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Merging Molecular, Materials, and Biological Design Elements in Catalysts
for Small Molecule Activation and Conversion

By

Peter T. Smith

A dissertation submitted in partial satisfaction of the
requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Christopher J. Chang, Chair

Professor Jeffrey R. Long

Professor Jeffrey A. Reimer

Summer 2020

Merging Molecular, Materials, and Biological Design Elements in Catalysts
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by Peter T. Smith

Abstract

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Peter T. Smith

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Christopher J. Chang, Chair

Understanding and manipulating transformations of CO_2 , O_2 , H_2O , NO_3^- , CH_4 , and N_2 is crucial for establishing sustainable energy cycles, and using inputs such as electricity or light allows coupling of these reactions to renewable sources. Developing platforms that can activate these molecules is a continuous challenge and must be approached from many directions. As such, we take inspiration from homogeneous molecular, heterogeneous materials, and biological enzyme catalysis to create more effective platforms. This dissertation describes this general approach and then focuses on a supramolecular strategy that integrates the structural tunability of molecular porphyrin catalysts into a rigid and porous architecture that benefits from a materials-inspired high surface area. This platform is widely applicable, showing various improvements in the catalysis of CO_2 , O_2 , and H_2O reduction. We also present a bio-molecular platform that combines a synthetic porphyrin catalyst with bio-inspired additives that can function as electron and proton mediators resulting in improved CO_2 reduction. Overall, our general strategy for blurring the lines between molecular, materials, and biological fields of catalysis has proven fruitful and aids in the rational design of more optimized systems.

For me and my family

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Chapter 1

Hybrid Catalysts for Artificial Photosynthesis: Merging Approaches from Molecular, Materials, and Biological Catalysis

Portions of this work were published in the following scientific journal:

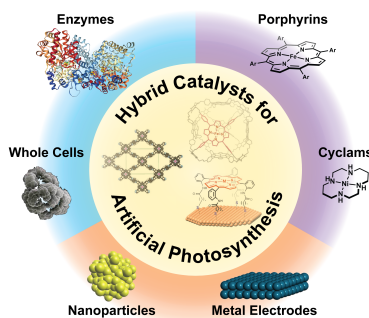
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Abstract

Increasing demand for sustainable energy sources continues to motivate the development of new catalytic processes that store intermittent energy in the form of chemical bonds. In this context, photosynthetic organisms harvest light to drive dark reactions reducing carbon dioxide, an abundant and accessible carbon source, to store solar energy in the form of glucose and other biomass feedstocks. Inspired by this biological process, the field of artificial photosynthesis aims to store renewable energy in chemical bonds spanning fuels, foods, medicines, and materials using light, water, and CO_2 as the primary chemical feedstocks, with the added benefit of mitigating the accumulation of CO_2 as a greenhouse gas in the atmosphere. As such, devising new catalyst platforms for transforming CO_2 into value-added chemical products is of importance. Historically, catalyst design for artificial photosynthesis has been approached from the three traditional fields of catalysis: molecular, materials, and biological. In this Chapter, we show progress from our laboratory in constructing new hybrid catalysts for artificial photosynthesis that draw upon design concepts from all three of these traditional fields of catalysis and blur the boundaries between them. Starting with molecular catalysis, we incorporated biological design elements that are abundant in enzymes into synthetic systems. Specifically, we demonstrated that proper positioning of intramolecular hydrogen bond donors or addition of intermolecular multi-point hydrogen bond donors with classic iron porphyrin and nickel cyclam platforms can substantially increase rates of CO_2 reduction and break electronic scaling relationships. In parallel, we incorporated a key materials design element, namely high surface area and porosity for maximizing active site exposure, into molecular systems. A supramolecular porous organic cage molecule was synthesized with iron porphyrin building blocks, and the porosity was observed to facilitate substrate and charge transport through the catalyst film. In turn, molecular design elements can be incorporated into materials catalysts for CO_2 reduction. First, we utilized molecular synthons in a bottom-up reticular approach to drive polymerization/assembly into a bulk framework material. Second, we established an organometallic approach in which molecular ligands, including chelating ones, are adsorbed onto a bulk inorganic solid in order to create and tune new active sites on surfaces. Finally, we describe two examples in which molecular, materials, and biological design elements are all integrated to catalyze the reduction of CO_2 into CH_4 using a hybrid biological-materials interface with sustainably-generated H_2 as the reductant, or to reduce CO into value-added C_2 products acetate and ethanol using a hybrid molecular-materials interface to construct a biomimetic, bimetallic active site. Taken together, our program in catalysis for energy and sustainability has revealed that combining more conventional design strategies in synergistic ways can lead to advances in artificial photosynthesis.



Introduction and Dissertation Overview

In this first chapter, we introduce the general theme of our research in which we construct new electrochemical catalysis platforms that merge design elements from molecular, materials, and biological catalysts. This approach aims to combine the beneficial aspects of these three distinct fields in an effort to overcome some of the traditional drawbacks that each also present. In Chapters 2, 3, and 4 we focus on a supramolecular porphyrin box platform that combines the synthetic tunability of molecular catalysts with the high surface area and porosity of materials catalysts. This platform was applied to the CO₂, O₂, and H₂O reduction reactions. In Chapter 5, we focus on a hybrid bio-molecular approach to CO₂ reduction that uses a synthetic molecular catalyst and takes inspiration from biology to design additives that enhance electron and proton delivery to the catalyst. This theme is continued in the appendices which detail preliminary results from several projects that are ongoing. We begin with an emphasis on the transformation of CO₂, and then we broaden our approach to include the activation and conversion of O₂, H₂O, NO₃⁻, CH₄, and N₂.

Increasing human consumption of fossil fuels continues to contribute to adversely high levels of atmospheric CO₂ and a changing climate on the planet.¹ Photosynthesis offers a blueprint to mitigating this global problem by converting intermittent light energy into electrical current for converting CO₂ and H₂O into sugars for sustainable energy storage.² Artificial photosynthesis has the potential to expand this process, where electricity derived from sustainable sources can drive electrocatalytic generation of value-added products.^{3,4} Characteristics used to benchmark catalyst performance for electrochemical CO₂ reduction include overpotential, product selectivity, Faradaic efficiency (FE), current density, turnover frequency (TOF), and turnover number (TON).⁵ However, simultaneously optimizing each of these parameters using a single catalyst remains a significant challenge.^{6,7}

Electrocatalytic CO₂ reduction is generally performed in a liquid electrolyte using one of three traditional catalytic approaches: molecular, materials, or biological. *Molecular catalysts* refer to discrete, synthetic molecules that may either be dissolved in the electrolyte (homogeneous) or attached directly to an inert electrode (heterogeneous). *Materials catalysts* are defined as bulk or nanoparticulate solids—typically metals or semiconductors—that promote reactions at the heterogeneous interface with electrolyte and generally exhibit a distribution of active sites. *Biological catalysts* refer to either isolated enzymes or entire microorganisms, including both wild-type and genetically-modified forms.

Seminal advances in CO₂ reduction have been achieved using molecular metal complexes supported by macrocyclic porphyrin, phthalocyanine, and cyclam ligands, as well as heteroleptic complexes bearing polypyridines, *N*-heterocyclic carbenes, carbonyls, or phosphines.^{8,9} Mechanistic studies for molecular catalysts are tractable and show promise for rational optimization, and attachment to conductive heterogeneous supports can improve activity and aqueous compatibility.¹⁰ Separately, materials catalysts for CO₂ reduction have witnessed an expansion of recent activity, predominantly using gold-, silver-, and copper-based materials.^{11,12} Materials catalysts show promise for generating more highly reduced products beyond CO and formate, as well as value-added C-C coupled products, but mechanistic studies *in operando* to inform future design are challenging relative to molecular catalysts. Finally, using electrical input to drive catalysis with isolated enzymes¹³ or microorganisms¹⁴ can enable multi-step conversions

with selectivities or rates that transcend both molecular or materials systems. Challenges of such biological approaches include maintaining enzyme stability outside the native cellular environment, interfacing the complex biological components with an electrode, and balancing biosynthesis of a desired chemical product with the metabolic needs of living organisms.

We have initiated a program seeking to merge concepts from all three traditional fields of catalysis to pursue new artificial photosynthesis platforms that blur the boundaries between these often disparate research domains. In doing so, we have demonstrated that hybrid catalysts often exhibit significant synergistic effects, whereby TOF, product selectivity, energetic efficiency, or catalyst stability of the hybrid catalyst are improved compared to any traditional approach alone. In this Chapter, we describe our laboratory's progress in incorporating biological and materials designs into molecular systems, molecular designs into materials systems, and hybrid platforms that combine molecular, materials, and biological approaches to harness benefits inherent to each.

Biological Design Elements Applied to Molecular Catalysts

Enzymes have evolved to catalyze reactions relevant to sustainable energy conversion with high TOF and selectivity using Earth-abundant components.^{2,13} Direct synthetic mimicry of such redox enzyme active sites encounters difficulties in replicating catalytic activity because of removal of the protective and structure-enforcing protein that surrounds the active site.¹⁵ As such, we and others have pursued a functionally bioinspired approach to drive new synthetic designs for robust molecular catalysts. For example, our laboratory has previously reported a number of molecular catalysts for hydrogen evolution that are compatible with water or even operate at neutral pH,¹⁶⁻¹⁹ including one where proper placement of pyrazine redox reservoirs enables catalysis in a fashion reminiscent of the positional dependence of redox-active cofactors in metalloenzymes.²⁰ More recently, our focus has shifted to the development of CO₂ reduction catalysts, drawing inspiration from Ni-Fe carbon monoxide dehydrogenase (CODH) enzymes as highlighted in Figure 1.1. Here, the confined active site and second-sphere hydrogen bond network work in concert to enable nucleophilic attack of CO₂ and subsequent C-O bond scission.^{21,22}

Structural and Electronic Tuning of a Bioinspired Metal Active Site. The CO₂ reduction activity of NiFe-CODH is due in part to its highly nucleophilic low-valent nickel center.²¹ As such, low-valent nickel complexes supported by N₄-macrocyclic ligands have featured prominently as electrocatalysts for the conversion of CO₂ to CO,²³ including [Ni(cyclam)]²⁺ and derivatives, which exhibit excellent selectivity for CO₂ reduction over competitive proton reduction.²⁴ However, tunability of these systems is challenging to predict because activity depends strongly on macrocycle size, solution configuration, and N-alkylation.^{25,26}

We sought to replicate the nucleophilic character of the active nickel center in CODH through the use of electron-rich N-heterocyclic carbene (NHC)-pyridine ligands and prepared a series of nickel bis(imidazolylpyridine) (bimpy) complexes featuring various bridgehead linker lengths (Figure 1.2A).²⁷ Increasing the number of methylene units (*n*) in the linker enables geometric tunability at nickel from square planar to distorted tetrahedral. These changes are reflected in the electrochemistry *via* a systematic positive shift of the Ni^{I/0} reduction potentials over 230 mV, with the *n*=3 complex displaying the most positive reduction potential. This structural tunability is reminiscent of entatic states of blue copper proteins, which adopt a geometry in between square planar and tetrahedral to minimize structural reorganization upon redox changes.²⁸ All three **Ni(bimpy)** complexes selectively reduce CO₂ to CO in acetonitrile with added water as the proton source.

We expanded this platform to prepare propyl-bridged nickel complexes bearing expanded π -systems on either the pyridine group (*i.e.*, isoquinoline) or the imidazolyl group (*i.e.*, benzimidazolyl) (Figure 1.2B).²⁹ Varying the location of the expanded π -system alters the electronics at the nickel center and affects electrocatalytic CO₂ reduction activity, with isoquinoline derivative [Ni(^{Pr}bimiq1)](PF₆)₂ (^{Pr}bimiq1 = bis(3-(imidazolyl)isoquinolynyl)propane) exhibiting an onset potential >200 mV more positive than the other members of the series and a FE of 90% for CO. Furthermore, [Ni(^{Pr}bimiq1)](PF₆)₂ is efficient for photocatalytic reduction of CO₂ to CO in conjunction with a photosensitizer and amine donor, achieving TON of 98,000 and TOF of 3.9 s⁻¹ under conditions of relevant solar intensity (Figure 1.2C) with a >3000-fold rate improvement over the first-generation system.

Installation of Pendant Relays in the Catalyst Second Coordination Sphere. Enzyme activity depends on precisely tuned networks of non-covalent interactions that modulate reduction potentials, assist in proton transfer, and appropriately (de)stabilize intermediates or transition states. In NiFe-CODH, hydrogen bonding between histidine and lysine residues stabilizes the CO₂ adduct and assists in C-O cleavage (Figure 1.1).²¹ Mimicking this biological design strategy, various second-sphere pendants have been incorporated into molecular electrocatalysts for a variety of transformations including CO₂ reduction.³⁰⁻³⁷ Notably, state-of-the-art iron porphyrins bearing pendant phenol or trimethylanilinium groups have shown impressive catalytic enhancements that are attributed to the proton relays/hydrogen bond donors or electrostatic compensation groups.^{30,38} Given the critical role of amino acid positioning in enzymatic active sites, we became interested in the precise positional dependence of second-sphere donors for molecular CO₂ reduction catalysis.

To meet this goal, we prepared four isomers of iron tetraphenylporphyrin featuring one pendant amide ($pK_a \sim 19$ in DMSO) (Figure 1.3A).³² Pendant amides were placed proximal (1) or distal (2) to the porphyrin plane, and *ortho*-functionalized isomers could be expected to engage in intramolecular interactions with an iron-bound CO₂ intermediate, while *para*-functionalized analogues would not. All four isomers reduce CO₂ into CO as the only product in DMF with phenol as the proton source. Iron porphyrins with simple electron donating/withdrawing groups display a linear scaling relationship between the formal Fe^{I/0} reduction potential (E_{cat}^0) and maximum TOFs (TOF_{max}) (Figure 1.3B, dashed line). In contrast, both *ortho*-amide-functionalized porphyrins deviate from this relationship, implying that through-space interactions involving the pendant amide contribute in some way to the increased TOF_{max}. All isomers exhibit 1st-order dependencies on [CO₂], [PhOH], and [catalyst], suggesting that the pendant group does not drastically alter the mechanism. Equilibrium binding constants for CO₂ are ~ 5 times larger for the *ortho*- compared to the *para*- or unfunctionalized catalysts, consistent with the hypothesis that second-sphere amides assist in stabilizing Fe-bound CO₂. A two-orders-of-magnitude increase in TOF_{max} for the distal isomer **Fe-*ortho*-2-amide** compared to the proximal isomer **Fe-*ortho*-1-amide**, along with primary kinetic isotope effects between 1.5-2, suggest that distal NH positioning allows for more productive hydrogen bonding and proton relay interactions during the rate-determining step. A number of catalytically-relevant parameters may ultimately be tuned as a function of pendant group identity and location, including solvation, speciation, or substrate trajectory/orientation. Currently, we are exploring these ideas on polypyridyl systems with the Long laboratory.³⁹

Cooperative, Multi-Point Donors for Catalytic Enhancement. We next sought to further expand this concept of second-sphere tuning to multi-point interactions. Indeed, in NiFe-CODH, the interactions between lysine and histidine residues and a Lewis acidic iron are believed to work in concert to stabilize a bound CO₂ (Figure 1.1). This cooperative approach has been applied in organocatalysis, where dual hydrogen bonding interactions from a (thio)urea catalyst activate carbonyl-containing substrates towards nucleophilic attack.⁴⁰ The precedent for (thio)ureas to participate in oxyanion binding suggested to us that such moieties could (de)stabilize species relevant to CO₂ reduction and accelerate catalytic turnover.

Using Ni(cyclam)²⁺ as a catalyst for CO₂ reduction to CO,⁴¹ we observed a concentration-dependent increase in peak catalytic current in acetonitrile upon addition of **urea 1**. In contrast, **amide 2** lacks the ability to participate in cooperative interactions and shows minimal

enhancement. Importantly, the pK_a values in acetonitrile for **urea 1** and **amide 2** are 22.3 and 24.3, respectively. In an attempt to disambiguate the role of acidity from cooperativity, we selected a series of cationic and neutral acids of comparable or slightly greater acidity that could not form cooperative hydrogen bond interactions with CO_2 . In this study, we do not account for homoconjugation effects, which can be significant in acetonitrile. A comparison of peak catalytic current in the presence of the same amount of each acidic additive shows that the control acids do enhance CO_2 catalysis (as expected for a proton-dependent process), but not to the extent observed with the cooperative **urea 1** (Figure 1.4). **Urea 1** results in an approximately four-fold higher TOF than expected based on its pK_a , an observation attributed to productive two-point hydrogen bonding. **Ni(cyclam)**²⁺ remains highly selective for CO production in the presence of urea additive, with a FE of 91% and no H_2 detected. This work shows that cooperative binding can be used as an effective bioinspired design element for molecular catalysis.

Materials Design Elements Applied to Molecular Catalysts

Many molecular catalysts for CO₂ reduction suffer from poor aqueous compatibility and low current density, parameters for which materials catalysts frequently excel. As such, we sought to use materials design elements to develop molecular catalysts that retain the tunability of discrete molecular units but exploit advantages of heterogeneous materials. In an initial foray into this area, we reported electrochemical proton reduction with a molybdenum disulfide complex supported by polypyridyl ligands, which mimics the catalytically relevant edge sites of bulk molybdenum disulfide materials.¹⁸

As another example of a materials design element, catalysts with high surface area eliminate catalytically inactive bulk material and improved substrate delivery. In this context, porous organic cages (POCs) offer an attractive platform for translating permanent porosity from materials to molecular catalysts because homogeneous supramolecules of designable sizes and shapes can be synthesized through robust covalent bonds.⁴² Additionally, the solubility of POCs facilitates characterization and processing.⁴³ Electrocatalysts based on porous molecules constructed with metal nodes have been reported,^{44,45} but activity is low in part because metal-organic cages are labile and highly charged, which can cause detrimental electrostatic interactions with an electrode. By changing these charged nodes with all-organic linkers, we sought to improve charge-transport properties and long-term stability.

With the Kim laboratory, we focused on a POC constructed from six tetraphenylporphyrins linked through imine bonds for CO₂ reduction (Figure 1.5A).⁴⁶ We chose a porphyrin-based system with known CO₂ reduction activity,⁴⁷ so we could study the effects of supramolecular porosity. The porphyrin box is resistant to hydrolysis and is readily metalated with iron to afford **Fe-PB** with six catalytic centers per cage. **Fe-PB** was deposited onto a carbon electrode and studied as a heterogeneous molecular catalyst in neutral aqueous electrolyte.⁴⁸ Scan rate dependence of the Fe^{II/I} couple revealed that **Fe-PB** electrodes have nearly twice as many electrochemically active metal centers as **Fe-TPP** electrodes for the same loading. This indicates that **Fe-PB** is in greater electrical contact with the electrode, which we propose is due to decreased molecular aggregation that can slow charge transfer and lower the amount of charge-balancing electrolyte that can enter the heterogeneous film. During 1 h electrolyses, **Fe-PB** displays improved FE, reaching 100% for CO. After 24 h electrolysis, **Fe-PB** generates twice the volume of CO compared to **Fe-TPP** while maintaining 85% FE (Figure 1.5B). At negative potentials where catalysis is not limited by electron transfer, the difference in specific current density for CO (j_{CO}) increases between **Fe-TPP** and **Fe-PB** electrodes (Figure 1.5C), indicating that mass transport is more facile in the porous **Fe-PB** electrode. We recently extended this porphyrin box system to the O₂ reduction reaction where supramolecular site isolation controls product selectivity.⁴⁹

Molecular Design Elements Applied to Materials Catalysts

Applying elements of molecular chemistry to materials catalysis can overcome challenges of tunability and rational design. This strategy can take a bottom-up approach, where molecular catalysts are used to generate an extended material whose properties vary as a function of the size, geometry, or electronics of the building blocks.⁵⁰ A complementary top-down, or “organometallic coordination chemistry,” approach involves coordination of ligands to a bulk metal or nanoparticle surface to alter the band structure, induce surface restructuring, or improve stability by preventing Ostwald ripening.⁵¹ We highlight examples that have established the feasibility of both approaches in the molecular design of materials catalysts for CO₂ reduction.

Covalent Organic Frameworks as Reticular Materials for Heterogenization of Molecular Catalysts. Metal-organic frameworks (MOFs)⁵²⁻⁵⁴ and covalent organic frameworks (COFs)⁵⁵⁻⁵⁷ are customizable reticular materials whose properties can be tuned as a function of the constituent molecular components. They are thus attractive platforms for artificial photosynthesis applications ranging from CO₂ capture⁵⁸ to charge transport.⁵⁹ With the Yaghi laboratory, we chose to heterogenize molecular cobalt porphyrin catalysts into a materials COF platform owing to their precedent for CO₂ reduction⁴⁷ and square molecular shape. Condensation of cobalt tetra(aminophenyl)porphyrin [Co(TAP)] with 1,4-benzenedicarboxaldehyde yields the porous two-dimensional **COF-366-Co** (Figure 1.6).⁶⁰ When deposited on carbon electrodes, this COF shows stable CO₂ reduction activity for over 24 h in neutral aqueous electrolyte with a FE of 90% for CO at 550 mV overpotential. The initial TOF (TOF_{init}) and TON after 24 h (TON_{24h}) per electrochemically-active Co centers were 2,500 h⁻¹ and 34,000, respectively. These values represent a 4-fold improvement in activity compared with the molecular analog **Co(TAP)** (Figure 1.7). We hypothesized that increasing the COF pore size would facilitate mass transport to/from the active sites, so the pore-expanded **COF-367-Co** was prepared using biphenyl linkers. The greater porosity of **COF-367-Co** results in a TON_{24h} of 48,000 while maintaining 91% CO FE (Figure 1.7). Additional tunability was achieved with mixed-metal COFs, where a percentage of cobalt porphyrin sites are replaced with isostructural but inactive copper porphyrins (**COF-367-Co(10%)** and **COF-367-Co(1%)**, Figure 1.6). Dilution of the cobalt active sites with copper results in substantial improvements in TOF_{init} and TON_{24h} to 9,400 h⁻¹ and 296,000, respectively, with **COF-367-Co(1%)**, representing a 26-fold improvement in activity of the hybrid catalyst compared to purely molecular **Co(TAP)**. Moreover, X-ray absorption shows that the framework causes greater delocalization of the cobalt electron density. In this manner, the COF can be thought of as a materials analog of a redox non-innocent ligand.

We then rationalized that this materials framework would be sensitive to electronic modifications of the struts, and hence molecular design of these struts could be used to tune catalysis. Condensation of **Co(TAP)** with electron-rich or -deficient 1,4-benzenedicarboxaldehydes results in reticular, oriented COFs on a highly ordered pyrolytic graphite electrode (Figure 1.6).⁶¹ X-ray absorption shows that **COF-366-Co** has the most electron-rich cobalt centers, followed by **COF-366(OMe)₂-Co**, **COF-366(F)₄-Co**, and finally **COF-366-F-Co**. This unexpected trend was corroborated by cyclic voltammetry and demonstrates that electronic structure-function relationships from molecular chemistry do not always translate directly to extended materials. Investigating the electrocatalytic performance showed that the electron-deficient **COF-366-F-Co** has the greatest current density at 550 mV overpotential for CO

production. Recently, work by other labs have continued applying MOFs and COFs to photo- and electrochemical CO₂ conversion.⁶²⁻⁶⁶

Modulating Materials Catalyst Performance via Molecular Surface Coordination Chemistry. Gold nanoparticles (Au NPs) have been extensively studied for CO₂ reduction due to their high activity for CO production at relatively low overpotentials.⁶⁷ However, selectivity for CO₂ over proton reduction remains a challenge. Although efforts to improve catalyst efficiency through variation in size, shape, or defect sites have yielded valuable insights,⁶⁸⁻⁷⁰ a more modular molecular approach is desirable and complementary to these nanoscience approaches. We therefore sought to tune product selectivity through surface functionalization with NHC ligands, which can form robust bonds to gold.⁷¹⁻⁷⁶ We performed ligand exchange with a monodentate NHC, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, on oleylamine-capped Au NPs to afford functionalized **Au-Cb NP** (Figure 1.8A). A carbene-free control (**Au NP/C**) was prepared by loading Au NPs onto carbon black to prevent sintering then thermal annealing to remove oleylamine ligands. Electrolysis shows a consistent improvement in selectivity for CO production using **Au-Cb NP** compared to **Au NP/C** (Figure 1.9A), illustrating the synergy of binding non-catalytic molecules onto a materials catalyst.⁷⁷ For example, at 460 mV overpotential, **Au-Cb NP** gives 83% FE for CO compared to 53% for **Au NP/C** while also exhibiting a 7.6-fold increase in current density (Figure 1.9B). DFT calculations suggest that strong NHC-Au bonding can destabilize Au-Au bonding, leading to surface restructuring and an increase in defect sites with improved catalytic activity for CO₂ reduction.

The above example demonstrates that selectivity for materials catalysts can be tuned using surface-bound ligands, however, the long-term catalytic stability of **Au-Cb NP** is relatively poor. To address this, we applied a common strategy in coordination chemistry for preventing ligand dissociation—the chelate effect. A tridentate NHC ligand suitable for surface coordination was designed to reduce lability (Figure 1.8B).⁷⁸ Accordingly, palladium (**Pd**) foil electrodes were functionalized with the tridentate molecular ligand **timtmb**^{Me} and investigated for electrochemical CO₂ reduction under neutral, aqueous conditions. **Pd-timtmb**^{Me} electrodes display a pronounced increase in catalytic current compared to bare Pd foil, along with a 265 mV positive shift in onset potential (Figure 1.10A). Electrolysis reveals that bare **Pd** foil generates CO as the major carbon-containing product with less than 30% FE, whereas **Pd-timtmb**^{Me} generates formate with greater than 80% FE and only 4% FE for CO. The improved selectivity and current density for CO₂ reduction into formate was maintained for 6 h with the tripodal chelating ligand. When a control monodentate NHC ligand, **mimtmb**^{Me}, was used to functionalize the Pd surface (**Pd-mimtmb**^{Me}), the selectivity for C₁ products fell dramatically within 2 h, demonstrating the increased stability imparted by the chelation strategy (Figure 1.10B).

Integrating Biological, Molecular, and Materials Catalysts

In this final section, we summarize our efforts to integrate biological, molecular, and materials catalysts into hybrid platforms for the transformation of CO₂ into value-added products that are challenging to obtain with any one of these approaches alone. The hybrid catalyst approach to artificial photosynthesis enables separate optimization of key chemical steps in a given process, including light absorption, charge separation, transformation of electrical to chemical energy, and catalytic conversion.

Interfacing Biological Organisms with Materials Electrodes via Hydrogen as a Soluble Molecular Mediator. Integration of biological components into artificial photosynthetic schemes provides an attractive means to affect transformations that may be inaccessible using synthetic catalysts while taking advantage of the exquisite selectivities, high rates, and energetic efficiencies of enzymes. Many efforts domain have focused on attaching enzymes to electrodes,^{13,79-84} which has merits where good stability and electrical contact can be achieved outside the protective cell environment. A complementary approach uses whole-cell chemotrophic organisms that can interface with an electrode either *via* direct electron transfer⁸⁵⁻⁸⁷ or the intermediacy of a soluble electron carrier.⁸⁸⁻⁹² The bacterium *Ralstonia eutropha* is a popular host in this regard, with wildtype and engineered strains generating poly-hydroxybutyric acid⁹² and C₃-^{91,92} or C₄+ alcohols,^{89,92} respectively. However, the requisite aerobic growth environment for *R. eutropha* can present incompatibilities with reductive electrochemical conditions (poor FE, generation of reactive oxygen species, and explosion hazards with H₂).

In work with the M. Chang laboratory, we identified the obligate anaerobe *Methanosarcina barkeri*, a methanogen that reduces CO₂ to CH₄, as an organism to interface with H₂-generating (photo)electrodes without genetic modification (Figure 1.11A).⁹⁰ Conceptually, this work mimics photosynthesis by performing light harvesting and dark CO₂ fixation reactions separately. Specifically, we couple a materials catalyst as an artificial hydrogenase to convert electrical current into a molecular chemical reductant (H₂), then use this reductant for a biological CO₂ fixation scheme. Because the electrons can come from a number of sustainable energy sources, this bio-inorganic platform serves a single-cell version of the multi-cellular leaf but is not limited by the source of energy from sunlight.

Using a two-chamber electrochemical cell (Figure 1.11B), a culture of *M. barkeri* was added to the catholyte to use reducing equivalents from the electrogenic H₂ to reduce CO₂ to CH₄. Galvanostatic electrolysis using a platinum cathode as a materials H₂ evolution catalyst showed sustained production of CH₄ over 3 days with 74-86% FE depending on current (Figure 1.11C). A 7-day electrolysis demonstrated the long-term ability of a single culture to generate CH₄ with no loss in performance, requiring only replenishment of the CO₂ atmosphere every 24 hours. Inspired by nickel-dependent hydrogenases, we prepared nanoparticulate nickel sulfide as an economical replacement for the platinum electrode and observed comparable CH₄ generation, although ~300 mV larger overpotential was required for similar current density. Finally, we demonstrated photoelectrochemical and fully light-driven CH₄ generation using visible irradiation and single- or tandem photoelectrodes. Taken together, this hybrid system harnesses the individual strengths of light absorption and charge separation by synthetic electrodes and photoelectrodes, efficient H₂

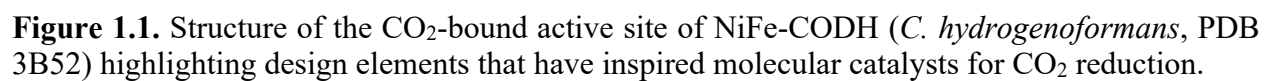
evolution catalysis, and multi-step reduction cascades near their thermodynamic potential enabled by the enzymes in a living, recyclable biocatalyst.

Molecular Cages Assembled at Materials Surfaces as Biomimetic Active Sites. In a final example, we sought to utilize biological principles to construct new molecular-material interfaces for carbon fixation, with an eye toward producing C-C coupled products. In this context, compared to the numerous strategies for conversion of CO₂ to CO, approaches for further reduction of CO remain underdeveloped. Copper electrodes show promise in this area due to their unique ability to generate ethylene, ethanol, acetate, propanol, and other reduced multi-carbon products.^{93,94} These studies and others^{12,95-98} have demonstrated the importance of surface structure and the electrode-electrolyte interface in determining product selectivity. However, control of the surface morphology and subsequent effects on selectivity remain difficult to predict.¹²

To address some of these challenges, we sought to apply the rational tunability of molecular chemistry and second-sphere design elements from biology to a heterogeneous polycrystalline copper electrode for CO reduction.⁹⁹ Specifically, tetrapodal porphyrins were used to form self-assembled monolayers of supramolecular cages on the copper surface (Figure 1.12A), where the porous structure maintains the ability of reactants to access the electrode. This platform offers the permanent porosity of MOFs/COFs/POCs by taking advantage of the chelate effect and directly coupling the molecular cavity to an electrically-active materials surface. Indeed, the FE for CO reduction to acetate and ethanol in 0.1 M KOH is dramatically enhanced at low overpotentials on cage-functionalized copper surfaces compared to bare copper. Furthermore, acetate and ethanol yields show a dependence on the length of the linker joining the porphyrin to the surface (Figure 1.12B), indicating that product selectivity is driven in part by differences in the molecular environment above the metal surface. Amides in the linkers have the potential to interact with surface-bound intermediates *via* hydrogen bonding akin to an enzyme. Further tunability can be achieved through metallation of the porphyrin units to create bimetallic active sites reminiscent of redox enzymes including cytochrome *c* oxidase. Under optimized conditions at -0.4 V vs. RHE, iron-containing cages show the highest selectivity for C₂ products (57% ethanol, 24% acetate, and 2% ethylene) (Figure 1.12C). This work demonstrates how bioinspired molecules featuring enzyme-like cavities, hydrogen bond donors, and auxiliary metal sites can work synergistically with a heterogeneous metal surface to promote selective CO reduction that cannot be accomplished with any individual design strategy.

Conclusion

Artificial photosynthesis is a promising approach for storing renewable energy in chemical bonds, and the challenge of simultaneously optimizing activity, stability, selectivity, and energetic efficiency necessitates the development of improved catalysts. This chapter has summarized our progress in merging design elements from molecular, materials, and biological systems to better facilitate electrochemical carbon fixation. Our findings exemplify how these traditional fields of catalysis can be synergistically coupled to yield next-generation platforms. Moving forward, we envision that the broader use of synergistic design will advance basic and translational research for sustainable synthesis by judiciously combining components of the three major fields of catalysis: homogeneous/molecular, heterogeneous/materials, and biological. In addition to new catalyst design, mechanistic studies to inform design strategies involving pre-bending of CO₂, relative positioning of intermediates along the catalytic cycle, and how confinement and supramolecular effects can influence catalyst speciation remain at the forefront of this growing area of research.



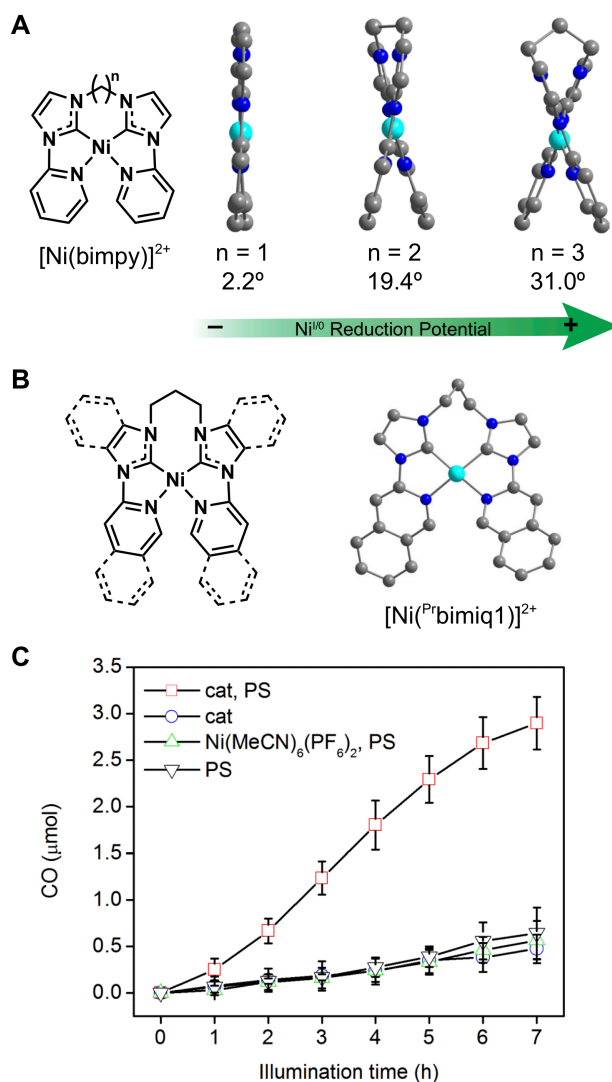


Figure 1.2. (A) First-generation $[\text{Ni}(\text{Rbimpy})](\text{PF}_6)_2$ complexes showing an increased flexibility as the bridgehead linker is increased. (B) Second-generation complexes with expanded π -systems, with $[\text{Ni}(\text{Prbimiq1})](\text{PF}_6)_2$ shown as the optimized structure. (C) Photocatalytic CO_2 -to-CO conversion in acetonitrile containing 0.07 M triethylamine using 0.2 μM cat, $[\text{Ni}(\text{Prbimiq1})](\text{PF}_6)_2$, in the presence or absence of 0.2 mM photosensitizer, PS, $\text{Ir}(\text{ppy})_3$.

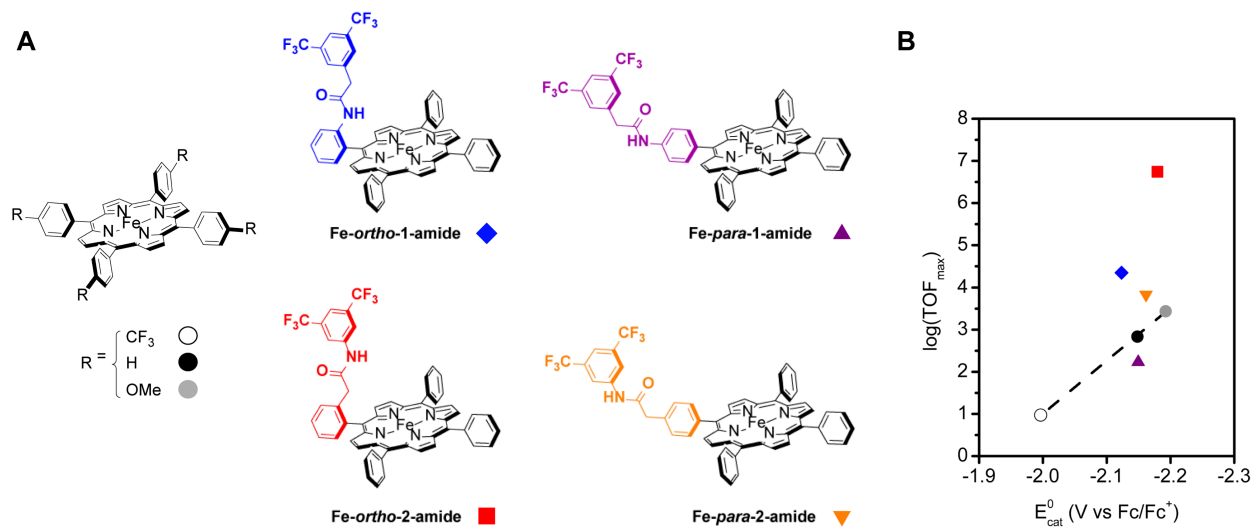


Figure 1.3. (A) Four isomers of amide-functionalized iron tetraphenylporphyrins, along with electronic control porphyrins. (B) Correlation between $\log(\text{TOF}_{\text{max}})$ and E_{cat}^0 for amide-functionalized porphyrin catalysts and electronic control porphyrins. TOF_{max} values were determined in DMF with 100 mM phenol and 0.23 M CO_2 . **Fe-ortho-2-amide** with proper placement of the hydrogen-bond pendant exhibits the greatest breaking of electronic scaling relationships.

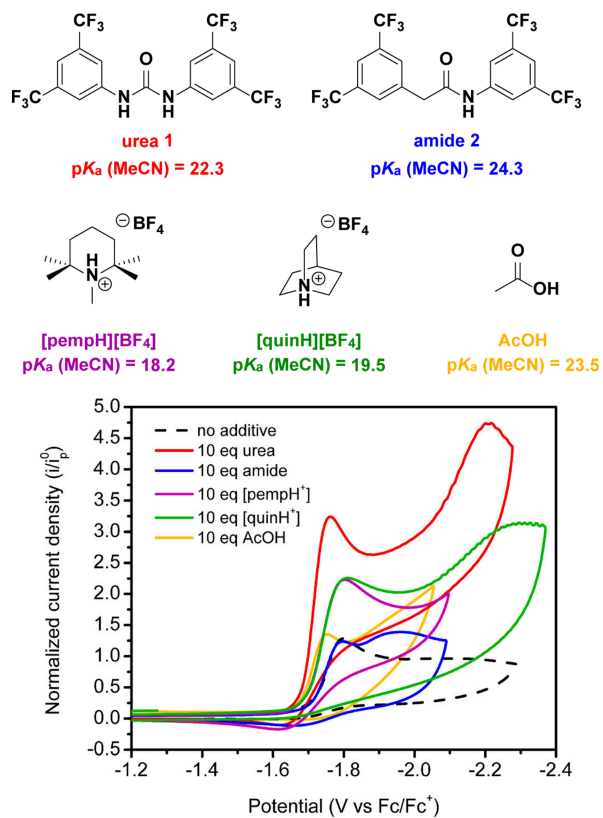


Figure 1.4. Catalytic CV responses of [Ni(cyclam)][PF₆]₂ (1 mM) under CO₂ in the presence of 10 equiv of each additive in 0.1 M TBAPF₆ in MeCN showing the improved effect of two-point binding. Current has been normalized to i_p^0 , the peak current under Ar.

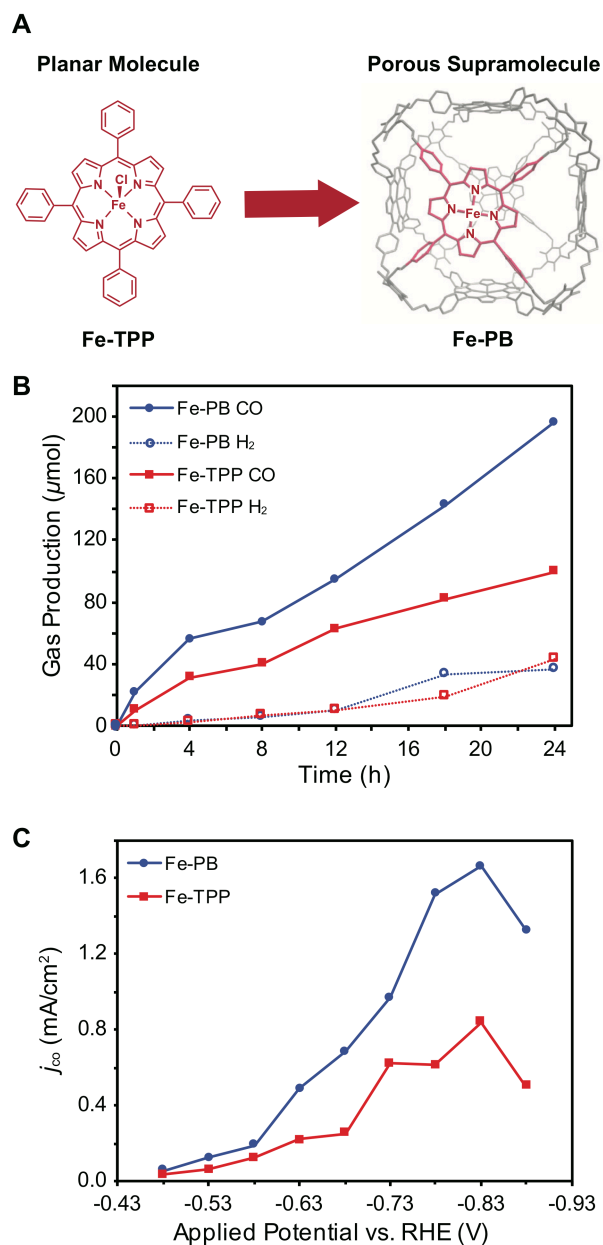


Figure 1.5. (A) Structures of **Fe-TPP** and **Fe-PB**, which features a permanent pore. (B) Gas production over 24 h at -0.63 V vs. RHE in pH 7.3 0.5 M aq. KHCO_3 saturated with CO_2 . (C) CO specific current densities for 1 h electrolyses. The porous **Fe-PB** supramolecule outperforms **Fe-TPP** by increasing electrical contact and providing a porous pocket for greater substrate access.

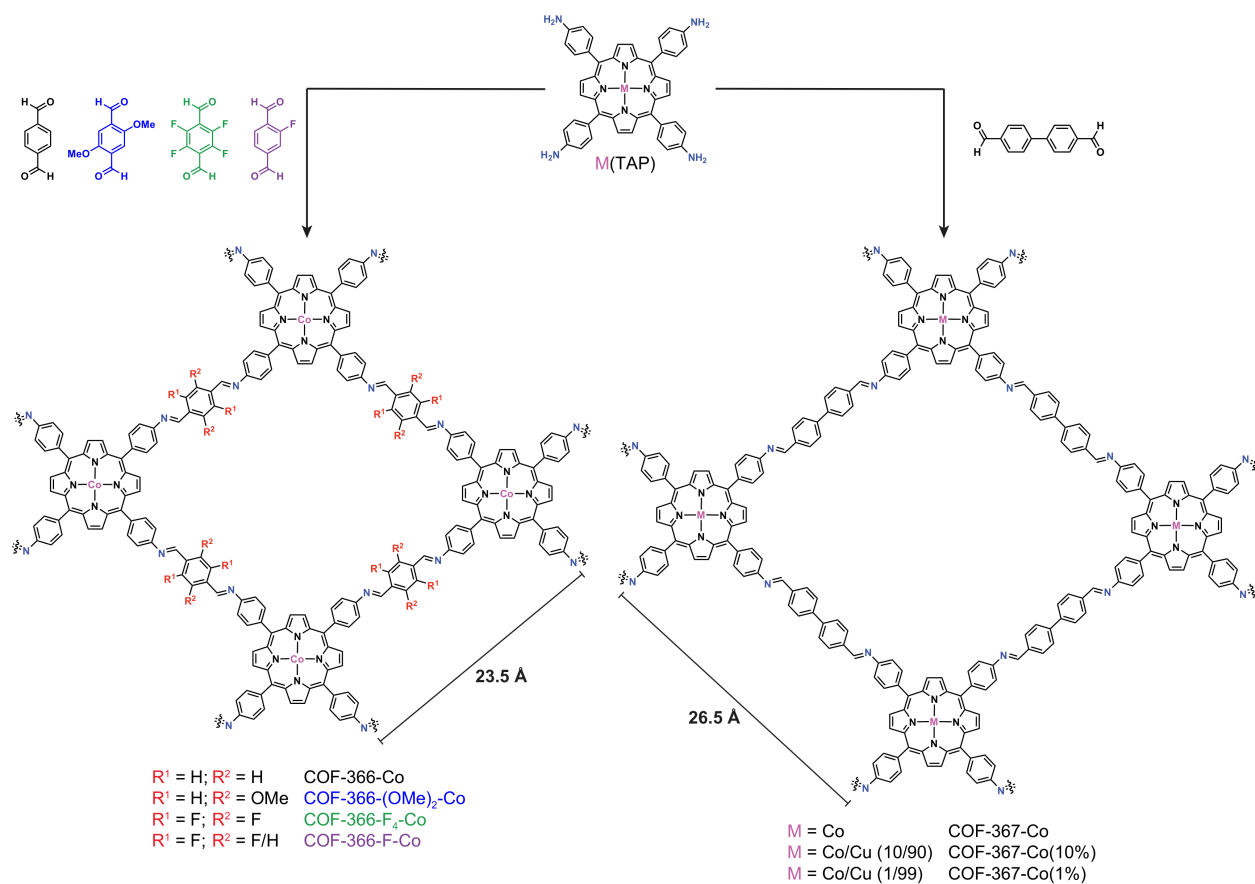


Figure 1.6. Incorporation of molecular cobalt porphyrin catalysts into heterogeneous **COF-366** and **COF-367** derivatives with various linkers to control the framework electronics and porosity.

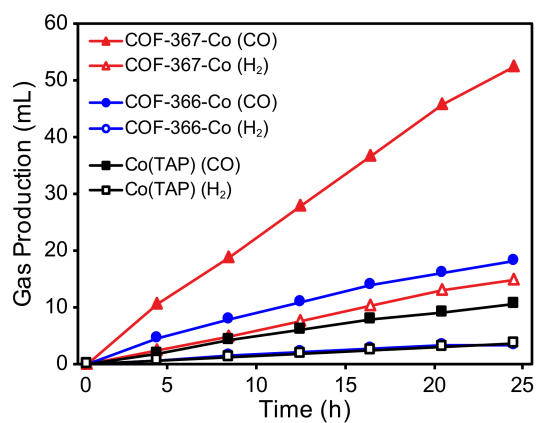


Figure 1.7. CO and H₂ generation by **COF-367-Co**, **COF-366-Co**, and **Co(TAP)** during 24 h electrolyses at -0.67 V vs. RHE in pH 7.3 0.5 M aq. KHCO₃ saturated with CO₂.

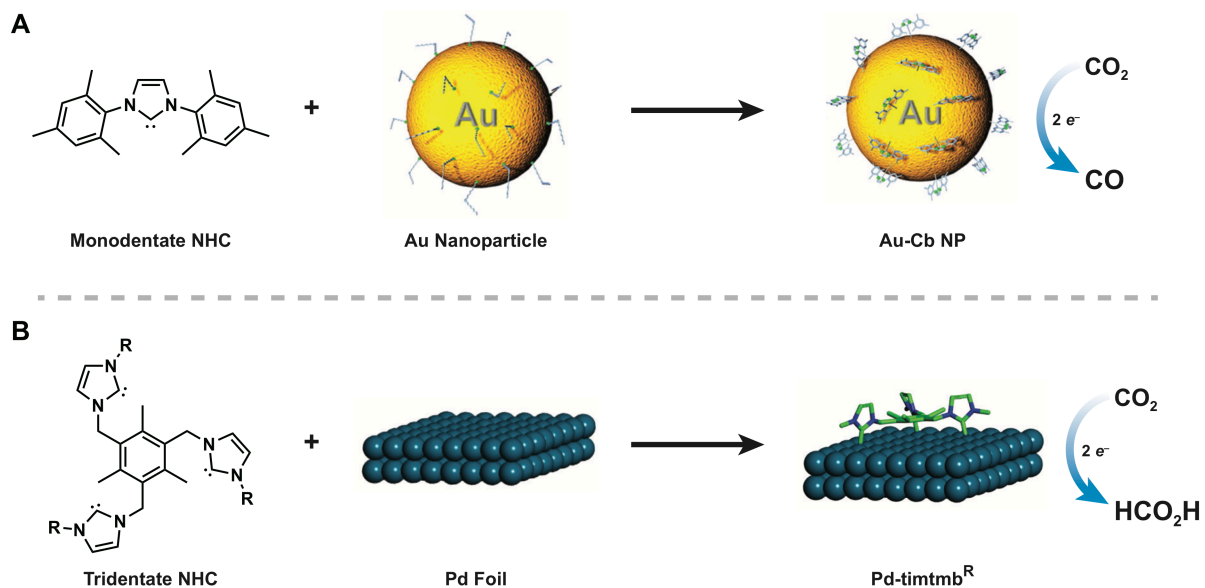


Figure 1.8. (A) Monodentate NHC coordination to Au nanoparticles for CO_2 reduction into CO, and (B) tridentate NHC coordination to Pd foil for CO_2 reduction into formate, highlighting the ability of ligands to tune product selectivity of materials catalysts.

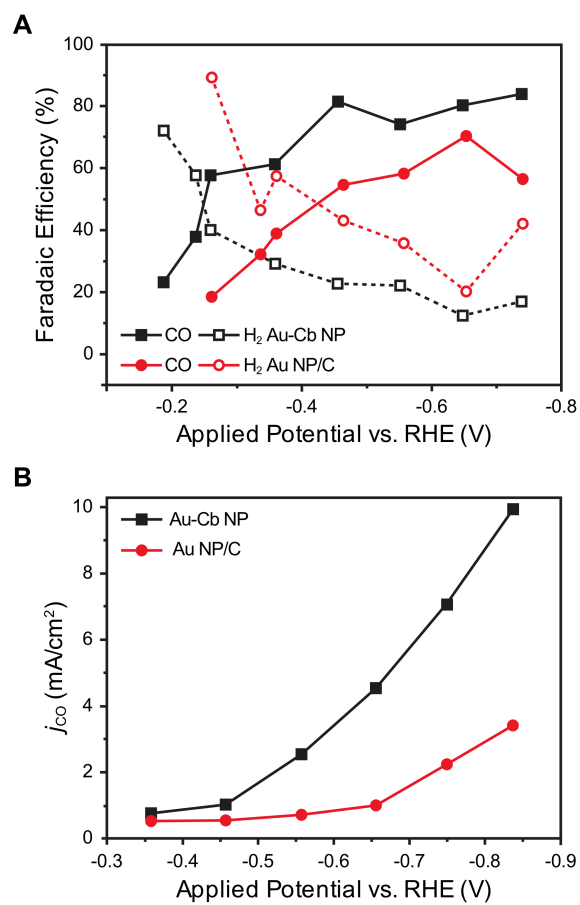


Figure 1.9. (A) FEs for CO and H₂ over a range of applied potentials, and (B) CO specific current densities for carbene-functionalized and unfunctionalized Au NPs.

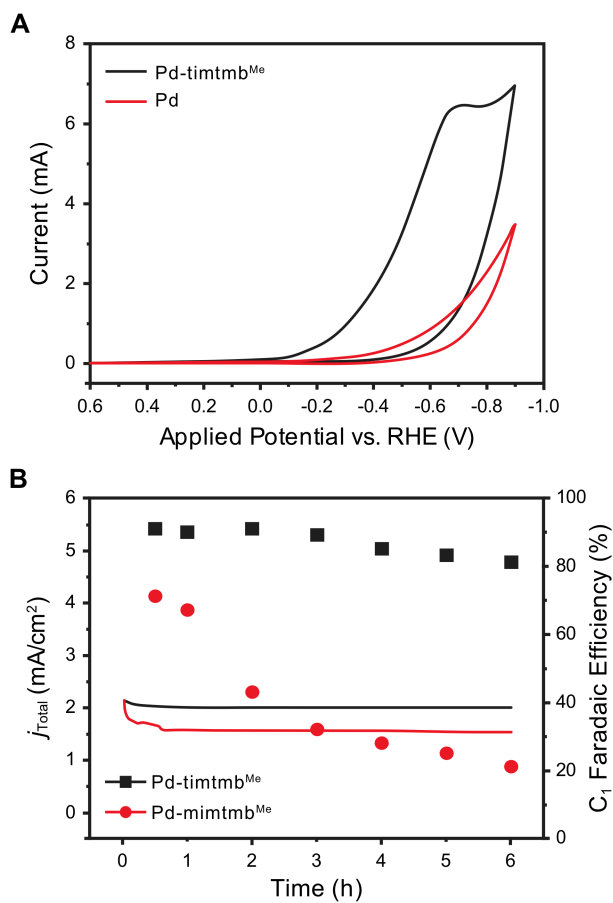


Figure 1.10. (A) CVs of bare Pd foil and Pd foil functionalized with the tridentate ligand **timtmb**^{Me}. (B) Long term electrolyses at -0.57 V vs. RHE in 0.5 M aq. KHCO₃ saturated with CO₂ showing the current density and FE for CO + formate.

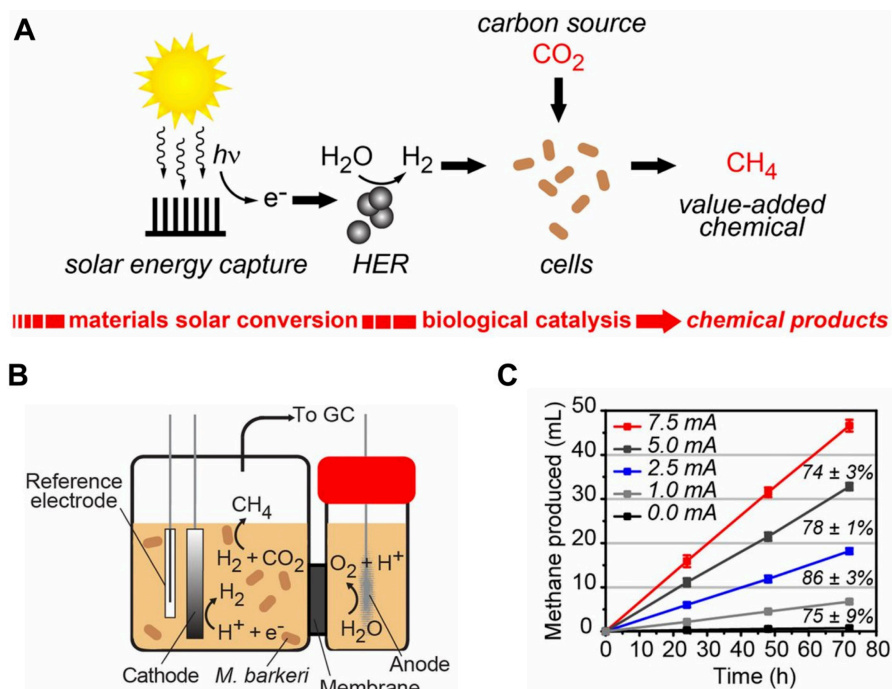


Figure 1.11. (A) General schematic illustrating integration of a (photo)electrode with biological catalysis for CO₂ reduction. (B) Electrolytic cell used for H₂ evolution at an electrode and subsequent CO₂ reduction to CH₄ by *M. barkeri*. (C) Cumulative CH₄ generated and associated FEs at various controlled currents. This hybrid catalyst system enables efficient product generation by integrating an artificial hydrogenase with a living biocatalyst.

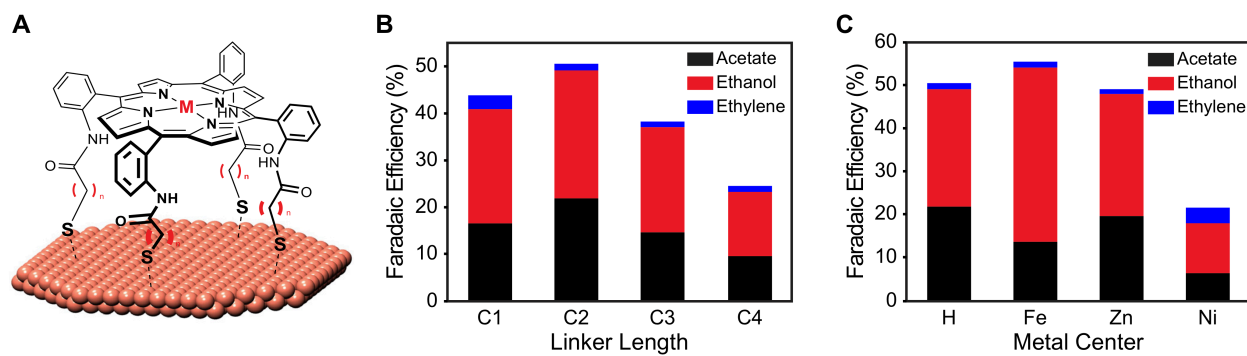


Figure 1.12. (A) Schematic of the molecular porphyrin cage on a copper surface illustrating the variable linker lengths and metal center in the porphyrin ligand. FEs for CO reduction at -0.55 V vs. RHE as a function of (B) linker length with $M=H$ or (C) metal ion incorporation with C2 linker lengths.

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Chapter 2

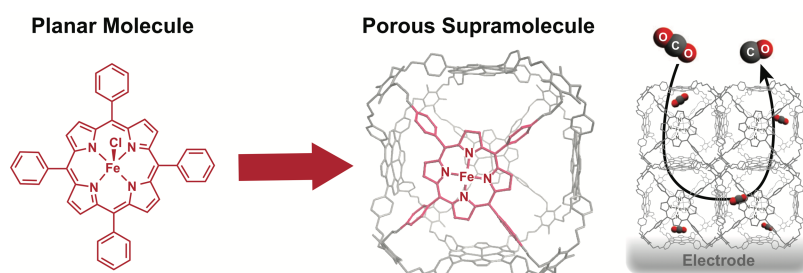
Iron Porphyrins Embedded into a Supramolecular Porous Organic Cage for Electrochemical CO₂ Reduction in Water

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Abstract

We report the use of a porous organic cage composed of six iron tetraphenylporphyrins as a supramolecular catalyst for electrochemical CO₂-to-CO conversion. This strategy enhances active site exposure and substrate diffusion relative to the monomeric catalyst, resulting in CO generation with near-quantitative Faradaic efficiency in pH 7.3 water, with activities reaching 55,250 turnovers. These results provide a starting point for the design of supramolecular catalysts that can exploit the properties of the surrounding matrix yet retain the tunability of the original molecular unit.



Introduction

The previous chapter introduced the concept of merging molecular and materials design elements in the form of supramolecular cage catalysts. Here, we provide further detail on the design and synthesis of this porphyrin box hybrid catalyst platform, and we demonstrate catalytic activity for CO₂ reduction. This work opens up applications in electrocatalysis that have not been explored using porous organic cages.

Electrochemical CO₂ reduction is an attractive approach to developing energy-efficient CO₂ fixation processes, but such systems necessitate selective product generation over long-term electrolysis at low overpotential.¹ In this context, water is an abundant and benign proton source for CO₂ reduction; however, it can promote catalyst degradation and off-target H₂ evolution. Materials catalysts can exhibit aqueous compatibility, but often are difficult to tune for selectivity due to shortcomings in molecular-level control.²⁻⁵ Homogeneous molecular catalysts can reduce CO₂ into value-added products such as CO⁶⁻¹⁰ yet often require organic solvent. CO₂ reduction by water-soluble catalysts is rare,^{11,12} but methods for catalyst immobilization¹³⁻¹⁶ or deposition¹⁷⁻²³ onto an electrode can permit the use of aqueous electrolytes. As such, we have initiated a program using multiple approaches for electrochemical carbon fixation that integrate tunable molecular catalysts into hybrid materials to endow aqueous stability and to organize catalysts at the electrode so as to encourage productive interactions with the substrate.²⁴⁻²⁷

Against this backdrop, we were inspired by supramolecular vessels for catalysis wherein control of the spatial arrangement of both catalyst and substrate is emphasized.²⁸⁻³⁴ In this group, porous organic cages (POCs) are unique hybrid structures that combine molecular tunability and solubility with materials-like structural porosity.³⁵⁻³⁷ These cages are built from subunits connected through covalent linkages to form an inner cavity without the high charge buildup associated with metal-templated vessels³⁸ that could complicate electrochemical behavior, making such applications rare,^{39,40} especially in electrocatalysis.³⁴ POCs can possess large surface areas,^{41,42} exhibit high chemical stability,⁴²⁻⁴⁵ and be easily processed due to their solubility.⁴⁶ Advances in POC synthesis have enabled applications in host-guest chemistry,^{47,48} gas uptake and separation,⁴⁹ nanoparticle synthesis,^{50,51} porous additives in materials,⁵² liquids,^{53,54} and cell membranes,⁵⁵ as well as building blocks in extended frameworks⁵⁶ and polymers.⁵⁷

Here, we install iron tetraphenylporphyrin (**Fe-TPP**), an established catalyst for the electroreduction of CO₂ to CO, into a rhombicuboctahedral POC to increase the electrochemically active surface area and facilitate mass transport (Scheme 2.1). The porphyrin box (**PB**) was synthesized by condensing six tetraformylphenylporphyrins and eight triamine linkers.⁵⁵ The chloroiron(III) porphyrin box (**Fe-PB**) was next obtained using FeBr₂ and 2,6-lutidine then treating with aq. NaCl (Figure 2.1A). Complete metalation was verified using UV/Vis spectroscopy and MALDI mass spectrometry, and ¹H NMR spectroscopy shows that the POC symmetry is conserved after metalation (Figures 2.4-2.7). These data are consistent with previously reported crystal structures of this porphyrin box architecture.^{42,55}

Results and Discussion

The porosity of **Fe-PB** was probed with gas sorption studies. Figure 2.1B depicts CO₂ sorption isotherms for **Fe-PB** powder samples at 273 and 298 K. **Fe-PB** exhibits 5.85 wt% CO₂ uptake at 273 K, and 3.67 wt% at 298 K. Unusually, N₂ sorption at 77 K is linear, but CO₂ sorption at 195 K allows for estimation of the Brunauer–Emmett–Teller (BET) surface area as 490 m²/g (Figure 2.8), which is comparable to many porous organic molecular solids.⁵⁸ We hypothesize that this porosity can facilitate diffusion of CO₂ to the catalytic active sites within **Fe-PB**.

Cyclic voltammetry (CV) of **Fe-PB** in *N*-methyl-2-pyrrolidinone (NMP) shows three redox waves at -0.62, -1.52, and -2.11 V vs. ferrocene/ferrocenium (Fc/Fc⁺) assigned to the formal Fe^{III}/Fe^{II}, Fe^{II}/Fe^I, and Fe^I/Fe⁰ couples, respectively (Figure 2.9). These redox features closely resemble **Fe-TPP**, indicating little difference in the electronic structure of the metalloporphyrins. Scan rate dependence studies of the Fe^{II}/Fe^I wave, which is unaffected by changes in ligand coordination and residual proton reduction, indicate that **Fe-PB** is freely diffusing (Figure 2.10). At more negative potentials, an irreversible reduction of the ligand is observed, similar to **Fe-TPP** (Figure 2.11). After saturation with CO₂ and addition of 1 M phenol as an acid source, the Fe^I/Fe⁰ wave becomes an intense, irreversible peak as shown in Figure 2.2A, suggesting the catalytic reduction of CO₂. Titration of phenol reveals that the rate of catalysis is proton dependent (Figure 2.12).

We next extended this CO₂ reduction activity to aqueous conditions by depositing **Fe-PB** onto a glassy carbon electrode that was first coated with carbon nanotubes. CV scans of heterogeneous **Fe-PB** in 0.5 M aq. KHCO₃ (pH 7.3) electrolyte under N₂ show weak redox waves at 0.28 V and -0.33 V vs. the reversible hydrogen electrode (RHE) (Figure 2.2B). At potentials more negative than -0.75 V vs. RHE a large cathodic current is observed due to H₂ evolution. After saturation with CO₂, there is a more dramatic current increase as well as a positive shift of the onset potential, suggesting catalytic CO₂ reduction. We compared **Fe-TPP** as a control catalyst, depositing six-molar equivalents of **Fe-TPP** compared to **Fe-PB** onto the electrode in order to normalize to the total number of iron centers. CVs also suggest CO₂ reduction by this monomeric catalyst; however, the lower current intensities observed for **Fe-TPP** compared to **Fe-PB** indicate an inferior catalytic response for the former.

To further elucidate the impact of the high surface area structure on the subsequent catalytic performance, we measured electroactive surface areas of the heterogeneous electrodes. Figure 2.2C-D shows the scan rate dependence of the Fe^{II}/Fe^I reduction for **Fe-PB** and **Fe-TPP**. Both electrodes were constructed by depositing 6.78 nmol/cm² of iron onto the electrode surface, corresponding to 1.13 nmol/cm² of **Fe-PB** and 6.78 nmol/cm² of **Fe-TPP**. Plots of the peak current versus scan rate gave linear relationships (Figure 2.14), indicating catalyst immobilization and allowing calculation of the number of electrochemically active iron centers (EA-Fe). The **Fe-PB** electrode displayed 3.7 nmol EA-Fe/cm², whereas the **Fe-TPP** electrode only had 2.5 nmol EA-Fe/cm². This value corresponds to 54% of iron sites being active in **Fe-PB** compared to only 38% in **Fe-TPP**. The larger percentage of EA-Fe in the **Fe-PB** electrode is indicative of the surface area afforded by the permanently porous cage, which likely deters the aggregation of flat porphyrin molecules that can lead to inactive catalysts due to poor electron transfer or limited substrate/electrolyte accessibility.

Controlled potential electrolyses (CPEs) were then performed in 0.5 M aq. KHCO_3 saturated with CO_2 revealing CO and H_2 as the only detectable reduction products (Figure 2.16-2.18). The highest CO: H_2 selectivities after 1 h were observed at an applied potential of -0.63 V vs. RHE, corresponding to an overpotential of 510 mV (Figure 2.3A). For **Fe-PB**, CO was generated with $100 \pm 2\%$ (average of three replicates) Faradaic efficiency (FE) and just $2 \pm 1\%$ FE for H_2 . For **Fe-TPP**, CO and H_2 were produced with $96 \pm 3\%$ and $6 \pm 2\%$ FEs, respectively. Electrodes prepared without catalyst or with free-base **PB** yielded H_2 with $>97\%$ FE after 24 h CPEs (Figure 2.19-2.22). **Fe-PB** generated 200 μmol of CO after 24 h electrolysis at -0.63 V vs. RHE, double that of **Fe-TPP**, and the CO FE was more stable over long-term CPEs, dropping only to 85% compared to 70% for **Fe-TPP** (Figure 2.3B-C). Furthermore, **Fe-PB** exhibited a turnover number per electroactive iron (TON) of 6,280 after 1 h, corresponding to a turnover frequency (TOF) of 1.74 s^{-1} , and a TON of 55,250 after 24 h ($\text{TOF} = 0.64 \text{ s}^{-1}$).⁵⁹ In contrast, **Fe-TPP** attained a TON of 3,380 after 1 h ($\text{TOF} = 0.94 \text{ s}^{-1}$), and a TON of 32,770 after 24 h ($\text{TOF} = 0.38 \text{ s}^{-1}$). The larger TON and TOF values for **Fe-PB** support that our supramolecular approach more efficiently exposes catalytic sites and show that **Fe-PB** is one of the most efficient molecular catalysts for CO_2 reduction in heterogeneous aqueous conditions (Table 2.6). Both **Fe-PB** and **Fe-TPP** exhibit slight decreases in TOF and current density after extended CPEs that may be attributed to catalyst deactivation or detachment. However, CO production continues at an enhanced rate for **Fe-PB** versus **Fe-TPP**, and MALDI-MS, UV/Vis and CV analysis of **Fe-PB** after 24 h CPE do not indicate degradation of the supramolecular catalyst (Figure 2.23). Further optimizing electrode construction may thus increase performance.

Interestingly, the CO specific current density for **Fe-PB** was consistently larger than that for **Fe-TPP**, yet Tafel analysis suggests that the mechanism for CO_2 reduction by **Fe-TPP** does not change significantly after being embedded into the supramolecular **Fe-PB** (Figure 2.3D-E). Tafel slopes of 165 and 175 mV/decade are similar to each other and slightly higher than the 118 mV/decade slope expected for rate-limiting single-electron transfer from **Fe-PB** or **Fe-TPP** to CO_2 , therefore either adsorption of CO_2 or desorption of CO are also rate-limiting.^{21,22} Also, the difference in CO specific current density becomes larger at higher overpotentials where mass transport is a limiting factor for catalysis, further indicating that the porosity of **Fe-PB** facilitates CO_2 diffusion towards active sites. These results are consistent with the notion that the greater exposure of iron sites observed in the POC **Fe-PB** catalyst as well as the potentially greater diffusion and local concentration of CO_2 in the hydrophobic cavity are primarily responsible for the enhanced catalysis. Figure 2.3F depicts the proposed mechanism by which **Fe-PB** facilitates diffusion of substrate and electrolyte throughout an array of readily accessible catalytic metal centers as opposed to aggregation of planar **Fe-TPP** molecules that can diminish the number of electrochemically accessible and active metal centers.

Conclusion

In summary, we have applied a POC platform containing iron porphyrins to CO₂ reduction catalysis. In pH 7.3 aqueous conditions, CO is generated with near-quantitative selectivity by the **Fe-PB** supramolecular catalyst. The porous architecture of **Fe-PB** results in a higher percentage of electroactive iron centers in the cage hybrid compared to the monomeric metalloporphyrin, facilitating CO production with superior rate, current density, and longevity. Embedding the **Fe-TPP** unit within the POC does not significantly alter the mechanism, suggesting that POC architectures can enhance catalysis while retaining the properties of the original building block. We anticipate that the ease of processing and potential modularity of this approach will open up more applications for POCs in catalysis.

Materials and Methods

General Methods. All reagents and solvents were purchased from commercial sources and used without further purification unless specified. Carbon dioxide (99.99%), carbon monoxide (99.5%), hydrogen (99.999%), ethylene (99.9%), argon (99.999%) and nitrogen (99.998%) were purchased from Praxair. Multi-walled carbon nanotubes (MWCNTs), anhydrous *N*-methyl-2-pyrrolidinone (NMP), *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB), and electrochemical grade *n*Bu₄NPF₆ were purchased from Sigma-Aldrich and used as received. 2,6-Lutidine was purchased from Sigma-Aldrich and dried over AlCl₃ then purified by distillation. Tetraphenylporphyrin iron(III) chloride and FeBr₂ were purchased from Strem Chemicals and used as received. The free-base **PB** was synthesized and characterized as previously described.⁵⁵ THF and CH₃CN were dried using a JC Meyer solvent purification system. Deionized water was obtained from a Millipore Autopure system. UV/Vis spectra were collected using an Agilent Cary 60 spectrophotometer at room temperature. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry spectra were obtained using an Applied Biosystems Voyager DE Pro at the QB3 Mass Spectrometry Facility at the University of California, Berkeley. FT-IR spectra were collected using a Bruker ALPHA-P spectrometer. NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz. Chemical shifts for ¹H spectra are reported in ppm relative to residual protiated solvent.

Gas Sorption Measurements. Gas sorption isotherms of **Fe-PB** were measured with an Autosorp-iQ volumetric adsorption analyzer. Typically, a sample of as-synthesized material (~30 mg) was loaded and, prior to the measurements, residual solvents were evacuated by heating to 100 °C under high vacuum (10⁻² Pa) overnight. Sorption isotherms were measured for nitrogen using liquid nitrogen (for 77 K) and for CO₂ using a dry-ice/acetone dewar (for 195 K) or a chiller circulator dewar (for 273 and 298 K).

Cyclic Voltammetry. Cyclic voltammetry experiments were performed using either a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat or a CH Instruments, Inc. 600E potentiostat.

Aqueous voltammetry studies were performed with a three-electrode cell equipped with a glassy carbon disk (3.0 mm diameter) working electrode (BASi), a platinum wire counter electrode, and a Ag/AgCl reference electrode. The electrolyte used was 0.5 M aq. KHCO₃ prepared as previously described²⁴ and saturated with either CO₂ or N₂ at 1 atm. No iR compensation was applied. The Ag/AgCl (sat. KCl) reference electrode was externally calibrated to potassium ferricyanide in 0.5 M aq. KHCO₃ saturated with CO₂ at pH 7.3.

For organic homogeneous electrochemistry, a three-electrode cell equipped with a glassy carbon disk (3.0 mm diameter) working electrode, a platinum wire counter electrode, and a Ag wire in a porous Vycor tipped glass tube filled with electrolyte as a pseudo-reference electrode. The electrolyte was 0.1 M *n*Bu₄PF₆ in NMP or CH₃CN freshly prepared with anhydrous solvent and saturated with either CO₂ or N₂ at 1 atm. Cyclic voltammograms were obtained after iR compensation. Potentials were subsequently referenced against ferrocene/ferrocenium used as an internal standard.

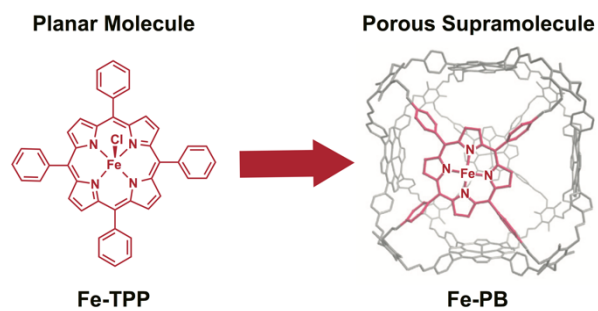
Preparative Scale Electrolysis. Controlled potential electrolyses were performed using either a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat or a CH Instruments, Inc. 600E potentiostat. A custom-made three-piece glass electrochemical cell was used, including a working compartment body, a working compartment lid, and a counter compartment body. A cation exchange membrane (Nafion 117) separates the working electrode and Ag/AgCl (sat. KCl) reference electrode from the graphite counter electrode. This experimental setup has been described elsewhere.^{24,27,60,61} The electrolyte used was 0.5 M aq. KHCO_3 prepared as previously described²⁴ and sparged with CO_2 for 15 min immediately before electrolysis. No iR compensation was applied. Once assembled, an internal standard of 1 mL ethylene was injected into the headspace for GC analysis. Electrolysis was then performed at a constant potential for a specified amount of time. After this period, the headspace was immediately analyzed by GC, and the amount of gas generated was determined on the basis of the internal standard and from calibration curves plotted from injecting known amounts of CO , H_2 , and ethylene into the GC (Figure 2.26-S2.27). Gas production was measured on an SRI gas chromatography instrument (model #8610C) equipped with a Haysep D column (1/8" $\times$ 6') and a 13X Mol Sieve column (1/8" $\times$ 6'). Ethylene was used as an internal standard. Carbon monoxide was quantified using flame ionization detector (FID) equipped with a methanizer and hydrogen was quantified using a thermal conductivity detector (TCD). No liquid products were detected by ^1H NMR.

Preparation of Working Electrodes. For cyclic voltammetry experiments, a glassy carbon (GC) disk electrode (0.071 cm^2) was thoroughly polished with 0.5 μm alumina powder, rinsed with isopropanol, and dried in air. To increase conductivity, a dispersion of MWCNTs in *i*PrOH (1 mg/mL) was sonicated for 20 min, and then 10 μL was slowly deposited onto the 3 mm diameter GC electrode and dried in air. Then, either 7.1 μL of a **Fe-PB** solution in THF (0.1 mg/mL) or 6.8 μL of a **Fe-TPP** solution in THF (0.05 mg/mL) was deposited on top of the MWCNT/GC electrode and allowed to dry in air. This preparation results in 0.14 mg/cm^2 of MWCNTs and either 0.01 mg/cm^2 (1.13 nmol/cm^2) of **Fe-PB** or 0.005 mg/cm^2 (6.78 nmol/cm^2) of **Fe-TPP**.

For controlled potential electrolyses, a glassy carbon plate electrode (2.25 cm^2) was thoroughly polished with 0.5 μm alumina powder, rinsed with isopropanol, and dried in air. A dispersion of MWCNTs in *i*PrOH (2 mg/mL) was sonicated for 20 min, and then 190 μL was slowly deposited onto the GC plate electrode and thoroughly dried in air. Then, either 225 μL of a **Fe-PB** solution in THF (0.2 mg/mL) or 214 μL of a **Fe-TPP** solution in THF (0.1 mg/mL) was deposited on top of the MWCNT/GC electrode and allowed to dry in air. This electrode was then thoroughly rinsed with *i*PrOH, H_2O , and 0.5 M aq. KHCO_3 , and then dried in air again. This preparation results in 0.17 mg/cm^2 of MWCNTs and either 0.02 mg/cm^2 (2.26 nmol/cm^2) of **Fe-PB** or 0.01 mg/cm^2 (13.56 nmol/cm^2) of **Fe-TPP**.

Synthesis of Fe-PB. In a dry glovebox with a dinitrogen atmosphere, a 100 mL two-neck flask equipped with a condenser was charged with free-base **PB** (28 mg, 3.4 μmol), FeBr_2 (72.5 mg, 0.340 mmol, 100 equiv.), and THF (45 mL). Outside the glovebox, 2,6-lutidine (12 μL , 0.10 mmol, 30 equiv.) was injected under N_2 , and the mixture was heated at 70 $^\circ\text{C}$ for 12 h. After cooling to room temperature, the reaction was opened to air, and the solvent was removed under reduced pressure. The brown residue was taken up in CH_2Cl_2 (50 mL), washed with water (4 $\times$ 50 mL), and then with saturated $\text{NaCl}_{(\text{aq})}$ (2 $\times$ 50 mL). The organic layer was separated, additional saturated $\text{NaCl}_{(\text{aq})}$ (100 mL) was added, and the mixture was vigorously stirred for 30 min. The organic layer

was decanted and dried over anhydrous Na_2SO_4 . Solvent was removed under reduced pressure, and the dark brown residue was dried *in vacuo*. Next, Et_2O (20 mL) was added, and after sonicating for 1 min, the product was recovered by vacuum filtration and washed with additional Et_2O (3 x 5 mL). **Fe-PB** was obtained as a brown powder (25 mg, 84% yield). MALDI-MS (matrix: DCTB) m/z calcd. for $\text{C}_{552}\text{H}_{624}\text{Cl}_5\text{Fe}_6\text{N}_{48}\text{O}_{24}$ $[\text{M} - \text{Cl}]^+$: 8826.38, found: 8826.84, m/z calcd. for $\text{C}_{552}\text{H}_{624}\text{Cl}_6\text{Fe}_6\text{N}_{48}\text{O}_{24}$ $[\text{M}]^+$: 8861.34, found: 8861.19. Elemental analysis calcd for $(\text{C}_{552}\text{H}_{624}\text{Cl}_6\text{Fe}_6\text{N}_{48}\text{O}_{24})(\text{H}_2\text{O})_3(\text{CH}_2\text{Cl}_2)_7$: C, 70.59; H, 6.82; N, 7.07. Found: C, 71.03; H, 7.01; N, 6.62. UV/Vis (CH_2Cl_2) λ_{abs} 378, 419, 510, 582 nm.



Scheme 2.1. Supramolecular structure of **Fe-PB** composed of six **Fe-TPP** monomer building blocks. The alkyl chains and counterions are not shown in the molecular model for clarity.

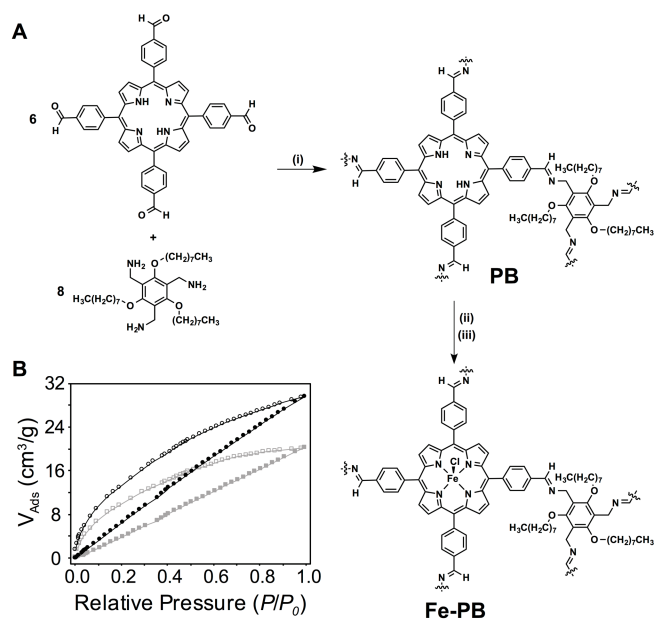


Figure 2.1. (A) Synthesis of the porous organic cage **Fe-PB**. (i) Trifluoroacetic acid (cat.), CHCl_3 , 55 °C, 12 h, 95%; (ii) FeBr_2 , 2,6-lutidine, THF, 70 °C, 12 h; (iii) O_2 , CH_2Cl_2 , sat. $\text{NaCl}_{(\text{aq})}$, RT, 30 min, 84% (2 steps). (B) CO_2 sorption isotherms for **Fe-PB** at 273 K (black) and 298 K (grey). Adsorption: filled symbols; desorption: open symbols.

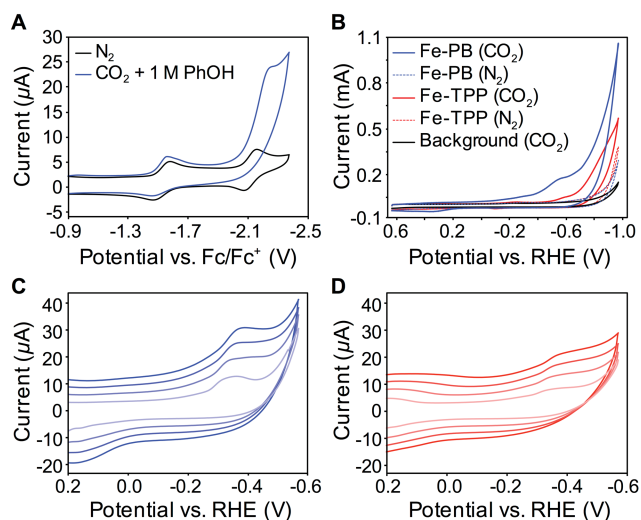


Figure 2.2. (A) CVs of 0.2 mM **Fe-PB** in NMP containing 0.1 M $n\text{Bu}_4\text{NPF}_6$ under N_2 and under CO_2 with added 1 M phenol at scan rates of 0.1 V/s. (B) CVs of **Fe-PB** (blue), **Fe-TPP** (red), and electrode background (black) in 0.5 M aq. KHCO_3 saturated with CO_2 or N_2 at scan rates of 0.1 V/s. Scan rate dependence (0.025-0.1 V/s) of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ reduction for (C) **Fe-PB** and (D) **Fe-TPP** under N_2 in 0.5 M aq. KHCO_3 . Each heterogeneous electrode used was constructed by depositing 6.78 nmol Fe/cm^2 .

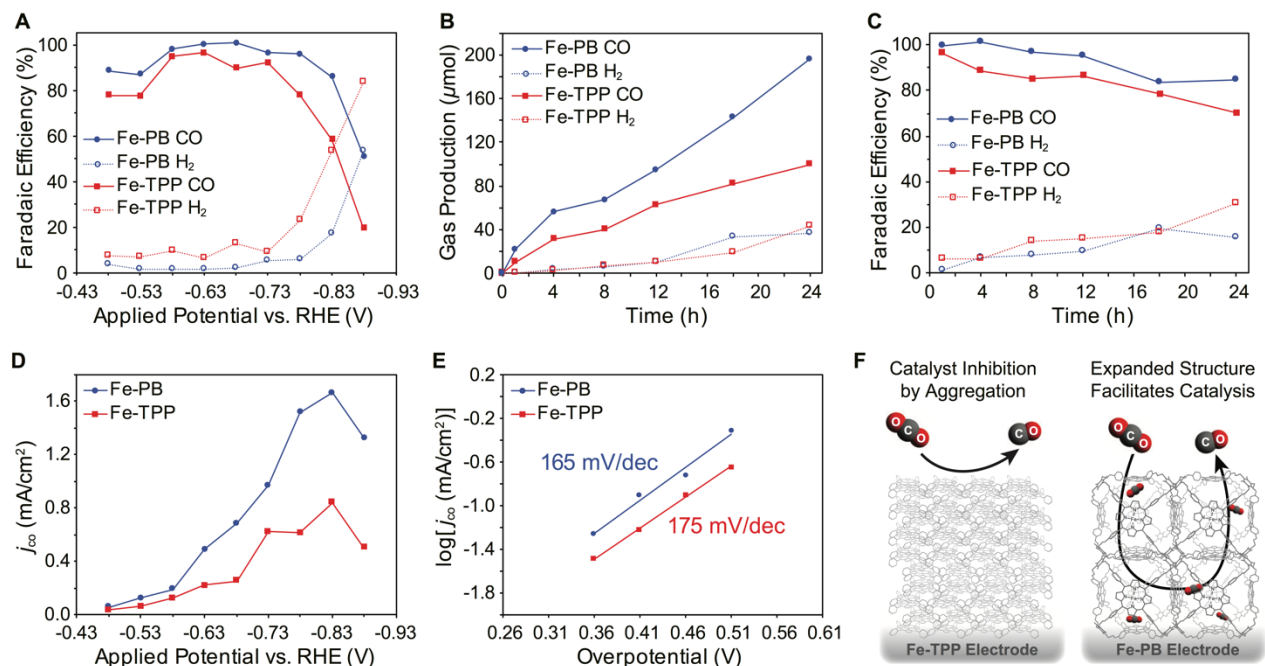
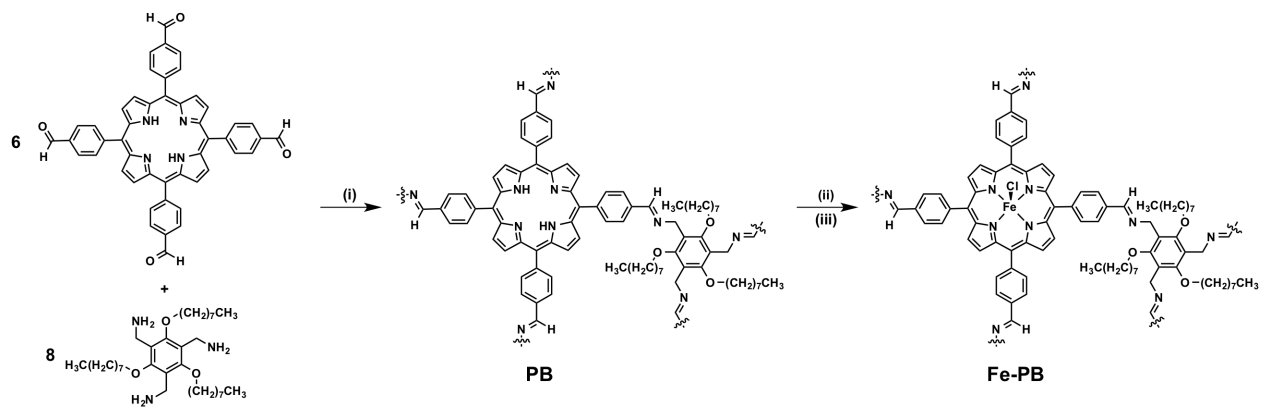


Figure 2.3. (A) Faradaic Efficiencies (FEs) for CO and H₂ by **Fe-PB** and **Fe-TPP** over a range of applied potentials after 1 h electrolysis. (B) Gas production and (C) CO and H₂ FEs during 24 h electrolyses at -0.63 V vs. RHE in 0.5 M aq. KHCO₃ saturated with CO₂. (D) CO specific current densities for **Fe-PB** and **Fe-TPP**. (E) Tafel plots for **Fe-PB** and **Fe-TPP**. Each electrode used for electrolysis experiments was constructed by depositing 13.56 nmol Fe/cm². (F) Proposed model by which the permanently porous supramolecular **Fe-PB** facilitates diffusion of substrate and electrolyte around the catalytic iron centers



Scheme 2.2. Synthetic scheme for the preparation of the porous organic cage Fe-PB. (i) Trifluoroacetic acid (cat.), CHCl_3 , 55 °C, 12 h; (ii) FeBr_2 , 2,6-lutidine, THF, 70 °C, 12 h; (iii) O_2 , CH_2Cl_2 , sat. $\text{NaCl}_{(\text{aq})}$, RT, 30 min

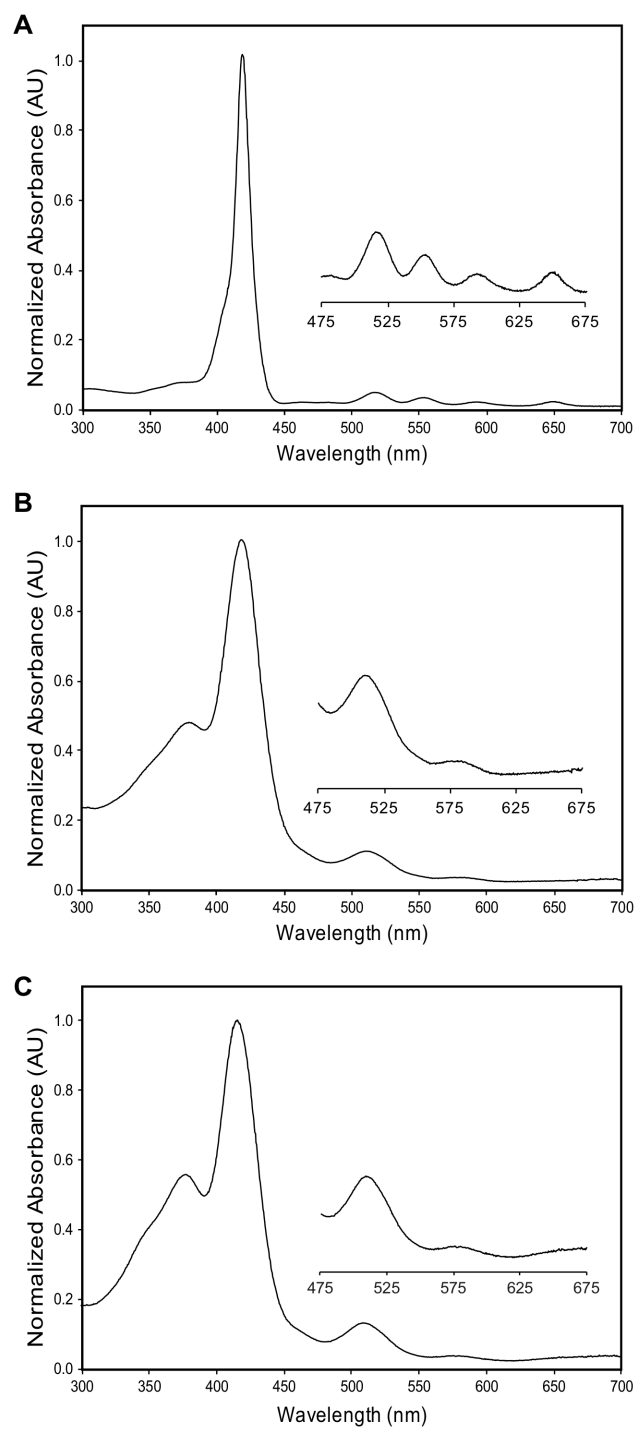


Figure 2.4. UV/Vis spectra in CH_2Cl_2 of free-base **PB** (A), **Fe-PB** (B), and **Fe-TPP** (C).

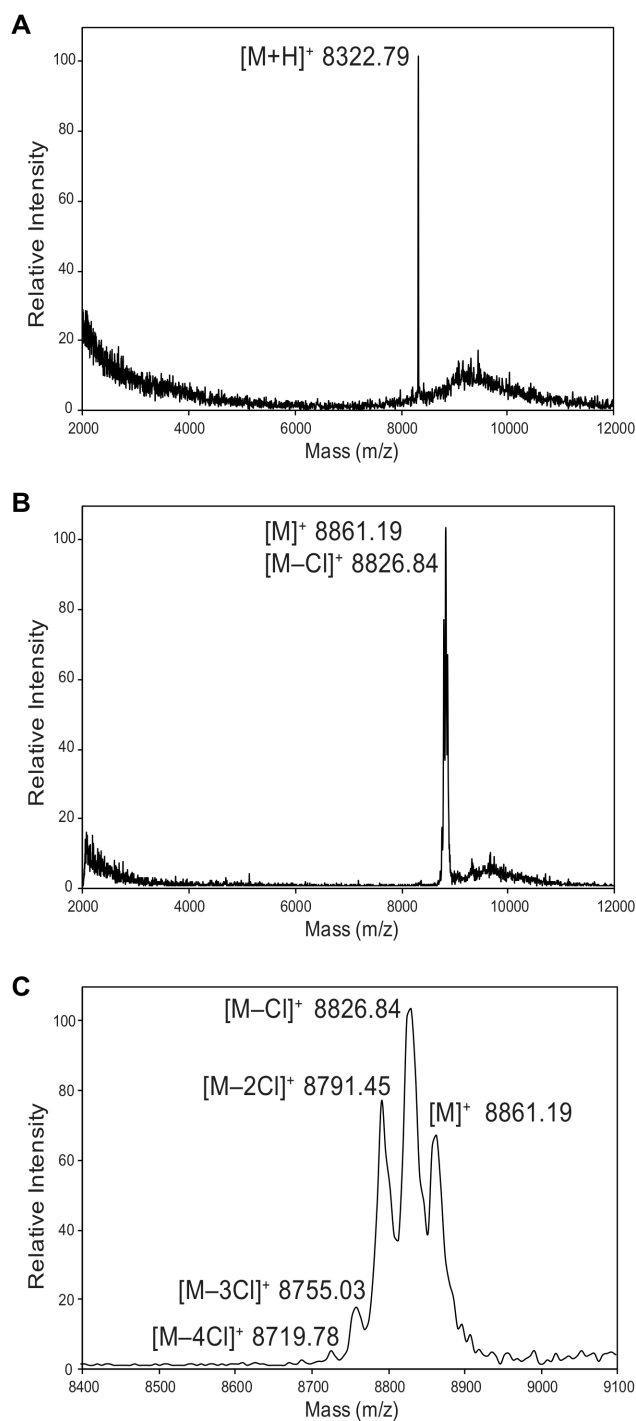


Figure 2.5. MALDI-MS of the free-base **PB** with dithranol as the matrix (A) and **Fe-PB** with DCTB as the matrix (B, C). m/z calcd. for $C_{552}H_{624}Cl_6Fe_6N_{48}O_{24}$ $[M]^+$: 8861.34, found: 8861.19, m/z calcd. for $C_{552}H_{624}Cl_5Fe_6N_{48}O_{24}$ $[M - Cl]^+$: 8826.38, found: 8826.84, m/z calcd. for $C_{552}H_{624}Cl_4Fe_6N_{48}O_{24}$ $[M - 2Cl]^+$: 8791.41, found: 8791.45, m/z calcd. for $C_{552}H_{624}Cl_3Fe_6N_{48}O_{24}$ $[M - 3Cl]^+$: 8754.44, found: 8755.03, m/z calcd. for $C_{552}H_{624}Cl_2Fe_6N_{48}O_{24}$ $[M - 4Cl]^+$: 8719.47, found: 8719.78. The loss of multiple counterions while maintaining $m/z = +1$ for organometallic compounds has been observed by MALDI-MS and may be due to reduction by the matrix.⁶²

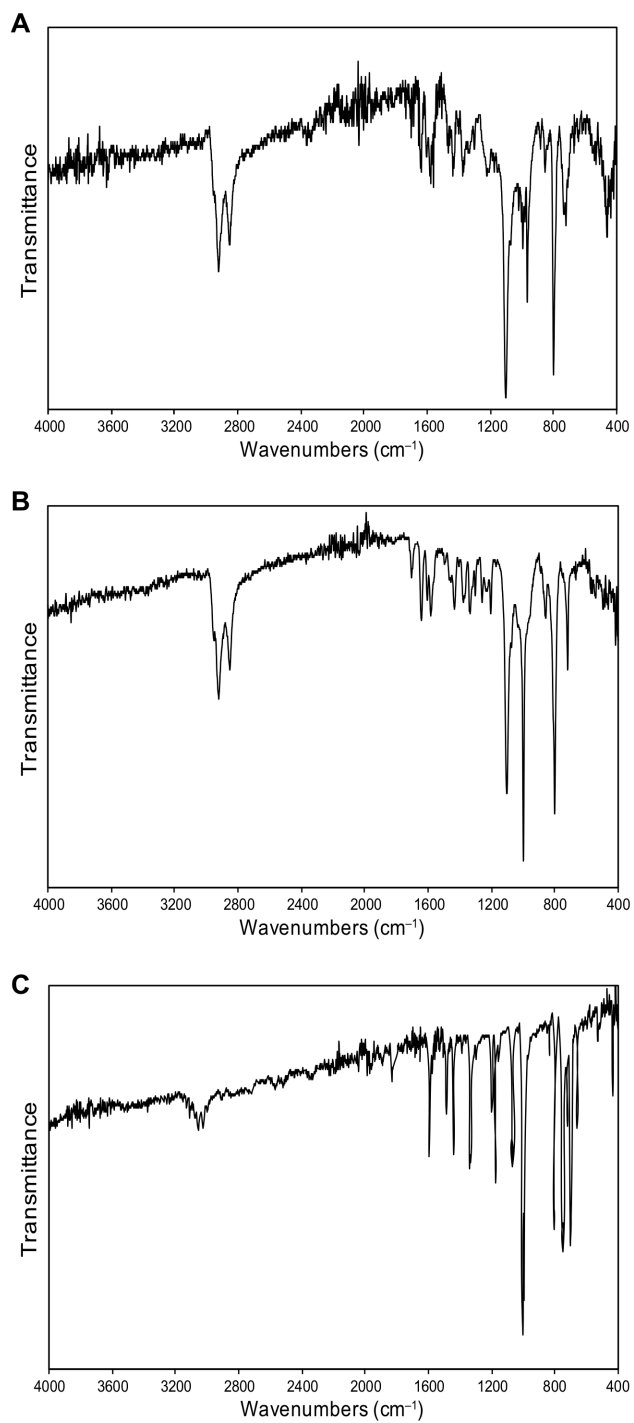


Figure 2.6. IR spectra of the free-base **PB** (A), **Fe-PB** (B), and **Fe-TPP** (C).

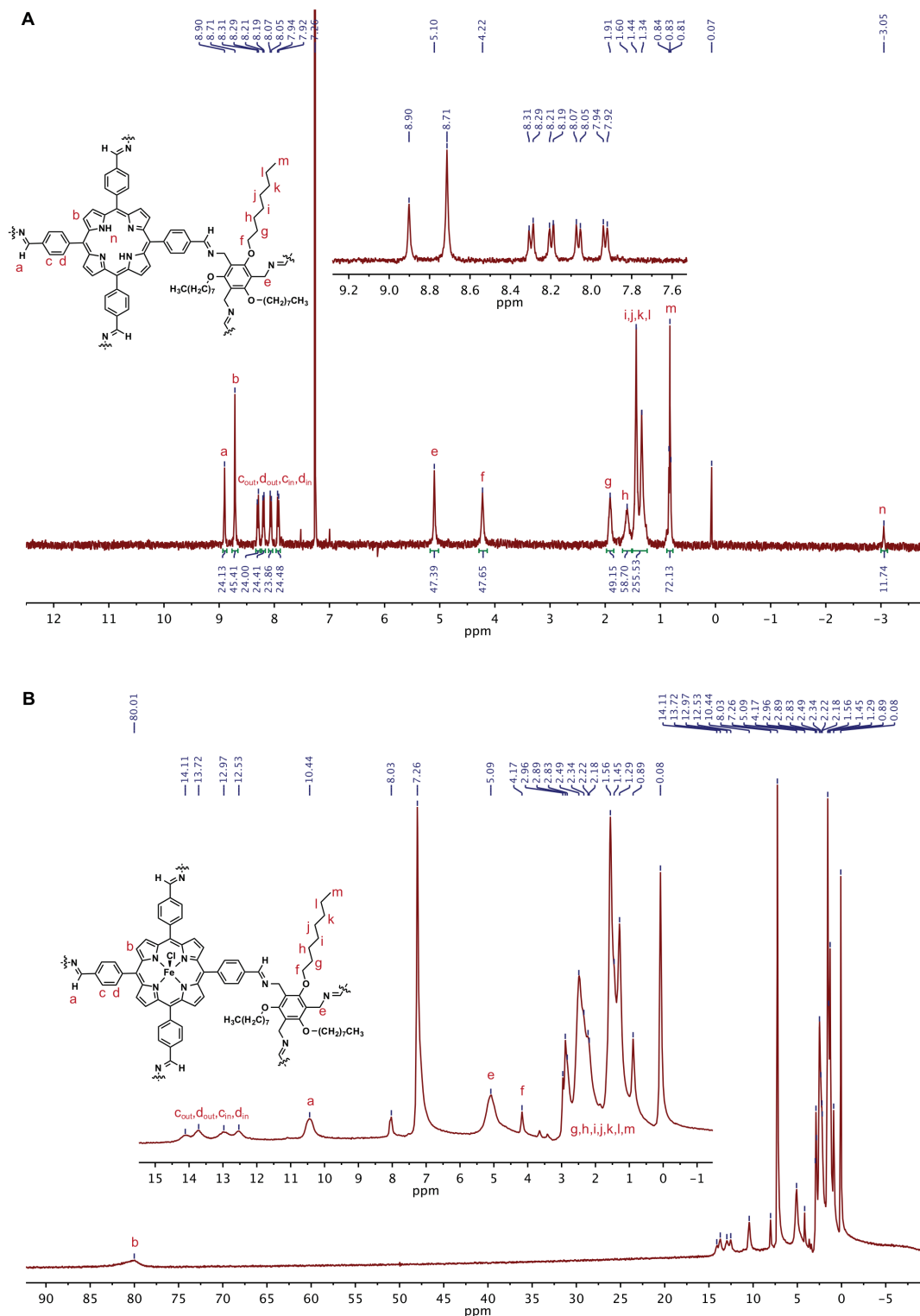


Figure 2.7. ^1H NMR spectra of (A) free-base **PB** and (B) **Fe-PB** measured in CDCl_3 at room temperature. The paramagnetic **Fe-PB** maintains the high symmetry of the rhombicuboctahedral structure. Peaks at 8.03, 2.96 and 2.89 ppm are attributed to residual *N,N*-dimethylformamide, and the peak at 0.08 ppm is attributed to residual silicone grease.

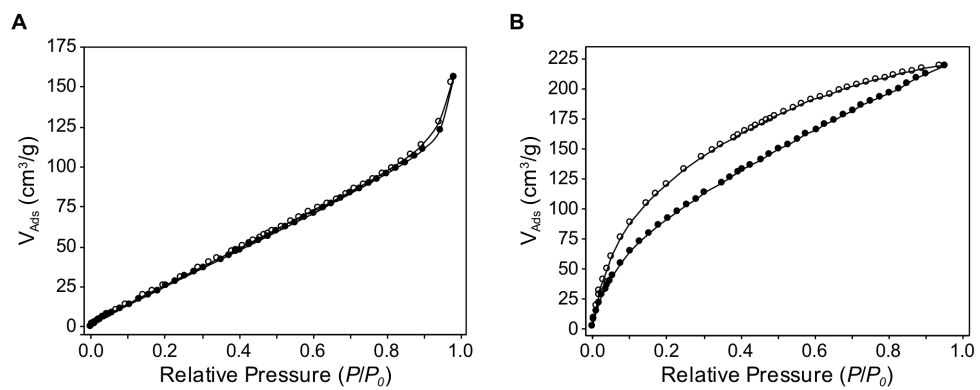


Figure 2.8. (A) N₂ sorption isotherm at 77 K for **Fe-PB**. (B) CO₂ sorption isotherm at 195 K for **Fe-PB**. Filled symbols indicate adsorption and unfilled symbols indicate desorption.

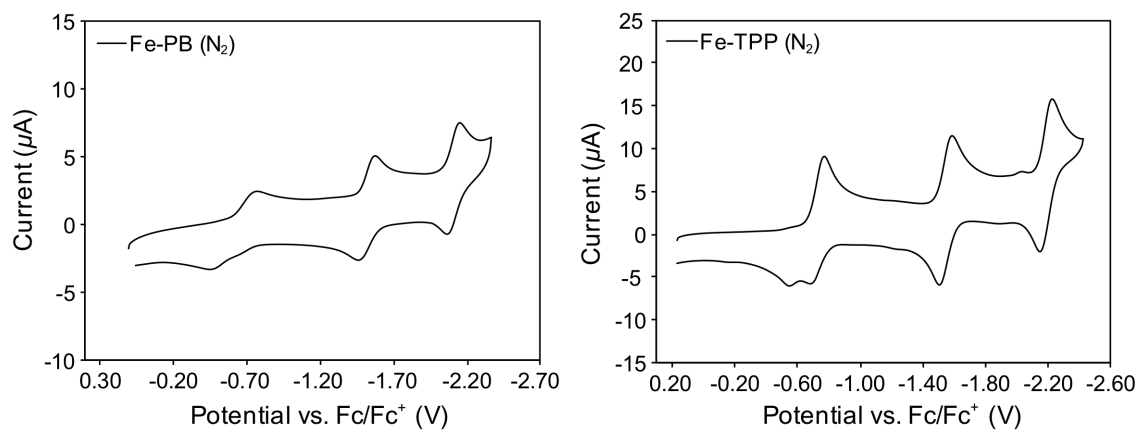


Figure 2.9. CVs of 0.2 mM **Fe-PB** and 1.2 mM **Fe-TPP** in NMP containing 0.1 M *n*Bu₄NPF₆ under N₂ at a scan rate of 0.1 V/s.

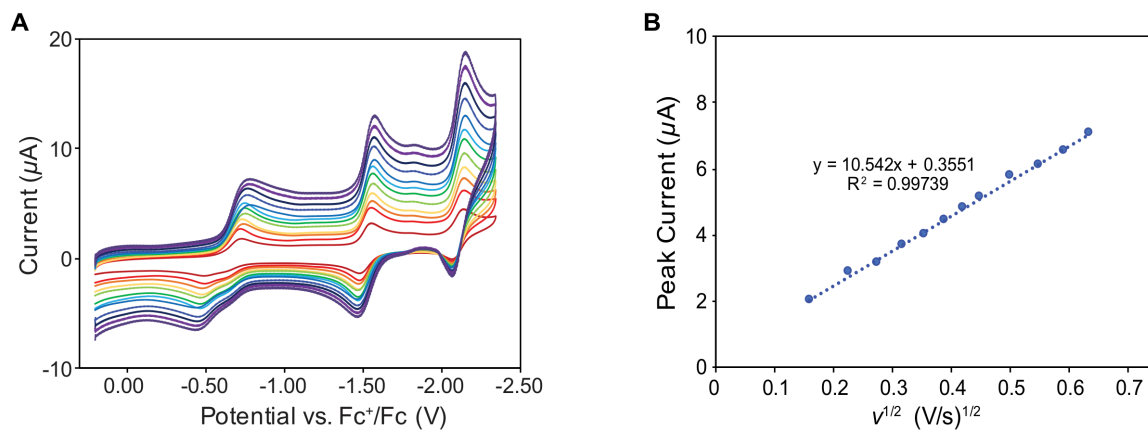


Figure 2.10. (A) CVs showing the scan rate dependence of 0.2 mM **Fe-PB** in 0.1 M *n*Bu₄NPF₆ in NMP electrolyte under N₂. (B) Plot of the Fe^{II}/Fe^I peak current for **Fe-PB** versus the square root of the scan rate.

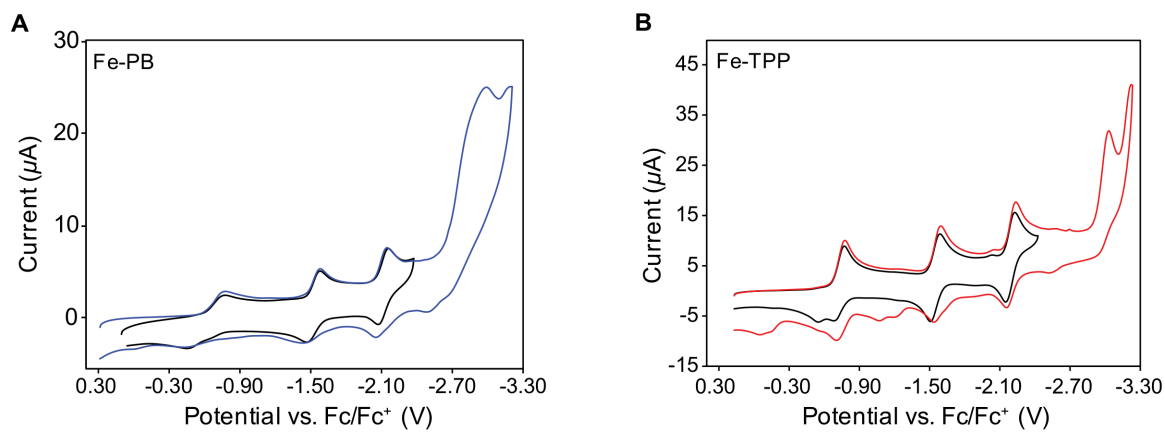


Figure 2.11. Extended CVs over a larger potential window of (A) 0.2 mM **Fe-PB** and (B) 1.2 mM **Fe-TPP** with 0.1 M $n\text{Bu}_4\text{NPF}_6$ in NMP electrolyte under N_2 .

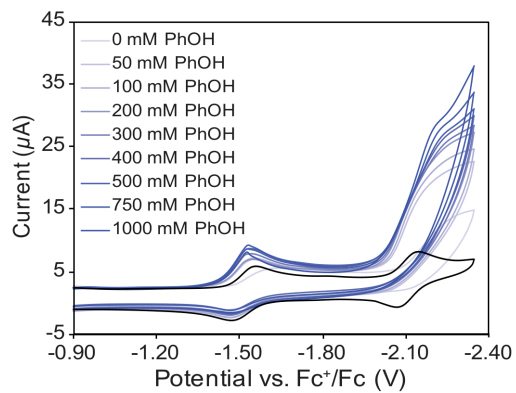


Figure 2.12. Phenol titration (0-1000 mM) into 0.2 mM **Fe-PB** with 0.1 M $n\text{Bu}_4\text{NPF}_6$ in NMP electrolyte saturated with CO_2 . The CV trace shown in black is for **Fe-PB** under N_2 .

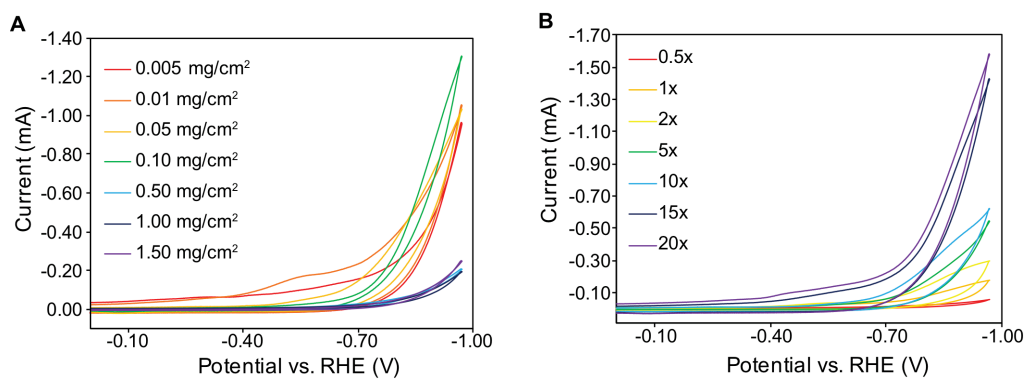


Figure 2.13. (A) CV scans of **Fe-PB** with catalyst loading ranging from 0.005 mg/cm² to 1.50 mg/cm² deposited on top of 0.14 mg/cm² MWCNTs. (B) CV scans of **Fe-PB** with varying MWCNT:catalyst mass ratio ranging from 0.001-0.2 mg/cm² MWCNTs with fixed 0.01 mg/cm² **Fe-PB**. CVs were obtained in 0.5 M aq. KHCO₃ saturated with CO₂ at 0.1 V/s.

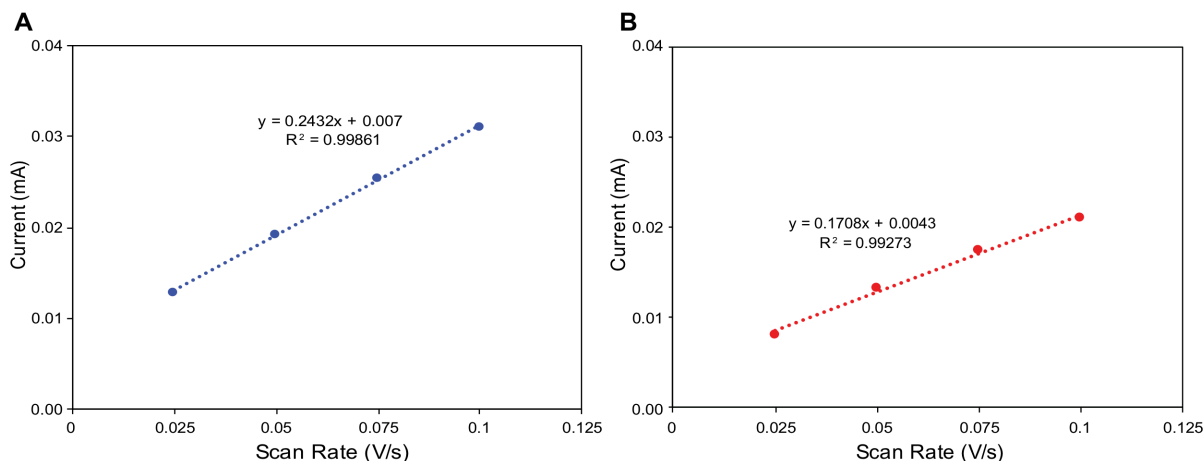


Figure 2.14. Plot of $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ peak currents as a function of scan rate for **Fe-PB** (A) and **Fe-TPP** (B). The scan rate dependence of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ peak currents for each catalyst was determined by taking CVs in 0.5 M aq. KHCO_3 saturated with N_2 . The heterogeneous electrodes were prepared with a 0.071 cm^2 glassy carbon disk as described above.

The surface concentration of electroactive sites, Γ , was then determined using the following equation:

$$i_p = n^2 F S \Gamma \frac{F v}{4 R T}$$

where i_p is the peak current of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ reduction, n is the number of electrons, F is Faraday's constant, S is the geometrical surface area of the electrode, v is the scan rate, R is the gas constant, and T is the temperature. The number of electrons, n , is taken to be 1 for the single electron reduction of Fe^{II} to Fe^{I} . This treats each iron porphyrin moiety in **Fe-PB** or **Fe-TPP** as independent of one another, and thus the surface concentration of electroactive iron centers is determined.

Table 2.1. Changes in electroactive surface area for different amounts of **Fe-PB** and **Fe-TPP** catalyst deposited onto the heterogeneous MWCNT coated electrode. The number of electroactive iron centers was determined following the same procedure described in Figure 2.14 by measuring the scan rate dependence of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ peak current in 0.5 M aq. KHCO_3 saturated with N_2 .

Catalyst	Amount of Catalyst Added (nmol/cm ²)	Amount of Fe Added (nmol Fe/cm ²)	Electroactive Surface Area (nmol EA-Fe/cm ²)	Percentage of Electroactive Fe Sites	Fe-PB:Fe-TPP EA Surface Area
Fe-PB	0.565	3.39	3.4	100%	1.2
Fe-TPP	3.39	3.39	2.8	84%	
Fe-PB	1.13	6.78	3.7	54%	1.4
Fe-TPP	6.78	6.78	2.5	38%	
Fe-PB	2.26	13.56	1.6	12%	1.2
Fe-TPP	13.56	13.56	1.3	10%	
Fe-PB	5.65	33.90	0.8	2%	0.4
Fe-TPP	33.90	33.90	2.2	6%	

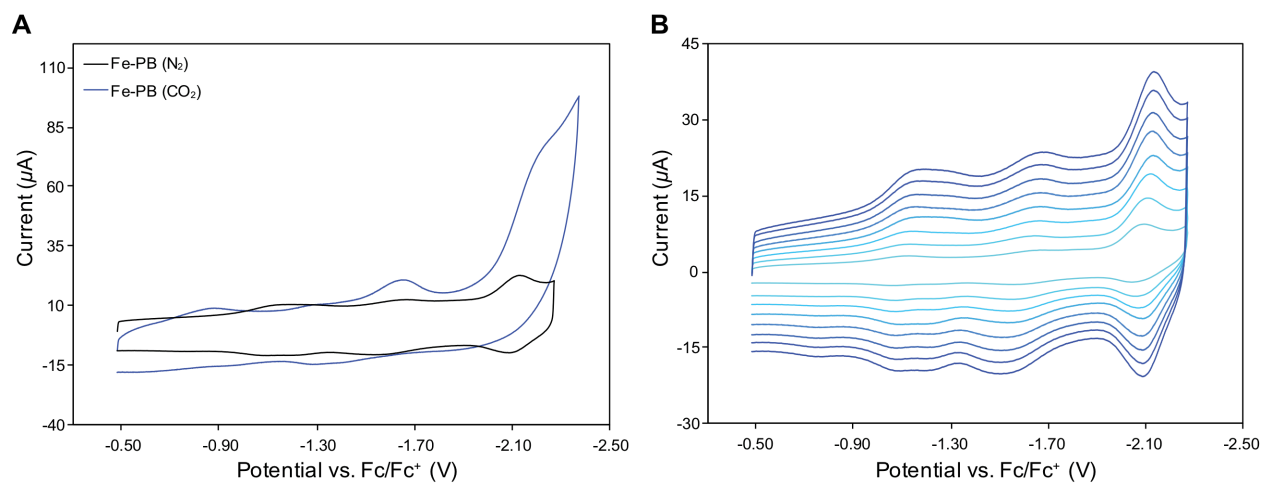


Figure 2.15. CVs of Fe-PB deposited onto 0.071 cm² glassy carbon disk electrode first coated with MWCNTs in acetonitrile with 0.1 M *n*Bu₄NPF₆ saturated with N₂ or CO₂ (A) and the scan rate dependence from 25 to 200 mV/s saturated with N₂ (B).

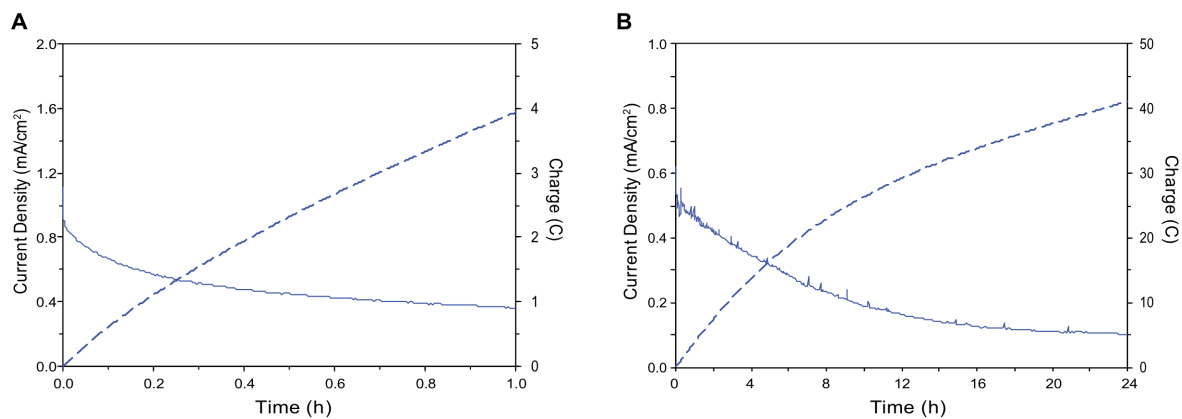


Figure 2.16. Representative electrolyses of **Fe-PB** at an applied potential of -0.63 V vs. RHE for 1 h (A) and for 24 h (B). Solid lines correspond to current density and dashes lines correspond to charge accumulation.

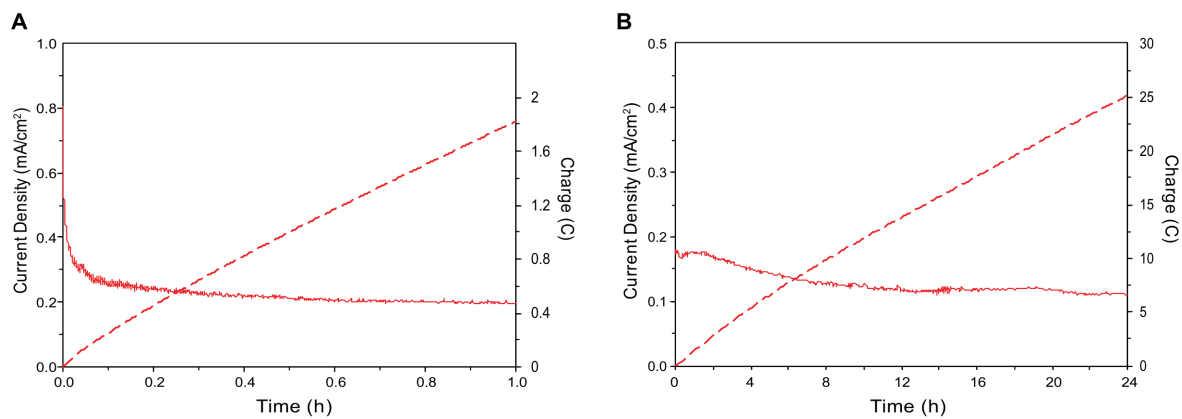


Figure 2.17. Representative electrolyses of **Fe-TPP** at an applied potential of -0.63 V vs. RHE for 1 h (A) and for 24 h (B). Solid lines correspond to current density and dashes lines correspond to charge accumulation.

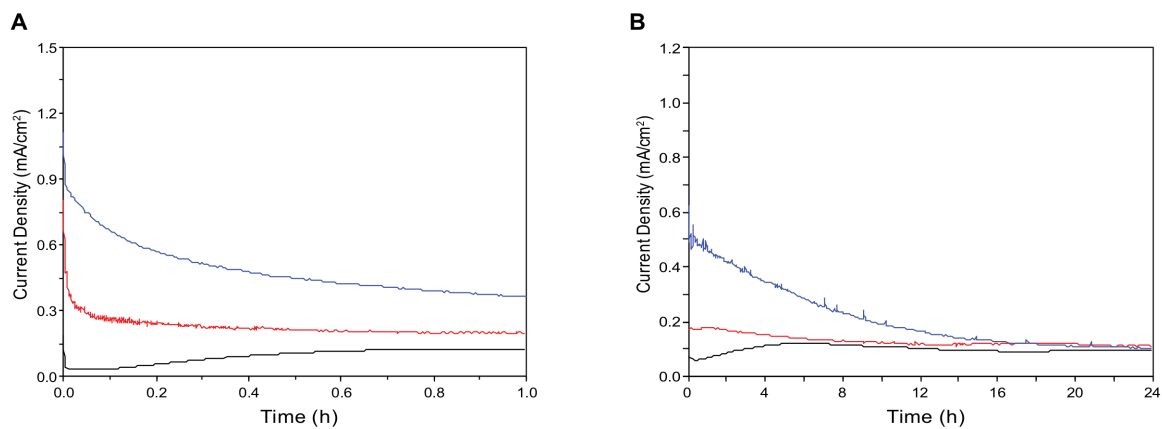


Figure 2.18. Comparison of the current densities observed for **Fe-PB** (blue), **Fe-TPP** (red), and bare MWCNTs (black) during 1 h (A) and 24 h (B) electrolyses at an applied potential of -0.63 V vs. RHE.

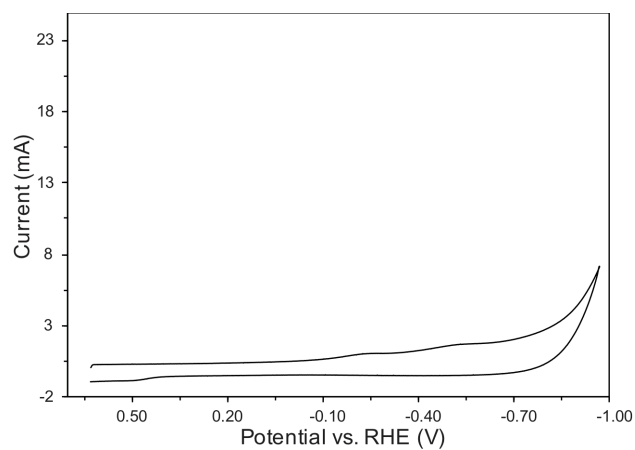


Figure 2.19. CV of 2.25 cm² GC plate electrode coated with 0.17 mg/cm² MWCNTs with no added catalyst in 0.5 M aq. KHCO₃ saturated with CO₂.

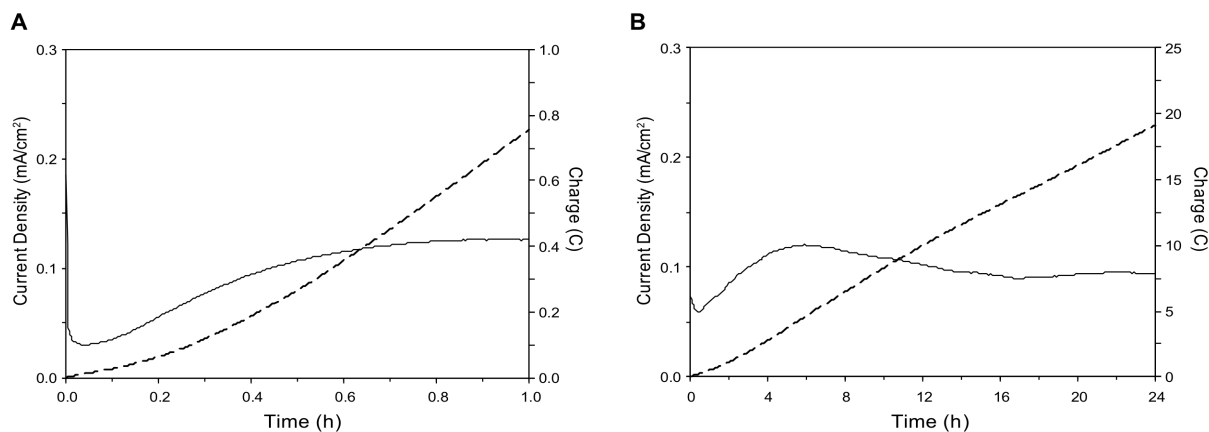


Figure 2.20. Electrolysis of 2.25 cm² GC plate electrode coated with 0.17 mg/cm² MWCNTs with no added catalyst. A potential of −0.63 V vs. RHE was applied for 1 h (A) and for 24 h (B) with 0.5 M aq. KHCO₃ saturated with CO₂ as the electrolyte. Solid lines correspond to current density and dashes lines correspond to charge accumulation. H₂ was the major product as shown in Table S4 below.

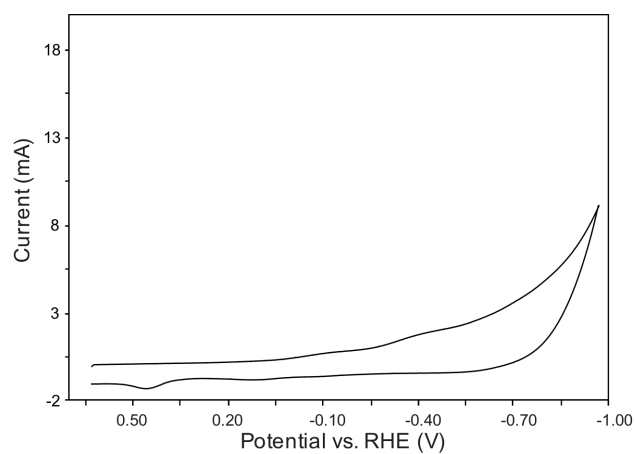


Figure 2.21. CVs of free-base **PB** in 0.5 M aq. KHCO_3 saturated with CO_2 after deposition onto a MWCNT coated GC disk electrode with same molar loading as **Fe-PB** (2.26 nmol/cm^2).

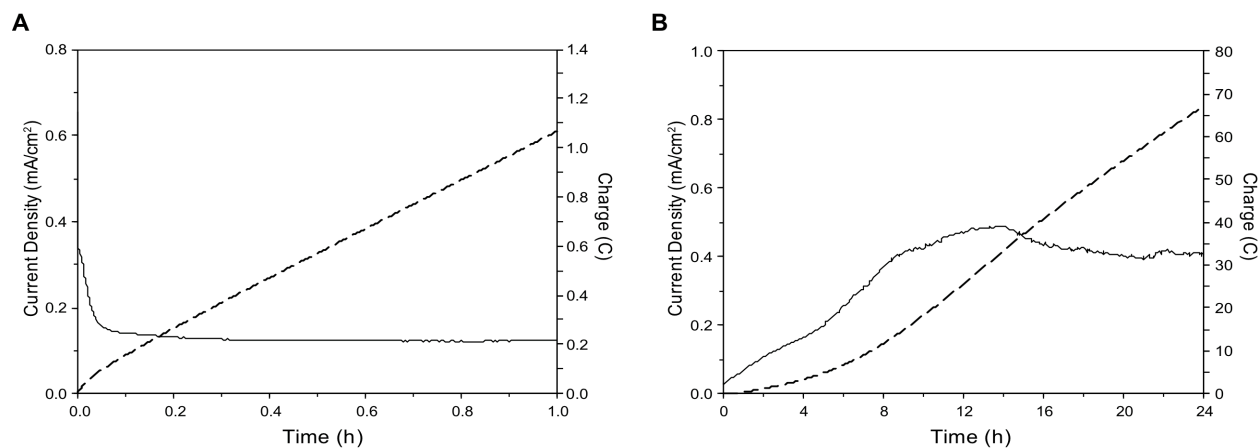


Figure 2.22. Electrolysis of free-base **PB** at an applied potential of -0.63 V vs. RHE for 1 h (A) and for 24 h (B) with 0.5 M aq. KHCO_3 saturated with CO_2 as the electrolyte. Solid lines correspond to current density and dashes lines correspond to charge accumulation. H_2 was the major product as shown in Table S5 below.

Table 2.2. Long-term controlled potential electrolyses of **Fe-PB**. Volume of CO and H₂ produced over time during electrolysis of **Fe-PB** at an applied potential of –0.63 V vs. RHE.

Time (h)	Total Charge (C)	Volume CO (mL)	FE CO (%)	Volume H ₂ (mL)	FE H ₂ (%)
1	3.95	0.50	100.3	0.01	1.3
4	9.84	1.26	101.3	0.08	6.8
8	12.30	1.51	97.0	0.12	7.9
12	17.64	2.12	94.9	0.22	9.7
18	30.12	3.20	83.8	0.75	19.6
24	41.16	4.40	84.5	0.82	15.7

Table 2.3. Long-term controlled potential electrolyses of **Fe-TPP**. Volume of CO and H₂ produced over time during electrolysis of **Fe-TPP** at an applied potential of −0.63 V vs. RHE.

Time (h)	Total Charge (C)	Volume CO (mL)	FE CO (%)	Volume H ₂ (mL)	FE H ₂ (%)
1	1.83	0.23	96.5	0.01	4.6
4	6.21	0.70	88.6	0.05	6.1
8	8.34	0.90	85.1	0.15	14.2
12	12.84	1.41	86.6	0.24	14.8
18	18.46	1.84	78.6	0.42	17.9
24	25.14	2.23	70.0	0.97	30.5

Table 2.4. Long-term controlled potential electrolyses of MWCNT coated glassy carbon electrode (no catalyst). Volume of CO and H₂ produced over time during electrolysis of MWCNTs at an applied potential of −0.63 V vs. RHE.

Time (h)	Total Charge (C)	Volume CO (mL)	FE CO (%)	Volume H ₂ (mL)	FE H ₂ (%)
1	0.76	0.00	—	0.10	99.2
24	19.22	0.01	0.2	2.38	97.7

Table 2.5. Long-term controlled potential electrolyses of free-base **PB**. Volume of CO and H₂ produced over time during electrolysis of free-base **PB** at an applied potential of –0.63 V vs. RHE.

Time (h)	Total Charge (C)	Volume CO (mL)	FE CO (%)	Volume H ₂ (mL)	FE H ₂ (%)
1	1.07	0.01	8.1	0.11	83.3
24	67.54	0.03	0.3%	8.87	103.7

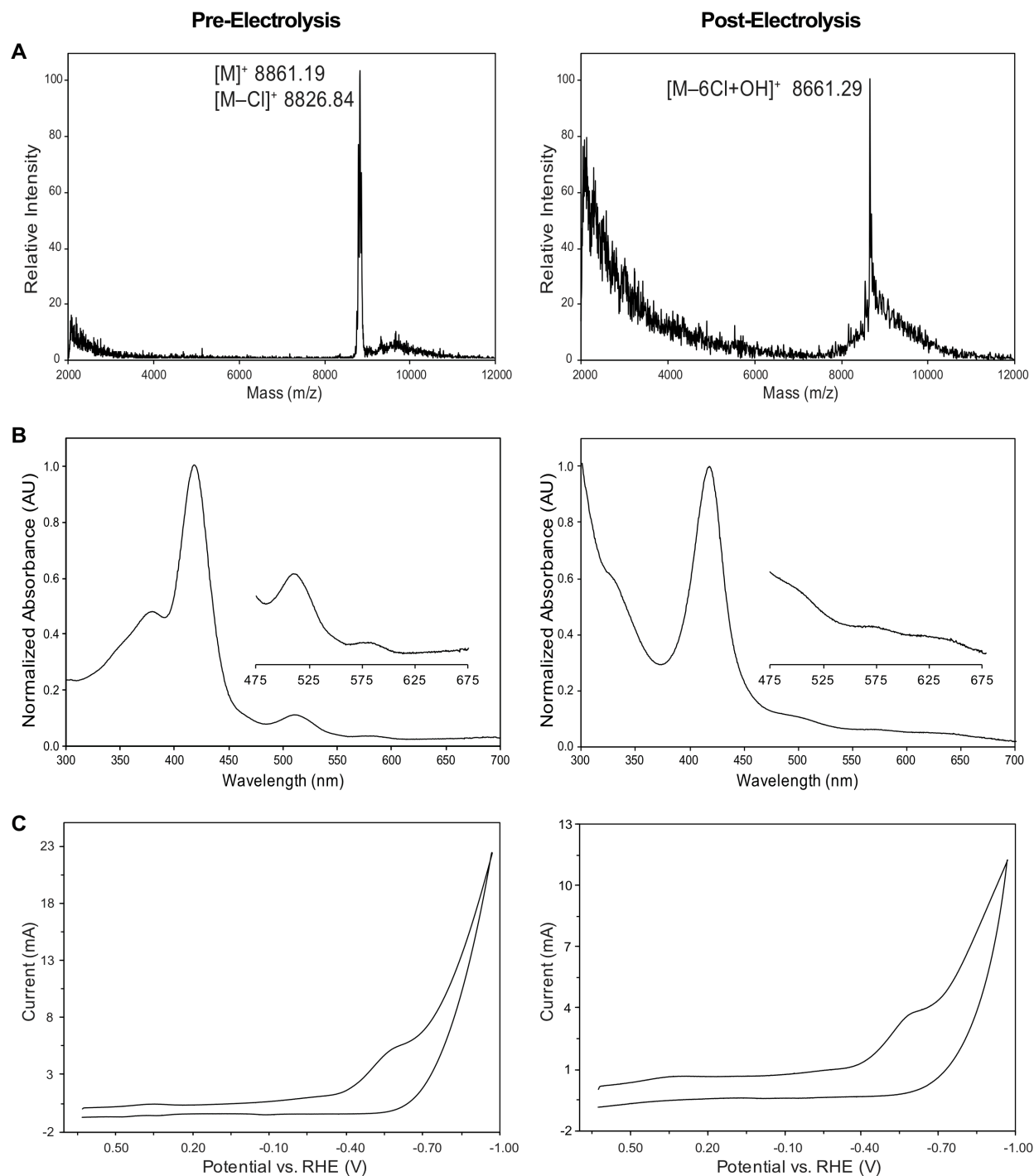


Figure 2.23. MALDI-MS (A), UV/Vis (B), and CV (C) of **Fe-PB** before and after a 24 h long-term electrolysis at -0.63 V vs. RHE. The changes observed in the MALDI-MS and UV/Vis spectra for **Fe-PB** are indicative of exchange of the axial ligands on the Fe^{III} metal centers and not decomposition of the metalloporphyrin cage molecule. CVs were obtained using the 2.25 cm^2 glassy carbon plate working electrode prepared for the bulk electrolyses, and the CV collected post-electrolysis was conducted in fresh electrolyte.

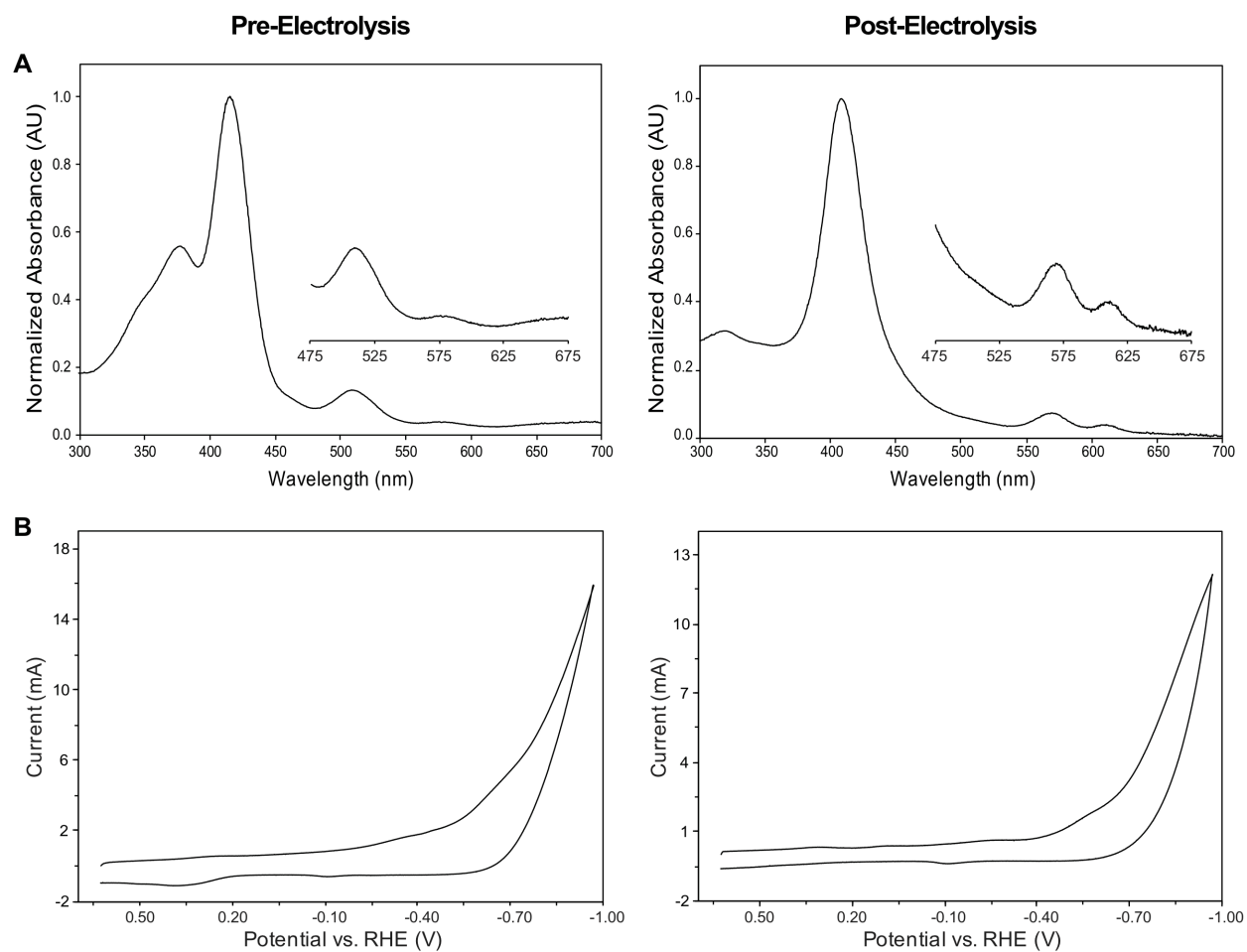


Figure 2.24. UV/Vis (A) and CV (B) of Fe-TPP before and after a 24 h long-term electrolysis. CVs were obtained using the 2.25 cm² glassy carbon plate working electrode prepared for the bulk electrolyses, and the CV collected post-electrolysis was conducted in fresh electrolyte.

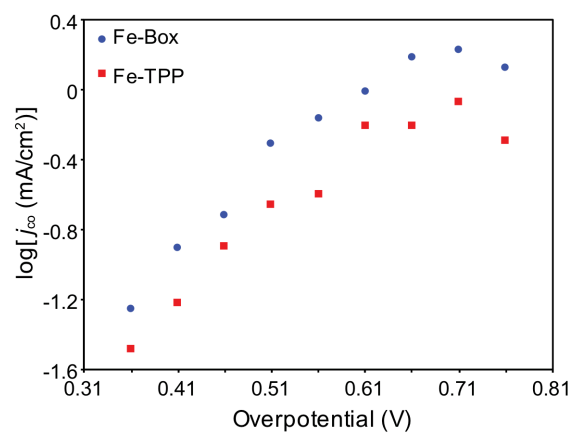


Figure 2.25. Plot of the $\log[\text{CO specific current density}]$ versus the applied overpotential for a series of 1 h electrolyses with **Fe-PB** and **Fe-TPP**.

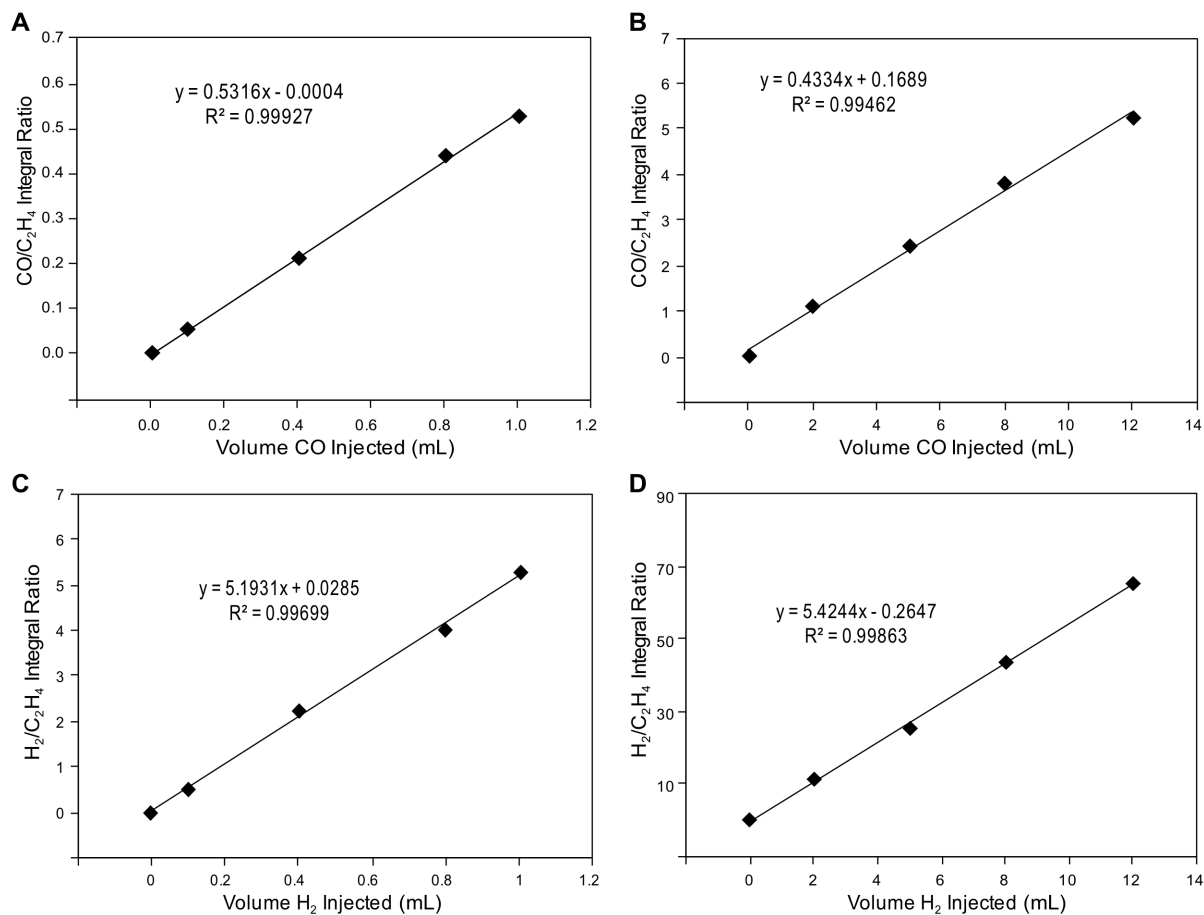


Figure 2.26. Gas chromatography calibration curves for CO and H_2 with C_2H_4 as an internal standard. (A) CO detection at low volumes with high gain FID, (B) CO detection at high volumes with low gain FID, (C) H_2 detection at low volumes, and (D) H_2 detection at high volumes.

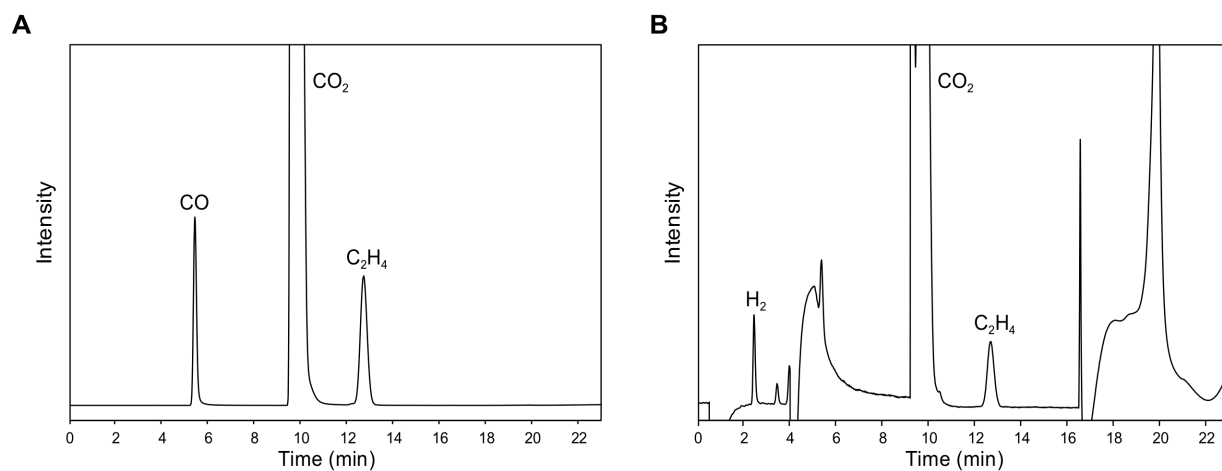


Figure 2.27. Representative GC traces showing the separation and identification of CO, H₂, CO₂, and C₂H₄ with an FID (A) and a TCD (B).

Table 2.6. Performances of selected recent molecular catalysts immobilized or deposited onto heterogeneous electrodes for electrochemical CO₂ reduction to CO in aqueous media.

Catalyst	Electrolyte (pH)	Potential vs. RHE	Time	Average CO Specific Current Density	Products (FE)	TON (CO)	TOF (CO)	Ref.
Fe-PB	0.5 M KHCO ₃ (7.3)	−0.63 V	1 h	0.49 mA/cm ²	CO (100%) H ₂ (2%)	6,280	1.74 s ^{−1}	This work
Fe-PB	0.5 M KHCO ₃ (7.3)	−0.63 V	24 h	0.2 mA/cm ²	CO (85%) H ₂ (16%)	55,250	0.64 s ^{−1}	This work
Fe-TPP	0.5 M KHCO ₃ (7.3)	−0.63 V	1 h	0.22 mA/cm ²	CO (96%) H ₂ (6%)	3,380	0.94 s ^{−1}	This work
Fe-TPP	0.5 M KHCO ₃ (7.3)	−0.63 V	24 h	0.12 mA/cm ²	CO (70%) H ₂ (31%)	32,770	0.38 s ^{−1}	This work
COF-366-Co	0.5 M KHCO ₃ (7.3)	−0.67 V	24 h	1.6 mA/cm ²	CO (90%) H ₂ (16%)	34,000	0.69 s ^{−1}	24
COF-367-Co	0.5 M KHCO ₃ (7.3)	−0.67 V	24 h	2.7 mA/cm ²	CO (83%) H ₂ (23%)	48,000	0.53 s ^{−1}	24
COF-367-Co(10%)	0.5 M KHCO ₃ (7.3)	−0.67 V	4 h	0.5 mA/cm ²	CO (68%) H ₂ (35%)	17,280	1.2 s ^{−1}	24
COF-367-Co(1%)	0.5 M KHCO ₃ (7.3)	−0.67 V	4 h	0.2 mA/cm ²	CO (50%) H ₂ (46%)	37,440	2.6 s ^{−1}	24
Co-TAP	0.5 M KHCO ₃ (7.3)	−0.67 V	24 h	0.5 mA/cm ²	CO (80%) H ₂ (26%)	8,300	0.1 s ^{−1}	24
TCPP-Co	0.5 M KHCO ₃ (7.3)	−0.7 V	7 h	~0.5 mA/cm ²	CO (50%)	1,400	0.06 s ^{−1}	63
CoPc/CNT	0.1 M KHCO ₃ (6.8)	−0.63 V	10 h	9.2 mA/cm ²	CO (92%) H ₂ (6.4%)	97,000	2.7 s ^{−1}	23
CoPc-CN/CNT	0.1 M KHCO ₃ (6.8)	−0.63 V	1 h	14.7 mA/cm ²	CO (98%) H ₂ (3.3%)	14,760	4.1 s ^{−1}	23
Co-TPP	0.5 M KHCO ₃ (7.3)	−0.67 V	4 h	2.9 mA/cm ²	CO (91%) H ₂ (9%)	1,118	0.08 s ^{−1}	22
Fe-CAT	0.5 M NaHCO ₃ (7.3)	−0.59 V	3 h	~0.14 mA/cm ²	CO (90%)	N/A	N/A	13
Fe-CATpyr	0.5 M NaHCO ₃ (7.3)	−0.59 V	12 h	~0.14 mA/cm ²	CO (85%)	813	0.02 s ^{−1}	13
Fe-CAT-CNT	0.5 M NaHCO ₃ (7.3)	−0.62 V	3 h	~0.12 mA/cm ²	CO (80%)	532	0.05 s ^{−1}	14
Fe-TPP-CNT	0.5 M NaHCO ₃ (7.3)	−0.62 V	3 h	~0.05 mA/cm ²	CO (51%)	N/A	N/A	14
WSCAT	0.1 M KCl + 0.5 M KHCO ₃ (7.3)	−0.52 V	30 h	0.9 mA/cm ²	CO (90%)	N/A	N/A	64
CoFPc	0.5 M KHCO ₃ (7.2)	−0.8 V	2 h	4.1 mA/cm ²	CO (93%) H ₂ (6%)	11,520	1.6 s ^{−1}	21
Mn(bpy)(CO) ₃ Br-Nafion	30 mM Na ₂ HPO ₄ + 30 mM NaH ₂ PO ₄ (7.0)	−0.87 V	4 h	N/A	CO (51%) H ₂ (24%)	471	0.03 s ^{−1}	18
Mn-pyr	0.5 M KHCO ₃ (7.4)	−0.67 V	8 h	0.13 mA/cm ²	CO (25%) H ₂ (59%)	1,400	0.05 s ^{−1}	16
CoPc	0.1 M NaH ₂ PO ₄ (4.7)	−0.75 V	2 h	0.22 mA/cm ²	CO (36%) H ₂ (41%)	4,500	0.6 s ^{−1}	20
CoPc-P4VP	0.1 M NaH ₂ PO ₄ (4.7)	−0.75 V	2 h	1.8 mA/cm ²	CO (89%) H ₂ (5%)	34,000	4.8 s ^{−1}	20

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Chapter 3

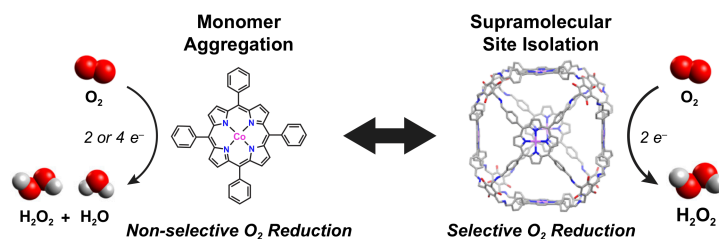
Supramolecular Tuning Enables Selective Oxygen Reduction Catalyzed by Cobalt Porphyrins for Direct Electrosynthesis of Hydrogen Peroxide

Portions of this work were published in the following scientific journal:

Smith, P. T.; Kim, Y.; Benke, B. P.; Kim, K.; Chang, C. J., Supramolecular Tuning Enables Selective Oxygen Reduction Catalyzed by Cobalt Porphyrins for Direct Electrosynthesis of Hydrogen Peroxide. *Angewandte Chemie International Edition*. **2020**, 59 (12), 4902-4907.

Abstract

We report a supramolecular design strategy for promoting the selective reduction of O_2 for direct electrosynthesis of H_2O_2 . Specifically, we utilized cobalt tetraphenylporphyrin (**Co-TPP**), an oxygen reduction reaction (ORR) catalyst with highly variable product selectivity, as a building block to assemble the permanently porous supramolecular cage **Co-PB-1(6)** bearing six **Co-TPP** subunits connected through twenty-four imine bonds. Reduction of these imine linkers to amines yields the more flexible cage **Co-rPB-1(6)**. Both **Co-PB-1(6)** and **Co-rPB-1(6)** cages produce 90-100% H_2O_2 from electrochemical ORR catalysis in neutral pH water, whereas the **Co-TPP** monomer gives a 50% mixture of H_2O_2 and H_2O . Bimolecular pathways have been implicated in facilitating H_2O formation, therefore, we attribute this high H_2O_2 selectivity to site isolation of the discrete molecular units in each supramolecule. The ability to control reaction selectivity in supramolecular structures beyond traditional host-guest interactions offers new opportunities for designing such architectures for a broader range of catalytic applications.



Introduction

Continuing with the work described in Chapter 2, we expand the range of electrochemical reactivity that supramolecular cages are capable of and reveal unique advantages. In this chapter, we focus on the oxygen reduction reaction using the cobalt analog of our porphyrin box platform. In addition to improving catalysis through improved charge transport and substrate diffusion as seen in Chapter 2, we now exploit the site isolation benefits for selective catalysis that are a result of the permanently porous rigid structure.

The oxygen reduction reaction (ORR) is a central chemical transformation for biological and chemical energy conversion and storage, and can proceed through either a 2 e⁻ pathway to produce H₂O₂ or a 4 e⁻ pathway to produce H₂O.¹⁻⁴ Using electricity offers the possibility to drive this process with sustainable energy input, and in the context of molecular catalysts, structural and functional mimics of cytochrome *c* oxidase enzymes that perform ORR in biology have focused on the selective formation of H₂O to better understand multielectron small molecule activation and develop efficient fuel cells.⁵⁻⁹ Alternatively, H₂O₂ is a valuable oxidant, energy carrier, and commodity chemical, and using electricity for H₂O₂ production presents an environmentally green alternative to the traditional anthraquinone process for its synthesis,¹⁰⁻¹⁵ with the key challenge to avoid further reduction to more thermodynamically favored H₂O product. Along these lines, molecular catalysts offer a precise approach to active site engineering, and elegant strategies have been devised to guide ORR to the 4 e⁻ pathway, including constructing bimetallic platforms,¹⁶⁻²² appending intramolecular proton sources,²³⁻²⁷ and integrating electron reservoirs.^{28,29} In contrast, development of molecular ORR electrocatalysts to selectively produce H₂O₂ has received less attention, focusing primarily on mononuclear cobalt or manganese complexes supported by a limited set of tetradentate ligands.³⁰⁻³⁵ Moreover, most molecular ORR electrocatalysts require organic solvents and proton donors, with aqueous conditions using heterogeneous or immobilized versions being limited to acidic or alkaline conditions. Only a few catalysts show efficient ORR in water at neutral pH, and these examples generate primarily H₂O as the 4 e⁻ reduction product.³⁶⁻³⁹ Herein, we present a supramolecular design strategy to develop catalysts that can selectively generate H₂O₂ as the 2 e⁻ reduction product from electrochemical ORR and operate in water at neutral pH. Site isolation of molecular cobalt tetraphenylporphyrin (**Co-TPP**) active sites within a porous organic cage (POC) architecture enables ORR catalysis for direct electrosynthesis of H₂O₂, where the resultant porphyrin boxes, **Co-PB-1(6)** and **Co-rPB-1(6)**, achieve 90-100% selectivity by avoiding formation of bimetallic active sites that can promote off-pathway reduction to H₂O (Scheme 3.1). The POC structure offers an improvement over free monomer **CoTPP** that generates a 50%/50% mixture of H₂O₂ and H₂O from ORR. This work presents an alternative strategy for exploiting supramolecular cavities for selective catalyst design beyond traditional host-guest interactions that favor substrate binding and/or product release or increasing catalyst stability by preventing intermolecular decomposition.^{40,41}

In designing molecular catalysts for selective electrochemical ORR to H₂O₂ over H₂O that operate in water at neutral pH, we considered the fact that catalyst immobilization can impart aqueous compatibility, but also promote formation of intermolecular bimetallic aggregates that facilitate reduction to increase off-pathway H₂O production.⁴²⁻⁴⁵ As such, we pursued a design strategy of site isolation, where we reasoned that supramolecular-induced separation of molecular units could promote the 2 e⁻ reduction pathway for direct electrosynthesis of H₂O₂ and disfavor

the 4 e⁻ reduction to H₂O. Indeed, complementary materials approaches for H₂O₂ electrosynthesis that exploit site isolation include dispersed and single-atom materials,^{46,47} metal organic frameworks and related reticular materials,⁴⁸⁻⁵⁰ graphite-conjugated catalysts,⁵¹ and phase-transfer catalysis.⁵² In this context, POCs are appealing supramolecular platforms that combine the synthetic tunability of molecular catalysts with the high surface area of materials catalysts, and advances continue to showcase the variety of POCs that can be synthesized.^{53,54} Large, rigid POCs have the potential to incorporate multiple non-interacting active sites. This broad structural diversity in combination with soluble processing that is not possible with most heterogeneous materials has led to POC applications in gas separation,⁵⁵ artificial ion channels,⁵⁶ nanoparticle encapsulation,⁵⁷ batteries,⁵⁸ and supramolecular allostery.⁵⁹ The molecular structure of POCs also facilitates post-synthetic modifications where more robust and intricate cages can be obtained.⁶⁰⁻⁶² This strategy has been used to synthesize binding sites in a POC for molecular recognition⁶³ and for constructing POCs capable of hydrogen isotope separation.⁶⁴ Of particular interest to our electrocatalysis program in water⁶⁵⁻⁶⁷ is the development of a porphyrin POC that is resistant to hydrolytic decomposition,⁶⁸⁻⁷⁰ which we have used to create a porous iron porphyrin catalyst for CO₂ reduction where the permanent porosity increases the density of electrochemically-active sites for catalysis as well as transport of gaseous substrates and products.⁷¹

Results and Discussion

To synthesize the supramolecular catalysts, we first prepared the free-base porphyrin box, **PB-1(6)**, through condensation of six tetraformylphenyl porphyrins with eight tripodal triamines bearing hexyloxy solubilizing groups.⁶⁹ Treatment of **PB-1(6)** with excess NaBH₄ reduces the twenty-four imine bonds to amines yielding the reduced porphyrin box, **rPB-1(6)**, as shown in Scheme 3.2. MALDI-MS shows the expected mass increase after reduction (Figure 3.5), and IR shows the disappearance of the imine absorption band (Figure 3.15). Furthermore, ¹H NMR shows the disappearance of the imine peak and subsequent broadening of the remaining resonances, which we attribute to a large degree of conformational heterogeneity. Using analogous methods to our previous work,^{69,71} cobalt was introduced into all six porphyrin moieties in both **PB-1(6)** and **rPB-1(6)** by heating with CoCl₂ and 2,6-lutidine in THF (Scheme 3.2). MALDI-MS and UV/Vis show complete metalation for each catalyst (Figures 3.6-3.7, 3.9-3.13). The porous nature of **Co-PB-1(6)** was confirmed with N₂ sorption analysis giving a Brunauer-Emmett-Teller surface area of 562 m²/g (Figure 3.18), which is in agreement with our previous report on **Zn-PB-1(6)**.⁶⁹ In contrast, N₂ sorption studies showed **Co-rPB-1(6)** to be relatively non-porous with a surface area of 23 m²/g. Molecular dynamics (MD) simulations support these data and suggest that **PB-1(6)** is a rigid structure that maintains an inner pore, whereas the more flexible amine linkers in **rPB-1(6)** result in partial cage collapse as has been observed in other imine-reduced POCs.⁷²⁻⁷⁴

Each catalyst was heterogenized into inks composed of multi-walled carbon nanotubes (MWCNTs) and Nafion in THF and deposited onto glassy carbon disc electrodes. This protocol lowers the amount of catalyst required, improves electrical contact, and enables the use of benign aqueous electrolytes. Catalyst inks were formulated from THF mixtures containing 2 mg/mL MWCNTs and 10 μ L/mL 5% Nafion with either 0.3 mM **Co-PB-1(6)**/**Co-rPB-1(6)** catalyst or 1.8 mM **Co-TPP** catalyst, which normalizes the number of cobalt atoms. Electrochemical characterization was subsequently carried out in aqueous solutions buffered to neutral pH with phosphate. For each catalyst, cyclic voltammetry (CV) measurements show a clear Co^{III}/Co^{II} reduction wave under N₂ with peak currents that scale linearly with scan rate (Figure 3.1A). The peak potential at the Co^{III}/Co^{II} reduction is 0.54 V for **Co-TPP**, 0.55 V for **Co-PB-1(6)**, and 0.40 V for **Co-rPB-1(6)**. The negative shift in reduction potential for **Co-rPB-1(6)** is likely a result of the more electron-donating effect of the twenty-four amine substituents in the reduced cage relative to imine linkages in **Co-PB-1(6)**. The Co^{III}/Co^{II} wave for **Co-TPP** is irreversible, whereas **Co-PB-1(6)** and **Co-rPB-1(6)** display broadened re-oxidation waves, and at slow scan rates more minor redox features are observable, suggesting a distribution of closely related active sites in the catalyst films. Analysis of the scan rate dependence of the Co^{III}/Co^{II} reduction waves yields the number of electrochemically active cobalt centers (EA_{Co}) in each heterogeneous film.^{71,75} For **Co-TPP**, **Co-PB-1(6)**, and **Co-rPB-1(6)**, the observed EA_{Co} were 6.3 nmol/cm², 9.1 nmol/cm², and 4.2 nmol/cm², respectively. The amount of catalyst ink added to each electrode contained 91.8 nmol/cm² of cobalt centers, so the percentage of EA_{Co} in the **Co-TPP**, **Co-PB-1(6)**, and **Co-rPB-1(6)** electrodes were 6.8%, 9.9%, and 4.6%, respectively. These values are in the range observed for other molecular catalysts adsorbed onto heterogeneous supports in a similar manner.^{76,77} **Co-PB-1(6)** exhibits the largest percentage of EA_{Co}, which agrees with our previous studies suggesting that the porosity enhances active site exposure.⁷¹ **Co-rPB-1(6)** has the lowest percentage of EA_{Co}, which we attribute to the loss in porosity after imine reduction observed by gas sorption and MD.

We speculate that this observed loss of porosity upon imine reduction produces less accessible pores for electrolyte to enter and balance the applied negative potential, thus limiting the EA_{Co} .

After saturating the aqueous electrolyte with O_2 , CVs show large current enhancements at positively shifted Co^{III}/Co^{II} waves, indicating catalysis of the ORR (Figure 3.1B). The catalytic onset potentials, defined as the potential at half the peak catalytic current ($E_{cat/2}$), are 0.60 V for **Co-TPP**, 0.63 V for **Co-PB-1(6)**, and 0.48 V for **Co-rPB-1(6)**. The standard reduction potentials in pH 7 water for the $2 e^-$ reduction of O_2 into H_2O_2 is 0.70 V vs. RHE, while for the $4 e^-$ reduction of O_2 into H_2O it is 1.23 V.⁷⁸ Thus, it is clear that cobalt porphyrin molecular and supramolecular catalysts are primed for low overpotential H_2O_2 generation, with the $E_{cat/2}$ of **Co-PB-1(6)** occurring at a H_2O_2 overpotential of just 70 mV. CVs of an electrode modified with catalyst-free ink shows a catalytic O_2 reduction current with a more negative $E_{cat/2}$ of 0.28 V, subsequent to a reversible wave indicating poor catalysis with formation of superoxide (Figure 3.19).

A rotating ring-disk electrode (RRDE) was used to quantify the formation of H_2O_2 upon ORR. Figure 3.2A shows the RRDE responses for each catalyst in which significant ring currents are observed, indicating H_2O_2 generation. The product selectivity for ORR for each catalyst can then be calculated and is plotted as a function of applied potential in Figure 3.2B. **Co-TPP** displays minimal product selectivity with ca. 50% Faradaic efficiency for H_2O_2 , which is common with mononuclear cobalt porphyrins^{23,27,43,79} and may be attributed to catalyst aggregation that creates intermolecular active sites that can catalyse the off-pathway $4 e^-$ reduction of O_2 into H_2O . The selectivity of porphyrin ORR catalysts is also known to be highly dependent on the proton source⁹ and catalyst medium.⁸⁰ In contrast, both **Co-PB-1(6)** and **Co-rPB-1(6)** show high selectivity for the $2 e^-$ reduction of O_2 into H_2O_2 , attaining 100% H_2O_2 generation near the $E_{cat/2}$. Product selectivity drops slowly to ca. 90% upon scanning up to 500 mV more negative for each catalyst. We attribute this enhancement in ORR selectivity to H_2O_2 product to the site isolation imparted by the supramolecular arrangement of the cobalt centers. Whereas intermolecular aggregation with the supramolecular catalysts is possible, the high observed H_2O_2 product selectivity suggests that it is deterred, presumably due to the presence of hexyloxy alkyl chains that prevent close contacts between cages. Additionally, the partial cage collapse observed for **Co-rPB-1(6)** does not appear to be significant enough to facilitate formation of bimetallic sites, as MD simulations show a distance of at least 9 Å between opposing porphyrins within individual cages. The catalyst-free ink is capable of the ORR at more negative potentials, but the H_2O_2 selectivity is highly potential dependent, ranging from 43-79% over the same potential regime tested for the Co porphyrin cage systems (Figure 3.20).

To compare the rates of ORR catalysis for **Co-TPP**, **Co-PB-1(6)**, and **Co-rPB-1(6)**, we can estimate the turnover frequencies (TOF) from the observed current densities at various rotation rates. However, typical Koutecky-Levich (K-L) analysis of all three catalysts gave electron transfer values inconsistent with RRDE data where H_2O_2 is quantified, indicating that the assumptions for K-L analysis, including ideal mass transport and a single-step reaction, do not apply in these heterogenized supramolecular catalyst conditions.⁸¹ In particular, rotating disk electrode analysis shows that each catalyst displays two closely-spaced catalytic waves, indicating that multiple mechanisms are taking place (Figure 3.21). Instead, we approximate the observed catalytic currents as kinetic currents in order to compare potential dependent TOFs for H_2O_2 for these tested conditions. Specific current densities for H_2O_2 generation were obtained by

multiplying the observed disk current by the Faradaic efficiency for H_2O_2 at each potential. Additionally, TOF values were calculated either per the total amount of added Co or per the EA_{Co} determined in each electrode. Plots of $\log(\text{TOF})$ vs. H_2O_2 overpotential could then be constructed as shown in Figure 3 in which $\log(\text{TOF})$ increases at larger overpotentials until a plateau is reached indicating that the catalyst is fully reduced and the maximum observed rate constant (k_{obs}) is attained. The estimated rates are competitive with state-of-the-art molecular catalysts for selective H_2O_2 formation at low overpotential.^{33,34,51} When normalizing the estimated TOFs to the total amount of cobalt added to each electrode (Figure 3.3A), **Co-PB-1(6)** and **Co-rPB-1(6)** show identical maximum TOFs ($\text{TOF}_{\text{max}} = k_{\text{obs}}$) of 0.08 s^{-1} , which is double the 0.04 s^{-1} for **Co-TPP**. These values are comparable, suggesting that the supramolecular structure has a greater effect on catalytic selectivity rather than activity. The higher observed TOF_{max} for **Co-PB-1(6)** compared to **Co-TPP** could be result of the greater percentage of active cobalt site due to improved porosity, whereas the increase in TOF_{max} for **Co-rPB-1(6)** despite its reduced porosity is more likely a result of increased number of electron-donating substituents, as evidenced by its shift in catalytic $E_{\text{cat}/2}$ relative to monomer and porous box congeners. Indeed, a linear scaling relationship correlating $\log(\text{TOF})$ and the $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ reduction potential is typically observed.³⁴ Another possibility is that the pendant amines in **Co-rPB-1(6)** act as intramolecular proton relays that can accelerate catalysis, which will be probed in future studies. If the rates are instead normalized to the amount of EA_{Co} in each electrode (Figure 3.3B), then **Co-rPB-1(6)** exhibits an increase in TOF_{max} to 1.55 s^{-1} compared to 0.77 s^{-1} and 0.65 s^{-1} for **Co-PB-1(6)** and **Co-TPP**, respectively. In this comparison, **Co-rPB-1(6)** shows a more pronounced increase in TOF that overrides its relative lack of porosity.

Conclusion

To close, we have established a supramolecular approach to electrochemical ORR catalysis in neutral pH water where site isolation and porosity synergistically aid in favoring the 2 e^- reduction to generate H_2O_2 with 100% selectivity over the more thermodynamically favored 4 e^- H_2O product. Moreover, the supramolecular imine cage structure can be further tuned by chemical reduction to an amine cage that is a more flexible and electron-rich supramolecular catalyst. This supramolecular tuning resulted in a catalyst with superior TOF that maintains high selectivity for H_2O_2 . In addition to furthering the applications of POCs for catalysis, we have demonstrated that POCs are amenable to both modular and sequential tuning of the molecular structure that can be exploited for optimizing catalyst performance. This work provides a starting point for the use of supramolecular chemistry in an alternative and complementary way to conventional strategies that exploit porous structures to favor substrate binding and/or product release by host-guest interactions and disfavor larger substrates, or increase catalyst stability by preventing intermolecular decomposition pathways. In this case, the supramolecular structure site isolates the discrete molecular unit in order to promote selective chemistry beyond the molecule itself.

Materials and Methods

General Methods. All reagents and solvents were purchased from commercial sources and used without further purification unless specified. Oxygen (99.99%) and nitrogen (99.998%) were purchased from Praxair. Multi-walled carbon nanotubes (MWCNTs) were purchased from Sigma-Aldrich and were washed with 10% HCl followed by deionized water until the filtrate was neutral and then dried *in vacuo* before use. 2,6-Lutidine was purchased from Sigma-Aldrich and dried over AlCl₃ then purified by distillation. Co(II) tetraphenylporphyrin (**Co-TPP**) was purchased from Frontier Scientific and CoCl₂ was purchased from Strem Chemicals and used as received. Sodium phosphate monobasic, sodium phosphate dibasic and Nafion 117 solution (5%) were purchased from Sigma-Aldrich and used as received. The free-base porphyrin box was synthesized and characterized as previously described.⁶⁹ THF was dried using a JC Meyer solvent purification system. Deionized water was obtained from a Millipore Autopure system. UV/Vis spectra were collected using an Agilent Cary 60 spectrophotometer at room temperature. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry spectra were obtained using an Applied Biosystems Voyager DE Pro at the QB3 Mass Spectrometry Facility at the University of California, Berkeley. FT-IR spectra were collected using a Bruker ALPHA-P spectrometer. NMR spectra were recorded on a Neo-500 Bruker spectrometer. Computations were performed in the Molecular Graphics and Computation Facility at the University of California, Berkeley.

Gas Sorption Measurements. Gas sorption isotherms of **Co-PB-1(6)** and **Co-rPB-1(6)** were measured with a BELSORP-max volumetric adsorption analyzer. Typically, a sample of as-synthesized material (~40 mg) was loaded and, prior to the measurements, residual solvents were evacuated by heating to 100 °C under high vacuum (10⁻² Pa) overnight.

Electrochemistry. All electrochemistry experiments were performed using a BioLogic VSP-300 potentiostat at RT. The electrolyte used was 0.1 M potassium phosphate buffer at pH 7 saturated with either N₂ or O₂. A platinum coil counter electrode (BASi) and an aqueous Ag/AgCl sat. KCl reference electrode (BASi) were used for all experiments. No iR compensation was applied.

Cyclic Voltammetry. Aqueous voltammetry studies were performed with a three-electrode cell equipped with a glassy carbon disk (5.0 mm diameter) working electrode (Pine Research Instrumentation), a platinum coil counter electrode (BASi), and a Ag/AgCl sat. KCl reference electrode (BASi). The electrolyte was sparged with N₂ or O₂ for 10 min before obtaining CVs. Three CV scans were performed prior to data collection.

Rotating Ring-Disk Electrode Voltammetry. RRDE experiments were conducted using a 5 mm diameter glassy carbon disk electrode with a platinum ring electrode in a ChangeDisk assembly attached to a Modulated Speed Rotator (Pine Research Instrumentation). The ring collection efficiency was determined to be 0.24 using potassium ferricyanide dissolved in neutral phosphate buffer. The disk electrode was modified with catalyst ink (*vide infra*) prior to determining the ring collection efficiency in order to account for the modified electrode geometry and surface roughness.⁸¹ The ring electrode potential was set to 1.2 V vs. Ag/AgCl to oxidize the collected H₂O₂ without any observable oxidation of H₂O. Linear sweep voltammograms were performed at 20 mV/s with 250 rpm rotation rate. The integrity of the catalyst film was observed to decline at faster rotation rates. Three LSV scans were performed prior to data collection.

Preparation of Working Electrodes. The glassy carbon (GC) disk electrode (0.196 cm²) was thoroughly polished with 0.5 μm alumina powder, rinsed with isopropanol, and dried in air. Catalyst inks were prepared by first dispersing 2 mg/mL of MWCNTs in THF by sonication for 30 min. This mixture was then added to solid catalyst to give a concentration of 0.3 mM for **Co-PB-1(6)** and **Co-rPB-1(6)** or 1.8 mM for **Co-TPP**, thus normalizing the number of cobalt atoms in each ink. Then, 10 μL of Nafion 5% solution was added per 1 mL of ink solution. The mixture was sonicated for another 30 min. To the 5 mm diameter glassy carbon disk electrode was added 10 μL of the ink solution, which was dried in air prior to use.

Electrochemically Active Surface Area. Scan rate dependence was performed at 100, 200, 300, 400, and 500 mV/s at the Co^{III}/Co^{II} redox couple for each catalyst in 0.1 M pH 7 phosphate buffer saturated with N₂. The number of electroactive Co centers in the catalyst films (Γ , mol/cm²) was determined using the Equation 1:

$$i_p = n^2 F S \Gamma \frac{F \nu}{4 R T} \quad \text{Equation 1}$$

where i_p is the peak current of the Co^{III}/Co^{II} redox couple, n is the number of electrons ($n = 1$), F is Faraday's constant (96485 C/mol), S is the geometrical surface area of the electrode (0.196 cm²), ν is the scan rate in V/s, R is the gas constant (8.314 J/K mol), and T is the temperature (298 K). The number of electrons, n , is taken to be 1 for the single electron transfer. This treats each cobalt porphyrin moiety as independent of one another.^{71,75}

Oxygen Reduction Analysis. Using the results from RRDE analysis, hydrogen peroxide product selectivity as a function of the applied potential (E) was determined using Equation 2:

$$\% H_2O_2(E) = 200 \times \frac{\frac{i_r(E)}{N_c}}{i_d(E) + \frac{i_r(E)}{N_c}} \quad \text{Equation 2}$$

where $i_d(E)$ is the observed disk current and $i_r(E)$ is the observed ring current at the potential E , and N_c is the measured collection efficiency for the modified RRDE (*vide supra*).²⁰

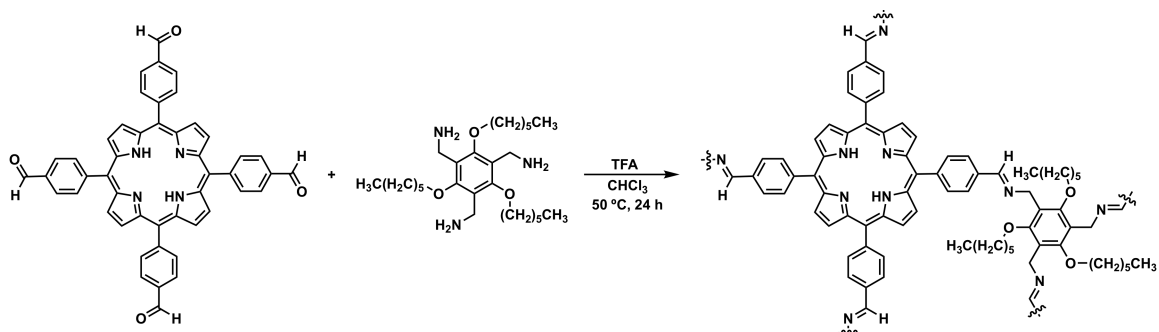
The turnover frequency (TOF) for H₂O₂ production by each catalyst was approximated from the RRDE data using Equation 3:

$$TOF = \frac{j_{H_2O_2}(E)}{1000 F n \Gamma_{Co}} \quad \text{Equation 3}$$

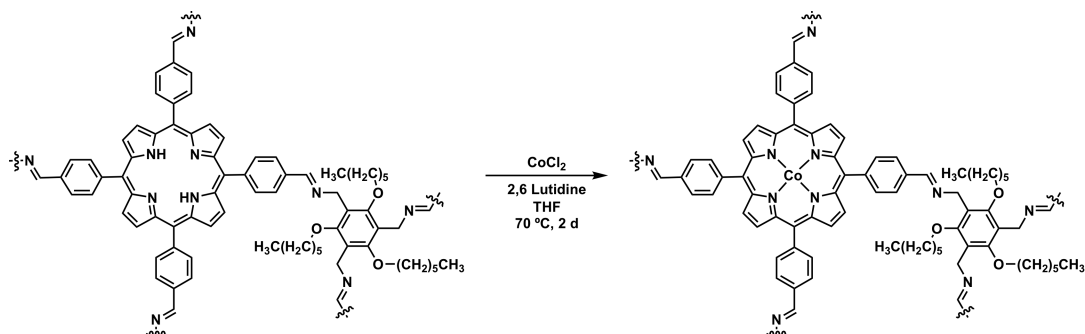
where $j_{H_2O_2}(E)$ is the potential dependent current density (mA/cm²) at the disk electrode multiplied by the potential dependent Faradaic efficiency for H₂O₂, F is Faraday's constant (96485 C/mol), n is the number of electrons transferred per reduced O₂ and is taken to be 2 for the production of H₂O₂, and Γ_{Co} is the number of cobalt centers (mol/cm²) on the electrode, either as the total amount added or the number of electrochemically active metals.^{51,82}

Computational Details. Structural geometry optimizations were performed starting from the crystal structure of **PB-1(4)**.⁶⁸ Using Maestro, atoms were added to give the **PB-1(6)** structure and

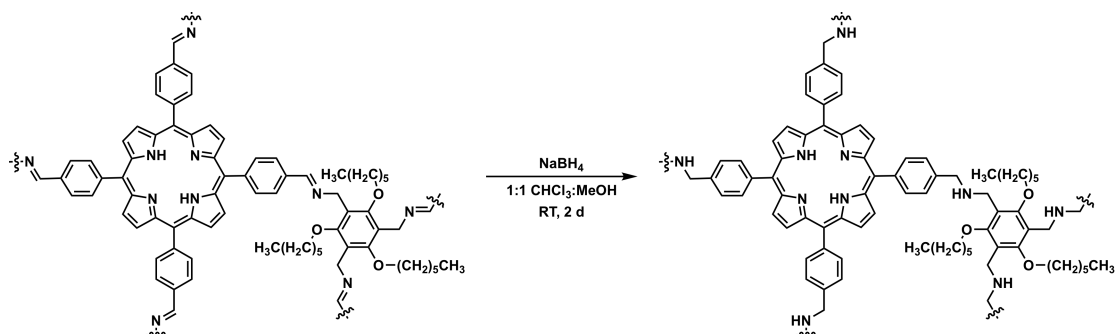
the **rPB-1(6)** structure. An initial geometry optimization of each molecule was performed using MacroModel minimization with the OPLS3e force field. The PRCG method was used with gradient convergence of $0.05 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$. Next, to better sample the conformational space of the porous organic cages, high temperature molecular dynamics simulations were performed using Desmond.⁸³ The OPLS3e force field was used at 700 K for 20 ns with a time interval of 5 ps. Finally, each structure obtained along the molecular dynamics trajectories was geometry optimized using MacroModel minimization with the OPLS3e force field as above, and then the lowest energy conformer was identified.



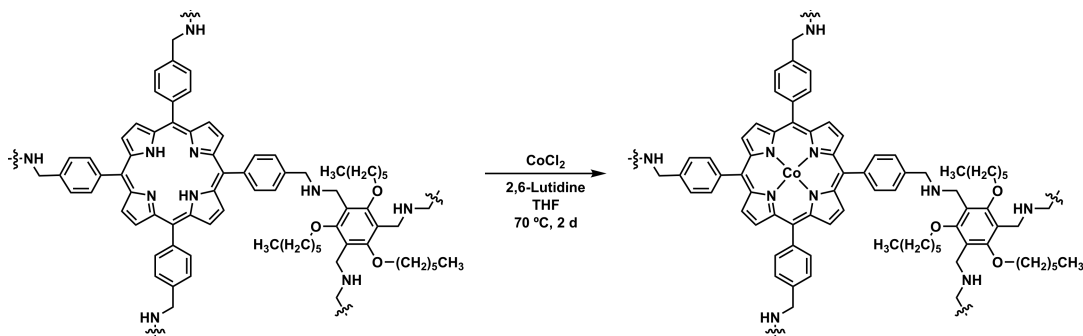
Synthesis of PB-1(6). PB-1(6) was synthesized following our previous report.⁶⁹ ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 24H), 8.72 (s, 48H), 8.30 (d, *J* = 7.8 Hz, 24H), 8.20 (d, *J* = 7.8 Hz, 24H), 8.08 (d, *J* = 7.8 Hz, 24H), 7.94 (d, *J* = 7.8 Hz, 24H), 5.11 (s, 48H), 4.25 (m, 48H), 1.94 (m, 48H), 1.53-1.47 (m, 48H), 1.44 (m, 96H), 0.98 (t, *J* = 6.3 Hz, 72H), −3.05 (s, 12H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 160.7, 159.3, 144.4, 136.0, 135.2, 128.1, 124.6, 123.0, 119.9, 76.2, 54.8, 32.0, 30.1, 25.7, 22.9, 14.5 ppm. MALDI-MS (matrix: DCTB) *m/z* calcd. for C₅₀₄H₅₄₀N₄₈O₂₄ [M]⁺: 7653.27, found: 7653.47. FT-IR (solid) 2927, 1641, 1259, 1102, 966, 800 cm^{−1}. UV/Vis (THF) λ_{abs} 418, 516, 552, 594, 650 nm.



Synthesis of Co-PB-1(6). Under a dinitrogen atmosphere, **PB-1(6)** (50 mg, 6.5 μmol) and CoCl₂ (85 mg, 0.65 mmol, 100 equiv.) were dissolved in anhydrous THF (40 mL). Subsequently, 2,6-lutidine (23 μL, 0.20 mmol, 30 equiv.) was injected, and the reaction mixture was heated at 70 °C for 2 d. After cooling to room temperature, solvent was removed under reduced pressure. Then, acetonitrile (25 mL) was added, and after sonication for 30 s to suspend the product, the mixture was transferred to a conical tube and centrifuged. The supernatant was then decanted off. This washing cycle with acetonitrile was repeated eight times. Next, the product was suspended again in acetonitrile (25 mL) and allowed to soak overnight at room temperature. After vacuum filtration and further washing with methanol and dichloromethane, **Co-PB-1(6)** was obtained as a dark red-brown powder in quantitative yield. MALDI-MS (matrix: DCTB) *m/z* calcd. for C₅₀₄H₅₂₈Co₆N₄₈O₂₄ [M]⁺: 7994.77, found: 7994.64. Anal. calcd. for (C₅₀₄H₅₂₈Co₆N₄₈O₂₄)(CH₂Cl₂)₈: C, 70.89; H, 6.32; N, 7.75. Found: C, 71.27; H, 5.80; N, 8.04. FT-IR (solid) 2923, 1644, 1350, 1103, 1000, 798, 715 cm^{−1}. UV/Vis (THF) λ_{abs} 417, 529 nm.

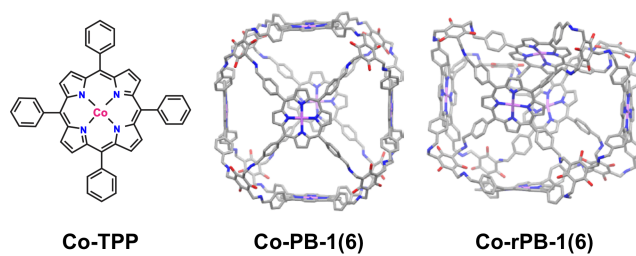


Synthesis of rPB-1(6). In a 50 mL two-neck round bottom flask, **PB-1(6)** (100 mg, 0.013 mmol) was dissolved in CHCl_3 (16 mL). Methanol (16 mL) was then added, and the mixture was sparged with N_2 for 10 min. Next, NaBH_4 (48 mg, 1.3 mmol, 100 equiv.) was added, and the reaction mixture was stirred at room temperature under N_2 overnight. A second portion of NaBH_4 (48 mg, 1.3 mmol, 100 equiv.) was then added and stirring was continued for 15 h. The reaction mixture becomes more homogeneous throughout the course of the reaction. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and then washed four times with H_2O (20 mL). The organic phase was isolated and the solvent was removed by rotary evaporation. The purple residue was then suspended in methanol (10 mL) and sonicated for 2 min. Vacuum filtration and additional washing with methanol yielded a shiny purple solid (100 mg, 99% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.76 (s, 48H), 8.09–7.71 (m, 96H), 4.19 (br s, 144H), 2.27 (br s, 24 H), 2.03 (br s, 48H), 1.74 (br s, 48H), 1.52 (br s, 96 H), 1.00 (br s, 72H), -3.10 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 158.0, 140.6, 134.8, 130.9, 126.2, 123.9, 120.0, 76.0, 54.4, 44.7, 32.0, 30.9, 26.2, 23.0, 14.4 ppm. MALDI-MS (matrix: DCTB) m/z calcd. for $\text{C}_{504}\text{H}_{588}\text{N}_{48}\text{O}_{24}$ $[\text{M}]^+$: 7701.64, found: 7701.65. FT-IR (solid) 2961, 1579, 1259, 1090, 1017, 966, 797 cm^{-1} . UV/Vis (THF) λ_{abs} 415, 514, 550, 592, 650 nm.

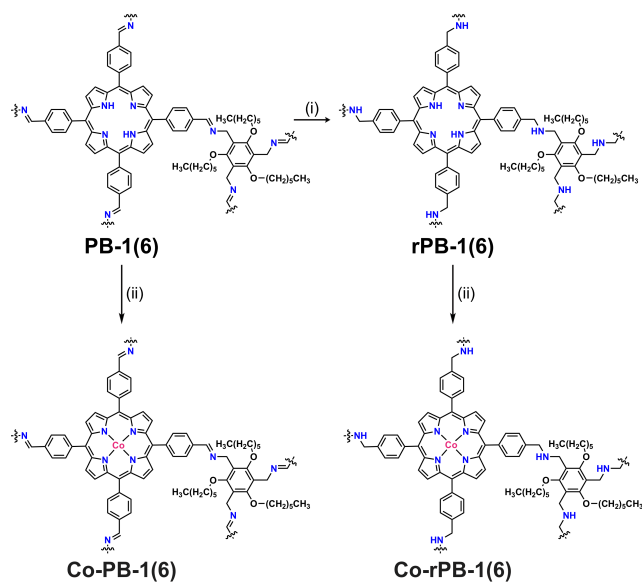


Synthesis of Co-rPB-1(6). Cobalt metalation of **rPB-1(6)** was carried out in a similar manner to that for metalation of **PB-1(6)**. Under a dinitrogen atmosphere, **rPB-1(6)** (50 mg, 6.5 μmol) and CoCl_2 (84 mg, 0.65 mmol, 100 equiv.) were dissolved in anhydrous THF (40 mL). Subsequently, 2,6-lutidine (23 μL , 0.19 mmol, 30 equiv.) was injected, and the reaction mixture was heated at 70 $^\circ\text{C}$ for 2 d. After cooling to room temperature, solvent was removed under reduced pressure. Then, acetonitrile (25 mL) was added, and after sonication for 30 s to suspend the product, the mixture was transferred to a conical tube and centrifuged. The supernatant was then decanted off. This washing cycle with acetonitrile was repeated 8 times. Next, the product was suspended again in acetonitrile (25 mL) and allowed to soak overnight at room temperature. After vacuum filtration

and further washing with methanol and dichloromethane, **Co-rPB-1(6)** was obtained as a dark purple-brown powder in quantitative yield. MALDI-MS (matrix: DCTB) m/z calcd. for $C_{504}H_{576}Co_6N_{48}O_{24}$ $[M]^+$: 8043.15, found: 8043.26. Anal. calcd. for $(C_{504}H_{588}Co_6N_{48}O_{24})(CH_2Cl_2)_8(CH_3CN)_2$: C, 70.38; H, 6.85; N, 7.95. Found: C, 70.71; H, 6.53; N, 8.21. FT-IR (solid) 2924, 1578, 1350, 1206, 1152, 1100, 999, 796, 717, 505 cm^{-1} . UV/Vis (THF) λ_{abs} 416, 533 nm.



Scheme 3.1. Chemical structure of **Co-TPP** and computed lowest energy conformational models of **Co-PB-1(6)** and **Co-rPB-1(6)**. Hydrogen atoms and alkyl chains are omitted for clarity.



Scheme 3.2. Synthesis of the reduced porphyrin box **rPB-1(6)** from **PB-1(6)** and the catalysts **Co-PB-1(6)**, and **Co-rPB-1(6)**. (i) NaBH₄, 1:1 CHCl₃:MeOH, RT, 48 h. (ii) CoCl₂, 2,6-lutidine, THF, 70 °C, 48 h.

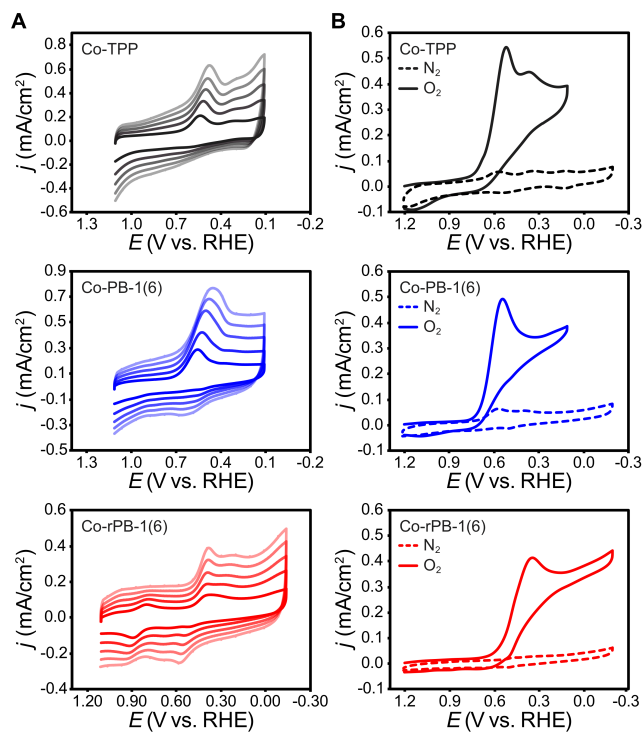


Figure 3.1. (A) CVs under N₂ at 100-500 mV/s scan rates of **Co-TTP** (black), **Co-PB-1(6)** (blue), and **Co-rPB-1(6)** (red) in pH 7 phosphate buffer. (B) CVs under N₂ (dashed) and O₂ (solid) atmosphere at 20 mV/s scan rates. All CVs were performed starting with the reductive sweep.

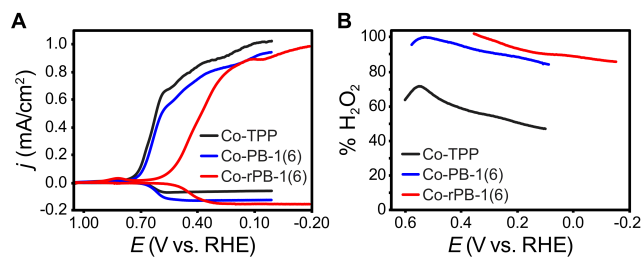


Figure 3.2. (A) RRDE data at 250 rpm and 20 mv/s in pH 7 phosphate buffer. (B) The corresponding H₂O₂ Faradaic efficiencies for each catalyst as a function of the applied potential.

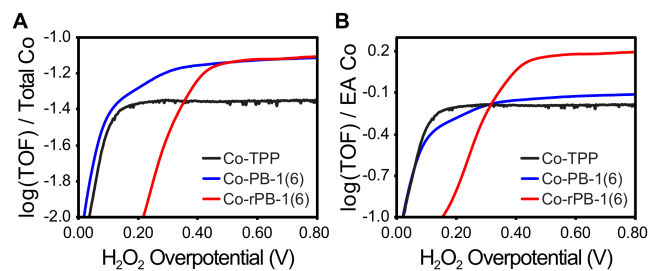


Figure 3.3. Plots of the $\log(\text{TOF})$ vs. overpotential for H_2O_2 production. (A) TOFs normalized per the total amount of Co added to each electrode. (B) TOFs normalized per the amount of EA_{Co} measured in each electrode.

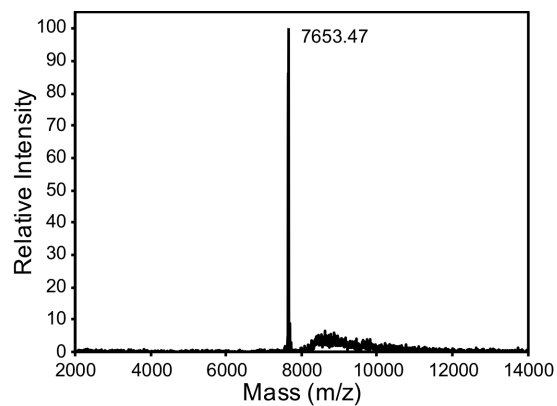


Figure 3.4. MALDI-MS spectrum with DCTB matrix of **PB-1(6)**. m/z calcd. for $C_{504}H_{540}N_{48}O_{24}$ $[M]^+$: 7653.27, found: 7653.47.

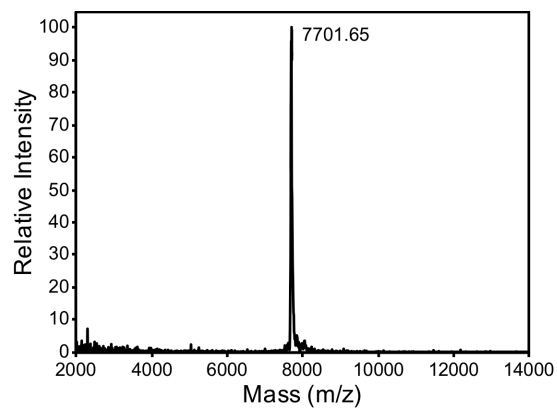


Figure 3.5. MALDI-MS spectrum with DCTB matrix of **rPB-1(6)**. m/z calcd. for $C_{504}H_{588}N_{48}O_{24}$ $[M]^+$: 7701.64, found: 7701.65.

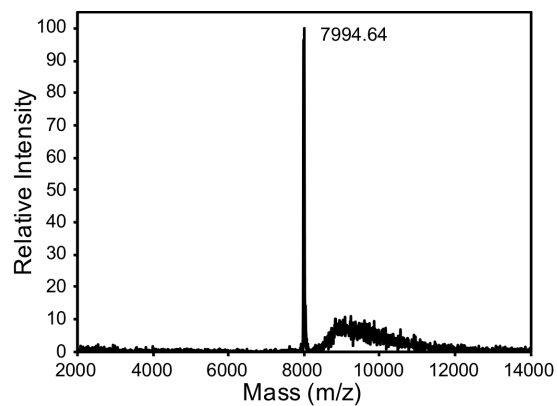


Figure 3.6. MALDI-MS spectrum with DCTB matrix of **Co-PB-1(6)**. m/z calcd. for $C_{504}H_{528}Co_6N_{48}O_{24} [M]^+$: 7994.77, found: 7994.64.

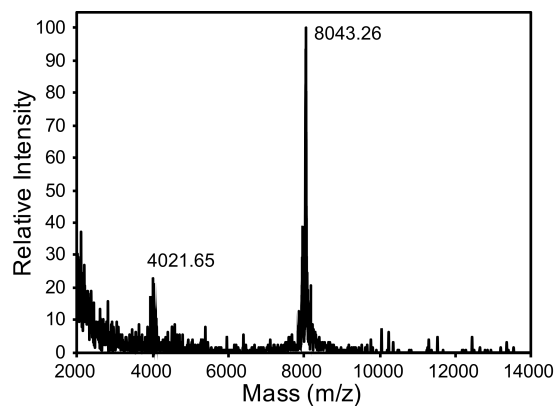


Figure 3.7. MALDI-MS spectrum with DCTB matrix of **Co-rPB-1(6)**. m/z calcd. for $C_{504}H_{576}Co_6N_{48}O_{24}$ $[M]^+$: 8043.15, found: 8043.26. m/z calcd. for $C_{504}H_{576}Co_6N_{48}O_{24}$ $[M]^{2+}$: 4021.58, found: 4021.65.

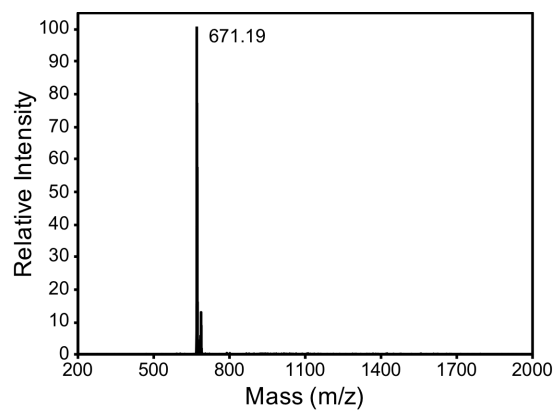


Figure 3.8. MALDI-MS spectrum with DCTB matrix of **Co-TPP**. m/z calcd. for $C_{44}H_{28}CoN_4 [M]^+$: 671.16, found: 671.19.

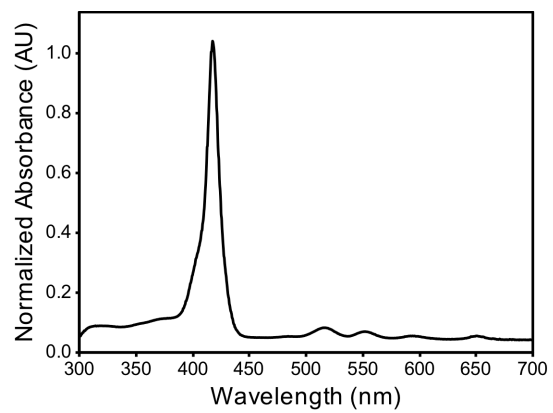


Figure 3.9. UV/Vis spectrum of **PB-1(6)** in THF. λ_{abs} 418, 516, 552, 594, 650 nm.

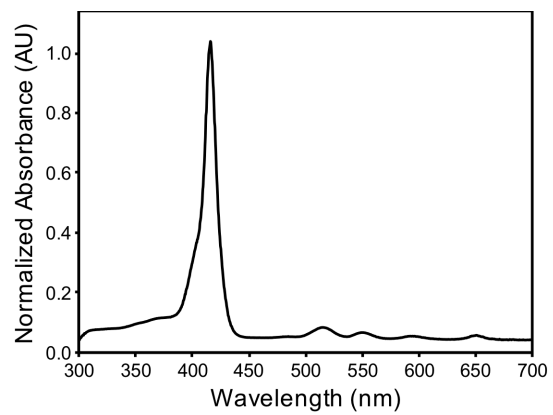


Figure 3.10. UV/Vis spectrum of **rPB-1(6)** in THF. λ_{abs} 415, 514, 550, 592, 650 nm.

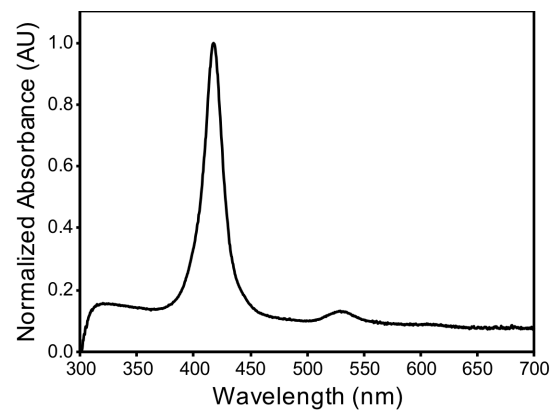


Figure 3.11. UV/Vis spectrum of **Co-PB-1(6)** in THF. λ_{abs} 417, 529 nm.

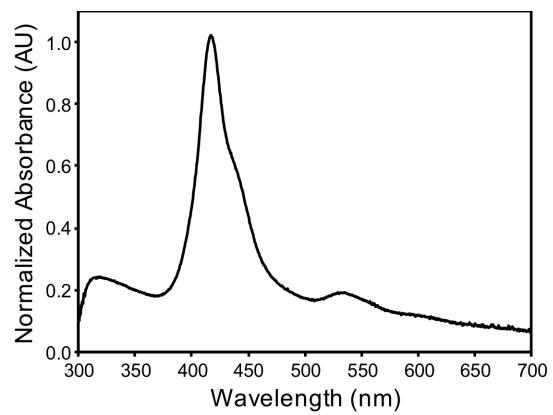


Figure 3.12. UV/Vis spectrum of **Co-rPB-1(6)** in THF. λ_{abs} 416, 533 nm.

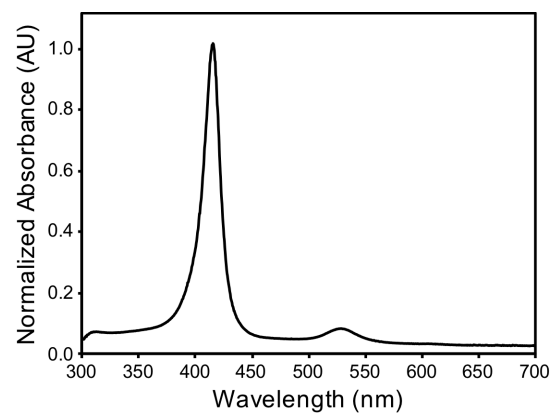


Figure 3.13. UV/Vis spectrum of **Co-TPP** in THF. λ_{abs} 415, 529 nm.

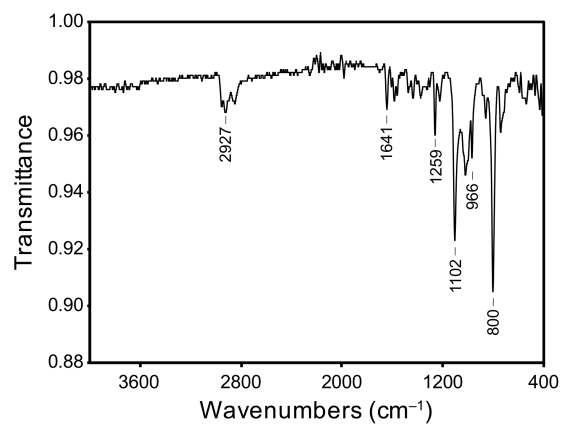


Figure 3.14. FT-IR spectrum of **PB-1(6)**. Imine stretching peak observed at 1641 cm⁻¹.

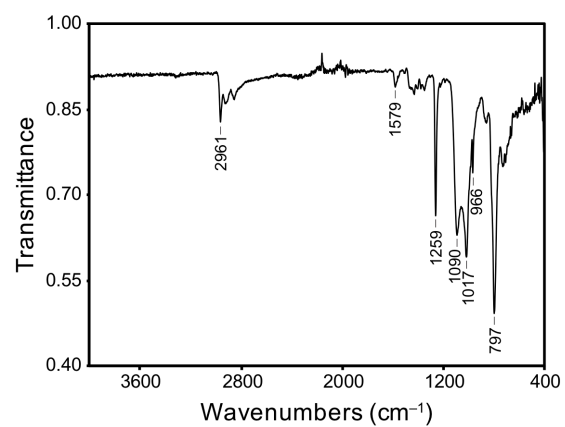


Figure 3.15. FT-IR spectrum of **rPB-1(6)**.

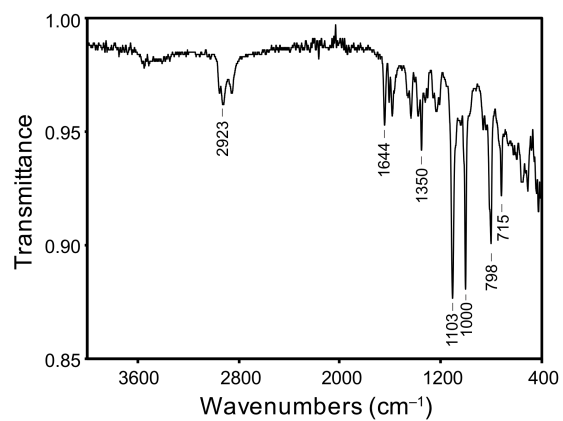


Figure 3.16. FT-IR spectrum of **Co-PB-1(6)**. Imine stretching peak observed at 1644 cm⁻¹.

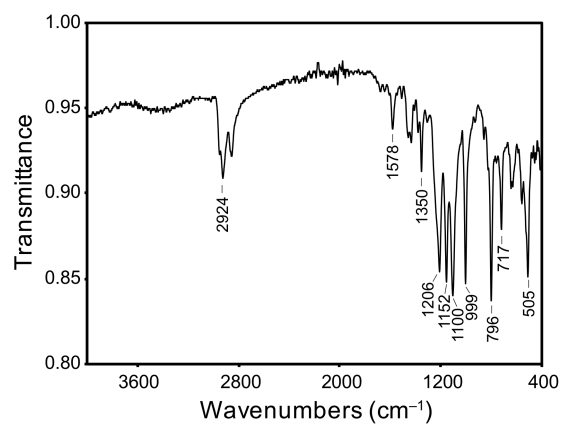


Figure 3.17. FT-IR spectrum of **Co-rPB-1(6)**.

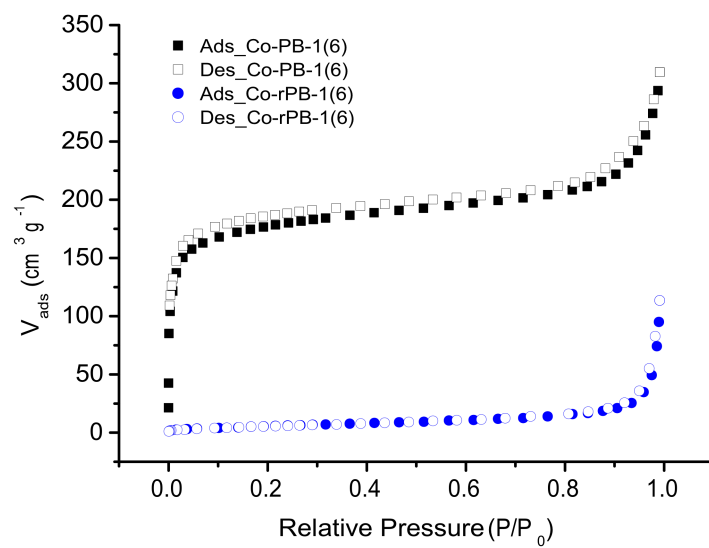


Figure 3.18. N₂ sorption isotherms for **Co-PB-1(6)** (black) and **Co-rPB-1(6)** (blue) at 77 K.

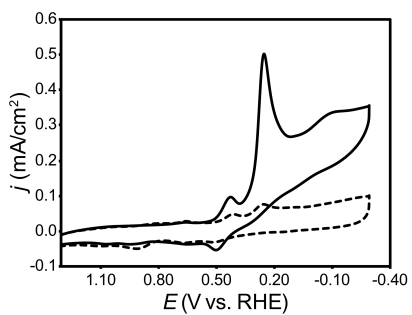


Figure 3.19. CV of catalyst-free ink at 20 mV/s under N₂ and O₂. The presence of a small reversible wave under O₂ prior to the observed catalytic current indicates that the background MWCNTs are participating in the reversible one electron reduction of O₂ to superoxide, O₂^{•−}.

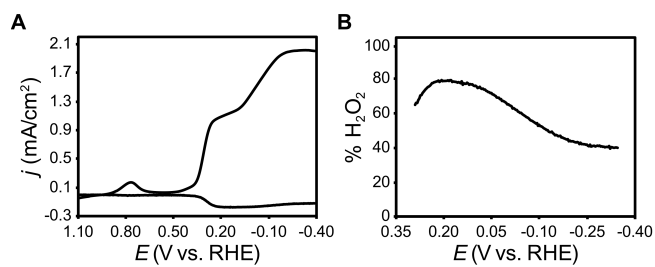


Figure 3.20. (A) RRDE of catalyst-free ink at 20 mV/s and 250 rpm under O₂. (B) The corresponding H₂O₂ Faradaic efficiency as a function of applied potential.

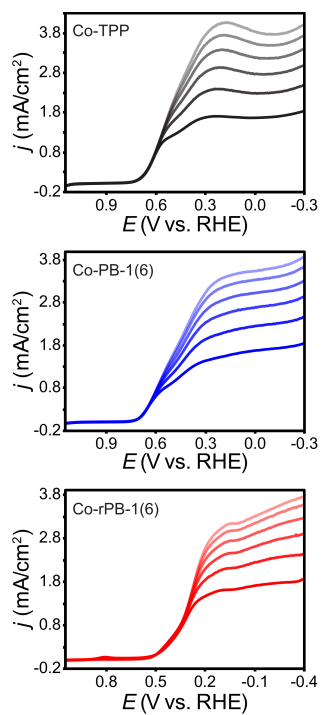


Figure 3.21. RDE traces of **Co-TPP** (black), **Co-PB-1(6)** (blue), and **Co-rPB-1(6)** (red) under O_2 at 250, 500, 750, 1000, 1250, and 1500 rpm at 20 mV/s. Multiple reduction events are observed suggesting multiple mechanisms. At these elevated rotation rates, catalyst ink was observed to physically detach from the electrode, further precluding the use of K-L analysis.

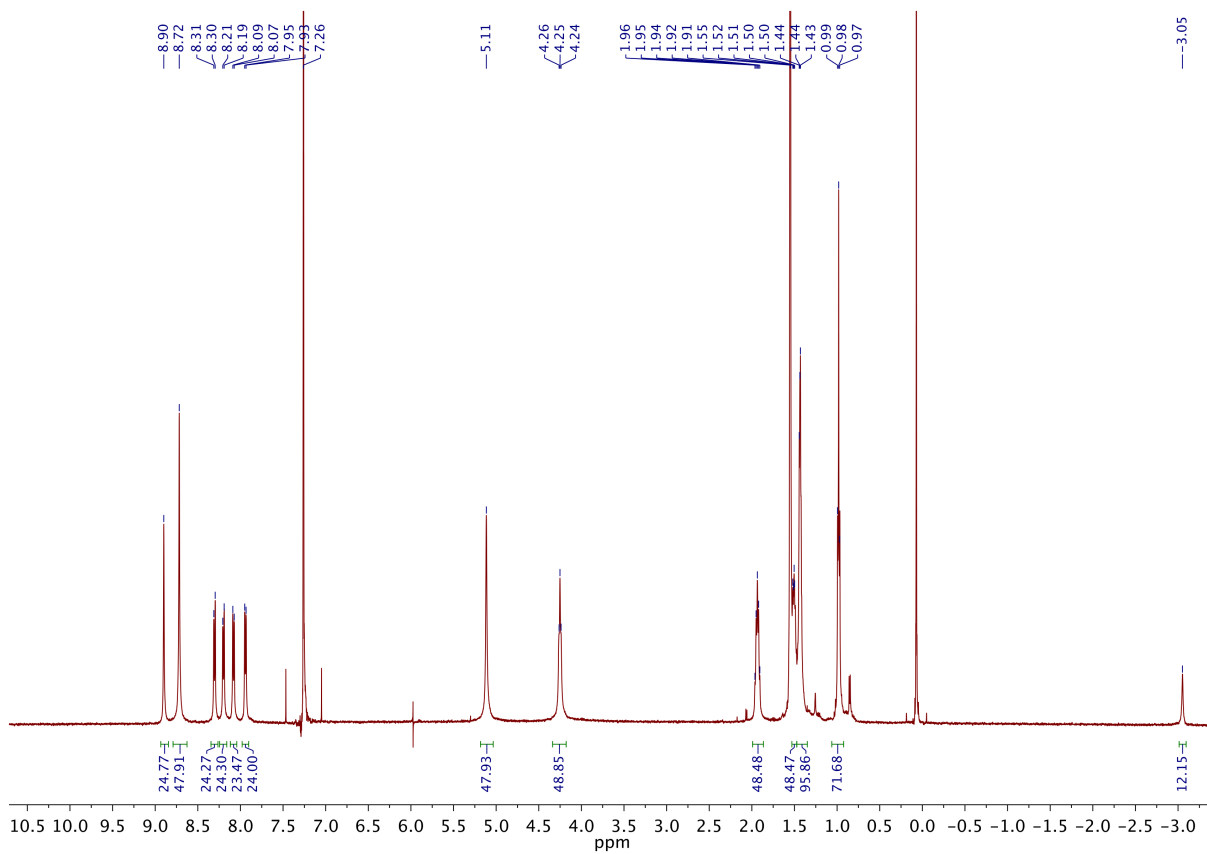


Figure 3.22. ^1H NMR (500 MHz) spectrum of **PB-1(6)** in CDCl_3 .

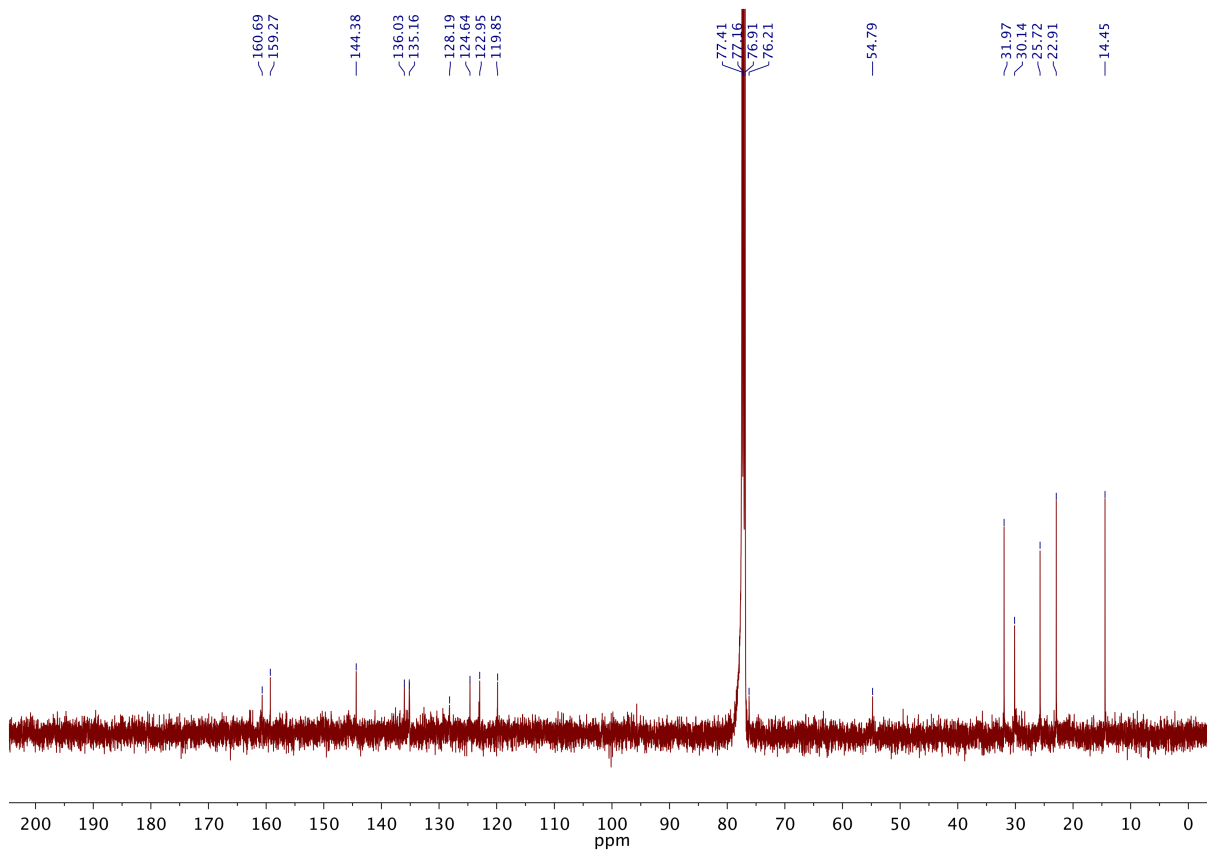


Figure 3.23. ¹³C NMR (126 MHz) spectrum of **PB-1(6)** in CDCl₃.

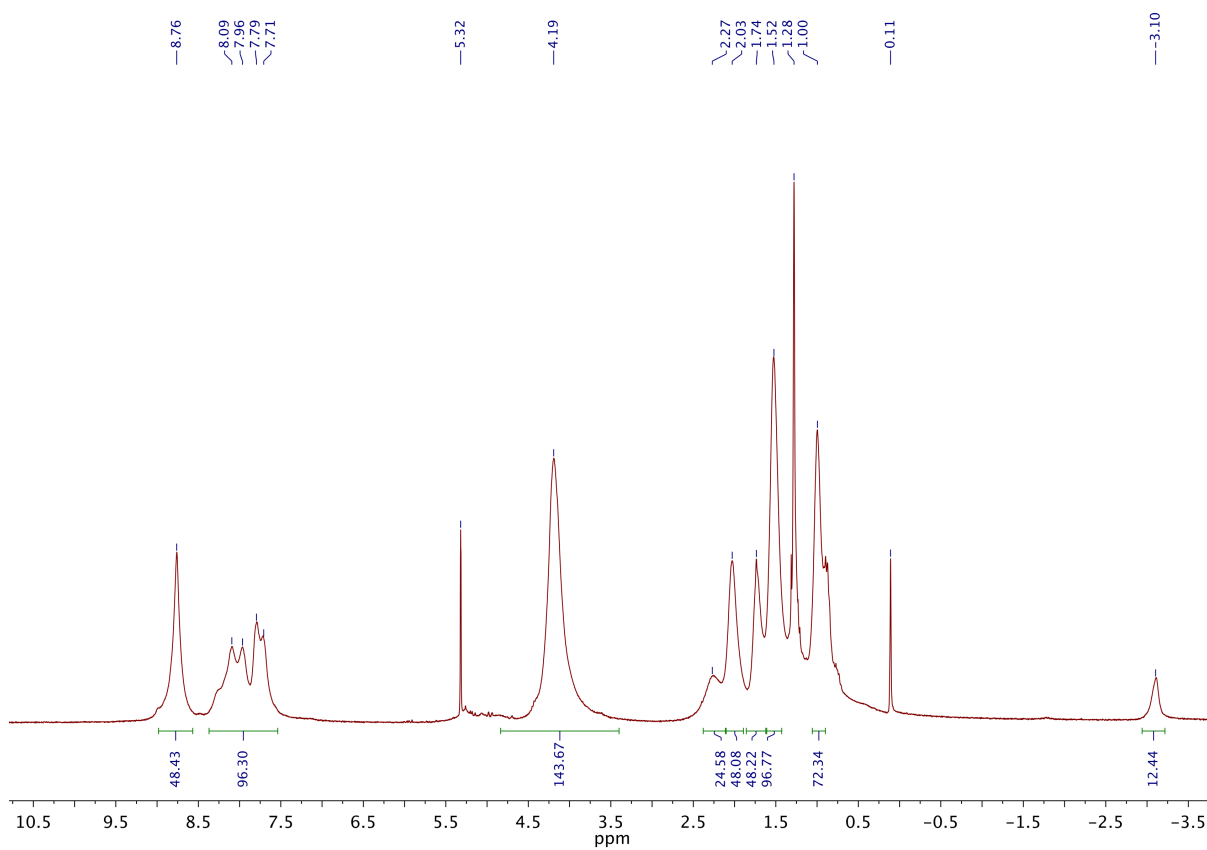


Figure 3.24. ^1H NMR (500 MHz) spectrum of **rPB-1(6)** in CD_2Cl_2 . Residual grease is observed at 1.28 and 0.11 ppm.

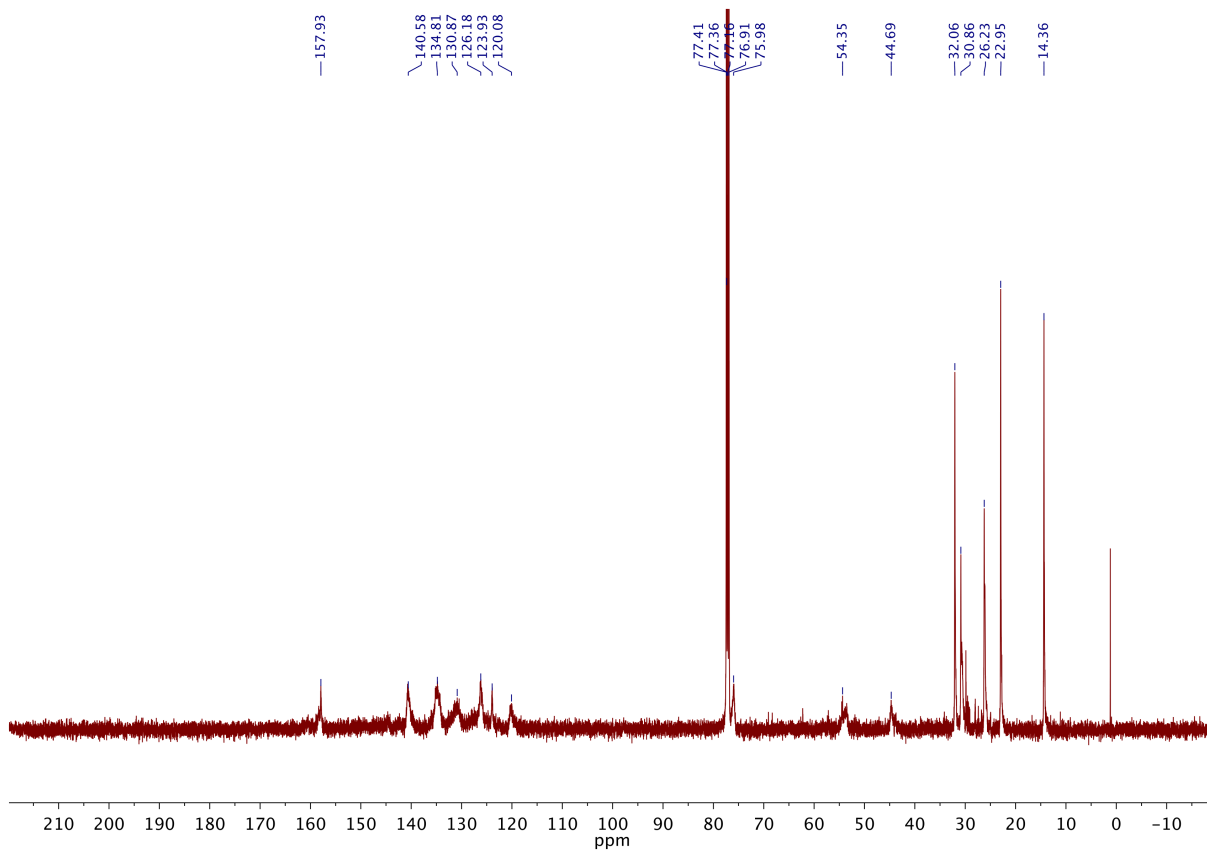


Figure 3.25. ¹³C NMR (126 MHz) spectrum of **rPB-1(6)** in CDCl₃.

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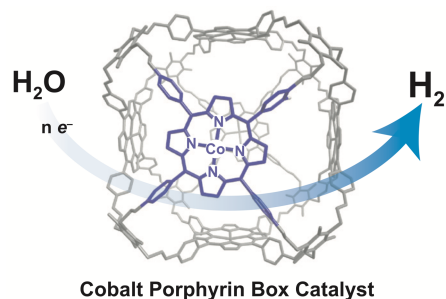
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Chapter 4

Cobalt Porphyrins Embedded into a Supramolecular Porous Organic Cage for Electrochemical Reduction of Water to Hydrogen

Abstract

We report a supramolecular porous organic cage composed of cobalt porphyrins as an efficient catalyst for electrochemical reduction of water to hydrogen at neutral pH. The supramolecular architecture is shown to be an advantageous parameter for tuning catalytic activity over the parent porphyrin congener.



Introduction

The generation of high-purity hydrogen gas from renewable sources as a fuel or feedstock for industrial synthesis is an attractive alternative over conventional energy-intensive and environmentally harmful processes such as natural gas reforming.¹ In this context, water is an abundant source of protons that can be electrochemically reduced to form hydrogen, and the development of catalysts for this transformation using earth-abundant metals has been the subject of intense research.²⁻⁴ Electrochemical hydrogen evolution using a variety of cobalt complexes has been thoroughly investigated,⁵⁻⁸ and cobalt porphyrins in particular have been extensively shown to be efficient hydrogen evolving catalysts in homogeneous organic or aqueous conditions,^{9,10} as catalyst films,¹¹⁻¹⁴ and even within artificial enzymes.^{15,16} More broadly, porphyrin-based catalysts have proven to be privileged scaffolds for other small-molecule activation reactions owing to facile tuning of porphyrin electronics and associated outer-coordination sphere.¹⁷⁻²² In materials platforms for energy catalysis, a common strategy for tuning catalytic activity is altering the nanostructure of the electrode material in an effort to elucidate how different shapes, sizes, or assemblies can influence the active sites.²³⁻²⁹ On the other hand, the supramolecular architecture of electrochemical molecular catalysts is rarely probed as a feature that can modify catalytic activity,³⁰⁻³⁵ although recent extended framework materials can be rationalized as embedding molecular catalysts into tailored matrices.³⁶⁻⁴² Along these lines, we report here an investigation into the effects of supramolecular porosity in a cobalt porphyrin-based porous organic cage for electrocatalytic hydrogen evolution from water.

Based on recent work from our laboratories using a porous architecture to enhance the electrochemical activity of a molecular catalyst for CO₂ reduction,⁴³ we reasoned that a catalyst capable of proton reduction would likewise benefit from being incorporated into a platform with permanent porosity that more efficiently exposes the active sites. We have focused on exploring porous organic cages (POCs) as catalyst platforms due to the ability to rationally design permanently porous supramolecules built from purely covalent linkages,^{44,45} which can provide both chemical and electrochemical stability.⁴⁶⁻⁴⁸ POCs are effective at gas adsorption and separation^{49,50} as well as promoting gas solubility in liquids.⁵¹ Thus, we developed a synthesis for a rhombicuboctahedral POC that is composed of six cobalt tetraphenylporphyrin (**Co-TPP**) units covalently linked through imine bonds, **Co-PB** (Scheme 4.1). We have previously demonstrated the utility of this porphyrin box platform as synthetic ion channels⁵² and catalysts for electrochemical CO₂ reduction.⁴³ Our research efforts are revealing porphyrin-based POCs to be a versatile and modular system where metal and strut substitutions can enable a broad range of applications.

Results and Discussion

To start, the free-base porphyrin box was first obtained by imine condensation between six tetra(formylphenyl)porphyrins and eight triamine linkers bearing solubilizing alkyl groups (Scheme 4.2). Successful and complete metalation of all six porphyrin moieties in the porphyrin box using CoCl_2 to obtain **Co-PB** was confirmed using MALDI mass spectrometry and UV/Vis spectroscopy (Figure 4.4-4.5). In addition, gas sorption studies of **Co-PB** show permanent porosity and indicate a Brunauer–Emmett–Teller surface area of $519 \text{ m}^2/\text{g}$ (Figure 4.6).

In order to use an aqueous electrolyte, the **Co-PB** catalyst was heterogenized by drop-casting onto a glassy carbon working electrode that had first been coated with carbon nanotubes to enhance conductivity. Linear sweep voltammograms (LSVs) of this heterogeneous **Co-PB** electrode in 1 M pH 7 phosphate buffer show a large cathodic current enhancement when scanning beyond -0.5 V vs. the reversible hydrogen electrode (RHE), suggesting catalytic proton reduction (Figure 4.1A). For comparison, we investigated **Co-TTP** as a hydrogen evolving catalyst under these conditions since it is the base unit of the **Co-PB** architecture. Six molar equivalents of **Co-TTP** were deposited onto the electrode in order to normalize to the number of Co centers in the **Co-PB** and **Co-TTP** heterogeneous catalyst films. Accordingly, LSV responses of this **Co-TTP** electrode show a much weaker current enhancement with an onset potential for HER shifted slightly more negative compared to **Co-PB**, which possesses electron-withdrawing imine groups.

Interestingly, Tafel analysis in Figure 4.1B indicates that the supramolecular **Co-PB** catalyst displays improved kinetics compared to the **Co-TTP** molecule. **Co-PB** exhibits a Tafel slope of $119 \text{ mV}/\text{dec}$, which is in agreement with the theory that a single electron transfer to a proton from water is rate-determining.⁵³ In contrast, **Co-TTP** has a larger Tafel slope of $170 \text{ mV}/\text{dec}$. We speculate that this observed difference may be attributed to inferior electron transfer throughout the **Co-TTP** catalyst film or to a lower local concentration of water within the film, where the structural porosity of **Co-PB** may facilitate in the delivery of both electrons and protons to the active Co centers. Heterogeneous molecular electrocatalysts commonly suffer from large Tafel slopes indicating that the initial electron transfer is greatly hindered; therefore, embedding the catalyst into a supramolecular platform may accelerate this rate-limiting step by facilitating charge, electrolyte, and substrate transport.

The electrochemically active surface areas of the **Co-PB** and **Co-TTP** heterogeneous electrodes were further analyzed by measuring the scan rate dependence of the reversible $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ redox couple observed at 0.76 V vs. RHE for both **Co-PB** and **Co-TTP** in 1 M pH 7 phosphate buffer (Figure 4.2). Both catalyst films were prepared by depositing $13.8 \text{ nmol}/\text{cm}^2$ of Co centers ($2.3 \text{ nmol}/\text{cm}^2$ of **Co-PB** and $13.8 \text{ nmol}/\text{cm}^2$ of **Co-TTP**). Variation of the peak current with the scan rate was linear for both catalysts, (Figure 4.8) indicating catalyst immobilization and revealing that the **Co-PB** electrode had $1.0 \pm 0.1 \text{ nmol}/\text{cm}^2$ of electrochemically active Co centers compared to $0.2 \pm 0.05 \text{ nmol}/\text{cm}^2$ in the **Co-TTP** electrode. This corresponds to just 1.4% of Co centers being electroactive in the **Co-TTP** film, whereas 7.2% of the Co centers are electroactive in the **Co-PB** film, resulting in a 5-fold enhancement in electrochemically active surface area observed for the supramolecular **Co-PB** catalyst over the **Co-TTP** molecule, suggesting that the greater porosity can contribute to making the active sites more accessible in the film. Indeed,

aggregation of planar macrocyclic catalysts has been shown to greatly hinder electrocatalytic activity.⁵⁴

With these data in hand, we performed controlled potential electrolyses with both **Co-PB** and **Co-TTP** heterogeneous electrodes (13.8 nmol/cm² Co deposited for each) in 1 M pH 7 phosphate buffer. A potential of -0.6 V vs. RHE was applied for 24 h, and **Co-PB** and **Co-TTP** passed 114 C and 52 C, respectively (Figure 4.3). Analyzing the headspace after each experiment by gas chromatography revealed that both catalysts gave *ca.* 100% Faradaic efficiency for hydrogen evolution, with **Co-PB** producing more than double the amount of H₂ compared to **Co-TTP**. For **Co-PB**, these results correspond to a turnover number (TON) of 19,030 [TON per electroactive Co (TON_{EA}) = 262,660] and an average turnover frequency (TOF) of 0.22 s⁻¹ [TOF per electroactive Co (TOF_{EA}) = 3.04 s⁻¹]. For **Co-TTP**, these data give a TON of 8,710 (TON_{EA} = 601,090) and an average TOF of 0.10 s⁻¹ (TOF_{EA} = 6.96 s⁻¹). The data support the notion that the supramolecular structure allows for more of the deposited catalytic cobalt porphyrin moieties to participate in hydrogen evolution. Normalizing to the number of electroactive Co centers reveals that the monomeric **Co-TTP** catalyst can outperform **Co-PB**, but not to an extent large enough to generate more hydrogen product. We attribute this slight difference in the intrinsic catalytic activity by the presence of electron-withdrawing imine groups present in the **Co-PB** catalyst, which may reduce the nucleophilicity of the metal center compared to **Co-TTP** at the same applied potential. Nevertheless, the supramolecular architecture enables the **Co-PB** catalyst to electrochemically generate significantly more hydrogen than the monomeric analogue **Co-TTP**, under identical conditions and at an overpotential of just 0.6 V, which compares favorably with canonical hydrogen evolving molecular catalysts under neutral aqueous conditions.²

Conclusion

In summary, we have demonstrated that porphyrin box POCs with Co centers are effective catalysts for electrochemical hydrogen evolution from water. Tafel analysis reveals that electron transfer and proton availability are superior for the **Co-PB** catalyst over its **Co-TPP** counterpart, and the measured electrochemically active surface areas show that the **Co-PB** electrode displays more than 5 times as many electroactive Co centers over **Co-TPP**. These data further establish this supramolecular approach as an effective strategy to enhance catalytic activity of molecular electrocatalysts. We anticipate that the versatility of porous organic cages as a supramolecular platform for developing tunable and efficient catalysts will continue to expand, particularly for reactions that can be effected by sustainable electrical and/or light energy input.

Materials and Methods

General Methods. All reagents and solvents were purchased from commercial sources and used without further purification unless specified. Hydrogen (99.999%), ethylene (99.9%), argon (99.999%) and nitrogen (99.998%) were purchased from Praxair. Multi-walled carbon nanotubes (MWCNTs) were purchased from Sigma-Aldrich and were washed with 10% HCl followed by deionized water until the filtrate was neutral and then dried *in vacuo* before use. 2,6-Lutidine was purchased from Sigma-Aldrich and dried over AlCl_3 then purified by distillation. Co(II) tetraphenylporphyrin and CoCl_2 were purchased from Strem Chemicals and used as received. Chelex chelating resin, sodium phosphate monobasic, and sodium phosphate dibasic were purchased from Sigma-Aldrich and used as received. The free-base porphyrin box was synthesized and characterized as previously described.⁵² THF and CH_3CN were dried using a JC Meyer solvent purification system. Deionized water was obtained from a Millipore Autopure system. UV/Vis spectra were collected using an Agilent Cary 60 spectrophotometer at room temperature. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry spectra were obtained using an Applied Biosystems Voyager DE Pro at the QB3 Mass Spectrometry Facility at the University of California, Berkeley. FT-IR spectra were collected using a Bruker ALPHA-P spectrometer.

Gas Sorption Measurements. Gas sorption isotherms of **Co-PB** were measured with an Autosorp-iQ volumetric adsorption analyzer. Typically, a sample of as-synthesized material (~30 mg) was loaded and, prior to the measurements, residual solvents were evacuated by heating to 100 °C under high vacuum (10^{-2} Pa) overnight. Sorption isotherms were measured for CO_2 using a dry-ice/acetone dewar (for 195 K).

Cyclic Voltammetry. Cyclic voltammetry experiments were performed using either a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat or a CH Instruments, Inc. 600E potentiostat.

Aqueous voltammetry studies were performed with a three-electrode cell equipped with a glassy carbon disk (3.0 mm diameter) working electrode (BASi), a platinum wire counter electrode, and a Ag/AgCl reference electrode. The electrolyte used was 1 M aq. potassium phosphate buffer with pH 7 and sparged with Ar. The electrolyte was pre-treated with Chelex resin overnight to remove any trace metal ion impurities.⁵⁵ No iR compensation was applied.

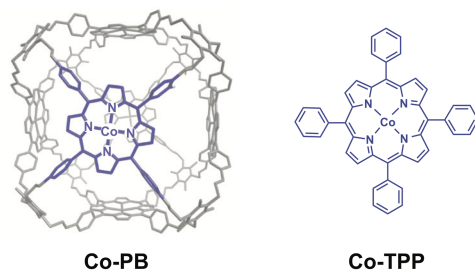
Preparative Scale Electrolysis. Controlled potential electrolyses were performed using either a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat or a CH Instruments, Inc. 600E potentiostat. A custom-made three-piece glass electrochemical cell was used (Adams & Chittenden Scientific Glass), including a working compartment body, a working compartment lid, and a counter compartment body. A cation exchange membrane (Nafion 117) separates the working electrode and Ag/AgCl (sat. KCl) reference electrode from the graphite rod counter electrode. This experimental setup is a smaller version of what we have described elsewhere.^{37,56-58} The cathode compartment holds 50 mL of electrolyte and the anode compartment holds 12 mL of electrolyte. The electrolyte used was 1 M aq. potassium phosphate buffer with pH 7 and sparged with Ar for 20 min immediately before electrolysis. The electrolyte was pre-treated with Chelex resin overnight to remove any trace metal ion impurities.⁵⁵ Once assembled, an internal standard of 0.5 mL ethylene was injected into the headspace for GC analysis. Electrolysis was then

performed at a constant potential for a specified amount of time. No iR compensation was applied. After this period, the headspace was immediately analyzed by GC, and the amount of gas generated was determined on the basis of the internal standard and from calibration curves plotted from injecting known amounts of H₂ and ethylene into the GC. Gas production was measured on an SRI gas chromatography instrument (model #8610C) equipped with a Haysep D column (1/8" × 6') and a 13X Mol Sieve column (1/8" × 6'). Hydrogen and ethylene were quantified using a thermal conductivity detector (TCD).

Preparation of Working Electrodes. For cyclic voltammetry experiments, a glassy carbon (GC) disk electrode (0.071 cm²) was thoroughly polished with 0.5 μm alumina powder, rinsed with isopropanol, and dried in air. To increase conductivity, a dispersion of MWCNTs in *i*PrOH (1 mg/mL) was sonicated for 20 min, and then 10 μL was slowly deposited onto the 3 mm diameter GC electrode and dried in air. Then, either 14.2 μL of a **Co-PB** solution in THF (0.1 mg/mL) or 6.6 μL of a **Co-TPP** solution in THF (0.1 mg/mL) was deposited on top of the MWCNT/GC electrode and allowed to dry in air. This electrode was then thoroughly rinsed with *i*PrOH, H₂O, and 1 M pH 7 phosphate buffer, and then dried in air again. This preparation results in 0.14 mg/cm² of MWCNTs and either 0.02 mg/cm² (2.31 nmol/cm²) of **Co-PB** or 0.01 mg/cm² (13.84 nmol/cm²) of **Co-TPP**.

For controlled potential electrolyses, a glassy carbon plate electrode (2.25 cm²) was thoroughly polished with 0.5 μm alumina powder, rinsed with isopropanol, and dried in air. A dispersion of MWCNTs in *i*PrOH (2 mg/mL) was sonicated for 20 min, and then 190 μL was slowly deposited onto the GC plate electrode and thoroughly dried in air. Then, either 450 μL of a **Co-PB** solution in THF (0.1 mg/mL) or 209 μL of a **Co-TPP** solution in THF (0.1 mg/mL) was deposited on top of the MWCNT/GC electrode and allowed to dry in air. This electrode was then thoroughly rinsed with *i*PrOH, H₂O, and 1 M pH 7 phosphate buffer, and then dried in air again. This preparation results in 0.17 mg/cm² of MWCNTs and either 0.02 mg/cm² (2.31 nmol/cm²) of **Co-PB** or 0.01 mg/cm² (13.84 nmol/cm²) of **Co-TPP**.

Synthesis of Co-PB. Under a dinitrogen atmosphere, free-base porphyrin box (25 mg, 2.9 μmol) and CoCl₂ (40 mg, 0.31 mmol, 106 equiv.) were dissolved in anhydrous THF (50 mL). Subsequently, 2,6-lutidine (10 μL, 0.083 mmol, 29 equiv.) was injected, and the reaction mixture was heated at 70 °C for 12 h. After cooling to room temperature, solvent was removed under reduced pressure. Then, acetonitrile (25 mL) was added, and after sonication for 30 s to suspend the product, the mixture was transferred to a conical tube and centrifuged. The supernatant was then decanted off. This washing cycle with acetonitrile was repeated six times. **Co-PB** was obtained as a dark red-purple powder (95% yield). MALDI-MS (matrix: DCTB) *m/z* calcd. for C₅₅₂H₆₂₄Co₆N₄₈O₂₄ [M]⁺: 8667.52, found: 8667.48. Elemental analysis calc. for C₅₅₂H₆₂₄Co₆N₄₈O₂₄(C₂H₆O)₂: C, 76.22; H, 7.24; N, 7.72. Found: C, 75.97; H, 7.28; N, 7.58. UV/Vis (CH₂Cl₂) λ_{abs} 418, 531 nm.



Scheme 4.1. The porous organic cage catalyst **Co-PB** (left) and its monomeric analog **Co-TPP** (right). Alkyl chains are omitted in the molecular model for clarity.

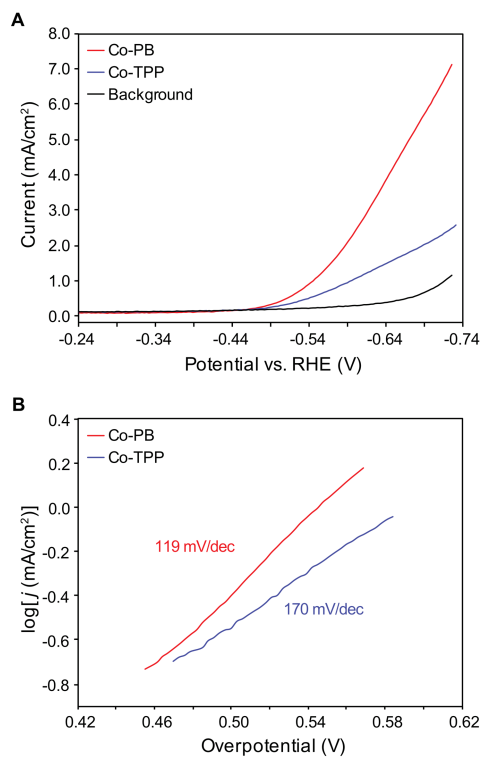


Figure 4.1. (A) LSV traces for **Co-PB** (red), **Co-TPP** (blue), and electrode background (black) obtained in 1 M pH 7 phosphate buffer saturated with N₂. (B) Corresponding Tafel plot for **Co-PB** and **Co-TPP** catalysts. Each catalyst electrode was prepared by depositing 13.8 nmol/cm² of Co centers (2.3 nmol/cm² of **Co-PB** and 13.8 nmol/cm² of **Co-TPP**).

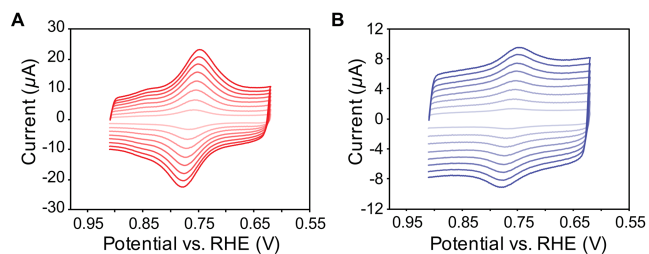


Figure 4.2. Scan rate dependence from 0.025-0.2 V/s of the $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ redox couple for **Co-PB** (A) and **Co-TPP** (B) catalyst films in 1 M pH 7 phosphate buffer saturated with N_2 . Each catalyst electrode was prepared by depositing $13.8 \text{ nmol}/\text{cm}^2$ of Co centers ($2.3 \text{ nmol}/\text{cm}^2$ of **Co-PB** and $13.8 \text{ nmol}/\text{cm}^2$ of **Co-TPP**).

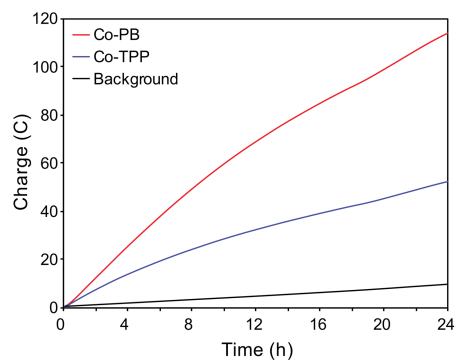
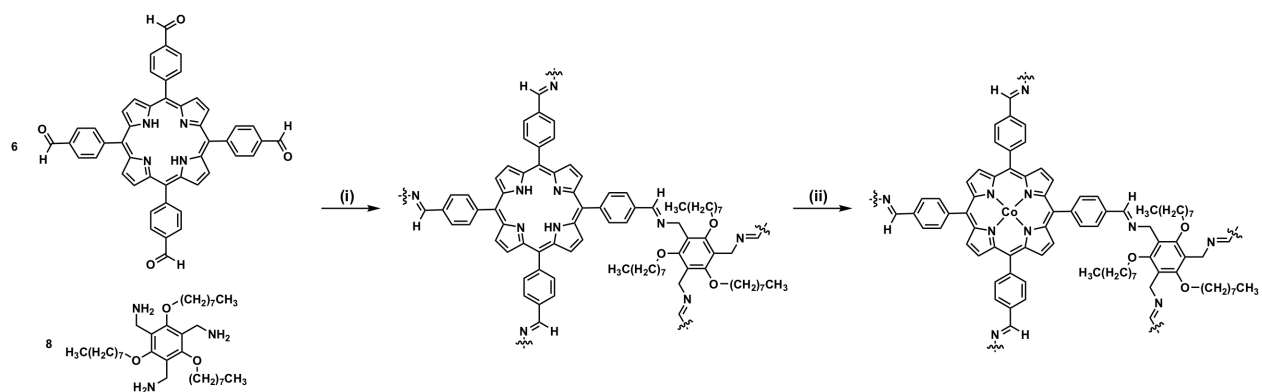


Figure 4.3. Charge accumulation during long-term controlled potential electrolyses with **Co-PB** (red), **Co-TPP** (blue), and electrode background (black) at -0.6 V vs. RHE in 1 M pH 7 phosphate buffer saturated with Ar. Each catalyst electrode was prepared by depositing 13.8 nmol/cm^2 of Co centers (2.3 nmol/cm^2 of **Co-PB** and 13.8 nmol/cm^2 of **Co-TPP**).



Scheme 4.2. Synthetic scheme for the preparation of the porous organic cage **Co-PB**. (i) Trifluoroacetic acid (cat.), CHCl_3 , 55°C , 12 h; (ii) CoCl_2 , 2,6-lutidine, THF, 70°C , 12 h.

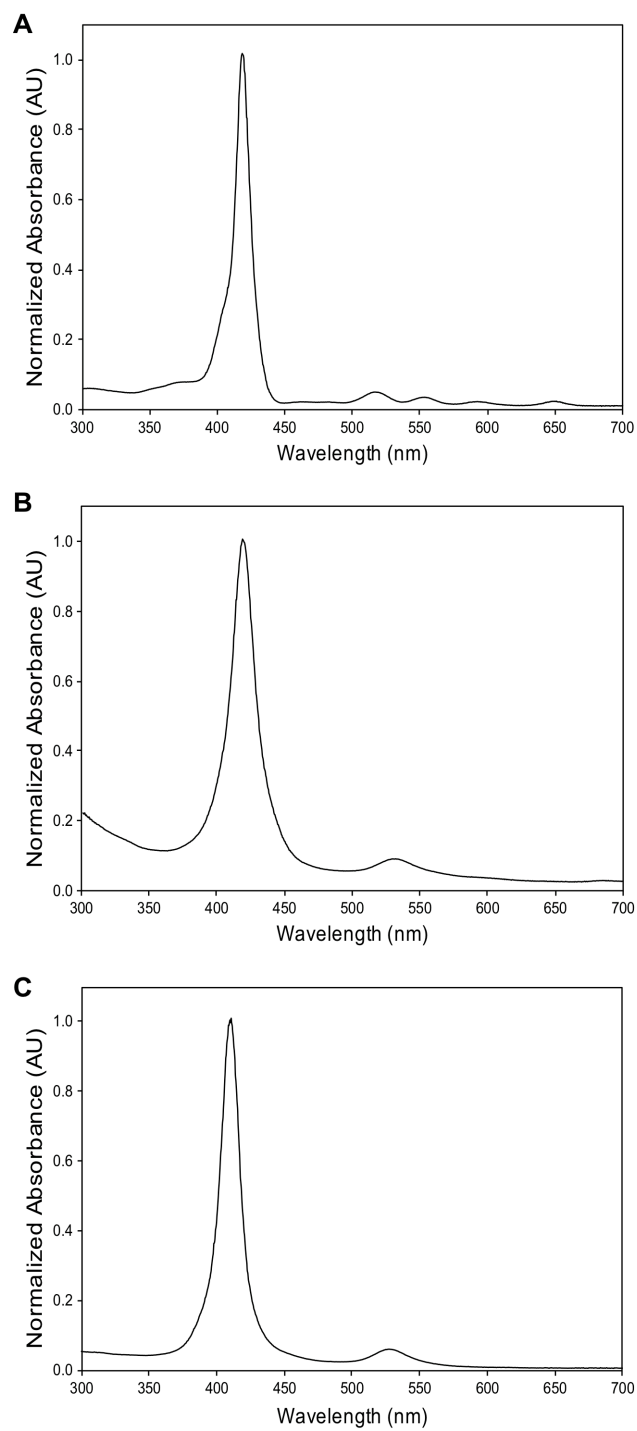


Figure 4.4. UV/Vis spectra of (A) free-base porphyrin box (B) Co-PB, and (C) Co-TPP.

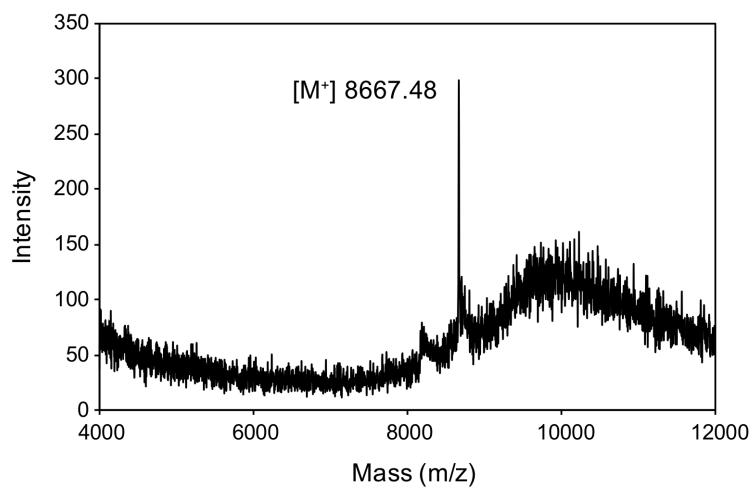


Figure 4.5. MALDI-MS spectrum of **Co-PB** (DCTB matrix).

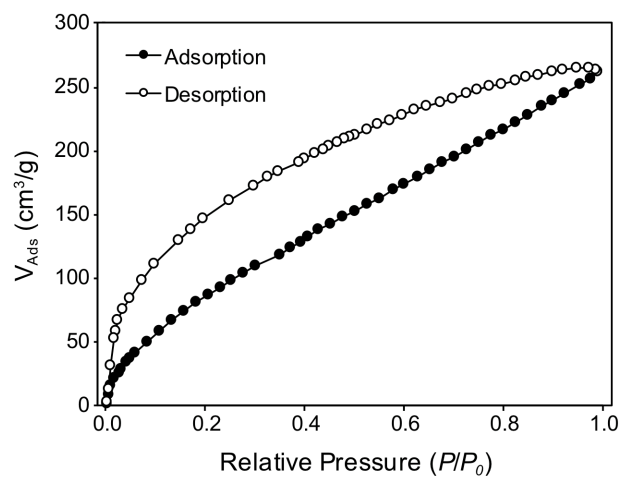


Figure 4.6. CO₂ sorption isotherms for **Co-PB** at 195 K.

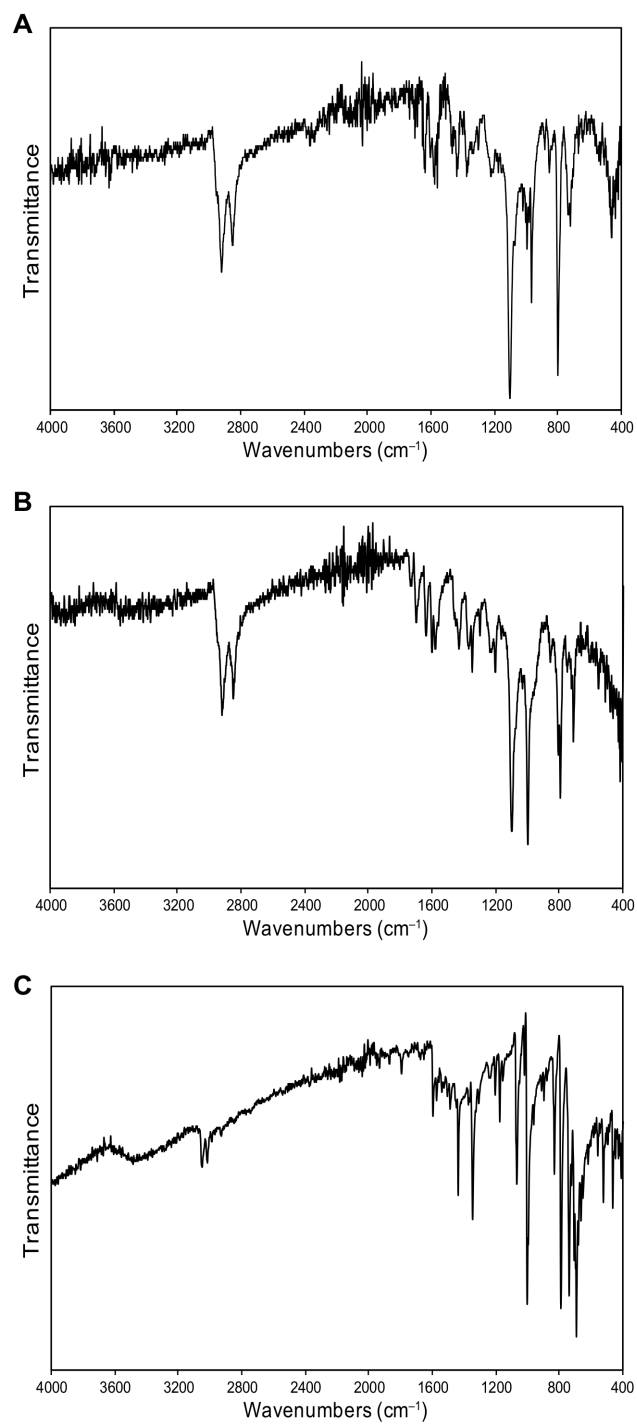


Figure 4.7. IR spectra of (A) free-base porphyrin box, (B) **Co-PB**, and (C) **Co-TPP**.

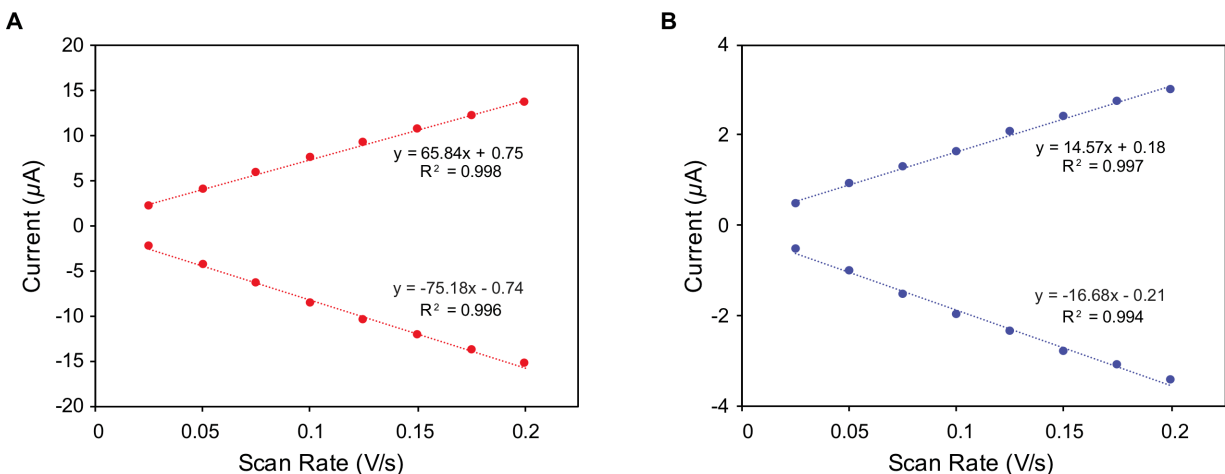


Figure 4.8. Scan rate dependence from 0.025-0.2 V/s of the $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ redox couple for **Co-PB** (A) and **Co-TPP** (B) catalyst films in 1 M pH 7 phosphate buffer saturated with N_2 . Each catalyst electrode was prepared by depositing $13.8 \text{ nmol}/\text{cm}^2$ of Co centers ($2.3 \text{ nmol}/\text{cm}^2$ of **Co-PB** and $13.8 \text{ nmol}/\text{cm}^2$ of **Co-TPP**). The number of electroactive Co centers in the catalyst films (Γ , mol/cm^2) was determined from these plots using the following equation:

$$i_p = n^2 F S \Gamma \frac{Fv}{4RT}$$

where i_p is the peak current of the $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ redox couple, n is the number of electrons, F is Faraday's constant, S is the geometrical surface area of the electrode, v is the scan rate, R is the gas constant, and T is the temperature. The number of electrons, n , is taken to be 1 for the single electron transfer. This treats each cobalt porphyrin moiety in **Co-PB** or **Co-TPP** as independent of one another.

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Chapter 5

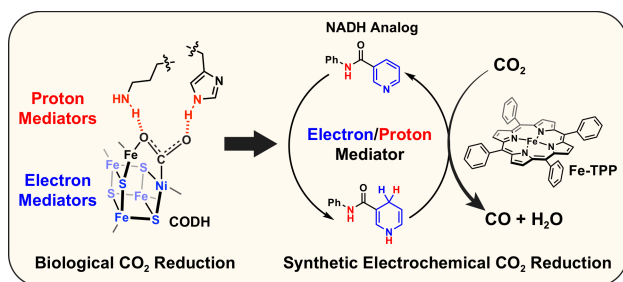
An NADH-Inspired Redox Mediator Strategy to Promote Second-Sphere Electron and Proton Transfer for Cooperative Electrochemical CO₂ Reduction Catalyzed by Iron Porphyrin

Portions of this work were published in the following scientific journal:

Smith, P. T.; Weng, S.; Chang, C. J., An NADH-Inspired Redox Mediator Strategy to Promote Second-Sphere Electron and Proton Transfer for Cooperative Electrochemical CO₂ Reduction Catalyzed by Iron Porphyrin. *Inorganic Chemistry*. **2020**, 59 (13), 9270-9278.

Abstract

We present a bioinspired strategy for enhancing electrochemical carbon dioxide reduction catalysis by cooperative use of base-metal molecular catalysts with intermolecular second-sphere redox mediators that facilitate both electron and proton transfer. Functional synthetic mimics of the biological redox cofactor NADH, which are electrochemically stable and are capable of mediating both electron and proton transfer, can enhance the activity of an iron porphyrin catalyst for electrochemical reduction of CO_2 to CO , achieving a 13-fold rate improvement without altering the intrinsic high selectivity of this catalyst platform for CO_2 versus proton reduction. Evaluation of a systematic series of NADH analogs and redox-inactive control additives with varying proton and electron reservoir properties reveals that both electron and proton transfer contribute to the observed catalytic enhancements. This work establishes that second-sphere dual control of electron and proton inventories is a viable design strategy for developing more effective electrocatalysts for CO_2 reduction, providing a starting point for broader applications of this approach to other multi-electron, multi-proton transformations.



Introduction

As discussed in Chapter 1, our lab aims to merge aspects of molecular, materials, and biological catalysts to improve the efficiency and control the selectivity of electrochemical reactions. In Chapters 2, 3, and 4, we focused on a porphyrin box platform that combines molecular and materials design elements. In this chapter, we now take inspiration from biology to develop a hybrid bio-molecular strategy for improved CO₂ reduction.

Catalyzing the CO₂ reduction reaction by electrochemical means offers an approach for converting this greenhouse gas into value-added chemical products with sustainable energy input.¹⁻¹⁵ Efforts in molecular electrocatalysts for CO₂ reduction have predominantly focused on the 2-electron/2-proton reduction of CO₂ into CO, which can then be fed into numerous existing industrial processes for chemical synthesis. Iron porphyrins, in particular, have been the subject of extensive research owing to their high selectivity for CO₂ versus proton reduction, structural tunability, and compatibility with various electrolyte media.¹⁶⁻²⁴ Beyond this platform and other privileged primary coordination sphere motifs, approaches to enhance CO₂ reduction catalysis with secondary coordination sphere pendants have largely focused on improving the delivery of protons using intramolecular proton relays and/or stabilization of metal-bound CO₂ intermediates via hydrogen bonding.^{17,18,25-39} Additionally, reduced CO₂ intermediates can be captured by inter/intra-molecular Lewis acid cations⁴⁰⁻⁴² or intramolecular charge-compensation moieties, such as ammonium^{21,43} or imidazolium groups.⁴⁴⁻⁴⁶

In addition to proton control, strategies for facilitating electron delivery from the secondary coordination sphere for CO₂ reduction have also been explored. One elegant example from Shafaat's laboratory embeds nickel cyclam, a classic CO₂ reduction catalyst, within a blue copper protein that acts as an outer-sphere electron reservoir to enhance activity.⁴⁷ We have also shown that reticular materials can influence CO₂ selectivity and activity by electronic delocalization in the secondary coordination sphere.^{48,49} Redox-active ligands based on polypyridines,⁵⁰⁻⁵⁵ imines,⁵⁶ and porphyrins^{57,58} can also be employed for CO₂ reduction, where ligand-centered reductions offer the advantage of removing electron density away from the metal center to diminish metal hydride formation and off-pathway H₂ evolution.⁵⁹ Our laboratory and Miller's laboratory have identified molecular terpyridine-based iron complexes that are highly active CO₂-to-CO electrocatalysts that operate at extremely low overpotentials due to electronic delocalization.^{54,55} Finally, bulk electron transfer can be improved by electrode surface attachment.⁶⁰⁻⁶⁴

Against this backdrop of literature showing benefits of either second-sphere proton or electron control for electrochemical CO₂ reduction catalysis, we sought to develop a second-sphere approach that enables dual management of both electron *and* proton inventories. Our synthetic efforts are inspired by biological CO₂ reduction enzymes. Included are carbon monoxide dehydrogenases (CODH)⁶⁵ and formate dehydrogenases⁶⁶ that couple primary active sites with properly positioned second-sphere proton relays and electron reservoirs to enable catalysis near thermodynamic potentials (Scheme 5.1). Such enzymes can be utilized for electrochemical CO₂ reduction,^{67,68} but challenges associated with direct electron transfer from electrodes to buried active sites within these macromolecules in the absence of their native redox partners in the cell requires the addition of small-molecule redox mediators like ferrocenes, viologens, and quinones.^{69,70} To pursue such biology-to-chemistry concept transfer, we turned to the use of

organic cofactors such as nicotinamide adenine dinucleotide (NAD^+/NADH) that can facilitate both electron and proton transfer. However, NADH and various synthetic organic analogs are often incompatible with electrochemically-driven catalytic cycles due to formation of radical intermediates leading to decomposition.⁷¹ As such, we sought to overcome this challenge by judicious choice of catalyst and electron-proton mediator components with matched reduction potentials to avoid these off-cycle decomposition pathways.

In this report, we present a cooperative electrochemical CO_2 reduction strategy that combines a base-metal molecular catalyst in the primary coordination sphere with intermolecular NADH -like redox mediators that facilitate electron and proton transfer from the secondary coordination sphere (Scheme 5.1). We chose *N*-phenylnicotinamide (**1**) as a dual electron-proton mediator that possesses a basic pyridine and promotes 2-electron/2-proton transfer pathways, coupled to the classic iron tetraphenylporphyrin (**Fe-TPP**) electrocatalyst system for CO_2 reduction. As reduction of pyridine heterocycles can give 1,2- or 1,4-dihydropyridine regioisomers,⁷² we exploited this property to evaluate the *N*-phenylisonicotinamide (**2**) isomer as an additional electron-proton mediator. When added in catalytic amounts, both **1** and **2** significantly enhance CO formation during electrochemical CO_2 reduction catalyzed by **Fe-TPP** with up to a 13-fold improvement in catalytic activity without sacrificing CO_2 versus proton substrate selectivity. Further studies with a systematic series of control additives reveals that both proton and electron reservoir capacities contribute to the observed second-sphere driven improvements in electrochemical CO_2 reduction efficiency. This work provides a starting point for designing catalysts for a broader range of multielectron, multiproton transformations with second-sphere additives or pendants that can manage both electron and proton inventories.

Results and Discussion

NADH Analogs Show Enhanced Current Activity in the Presence of External Proton Sources. We initiated our studies by evaluating the electrochemical behavior of NADH analogs in the presence of external proton sources with the goal of developing electron-proton redox mediators with multielectron, multiproton capabilities and electrochemical stability. As a starting point, the cyclic voltammogram (CV) of **1** under an N₂ atmosphere in anhydrous DMF electrolyte shows an irreversible reduction with a peak potential at -2.52 V vs. Fc/Fc⁺ (Figure 5.1). This result suggests an EC mechanism in which the 1-electron reduced species undergoes a rapid chemical reaction. The CV of the isomeric analog **2** shows a similar EC wave but at a more positive peak potential of -2.21 V. Upon titration of phenol as a proton source into the solution of **1** or **2** under an N₂ atmosphere, we observe a positive shift in peak potential and concomitant increase in peak current in a dose-dependent manner until a saturation level is reached above 5 equiv. of added phenol. The peak potentials for **1** and **2** in the presence of excess phenol are -2.40 and -2.14 V, respectively. Integration of the reduction waves for **1** and **2** in the absence of phenol gives $29.8\ \mu\text{C}$ and $29.6\ \mu\text{C}$ of charge, respectively, whereas in the presence of 100 mM phenol electrochemical reductions of **1** and **2** consume $63.0\ \mu\text{C}$ and $72.6\ \mu\text{C}$, respectively. These data suggest a transition from a 1-electron to a 2-electron reduction process with added acid, which is reminiscent of the ECEC mechanism that is classically observed for quinone species in the presence of proton sources.⁷³ We speculate that hydrogen bonding between the basic pyridine nitrogen and acidic phenol trigger the positive shift in onset potential, and protonation after the initial 1-electron reduction step produces a species that is more easily reduced than **1**, so an overall 2-electron/2-proton reduction process is facilitated as more phenol is added. This reaction leads to the proposed dihydropyridines **1'** and **2'** as shown in Scheme 5.2. A new oxidation wave is also observed at -0.61 V for **1** and at -0.24 V for **2** (Figures 5.8-5.10), indicative of oxidation of the incipient dihydropyridine intermediate. After titration of 5 equiv. of phenol, the CVs show complete conversion to an ECEC mechanism, establishing the potential for NADH analogs **1** and **2** in the presence of complementary acid sources to act as 2-electron/2-proton mediators, while also tuning redox potentials to more positive potentials.

CVs of the structurally similar *N*-phenylpicolinamide (**3**) exhibits a similar ECEC type wave upon phenol titration with a peak potential of -2.33 V (Figure 5.10). Interestingly, the unsubstituted nicotinamide exhibits different behavior with CVs revealing a more negative reduction potential of -2.57 V in the presence of 100 mM phenol and a peak area that does not double as expected for a 2-electron process, suggesting an undesired reduction mechanism (Figure 5.14). Dose-dependent titration of phenol at concentrations of up to 500 mM with additives **1-3** under an N₂ atmosphere showed no change in ECEC waves, and subsequent saturation of the electrolyte with CO₂ afforded identical CV responses observed under an N₂ atmosphere. Taken together, these observations establish that these synthetic NADH analogs can serve as 2-electron/2-proton reservoirs in the presence of a complementary proton source, and that the reduced additives neither behave as CO₂ reduction nor proton reduction electrocatalysts on the CV timescale (Figures 5.15-5.17).

Controlled Potential Electrolysis Experiments on NADH Analogs Provide Evidence for Dihydropyridine Formation. To provide further evidence to support the 2-electron behavior in these synthetic NADH analogs, we performed controlled potential electrolysis (CPE) on 5 mM

solutions of **1** and **2** at -2.4 V vs. Fc/Fc^+ with 500 mM PhOH under a CO_2 atmosphere. The CPE data show that the overall charge consumed is close to the 2 electrons per molecule stoichiometry that would theoretically yield the reduced dihydropyridines **1'** or **2'**, respectively (Figure 5.2). The catholyte consisted of 10 mL of 5 mM solutions of each additive, which would require 9.6 C for a complete 2-electron reduction. Electrolysis of **1** led to rapid charge consumption during the first 5 hours, but then required over 25 h of electrolysis for complete reduction (Figure 5.2). This behavior is likely due to low current density at this applied potential, which is at the peak potential for the reduction of **1** (Figure 5.1). Notably, more negative applied potentials were avoided to minimize background hydrogen evolution at the glassy carbon electrode. In contrast, **2** is fully reduced after 1.5 h of electrolysis, quickly consuming a full 9.6 C as a result of the more positively shifted reduction potential of **2** relative to **1**, where the electron-withdrawing group of the former is now located on the 4-position. The applied potential of -2.4 V is now 260 mV more negative than the peak potential for the reduction of **2**, so that the rate of reduction of **2** is primarily limited by diffusion whereas reduction of **1** is limited by diffusion as well as electron transfer. We attribute the slight excess of charge consumed to background hydrogen evolution, which was detected by gas chromatography (GC). No reduced carbon products were detected, confirming that the electrochemically-generated dihydropyridines do not directly react with CO_2 , as has been observed in other organohydride systems.⁷⁴ Indeed, the hydricity values of a range of substituted dihydropyridines have been reported and are not strong enough to reduce CO_2 into formate.⁷⁵

We also performed a direct chemical reduction of **1** using LiAlH_4 with an anaerobic aqueous workup to give **1'**. ESI mass spectrometry shows an m/z increase of 2, consistent with dihydropyridine formation. Moreover, the UV/Vis absorption spectrum of starting additive **1** shows a single absorption at 250 nm, but spectra of the products of both chemical and electrochemical reduction of **1** show the same prominent absorption band at 355 nm (Figure 5.3A). Interestingly, this absorption behavior is similar to that of NAD^+/NADH ,⁷⁶ suggesting a similar change to the aromatic pyridine π system in this synthetic analog. Furthermore, the ^1H NMR spectrum of chemically synthesized **1'** shows nearly complete consumption of starting material and the formation of new peaks at 3.10, 4.56, 5.94, and 7.08 ppm consistent with allylic and vinylic protons in the proposed dihydropyridine structure (Figure 5.3B). Full peak assignment is provided in Figure 5.21. Exposure of **1'** to air leads to rapid re-formation of **1** as observed by ^1H NMR, indicating the reversible redox nature of this additive.

Synthetic NADH Analogs Promote Higher Catalytic Current for Iron Porphyrin in the Presence of CO_2 . We next tested the ability of **1** to act as an electron-proton transfer mediator for the CO_2 reduction reaction catalyzed by **Fe-TPP**. The peak reduction potentials for **1** and **2** in the presence of excess phenol are -2.40 and -2.14 V, respectively, which lie in the same range as the formal $\text{Fe}^{\text{I}}/\text{Fe}^0$ reduction at -2.15 V with **Fe-TPP** where CO_2 reduction occurs.¹⁶ Titration of phenol into a DMF electrolyte solution of **Fe-TPP** saturated with CO_2 shows the expected significant increase in catalytic current with peak shaped waves indicative of fast catalysis (Figure 5.22). We then repeated this CV experiment with the addition of either 1 or 5 equiv. of additives **1** and **2** (Figures 5.23-5.26). At low concentrations of phenol, the reductions of **1** and **2** are clearly observable in the range of the catalytic CO_2 reduction wave. Figure 5.4 shows the overlaid CV traces at the highest phenol concentration of 500 mM with the catalytic currents normalized to the 1-electron peak height for the formal $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ reduction of **Fe-TPP**, i_p^0 . With 1 equiv. of **1**, a modest increase in peak catalytic current is observed at -2.25 V relative to **Fe-TPP** alone. However, **1** has

a peak reduction potential of -2.40 V under these conditions, which is reflected by a larger difference in catalytic current with added **1** at more negative potentials in Figure 5.4. In contrast, additive **2** has a peak reduction potential of -2.14 V under these conditions, which more closely matches where **Fe-TPP** catalyzes CO_2 reduction. This redox matching results in a more significant increase in peak catalytic current in the presence of 1 equiv. of NADH analog **2** compared to **1**, with further amplification in the presence of 5 equiv. of additive. Taken together, these results suggest that additives **1** and **2** can participate as co-catalysts with **Fe-TPP** for cooperative electrochemical CO_2 reduction.

Controlled Potential Electrolysis Experiments Confirm that NADH Analogs Enhance Electrochemical CO_2 Reduction Catalyzed by Iron Porphyrin. We then performed CPE experiments to quantify product formation for electrochemical CO_2 reduction reactions catalyzed by **Fe-TPP** in the absence or presence of the NADH analogs **1** and **2** in addition to a broader set of NADH mimics (Scheme 5.3). CPEs were conducted with 0.5 mM **Fe-TPP**, 0.5 mM additive, and 500 mM phenol under CO_2 for 16 h at -2.4 V vs. Fc/Fc^+ . Charge accumulation over time is plotted in Figure 5.5, and a summary of the data is listed in Table 5.1. With no additive, 4.9 mL of CO were generated. In comparison, addition of 1 equiv. of **1** yielded over 3 times as much CO under the same conditions, establishing the ability for **1** to increase the catalytic activity of **Fe-TPP** for CO_2 reduction. Moreover, addition of 1 equiv. of **2** yields 3.7 times as much CO as **Fe-TPP** alone, highlighting the redox tunability of these nicotinamide additives. Additive **3** yields a similar increase in CO production. Current density over time is plotted in Figure 5.29 showing that the current for each experiment drops significantly over the long-term CPEs, which may be due to the relatively negative applied potential of -2.4 V that accelerates catalyst decomposition. All experiments revealed CO to be the major product accounting for approximately 90-100% Faradaic efficiency (FE) consistent with the high selectivity for iron porphyrin catalysts and showed that these cooperative electron-proton redox mediators improved catalytic activity without sacrifices in catalytic selectivity.^{16,18,23,24} Indeed, only trace amounts of H_2 were detected by GC (Table 5.2), and no liquid products were detected by ^1H NMR spectroscopy. Noting that some dihydropyridines may be capable of reducing CO_2 into formate via hydride transfer,⁷⁷ the formation of CO as the sole reduced carbon product in this system suggests a different mechanism for enhanced electron and proton transfer with catalysis occurring at **Fe-TPP**. Along these lines, an elegant related study by Anson and Stahl showed an increase in current density for reduction of O_2 into H_2O_2 and H_2O using quinones as electron-proton mediators.⁷⁸ Similarly, aminoxyl radicals can aid in electron-proton transfer for catalytic electrochemical oxidations.⁷⁹

The observed rate constants (k_{obs}) can be estimated from the CO-specific current densities (j_{CO}) since the charge consumed is directly associated with catalyst turnover.⁸⁰ The common foot-of-the-wave analysis determining rate constants from CV traces is not applicable in this system because the reduction of **1** occurs more negative the **Fe-TPP** foot-of-the-wave whereas the reduction of **2** occurs more positive the **Fe-TPP** foot-of-the-wave, which obscures this type of analysis. As such, we used the average j_{CO} from direct product detection and quantification with the assumption that the redox mediator did not change the rate-determining step for **Fe-TPP** catalysis as product distributions were identical with and without the additive. Using this method, the maximum turnover frequency ($\text{TOF}_{\text{max}} = k_{\text{obs}}$) for 0.5 mM **Fe-TPP** under CO_2 in the presence of 500 mM phenol was estimated to be $5.24 \times 10^4 \text{ s}^{-1}$, which is in agreement with literature reports under conditions of large proton excess.^{21,36,45,80} In the presence of 1 equiv. of **1** or **2**, patent

increases in the **Fe-TPP** TOF_{max} are observed with estimated values of $5.00 \times 10^5 \text{ s}^{-1}$ and $7.01 \times 10^5 \text{ s}^{-1}$, respectively. These values correspond to 9.5- and 13.4-fold increases in rate, respectively. Catalytic Tafel plots could then be constructed to visualize the relationship between TOF and overpotential.⁸⁰ Figure 5.6 depicts the Tafel plots for **Fe-TPP** in the absence and presence of synthetic NADH analogs **1** and **2** further demonstrating the substantial rate enhancement for CO production by **Fe-TPP** in the presence of these two additives.

We next expanded these studies to the broader set of NADH mimics to decipher contributions of electron and proton relays in a systematic fashion (Scheme 5.3). First, pyridine additive **4** was tested to probe the role of the basic nitrogen atom in the observed catalytic enhancements. It has previously been hypothesized that pyridine additives can coordinate to cobalt phthalocyanine catalysts to increase their nucleophilicity and CO₂ reduction activity.⁸¹ However, CPE of **Fe-TPP** with 1 equiv. of **4** does not show a significant increase in charge consumption and CO production (Figure 5.5, Table 5.1) relative to **Fe-TPP** alone. Second, the methylated pyridinium additive **5**, a closer structural mimetic of NAD⁺, was used to determine the importance of the ECEC mechanism because this charged pyridinium also undergoes two sequential reductions, the first of which is proton-independent (Figure 5.12). CPE of **Fe-TPP** with 1 equiv. of **5** shows a similarly high rate of charge consumption and current density as observed with additives **1-3** (Figure 5.5, Figure 5.29). However, after this initial increase, the catalytic current decreases dramatically and the cumulative CO production is comparable to that of **Fe-TPP** alone, which we attribute to the formation of radical anions that dimerize or decompose catalyst. Figure 6 further shows that the log(TOF)-overpotential relationship for **Fe-TPP** is not significantly changed upon addition of **4** or **5**.

Additional synthetic NADH analogs were then investigated as additives to probe contributions of second-sphere electron and proton relays to enhanced CO₂ catalysis. CPE experiments were performed using benzanilide **6** as a redox-inactive additive that retains the amide substituent. Previous work from our laboratory demonstrated that intramolecular amide pendants can significantly enhance the reduction of CO₂ to CO with proper second-sphere positioning.²⁹ In agreement with that study, the CPE experiments performed with **Fe-TPP** and 1 equiv. of **6** lead to improved rates of CO production (5.9-fold increase), but not to the levels achieved with additives **1-3** seen in Figure 5.6 that possess both electron and proton transfer capabilities (9.5- to 13.4-fold rate increases). Indeed, CVs of **6** in the presence of phenol do not show the ECEC behavior observed with additives **1-3**. Consistent with **6** being a proton-only reservoir, a catalytic wave is observed with a peak area that more than triples with increasing phenol concentration (Figure 5.13). Finally, we tested pyridine amide additive **7**, where the amide nitrogen atom is methylated to remove benefits of hydrogen bonding and/or proton relays, but retains the redox-active reservoir. As observed with proton-only **6**, electron-only additive **7** increases charge consumption and rates of CO production compared to **Fe-TPP** alone (8.4-fold) but not to the same extent as NADH analogs **1-3** that have the capacity for both electron and proton management (Figure 5.6, Figure 5.31). Interestingly, the enhanced catalysis with additive **1** is not simply a summation of the benefits provided by hydrogen bonding or proton donation with **6** and by electron transfer with **7**, suggesting a more complex interplay. Nevertheless, these data suggest the participation of both electron and proton relay components in enhancing electrochemical CO₂ reduction catalysis, as NADH analogs that possess dual electron-proton redox reservoir capabilities are superior to additive that only have either electron or proton transfer capacity.

Finally, as NADH analog **2** showed the highest activity enhancements for electrochemical CO₂ reduction, we performed further dose-dependent CPE experiments with this additive. Figure 5.7 compares relative current density and charge accumulation values during 1 h of electrolysis at –2.4 V with **Fe-TPP** under a CO₂ atmosphere and 0, 1, 5, 10, or 15 equiv. of additive **2**. Addition of 1 equiv. of **2** leads to a significant enhancement in average current density to 4.19 mA/cm², compared to 1.64 mA/cm² with **Fe-TPP** alone. However, increasing doses of **2** to 5, 10 or 15 equiv. provides only a modest further current density enhancement. We speculate that this saturation behavior could be due to inherent rate limitations of the parent **Fe-TPP** catalysis and/or insufficient electrolysis to reduce enough **2** to couple to **Fe-TPP** to be effective in the catalytic cycle, as the two components must interact intermolecularly. Further experiments beyond the scope of this work are required to elucidate such complex mechanistic details.

Conclusion

In summary, we have presented a strategy for enhancing electrochemical CO₂ reduction catalysis through the use of second-sphere additives that have dual electron-proton reservoir capabilities. We establish this concept using synthetic NADH analogs as electron-proton mediators with the molecular CO₂ reduction catalyst **Fe-TPP**. Indeed, although extensive efforts have provided valuable design strategies for facilitating second-sphere proton transfer for electrochemical CO₂ reduction, our findings show that such electrocatalysts can be further augmented by adding electron transfer relays as well. Specifically, the NADH-inspired nicotinamide-based additives **1-3** undergo an ECEC reduction pathway to subsequently serve as intermolecular electron-proton sources for CO₂ reduction catalyzed by **Fe-TPP**. Dihydropyridine intermediates, which can be generated by chemical or electrochemical means, can be re-oxidized in air thermally or through anodic electrochemistry back to the starting nicotinamide to complete the electrochemical cycle.

A key design feature that emerges from this study is to precisely match the redox potentials of the primary-sphere molecular catalyst and second-sphere electron-proton mediator to promote productive multi-electron, multi-proton chemistry. For the 2-electron/2-proton conversion of CO₂ to CO, catalytic rates for reduction can be augmented by up to 13.4-fold in the presence of the electron-proton mediator without sacrificing the high selectivity of **Fe-TPP** for CO₂ versus proton reduction. The cooperative second-sphere approach complements work on CO₂ hydrogenation catalysts, where metal-hydrides simultaneously deliver electrons and protons.^{59,82-84} Indeed, few organic hydrides are strong enough donors to reduce CO₂ directly,^{72,75} and those that can be regenerated encounter slow rates of hydride transfer that limit integration into photo- or electrocatalytic cycles.^{74,85} This cooperative, bioinspired approach to electrocatalysis, which leverages primary metal centers with secondary dual electron-proton reservoirs, should be applicable to a broader array of chemical transformations where bond activation and catalytic turnover relies on controlling both electron and proton inventories.

Materials and Methods

General Materials and Methods. Fe(III) tetraphenylporphyrin chloride (**Fe-TPP**) was purchased from Frontier Scientific and used as received. Additive **1** was purchased from Santa Cruz Biotechnologies. Additive **2** was purchased from Combi-Blocks. Additive **4** was purchased from Sigma-Aldrich. Additive **6** was purchased from AK Scientific. Phenol and electrochemical grade tetrabutylammonium hexafluorophosphate (TBAPF₆) were purchased from Sigma-Aldrich and used as received. Carbon dioxide (99.99%) and nitrogen (99.998%) were purchased from Praxair. All other reagents and solvents were purchased from commercial sources and used without further purification unless specified. *N,N*-Dimethylformamide (DMF) and tetrahydrofuran (THF) were dried using a JC Meyer solvent purification system. UV/Vis spectra were collected using an Agilent Cary 60 spectrophotometer or an Agilent 8453 spectrophotometer at room temperature. NMR spectra were recorded on Bruker spectrometers operating at 400 or 500 MHz as noted. Chemical shifts for ¹H and ¹³C spectra are reported in parts per million relative to residual protiated solvent. ESI-MS data were obtained using an Advion mass spectrometer.

Cyclic Voltammetry Methods. Cyclic voltammetry experiments were performed using a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat. A 10 mL 2-neck pear-shaped flask was equipped with a glassy carbon disk (3.0 mm diameter, BASi) working electrode, a platinum wire counter electrode, and a Ag wire contained in a porous Vycor tipped glass tube filled with electrolyte as a pseudo-reference electrode. Before use, the working electrode was thoroughly polished with 0.05 μm alumina powder on a felt pad. The electrolyte was 0.1 M TBAPF₆ in DMF freshly prepared with anhydrous solvent and saturated with either CO₂ or N₂ by sparging for 20 minutes. Gas flow was continued throughout the experiment with sparging in between scans and blanketing the solvent during scans. Cyclic voltammograms were obtained with internal resistance compensation measured immediately prior to each scan. At the conclusion of the experiment, potentials were referenced against the ferrocene/ferrocenium redox couple of added ferrocene.

Controlled Potential Electrolysis Methods. Controlled potential electrolysis experiments were performed using either a Bioanalytical Systems, Inc. (BASi) Epsilon potentiostat or a BioLogic VSP-300 potentiostat. Experiments were performed in a custom-made, gas-tight PEEK cell that is a miniaturized version of one previously reported by our laboratory.⁸⁶ The working chamber (10 mL liquid volume) and counter chamber (3 mL liquid volume) were separated by an ultra-fine glass frit (Ace Glass). A 1 cm² glassy carbon plate (Tokai Carbon) attached to a stainless steel rod with silver epoxy and covered with Loctite epoxy was used as the working electrode. A 1 cm diameter graphite planchet (Ted Pella) connected to a platinum wire was used as the counter electrode, and an Ag wire in a Vycor tipped glass tube filled with electrolyte was used as a pseudo-reference electrode. The working compartment was filled with 10 mL of a 0.5 mM solution of **Fe-TPP** dissolved in 0.1 M TBAPF₆ in DMF containing 0.5 M phenol as a proton source and any of the additives **1-7**. The counter electrode chamber was filled with 3 mL of a 20 mM solution of tetrabutylammonium acetate dissolved in 0.1 M TBAPF₆ in DMF. This soluble source of acetate was sacrificially oxidized to generate CO₂ and ethane, thereby avoiding GC detection of solvent or anode oxidation byproducts. Both compartments were sealed to be gastight. The working compartment was sparged with CO₂ for 20 min, then sealed and injected with 0.5 mL of ethane as a gaseous internal standard. A CV scan was collected prior to the electrolysis to calibrate the potential. The electrolyte solution was constantly stirred during the electrolysis with a 1 cm stirbar.

At the conclusion of the experiment, the headspace was injected directly into an SRI-GC (model #8610C) equipped with 6' Haysep D and 13X molecular sieve chromatographic columns. Carbon monoxide and ethane were quantified using an in-line flame ionization detector (FID) equipped with a methanizer, and hydrogen and ethane were quantified using a thermal conductivity detector (TCD). Analytes of interest were quantified by comparing a ratios of analyte/internal stand peak integrals to a calibration curve with known amounts of analyte.

Turnover Frequency Calculations. The turnover frequency was estimated from the average current densities during each controlled potential electrolysis using methods developed by Savéant and coworkers.⁸⁰ The average CO specific current density was obtained by averaging each recorded current density data point over the 16 h electrolysis experiments and then multiplying by the CO Faradaic efficiency determined by gas chromatography. The observed rate constant (k_{obs}) was then estimated using equation 1:

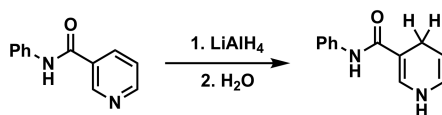
$$\frac{I}{F} = \sqrt{2k_{obs}C_A^0D_p} \frac{C_p}{1 + \exp\left[\frac{F}{RT}(E - E_{redox}^0)\right]} \quad (\text{Equation 1})$$

Where I is the CO specific current density, F is the Faraday constant, E is the applied potential of -2.4 V vs. Fc/Fc^+ , E_{redox}^0 is the $\text{Fe}^{\text{I}}/\text{Fe}^0$ redox potential of **Fe-TPP** in the absence of substrate measured to be -2.05 V vs. Fc/Fc^+ , R is the ideal gas constant ($8.314 \text{ J K}^{-1} \text{ mol}^{-1}$), T is the temperature (298 K), C_A^0 is the concentration of CO_2 saturated in DMF ($2.3 \times 10^{-4} \text{ mol cm}^{-3}$), D_p is the diffusion coefficient of **Fe-TPP** determined using scan rate dependence of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$ reduction ($8.0 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$), and C_p is the concentration of catalyst ($5.0 \times 10^{-7} \text{ mol cm}^{-3}$).

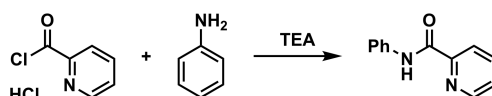
From the estimated k_{obs} value, the turnover frequency could then be calculated using equation 2:

$$TOF = \frac{k_{obs}}{1 + e^{\left[\frac{F}{RT}(E - E_{redox}^0)\right]}} \quad (\text{Equation 2})$$

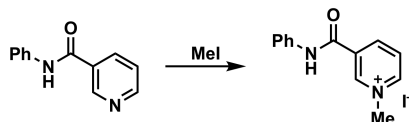
In this approximation, we estimate that the mechanism for CO_2 reduction catalyzed by **Fe-TPP** is unchanged in the presence of additive with each turnover requiring 2 molecules of catalyst. Under the applied potential of -2.4 V vs. Fc/Fc^+ , the denominator of equation 2 approaches 1.0, and k_{obs} is equal to the maximum turnover frequency.



Synthesis of 1'. In a dry glovebox with a dinitrogen atmosphere, **1** (200 mg, 1.0 mmol, 1.0 equiv.) and LiAlH₄ (76 mg, 2.0 mmol, 2.0 equiv.) were added to a 100 mL round bottom flask. THF (6 mL) was added, and the reaction mixture immediately turns bright yellow and then orange and appears heterogeneous. After stirring for 3 h at RT, the reaction mixture was cooled in an ice bath, and 12 mL of H₂O, pre-sparged with N₂ for 10 min, was slowly added dropwise. The resulting precipitate was quickly recovered by vacuum filtration exposed to air. The solid was washed with H₂O, CH₃OH, and then dried in vacuo. Product **1'** was isolated as a pale yellow solid and stored under N₂. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 7.72 (br s, 1H), 7.61 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.23 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.09 (d, *J* = 5.4 Hz, 1H), 6.96 (m, 1H), 5.94 (m, 1H), 4.56 (m, 1H), 3.11 (dd, *J* = 3.5, 1.6 Hz, 2H) ppm. ESI-MS *m/z* calcd. for C₁₂H₁₃N₂O [M + H]⁺: 201.1, found: 201.0. UV/Vis (DMF) λ_{abs} 355 nm.

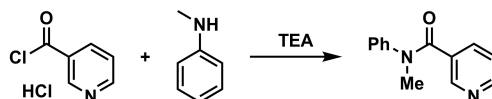


Synthesis of N-Phenylpicolinamide (3). Following a modified literature report,⁸⁷ aniline (0.34 mL, 3.75 mmol, 1.0 equiv.), picolinoyl chloride hydrochloride (1.0 g, 5.62 mmol, 1.5 equiv.), and triethylamine (1.57 mL, 11.23 mmol, 3.0 equiv.) were dissolved in anhydrous THF (7 mL) under N₂ atmosphere. The reaction mixture was stirred for 2 h at RT, then diluted with ethyl acetate. The organic phase was added to a separatory funnel and washed with H₂O, sat. NaHCO₃, and brine, then isolated and dried over Na₂SO₄. After filtration and removal of solvent by rotary evaporation, the yellow oil was purified by column chromatography using silica eluting with 9:1 hexane:ethyl acetate. The second fraction was collected and isolated as a white/yellow solid. Recrystallization from hot hexane yielded **3** as white, needle shaped crystals. Spectroscopic data is in good agreement with the literature report. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 8.75 (m, 1H), 8.17 (m, 1H), 8.08 (m, 1H), 7.91 (m, 2H), 7.68 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.36 (m, 2H), 7.12 (m, 1H) ppm. ESI-MS *m/z* calcd. for C₁₂H₁₁N₂O [M + H]⁺: 199.1, found: 199.0.

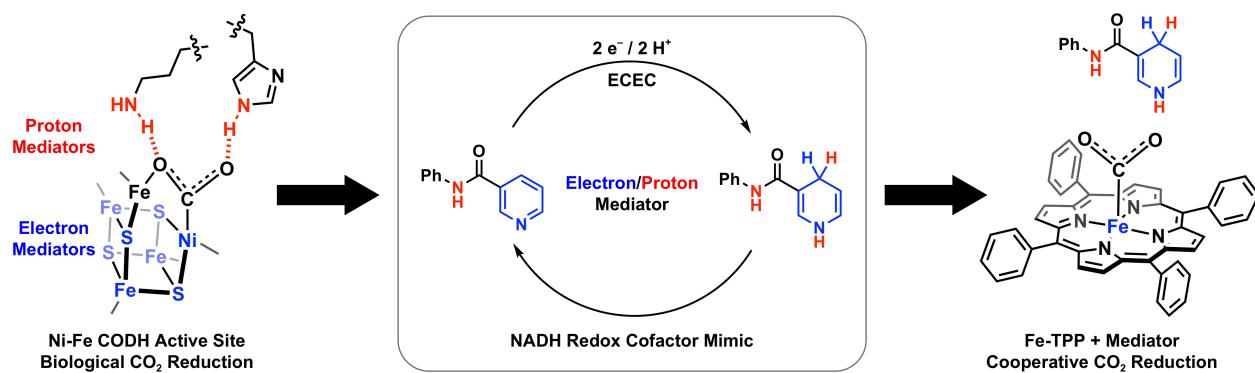


Synthesis of N-Methyl-N'-Phenylnicotinamide (5). Following a modified literature report,⁸⁸ compound **1** (50 mg, 0.25 mmol, 1.0 equiv.) was dissolved in ethanol (0.8 mL), then a solution of methyl iodide (40 μL, 0.64 mmol, 2.5 equiv.) in acetone (0.4 mL) was added. The reaction mixture was stirred overnight at 40 °C. Solvent was removed by rotary evaporation, then the residual solid was suspended in CH₂Cl₂, filtered and washed with more CH₂Cl₂ to give **5** as a white solid with quantitative yield. ¹H NMR (300 MHz, Acetone-*d*₆) δ 10.01 (s, 1H), 9.24 (d, *J* = 5.9 Hz, 1H), 9.17

(d, $J = 8.2$ Hz, 1H), 8.37 (m, 1H), 8.06 (m, 2H), 7.39 (dd, $J = 8.4, 7.5$ Hz, 2H), 7.18 (m, 1H), 4.72 (s, 3H) ppm. ESI-MS m/z calcd. for $C_{13}H_{13}N_2O$ $[M - I^-]^+$: 213.1, found: 213.0



Synthesis of *N*-Methyl-*N*-Phenylnicotinamide (7). Following a similar protocol as with **3** above, in a 20 mL scintillation vial, *N*-methylaniline (0.41 mL, 3.75 mmol, 1.0 equiv.), nicotinoyl chloride hydrochloride (1.0 g, 5.62 mmol, 1.5 equiv.), and triethylamine (1.57 mL, 11.23 mmol, 3.0 equiv.) were dissolved in CH_2Cl_2 (7 mL) under N_2 atmosphere. The reaction mixture was stirred overnight at RT. The reaction mixture was added to a separatory funnel and washed with H_2O , sat. $NaHCO_3$, and brine, then isolated and dried over Na_2SO_4 . After filtration and removal of solvent by rotary evaporation, the yellow oil was purified by column chromatography using silica eluting with 9:1 hexane: CH_2Cl_2 to give **7** as a clear, viscous oil. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.46 – 8.37 (m, 2H), 7.67 – 7.60 (m, 1H), 7.33 – 7.14 (m, 6H), 3.39 (s, 3H). ESI-MS m/z calcd. for $C_{13}H_{13}N_2O$ $[M + H]^+$: 213.1, found: 213.0



Scheme 5.1. Bioinspired Design of Second-Sphere Additives that Enable Dual Electron and Proton Control for Facilitating Electrochemical CO₂ Reduction Catalyzed by Iron Tetraphenylporphyrin (Fe-TPP)

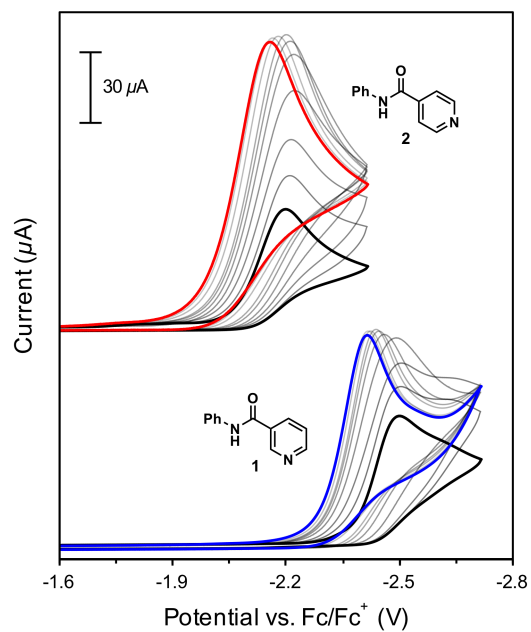
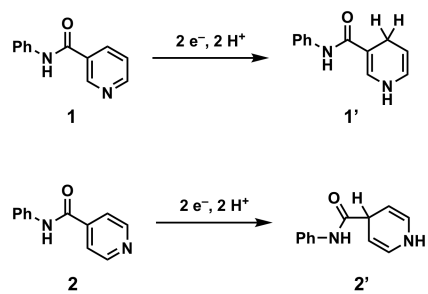


Figure 5.1. Cyclic voltammograms of 5 mM of NADH analogs **1** (blue) and **2** (red) in 0.1 M TBAPF₆ DMF electrolyte under an N₂ atmosphere with titration of 0-100 mM phenol. Scan rate = 100 mV/s.



Scheme 5.2. Reductions of NADH Analogs 1 and 2 Produce the Corresponding 1,4-Dihydropyridines, 1' and 2'

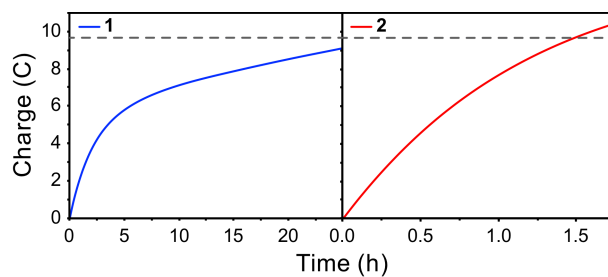


Figure 5.2. Controlled potential electrolyses showing charge consumption of 5 mM of NADH analogs **1** (blue) and **2** (red) at -2.4 V vs. Fc/Fc^+ in 0.1 M TBAPF_6 DMF electrolyte containing 500 mM phenol under a CO_2 atmosphere. The grey dashed line denotes the charge required for complete 2-electron reduction of **1** and **2**.

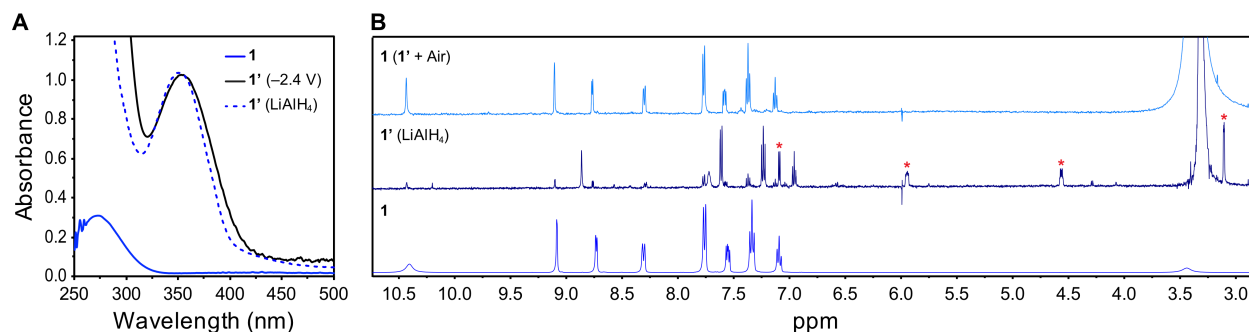


Figure 5.3. (A) Overlaid UV/Vis spectra in DMF solution of **1** (solid blue) and **1'** synthesized by either chemical reduction with LiAlH₄ (dashed blue) or by electrochemical reduction at -2.4 V in the presence of excess phenol (black). (B) Overlaid ¹H NMR spectra in DMSO-d₆ of **1**, **1'** synthesized by chemical reduction with LiAlH₄, and **1** obtained by oxidation of **1'** upon exposure to air. Peaks labeled with asterisks are assigned to the newly formed allylic and vinylic protons. Peaks between 3.3 and 3.5 ppm are assigned to residual water.

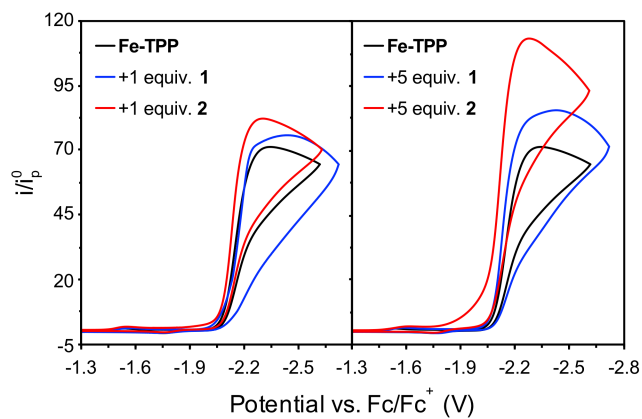
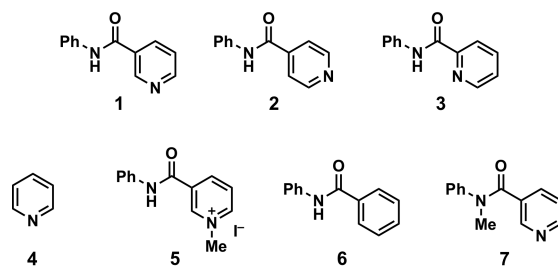


Figure 5.4. CVs of **Fe-TPP** (black) in the presence of 1 equiv. or 5 equiv. of additives **1** (blue) or **2** (red) in 0.1 M TBAPF₆ DMF electrolyte containing 500 mM phenol under a CO₂ atmosphere. Current is normalized to the formal Fe^{II}/Fe^I reduction of **Fe-TPP**, i_p^0 .



Scheme 5.3. Chemical Structures of Synthetic NADH-Type Additives 1-7

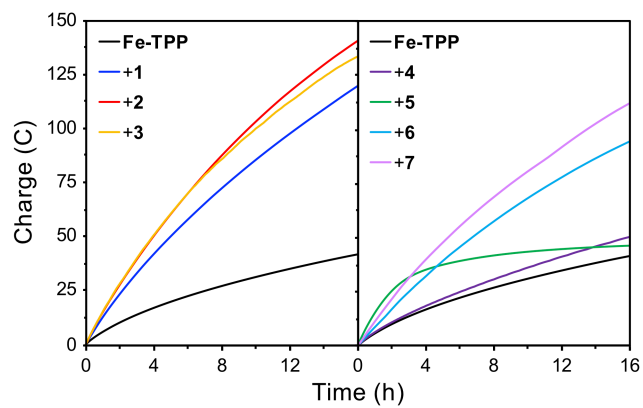


Figure 5.5. CPEs of 0.5 mM **Fe-TPP** in the presence of 1 equiv. of additives **1-7** in 0.1 M TBAPF₆ DMF electrolyte containing 500 mM phenol under CO₂ performed at -2.4 V vs Fc/Fc⁺.

Table 5.1. CPE Data Summarizing Effects of NADH-Type Additives on Electrochemical CO₂ Reduction Catalyzed by Iron Porphyrin

Catalysts	Charge (C)	Vol. (mL) ^a	CO	FE _{CO} (%) ^a	Avg. j_{CO} (mA cm ⁻²) ^b	TOF _{max} (s ⁻¹) ^c
Fe-TPP	41.8	4.9		93	0.67	5.24 x 10 ⁴
+1	119.2	15.0		86	2.07	5.00 x 10 ⁵
+2	141.0	17.9		108	2.45	7.01 x 10 ⁵
+3	132.7	16.8		87	2.31	6.23 x 10 ⁵
+4	50.4	6.0		94	0.82	7.85 x 10 ⁴
+5	46.0	5.4		92	0.74	6.39 x 10 ⁴
+6	94.5	11.9		104	1.63	3.10 x 10 ⁵
+7	112.5	14.2		100	1.95	4.44 x 10 ⁵

CPEs performed with 0.5 mM **Fe-TPP**, with or without 0.5 mM the synthetic NADH analog as an additive, at a potential of -2.4 V vs. Fc/Fc⁺ in 0.1 M TBAPF₆ DMF electrolyte containing 500 mM phenol under a CO₂ atmosphere for 16 h. ^a Determined using gas chromatography equipped with a flame ionization detector and a known calibration curve. Faradaic efficiency (FE) values are estimated to have an error of ±10%. ^b Determined by averaging the observed current density during each 16 h electrolysis experiment and multiplying by the FE_{CO}. ^c Estimated from the average j_{CO} during each electrolysis (see Supporting Information).

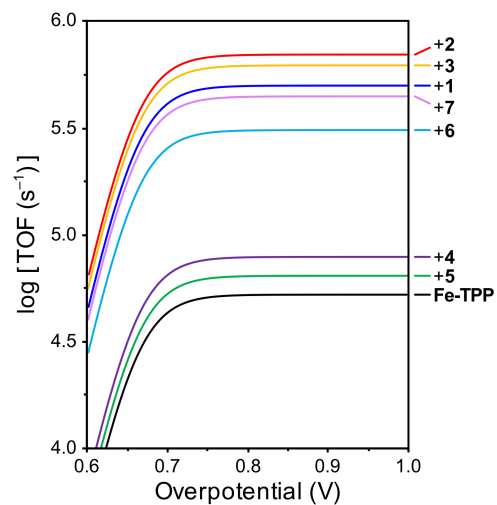


Figure 5.6. Catalytic Tafel plots for **Fe-TPP** in the absence or presence of 1 equiv. of NADH mimics **1-7** derived from the k_{obs} values estimated from controlled potential electrolysis experiments.

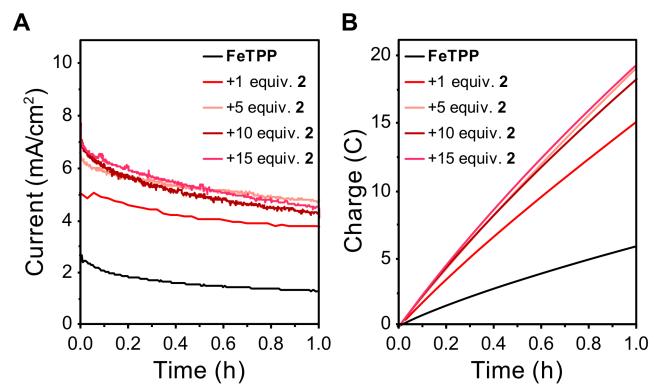


Figure 5.7. CPEs of 0.5 mM **Fe-TPP** in the presence of 0-15 mM additive **2** in 0.1 M TBAPF₆ DMF electrolyte containing 500 mM phenol under a CO₂ atmosphere plotting (A) current density and (B) charge accumulation over a period of 1 h at -2.4 V vs. Fc/Fc⁺.

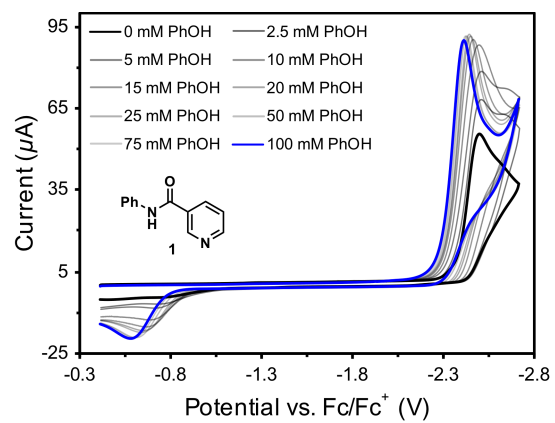


Figure 5.8. Full CVs of **1** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

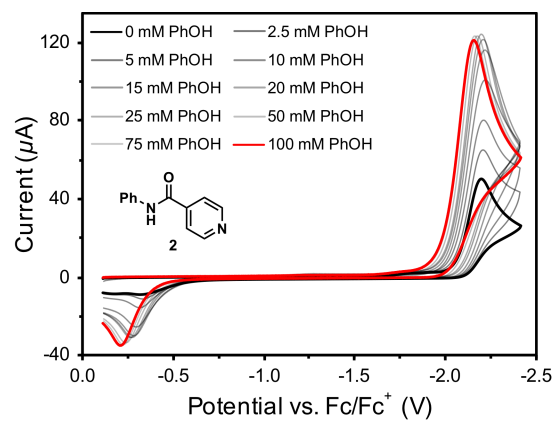


Figure 5.9. Full CVs of **2** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

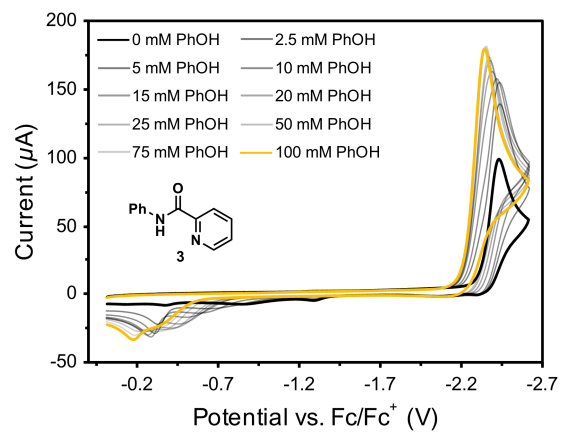


Figure 5.10. Full CVs of **3** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

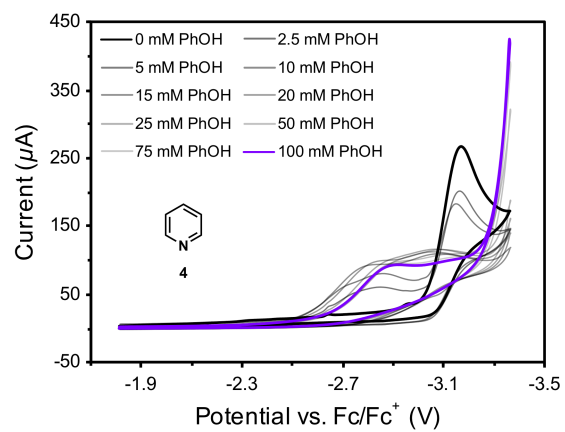


Figure 5.11. CVs of **4** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

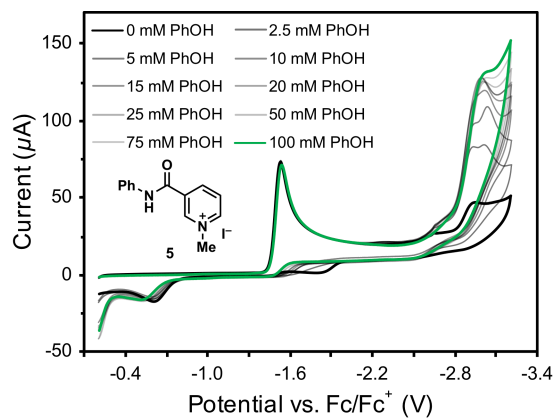


Figure 5.12. CVs of **5** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

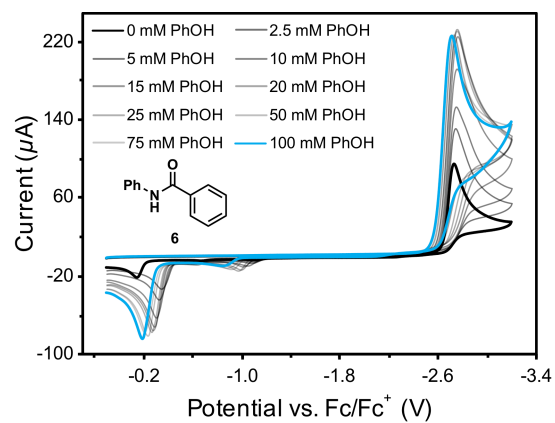


Figure 5.13. CVs of **6** (5 mM) in the presence of 0-100 mM phenol under N₂ atmosphere in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

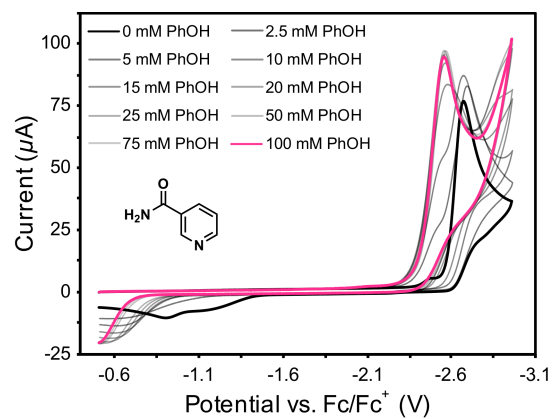


Figure 5.14. CVs of **Nicotinamide** (5 mM) in the presence of 0-100 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

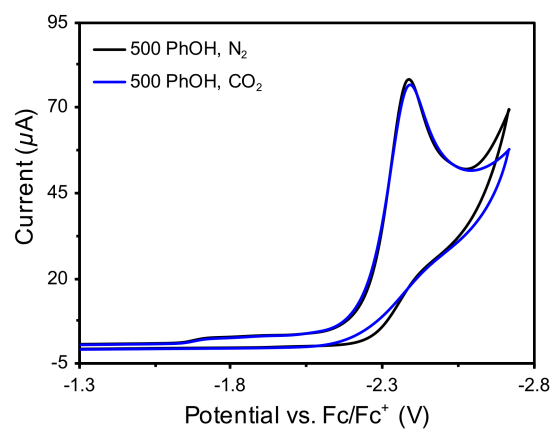


Figure 5.15. CVs of **1** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (blue) at a scan rate of 100 mV/s.

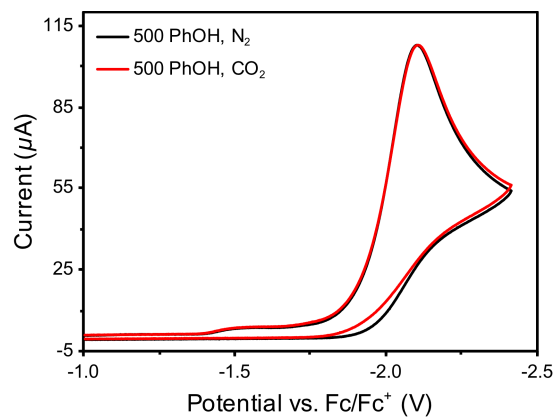


Figure 5.16. CVs of **2** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (red) at a scan rate of 100 mV/s.

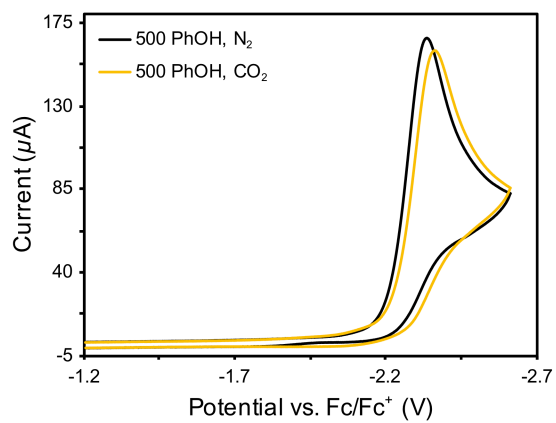


Figure 5.17. CVs of **3** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (yellow) at a scan rate of 100 mV/s.

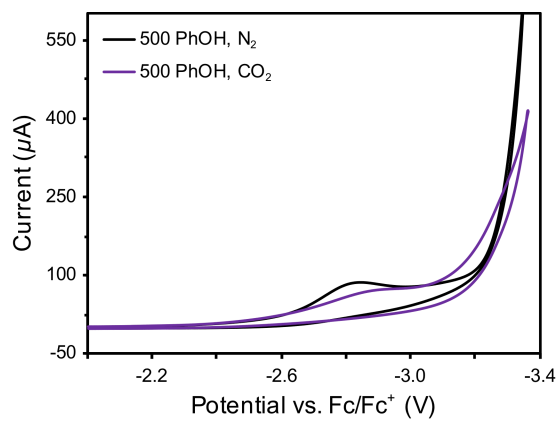


Figure 5.18. CVs of **4** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (purple) at a scan rate of 100 mV/s.

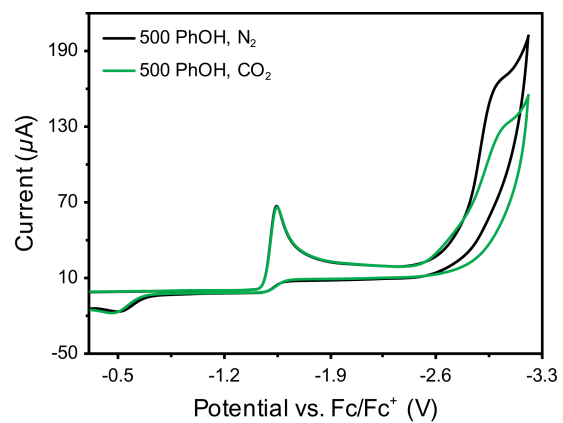


Figure 5.19. CVs of **5** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (green) at a scan rate of 100 mV/s.

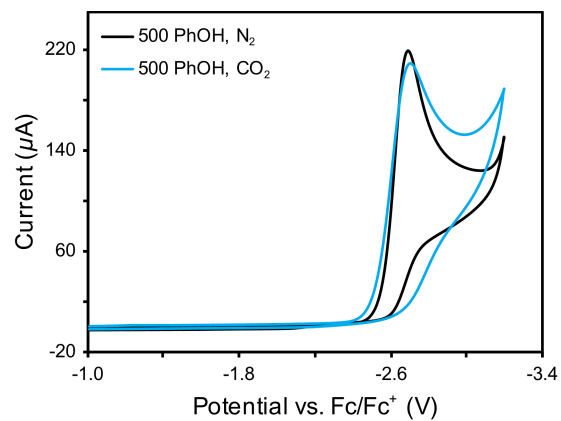


Figure 5.20. CVs of **6** (5 mM) with 500 mM phenol in 0.1 M TBAPF₆ in DMF saturated with N₂ (black) or CO₂ (cyan) at a scan rate of 100 mV/s.

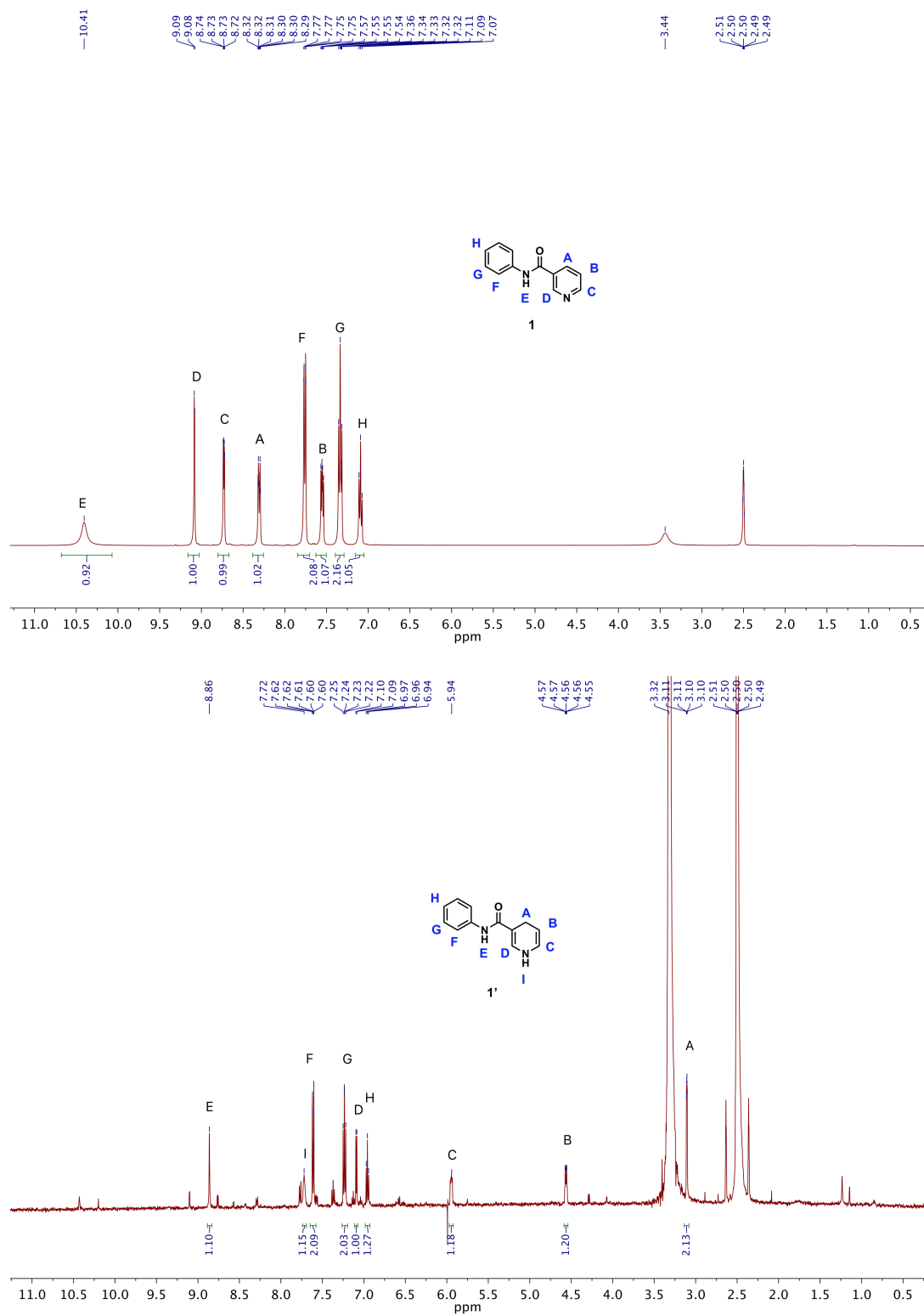


Figure 5.21. ^1H NMR spectra of **1** and **1'** in DMSO-d_6 with peak assignment.

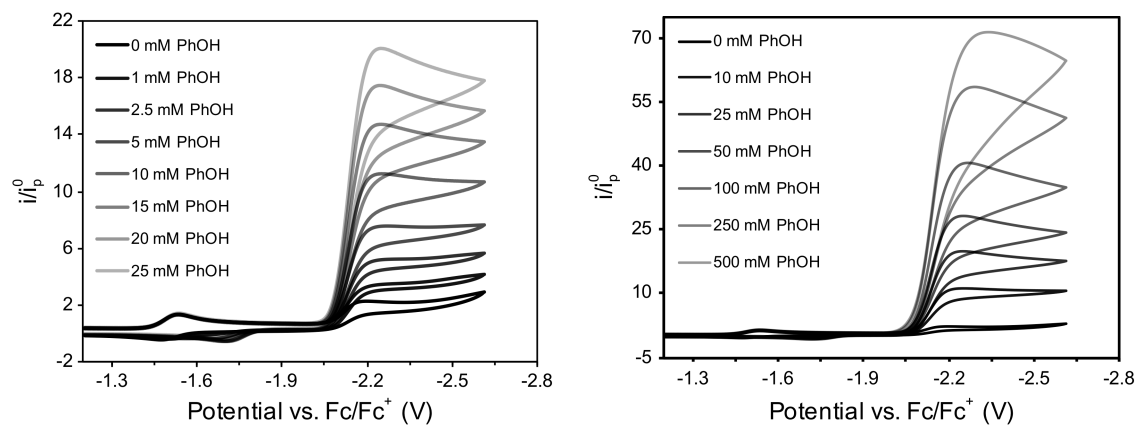


Figure 5.22. CVs of **Fe-TPP** (1 mM) in the presence of 0-500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

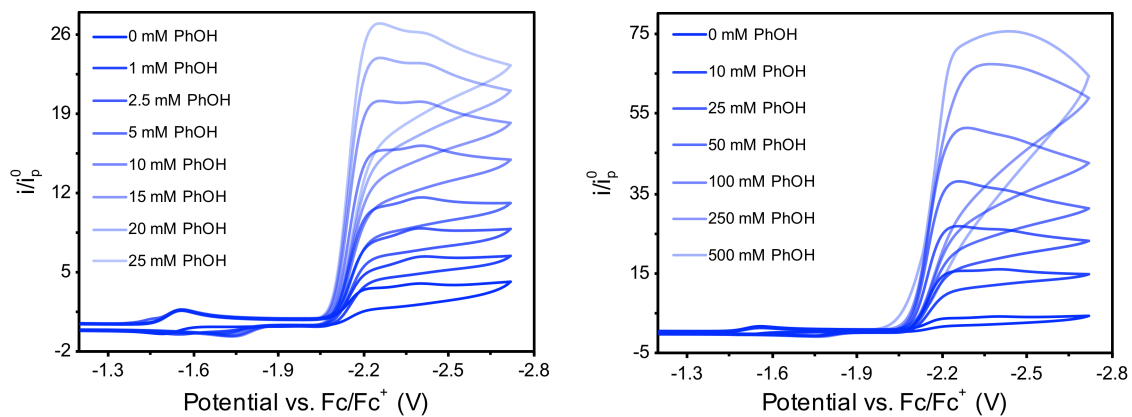


Figure 5.23. CVs of Fe-TPP (1 mM) in the presence of 1 equiv. of **1** and 0-500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

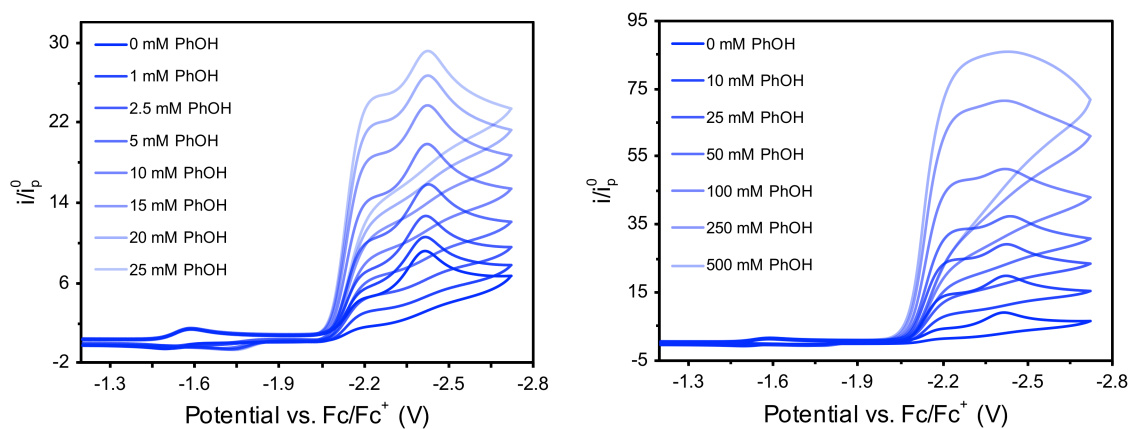


Figure 5.24. CVs of **Fe-TPP** (1 mM) in the presence of 5 equiv. of **1** and 0-500 mM phenol under CO_2 atmosphere (0.23 M) in 0.1 M $TBAPF_6$ in DMF at a scan rate of 100 mV/s.

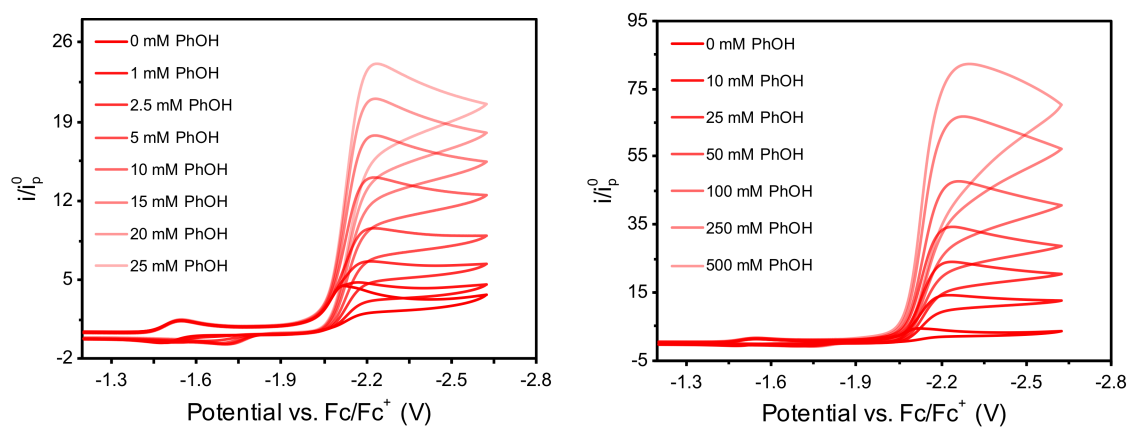


Figure 5.25. CVs of Fe-TPP (1 mM) in the presence of 1 equiv. of **2** and 0-500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

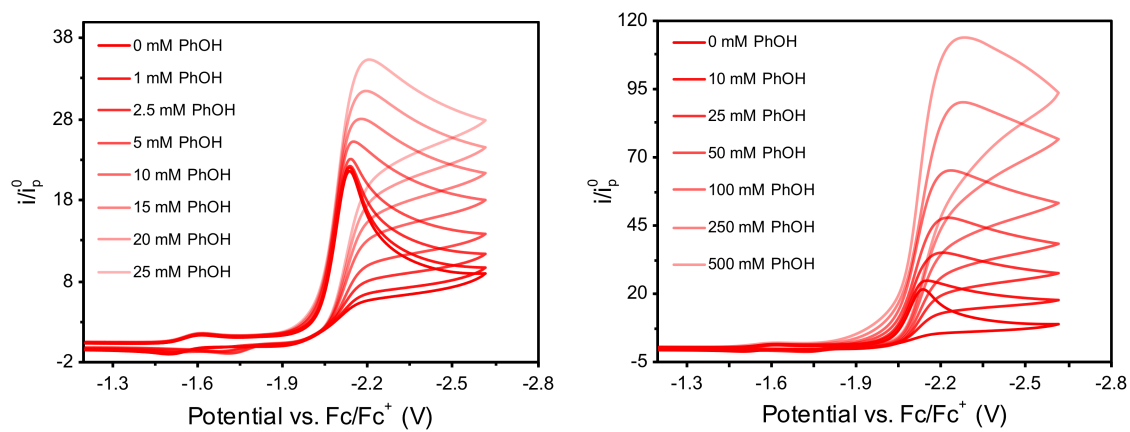


Figure 5.26. CVs of Fe-TPP (1 mM) in the presence of 5 equiv. of **2** and 0-500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

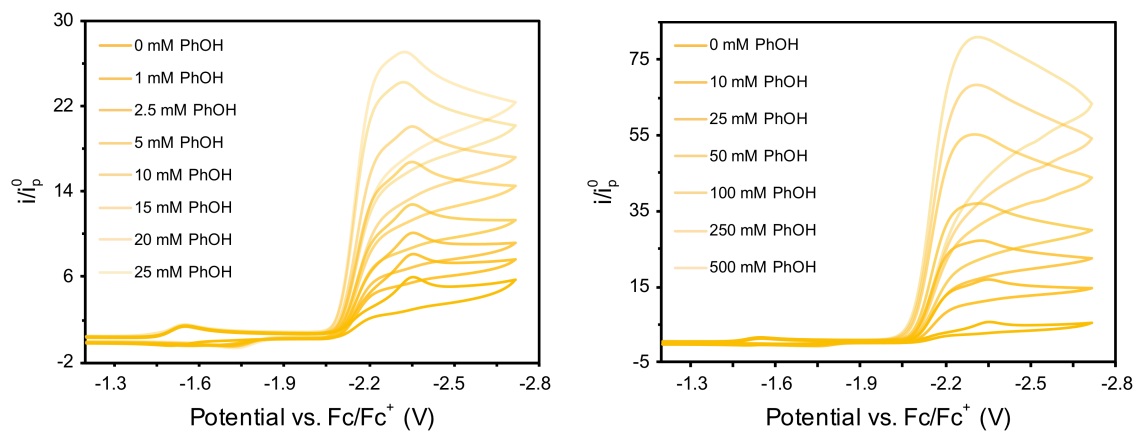


Figure 5.27. CVs of **Fe-TPP** (1 mM) in the presence of 1 equiv. of **3** and 0-500 mM phenol under CO_2 atmosphere (0.23 M) in 0.1 M $TBAPF_6$ in DMF at a scan rate of 100 mV/s.

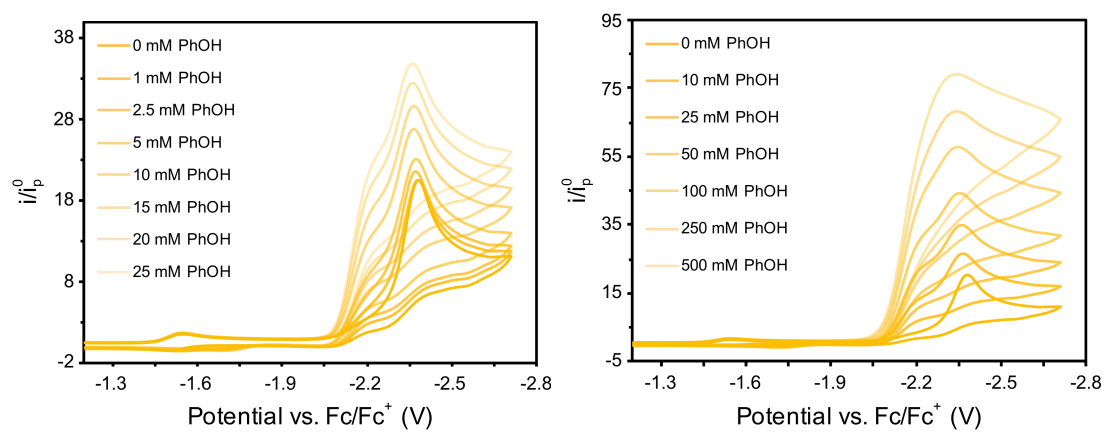


Figure 5.28. CVs of Fe-TPP (1 mM) in the presence of 5 equiv. of **3** and 0-500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at a scan rate of 100 mV/s.

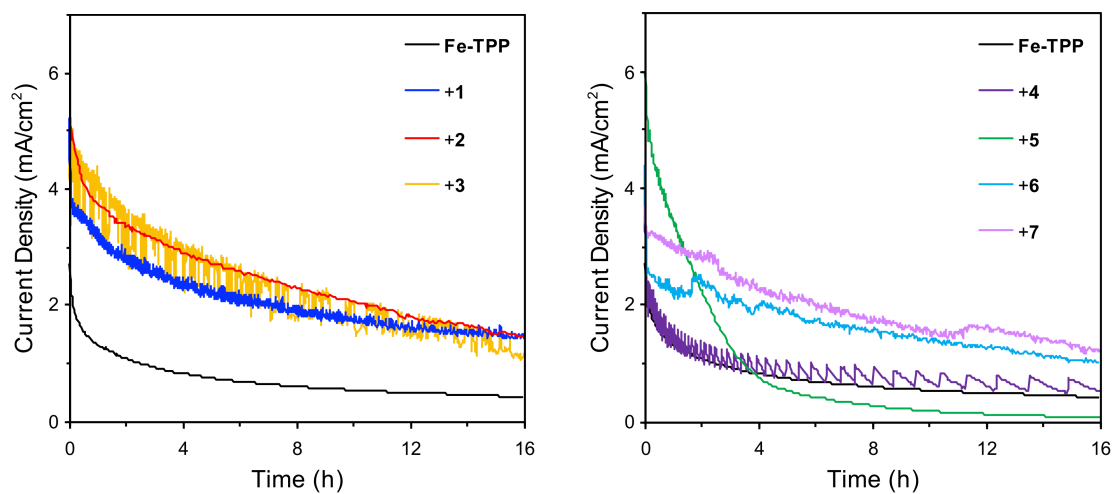


Figure 5.29. CPEs showing current density over time for 0.5 mM **Fe-TPP** with added 0.5 mM additive and 500 mM phenol under CO₂ atmosphere (0.23 M) in 0.1 M TBAPF₆ in DMF at -2.4 V vs. Fc/Fc⁺ for 16 h.

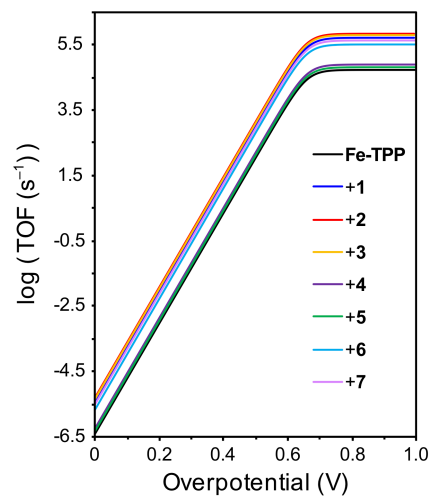


Figure 5.30. Full Tafel plot showing the intrinsic turnover frequencies for each system at zero overpotential.

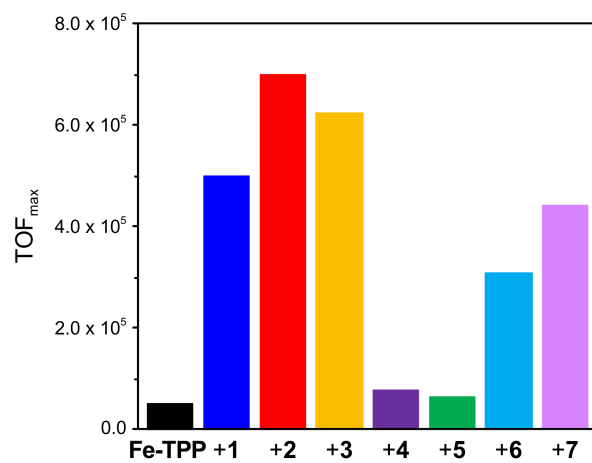


Figure 5.31. Bar graph comparing the TOF_{max} values for each system.

Table 5.2. Data for CO and H₂ product selectivity during 16 h CPEs at –2.4 V vs. Fc/Fc⁺ using 0.5 mM **Fe-TPP** with 0.5 mM additive in 0.1 M TBAPF₆ DMF electrolyte under CO₂.

Catalysts	Charge (C)	Vol. CO (mL)	FE _{CO} (%)	FE _{H₂} (%)
Fe-TPP	41.8	4.9	93	1
+ 1 equiv. 1	119.2	15.0	86	16
+ 1 equiv. 2	141.0	17.9	108	1
+ 1 equiv. 3	132.7	16.8	87	0
+ 1 equiv. 4	50.4	6.0	94	1
+ 1 equiv. 5	46.0	5.4	92	1
+ 1 equiv. 6	94.5	11.9	104	0
+ 1 equiv. 7	112.5	14.2	100	0

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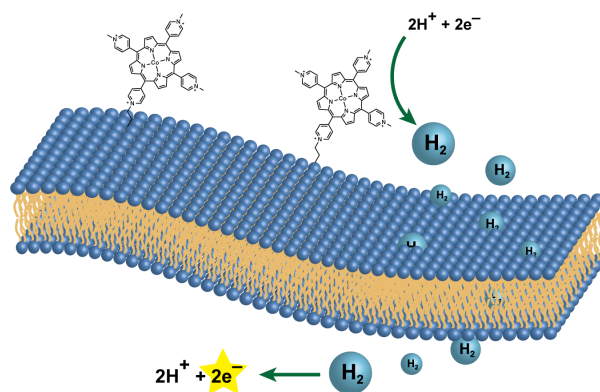
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Appendix A

Covalent Attachment of Molecular Proton Reduction Catalysts onto the Cell Membrane of Denitrifying Bacteria

Abstract

We present preliminary work towards the construction of a hybrid molecular-biological platform for the electrochemical reduction of nitrate into dinitrogen (N_2). We take advantage of *Paracoccus denitrificans*, a denitrifying bacterium with established enzymatic pathways for the reduction of nitrate into nitrite and then ultimately into N_2 . To interface this microbe with an electrochemical source of energy, we use electro-generated H_2 as a soluble source of reducing equivalents that can be taken up by the bacteria and converted to electrons by hydrogenase enzymes. This can be done using H_2 generated at the electrode surface, which then diffuses to the cells. Alternatively, we attempt to covalently attach molecular catalysts for proton reduction directly to the outer membrane of the bacteria in order to generate the reducing equivalents at the surface of the bacteria for immediate uptake. This work begins to establish methods for making molecular-biological hybrids that operate under electrochemical conditions and methods for the quantification of nitrate and nitrite during the denitrification process.



Introduction

In this appendix, we continue exploring approaches for hybrid bio-molecular catalyst platforms. But, instead of simply taking inspiration from biology in the design of molecular catalysts, we use a living organism itself to drive redox enzyme catalysis and we attempt to interface it with molecules that can provide the necessary reducing equivalents.

The nitrogen cycle involves four main processes.¹ First, fixation is the conversion of N_2 into NH_3 and is performed by bacteria. Second, nitrification is the conversion of NH_3 into nitrate and nitrite. Third is the reverse process of denitrification, where bacteria convert nitrate and nitrite into N_2 . Finally, the fourth process is assimilation wherein plants and animals incorporate nitrate and NH_3 into their biomass. This cycle is crucial for life since the nitrogen in N_2 is largely unavailable until it is transformed into NH_3 or nitrate. However, human activity has disrupted the nitrogen cycle because of the immense use of fertilizers for agriculture. The Haber-Bosch process allows for the industrial fixation of N_2 into NH_3 , which can then be incorporated into various fertilizers, the overuse of which can have serious detrimental impacts on the environment. Most notably is fertilizer runoff, which causes eutrophication wherein bodies of water containing excess minerals and nutrients experience dense growth of cyanobacteria, algae, and plants that ultimately depletes dissolved oxygen leading to loss of animal life.² Additionally, fossil fuel combustion can often release various nitrogen oxides that are greenhouse gases and that contribute to air pollution.³ Because of this, it is of interest to develop various means to purify water from excess fertilizers. An industrial process for denitrification is necessary to counteract the industrial fixation and nitrification that we rely so heavily on.

Catalysts for denitrification, the reduction of nitrate into N_2 , have not been extensively developed despite the appeal of driving this conversion electrochemically.⁴ Complete conversion into N_2 requires two nitrate molecules and a total of ten electrons and twelve protons. Such transformation is desirable for groundwater remediation as discussed above. Alternatively, nitrate can be reduced by eight electrons and ten protons into NH_3 as a potential alternative to the Haber-Bosch process using more renewable energy sources. A range of heterogeneous catalysts have been, and with transition metal electrodes the main products are NH_3 and hydroxylamine.⁵ For nitrate reduction into N_2 , a palladium/copper alloy electrocatalyst where the copper helps with the first reduction of nitrate into nitrite while palladium steers the final selectivity towards N_2 .⁶ Currently, only a few recently reported molecular species are capable of catalyzing the electrochemical reduction of nitrate or nitrite. First, cobalt complexes using redox-active cyclam derivatives were shown to catalyze the reduction of nitrate or nitrite into NH_3 in aqueous electrolyte,^{7,8} and chromium cyclam could catalyze the reduction of nitrate into nitrite although it adsorbs onto the mercury electrode.⁹ Also, a cobalt metalloprotein catalyst was reported for the electrochemical reduction of nitrite to NH_3 at neutral pH with 90% Faradaic efficiency.¹⁰ Taken together, the results of heterogeneous and homogeneous catalysis with nitrate indicate that selective formation of N_2 as the final product is still not readily attainable.

In this context, it is appealing to consider biological approaches to denitrification catalysis since various microbes are already capable of selectively catalyzing this multi-electron-multi-proton reduction. However, the challenge with this is interfacing the living organism with an electrochemical platform. This can be approached in two primary ways, one being using biofilms

on the electrode surface and the other using dispersed bacteria in the electrolyte.¹¹ Few examples have been able to demonstrate direct electron transfer from an electrode to a living microbe, and most platforms rely on soluble redox mediators to deliver electrons from the electrode to enzymes in the cell. One potential redox mediator of interest to us is H_2 since it can be readily generated electrochemically with numerous proton reduction catalysts and many bacteria possess hydrogenase enzymes that catalyze the interconversion of H_2 and 2 electrons and 2 protons.¹² Our laboratory has previously explored this strategy, as described in Chapter 1, where we interfaced H_2 evolving platinum electrodes or nickel-sulfide nanoparticles with a microbe capable of using H_2 and CO_2 to selectively generate CH_4 .¹³ In this approach, catalyst optimization for proton reduction was relatively easy whereas no molecular catalysts and few materials catalysts can selectively reduce CO_2 into CH_4 . We hypothesize that this strategy can be extended to other microbes to catalyze other transformations that use electrochemically-generated H_2 as the soluble source of reducing equivalents.

Herein, we describe our efforts towards synthesizing proton reduction catalysts that have reactive handles for the labeling of the cell membrane of *Paracoccus denitrificans* for rapid delivery of reducing equivalents that can be used for the reduction of nitrate into N_2 . We begin by designing and synthesizing various cobalt porphyrins that are water soluble and that we can readily attach an array of reactive groups that can potentially covalently attach to the cell membrane. We also develop cobalt polypyridine proton reduction catalysts as alternatives to the porphyrins. We apply these catalysts to various cell labeling techniques and then investigate the effects on denitrification catalysis. We developed methods to monitor the activity of *P. denitrificans* and to accurately quantify the amounts of nitrate and nitrite in solution. Further optimization of this system is required, but we present a strong foundation for developing covalently linked molecular-biological hybrid catalysts for electrochemical nitrate reduction.

Results and Discussion

Design and Synthesis of Proton Reduction Catalysts. Cobalt porphyrins have been extensively studied for their proton reduction activity in a wide range of conditions, including physiological conditions that are relevant for our work. The media used for our bacteria is neutral, therefore, the proton reduction catalyst must be able to operate at neutral pH. We chose to use tetra(4-pyridyl)porphyrin as a starting compound, since alkylation of the pyridine nitrogen atoms will create a tetra-cationic species that can be water soluble and that can possess reactive handles for cell membrane labeling (Scheme A.1). Using this approach, we could synthesize cationic cobalt porphyrins bearing a single moiety that can be used in click chemistry labeling or that is known to be reactive directly with amino acids such as lysine or cysteine. To begin, the tetra(4-pyridyl)porphyrin was mono-alkylated with the desired reactive handle for cell labeling by reacting in DMF at 100 °C with 10-20% yield after isolation by column chromatography on silica using CHCl₃/MeOH. Then the remaining three pyridine nitrogens were alkylated with methyl iodide, and repeated anion exchanges yielded the pure product that could then be metalated with cobalt. This strategy proved to be useful in appending a range of potential bioconjugation moieties including azides for click chemistry, alkanes for lipid insertion, NHS esters for amine labeling, or maleimides for cysteine labeling. One potential problem with cell labeling with synthetic molecules is their cytotoxicity. This is likely a factor of the extent of cell labeling and which attachment strategy is used, but porphyrins themselves are a concern because of their extensive use in photodynamic therapy where the porphyrins aid in the formation of reactive oxygen species that kills cells.¹⁴

CVs were performed using the bacteria minimal media as the electrolyte to verify that these cationic cobalt porphyrins exhibit catalytic behavior. Figure A.1 shows the CVs for the tetra-methylated pyridinium cobalt porphyrin, CoTMPyP, as well as the derivative bearing a single azide substituent. Both complexes show large increases in current upon application of a potential negative of -1.0 V vs. SHE. While this potential is relatively negative, the background CV for the glassy carbon shows no catalytic current, suggesting that these cobalt porphyrins are active above the background level and that the azide modification does not hinder catalysis.

In addition to cobalt porphyrins, we investigated cobalt polypyridine complexes that our laboratory has developed previously for proton reduction at neutral pH. These polypyridine ligands have very extensive synthetic tunability so that we can readily incorporate reactive groups onto them, and they can also be tuned to operate at potentials slightly less negative compared to cobalt porphyrins. This is important in order to minimize the extent of background proton reduction occurring at the electrode and to amplify the effects of cell surface attachment. We developed two primary catalysts, one a PY5Me₂ complex and the other a bpyPY2Me complex. Our laboratory already had a bpyPY2Me functionalized with a carboxylate, so a simple coupling reaction with *N*-hydroxysuccinimide gave the NHS ester (Scheme A.2). For the PY5Me₂, the synthesis of a derivative with an amino group has been reported, however, conversion of this to an ester or an amide would make the catalyst slightly electron-rich and shift the reduction potential more negative. Since these catalysts already operate at relatively negative potentials and typically use mercury electrodes when performing electrochemical proton reduction, we decided to avoid this route. Instead, appending a carboxylic acid directly to the PY5Me₂ ligand and subsequent conversion would put the heteroatom away from the pyridine structure, thereby acting as an

electron-withdrawing group, which should shift the potential for proton reduction catalysis more positive, as has been shown with the trifluoromethyl derivative.¹⁵ We approached this synthesis as shown in Scheme A.3, first converting the cyano group to a protected carboxylic acid that is compatible with the general PY5 synthesis and then deprotecting and performing the amide coupling with an amino alkyl azide.

Nitrate and Nitrite Quantification. To monitor the denitrification activity of our system, it is necessary to track the products formed and consumed over time. With the bacteria *P. denitrificans*, this denitrification is a stepwise enzymatic pathway where nitrate is first reduced into nitrite, then nitrite is reduced into nitric oxide, two molecules of nitric oxide are reduced to give nitrous oxide, and finally nitrous oxide is reduced into N₂ (Figure A.2).^{16,17} To monitor the course of this reaction, we used a known method for nitrate and nitrite detection termed the Griess assay, wherein the sample is split in two and nitrite is first detected spectrophotometrically after reaction with sulfanilamide and naphthalene ethylenediamine.¹⁸ Then the rest of the sample is treated with vanadium chloride to reduce any nitrate into nitrite, and this new quantity for total nitrite is quantified and subtraction of the first nitrite quantification gives the amount of nitrate. We chose not to directly monitor nitric oxide or nitrous oxide, but could detect N₂ by gas chromatography. Following literature reports for the Griess assay was not immediately successful, and this detection protocol required extensive optimization to give reliable and accurate measurements. The steps for this optimized procedure are given in the Materials and Methods section below (Scheme A.4).

Thus, the expected results would be for nitrate concentration to decrease while nitrite concentration begins to increase. Then the nitrite concentration should decrease as it is further reduced, and finally the N₂ quantity should increase as the final product. To verify this technique, we monitored the enzymatic activity of *P. denitrificans* in anaerobic test tubes using acetate as the source of electrons for nitrate reduction. As expected, we see the starting 30 mM concentration of nitrate quickly drop to 0 mM while the concentration of nitrite increases over the first 20 h and then decreases down to 0 mM (Figure A.3). For these initial experiments, we did not quantify the N₂ formation, but these assays provide good insight into the rate of denitrification by the bacteria.

Interfacing Denitrifying Bacteria with Heterogeneous Electrodes. Next, we used an electrochemical cell instead of the anaerobic tubes and added the suspended bacteria in minimal media to the working chamber. Using the same 30 mM starting concentration of nitrate as with the acetate experiments, we used a platinum working electrode and applied a potential of -0.75 V vs. Ag/AgCl for 72 h while periodically removing 0.5 mL aliquots via a syringe to minimize exposure to air and then immediately froze the samples until analysis. Over the 72 h, the concentration of nitrate only fell to approximately 20 mM and nitrite concentration detected increased to approximately 5 mM (Figure A.4). These results indicate that the bacteria are not receiving sufficient reducing equivalents from the electro-generated H₂ to drive the denitrification of 30 mM nitrate. The current density at this potential was close to 0.02 mA/cm², so we repeated the electrolysis experiment using a controlled current at an elevated 1 mA/cm². However, again the cells are unable to consume the 30 mM nitrate after 72 h. If we look at the charge requirements for this transformation, there is 30 mM nitrate in 50 mL of electrolyte, and each nitrate molecule needs to be reduced by 5 electrons to give N₂. This would require 723.6 C to be passed to make H₂ and then assume that all of this H₂ is successful consumed by the bacteria. In our experiments, the

platinum electrode passes 50 C or 110 C over 90 h in minimal media when -1.0 or -1.2 V vs Ag/AgCl is applied.

We next decided to investigate lower concentrations of starting nitrate substrate. The Environmental Protection Agency and the World Health Organization have set the maximum contaminant level for nitrate as 10-50 ppm, which corresponds to approximately $800\ \mu\text{M}$ nitrate. Thus, we chose to use 1 mM nitrate as the starting concentration, which would require 24.1 C for complete reduction. Now, we are able to see the complete consumption of nitrate within 20 h and the formation of 1 mM nitrite after 20 h that then is completely consumed after 30 h (Figure A.5). This indicates that the bacteria can catalyze denitrification under these conditions.

Subsequently, the working electrode was changed to glassy carbon since we want a more inert electrode material that can transfer electrons to the molecular cobalt catalyst once they are added to the system. Using the glassy carbon electrode with bacteria that are not labeled with catalyst should lead to no denitrification activity, however, we observed that the cells are able to consume both nitrate and nitrite over 60 h when -0.8 V vs. Ag/AgCl is applied, suggesting that there is some reductant present that allows the bacteria to reduce 1 mM nitrate (Figure A.6). This could be from the low level of background proton reduction on the glassy carbon, or from some unknown source of electrons.

We performed a series of experiments to then determine how to minimize this background level of nitrate reduction. First, we prepared the electrochemical experiment with 1 mM nitrate but did not add any bacteria and did not apply any potential. Over 80 h the concentration of nitrate remained unchanged and no nitrite was detected indicating that there is no physical loss of the substrate in the experimental design such as through the ion exchange membrane. Next, we setup the electrochemical experiment with 1 mM nitrate and prepared the bacteria in two ways. One by growing the bacteria in rich media and then washing with minimal media and adding to the cell. The other method we grew the bacteria in rich media and then mimicked the cell labeling procedure by washing with PBS, incubating with PBS for 1 h, washing and incubating with PBS for another 1 h, washing with minimal media, and then adding to the cell. No potential was applied, and in the first method, the nitrate concentration slowly decreases and the nitrite concentration slowly increases over 100 h but is not completely consumed (Figure A.7). In the second method, the nitrate and nitrite are both completely consumed within 50 h. There is no electro-generated H_2 in these experiments, so the bacteria must be obtaining the reducing equivalents from a different source, and the experiment that involves the lengthy washing and PBS incubation must have a greater amount of these reducing equivalents available. We also monitored the denitrification activity in anaerobic tubes containing 1 mM nitrate. With the bacteria and acetate as the added electron donor the nitrate and nitrite are consumed within 20 h, and when no acetate is added, the nitrate concentration slowly decreases and the nitrite concentration slowly increases over 80 h (Figure A.8). This again indicates that there is some background denitrification activity with no added electron donor. At this stage, it is unclear what is causing this activity, but there may be strategies to help starve the cells to prevent accumulation of reductants. Alternatively, we can try increasing the starting nitrate concentration to 10 mM to minimize this background activity.

Cell Labeling with Molecular Catalysts. For the labeling of the cell membrane, we first performed experiments using click chemistry and commercially available fluorophores. Scheme

A.5 depicts the general strategy of non-specific attachment of a cyclooctyne group using amide coupling with the commercially available NHS ester. Subsequent treatment with a fluorophore, Cy3, bearing an azide moiety enables labeling with the fluorophore through a strain-promoted reaction to avoid an addition of copper for click chemistry. The labeled cells were then imaged by confocal microscopy, and Figure A.9 shows good overlay of the dye fluorescence with the bright-field image of the bacteria indicating that this click chemistry strategy is attaching the dye to the cells. We also repeated this labeling experiment using a free base pyridinium porphyrin functionalized with an azide group. This structure is given in Scheme A.1, but we are using the non-metalated species for this labeling strategy because non-metalated porphyrins exhibit red fluorescence upon irradiation with UV light, so we could potentially also visualize the membrane labeling with our synthesized compound. Figure A.10 also shows fluorescence of the cells after labeling indicating that the porphyrins are attaching to the cell.

While the above confocal microscopy images are promising, the resolution is too low to verify the localization of the dyes at the cell membrane because the bacteria cells are so small. It is possible that dye or porphyrin is entering into the cell, and this cannot be readily differentiated from specific covalent labeling of the outer cell membrane. We attempted to improve upon this using super resolution fluorescence microscopy. The Biological Imaging Facility was used for structured illumination microscopy of the dye labeled cells, and preliminary results seemed to suggest that the dye was localized to the membrane of the bacteria cells. Additional experiments using this imaging technique are necessary.

Denitrification Activity with Labeled Bacteria. We first confirmed that the click chemistry labeling procedure does not hinder the denitrification activity of the bacteria by monitoring the nitrate and nitrite concentrations of a suspension of acetate-fed bacteria labeled with just the NHS-DBCO click chemistry precursor and also with the Cy3 dye and fed acetate. Figure A.11 shows the consumption of 30 mM nitrate, formation of nitrite, and consumption of nitrite using cells labeled with NHS-DBCO and cells labeled with DBCO and then Cy3. The denitrification activity are both comparable to that of unlabeled cells shown in Figure A.3, indicating that this click chemistry protocol is bio-compatible.

We next extended this cell labeling protocol to our azide functionalized cobalt porphyrins and investigated the electrochemistry of the labeled cells. The cobalt porphyrin labeled bacteria were added to the electrochemical cell equipped with a glassy carbon electrode, and CVs taken show a large increase in current at -1.2 V vs. Ag/AgCl while CVs of unlabeled bacteria show no change in current from background (Figure A.12). This suggests that the catalytic proton reduction activity of the cobalt porphyrins is preserved after being covalently attached to the bacteria. We then performed controlled potential electrolysis experiments on these labeled and unlabeled cells and monitored the conversion of 1 mM nitrate. The control unlabeled cells show the consumption of nitrate and nitrite in 20 h as expected, but the porphyrin labeled cells take over 90 h to consume the nitrate and nitrite (Figure A.13). This indicates that the labeling is hindering the denitrification activity.

A final set of control experiments were performed to verify that labeling is hindering denitrification activity. The reduction of 30 mM nitrate using acetate in anaerobic tubes was repeated using bacteria labeled with the two different cobalt porphyrin azides, one with an alkyl

linker and the other with a PEG linker. Figure A.14 shows the nitrate and nitrite concentrations that slowly decrease or increase, respectively, over 100 h. This activity is much slower than that of the unlabeled cells shown in Figure A.3. Additionally, this activity is worse than that for the bacteria labeled with just NHS-DBCO or with Cy3 as shown in Figure A.11. From these results, we can conclude that while the click chemistry protocol is not damaging to the bacteria, the labeling with cobalt porphyrins does diminish the denitrification. This may be due to the cytotoxic nature of porphyrins, therefore, moving forward it will be necessary to investigate the polypyridine catalysts and verify whether or not they are cytotoxic.

Conclusion and Future Directions

In summary, we have described our efforts in developing hybrid molecular-biological catalyst platforms that interface synthetic molecular catalysts for proton reduction with living bacteria for nitrate reduction. This work aims to continue expanding our theme of hybridizing the three main elements of molecular, materials, and biological catalysts in unique ways. There are two main challenges that have been identified that need to be resolved for this hybrid platform to be successful. First, the concentration of nitrate substrate needs to be optimized since too much nitrate leads to slow catalysis and extremely long electrolysis experiments while too little nitrate can be reduced by the bacteria enzymes without adding an extrinsic electron source, potentially because of stored amounts of electron donors already present in the cells. It may also be possible to deplete the cells of these electron donors prior to their use in our experimental setup. Second, cell labeling with synthetic molecular catalysts, particularly with porphyrins, appears to be fairly cytotoxic. Nonetheless, the activity of this hybrid platform shows promise as we are able to make synthetic proton reduction catalysts with bioconjugation handles, we are able to label denitrifying bacteria using click chemistry, and we are able to monitor the denitrification activity by following the nitrate and nitrite concentrations over time. The main challenges have been identified, or resolved in the case of nitrate and nitrite detection, so further optimization has a clear path forwards.

Materials and Methods

General Methods. The *Paracoccus denitrificans* bacteria were purchased from the DSMZ-German Collection of Microorganisms and Cell Cultures and stored in a $-80\text{ }^{\circ}\text{C}$ freezer. Sulfo-NHS DBCO and Cy3-azide were purchased from Click Chemistry Tools. Electrochemistry experiments were performed using a custom made two-compartment glass cell as described in Chapters 2-4. The glass cells were dried in an oven overnight at $200\text{ }^{\circ}\text{C}$ and assembled in front of a flame immediately before use. All components that cannot be heated were thoroughly disinfected using ethanol. The rich media used for bacteria growth was composed of 5 g peptone and 3 g meat extract in 1000 mL deionized water with pH 7. The minimal media composition is previously reported with the trace elements TE-3-Zn.¹⁹ Phosphate buffer saline (PBS-1X) was purchased sterile from Corning. All media was autoclaved before use. Cells were grown by inserting a sterile pipette into the frozen pellet and swirling the residue into a flask containing rich media and then grown in an incubator at $30\text{ }^{\circ}\text{C}$.

General Procedure for Monitoring Denitrification Activity. Bacteria were grown in rich media at $30\text{ }^{\circ}\text{C}$ for 3 days then centrifuged. If labeling the cells using click chemistry, follow the procedure below. If not labeling the cells, then the bacteria pellet was washed 4 times with minimal media. The bacteria were diluted with minimal media to an OD_{600} of 0.65. Using a sterile 3 M solution of KNO_3 , nitrate was added to give a starting concentration of 30 or 1 mM. If acetate is added to the experiment, then this is done with a sterile 6 M NaOAc solution. The bacteria solutions are then added to either an anaerobic tube or to the working chamber of an assembled electrochemical cell. The counter chamber was filled with a nitrate solution in minimal media with no added bacteria. The anaerobic tubes were sealed with a septum and crimped closed and the electrochemical cell was closed with the working, counter, and reference electrodes attached. The systems were then sparged with N_2 for 20 minutes and then shaken or stirred at $30\text{ }^{\circ}\text{C}$. A sterile syringe and needle were used to periodically remove 0.5 mL aliquots, which were then syringe filtered into tubes and frozen until analysis for nitrate and nitrite concentrations.

General Procedure for Cell Labeling Using Click Chemistry. The cell culture in rich media was transferred to a test tube and centrifuged for 10 min at 2500 g and then the media was removed and the pellet suspended in PBS. The tube was vortexed and then centrifuged again for 10 min. This washing with PBS was performed 4 times. The bacteria were suspended in PBS to an OD_{600} of 1.0, then for every 1 mL of suspension, 100 μL of a solution of sulfo-NHS-DBCO in PBS (1 mg/mL) was then added and the tube was vortexed and then shaken at RT for 1 h. Centrifugation and washing with PBS was repeated 4 times. PBS was added to the tube to again give an OD_{600} of 1.0, and then for every 1 mL of suspension, 2 μL of a solution of azide dye or catalyst in DMSO (10 mM) was added and the tube was vortexed and shaken at RT for 1 h. Centrifugation and washing with minimal media was then performed.

Procedure for Quantifying Nitrate and Nitrite.

Reagents:

- SULF
 - 2% in 1.2 M HCl
 - 200 mg Sulfanilamide, 9 mL H_2O , 1 mL HCl (37%)
- NEDD

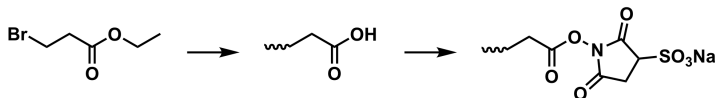
- 0.2% in H₂O
 - 10 mg *N*-1-(Naphthyl)ethylenediamine dihydrochloride, 10 mL H₂O
- VCl₃
 - ~saturated in 1 M HCl
 - 80 mg VCl₃, 9.16 mL H₂O 0.84 mL HCl (37%)
- NO_x Reagent
 - 5 parts VCl₃, 1 part NEDD, 1 part SULF
- Griess Reagent
 - 5 parts 1 M HCl, 1 part NEDD, 1 part SULF

Notes:

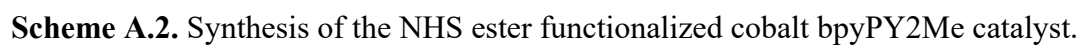
- Working range of assay is ~0-50 μ M
- Nitrate and Nitrite standards range from 0.1 to 50 mM
- Dilute standards 1/1000 before use
- Dilute samples either 1/1000 or 1/100 before use depending on initial concentration
- Reaction of Nitrite with SULF and NEDD is rapid and reaction of Nitrate with VCl₃ is much slower
- Acidic VCl₃ solution will also reduce Nitrite, so Nitrite must be consumed by Griess reagents before reduction by VCl₃
- Each 96-well plate used must have a set of calibration samples

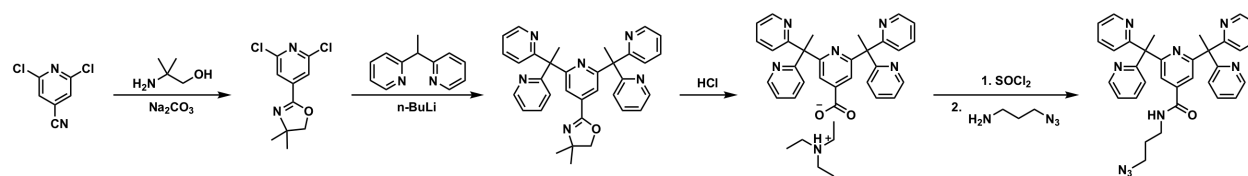
Procedure:

1. Prepare or thaw Nitrate and Nitrite calibration samples and testing samples.
2. Dilute all samples with water to appropriate final concentration range.
3. Add 180 μ L of sample to separate wells in a 96-well plate.
 - a. First row: Nitrate calibration samples and NO_x blank (H₂O only)
 - b. Second row: Nitrite calibration samples and Griess blank (H₂O only)
 - c. Third row: Test samples for NO_x detection
 - d. Fourth row: Test samples for Nitrite detection
4. Prepare all reagents listed above.
5. Add 150 μ L of NO_x reagent to the Nitrate calibration and NO_x sample wells.
6. Add 150 μ L of Griess reagent to the Nitrite calibration and Nitrite sample wells.
7. Incubate the plate at 40 °C covered with foil for 1 h.
8. Measure the absorbance at 540 nm using a plate reader.
9. Data analysis:
 - a. Subtract absorbance from the NO_x and Griess blank wells.
 - b. Plot the Nitrate and Nitrite calibration absorbances versus their concentration, including zero absorbance, to make the two calibration curves.
 - c. Subtract the Nitrite absorbance from the NO_x absorbance for the test samples.
 - d. Use the calibration curves to calculate the Nitrate and Nitrite concentrations, making sure to account for any differences in sample dilution.

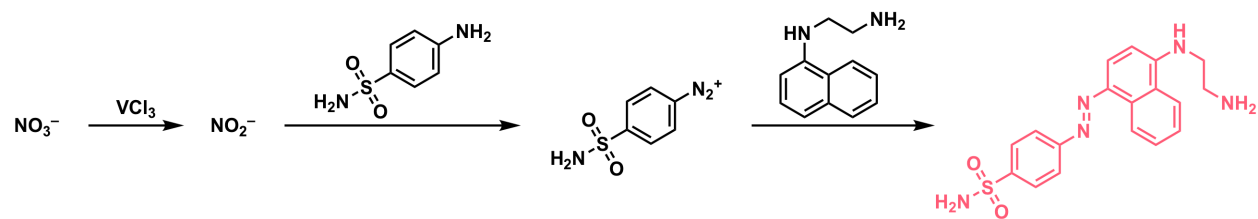


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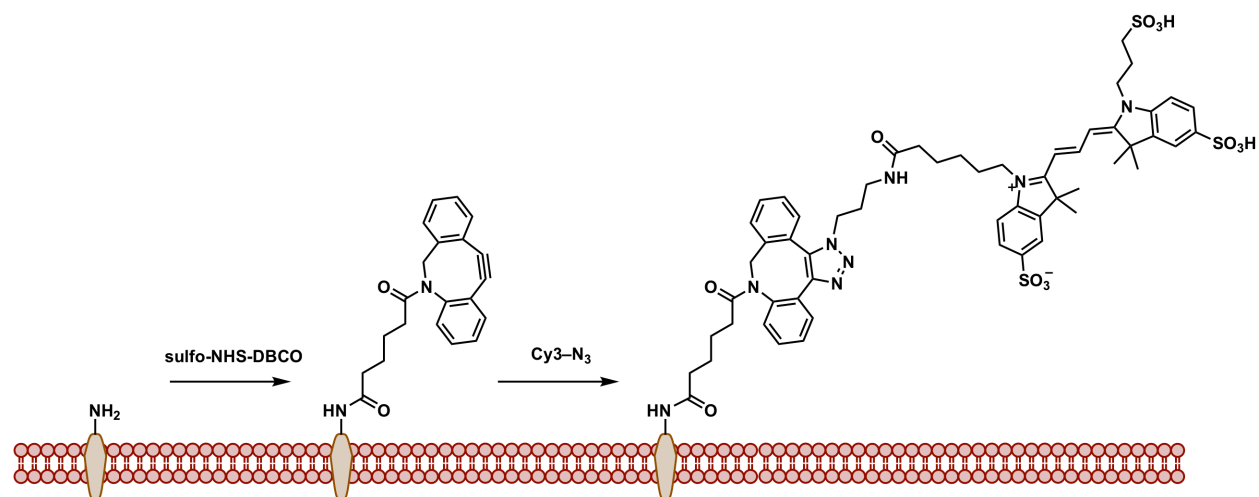




Scheme A.3. Synthesis of the PY5Me₂ ligand functionalized with a carboxylate allowing for functionalization, such as with the azide shown.



Scheme A.4. Spectrophotometric detection of nitrate and nitrite.



Scheme A.5. Scheme for the non-specific labeling of cell surface amines using sulfo-NHS-DBCO and the subsequent strain-promoted click reaction using the fluorophore Cy3 bearing an azide group.

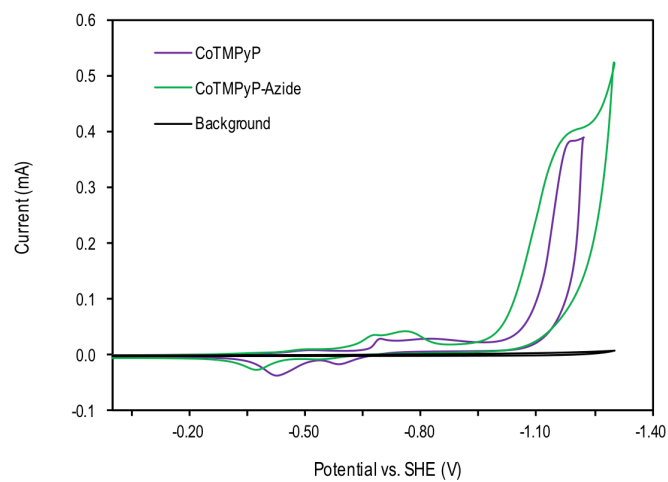


Figure A.1. CVs of the tetra methylated pyridinium cobalt porphyrin, CoTMPyP and the mono-azide functionalized derivative in minimal media using a glassy carbon electrode.

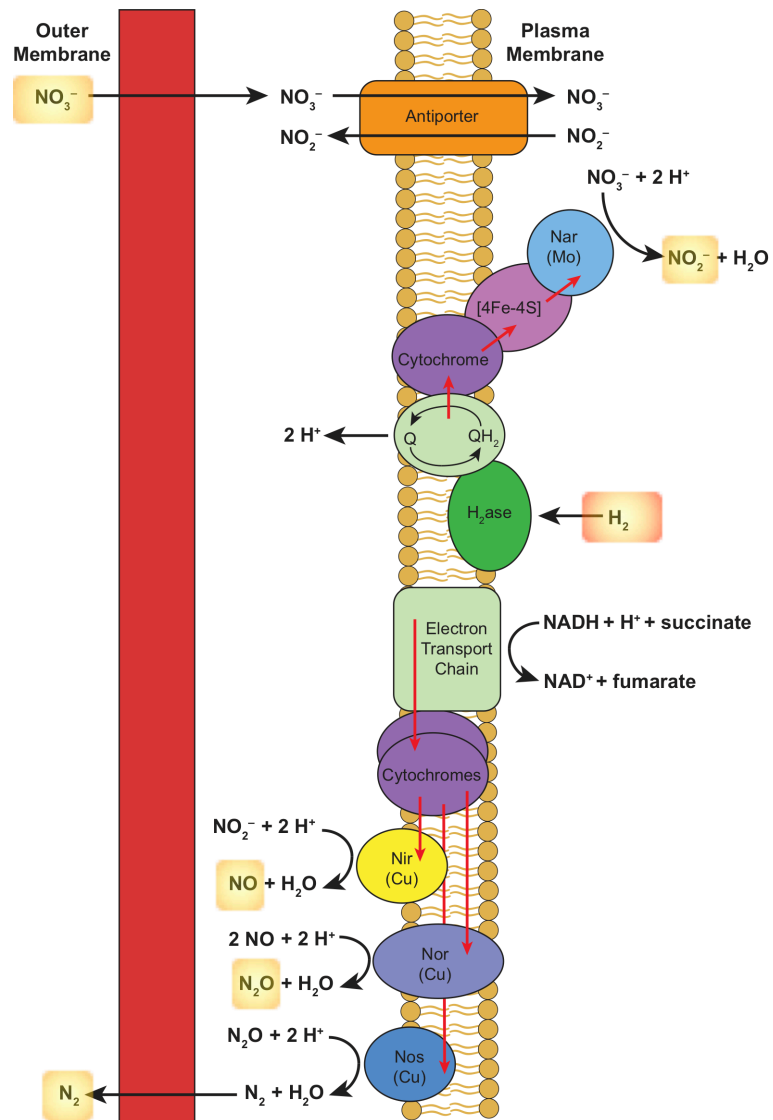


Figure A.2. Diagram summarizing the enzymatic pathways for denitrification in *P. denitrificans*.

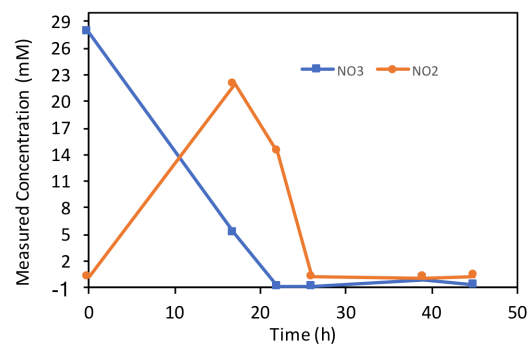


Figure A.3. Nitrate and nitrite concentrations detected in an anaerobic tube filled with *P. denitrificans* with acetate as the electron donor.

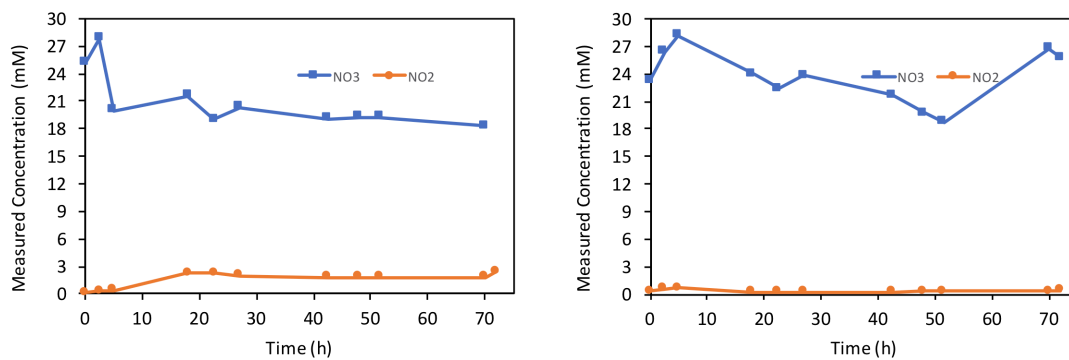


Figure A.4. Electrolysis at -0.75 V vs. Ag/AgCl using platinum electrodes and 30 mM nitrate. The experiment on the left contains the added bacteria showing only modest substrate consumption, and the experiment on the right has no added bacteria showing no nitrite formation.

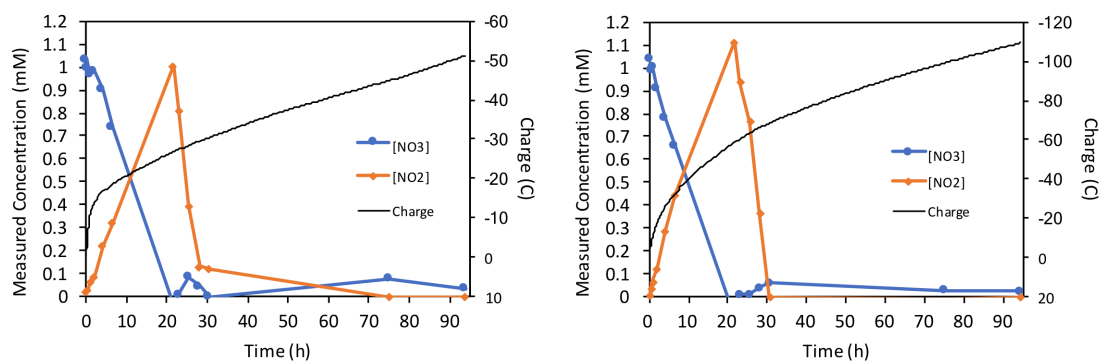


Figure A.5. Electrolysis of bacteria dispersions containing 1 mM nitrate using platinum electrodes at either -1.0 V (left) or -1.2 V (right) vs. Ag/AgCl.

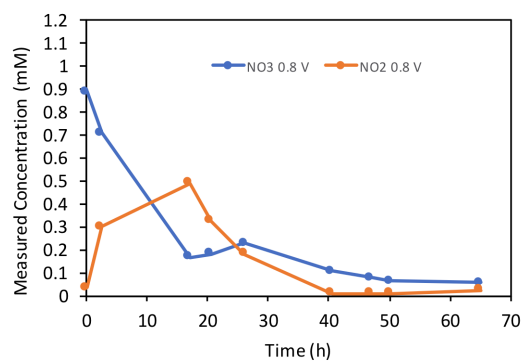


Figure A.6. Electrolysis of bacteria dispersions containing 1 mM nitrate using a glassy carbon electrode at -0.8 V vs. Ag/AgCl.

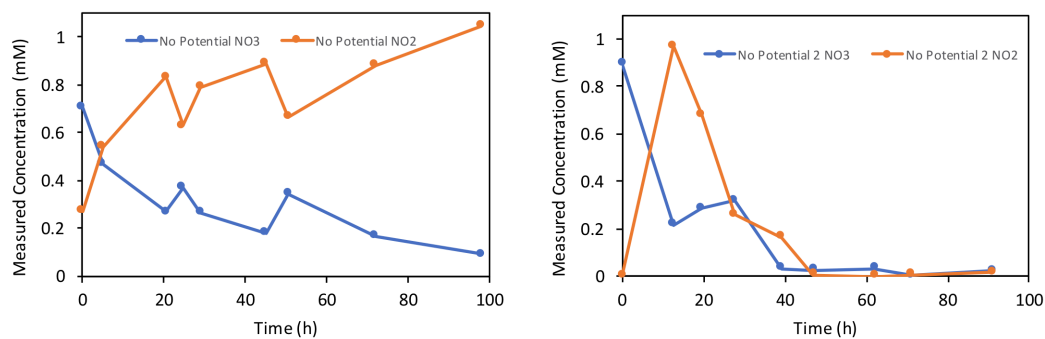


Figure A.7. Nitrate and nitrite concentrations monitored in bacteria solutions in the electrochemical cell with no applied potential. Left: bacteria prepared by one round of washing with minimal media. Right: bacteria prepared mimicking the click chemistry labeling protocol.

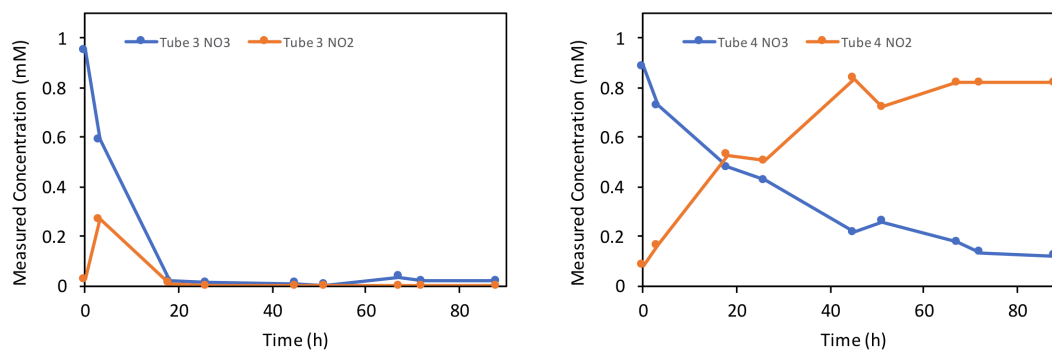


Figure A.8. Nitrate and nitrite concentrations monitored in bacteria solutions in anaerobic tubes containing 1 mM nitrate with added acetate (left) or without added acetate (right).

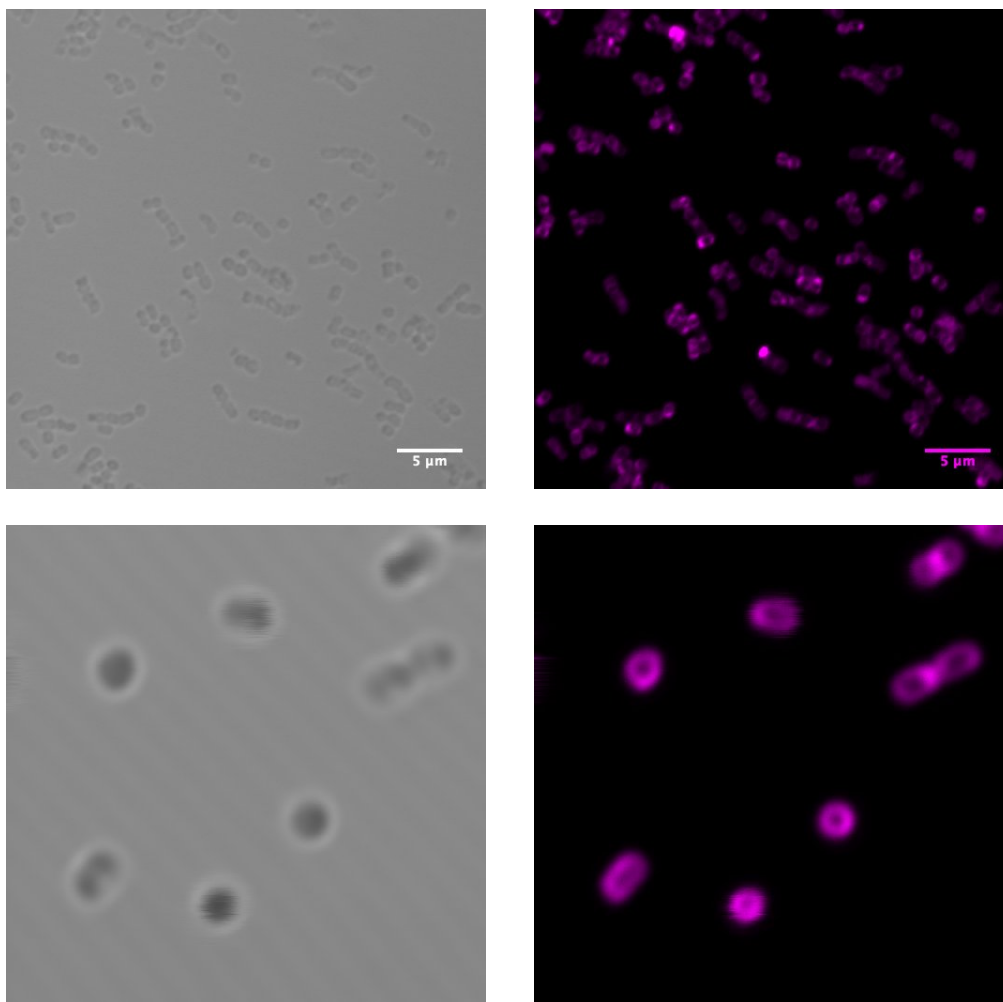


Figure A.9. Confocal microscopy images of *P. denitrificans* labeled with sulfo-NHS-DBCO and then Cy3-N₃.

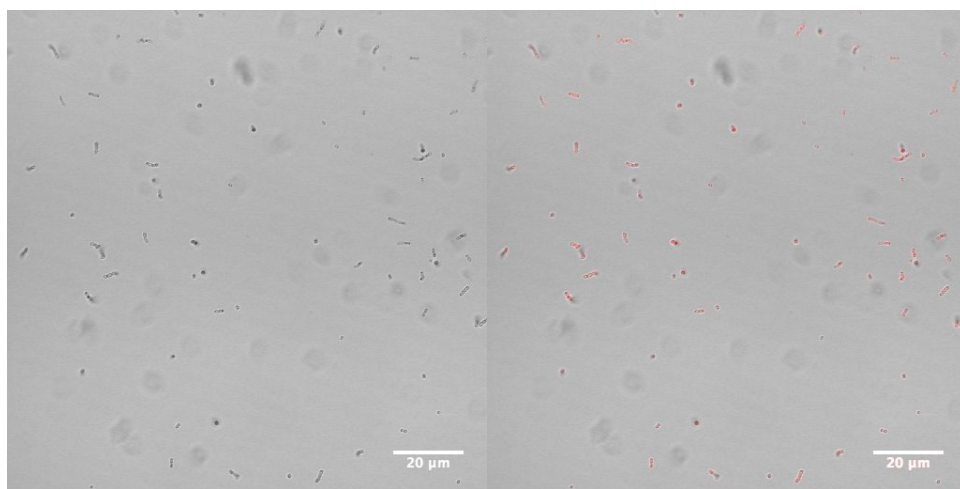
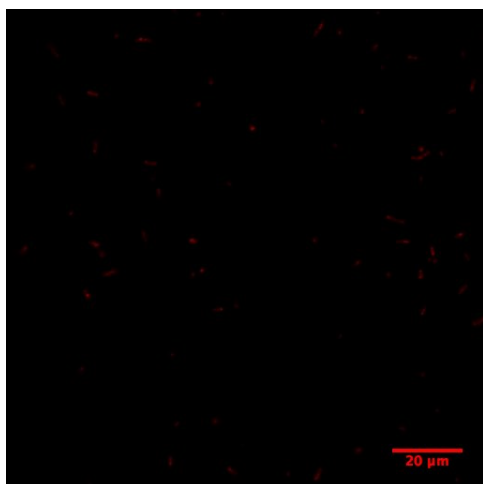


Figure A.10. Confocal microscopy images of *P. denitrificans* labeled with sulfo-NHS-DBCO and then the azide functionalized free base porphyrin.

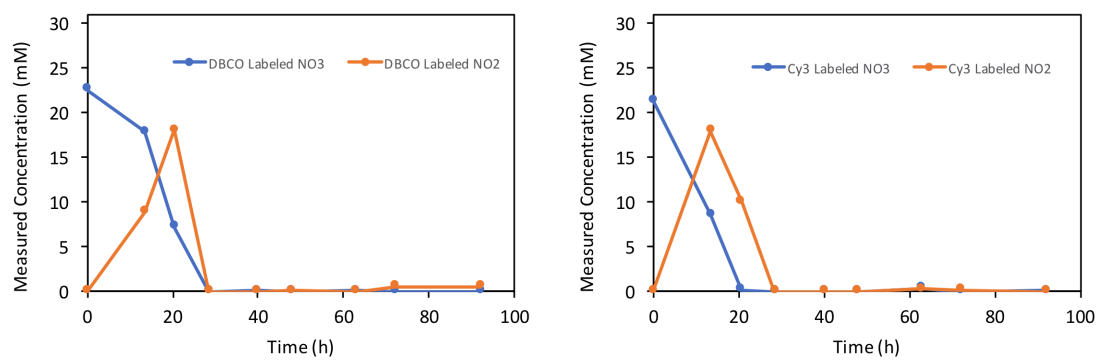


Figure A.11. Nitrate and nitrite concentrations in anaerobic test tubes containing *P. denitrificans* and 30 mM nitrate and 60 mM acetate. Left: cells labeled with sulfo-NHS-DBCO. Right: cells labeled with sulfo-NHS-DBCO and then with Cy3-N₃.

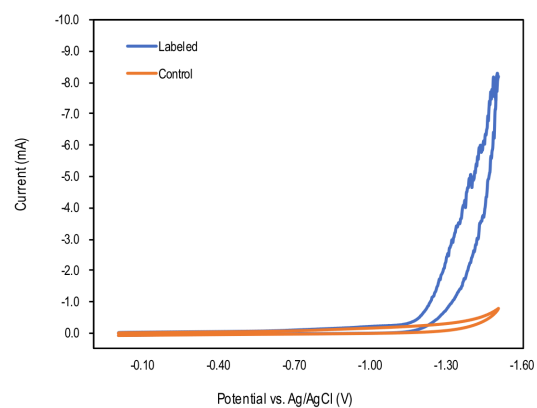


Figure A.12. CVs of bacteria covalently labeled with cobalt porphyrin compared to unlabeled bacteria in minimal media.

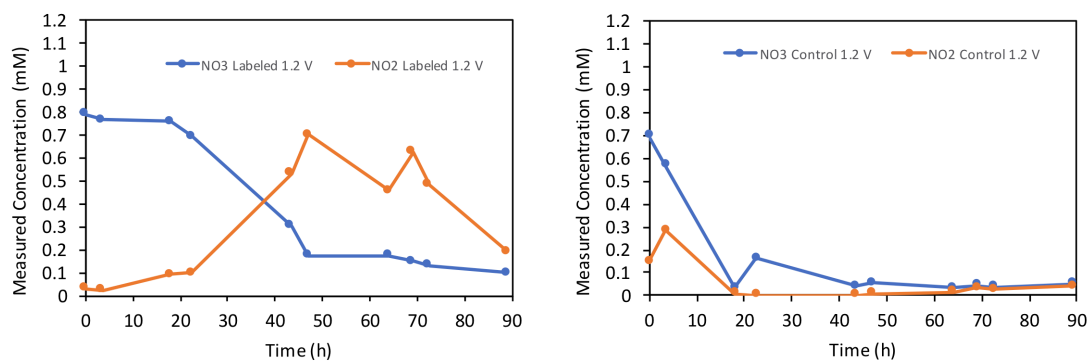


Figure A.13. Nitrate and nitrite concentrations during electrolyses at -1.2 V vs. Ag/AgCl using bacteria labeled with cobalt porphyrin (left) or unlabeled bacteria (right).

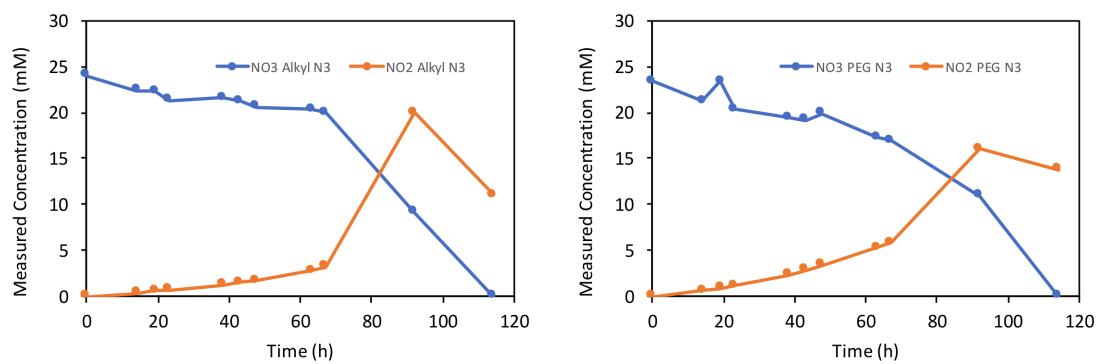


Figure A.14. Nitrate and nitrite concentrations in anaerobic tubes containing acetate with bacteria labeled with cobalt porphyrins bearing either alkyl (left) or PEG (right) linkers.

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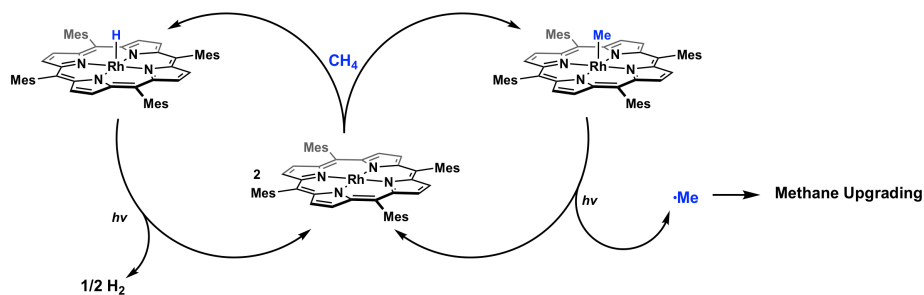
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Appendix B

Photochemical Methane Functionalization Using Rhodium Porphyrins and Progress Towards Homogeneous Methane Catalysis

Abstract

Methane is the simplest C₁ hydrocarbon, but it is currently not exploited for many synthetic applications. Here, we present a strategy that takes advantage of the ability for rhodium porphyrins to cleave a C-H bond in methane to make rhodium-methyl complexes. Photolysis of these species liberates methyl radicals, which we demonstrate can be captured by a range of organic and inorganic substrates to make methylated compounds. This type of methane functionalization is unprecedented in the literature, but our reactions are limited by zero or minimal turnover of the rhodium porphyrin catalyst. Nonetheless, stoichiometric conversion of methane is still remarkable, and further optimization of this platform could improve the catalytic nature.



Introduction

Methane is the primary component of natural gas, which requires specialized equipment to capture, otherwise it is burnt off as waste to make CO₂ as a less detrimental greenhouse gas. If the natural gas can be captured and transported, then the primary applications are as a general energy source upon burning or reforming it into CO and H₂ mixtures.¹ There are no synthetic applications for methane despite it being the simplest C₁ hydrocarbon and the prevalence of methyl groups in organic chemistry. The “magic methyl” effect wherein the presence of a single methyl substituent can greatly influence the binding of small molecules to proteins incentivizes strategies for readily incorporating methyl groups at specific sites.² Many efforts have been reported in literature in attempts to make methane functionalization strategies, most of them focusing on the oxidation of methane into methanol, which is of interest since it can potentially allow for a significantly simpler route to methanol synthesis from methane which currently requires steam reformation into syngas and then methanol synthesis.³ Finding additional synthetic routes could expand the applications for methane, which could help to counter the emissions of methane and CO₂ greenhouse gases.

Rhodium porphyrins are a unique group of metal complexes that have demonstrated activation of methane as well as various other small molecules. Pioneering work by the Wayland laboratory shows that rhodium porphyrins react with methane in a termolecular transition state involving two rhodium(II) porphyrins.⁴ Each rhodium(II) center behaves as a metalloradical to cleave a C-H bond in methane to generate a rhodium-methyl porphyrin and a rhodium-hydride porphyrin. While thermodynamically favorable, the termolecular nature of the reaction hinders the kinetics. This can be overcome by synthesizing cofacial rhodium porphyrins.⁵ While an extensive amount of work has been done exploring similar types of metalloradical reactivity of rhodium porphyrins,⁶⁻¹¹ there has not been much more work investigating methane reactivity. These rhodium porphyrins offer an approach to activate and cleave methane under relatively mild conditions, therefore, it is a good starting point for investigating the functionalization of methane using molecular homogeneous conditions.

In this section, we describe our efforts to exploit the methane activation properties of rhodium porphyrins to transfer methyl groups onto appropriate substrates. Since the activation of methane by rhodium porphyrins is established, we focus on using light to cleave the Rh-CH₃ bond to generate methyl radicals. Screening of various substrates reveals that these methyl radicals can be captured to make methylated products. The catalytic nature of these reactions is still quite slow with small or zero turnover numbers, but this work is a solid starting point for a diverse range of methane functionalization reactions.

Results and Discussion

Benzene-to-Toluene Conversion Using Methane. We began this investigation after noticing that the synthesis of bare rhodium(II) porphyrins involves the photolysis of $\text{Rh}^{\text{III}}\text{-CH}_3$ porphyrins in benzene and that toluene is one of the products (Scheme B.1). This indicates that methyl radicals are liberated and can add to the solvent benzene rings. (Scheme B.2) It is assumed that H_2 is another product of this reaction, but it is not observed in these stoichiometric reactions that are often performed in deuterated benzene on NMR scale. We decided to perform this photolysis using TMP-Rh-CH_3 under a methane atmosphere to determine if catalytic toluene formation can occur. In our initial experiments performed at elevated temperature, proton NMR revealed peaks for toluene, identified by the methyl protons, as well as a peak for H_2 that both appeared to increase over extended photolysis. This provided the first indication that catalytic methane functionalization may be possible, although this first reaction was crude and toluene is not typically seen as value added compared to benzene. Looking more closely at this photolysis reaction by proton NMR reveals that the Rh-CH_3 bond is cleaved within 1 h using only blue light, but the product appears to be a Rh-H species, which is not cleaved unless extended photolysis using UV light >350 nm is used.

Next, we screened conditions for benzene methylation at slightly larger scale using pressure tubes sealed with a custom-made Swagelok manifold allowing for pressurization of the glass tubes capable of being irradiated (Figure B.1). We primarily used TMP-Rh-CH_3 in benzene and screened concentration, irradiation, temperature, pressure, and time. With our most common conditions employing 10 mM TMP-Rh-Me and heating at 120°C under 10 atm of CH_4 , we could detect the formation of 12-14 mM toluene (Table B.1). Although small, these results do indicate turnover and catalytic methane activation. One potential problem is that the methane activation step is quite slow, so there is not a significant amount of methyl radical generation over the 2 day reactions. To circumvent this, we also synthesized bimetallic cofacial rhodium porphyrins that are known to activate CH_4 significantly faster through the same mechanism.¹² Using 5 mM of this dimer under the same reaction conditions, we detected the formation of 36 mM toluene. These results represent a relatively significant amount of turnover, indicating that rhodium porphyrins can be successfully used for photocatalytic methane functionalization. Another problem could be that while methyl radicals are being generated, rhodium hydride complexes are also being generated. We know that these suffer from slower photolysis, which could further hinder rhodium turnover, but it is also possible that the methyl radicals can simply abstract these H atoms to reform CH_4 since this is the weakest bond in the system. In many of our experiments, we also detected the formation of biphenyl, which suggests that there is activation of sp^2 C-H bonds. This is known from the literature to occur with non-coordinated rhodium(III) porphyrins and not with rhodium(II),¹³ therefore, rhodium oxidation could be a possible catalyst inactivation pathway since it would not be able to activate CH_4 anymore.

Interestingly, when using toluene as the solvent for methane activation and photolysis with rhodium porphyrins, xylenes could be detected as products. Starting with 10 mM TMP-Rh-CH_3 in toluene, irradiation at 120°C under 10 atm CH_4 gave two GCMS peaks that we assign to *ortho*- and *para*-xylene. The concentrations of products were 7.3 and 7.7 mM, indicating that catalysis with rhodium did occur, although with low turnover. This reaction is of interest because it begins

to show other potential substrates for methane functionalization using rhodium porphyrins, and xylenes are actually value-added products because of their extensive use in polymer synthesis.

Additionally, we looked at several alternative aromatic substrates including lutidine, quinaldine, and *N*-methylimidazole. Such heterocycles are typical substrates for Minisci reactions involving the addition of a radical and subsequent oxidation because of the greater electrophilicity of the aromatic systems. We are able to detect minor amounts of methylated product by GCMS when using lutidine or quinaldine as the substrate when using acidic conditions similar to Minisci reactions. Excess trifluoroacetic acid was added to the reactions performed in dichloroethane, and with 1 equiv. of TMP-Rh-CH₃, approximately 5% yield of methylated quinaldine was detected. However, using conditions similar to those above for benzene methylation did not give any detectable product, likely because of the competing reaction with benzene solvent.

Nickel Cross-Coupling of Aryl Halides with Methane. In recent years, metallaphotoredox chemistry has gained significant attention due to the ability to access unique reactivity using light energy.¹⁴ This, in combination with extensive work on nickel catalyzed cross-couplings,^{15,16} has yielded a broad understanding of radical reactions controlled by homogeneous metals complexes. Because we believe that photolysis of methylated rhodium porphyrins can readily release methyl radicals, it seemed logical to combine this approach with a nickel cross-coupling scheme. While such cross-coupling approaches have been successful in synthesizing a diverse array of organic products, simply methylation of aryl or alkyl halides using the strategy is rare. There are limited examples that use peroxide precursors that can decompose into methyl radicals, which is promising for our intentions.^{17,18} In contrast, trifluoromethylation or difluoromethylation strategies are abundant in the literature.¹⁹⁻²¹

To test this hypothesized cross-coupling with methane, we pre-synthesized the product of oxidative addition of the aryl halide to nickel(0) and screened conditions using this as the methyl radical trap leading to the toluene derivative product. With this approach, we remove any problems that may be associated with nickel catalysis in our systems. This may be an issue because nickel catalyzed cross-couplings are rarely performed in non-polar solvents such as benzene, and polar solvents such as DMF are generally preferred due to improved reduction of nickel by the excess heterogeneous metal. However, along these lines we did eventually demonstrate that such reduction can occur in benzene by starting with the nickel(II) salt NiBr₂ rather than Ni(COD)₂ and observing product formation indicating that the starting nickel(II) is being reduced under our experiment conditions. For most of our studies we used the di-*tert*-butylbipyridine, dtbbpy, ligand with nickel, and the main aryl halide substrate investigated was *p*-trifluoromethyl-bromobenzene. The pre-synthesized nickel complex was made by first combining Ni(COD)₂ with 1 equiv. of the dtbbpy ligand to give a dark purple solution. The aryl halide *p*-CF₃-bromobenzene was then added to give an orange solution that could be purified by filtration (Scheme B.3). Using this complex with 1 equiv. of TMP-Rh-CH₃, photolysis yielded the desired product in high yield in several solvents. Up to 64% yield was detected by GCMS when using benzene as the solvent and irradiating with a blue LED. This result is quite promising for the development of a methane cross-coupling platform. This also opens up the ability to do stepwise methane functionalization, wherein methane is first reacted with a rhodium(II) porphyrin to give the activated Rh-CH₃ and Rh-H products, which can be subsequently irradiated in the presence of the nickel and aryl halide species to give the desired product. Since this would require significant amounts of the porphyrin, which

has fairly low solubility, it is more desirable to make this functionalization strategy catalytic in rhodium.

In our most ambitious catalytic strategy, we attempted to merge this strategy for photogeneration of methyl radicals from rhodium porphyrins and methane with existing metallaphotoredox approaches. This involves using an Ir(ppy)₃ photosensitizer, an electron donor such as an amine or halide, and the catalytic nickel complex. Results from these experiments are given in Table B.2. Interestingly, the desired cross coupled product, *p*-trifluoromethyl-toluene was detected when using TMP-Rh-CH₃, but unfortunately, this photoredox approach failed to show any signs of catalysis with rhodium. Only sub-stoichiometric quantities of product were detected. Moving forward, we decided to remove the photoredox component of this proposed catalytic cycle in order to simplify the mechanism and lower the number of parameters requiring optimization.

We next screened conditions using an excess amount of metal reductant that can provide reducing equivalents for nickel turnover as shown in Scheme B.4. Table B.2 lists the results of extensive screening typically using TMP-Rh-CH₃ with zinc as the heterogeneous reductant. With 100 mM aryl bromide substrate, 5 mM TMP-Rh-CH₃ was used while screening different solvents and irradiation conditions. A large portion of this experiments yielded slightly more than 5 mM of the desired toluene derivative product. This indicates that there is a minor amount of methane activation and functionalization catalysis occurring with the rhodium porphyrin since the stoichiometric reactions with TMP-Rh-CH₃ and nickel discussed above only gave yields up to 64%. While this suggests catalysis, the turnover is still minimal. Increasing the concentration of TMP-Rh-CH₃ to 10 mM could give more than 11 mM product, but this turnover is still too low. Switching to the rhodium dimer species gave similar results despite the faster kinetics for CH₄ activation. It is possible that the dimer species suffers more than the monomeric rhodium complex from the reductive elimination of a Rh-CH₃ unit with a Rh-H unit to reform CH₄ since they are intramolecularly linked to each other, thereby counteracting the benefits of faster C-H activation. During the course of this screening, the bi-aryl side product was also detected indicating coupling of the aryl-bromide substrate. It has been reported in the literature that rhodium(II) porphyrins can react with aryl halides in an S_NAr fashion at high temperatures, so it is possible that this also occurs in our system and that subsequent photolysis could yield the dimer.²² To circumvent this, we changed the substrate from *p*-CF₃-bromobenzene either *o*-CF₃-bromobenzene, *p*-CF₃-chlorobenzene, or 1-bromonaphthalene, which should all be less reactive with rhodium(II). These different substrates still yielded the expected products, which shows that we can begin to explore the substrate scope, however, there is no significant change in the turnover numbers. An additional problem could be with the nickel catalysis and the heterogeneous reductant not being effective in non-polar solvents.²³ Changing the starting nickel from Ni(COD)₂ to NiBr₂-glyme gave similar results, however, indicating that zinc is capable of reducing nickel(II) under these conditions. Additionally, we attempted this rhodium catalysis using either 1 equiv. of Ni(COD)₂ and ligand relative to the aryl halide substrate, or with an excess of the pre-synthesized product of oxidative addition to nickel. No significant improvement was observed using the standard conditions of 120 °C with 10 atm CH₄ and increasing the concentration of TMP-Rh-CH₃ appeared to hinder the product formation. We next hypothesized that the irradiation conditions may hinder the CH₄ activation mechanism, so we performed the experiment with the irradiation being turned on and off every six hours. Interestingly, there was a slight increase in product formation up to 9% yield when starting with 5 mol% TMP-Rh-CH₃. Finally, we hypothesized that the high temperature may

be encouraging undesired reactivity, so we performed these photolysis experiments at room temperature for more extended reaction times since the CH₄ activation is significantly slower at lower temperature. Interestingly, using 5 mol% TMP-Rh-CH₃ and 1 equiv. of nickel and ligand to avoid the use of a reductant, 8.8% yield product was detected with 7.4 mM toluene also being formed. In most of these reactions performed at high temperature toluene was not detected indicating that the nickel was a better acceptor than the solvent or that there is another pathway for methyl radical consumption. However, this room temperature reaction did yield methane to give an overall concentration of CH₄ functionalization products of 16.2 mM after starting with 5 mM TMP-Rh-CH₃. More optimization of these reaction conditions is necessary, but this demonstrates that we can combine rhodium with nickel catalysis to develop methane cross coupling.

Methane Borylation. Another potential strategy for methane functionalization involves borylation. Aryl and alkyl boronic acids or esters are extremely useful building blocks used in coupling reactions. Two examples have demonstrated that traditional rhodium, iridium, and ruthenium catalysts for C-H borylation are capable of borylating methane at elevated temperature and pressure with modest turnover numbers.^{24,25} This reaction had not been explored in depth previously, but it presents a logical strategy for homogeneous functionalization of methane since the catalysts are well studied for other alkane substrates. Various photocatalytic radical borylation strategies have also been reported in recent years, providing evidence that organic radicals can add to activated diboron substrates to yield the borylated product.^{26,27} Furthermore, alkyl boronic esters can be readily oxidized to give alcohols, which in the case of borylated methane could provide a route to methanol synthesis from methane. While the ideal route for methane oxidation into methanol would use O₂, this strategy of borylation then oxidation with hydrogen peroxide offers a potential route to methanol that easily avoids the challenge of over-oxidation.

Our screening efforts for methane borylation using rhodium porphyrin photocatalysis are summarized in Table B.3. Beginning with B₂Pin₂ as the substrate with TMP-Rh-CH₃, no Me-BPin could be detected after photolysis under methane in a range of solvents. We then switched to B₂Cat₂ as the substrate since it is more commonly used in radical-based borylations because of its greater electrophilicity. Now, performing the photolysis of TMP-Rh-CH₃ under N₂ with excess B₂Cat₂. The desired product Me-BCat is fairly unstable and difficult to detect by GCMS, so the reaction workup involved treatment of the reaction mixture with excess trimethylamine and pinacol to convert any catechol esters to pinacol esters. Using 5 mM TMP-Rh-CH₃ with 50 mM B₂Cat₂ failed to give any product, but after increasing the B₂Cat₂ concentration to 200 mM we were able to detect the formation of Me-BPin in approximately 50% yield relative to the TMP-Rh-CH₃, indicating that B₂Cat₂ is a suitable acceptor the methyl radical generated upon photolysis. We next explored conditions amenable to catalysis by pressurizing with CH₄ and heating the reactions. Using 5 mM TMP-Rh-CH₃ with a large excess of 200 mM B₂Cat₂, we were able to detect up to 4 mM Me-BPin product formation, which is larger than the reactions performed under N₂, but still does not clearly show rhodium turnover. During this screening, we also began to observe the formation of H-BPin and Ph-Bpin, which may be forming through solvent borylation. Starting with TMP-Rh(II), we were able to detect similar amounts of product, indicating that both methane activation and functionalization can be accomplished in a single flask, although with low yield.

Next, we explored the addition of silanes for improving the catalytic activity hypothesizing that an excess H atom donor could aid in turning over the rhodium catalyst (Scheme B.5). We used dimethyl ethylsilane, which can also act as a reductant allowing us to use TMP-Rh-I as the starting pre-catalyst. TMP-Rh-I is reduced *in situ* to TMP-Rh-H which can then be photolysed or eliminate H₂ to give TMP-Rh(II) that can activate methane. Me-BPin product was detected under these conditions, with 6.2 mM product formed after starting with 5 mM TMP-Rh-I and heating with irradiation for two days. This result represents a significant amount of methane activation and functionalization since we do not start off with the methylated rhodium porphyrin. Unfortunately, further screening could not improve upon this result, however, this shows great promise for the photocatalytic activity of rhodium porphyrins for direct methane functionalization.

Hydromethylation of Alkenes. Alkene functionalization strategies offer enormous levels of structural diversification, however, simple hydromethylation strategies are not readily available despite the potential benefits of being able to install methyl substituents. Various hydrofunctionalization strategies have been developed taking advantage of Mn, Fe, and Co hydrides for functionalization strategies going through radical intermediates,²⁸ and we have used this literature as a starting point for extending our rhodium porphyrin strategy of generating methyl radicals to attempt to functionalize alkenes with methane. One example of note for hydromethylation uses a Sc catalyst for methane activation and conversion, but turnover is limited and reaction times are extremely long.²⁹ Another example of hydromethylation is more efficient across a range of substrates but does not use methane as the source of methyl groups.³⁰ In Scheme B.6, we propose a mechanism for hydromethylation of alkenes using rhodium porphyrins to accomplish the complete addition of methane across a double bond.

We used dimethyl fumarate as an electron-poor alkene for the substrate of potential hydromethylation using methane. When attempting the reaction starting with TMP-Rh-Me, no product was detected, indicating that the substrate does not readily accept the methyl radical. However, when starting with the bare TMP-Rh(II), we did detect several functionalization products as shown in Scheme B.7. Under these conditions, methane activation must occur *in situ* prior to photolysis and functionalization. This activation generates both TMP-Rh-CH₃ and TMP-Rh-H. It is known from the literature that the hydrogen atom in TMP-Rh-H can be readily abstracted, and it is possible that this H atom source is necessary for the hydromethylation reaction to occur, as proposed in Scheme B.6. The detected products are low yielding relative to the dimethyl fumarate substrate, indicating limited turnover, but this reaction does represent another example of a single-pot methane activation and functionalization reaction with decent yield relative to the rhodium porphyrin. The detected products of the reaction are the desired hydromethylation product as well as the oxidized methylated product and the product of alkene reduction. This suggests that the desired product can be formed by H atom abstraction and the oxidized methylated product can be formed by H atom elimination. Since TMP-Rh-H can behave as an H atom donor and can also be photolyzed under these conditions, it likely accounts for the direct reduction of the alkene. Although no catalysis is observed, this reactivity is noteworthy.

Carboxylation of Methane. The direct carboxylation of methane using CO₂ to yield acetic acid is of great interest because it combines two abundant greenhouse gases to synthesize a highly value commodity chemical. The catalytic carboxylation of aryl and alkyl halides using nickel or copper has been heavily developed in recent years and relies on oxidative addition of the substrate

and insertion of CO₂ to generate the carboxylated product.^{31,32} From our investigation into nickel cross-coupling reactions using methane, we believe that nickel can readily accept the photo-generated methyl radicals from rhodium porphyrins. Therefore, it may be possible to couple this with CO₂ insertion to develop a methane carboxylation platform. For nickel catalyzed carboxylations, it has been observed that the CO₂ insertion primarily occurs at the nickel(I) alkyl state.³³ In our work investigating nickel cross-coupling with methane and rhodium porphyrins, we showed that the photogenerated methyl radical can add to the nickel(II) species to give the product. Literature for these types of nickel radical coupling reactions have suggested that the radical can also add to the nickel(0) species prior to oxidative addition of the substrate.³⁴ Thus, it may be possible for our system to generate nickel(I) methyl species, either through addition to nickel(0) or reduction of a nickel(II) or nickel(III) methyl complex, that can undergo CO₂ insertion and liberate acetate (Scheme B.8).

To begin screening, we used TMP-Rh-CH₃ and nickel bearing phenanthroline ligands, which have shown the most success for nickel catalyzed carboxylations. We focused on stoichiometric transfer of the methyl group since we know that catalytic methane activation and photolysis is slow. Thus, most reactions were performed at room temperature under 1 atm of CO₂ with irradiation from blue LEDs. We screened various solvents, additives, and altered the nickel ligand, but most results were inconclusive. We obtained a couple of promising hits using DME as the solvent with LiCl additive and varying the sterics of the nickel ligand with neocuproine, bathocuproine, and diphenylphenanthroline. After the reaction, the solvent was removed, and the residue was acidified and analyzed by NMR spectroscopy. Proton NMR suggested approximately 5-7% yield of acetate formation, however, there is some ambiguity to these results because the peak for acetate is both proton and carbon NMR appears in a range where common laboratory impurities appear, and we did not observe a carbonyl carbon peak in carbon NMR, although the concentrations may have been too low. We then synthesized the isotopically labeled TMP-Rh-¹³CH₃ by using labeled methyl iodide and repeated the carboxylation reactions. Unfortunately, we were unable to see clear evidence of an isotopically labeled acetate product. While we did not observe clear product formation for this proposed methane carboxylation, this strategy is worth pursuing because of the huge increase in value upon combining methane and CO₂ to make acetic acid, and significant amount of literature and our above results on methane functionalization suggest that this may be feasible.

Conclusion and Future Directions

In this Appendix, we have outlined our strategy for the photochemical functionalization of methane using rhodium porphyrins. We have built upon the known methane reactivity of rhodium porphyrins to extend their applications towards the synthesis of methylated substrates. The rhodium-methyl bond can be readily cleaved upon irradiation to give methyl radicals. Recent years have seen an enormous amount of work on synthetic organic strategies using photoredox chemistry that is built upon radical intermediates. Using this work as a starting point, we identified a group of substrates that can accept the photo-generated methyl radical to give the methylated product. Methylation of arenes can be accomplished directly in a Minisci type fashion, or coupled with a Ni cross-coupling strategy to convert aryl halides into the toluene derivatives. Methane borylation also showed promise by using B_2Cat_2 as the radical acceptor giving modest yields of the Me-BPin product. Finally, hydromethylation of alkenes gave a hit using this strategy of methyl radical generation.

Moving forward, the primary challenge is understanding what is preventing further turnover of the rhodium porphyrin catalysts. Direct benzene-to-toluene conversion using bimetallic rhodium porphyrins gave turnover numbers that clearly indicate that catalysis can be achieved in these systems. However, other functionalization approaches were severely limited in turnover. We have recently been constructing a steel reactor equipped with a window in it that can allow for application of higher methane pressure while still allowing for irradiation with light. It is also possible to further develop these transformations as stoichiometric with respect to the rhodium porphyrin. Nonetheless, the results presented here demonstrate multiple examples of methane activation and functionalization using heat and light energy to incorporate methane into various organic products.

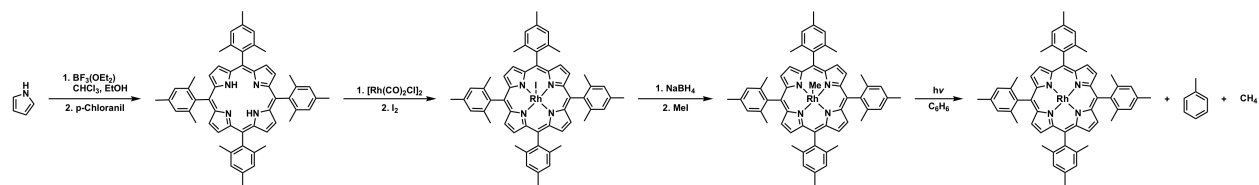
Materials and Methods

General Methods. All reactions for screening were prepared in a glovebox using dried and degassed solvents. High purity gases were purchased from Praxair. Most of the rhodium porphyrin complexes were synthesized following modified procedures to Wayland's reports.^{4,35} Product detection was performed by GCMS and yields were determined after making calibration curves of the various products and substrates. Mesitylene was also added to the sample prior to injection as an internal standard.

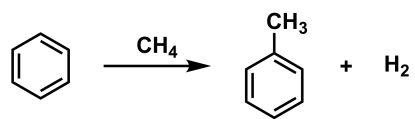
Reaction Setup in NMR Tubes. Heavy walled NMR tubes rated to 200 psi or medium walled NMR tubes rated to 100 psi were purchased from Wilmad. These tubes were oven dried and then transferred to a nitrogen-filled glovebox. Reagents and solvents were prepared in the glovebox, and for reactions that appeared slightly heterogeneous, a micro stir bar was added to provide agitation. The tubes were closed with the piston valve, removed from the glove box and connected to a Schlenk line, where the reactions mixtures were further degassed by three freeze-pump-thaw cycles. The tube was then connected to a CH₄ tank and slowly pressurized and then sealed. The tube was then clamped to a stir plate with an oil bath and irradiated and heated. Upon completion of the experiment, the heating was stopped, the tube was carefully vented, and then the reaction mixture was transferred to a vial, diluted with a solution of mesitylene in acetone, and then filtered before analysis by GCMS. It is important to note that the pressure in the NMR tubes is not known to be maintained throughout the experiments, and the venting step occasionally revealed that the pressure had been lost during the course of the reaction. To help limit this, PEEK plugs were screwed on top of the valve cap adapters after being closed following pressurization. These additional plugs can provide an extra barrier in the event of inadequate sealing of the o-ring in the piston valve.

Reaction Setup in Pressure Tubes. We used 15 mL pressure tubes purchased from Ace Glass that are rated for 150 psi at 120 °C. A Kalrez o-ring was used with a PTFE cap that has a NPT threaded hole drilled through, also purchased from Ace Glass. Steel fittings and valves purchased from Swagelok, and steel tubing and pressure gauges were purchased from McMaster-Carr. These parts were used to assemble a manifold that allows for easy exchange of the atmosphere in the pressure tubes and subsequent pressurization and irradiation for prolonged reaction times. For the reaction setup, the glass pressure tubes equipped with a stir bar were dried in an oven overnight and then transferred into a nitrogen atmosphere glovebox along with the PTFE plug/valve manifolds. The reagents and solvents were measured in the glovebox and added to the pressure tubes, then sealed with the PTFE plugs and all of the valves were closed to maintain the inert nitrogen atmosphere in the reaction tubes. The closed tubes were then removed from the glovebox, clamped to a stir plate with a clean oil bath behind a blast shield, and connected to the CH₄ gas tank using the Swagelok Quick-connects. A low pressure of CH₄ was applied and the top valve was opened to air to allow for purging of the connection tubing with CH₄. Subsequently, this three-way valve was turned to fill the pressure tube, and the second outlet valve was opened to begin purging the headspace of the pressure tube with CH₄. Once adequately purged, the outlet valve was closed and the CH₄ pressure was slowly increased to the desired level. Finally, the inlet valve to the pressure tube was closed and the tubing connecting the gas tank was removed. Heating and irradiation could then be applied. If no heating was applied, then a fan was used to cool the reaction flasks and limit heating from the light source. Upon completion of the experiment, the heating and

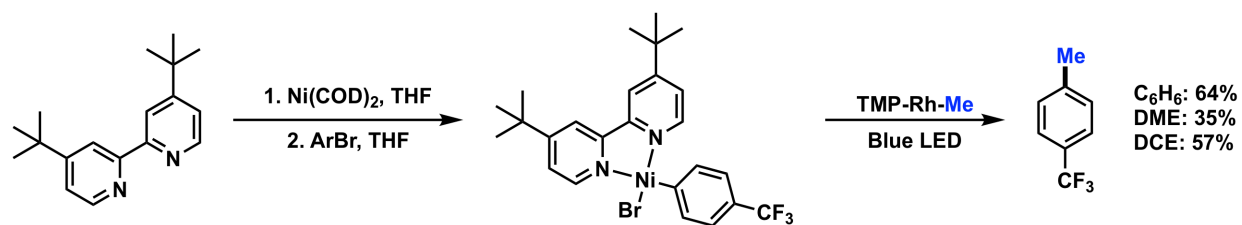
irradiation were turned off, the reaction mixture was allowed to cool to room temperature, and then the pressure was slowly vented by opening an outlet valve. The reaction mixture was then transferred to a vial, diluted with a solution of mesitylene in acetone, and then filtered before analysis by GCMS. It is important to take the necessary safety precautions while pressurizing glass flasks with a flammable gas. All reactions were performed within a closed fume hood with a blast shield closely surrounding the stir plate holding the reactions. Connection and disconnection to the gas source were performed while wearing protective gloves in case of glass breaking. The tubes were not over-pressurized while heating since the pressure increases at higher temperature. UV resistant acrylic sheets were also used to block the intense light from escaping the hood.



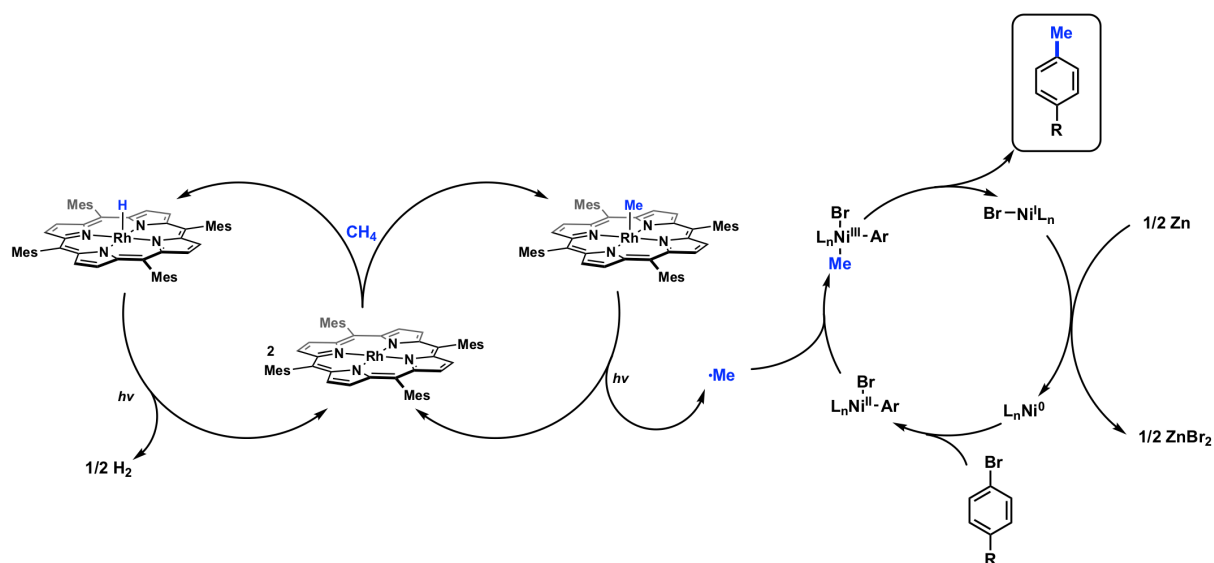
Scheme B.1. Synthesis of the sterically hindered TMP-Rh involving the alkylation of the reduced rhodium to make TMP-Rh-CH₃ and the subsequent photolysis that gives the bare metalloporphyrin as well as toluene, indicating transfer of a methyl group to the solvent.



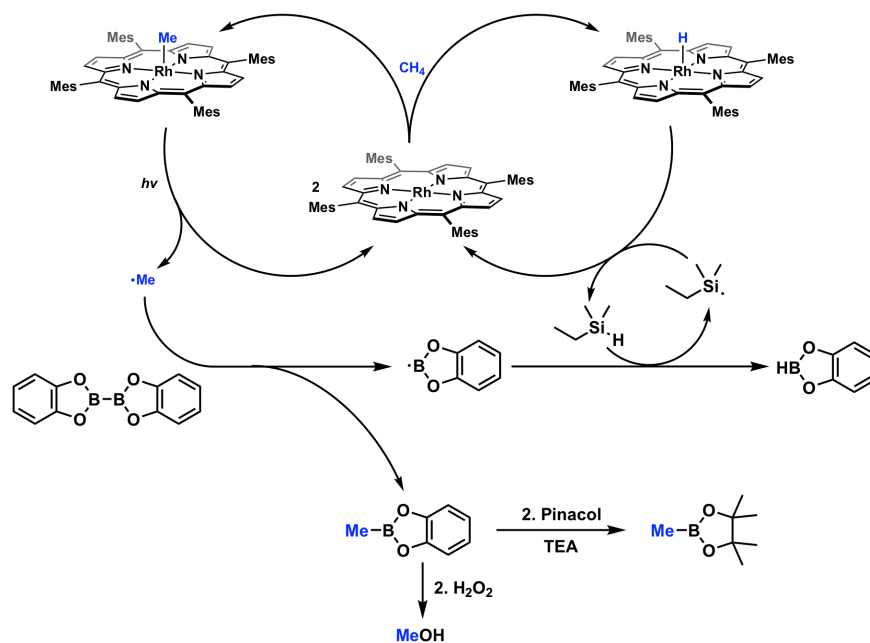
Scheme B.2. Balanced reaction for the functionalization of methane using benzene as the substrate to give toluene and H₂.



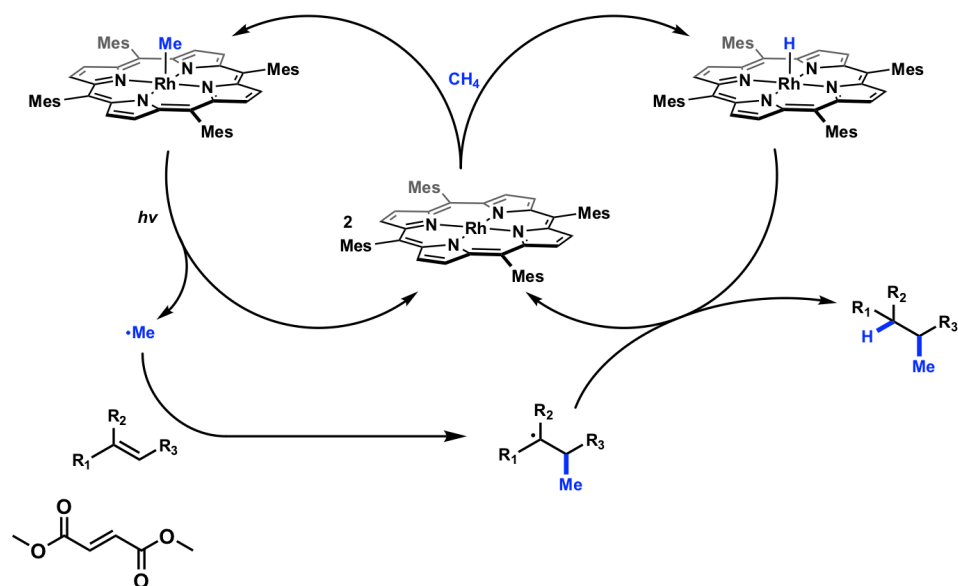
Scheme B.3. Synthesis of the product of oxidative addition of the aryl halide substrate to nickel, and the subsequent reaction with TMP-Rh-CH₃ with photolysis to give the toluene product.



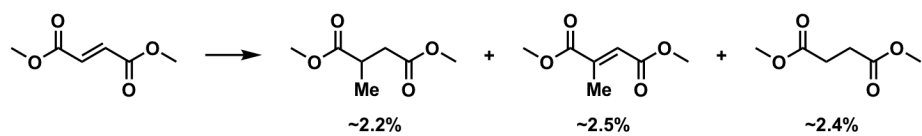
Scheme B.4. Proposed mechanism for methane cross-coupling using rhodium porphyrins for the methane activation, irradiation for generating methyl radicals, and nickel catalysis for trapping the methyl radical and coupling it to an aryl halide.



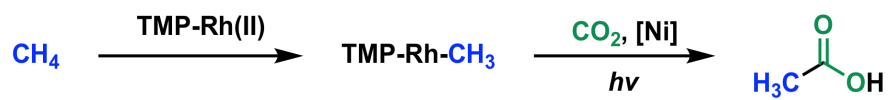
Scheme B.5. Proposed mechanism for methane borylation using rhodium porphyrins and methane with photo-generation of methyl radicals that are trapped by B_2Cat_2 . Workup involves conversion to the more stable Me-BPin product or oxidation to methanol.



Scheme B.6. Proposed mechanism for hydromethylation of alkenes using rhodium porphyrins for methane activation and irradiation for the liberation of methyl radicals.



Scheme B.7. Products of the attempted hydromethylation of dimethyl fumarate using TMP-Rh-I and methane.



Scheme B.8. General scheme for methane activation by a rhodium porphyrin and subsequent carboxylation using nickel photocatalysis to give acetic acid.

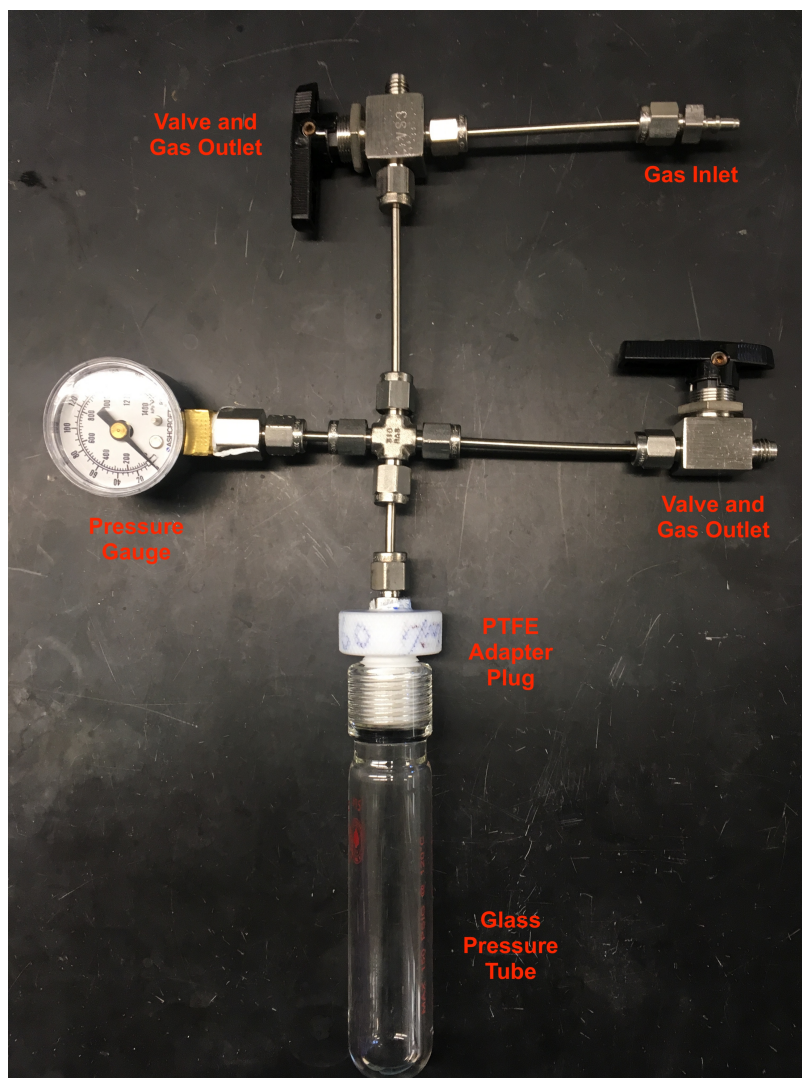


Figure B.1. Photograph of the glass pressure tube and custom tubing/valve attachments that allow for purging of the atmosphere and pressurization as well as heating and irradiation.

Table B.1. Summary of screening conditions and results for benzene/arene methylation.

	Substrate	Conc.	Rh	Rh Conc.	Additive	Solvent	Light	Temp.	Pressure	Time	Results
1	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	440 nm LED 200 W Hg Lamp	100 °C	10 atm CH ₄	2 d	Sub-stoichiometric
2	Benzene	-	TMP-Rh(ID)	10 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	9.5 mM toluene, <1.5 mM biphenyl
3	Benzene	-	Bimetallic Rh-Me	5 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	36.1 mM toluene, <3.9 mM biphenyl
4	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	12.7 mM toluene, <4.8 mM biphenyl
5	Benzene	-	TDthP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	1.7 mM toluene, <3.3 mM biphenyl
6	Toluene	-	TMP-Rh-Me	10 mM	-	0.5 mL toluene	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	7.3 mM and 7.7 mM xylenes
7	Benzene	-	TMP-Rh-Me	10 mM	0.5 mL C ₆ F ₁₄	0.5 mL C ₆ H ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	4.1 mM toluene, <2.6 mM biphenyl
8	Benzene	-	TMP-Rh-Me	40 mM	-	0.5 mL C ₆ H ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	14.1 mM toluene, <11.3 mM biphenyl
9	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	150 W Xe Lamp	120 °C	10 atm 9:1 CH ₄ :O ₂	2 d	<0.5 mM toluene, <1.3 mM biphenyl
10	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	on/off, 300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	13.9 mM toluene, <3.2 mM biphenyl
11	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	3.5 d	10.7 mM toluene, <6.2 mM biphenyl
12	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	300 W Xe Lamp	175 °C	6.8 atm CH ₄	2.5 d	5.7 mM toluene, <24.3 mM biphenyl
13	Benzene	-	TMP-Rh-Me	5 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	4.7 mM toluene, <5.7 mM biphenyl
14	Benzene	-	TMP-Rh-Me	1 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	0.85 mM toluene
15	Quinaldine	200 mM	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	No Product, 6 mM toluene
16	N-Methylimidazole	200 mM	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	No Product, 3 mM toluene
17	Benzene	-	TMP-Rh-Me	10 mM	200 mM MeEtSiH	0.5 mL C ₆ H ₆	300 W Xe Lamp	175 °C	6.8 atm CH ₄	2 d	1 mM toluene, <2.1 mM biphenyl
18	Toluene	-	TMP-Rh-Me	10 mM	-	0.5 mL toluene	300 W Xe Lamp	175 °C	6.8 atm CH ₄	2 d	5.3 mM and 5.2 mM xylenes
19	Benzene	-	Bimetallic Rh-Me	5 mM	-	0.9 mL C ₆ H ₆	200 W Hg Lamp	RT	10 atm CH ₄	3 d	23 mM toluene, <1.8 mM biphenyl
20	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	440 nm LED 200 W Hg Lamp	RT	10 atm CH ₄	5 d	~1.1 mM toluene, <3.5 mM biphenyl
21	Benzene	-	TMP-Rh-Me	10 mM	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	RT	10 atm CH ₄	5 d	13.8 mM toluene, <2.2 mM biphenyl

Table B.2. Summary of screening conditions and results for methane cross coupling.

	Substrate	Conc.	Rh	Ni	Ligand	Ir	Additive	Solvent	Light	Temp.	Pressure	Time	Results
1	p-CF ₃ - bromobenzene	47.7 mM	2 mol%	1 mol% NiBr ₂	1 mol% dtbbpy	1 mol%	1.1 equiv. Quinuclidine	0.35 mL C ₆ D ₆	>345 nm, 150 W	100 °C	1 atm CH ₄	48 h	No product. Quinuclidine binding to Rh observed by NMR
2	p-CF ₃ - bromobenzene	47.7 mM	2 mol%	1 mol% NiBr ₂	1 mol% dtbbpy	1 mol%	1.1 equiv. Quinuclidine	0.35 mL DMSO- d ₆	>345 nm, 150 W	100 °C	1 atm CH ₄	48 h	No product
3	dtbbpy-Ni(p- CF ₃ Ph)(Br)	5.6 mM	1 equiv.	-	-	-	None	0.1 mL C ₆ D ₆	16 W Blue LED	RT	1 atm N ₂	48 h	64% yield
4	dtbbpy-Ni(p- CF ₃ Ph)(Br)	5.6 mM	1 equiv.	-	-	-	None	0.1 mL DCE	16 W Blue LED	RT	1 atm N ₂	48 h	57% yield
5	dtbbpy-Ni(p- CF ₃ Ph)(Br)	5.6 mM	1 equiv.	-	-	-	None	0.1 mL DME	16 W Blue LED	RT	1 atm N ₂	48 h	35% yield
6	p-CF ₃ - bromobenzene	100 mM	5 mol%	1 mol% NiBr ₂	1 mol% dtbbpy	1 mol%	2 equiv Na ₂ CO ₃	0.2 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	48 h	No product
7	p-CF ₃ - bromobenzene	100 mM	5 mol%	1 mol% NiBr ₂	1 mol% dtbbpy	1 mol%	2 equiv Na ₂ CO ₃	0.2 mL DCE	16 W Blue LED	RT	10 atm CH ₄	48 h	No product
8	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	10 mol% dtbbpy	1 mol%	2 equiv Na ₂ CO ₃	0.1 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	36 h	3% yield
9	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	10 mol% dtbbpy	1 mol%	2 equiv Na ₂ CO ₃	0.1 mL DCE	16 W Blue LED	RT	10 atm CH ₄	36 h	1% yield
10	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	1 mol%	2 equiv K ₃ PO ₄	0.1 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	2 d	2.3% yield
11	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	1 mol%	2 equiv K ₃ PO ₄	0.1 mL C ₆ D ₆	>345 nm, 40 W	RT	10 atm CH ₄	2 d	3.4% yield
12	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	1 mol%	2 equiv K ₃ PO ₄	1 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	2 d	4.2% yield
13	dtbbpy-Ni(p- CF ₃ Ph)(Br)	5.6 mM	1 equiv.	-	-	-	10 equiv. DF	0.1 mL C ₆ D ₆	16 W Blue LED	RT	1 atm N ₂	48 h	48% toluene prod. ~30% tri-coupled, ~20% methyl alkene
14	dtbbpy-Ni(p- CF ₃ Ph)(Br)	5.6 mM	1 equiv.	-	-	-	CO	0.1 mL C ₆ D ₆	16 W Blue LED	RT	1 atm CO	48 h	No reaction. CO probably coordinates Ni
15	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	-	2.2 equiv. Mn	0.1 mL C ₆ D ₆	>345 nm, 40 W	RT	10 atm CH ₄	1 d	4.1% yield
16	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	-	2.2 equiv. Mn	0.1 mL MA	>345 nm, 40 W	RT	10 atm CH ₄	1 d	2.2% yield
17	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	-	2.2 equiv. Mn	0.1 mL C ₆ D ₆	>345 nm, 50 W	RT	10 atm CH ₄	6 d	2.0% yield
18	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	-	2.2 equiv. Zn	0.1 mL C ₆ D ₆	>345 nm, 50 W	RT	10 atm CH ₄	6 d	4.6% yield
19	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	1 mol%	2 equiv. DIEA	0.1 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	2 d	1.3% yield. SM consumed?
20	p-CF ₃ - bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	1 mol%	TPPS-SH + Na ₂ CO ₃	1 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	2 d	1.8% yield
21	dtbbpy-Ni(p- CF ₃ Ph)(Br)	100 mM	5 mol%	10 mol% Ni(COD) ₂	12 mol% dtbbpy	-	2.2 equiv. Zn	0.1 mL C ₆ D ₆	>345 nm, 100 W	RT	10 atm CH ₄	3 d	4.6% yield
22	dtbbpy-Ni(p- CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	-	None	0.1 mL C ₆ D ₆	>345 nm, 150 W	RT	10 atm CH ₄	36 h	3% yield (61% from Rh)

23	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	0.1 mL DFB	>345 nm, 150 W	RT	10 atm CH ₄	36 h	1.6% yield (31% from Rh)
24	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	0.1 mL DCE	>345 nm, 150 W	RT	10 atm CH ₄	36 h	4.4% yield (87% from Rh)
25	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	0.1 mL DCE	>345 nm, 150 W	RT	10 atm CH ₄	36 h	3% yield (59% from Rh)
26	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	0.1 mL THF	>345 nm, 150 W	RT	10 atm CH ₄	36 h	0.7% yield (14% from Rh)
27	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	0.1 mL DMA	>345 nm, 150 W	RT	10 atm CH ₄	36 h	0.7% yield (14% from Rh)
28	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	1 mL C ₆ D ₆	>345 nm, 150 W	RT	10 atm CH ₄	24 h	4.5% yield (90% from Rh)
29	dtbbpy-Ni(p-CF ₃ Ph)(Br)	100 mM	5 mol%	-	-	None	1 mL DCE	>345 nm, 150 W	RT	10 atm CH ₄	24 h	Exposed to air, barely any product, lots of aryl bromide (13.5 mM Ar-Br)
30	p-CF ₃ -bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DCE	>345 nm, 150 W	RT	10 atm CH ₄	24 h	2.8% yield
31	p-CF ₃ -bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	>345 nm, 150 W	RT	10 atm CH ₄	24 h	5.5% yield. O-ring dissolved
32	p-CF ₃ -bromobenzene	100 mM	10 mol%	10 mol% Ni(COD) ₂	dtbbpy	2 equiv K ₃ PO ₄	1 mL C ₆ H ₆	>345 nm, 150 W	RT	10 atm CH ₄	5 d	7.5% yield
33	p-CF ₃ -bromobenzene	100 mM	10 mol%	10 mol% Ni(COD) ₂	dtbbpy	2 equiv K ₃ PO ₄	1 mL DME	>345 nm, 150 W	RT	10 atm CH ₄	5 d	8.7% yield. O-ring dissolved. Pressure lost and solids stick to glass above solvent after a while.
34	p-CF ₃ -bromobenzene	100 mM	10 mol%	10 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	>345 nm, 150 W	RT	10 atm CH ₄	42 h	11.5% yield
35	p-CF ₃ -bromobenzene	100 mM	10 mol%	10 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Mn	1 mL DME	>345 nm, 150 W	RT	10 atm CH ₄	42 h	11.6% yield. No SM left. Lots of Ar-Ar product
36	p-CF ₃ -bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	>345 nm, 150 W	80 °C	10 atm CH ₄	2 d	5.4% yield
37	p-CF ₃ -bromobenzene	100 mM	5 mol%	10 mol% Ni(COD) ₂	dtbbpy	2 equiv K ₃ PO ₄	1 mL DME	>345 nm, 150 W	80 °C	10 atm CH ₄	2 d	0.6% yield
38	p-CF ₃ -bromobenzene	100 mM	5 mol%	5 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL C ₆ D ₆	>345 nm, 150 W	80 °C	10 atm CH ₄	2 d	4.6% yield
39	p-CF ₃ -bromobenzene	100 mM	5 mol%	5 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	>345 nm, 150 W	80 °C	10 atm CH ₄	2 d	4.6% yield
40	p-CF ₃ -bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL C ₆ H ₆	>345 nm, 150 W	80 °C	10 atm CH ₄	48 h	5.2% yield
41	p-CF ₃ -bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	>345 nm, 150 W	80 °C	10 atm CH ₄	48 h	4.9% yield
42	p-CF ₃ -bromobenzene	100 mM	5 mol%	1 equiv. Ni(COD) ₂	1.2 equiv. dtbbpy	-	1 mL C ₆ D ₆	>345 nm, 300 W	120 °C	10 atm CH ₄	48 h	5.3% yield
43	p-CF ₃ -bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL DME	on/off, >3 45 nm, 300 W	120 °C	10 atm CH ₄	4 d	7.4% yield
44	p-CF ₃ -bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL C ₆ D ₆	on/off, >3 45 nm, 300 W	120 °C	10 atm CH ₄	4 d	9.0% yield
45	p-CF ₃ -bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	dtbbpy	2.2 equiv. Zn	1 mL C ₆ D ₆	>305 nm, 300 W	120 °C	10 atm CH ₄	4 d	6.5% yield

46	p-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL DME	>305 nm, 300 W	120 °C	10 atm CH ₄	4 d	7.7% yield
47	p-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	6.4% yield
48	p-CF ₃ - chlorobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	6.4% yield
49	p-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	5.5% yield
50	p-CF ₃ - chlorobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	200 W Hg Lamp	120 °C	10 atm CH ₄	2 d	5.4% yield
51	o-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	~6.1% yield
52	1-bromonaphthalene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	<~7.3% yield
53	o-CF ₃ - bromobenzene	100 mM	10 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 Zn + 1.0 Et ₄ NI	1 mL DME	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	~6.0% yield
54	o-CF ₃ - bromobenzene	100 mM	10 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 Mn + 1.0 Et ₄ NI	1 mL DME	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	~6.5% yield
55	dtbbpy-Ni(p- CF ₃ ,Ph)(Br)	100 mM	10 mol%	-	-	-	None	0.5 mL C ₆ H ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	7.9% yield, 4.7 mM toluene
56	dtbbpy-Ni(p- CF ₃ ,Ph)(Br)	100 mM	10 mol%	-	-	-	None	0.5 mL DME	300 W Xe Lamp	120 °C	10 atm CH ₄	2 d	7.1% yield
57	o-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL C ₆ D ₆	None	120 °C	10 atm CH ₄	5 d	3.7% yield
58	o-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn	1 mL DME	None	120 °C	10 atm CH ₄	5 d	3.6% yield
59	o-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn + Silane	1 mL C ₆ D ₆	None	120 °C	10 atm CH ₄	44 h	3.5% yield
60	o-CF ₃ - bromobenzene	100 mM	5 mol% TMF- Rh-1	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	2.2 equiv. Zn + Silane	1 mL C ₆ D ₆	None	120 °C	10 atm CH ₄	44 h	No product detected
61	dtbbpy-Ni(p- CF ₃ ,Ph)(Br)	100 mM	5% Rh- Dimer	-	-	-	None	0.5 mL C ₆ H ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	~13.2% yield, 3.8 mM toluene. Poor solubility of Ni complex. Some solvent evaporated.
62	o-CF ₃ - bromobenzene	100 mM	5 mol%	20 mol% NiBz ₂ -glyme	25 mol% dtbbpy	-	3 equiv. Zn	1 mL C ₆ D ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	5.2% yield, ~0.6 mM toluene
63	o-CF ₃ - bromobenzene	100 mM	5 mol% 5% Rh- Me	20 mol% NiBz ₂ -glyme	25 mol% dtbbpy	-	3 equiv. TDAE	1 mL C ₆ D ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	No product, 12.7 mM toluene
64	o-CF ₃ - bromobenzene	100 mM	5% Rh- Dimer	20 mol% Ni(COD) ₂	25 mol% dtbbpy	-	3 equiv. Zn	0.5 mL C ₆ H ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	10.4% yield, no toluene
65	o-CF ₃ - bromobenzene	100 mM	5 mol% 5% Rh- Me	1 equiv. Ni(COD) ₂	1.2 equiv. dtbbpy	-	-	0.5 mL C ₆ H ₆	200 W Hg Lamp	RT	10 atm CH ₄	5 d	8.8% yield, 7.4 mM toluene
66	o-CF ₃ - bromobenzene	100 mM	5% Rh- Dimer	1 equiv. Ni(COD) ₂	1.2 equiv. dtbbpy	-	-	1 mL C ₆ D ₆	200 W Hg Lamp	RT	10 atm CH ₄	6 d	9.8% yield, no toluene
67	o-CF ₃ - bromobenzene	100 mM	5% Rh- Me Dimer	1 equiv. Ni(COD) ₂	1.2 equiv. dtbbpy	-	-	1 mL C ₆ H ₁₂	200 W Hg Lamp	RT	10 atm CH ₄	6 d	8.4% yield

Table B.3. Summary of screening conditions and results for methane borylation.

	Substrate	Conc.	Rh	Additives	Additives	Solvent	Light	Temp.	Pressure	Time	Results
1	B ₂ Pin ₂	4.85 mM	20 mol%	-	-	C ₆ D ₆	>345 nm, 150 W	100 °C	1 atm CH ₄		Ph-Bpin and small amount of HBpin observed by GCMS and NMR
2	B ₂ Pin ₂	47.6 mM	2 mol%	-	-	0.35 mL C ₆ D ₆	>345 nm, 150 W	100 °C	1 atm CH ₄	48 h	
3	B ₂ Cat ₂	47.6 mM	2 mol%	-	-	0.35 mL C ₆ D ₆	>345 nm, 150 W	100 °C	1 atm CH ₄	48 h	
4	B ₂ Pin ₂	47.6 mM	2 mol%	-	-	0.25 mL C ₆ D ₆	>345 nm, 150 W	RT	10 atm CH ₄	48 h	Ph-Bpin observed by GCMS
5	B ₂ Pin ₂	47.6 mM	2 mol%	-	-	0.25 mL 8:2 C ₆ D ₆ :DMA	>345 nm, 150 W	RT	10 atm CH ₄	48 h	No product
6	B ₂ Pin ₂	47.6 mM	2 mol%	-	-	0.25 mL 8:2 C ₆ D ₆ :MeOH	>345 nm, 150 W	RT	10 atm CH ₄	48 h	No product
7	B ₂ Pin ₂	47.6 mM	2 mol%	-	-	0.25 mL 8:2 C ₆ D ₆ :lutidine	>345 nm, 150 W	RT	10 atm CH ₄	48 h	No product
8	B ₂ Pin ₂	100 mM		-	-	8:2 C ₆ D ₆ :DMA	16 W Blue LED	RT	10 atm CH ₄	48 h	N/A
9	B ₂ Pin ₂	100 mM		-	-	8:2 DCE:DMA	16 W Blue LED	RT	10 atm CH ₄	48 h	N/A
10	B ₂ Cat ₂	50 mM	5 mM	-	-	0.5 mL DMA	456 nm LED	RT	1 atm N ₂	24 h	No product detected after pinacol workup
11	B ₂ Cat ₂	50 mM	5 mM	-	-	0.5 mL DME	456 nm LED	RT	1 atm N ₂	24 h	No product detected after pinacol workup
12	B ₂ Cat ₂	50 mM	5 mM	50 mM DMAP	-	0.5 mL DME	456 nm LED	RT	1 atm N ₂	24 h	No product detected after pinacol workup
13	B ₂ Cat ₂	50 mM	5 mM	50 mM DMAP	-	0.5 mL C ₆ D ₆	456 nm LED	RT	1 atm N ₂	24 h	No product detected after pinacol workup
14	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL C ₆ D ₆ + 0.1 mL DMA	16 W Blue LED	RT	1 atm N ₂	24 h	~3.3 mM Me-Bpin formed
15	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL DCE + 0.1 mL DMA	16 W Blue LED	RT	1 atm N ₂	24 h	~3.7 mM Me-Bpin formed
16	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL DME + 0.1 mL DMA	16 W Blue LED	RT	1 atm N ₂	24 h	~1.3 mM Me-Bpin formed
17	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL DCE + 0.1 mL DMA	16 W Blue LED	RT	10 atm CH ₄	60 h	~2.4 mM Me-Bpin formed
18	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL C ₆ D ₆ + 0.1 mL DMA	16 W Blue LED	RT	10 atm CH ₄	60 h	~2.3 mM Me-Bpin formed
19	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	16 W Blue LED	100 °C	10 atm CH ₄	3 d	3.74 mM Me-Bpin, ~4 mM Ph-Bpin, 77.7 mM B ₂ Pin ₂
20	B ₂ Cat ₂	200 mM	5 mM TXP-Rh-Me	-	-	0.5 mL C ₆ D ₆	16 W Blue LED	RT	10 atm CH ₄	3 d	3.13 mM Me-Bpin formed
21	B ₂ Cat ₂	200 mM	5 mM TXP-Rh-Me	-	-	0.5 mL C ₆ D ₆	16 W Blue LED	100 °C	10 atm CH ₄	3 d	3.21 mM Me-Bpin formed
22	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	2.79 mM Me-Bpin, ~5 mM Ph-Bpin, 84.9 mM B ₂ Pin ₂
23	B ₂ Pin ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	1.81 mM Me-Bpin, 8.85 mM H-Bpin, ~65 mM Ph-Bpin, 145.7 mM B ₂ Pin ₂
24	B ₂ Cat ₂	200 mM	5 mM TXP-Rh-Me	-	-	0.5 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	3.7 mM Me-Bpin, ~3 mM Ph-Bpin, 20.3 mM B ₂ Pin ₂
25	B ₂ Pin ₂	200 mM	5 mM TXP-Rh-Me	-	-	0.5 mL C ₆ D ₆	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	1.1 mM Me-Bpin, 5.2 mM H-Bpin, ~35 mM Ph-Bpin, 170.1 mM B ₂ Pin ₂

26	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.4 mL C ₆ H ₆ + 0.1 mL DMA	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	4.0 mM Me-Bpin, no Ph-Bpin or B ₂ Pin ₂ observed by GC
27	B ₂ Cat ₂	200 mM	5 mM TXP-Rh-Me	-	-	0.4 mL C ₆ H ₆ + 0.1 mL DMA	300 W Xe Lamp	120 °C	10 atm CH ₄	24 h	3.5 mM Me-Bpin, no Ph-Bpin or B ₂ Pin ₂ observed by GC
28	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL Toluene	300 W Xe Lamp	120 °C	1 atm N ₂	2 d	1.5 mM Me-Bpin, <~4.3 mM Tol-Bpin, 27.9 mM B ₂ Pin ₂
29	B ₂ Cat ₂	200 mM	None	-	-	0.5 mL C ₆ D ₆	200 W Hg Lamp	RT	1 atm N ₂	2 d	No Ph-Bpin detected
30	B ₂ Cat ₂	200 mM	None	-	-	0.5 mL C ₆ D ₆	None	120 °C	1 atm N ₂	2 d	Ph-Bpin detected
31	HBCat	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	2.0 mM Me-Bpin
32	HBPIn	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	150 W Xe Lamp	120 °C	10 atm CH ₄	2 d	~0.7 mM Me-Bpin
33	B ₂ Cat ₂	200 mM	5 mM TMP-Rh(II)	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	4 d	2.0 mM Me-Bpin, Toluene observed by GCMS
34	B ₂ Cat ₂	200 mM	5 mM TMP-Rh(II)	-	-	0.4 mL C ₆ H ₆ + 0.1 mL DMA	440 nm LED	120 °C	10 atm CH ₄	4 d	~1.4 mM Me-Bpin
35	B ₂ Hex ₂	200 mM	5 mM TMP-Rh(II)	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	~1.3 mM Me-Bpin, 55.4 mM B ₂ Pin ₂ , ~4.7 mM mM Ph-Bpin
36	B ₂ Cat ₂	200 mM	5 mM TMP-Rh(II)	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	2.23 mM Me-Bpin, 71.3 mM B ₂ Pin ₂ , ~1.6 mM Ph-Bpin
37	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	6.2 mM Me-Bpin, 80.9 mM B ₂ Pin ₂ , ~0.9 mM Ph-Bpin
38	B ₂ Cat ₂	200 mM	5 mM TXP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	2.35 mM Me-Bpin, 22.4 mM B ₂ Pin ₂ , ~0.3 mM Ph-Bpin
39	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.4 mL C ₆ H ₆ + 0.1 mL DMA	440 nm LED	120 °C	10 atm CH ₄	44 h	~1.7 mM Me-Bpin
40	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	44 h	3.4 mM Me-Bpin, 54.2 mM B ₂ Pin ₂ , ~2.5 mM Ph-Bpin
41	B ₂ Cat ₂	200 mM	10 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	1.5 mM Me-Bpin, 70.7 mM B ₂ Pin ₂ , ~0.8 mM Ph-Bpin
42	B ₂ Cat ₂	200 mM	10 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	RT	10 atm CH ₄	2 d	1.7 mM Me-Bpin, 70.1 mM B ₂ Pin ₂
43	B ₂ Cat ₂	200 mM	5 mM Bimetallic Rh-Me	-	-	0.5 mL C ₆ D ₆	440 nm LED	120 °C	10 atm CH ₄	2 d	5.8 mM Me-Bpin, 71.8 mM B ₂ Pin ₂ , ~1.4 mM Ph-Bpin
44	B ₂ Cat ₂	200 mM	10 mM Rh-Me	-	-	0.5 mL C ₆ D ₆	440 nm LED	RT	10 atm CH ₄	2 d	5.5 mM Me-Bpin, 64.4 mM B ₂ Pin ₂ , ~0.6 mM Ph-Bpin
45	B ₂ Pin ₂	200 mM	10 mM TMP-Rh-Me	-	-	0.5 mL C ₆ D ₆	440 nm LED	100 °C	10 atm CH ₄	1 d	5.1 mM Me-Bpin, 201 mM B ₂ Pin ₂ , 0.8 mM Ph-Bpin, ~1.1 mM H-Bpin, 1.8 mM toluene
46	B ₂ Pin ₂	200 mM	10 mM TMP-Rh-Me	-	-	0.5 mL DME	440 nm LED	100 °C	10 atm CH ₄	1 d	3.0 mM Me-Bpin, 148.2 mM B ₂ Pin ₂ , ~1.0 mM H-Bpin
47	B ₂ Pin ₂	200 mM	10 mM TMP-Rh-Me	-	-	0.5 mL C ₆ H ₁₂	440 nm LED	100 °C	10 atm CH ₄	1 d	1.4 mM Me-Bpin, 195.9 mM B ₂ Pin ₂ , ~1.2 mM H-Bpin
48	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	100 °C	10 atm CH ₄	1 d	3.34 mM Me-Bpin, 54.6 mM B ₂ Pin ₂ , 6.4 mM Ph-Bpin
49	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	100 °C	10 atm CH ₄	1 d	~1.6 mM Me-Bpin, 60.4 mM B ₂ Pin ₂ , ~2.1 mM Ph-Bpin
50	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	100 °C	10 atm CH ₄	1 d	~1.7 mM Me-Bpin, 61 mM B ₂ Pin ₂ , 2.2 mM Ph-Bpin
51	B ₂ Cat ₂	200 mM	5 mM TMP-Rh-I	-	-	0.5 mL C ₆ D ₆	440 nm LED	100 °C	10 atm CH ₄	1 d	~1.4 mM Me-Bpin, 65.6 mM B ₂ Pin ₂ , ~1.6 mM Ph-Bpin

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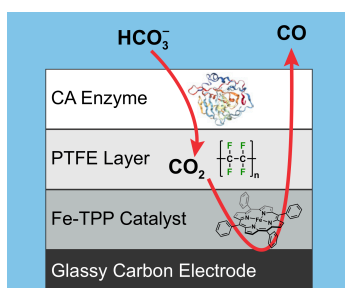
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Appendix C

Improved CO₂ Reduction by Mimicking the Confined Catalysis of the Carboxysome

Abstract

In this Appendix, we describe our efforts towards the combining a synthetic molecular catalyst and a biological enzyme in a hybrid heterogeneous platform for improved electrochemical reduction of CO₂. Importantly, this section includes a protocol for constructing robust, hydrophobic electrodes that immobilize molecular catalysts and any additives onto a heterogeneous electrode surface. This enables rapid translation to heterogeneous conditions with improved stability of the molecular-electrode interaction as well as improved selectivity for CO₂ versus H₂O diffusion into the electrode catalyst layer.



Introduction

As described in Chapters 1 and 2, CO₂ capture and conversion is a critical challenge that necessitates solutions to help combat anthropogenic climate change. Portions of this dissertation have focused on conversion of CO₂ into value-added products including CO wherein only the catalyst structure is thoroughly investigated and the experimental conditions are primarily chosen to limit any undesired side pathways and to amplify the catalyst performance. This involves using high-purity CO₂ gas as the substrate and saturating the organic or aqueous electrolyte with it. In contrast, our lab has put less emphasis on the engineering of CO₂ conversion platforms that can operate effectively under less ideal conditions.

In this context, it is important to understand some of the approaches that are used or being developed for CO₂ capture. Absorption of CO₂ using solutions of amines is the primary method for CO₂ capture from flue gas, which yields highly concentrated aqueous solutions.¹ Additionally, aqueous solutions of alkali hydroxides can absorb CO₂ to make concentrated carbonate solutions.² Currently, the processes for CO₂ capture and CO₂ conversion have remained largely separate from each other. This is often because the conditions for these two processes are not typically compatible. The work in this Appendix is a starting point for new electrode fabrication strategies to enhance CO₂ reduction under ideal and non-ideal conditions.

In recent years, a larger emphasis has been placed on electrode construction techniques that selectively allow CO₂ substrate to access the active sites. This is typically done by coating a metal electrode with a hydrophobic polymer such as polytetrafluoroethylene (PTFE). The layer of PTFE does not hinder the entry and diffusion of dissolved CO₂ gas, but it does greatly limit the extent of H₂O diffusion to the catalyst. This greatly diminishes the undesired proton reduction pathway, leading to enhanced selectivity for CO₂ reduction. This approach has also been coupled with immobilized nanoparticle catalysts,³ but not thoroughly investigated using immobilized molecular catalysts, which are commonly immobilized in hydrophilic polymers.⁴⁻⁶ Finally, another approach to increase CO₂ reduction selectivity and activity is using flow cells, where these gas diffusion electrodes are used in cells that continuously flow CO₂ gas over them.⁷ By removing the solvent from this cell compartment, the off-pathway proton reduction is even further diminished. High concentrations of CO₂ gas can be delivered, resulting in very high specific current densities, which is a crucial parameter for making such CO₂ conversion processes industrially feasible.

In nature, the key process for CO₂ capture and conversion is photosynthesis. Since air is the source of CO₂ for photosynthesis and air is only ~0.05% CO₂ and contains ~20% O₂, selective transformation of CO₂ is a large challenge. In photosynthetic bacteria, this challenge is overcome by carboxysome protein structures. Outside the carboxysome, the standard CO₂/HCO₃⁻ equilibrium is attained, whereas inside the carboxysome a high concentration of carbonic anhydrase enzymes and RuBisCO enzymes are localized. This localization allows for rapid conversion of HCO₃⁻ back into CO₂ once it diffuses into the carboxysome.⁸ This process creates a locally elevated concentration of CO₂ within the carboxysome, which saturates the RuBisCO enzymes as they fix CO₂. We envision that this strategy of using the carbonic anhydrase enzyme to elevate the CO₂ concentration near the active sites can also be applied to synthetic molecular catalysts. An extensive amount of research has been reported using carbonic anhydrase in various strategies for CO₂ capture.^{9,10} These typically involve the conversion of CO₂ from air or flue gas

into solutions of HCO_3^- , thus trapping the CO_2 in a more processable form. For our work, we aim to use carbonic anhydrase primarily for the dehydration of HCO_3^- into CO_2 for integration into our existing CO_2 conversion strategies.

Herein, we present our initial results in developing a hydrophobic electrode containing an immobilized molecular catalyst for CO_2 reduction and coupling it to immobilized carbonic anhydrase enzymes for improved CO_2 capture. This Appendix also includes details on construction of a gas diffusion electrode design that greatly improves that activity of heterogenized molecular electrocatalysts under aqueous conditions.

Results and Discussion

First, we used the molecular catalysts Fe-TPP and Co-TPP to optimize the construction of a durable gas diffusion electrode (GDE). Our previous work discussed in Chapters 2 and 4 also used these molecular catalysts for heterogeneous CO₂ or proton reduction. For these systems, our heterogenization procedure involved first coating a glassy carbon electrode with carbon nanotubes, then dropcasting a solution of catalyst on top. While this method gave good electrochemical responses, it suffered from catalyst desorption during long term electrolysis seen by decreasing current densities. In Chapter 3, we improved upon this protocol by first combining the carbon nanotubes and the molecular catalyst in solution with the addition of Nafion as a binding polymer. This mixture was sonicated thoroughly to disperse the catalyst as it adsorbs onto the nanotubes before it was dropcast onto the electrode, which resulted in a more robust film required for the rotating disk electrode used in that study. Here, we further improve upon this heterogenization of molecular electrocatalysts by constructing GDEs based on carbon black and poly(tetrafluoroethylene), PTFE. In this procedure, we sonicate a mixture of catalyst, Vulcan carbon black, and PTFE and dropcast it onto the electrode. Subsequently, an outer layer of PTFE is applied and the electrode is dried at elevated temperature. Now, we are adsorbing the molecular catalyst onto the high surface area conductive Vulcan carbon black, which plays the same role as carbon nanotubes but is significantly cheaper. We also include PTFE as the binder that also makes the catalyst layer more hydrophobic. The outer PTFE layer seals in the catalyst layer to make a highly durable electrode. The other major advantage of this hydrophobicity is the preference for CO₂ entry over H₂O entry. This greatly minimizes any undesired proton reduction, greatly increasing the activity and selectivity for CO₂ reduction.

We first used this GDE preparation containing Fe-TPP as the molecular catalyst. Fe-TPP already exhibits high selectivity for CO₂ reduction into CO, reaching 100% Faradaic efficiency, and this GDE preparation maintains this high selectivity at an applied potential of -0.67 V vs RHE. The advantage that this GDE method offers is that the current density at this applied potential is more than four times larger than that obtained using our previous immobilization strategies, and this current density is maintained during prolonged electrolysis (Table C.1). The hydrophobic GDE design likely increases in concentration of CO₂ that enters the catalyst layer resulting in larger CO specific current densities while also preventing loss of catalyst by desorption since it is encased on the electrode by a PTFE layer. We next applied this GDE strategy to the Co-TPP molecular catalyst. Previously, Co-TPP proved to be an unselective CO₂ reduction catalyst giving only ~60% Faradaic efficiency for CO under the same conditions as Fe-TPP. However, Co-TPP offers an advantage over Fe-TPP in that it can operate at lower overpotentials. By incorporating Co-TPP into a GDE, we observed that the CO Faradaic efficiency increased to approximately 100% over a wide applied potential range of -0.47 to -0.77 V vs RHE. Additionally, the CO specific current density for these Co-TPP electrodes could reach up to 4 mA/cm^2 . Such activity and selectivity put this platform on par with the best heterogenized molecular catalysts for CO₂ reduction into CO.

Next, we aimed to interface this GDE platform with carbonic anhydrase (CA) or synthetic CA mimics in order to increase the local CO₂ concentration at the electrode. CA catalyzes the rapid interconversion of CO₂ and HCO₃⁻, so by incorporating CA into the electrode assembly, we envision that the local concentration of CO₂ at the electrode catalyst film will be elevated, thus

leading to enhanced catalysis. To do this, our strategy is to simply add a layer of immobilized enzyme on top of the outer PTFE layer of the GDE. This should allow for rapid conversion of HCO_3^- in solution into CO_2 that can directly diffuse into the GDE, which should allow for more substrate to enter compared to relying on the uncatalyzed equilibrium between dissolved HCO_3^- and CO_2 . Enzyme immobilization is a large field of research and can be approached with either covalent or non-covalent methods.^{11,12} The primary challenge with these techniques, however, is maintaining the enzymatic activity after immobilization. This requires minimal changes to the protein structure as well as a local environment that is compatible with the enzyme reaction. For our work, we chose to immobilize CA non-covalently by entrapping it within a polymer film. This technique has been used to immobilization of redox-active enzymes onto electrode surfaces, and we used a similar reported technique, despite CA not being a redox enzyme. This strategy begins with the Nafion polymer binder that has cation exchange properties due to the acidic sulfonate moieties. While Nafion is a good binder, as it was used in Chapter 3, it is acidic and typically not readily compatible with enzymes. The Minteer lab has demonstrated that Nafion can be converted into film with improved diffusion of large redox species that maintains enzyme activity as a heterogeneous film by adding tetraalkyl ammonium halides to the Nafion mixture in a cation-exchange process.¹³ These more hydrophobic polymers can then be mixed with the enzyme and drop-cast onto an electrode surface to yield the immobilized enzyme film. We copied this process using CA to make films on top of the GDEs containing molecular catalysts for CO_2 reduction. This approach is appealing because the reagents are commercially available and no synthesis is required.

We used tetrabutylammonium bromide in our modified Nafion films and investigated various ratios of enzyme to binder. The Nafion solution is in ethanol, and the enzyme solution is in either water or phosphate buffer. It is important to avoid high concentrations of anions, such as in phosphate buffer saline, since these anions can bind and inhibit CA. Since the outer GDE PTFE layer is highly hydrophobic, it is important for the ethanol-water mixture containing Nafion and CA not be too polar because this will result in droplets forming on the GDE rather than an even layer. Typically, a 1 to 1 mixture is used, and the enzyme concentration is 10 mg/mL.

To begin, we immobilized Fe-TPP as the CO_2 reduction catalyst and investigated its ability to reduce CO_2 from HCO_3^- electrolyte.¹⁴ Using the Fe-TPP GDE in 0.5 M KHCO_3 electrolyte saturated with N_2 and depending on the uncatalyzed HCO_3^- dehydration resulted in just 37% Faradaic efficiency for CO formation, with the remaining current going towards the production of H_2 . In contrast, if a layer of CA is added on top of the Fe-TPP GDE, then the product selectivity for CO_2 reduction via HCO_3^- switches to 70% for CO. This simple electrode modification demonstrates how we can begin to exploit a biological enzyme to more readily deliver CO_2 substrate to a synthetic electrocatalyst. We are now optimizing the enzyme immobilization strategy to maintain the CA activity as high as possible, and we are integrating this system with other canonical CO_2 reduction catalysts, including Ni cyclam, $\text{Re}(\text{bpy})(\text{CO})_3\text{Cl}$, and Co phthalocyanine, to establish the broad applicability of our hybrid bio-molecular electrode design.

In addition to CO_2 reduction via HCO_3^- , we investigated the ability for CA to aid in the reduction of low concentrations of CO_2 . To do this, we set up our electrochemical cell using a standard Fe-TPP GDE and a phosphate buffer electrolyte that had the CA enzyme dissolved in it. The electrolyte was sparged with N_2 , and then a small amount of CO_2 was injected into the headspace. For this strategy, we envision that CA will help with the dissolution of CO_2 in the

electrolyte because of the catalyzed hydration reaction can act as a CO₂ capture mechanism. Then the reverse dehydration could result in a greater concentration of dissolved CO₂. Since this begins with CO₂ only in the headspace, extended 18 h electrolyses were required to observe a difference in activity. With no added CA, about 15% CO was detected, whereas with CA about 24% CO was detected. This is a fairly modest increase in CO Faradaic efficiency over long term electrolysis, but it provides a starting point for using CA to capture low levels of CO₂ for conversion.

While our preliminary results show modest improvements in CO production with the addition of CA enzyme, further optimization is required. One potential issue with our approach is that Nafion as well as the modified tetraalkyl ammonium Nafion are typically selective against anions. This is a problem for us because we want HCO₃⁻ to be able to readily diffuse into the enzyme film for conversion into CO₂. The modified Nafion does improve on anion permeability, but other polymer binders are worth investigation, including chitosan, which is a polysaccharide that has also been used in various enzyme immobilization strategies. One additional point of optimization with our platform is the electrolyte, specifically the pH. Under the primary conditions that we investigated of 0.5 M KHCO₃ saturated with N₂, the pH is slightly basic at 8.6. However, basic pH facilitates the hydration of CO₂ while we want to favor the dehydration of HCO₃⁻ in our system. In the carboxysome, the pH is also slightly basic in order to optimize RuBisCO activity, but it is proposed that a more acidic carboxysome could be beneficial in increasing the rate of CO₂ fixation.⁸ For our system, further screening the pH as well as the concentration of KHCO₃ is necessary.

Conclusion and Future Directions

Thus far, we have established a reliable method for constructing hydrophobic gas diffusion electrodes containing immobilized molecular catalysts for CO₂ reduction. This method creates more robust heterogeneous molecular catalyst electrodes that hinder catalyst desorption so that activity is maintained throughout the electrolysis experiments. Further, the hydrophobic layer significantly increases the CO₂ reduction selectivity. These two factors in combination lead to elevated current densities without having to perform any synthetic modifications to the catalyst itself. Preliminary results for the inclusion of the carbonic anhydrase enzyme into these gas diffusion electrodes have shown promise for catalyzing the reduction of CO₂ from bicarbonate solutions.

Moving forward, we envision that this approach for simultaneous CO₂ capture and conversion will prove to be a versatile hybrid platform that combines biological CO₂ capture mechanisms with an array of synthetic molecular catalysts. More optimization is required regarding the immobilization of carbonic anhydrase and the correct ratio of enzyme or enzyme mimic to polymer binder. However, this strategy may prove to be effective for such applications as the reduction of CO₂ at low concentration or potentially directly from air or from flue gas, where we hypothesize that the combined enzyme and hydrophobic layers will selectively allow for primarily CO₂ to access the catalyst layer so that it is unaffected by contaminants such as oxygen and sulfides.

Materials and Methods

Gas Diffusion Electrode Construction. First, an ink was made containing 20 mg carbon black in 2 mL THF with 1.5 mM molecular catalyst. Then 100 μL of 10% PTFE (aq) was added to the ink, and the mixture was sonicated for 30 minutes to fully disperse the catalyst and support. Subsequently, a pipettor was used to slowly add 200 μL of ink onto a 1 cm^2 glassy carbon electrode. Just before the THF fully dries in air, an outer layer of 100 μL of 1% PTFE (aq) was added. This aqueous layer was allowed to partially dry in air over approximately 30 minutes. Finally, the entire electrode was placed inside a tube furnace and heated under slow N_2 flow at 70 $^\circ\text{C}$ for 30 minutes, then at 200 $^\circ\text{C}$ for 1 hour before cooling and using for electrolysis. The 1 cm^2 glassy carbon electrodes used for electrolysis experiments were constructed by the standard silver epoxy and outer epoxy casing but with an orientation so that the exposed glassy carbon surface is parallel to the length of the attached steel rod. This allows for easy placement inside the tube furnace without the ink and PTFE layers falling off. This procedure can be readily scaled up or down to different sized working electrodes. Figure C.3 shows an example of the final GDE.

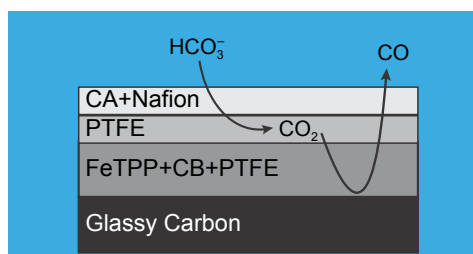


Figure C.1. Proposed strategy for heterogeneous CO_2 capture and conversion from bicarbonate using immobilized carbonic anhydrase and molecular catalyst gas diffusion electrode.

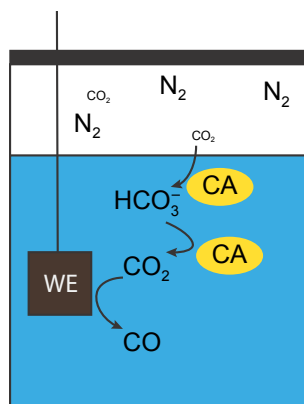


Figure C.2. Proposed strategy for capturing low concentration CO₂ using carbonic anhydrase.



Figure C.3. Example image of a completed gas diffusion electrode.

Table C.1. Summary of electrolysis results using gas diffusion electrodes and carbonic anhydrase.

Catalyst	Applied Potential (vs RHE)	Time (h)	Charge (C)	Avg. Current Density (mA/cm ²)	FE CO	FE H ₂	FE CH ₄	Total FE	Comments
FeTPP 1.5 mM	-0.772	1.00	12.19	3.39	73.81	27.95	0.04	101.79	
FeTPP 1.5 mM	-0.672	1.00	7.78	2.16	101.28	8.01	0.00	109.28	
FeTPP 1.5 mM	-0.622	1.00	3.52	0.98	102.84	9.45	0.00	112.29	
CoTPP GDE	-0.572	1.00	7.44	2.07	103.76	5.60	0.00	109.35	
CoTPP GDE	-0.672	1.00	11.54	3.21	103.03	5.05	0.00	108.08	
CoTPP GDE	-0.472	1.00	2.25	0.63	105.74	9.65	0.00	115.39	
CoTPP GDE	-0.772	1.00	13.28	3.69	101.11	3.46	0.00	104.57	
FeTPP no CO ₂	-0.672	1.00	2.42	0.67	43.04	53.34	0.07	96.45	100 μ L 1:1 PBS:Naïon. N ₂ sparged
FeTPP no CO ₂	-0.672	1.00	1.41	0.39	61.48	32.43	0.00	93.91	50 μ L 1:1 PBS:Naïon. N ₂ sparged. Some cat falls off
FeTPP + CA no CO ₂	-0.672	1.00	2.32	0.64	43.54	60.19	0.35	104.08	GC GDE. 10 mg/mL CA H ₂ O. 100 μ L 1:1 CA:Naïon on PTFE. N ₂ sparged.
FeTPP no CO ₂	-0.672	1.00	2.97	0.83	36.99	68.69	0.13	105.82	GC GDE. 100 μ L 1:1 PBS:Naïon on PTFE. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	3.00	4.54	0.42	69.97	38.31	0.34	108.63	GC GDE. 10 mg/mL CA H ₂ O. 100 μ L 1:1 CA:Naïon on PTFE. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	1.00	1.60	0.44	45.91	25.63	7.30	78.84	GC GDE. 0.1 M KPB pH 7. N ₂ sparge. 2 mL CO ₂ . 10 mg CA added to 50 mL catholyte
FeTPP + 10mg CA	-0.672	1.00	0.35	0.10	19.94	81.43	0.00	101.37	GC GDE. 0.1 M KPB pH 7. N ₂ sparge. 2 mL CO ₂ . 10 mg CA added to 50 mL catholyte
FeTPP + 10mg CA	-0.672	1.00	0.55	0.15	18.32	56.78	0.39	75.49	GC GDE. 0.1 M KPB pH 7. N ₂ sparge. 2 mL CO ₂ . No CA added
FeTPP + 10mg CA	-0.672	18.00	10.79	0.17	24.34	73.65	0.10	98.09	GC GDE. 0.1 M KPB pH 7. N ₂ sparge. 2 mL CO ₂ . 10 mg CA added to 50 mL catholyte
FeTPP + 0mg CA	-0.672	18.00	17.31	0.27	15.18	80.01	0.68	95.87	GC GDE. 0.1 M KPB pH 7. N ₂ sparge. 2 mL CO ₂ . No CA added
CoTPP + CA no CO ₂	-0.672	1.00	5.51	1.53	40.51	57.90	0.00	98.41	GC GDE. 10 mg/mL CA H ₂ O. 100 μ L 1:1 CA:Naïon on PTFE. N ₂ sparged.
CoTPP no CO ₂	-0.672	1.00	4.04	1.12	47.45	58.19	0.00	105.64	GC GDE. No CA. 100 μ L 1:1 H ₂ O:Naïon on PTFE. N ₂ sparged.
CoTPP + CA no CO ₂	-0.672	1.00	2.57	0.71	18.96	74.98	0.00	93.94	GC GDE. 10 mg/mL CA H ₂ O. 200 μ L 1:1 CA:Naïon on PTFE. N ₂ sparged.

CoTPP + CA no CO ₂	-0.672	1.00	2.40	0.67	18.40	79.19	0.00	97.58	GC GDE. 10 mg/mL CA H ₂ O. 150 μ L 1:1 CA:Nafion on PTFE. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	1.00	1.00	0.28	20.43	45.35	0.00	65.78	GC GDE. 10 mg/mL CA H ₂ O. 100 μ L 1:1 CA:Nafion on PTFE. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	1.00	1.04	0.29	23.55	65.90	0.00	89.45	GC GDE. 10 mg/mL CA H ₂ O. 200 μ L 1:1 CA:Nafion on PTFE. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	18.00	17.47	0.27	25.87	77.30	0.10	103.26	GC GDE. 10 mg/mL CA H ₂ O. 100 μ L 1:1 CA:Nafion on PTFE. Dried. N ₂ sparged.
FeTPP + CA no CO ₂	-0.672	15.00	7.93	0.15	28.54	67.00	1.87	97.41	GC GDE. 10 mg/mL CA 0.1 M KPB. 50 μ L CA + 100 μ L TBAB-Naf. 0.1 M KPB pH 7 + 10 mM KHCO ₃ . N ₂
FeTPP no CO ₂	-0.672	15.00	16.98	0.31	31.01	73.21	0.15	104.37	GC GDE. No CA. 50 μ L 0.1 M KPB + 100 μ L TBAB-Naf. 0.1 M KPB pH 7 + 10 mM KHCO ₃ . N ₂
FeTPP + CA no CO ₂	-0.672	1.00	2.82	0.78	27.10	60.44	0.31	87.85	GC GDE. 10 mg/L CA H ₂ O. 50 μ L CA + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . N ₂
FeTPP no CO ₂	-0.672	1.00	0.79	0.22	44.65	37.51	0.00	82.16	GC GDE. No CA. 50 μ L H ₂ O + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . N ₂
FeTPP + CA no CO ₂	-0.672	15.00	10.62	0.20	46.16	57.35	0.28	103.80	GC GDE. 10 mg/L CA H ₂ O. 50 μ L CA + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . N ₂
FeTPP no CO ₂	-0.672	15.00	22.81	0.42	34.03	70.04	0.02	104.10	GC GDE. No CA. 50 μ L H ₂ O + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . N ₂
FeTPP + CA + CO ₂	-0.672	1.00	6.19	1.72	103.05	3.57	0.15	106.77	GC GDE. 10 mg/L CA H ₂ O. 50 μ L CA + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . CO ₂
FeTPP + CO ₂	-0.672	1.00	2.44	0.68	100.21	6.89	0.00	107.10	GC GDE. No CA. 50 μ L H ₂ O + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . CO ₂
FeTPP + CA + CO ₂	-0.672	15.00	39.27	0.73	69.26	9.89	0.20	79.35	GC GDE. 10 mg/L CA H ₂ O. 50 μ L CA + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . CO ₂
FeTPP + CO ₂	-0.672	15.00	64.56	1.20	57.07	8.29	0.02	65.38	GC GDE. No CA. 50 μ L H ₂ O + 50 μ L TBAB-Naf. 0.5 M KHCO ₃ . CO ₂
FeTPP + ZnCylen	-0.672	15.00	14.20	0.26	32.22	74.35	0.05	106.62	10 mg/mL Zn H ₂ O. 25 μ L + 25 μ L TBAB-Naf. Dry electrode. 0.5 M KHCO ₃ . N ₂
FeTPP + ZnCylen	-0.672	15.00	13.18	0.24	33.56	68.06	0.04	101.66	10 mg/mL Zn H ₂ O. 50 μ L + 100 μ L TBAB-Naf. Dry electrode. 0.5 M KHCO ₃ . N ₂
FeTPP + ZnCylen	-0.672	15.00	25.55	0.47	33.75	53.24	0.11	87.10	10 mg/mL Zn H ₂ O. 25 μ L + 25 μ L TBAB-Naf. Wet electrode. 0.5 M KHCO ₃ . N ₂
FeTPP + ZnCylen	-0.672	15.00	15.55	0.29	44.18	55.71	0.04	99.93	10 mg/mL Zn H ₂ O. 50 μ L + 100 μ L TBAB-Naf. Wet electrode. 0.5 M KHCO ₃ . N ₂

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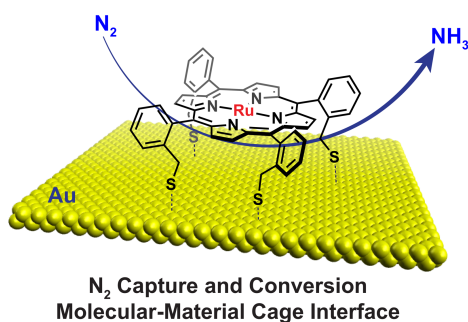
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Appendix D

Design and Synthesis of Ruthenium Porphyrins for Facilitating Electrochemical N₂ Fixation at Gold Electrodes

Abstract

We describe the synthesis of a small library of ruthenium-containing macrocyclic complexes as components in a hybrid molecular-materials electrode platform for the electrochemical reduction of N_2 into NH_3 . It is hypothesized that the inclusion of potential N_2 -binding metal complexes at an electrode surface can act to pre-concentrate the substrate to be more readily reduced by electrons at the electrode. Ruthenium complexes, particularly ruthenium porphyrin, have been shown to bind N_2 . Thus, a target molecule was designed being a ruthenium “picket-fence” porphyrin bearing thiol groups. This structure is believed to be able to bind to the surface of a gold electrode in a table-top fashion so as to make supramolecular cages on the surface of the electrode with small metal-metal distances.



Introduction

This appendix demonstrates another approach that our lab has taken for molecular-materials hybrids. Chapter 1 discussed a platform for ligating porphyrins onto an electrode surface for CO reduction. Here, we expand this work and take a similar approach for improving the reduction of dinitrogen.

The transformation of dinitrogen (N_2) into ammonia (NH_3) represents a process crucial for all life to succeed, in particular human activity. All nitrogen containing organic molecules including the building blocks for proteins and nucleic acids that are essential for life are acquired through this fixation process, and only a select number of organisms are capable of converting N_2 into NH_3 .¹ Furthermore, human-driven N_2 fixation through the Haber-Bosch process can be viewed as an equally important process for generating bioavailable nitrogen. While the Haber-Bosch process has been vital for the development of large-scale agriculture, it is an intensive process that consumes approximately 1-2% of the world's energy supply each year.²

Electrochemistry offers several potential methods for improving the efficiency of N_2 fixation. First, a major energy sink for the Haber-Bosch process is the purification of H_2 , typically by steam reformation of natural gas. As an alternative, electrolysis of water has the potential to generate high-purity H_2 directly from water using electricity,³ which can further be coupled to renewable sources such as solar or wind. Another possible alternative is the direct electrochemical reduction of N_2 into NH_3 . This is an 8-electron/8-proton transformation, and the past couple years have seen a big surge in research developing materials catalyst platforms that can drive this transformation.⁴⁻⁶

While this rapid increase in research output on electrochemical N_2 fixation is necessary and welcome, there has also been a significant amount of concern regarding the accuracy and reproducibility of some results.⁷⁻⁹ The reasoning for this questioning is the abundance of nitrogen-containing contaminants present in N_2 and Ar gases as well as on common laboratory surfaces. Such contaminants, including NH_3 itself as well as nitrate, nitrite, and nitric oxide, can be present in commercial N_2 sources, especially in isotopically labeled $^{15}\text{N}_2$, which is used for crucial experiments in determining the source of NH_3 formation.^{10,11} This necessitates the purification of gases, which can be prohibitively expensive for labeled $^{15}\text{N}_2$. Additionally, reductive decomposition of nitrogen-containing catalyst materials can lead to NH_3 formation. Thus, sufficient purification and cleaning is required as well as avoiding catalysts with high nitrogen content to minimize false positive results.

In addition to N_2 being a highly inert substrate, its concentration in aqueous electrolytes is extremely low. This results in a small number of N_2 molecules that are actually near the electrode and capable of being reduced. In comparison, aqueous electrolyte has an abundance of water molecules that favor the reduction of protons into H_2 . To overcome this challenge, we envision that the inclusion of metal complexes capable of binding N_2 at the electrode surface can enhance the local substrate concentration for reduction into NH_3 . We are pursuing this strategy primarily using ruthenium porphyrins, which have long been known to be able to bind to N_2 , as well as the various reduced intermediates leading to NH_3 .¹²⁻¹⁴

Herein, we developed a synthetic protocol for the synthesis of a library of ruthenium porphyrins and other molecules to be used as additives on gold electrodes that can catalyze the reduction of N_2 into NH_3 with modest activity. This Appendix focuses on the synthetic efforts of this project, and preliminary results indicate that the addition of ruthenium porphyrins can increase the selectivity for N_2 reduction over proton reduction, presumably by increasing the local substrate concentration at the electrode surface.

Results and Discussion

We began with the synthesis of a range of porphyrins that lack the ability to coordinate directly to the electrode surface. This approach simplifies the synthesis, thus allowing for a more diverse selection of porphyrin complexes to be rapidly made as well as simplifying the electrode preparation procedure. The scope of porphyrins utilized for this initial work is depicted in Scheme D.1. This involved varying the electronic substituents and the steric bulk on the *meso* phenyl rings. Porphyrin ligands were either purchased directly from Frontier Scientific or synthesized following standard procedures established by Adler and Lindsey.¹⁵⁻¹⁸ Additionally, we pursued simple phthalocyanine ligands. Metalation procedures required some optimization beyond literature reports. For metalation with ruthenium the most reliable procedure involves heating a solution of porphyrin in decalin at high temperatures with slow addition of $\text{Ru}_3(\text{CO})_{12}$.¹⁹ This leads to nearly quantitative conversion, and a simple procedure of filtering through an alumina plug and increasing the polarity of the solvent from hexane to dichloromethane, and then to 5% methanol in dichloromethane yields the desired product. Since this method requires heating to 190 °C, we attempted to develop milder ruthenium metalation procedures. We attempted to use $\text{Ru}(\text{DMF})_6(\text{OTf})_2$ in DMF at 60 °C, as well as RuCl_3 or $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$, but unfortunately, we had limited success and chose to maintain the high temperature metalation strategy.

The product of metalation using $\text{Ru}_3(\text{CO})_{12}$ is a ruthenium porphyrin with a bound CO ligand, which can be clearly observed by MALDI mass spectrometry. This presents a potential problem since we want the ruthenium porphyrin to be able to bind to N_2 , and the CO ligand blocks a coordination site as well as pulls electron density away from the metal center which may weaken the Ru- N_2 interaction. Thus, we investigated the photolysis of the CO ligand to make solvent or N_2 -bound ruthenium porphyrins for use in the electrode labeling (Scheme D.2). Literature reports have demonstrated this reaction on the NMR scale, but we required a larger scale reaction. This was accomplished using pressure tube and prolonged photolysis over 2 days. The product of the photolysis is highly air sensitive, therefore, the subsequent electrode labeling and electrochemical cell setup need to be performed in anaerobic conditions. We set up a glovebag with a continuous flow of high purity N_2 to do this electrode labeling and cell setup, however, the subsequent electrolysis did not reveal a difference in Faradaic efficiency for NH_3 compared to the CO-bound ruthenium porphyrin. Because of this and the complicated nature of having an anaerobic setup, we chose to continue using the CO-bound ruthenium porphyrins. Literature reports on ruthenium porphyrins have demonstrated the binding of multiple ligands including two CO, two pyridine, or two N_2 , as well as one N_2 and one alkylamine or imidazole ligand.^{12,13,20,21} This suggests to us that the CO ligand may not significantly hinder the N_2 capture mechanism that we are proposing.

To expand the library of porphyrins, we sought to synthesize ruthenium picket-fence porphyrins that bear thiols to allow for coordination to the electrode surface in a table-top manner. This is a direct expansion of our laboratory's work with thiol-functionalized porphyrins bound to copper electrodes for electrochemical CO reduction.²² Upon coordination to the surface, it is hypothesized that supramolecular cages are formed at the molecular-materials interface that act as unique active sites. The distance between the electrode and the porphyrin can be tuned by varying the length of the picket-fence linkers, and the metal center of the porphyrins can be changed to create bimetallic active sites. In this CO reduction system, the amide N-H groups within each cage may behave as hydrogen bond donors or proton relays that facilitate catalysis. We began our efforts

using the C1 amide linker length picket-fence porphyrin synthesized previously and attempting to metalate with ruthenium (Scheme D.3). Unfortunately, the desired product was not detected after the ruthenium metalation at 190 °C. We believe these harsh conditions cleave the C-S bonds in the porphyrin. It is also possible that unselective C-H activation by ruthenium decomposes the porphyrin ligand. We observed by MALDI mass spectrometry that these conditions can cleave aryl and alkyl C-S bonds as well as benzyl halides.

In addition to investigating ruthenium porphyrins with four ligating moieties, we designed a porphyrin bearing a single thioacetate group on a *meso* phenyl ring. With this additive, the ruthenium porphyrin may bind the electrode surface such that it may be able to position bound N₂ parallel to the electrode. The drawbacks of this approach are that the porphyrins can form a denser monolayer that hinders substrate and product diffusion, and this single binding point makes a less robust interaction with the electrode. Nonetheless, we were able to synthesize the structure shown in Scheme D.4, where the aniline group of the porphyrin can survive the high temperature metalation prior to introduction of the thioacetate group. Unfortunately, this strategy was not successful when using the tetra-*o*-aminophenylporphyrin to obtain the original product in Scheme D.3.

Moving forward, DFT calculations suggested to us that for optimal electron transfer from the electrode to a ruthenium-bound N₂ molecule, the size of the molecular cage structure must be minimized. This led to a revision in the design of porphyrin capable of coordinating to the electrode to form N₂-concentrating cages. The target porphyrin ligand possesses the standard tetraphenylporphyrin base, and each *meso* phenyl ring bears methanethiol substituents at the *ortho* positions (Scheme D.5). With this design, we maintain the ruthenium porphyrin and the ability to coordinate four thiols to the electrode surface, but we shorten the distance between the electrode and the porphyrin ring.

Synthesis of the new target porphyrin, **RuPC₁SAc**, also proved challenging due to the harsh ruthenium metalation conditions and the fragile thioacetate functional groups. This required a strategy for metalating with ruthenium prior to installation of the thioacetates. The procedure that proved successful is depicted in Scheme D.6 and begins with the synthesis of a porphyrin bearing methoxymethyl substituents at each *ortho* position. The rationale here was that methoxy groups were known to be compatible with the high temperature metalation conditions, and ether cleavage and halogenation has been reported previously.²³ Conversion to simple benzyl halides would then enable facile displacement with thioacetate to yield the desired product.

To begin, we synthesized the *ortho*-methoxymethyl benzaldehyde starting material and then subjected it to the standard porphyrin synthesis procedure, giving the desired porphyrin in 12% yield. The *ortho* substituents proved bulky enough to limit the rotation of the *meso* phenyl rings, resulting in a mixture of atropisomers. We continued through with the synthesis using the mixture of atropisomers rather than purifying out the desired $\alpha,\alpha,\alpha,\alpha$ atropisomer since the final electrode functionalization step is performed at elevated temperature, which should allow for free rotation of the substituents and binding to the surface in the desired fashion. Next, the ruthenium metalation was performed at 190 °C, and no issues were observed, giving the metalloporphyrin product in 68% yield. Finally, the methoxy deprotection and thioacetate substitution were performed in two steps. First, trimethylsilyl iodide with sodium iodide were used to cleave the methoxy groups and introduce iodides. This product proved to be quite sensitive to hydrolysis, so

was not completely isolated. After a quick work-up using a separatory funnel, sodium thioacetate was added to displace the benzyl iodides. Finally, column chromatography gave the final **RuPC₁Sac** product in 63% yield. This mixture of atropisomers was characterized by NMR spectroscopy and MALDI mass spectrometry.

With the desired ruthenium porphyrin in hand, our laboratory is screening electrochemical conditions for the reduction of N₂ into NH₃. Preliminary results indicate that among the non-ligating ruthenium porphyrins, the electron-rich and sterically unhindered tetra(4-methoxyphenyl)porphyrin additive is most effective at increasing the N₂ reduction activity of the gold electrode. Also, the use of **RuPC₁Sac** to make supramolecular cages at the gold electrode further enhances the Faradaic efficiency for NH₃ formation, likely due to the more porous nature that allows for better substrate access and positioning at the electrode for reduction.

Conclusion and Future Directions

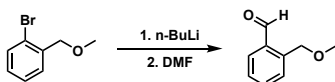
In summary, we have devised a successful strategy for synthesizing ruthenium porphyrins bearing *ortho* thiomethyl substituents that enable binding to a gold electrode surface with a small distance between the ruthenium metal and the gold surface. The delicate nature of the thioacetate substituents and the harsh ruthenium metalation conditions required us to devise a unique metalloporphyrin synthetic scheme that takes advantage of methoxy protecting groups that are robust enough for the high temperature metalation step and can subsequently be transformed into the desired thioacetates. We also synthesized a range of ruthenium porphyrins bearing different electron-donating or electron-withdrawing substituents as well as porphyrins with various degrees of steric hindrance. This group of molecules is used for non-covalent absorption onto the electrode, but their facile synthesis enables more rapid screening of the effects on electrochemical performance.

Currently, work in our lab is continuing to verify and optimize the electrochemical N₂ reduction activity of these ruthenium porphyrin-gold electrode hybrid catalysts. Promising results indicate that the addition of surface-bound ruthenium porphyrins increase the Faradaic efficiency for NH₃ compared to bare gold alone or with non-covalently bound ruthenium porphyrins. Further optimization of electrode construction and electrolysis conditions, including N₂ pressure and electrolyte composition, is ongoing.

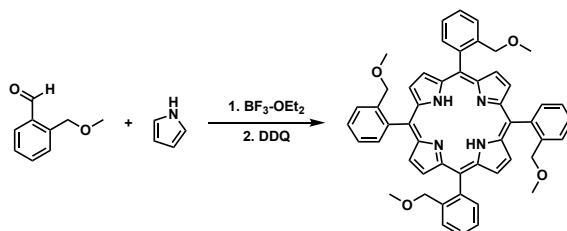
Materials and Methods

General Materials and Instrumentation. All reagents and solvents were purchased from commercial sources and used without further purification unless specified. Ultra-high purity nitrogen (99.999%) and argon (99.999%) were purchased from Praxair. Labeled $^{15}\text{N}_2$ (98 atom% ^{15}N , 364584-1L), decalin, potassium thioacetate, *n*-butyllithium, trimethylsilyl iodide, and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) were purchased from Sigma-Aldrich and used as received. $\text{Ru}_3(\text{CO})_{12}$ was purchased from Strem and used as received. 1-Bromo-2-(methoxymethyl)benzene was purchased from Oakwood Chemical and used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Tetra-(2-methylphenyl)porphyrin and tetra-(2-ethylphenyl)porphyrin were synthesized following standard procedures in refluxing propionic acid.¹⁵ Tetra-(2-(thioacetylmethyl)phenyl)porphyrin was synthesized following reported procedures.^{24,25} Anhydrous solvents were obtained from a JC Meyer solvent purification system. Deionized water was obtained from a Millipore Autopure system. Silica gel (SiliCycle, 40-63 μm , 230-400 mesh) and aluminum oxide (activated, basic, Brockmann grade I, 58 Å) were used for column chromatography. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry spectra were obtained using an Applied Biosystems Voyager DE Pro at the QB3 Mass Spectrometry Facility at the University of California, Berkeley. NMR spectra were recorded on Bruker spectrometers at room temperature, and chemical shifts are reported in ppm relative to residual solvent.

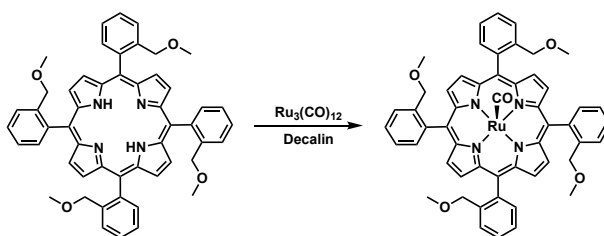
General Ruthenium Metalation Protocol. The free-base porphyrin was dissolved in decalin (10 mL) at a concentration of approximately 10 mg/mL, and the mixture was sparged with N_2 . The reaction mixture was then heated to 190 °C with stirring under N_2 , and solid $\text{Ru}_3(\text{CO})_{12}$ (97 mg, 0.15 mmol) was added in ~ 10 mg portions until the red fluorescence of the free-base porphyrin under UV illumination disappeared, typically between 2-4 h. After cooling to room temperature, the crude reaction mixture was poured on top of an alumina plug and washed extensively with hexane to remove decalin solvent. The eluant was then ramped to 1:1 hexane: CH_2Cl_2 and then 100% CH_2Cl_2 to elute any unreacted free-base porphyrin, then to 5% MeOH in CH_2Cl_2 to elute the product. After rotary evaporation and drying *in vacuo*, the ruthenium porphyrin product was obtained as an orange solid.



2-(Methoxymethyl)benzaldehyde. In a Schlenk flask under a N_2 atmosphere, 1-bromo-2-(methoxymethyl)benzene (5.1 g, 25.4 mmol) was dissolved in anhydrous THF (90 mL) and cooled to -78 °C in a dry ice/isopropanol bath. *n*-Butyllithium (2.5 M, 12.2 mL, 30.5 mmol) was then added dropwise, and the reaction was stirred for 1.5 h. Anhydrous DMF (3.9 mL, 50.8 mmol) was then added dropwise, and the reaction mixture was stirred for 2 h while warming to room temperature. The reaction mixture was then quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$. The mixture was then extracted with ethyl acetate, and the organic phase was separated and dried by rotary evaporation to give a yellow oil. The crude product was then passed through a silica plug eluting with 9:1 hexane:EtOAc to give the pure product as a clear oil (3.0 g, 78% yield). Spectroscopic data were consistent with literature reports.²⁶ ^1H NMR (400 MHz, CDCl_3) δ 10.20 (s, 1H), 7.85 (dd, J = 7.5, 1.2 Hz, 1H), 7.75-7.55 (m, 2H), 7.52-7.40 (m, 1H), 4.86 (s, 2H), 3.47 (s, 3H) ppm.

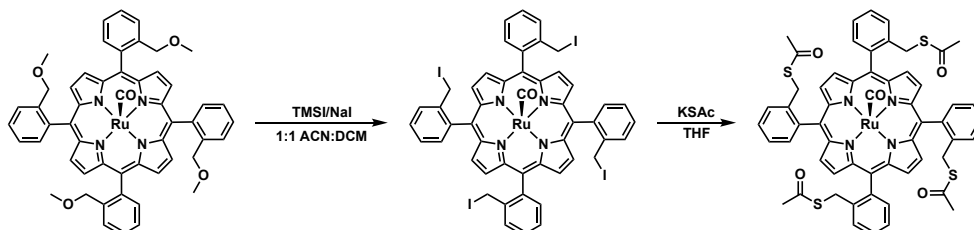


Tetra-(2-(methoxymethyl)phenyl)porphyrin. In a two-neck round bottom flask equipped with a condenser, 2-(methoxymethyl)benzaldehyde (1.5 g, 10 mmol) and pyrrole (0.69 mL, 10 mmol) were dissolved in CH₂Cl₂ (1000 mL), and then the mixture was sparged with N₂ for 10 minutes. Trifluoroacetic acid (0.77 mL, 10 mmol) was then added dropwise, and the reaction was stirred at room temperature in the dark for 2 h. Chloranil (2.5 g, 10 mmol) was then added and the reaction was heated to reflux for 2 h. The solvent was removed by rotary evaporation, and then the crude material was filtered through an alumina plug eluting with 9:1 CH₂Cl₂:EtOAc. The filtrate was dried and then dissolved in toluene (100 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (2.3 g, 10 mmol) was added and the mixture was heated to reflux for 1 h to oxidize any remaining chlorin impurities. Filtering through successive silica and then alumina plugs eluting with 9:1 CH₂Cl₂:EtOAc yielded the pure purple product as a mixture of atropisomers (227 mg, 12% yield). ¹H NMR (600 MHz, CDCl₃) δ 8.80-8.58 (m, 8H), 8.14-7.99 (m, 4H), 7.97-7.91 (m, 4H), 7.84 (m, 4H), 7.65 (m, 4H), 4.19-4.05 (m, 8H), 2.95-2.79 (m, 12H), -2.64 (s, 2H) ppm. ¹³C {¹H} NMR (151 MHz, CDCl₃) δ 140.33, 140.30, 140.26, 140.24, 140.21, 140.02, 139.96, 139.92, 139.87, 134.15, 134.11, 134.10, 134.08, 131.09, 128.93, 126.81, 126.74, 126.67, 126.65, 126.59, 125.73, 125.71, 125.69, 117.82, 117.77, 117.75, 72.95, 72.92, 72.89, 72.87, 58.32, 58.27, 58.25 ppm. MALDI-MS (matrix: DCTB) *m/z* calcd. for C₅₂H₄₆N₄O₄ [M]⁺: 790.35, found: 790.39.

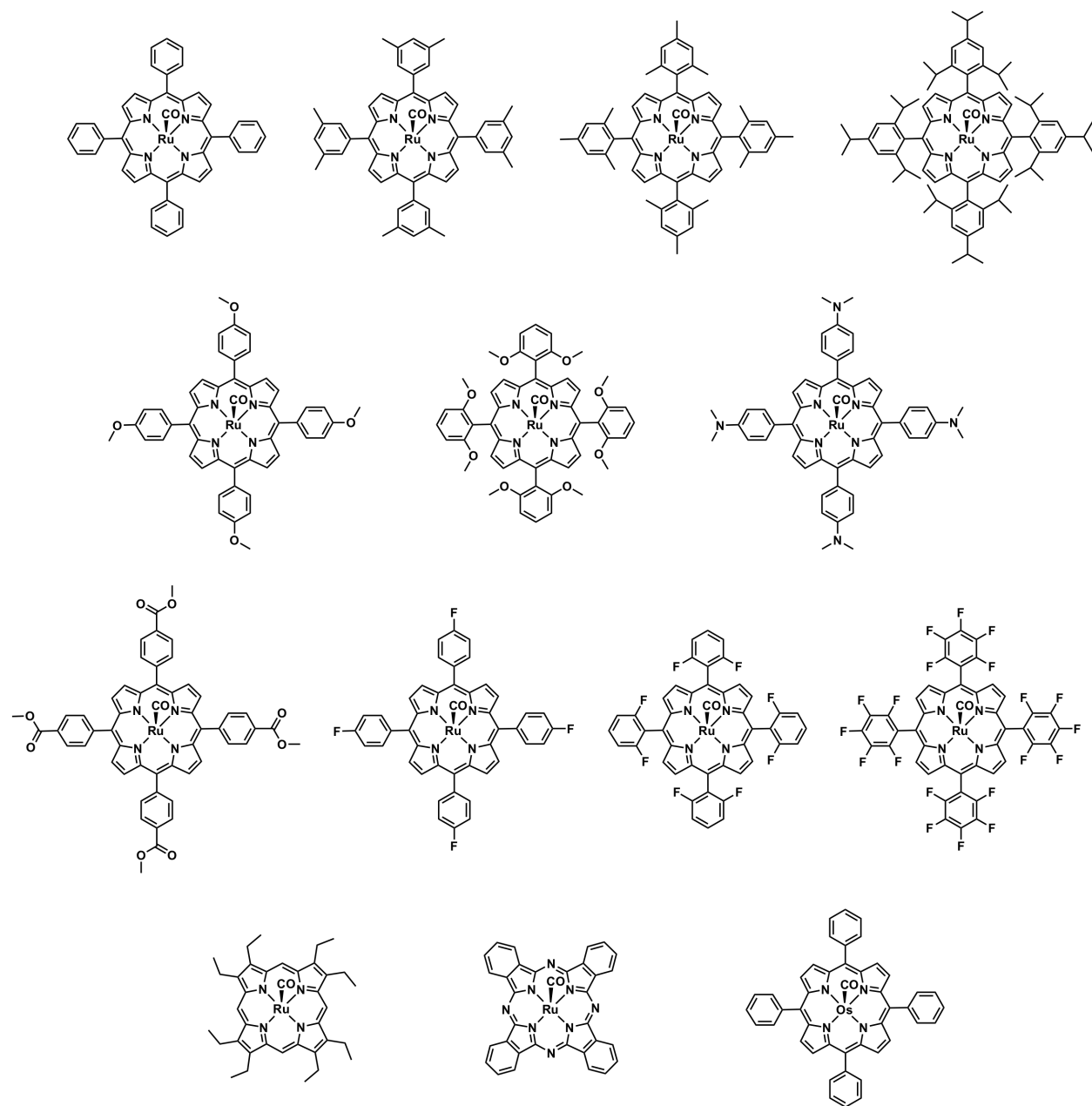


Ru^{II} carbonyl tetra-(2-(methoxymethyl)phenyl)porphyrin. Tetra-(2-(methoxymethyl)phenyl)porphyrin (100 mg, 0.13 mmol) was dissolved in decalin (10 mL) and the mixture was sparged with N₂. The reaction mixture was then heated to 190 °C with stirring under N₂, and solid Ru₃(CO)₁₂ (97 mg, 0.15 mmol) was added in ~10 mg portions until the red fluorescence of the free-base porphyrin under UV illumination disappeared after 4 h. After cooling to room temperature, the crude reaction mixture was poured on top of an alumina plug (5 cm x 5 cm) and washed extensively with hexane to remove decalin solvent. The eluant was then ramped to 1:1 hexane:CH₂Cl₂ and then 100% CH₂Cl₂ to elute any unreacted free-base porphyrin, then to 5% MeOH in CH₂Cl₂ to elute the product as a mixture of atropisomers. After rotary evaporation and drying *in vacuo*, the product was obtained as an orange solid (79 mg, 68% yield). ¹H NMR (600 MHz, THF-*d*₈) δ 8.53-8.37 (m, 8H), 8.19-8.05 (m, 3H), 7.95 (m, 1H), 7.90-7.82 (m, 4H), 7.78-7.73 (m, 4H), 7.67-7.56 (m, 4H), 4.14-3.94 (m, 8H), 2.83-2.65 (m, 12H) ppm. ¹³C NMR (151 MHz, THF-*d*₈) δ 181.22, 145.07, 145.05, 144.96, 144.92, 144.86, 141.77, 141.70, 141.64, 140.98,

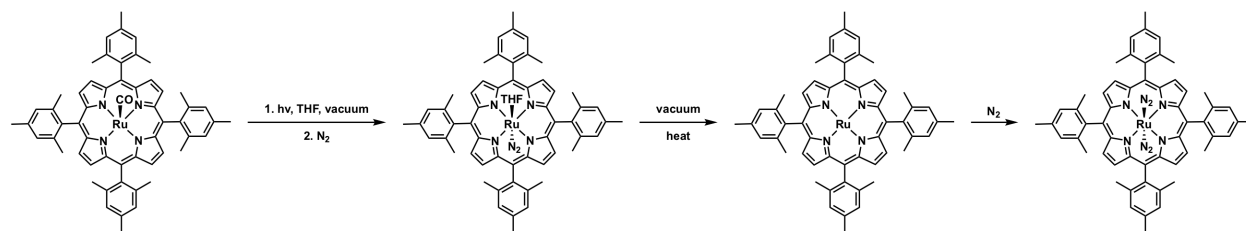
140.89, 140.86, 140.78, 140.75, 134.70, 134.64, 134.62, 134.45, 134.27, 132.22, 132.19, 132.16, 132.14, 132.12, 129.20, 129.15, 127.76, 127.70, 127.66, 127.61, 127.47, 127.40, 126.61, 126.58, 126.52, 126.49, 126.13, 126.10, 125.96, 120.44, 120.42, 73.98, 73.95, 73.92, 73.89, 73.60, 73.58, 58.36, 58.33, 58.12, 58.09, 58.07 ppm. MALDI-MS (matrix: DCTB) m/z calcd. for $C_{53}H_{44}N_4O_5Ru$ $[M]^+$: 918.24, found: 918.29; m/z calcd. for $C_{52}H_{44}N_4O_4Ru$ $[M-CO]^+$: 890.24, found: 890.30.



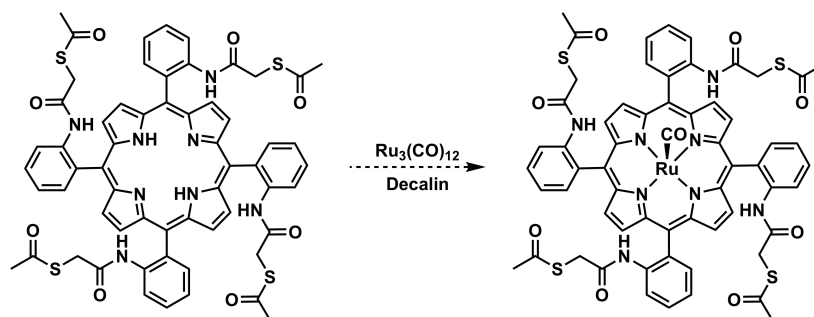
RuPC₁SAC. In a Schlenk flask under N₂, Ru^{II} carbonyl tetra-(2-(methoxymethyl)phenyl)porphyrin (40 mg, 0.044 mmol) and NaI (0.26 g, 1.74 mmol) were dissolved in an anhydrous mixture of 1:1 acetonitrile:CH₂Cl₂ (10 mL). Trimethylsilyl iodide (1 M in CH₂Cl₂, 1.74 mL, 1.74 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with CH₂Cl₂ then washed with sat. Na₂S₂O₃(aq.), H₂O, sat. NaCl(aq.), and then dried over Na₂SO₄. The solvent was then removed by rotary evaporation, and the solid residue was dissolved in THF (10 mL). The reaction was put back under N₂, and potassium thioacetate (40 mg, 0.35 mmol) was added. After stirring for 15 h at room temperature, the reaction mixture was concentrated by rotary evaporation, dissolved in CH₂Cl₂ and washed with H₂O, sat. NaCl(aq.), and then dried over Na₂SO₄. Column chromatography on silica gel eluting with CH₂Cl₂ gave the orange solid product as a mixture of atropisomers (30 mg, 63% yield). ¹H NMR (600 MHz, THF-*d*₈) δ 8.50-8.40 (m, 8H), 8.17-7.93 (m, 4H), 7.81-7.67 (m, 8H), 7.66-7.54 (m, 4H), 4.02-3.71 (m, 8H), 2.02-1.79 (m, 12H) ppm. ¹³C{¹H} NMR (151 MHz, THF-*d*₈) δ 194.75, 194.36, 194.32, 194.28, 194.10, 194.08, 145.31, 145.20, 145.13, 145.03, 142.95, 142.90, 142.77, 141.02, 140.82, 139.76, 139.64, 139.50, 135.08, 135.00, 134.95, 134.88, 134.65, 132.63, 132.50, 132.42, 132.36, 130.06, 129.96, 129.80, 129.78, 129.71, 126.69, 126.66, 126.27, 126.20, 120.58, 120.48, 120.36, 120.33, 120.26, 33.15, 33.08, 32.97, 32.90, 32.77, 32.71, 32.64, 30.82, 30.50, 29.94, 29.91, 29.89, 29.87, 29.85, 29.81, 29.12 ppm. MALDI-MS (matrix: DCTB) m/z calcd. for $C_{57}H_{44}N_4O_5RuS_4$ $[M]^+$: 1094.12, found: 1094.61.



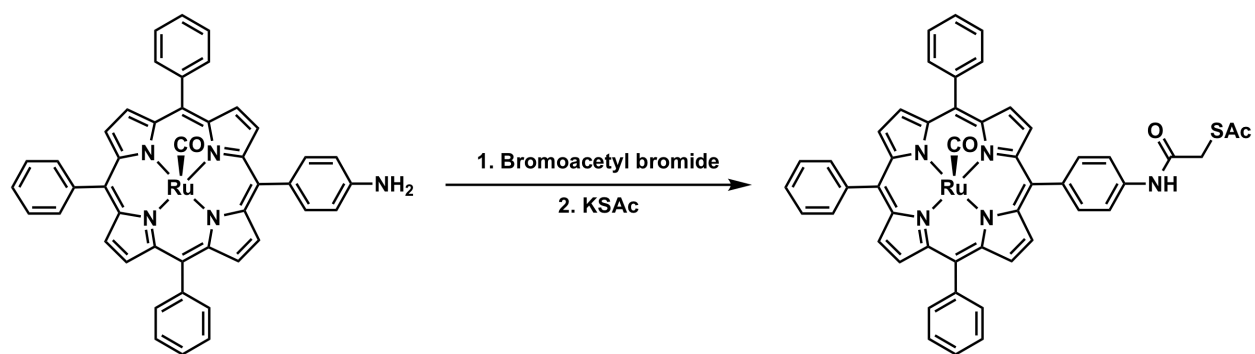
Scheme D.1. The series of ruthenium or osmium metalloporphyrins functionalized with various electron-donating or electron-withdrawing groups or sterically bulky substituents.



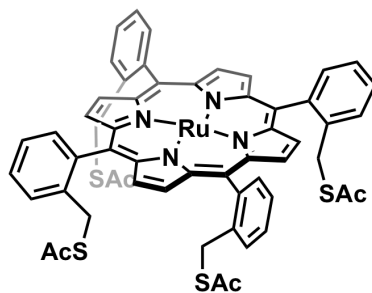
Scheme D.2. Photolysis of the ruthenium-bound carbonyl ligand that is formed after metalation with Ru₃(CO)₁₂ and subsequent exposure to N₂ to give the N₂-bound complex.



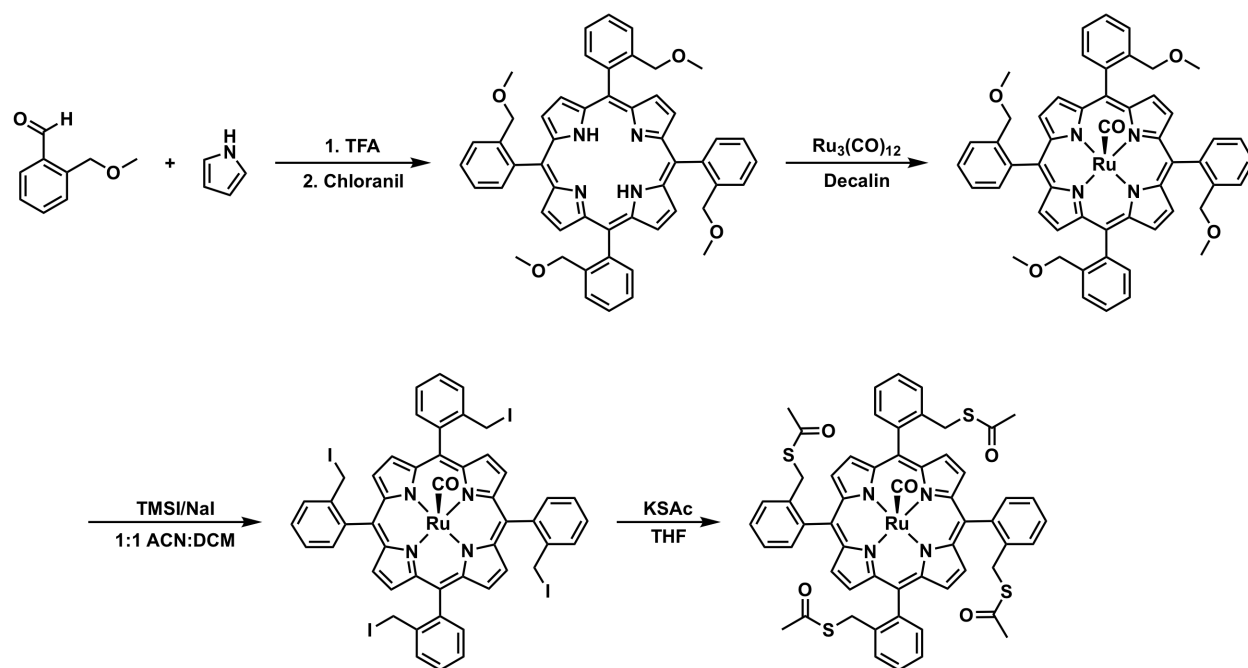
Scheme D.3. Attempted ruthenium metalation of the C₁ thioacetate picket-fence porphyrin that we previously used for CO reduction.



Scheme D.4. Synthesis of a ruthenium porphyrin bearing a single thioacetate group for binding to the electrode surface in a perpendicular fashion.



Scheme D.5. Desired ruthenium porphyrin structure bearing the DFT-optimized cage structure that minimizes the distance between the porphyrin and the electrode.



Scheme D.6. Synthetic scheme to obtain **RuPC₁SAC**.

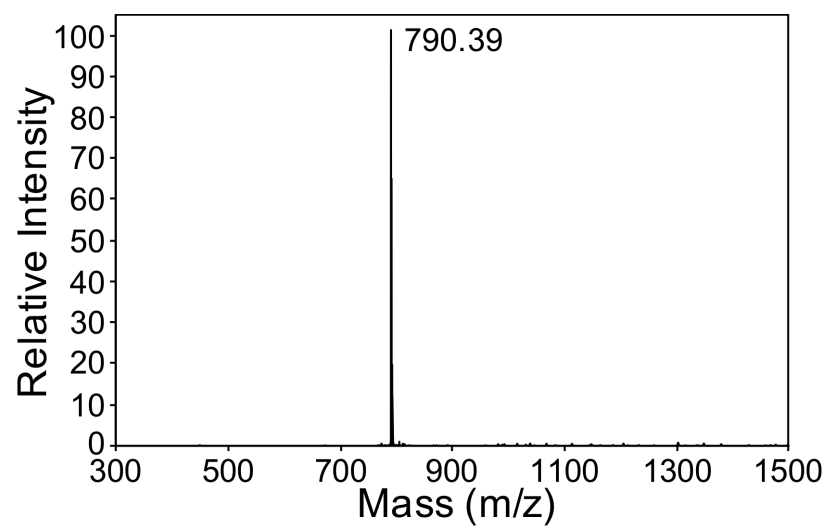


Figure D.1. MALDI-MS spectrum of tetra-(2-(methoxymethyl)phenyl)porphyrin.

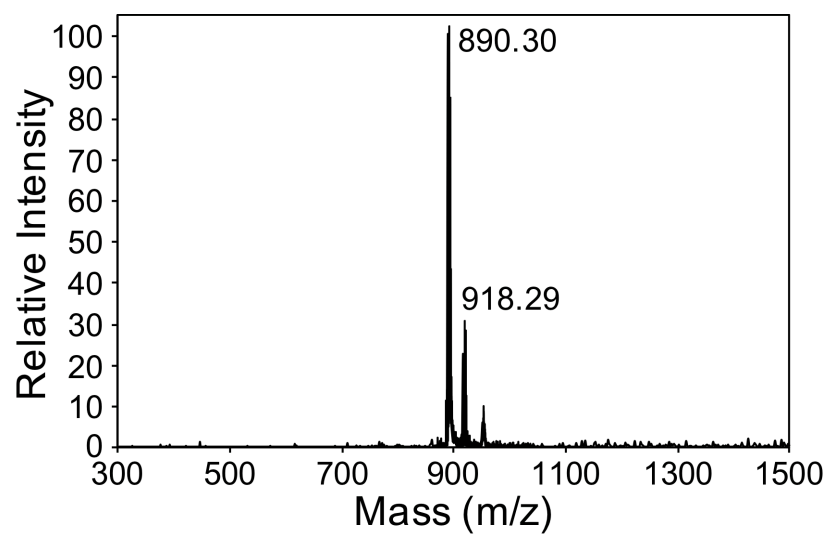


Figure D.2. MALDI-MS spectrum of Ru^{II} carbonyl tetra-(2-(methoxymethyl)phenyl)porphyrin.

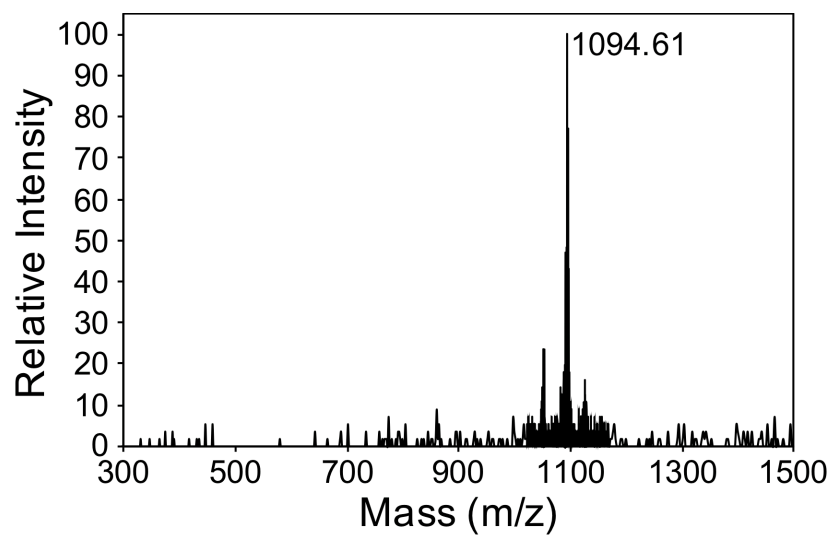


Figure D.3. MALDI-MS spectrum of **RuPC₁SAc**.

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