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Mononuclear tris(2-mercapto-1-arylimidazolyl)hydroborato complexes of zinc, [Tm^{Ar}]ZnX: structural evidence that a sulfur rich coordination environment promotes the formation of a tetrahedral alcohol complex in a synthetic analogue of LADH

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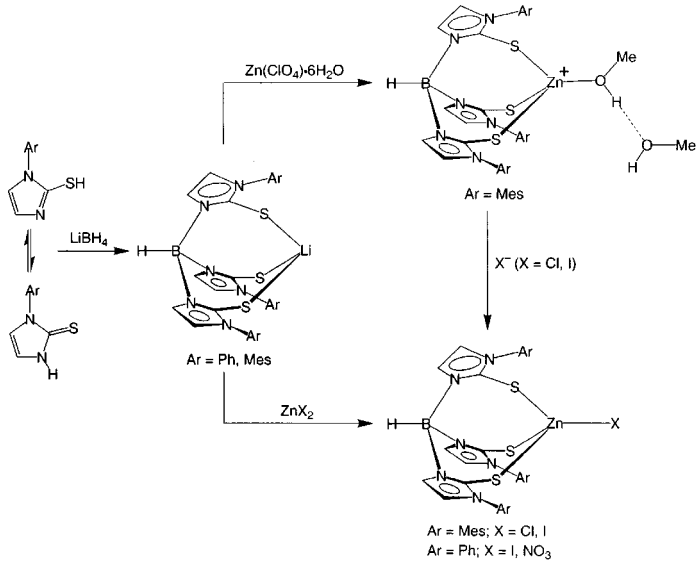
The tris(2-mercapto-1-mesitylimidazolyl)borate ligand, [Tm^{Mes}]$^-$, has been used to synthesize {[Tm^{Mes}]Zn-(HOMe)}$^+$, a stable monomeric tetrahedral zinc–methanol complex which resembles the proposed alcohol intermediate in the catalytic cycle of the mechanism of action of liver alcohol dehydrogenase.

The active sites of many zinc enzymes are composed of tetrahedral zinc centers surrounded by a water molecule and a combination of nitrogen, oxygen and sulfur donors derived from amino acid residues of the protein backbone, and may be generally represented as {[$N_xO_yS_z$]Zn^{II}(OH$_2$)}, where $x + y + z = 3$.[1] Although structurally similar, it is evident that the compositions of the {[$N_xO_yS_z$]Zn^{II}(OH$_2$)} active sites are highly varied, ranging from nitrogen rich carbonic anhydrase (CA), {[N$_3$]Zn^{II}(OH$_2$)}, to sulfur rich liver alcohol dehydrogenase (LADH), {[NS$_2$]Zn^{II}(OH$_2$)}.[1] Correspondingly, the chemistry performed by each of these enzymes is distinctly different: for example, CA is a hydrolytic enzyme, whereas LADH is responsible for the oxidation of alcohols.[1] In order to understand why Nature has elected to use different amino acid residues to promote different chemical transformations of zinc enzymes, it is essential to understand how the chemistry of zinc is modified by various donor groups. Here, we describe the syntheses of tetrahedral zinc complexes in a sulfur rich environment of relevance to LADH chemistry,[2] including the structural characterization of an alcohol complex.

Although a large number of [S$_3$] donor ligands are known, many of these are unsuitable for modeling aspects of bioinorganic zinc chemistry since they do not have the ability to inhibit the formation of six-coordinate sandwich complexes. For example, crown thioethers, such as 1,4,7-trithiacyclononane, are insufficiently sterically demanding and do not provide a protective pocket about a metal center that prevents the formation of six-coordinate sandwich complexes.[3] Tripodal thioethers, such as Rabinovich's {MeSi(CH$_2$SMe)$_3$},[4] and Riordan's [RB(CH$_2$SMe)$_3$]$^-$ (R = CH$_2$SMe, Ph, Fc)[5] and [PhB(CH$_2$SR)$_3$]$^-$ (R = Ph,[6] Bu^t [7]) offer much more potential for providing well defined and sterically encumbered coordination sites than their cyclic counterparts. However, of these ligands, only the *tert*-butyl substituted [PhB(CH$_2$SBu^t)$_3$]$^-$ derivative has been reported to be a 'tetrahedral enforcer';[7] thus, a methyl substituent on sulfur does not prevent the formation of six-coordinate compounds, *e.g.* [RB(CH$_2$SMe)$_3$]$_2$Co (R = CH$_2$SMe, Ph).[5a,b]

We are particularly interested in the application of sterically demanding tripodal ligands in which the sulfur atoms are devoid of additional substituents: ligation of this type should more closely resemble that of the negatively charged cysteine thiolates (RS$^-$) at the active site of LADH[1] than would coordination of a thioether (RSR) function. Thus, we considered that modification of Reglinski's tris(mercaptomethylimidazolyl)borate ligand [Tm^{Me}]$^-$,[8] by incorporation of bulky substituents on the imidazolyl rings, could provide a coordination environment that would allow for the isolation of monomeric species of relevance to the mechanism of action of LADH, such as four-coordinate alcohol complexes. Indeed, the aryl substituted ligands [Tm^{Ph}]$^-$ and [Tm^{Mes}]$^-$ are readily obtained by heating LiBH$_4$ with 3 equivalents of 2-mercaptophenylimidazole and 2-mercaptomesitylimidazole,[9] respectively (Scheme 1).



Scheme 1

A critical step in the proposed mechanism of action of LADH involves displacement of water from the active site to give a tetrahedral zinc–alcohol complex, {[NS$_2$]Zn^{II}(HOR)}, as an essential intermediate.[1] Despite their relevance, however, there are no mononuclear tetrahedral zinc complexes of aliphatic alcohols listed in the Cambridge Structural Database,[10] even though there are a substantial number of five- and six-coordinate derivatives.[11] It is, therefore, significant that the cationic alcohol complex {[Tm^{Mes}]Zn(HOMe)}$^+$ may be obtained by reaction of Li[Tm^{Mes}] with Zn(ClO$_4$)$_2$ in methanol (Scheme 1).

The molecular structure of {[Tm^{Mes}]Zn(HOMe)}$^+$ has been determined by X-ray diffraction (Fig. 1), which demonstrates that the [Tm^{Mes}] ligand adopts a propeller configuration.[12] Solution ^{1}H NMR spectroscopic studies indicate that this configuration is also rigid on the NMR time-scale at room temperature. For example, the two *ortho*-methyl groups of each mesityl substituent are chemically inequivalent in the ^{1}H NMR spectrum, thereby indicating that both inversion of the propeller configuration and rotation about the C–N bond are slow on the NMR time-scale.

The zinc coordination geometry in {[Tm^{Mes}]Zn(HOMe)}$^+$ resembles aspects of that in LADH. For example, the Zn–O and average Zn–S bond lengths in {[Tm^{Mes}]Zn(HOMe)}$^+$ {1.993(3) and 2.32[1] Å, respectively} are comparable to those in the

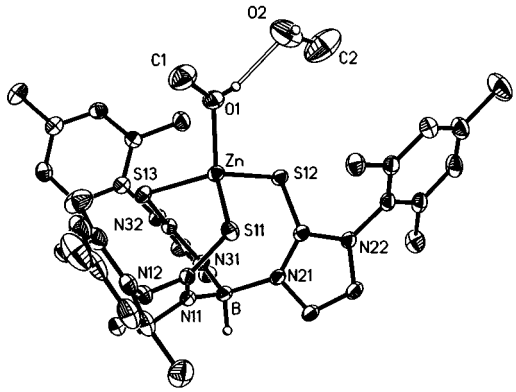


Fig. 1 Molecular structure of $\{[Tm^{Mes}]Zn(HOMe)_2\}^+$ (counter ion omitted for clarity). Selected bond lengths (Å) and angles (°): Zn–O(1) 1.993(3), Zn–S(11) 2.338(1), Zn–S(12) 2.320(1), Zn–S(13) 2.313(1); O(1)–Zn–S(11) 111.37(9), O(1)–Zn–S(12) 105.56(1), O(1)–Zn–S(13) 109.68(9).

$C_6F_5CH_2OH$ adduct of LADH (2.0 and 2.2 Å, respectively).[13] Also noteworthy is the observation that the hydroxy group of the coordinated alcohol of $\{[Tm^{Mes}]Zn(HOMe)\}^+$ participates in a hydrogen bonding interaction with an additional molecule of methanol. This interaction may be viewed as mimicking the hydrogen bond network at the active site of LADH which serves as a relay for proton transfer to the solvent.[13,14] In fact, the hydrogen bonded O···O separation of 2.58 Å between $\{[Tm^{Mes}]Zn(HOMe)\}^+$ and MeOH is effectively identical to that between the zinc bound alcohol at the active site of LADH and Ser–48 (2.6 Å).[13]

The facile isolation of a tetrahedral alcohol complex $\{[Tm^{Mes}]Zn(HOMe)\}^+$ using the tripodal $[S_3]$ tris(mercaptomesitylimidazolyl) ligand is particularly interesting given that the tripodal $[N_3]$ donor tris(imidazolyl)phosphine ligand $[Pim^{Bu^t,Pr^i}]$ yields a zinc hydroxide complex, $\{[Pim^{Bu^t,Pr^i}]ZnOH\}^+$,[15] upon reaction with $Zn(ClO_4)_2$ in methanol. Furthermore, tris(pyrazolyl)hydroborato zinc hydroxide complexes $[Tp^{RR'}]ZnOH$ have also been synthesized using methanol as solvent, in accord with the fact that simple alkoxide derivatives $[Tp^{RR'}]ZnOR$ are extremely sensitive to hydrolysis.[16] In contrast, ^1H NMR spectroscopy and mass spectrometry demonstrate that solutions of $\{[Tm^{Mes}]Zn(HOMe)\}^+$ in methanol are reasonably stable in the presence of water.

The above observations strongly indicate that the sulfur rich coordination environment provided by $[Tm^{Mes}]$ stabilizes alcohol binding to zinc. As such, it suggests that one of the reasons why LADH utilizes a sulfur rich coordination environment is to increase the stability of the required alcohol intermediate with respect to that of an aqua species.[17] In support of this notion, there is only one other structurally characterized complex listed in the Cambridge Structural Database which contains methanol coordinated to a tetrahedral zinc center, and it also possesses a sulfur rich $\{[S_3]Zn(HOMe)\}$ coordination environment; this entity is, however, a portion of a complex polymeric structure, *catena*-$(\mu$-SPh$)[(\mu$-SPh$)_6Zn_4$(MeOH)(SPh)].[18]

Although not readily displaced by water, the methanol ligand in $\{[Tm^{Mes}]Zn(HOMe)\}^+$ is displaced by anions to give neutral $[Tm^{Mes}]ZnX$ derivatives, which may also be obtained by the direct reaction of $Li[Tm^{Mes}]$ with ZnX_2 (Scheme 1). The corresponding $[Tm^{Ph}]ZnX$ (X = I, NO_3) derivatives may be obtained in an analogous manner. The molecular structures of $[Tm^{Mes}]ZnX$ (X = Cl, I) and $[Tm^{Ph}]ZnX$ (X = I, NO_3) have been determined by X-ray diffraction, thereby confirming the monomeric nature of the complexes.[12] It is also worth noting that the nitrate ligand in $[Tm^{Ph}]Zn(ONO_2)$ is coordinated in a unidentate, and not bidentate, manner, thus demonstrating that the $[Tm^{Ph}]^-$ ligand strongly favors tetrahedral coordination in zinc chemistry.

In conclusion, a monomeric tetrahedral zinc–alcohol complex has been obtained using the anionic $[Tm^{Mes}]^-$ sulfur rich donor ligand. The successful isolation of $\{[Tm^{Mes}]Zn(HOMe)\}^+$, and its stability towards water, suggest that sulfur rich coordination sites promote the formation of alcohol adducts. Thus, because such species are essential intermediates in the mechanism of action of LADH, one of the reasons why LADH possesses a sulfur rich active site may be to promote the binding of alcohol to zinc at the active site.

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Notes and references

1 (*a*) B. L. Vallee and D. S. Auld, *Acc. Chem. Res.*, 1993, **26**, 543; (*b*) R. H. Holm, P. Kennepohl and E. I. Solomon, *Chem. Rev.*, 1996, **96**, 2239; (*c*) W. N. Lipscomb and N. Sträter, *Chem. Rev.*, 1996, **96**, 2375; (*d*) E. Kimura, T. Koike and M. Shionoya, *Struct. Bonding* (*Berlin*), 1997, **89**, 1; (*e*) S. Lindskog, *Pharmacol. Ther.*, 1997, **74**, 1; (*f*) K. E. Hightower and C. A. Fierke, *Curr. Opin. Chem. Biol.*, 1999, **3**, 176.

2 For studies modeling aspects of LADH structure and chemistry, see: C. Bergquist and G. Parkin, *Inorg. Chem.*, 1999, **38**, 422; C. Kimblin and G. Parkin, *Inorg. Chem.*, 1996, **35**, 6912; S. C. Shoner, K. J. Humphreys, D. Barnhart and J. A. Kovacs, *Inorg. Chem.*, 1995, **34**, 5933; E. Kimura, M. Shionoya, A. Hoshino, T. Ikeda and Y. Yamada, *J. Am. Chem. Soc.*, 1992, **114**, 10 134; J. F. J. Engbersen, A. Koudijs and H. C. van der Plas, *J. Org. Chem.*, 1990, **55**, 3647; R. M. Kellogg and R. P. Hof, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1651; B. Muller, A. Schneider, M. Tesmer and H. Vahrenkamp, *Inorg. Chem.*, 1999, **38**, 1900.

3 W. N. Setzer, C. A. Ogle, G. S. Wilson and R. S. Glass, *Inorg. Chem.*, 1983, **22**, 266; H. J. Küppers, K. Wieghardt, B. Nuber and J. Weiss, *Z. Anorg. Allg. Chem.*, 1989, **577**, 155.

4 H. W. Yim, L. M. Tran, E. D. Dobbin, D. Rabinovich, L. M. Liable-Sands, C. D. Incarvito, K.-C. Lam and A. L. Rheingold, *Inorg Chem.*, 1999, **38**, 2211.

5 (*a*) C. Ohrenberg, P. H. Ge, P. Schebler, C. G. Riordan, G. P. A. Yap and A. L. Rheingold, *Inorg. Chem.*, 1996, **35**, 749; P. Ge, B. S. Haggerty, A. L. Rheingold and C. G. Riordan, *J. Am. Chem. Soc.*, 1994, **116**, 8406; (*c*) P. J. Schebler, C. G. Riordan, L. Liable-Sands and A. L. Rheingold, *Inorg. Chim. Acta*, 1998, **270**, 543; (*d*) C. Ohrenberg, M. M. Saleem, C. G. Riordan, G. P. A. Yap, A. K. Verma, A. L. Rheingold, *Chem. Commun.*, 1996, 1081.

6 C. Ohrenberg, C. G. Riordan, L. Liable-Sands and A. L. Rheingold, *Coord. Chem. Rev.*, 1998, **174**, 301.

7 P. J. Schebler, C. G. Riordan, I. A. Guzei and A. L. Rheingold, *Inorg. Chem.*, 1998, **37**, 4754.

8 M. Garner, J. Reglinski, I. Cassidy, M. D. Spicer and A. R. Kennedy, *Chem. Commun.*, 1996, 1975; J. Reglinski, M. Garner, I. D. Cassidy, P. A. Slavin, M. D. Spicer and D. R. Armstrong, *J. Chem. Soc., Dalton Trans.*, 1999, 2119.

9 K. Matsuda, I. Yanagisawa and Y. Isomura, *Synth. Commun.*, 1997, **27**, 3565.

10 CSD Version 5.17. 3D Search and Research Using the Cambridge Structural Database, F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, 1993, vol. 8(1), pp. 1 & 31–37.

11 For recent examples, see: T. Brandsch, F.-A. Schell, K. Weis, M. Ruf, B. Müller and H. Vahrenkamp, *Chem. Ber./Recueil*, 1997, **130**, 283 and references therein.

12 $\{[Tm^{Mes}]Zn(HOMe)_2\}(ClO_4)$ is monoclinic, $P2_1/n$, a = 13.5920(11) Å, b = 16.3598(12) Å, c = 20.1484(15) Å, β = 92.037(2)°, V = 4477.4(6) Å^3, T = 233 K, $R1$ = 0.0477, $wR2$ = 0.1036 for 10237 reflections. CCDC 182/1439. See http://www.rsc.org/suppdata/cc/1999/2301/ for crystallographic files in .cif format.

13 S. Ramaswamy, H. Eklund and B. V. Plapp, *Biochemistry*, 1994, **33**, 5230.

14 For studies on Co and Ni complexes which model aspects of hydrogen bonding interactions at the active sites of zinc enzymes, see: C. J. Boxwell and P. H. Walton, *Chem. Commun.*, 1999, 1647; L. Cronin, B. Greener, M. H. Moore and P. H. Walton, *J. Chem. Soc., Dalton Trans.*, 1996, 3337.

15 C. Kimblin, W. E. Allen and G. Parkin, *J. Chem. Soc., Chem. Commun.*, 1995, 1813.

16 See, for example: C. Bergquist and G. Parkin, *Inorg. Chem.*, 1999, **38**, 422; M. Ruf, F. A. Schell, R. Walz and H. Vahrenkamp, *Chem. Ber./Recueil*, 1997, **130**, 101; R. Alsfasser, M. Ruf, S. Trofimenko and H. Vahrenkamp, *Chem. Ber.*, 1993, **126**, 703.

17 In this regard, it has been suggested that the two negative cysteine thiolate residues serve to reduce the tendency to form a zinc hydroxide species and thereby increase the propensity for a coordinated water molecule to be replaced by an alcohol. See ref. 1(*a*).

18 I. G. Dance, *J. Am. Chem. Soc.*, 1980, **102**, 3445.

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