Applications of tripodal [S_3] and [Se_3] L_2X donor ligands to zinc, cadmium and mercury chemistry: organometallic and bioinorganic perspectives†

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The tripodal *tris*(2-mercapto-1-R–imidazolyl)hydroborato ligand system, [Tm^R], and its selenium counterpart, [Tse^R], provide useful platforms for investigating organometallic and bioinorganic aspects of the chemistry of zinc, cadmium and mercury in sulfur-rich and selenium-rich coordination environments. For example, the tridentate [Tm^R] ligand provides an [S_3] donor array that is of use for mimicking aspects of zinc enzymes and proteins that have sulfur-rich active sites, such as the Ada DNA repair protein. With respect to mercury, an interesting application of the [Tm^{Bu^t}] ligand is the synthesis of the mercury alkyl compounds [Tm^{Bu^t}]HgR (R = Me, Et) that react with PhSH to yield [Tm^{Bu^t}]HgSPh and RH, a reaction that emulates mercury detoxification by the organomercurial lyase, *MerB*. In addition to the tridentate [Tm^R] and [Tse^R] ligands, applications of the bidentate counterparts, [Bm^R] and [Bse^R] are also described.

1 Introduction

Tripodal ligands, in their simplest form, provide three donor atoms with a distinct preference for coordinating to a metal in a facial rather than meridional manner.[1] As such, tripod ligands are often viewed as inorganic counterparts to cyclopentadienyl and benzene ligands. The widespread application of tripod ligands is largely a consequence of the fact that the steric and electronic properties of tripod ligands can be modified extensively, and to a much greater degree than is possible by simply introducing substituents on cyclopentadienyl and benzene ligands. For example, $[PhB(CH_2PR_2)_3]^-$ and $[PhB(CH_2SR)_3]^-$ are two structurally related tripod ligands that feature different donor atoms and confer different chemical properties.[2] Furthermore, a large degree of modification is possible even if one maintains a common donor array. For example, the electronic properties of a metal center can be dramatically influenced according to whether the tripod ligand employed is a "neutral" L_3 donor or an "anionic" X_3 donor,[3] or intermediate variants, as illustrated by the series of [N_3]-donors: *tris*(pyrazolyl)-methane (L_3),[4] *tris*(pyrazolyl)hydroborato (L_2X),[5] and *tris*[(amido)methyl]ethane (X_3),[6] as illustrated in Fig. 1.

Our first interest in tripod ligands was concerned with the [N_3]-donor *tris*(pyrazolyl)hydroborato [$Tp^{RR'}$] class of ligands (Fig. 2).[5] Specifically, we considered that this ligand system would be amenable to synthesizing an isostructural series of alkyl and hydride derivatives of the main group and transition elements, [$Tp^{RR'}$]MR and [$Tp^{RR'}$]MH, a proposal that was

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† Dedicated to the memory of Swiatoslaw ("Jerry") Trofimenko, whose landmark discovery of the synthesis of poly(pyrazoly)borate ligands made this research possible.

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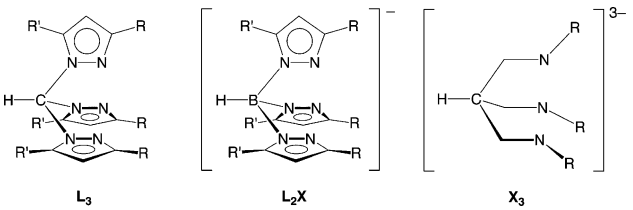


Fig. 1 Tripodal L_3, L_2X and X_3 [N_3]-donor ligands.

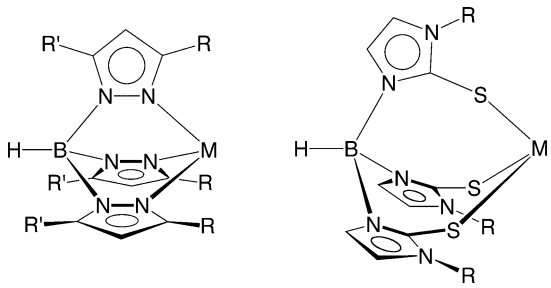
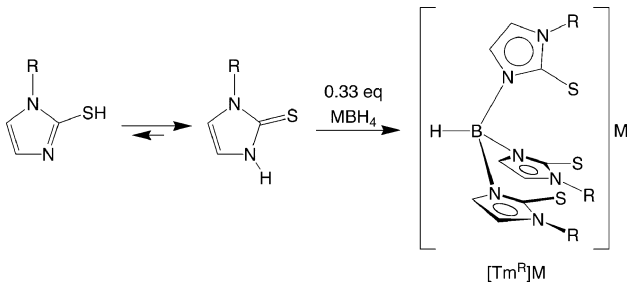


Fig. 2 [N_3]-donor [$Tp^{RR'}$] and [S_3]-donor [Tm^R] ligands.



Scheme 1

borne out with the isolation of such derivatives for Be,[7] Mg,[8] Zn,[9] Cd[10] and Fe.[11]

In view of the success in synthesizing alkyl and hydride derivatives, together with Vahrenkamp, we extended our studies to prepare the monomeric zinc hydroxide compound [$Tp^{Bu^t,Me}$]ZnOH, with the specific intent that it would serve as a synthetic analogue of the zinc enzyme carbonic anhydrase.[12,13] Indeed, with the pyrazolyl groups mimicking the three histidines, [$Tp^{Bu^t,Me}$]ZnOH proved to be an excellent structural and functional model for carbonic anhydrase.[12,14,15] Shortly thereafter, we obtained a more accurate structural model for carbonic anhydrase, namely {[Pim^{Pr^i,Bu^t}]ZnOH}$^+$, by using the sterically demanding neutral *tris*[2-(1-isopropyl-4-*tert*-butylimidazolyl)]phosphine ligand, [Pim^{Pr^i,Bu^t}].[16,17]

While histidine is the most commonly encountered metal-binding residue in zinc enzymes,[18] other residues such as glutamate, aspartate and cysteine are also utilized, and the precise combination is largely responsible for dictating the properties of the enzyme.[18,19] Some enzymes, in fact, use only cysteine residues to bind the zinc, as illustrated by 5-amino-levulinate dehydratase (ALAD).[20] Accurate synthetic modeling of such enzymes naturally requires the use of [S_3] tripod ligands, thereby providing the impetus for us to investigate the use of such ligands. In particular, the *tris*(2-mercapto-1-R–imidazolyl)hydroborato ligand system, [Tm^R] (Fig. 2),[21,22] was appealing for this purpose. The present article provides an account of our application of [Tm^R] and related ligands to the chemistry of zinc, cadmium and mercury, focusing on organometallic and bioinorganic perspectives.[23]

2 *Tris*(2-mercapto-1-R–imidazolyl)hydroborato ligands

The highly successful application of the [$Tp^{RR'}$] ligand system owes much to the fact that the method of synthesis, namely the reaction of a pyrazole ($Hpz^{RR'}$) with an alkali metal borohydride, M[BH_4], is exceedingly general; as such, a large variety of [$Tp^{RR'}$] derivatives that feature substituents with diverse electronic and structural features is available.[5] In 1996, Reglinski and Spicer reported an important development of this basic type of reaction.[21a] Specifically, 2-mercapto-1-methylimidazole (methimazole) was shown to react with $NaBH_4$ in a melt to yield [Tm^{Me}]Na (Scheme 1). A large variety of other [Tm^R]M derivatives have subsequently been synthesized and are frequently referred to as "soft" analogues of [$Tp^{RR'}$] ligands.[21]

Since 2-mercaptoimidazole compounds typically exist as their thione tautomers (Scheme 1), the sulfur atoms of [Tm^R] ligands are often described as possessing "thione" rather than "thiolate" character. However, while the anionic form of the [Tm^R]$^-$ ligand may certainly be represented by a resonance structure with three C=S thione groups in which each sulfur atom is a "neutral" donor, with the formal charge being localized on boron, it must be emphasized that this description should not be taken too literally because the sulfur atoms actually bear a substantial negative charge. For example, the NBO charges on sulfur in [Tm^{Me}]$^-$ are −0.36.[24] There are two reasons for the negative charge on the sulfur atoms in the [Tm^R]$^-$ ligand. Firstly, and most obviously, the closed shell ligand bears a negative charge, whereas thioketones are neutral. Secondly, a resonance interaction of the nitrogen lone pairs of the mercaptoimidazole moiety induces a negative charge on the sulfur atoms as illustrated in Fig. 3. This is by no means a new concept since previous studies have shown that the calculated charge on sulfur in thioformaldehyde $H_2C{=}S$ is almost zero (−0.05) whereas that in thiourea $(H_2N)_2C{=}S$ is substantially negative (−0.37).[25] In addition to calculations, experimental evidence to support the notion that the sulfur atom of the mercaptoimidazolyl moiety bears a substantial negative charge is provided by the simple observation that the sulfur atom of a mercaptoimidazole compound is a much better hydrogen bond acceptor than that of a simple thioketone.[25,26] Vahrenkamp's notion that [Tm^R] ligands represent "tame" thiolates[21e] is, therefore, most appropriate.

While [Tm^R] ligands are similar to [$Tp^{RR'}$] and [Cp^R] ligands in the sense that all are L_2X ligands according to the Covalent Bond Classification method,[3] there are several important differences. For example, the [Tm^R] and [$Tp^{RR'}$] ligands have different numbers of spacer atoms between the boron and the respective donor, *i.e.* there are two atoms between boron and the sulfur donor in [Tm^R], but only one atom between boron and the nitrogen donor in [$Tp^{RR'}$]. As a result of this different

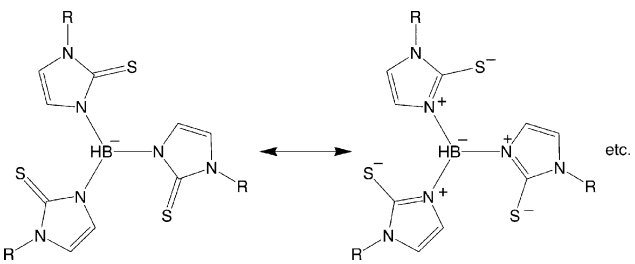


Fig. 3 Resonance structures for the closed-shell [Tm^R]$^-$ anion.

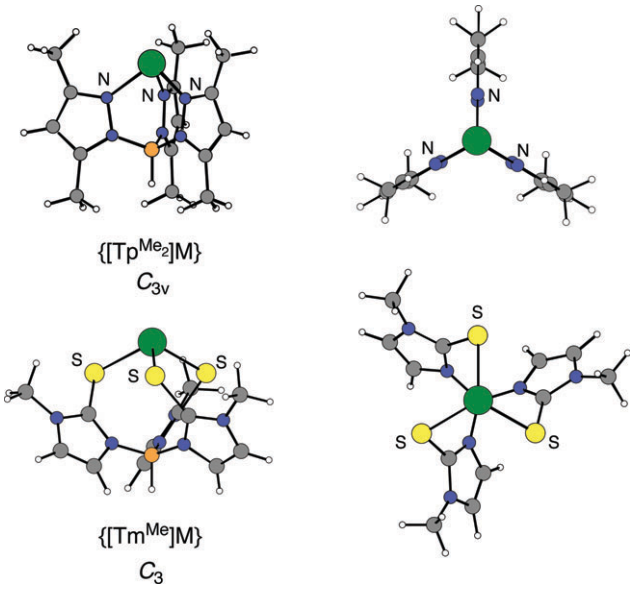


Fig. 4 Comparison of the coordination geometries of $\{[Tp^{RR'}]M\}$ and $\{[Tm^{R}]M\}$ moieties as illustrated for R = R′ = Me. Whereas $\{[Tp^{RR'}]M\}$ adopts a C_{3v} symmetric structure, $\{[Tm^{R}]M\}$ is chiral with C_3 symmetry.

linker size, the $[Tm^{R}]$ and $[Tp^{RR'}]$ exhibit different geometrical preferences.

Firstly, while coordination of both $[Tm^{R}]$ and $[Tp^{RR'}]$ ligands result in cage-like structures, the $\{[Tm^{R}]M\}$ moiety consists of three *eight*-membered rings, whereas that for the $\{[Tp^{RR'}]M\}$ moiety is composed of three *six*-membered rings. Secondly, whereas the $\{[Tp^{RR'}]M\}$ moiety typically adopts C_{3v} symmetry,[27] the $\{[Tm^{R}]M\}$ moiety adopts only C_3 symmetry due to a propeller-like twist of the ligand that is required to maintain reasonable bond lengths and angles for each of the three eight-membered rings (Fig. 4). As such, the $\{[Tm^{R}]M\}$ moiety is inherently chiral and NMR spectroscopic studies indicate that the barrier to enantiomer interconversion may be substantial on the NMR timescale.[28]

Another consequence of the different linker size is that the preference for simple κ^3-S_3 coordination using all three sulfur atoms of the $[Tm^{R}]$ ligand is often reduced compared to the corresponding κ^3-N_3 coordination observed for $[Tp^{RR'}]$ ligands. In particular, the $[Tm^{R}]$ ligand often binds with κ^2-S_2 or κ^3-S_2H coordination modes (Fig. 5), as illustrated by $[Tm^{Bu^t}]_2Zn$[21e] and $[Tm^{Ph}]_2M$ (M = Fe, Co),[29] respectively. The larger size of the linker also makes it possible for the $[Tm^{R}]$ ligand to coordinate with an "inverted" κ^4-coordination mode (Fig. 5), *e.g.* $[Tm^{Me}]_2Pb$,[30] a geometry that is not possible for $[Tp^{RR'}]$ ligands. It is, therefore, evident that $[Tm^{R}]$ is a rather flexible ligand that adopts a coordination mode which depends on the electronic nature and steric demands of the metal center. An illustration of the role that steric interactions may play is provided by the observation that the $[Tm^{R}]$ ligands of $[Tm^{R}]_2Fe$ adopt a κ^3-S_3 coordination mode for R = Me,[31] but a κ^3-S_2H coordination mode for R = Ph.[29]

A final important distinction between $[Tp^{RR'}]$ and $[Tm^{R}]$ ligands is that the longer linker for $[Tm^{R}]$ makes it possible for the B–H bond to be cleaved and the so-generated $B(mim^{R})_3$ ligand may coordinate in a κ^4-manner *via* the boron and three sulfur donors. The derived compounds, $\{[\kappa^4\text{-}B(mim^{R})_3]M\}$ (Fig. 5), are called "metallaboratranes" and represent an interesting class of molecules that feature metal-to-ligand M→B dative bonds.[1f–k]

IR spectroscopic studies on a variety of metal carbonyl compounds indicate that the $[Tm^{R}]$ ligand is more strongly

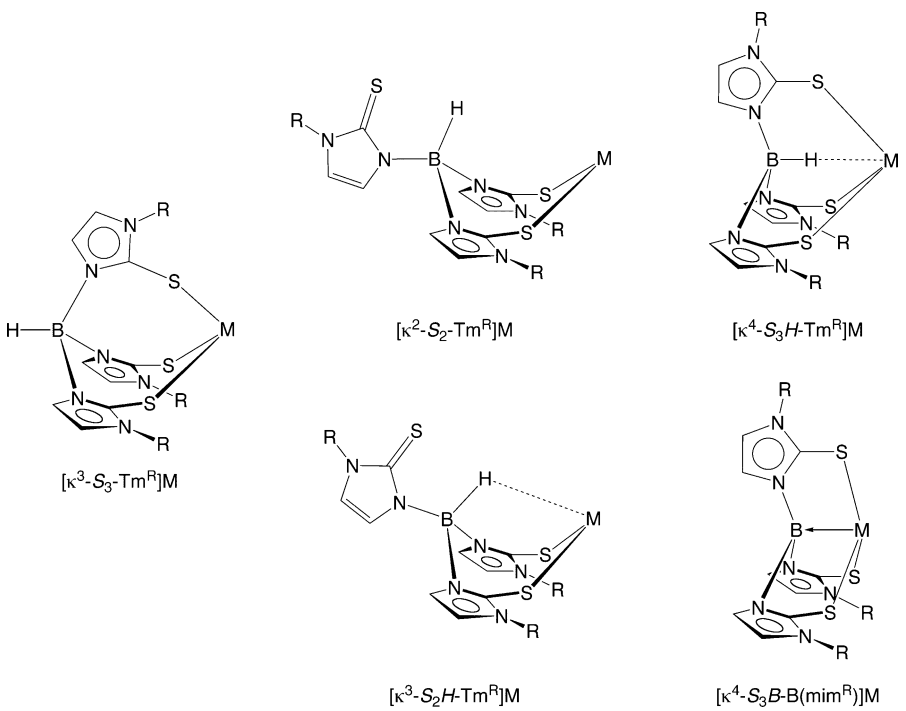
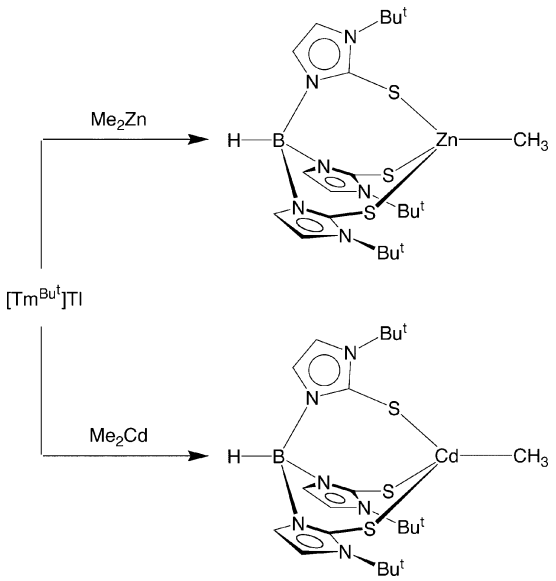


Fig. 5 Some coordination modes of $[Tm^{R}]$ and $B(mim^{R})_3$ ligands.



Scheme 2

electron donating than both [$Tp^{RR'}$] and [Cp^{R}] counterparts.[32] While the different electronegativities of the donor atoms provide an important component in determining the electron donating properties of the respective ligands, it is important to note that [Tm^{R}], [$Tp^{RR'}$] and [Cp^{R}] ligands have different σ and π-donor/acceptor characteristics and that these may also influence the electron donating properties.[21b,32] For example, while the principal σ bonding modes are similar for both [Tm^{R}] and [$Tp^{RR'}$] ligands, the sulfur atoms of the [Tm^{R}] ligand has an additional lone pair that may serve as a π-donor function and thereby influence the electron donating properties of this ligand. In contrast, [Cp^{R}] ligands have π-acceptor orbitals that play an important role in bonding and thereby reduce the overall electron donating properties of the ligand. As such, the electron donating properties of these classes typically increase in the sequence [Cp^{R}] < [$Tp^{RR'}$] < [Tm^{R}].

With respect to steric properties, [Tm^{R}] ligands are less sterically demanding than [$Tp^{RR'}$] ligands because the substituents on the former are more distant from the metal center. Specifically, the substituents on [Tm^{R}] are located three atoms away from the metal center, whereas the 3-substituents on [$Tp^{RR'}$] are only located two atoms away (Fig. 4). Thus, cone angles for the ligands typically increase in the sequence [Cp] < [Tm^{R}] < [$Tp^{RR'}$].

Table 1 M–C bond lengths for [Tm^{Bu^t}]MR complexes (M = Zn, Cd, Hg)

	d(M–C)/Å	Ref.
[Tm^{Bu^t}]ZnMe	1.973(3)	33
[Tm^{Bu^t}]CdMe	2.152(4)	35
[κ^1-Tm^{Bu^t}]HgMe	2.073(7), 2.069(6)[a]	36
[κ^1-Tm^{Bu^t}]HgEt	2.093(3)	36
[κ^3-Tm^{Bu^t}]$HgCH_2CN$	2.141(9)	36

[a] Values for two different crystalline forms.

3 [Tm^{R}]MR alkyl derivatives of zinc, cadmium and mercury

3.1 Syntheses and structures of [Tm^{R}]MR

The monomeric zinc methyl compound [Tm^{Bu^t}]ZnMe is obtained *via* the reaction of [Tm^{Bu^t}]Tl[1g] with Me_2Zn (Scheme 2) and the molecular structure, as determined by X-ray diffraction, is illustrated in Fig. 6.[33] Despite the sulfur-rich coordination environment, the Zn–C bond length of [Tm^{Bu^t}]ZnMe [1.973(3) Å; Table 1] is very similar to that of the [Tp^{Bu^t}]ZnMe analogue [1.971(4) Å].[34] Spectroscopically, the methyl group of [Tm^{Bu^t}]ZnMe is characterized by a singlet at δ 0.28 in the ^{1}H NMR spectrum and a quartet at δ −8.5 ($^1J_{C-H}$ = 119 Hz) in the ^{13}C NMR spectrum.

The cadmium counterpart [Tm^{Bu^t}]CdMe is likewise obtained *via* treatment of [Tm^{Bu^t}]Tl with Me_2Cd (Scheme 2) and has been structurally determined by X-ray diffraction (Fig. 6; Table 1).[35] In addition, the cadmium–methyl group is characterized by a signal at 0.37 ppm in the ^{1}H NMR spectrum which exhibits ^2J coupling to ^{111}Cd (67.1 Hz) and ^{113}Cd (70.0 Hz),[35] with values that are comparable to those of [$Tp^{Bu^t,Me}$]CdMe (71 and 74 Hz, respectively).[10]

In marked contrast to the tetrahedral geometries observed for [Tm^{Bu^t}]ZnMe and [Tm^{Bu^t}]CdMe, linear geometries are adopted by the mercury alkyl compounds [Tm^{Bu^t}]HgMe (Fig. 7; Table 1) and [Tm^{Bu^t}]HgEt that are obtained *via* the reactions of [Tm^{Bu^t}]K with RHgX (Scheme 3).[36] While the κ^1-coordination mode of the [Tm^{Bu^t}] ligand in [Tm^{Bu^t}]HgR (R = Me, Et) provides an interesting distinction with the κ^3-coordination mode adopted by the zinc and cadmium congeners,[37] it is pertinent to note that linear geometries are prevalent for mercury alkyl compounds.[38] In this regard, it is noteworthy that the cyanomethyl complex [Tm^{Bu^t}]$HgCH_2CN$, obtained from the reaction between [Tm^{Bu^t}]K, EtHgCl and KBH_4 in

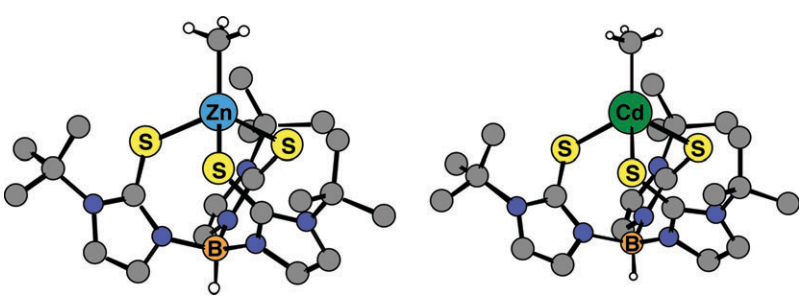


Fig. 6 Molecular structures of [Tm^{Bu^t}]ZnMe and [Tm^{Bu^t}]CdMe.

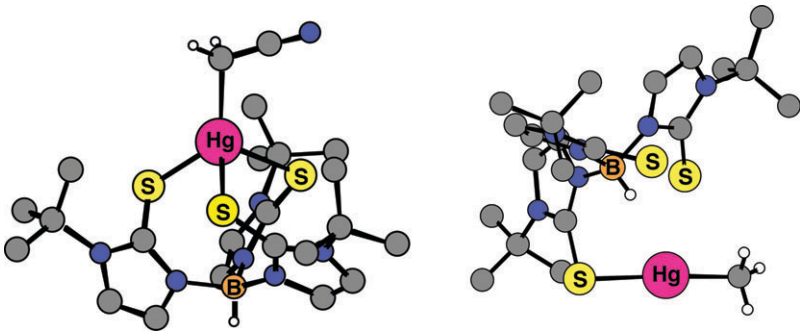
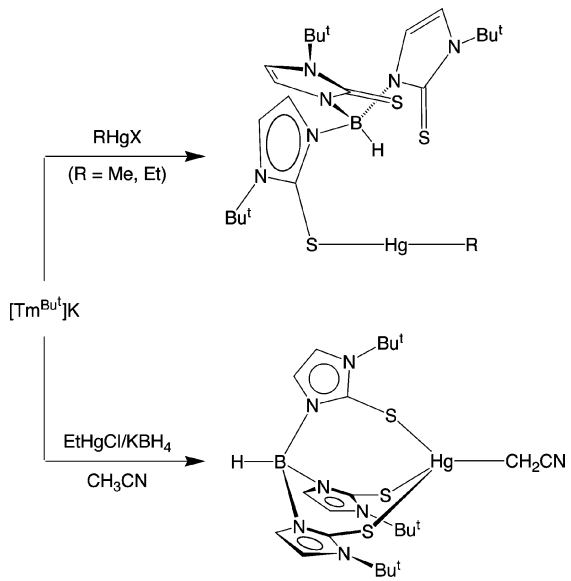


Fig. 7 Molecular structures of $[Tm^{Bu^t}]HgCH_2CN$ and $[Tm^{Bu^t}]HgCH_3$.



Scheme 3

MeCN (Scheme 3), actually adopts κ^3-coordination of the $[Tm^{Bu^t}]$ ligand giving a four-coordinate pseudo-tetrahedral mercury center (Fig. 7).

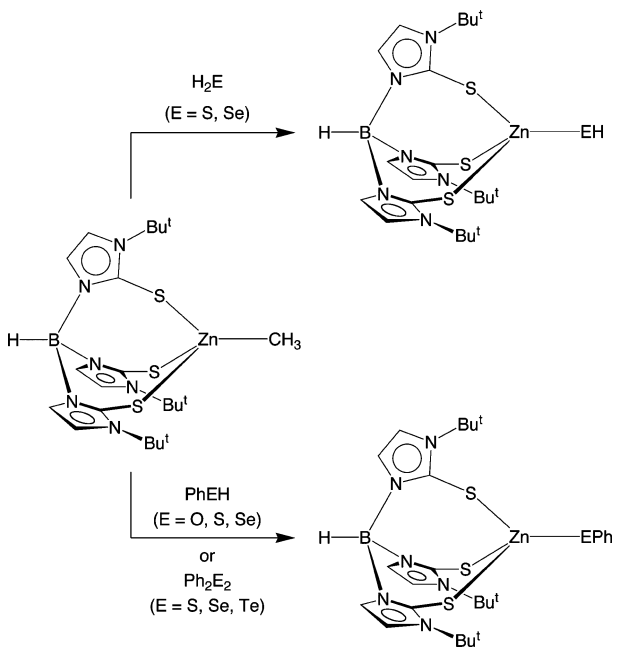
The observation of both linear and tetrahedral coordination geometries for $[Tm^{Bu^t}]HgR$ (R = Me, Et, CH_2CN) in the solid state suggests that interconversion between κ^1 and κ^3-isomers may be facile. In support of this notion, ^1H NMR spectroscopic studies on $[Tm^{Bu^t}]HgR$ (R = Me, Et) indicate that the molecules are highly fluxional. At low temperature, a spectrum consistent with a $[\kappa^3\text{-}Tm^{Bu^t}]HgR$ pseudo-tetrahedral structure is observed, but as the temperature is raised, an equilibrium between κ^1- and κ^3-isomers is observed.

3.2 Reactivity of $[Tm^R]MR$: access to chalcogenolate complexes and analysis of M–ER bonds

The zinc methyl compound $[Tm^{Bu^t}]ZnMe$ provides a means to synthesize a variety of other $[Tm^{Bu^t}]ZnX$ derivatives *via* reactivity of the Zn–C bond, as illustrated in Scheme 4. Of particular note, the hydrosulfido and hydroselenido compounds, $[Tm^{Bu^t}]ZnSH$ and $[Tm^{Bu^t}]ZnSeH$, are obtained *via* the reaction of $[Tm^{Bu^t}]ZnMe$ with H_2S and H_2Se, respectively,[39] with the latter complex being the first structurally characterized zinc–hydroselenido compound (Fig. 8).

Similarly, the series of phenylchalcogenolate compounds $[Tm^{Bu^t}]ZnEPh$ are obtained *via* reaction of $[Tm^{Bu^t}]ZnMe$ with either PhEH (E = O, S, Se) or Ph_2E_2 (E = S, Se, Te). Likewise, $[Tm^{Bu^t}]CdMe$ provides access to $[Tm^{Bu^t}]CdEPh$ (E = S, Se, Te) *via* treatment with PhSH, PhSeH, and Ph_2Te_2, respectively (Scheme 5). The phenoxide derivative $[Tm^{Bu^t}]$-CdOPh, however, was not isolated from the corresponding reaction of $[Tm^{Bu^t}]CdMe$ with PhOH, which preferentially resulted in the formation of $[Tm^{Bu^t}]_2Cd$ due to facile ligand redistribution. Isolation of a cadmium aryloxide is, nevertheless, facilitated by the use of bulky substituents and thus $[Tm^{Bu^t}]CdOAr'$ may be obtained by treatment of $[Tm^{Bu^t}]CdMe$ with Ar′OH (Ar′ = 2,6-$Ph_2C_6H_3$). The mercury alkyl compounds $[Tm^{Bu^t}]HgR$ (R = Me, Et) also react with PhSH to yield $[Tm^{Bu^t}]HgSPh$,[36] a reaction that will be discussed in more detail in Section 3.3.

The structural characterization of the series of zinc and cadmium chalcogenolate complexes $[Tm^{Bu^t}]MEAr$ is significant because such series are very rare, with the only other examples being $Cp^*_2Zr(EPh)_2$[40] and $[Tp^{Me_2}]_2SmEAr$.[41,42] The most interesting aspect of these chalcogenolate complexes pertains to the variation of M–E bond lengths which are



Scheme 4

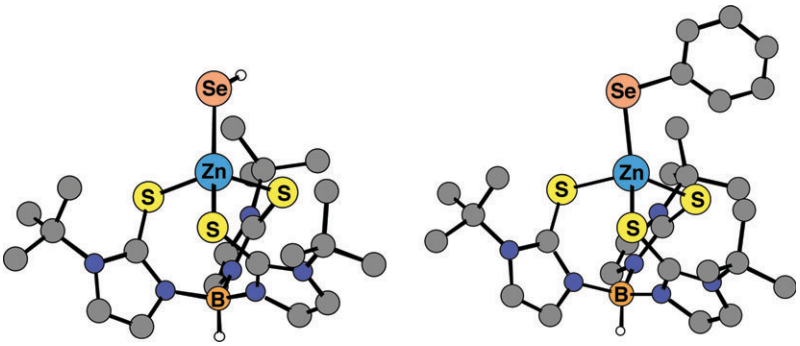
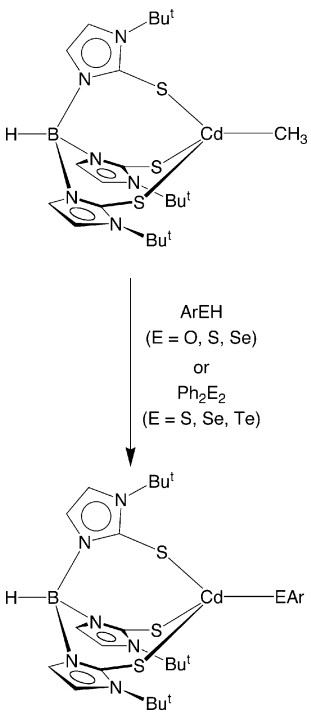


Fig. 8 Molecular structures of [Tm$^{Bu^t}$]ZnSeH and [Tm$^{Bu^t}$]ZnSePh.

summarized in Table 2 and Fig. 9. Of particular note, the difference in M–O and M–S bond lengths for [Tm$^{Bu^t}$]ZnEPh (0.35 Å) and [Tm$^{Bu^t}$]CdEAr (0.35 Å) corresponds much more closely to the difference in covalent radii of O and S (0.30 Å) than do the corresponding values for Cp*$_2$Zr(EPh)$_2$ (0.53 Å) and [Tp^{Me_2}]$_2$SmEAr (0.70 Å). As such, the M–O bond lengths in the Zr and Sm compounds are shorter than would otherwise be expected on the basis of the respective M–E (E = S, Se, Te) bond lengths.

Anomalously short metal–ligand covalent bonds may be rationalized by either an ionic component or a π-component to the bonding, but the significance of these components on metal alkoxide and thiolate bond lengths is controversial. For example, Barron *et al.* have proposed that the short Al–O bond lengths in R$_2$AlOR′ and R$_2$Al(OR′)L is due to π-donation from oxygen to aluminium,[43] whereas Power and co-workers have concluded that the short M–ER bond lengths in R$_2$MER′ (M = Al, Ga; E = O, S) are due to an ionic component to the bonding.[44] Calculations on [Tm$^{Bu^t}$]ZnEPh, [Tm$^{Bu^t}$]CdEPh, Cp*$_2$Zr(EPh)$_2$, and [Tp]$_2$LnEPh (Ln = La, Lu) indicate that the polarity (as judged by the NBO charges) of the M–O bond increases dramatically across the series Cd ≈ Zn < Zr < Ln,[45] thereby supporting the suggestion that the short M–O bond lengths for the latter compounds may be attributed to ionic effects. Furthermore, additional calculations provide evidence that π-effects are not significant in influencing the M–E bond lengths in these systems.



Scheme 5

Table 2 Variation of M–EAr bond lengths (Ar = Ph unless otherwise stated otherwise; Data taken from ref. 35)

	[Tm$^{Bu^t}$]CdEAr	[Tm$^{Bu^t}$]ZnEAr	Cp*$_2$Zr(EAr)$_2$	[Tp^{Me_2}]$_2$SmEAr
O	2.109(6)[a]	1.925(4)	1.989(3)	2.159(2)[b]
S	2.4595(7)[c]	2.272(1)	2.522(1)	2.8620(9)[d]
Se	2.5595(5)	2.394(1)	2.651(3)	2.9390(3)
Te	2.7097(5)	2.568(1)	2.87(2)	3.1874(4)

[a] Ar = 2,6-C$_6$H$_3$Ph$_2$. [b] Ar = *p*-OC$_6$H$_4$Bu^t. [c] *d*(Cd–S) = 2.465(1) Å for Ar = *p*-SC$_6$H$_4$Me. [d] Ar = *p*-OC$_6$H$_4$Me.

3.3 Protolytic cleavage of the mercury–alkyl bonds in [Tm$^{Bu^t}$]HgR by PhSH as a functional model for mercury detoxification by organomercurial lyase, *MerB*

The reactivity of [Tm$^{Bu^t}$]HgR towards PhSH is of considerable significance with respect to mercury detoxification. In this regard, organomercury compounds are highly toxic because

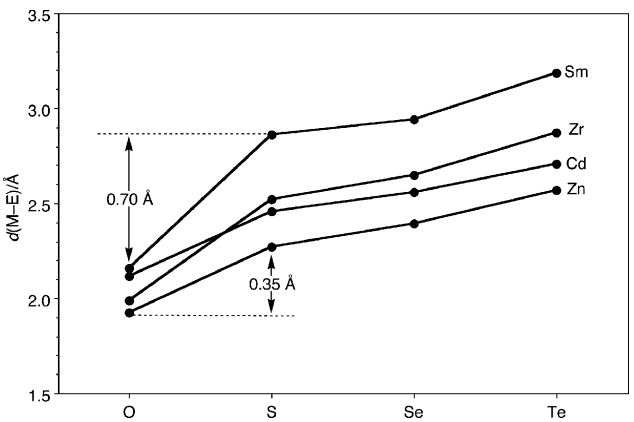


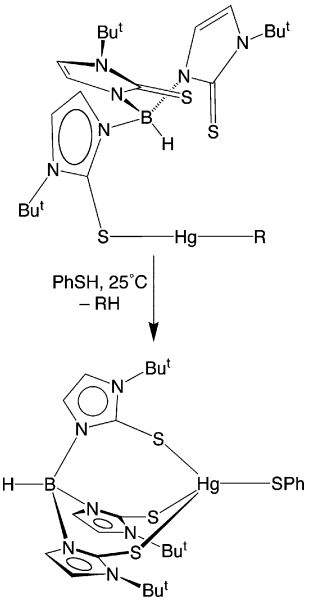
Fig. 9 Variation in experimental M–E bond length for [Tm$^{Bu^t}$]-ZnEPh, [Tm$^{Bu^t}$]CdEAr, Cp*$_2$Zr(EPh)$_2$, and [Tp^{Me_2}]$_2$SmEAr (reproduced from ref. 35 with permission of The Royal Society of Chemistry).

(*i*) they coordinate so strongly to protein residues, (*ii*) they are capable of crossing the blood–brain barrier, and (*iii*) the Hg–R bond is kinetically stable towards protolytic cleavage in aqueous solution. Detoxification of organomercury compounds is achieved in Nature by the combined action of two enzymes, namely: (*i*) bacterial organomercurial lyase (*MerB*), which achieves protolytic cleavage of the otherwise inert Hg–R bond and (*ii*) mercuric ion reductase (*MerA*), which reduces Hg(II) to less toxic elemental mercury, Hg(0).[46,47]

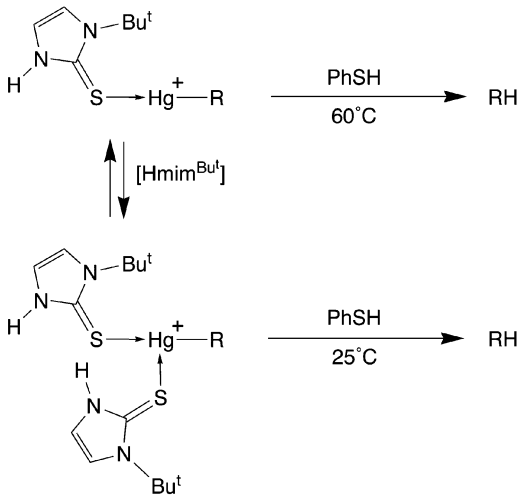
MerB obtained from *E. coli* (R831b) has four cysteine residues that are crucial for enzymatic activity, of which one plays a structural role and three serve the combined roles of binding the $[HgR]^+$ substrate and protolytically cleaving the mercury alkyl group.[46,48,49] Since the $[Tm^{Bu^t}]$ ligand presents a sulfur-rich coordination environment, the alkyl complexes $[Tm^{Bu^t}]HgR$ provide an excellent means of investigating the mechanism of action of *MerB* in a synthetic analogue system. In this regard, the monodentate κ^1-coordination mode of the $[Tm^{Bu^t}]$ ligand observed for $[Tm^{Bu^t}]HgMe$ and $[Tm^{Bu^t}]HgEt$ shows a close correspondence to the means by which mercury has been proposed to coordinate to the protein in the mercury dithiothreitol complex of *MerB*.[50]

Significantly, the elimination of RH upon treatment of $[Tm^{Bu^t}]HgR$ (R = Me, Et) with PhSH (a simple mimic for a cysteine thiol) represents an interesting example of facile Hg–C bond cleavage by a thiol in a sulfur coordination environment (Scheme 6). The mechanism of cleavage of the Hg–C bond is of key importance and it has been noted previously that two-coordinate mercury alkyl compounds of the type X–Hg–R are inert towards such cleavage.[51,52] The high reactivity of $[Tm^{Bu^t}]HgMe$ and $[Tm^{Bu^t}]HgEt$ is, therefore, attributed to the ability of these molecules to access κ^2- or κ^3-isomers.

Evidence that the coordination number may have a significant impact on the reactivity of the Hg–C bond in this system is provided by the observation that the 1-*tert*-butylimidazole-2-thione derivatives $\{[Hmim^{Bu^t}]HgR\}^+$, in which the $Hmim^{Bu^t}$ ligand emulates the κ^1-coordination mode of the $[Tm^{Bu^t}]$ ligand, do not react with PhSH under comparable conditions, but require heating to 60 °C to proceed rapidly (Scheme 7). However, upon addition of $Hmim^{Bu^t}$ to a mixture of $\{[Hmim^{Bu^t}]HgEt\}[BF_4]$ and PhSH, elimination of EtH occurs rapidly at room temperature. This observation is consistent with the formation of a higher coordinate species $\{[Hmim^{Bu^t}]_n$-$HgEt\}^+$ that is more susceptible to Hg–C protolytic cleavage than is two-coordinate $\{[Hmim^{Bu^t}]HgEt\}^+$. A consideration of these observations suggests that, of the three nonstructural cysteine residues of *MerB* that are essential for enzymatic activity, one cysteine is required to coordinate $[HgR]^+$ in a linear manner, a second cysteine is required to activate the Hg–alkyl group towards protolytic cleavage, while the third cysteine is required to effect the cleavage reaction.



Scheme 6 (modified from ref. 36 with permission from Science).



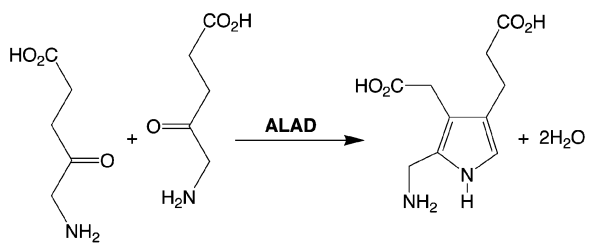
Scheme 7 (modified from ref. 36 with permission from Science.)

4 {[Tm^R]Zn} complexes as synthetic analogues of zinc enzymes

The $[Tm^R]$ ligand system provides a useful platform for obtaining synthetic analogues of zinc enzymes and proteins that have sulfur rich active sites such 5-aminolevulinate dehydratase and the Ada DNA repair protein.

4.1 5-Aminolevulinate dehydratase and lead poisoning

5-Aminolevulinate dehydratase (ALAD), also referred to as porphobilinogen synthase (PBGS), is an important enzyme that is present in all organisms which synthesize tetrapyrroles, and has the specific role of catalyzing the dimerization of 5-aminolevulinic acid (ALA) to porphobilinogen, a



Scheme 8

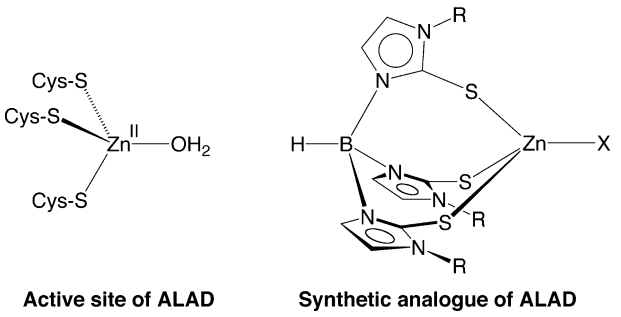


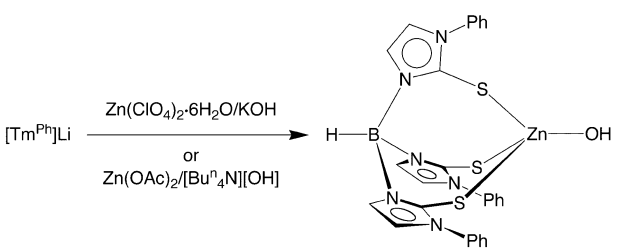
Fig. 10 Active site of ALAD and a synthetic analogue.

monopyrrole (Scheme 8).[53] ALAD is a zinc enzyme that contains both catalytic and structural zinc sites, of which the catalytic site has the uncommon composition of $[(Cys)_3Zn^{II}(OH_2)]$ (Fig. 10). As such, the three sulfur donors of the $[Tm^R]$ ligand system may be used to emulate the three cysteine residues in ALAD. In particular, the zinc hydroxide complex $[Tm^{Ph}]ZnOH$ complex may be obtained by (*i*) the reaction of $[Tm^{Ph}]Li$ with $Zn(ClO_4)_2$ in the presence of KOH and (*ii*) the reaction of $[Tm^{Ph}]Li$ with $Zn(OAc)_2$ in the presence of $[Bu_4^nN]OH$, as illustrated in Scheme 9.[54]

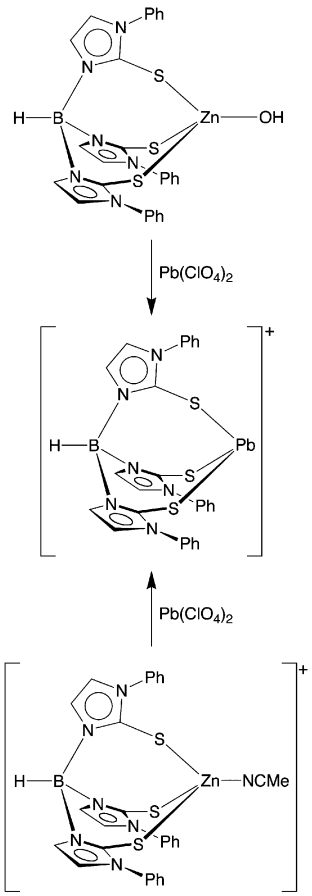
$[Tm^{Ph}]ZnOH$ is the first tetrahedral zinc hydroxide complex supported by a $[S_3]$ donor ligand to be structurally characterized by X-ray diffraction and the Zn–OH bond length [1.896(4) Å] is comparable to those for other monomeric tetrahedral zinc hydroxide complexes, namely the *tris*(pyrazolyl)hydroborato derivatives, $[Tp^{Bu^t,Me}]ZnOH$ [1.85 Å] and $[Tp^{Cum,Me}]ZnOH$ [1.85 Å], and the *tris*(imidazolyl)phosphine complex $\{[Pim^{Bu^t,Pr^i}]ZnOH\}^+$ [1.86 Å]. The mechanism of action of ALAD involves displacement of the aqua ligand by the substrate, ALA. A simple indication that displacement of the aqua ligand in such a coordination environment is facile is provided by protonation of $[Tm^{Ph}]ZnOH$ with $HClO_4$ in acetonitrile, in which the incipient aqua ligand is displaced by MeCN to give $\{[Tm^{Ph}]Zn(NCMe)\}^+$.[54,55]

An important facet of ALAD is concerned with lead poisoning. Indeed, the toxicological properties of lead, the most commonly encountered poisonous metal pollutant in the environment,[56,57] are a consequence of its interactions with proteins.[58–60] *Inter alia*, the debilitating effects of lead poisoning are attributed to the inability of lead-substituted ALAD to synthesize porphobilinogen, a monopyrrole which is essential for heme synthesis.[61–63] Furthermore, a secondary effect is that inactivation of ALAD results in a build-up of aminolevulinic acid, which itself is toxic.[62,64]

Lead poisoning involving ALAD has been modeled in a synthetic analogue system by observing that $[Tm^{Ph}]ZnOH$,



Scheme 9



Scheme 10

$[Tm^{Ph}]ZnI$ and $\{[Tm^{Ph}]Zn(NCMe)\}(ClO_4)$ react rapidly with $Pb(ClO_4)_2$ to give the lead complex $\{[Tm^{Ph}]Pb\}(ClO_4)$ (Scheme 10).[55] Measurement of the equilibrium constant for the reaction involving ligand exchange between $\{[Tm^{Ph}]Pb\}(ClO_4)$ and $Zn(ClO_4)_2$ in MeCN indicates that the preference of $[Tm^{Ph}]$ to coordinate Pb^{II} over Zn^{II} in this system is *ca.* 500 : 1, a value which clearly indicates that lead would show a strong thermodynamic tendency to displace zinc from sulfur rich active sites in enzymes. Despite this strong preference, however, the lead in $\{[Tm^{Ph}]Pb\}^+$ is replaced by zinc in the presence of NaI, a reaction that occurs because the above equilibrium is shifted to the right by precipitation of Pb^{II} as PbI_2.

The most notable feature of the molecular structure of $\{[Tm^{Ph}]Pb\}^+$, as illustrated in Fig. 11, is that the lead exhibits a trigonal pyramidal geometry which bears a close correspondence to the active site of Pb^{II}–ALAD.[64] This coordination geometry is markedly different to the four-coordinate nature of zinc in $\{[Tm^{Ph}]Zn(NCMe)\}^+$ and many other $[Tm^R]ZnX$ derivatives. As such, the comparison provides clear evidence that Pb^{II} and Zn^{II} attached to a common $[S_3]$ donor array have very different coordination preferences and that Pb^{II} has a much reduced tendency to bind an additional ligand. The reduced Lewis acidity of trigonal-pyramidal Pb^{II} compared to that of Zn^{II} was proposed to be a manifestation of the stereochemically active lone pair on Pb^{II} which tempers the effect (Fig. 12);[55] indeed, this notion has subsequently received support from theoretical calculations.[65]

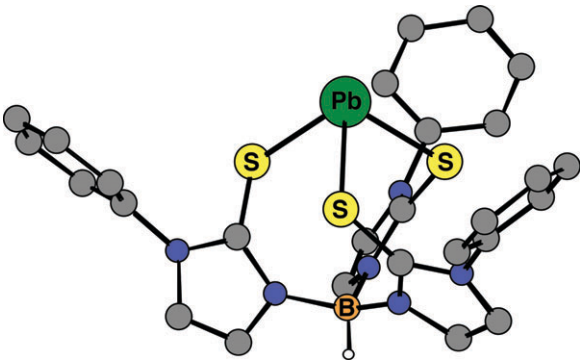


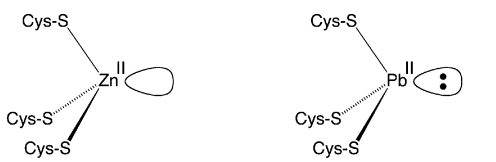
Fig. 11 Molecular structure of $\{[Tm^{Ph}]Pb\}^+$.

The reduced Lewis acidity of trigonal pyramidal Pb^{II} is of clear relevance to the inactivity of Pb^{II}–ALAD since the mechanism of action of ALAD requires activation of the ALA substrate by coordination of the ketone group to the metal center. The magnitude of the interaction is clearly dictated by the Lewis acidity of the metal center and, as such, Pb^{II}–ALAD would show a much reduced tendency to activate the ALA substrate (Fig. 12). Furthermore, analysis of the structures of a variety of lead compounds indicates that Pb^{II} shows a reduced tendency to adopt tetrahedral coordination; as such, it is evident that lead would also disrupt the structures of proteins if it substitutes a structural zinc site.[66]

4.2 The Ada DNA repair protein

4.2.1 Structural analogues. While the active sites of most zinc enzymes feature a zinc aqua or hydroxide group as the key component, there is also a class of zinc enzymes and proteins for which the reactivity centers on a zinc–thiolate linkage, as exemplified by the Ada DNA repair protein with a tetrahedral $[Cys_4Zn]$ active site.[67–70] Simple synthetic analogues for the $[(Cys)_4Zn]$ motif of the Ada protein are provided by the thiolate complexes $[Tm^R]ZnSPh$ (*e.g.* R = Ph, Bu^t), as illustrated in Scheme 4, in which the $[Tm^R]$ ligand serves the role of the three cysteine residues that remain bound to zinc during the course of the alkylation reaction.[71–73]

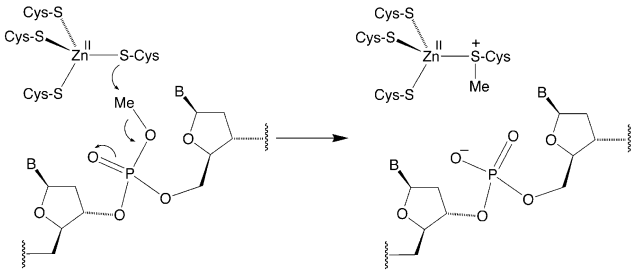
The Ada protein achieves the repair of damaged DNA by undergoing sacrificial alkylation of one of the zinc cysteine thiolate ligands (Scheme 11). This nucleophilic reactivity of the zinc–cysteine thiolate moiety of the Ada protein is particularly interesting in view of its lack of reactivity when it is a component of a structural site. As such, it has been postulated that N–H···S hydrogen bonding interactions between the



Trigonal Zn^{II}
Empty orbital
Strong Lewis acid
Activates substrates

Trigonal Pb^{II}
Lone pair orbital
Weak Lewis acid
Does not activate substrates

Fig. 12 Comparison of the properties of trigonal Zn^{II} and Pb^{II}.



Scheme 11

thiolate sulfur and amide groups of other residues provide a mechanism to modulate the reactivity of the zinc–cysteine thiolate moiety.[74,75] In this regard, the thiolate complexes $[Tm^R]ZnSCH_2C(O)N(H)Ph$ (R = Ph, Bu^t), which incorporate an N–H hydrogen bonding functionality, provide a more refined structural analogue for the Ada protein.[71b,76] The presence of hydrogen bonding interactions within $[Tm^R]ZnSCH_2C(O)N(H)Ph$ was confirmed by X-ray diffraction, as illustrated in Fig. 13. Selected data pertaining to the hydrogen bonding interactions are summarized in Table 3; for example, $[Tm^{Bu^t}]ZnSCH_2C(O)N(H)Ph$ is characterized by NH···S and N···S separations of 2.42 and 3.00 Å, respectively. These values are sufficiently short that the hydrogen bonding interaction must be considered significant.[77]

In addition to zinc thiolate derivatives, cationic mercaptoimidazole adducts $\{[Tm^{Ar}]Zn(Hmim^{Ar})\}^+$ with a tetrahedral $[ZnS_4]$ motif have also been synthesized (Scheme 12).[78] For both $\{[Tm^{Ph}]Zn(Hmim^{Ph})\}^+$ and $\{[Tm^{p\text{-}Tol}]Zn(Hmim^{p\text{-}Tol})\}^+$, the $Zn–S(Hmim^{Ar})$ bond lengths [2.326(1), R = Ph; 2.324(1) Å, R = *p*-Tol] are longer than that of Zn–SPh and $Zn–SCH_2C(O)N(H)Ph$, consistent with the dative covalent nature of the interaction with the mercaptoimidazole ligands.

4.2.2 Modeling the mechanism of action of the Ada DNA repair protein. Alkylation of a zinc–cysteine thiolate residue is the key step in the mechanism of action of the Ada DNA repair protein and may be modeled by the reactivity of $[Tm^R]ZnSR$ towards alkylating agents such as MeI. Indeed, $[Tm^R]ZnSR$ reacts rapidly with MeI to yield $[Tm^R]ZnI$ and RSMe.[71,72] A comprehensive evaluation of the reactivity of a series of zinc thiolate complexes, namely $[Tp^{RR'}]ZnSR$, $[HB(pz)_2(mim^R)]ZnSR$, $[HB(pz^R)(mim^R)_2]ZnSR$, and

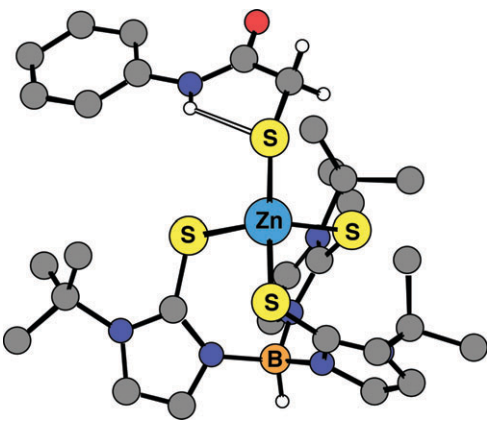


Fig. 13 Molecular structure of $[Tm^{Bu^t}]ZnSCH_2C(O)N(H)Ph$.

Table 3 Comparison of bond length data (Å) for $[Tm^R]ZnSCH_2C(O)N(H)Ph$ derivatives

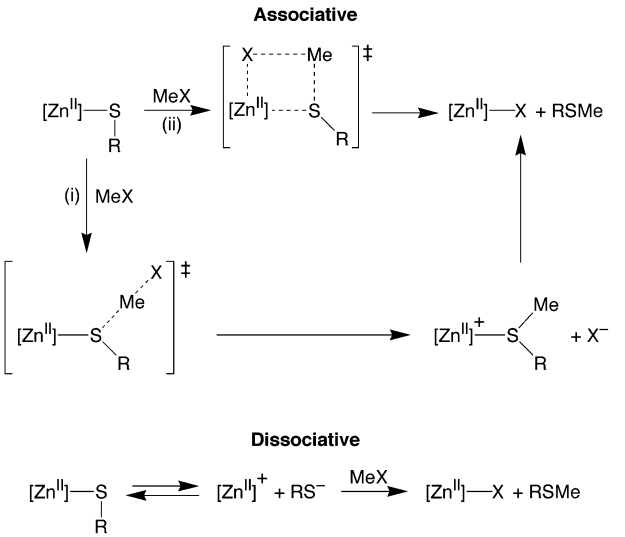
	$[Tm^{Bu^t}]Zn–SCH_2C(O)N(H)Ph$[a]	$[Tm^{Ph}]Zn–SCH_2C(O)N(H)Ph$[b]	$[Tm^{Ph}]Zn–SCH_2C(O)N(H)Ph\cdots O(H)Et$[b]
Zn–S(1)	2.356(1)	2.376(1)	2.359(1)
Zn–S(2)	2.362(1)	2.356(1)	2.344(1)
Zn–S(3)	2.367(1)	2.362(1)	2.361(7)
Zn–S(4)	2.290(1)	2.284(1)	2.267(1)
S(4)···H	2.42(4)	2.53(4)	2.46(3)
S(4)···N	3.004(4)	3.058(4)	2.987(3)

[a] Ref. 76. [b] Ref. 71*b*.

$[Tm^R]ZnSR$, in which the supporting ligand presents $[N_3]$, $[N_2S]$, $[NS_2]$ and $[S_3]$ donor arrays, demonstrates that the reactivity towards thiolate alkylation increases by four orders of magnitude across the series.[79]

On the basis of a variety of studies reported in the literature, there are two mechanistic extremes for zinc–thiolate alkylation, that are dissociative and associative in nature. Specifically, anionic $[Zn(SPh)_4]^{2-}$ is alkylated by $(MeO)_3PO$ *via* a mechanism that involves initial heterolytic dissociation generating an incipient thiolate anion,[80] while neutral derivatives such as $[Tp^{RR'}]ZnSR$,[79,81] $[Tm^R]ZnSR'$,[72,82] $[Ph(pz^{Bu^t})Bt^{Bu^t}]ZnSAr$,[83] $[HC(pz^{Me_2})_2(CMe_2S)]ZnX$,[84] $[HB(mim^R)_2(pz)]ZnSR$[85] and a series of other zinc thiolates,[86–90] are proposed to undergo alkylation without prior dissociation of RS^- (Scheme 13).

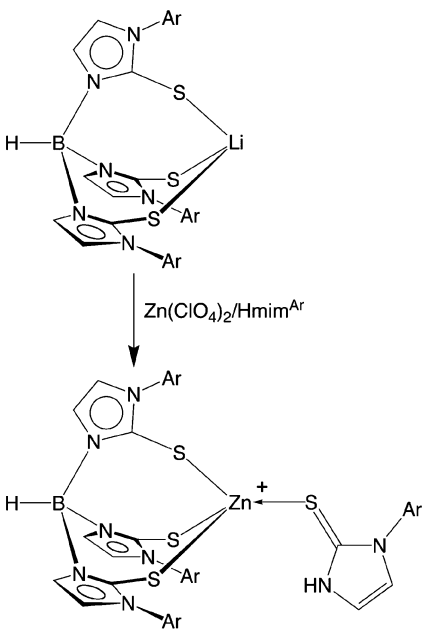
In an effort to discern further details concerned with the nature of alkylation reactions involving $[Tm^R]ZnSR$ derivatives, a series of kinetics studies were performed for the reaction of $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$ with MeI (Scheme 14).[76] However, the derived kinetics were incapable of distinguishing between associative and dissociative reaction mechanisms. Specifically, although the kinetics indicate a second order rate law, such an observation does not prove that the mechanism is associative because a dissociative reaction can also exhibit second order kinetics if re-coordination of RS^- to the zinc center competes with alkylation by MeI. Further evidence, however, was obtained by investigating the secondary deuterium kinetic isotope effect associated with the N–**H***···S (H* = H, D) hydrogen bonding interaction.



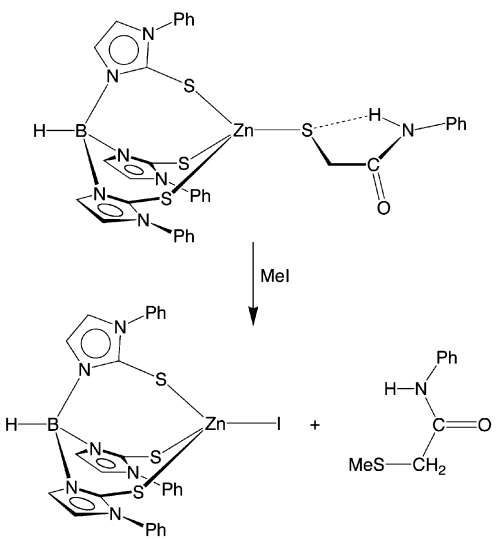
Scheme 13 (reproduced with permission from ref. 76. Copyright 2005, American Chemical Society).

In this regard, hydrogen bonding interactions have been postulated to provide a mechanism to modulate the reactivity of the zinc-cysteine thiolate moiety.[74,75] Evidence in support of this suggestion is provided by the observation that hydrogen bonded $LZnS[C_6H_4$-*o*-$NHC(O)R]$ derivatives exhibit a lower reactivity than the corresponding phenylthiolate complex LZnSPh towards alkyl halides.[82,83,86]

The influence of a hydrogen bonding interaction on a reaction mechanism may be probed by measurement of the kinetic deuterium isotope effect. In this regard, the kinetic isotope effect for alkylation of $[Tm^{Ph}]ZnSCH_2C(O)N(\mathbf{H}^*)Ph$ by MeI is characterized by a small normal (*i.e.* $k_H/k_D > 1$) value of $k_H/k_D = 1.16(1)$ at 0 °C, a value that is quite distinct



Scheme 12



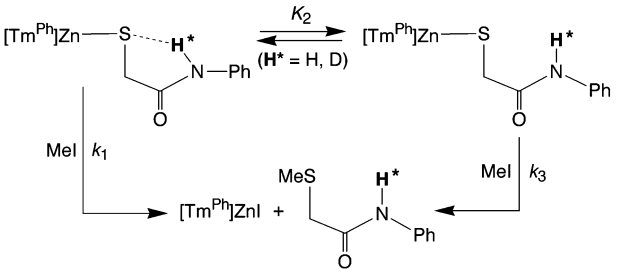
Scheme 14

from the substantial inverse (*i.e.* $k_H/k_D < 1$) value of 0.33 for alkylation of [Ph(pz$^{Bu^t}$)Bt$^{Bu^t}$]ZnS[C_6H_4-*o*-N**H***C(O)Bu^t] by $PhCH_2Br$.[83]

Disparate kinetic isotope effects for similar reactions are often an indication of the reactions being multistep and having different rate determining steps. For example, reductive elimination of C–H(D) bonds from a transition metal may be characterized by either normal or inverse kinetic isotope effects depending upon which step (reductive coupling or dissociation) is rate determining.[91] The observed KIE for a multistep reaction is a composite of the KIEs of all steps (including their microscopic reverse) up to, and including, the rate determining step. Therefore, a knowledge of the isotope effects for each individual step is required to establish whether or not a given mechanism is consistent with an observed KIE. However, the experimental determination of kinetic and equilibrium isotope effects of individual steps in a multistep reaction is difficult to achieve. For this reason, calculations have proven to be invaluable for providing a detailed understanding of measured isotope effects.[92] Therefore, a variety of isotope effects were calculated for steps pertaining to the alkylation of [Tm^{Ph}]ZnSCH$_2$C(O)N(**H***)Ph by MeI.

(i) Associative mechanisms: Isotope effects for (a) the interconversion of the hydrogen bonded and non-hydrogen bonded isomers of [Tm^H]ZnSCH$_2$C(O)N(H)Ph and (b) methylation of [Tm^H]ZnSCH$_2$C(O)N(H*)Ph by MeI.* With respect to an associative mechanism, two of the simplest possibilities, as illustrated in Scheme 15, involve (*i*) direct reaction of MeI with the N–H···S hydrogen bonded structure of [Tm^{Ph}]ZnSCH$_2$C(O)N(H)Ph (k_1) and (*ii*) isomerization to a non-hydrogen bonded structure ($K_2 = k_2/k_{-2}$) followed by rate-determining reaction with MeI (k_3). The significance of the latter mechanism is concerned with the aforementioned notion that N–H···S hydrogen bonding interactions temper the susceptibility of a thiolate ligand towards alkylation and thus dissociation may be required to facilitate alkylation of the sulfur.

The EIEs calculated for the various transformations pertaining to [Tm^H]ZnSCH$_2$C(O)N(H)Ph[93] are summarized in Table 4, which indicates that the EIE for the equilibrium between hydrogen bonded and non-hydrogen bonded isomers is calculated to be 0.98 at 0 °C (#1, Table 4); since the second step is expected to have a negligible isotope effect because the hydrogen bond plays no role, the KIE for the overall reaction



Scheme 15 (reproduced with permission from ref. 76. Copyright 2005, American Chemical Society).

is also estimated to be 0.98, which is not in accord with the normal KIE that is observed.

Two possible mechanisms for direct methylation (k_1 of Scheme 15) of the hydrogen-bonded isomer involve (*i*) rate-determining S_N2-like displacement of iodide by the coordinated zinc thiolate ligand (#2), and (*ii*) a four centered transition state which features Zn···I bond formation concomitant with Me···SR bond formation (#3); these isotope effects are also close to unity and not in accord with the observed normal KIE.

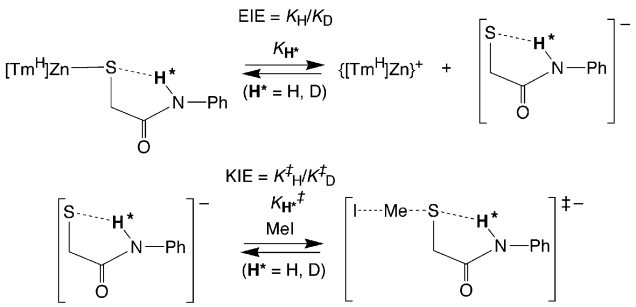
(ii) Dissociative mechanism: Equilibrium isotope effect for thiolate dissociation from [Tm^H]ZnSCH$_2$C(O)N(H)Ph and kinetic isotope effect for S_N2 displacement of I^- by [PhN(H*)C(O)CH$_2$S]$^-$.* In contrast to the isotope effects pertaining to an associative mechanism, the EIE for dissociation of [PhN(**H***)C(O)CH$_2$S]$^-$ from [Tm^H]ZnSCH$_2$C(O)N(**H***)Ph (Scheme 16) is *normal*, with a value of 1.21 at 0 °C (#4, Table 4). The second step of the dissociative mechanism involves S_N2 displacement of I^- by [PhN(**H***)C(O)CH$_2$S]$^-$ (Scheme 16). The KIE for this reaction is calculated to be inverse at all temperatures, with a value of 0.89 at 0 °C (#5, Table 4). The isotope effect is dominated by the component due to the N–H* stretch and is inverse because ν(N–H*) for the transition state [PhN(**H***)C(O)CH$_2$S···Me···I]$^{\ddagger -}$ is significantly higher in energy than that for [PhN(**H***)C(O)CH$_2$S]$^-$. However, since the inverse KIE for the second step opposes the normal EIE for the first step, the overall isotope effect is reduced from a value of 1.21 for the EIE to a value 1.08 at 0 °C.[94]

Examination of the isotope effects summarized in Table 4 indicate that all have small values, irrespective of whether the N–H···S hydrogen bonding interaction becomes stronger or weaker in the product. This insensitivity is due to the fact that

Table 4 Summary of isotope effects pertaining to zinc thiolate methylation at 0 °C (data taken from ref. 76)

	Reaction	Isotope effect
	[Tm^{Ph}]ZnSCH$_2$C(O)N(**H***)Ph + MeI $\xrightarrow{k_{H^*}}$ [Tm^{Ph}]ZnI + PhN(**H***)C(O)CH$_2$SMe	$k_H/k_D = 1.16(1)^a$
#1	H-bonded [Tm^H]ZnSCH$_2$C(O)N(**H***)Ph $\overset{K_{H^*}}{\rightleftharpoons}$ non-H-bonded [Tm^H]ZnSCH$_2$C(O)N(**H***)Ph	$K_H/K_D = 0.98^b$
#2	[Tm^H]ZnSCH$_2$C(O)N(**H***)Ph + MeI $\overset{K_{H^*}}{\rightleftharpoons}$ [Tm^H]ZnS(Me)CH$_2$C(O)N(**H***)Ph}$^+$ + I^-	$K_H/K_D = 0.94^b$
#3	[Tm^H]ZnSCH$_2$C(O)N(**H***)Ph + MeI $\xrightarrow{k_{H^*}}$ {[Tm^H]ZnSCH$_2$C(O)N(**H***)Ph}···MeI}$^{\ddagger c}$	$k_H/k_D = 1.00^b$
#4	[Tm^H]ZnSCH$_2$C(O)N(**H***)Ph $\overset{K_{H^*}}{\rightleftharpoons}$ {[Tm^H]Zn}$^+$ + PhN(**H***)C(O)CH$_2$S$^-$	$K_H/K_D = 1.21^b$
#5	PhN(**H***)C(O)CH$_2$S$^-$ + MeI $\xrightarrow{k_{H^*}}$ {PhN(H)C(O)CH$_2$S···Me···I}$^{-\ddagger d}$	$k_H/k_D = 0.89^b$

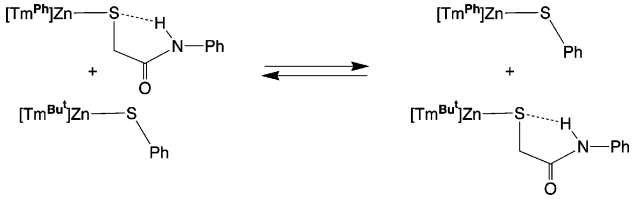
[a] Experimental value. [b] Calculated value. [c] Four-center transition state. [d] S_N2 transition state.



Scheme 16 (reproduced with permission from ref. 76. Copyright 2005, American Chemical Society).

the N–H stretch and out-of-plane bend are influenced oppositely as the strength of the N–H···S hydrogen bonding increases (Fig. 14). Nevertheless, even though the calculated isotope effects are small, the only mechanism that gives rise to a normal KIE is one involving a dissociative step (#4, Table 4). As such, the experimentally determined KIE of 1.16(1) is more in accord with a dissociative rather than associative mechanism. In essence, a normal KIE is a consequence of an increase in the hydrogen bonding interaction, and this is clearly facilitated by a sequence that involves an increase in negative charge on the sulfur. In this regard, it is possible that the stabilization afforded by the hydrogen bonding interaction could actually promote dissociation of the thiolate.

To procure further evidence for the feasibility of thiolate dissociation, experiments to probe for crossover products upon treatment of $[Tm^{Bu^t}]ZnSR$ with $[Tm^{Ph}]ZnSR'$, *i.e.* the formation of $[Tm^{Bu^t}]ZnSR'$ and $[Tm^{Ph}]ZnSR$, were investigated. Significantly, treatment of $[Tm^{Bu^t}]ZnSPh$ with $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$ results in the rapid formation of an equilibrium mixture with $[Tm^{Bu^t}]ZnSCH_2C(O)N(H)Ph$ and $[Tm^{Ph}]ZnSPh$ (Scheme 17), an observation that is consistent with (although not definitive proof of) facile thiolate dissociation.[71b] Further evidence for thiolate exchange is provided by the use of 2D-exchange spectroscopy (EXSY) to demonstrate the transfer of magnetization between the CH_2 groups of the $[SCH_2C(O)N(H)Ph]$ ligands in $[Tm^{Bu^t}]ZnSCH_2C(O)N(H)Ph$ and $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$. The observation of thiolate exchange is, therefore, consistent with a mechanism of thiolate alkylation that involves initial thiolate dissociation; however, the observation does not constitute definitive proof because other mechanisms, such as one involving formation of a dinuclear intermediate with two bridging thiolate ligands, could also account for the exchange.



Scheme 17

5 $[Bm^R]$ and $[pzBm^R]$ ligands: $[S_2]$ and $[NS_2]$ donors and synthetic analogues for liver alcohol dehydrogenase

In addition to the widespread use of *tris*(pyrazolyl)hydroborato ligands, their *bis*(pyrazolyl)hydroborato counterparts, $[Bp^{RR'}]$, have also received much attention.[5,95] For example, we employed $[Bp^{RR'}]$ ligands to prepare three-coordinate derivatives, *e.g.* $[Bp^{Bu^t}]ZnR$,[9c,96] that may be functionalized by insertion of unsaturated molecules (*e.g.* R_2CO, CO_2 and

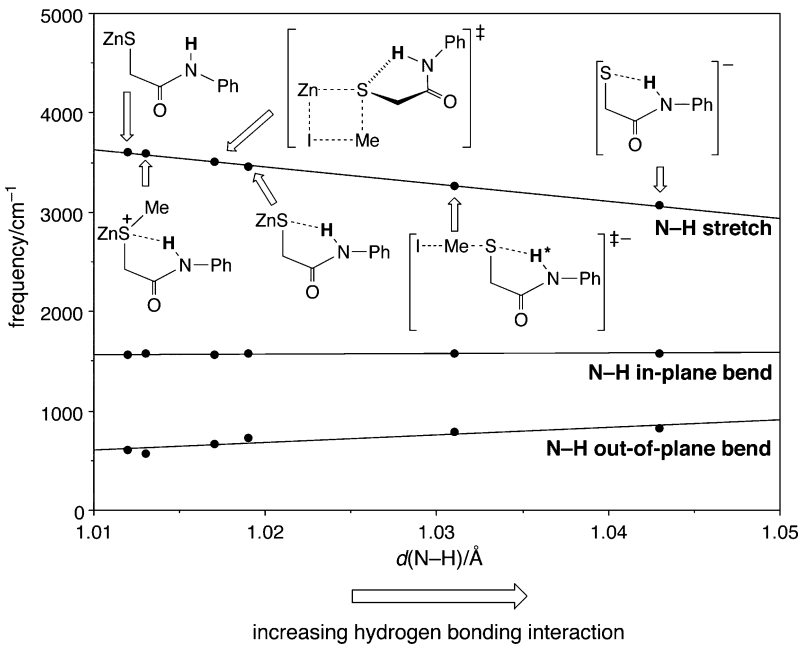


Fig. 14 Correlation of calculated N–H stretch, in-plane bend, and out-of-plane bend with d_{N-H} as an indicator of the strength of the hydrogen bonding interaction in various $\{PhN(H)C(O)CH_2S\}$ derivatives (modified with permission from ref. 76. Copyright 2005, American Chemical Society).

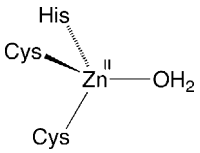
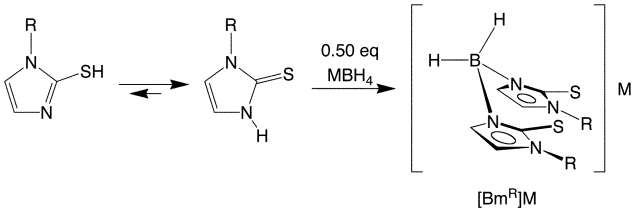


Fig. 15 Active site of liver alcohol dehydrogenase.

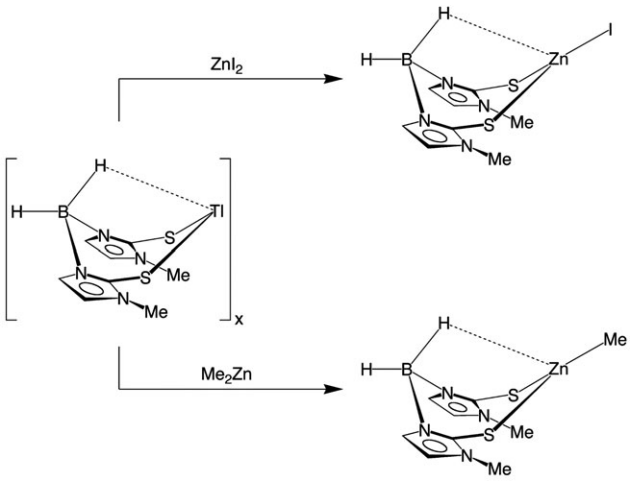
R_2CS) into the B–H group to obtain compounds that feature new facially tridentate [N_2O] and [N_2S] donor ligands that have potential for modeling certain zinc enzymes.[96,97] Vahrenkamp has also synthesized a [N_2S] ligand, namely K[(mim^R)Bp] *via* the reaction of K[Tp] and a mercaptoimidazole, Hmim^R, in a melt.[13f,98]

To extend our investigation to synthetic analogues for liver alcohol dehydrogenase, for which the active site has the {[S_2N]Zn(OH_2)} motif (Fig. 15),[99] we sought the complement of the above [N_2S] ligand. As such, we first required *bis*(mercaptoimidazolyl)hydroborato ligands, [Bm^R]. In this regard, [Bm^R] ligands may be synthesized by the reaction of H(mim^R) with MBH_4 in a 2 : 1 molar ratio (Scheme 18)[100,101] and, as anticipated, have also found widespread applications.[102] For example, with respect to zinc chemistry, the methyl and iodide complexes, [Bm^{Me}]ZnMe and [Bm^{Me}]ZnI, were obtained from the thallium derivative [Bm^{Me}]Tl by metathesis with Me_2Zn and ZnI_2, respectively (Scheme 19).[100] Furthermore, the homoleptic complex, [Bm^{Me}]$_2$Zn, may be obtained by a redistribution reaction of [Bm^{Me}]ZnMe in $CHCl_3$ (Scheme 20),[100] and also by the direct reaction of ZnX_2 with [Bm^{Me}]Na.[101]

X-Ray diffraction studies indicate that the bidentate coordination of the two sulfur donor atoms in [Bm^{Me}]ZnX derivatives[100,101] is supplemented, to varying degrees, by three-center–two-electron interactions with one of the B–H groups (Table 5).[103] For example, the Zn···B separation of 3.78 Å for [Bm^{Me}]$_2$Zn is substantially greater than those in [Bm^{Me}]ZnX complexes (2.82–2.94 Å), a difference that is in accord with the four-coordinate *vs.* "three coordinate" nature of the zinc centers. In addition to Zn···H–B three-center–two-electron interactions, an interesting difference between [Bm^{Me}]$_2$Zn and [Bm^{Me}]ZnX is that the [Bm^R] ligand in the former adopts a configuration which results in a "chair-like" eight-membered ring, as opposed to the "boat-like" rings present in "three coordinate" [Bm^{Me}]ZnX; the latter configuration is required to achieve a closer proximity between the metal and B–H group. Interestingly, the remote R substituents on the [Bm^R] ligand may exert an impact on the coordination geometry. For example, whereas [Bm^{Me}]$_2$Zn possesses Zn···B separations of 3.78 Å, the corresponding values for [Bm$^{Bu^t}$]$_2$Zn are considerably shorter (3.23 and 3.45 Å).[101]



Scheme 18

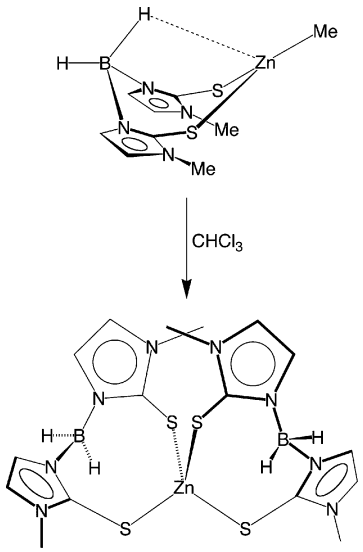


Scheme 19 (reproduced from ref. 100*a* with permission of The Royal Society of Chemistry).

Access to a tridentate [NS_2] donor ligand, namely [pzBm^{Me}], was provided by reaction of pyrazole with a *bis*(mercaptomethylimidazolyl)borate derivative (Scheme 21), from which the zinc complex [pzBm^{Me}]ZnI was obtained.[100b,104] The molecular structure of [pzBm^{Me}]ZnI was determined by X-ray diffraction, thereby demonstrating that the complex is indeed mononuclear with a distorted tetrahedral coordination geometry that resembles the active site of LADH.

A key step in the mechanism of action of LADH involves the formation of an alcohol complex (Scheme 22). In this regard, an important development with respect to the use of this class of [NS_2] donor ligand was provided by Vahrenkamp who introduced the [(pz^{Ph,Me})Bm$^{o\text{-}An}$] ligand derived from the reaction of 1-(*o*-anisyl)-2-thioimidazole, 3-phenyl-5-methylpyrazole and KBH_4.[13f,105,106] Specifically, this ligand allowed isolation of the ethanol complex, {[(pz^{Ph,Me})Bm$^{o\text{-}An}$]Zn(HOEt)}{ClO^4}·EtOH,[105] which provides the best structural model to date for LADH.

Since alcohol complexes of zinc in a sulfur-rich coordination environment are not well-known, it is pertinent to note



Scheme 20

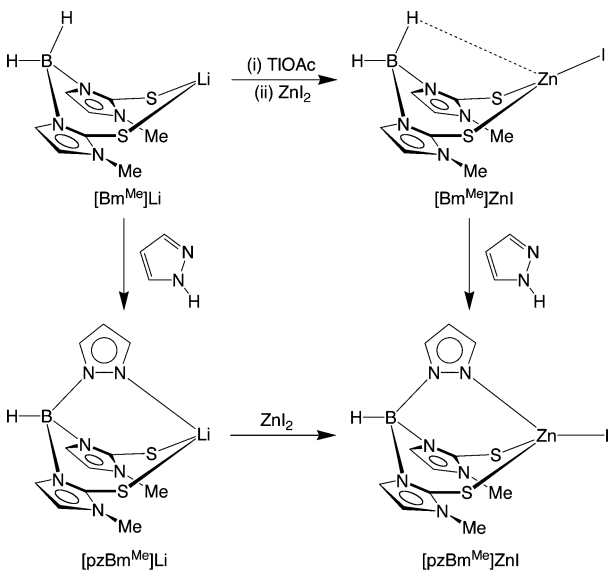
Table 5 [M···H–B] interactions in {[Bm^{R}]M} derivatives (data taken from ref. 100*a*)

	d(M···B)/Å	*d*(M···H)/Å
{[Bm^{Mes}]Li}$_2$	2.80, 3.09[a]	1.86, 2.34[a]
{[Bm^{Me}]Tl}$_x$	3.50	2.69
[Bm^{Me}]ZnI	2.94	2.06
[Bm^{Me}]ZnMe	2.88	1.77
[Bm^{Mes}]Zn(NO$_3$)	2.82	1.93
[Bm^{Me}]$_2$Zn	3.78	3.51

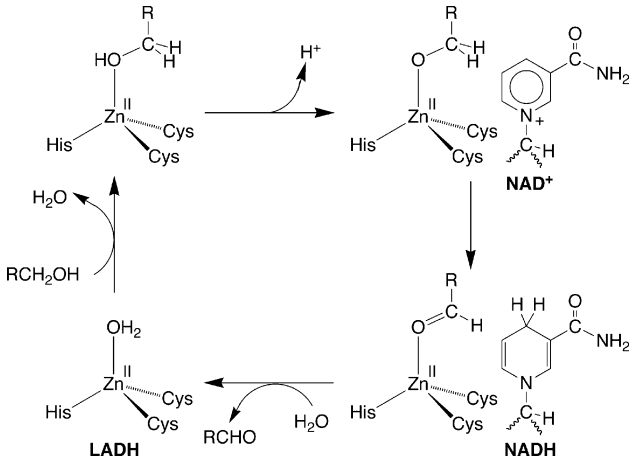
[a] Values for two independent molecules.

that related alcohol complexes employing an [S_3] donor ligand, namely {[Tm^{Mes}]Zn(HOMe)}$^+$ [21*d*] and {[Tm$^{Bu^t}$]-Zn(HOEt)}$^+$,[21*e*] have also been synthesized. The ability to isolate tetrahedral alcohol complexes {[(pz^{Ph,Me})Bm$^{o\text{-}An}$]-Zn(HOEt)}$^+$, {[Tm$^{Bu^t}$]Zn(HOEt)}$^+$ and {[Tm^{Mes}]Zn(HOMe)}$^+$ for these sulfur-rich ligand systems is in marked contrast to the fact that the tripodal [N_3] donor *tris*(imidazolyl)phosphine ligand [Pim$^{Bu^t,Pr^i}$] yields a zinc hydroxide complex, {[Pim$^{Bu^t,Pr^i}$]ZnOH}$^+$, upon reaction with Zn(ClO$_4$)$_2$ in methanol.[16] As such, the comparison indicates that the sulfur rich coordination environment provided by [Tm^{R}] and [(pz^{Ph,Me})Bm$^{o\text{-}An}$] ligands stabilizes coordination of the alcohol to zinc, thereby suggesting that one of the reasons why LADH utilizes a sulfur rich coordination environment is to promote coordination of the alcohol relative to that of water.

In addition to forming an alcohol complex, another important step of the mechanism of action of LADH (Scheme 22) involves the formation of a four-coordinate zinc alkoxide intermediate. While four-coordinate zinc alkoxide complexes are not well-characterized for synthetic analogues that employ a [NS_2] donor array, such complexes have been observed for [Tp$^{RR'}$] derivatives. For example, the zinc hydroxide [Tp$^{Bu^t,Me}$]ZnOH complex reacts with ROH (R = Me, Et, Pr^i, Bu^t) to generate [Tp$^{Bu^t,Me}$]ZnOR as a minor component of an equilibrium mixture (Scheme 23).[107–109] Although [Tp$^{Bu^t,Me}$]ZnOR are not readily isolated from the equilibrium



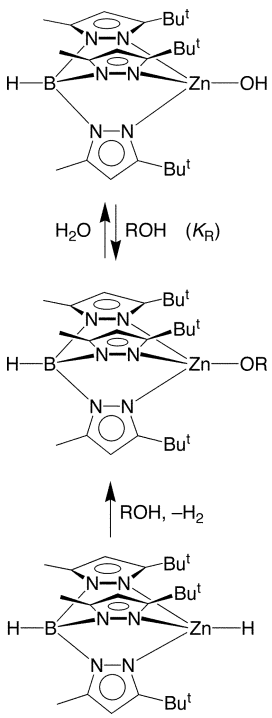
Scheme 21



Scheme 22 (reproduced with permission from ref. 13*a*. Copyright 2005, American Chemical Society).

mixture, the complexes may be isolated from the reaction of the hydride complex [Tp$^{Bu^t,Me}$]ZnH with the respective alcohol (Scheme 23). The methoxide complex [Tp^{Ph,Me}]ZnOMe · 2MeOH has also been obtained as a minor byproduct in the synthesis of [Tp^{Ph,Me}]ZnOH.[110]

The stability of tetrahedral zinc alkoxide complexes is of considerable relevance with respect to the mechanism of action of LADH, and the fact that simple zinc alkoxide complexes are very sensitive to hydrolysis suggests that the active site environment most likely plays an important role in stabilizing such species. In particular, hydrogen bonding interactions involving the alkoxide may provide such a mechanism.[111] Supporting this suggestion, the tetradentate [N_3S] ebnpa ligand, that features *two* hydrogen bond donors, has a significant effect on the relative stability of a zinc methoxide



Scheme 23

species.[112] Specifically, the equilibrium constant for methanolysis of $[(ebnpa)ZnOH]^+$ to give $[(ebnpa)ZnOMe]^+$ (3.0×10^{-1} at 304 K) is orders of magnitude greater than that for the corresponding reaction of $[Tp^{Bu^t,Me}]ZnOH$ with MeOH (1.4×10^{-3} at 300 K).

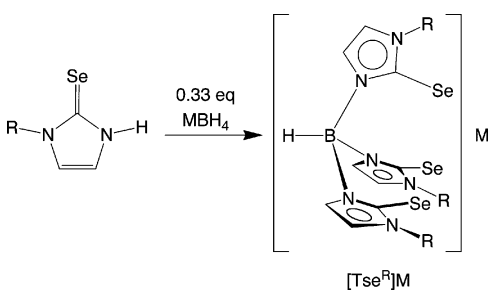
Another important step of the mechanism of action of LADH involves "hydride" transfer from the alkoxide to NAD^+. Evidence that such a transformation is possible for $[Tp^{Bu^t,Me}]ZnOR$ is provided by using *p*-nitrobenzaldehyde as a NAD^+ hydride acceptor mimic.[113] Thus, $[Tp^{Bu^t,Me}]ZnOEt$ reacts with ArCHO (Ar = p-$C_6H_4NO_2$) to yield $[Tp^{Bu^t,Me}]$-$ZnOCH_2Ar$ and MeCHO.

6 The next generation: $[Tse^R]$ and $[Bse^R]$, tridentate and bidentate selenium ligands

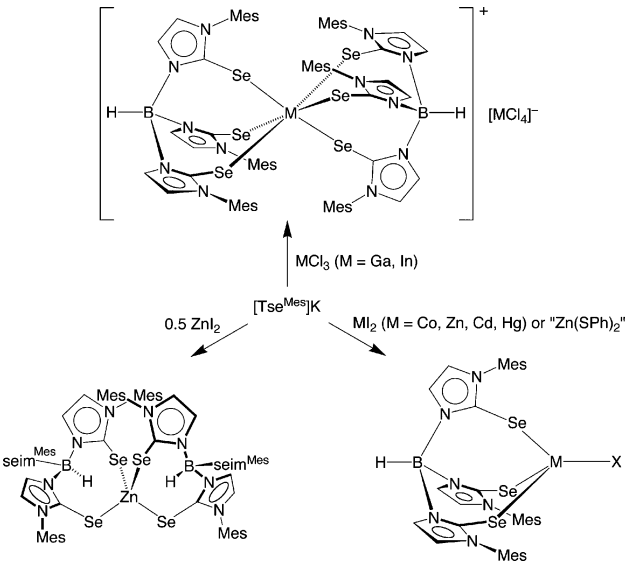
Since the $[Tm^R]$ ligand has proven to be versatile, we envisioned that a similar series of tripodal ligands that feature an L_2X [*Se*$_3$] donor array should be accessible and thereby provide a set of ligands with modified electronic properties. In this regard, it is worth noting that, in contrast to ubiquitous [*S*$_3$] tripodal donor ligands, their [*Se*$_3$] counterparts are uncommon.

Significantly, the *tris*(2-seleno-1-R–imidazolyl)hydroborato ligands may be obtained as alkali metal derivatives, $[Tse^R]M$ (R = Me, M = Na; R = Mes, M = K), *via* the reactions of MBH_4 with 1-R–imidazole-2-selone (R = Me, Mes)[114,115] as illustrated in Scheme 24.[116] $[Tse^R]M$ have been used to synthesize a variety of metal complexes,[116,117] with some zinc, cadmium and mercury complexes illustrated in Scheme 25. Furthermore, IR spectroscopic studies on $[Tse^R]Re(CO)_3$ indicate that the $[Tse^R]$ ligands are more strongly electron donating than Cp, Cp*, [Tp] and $[Tp^{Me_2}]$ ligands.[116] Thus, $[Tse^R]$ represents a new class of strongly electron donating ligand that has potential for studying the chemistry of both main group metals and transition metals.

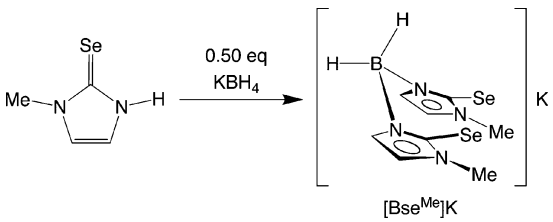
In addition to [*Se*$_3$]-donor tripodal ligands, the related [*Se*$_2$]-donor *bis*(2-seleno-1-methylimidazolyl)hydroborato ligand, $[Bse^{Me}]K$, has also been synthesized and investigated (Scheme 26).[116*b*,118] For example, $[Bse^{Me}]K$ reacts with ZnX_2 (X = Cl, I) in 1 : 1 and 2 : 1 molar ratios to give $\{[Bse^{Me}]ZnX\}_2$ and $[Bse^{Me}]_2Zn$, respectively (Scheme 27). Most interestingly, the $[Bse^{Me}]$ ligand is *not* merely a "heavier" version of the $[Bm^{Me}]$ sulfur congener. Thus, whereas $\{[Bse^{Me}]ZnI\}_2$ exists as a dimer, the sulfur counterpart $[Bm^{Me}]ZnI$ is a monomer.[100] Another interesting aspect of $\{[Bse^{Me}]ZnI\}_2$ is that the bridging entity is one of the 2-seleno-1-methylimidazolyl



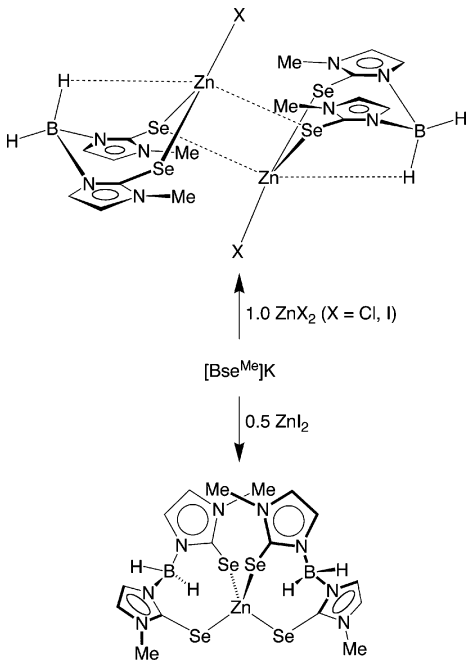
Scheme 24



Scheme 25 (reproduced from ref. 116*a* with permission of The Royal Society of Chemistry).



Scheme 26



Scheme 27 (reproduced from ref. 116*b* with permission of The Royal Society of Chemistry).

groups rather than the halide ligands.[119,120] The bridging interaction is, however, asymmetric such that the primary [*Se*, *Se*, *X*] coordination environment of the zinc centers in $\{[Bse^{Me}]ZnX\}_2$ may be described as trigonal planar.

In contrast to the unusual structures observed for $\{[Bse^{Me}]ZnX\}_2$ (X = Cl, I), $[Bse^{Me}]_2Zn$ exhibits the tetrahedral geometry that is common for zinc. A notable difference between $\{[Bse^{Me}]ZnX\}_2$ and $[Bse^{Me}]_2Zn$ pertains to the configuration of the $[Bse^{Me}]$ ligand. Thus, the eight-membered ring of the $\{[Bse^{Me}]Zn\}$ moiety of $[Bse^{Me}]ZnI$ adopts a "boat-like" configuration, whereas that of $[Bse^{Me}]_2Zn$ adopts a "chair-like" configuration. In accord with the different configurations, the Zn···B distances in $[Bse^{Me}]_2Zn$ (3.85 and 3.87 Å) are distinctly longer than that in $\{[Bse^{Me}]ZnI\}_2$ (3.10 Å) such that the "boat-like" configuration for the latter molecule allows the B–H group to come into closer proximity to the zinc center and participate in a three-center–two-electron B–H···Zn interaction.

8 Perspectives

The tripodal *tris*(2-mercapto-1-R–imidazolyl)hydroborato ligand system, $[Tm^R]$, and its selenium counterpart, $[Tse^R]$, may be viewed as $[S_3]$- and $[Se_3]$-donor analogues to the well-known $[N_3]$-donor *tris*(pyrazolyl)hydroborato ligands. The latter ligand system has been widely investigated and has been shown to have a multitude of applications. By analogy, it is anticipated that $[Tm^R]$ and $[Tse^R]$ ligands will also prove to be useful ligands for studying problems pertaining to coordination chemistry. In this regard, the present article has established bioinorganic and organometallic applications of these ligands with respect to the chemistry of zinc, cadmium and mercury. For example, the tridentate $[Tm^R]$ ligand provides an $[S_3]$ donor array that is of use for mimicking aspects of zinc enzymes and proteins that have sulfur-rich active sites, such as the Ada DNA repair protein. The versatility of this class of ligand has been extended by the synthesis of bidentate counterparts, $[Bm^R]$ and $[Bse^R]$, that provide $[S_2]$- and $[Se_2]$-donor arrays. Interestingly, the $[Bm^R]$ and $[Bse^R]$ ligands do not always adopt the same coordination modes. For example, whereas $[Bm^{Me}]ZnI$ is a monomer, the selenium counterpart $\{[Bse^{Me}]ZnI\}_2$ exists as a dimer in which selenium serves as a bridging atom. An interesting future challenge will be to synthesize the tridentate and bidentate tellurium counterparts, $[Te^R]$ and $[Bte^R]$, and develop their applications.

Acknowledgements

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