl}$  isotope effect on  $^1\text{H}$  and  $^{13}\text{C}$  in the NMR spectra as shown in Figure 4.

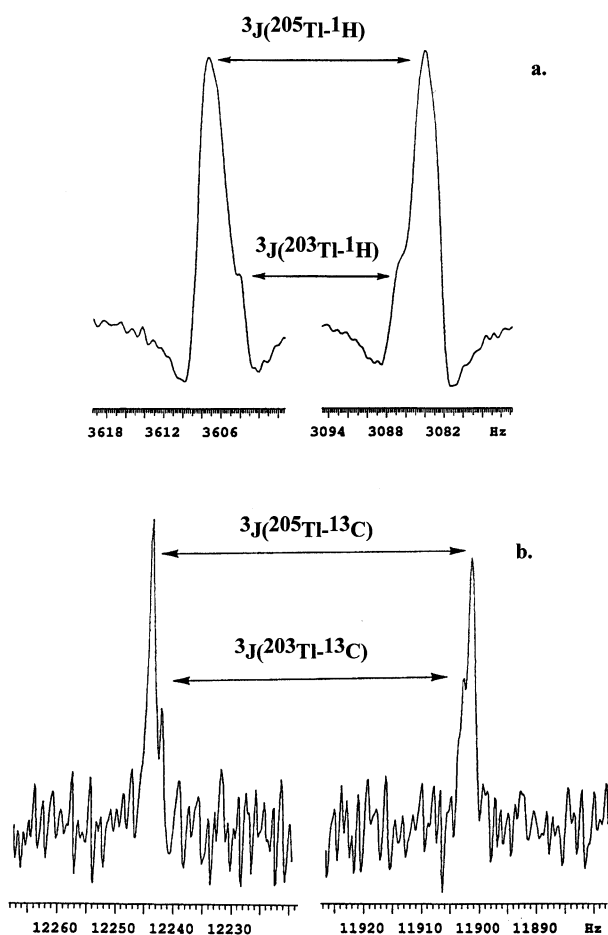


Figure 4. NMR spectra of  $[\text{Tl}(\text{L})]$  in DMSO showing the isotope effect in a. on  $\text{H}^3$  and in b. on  $\text{C}^4$

The presence of the two thallium isotopes induces a secondary isotope effect on  $^1\text{H}$  and  $^{13}\text{C}$  in the NMR spectra, which is also called isotope shift. This secondary isotope effect on nuclear shielding is defined as the difference ( $\Delta$ ) in the chemical shift ( $\delta$ ) of a nucleus N in the isotopomer with the heavier isotope  $^k\text{X}$  relative to the isotopomer with the lighter isotope  $^l\text{X}$  at a site  $n$  bonds away and expressed by<sup>[31]</sup>

$$^n\Delta\delta\text{N}(^k/^l\text{X}) = \delta\text{N}(^k\text{X}) - \delta\text{N}(^l\text{X})$$

The superscript  $n$  is the number of bonds between nuclei N and X. In most cases,<sup>[32]</sup> the chemical shift for the higher isotope is at a lower frequency, thus  $^n\Delta\delta\text{N}(^k/^l\text{X})$  is negative. This means that the heavier isotope causes increased shielding. In this study, the contrary is observed. Positive values of 0.625 ppb and 2.780 ppb are obtained for  $^3\Delta\delta\text{H}(^{205/203}\text{Tl})$  and  $^3\Delta\delta\text{C}(^{205/203}\text{Tl})$ , respectively. It is very difficult to comment on these data because to the best of our knowledge no such  $^3\Delta\delta\text{H}$  and  $^3\Delta\delta\text{C}$  are available in the literature for coordination compounds. However, similar values lying in the range  $-1.76$  to  $-0.88$  ppb are observed for  $^3\Delta\delta\text{F}$  in chlorofluorocarbons.<sup>[33]</sup>

For spin-spin coupling constants, the magnitude of the interaction  $J(\text{YZ})$ , expressed in Hz, also depends on the magnetogyric ratio of the Y and Z nuclei, and when a nucleus  $^m\text{Y}$  is replaced by an isotopic species  $^n\text{Y}$ , the ratio  $J(^m\text{YZ})/J(^n\text{YZ})$  is equal to  $\gamma(^m\text{Y})/\gamma(^n\text{Y})$ . According to Figure 4, the ratios  $^3J(^{203}\text{Tl}-^1\text{H})/^3J(^{205}\text{Tl}-^1\text{H})$  and  $^3J(^{203}\text{Tl}-^{13}\text{C})/^3J(^{205}\text{Tl}-^{13}\text{C})$  are equal to 0.9886 and 0.9915, respectively, while  $\gamma(^{203}\text{Tl})/\gamma(^{205}\text{Tl}) = 0.9902$  confirming thus an isotope effect on coupling constants. If the isotopically substituted nucleus Y ( $^m\text{Y}/^n\text{Y}$  substitution) is involved in spin-spin interaction, one can measure a primary isotope effect on the coupling constant<sup>[32]</sup> defined as

$$^{p,q}\Delta J_{\text{X}} = \frac{\gamma(^m\text{Y})}{\gamma(^n\text{Y})} J(^m\text{X}^n\text{Y}) - J(^n\text{X}^m\text{Y}) \quad \text{with } n > m$$

where  $p$  and  $q$  denote the number of bonds separating the site of isotopic substitution and each of the two nuclei involved in spin-spin coupling. From  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra,  $^{0,3}\Delta J_{\text{H}}$  and  $^{0,3}\Delta J_{\text{C}}$  values of 0.86 Hz and  $-0.43$  Hz, respectively, are obtained only from the imine proton  $\text{H}^3$ , and the carbon atom  $\text{C}^4$ , these two atoms having the largest coupling constant with  $\text{Tl}^{\text{III}}$ . These rather low  $^{0,3}\Delta J_{\text{H}}$  and  $^{0,3}\Delta J_{\text{C}}$  values, which do not exceed 0.2% of the coupling constants, represent an effect through three bonds. Data on isotope effects for the coupling constants between heavy isotopes other than protons are more documented for organic compounds,<sup>[32,34]</sup> but nonexistent in coordination chemistry. However, the largest  $^1J(^{13}\text{C}-\text{Tl})$  values have been measured for mono- and dicyano complexes of  $\text{Tl}^{\text{III}}$ , with  $^{0,1}\Delta J$  visualized in the spectra,<sup>[35]</sup> but not investigated. Any discussion of these isotope effect values would require theoretical developments.<sup>[34]</sup> Yet, what can be said is that the observation of an isotope effect implies a strong Tl–ligand coordination bond.

## Conclusion

We have shown that tripodal Schiff base phenol complexes derived from salicylaldehyde, *tren* and the acidic  $\text{Ga}^{\text{III}}$ ,  $\text{In}^{\text{III}}$ , and  $\text{Tl}^{\text{III}}$  metal ions could be easily prepared without noticeable imine hydrolysis. The accurate structure of all the complexes show a constant coordinating pattern

of the tripodal ligand that acts as a hexadentate ligand, giving isostructural species from Ga<sup>III</sup> to Tl<sup>III</sup>. Further, NMR-spectroscopic data strongly support that the rigid structure in the solid state is maintained in DMSO or CDCl<sub>3</sub> solutions. Consequently, these facts involve a strong coordination of the metal ions. This characteristic is very favorable for biomedical applications. Investigations concerning this topic are currently underway and the results will be described elsewhere.

## Experimental Section

**General Remarks:** Tris(aminoethyl)amine (*tren*) and hydrated metal salts [Ga(NO<sub>3</sub>)<sub>3</sub>, In(NO<sub>3</sub>)<sub>3</sub> and Tl(NO<sub>3</sub>)<sub>3</sub>] were obtained from Acros. 5-Bromosalicylaldehyde was obtained from Lancaster. All chemicals were used without further purification. Thallium is highly poisonous and should be handled with caution.<sup>[36]</sup> – NMR spectra were recorded with a Varian U400 spectrometer (operating at 100.58 MHz for <sup>13</sup>C). Each spectrum was referenced to the solvent used at room temperature. – Mass spectrometry (FAB<sup>+</sup> mode) experiments were run in a 3-nitrobenzyl alcohol matrix with a Nermag R10 spectrometer. – Infrared spectra were recorded as KBr disks in the range 400–4000 cm<sup>−1</sup> with a Nicolet Impact 400 spectrometer. – Elemental analysis for C, H and N were performed by the Service Central d'Analyses (CNRS) at Vernaison (France).

**Synthesis of Tris[(5-bromosalicylidene)aminoethyl]amine (H<sub>3</sub>L):** The ligand tris[(5-bromosalicylidene)aminoethyl]amine (H<sub>3</sub>L) was prepared according to the method reported in the literature.<sup>[7]</sup> To a warm solution of 5-bromosalicylaldehyde (6.03 g, 30 mmol) in absolute ethanol (100 mL) was added a solution of tris(aminoethyl)amine (1.46 g, 10 mmol) in EtOH (40 mL). After the addition was complete, the resulting bright yellow suspension was heated at reflux for 20 min and then stirred at room temperature for 0.5 h. The mixture was cooled in an ice bath for 15 min, and the yellow microcrystals were collected by filtration, washed with cold EtOH (40 mL) and Et<sub>2</sub>O. The solid was dried under vacuum. Yield 5.36 g (77%). M.p. 145–146 °C (ref.<sup>[7]</sup> 144–145 °C). Slow evaporation of the solvent from the filtrate yielded suitable crystals for X-ray diffraction studies.

**Synthesis of the Complexes, General Procedure:** [M(L)] complexes were prepared as follows. To a suspension of the ligand H<sub>3</sub>L (1 mmol) in methanol (25 mL), was added NaOH (0.12 g, 3 mmol in 10 mL of MeOH). To this homogeneous solution was added the metal nitrate in methanol (1 mmol in 25 mL). A precipitate formed immediately. The mixture was stirred at reflux for 15 min and then cooled to room temperature. The solid was filtered off; washed with methanol (2 × 20 mL) and diethyl ether (2 × 10 mL), and then dried in vacuum. Slow concentration of the filtrate over a period of two weeks yielded suitable crystals for X-ray diffraction studies.

**[Ga(L)] (1):** Yield: 0.720 g, 94%. – C<sub>27</sub>H<sub>24</sub>Br<sub>3</sub>Ga<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: calcd. C 42.56, H 3.17, N 7.35; found C 42.55, H 3.51, N 7.08. – <sup>13</sup>C NMR (CDCl<sub>3</sub>, room temp.): δ = 57.2 (C<sup>1</sup>), 61.7 (C<sup>2</sup>), 105.1 (C<sup>8</sup>), 118.4 (C<sup>4</sup>), 125.2 (C<sup>6</sup>), 135.8 (C<sup>9</sup>), 137.5 (C<sup>7</sup>), 167.9 (C<sup>5</sup>), 169.6 (C<sup>3</sup>). – IR (KBr):  $\tilde{\nu}$  = 3047 (weak, C–H phenyl), 2877, 2840 (s, C–H aliphatic), 1622 (very strong, C=N imine), 1182 (s, C–O) cm<sup>−1</sup>. – MS (FAB<sup>+</sup>): *m/z* (%) = 763 (100) [M + H]<sup>+</sup>.

**[In(L)] (2):** Yield: 0.605 g, 75%. – C<sub>27</sub>H<sub>24</sub>Br<sub>3</sub>In<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: calcd. C 40.18, H 3.00, N 6.94; Br, 29.70; found C 39.71, H 2.94, N 6.77; Br, 29.36. – IR (KBr):  $\tilde{\nu}$  = 3048 (weak, C–H phenyl), 2908, 2846

(s, C–H aliphatic), 1627 (very strong, C=N imine), 1169 (s, C–O) cm<sup>−1</sup>. – MS (FAB<sup>+</sup>): *m/z* (%) = 807 (100) [M + H]<sup>+</sup>.

**[Tl(L)] (3):** Yield: 0.848 g, 95%. – C<sub>27</sub>H<sub>24</sub>Br<sub>3</sub>TlN<sub>4</sub>O<sub>3</sub>: calcd. C 36.17, H 2.70, N 6.25; Br, 26.74; found C 35.76, H 2.77, N 6.18; Br, 26.53. – <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, room temp.): δ = 55.2 (C<sup>1</sup>), 55.7 (C<sup>2</sup>, <sup>2</sup>*J* = 193.03 Hz), 102.1 (C<sup>8</sup>, <sup>5</sup>*J* = 32.59 Hz), 120.0 (C<sup>4</sup>, <sup>3</sup>*J* = 342.05 Hz), 125.2 (C<sup>6</sup>, <sup>3</sup>*J* = 160.10 Hz), 135.1 (C<sup>9</sup>, <sup>4</sup>*J* = 10.44 Hz), 136.5 (C<sup>7</sup>, <sup>4</sup>*J* = 40.19 Hz), 170.2 (C<sup>3</sup>, <sup>2</sup>*J* = 93.96 Hz), 172.1 (C<sup>5</sup>, <sup>2</sup>*J* = 195.85 Hz). – IR (KBr):  $\tilde{\nu}$  = 3047 (weak, C–H phenyl), 2877, 2840 (s, C–H aliphatic), 1622 (very strong, C=N imine), 1182 (s, C–O) cm<sup>−1</sup>. – MS (FAB): *m/z* (%) = 897 (100) [M + H]<sup>+</sup>.

**X-ray Crystallographic Study:** The main crystallographic features, the strategy used for the crystal structure determination, and its results are gathered in Table 1. Data collections were carried out at room temperature. The *U*<sub>iso</sub> values of the H atoms have been fixed to 1.2 × *U*<sub>equiv</sub> of the C atoms they are attached to. The structures were solved by direct methods (SIR92).<sup>[37]</sup> Crystallographic data (excluding structure factors), for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152917, -152918, -152919, -152920 for [Tl(L)], [In(L)], [Ga(L)] and H<sub>3</sub>L, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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