

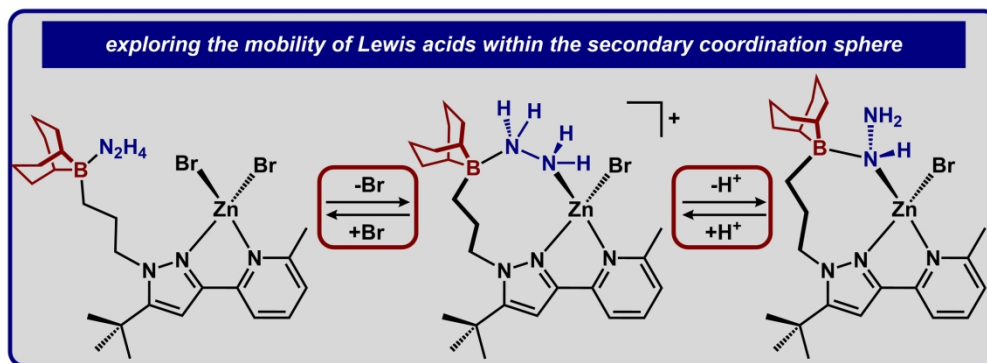


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Mobility of Lewis Acids within the Secondary Coordination Sphere: Toward a Model for Cooperative Substrate Binding

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Distance dependence of appended Lewis acids in N₂H₄ binding and deprotonation was evaluated within a series of zinc complexes. Variation of spacer-length to a tethered trialkylborane Lewis acid revealed distinct preferences for binding and stabilization of the resulting deprotonated N₂H₃⁻ unit.

Acidic/basic residues within the secondary coordination sphere of metalloenzyme active sites are often critical for structure regulation and/or reactive-intermediate stabilization.¹ These interactions occur in a dynamic protein environment where acidic residues are highly flexible and mobile. For example, in the active site of type II β -carbonic anhydrase, an aspartate residue (Asp44) gates reactivity to a Zn-OH: initially binding to Zn, then migrating 1.5 Å to hydrogen bond with Zn-OH₂.² Similarly, a recent report of Mo-nitrogenase revealed a dynamic multi-metallic cofactor, where the nitrogen reduction sequence is proposed to involve dynamic rotation and substrate/H-bonding interactions.³

Synthetic models containing pre-arranged secondary sphere groups can provide insight into the roles through which acidic groups facilitate substrate binding.⁴ While such models often use rigid molecular scaffolds to provide critical snapshots of donor/acceptor adducts, they do not capture mobility-dependent reactivity. Modelling mobility of an acidic residue within the secondary coordination sphere is synthetically challenging.⁵

Our group is working to evaluate how the precise structural, electronic, and cooperative modes in the secondary coordination sphere can be used to regulate reactivity.⁶ Recently, our lab investigated the role of ligand-appended acidic groups in homolytic bond scission of hydrazine by

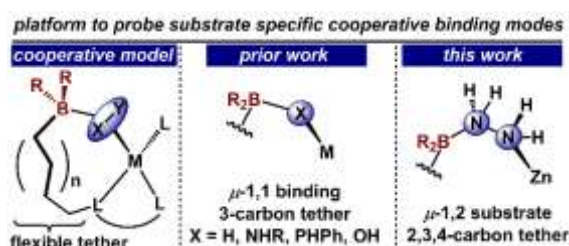


Fig. 1 Left: Conceptual design. Right: specific substrates investigated in this study and their potential binding modes.

transition metal complexes.⁷ A key design aspect in those studies was the flexibility of the tethered trialkylborane Lewis acid, which enabled acid/base interactions to occur in *both* the primary (cooperatively with the transition metal) and secondary (independent of metal) spheres. A first-generation ligand, ³-BBN^{tBu}, containing a 3-carbon alkyl tether between the Lewis acid and the bidentate ligand was synthesized by hydroboration of 2-(1-allyl-5-(*tert*-butyl)-1*H*-pyrazol-3-yl)-6-methylpyridine with 9-borabicyclo[3.3.1]nonane (BBN).⁸ While this tether length stabilized monoatomic ligands (e.g. -NH₂) cooperatively with iron (Fig. 1), we obtained divergent results when attempting to sequester a diatomic substrate, cyanide.⁹ These disparate results highlight a Lewis acid dependence on substrate binding and illustrate a need to establish parameters (e.g. tether length) that maximize binding for a given substrate. Minimizing the energy requirement for cooperative acid-substrate-metal interaction will provide design cues that will enable the use of less-acidic Lewis acids, and ultimately facilitate product release—a challenge for catalytic turnover.

To probe distance relationships between the Lewis acid and a given substrate, we evaluated a set of compounds where: 1) the Lewis acid is held constant (9-BBN), 2) the alkyl tether length is systematically varied from 2 to 4 methylene (-CH₂-) units, and 3) the substrate contained variable bonding modes (Fig. 1). Zn was selected to ensure a consistent coordination geometry, and hydrazine (N₂H₄) was selected as the substrate (Fig. 1). Cooperative binding of N₂H₄ between the two Lewis acids, Zn²⁺

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and trialkylborane, must involve coordinating each of the two lone pairs (i.e. μ -1,2- N_2H_4).

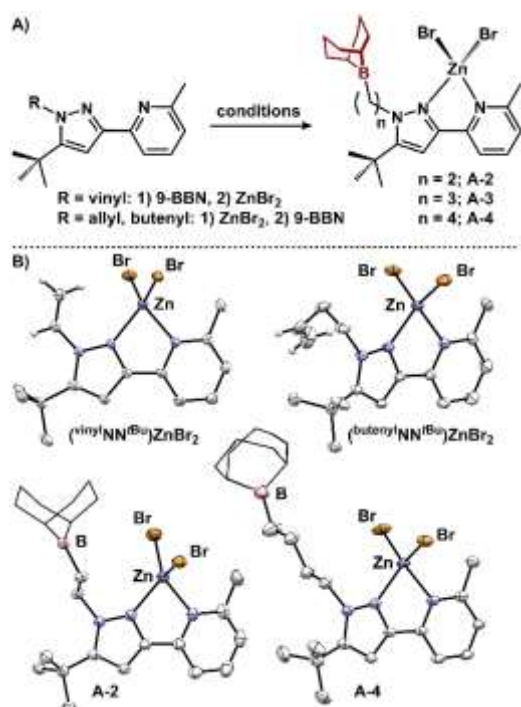


Fig. 2 A) Synthesis of complexes **A**. B) Molecular structures (50% probability ellipsoids) of **A-2** and **A-4** as well as their vinyl and butenyl precursors, respectively. H-atoms not attached to alkenyl moieties are omitted for clarity.

The two- and four-carbon length precursor ligands, $^{vinyl}NN^{tBu}$ and $^{butenyl}NN^{tBu}$, were prepared by adapted literature procedures (see SI). Initial metalation strategies of the new ligands mirrored our synthesis of ($^{3-BBN}NN^{tBu}$)ZnBr₂ (**A-3**; **3** denotes tether length, **A** denotes compound series).⁸ Stirring a CH₂Cl₂ solution of $^{vinyl}NN^{tBu}$ or $^{butenyl}NN^{tBu}$ with ZnBr₂ furnished ($^{vinyl}NN^{tBu}$)ZnBr₂ and ($^{butenyl}NN^{tBu}$)ZnBr₂ as white powders (Fig. 2). Whereas late-stage hydroboration of ($^{butenyl}NN^{tBu}$)ZnBr₂ with 9-BBN proceeded (RT, THF, 18 hr) to afford ($^{4-BBN}NN^{tBu}$)ZnBr₂ (**A-4**), ($^{vinyl}NN^{tBu}$)ZnBr₂ was obstinate to hydroboration. The molecular structures of ($^{vinyl}NN^{tBu}$)ZnBr₂ and ($^{butenyl}NN^{tBu}$)ZnBr₂ (Fig. 2B) determined by single crystal X-ray diffraction (SC-XRD) revealed a potential origin of the difference in hydroboration reactivity. Although hydroboration of vinyl substituents is generally facile with 9-BBN,¹⁰ ($^{vinyl}NN^{tBu}$)ZnBr₂ possesses two large steric moieties, the $-C(CH_3)_3$ and ZnBr₂, that render the vinyl group inaccessible.¹¹ To overcome this challenge, we pursued an early-stage hydroboration. Treating $^{vinyl}NN^{tBu}$ with 9-BBN generated $^{2-BBN}NN^{tBu}$ *in situ*, which was metalated with ZnBr₂ in one-pot to afford ($^{2-BBN}NN^{tBu}$)ZnBr₂ (**A-2**). Spectroscopically and structurally, **A-2** and **A-4** are similar to **A-3**. The distance between the two acidic centres, Zn and the trialkylborane, increases by *ca.* 1 Å for each additional $-CH_2-$ unit added to the tether length (Zn-B: **A-2** = 4.76_{ave}; **A-3** = 5.82; **A-4** = 6.57 Å).¹² This trend suggests the system is well-suited for a distance-dependent cooperativity study.

Our previous studies revealed the three-carbon tether was ideally suited for cooperative binding of a wide range of μ -1,1 substrates,⁸⁻⁹ however, we hypothesized a distinct tether length

would be needed for a μ -1,2 substrate. We used hydrazine (N_2H_4) to investigate this hypothesis. Previously, we demonstrated that the trialkylborane of **A-3** could capture a single equivalent to N_2H_4 to afford ($^{3-BBN}NN^{tBu}$)ZnBr₂(N_2H_4) (**B-3**), where the terminal $-NH_2$ lone-pair is uncoordinated.¹³ The series of complexes **B** were synthesized by standard protocols and all share similar spectroscopic properties.⁸ Structurally, the coordination environment at Zn is unperturbed and the distances between the two acidic sites, Zn and boron, are variable and range from 4.80 (**B-2**) to 7.38 Å (**B-4**). All display weak intra- (**B-2** and **B-3**) or intermolecular (**B-4**) $NH\cdots Br$ hydrogen bonding interactions¹⁴ that result in the N_2H_4 moieties being nearly equidistant (ave = 4.36 \pm 0.17 Å) to a Zn atom of the same, or an adjacent molecule.

Halide abstraction from complexes **B** with Tl^+ afforded cationic complexes, [$^{n-BBN}NN^{tBu}$]ZnBr(N_2H_4)[X], (**C-2-C-4**; X = OTf, PF₆) and were subjected to SC-XRD studies (Fig. 3). Each complex displays a C₁ symmetric tetrahedral bromido-Zn (τ_4 = 0.83-0.85) chelated by the $^{n-BBN}NN^{tBu}$ ligand. The fourth coordination site is occupied by a hydrazine ligand bridging to the appended trialkylborane (i.e. Zn-NH₂NH₂-BR₃). Across the series of compounds, the Zn-N₂H₄ bond distance elongates from 2.0256(11) – 2.0892(15) Å (**C-2** < **C-3** < **C-4**) as the tether length to the trialkylborane increases (Δ = 0.055 Å). This trend is also observed, though to a lesser degree, in the B-N₂H₄ distance where **C-2** is shorter (1.6463(18) Å) in comparison to **C-3** and **C-4** (1.675(2) and 1.668(2) Å, respectively). Both the R₃B-N₂H₄¹⁵ and Zn-N₂H₄ distances¹⁶ are comparable to related species. The interactions of N_2H_4 with the two Lewis acids, Zn and boron, force a nearly fixed distance from one another with variation of only 0.33 Å across the **C** series (contrasting with the **B** series; Δ Zn-B = 2.58 Å), highlighting the accordion-like flexibility of the acidic trialkylborane.

The solid-state data of **C-2** revealed both the shortest Zn-N and B-N contacts suggesting that this binding pocket is best suited for favourable host/guest interactions with N_2H_4 . Variable temperature NMR spectra provided additional support. At 25 °C, complexes **C** display C_s symmetric spectra that suggest a dynamic process. Upon cooling, each undergo broadening with a coalescence temperature of T_c = 276, 260, and 240 K for **C-2**, **C-3**, and **C-4**, respectively. For each complex, we propose this dynamic process is the same. From the coalescence temperature of **C-2** in CDCl₃, we obtained an activation energy barrier for this process of 12.8 \pm 0.1 kcal/mol (see SI). This value is similar to a previously reported on/off binding event between Zn and a ligand-tethered amine (13 kcal/mol).¹⁷ Across the series of compounds **C**, this energy varies by \sim 1.5 kcal/mol. Complex **C-4** displays both the lowest barrier for activation (11.5 kcal/mol), as well as the longest Zn-N₂H₄ bond distance.

Two limiting dynamic acid/base interactions are possible in complexes **C**: 1) Zn-N₂H₄ bond scission, or 2) R₃B-N₂H₄ bond scission. The latter was probed by attempting to form a borane-free analogue of complexes **C**. Treating ($^{butyl}NN^{tBu}$)ZnBr₂, a borane-free surrogate where the alkyl-BBN portion of the ligand was replaced with *n*-butyl, N_2H_4 caused immediate demetalation of the ligand. These results suggest that boron-

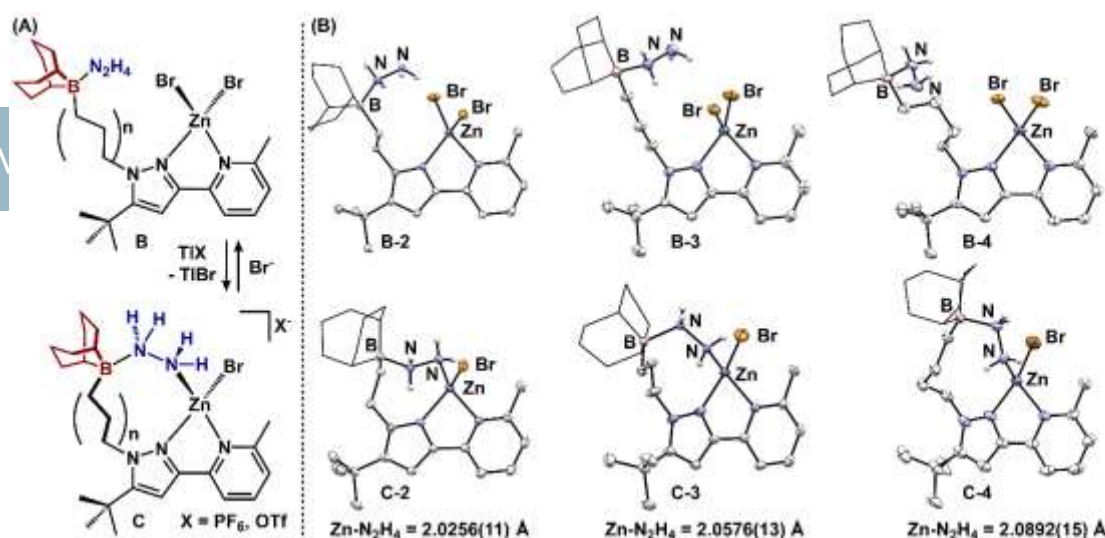


Fig. 3 A) Reversible formation of C from B. B) Molecular structures (50% probability ellipsoids, only H-atoms attached to heteroatoms are displayed). B-3 is previously reported.⁸

nitrogen bond scission in complexes C may result in decomposition, and highlights the requirement of an appended Lewis acid for stability. To ascertain the differences in Lewis acid strengths, we measured solution Gutmann-Beckett acidities.¹⁸ These data show that the Zn in C-2 is significantly more acidic than the appended borane (acceptor number = 66.3 vs. 25.0; see SI). The acceptor numbers suggest that a competitive base may promote dissociation of the weaker acid.¹⁹ Treating compounds C with 1.5 equiv. [Bu₄N][Br] rapidly regenerated compounds B, highlighting the lability of the Zn-N₂H₄ bond (Fig. 3A).²⁰ This result highlights the challenges of experimentally measuring and comparing Lewis acidities: due to hard/soft-acid/base mismatches and steric considerations, measured acidities are substrate specific and do not always correspond to accessible acidities.²¹

We propose the dynamic solution behaviour for complexes C is the result of dissociation of the Zn-N₂H₄ bond (Fig. 4, top). Thermodynamically, the tether length has minimal effect on the Zn-N₂H₄ bond dissociation energy.²² We computationally probed the electron density distribution of the Zn-N₂H₄ unit via density functional theory (DFT) methods. Complexes C were analysed at the B3LYP/6-311+G(2d,p) (CH₂Cl₂) level of theory for all atoms except Zn (6-311+G(2d) level). Natural bond orbital analyses are consistent with the extracted thermodynamic parameters from NMR spectroscopy: changing tether length results in minimal variation to the natural charges or bond indices. Kinetically, the tether length has a clear effect. Measured rates of Zn-N₂H₄ on/off binding at the coalescence temperature, k_c , for each complex follows the trend C-2 > C-3 > C-4.²³ This trend can be rationalized in terms of the distances between the two acidic residues, Zn and boron, in complexes B and C. As the tether length is increased, the rate of on/off binding is slowed because the distance between the two acids increases.

The acidification of hydrazine by Lewis acids was probed through DFT assessment of C-3, N₂H₄, and its adduct with 9-methyl-9-borabicyclo[3.3.1]nonane (9-Me-9-BBN).²⁴ Upon coordination of N₂H₄ to 9-Me-9-BBN, the proximal N-H protons

are acidified by 20 pK_a units (Fig 4B). In C-3, the N-H protons are further acidified by ca. 10 pK_a units. Notably, the Lewis acidic Zn in C-3 acidifies the N-H protons to a greater extent (pK_a = 24.9 vs. 26.9; Fig. 4B, right) than the trialkylborane, supporting the measured acceptor numbers.²⁵ Overall, these data indicate that the addition of both Zn and boron Lewis acids serve additive roles to increase the acidity of coordinated N₂H₄.

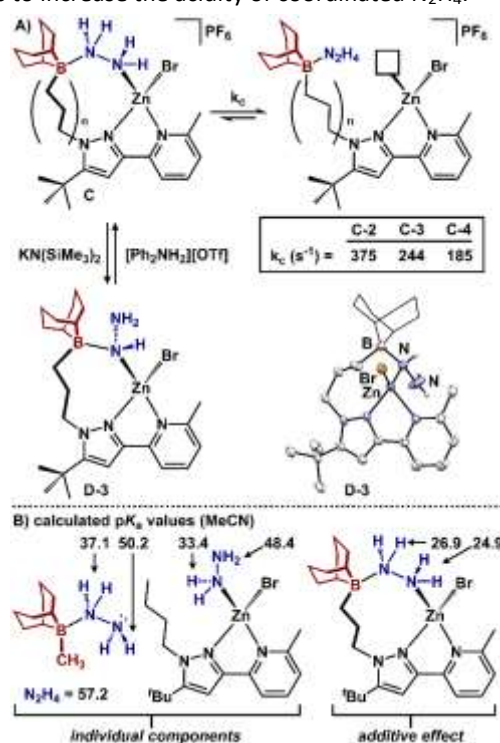


Fig. 4 A) Top: Dynamic solution behaviour of complexes C. Left: reversible deprotonation of C-3 to form D-3 and molecular structure of D-3 (50% probability ellipsoids, only H-atoms attached to heteroatoms displayed). B) Calculated pK_a values.

We assessed the viability of deprotonating the cooperatively captured N₂H₄. Treating a THF solution of C-3 with KN(SiMe₃)₂ at low temperature resulted in formation of HN(SiMe₃)₂ and a C₁ symmetric complex by ¹H NMR spectroscopy—consistent with formation of a [N₂H₃]¹⁻ moiety

and production of (^{3-BBN}NN^{tBu})ZnBr(N₂H₃) (**D-3**).²⁶ In contrast, when similar reactions were attempted for the other tether lengths to form **D-2** and **D-4**, we observed either demetalation or an intractable mixture (see SI), illustrating a unique stabilizing effect for the 3-carbon variant.

Due to the multiple bonding modes possible with [N₂H₃]¹⁻,²⁷ the solid-state structure was determined by SC-XRD. **D-3** represents the first structurally characterized example of a Zn hydrazido¹⁻ complex. Both boron and Zn are attached to the same nitrogen of the hydrazido ligand (Fig. 4, bottom). Deprotonation results in a decrease in both the Zn-N (1.973(2); Δ = 0.074 Å) and B-N (1.630(4); Δ = 0.027 Å) bond lengths, compared to **C-3**. In **D-3**, the terminal -NH₂ does not interact with Lewis acidic residues and the N-N distance is identical to **C-3**. The tandem Lewis acid/metal stabilization of [N₂H₃]¹⁻ in **D-3**, is reminiscent of the vanadium Lewis acid/base triad that employed a weakly acidic, but rigid, tetramethyl-1,3,2-dioxaborolane Lewis acid (B-N₂H₃ = 1.623(4) Å).²⁸

The structure of **D-3** is unique to the series because the 3-carbon tether can accommodate both μ-1,1 and μ-1,2 ligands (N₂H₃ and N₂H₄). The ability to stabilize both types of substrates enables facile rearrangement upon deprotonation of **C-3** to form **D-3**. Importantly, this process is reversible; treating **D-3** with [Ph₂NH][OTf] quantitatively regenerates **C-3** (Fig. 4, left). The mobility of the Lewis acid is highlighted for complexes **B-3**, **C-3**, and **D-3**. While operating independently, the boron atom is located 5.41 Å away from Zn (**B-3**). Upon forming a cooperative interaction with Zn in **C-3** to capture a diatom, N₂H₄, the Zn-B distance decreases to 3.95 Å (Δ = 1.46 Å). Finally, following deprotonation, cooperative stabilization of the same N-atom in N₂H₃ decreases the Zn-B distance to 3.06 Å. Overall, the Lewis acid exhibits mobility of 2.35 Å, mirroring the distance traversed by amino acids in metalloenzymes during turnover.^{1a, 2}

We have described a system where it is possible to probe distant-dependent substrate-Lewis acid relationships. The trialkylborane in this system was tethered by -(CH₂)_n- units at defined distances, from a substrate. Of note, the three-carbon tether affords the most versatility in terms of substrate accommodation. Our results suggest that while a certain tether length may provide an ideal fit for a given substrate, the versatility of the three-carbon tether may be the most useful for stabilizing a variety of high-energy reduction products of a single substrate (e.g. N_xH_y from N₂). Further work from our lab is investigating both of these aspects.

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Conflicts of interest

There are no conflicts to declare.

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