

Synthesis and structure of a nitrogen/sulfur-ligated zinc hydroxide complex†

Lisa M. Berreau,*^a Russell A. Allred,^a Magdalena M. Makowska-Grzyska^a and Atta M. Arif^b

^a Department of Chemistry and Biochemistry, Utah State University, 0300 Old Main Hill, Logan, UT 84322-0300, USA. E-mail: berreau@cc.usu.edu

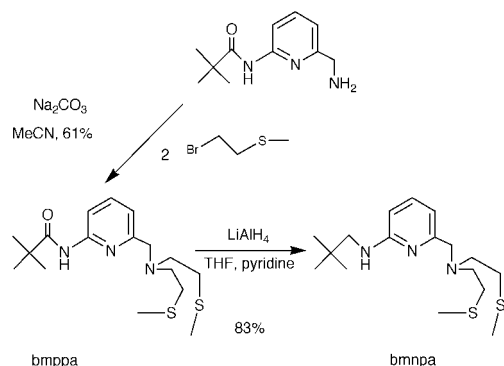
^b Department of Chemistry, University of Utah, 315 S. 1400 E., Salt Lake City, Utah 84112 USA

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Using a novel secondary amine-appended nitrogen/sulfur ligand, the first example of a nitrogen/sulfur-ligated zinc hydroxide complex, a species relevant to the active forms of several zinc-containing metalloenzymes, has been prepared and structurally characterized.

Zinc-containing metalloenzymes utilize active site structural motifs of varying nuclearity and supporting primary and secondary coordination environments to catalyze a diverse array of chemical transformations.¹ Distinctive among active site structures in these enzymes are those which have sulfur ligation to a Zn(II) ion that also binds a water/hydroxo moiety that is directly involved in catalysis.^{1a} Specifically, the presence of cysteine sulfur ligation at the mononuclear Zn(II) active site ions of alcohol dehydrogenase,² peptide deformylase,³ cytidine deaminase,⁴ spinach carbonic anhydrase,⁵ and at one of the two active site Zn(II) ions found in the metallo- β -lactamases from *B. fragilis*, *B. cereus*, and *A. hydrophila*,⁶ has prompted research efforts toward the goal of generating Zn(II) complexes, supported by a mixed nitrogen/sulfur coordination environment, that possess an available coordination position for water/hydroxo binding.⁷ However, despite the construction of several new ligand systems, a discrete zinc hydroxide species supported by a metal coordination sphere possessing sulfur donors has remained elusive, in part because of the tendency of thiolate ligands to produce oligomeric structures.⁸ Herein we describe the synthesis and structural characterization of the first zinc hydroxide complex supported by a mixed nitrogen/sulfur ligand environment.

Reasoning that hydrogen bonding interactions might prove useful toward the stabilization and isolation of a nitrogen/sulfur-ligated zinc hydroxo species,⁹ we prepared a new ligand system, *N*-bis-2-(methylthio)ethyl-*N*-(6-neopentylamino-2-pyridylmethyl)amine (bmnpa, Scheme 1), that combines a nitrogen/sulfur coordination environment with a secondary amine functionality that may serve as a hydrogen bond donor in metal complexes. As shown in Scheme 1, this ligand was prepared *via* a two-step reaction sequence. Treatment of 2-pivalolylamido-



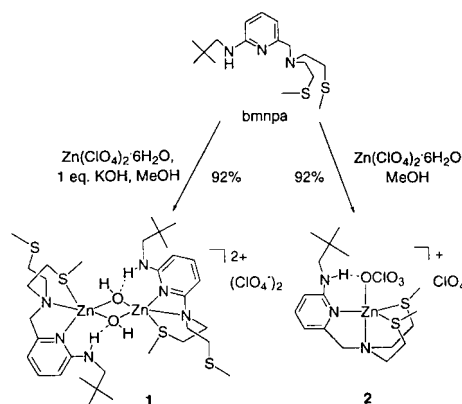
Scheme 1

† Electronic supplementary information (ESI) available: synthesis and characterization of ligands and complexes. See <http://www.rsc.org/suppdata/cc/bo/b003144p/>

6-aminomethylpyridine¹⁰ with 2 equivalents of 1-bromo-2-methylthioethane yielded *N*-bis-2-(methylthio)ethyl-*N*-(6-pivaloylamido-2-pyridylmethyl)amine (bmppa) in 61% yield.† Reduction of bmppa with LiAlH₄ in THF-pyridine followed by purification by column chromatography yielded the desired bmnpa ligand.‡ Zinc complexation of bmnpa was achieved *via* admixture of equimolar amounts of bmnpa, Zn(ClO₄)₂·6H₂O and KOH (Scheme 2) in methanol at ambient temperature followed by crystallization from MeCN–Et₂O, which produced a colorless crystalline material with an analytical composition consistent with the empirical formula [(bmnpa)Zn(OH)]ClO₄ **1**.§¶ It is notable that in the absence of added KOH, a different zinc complex is generated. Specifically, treatment of bmnpa with Zn(ClO₄)₂·6H₂O in MeOH followed by crystallization from MeCN–Et₂O yielded [(bmnpa)Zn(ClO₄)](ClO₄) **2** (Scheme 2), which deposited as plate-type crystals.¶¶

X-Ray crystallographic analysis of **1** revealed an asymmetric, dinuclear nitrogen/sulfur-ligated zinc hydroxide structure (Fig. 1, top), with only one of the two available thioether sulfur donors ligated to each Zn(II) center. The five-coordinate zinc ions, which are related by an inversion center, exhibit a slightly distorted trigonal bipyramidal geometry ($\tau = 0.80$)¹¹ with the pyridyl nitrogen [Zn(1)–N(2) 2.068(3) Å], a thioether sulfur [Zn(1)–S(1) 2.514(1) Å] and a hydroxide oxygen atom [Zn(1)–O(1) 1.974(3) Å] occupying equatorial positions. The observed Zn(1)–O(1) bond length falls within the range (*ca.* 1.9–2.3 Å) of distances previously reported for bridging hydroxo moieties in multinuclear zinc complexes.¹² The second zinc oxygen bond [Zn(1)–O(1')] is slightly longer [2.028(3) Å] and is a structural component of a six-membered ring [Zn(1)–O(1')···H–N(3)–C(9)–N(2)]¹³ created by a hydrogen bonding interaction between the secondary amine hydrogen [N(3)–H] and a lone pair on the hydroxyl oxygen [O(1')···N(3) 2.82 Å, O(1')···H–N(3) 161.0°].¹⁴ Because this intramolecular hydrogen bonding interaction involves the longer Zn(1)–O(1') bond, it appears to contribute toward the stabilization of the asymmetric dinuclear Zn₂(OH)₂ core.

Complex **2** is mononuclear in the solid state (Fig. 1, bottom), adopting a distorted trigonal bipyramidal geometry ($\tau = 0.65$)



Scheme 2

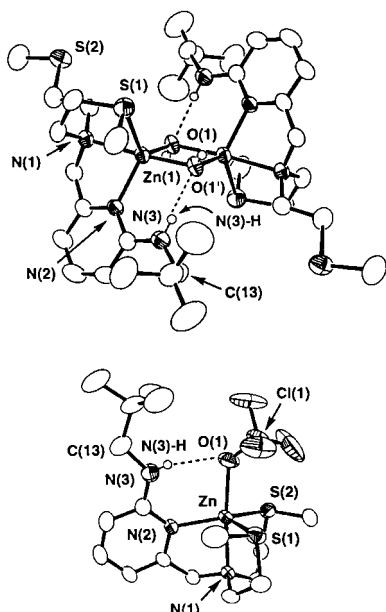


Fig. 1 Drawings of the cationic portions of the X-ray crystal structures of **1** (top) and **2** (bottom). All ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): **1**: Zn(1)–O(1) 1.974(3), Zn(1)–S(1) 2.514(1), Zn(1)–N(1) 2.189(3), Zn(1)–N(2) 2.068(3), Zn(1)–O(1') 2.028(3); S(1)–Zn(1)–N(1) 82.8(1), N(1)–Zn(1)–N(2) 80.70(12), N(2)–Zn(1)–O(1) 114.2(1), N(2)–Zn(1)–O(1') 102.6(1), N(1)–Zn(1)–O(1) 98.7(1), N(1)–Zn(1)–O(1') 174.5(1), S(1)–Zn(1)–O(1) 126.8(1), S(1)–Zn(1)–O(1') 91.7(1); **2**: Zn–O(1) 2.174(3), Zn–S(1) 2.432(1), Zn–S(2) 2.390(1), Zn–N(1) 2.191(3), Zn–N(2) 2.042(3); O(1)–Zn–N(1) 174.8(1), N(2)–Zn–S(2) 136.1(1), N(2)–Zn–S(1) 109.3(1), S(1)–Zn–S(2) 111.8(1).

with both thioether sulfur atoms of the ligand bound to the Zn(II) center [Zn–S(1) 2.432(1) Å, Zn–S(2) 2.390(1) Å] in the equatorial plane. The Zn–S bond distances of **2** fall between those reported for the monomeric, four-coordinate [(Ph₂CHS)Bp^{But, Pri}]₂ZnI [2.460(2) Å]^{7b} and [HB(tim^{Me})₂pz]₂ZnI [2.320(2), 2.352(2) Å]^{7c} complexes, but are slightly shorter than the Zn–S(1) distance found in **1** [2.514(1) Å]. Located *trans* to the apical nitrogen atom in **2** is a coordinated perchlorate anion [Zn–O(1) 2.174(3) Å]. An intramolecular hydrogen bonding interaction between the zinc-bound oxygen atom of this anion and the secondary amine donor [O(1)⋯N(3) 2.93 Å, N(3)–H⋯O(1) 158°] is present in the solid state.

Importantly, the isolation of complex **1** confirms the feasibility of using ligand systems possessing a single hydrogen bond donor to stabilize biologically relevant metal hydroxide species. Evidence for the hydrogen bonding interaction found in the solid state between the metal-bound hydroxide and the secondary amine proton [N(3)–H] in **1** remaining intact in solution is derived from examination of ¹H NMR spectra of the complex obtained in dry CD₃CN. Specifically, the N(3)–H resonance of **1**, which is found as a broad triplet at δ 8.97 (*J* 6.3 Hz), with the observed multiplicity being indicative of a slow rate of exchange and coupling with the adjacent methylene unit [C(13)–H₂, δ 2.71, *d*, *J* 6.3 Hz], is shifted significantly downfield from the position of the same resonance in the free ligand [N(3)–H, δ 5.01]. This deshielding of the N(3)–H resonance in **1** indicates a decrease in the electron density surrounding this proton due to its involvement in a hydrogen bonding interaction. It is also intriguing that the chemical shift of the secondary amine proton of the bmnpa ligand is highly dependent upon the nature of the anions present in zinc complexes, as **2** exhibits a N(3)–H resonance at δ 5.79.

In summary, we have synthesized a new secondary amine-appended nitrogen/sulfur ligand system and have utilized it to prepare and structurally characterize the first example of a nitrogen/sulfur-ligated zinc hydroxide complex. As such, it is the first relevant synthetic complex for the catalytic site of several nitrogen/sulfur-ligated zinc enzymes that possess a water/hydroxo moiety that is directly involved in catalysis. The results

outlined herein lay the groundwork for extensive reactivity studies directed at examining the influence of sulfur ligation on the reactivity of a zinc hydroxide moiety toward a variety of biologically-relevant substrates including alcohols, amides and CO₂.

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Notes and references

‡ Characterized by ¹H and ¹³C NMR, FTIR, HRFAB-MS and CHN analysis.

§ Characterized by ¹H and ¹³C NMR, FTIR and CHN analysis.

¶ *Crystal data*: for **1**: C₁₇H₃₂ClN₃O₈S₂Zn, *M* = 523.4, monoclinic, space group *P*2₁/*n*, *a* = 11.5830(3), *b* = 17.1392(6), *c* = 12.1278(5) Å, β = 98.964(2)°, *V* = 2378.25(14) Å³, *Z* = 4, *T* = 200 K, μ = 1.352 mm⁻¹. Using Mo-Kα radiation (0.71073 Å), a total of 9424 reflections were collected (5.94 < 2θ < 54.98°), of which 5303 were independent. Refinement converged to *R*₁ = 0.0507, *wR*₂ = 0.1180 (*I* > 2σ*I*) and *R*₁ = 0.0764, *wR*₂ = 0.1317 (all data). The perchlorate anion was disordered over more than two orientations, with some overlapping of the oxygen positions. For **2**: C₁₇H₃₁Cl₂N₃O₈S₂Zn, *M* = 605.8, monoclinic, space group *P*2₁/*a*, *a* = 16.0431(9), *b* = 9.2753(3), *c* = 19.5165(11) Å, β = 111.1170(16)°, *V* = 2709.1(2) Å³, *Z* = 4, *T* = 200 K, μ = 1.301 mm⁻¹. Using Mo-Kα radiation (0.71073 Å), a total of 14106 reflections were collected (6.16 < 2θ < 65.24°), of which 8382 were independent. Refinement converged to *R*₁ = 0.0602, *wR*₂ = 0.1481 (*I* > 2σ*I*) and *R*₁ = 0.1009, *wR*₂ = 0.1688 (all data). The noncoordinated perchlorate anion and the *tert*-butyl group both exhibit *ca.* 60% orientational disorder.

CCDC 182/1700. See <http://www.rsc.org/suppdata/cc/b0/b003144p/> for crystallographic files in .cif format.

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- Average deviation from planarity of the atoms in the six-membered ring is 0.0965 Å.
- A hydrogen-bonding interaction was also found between the hydroxyl proton [O(1)–H] and oxygen atoms of the disordered, non-coordinated perchlorate anion.