Harnessing the Oxidative Power of Monooxygenases through Electrochemistry

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A newly designed bioinspired electrocatalyst unlocks the oxidative power of dioxygen to functionalize unactivated C–H bonds and olefins.

Nature has evolved to utilize the oxidative power of dioxygen with the aid of transition metal cofactors to facilitate difficult chemical transformations of unactivated hydrocarbons. In our bodies, a family of Fe-porphyrin dependent metalloenzymes, known as cytochrome P450s (Cyt. P450s) perform monooxygenase chemistry through reductive activation of dioxygen to insert an O atom into a saturated C–H bond or olefin. This oxygenation reaction is a crucial step in the biogenesis of essential steroidal molecules and the metabolism of pharmaceutical drugs and xenobiotics. The key intermediate responsible for this transformation is a high valent Fe(IV) oxo-π-cation radical complex, compound 1 (Figure 1). In order for catalytic O₂ activation to occur, most Cyt. P450 enzymes require delivery of electrons via exogenous proteins known as reductases. In this issue of ACS Central Science, Mukherjee and Dey report the immobilization of a Cyt. P450 model complex (Fe-“picket-fence” porphyrin, FePf) atop an alkylthiol-derived self-assembled monolayer (SAM) modified electrode, yielding a new electrocatalyst for the hydroxylation and epoxidation of alkanes and olefins (Figure 1). Unlike Cyt. P450 or synthetic porphyrin model complexes, electrocatalysis is achieved without the requirement of exogenous electron donors or strong chemical oxidants utilizing solely O₂ and electrochemically derived electrons. Careful modulation of the SAM composition and FePf binding pocket reveals the electrochemical and chemical factors governing both catalyst efficiency and selectivity.

In Cyt. P450, O₂ coordinates to a reduced ferrous center, where addition of an electron and proton yields the ferric hydroperoxide complex, Fe³⁺(P450)–OOH. Heterolytic O–O cleavage is then promoted by the so-called “push–pull” machinery where strong axial cysteine donation coupled with hydrogen bonding to the terminal oxygen atom of the hydroperoxide in the distal pocket leads to the generation of the active oxidizing intermediate, Fe⁴⁺(P450°°)═O (compound 1) and H₂O (Figure 1). In their report, Mukherjee and Dey rationalized that the key to making a successful electrocatalyst capable of oxygenating strong C–H substrates was through stabilization of the electrochemically generated Fe⁴⁺(Pf°°)═O. Under fast electron transfer conditions, Fe⁴⁺(Pf°°)═O is rapidly reduced owing to its high reduction potential (E_red = 0.95–1.4 V vs. NHE), thereby quenching the reactive intermediate before it encounters substrate and thereby lowering faradaic efficiency. Careful tuning of the electron transfer rate through modulating the length of the SAM alkylthiol diluent was necessary to minimize electrochemical catalyst quenching, while maximizing the catalyst turnover frequency. This was accomplished by utilizing an octanethiol diluent which allowed for oxygen incorporation into various alkanes and alkenes in water at a mild potential (−100 mV vs. NHE) and in good faradaic yields (up to 72%). Perhaps the most impressive transformation is the hydroxylation of cyclohexane to cyclohexanol (TON = 21 000) without further oxidation to cyclohexanone; similar oxidations using homogeneous catalysts frequently exhibit over oxidation resulting in a mixture of products.
Analysis of substrates containing multiple functionalizable but inequivalent C−H bonds reveals surprising regioselectivity. Electrocatalytic oxidation of adamantane by FePf results in the preference to hydroxylate the stronger secondary C−H bond over the weaker tertiary C−H bond (3:2 ratio). Likewise, oxidation of ethylbenzene results in oxygen incorporation at both the benzylic and primary carbon positions (3:1 ratio), a highly unusual observation given the benzylic C−H bond is 13 kcal/mol weaker than the primary C−H bond. The origins of this unexpected regioselectivity can be traced to the steric environment of the distal binding pocket. The presence of four bulky pivaloyl groups surrounding the oxo core leaves a narrow window by which substrate can access the catalytic center, resulting in a slower oxidation rates for higher substituted carbon centers despite containing more easily modifiable (weaker) bonds. Comparison of FePf with an analogue where the distal binding site is opened through removal of two pivaloyl groups (FehPf) results in the expected preference for the oxidation of weaker C−H bonds.

While hydroxylation of cyclohexane is fairly efficient (72% faradaic yield, defined as moles product/total moles of e− consumed ×100%), the FePf catalyst is susceptible to production of partially reduced oxygen species during catalysis reflected by a H2O2 faradaic yield of 10%. Production of H2O2 highlights the multifaceted interplay between chemical and electrochemical processes whereby dissociation of H2O2 from FeIIIPf−OOH—initiated either through protonation of the hydroperoxide moiety or deleterious reduction of the metal center—competes with O−O bond heterolysis. Kinetic isotope studies reveal both a substrate (KIE) and solvent (KSIE) isotope effect indicating O−O bond heterolysis in FeIIIPf−OOH and oxidation of substrate by FeIV(PPf)O proceed at similar rates. Introduction of additional pendent proton relay moieties in the distal binding pocket may serve as an attractive future design element, mimicking the push−pull machinery in Cyt. P450s and acting to enhance the rate of O−O bond heterolysis relative to H2O2 dissociation.

Heterogenization of homogeneous electrocatalysts, as demonstrated by Mukherjee and Dey, is desirable due to the numerous advantages enjoyed by structurally immobilized species, including site isolation, flexibility of the solvent.

Figure 1. Schematic representation inspired by the catalytic cycle of Cyt. P450 showing substrate hydroxylation by the electrocatalyst FePf immobilized on a SAM modified gold electrode as reported by Mukherjee and Dey. Highlighted in yellow is the active catalytic intermediate responsible for substrate oxidation, compound 1.
Strategic design and development of electrocatalysts capable of oxidizing unactivated hydrocarbons at ambient conditions are an appealing alternative to the energy intensive steam cracking and reforming processes currently utilized to functionalize saturated alkanes.\(^9\) However, challenges remain in refining these electrocatalysts, including improving faradic efficiency and preventing passivation or decomposition of the catalytic surface, which is observed in FePf following electrolysis. Interestingly, these same obstacles exist in the P450 enzyme, but nature has cleverly employed several mechanisms to increase catalyst efficiency and lifetime. Substrate recognition sequences gate the activation of the Fe-center for O\(_2\) binding until substrate coordination,\(^1\) and hole-hopping pathways remove harmful oxidizing equivalents from the active site in the absence of substrate.\(^10\) While it is difficult—and perhaps unproductive—for synthetic chemists to exactly model all the aspects present in an enzyme active site, we should take advantage of the lessons learned from millions of years of evolution to sharpen and direct our questioning of what key factors are required in designing a successful catalyst.

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