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Bioinorganic Chemistry of Group 12 Complexes Supported by Tetradentate Tripodal Ligands Having Internal Hydrogen-Bond Donors

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Inspired by the proposed role of secondary hydrogen-bonding interactions in modulating the chemistry of mononuclear zinc centers in metalloenzymes, zinc complexes supported by tetradentate tripodal ligands having one or more internal hydrogen-bond donors have been prepared, characterized, and investigated for biologically relevant reactivity. Complexes of this class have been examined in terms of water activation and CO_2 reactivity, alcohol/alkoxide coordination, and amide methanolysis and phosphate ester hydrolysis reactivity. The results of these studies indicate that the presence of internal hydrogen-bond donors will lower the pK_a of a zinc-bound water molecule, stabilize zinc alkoxide species with respect to hydrolysis, and enhance the phosphate ester cleavage reactivity of mononuclear zinc complexes. In addition, use of tripodal ligands having a single internal hydrogen-bond donor has enabled the isolation of a novel cadmium hydroxide complex and examination of its CO_2 chemistry, as well as the identification of a novel amide cleavage reaction which proceeds by initial formation of a deprotonated amide intermediate.
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Introduction

Secondary hydrogen-bonding interactions are suggested to play important roles in modulating the chemistry of mononuclear zinc centers in metalloenzymes.[1,2] For example, as outlined below for specific enzymes, these interactions have been proposed to: (1) influence the pK_a of a zinc-bound water molecule, (2) orient a substrate or nucleophile for catalysis, (3) stabilize a transition state or reactive species, or (4) activate a substrate for a reaction (e.g. hydrolysis). Over the past few years, several laboratories have worked toward understanding the influence of hydrogen bonding on the chemistry of zinc centers by examining the chemistry of synthetic zinc complexes supported by novel tripodal tetradentate chelate ligands containing internal hydrogen-bond donors. In an approach akin to metal ion substitution studies of zinc enzymes, in some cases analog complexes of the heavier group 12 metals have also been prepared, characterized, and examined for biologically relevant reactivity. Overall, these studies have provided important new fundamental chemical insight with which to evaluate the proposed role of secondary hydrogen bonding in the catalytic cycles of zinc enzymes.

Carbonic anhydrases (CAs) catalyze the reversible hydration of carbon dioxide to form hydrogen carbonate. These enzymes are classified in four distinct classes, designated α-, β-, γ- and δ-CAs.[3] In the first three classes, a mononuclear zinc center mediates the hydrolysis of CO_2 by a two-step mechanism.[4] In the first step, a zinc-bound hy-

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droxide serves as a nucleophile for attack on CO_2. The second step involves regeneration of the active site Zn–OH moiety through water activation. In the active site of a typical mammalian α-type carbonic anhydrase (e.g. carbonic anhydrase II), the resting state tetrahedral zinc center, ligated by three histidine ligands and one hydroxide/water ligand [$(N_{His})_3Zn–OH$], acts as a hydrogen-bond donor to an active-site threonine residue (Thr-199, Figure 1). This interaction is suggested to be important toward determining the pK_a of the $Zn–OH_2$ moiety and orienting the hydroxide lone pair for attack on CO_2.[5,6] Hydrogen bonding involving Thr-199 is also suggested to be important for stabilization of the transition state and product-bound forms of the enzyme. Notably, an X-ray structure of carbonic anhydrase II shows that the zinc-bound hydroxide oxygen atom also accepts hydrogen bonds from the surrounding water molecules (Figure 1).[7]

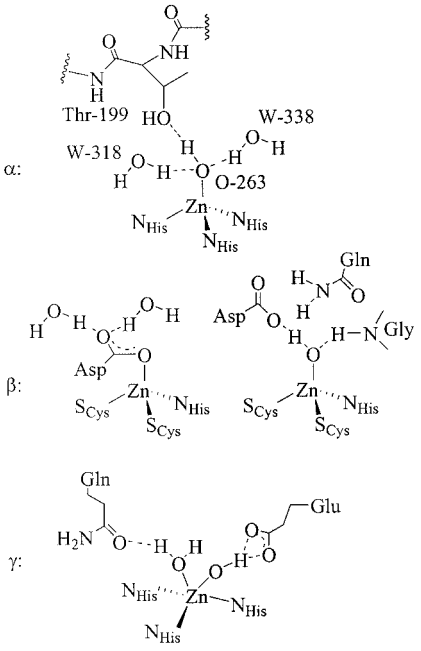

Figure 1. Active-site primary and secondary coordination environments of α-, β-, and γ-type carbonic anhydrases.

The β-type CAs contain a mononuclear zinc center ligated by two conserved cysteine residues, one conserved histidine residue, and an aspartate or water ligand (Figure 1).[8–12] On the basis of the X-ray structure of the *P. sativum* β-CA, secondary hydrogen-bonding interactions involving active site aspartate, glutamine, and glycine residues are suggested to be involved in catalysis.[9] In the γ-CA "Cam" from the archaeon *Methanosarcina thermophila*, a trigonal-bipyramidal zinc center is ligated by three histidine residues and two water/hydroxo ligands (Figure 1).[13,14] Hydrogen-bonding interactions are present between the water/hydroxo ligands and two active-site residues (Gln-75 and Glu-62). The glutamate residue has also been implicated in proton transfer and in stabilization of a hydrogen carbonate bound form of the enzyme. Finally, a δ-type carbonic anhydrase, TWCA1, from the marine diatom *Thalassiosira weissflogii*, has been identified as having an $(N_{His})_3Zn–OH_2/OH$ motif akin to α-type CAs.[15] Notably, under conditions wherein the level of TWCA1 is low in *T. weissflogii*, a putative naturally occurring, cadmium-containing carbonic anhydrase (CDCA1) has been identified.[16] The sequence of CDCA1 is significantly different from those of all other classes of CAs.[17] X-ray absorption spectroscopic studies suggest that the cadmium center in CDCA1 is tetrahedral and is ligated by two or more cysteine thiolates and a water molecule.[17]

Liver alcohol dehydrogenase (LADH) catalyzes the oxidation of alcohols to aldehydes and ketones using NAD^+ as a cofactor.[18] The resting state form of the enzyme contains a tetrahedral $(N_{His})(S_{Cys})_2Zn–OH_2$ center, with a nearby serine residue (Ser-48) positioned to form a hydrogen-bonding interaction with the zinc-bound water molecule (Figure 2).[18] In a proposed catalytic cycle for LADH, the active-site water molecule is replaced by the alcohol substrate.[19] An X-ray crystallographic study of $C_6F_5CH_2OH$ bound to the active-site zinc center of LADH suggests the presence of a hydrogen-bonding interaction between the hydroxy proton of the zinc-bound alcohol and the oxygen atom of Ser-48.[20] Following deprotonation of the zinc-bound alcohol, Ser-48 is proposed to form a strong hydrogen-bonding interaction with the alkoxide oxygen atom.[21,22] This interaction is then proposed to weaken upon hydride transfer and formation of a zinc-bound aldehyde or ketone product.[22] Notably, X-ray crystallographic studies of formamide-[23–25] and sulfoxide-inhibited[26,27] forms of LADH also indicate the presence of hydrogen bonding between the zinc-bound oxygen atom of the inhibitor and Ser-48.

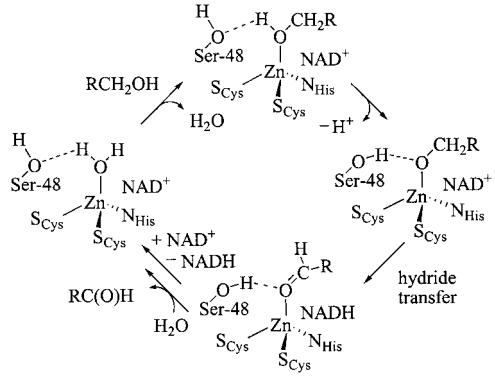

Figure 2. Hydrogen-bonding interactions proposed in the catalytic cycle of liver alcohol dehydrogenase.

Zinc enzymes that catalyze the hydrolysis of amide bonds in many cases have active-site residues within hydrogen-bonding distance of the metal-bound water and/or the substrate carbonyl group.[28,29] For example, in the active site of carboxypeptidase A, hydrogen-bonding interactions involving several residues (Glu-270, Arg-71, Arg-127, Asn-144, Arg-145, and Tyr-248) have been identified (Figure 3).[30,31]

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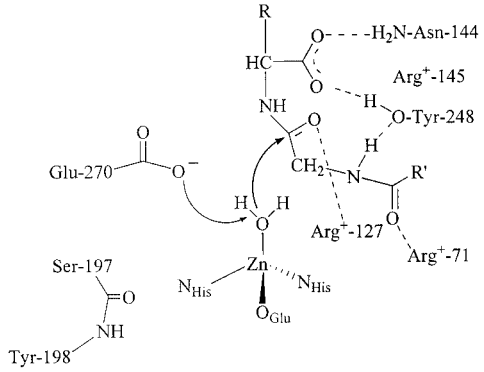

Figure 3. Proposed secondary interactions in the active site of carboxypeptidase A in the presence of substrate.

Similary, within the active site of several metalloenzymes that catalyze the hydrolysis of phosphate ester linkages, are positively charged amino acid side chains that are proposed to stabilize the transition state by hydrogen bonding and/or provide a proton for the leaving group. For example, in the catalytic cycle of alkaline phosphatase, phosphate monoester hydrolysis involves substrate interactions with arginine guanidinium and histidine imidazolium groups.[32]

In this Microreview, I summarize recent advances in the use of tripodal tetradentate ligand systems having internal hydrogen-bond donors in studies directed at evaluating the influence of secondary interactions on chemical reactions of relevance to carbonic anhydrase, liver alcohol dehydrogenase, and amide and phosphate ester hydrolyzing enzymes. In an ideal scenario, such studies would be performed using a tetrahedral enforcing ligand having internal hydrogen-bond donors, as this type of ligand would provide the most accurate mimic of both the primary and secondary coordination environment of the biological metal centers described above. However, despite recent attempts to incorporate secondary hydrogen-bond donors into tetrahedral enforcing ligands,[33] little coordination chemistry of such systems has been reported.

Water Activation: (Aqua)- and (Hydroxo)zinc Complexes

A key step in the catalytic cycle of several zinc enzymes, including carbonic anhydrases, is the activation of a water molecule to produce a reactive Zn–OH moiety. To gauge the influence of secondary hydrogen bonding on the acidity of a metal-bound water molecule, Mareque-Rivas and co-workers have examined the acidity of a $Zn–OH_2$ moiety supported by a variety of tripodal N_4-donor ligands having internal hydrogen-bond donors.[34,35] For ligands having a primary amine hydrogen-bond donor [bpapa, bapapa, tapa; Figure 4 (left)], the acidity of the $Zn–OH_2$ moiety increases by ca. 0.7–0.9 pK_a units per hydrogen-bond donor present in the chelate ligand. This can be rationalized by the fact that the formation of hydrogen-bonding interactions with the zinc-bound water molecule withdraws electron density from the water molecule, thus lowering the pK_a value. Notably, a parallel study involving neopentylamine-appended ligands [bpnpa, bnpapa, tnpa; Figure 4 (right)] yielded a different result. Specifically, the ligand system having the largest number of internal hydrogen-bond donors (tnpa) was found to produce an (aqua)zinc complex that was intermediate in acidity between complexes supported by ligands having one (bpnpa) or two (bnpapa) internal hydrogen-bond donors. This difference may be due to steric effects involving the bulkier neopentylamine hydrogen-bond donors. In this regard, X-ray structures of zinc hydroxide complexes of both the bnpapa and tnpa ligands have been reported (Figure 5).[35,36] In $[(bnpapa)Zn–OH]ClO_4$, the zinc-bound hydroxide oxygen atom accepts two hydrogen bonds from the neopentylamine donors. These secondary interactions are characterized by a heteroatom N···O distance of ca. 2.73 Å. In $[(tnpa)Zn–OH]ClO_4$, the hydroxide oxygen atom also accepts two hydrogen bonds from the supporting chelate ligand. However, in this complex the average heteroatom distance is longer [$N···O_{avg}$ 2.82 Å; $N···O_{avg}$ 2.88 Å (two independent X-ray structures reported)].[35,36] Notably, this change in the secondary hydrogen-bonding interactions does not produce a significant difference in the Zn–O(H) bond length {$[(bnpapa)Zn–OH]ClO_4$, 1.941(3) Å; $[(tpna)Zn–OH]ClO_4$ [1.9315(8) Å, 1.957(2) Å]}.

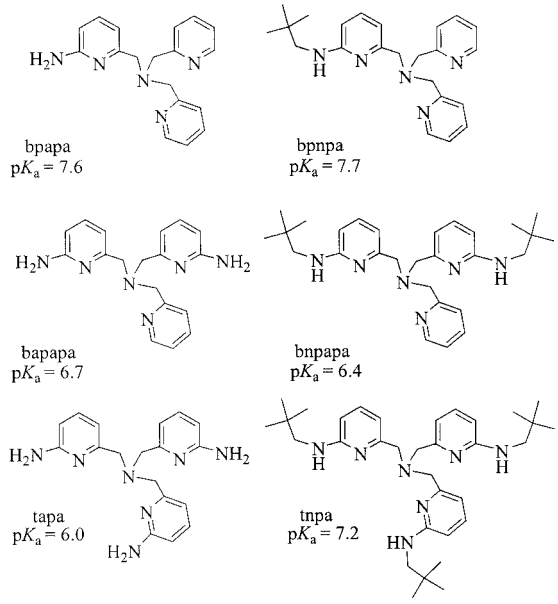

Figure 4. Tetradentate, tripodal chelate ligands having internal hydrogen-bond donors. The pK_a values for the $[(ligand)Zn–OH_2]^{2+}$ complexes are given.

Chin and co-workers have determined the acidity of a zinc-bound water molecule in complexes supported by tetradentate tripodal N_3O-type ligands having internal hydrogen-bond donors.[37] A Zn^{II} complex of the L2 ligand (Figure 6), which has two internal primary amine hydrogen-bond donors, has more acidic pK_a values than a Zn^{II} complex of the L1 ligand. These values, determined by potentiometric titration, are for ionization of the pendant alcohol of the chelate ligand and a zinc-bound water molecule, albeit the individual values have not been definitively as-

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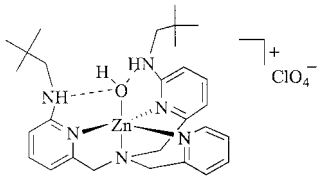
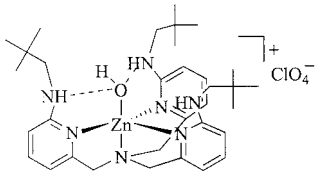


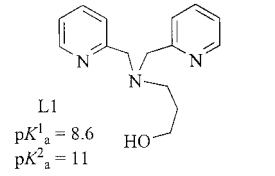
[(bnpapa)Zn-OH]ClO_4



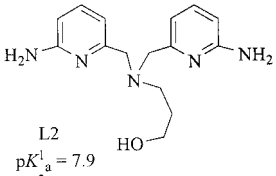
[(tnpa)Zn-OH]ClO_4

Figure 5. Mononuclear zinc hydroxide complexes of tripodal ligands having internal hydrogen-bond donors.

signed. As with the ligand systems described above, the enhanced acidity for the zinc-bound water molecule is attributed to secondary hydrogen-bonding interactions involving the ligand amine groups. To date, no X-ray structural characterization data has been reported for (aqua)- or (hydroxo)-zinc derivatives of the L1 or L2 ligands.



L1
$pK^1_a = 8.6$
$pK^2_a = 11$



L2
$pK^1_a = 7.9$
$pK^2_a = 10$

Figure 6. N_3O-donor ligands. pK_a values are given for the [(ligand)-Zn–OH_2]$^{2+}$ complexes.

Metal Hydroxide/CO_2 Chemistry

As noted above, studies of both α- and γ-carbonic anhydrases suggest that HCO_3^- binding to the zinc ion is stabilized by hydrogen-bonding interactions.[14,38] Interestingly, several isolated mononuclear metal hydrogen carbonate complexes also demonstrate both hydrogen-bond-donor and -acceptor interactions involving the metal-bound hydrogen carbonate ligand.[39–43] To date, a mononuclear zinc hydrogen carbonate complex of relevance to carbonic anhydrase has not been structurally characterized. However, Masuda and co-workers recently reported that a zinc hydroxide complex of the tnpa chelate ligand {[(tnpa)Zn–OH]ClO_4, Figure 5} undergoes reaction in the presence of CO_2 to produce a putative zinc hydrogen carbonate complex, which has been characterized by ^{1}H and ^{13}C NMR and electrospray mass spectrometry.[36] In the proton NMR spectrum in [D_6]DMSO, evidence for the formation of the hydrogen carbonate complex is derived from a shift of the neopentylamine proton resonance from δ = 9.21 ppm in the hydroxide complex to δ = 7.71 ppm in the hydrogen carbonate complex. In the ^{13}C NMR spectrum in CD_3OD, a new resonance at δ = 160.8 ppm has been assigned as the sp^2 carbon atom of the coordinated hydrogen carbonate ligand. The strongest evidence for the formation of [(tnpa)-Zn(HCO_3)]ClO_4 comes from electrospray mass spectrometry where a new isotope cluster is found at m/z = 670.3. This value corresponds to the cationic formula [(tnpa)-Zn(HCO_3)]$^+$. The reaction to produce [(tnpa)Zn(HCO_3)]-ClO_4 is reversible, as purging with argon results in the regeneration of the spectroscopic signals associated with [(tnpa)Zn–OH]ClO_4. Recently, the same laboratory reported that [(bnpapa)Zn–OH]ClO_4[35,44] (Figure 5) undergoes reaction with CO_2 to produce a zinc hydrogen carbonate species, [(bnpapa)Zn(HCO_3)]ClO_4.[45] Though not relevant to carbonic anhydrases, we note that in the presence of H_2O_2, this hydrogen carbonate complex undergoes further reaction with a zinc hydroperoxide intermediate, [(bnpapa)Zn–OOH]ClO_4, to produce a novel dinuclear zinc peroxocarbonate complex, [(bnpapaZn)$_2$(O_3CO)](ClO_4)$_2$.[45] X-ray crystallographic studies of this peroxocarbonate complex indicate stabilization of peroxocarbonate dianion coordination by hydrogen-bonding interactions involving the bnpapa supporting chelate ligand.

In reactions with relevance to β-type CAs and the novel cadium-containing carbonic anhydrase that was recently reported,[16,17] we have examined the CO_2 reactivity of dinuclear zinc and cadmium hydroxide complexes, [(benpaZn)$_2$-(μ-OH)$_2$](ClO_4)$_2$[46] and [(bmnpaCd)$_2$(μ-OH)$_2$](ClO_4)$_2$, supported by tripodal N_2S_2 chelate ligands containing a single internal hydrogen-bond donor (Scheme 1).[47,48] For the zinc complex, the reaction with CO_2 leads to the formation of a bridging carbonate complex, [(benpaZn)$_2$(μ-CO_3)]-(ClO_4)$_2$, having bidentate carbonate coordination to both zinc centers. The reaction of [(bmnpaCd)$_2$(μ-OH)$_2$](ClO_4)$_2$ with CO_2 leads to the formation of [(bmnpaCd)$_2$(μ-CO_3)]-(ClO_4)$_2$, a dinuclear complex wherein the carbonate ligand is coordinated in a bidentate fashion to one Cd^{II} center and in an anisobidentate mode to the other Cd^{II} ion. Notably, while addition of water to the zinc carbonate complex results in the release of CO_2 and the regeneration of [(benpaZn)$_2$(μ-OH)$_2$](ClO_4)$_2$, the cadmium carbonate complex exhibits no reaction in the presence of water. This difference in reactivity may be due to several factors, including the weak nature of thioether ligation to Zn^{II}.[49,50] In [(benpaZn)$_2$(μ-CO_3)](ClO_4)$_2$, long Zn–S interactions [2.561(1) Å and 2.594(1) Å] suggest the possibility that a coordinated thioether may dissociate or could possibly be displaced in favor of a water ligand. Water coordination could facilitate the hydrolysis of the bridging carbonate moiety and the release of CO_2. Subtle differences in hydrogen-bonding interactions involving the bridging carbonate ligands in [(benpaZn)$_2$(μ-CO_3)](ClO_4)$_2$ and [(bmnpaCd)$_2$(μ-CO_3)](ClO_4)$_2$ may also contribute to the observed differences in CO_2 release reactivity.

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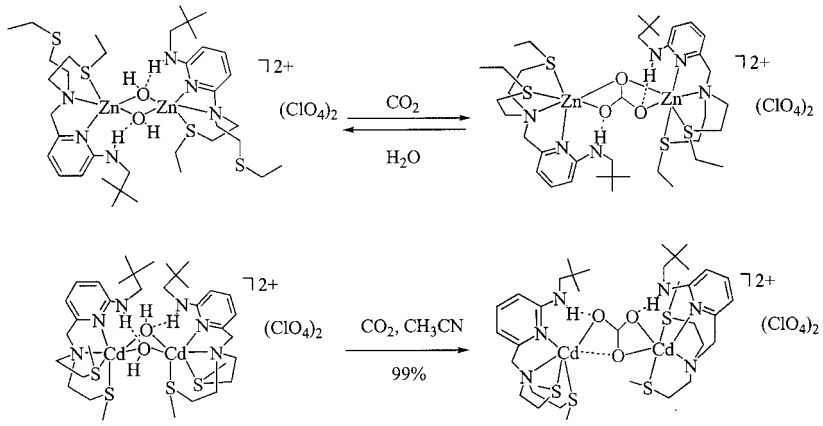

Scheme 1. CO_2 reactivity of N_2S_2-ligated zinc and cadmium hydroxide complexes.

Nitrogen/Sulfur-Ligated Zinc–Alcohol, –Aryloxide, and –Alkoxide Complexes

Comparative structural studies of mononuclear zinc–alcohol, –formamide, and –sulfoxide complexes, supported by the N_2S_2-donor chelate ligands bmapa {[(6-amino-2-pyridyl)methyl]bis[2-(methylthio)ethyl]amine} and bmpa {bis-[2-(methylthio)ethyl][(2-pyridyl)methyl]amine} (Figure 7), revealed, in some cases, differences as a consequence of the presence of a hydrogen-bond-donor amine group in the former ligand.[51,52] For example, while mononuclear bmapa- and bmpa-ligated zinc–methanol complexes showed no difference in the Zn–O(alcohol) distance, a subtle elongation (ca. 0.025 Å) was identified for the Zn–O(formamide) distances in [(bmapa)Zn(DMF)]$(ClO_4)_2$ and [(bmapa)-Zn(NMF)]$(ClO_4)_2$ relative to their bmpa-ligated analogs. This bond lengthening may be due to the removal of electron density from the formamide carbonyl unit through the intramolecular hydrogen-bonding interaction, which would make the formamide a weaker donor to the cationic zinc center. However, alternative rationales for the Zn–O bond elongation in the bmapa-ligated zinc–formamide derivatives must also be considered. For example, the presence of the secondary amine group may impart additional steric hindrance that is responsible for the slight Zn–O(formamide) bond elongation. In addition, the amine substituent on the pyridyl ring of the bmapa ligand makes this heterocycle a slightly better base (pyridine: pK_a = 5.14; 2-aminopyridine: pK_a = 6.71) and thus a better donor to the zinc center.[53,54] This could result in a slightly decreased Lewis acidity for the zinc center in the bmapa-ligated derivatives. Overall, the degree to which each of these factors influences the neutral oxygen-donor binding properties of the N_2S_2-ligated zinc center remains to be fully elucidated.

As noted above, a mononuclear nitrogen/sulfur-ligated zinc–alkoxide derivative is proposed as the active species for hydride transfer in the catalytic cycle of liver alcohol dehydrogenase.[19] To examine the influence of hydrogen bonding on the formation and reactivity of nitrogen/sulfur-ligated zinc–aryloxide and –alkoxide complexes, two new tetradentate tripodal ligand systems containing one or more internal hydrogen-bond donors were employed

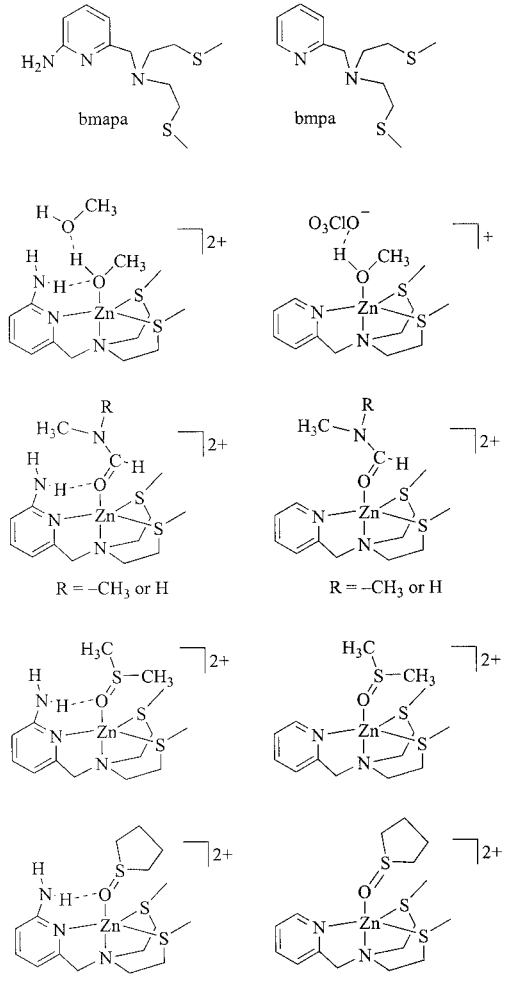

Figure 7. Zinc–alcohol, –formamide, and –sulfoxide complexes of the bmapa and bmpa ligands. All complexes have perchlorate counteranions.

(Figure 8).[46,55] Using the bmnpa and benpa ligands, a series of mononuclear N_2S_2-ligated zinc–aryloxide complexes were prepared and characterized.[46] In each complex, a hydrogen-bonding interaction is present between the zinc-bound aryloxide oxygen atom and the secondary amine moiety of the supporting chelate ligand. ^{1}H NMR

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studies of this family of complexes indicated that this hydrogen-bonding interaction is perturbed upon change in the basicity of the aryloxide ligand. Specifically, whereas in the *p*-methoxyphenolate complex [(benpa)Zn(*p*-$OC_6H_4OCH_3$)]ClO_4 the secondary amine N–H resonance is found at δ = 9.97 ppm (CD_3CN, ambient temperature), in the *p*-nitrophenolate complex [(benpa)Zn(*p*-$OC_6H_5NO_2$)]ClO_4 the same resonance is found at δ = 8.93 ppm. The downfield position of the N–H resonance in the *p*-methoxyphenolate derivative relative to the *p*-nitrophenolate analog indicates that a stronger hydrogen-bonding interaction is present in [(benpa)Zn(*p*-$OC_6H_4OCH_3$)]ClO_4. This is consistent with the relative basicity of the two anions (*p*-methoxyphenol: pK_a = 10.2; *p*-nitrophenol: pK_a = 7.14).

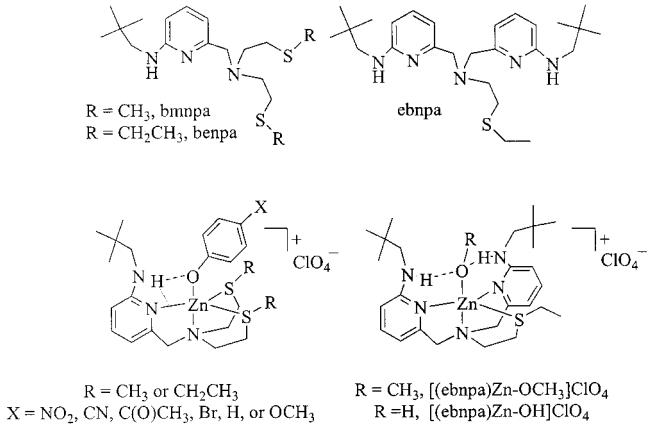
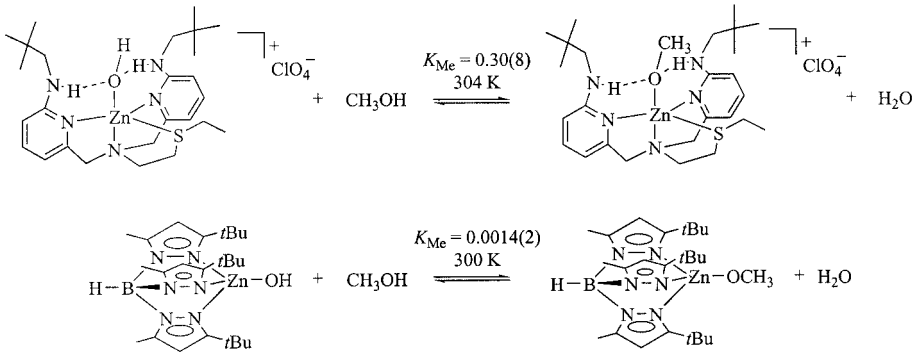


Figure 8. Top: Tripodal tetradentate nitrogen/sulfur ligands containing internal hydrogen-bond donors. Bottom: Mononuclear zinc–aryloxide and –methoxide/hydroxide complexes.

Particularly interesting results were obtained using the tripodal N_3S-donor ebnpa {[2-(ethylthio)ethyl]bis[(6-neopentylamino-2-pyridyl)methyl]amine} ligand (Figure 8).[55] The mononuclear zinc–methoxide and –hydroxide complexes, [(ebnpa)Zn–OCH_3]ClO_4 and [(ebnpa)Zn–OH]ClO_4, were isolated and characterized. Notably, determination of the equilibrium constant for the methanolysis of the hydroxide derivative revealed a value [K_{Me} (304 K) = 0.30(8)] that is orders of magnitude greater than that of an equilibrium involving Zn–OH and Zn–OCH_3 derivatives of the hydrophobic $Tp^{tBu,Me}$ ligand [$Tp^{tBu,Me}$ = tris(3-*t*Bu-5-Me-pyrazolyl)hydroborate, Scheme 2] [K_{Me} (300 K) = $1.4(2)\cdot10^{-3}$].[56,57] Examination of the temperature dependence of the equilibrium constants for the ebnpa- and $Tp^{tBu,Me}$-ligated systems yielded ΔH_{Me} = –0.9 kcal/mol and 1.2(1) kcal/mol, respectively. The negative ΔH_{Me} value for the ebnpa-ligated system indicates that spontaneous alkoxide formation will occur from a zinc hydroxide precursor at low temperature. In contrast, the positive ΔH_{Me} value for the $Tp^{tBu,Me}$-ligated system indicates that alkoxide formation from a zinc hydroxide species is thermodynamically unfavorable at all temperatures. Overall, this work has implications for the catalytic cycle of LADH as it suggests that active-site ligand effects, including hydrogen-bonding interactions involving Ser-48, likely influence the hydrolytic stability of the proposed zinc–alkoxide moiety in the catalytic cycle.

Amide Cleavage

Secondary hydrogen-bonding interactions are proposed to play important roles in the amide hydrolysis reactions mediated by carboxypeptidase A and other metalloamidases. For example, hydrogen bonding may be involved in the activation of the amide carbonyl moiety, and/or in transition-state stabilization. To probe the influence of hydrogen bonding on amide cleavage reactivity, Mareque-Rivas and co-workers have examined the amide cleavage properties of tripodal N_4-ligated systems having one internal amide substrate and from zero to two internal hydrogen-bonding interactions involving the zinc-bound amide carbonyl oxygen atom (Figure 9).[58–60] X-ray crystallographic studies of [(ppbpa)Zn]$(ClO_4)_2$, [(amppa)Zn]$(ClO_4)_2$ (amppa = [(6-amino-2-pyridyl)methyl]{[6-(pivaloylamido)-2-pyridyl]-methyl}[(2-pyridyl)methyl]amine) and [(bampa)Zn]$(ClO_4)_2$ (bampa = bis[(6-amino-2-pyridyl)methyl]{[6-(pivaloylamido)-2-pyridyl]methyl}amine) revealed that each complex contains a distorted trigonal-bipyramidal zinc center with the tertiary amine and the amide oxygen donors of the chelate ligand in the axial positions.[59,61] Comparison of the zinc–ligand distances in this series of complexes indicated that as the number of internal hydrogen-bonding interactions involving the coordinated amide oxygen atom increased, the Zn–O(amide) bond elongated by ca. 0.02 Å and the Zn–N(*tert*-amine) shortened by ca. 0.02–0.03 Å



Scheme 2. Zinc–hydroxide/methoxide equilibria.

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(Figure 9). Notably, the magnitude of this elongation of the Zn–O bond in this series of complexes per hydrogen-bond donor is identical to that found upon comparison of the Zn–O bond lengths in the N_2S_2-ligated zinc–formamide complexes {[(bmapa)Zn(DMF)]$(ClO_4)_2$, [(bmapa)Zn(NMF)]-$(ClO_4)_2$, Figure 7} vs. structurally similar compounds lacking the internal hydrogen-bond donor {[(bmpa)Zn(DMF)]-$(ClO_4)_2$, [(bmpa)Zn(NMF)]$(ClO_4)_2$, Figure 7}.[52] The hydrogen-bonding interactions for the complexes shown in Figure 7 and Figure 9 may all be classified as moderate hydrogen bonds.[62]

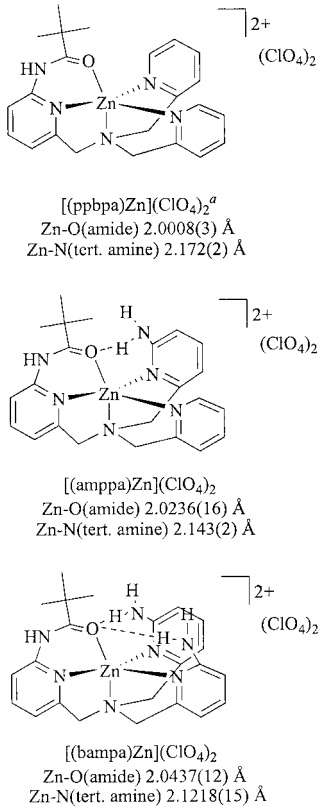

Figure 9. Amide-appended complexes containing zero to two internal hydrogen-bond donors.[63]

Treatment of the amide-appended zinc complexes shown in Figure 9 with 1 equiv. of $Me_4NOH{\cdot}5H_2O$ in methanol at 50(1) °C results in amide alcoholysis to produce 1 equiv. each of methyl trimethylacetate and Me_4NClO_4, and one or more zinc complexes of a modified chelate ligand having a new primary amine appendage derived from the cleavage of the amide moiety. For example, the reaction of [(ppbpa)-Zn]$(ClO_4)_2$ under the conditions cited above produces a mixture of zinc–hydroxide and –methoxide complexes of the ambpa {[(6-amino-2-pyridyl)methyl]bis[(2-pyridyl)-methyl]amine}. Mareque-Rivas and co-workers have shown that the half-life for the amide methanolysis reaction in the series of complexes shown in Figure 9 increases dramatically with the addition of each internal hydrogen-bond donor. Specifically, the half-life for the amide bond in [(ppbpa)Zn]$(ClO_4)_2$ is ca. 0.4 h, whereas for [(amppa)-Zn]$(ClO_4)_2$ and [(bampa)Zn]$(ClO_4)_2$, the half-life is ca. 9 h and ca. 320 h, respectively.[59] To interpret these results, as well as other amide cleavage studies involving similar complexes reported in the literature, we thought it essential to further investigate the reaction mechanism of amide cleavage operative in these systems. In this regard, we recently completed kinetic and mechanistic studies of the amide methanolysis reaction of [(ppbpa)Zn]$(ClO_4)_2$.[61] As depicted in Scheme 3, these studies revealed that the treatment of [(ppbpa)Zn]$(ClO_4)_2$ with 1 equiv. of $Me_4NOH{\cdot}5H_2O$ in methanol/acetonitrile solution at ambient temperature results in the stoichiometric formation of a deprotonated amide intermediate complex, [(ppbpa$^-$)Zn]ClO_4, which was isolated and characterized (^{1}H and ^{13}C NMR, FTIR, and elemental analysis). Heating of analytically pure [(ppbpa$^-$)-Zn]ClO_4 in methanol/acetonitrile solution at 65(1) °C results in amide methanolysis. Kinetic studies of this reaction revealed a first-order dependence on both [(ppbpa$^-$)Zn]-ClO_4 and methanol in the rate-determining step. Analysis of the rate of decay of a ^{1}H NMR signal of [(ppbpa$^-$)Zn]-ClO_4 as a function of time yielded activation parameters that are consistent with an intramolecular amide-cleavage process [$\Delta H^{\ddagger}$ = 15.0(3) kcal/mol, $\Delta S^{\ddagger}$ = –33(1) eu].[63] On the basis of this data and other experiments, a reaction mechanism was proposed in which the deprotonated amide species [(ppbpa$^-$)Zn]ClO_4 is an intermediate produced prior to the rate-limiting step.[61] The reaction of this intermediate with methanol is proposed to produce a Lewis activated type structure from which amide cleavage is initiated. The rate-determining step in this reaction pathway should be either the attack of the zinc-bound alkoxide nucleophile at the amide carbonyl carbon atom or the breakdown of the resulting tetrahedral intermediate. On the basis of these kinetic and mechanistic studies, we suggest that the slowing of the rate of amide methanolysis for the series of complexes shown in Figure 9 results from steric hindrance imparted by the hydrogen-bond donor amine groups, which limits the approach of the nucleophile to the amide carbonyl carbon atom, or from stabilization of the tetrahedral intermediate by hydrogen-bonding interactions. Further experiments directed at differentiating between these possibilities are underway.

Notably, a Zn^{II} complex of the N_2S_2 donor ligand bmppa (Scheme 4) also undergoes amide methanolysis in the presence of $Me_4NOH{\cdot}5H_2O$ in methanol-containing solutions.[64] In addition, we have discovered that Cd^{II} and Hg^{II} analogs, [(bmppa)Cd(ClO_4)]ClO_4 and [(beppa)-Hg(ClO_4)]ClO_4, also undergo amide methanolysis under similar conditions.[64,65] The X-ray structures of these heavier group 12 analogs provide evidence that simultaneous amide oxygen and anion coordination can occur. Specifically, in the solid-state structures of [(bmppa)Cd(ClO_4)]-ClO_4 and [(beppa)Hg(ClO_4)]ClO_4 (Figure 10) a weak perchlorate interaction yields a six-coordinate cation having a distorted trigonal-prismatic geometry. Interestingly, the metal-bound oxygen atom of the coordinated perchlorate anion is positioned adjacent to the amide carbonyl oxygen atom in an arrangement that may be relevant to the proposed active form of the metal complexes for amide meth-

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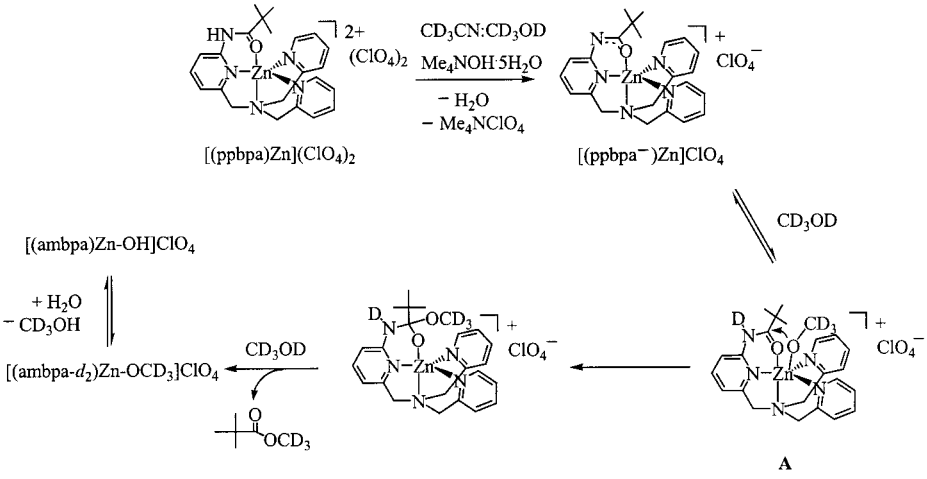
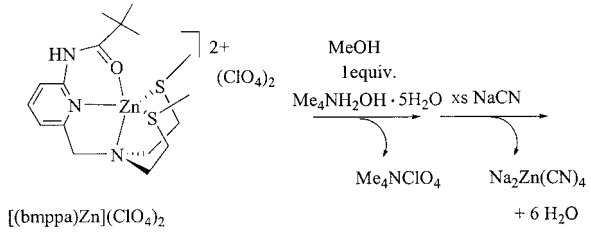
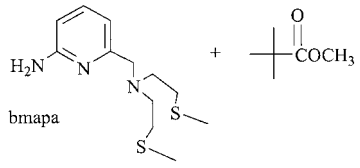


Scheme 3. Proposed mechanistic pathway of the amide methanolysis for $[(ppbpa)Zn](ClO_4)_2$.

anolysis (Scheme 3, "A"). Preliminary mechanistic studies indicate that the amide-cleavage reactions of $[(bmppa)Cd(ClO_4)]ClO_4$ and $[(beppa)Hg(ClO_4)]ClO_4$ also proceed by the formation of an intermediate deprotonated amide complex.





Scheme 4. Amide methanolysis reaction of $[(bmppa)Zn](ClO_4)_2$.

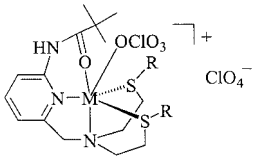


Figure 10. Drawing of the cationic portions of $[(bmppa)M(ClO_4)]ClO_4$ ($M = Cd^{II}$ or Hg^{II}).

The studies outlined above indicate that group 12 complexes supported by tripodal ligands having a single internal amide appendage exhibit novel amide-cleavage reactivity in basic methanol solution. This is interesting in that amide-appended tetradentate tripodal ligands have been used to stabilize a variety of 3d-metal complexes of relevance to biological systems, including metal hydroxide complexes, without any reported amide-cleavage side reactions. For example, Borovik has used amide-appended tripodal, trianionic ligands to stabilize a variety of terminal M–X (M = Fe, Mn; X = O, OH, S, Se, NHR, NR) complexes.[66,67] Masuda has also demonstrated that amide-appended tetradentate tripodal N_4-donor ligands can be used to stabilize a variety of novel copper– and/or iron–hydroxo, –hydroperoxo, and –alkylperoxo species.[68–73] These latter complexes are particularly interesting in that each contains the {[6-(pivaloylamido)-2-pyridyl]methyl}amine structural component within the supporting chelate ligand. Further studies are clearly needed to determine how changes in the nature of the metal ion influence the amide-cleavage reactivity.

Phosphate Ester Coordination and Hydrolysis

There is considerable current interest in the development of synthetic compounds that catalyze the selective and/or catalytic hydrolysis of phosphate esters.[74–90] In this contribution, discussion in this area is limited to recent studies of phosphate ester coordination and hydrolysis mediated by zinc complexes of tetradentate tripodal ligands having internal hydrogen-bond donors.

Mareque-Rivas and co-workers recently compared the phosphate monoester binding properties of $[(bapapa)Zn(OH_n)]^{2+}$ (n = 1 or 2; pK_a = 6.7) and $[(tpa)Zn(OH_2)]^{2+}$ (Figure 11).[91] In aqueous solution at pH = 7, the former compound exhibits a higher affinity for $PhOPO_3^{2-}$ coordination ($\log K = 3.6 \pm 0.1$) than the tpa-ligated analog complex ($\log K = 4.4 \pm 0.1$). Although an X-ray structure of a phosphate monoester adduct was not reported for either system, X-ray crystallographic characterization of a zinc nitrate complex of the bapapa ligand, $[(bapapa)Zn(NO_3)]NO_3$, showed that the zinc-bound oxygen atom of the anion can participate in two moderate hydrogen-bonding interactions [O(1)···$N(amine)_{avg}$ 2.93 Å] with the supporting chelate ligand. Presumably, the bound phosphate ester monoanion can coordinate in a similar fashion.

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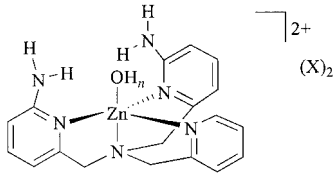
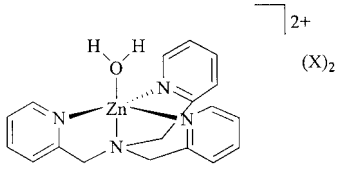
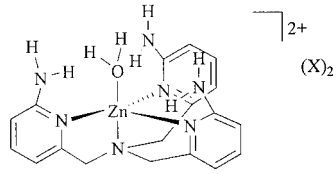


[(bapapa)Zn(H$_2$O)](X)$_2$
n = 1 or 2 at pH = 7; pK_a = 6.7



[(tpa)Zn(H$_2$O)](X)$_2$
pK_a = 8.1

Figure 11. Mononuclear zinc complexes used to evaluate the influence of hydrogen bonding on the phosphate ester coordination.



[(tapa)Zn(H$_2$O)](X)$_2$

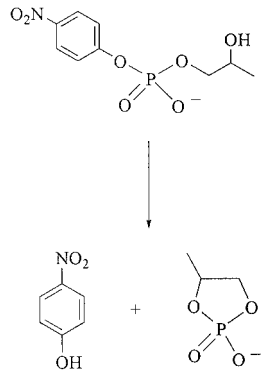
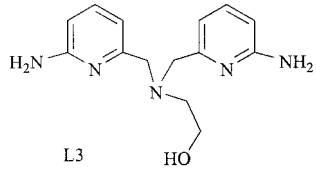


Figure 12. Top: Drawing of [(tapa)Zn(H$_2$O)](X)$_2$. Bottom: Intramolecular transesterification reaction of 2-hydroxypropyl 4-nitrophenyl phosphate.

A dinuclear zinc–phosphate diester complex, [{(bpapa)Zn}$_2$(μ-DMP)$_2$](PF$_6$)$_2$ (DBP = dibenzyl phosphate) having one internal hydrogen-bond donor per chelate ligand has been characterized by X-ray crystallography.[92] At each zinc center in [{(bpapa)Zn}$_2$(μ-DMP)$_2$](PF$_6$)$_2$, a bound phosphate diester oxygen atom accepts one hydrogen-bonding interaction from the amine group of the supporting chelate ligand. In solution [CD$_3$CN/D$_2$O (pD = 7.4)], using ^{31}P NMR spectroscopy as a detection method, it was found that the affinity of the [(bpapa)Zn(OH/H$_2$O)]$^{2+}$ cation for DBP$^-$ was higher than that of [(tpa)Zn(H$_2$O)]$^{2+}$, which is similar to the reactivity found for the phosphate monoester binding studies described above.

In further investigations of the impact of secondary hydrogen-bonding interactions on the phosphate ester reactivity of zinc complexes, Mareque-Rivas and Williams recently reported a comparative study of the transesterification of 2-hydroxypropyl 4-nitrophenyl phosphate catalyzed by [(tapa)Zn(H$_2$O)]$^{2+}$ (Figure 12) and [(tpa)Zn(H$_2$O)]$^{2+}$ (Figure 11).[93] Notably, the rate of cyclization of the substrate is accelerated 3·10^6-fold by [(tapa)Zn(H$_2$O)]$^{2+}$ and 4·10^3-fold by [(tpa)Zn(H$_2$O)]$^{2+}$. The significant rate enhancement found for [(tapa)Zn(H$_2$O)]$^{2+}$ was attributed to enhanced stabilization of the dianionic intermediate that is formed in the rate-limiting step of the transesterification reaction, presumably by hydrogen-bonding interactions.

Studies of phosphate ester transesterification and hydrolysis have also been reported using tripodal N$_3$O-donor ligands having a variable number of internal hydrogen-bond donors.[37] Treatment of Zn^{II} complexes of the L1–L3 ligands (Figure 6 and Figure 13) with bis(*p*-nitrophenyl) phosphate (BNP) results in the production of either phosphate ester transesterification or hydrolysis products, depending on the identity of the supporting chelate ligand. For L1 and L2 (Figure 6), *p*-nitrophenol and the *O*-phosphorylated chelate ligand are generated, indicating a transesterification reaction pathway involving the alkoxide moiety of the chelate ligand. For L3 (Figure 13), only phosphate ester hydrolysis products are produced.



L3

Figure 13. L3 ligand.

Comparison of the reactivity of the zinc complex of L2 (second-order rate constant: 9.7·10^{-2} M^{-1} s^{-1}) vs. the spontaneous hydrolysis of BNP at pH = 7.0 and 25 °C reveals an acceleration of approximately six orders of magnitude. This rate acceleration was attributed to the involvement of an alkoxide (vs. hydroxide) nucleophile and the presence of secondary hydrogen-bonding interactions. The presence of the hydrogen-bond donors may provide additional Lewis acid activation for the zinc-bound substrate, or as suggested above, may stabilize a dianionic intermediate in the transesterification reaction. Further evidence for the impact of secondary hydrogen bonding is derived from the comparison of the second-order rate constants for BNP transesterification mediated by the zinc complex of L1 (4.2·10^{-4} M^{-1}s^{-1}) vs. that of L2, which reveals a 230-fold reactivity increase. For the phosphate ester hydrolysis reaction catalyzed by the zinc complex of L3, which includes two internal hydrogen-bond donor groups, the rate acceleration is ca. 10^5 over that of the uncatalyzed reaction.

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Conclusions

Through studies of synthetic zinc complexes supported by tetradentate tripodal ligands containing one or more internal hydrogen-bond donors, chemical precedent has been elucidated which can be used to interpret the proposed roles for secondary hydrogen bonding in modulating the chemistry of mononuclear zinc centers in biological systems. For example, by using synthetic complexes, it has been determined that the presence of hydrogen-bond donors to a zinc-bound water molecule reduces the pK_a of the bound water by 0.7–0.9 pK_a units per secondary interaction. This result has relevance to carbonic anhydrases (CAs), where the formation of a zinc hydroxide moiety is required for CO_2-hydration reactivity. Hydrogen-bonding interactions are also likely important toward influencing the hydroxide and hydrogen carbonate anion coordination within the active site of CAs. In regard to the latter, spectroscopic evidence has been recently reported for the formation of a novel mononuclear zinc hydrogen carbonate complex supported by a tripodal ligand having three internal hydrogen-bond donors. Use of an N_2S_2-donor chelate ligand having one internal hydrogen-bond donor has enabled the isolation of a novel Cd–OH complex. This complex is reactive toward CO_2, thus providing the first chemical precedent relevant to the reactivity of a recently reported naturally occurring cadmium-containing carbonic anhydrase. The catalytic cycle of liver alcohol dehydrogenase is proposed to involve hydrogen-bonding interactions between a zinc-coordinated neutral oxygen donor or an alkoxide ligand and a nearby serine residue. Comparative structural studies of tripodal N_2S_2-ligated zinc–alcohol, –formamide, and –sulfoxide complexes revealed only minor perturbations in Zn–O bonding as a consequence of the presence of an internal hydrogen-bond donor. However, studies of the methanolysis reactivity of an N_3S-ligated zinc–hydroxide complex revealed that the presence of internal hydrogen-bond donors enhances the stability of a zinc–methoxide species with respect to hydrolysis. This result indicates that hydrogen bonding involving Ser-48 in LADH may play an important role in stabilizing the proposed zinc–alkoxide species.

Amide methanolysis reactivity has been identified for group 12 complexes of tetradentate tripodal N_4- and N_2S_2-donor ligands having one internal amide appendage. Kinetic and mechanistic studies of the amide methanolysis reaction of one N_4-ligated system indicate a novel reaction pathway involving initial formation of a deprotonated amide intermediate. Incorporation of hydrogen-bond donors into this N_4-donor ligand, such that they interact with the zinc-bound amide oxygen atom, significantly slows the rate of amide methanolysis. This may be the result of steric hindrance and/or hydrogen-bond stabilization of a tetrahedral intermediate. Importantly, these systems now provide a unique opportunity to systematically examine an amide-cleavage process as a function of both supporting ligand and metal ion present in the complex. Such studies are expected to provide additional insight into how secondary interactions, including hydrogen bonding, influence amide-cleavage reactions.

The presence of hydrogen-bond donors in a tetradentate tripodal N_4-ligated zinc complex enhances the affinity of the zinc center for coordination of a phosphate ester monoanion. In terms of phosphate ester hydrolysis reactivity, zinc complexes having internal hydrogen-bond donors have been found to exhibit significant rate enhancement over analogs lacking such secondary interactions. These combined results provide chemical precedent to support the notion that hydrogen bonding interactions play an important role in modulating biological phosphate ester cleavage reactions.

Acknowledgments

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