

# Molecular Bio-inspired Strategies for the Design of Electrocatalytic Systems

Victor Mougel\*

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**Abstract:** This perspective article delves into the realm of bio-inspired catalysis, highlighting the valuable insights gleaned from enzymatic systems for the design of advanced electrocatalysts. We focus here on three key aspects to mimic: the structure of enzymatic active sites, the essential functions to enable catalytic activity as well as key elementary steps of reaction mechanisms employed by enzymes to ensure maximum efficiency and selectivity. Our research group's contributions to these areas are highlighted, including the synthesis and catalytic activity of cobalt(III) pyridinethiolate complexes, the exploration of bimetallic sites mimicking biological carbon dioxide reductases and of all-ferrous  $\text{Fe}_4\text{S}_4$  clusters as mimics of FeP active sites, and the integration of concerted proton-electron transfer (CPET) mediators for the generation of metal hydride species. We emphasize the potential of these bio-inspired approaches in advancing electrocatalyst design and their relevance to molecular catalysis.

**Keywords:** Bio-inspired chemistry · Catalysis ·  $\text{CO}_2$  reduction · Coordination chemistry · Electrochemistry



**Victor Mougel** is currently serving as a tenure track assistant professor of Inorganic Chemistry in the Department of Chemistry and Applied Biosciences at ETH Zürich, a position he has held since December 2018. His academic journey began with a Bachelor's and Master's degree in Chemistry from the ENS of Lyon. He pursued his doctoral studies at the University of Grenoble, working under the guidance of Prof. Marinella Mazzanti.

After completing his PhD, he joined ETH Zürich as an ETH Fellow, in the group of Prof. Christophe Copéret. In 2016, he started his independent career as a CNRS associate researcher at Collège de France in Paris. Currently, his research interests revolve around the electrochemical activation of small molecules, drawing inspiration from enzymatic systems in a bio-inspired approach.

## Introduction

The endeavor to design effective and efficient electrocatalysts is a crucial component in the pursuit of identifying fossil-fuel free routes to key base chemicals. With challenges related to cost, stability, and activity, the field continually seeks innovative strategies to overcome these hurdles.

Nature presents itself as a master innovator in that context: enzymes, nature's own catalysts, perform a wide variety of complex chemical transformations under mild conditions with unique efficiencies and selectivities. Bio-inspired strategies, drawing inspiration from the structure and function of enzymatic systems, have shown in this context significant potential in improving electrocatalyst design. These strategies can help overcome the challenges of designing electrocatalysts with high activity, selectivity, and stability, while also addressing issues related to material scarcity and environmental sustainability.

In this context, our group has been exploiting bio-inspired strategies at multiple scales, taking inspiration from the macroscale (shape of some living organisms such as newt gills), the microscale (secondary coordination sphere of enzymatic systems,

electron/proton transfer chains) as well as at the molecular level (structure and elemental composition of the active site).<sup>[1]</sup>

This article provides a perspective on recent work developed in our group, focusing on bio-inspired strategies introduced at the molecular level to design new catalytic approaches for the electrochemical reduction of  $\text{CO}_2$ . The forthcoming sections elaborate on three core strategies derived from enzymes explored by our team: mimicking active site structures, emulating functions, and replicating key features of enzymatic reaction mechanisms.

## Bio-inspired Strategies for $\text{CO}_2$ Electroreduction

Aiming at developing  $\text{CO}_2$  reduction catalysts, the biological carbon dioxide reductases, namely the Carbon Monoxide Dehydrogenases (CODH) and the Formate Dehydrogenases (FDH) enzymes offer a very good source of inspiration. These enzymes serve in natural systems as efficient catalysts in the transformation of  $\text{CO}_2$  as a substrate to CO and HCOOH or a product from their oxidation. One interesting commonality shared by these enzymes is the presence of thiolate ligands directly coordinated to the enzymatic active sites. However, despite their prevalence in biological  $\text{CO}_2$  reductases, the use of thiolate ligands in the design of  $\text{CO}_2$  reduction catalysts remained surprisingly underexplored in the literature.<sup>[2–5]</sup>

To address this knowledge gap, our research group investigated the synthesis and catalytic activity of complexes of earth-abundant metals bearing thiolate ligands. Thiolate ligands possess soft Lewis base properties and contribute to increased electron density on reduced metals, promoting strong metal–ligand covalency. These characteristics are important to enhance the reactivity of reduced complexes with  $\text{CO}_2$ . However, due to their anionic nature, thiolate ligands also impede the reduction of the complex, necessitating higher cathodic potentials for the generation of active species, *in fine* translating to increased overpotentials and lower turnover numbers. Aiming at modulating the electronic influence of anionic thiolate ligands *via* their combination with neutral nitrogen ligands, we explored the use of 2-pyridinethi-

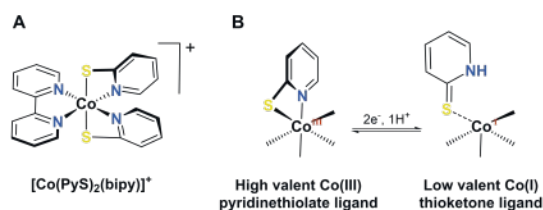
\*Correspondence: Prof. Dr. V. Mougel, E-mail: mougel@inorg.chem.ethz.ch

Department of Chemistry and Applied Biosciences, Laboratory of Inorganic Chemistry, ETH Zürich, Vladimir Prelog Weg. 1-5, CH-8093 Zürich

olate (PyS) ligands, in combination with substituted bipyridine (bpy) ligands.

While exploring a large number of different first row transition metals, we identified Co as being the most promising electrocatalyst for CO<sub>2</sub> reduction.

We focused on a series of cobalt(III) pyridinethiolate complexes, demonstrating that [bipyridine-bis-(2pyridinethiolato)-cobalt(III)-hexafluorophosphate] ([Co(PyS)<sub>2</sub>(bipy)](PF<sub>6</sub>), Scheme 1A) in particular serves as a highly selective catalyst for formate production.<sup>[6]</sup> This catalyst operates at a very low overpotential of 110 mV while achieving high turnover frequency (TOF) of 10 s<sup>-1</sup>.



Scheme 1. **A:** [Co(PyS)<sub>2</sub>(bipy)]<sup>+</sup> complex; **B:** resonance structure of the PyS ligand in function of Co oxidation state.

The figures of merit of molecular electrocatalysts can typically be compared *via* log(TOF) vs overpotential plots, such as represented in Fig. 1. Catalysts displaying the best performances can be found in the top left corner of the plot, *i.e.* showing high TOFs at modest overpotentials. Fig. 1 highlights that [Co(PyS)<sub>2</sub>(bipy)]<sup>+</sup> stands among the best catalysts for the CO<sub>2</sub> electroreduction to formate, in particular displaying improved performances with respect to other Co-based catalysts. To rationalize this improved activity, we carried out density functional theory studies and electrokinetic analysis. We were able to propose a reaction mechanism for the CO<sub>2</sub> reduction process and identified the unique role of the pyridinethiolate ligand to enable high catalytic turnover. When bound to the complex in its oxidized state (Co(III)), the ligand binds in a bidentate mode, with the pyridine nitrogen and S atom presenting a thiolate character. Upon reduction of the complex to the low valent Co(I) state, the ligand binds in a monodentate fashion, being solely bound *via* the S atom, then presenting a thioketone character while the pyridine nitrogen is protonated (Scheme 1B). This modulation of hapticity, resulting from the thioketone/thioenol resonance forms of the ligands, is key for activity, as the decoordination/protonation of the pyridine nitrogen generates a highly reactive coordinatively unsaturated Co(I) complex. This allows the direct protonation of the Co center to generate a Co(III) hydride species of high hydricity (38 kcal/mol), enabling its transfer to CO<sub>2</sub>, generating formate.

Moving beyond single-metal centers, our research also delved into the role of bimetallic sites, a common feature in both families of CODH enzymes. We focused specifically on the Mo-Cu bimetallic active site of CODH2. We synthesized and examined a molecular complex, [(bdt)Mo<sup>VI</sup>(O)S<sub>2</sub>Cu<sup>I</sup>(CN)]<sup>2-</sup>, that mimics the active site of the CODH2 enzyme (Fig. 2). This complex was found to be electrocatalytically active for the selective reduction of CO<sub>2</sub> to formic acid. The difference in product selectivity compared to the enzyme it models (formate vs. CO) was particularly surprising and drove us to further investigate the origin of this selectivity shift.

Utilizing a combination of *in situ* infrared spectroelectrochemical studies and density functional theory, we demonstrated that the complex was only a pre-catalyst, while the active catalyst is generated upon reduction in the presence of CO<sub>2</sub>. We found that the two-electron reduction of [(bdt)Mo<sup>VI</sup>(O)S<sub>2</sub>Cu<sup>I</sup>(CN)]<sup>2-</sup> triggers the transfer of the oxo moiety to CO<sub>2</sub>, forming CO<sub>3</sub><sup>2-</sup> and the com-

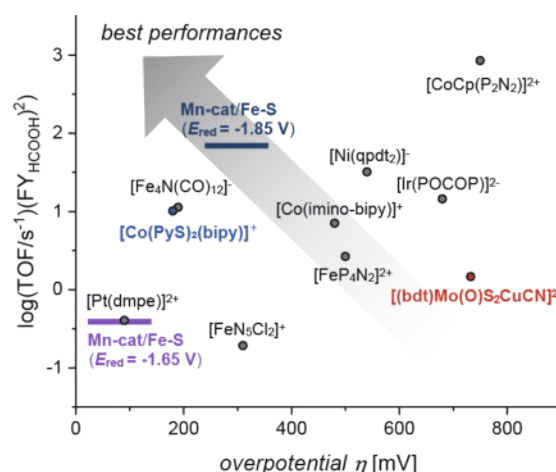


Fig. 1. Comparison of the performance among reported catalytic CO<sub>2</sub> Reduction Reaction (CO<sub>2</sub>RR) systems selective for formic acid production. The bars indicate the range of overpotential for the Mn<sup>I</sup>-cat/Fe-S system, to account for the uncertainties related to the actual pK<sub>a</sub> value of the proton source in the organic electrolyte solution.

plex [(bdt)Mo<sup>IV</sup>S<sub>2</sub>Cu<sup>I</sup>(CN)]<sup>2-</sup>. This more coordinatively unsaturated complex can be further reduced by one-electron reduction to generate the active catalyst. Its protonation yields a reactive Mo<sup>V</sup>-H hydride intermediate, which reacts with CO<sub>2</sub> to afford formate as the main reduction product from CO<sub>2</sub> reduction (Scheme 2). However, despite presenting a closer analogy with the enzymatic active site than the Co complex introduced earlier in text, its catalytic performances were more modest, as highlighted in Fig. 1, lying in the bottom right corner of the log(TOF) vs. η plot.

This difference of activity further stresses a key challenge in the electroreduction of CO<sub>2</sub> to formic acid: in the vast majority of reaction mechanisms leading to formate/formic acid, a metal hydride (M-H) site is involved. This M-H site needs to display a strong hydride donor ability (Δ°G<sub>H</sub> < 44 kcal/mol) to enable the hydride transfer to CO<sub>2</sub>. In the particular context of the electrochemical generation of metal hydrides, the metal center must be overall reduced by two electrons, occurring in a stepwise fashion with a protonation step (Fig. 3).<sup>[7,8]</sup> Such sequential processes involve the transfer of electrons and protons from different sources (the solid electrode and the electrolyte, respectively). From a thermodynamic perspective, achieving highly reactive metal hydride species hence involves the generation of highly reduced oxidation states of the metal center or the use of strong acids. These two points constitute significant hurdles for the generation of M-H species in an electrocatalytic context: the use of strong acids typically results in the direct protonation of the formed M-H species, consuming it as soon as generated and releasing H<sub>2</sub>, while the required electrogenerated highly reactive doubly reduced metal centers may not exist at all under electrochemical conditions. Such species are indeed often extremely reducing and may lie beyond the solvent wall or be able to reduce the substrate before being protonated.

To mitigate this issue and enable hydride formation using mild acid sources at modest applied potentials, we explored the use of concerted proton-electron transfer (CPET) mediators for the

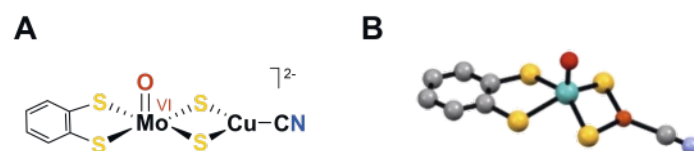
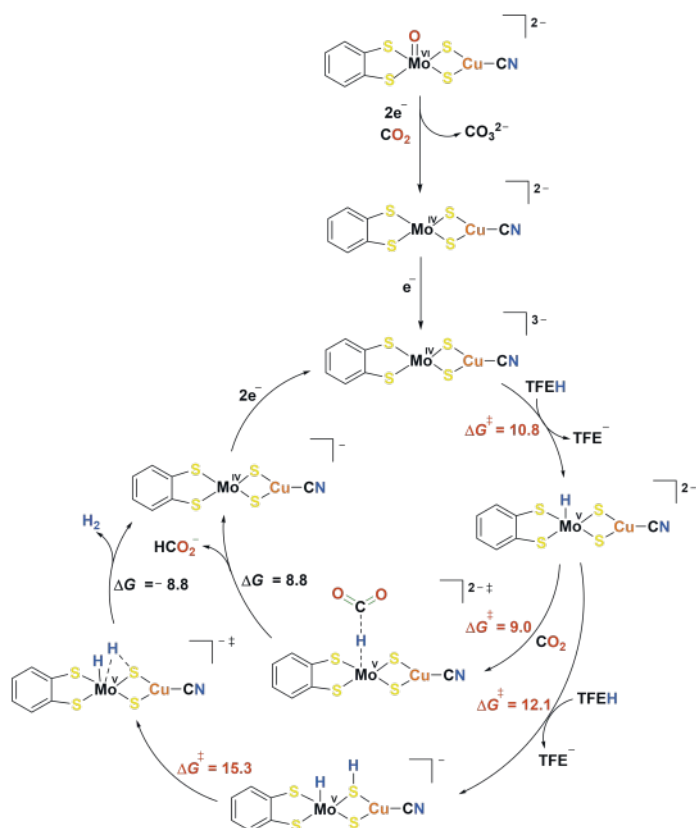


Fig. 2. **A:** formula and **B:** single crystal X-ray diffraction structure of [(bdt)Mo<sup>VI</sup>(O)S<sub>2</sub>Cu<sup>I</sup>(CN)]<sup>2-</sup>.



Scheme 2. Proposed reaction mechanisms of  $\text{CO}_2$  reduction to formate and hydrogen by complex  $[(\text{bdt})\text{Mo}^{\text{V}}(\text{S})_2\text{Cu}(\text{CN})]^{2-}$  obtained from the pre-catalyst  $[(\text{bdt})\text{Mo}^{\text{V}}(\text{O})(\text{S})_2\text{Cu}(\text{CN})]^{2-}$ . The relative Gibbs free energies ( $\Delta G$ , kcal  $\text{mol}^{-1}$ ) and transition state barriers ( $\Delta G^\ddagger$ , kcal  $\text{mol}^{-1}$ ) are given relative to the preceding intermediate. The standard one-electron reduction potential ( $E^0$ , V) is given vs.  $\text{Fc}/\text{Fc}^+$ .

generation of metal hydride species. In a CPET, both a proton and an electron are transferred simultaneously, being co-localized as a hydrogen atom or originating from two different locations (multi-site CPET). In an electrocatalytic context, a CPET mediator can collect an electron at the electrode, a proton in the electrolyte and transfer them simultaneously to a substrate<sup>[9–13]</sup> Such concerted steps have been shown to be kinetically advantageous over the stepwise transfer of a proton and an electron (Fig. 3).<sup>[14,15]</sup> In addition to its kinetic interest, the use of such mediators in an electrocatalytic context could have a significant advantage from a selectivity point of view. The CPET mediated generation of hydride species would allow to employ milder proton sources, which could effectively reduce the likelihood of the hydride species being quenched to produce  $\text{H}_2$ , a key factor for achieving high selectivity when  $\text{H}_2$  is not the intended product. Such use of a CPET mediator in facilitating the electrocatalytic production of a metal hydride had never been reported in a catalytic context, but was not unprecedented in Nature: it had been recently reported that the very reactive iron hydride species found in the Fe-Fe hydrogenase enzyme is generated *via* a CPET mediated mechanism.<sup>[16–18]</sup> These CPET steps were promoted by iron sulfur cubane clusters ( $\text{Fe}_4\text{S}_4$  clusters). The ability of  $\text{Fe}_4\text{S}_4$  clusters to mediate CPET had been demonstrated in a stoichiometric way by the early work of Saouma and Mayer,<sup>[19]</sup> but had never been explored in a catalytic way.

Based on these studies, we decided to investigate the use of synthetic  $\text{Fe}_4\text{S}_4$  clusters as CPET mediators for the electroreduction of  $\text{CO}_2$  to formic acid. We were in particular interested by their very low reorganization energy, which is key to the high efficiency of electron transfers in enzymatic systems,<sup>[20,21]</sup> as this

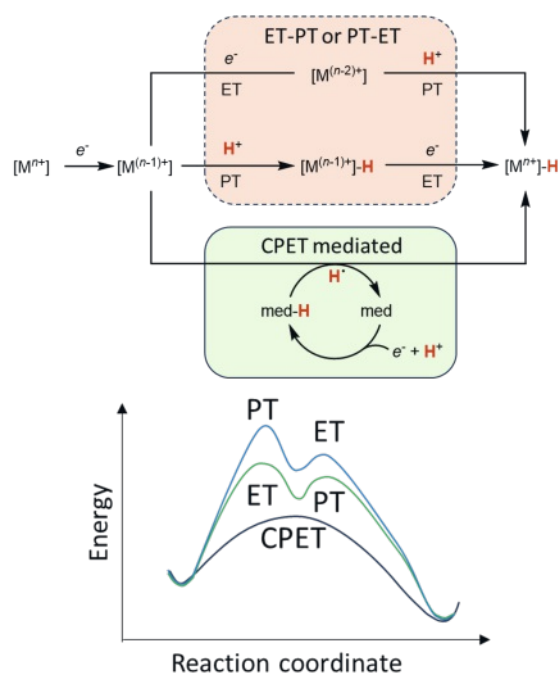


Fig. 3. (top) Generation of M-H species *via* stepwise electron-proton transfer (ET-PT or PT-ET) and CPET processes; (bottom) schematic associated energy profiles.

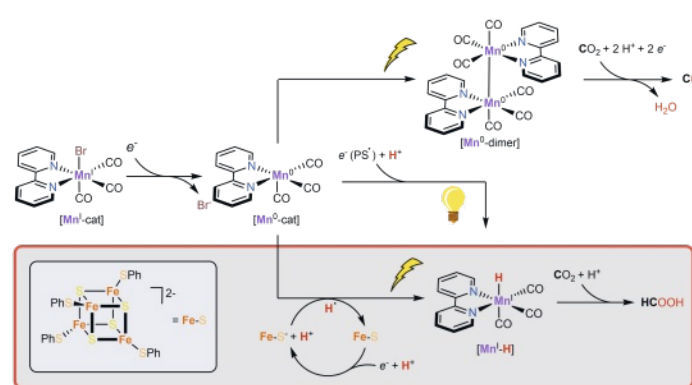
is highly desirable for an efficient (re)generation when used as a CPET mediator. The CPET mediator is not itself a catalyst, and we selected  $[\text{Mn}^{\text{I}}(\text{bpy})(\text{CO})_3\text{Br}]$  (**Mn<sup>I</sup>-cat**) given its divergent behavior in the electrochemical and photochemical  $\text{CO}_2$  Reduction Reactions ( $\text{CO}_2\text{RR}$ ) (Scheme 3, top arrows). It produces  $\text{CO}$  under electrochemical conditions<sup>[22]</sup> while generating  $\text{HCOOH}$  as the major product in photochemical conditions.<sup>[23,24]</sup> This shift in selectivity is a direct consequence from the catalytic reaction pathway: the carbon-centered activation of  $\text{CO}_2$  under electrochemical conditions results in  $\text{CO}$  being the primary product, whereas the formation of a manganese(I) hydride species ( $\text{Mn}^{\text{I}}\text{-H}$ ) under photochemical conditions enables the production of  $\text{HCOOH}$  (Scheme 3, bottom).<sup>[24]</sup>

Combining the synthetic iron-sulfur cluster  $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$  (**FeS**) as a CPET mediator with **Mn<sup>I</sup>-cat**, we were able to promote the targeted electrocatalytic formation of a  $\text{Mn}^{\text{I}}\text{-H}$  species and shift the  $\text{CO}_2\text{RR}$  selectivity of **Mn<sup>I</sup>-cat** from  $\text{CO}$  to  $\text{HCOOH}$  (Scheme 3).<sup>[25]</sup> This  $\text{Mn}^{\text{I}}\text{-H}$  species was generated at minimum thermodynamic cost, operating at the lowest overpotential for the  $\text{CO}_2\text{RR}$  to  $\text{HCOOH}$  reported to date (Fig. 1).

Besides this specific catalytic example, we expanded this strategy to experimentally validate the boundary conditions for the choice of CPET mediators for the electrochemical generation of metal hydrides. We could experimentally demonstrate that the relationship between the bond dissociation free energy (BDFE) of the CPET mediator ( $\text{med-H}$ ) and targeted M-H species had to be chosen so that  $\text{BDFE}^{\text{M-H}} > \text{BDFE}^{\text{med-H}}$ . This proof of concept paves the route for the generalization of this approach to other M-H species and catalytic reactions. This strategy has notably now just been used to promote hydrogenation reactions selectively, avoiding the competing hydrogen evolution reaction.<sup>[26]</sup>

All biological  $\text{CO}_2$  reductase enzymes are restricted to the two-electron reduction products of  $\text{CO}_2$ , namely  $\text{CO}$  for the CODH enzyme and formic acid for the FDH. However, the nitrogenase enzyme, catalyzing in natural systems the reduction of dinitrogen to ammonia, has shown a remarkable capability to surpass this two-electron reduction limit. Different families of nitrogenases and cofactors were indeed proven able to mediate the reduction of





Scheme 3. Reaction pathways and associated product selectivity for **Mn<sup>I</sup>-cat** catalyzed CO<sub>2</sub> reduction under electro- and photochemical conditions.

CO<sub>2</sub> to a vast series of products, ranging from formate and carbon monoxide to methane and longer hydrocarbons such as ethylene and ethane.<sup>[27–30]</sup> Such reductions involve 8, 12 or even 14 electron reduction, much beyond the 2-electron processes typically found in other biological CO<sub>2</sub> reductases.

The discovery of nitrogenase's potential in the realm of CO<sub>2</sub> reduction points to new research directions. While the enzyme does not naturally perform these reactions in biological systems, it nonetheless demonstrates the feasibility of such complex multi-electron reductions using molecular catalysts. The key to unlocking this potential further might lie in our understanding of this enzyme's structure and function, and how we can manipulate and incorporate these properties in the design of molecular electrocatalysts. Of particular interest for us was the demonstration that the Fe<sub>4</sub>S<sub>4</sub> cluster of the iron protein (FeP) of the nitrogenase was found competent to mediate the reduction of CO<sub>2</sub> to hydrocarbons.<sup>[29]</sup> However, from a synthetic point of view, no mimic of the all-ferrous active site of the FeP, proposed to be catalytically active here, was known in the literature. We hence focused our efforts to attempt to isolate such a highly reduced Fe<sub>4</sub>S<sub>4</sub>, bearing four thiolate ligands. A significant obstacle to synthesizing a Fe<sub>4</sub>S<sub>4</sub> cluster of this type is its extreme sensitivity towards oxidative degradation. As a result, [Fe<sub>4</sub>S<sub>4</sub>(SR)<sub>4</sub>]<sup>4-</sup> is the only known analogue of the [Fe<sub>4</sub>S<sub>4</sub>(SR)<sub>4</sub>]<sup>n-</sup> (n = 0–4) redox series that hasn't been synthetically isolated. The all-ferrous state, also known as the superreduced state of the Fe<sub>4</sub>S<sub>4</sub> core, [Fe<sub>4</sub>S<sub>4</sub>]<sup>0</sup>, was first detected electrochemically in 1984 by Pickett<sup>[31]</sup> using a synthetic model of the biologically relevant [Fe<sub>4</sub>S<sub>4</sub>(S<sup>Cys</sup>)<sub>4</sub>]<sup>n-</sup> site, [Fe<sub>4</sub>S<sub>4</sub>(SPh)<sub>4</sub>]<sup>n-</sup>.<sup>[32,33]</sup> This state was later suggested to exist in the nitrogenase FeP,<sup>[34–36]</sup> but the complex nature of the FeP's enzymatic system has hindered precise determination of the superreduced FeS core's key structural and electronic parameters.

The discovery of the all-ferrous state in biological systems ignited an intense pursuit for well-defined, physiologically relevant molecular models.<sup>[37–40]</sup> However, the ligands used for isolating the few reported models, such as NHC and cyanide, display non-negligible π-backbonding properties, which differ significantly from the biologically relevant thiolate ligands. These discrepancies could modify the cluster's reactivity and spectroscopic properties due to differences in metal–ligand orbital interaction energy and ligand field strength.

In FeP, the Fe<sub>4</sub>S<sub>4</sub>'s placement at the positive end of four α-helix dipoles and the unique hydrogen bonding patterns surrounding the cluster are believed to stabilize the superreduced state.<sup>[41]</sup> Aiming to replicate these stabilizing effects, we selected the bulky thiolate ligand DmpS<sup>-</sup> (2,2'',4,4'',6,6''-hexamethyl-1,1':3',1''-terphenyl-2'-thiolate) as a suitable candidate because it is known for its capacity to pack redox-innocent K<sup>+</sup> ions into the molecular as-

sembly upon coordination to metal centers *via* cation-π interaction (Scheme 4).<sup>[42,43]</sup> By adopting this strategy, we managed to isolate the first all-ferrous [Fe<sub>4</sub>S<sub>4</sub>]<sup>0</sup> cluster with biologically relevant thiolate ligands.<sup>[44]</sup> We established that this method, by adjusting the charge needed to stabilize different Fe<sub>4</sub>S<sub>4</sub> oxidation states with the number of potassium cations, facilitated the creation of the first series of thiolate-supported FeS cubanes encompassing all oxidation states within the Fe<sup>II</sup>/Fe<sup>III</sup> redox couples. This series ranged from all-ferric ([Fe<sub>4</sub>S<sub>4</sub>]<sup>4+</sup>) to all-ferrous ([Fe<sub>4</sub>S<sub>4</sub>]<sup>0</sup>), allowing a thorough analysis of the variation of the structural and electronic properties along the series.

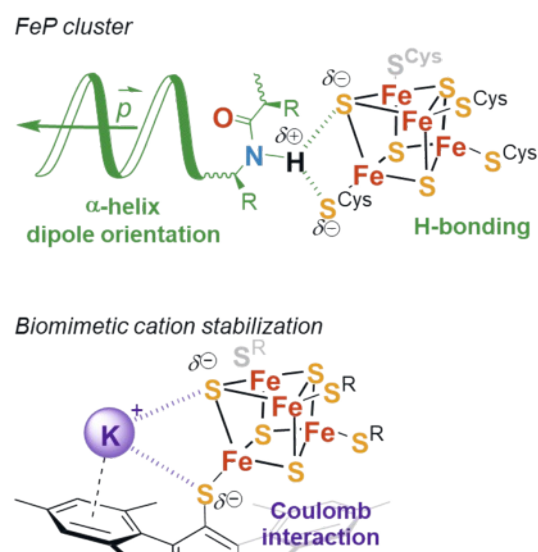
Electrochemical investigations highlighted the stabilization provided by the K<sup>+</sup> cations. While only the [Fe<sub>4</sub>S<sub>4</sub>]<sup>2+/3+</sup> and [Fe<sub>4</sub>S<sub>4</sub>]<sup>3+/4+</sup> redox couples can be accessed using [<sup>n</sup>Bu<sub>4</sub>N][PF<sub>6</sub>]<sup>-</sup> as electrolyte, using K[BarF<sub>2,4</sub>]<sup>-</sup> as electrolyte allows complete traversal of relevant oxidation states within a potential window, ΔV, of only 1.27 V (Fig. 4). This cation-provided stabilization was most potent for the most reduced cluster state, shifting the all-ferrous cluster's redox potential by approximately 1.6 V to more anodic potentials.

However, this strong stabilization effect can also dampen the reduced clusters' reactivity. Current research efforts in our group focus on potentially liberating this stored electrochemical energy and exploring the activation of small molecules with such Fe<sub>4</sub>S<sub>4</sub> analogs.

## Conclusions and Outlook

The few examples from our recent work introduced in this perspective article emphasize the strength of the bio-inspired approach in the realm of molecular catalysis. Exploring the complex nature of enzymes provides unique insights on the key aspects to be mimicked to enable catalytic activity, leading to new pathways for the design of advanced electrocatalysts. Three key facets of enzymatic catalysis have emerged as particularly instructive for our group.

The first and most straightforward step is to gain inspiration from the structure of enzymatic active sites, informing more effective catalyst designs regarding the choice of metal to be used, the primary and secondary coordination spheres to replicate to enable catalytic activity, *etc.* The creation of bimetallic Mo-Cu CODH mimics and all-ferrous Fe<sub>4</sub>S<sub>4</sub> clusters underlines how bio-



Scheme 4. Synthetic strategy utilized for the isolation and characterization of the redox series K<sub>n</sub>[Fe<sub>4</sub>S<sub>4</sub>(DmpS)<sub>4</sub>] (n = 0–4). (top) Stabilization of reduced FeS cubanes in enzymes; (bottom) strategy deployed in our studies, based on K<sup>+</sup>-π cation interactions.

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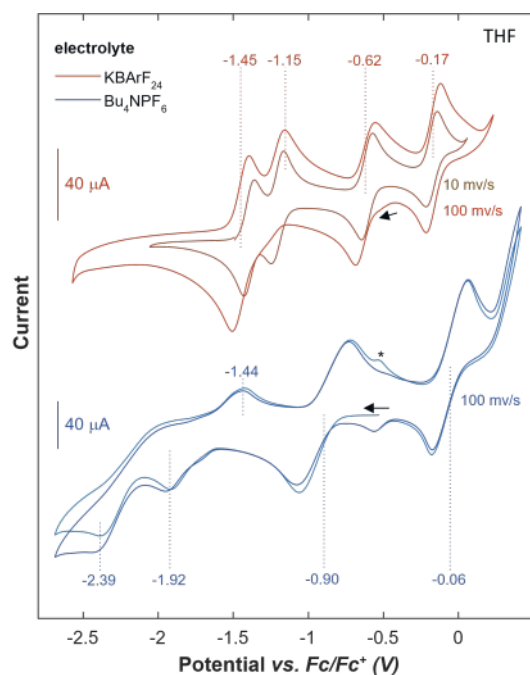


Fig. 4. Electrochemical traverse of the  $[\text{Fe}_4\text{S}_4]^{0/+2+/3+/4+}$  redox series. (top two traces) Cyclic voltammograms of  $[\text{Fe}_4\text{S}_4(\text{SDmp})_4]^{3+}$  recorded in THF containing 0.3 M  $\text{K}[\text{BArF}_{2.4}]$  recorded with scan rates of  $10 \text{ mV s}^{-1}$  and  $100 \text{ mV s}^{-1}$ . (bottom two traces) Cyclic voltammograms of  $[\text{Fe}_4\text{S}_4(\text{SDmp})_4]^{3+}$  recorded with a scan rate of  $100 \text{ mV s}^{-1}$  in THF containing 0.3 M  $[\text{tBu}_4\text{N}][\text{PF}_6]$  (blue lines), respectively, as electrolyte.

mimetic structural considerations can impact the reactivity and performances of bio-inspired molecular complexes.

Furthermore, moving beyond exact structural mimicry to draw inspiration from the functionality of enzymatic systems can yield a greater flexibility in design. The development of cobalt(III) pyridinethiolate complexes serves as a testament to this approach, presenting an innovative path to replicating enzymatic functions in artificial electrocatalysts.

Last, the detailed understanding of the unique reaction mechanisms of enzymes enables the exploration of novel catalytic strategies. The incorporation of concerted proton–electron transfer mechanisms into our designs stands as an example of this strategic innovation.

These three facets – structure, function, and mechanism – will continue to serve as a robust framework for the research developed in our group. By deepening our understanding of biological systems and harnessing their ingenuity, we believe that substantial strides in the performances and sustainability of electrocatalysts can be made. It should be noted, in addition, that these concepts equally apply to heterogeneous catalysis, further extending the potential reach of such bio-inspired strategies.

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