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Cyclophanes as platforms for reactive multimetallic complexes

Ricardo B. Ferreira, Leslie J. Murray*

Center for Catalysis and Florida Center for Heterocyclic Chemistry, Department of Chemistry, University of Florida, Gainesville, FL 32611, USA.

CONSPECTUS.

Multimetallic cofactors supported by weak-field donors frequently function as reaction centers in metalloproteins, and many of these cofactors catalyze small molecule activation (*e.g.*, N₂, O₂, CO₂) with prominent roles in geochemical element cycles or detoxification. Notable examples include the iron-molybdenum cofactor of the molybdenum-dependent nitrogenases, which catalyze N₂ fixation, and the NiFe₄S₄ cluster and the Mo(O)SCu site in various carbon monoxide dehydrogenases. The prevailing proposed reaction mechanisms for these multimetallic cofactors relies on a cooperative pathway, in which the oxidation state changes are distributed over the aggregate coupled with orbital overlap between the substrate and more than one metal ion within the cluster. Such cooperativity has also been proposed for chemical transformations at the surfaces of heterogeneous catalysts. However, the design details that afford cooperative effects and allow such reactivity to be harnessed effectively in homogeneous synthetic systems remain unclear. Relatedly, hydride donors ligated to these metal cluster cofactors are suggested as precursors to the state that reacts with substrates; here too, however, the reactivity of hydride-decorated clusters supported by weak-field ligands is underexplored.

Inspired by the reactivity potential of multimetallic assemblies evidenced in biological systems, approaches to design, synthesize, and evaluate reactivity of polynuclear metal compounds have been actively explored. In a similar vein to the templating function afforded by enzyme active sites, a carefully engineered organic ligand can be employed to control metal nuclearity of the complex and the local coordination environment of each metal center. This Account presents our efforts within this field, beginning with ligand design considerations followed by a survey of observed small molecule activation by trimetallic cyclophanates. We highlight the distinct reactivity outcomes accessed by multimetallic compounds as compared to aggregates that assemble in reaction mixtures from monometallic precursors. Contributing to the opportunity for programmed cooperativity in these designed multimetallic compounds, the cyclophane also dictates the orientation of substrate binding and metal-substrate interactions, which has a prominent influence on reactivity. For example, the dinitrogen-tricopper(I) cyclophanate reacts with dioxygen with markedly different results as compared to monocopper compounds. As an unexpected outcome, one series of tricopper compounds were discovered to be competent catalysts for carbon dioxide reduction to oxalate - a formally one-electron process - hinting at an inherently broader reaction scope for weak-field clusters at lowering the barrier for one-electron pathways as

*Corresponding Author murray@chem.ufl.edu.

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well as multielectron redox transformations. Further reflecting the role of the ligand in tuning reactivity, the trimetallic trihydride cluster compounds, $[M_3(\mu-H)_3]^{3+}$ ($M = Fe^{II}, Co^{II}, Zn^{II}$), demonstrate substrate specificity for CO_2 over various other unsaturated molecules and surprising stability towards water. This series reflects the role of the local environment of a shallow ligand pocket to control substrate access. Summed together, the systems described here evidence the anticipated cooperative reactivity accessed in designed multimetallic species vs. self-assembled monometallic systems (*e.g.*, O_2 activation and O-atom transfer) as well as control of substrate access by seemingly subtle structural effects. Indeed, future efforts aim to interrogate the limits of cooperativity in these systems as well as the role of ligand dynamics and sterics on reactivity.

Graphical Abstract

INTRODUCTION

Small molecules (*e.g.*, O_2 , N_2 , and CO_2) are central to biogeochemical cycles, and are abundant potential chemical feedstocks as heteroatom sources in the synthesis of fine chemicals or as carbon-neutral fuels. However, most of these small molecules are challenging to activate and the thermodynamically-favored chemical transformations of these substrates require multi-electron multi-proton redox processes to generate X-H bonds, where X = C, N, and O.¹ By comparison, single-electron transfer events are significantly more energy intensive, as evidenced by the aqueous reduction potentials for the CO_2/CO_2^- couple ($E_{1/2} = -1.90$ V vs. NHE) as compared to that for the $CO_2/HCOOH$ and CO_2/CH_4 couples ($E_{1/2} = -0.61$ and -0.24 V, respectively).² This Account highlights our efforts to develop synthetic complexes that facilitate such multi-electron redox events coupled to bond formation events.

A recurrent theme in metalloenzymes that activate these substrates is the use of polynuclear clusters supported typically by weak-field donors as reaction centers.³ For example, dinitrogen fixation is catalyzed by nitrogenases for which N_2 binding and reduction occurs at an iron-rich octanuclear metal cluster housed within the active site.^{4,5} Similarly, multinuclear copper(I) assemblies activate dioxygen for O_2 transport (*e.g.*, hemocyanin), O-atom incorporation into organic substrates (*e.g.*, tyrosinase), or reduction of dioxygen to water (*e.g.*, multicopper oxidases). Biological precedent highlights the design criteria for accessing synthetic systems with analogous reactivity; namely, complexes with multiple metal cations in close proximity supported by weak-field donors. The reactivity of these polynuclear metal active sites is proposed to rely on metal-ion redox cooperativity, *i.e.*, the

distribution of the cost to effect the necessary oxidation state changes across multiple metal centers, together with the expanded frontier orbital interactions between substrates and the multiple metal ions.^{6–10} Indeed, such cooperativity is readily apparent in synthetic dimetallic catalysts that effect oxidative addition or reductive elimination in which both metal ions undergo a change in their formal oxidation number.^{11–13} As highlighted recently, multiple metal sites in a catalyst can improve conversion values (*e.g.*, number of turnovers) and product selectivity.^{14,15} Analogous trends are also observed for higher nuclearity compounds, supporting a multinuclear hypothesis for multi-electron redox processes.^{16–19}

DESIGNED MULTIMETALLIC COMPOUNDS

The two strategies for synthesizing multimetallic compounds rely on (*i*) self-assembly of discrete monometallic precursors or (*ii*) a carefully constructed organic ligand to template multiple metal binding sites. The former provides unique advantages with respect to ease of synthesis and access to diverse structures, but lacks the control frequently required to test hypotheses. Our focus is on the latter approach wherein we aim to delineate the criteria that govern cooperative reactivity by evaluating reactivity across a pseudo-isostructural series of compounds. The main challenges with a ligand-based approach, however, are the design and synthesis of ligand scaffolds for which (*i*) electronic and steric effects can be readily tuned, (*ii*) nuclearity and ligand field match predictions, (*iii*) substrates can access one or more metal centers, and (*iv*) sufficient steric protection limits cluster aggregation. This list of desirable properties presents unique challenges in molecular design. For example, one of the first examples of a designed ligand for metal clusters is the trithiolate ligand from Holm and coworkers, which supports subsite-differentiated [4Fe-4S] clusters.^{20,21} Expectedly, this ligand provided a modular and rational route to the related heterometallic [MFe₃S₄] cubanes as well as the [4Fe-4Se] analogs,²² but this and related ligands were challenging to synthesize and few derivatives have been reported.

From a biomimetic perspective, substrates can bridge weakly- or non-interacting metal centers, leading to cooperative substrate bond scission and affording intermediates or products in which the metal ions are strongly-coupled. For example, diiron and dicopper active sites frequently bind and activate O₂ between both metals;^{23–25} here, one can simplistically envision one protein function as precluding metal-metal bond formation or unreactive single-atom (*e.g.*, oxide, hydroxide) bridged centers. Consistently, examples of monometallic systems that take advantage of this substrate-gated cooperativity abound with numerous examples of aggregates of monometallic complexes bridged by ligands derived from O₂, N₂, and CO₂ and other small molecules.^{26–28} Unfortunately, however, this type of cooperativity in synthetic systems can result in thermodynamically-favored products that lack the reactivity of the related enzyme systems.^{29–35} Such an approach has distinct benefits as compared to single-atom or metal-metal bonded clusters: the multimetallic complex can be treated as an assembly of non-interacting monometallic species. A caveat to this approach is that the ligand architecture must limit flexibility to enforce the desired reactivity. For example, Karlin and coworkers reported the tricopper(I) complex of a ligand with three bis(ethylene-2-pyridyl)aminomethyl arms with the intention of modeling the active site of multicopper oxidases (MCOs). However, inter- and intramolecular O₂ activation at pairs of copper centers was observed rather than [Cu₃O₂]³⁺ transients.^{36,37}

Notable relevant examples of designed multimetallic compounds have been reported recently. Betley and coworkers have explored a series of trimetallic complexes for Mn, Fe, and Co in which ligand parameters are tuned to modulate metal-metal interactions. One result is their reactivity studies on the N-N and N=N scission by a triiron complex, which provide support for the polynuclear hypothesis in nitrogenase.^{18,19,38–40} The three-fold symmetric ligand pioneered by Agapie and coworkers templates sub-site differentiated metal-oxide and metal-halide clusters analogous to Holm's MFe_3S_4 clusters.^{41,42} Here, controlled access to heterometallic cubane clusters was instrumental in testing the hypothesis that redox innocent cations primarily serve to tune the reduction potentials of mimics of the water oxidizing cluster in Photosystem II.

CYCLOPHANE-BASED LIGAND ($\text{H}_3\text{L}^{\text{Et/Me}}$)

We sought access to multimetallic complexes that could readily straddle substrate-gated cooperativity and that of single-atom bridged clusters (*e.g.*, metal chalcogenide clusters). Inspired by dimetallic cryptates,^{43–45} we leveraged molecular receptor design concepts to develop trinucleating macrobicyclic ligands, which enforce predictable coordination environments and metal-metal separations. From work by Anslyn and others,^{46,47} 1,3,5-triethylbenzene derivatives were attractive building blocks as the sterics of this platform favor ring closure, and as the anticipated metal-metal spacing can support either bridging single-atom donors (*e.g.*, $\text{M}_3(\mu_3\text{-X})$ or $\text{M}_3(\mu_3\text{-X})(\mu_3\text{-Y})$) or diatomic species. Moreover, the precursors for the 1,3,5-triethylbenzene platforms are amenable to diverse coupling strategies, allowing access to a library of ligands spanning a breadth of electronic and steric effects (Scheme 1).

One important consideration is an appropriate reference for reactivity of the isolated metal centers to demonstrate the benefit of cooperativity by design. β -diketiminates (BDI) provide an excellent entry point in that regard as the reactivity of BDI complexes comprising early to late and 1st to 3rd row transition metals has been examined.⁴⁸ Moreover, substrate activation by assynthesized or chemically-reduced species is reported for BDI-metal complexes, implying a similar or greater breadth of reactivity for the multimetallic congeners. For example, β -diketiminatocopper(I) complexes cleave O_2 and reduction of iron(II) and cobalt(II) complexes leads to N_2 activation.^{49–51} The weak-field *cis-N,N*-chelate ligand also affords metal σ - and π -type frontier orbitals oriented towards the internal cavity of the cyclophane, priming the system for substrate-gated cooperativity (Figure 1).⁵²

The target ligand was readily synthesized by condensation of 1,3,5-tri(aminomethyl)-2,4,6-triethylbenzene with the monoketal-protected acetylacetone (Figure 2), and the solid state structure of the ligand is consistent with our expectation.⁵³ From structural data on BDI complexes, one can predict a metal-metal separation of 3–4.5 Å, which is a distance range ideally suited to limit strong direct metal-metal interactions, yet sufficiently close to be bridged by mono-, di-, and tri-atomic ligands.⁵³ Gratifyingly, this predicted range of distances correlates with those observed in the synthesized complexes hitherto reported, spanning late first-row transition and main-group metals.^{53–59} This cyclophane is more flexible than might be initially assumed; small variations are observed as the ligand framework can adopt C_{2v} or D_{3h} symmetry depending on metal ion and bridging ligand type

and, more impressively, the triAl complex exhibits a single *trans*- β -diketimine arm in its solid state structure.

Small molecule activation using trimetallic complexes

These trimetallic cyclophanates were viewed as excellent entry points to probe metal-ion redox cooperativity in single-atom bridged clusters or by a substrate-gated process. For the latter, we require complexes in which ancillary donors are absent because we reasoned that these donors likely hinder substrate internalization or their dissociation can complicate reaction kinetics. To that end, the section below details our efforts to generate and evaluate the reactivity of stable or transient halide-free trimetallic complexes (*e.g.*, $M^I_3L^{Et/Me}$) followed by studies on μ_3 -X trimetallic compounds (X = S, N).

As a foray into substrate-gated cooperativity, we sought to mimic the reactivity of the tricopper active sites in MCOs. Reaction of the deprotonated ligand with a copper(I) source afforded the tricopper(I) cyclophanate in which the identity of the guest within the central cavity is dependent on the counteranion. Use of CuCl results in the μ_3 -chlorotricopper(I) compound, $[Cu_3ClL^{Et/Me}]^-$, whereas $[Cu(OTf)]_2(C_7H_8)$ under a dinitrogen atmosphere affords the (μ - η^1 : η^2 : η^1 - dinitrogen)tricopper(I) complex, $Cu_3(N_2)L^{Et/Me}$ – the first example of a molecular copper(I)-dinitrogen species (Figure 3).^{54,55} Vibrational spectra recorded on $Cu_3(N_2)L^{Et/Me}$ suggest an activated N_2 molecule ($\nu_{N-N} = 1952\text{ cm}^{-1}$ vs. 2331 cm^{-1} for free N_2), which is counter to the expectations that copper(I) is a poor π -bonding metal.⁵⁵ This apparent activation is contrasted to crystallographic N-N distances (1.0854 – $1.0956\text{ \AA}$ vs. $1.10\text{ \AA}$ for free N_2) as well as DFT calculations, which suggest a host-guest interaction.⁶⁰ Intriguingly, the differences between the electronic absorption spectra of $[Cu_3ClL^{Et/Me}]^-$ and $Cu_3(N_2)L^{Et/Me}$ point to a copper-dinitrogen charge transfer band in the visible spectrum, implying possible photochemical activation of substrates. Consistent with weak Cu- N_2 interactions, the bound N_2 can be readily exchanged or displaced by substrates. For example, reaction of $Cu_3(N_2)L^{Et/Me}$ with N_2O or other O-atom sources (*e.g.*, PhIO, Me_3NO) affords the μ_3 -oxidotricopper complex, $Cu_3OL^{Et/Me}$ (Figure 3).⁶¹ Similarly, reaction with S_8 or Se metal yields the structurally-related $Cu_3OL^{Et/Me}$ (E = μ_3 -S, μ_3 -Se) compounds (Figure 3).^{54,62}

In contrast to reported Cu_xE_y complexes (x = 3, y = 2), the $Cu_3EL^{Et/Me}$ (E = O, S, Se) series is atypical as E-E bonding interactions are not present and the bond metrics within the cyclophanate series are comparable.⁶³ Consequently, we had a unique opportunity to probe copper-chalcogen bonding and add to ongoing discussion of copper-chalcogen covalency. From computational methods benchmarked to chalcogen K-edge and Cu K- and $L_{2,3}$ -edge X-ray absorption spectra and UV/visible/nIR spectra, we surmise that the $[Cu_3E]^{3+}$ cores (E = O, S, Se) are highly covalent and that formal oxidation state assignments (*i.e.*, E^{2-} and $Cu^ICu^{II}_2$) are misleading. Such covalency is invoked typically for formally Cu^{III} species whereas our data are for lower formal copper oxidation states (*i.e.*, $Cu^ICu^{II}_2$), reinforcing that late transition metals engage in markedly more covalent metal-ligand interactions rather than the Lewis acid-base model of classical ligand field theory.

Our bonding analysis indicated that the LUMO of $\text{Cu}_3\text{SL}^{\text{Et/Me}}$ and $\text{Cu}_3\text{SeL}^{\text{Et/Me}}$ corresponds to a pseudo- a_2'' Cu-S/Se π^* orbital in idealized D_{3h} symmetry. Consistently, X-band EPR spectra of $[\text{Cu}_3\text{SL}^{\text{Et/Me}}]^-$, generated by reduction of $\text{Cu}_3\text{SL}^{\text{Et/Me}}$ with $\text{Cp}2^*\text{Co}$, exhibits a 10-line absorption, corresponding to a SOMO delocalized over three Cu nuclei ($I = 3/2$).⁵⁴ Whereas the neutral complexes are air-stable, the $[\text{Cu}_3\text{SL}^{\text{Et/Me}}]^-$ anions (E = S, Se) react readily with O_2 to regenerate the parent $\text{Cu}_3\text{SL}^{\text{Et/Me}}$. To our surprise, the reduced complexes are also competent catalysts for the homocoupling of CO_2 to oxalate, exhibiting a countercation and solvent dependence with more Lewis acidic cations and less coordinating solvents enhancing reaction rate. Although the mechanistic studies remain ongoing, this system adds to precedent for copper as predisposed for reductive CO_2 homocoupling rather than CO or formate synthesis. We speculate that CO_2 interacts with Cu centers on the edge of the cluster by a mechanism analogous to that proposed for nitrous oxide reductase as the μ_3 -chalcogenide is likely inaccessible.⁶²

Returning to mimicking MCO reactivity, $\text{Cu}_3(\text{N}_2)\text{L}^{\text{Et/Me}}$ reacts rapidly with O_2 to generate reactive transient(s) capable of C-H bond activation and O-atom transfer to toluene and ethylbenzene with formation of $\text{Cu}_3\text{SL}^{\text{Et/Me}}$. The O O vectors in reported di(μ -oxo)tricopper compounds supported by *cis*-*N,N*chelating ligands are perpendicular to the tricopper plane and coplanar with the N atoms of the supporting ligands. Thus, each metal center utilizes a frontier orbital of nominal Cu-N_{ligand} σ^* character with $3d_{xz}$ parentage to donate into the O_2 π^* orbital, leading to O_2 bond scission. These frontier orbitals ultimately afford the Cu-O σ -interactions between each O-atom and the three Cu centers. Contrastingly, reorienting the O O vector as enforced by $[\text{L}^{\text{Et/Me}}]^-$ to within the copper plane results in a bonding picture in which the same metal frontier orbital instead engages in the delocalized π -bonding interaction with one O-atom; that is, the bonding orbital analogous to the pseudo a_2' LUMO in the $\text{Cu}_3\text{EL}^{\text{Et/Me}}$ compounds. From broken symmetry DFT calculations, the out-of-plane p_π orbital of the second O atom is the major contributor to the β LUMO, implying oxyl-like character although the bonding in the $[\text{Cu}_3\text{O}_2]^{3+}$ cluster is highly covalent. This orbital is the H-atom acceptor orbital and subsequent radical rebound liberates the hydroxylated hydrocarbon. Indeed, the reactivity and electronic structure differences compared to self-assembled analogs highlights the subtle geometric and consequent electronic constraints afforded by enzyme active sites, and provides context for H-atom abstraction vs. O-atom transfer reactivity reported previously for oxygenated copper BDI transients. Surprisingly, the cluster product of O_2 activation and O-atom transfer, $\text{Cu}_3(\mu_3\text{-O})\text{L}^{\text{Et/Me}}$, is itself reactive with dioxygen to afford a transient purple intermediate, which ultimately decomposes under an O_2 atmosphere. Dioxygen activation by the product cluster from a monooxygenase-like reaction in the absence of an exogenous reductant is unprecedented, and evidences the power of modulating metal-dioxygen orbital overlap in tuning reactivity.

Inspired by precedent for N_2 activation by BDI complexes, we sought to examine the influence of the arrangement of metal ion in our complexes on N_2 bond scission.^{53,57,64} Tri-Mn, -Fe, and -Co cyclophane complexes were readily synthesized with halide ions completing the coordination sphere (Figure 4). Employing the iron congener as our entry point, reduction of $\text{Fe}_3\text{Br}_3\text{L}^{\text{Et/Me}}$ with KC_8 affords a tri(μ -amido/imido)triiron product, $\text{Fe}_3(\text{NH}_x)_3\text{L}^{\text{Et/Me}}$, with metal oxidation states and the protonation state of N ligands inferred

from simulations of variable-temperature and variable-field (VT/VH) Mößbauer spectra (Figure 4). Labeling studies confirm that the amide or imide ligands are derived from atmospheric dinitrogen.⁶⁴ The reactivity observed is a departure from that of the monometallic analogs for which discrete N₂ adducts or isolable di(μ -nitride) compounds are observed. Contrastingly, the cyclophanate system funnels to the protonated N donor ligands and is competent for multiple rounds of N₂ activation with a net 1.5 N₂ activated per triiron complex. The product stoichiometry also implies at least one intercomplex N₂ activation step. Attempts to stall this reaction at the nitride-bridged compounds have been unsuccessful, consistent with the initial N₂ bond activation being rate controlling. The relationship between structure and the enhanced reactivity towards N₂ remain unclear; possible reasons are instability of a K⁺ adduct of a transient anionic di(μ -nitride) or an intercomplex-only dinitrogen activation wherein nitride compounds are more readily reduced than the precursors.^{58,64}

The structure of the tricopper-dinitrogen complex provides a snapshot of that for a possible triiron(I)-dinitrogen transient, suggesting that an intracluster pathway relying on substrate-gated cooperativity may be integral to N₂ activation. Insofar as intermediates upon reduction of Fe₃Br₃L^{Et/Me} remain elusive, we instead sought to benchmark the reactivity of possible intercluster intermediates, *viz.* nitridotriiron bromide cyclophanates.⁶⁵ Dinitrogen binding is not observed to members of the series, Fe₃(μ_3 -N)Br_xL^{Et/Me} (x = 0, 1, or 2), but chemical reduction of these compounds results in dinitrogen activation (*vide infra*), supporting an intercluster pathway as possible.

Part of our impetus for developing macrobicyclic ligands was to correlate donor atom identity with reactivity. To that end, the triiron(II) tribromide complex provides facile access to sulfide-bridged triiron compounds, Fe₃S₃L^{Et/Me} and Fe₃(μ_3 -S)Br₂L^{Et/Me}. Reduction of Fe₃(μ_3 -S)Br₂L^{Et/Me} with excess Na/Hg affords the related Fe₃(μ_3 -S)Br₂L^{Et/Me}; all three sulfide-bridged compounds are new members of the iron-sulfur cluster family, the trisulfide being the first planar [3Fe-3S] cluster. As a convergence of research foci on the reactivity of sulfide-, nitride-, and hydride-bridged triiron complexes, we examined catalytic silylation of dinitrogen by a series of triiron cyclophanates in which bridging ligands and metal oxidation states vary (Table 1).⁶⁷ All tested complexes were effective at catalyzing N(Me₃Si)₃ production from N₂ using KC₈ and Me₃SiCl as the electron and silyl cation source, respectively; the parent Fe₃Br₃L^{Et/Me} and Fe₃Br₃L^{Et/Me} (entries 1 and 8) are two of the most effective known catalysts with respect to electron efficiency. However, a weak correlation is observed: π -donor ligands are generally superior to π -acid and strong σ -donors, consistent with the expected trend in metal-dinitrogen π -backbonding as a function of ancillary ligands. For example, Fe^{III}₃(μ -S)₃L^{Et/Me} and Fe^{II}₃Br₃L^{Et/Me} are comparable catalysts whereas Fe^{II}₃(μ -H)₃L^{Et/Me} and (Fe^ICO)₂Fe^{II}(μ_3 -H)L^{Et/Me} are the least effective (entries 4 and 5). Notably, Fe₃(μ_3 -N)L^{Et/Me} accumulates to varying extents in product mixtures, implying that bridging ligands are labile and susceptible to dissociation under reducing conditions and that N-atoms derived from N₂ can be effectively incorporated into the cluster. This observation bears strong resemblance to S²⁻ dissociation reported for FeMoco and vanadium molybdenum cofactor (or VMoco) under catalytic turnover or in the presence of CO.⁶⁶ The mechanism of ligand substitution upon reduction remains to be

determined, but suggests that exogenous sulfide may serve to stabilize Fe- and V- Moco in the absence of substrate.

Related to our interest in accessing bond activation by low-valent metal centers, we targeted hydride-bridged multimetallic compounds because hydrides can serve as masks of low-valent centers. Facile access to an $M_3(\mu\text{-H})_3\text{L}^{\text{Et/Me}}$ series ($M = \text{Fe, Co, Zn}$) is possible by reaction of an alkali trialkylborohydride with the corresponding $M_3X_3\text{L}^{\text{Et/Me}}$ complex ($X = \text{Cl}^-, \text{Br}^-$). In contrast to work from monometallic analogs,⁶⁸ thermal or photochemical reductive elimination is not observed for the triFe and triCo tri(hydride) compounds. Given that the order of N_2 binding and H_2 reductive elimination from the E_4 state of FeMoco is unclear, we surveyed the reaction of the $[\text{Fe}_3\text{H}_3]^{3+}$ compound with various substrates and discovered a very substrate specific insertion reactivity towards carbon dioxide. This specificity persists across the series with the triZn congener even being unreactive towards water over 24 h (Figure 5).⁵⁶ Given the invariance of reactivity as a function of metal ion type, the ligand is the likely source of the specificity and substrate selection and dictated by the electrostatics of the pocket surrounding the hydride donor. Changes to the cyclophane ligand to modulate these electrostatics will be key to identifying the factors responsible for this substrate selectivity. Here then, the ligand bears analogy to enzymes in which the substrate access channels enforce specific selection criteria on substrates. Our results also complement prior work in which the internal binding sites of macrobicyclic di- and monometallic compounds enforce size selection criteria on ligand guests. If correct, the ease with which a seemingly surface exposed reactive site exerts control over reactivity is a promising area of exploration in catalyst design.

Given the CO_2 reactivity, we then examined small molecule substrates for which insertion chemistry is challenging. The tri(μ -hydride) complexes were unreactive towards dinitrogen even with heating; however, CO reacts upon mixing with $\text{Fe}_3\text{H}_3\text{L}^{\text{Et/Me}}$ at ambient temperature to evolve H_2 and form the dicarbonyl hydride complex, $(\text{Fe}^{\text{I}}\text{CO})_2\text{Fe}^{\text{II}}(\mu_3\text{-H})\text{L}^{\text{Et/Me}}$. Results from crossover experiments are consistent with an intramolecular pathway for H_2 loss, which also agrees with the stoichiometry of the isolated product. We intimate that the $[\text{Fe}_3\text{H}_3]^{3+}$ cluster is fluxional, leading to available sites for CO coordination and contracting the H-H distance for reductive elimination. Conceptually, this hypothesis agrees with the trend observed in our catalytic silylation chemistry and the observed D_{3h} vs. C_{2v} symmetry of $\text{Fe}_3\text{Cl}_3\text{L}^{\text{Et/Me}}$ in solution vs. solid state, respectively. Each Fe center in $(\text{Fe}^{\text{I}}\text{CO})_2\text{Fe}^{\text{II}}(\mu_3\text{-H})\text{L}^{\text{Et/Me}}$ is high-spin based on VT/VH Mößbauer measurements; few examples of $S_{\text{Fe}} = 3/2$ Fe^{I} -CO fragments are known.⁶⁹ Indeed, the reactivity profile of $(\text{Fe}^{\text{I}}\text{CO})_2\text{Fe}^{\text{II}}(\mu_3\text{-H})\text{L}^{\text{Et/Me}}$ reflects this electronic structure with thermally-accessible H_2 oxidative addition and reformation of $\text{Fe}_3\text{H}_3\text{L}^{\text{Et/Me}}$ being possible.

Two plausible mechanisms for H_2 reductive elimination observed from $\text{Fe}_3\text{H}_3\text{L}^{\text{Et/Me}}$ in the presence of CO are: (i) CO binding to $[\text{Fe}_3\text{H}_3]^{3+}$ concomitant with ligand reorganization and contraction of the H-H distance, which favors reductive elimination or (ii) an equilibrium between $[\text{Fe}_3(\mu\text{-H})_3]^+$ and a Kubas type complex, $[\text{Fe}_3(\text{H})(\text{H}_2)]^{3+}$, with the latter being trapped by CO. Pathway (ii) would appear incongruent with the CO_2 insertion reactivity as we might anticipate other possible products (*e.g.*, C=O bond scission) from low-valent Fe centers; however, one can envision a kinetic condition in which competition between

insertion vs. H₂ reductive elimination leads to the observed outcome. Ambiguity remains as to the nature of the H-H bond forming event (*i.e.*, homolytic vs. heterolytic pathway). Undoubtedly, the breadth of accessible reaction manifolds for these hydrides (*i.e.*, hydride, H-atom, proton) provide precedent for the proposed diverse reactivities for comparable proposed metal hydride intermediates of metallocofactors.⁵⁶

CONCLUDING REMARKS

Recent work on polynuclear metal complexes actualizes the *ex vivo* reactivity promised from metal cluster cofactors in metalloproteins, opening new opportunities to interrogate the reaction mechanisms for small molecule activation at biological clusters. In particular, we have demonstrated that macrobicyclic ligands provide unique advantages over previously explored approaches (*e.g.*, substrate specificity). These trimetallic complexes can activate N₂, CO₂, and O₂, with triiron and tricopper compounds serving as catalysts for reduction of the former two substrates. The reactivity observed differs from that of the monometallic analogs and thereby evidences the potential for designed redox cooperativity in small molecule activation. For example, monoiron complexes are not similarly effective catalysts for N₂ fixation and the monocopper compounds afford oxygenated intermediates that are not competent for C-H activation and O-atom transfer. Future directions aim to harness these design approaches to enable catalytic rather than stoichiometric transfer reactions employing N₂, CO₂, or O₂.

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Biographical Information

Ricardo B. Ferreira was born in Brazil, received his B.S. and M.Sc. degrees in Chemistry from University of Campinas. He joined the laboratory of Dr. Murray in 2013 as a graduate student and got his Ph.D. in Chemistry from University of Florida in 2018.

Leslie J. Murray was born in Trinidad & Tobago, received B.A. degrees in Chemistry and Biology from Swarthmore College and a Ph.D. in Inorganic Chemistry from M.I.T under Stephen Lippard. After a subsequent postdoctoral appointment in Jeffrey Long's group (UC, Berkeley), he began his independent career at the University of Florida, where he is currently an Associate Professor.

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Figure 1.
Qualitative frontier molecular orbitals for a C_{2v} ML_2 complex considering a BDI chelate.

Figure 2.
Synthesis of cyclophane-based trinucleating ligand $H_3L^{Et/Me}$.⁵³

Figure 3. Synthesis of tricopper complexes using the macrobicyclic ligand $H_3L^{Et/Me}$ ^{54,55}

Figure 4. Synthesis of triiron complexes using the macrobicyclic ligand $\text{H}_3\text{L}^{\text{Et/Me}}$.

Figure 5.
Reactivity of trizinc complexes containing the $H_3L^{Et/Me}$ macrobicyclic ligand⁵⁶

Scheme 1.

Table 1.

Catalytic dinitrogen silylation by triiron complexes.

Entry ^a	Triiron Complex	N(SiMe ₃) ₃ /Fe ₃ (yield in %)
1	Fe ₃ Br ₃ L ^{Et/Me}	57 ± 7 (34) 83 ± 7 (50) ^b
2	Fe ₃ Cl ₃ L ^{Et/Me}	45 ± 7 (27)
3	Fe ₃ F ₃ L ^{Et/Me}	64 ± 6 (38)
4	Fe ₃ H ₃ L ^{Et/Me}	34 ± 5 (20)
5	(FeCO) ₂ Fe(μ ₃ -H)L ^{Et/Me}	35 ± 3 (21)
6	Fe ₃ Br ₂ (μ ₃ -N)L ^{Et/Me}	51 ± 4 (31)
7	Fe ₃ (μ ₃ -N)L ^{Et/Me}	43 ± 3 (26)
8	Fe ₃ S ₃ L ^{Et/Me}	58 ± 1 (35)

^aReaction conditions unless stated otherwise: 500 equiv. of KC₈ and 500 equiv. of TMSCl after 24 h at room temperature in triplicate. The solvent was Et₂O:PhMe 9:1. N(SiMe₃)₃ was quantified by acidolysis followed by ¹H-NMR;

^bresult after 96 h at -34 °C. Adapted from ref. 67.