Electrocatalytic Oxygen Reduction at Multinuclear Metal Active Sites Inspired by Metalloenzymes

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Polymer electrolyte fuel cells (PEFCs) are a clean, sustainable device to convert chemical energy to electricity and can provide power for automobiles, trains, and ships. In PEFCs, the oxygen reduction reaction (ORR) occurs at the cathode and is catalyzed at electrocatalysts. The activity of ORR electrocatalysts is known to limit the overall performance of PEFCs because the ORR is more sluggish than the hydrogen oxidation reaction at the anode. In the state-of-the-art PEFC, platinum group metal (PGM)-based ORR electrocatalysts are used. Since PGMs are rare and expensive, highly active and durable non-PGM ORR electrocatalysts are required for widespread applications of PEFCs. In nature, metalloenzymes such as cytochrome c oxidase and multicopper oxidases efficiently catalyze the ORR and utilize multinuclear iron and/or copper complexes as active sites. The structure of these active sites and enzyme reaction mechanisms would give us design concepts of artificial non-PGM electrocatalysts for the ORR, possibly leading us to develop next-generation non-PGM electrocatalysts. Herein, recent research progress on understanding enzymatic ORR reaction mechanisms and developing non-PGM ORR electrocatalysts is reviewed from the viewpoint of bio-inspired approaches.

Keywords Oxygen reduction reaction; Nonprecious metal catalyst; Electrocatalysis; Metalloenzyme; Polymer electrolyte fuel cell

I. INTRODUCTION

Polymer electrolyte fuel cells (PEFCs) are a clean, sustainable device to produce electricity, heat and water from oxygen and hydrogen. PEFCs can be used to power vehicles (fuel cell vehicles, FCVs), trains, ships and forklifts, which can be used even inside the buildings because of no emission of harmful gases. PEFCs can work efficiently with no limitation by the Carnot cycle [1, 2]. The efficiency of PEFCs is defined by the overpotentials (energy loss) observed for the two half-reactions in the PEFC, the hydrogen oxidation reaction (HOR) at the anode (H₂ → 2H⁺ + 2e⁻, E° = 0.00 V vs. SHE) and the oxygen reduction reaction (ORR) at the cathode (O₂ + 4e⁻ + 4H⁺ → 2H₂O, E° = +1.23 V vs. SHE). In theory, PEFCs produce a voltage of 1.23 V, which is the difference between the formal potentials of the HOR and ORR. In practice, cell voltages produced for PEFCs are less than 1.23 V because of the overpotential of the HOR and ORR. State-of-the-art electrocatalysts for the HOR show almost no energy loss, overpotential of more or less 5 mV because of the low energy barrier for H–H breakage. On the other hand, the ORR involves the four-proton and four-electron transfer and requires overpotential in the range typically between 300 and 400 mV [3]. Thus, developing highly active ORR electrocatalysts is the key to improving the overall performance of PEFCs. The ORR can
also proceed by two-proton and two-electron transfer to a byproduct hydrogen peroxide ($\text{H}_2\text{O}_2$; $\text{O}_2 + 2\text{e}^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2$, $+0.695 \text{ V vs. SHE}$). The product selectivity for the ORR contributes to not only increasing cell voltage but also long-term stability: $\text{H}_2\text{O}_2$ can be decomposed to hydroxyl radical species, which destroy catalysts and polymer electrolyte membranes [4]. Thus, many efforts have been devoted to improving the efficiency and selectivity of the ORR electrocatalysts.

Developing highly efficient and durable ORR electrocatalysts based on nonprecious metals such as 3d transition metals is challenging. In the most advanced PEFC, Pt-based nanostructured electrocatalysts are used [3, 5–8] because Pt is known to show the highest ORR activity in the metals. The U.S. Department of Energy (DOE) set a platinum group metal (PGM) target of 0.125 kW rated gPGM, which corresponds to ca. 11.3 gPGM per midsize sedan vehicle powered by a PEFC (90 kW gross), by the year 2020, where the PGM mass used for the anode and cathode is 2.3 and 9 g, respectively [9, 10]. In a review paper describing PGM costs in FCVs [10], a PGM target of 0.0625 gPGM kW gross$^{-1}$ (ca. 6 gPGM vehicle$^{-1}$) was suggested considering both the cost to the consumer and the supply-demand relation in the precious metal markets. As a reference, the value of this target is almost the same as that of PGM contents used in a standard-size conventional vehicle (5.8–5.9 gPGM vehicle$^{-1}$), where catalytic converters require ca. 2.5 gPGM [11]. The development of highly active and durable non-PGM ORR electrocatalysts would allow us to achieve such targets, resulting in widespread commercialization of FCVs.

Solutions to developing highly active non-PGM electrocatalysts for the ORR could be found in natural catalysts. Metalloenzymes such as cytochrome $c$ oxidases (CcO) [12–14] and multicopper oxidases such as laccases (Lac) [15–19] efficiently and selectively catalyze the ORR. These metalloenzymes utilize multinuclear 3d metal complexes as catalytic reaction centers: a Fe–Cu dinuclear complex for CcO and a trinuclear copper complex for Lac. The structure of these active sites inspires us to design and synthesize non-PGM ORR electrocatalysts.

This review focuses on non-PGM-based ORR electrocatalysts particularly with multinuclear metal active sites, inspired by active sites of metalloenzymes.

II. NONPRECIOUS METAL OXYGEN REDUCTION ELECTROCATA-LYSTS WITH MULTINUCLEAR METAL ACTIVE SITES

A. Reaction mechanism

1. ORR reaction mechanisms for Pt-based electrocatalysts

Understanding the ORR reaction mechanism on Pt-based electrocatalysts, particularly the Pt(111) surface, would be helpful to clarify differences between Pt-based and non-PGM-based ORR electrocatalysts. The ORR is a multiple proton-electron transfer reaction and involves more than one intermediate. On the Pt(111) surface, the following associative reaction mechanism is proposed [20]:

$$\text{O}_2 + 4(\text{H}^+ + \text{e}^-) \rightarrow \text{OOH}_{\text{ad}} + 3(\text{H}^+ + \text{e}^-) \rightarrow \text{O}_{\text{ad}} + 2(\text{H}^+ + \text{e}^-) + \text{H}_2\text{O}$$

$$\rightarrow \text{OH}_{\text{ad}} + 1(\text{H}^+ + \text{e}^-) + \text{H}_2\text{O}$$

$$\rightarrow 2\text{H}_2\text{O},$$

where $\text{OOH}_{\text{ad}}$, $\text{O}_{\text{ad}}$, and $\text{OH}_{\text{ad}}$ indicate intermediate species adsorbed on the metal surface. Most potential dependence on the ORR for monometallic catalysts comes from the energy of these three intermediates. The binding energies of $\text{OOH}_{\text{ad}}$, $\text{O}_{\text{ad}}$, and $\text{OH}_{\text{ad}}$ are strongly correlated each other, so-called scaling relationships [20, 21]. Thermodynamic analysis based on the scaling relationships (volcano plots for the $\text{O}_{\text{ad}}$ binding free energy, $\Delta G_{\text{OH}}$) indicates that the first step involving $\text{OOH}_{\text{ad}}$ and the last step involving $\text{OH}_{\text{ad}}$ govern limiting potentials, at which all the reaction steps are downhill in free energy, for all the transition metals [20]. Pt(111) lies closest to the top of the limiting potential volcano, compared with the (111) facets for the other transition metals (Figure 1) [20, 22]. The high catalytic activity of Pt(111) initiates ORR studies on bimetallic alloy (111) surfaces such as PtNi(111) [6, 23] and high index surfaces such as Pt(331) = 3(111)-(111) [24].

One of the challenges for developing Pt-based ORR electrocatalysts is breaking the scaling relationships. The value of theoretical overpotentials is limited by the scaling relationships for the Pt-based electrocatalysts. Synthetic strategies on breaking the scaling relationships, in other words, decoupling the electron transfer from the proton transfer

Figure 1: Volcano plots of experimental activity of PGM-based ORR electrocatalysts and limiting potential based on thermodynamic analysis. Adapted with permission from Ref. 20. Copyright 2018, American Chemical Society.
have been proposed for PGM electrocatalysts [20, 25]. Usually, in the associative reaction mechanism on the metal surface (mentioned above), proton and electron transfer pathways are coupled at each reaction step because the reaction barrier for proton transfer to surface-bound intermediates is estimated to be quite small, essentially the same order of magnitude as those in water [20, 26]. To decouple proton and electron transfer pathways, for example, pores and channels through nanoscopic confinement can be used to selectively stabilize one of the surface-bound intermediates, where a surface opposite to the adsorbate bond stabilizes OOHad via a hydrogen bond but is not close enough to interact with OHad [25, 27]. Such a selective interaction for the key intermediates could also be achieved with surface functionalization of the catalyst. Interestingly, metalloenzymes such as CcO and Lac use these strategies to break the scaling relationships [13, 20]. The reaction centers in metalloenzymes are typically placed in a pocket surrounded by residues of amino acids, which interact with the intermediates in the ORR via hydrogen bonding, resulting in decoupling the electron transfer from the proton transfer.

In the next section, the reaction mechanism of the ORR for non-PGM electrocatalysts including coordination compounds and metalloenzymes is discussed in detail.

2. O2 bonding form for mono- and multi-nuclear active sites of non-PGM metal complexes

Dioxygen (O2) binding to redox-active metal centers initiates the catalytic ORR for transition metal complexes (inner-sphere O2 reduction). Binding modes of O2 adducts have been intensively studied for many years particularly on iron porphyrin complexes because heme proteins such as hemoglobin, cytochrome P450 and CrO work for O2 transport and biosynthetic reactions that involve O2 binding, activation and reduction. Common coordination geometries of O2 to metal centers for copper complexes are shown in Figure 2. Redox-active metal centers give one electron to O2, yielding superoxo (O–O•−) intermediates and two-electron transfer produces peroxy intermediates [28–30]. For most of the mononuclear transition metal complexes, the ORR proceeds via end-on (η1) superoxo intermediates [30, 31]. Only a few examples of catalysis via side-on (η2) peroxy complexes were reported [30, 32–34]. In the case of multinuclear metal complexes, O2 can be sandwiched/bridged between more than two metal ions, giving peroxy species [Figure 2(b)]. This O2 bonding form is the key to efficiently and selectively reduce O2 to H2O. For example, mononuclear Co complexes show four-electron as well as two-electron ORR activity whereas Co cofacial dinuclear porphyrins and dimerized Co porphyrins selectively catalyze the four-electron reduction of O2 even in acidic media [35]. In nature, metalloenzymes of CcO and Lac efficiently catalyze the ORR at multinuclear metal active centers.

3. ORR reaction mechanism on metalloenzymes

Metalloenzymes such as Lac utilize multinuclear active sites for the ORR. Multicopper oxidases including Lac efficiently catalyze the ORR utilizing a multinuclear copper center [15, 18, 29]. Lac can be found in many organisms such as bacteria and fungi. The active site of Lac is composed of four copper centers: a mononuclear copper ion (type 1 site, T1) and a trinuclear cluster formed by a mononuclear (type 2 site, T2) and a dinuclear (type 3 site, T3)
copper center (Figure 3). The T1 site oxidizes organic substrates including a variety of phenolic compounds and then delivers the extracted electrons to the trinuclear cluster (T2 and T3), generating the fully reduced form. This fully reduced trinuclear cluster reduces O₂ to H₂O via two sequential two-electron transfer steps. O₂ binding to the fully reduced form initiates the first two-electron transfer from the T2 Cu¹ ion and one of the T3 Cu¹ ions to O₂, giving a peroxo intermediate (μ₁,1,2-peroxo structure, P₁). Two additional electrons are rapidly transferred from the other T3 Cu¹ ion and the T1 site, cleaving the O−O bond, followed by the formation of the native intermediate (NI). NI has bridging μ³-O²⁻ and μ²-OH⁻ ligands. In the presence of substrates NI is converted back to the fully reduced form, maintaining the catalytic cycle, whereas slowly decays to the resting oxidized form (RO) in the absence of substrate. T1-depleted Lac reacts with O₂ to generate P₁ but T2-depleted Lac does not, confirming that the catalytic ORR occurs at the trinuclear cluster of T2 and T3 but not at the T1 sites [15]. The T1 site works as an electron relay between substrates and the trinuclear cluster.

Note that a carboxylate group in the second coordination sphere of Lac is necessary for the O₂ activation. A highly conserved carboxylate residue of aspartic acid (Asp) is connected via hydrogen bonding network with the T2 copper site (Figure 3). DFT calculations on a relatively small model of the trinuclear cluster with O₂ [36] give an optimized structure with the μ−η¹−η¹−peroxo structure, where O₂ is sandwiched between the two T3 copper ions. This result disagrees with experimental results. An extended model including the trinuclear cluster and the Asp in the second coordination sphere produced the μ₁,1,2-peroxo structure P₁, which is in good agreement with experimental results [37]. The oxidation of two copper ions close to the Asp to CuII suggests that the electrostatic interactions and hydrogen bonds with the carboxylate group of the Asp cause a negative shift in the redox potentials of these copper ions [15]. Such a potential shift caused by weak interactions are often observed for redox cofactors in metalloproteins [38, 39].

Not only Lac but also heme-copper oxidases including CcO utilize multinuclear active sites for the catalytic ORR. CcO is a transmembrane metalloenzyme and located in the inner mitochondrial membrane of eukaryotes and in the cytoplasmic membrane of prokaryotes. At the terminal step of respiration, the catalytic ORR in CcO is coupled with proton-pumping (4 protons per turnover) across the membrane,
The ORR occurs at a dinuclear center containing a heme (high-spin heme a$_3$) and copper ion (Cu$_b$). CcO accepts electrons from a redox mediator of cytochrome c at the mixed-valent dinuclear copper site (Cu$_a$) and the electrons are transferred to a low-spin heme a, and then to the dinuclear center heme a$_3$Cu$_b$. The edge-to-edge distances from the Cu$_a$ center to heme a, heme a$_3$ and Cu$_b$ are ca. 12, 16, and 20 Å, respectively [12]. The Cu$_b$ site is placed 5.1 Å from the heme a$_3$ iron (PDB: 5B1B) [40].

The catalytic cycle of CcO is initiated by the reduction of a fully oxidized resting form in the dinuclear reaction center (Figure 4). The fully oxidized resting form has a trans-1,2-peroxo structure [Fe$^{III}$-(µ-1,2-O$^2$)-Cu$^{III}$] [41]. This resting form is converted by 6-electron and 4-proton transfer to the fully reduced state, R, with the five-coordinated high-spin Fe$^{III}$/Cu$^{II}$ state. In the catalytic cycle, O$_2$ binds to heme a$_3$ in the R state to generate the experimentally observable superxo intermediate, A [42, 43], involving a high- to low-spin transition for heme a$_3$ [12]. This A intermediate spontaneously decays to the PM state containing Fe$^{IV=O}$, Cu$^{II}$-OH, and a tyrosyl radical, where both the heme a and the Cu$_A$ center are oxidized. The free energy change of the conversion of A to PM is determined to be ca. 5 kcal mol$^{-1}$ based on DFT calculations [44, 45]. When both heme a and Cu$_A$ are reduced, the PR intermediate containing Fe$^{IV=O}$, Cu$^{II}$-OH and Tyr-O$^•$ moieties generates from A. Protonation of PR yields the F intermediate. The structure of R, A, PM, PR, and F intermediates is well established [12, 14].

The presence of a peroxo intermediate IF (Fe$^{III}$-O-O-Cu$^{III}$) and proton transfer pathways remain under debate [12, 46]. The presence of IF between A and PM intermediates is predicted by quantum chemical calculations [47, 48]. However, the IF state had not been observed experimentally because it has higher energy than the A state and an O-O cleavage barrier can be estimated to be 12.4 kcal mol$^{-1}$ using transition-state theory from the experimental time constant for the disappearance of A [44, 49]. Recent kinetic studies on Thermus thermophilus ba$_s$ oxidase at a low temperature of 10°C at pH 7 have revealed that electron transfer from the low-spin heme b to the heme a$_3$Cu$_b$ dinuclear active site (t ~ 11 ms) is approximately 10 times faster than the formation of the PR intermediate (t ~ 110 ms) [50]. This result clearly indicates that O$_2$2 is reduced prior to O-O bond cleavage. Theoretical studies also support that the transfer of a proton to the O$^•$ moiety is energetically required to reductively cleave the peroxodic O-O bond [14, 48, 50, 51]. It is most likely that the peroxo intermediate IF exists as resonance structures between Fe$^{III}$-O=OH-Cu$^{III}$ Tyr-O and Fe$^{III}$-OH-Cu$^{III}$ Tyr-O in Thermus thermophilus ba$_s$ oxidase [50]. Furthermore, a synthetic model of a heme-peroxo-copper complex and a phenol demonstrates that the O-O bond cleavage proceeds via hydrogen-bond assisted homolysis pathway [46]. These results imply that the tyrosine cross-linked to the histidine in the second coordination sphere plays an important role in decreasing the kinetic barrier to O-O bond cleavage for CcO.

Inspired by the active site of Lac, many multinuclear copper complexes as ORR catalysts have been studied. Homogeneous ORR catalysts based on dinuclear copper complexes can give mechanistic insights into ORR intermediates. Even in the case of mononuclear copper complexes such as [Cu(tmpa)(L)]$^{2+}$ (tmpa = tris(2-pyridylmethyl)amine, L = solvent), peroxo-bridged dinuclear intermediates can be involved for the ORR depending on the experimental condition [31, 52–56]. For example, a dinuclear copper complex with a (−(CH$_2$)$_3$)-linked bis[2-(2-pyridyl)ethyl]amine ligand selectively reduces O$_2$ to H$_2$O in acetone that contains decamethylferrocene (Fc$^+$) as the electron source and trifluoroacetic acid as the proton source [57]. In this catalytic system, four-electron transfer and four-proton transfer are decoupled: the electron transfer from Fe$^+$ to the dicopper complex is much faster than the proton transfer (Figure 5). The Cu$^{II}$/Cu$^{III}$ complex accepts two electrons from two Fe$^+$ molecules to form the Cu$^{III}$/Cu$^{II}$ intermediate. This intermediate reacts with O$_2$ to give a Cu$^{III}$/Cu$^{II}$ η$_2$:η$_2$-peroxo intermediate and then the subsequent two-electron transfer, which is the rate-determining step, cleaves the O–O bond, followed by the four-proton transfer to produce H$_2$O (Figure 5).

Another example of a dicopper(II) complex with a poly(pyridine–polyamide) ligand was reported to catalyze the O$_2$ reduction to H$_2$O in DMF as well as H$_2$O [58]. Control experiments using mononuclear Cu analogues showed lower selectivity for the O$_2$ reduction to H$_2$O, suggesting that the dicopper active site is important for the selective O$_2$ reduction to H$_2$O. Interestingly, O$_2^•$ is released in DMF from an intermediate compound, which is produced by the reaction between a Cu$^{II}$/Cu$^{III}$ intermediate and O$_2$, whereas O$_2^•$ is further reduced to H$_2$O in aqueous solutions, implying that the

Figure 5: Proposed ORR reaction mechanism of a dinuclear copper complex with a (−(CH$_2$)$_3$)-linked bis[2-(2-pyridyl)ethyl]amine ligand. Reprinted with permission from Ref. 57. Copyright 2012, Wiley-VCH.
polarity of the solvent used affects the product selectivity for homogeneous systems. Of course, only the use of dinculear copper cores is not enough to synthesize highly selective ORR catalysts. Ligand design is also important. A dicopper(II) complex with bridging phenolate and hydroxide ligands selectively reduces O$_2$ to H$_2$O$_2$, where a protonated hydroperoxo intermediate is observed [59]. The design and synthesis of bridging ligands for dinculear copper complexes remains challenging to synthesize highly active and selective ORR catalysts.

2. Heterogeneous catalysts with multinuclear copper complexes for the ORR

Practical ORR catalysts in PEFCs should be insoluble in water because the ORR catalysts should be placed on electrode substrates. Most of molecular-based catalysts show high catalytic activity in solution but not really on the electrode surface because of lacking the optimization of interfacial electron and/or proton transfer at the electrode surface.

One of the most active molecular-based heterogeneous catalysts is a dinculear copper(II) complex with 3,5-diamino-1,2,4-triazole ligands [Cu-Hdatrz, Figure 6(a)] [60]. Cu-Hdatrz is prepared from copper sulfate and Hdatrz in water in the co-presence of carbon support of Vulcan XC-72 (247 m$^2$ g$^{-1}$) [60] or Ketjen black ECP300 (813 m$^2$ g$^{-1}$) [61]. The carbon-supported Cu-Hdatrz is immobilized on the electrode surface with an ionomer of Nafion, which is a perfluorosulfonic acid polymer and works as a proton conductor as well as a binder between carbon supports. Although Cu-Hdatrz can be prepared in the absence of the carbon support [62] and then immobilized on carbon supports, the direct synthesis of Cu-Hdatrz on the carbon support provides a highly active ORR catalyst because the Cu-Hdatrz molecules are highly dispersed on the carbon support. Linear sweep voltammograms (LSVs) of Cu-Hdatrz/C under oxygen in the Britton-Robinson buffered aqueous solution containing 0.1 M NaClO$_4$ at pH 7 and 0.1 M NaOH at pH 13 gave onset potentials of 0.73 and 0.86 V vs. RHE for the ORR, respectively [60].

To gain insights into the ORR mechanism on Cu-Hdatrz, the oxidation state of the active species for Cu-Hdatrz/C under catalytic conditions was studied by in situ Cu K-edge XAS [61]. XAS is an element-specific technique and requires no crystalline samples, making it powerful to investigate heterogeneous (electro)catalysts [63]. Analysis of the X-ray absorption near edge structure (XANES) region allows us to obtain information on oxidation states of the target element. Potential dependent Cu K-edge XANES spectra of Cu-Hdatrz/C showed isosbestic points, indicating that two species are involved in the redox process. The spectra also showed a characteristic absorption peak at ca. 8981 eV under reductive conditions, which can be assigned to 1s to 4p$^\pi$ transition for CuI [Figure 7(a)] [61]. Thus, Cu-Hdatrz with Cu$^{II}$ is reduced to Cu$^{I}$ under catalytic conditions. Because the initial Cu-Hdatrz has a dinuclear Cu$^{II}$ core [62], the dinuclear Cu$^{II}$ core is reduced to Cu$^{I}$ and then the dinuclear Cu$^{I}$ active species catalyze the ORR. A Cu polynuclear assembly with Cu$^{I}$ sites is known to be a key to showing selective four-electron ORR, proved for mononuclear Cu complexes covalently immobilized on the surface of glassy carbon [64]. The pH-dependence of Cu-Hdatrz/C on the onset potential for the ORR gave a linear relationship with a slope of 26 mV per pH, which is equivalent to $-33$ mV per pH unit using a pH-independent reference electrode. Adapted with permission from Ref. 61. Copyright 2015, The Royal Society of Chemistry.

Figure 6: Molecular structures of (a) Cu-Hdatrz and (b) [Cu$^{I}$(7-N-Etppz(CH$_2$OH))]ClO$_4$. 

Figure 7: (a) In situ Cu K-edge XANES spectra of Cu-Hdatrz/Ketjen black in a neutral pH aqueous solution. (b) ORR performance of Cu-Hdatrz/Ketjen black using a rotating disk electrode at a rotation rate of 1600 rpm at different pHs under oxygen. (c) Plot of onset potentials for the ORR against pH. The plot gave a linear relationship with a slope of 26 mV per pH, equivalent to $-33$ mV per pH using a pH independent reference electrode. Adapted with permission from Ref. 61. Copyright 2015, The Royal Society of Chemistry.
bis(1-(4-ethylpiperazin-1-yl)propan-2-ol) was reported [Figure 6(b)] [65]. This compound was originally designed and synthesized as a biomimetic of the active site of the particulate methane monoxygenase (pMMO) in methanotrophic bacteria [66, 67]. To prepare the catalyst-modified electrode, the catalyst dissolved in acetonitrile was dropcast on to an electrochemically reduced carbon black modified screen-printed carbon electrode and then dried. The catalyst shows 4e⁻ reduction of O₂ with onset potentials of about 0.77 and 0.92 V vs. RHE with turnover frequencies (TOFs) of 12 s⁻¹ at pH 7 and 13, respectively. The use of a screen-printed ring-disk electrode-flow injection analysis system [68] confirms the generation of H₂O₂ with 21% during the ORR. Because trinuclear copper complexes have been synthesized and found to be ineffective towards the ORR [69–71], ligand design is critical for the synthesis of ORR active trinuclear copper complexes.

3. Self-assembled monolayers of multinuclear copper complexes on the gold surface

For molecular-based ORR electrocatalysts, different functional groups on ligands give a huge impact on the electrocatalytic activity. However, synthesis and characterization of molecular-based electrocatalysts is not straightforward and requires tremendous efforts and time. The use of thiol-ligands and the complexation of them with copper ions allow us to produce self-assembled monolayer (SAM)-based electrocatalysts on noble metal electrodes such as gold and silver via Au–S bonding. One of the advantages of SAM-based systems for the ORR is to study functional group effects of molecular-based catalysts on the ORR activity since SAMs can be easily prepared.

To understand the effect of functional groups of Cu-Hdatrz on the ORR activity, SAM-based model systems with different functional groups have been constructed on a gold electrode [72]. Ligands of 3-amino-1,2,4-triazole-5-thiol (AMT) and 1H-1,2,4-triazole-3-thiol (HT) were used to prepare SAMs on the gold surface, followed by the complexation with CuII ions (Figure 8). LSVs of the Cu complex SAMs with AMT and HT in the Britton-Robinson buffered aqueous solution at pH 7 under oxygen showed onset potentials for the ORR at 0.74 and 0.72 V vs. RHE, respectively. These onset potentials of Cu–AMT SAM are close to those of Cu-Hdatrz/C [60] and Cu-Htrz/C (Htrz = 1,2,4-triazole) [73], which are the counterparts in carbon-supported systems, respectively. These results indicate that SAM systems work as model systems for copper-based ORR catalysts on carbon supports. Notably, the introduction of perfluoroalkyl or alkyl chains to the AMT (Figure 8) modulates the oxygen mass-transfer (diffusion) properties but keeping the ORR kinetics. The perfluoroalkyl chains are vertically aligned to the gold surface, confirmed by vibrational sum frequency generation spectroscopy [72]. SAM-based model systems provide information on functional group effects on the ORR catalytic activity and the oxygen accessibility to the active site.

SAM-based electrocatalytic systems are also effective platforms to study electron and proton transfer kinetics for the ORR [74, 75]. A SAM-based dinuclear copper complex of 6-((3-(benzylamino)-1,2,4-triazol-5-yl)amino)hexane-1-thiol (CuBT'T) is constructed on Au electrodes and then covered with a monolayer 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) lipid containing a proton carrier of 1-dodecylbronic acid (DBA), which facilitates proton transfer to the copper complex via flip-flop diffusion (Figure 9). The ORR occurs at the dinuclear copper active site of CuBT'T. Protons and oxygen are delivered from the solution to CuBT'T through the DMPC monolayer. The presence of the hydrophobic DMPC lipid layer with the DBA proton carrier allows us to control the flux of hydrophilic protons to the CuBT'T catalyst. In the absence of the lipid layer, the dinuclear copper catalyst is exposed to the bulk electrolyte solution and protons can freely access the active site. In this case, protonation of the Cu–O–O–Cu adduct produces H₂O₂: 0.11 moles of H₂O₂ per mole of O₂ were consumed, which means a mixture of two and four electron transfer processes. In the presence of the DMPC lipid layer without DBA, no isotope effect was observed, indicating that the rate-determining step for the ORR does not involve protons and the catalyst predominantly reduces O₂ by one e⁻ to O²⁻. As the amount of DBA inside the lipid layer increases, the amount of H₂O₂ detected decreases and no H₂O₂ is detected with 10 mol% DBA in the lipid [74]. Changing the amount...
of DBA in the lipid layer controls the rate of proton transfer, whereas modifying the alkyl chain length of the SAM tunes the rate of electron transfer. Tuning relative rates of proton and electron transfer ($k_{H^+}/k_{e^-}$) allows the catalytic activity to be enhanced by ca. 300%, compared to the lipid-only case [75]. These results demonstrate that relative rates of proton and electron transfer to the dinuclear copper catalyst affect its activity and product selectivity. Note that a similar system but containing a mononuclear iron porphyrin as the SAM-based ORR catalyst is not able to break O–O bond before protonation and the selectivity of the catalyst cannot be improved beyond the SAM case in the absence of the lipid layer [74, 76]. This suggests that the dinuclear active site is able to cleave the O–O bond before protonation inside the lipid layer with a proton carrier but the mononuclear active site is not.

Multinuclear copper complexes can be tethered to not only Au but also carbon sheets. A dinuclear copper complex with 2,2″-((1H-1,2,3-triazole-1,4-diyl)-dipyridine is covalently linked to reduced graphene oxide (Figure 10) and shows high ORR activity and durability: an onset potential for the ORR at 0.95 V vs. RHE and $\Delta E_{1/2} = -4$ mV over 10000 continuous cycles in alkaline solution [77]. Since this covalently immobilized catalyst shows higher ORR activity than the corresponding physisorbed catalyst, this covalent immobilization approach could allow for enhancing the electron transfer between the catalyst and the supporting materials.

4. Multinuclear copper active sites embedded in carbon sheets for the ORR

SAM-based ORR electrocatalysts suggest that the immobilization of multinuclear metal active sites on conductive materials allow for improving the interfacial electron transfer rate, leading to the ORR electrocatalytic activity and durability. We can expect that active sites closer to conductive materials would give higher activity and durability. The incorporation of multinuclear active sites into conductive materials can, in principle, give highly efficient and durable electrocatalysts for the ORR.

One of the approaches to the incorporation of metal active sites into conductive materials such as carbon is pyrolysis. As non-PGM electrocatalysts, iron-based ORR electrocatalysts have been intensively studied and prepared in pyrolysis at high temperatures of 1073–1273 K [2]. As precursors, metal, nitrogen and carbon sources are used. Typically, simple metal salts and coordination compounds are used as metal sources. These are mixed with nitrogen-containing polymers as the nitrogen and carbon sources and then heated under ammonia. After heat treatments, metal, nitrogen-doped carbon (M/N/C) catalysts are obtained, where mainly four types of nitrogen are reported: pyrrolic nitrogen, pyridinic nitrogen, graphitic (quaternary) nitrogen and nitrogen-oxide. Usually, each content of these nitrogen species can be determined by using N 1s X-ray photoelectron spectroscopy (XPS) [78]. For Fe/N/C electrocatalysts, Mössbauer spectroscopy [79, 80], high-angle annular dark-field (HAADF) scanning transmittance electron microscopy (STEM), electron energy loss spectroscopy [81] and XAS [82] confirm that Fe ions are bonded to nitrogen atoms of N-doped carbon sheets to form metal-complex-like active sites $FeN_4$ ($M/N/C$: $M = metal$, $x$ = coordination number). Such active sites are mainly positioned at exposed ba-
The pyrolytic approach can be applied to precursors of multinuclear copper complexes. The mixture of Cu-Hdatrz and reduced graphene oxide (rGO) was heated at 1173 K under an inert atmosphere for a short period of time (45 s) [83]. The short period of time for heating has a great advantage of minimizing the fragmentation of coordination compound precursors during heating treatments [84]. LSVs of the heat-treated catalyst under oxygen showed an onset potential of 0.79 V vs. RHE at pH 7 for the ORR. This onset potential is more positive than that of the corresponding non-heated catalyst, Cu-Hdatrz/C [60], indicating that the heat treatment gave more active catalysts. Extended X-ray absorption fine structure (EXAFS) analysis of the heat-treated catalyst in the Cu K-edge region confirmed that Cu–N coordination bonds remained even after the heat treatment.

An ORR electrocatalyst with multinuclear copper active sites embedded into carbon sheets was prepared from a precursor mixture of a multinuclear copper complex with 1,2,4-triazolate (Cutrz) and graphene oxide (GO) in pyrolysis at 1173 K for 45 s under Ar [Figure 12(a)] [85]. Cutrz has a trinuclear copper core [86], which is similar to the active site of Lac. GO is an additional carbon source and can be converted to rGO during pyrolysis, involving the incorporation of MN, active sites into conductive sp² carbon networks [84]. The short-period heat treatment of the mixture of Cutrz and GO gave a Cu, N-doped carbon electrocatalyst (r[Cutrz/GO]). This electrocatalyst shows an onset potential of ca. 0.82 V vs. RHE in LSVs under oxygen and almost no catalytic activity loss after 8000 potential cycles in neutral media. The ORR activity of r[Cutrz/GO] is the highest activity at pH 7 in the copper-based ORR catalysts at that time. HAADF-STEM images demonstrate white spots [Figure 12(b)], which correspond to multinuclear copper cores that originate from the Cutrz precursor. Cu L-edge XAS of the powdery r[Cutrz/GO] showed characteristic peaks at 931 and 934 eV for CuII and CuI [Figure 12(c)], respectively, indicating that the catalyst contains CuI and CuII ions but no metallic copper, which was removed by an acid treatment. In situ Cu K-edge measurements of r[Cutrz/GO] in the XANES region captured the reduction of CuII to CuI under electrocatalytic conditions [Figure 12(d)], indicating that the reduction of the copper active sites initiates the ORR. Curve-fitting analysis of Fourier Transforms of
EXAFS data [Figure 12(e)] revealed the presence of multinuclear copper sites and an unsaturated coordination environment in r[Cutrz/GO]: coordination numbers of 2–3 for Cu−N and those of 0.5–1.5 for Cu···Cu. The Cu···Cu distance was determined to be 2.55 ± 0.01 Å at 0 V vs. RHE under oxygen. This distance falls in the distribution of intramolecular Cu···Cu distances of multinuclear CuI complexes [87], which indicates that the multinuclear copper cores remain even under catalytic conditions.

The short-period heat treatment of multinuclear copper complexes and a carbon source would allow us to incorporate multinuclear copper active sites into carbon sheets and produce highly active Cu/N/C electrocatalysts for the ORR. This synthetic approach can, in principle, be applied to other transition metals, making this approach open new possibilities for developing highly active and durable non-PGM-based electrocatalysts.

C. ORR electrocatalysts inspired by the active site ofCcO

Cu/N/C ORR electrocatalysts inspired by the multinuclear active site of Lac show high ORR activity in neutral and alkaline media but not in acidic media [60, 61, 85]. Such low catalytic activity in acidic media makes their practical application to cathodes in PEFCs difficult. In non-PGM ORR electrocatalysts, Fe/N/C ORR electrocatalysts have been intensively studied and are known to show relatively high ORR activity even in acidic media [1, 2]. The next target to developing practical non-PGM electrocatalysts in bio-inspired approaches would be Fe, Cu, N-doped carbon (Fe/Cu/N/C) electrocatalysts, inspired by the active site of CcO.

Biomimetic models of the active site of CcO have been studied to understand the role of the copper ion in the active site [14, 88]. In the case of simple iron porphyrins, only 5-coordinated FeII centers have a measurable O2 affinity, whereas O2 is not bonded to 4- or 6-coordinated centers, and the formation of the Fe−O2 adduct leads to O−O bond homolysis [88]. The O−O bond homolysis in iron porphyrins produces partially reduced oxygen species (PROS) such as an OH radical or H2O2, leading to the degradation of the catalyst. In contrast, O−O heterolysis occurs in CcO to minimize the production of PROS. CcO is believed to reduce oxygen by four electrons with > 99% selectively [89, 90], where slow electron transfer is rate-limiting [14]. Early electrochemical studies on biomimetic models of the active site of CcO suggest that the presence of the Cu ion gives no impact on the kinetics, stability and rates of the ORR under fast electron transfer regimes, whereas the Cu site works as a one-electron storage site in the limited electron flux [91]. However, recent electrochemical studies of CcO mimics suggest that the Cu site acts as the initial O2 binding site to form bridging heme−peroxo−Cu intermediates and suppresses the release of PROS depending on the experimental condition [92–94].

In Fe/Cu/N/C electrocatalysts, the co-presence of Cu and Fe in N-doped carbon electrocatalysts is also known to show synergistic effects on the ORR activity. A Fe/Cu/N/C electrocatalyst was prepared from the precursor mixture of chloro(protoporphyrinate)iron(III) (hemin), Cu-Hdatrz and oxidized Vulcan XC-72 (oV) in the short-period heat treatment at 1023 K under Ar for 45 s [Figure 13(a)] [95]. The Fe/Cu/N/C electrocatalyst shows higher ORR activity in the wide pH range from 1 to 13 than Fe/N/C and Cu/N/C, which are prepared from precursors of hemin/oV and Cu-Hdatrz/oV, respectively [Figure 13(b, c)]. Such synergistic effects of Fe and Cu for Fe/Cu/N/C prepared from other precursors are also reported on the ORR activity [96–101] as well as the mitigation of hydrogen peroxide yield [101].

The origin of the synergistic effect of Fe and Cu on the ORR activity and the reaction mechanism remains unclear. In a proposed mechanism, Fe3+−4N2 serves as the ORR active site and CuII redox couples shuttle electrons from the electrode to Fe sites during the ORR, resulting in acceleration of the reduction of intermediates of the ORR [98]. Fe and Cu L-edge XAS data of Fe/Cu/N/C reveal the variation of Fe and Cu electronic states toward higher and lower valence states, respectively, compared with Fe/N/C [102]. This result suggests that the interaction between the two metal centers promotes effective charge transfer. However, Fe and Cu K-edge XANES analysis of another Fe/Cu/N/C electrocatalyst shows interactions between Cu and Fe or electron transfer from Cu to Fe [100], which contradicts the L-edge XAS result that is mentioned above. As the reaction mecha-
nism on CeO is discussed, copper ions could interact with oxygen that is bonded to iron sites and then activate it for efficient O–O bond cleavage [103]. Further experimental studies including spectroscopic measurements and kinetic analysis [104] and theoretical studies [97] are needed to gain insights into the synergistic effect and reaction mechanism on Fe/Cu/N/C electrocatalysts.

III. CONCLUSIONS

This review focuses on metalloenzyme-inspired approaches to developing highly active non-PGM electrocatalysts for the ORR. Synthetic non-PGM electrocatalysts have advantages over PGM-based electrocatalysts and/or metalloenzymes: low material costs, small footprints (volume per active site) and tolerance to poisoning chemicals such as CO [105] and KSCN [106]. However, the improvement of the ORR activity and durability [107] of non-PGM electrocatalysts remains challenging despite many papers on them. Recent studies on 3Fe Mössbauer spectroscopy and low-temperature CO pulse chemisorption and temperature-programmed desorption (TPD) of Fe/N/C electrocatalysts revealed their TOFs of ca. 1.4 site s⁻¹ at +0.8 V vs. RHE [108]. This value is one or two orders of magnitudes smaller than those of metalloenzymes: TOFs of ca. 4×10² s⁻¹ for CeO and 20 s⁻¹ for Lac were estimated from catalytic electron transfer rates of > 3×10⁹ M⁻¹ s⁻¹ for CeO [19] and 1.5×10⁴ M⁻¹ s⁻¹ for Lac [109] in an O₂ saturated solution at c O₂ = 1.2×10⁻³ M. It is clear that there is a huge gap between synthetic non-PGM catalysts and metalloenzymes in activity at this moment. In other words, there is still room for drastic improvement of the catalytic activity of synthetic non-PGM electrocatalysts at least up to the enzymatic activity. We believe that bioinspired approaches would be the promising approach to developing next-generation non-PGM electrocatalysts for the ORR.

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