Cyclophanes as Platforms for Reactive Multimetallic Complexes

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CONSENSUS: 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 molybdenu

INTRODUCTION

Small molecules (e.g., O2, N2, and CO2) are central to biogeochemical cycles, and are abundant potential chemical feedstocks as heteroatoms 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 multielectron multiproton 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 CO2/CO2−couple (E1/2 = −1.90 V vs NHE) as compared to that for the CO2/HCOOH and CO2/CH4 couples (E1/2 = −0.61 and −0.24 V, respectively).2

This Account highlights our efforts to develop synthetic complexes...
that facilitate such multielectron 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. For example, dinitrogen fixation is catalyzed by nitrogenases for which N₂ binding and reduction occurs at an iron-rich octanuclear metal cluster housed within the active site. Similarly, multinuclear copper(I) assemblies activate dioxygen for O₂ 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 multielectron redox cooperativity, i.e., the distribution of the cost of these polynuclear metal active sites is proposed to rely on 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. 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. As highlighted recently, multiple metal sites in a catalyst can improve conversion values (e.g., number of turnovers) and product selectivity. Analogous trends are also observed for higher nuclearity compounds, supporting a multinuclear hypothesis for multielectron redox processes.

**DESIGNED MULTIMETALLIC COMPOUNDS**

The two strategies for synthesizing multimetallic compounds rely on (i) self-assembly of discrete mononuclear 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 co-workers, which supports subsite-differentiated [4Fe-4S] clusters. Expectedly, this ligand provided a modular and rational route to the related heterometallic [MFe₅S₄] cubanes as well as the [4Fe-4Se] analogues, but this and related ligands were challenging to synthesize and few derivatives have been reported.

From a biomimetic perspective, substrates can bridge weakly interacting or noninteracting 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 here, one can simply 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. Unfortunately, however, this type of cooperativity in synthetic systems can result in thermodynamically favored products that lack the reactivity of the related enzyme systems. 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 noninteracting monometallic species. A caveat to this approach is that the ligand architecture must limit flexibility to enforce the desired reactivity. For example, Karlin and co-workers 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.

Notable relevant examples of designed multimetallic compounds have been reported recently. Betley and co-workers have explored a series of trinuclear 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. The 3-fold symmetric ligand pioneered by Agapie and co-workers templates subsite differentiated metal–oxide and metal–halide clusters analogous to Holm’s MFe₅S₄.
clusters. 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 (H$_3$L$_{Et/Me}$)

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, 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, 1,3,5-triethylbenzene derivatives were attractive building blocks as the steric of this platform favor ring closure, and as the anticipated metal–metal spacing can support either bridging single-atom donors (e.g., M$_3$(μ$_3$-X) or M$_3$(μ$_2$-X)(μ$_1$-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 first to third row transition metals has been examined. Moreover, substrate activation by as-synthesized or chemically reduced species is reported for BDI activation. For example, β-diketiminatocopper(I) complexes cleave O$_2$ and reduction of iron(II) and cobalt(II) complexes leads to N$_2$ activation.

The target ligand was readily synthesized by condensation of 1,3,5-tri(aminomethyl)-2,4,6-triethylbenzene with the mono-ketal-protected acetylacetone (Figure 2), and the solid state structure of the ligand is consistent with our expectation. 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 triatomic ligands. 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. This cyclophane is more flexible than might be initially assumed; small variations are observed as the ligand framework can adopt C$_{2v}$a, D$_{3}$ 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$_3$L$_{Et/Me}$) 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 Cu$_3$(N$_2$)$_3$ complex, whereas Cu(OTf)$_2$(C$_7$H$_8$)$_2$ under a dinitrogen atmosphere affords the Cu$_3$(N$_2$)$_3$ complex, the first example of a molecular copper(I)–dinitrogen species (Figure 3).

Vibrational spectra recorded on Cu$_3$(N$_2$)$_3$L$_{Et/Me}$ suggest an activated N$_2$ molecule ($\nu_{\text{N}_2} = 1952$ vs 2331 cm$^{-1}$ for free N$_2$), which is counter to the expectations that copper(I) is a poor π-bonding metal. This apparent activation is contrasted to crystallographic N–N distances ($1.0854$–$1.0956$ vs $1.10$ Å for free N$_2$) as well as DFT calculations, which suggest a host–
guest interaction.\textsuperscript{60} Intriguingly, the differences between the electronic absorption spectra of \([	ext{Cu}_{3}E_{1}L_{4}^{E}/Me]^{−}\) and \([\text{Cu}_{3}(N)_{2}]L^{E}/Me\) point to a copper–dinitrogen charge transfer band in the visible spectrum, implying possible photochemical activation of substrates. Consistent with weak \(\text{Cu}–\text{N}_{2}\) interactions, the bound \(N_{2}\) can be readily exchanged or displaced by substrates. For example, reaction of \([\text{Cu}_{3}(N)_{2}]L^{E}/Me\) with \(N_{2}O\) or other \(O\) atom sources (e.g., PhIO, Me_{3}NO) affords the \(μ_{3}–\text{oxidotricopper complex, Cu}_{3}O_{3}L^{E}/Me\) (Figure 3).\textsuperscript{61} Similarly, reaction with \(S_{8}\) or \(Se\) metal yields the structurally related \(\text{Cu}_{3}E_{1}L^{E}/Me\) \((E = \text{S}, \text{Se})\) compounds (Figure 3).\textsuperscript{54,62}

In contrast to reported \(\text{Cu}_{3}E_{1}\) complexes \((x \leq 3, y \leq 2)\), the \(\text{Cu}_{3}E_{1}L^{E}/Me\) \((E = \text{O, S, Se})\) series is atypical as \(E–E\) bonding interactions are not present and the bond metrics within the cyclophanate series are comparable.\textsuperscript{63} Consequently, we have 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 \(\text{Cu}\) \(K\)- and \(L_{2,3}\)-edge X-ray absorption spectra and UV/visible/nIR spectra, we surmise that the \(\text{[Cu}_{3}E_{1}]^{3+}\) cores \((E = \text{O, S, Se})\) are highly covalent and that formal oxidation state assignments (i.e., \(E_{\text{π}}^{2−}\) and \(\text{Cu}_{3}^{\text{II}_{2}}\)) are misleading. Such covalency is invoked typically for formally \(\text{Cu}^{\text{III}}\) species whereas our data are for lower formal copper oxidation states (i.e., \(\text{Cu}_{3}^{\text{II}_{2}}\)), 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 \(\text{LUMO of Cu}_{3}E_{1}L^{E}/Me\) and \(\text{Cu}_{3}E_{1}L^{E}/Me\) corresponds to a pseudo-\(\text{π}^{*}\) \(\text{Cu}–\text{S/Se}\) \(\text{π}^{*}\) orbital in idealized \(D_{3h}\) symmetry. Consistently, X-band EPR spectra of \(\text{[Cu}_{3}E_{1}L_{4}^{E}/Me]\)\textsuperscript{−}\), generated by reduction of \(\text{Cu}_{3}E_{1}L_{4}^{E}/Me\) with \(\text{Cp}_{2}^{*}\text{Co}\), exhibits a 10-line absorption, corresponding to a SOMO delocalized over three \(\text{Cu}\) nuclei \((I = 3/2)\).\textsuperscript{54} Whereas the neutral complexes are air-stable, the \(\text{[Cu}_{3}E_{1}L_{4}^{E}/Me]\) \((E = \text{S, Se})\) react readily with \(O_{2}\) to regenerate the parent \(\text{Cu}_{3}E_{1}L_{4}^{E}/Me\). 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 mechanism studies remain ongoing, this system adds to precedent for copper as predisposed for reductive \(\text{CO}_{2}\) homocoupling rather than \(\text{CO}\) or formate synthesis. We speculate that \(\text{CO}_{2}\) interacts with \(\text{Cu}\) centers on the edge of the cluster by a mechanism analogous to that proposed for nitrous oxide reduction as the \(μ_{3}\)-chalcogenide is likely inaccessible.\textsuperscript{62}

Returning to mimicking MCO reactivity, \(\text{Cu}_{3}(N)_{2}L^{E}/Me\) 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 \(\text{Cu}_{3}O_{3}L^{E}/Me\). The \(O\)-\(O\) vectors in reported di(\(μ\)-oxo)tricopper compounds supported by \(\text{cis-N}_{2}N\) 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 \(\text{Cu}–\text{N}_{ligand} σ^{*}\) 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 \(\text{Cu}–O\) \(σ\)-interactions between each \(O\) atom and the three \(\text{Cu}\) centers. In contrast, reorienting the \(O\)-\(O\) vector as enforced by \([L^{E}/Me]^{−}\) 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-\(\text{π}^{*}\) \(\text{LUMO in the Cu}_{3}E_{1}L^{E}/Me\) compounds. From broken symmetry DFT calculations, the out-of-plane \(p_{e}\) orbital of the second \(O\) atom is the major contributor to the \(β\) \(\text{LUMO, implying oxyl-like character although the bonding in the [Cu}_{3}O_{2}]^{3+}\) 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, \(\text{Cu}_{3}(\text{μ}_{1}–\text{O})L^{E}/Me\), 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 monoxygenase-like reaction in the absence of an exogenous reductant is unprecedented, and evidence the

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**Figure 3.** Synthesis of tricopper complexes using the macrobicyclic ligand \(H_{3}L^{E}/Me\)\textsuperscript{54,55}
power of modulating metal-dioxygen orbital overlap in tuning reactivity.

Inspired by precedent for N₂ activation by BDI complexes, we sought to examine the influence of the arrangement of metal ion in our complexes on N₂ bond scission. 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 Fe₃Br₃LEt/Me with KC₈ affords a tri(μ-amido/imido)triiron product, Fe₃(NH₃)₃LEt/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. The reactivity observed is a departure from that of the monometallic analogues for which discrete N₂ adducts or isolable di(μ-nitride) compounds are observed. Contrastingly, the cyclophane 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 toward 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.

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 Fe₃Br₃LEt/Me remain elusive, we instead sought to benchmark the reactivity of possible intercluster intermediates, namely, nitridotriiron bromide cyclophanates. Dinitrogen binding is not observed to members of the series, Fe₃(μ₁-N)Br₃LEt/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, Fe₃S₃LEt/Me and Fe₃(μ₁-S)Br₃LEt/Me. Reduction of Fe₃(μ₁-S)Br₃LEt/Me with excess Na/Hg affords the related Fe₃(S⁻)Br₃LEt/Me, all three sulfide-bridged compounds are new members of the iron—sulfur cluster family, with 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). 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 Fe₃Br₃LEt/Me and Fe₃S₃LEt/Me (entries 1 and 8) are two of the most effective known catalysts with respect to

![Figure 4. Synthesis of triiron complexes using the macrobicyclic ligand H₃LEt/Me.](image)

**Table 1. Catalytic Dinitrogen Silylation by Triiron Complexes**

<table>
<thead>
<tr>
<th>entry</th>
<th>triiron complex</th>
<th>N(SiMe₃)₃/Fe₃ (yield in %)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Fe₃Br₃LEt/Me</td>
<td>57 ± 7 (34)</td>
</tr>
<tr>
<td>2</td>
<td>Fe₃Cl₂LEt/Me</td>
<td>48 ± 2 (77)</td>
</tr>
<tr>
<td>3</td>
<td>Fe₃P₃LEt/Me</td>
<td>64 ± 6 (38)</td>
</tr>
<tr>
<td>4</td>
<td>Fe₃H₃LEt/Me</td>
<td>34 ± 5 (20)</td>
</tr>
<tr>
<td>5</td>
<td>(FeCO)₃Fe(μ₁-H)LLEt/Me</td>
<td>35 ± 3 (21)</td>
</tr>
<tr>
<td>6</td>
<td>Fe₃Br₃(μ₁-N)LLEt/Me</td>
<td>51 ± 4 (31)</td>
</tr>
<tr>
<td>7</td>
<td>Fe₃(μ₁-N)₃LLEt/Me</td>
<td>43 ± 3 (26)</td>
</tr>
<tr>
<td>8</td>
<td>Fe₃S₃LLEt/Me</td>
<td>58 ± 1 (35)</td>
</tr>
</tbody>
</table>

*Reaction conditions unless stated otherwise: 500 equiv of KC₈ and 500 equiv of TMSCI 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. Result after 96 h at −34 °C. Adapted from ref 67.*
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, FeIII\((μ-S)\)LEx/Met and FeIII\(μ\)-BrLEx/Met are comparable catalyst whereas FeII\((μ-H)\)LEx/Met and (FeCO)FeII(μ-H)LEx/Met are the least effective (entries 4 and 5). Notably, FeII(μ-N)LEx/Met 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 S2²⁻ dissociation reported for FeMoco and vanadium molybdenum cofactor (or V-Moco) 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 M₃(μ-H)LEx/Met series (M = Fe, Co, Zn) is possible by reaction of an alkali trialkylborohydride with the corresponding M₃X₃LEx/Met complex (X = Cl⁻, Br⁻). In contrast to work from monometallic analogs,⁶⁸ thermal or photochemical reductive elimination is not observed for the triFe and triCo tri(μ-hydride) compounds. Given that the order of N₂ binding and H₂ reductive elimination from the E₄ state of FeMoco is unclear, we surveyed the reaction of the [Fe₃H₃]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 D₃h vs C₃v symmetry of Fe₃Cl₃LEx/Met in solution vs solid state, respectively. Each Fe center in (FeCO)₂FeII(μ-H)LEx/Met is high-spin based on VT/VH Mößbauer measurements; few examples of SFe= 3/2 Fe⁵⁻–CO fragments are known.⁶⁹ Indeed, the reactivity profile of (FeCO)₂FeIII(μ-H)LEx/Met reflects this electronic structure with thermally accessible H₂ oxidative addition and reformation of Fe₃H₃LEx/Met being possible.

Two plausible mechanisms for H₂ reductive elimination observed from Fe₃H₃LEx/Met in the presence of CO are (i) CO binding to [Fe₅H₃]⁶⁻ concomitant with ligand reorganization and contraction of the H=H distance, which favors reductive elimination, or (ii) an equilibrium between [Fe₅(μ-H)]⁷⁻ and a Kubas type complex, [Fe₅(H)(H₂)]⁷⁻, with the latter being trapped by CO. Pathway (ii) would appear incongruent with the CO₃ insertion reactivity as we might anticipate other possible products (e.g., C≡O bond scission). Given invariance of reactivity as a function of metal ion type, the ligand is the likely source of the specificity and substrate selectivity 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 CO₂ reactivity, we then examined small molecule substrates for which insertion chemistry is challenging. The tri(μ-hydride) complexes were unreactive toward dinitrogen even with heating; however, CO reacts upon mixing with Fe₃H₃LEx/Met at ambient temperature to evolve H₂ and form the dicarbonyl hydride complex, (FeCO)₂Fe(μ-H)LEx/Met. Results from crossover experiments are consistent with an intramolecular pathway for H₂ loss, which also agrees with the stoichiometry of the isolated product. We intimate that the [Fe₃H₃]⁶⁻ 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 D₃h vs C₃v symmetry of Fe₃Cl₃LEx/Met in solution vs solid state, respectively. Each Fe center in (FeCO)₂FeII(μ-H)LEx/Met is high-spin based on VT/VH Mößbauer measurements; few examples of SFe= 3/2 Fe⁵⁻–CO fragments are known.⁶⁹ Indeed, the reactivity profile of (FeCO)₂FeIII(μ-H)LEx/Met reflects this electronic structure with thermally accessible H₂ oxidative addition and reformation of Fe₃H₃LEx/Met being possible.

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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 evidence 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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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

**Notes**

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The authors declare no competing financial interest.

**Biographies**

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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 currently is an Associate Professor.

**ACKNOWLEDGMENTS**


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