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Bis-tridentate Chelates of an Asymmetric Ligand: X-ray Structures and Solution NMR Characterization of Divalent Zinc Triad Metal Ion Complexes of N-(2-pyridylmethyl)-N-(2-(methylthio)ethyl)amine

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Abstract

Divalent zinc triad metal ion complexes of type $M(L)_2(ClO_4)_2$ (L = N-(2-pyridylmethyl)-N-(2-(methylthio)ethyl)amine) with N_4S_2 metal coordination spheres were isolated and characterized by X-ray crystallography and variable temperature proton NMR. Although bis-tridentate chelates have nine geometric isomers, the crystallographically characterized complexes of all three metal ions had trans facial octahedral coordination geometry with C_i symmetry. Despite the low coordination number and geometric preferences of d^{10} metal ions, which facilitate inter- and intramolecular exchange processes, dilute solutions of these bis-tridentate chelates exhibited slow geometric isomerization. Symmetry, sterics and shielding arguments supported specific isomeric assignments for the major and minor chemical shift environments observed at low temperature. At elevated temperature, rapid intramolecular exchange occurred for all three complexes but slow intermolecular exchange on the coupling constant time scale was evidenced through detection of J_{HgH} interactions for $Hg(L)_2^{2+}$. These unusual observations are discussed in the context of the zinc triad metal ion coordination chemistry of related bis-tridentate chelates.

Keywords

Isomerization; NMR; Single crystal X-ray structure; Group 12; bis-tridentate chelate

INTRODUCTION

Divalent zinc triad metal ion complexes are prone to rapid intramolecular rearrangement and intermolecular exchange processes. The d^{10} electron configuration permits a wide range of coordination numbers and geometries, frequently leading to complicated solution speciation. Detailed analysis of the solution speciation of these metal ion complexes is hampered by the relatively limited number of techniques available to probe their coordination environments.

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The considerable bioactivity difference between zinc triad metals motivates parallel study of their coordination behavior in spite of the difficulties that must be overcome.¹⁻³

The limited degrees of freedom associated with multidentate ligand systems provide a convenient manner of limiting solution speciation.⁴⁻¹¹ Multidentate organic ligand complexes of diamagnetic zinc triad metals are amenable to characterization by NMR techniques. Although zinc does not have an isotope with favorable NMR properties, previous studies have revealed slow intermolecular ligand exchange on the proton and carbon NMR chemical shift time scales for zinc complexes of multidentate ligands.⁴ For Cd(II) and Hg(II) complexes, slow intermolecular exchange on the typically shorter J_{CdH} and J_{HgH} time scales, respectively, may be observed.⁴⁻¹¹ In addition, ^{113}Cd and ^{199}Hg NMR have been used as metallobioprobes for characterization of a variety of metal-substituted proteins.¹²⁻¹⁶

Previously we have reported solid- and solution-state characterization of group 12 metal ion bis-tridentate chelate complexes with symmetric pyridine-containing ligands bis(2-methylpyridyl)amine (**L**¹),^{8,9} bis(2-methylpyridyl)sulfide (**L**²)⁵ and 2,6-bis(methylthiomethyl)pyridine (**L**³).⁴ Conditions for slow intermolecular change were found for dilute solutions of these complexes in acetonitrile- d_3 . In this paper, the synthesis and characterization of $\text{M}(\text{ClO}_4)_2$ ($\text{M} = \text{Zn}(\text{II}), \text{Cd}(\text{II}), \text{Hg}(\text{II})$) complexes of the non- C_2 symmetric ligand N-(2-pyridylmethyl)-N-(2-(methylthio)ethyl)amine (**L**) are reported. X-ray crystallography revealed homologous trans facial octahedral $[\text{M}(\text{L})_2](\text{ClO}_4)_2$ complex structures. In dilute acetonitrile- d_3 solutions, each complex was in slow intermolecular exchange even at elevated temperatures. Furthermore, $[\text{M}(\text{L})_2]^{2+}$ are the first group 12 bis-tridentate chelates for which conditions favoring slow intramolecular isomerization have been accessible in acetonitrile- d_3 . These results are discussed in the context of the nine regular polyhedral forms of bis-tridentate chelate complexes.

EXPERIMENTAL

Methods and Materials

Solvents and reagents were of commercial grade and used as received unless otherwise stated. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, Georgia. J values are given in Hz. *Caution!* All the perchlorate salts of metal complexes included in this work were stable for routine synthesis and purification procedures. However, organic perchlorates are potentially explosive and should be handled with care.¹⁷

Solution-State NMR Spectroscopy

Proton NMR spectra were collected in 5 mm o.d. NMR tubes on a Varian Mercury 400VX NMR spectrometer operating in the pulse Fourier transform mode. Calibrated autopipets were used to prepare nominally 2 mM solutions for variable temperature NMR measurements by dissolution of elementally analyzed complexes. The sample temperature was maintained by

blowing chilled nitrogen over the NMR tube in the probe. Proton chemical shifts were measured relative to internal solvent but are reported relative to tetramethylsilane (TMS).

X-ray Crystallography

Selected crystallographic data are given in Tables 1 and 2. Data were collected on a Siemens P4 four-circle diffractometer using a graphite-monochromated Mo K α X-radiation ($\lambda = 0.71073$ Å). During data collection three standard reflections were measured after every 97 reflections. The structures were solved by direct methods and refined on F^2 by full-matrix least squares using the SHELXTL97 program package.^{18,19} All non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were refined as riding atoms with relative displacement parameters.

Synthesis of N-(2-pyridylmethyl)-N-(2-(methylthio)ethyl)-amine (L)

The ligand was prepared by adaptation of procedures for related ligands.²⁰ A solution of 2-chloroethyl methyl sulfide (2.4 mL, 24 mmol) in 20 mL deionized water was cooled to 0 °C in an ice bath. To this solution was added slowly with stirring a solution of 2-(aminomethyl)pyridine (2.1 mL, 20 mmol) in 35 mL methylene chloride. The mixture was then allowed to warm to room temperature. Over a 48-hour period, 12 mL of 2 M NaOH was added by syringe pump. The crude mixture was washed with 40 mL of 4 M NaOH. The organic phase was dried with sodium sulfate and filtered. Removal of methylene chloride yielded a brown liquid. Fractional vacuum distillation yielded **L** as a colorless oil (94 °C/0.05 mmHg, 1.8 g, 49%). (Found: C, 58.0; H, 7.8; N, 15.0. C₉H₁₄N₂S requires C, 59.3; H, 7.7; N, 15.4%) ¹H NMR (CD₃CN, -40 °C): δ 2.02 (3H, s, H_i), 2.62 (2H, t, J_{HH} 7, H_h), 2.73 (2H, t, J_{HH} 7, H_g), 3.83 (2H, s, H_f), 7.23 (1H, dd, J_{HH} 5, 7, H_b), 7.37 (1H, d, J_{HH} 8, H_d), 7.72 (1H, dt, J_{HH} 2, 8, H_c), 8.51 (1H, d, J_{HH} 5, H_a).

Preparation of Zn(L)₂(ClO₄)₂·H₂O (1a)

A solution of Zn(ClO₄)₂·6H₂O (190 mg, 0.50 mmol) in 3 mL acetonitrile was added to a solution of **L** (190 mg, 1.0 mmol) in 3 mL methanol with stirring. Pale pink crystals of **1a** (105 mg, 32.5%) suitable for X-ray crystallography were obtained in 5 mm glass tubes after a week by slow diffusion of the mixture into benzene. Mp: 188–189 °C. (Found: C, 33.4; H, 4.7; N, 8.8. Anal. C₁₈H₃₀Cl₂N₄O₉S₂Zn requires C, 33.4; H, 4.7; N, 8.7%) ¹H NMR (2 mM, CD₃CN, 60 °C): δ 1.92 (3H, s, H_i), 2.74 (2H, bs H_h), 2.96 (2H, bs H_g), 4.05 (1H, bs H_f), 4.22 (2H, bs, H_e), 7.60 (1H, dd, J_{HH} 5, 8, H_b), 7.65 (1H, d, J_{HH} 8 Hz, H_d), 8.14 (1H, dt, J_{HH} 1, 8, H_c), 8.21 (1H, bs, H_a).

Preparation of Cd(L)₂(ClO₄)₂·H₂O (1b)

A solution of Cd(ClO₄)₂·6H₂O (210 mg, 0.50 mmol) in 3 mL acetonitrile was added to a solution of **L** (190 mg, 1.0 mmol) in 3 mL methanol with stirring. Small, colorless crystals of **1b** (70 mg, 20 %) suitable for X-ray crystallography were obtained in 5 mm glass tubes after a week of slow diffusion into toluene. Mp: 163–165 °C. (Found: C, 31.3; H, 4.3; N, 8.1. C₁₈H₃₀CdCl₂N₄O₉S₂ requires C, 31.15; H, 4.4; N, 8.1) ¹H NMR (2 mM, CD₃CN, 20 °C): δ 1.98 (3H, s, H_i), 2.55 (1H, bs, H_g), 2.79 (2H, bs, H_h), 3.26 (1H, bs, H_{g'}), 3.66 (1H, bs, H_f), 4.06 (1H, bs, H_e), 4.27 (1H, bs, H_{e'}), 7.54 (1H, dd, J_{HH} 5, 8, H_b), 7.60 (1H, d, J_{HH} 8, H_d), 8.08 (1H, dt, J_{HH} 1, 8, H_c), 8.15 (1H, bs, H_a).

Preparation of the complex Hg(L)₂(ClO₄)₂ (1c)

A solution of Hg(ClO₄)₂·3H₂O (230 mg, 0.50 mmol) in 3 mL acetonitrile was added to a solution of **L** (190 mg, 1.0 mmol) in 3 mL methanol with stirring. Colorless small crystals of **1** (48 mg, 13%) suitable for X-ray crystallography were obtained in 5 mm glass tubes after 6 days of slow diffusion into benzene. Mp: 101–102 °C. (Found: C, 28.2; H, 3.6; N, 7.3.

$C_{18}H_{28}Cl_2HgN_4O_8S_2$ requires C, 28.3; H, 3.7; N, 7.3%) 1H NMR (2 mM, CD_3CN , 60 °C): δ 2.10 (3H, s, H_i), 2.92 (2H, bt, H_h), 3.07 (2H, bs, H_g), 4.03 (1H, bs, H_f), 4.26 (2H, s, J_{HgH} 70, H_e), 7.53 (1H, dd, J_{HH} 4,8, H_b), 7.56 (1H, d, J_{HH} 8, H_d), 8.04 (1H, dt, J_{HH} 2,7, H_c), 8.27 (1H, d, J = 4, H_a).

RESULTS

Crystal Structures of $M(L)_2(ClO_4)_2$ Complexes

Complexes $[Zn(L)_2](ClO_4)_2 \cdot H_2O$ (**1a**), $[Cd(L)_2](ClO_4)_2 \cdot H_2O$ (**1b**) and $[Hg(L)_2](ClO_4)_2$ (**1c**) contain $[M(L)_2]^{2+}$ dications (Figs. 2-4) and well-separated perchlorate anions. These are the first structurally characterized complexes of divalent zinc triad metal ions with an $N_4(SR)_2$ coordination sphere involving a non- C_2 symmetric ligand. Selected crystallographic data for complexes **1a–c** are given in Table 2. All three $[M(L)_2]^{2+}$ cations have trans facial octahedral geometry with the metal ion as an inversion center within a rectangular basal plane formed by the four nitrogen donor groups. Each pair of ligand nitrogens forms a pseudo-envelope chelate ring with the alkyl amino nitrogen on the flap (Fig. 1a). Complexes **1a** and **1b** are isostructural and isomorphous, containing twisted conformation N,S chelate rings with the ethylene carbons out of the plane formed by the other atoms (Fig. 1b). In contrast, these chelate rings have a pseudo-envelope conformation in **1c** with the ethylene carbons closest to S on the flaps (Fig 1c).

Crystal Structure of $Zn(L)_2(ClO_4)_2 \cdot H_2O$ (**1a**)

Seven structurally characterized complexes of Zn(II) with a $N_4(SR)_2$ coordination sphere have been reported.^{5,21–25} Complex **1a** contains a $[Zn(L)_2]^{2+}$ cation (Fig. 2), two perchlorate anions and a non-coordinated water molecule. The ligands have $N_{pyridyl}-N_{alkyl}-S$ angles of 66.4°. The planes formed by the coordinating atoms from each of the individual ligand are 2.88 Å apart. The methyl groups are oriented toward the opposing ligand in the crystal structure.

The intraligand $S-M-N_{alkyl}$ and $N_{alkyl}-M-N_{pyridyl}$ bond angles of 84.15(5)° and 79.80(5)° are closer to 90° than those observed for **1b** and **1c** in which the metal ions are larger. Shorter M–N and M–S distances are observed in complex **1a** than **1b** and **1c** as expected for the smaller zinc ion. The $Zn-N_{pyridyl}$ distance of 2.1059(19) Å is normal for six coordinate Zn(II) complexes.^{5,26–29} The $Zn-N_{alkyl}$ distance of 2.1773(17) Å is within the range (2.07–2.229 Å) reported for $N_4(SR)_2$ Zn(II) complexes. The Zn–S bond distance of 2.5978(13) Å is in the known range for six-coordinate thioether-containing complexes of Zn(II).^{5,23,25,30}

Crystal Structure of $Cd(L)_2(ClO_4)_2 \cdot H_2O$ (**1b**)

Similar to complex **1a**, complex **1b** consists of a $[Cd(L)_2]^{2+}$ cation (Fig. 3), two perchlorate anions and a non-coordinated water molecule. Distorted octahedral $[Cd(L)_2](ClO_4)_2$ is the only other structurally characterized Cd(II) complex with a $N_4(SR)_2$ coordination sphere.⁴ The ligands in **1b** have $N_{pyridyl}-N_{alkyl}-S$ angles of 69.1° forming coordinating atom planes that are 3.25 Å apart. The methyl groups are oriented toward the opposing ligand in the crystal structure as observed in **1a**.

The intraligand $S-M-N_{alkyl}$ and $N_{alkyl}-M-N_{pyridyl}$ bond angles of 80.24(4)° and 74.38(5)° are somewhat smaller in complex **1b** than in complex **1a**. The $Cd-N_{pyridyl}$ distance of 2.3132(17) Å is comparable to those (2.266–2.442 Å) found in pyridine-containing six-coordinate Cd(II) complexes.⁵ The $Cd-N_{alkyl}$ distance of 2.3826(17) Å resembles those found in the six coordinate complex $[Cd(TAT)](ClO_4) \cdot 0.5H_2O$ (TAT = 1,4,7-tris(o-aminobenzyl)-1,4,7-triazacyclononane).³¹ The Cd–S distance of 2.7115(7) Å is similar to other six coordinate thioether Cd(II) complexes.^{5,30,32}

Crystal Structure of $\text{Hg}(\text{L})_2(\text{ClO}_4)_2$ (**1c**)

Complex **1c** (Fig. 4) is the third structurally characterized complex of Hg(II) with a $\text{N}_4(\text{SR})_2$ coordination sphere.^{4,33} The other two complexes have significantly more trigonal prismatic coordination geometry, however in solution bis-tridentate chelates of divalent zinc triad metal ions typically exhibit exchange between as many as nine geometric isomers.⁹ The ligands have $\text{N}_{\text{pyridyl}}\text{--N}_{\text{alkyl}}\text{--S}$ angles of 77.8° , significantly larger than both **1a** and **1b**. The coordinated ligand atoms form planes that are 3.19 Å apart, further apart than **1a** but closer than **1b**. Unlike the complexes of the smaller metal ions, the methyl groups are oriented away from the opposing ligand in the crystal structure of **1c**.

Complex **1c** has intraligand S–Hg– N_{alkyl} and $\text{N}_{\text{alkyl}}\text{--Hg--N}_{\text{pyridyl}}$ bond angles of $80.41(7)^\circ$ and $73.26(8)^\circ$, respectively, which are very close to the bond angles observed for **1b**. The 2.424(2) Å Hg– $\text{N}_{\text{pyridyl}}$ distance is comparable to those observed in other six coordinate Hg(II) complexes including $[\text{Hg}(\text{L}^1)_2](\text{ClO}_4)_2$, [Bebout, 1998 #6] $[\text{Hg}(\text{L}^3)_2](\text{ClO}_4)_2$ ⁴ and $[\text{Hg}(\text{pyridine})_6](\text{CF}_3\text{SO}_3)_2$, [Aakesson, 1991 #57]. The 2.305(2) Å Hg– N_{alkyl} distance is slightly shorter than the range of 2.37(2) to 2.473(11) Å observed in the six coordinate complexes $[\text{Hg}(\text{TAT})](\text{ClO}_4)_2 \cdot 0.5\text{H}_2\text{O}$ ³¹ $[\text{Hg}(\text{TDO})](\text{PF}_6)_2$ (TDO = 1,4,10,13-tetrathia-7,16-diazacyclooctadecane)³⁵ and $[\text{Hg}([9]\text{aneN}_2\text{S})](\text{HgBr}_4)$ ($[9]\text{aneN}_2\text{S}$ = 1-thia-4,7-diazacyclononane).³³ In contrast, the Hg–S bond distance of 2.7989(13) Å is slightly longer than the previously reported range of 2.458 to 2.751 Å for six coordinate Hg(II) complexes involving thioether donors.^{5,33}

Solution state investigation of **L** coordination to divalent zinc triad metal ions

The solution state coordination chemistry of bis-tridentate chelates of **L** with divalent zinc triad perchlorates was studied in acetonitrile- d_3 using variable temperature ^1H NMR spectroscopy. The NMR samples were prepared from elementally analyzed, X-ray quality crystalline materials, creating samples with well defined metal-to-ligand mole ratios. The labeling scheme for the protons of **L** is provided in the introduction.

The proton NMR spectra of **1a–c** were qualitatively similar with severely broadened resonances for H_a , H_e , H_g and H_h at 20 °C (Fig. 5). Cooling to -40 °C had previously generated slow intermolecular exchange conditions on the J_{HH} , J_{CdH} and J_{HgH} time scales for related complexes.^{4,5,8,9} Although the proton NMR spectra of **1a–c** lacked evidence for J_{CdH} or J_{HgH} interactions at -40 °C, they were surprisingly complex. Resonances for H_b , H_c and H_d changed little upon cooling. In contrast, extensive geminal coupling of the methylene and ethylene protons appeared for all three complexes indicating the ligands remained tridentate on the J_{HH} time scale.^{8,9} Furthermore, major and minor environments were evident for some ligand protons. For example, the doublet with J_{HH} 5 Hz for H_a appeared at approximately 8.4 and 8.0 ppm in the minor and major environments, respectively, placing an upper limit of approximately 15 ms on their rate of exchange. Neither H_a environment grew in relative intensity following addition of excess ligand or metal salt to the samples (data not shown). As will be elaborated in the discussion, the simplest explanation for these observations is slow intramolecular exchange between isomeric bis-tridentate chelate forms.

Further proton spectra for these samples were collected at 20 °C intervals up to 80 °C (Fig. 5). Resonances were generally observed to broaden and coalesce as the temperature was raised until there were only nine ligand proton resonances. The coalescence temperature for the various peaks increased in the order $\text{Zn(II)} > \text{Cd(II)} > \text{Hg(II)}$. Interestingly, the major H_a resonance for **1a** originally got sharper as the temperature was raised. To determine whether additional exchange processes could be frozen out at lower temperature, a 2 mM solution of **1a** in acetone- d_6 was prepared. The proton NMR of **1a** was qualitatively similar at -40 °C in the two solvents (data not shown). Unfortunately, further cooling of the acetone- d_6 solution to

-90 °C resulted in broadening to extinction, foiling efforts to better characterize the species contributing to the major environment (data not shown). Further analysis of the H_a chemical shifts of $[M(L)_2]^{2+}$ as a function of temperature indicated near temperature independence for the minor resonance observed at low temperature, as expected for a single species. In contrast, the major resonance shifted significantly with temperature, consistent with an exchange equilibrium occurring on a submillisecond time scale. As a result, detailed quantitative analysis of the spectra for calculation of activation energies or accurate exchange rates is precluded.

Significantly, J_{HgH} 70 Hz involving H_e was observed for dilute solutions of **1c**, but only at elevated temperatures between 40 and 80 °C. Comparable magnitude coupling interactions between H_g and ^{199}Hg were also evident but poorly resolved. Notoriously rapid intermolecular exchange processes are commonly associated with coordination complexes of $Hg(II)$. Heteronuclear coupling between ^{199}Hg and ligand protons provides definitive evidence for slow intermolecular exchange. These coupling interactions indirectly suggest the ligands remain tridentate on the coupling constant time scale, since J_{HgH} have not been reported between ^{199}Hg and bidentate nitrogen or N,S donor ligands. Furthermore, this interaction was not observed in a more concentrated solution of **1c** (data not shown), likely because intermolecular exchange processes became more rapid. Significant broadening of resonances was observed for **1c** in dilute solution at 80 °C, suggesting intermolecular exchange at an appreciable rate. In contrast, resonances for **1a** and **1b** were still getting progressively sharper as the upper temperature limit for studies in acetonitrile- d_3 was approached.

Discussion

Detailed investigation of the coordination chemistry of divalent zinc triad metal ions is generally hampered by plasticity in coordination number and geometry, which leads to rapid intramolecular isomerization and intermolecular exchange rates. A variety of multidentate ligands have been used to create complexes with slow intermolecular exchange behavior on the NMR chemical shift and coupling constant time scales. Multidentate ligands have also provided group 12 coordination complexes in which different types of intramolecular exchange behavior was amenable to detailed characterization. Published studies have documented ligand-centered isomerization processes with no metal coordination changes³⁶ and slow intramolecular isomerization involving either changes in coordination number or identity of ligating atoms.^{10,37-39} In addition, exclusion of specific geometric isomers from solution equilibria has been observed.^{8,9} However, to the best of our knowledge only the novel $N_4(SR_2)_2$ coordination sphere divalent zinc triad metal ion complexes investigated here have enabled any characterization of individual geometric isomerization processes without cleavage of metal-ligand bonds.

Bis-tridentate chelates have nine regular polyhedral isomeric forms.⁹ A mechanism for concerted isomer interconversion without bond cleavage is depicted in Figure 6, patterned after the mechanism for racemization of tris-bidentate complexes described by Rodger and Johnson.⁴⁰ In this model, the terminal ligating atoms form 60° or 90° angles, respectively, around the central ligating atom in **1-4** and **5-6**. Polyhedra **1-4** can be interconverted, ostensibly without ligand reorganization, by rotation about a single pseudo- C_3 axis perpendicular to the planes formed by the ligating atoms of the individual ligands. Polyhedra **3-6** can be interconverted by rotation about an orthogonal pseudo- C_3 , but both ligand reorganization and changes in the relative orientation of the ligating atom planes occur. Repulsion-energy calculations have predicted octahedral isomers **1**, **3**, and **6** to be associated with potential energy minima.⁴¹ Calculations with updated methodologies have not been identified.

Another hurdle to detailed characterization of the coordination chemistry of divalent zinc triad metal ions is the limited number of applicable instrumental methods. X-ray crystallography

provides detailed bond lengths and bond angles, but these solid state measurements cannot be assumed to provide a complete description of solution species. Both kinetic and thermodynamic factors determine what crystallizes and crystallizes first from a mixture in solution and can favor isolation of minor solution species. All three divalent zinc triad metal ion complexes of type $M(L)_2(ClO_4)_2$ were isolated in bis-tridentate chelate form **1**. In contrast, bis-tridentate chelates of other pyridyl ligands have crystallized in different forms, and not necessarily the same form for all three metals (Table 3). Crystallization documents the presence of a complex with a particular structure in solution, but not its relative abundance. Furthermore, correlations between crystallographic and solution state methods have to be made especially carefully with divalent zinc triad metal ions in the context of the facility with which they normally undergo intramolecular isomerization and intermolecular exchange.

NMR is one of the most valuable solution methods for characterization of divalent zinc triad metal ion complexes of organic ligands because chemical shift, coupling constant and exchange time information can be collected simultaneously for selected nuclei. Furthermore, both cadmium and mercury have high natural abundance spin $I = 1/2$ isotopes. In the absence of coincidental chemical shifts and exchange processes faster than the chemical shift time scale in solution, the symmetry of complexes of form **1** and **4** would lead to a singlet methyl proton resonance and one discrete resonance for every other ligand proton. Similarly, asymmetric complexes of form **2**, **3** and **5** would have two singlet methyl proton resonances and discrete resonances for every other proton of both ligands. In contrast, complex **6** is a higher symmetry form with four pyridyl proton resonances, three methylene proton resonances and one methyl resonance expected. Either coincident chemical shifts or exchange rates faster than the chemical shift time scale can reduce the number of discrete proton resonances observed.

The proton NMR spectra of **1a-c** were strongly temperature dependent. At low temperature, extensive geminal coupling of methylene proton resonances provided definitive evidence for slow intermolecular exchange and preservation of all metal-ligand bonds. Even more significant were protons giving rise to two resonances in slow exchange on the chemical shift time scale of inequivalent intensity for all three metals. Detection of independent sets of ligand resonances for $[M(L)_2]^{2+}$ supports slow intramolecular geometric isomerization between bis-tridentate chelate forms on the NMR chemical shift time scale.

Structural and chemical shift considerations can be used to generate initial form assignments for the major and minor ligand environments observed in low temperature NMR experiments. Interligand steric interactions are anticipated to be greater in trigonal prismatic forms **2**, **4** and **5** than the octahedral complexes. However, in previous studies of bis-tridentate chelates the differences were not great enough to observe slow exchange between individual octahedral and trigonal prismatic forms.^{4,5,8,9} Strong geminal coupling of the methylene protons of **L**¹ provided evidence that form **6** was excluded from the solution equilibria between all or most of the other $[M(L)_2]^{2+}$ forms at low temperature.^{8,9} Similarly, geminal coupling is evident for both minor and major $[M(L)_2]^{2+}$ ligand environments observed at low temperature, leaving forms **1** and **3** as their most likely assignments.

Although some ligand protons only had one well-resolved resonance at -40 °C, for H_a there were two resonances with an approximate 0.4 ppm chemical shift differences. A difference of this magnitude is often induced by interactions with the ring current of opposing ligands in bis-chelates.^{8,9,11,42} Significantly, the enantiomeric **3** and **3'** forms have the pyridyl rings in close proximity where interactions could occur between them while form **1** does not. Based on this analysis, the minor low temperature species with H_a resonance only slightly upfield of free ligand at ~8.4 ppm is assigned to form **1**, which has C_i symmetry and one environment for each proton type. Assignment of the major ligand environment at ~8.0 ppm to chiral

enantiomeric forms **3** and **3'** then follows, but requires either widespread unresolved chemical shift differences or a rapid exchange process on the chemical shift time scale for the two ligands.

Significantly, for $\text{Zn}(\text{L})_2^{2+}$ the fairly sharp major ~ 8.0 ppm H_a resonance observed below 0°C began to broaden as the temperature approached -40°C , suggesting an exchange process was approaching the slow exchange limit. Unfortunately, while the proton spectra of $[\text{Zn}(\text{L})_2]^{2+}$ were qualitatively similar in acetone- d_6 and CD_3CN solutions at -40°C , further cooling of the acetone- d_6 sample resulted in broadening to extinction (data not shown). A suitable NMR solvent with lower freezing point could not be found. Since the slow exchange limit could not be reached for these H_a environments, neither the number of exchanged average species nor their NMR parameters could be readily determined experimentally. Given evidence for an exchange process, interconversion of complexes with forms **3** and **3'** through form **4** becomes an attractive hypothesis. Significantly, the interconversion of **3** and **3'** became rapid on the chemical shift time scale at a higher temperature for $\text{Zn}(\text{L})_2^{2+}$ than for the complexes involving larger metal ions and larger interligand separations.

Proposing involvement of a complex with trigonal pyramidal form **4** in low temperature equilibria, but not complexes with forms **2**, **2'**, **5** and **5'**, requires further comment. Examination of space filling crystal structure diagrams for **1a-1c** suggested that the trans facial orientation permitted the smallest interligand separation (Figs. S1-3). In structures **1a** and **1b**, for example, the thioether methyls extended more than halfway across the space between the donor atom planes associated with the two ligands. The opposing ligand had H_b of the pyridyl rings in distant opposition with the thioether methyl and aliphatic amine hydrogen blocking rotation in either direction. As a result, rotating through trigonal planar forms **2** and **2'** would require energetically demanding lengthening of many metal-ligand bonds. In contrast, form **4** has equivalent donor groups eclipsed and therefore has the potential to alter the angle between the planes formed by the donor atom. The energetic cost of lengthening a pair of M-L bonds can then be offset by shortening another pair without ligand reorganization. This model can also explain why the exchange rate between forms **3** and **3'** approaches the chemical shift time scale for Zn(II) but not its larger congeners. The distance separating the parallel donor atom planes of the two ligands is smaller for Zn(II) and interligand steric constraints would become significant with lesser deviations from parallel. As mentioned earlier, forms **5** and **5'** formally require increasing the N(1)-N(2)-S angle from 60° to 90° . The necessary ligand reorganization and requisite M-L bond stretches likely create an energy barrier that cannot be overcome on the chemical shift time scale at low temperature.

Thus, the simplest explanation for the low temperature proton NMR spectra of **1a-1c** is slow exchange on the chemical shift time scale between a complex of form **1** and an equilibrated form involving **3**, **3'** and **4** (or a variant with non-parallel donor atom planes). Assuming the concentration of the form most resembling **4** is modest compared to octahedral forms **3** and **3'**, the relative size of the two H_a peaks in the low temperature spectra suggests the stabilities of the three octahedral forms are comparable but form **1** is slightly less thermodynamically stable with all three metal ions. This is consistent with the conclusions of repulsion-energy calculations for bis-tridentate chelates of asymmetric ligands.⁴¹ As the temperature is increased, exchange with the other complexes becomes possible, particularly **6**, which allows exchange of methylene protons and collapses geminal coupling.

This model is fully consistent with the observed zinc triad metal ion coordination behavior of symmetric tridentate ligands **L¹**, **L²** and **L³** (Table 3). Differences in the nature of the central donor atom of these ligands typically impact speciation equilibria at temperatures approaching -40°C . Slow inversion at the secondary aliphatic amine excludes form **6** from low temperature equilibria for $\text{M}(\text{L}^1)_2^{2+}$.^{8,9} In contrast, thioethers have a much lower barrier to inversion and $\text{M}(\text{L}^2)_2^{2+}$ had no detectable geometric preferences.⁵ For $\text{M}(\text{L}^3)_2^{2+}$, ligand geometry suggests

form **6** is preferred, although rapid exchange between multiple forms including form **6** could not be distinguished.⁴

Interestingly, the bis-tridentate chelates of symmetric ligands had readily detected J_{HgH} and smaller J_{CdH} at low temperature for pyridyl and methylene protons (Table 3). These complexes were either in rapid intramolecular exchange on the chemical shift time scale or non-exchanging. Rapid intramolecular isomerization with preservation of bonding interactions leads to exchange averaged coupling constants. On the other hand, slow exchange on the chemical shift time scale for major and minor forms of $\text{M}(\text{L})_2^{2+}$ led to chemical shift differences of 0.4 ppm for H_a . Isomer interconversion at a rate which is slow relative to the chemical shift time scale but intermediate on the J_{MH} time scale for $\text{Hg}(\text{L})_2^{2+}$ and $\text{Cd}(\text{L})_2^{2+}$ would explain the absence of metal coupling satellites in low temperature proton NMR spectra.

In this study, samples that had exchange broadened NMR spectra at room temperature were also examined at higher temperature, resulting in coalescence and significant sharpening of some resonances. For $\text{Hg}(\text{L})_2^{2+}$, J_{HgH} 70 Hz with H_e was measurable at 40 °C and notably broadened at 80 °C. In addition, less distinct J_{HgH} with H_g was evident between 60 and 80 °C. At these temperatures, the intramolecular isomerization between bis-tridentate forms **1-6** has become rapid enough for exchange averaged chemical shifts and coupling constants to be observed. Increasing the sample concentration increased the rate of intermolecular exchange and obscured the J_{HgH} interactions. Although comparable J_{CdH} interactions were not observed for $\text{Cd}(\text{L})_2^{2+}$, their typically smaller magnitude and the comparable chemical shift behavior for all three zinc triad bis-tridentate chelates suggests that intermolecular exchange was slow even at elevated temperatures. Interestingly, exchange broadening of resonances has been observed for other bis-tridentate chelates at ambient temperature.⁹ Spectra were never taken at higher temperature to possibly distinguish between intramolecular and intermolecular exchange processes as the source of broadening.

Conclusions

An asymmetric tridentate ligand permitted more detailed comparisons of the coordination chemistry of divalent group 12 metal ions to be made than related symmetric ligands. Fortuitous crystallization of isostructural bis-tridentate zinc triad complexes allowed for detailed structural comparisons. Unfortunately, the properties of the crystallized complexes were incompatible with assignment to the predominant solution species at -40 °C and prospects for crystallizing additional species associated with the complex solution equilibria are limited.

These studies suggest the resilience of high coordination number divalent zinc triad metal ion complexes to intermolecular exchange may be obscured by intramolecular exchange processes. These findings need to be thoughtfully considered when designing experiments to probe the bioactivity differences of $\text{Zn}(\text{II})$, $\text{Cd}(\text{II})$ and $\text{Hg}(\text{II})$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Schematic diagrams of chelate ring conformations in complexes **1a-c**. a) Pseudo-envelope N,N chelate ring in all three complexes with N_{alkyl} out of plane formed by other atoms. b) Twisted N,S chelate ring in **1a** and **1b**. c) Pseudo-envelope N,S chelate ring in **1c** with C8 out of plane formed by other atoms.

Fig. 2.
Structure of $\text{Zn}(\text{L})_2^{2+}$ in **1a**. Thermal ellipsoids shown at 50% level.

Fig. 3.
Structure of $\text{Cd}(\text{L})_2^{2+}$ in **1b**. Thermal ellipsoids shown at 50% level.

Fig. 4.
Structure of $\text{Hg}(\text{L})_2^{2+}$ in **1c**. Thermal ellipsoids shown at 50% level.

Fig. 5. Variable temperature proton NMR spectra highlights: Nominally 2 mM CD₃CN (Left), **1b** (center) and **1c** (right) at (from top) 80, 60, 40, 20, 0, -20 and -40 °C.

Fig. 6. Model of concerted isomerization for asymmetric bis-tridentate chelates involving regular polyhedral forms.

Table 1

Crystallographic Data for complexes **1a–c**

Complex	Zn(L) ₂ (ClO ₄) ₂ ·H ₂ O (1a)	Cd(L) ₂ (ClO ₄) ₂ ·H ₂ O (1b)	Hg(L) ₂ (ClO ₄) ₂ (1c)
Empirical formula	C ₁₈ H ₃₀ Cl ₂ N ₄ O ₉ S ₂ Zn	C ₁₈ H ₃₀ CdCl ₂ N ₄ O ₉ S ₂	C ₁₈ H ₂₈ Cl ₂ HgN ₄ O ₈ S ₂
Formula weight	646.85	693.88	764.05
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	C2/c	C2/c	P2(1)/c
Crystal size (mm ³)	0.72 × 0.40 × 0.30	0.95 × 0.85 × 0.55	0.60 × 0.40 × 0.25
<i>a</i> (Å)	21.472(16)	20.807(8)	8.116(5)
<i>b</i> (Å)	10.014(6)	10.357(4)	13.048(8)
<i>c</i> (Å)	13.625(12)	13.487(5)	12.213(7)
<i>β</i> (°)	119.36(2)	115.659(6)	107.596(10)
<i>V</i> (Å ³)	2553(3)	2619.8(17)	1232.7(12)
<i>Z</i>	4	4	2
<i>ρ</i> _{calcd} (Mg m ⁻³)	1.683	1.759	2.058
<i>μ</i> (Mo Kα)(mm ⁻¹)	1.391	1.251	6.682
<i>T</i> (K)	93(2)	93(2)	93(2)
Total data	10202	8869	9910
Unique data	2845	2968	2758
Refined parameters	170	170	161
R1, ^a wR2 ^b [<i>I</i> > 2σ(<i>I</i>)]	0.0267, .0669	0.0257, 0.0633	0.0224, 0.0571
R1, ^a wR2 ^b (all data)	0.0304, .0690	0.0278, 0.0647	0.0251, 0.0587
GOF	1.035	1.088	1.056

^aR1 = Σ||*F*_o| - |*F*_c||/Σ|*F*_o|.^bwR2 = [Σ[w(*F*_o² - *F*_c²)²]/Σ[w(*F*_o²)²]^{1/2} GOF (Goodness of Fit) is defined as [w(*F*_o - *F*_c)/(n_o - n_v)]^{1/2} where n_o and n_v denote the number of data and variables, respectively.

Table 2
Selected Bond Distances (Å) and Bond Angles (deg) for complexes **1a–c**

	Zn(L)₂(ClO₄)₂•H₂O (1a)^a	Cd(L)₂(ClO₄)₂•H₂O (1b)^b	Hg(L)₂(ClO₄)₂ (1c)^c
M-N(1)	2.1059(19)	2.3133(17)	2.424(2)
M-N(2)	2.1773(17)	2.3826(17)	2.305(2)
M-S	2.5978(13)	2.7115(7)	2.7989(13)
N(2)-M-N(2)#1	180.0	180.0	180.0
N(2)-M-N(1)	79.80(5)	74.38(5)	73.26(8)
N(2)-M-N(1)#1	100.20(5)	105.62(5)	106.75(8)
N(2)-M-S#1	95.85(5)	99.76(4)	99.59(7)
N(2)-M-S	84.15(5)	80.24(4)	80.41(7)
N(1)-M-S	88.13(7)	87.84(5)	95.51(6)
N(1)-M-N(1)#1	179.999(1)	180.0	180.0
N(1)-M-S#1	91.87(7)	92.16(5)	84.49(6)
S-M-S#1	180.0	180.0	180.0

^a Symmetry transformations used to generate equivalent atoms: -x, -y+2, -z-1.

^b Symmetry transformations used to generate equivalent atoms: -x, -y+2, -z+2.

^c Symmetry transformations used to generate equivalent atoms: -x, -y+2, -z.

Overview of crystallographic and solution state proton NMR properties^a for bis-tridentate chelates of divalent zinc triad metal ions

Table 3

Properties		L ¹	L ²	L ³	L
Crystal Form ^b	Zn ²⁺ Cd ²⁺ Hg ²⁺	5, 5' 5, 5' 5, 5'	1 3, 3' 2, 2'	6 6 6	1 1 1
Low T NMR	<i>J</i> (M ¹ H) Inversion Py ¹ H sets CH ₂ ¹ H sets	¹¹³ Cd, ¹⁹⁹ Hg Slow One Two	¹⁹⁹ Hg Fast One One	¹⁹⁹ Hg NA One One	NA Slow > One ^c > Six ^d
Reference		8,9	5	4	This work

^a 2 mM, CD₃CN, -40 °C.

^b Refer to Figure 6; with C₂ symmetric ligands, groups 1,3,4 and 6 are identical, which increases the symmetry of all the complexes.

^c Major and minor resonances were resolved for H_a only.

^d More than three major and three minor methylene proton resonances were observed.