



Computational Study on Docking of Laccase and Cyanide-Bridged Ag-Cu Complex for Designing the Improved Biofuel Cell Cathode

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Abstract

The extrinsic catalytic properties of the laccase enzyme enable it to oxidize a wide range of metallic compounds, making it an essential enzyme for producing biofuel. We have employed computational and experimental approaches while searching cathode materials for biofuel cells composed of laccase and various metal complexes. Laccase is an oxygen-reducing copper enzyme. In this present study, we have focused on the complicated and hybrid systems of enzymes and metal complexes, which are quite different from the single-component system of metal complexes. We have obtained simple and reliable data of steric (crystal) structures and the corresponding electronic (optical, magnetic or electrochemical) properties and interpreted them with the conventional computational methods using the conceptual density functional theory (CDFT) framework. We have also applied some unique computational methods like molecular docking to observe the interaction pattern of laccase and a known cyanide-bridged trinuclear Ag-Cu-Ag complex. Electronic structures of the molecules and the prediction of folding of laccase enzyme were explained by the Fukui function which is supported by laccase-Ag-Cu-Ag complex docking. In this study, we have applied several computational to explore the laccase-metal complex hybrid system. Our findings can be applied in designing new compounds which can be used in growing biofuel and bioremediation industries.

Keywords: Laccase and cyanide-bridged Ag-Cu complex; Fukui function; DFT; Docking; Biofuel cell.

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1. Introduction

Because of multicopper oxidase-based biofuel cells use bio-based catalysts, they have the advantage to generate electricity at room temperature and low environmental load. A mediator that assists the donation and reception of the electron has been

also used for electron transfer between the electrode and laccase to improve electron transfer from cathode to laccase (near the T1 site). Typical examples of cyanide metal complex mediators for multicopper oxidase have been reported. For example, Bilirubin oxidase (BOD) from *Myrothecium verrucata*, a family of multicopper oxidase, with $E^{\circ} = 460$ mV could be mediated by cyanide metal complexes such as $[\text{W}(\text{CN})_8]^{3-/4-}$ ($E^{\circ} = 0.320$ V), $[\text{Os}(\text{CN})_8]^{3-/4-}$ ($E^{\circ} = 0.448$ V), and $[\text{Mo}(\text{CN})_8]^{3-/4-}$ ($E^{\circ} = 0.584$ V). In this way, one-directional electron transfer from cathode to oxygen could be realized generally. In biofuel cell cathode, to improve electron transfer between the electrode and laccase (e.g. from *Trametes versicolor* with $E^{\circ} = 580$ mV), several types of cyanide metal complexes have been investigated as promising mediators beside known good mediators such as $[\text{Cu}(\text{bpy})_3]^{2+}$ or “cyanide-bridged metal complexes” including $[\text{Fe}(\text{CN})_6]^{3-/4-}$.^[1] However, can such one-directional electron flow occurs under certain conditions? Even a mediator complex has the same values of redox potentials under a certain condition, it can also act as an opposite side redox mediator for another enzyme.

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Thus, in addition to “steric” docking factors for the hydrophobic pocket of laccase, an appropriate redox potential due to ‘electronic’ structures may be required. It is necessary to understand the applicability of various calculations when discussing hybrid systems and the three-dimensional and electronic structures of elements in calculations other than experiments.

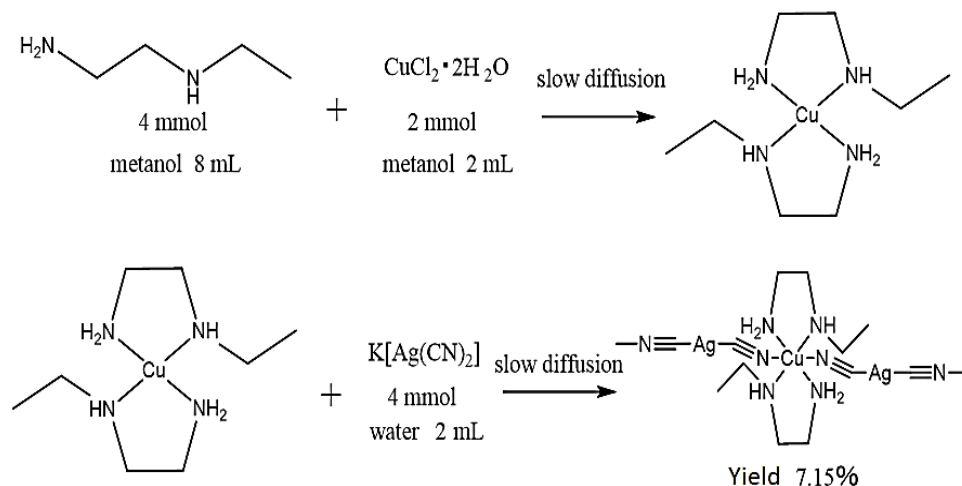
To date, we have systematically investigated for suitable electrochemical and sterical mediators to design electron-transfer improved biofuel cell cathode. Herein, we have referred a trinuclear cyanide-bridged Ag-Cu complex ($[\text{Cu}(\text{N-ethylethylenediamine})_2][\text{Ag}(\text{CN})_2]_2$)^[2] as a mediator of laccase and computational methods will be applied to validate the experimental findings. To improve electron transfer between the electrode and laccase, several types of metal complexes were investigated as mediators. In contrast to direct electron transfer, a mediator of metal complexes has advantage to conduct much current (an electrochemical feature) regardless of long-distance electron transfer required (a steric feature). Molecular docking of suitable compounds (both ligands and complexes) to the hydrophobic pocket of laccase is useful to predict the distance or path of electron transfer and their effectivity in biofuel cells. For such hydrophobic weak interactions, induced chirality (namely characteristic CD bands) from chiral (asymmetric) protein matrix proteins sometimes play a useful role in evaluating a supramolecular interaction even for achiral guests. In this way, we have also investigated some candidates of metal complexes for the mediator from several viewpoints. However, detailed comparison has not been carried out using suitable systems to date. Thus, we have tested various laccase/cyanide metal complexes as mediators and all complexes were examined and compared with various spectral measurements, electrochemical measurements, DFT (density functional theory) or protein-ligand docking calculations, etc.

2. Experimental section

We experimentally constructed the hybrid material of protein

and metal complex that is the subject of the present computational study. Since the components (laccase and a metal complex) are known substances, we only obtained characteristic experimental data for the purpose of confirmation (namely, changes before and after docking). Docking and redox behaviour could be confirmed similar to the related examples. Synthesis, crystal structure and characterization of a trinuclear cyanide-bridged Ag-Cu complex ($[\text{Cu}(\text{N-ethylethylenediamine})_2][\text{Ag}(\text{CN})_2]_2$) have been already illustrated in previous report^[2] as per given scheme below (Scheme 1). Preparation (yield: 7.15 %) was confirmed with IR [JASCO FT-IR 4200] spectra (2124 cm^{-1} for $\text{C}\equiv\text{N}$ band). According to the crystal structure, the complex has an octahedral geometry around the Cu centre (typically just like computational results) and it also afforded linear Ag-Cu-Ag structure exhibiting Jahn-Teller distortion. (Fig. 1a).

Docking of commercially available laccase from *Trametes versicolor* (confirmed similar folding features with Alfold2 based on crystal structure provided as PDB 1GYC) (Fig. 1b) and the complex were carried out in a similar procedure to the related linear cyanide-bridged Cu-M bimetallic coordination polymers^[1] and confirmed newly with Q-band ESR [JEOL JES-FA200] at 273 K ($g = 2.01$ for Cu-Ag complex and 2.064 for Cu-Ag complex and laccase), CV [BAS ALS DY2323] for Cu-Ag complex and laccase ($E^0 = 0.406; -0.237, -0.821\text{ V}$ Ag/AgCl), and UV-vis [JASCO V-560] and quenching of fluorescence [JASCO FP-6200] at 273 K as phosphate buffer solutions (Fig. 1c). As increasing the amount of added Cu-Ag complex detected with UV-vis spectra without refolding of laccase (Fig. 1d), decreasing of fluorescence intensity obeying Stern-Volmer equation suggested that docking of Cu-Ag complex into laccase molecule's specific sites on the surface quantitatively. It is becoming clear that even in cyanide-bridged complexes, small ones like the present one are included in as mediators, while large coordination polymers may potentially act in direct electron transfer. Electrochemical behaviour of laccase-complex composite (Fig. 1e) indicated that Cu-Ag complex could act as mediator between electrode



Scheme 1. Synthetic scheme for the preparation of $[\text{Cu}(\text{N-ethylethylenediamine})_2][\text{Ag}(\text{CN})_2]_2$ complex from N-ethylethylenediamine, copper(II) chloride dihydrate and potassium bis(cyanido) silver(I).

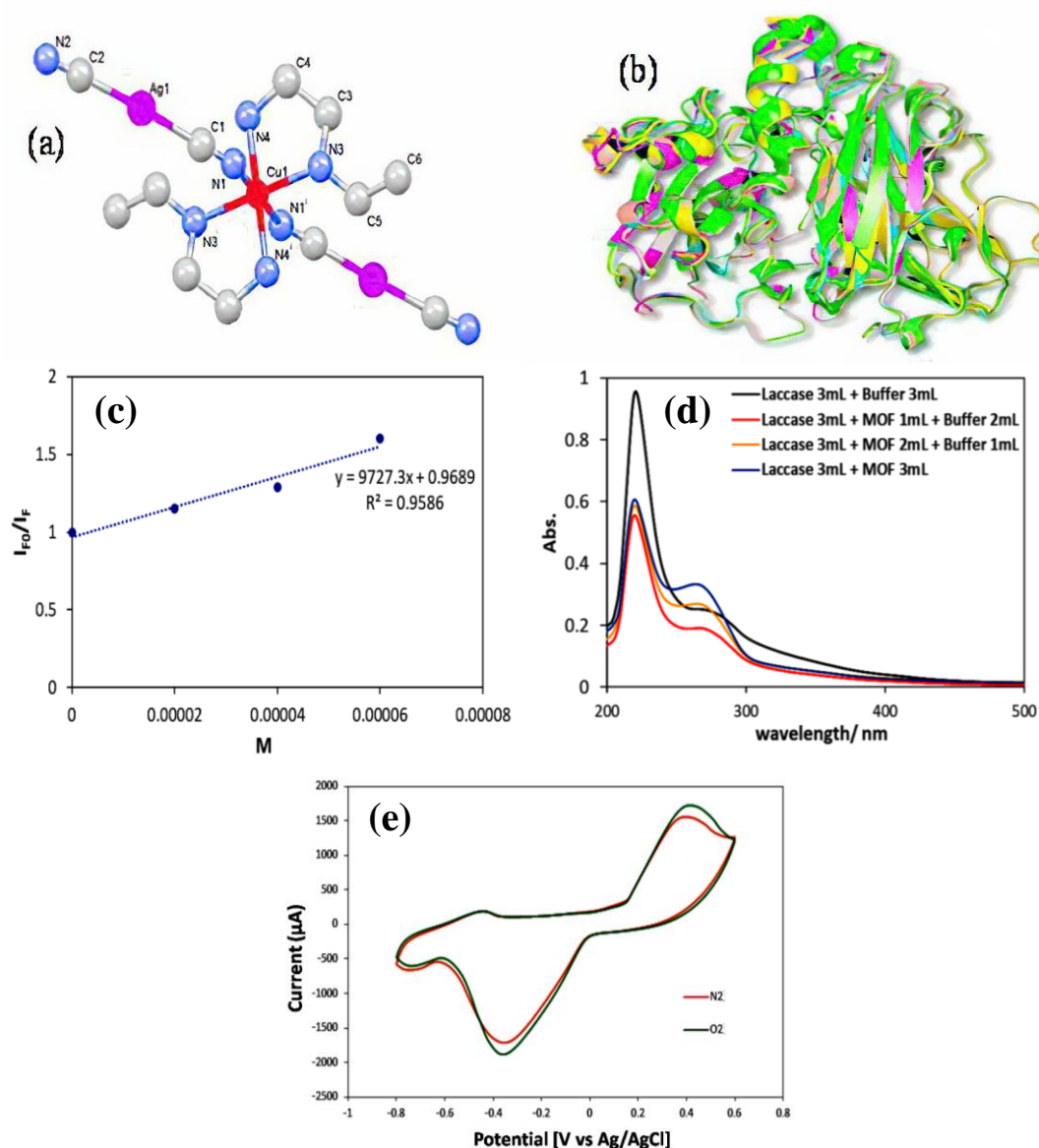


Fig. 1 (a) Crystal structure of complex,^[2] of which Cu atom affords tetragonally elongated octahedral geometry due to Jahn-Teller distortion, while Ag affords a linear geometry. (b) 3D structure of laccase by AlphaFold2, (c) Stern-Volmer plots of laccase (340 nm) for various concentration of complex, (d) UV-vis spectral changes of addition of solution of complex (MOF) into laccase corresponding to (c) and (e) CV for laccase-complex composite under N_2 and O_2 atmosphere.

and laccase. Laccase occurs four-electron reduction reactions of molecular oxygen by providing electron from the mediator, which was proved by comparison of nitrogen and oxygen purged solutions.

3. Computational Study

Conceptual density functional theory (CDFT)^[3-6] is a well-developed theory to find the stability and reactivity of the molecules. In CDFT there are local and global reactivity descriptors, which can describe the global (hardness, electrophilicity)^[5,6-8] and local (Fukui function, dual descriptor)^[9-14] properties of the molecules. To calculate the reactivity parameters, we first optimized all the studied molecules to obtain their ground state geometry with Gaussian 16 software package.^[15] All the geometries of the molecules

were optimized in the B3LYP/DEF2TZVP level of theory.^[16-18] Vibrational frequency analysis have also been carried out^[19-22] to ensure the true minima on the potential energy surface by using the same basis set and level of theory. The optimized structure and dual descriptor $\Delta f(r)$ from FMOs (Frontier molecular orbitals) of the complex are portrayed in Fig. 2 and Fig. 3 respectively. Local reactivity descriptors can be expressed with Fukui function ($f_k^{+/-}$)^[11,12] where (f_k) (Equation 1) identify the electrophilic centre (f_k^+) (Equation 2) identify the nucleophilic attacking atomic centre within the molecule and similarly dual descriptor $\Delta f(r)$ ^[13,14] (Equation 3) represents the nucleophilic region and electrophilic region of the molecules. They can be calculated by using the following equations.^[11-14]

Fukui function for electrophilic attack,

$$f_k^- = q_N^k - q_{N-1}^k \quad (1)$$

Fukui function for nucleophilic attack,

$$f_k^+ = q_{N+1}^k - q_N^k \quad (2)$$

where q_N^k , q_{N-1}^k , q_{N+1}^k are the atomic charge of neutral, cation, and anionic systems of the site atom k.

$$\text{Dual descriptor } (\Delta f(r)) = f_k^+ - f_k^- \quad (3)$$

If the $\Delta f = +$ ive, *i.e.* the site atom is favoured for nucleophilic attack. If the $\Delta f = -$ ive; which indicates that the site atom is favoured for an electrophilic attack.

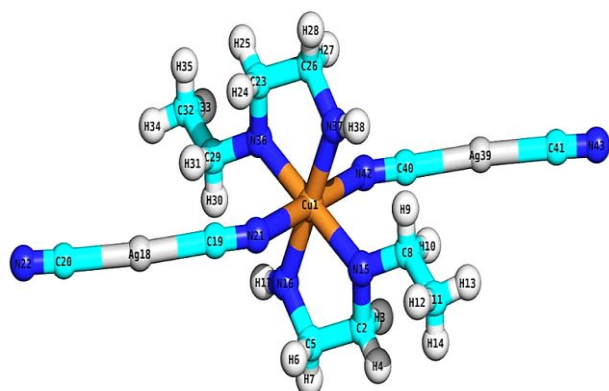


Fig. 2 Ground State geometry of the Cu-complex with Energy (E) = -2841.913 Hartree (at B3LYP/DEF2TZVP level of theory).

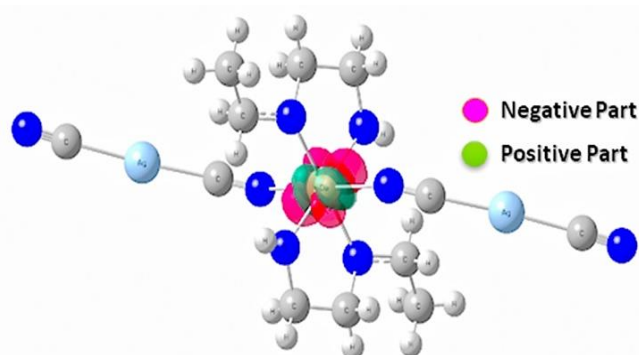


Fig. 3 Dual descriptor $\Delta f(r)$ from FMOs (Frontier molecular orbitals) of the complex. The pink colour represents the nucleophilic region and green represents the electrophilic region of the molecules [At 0.002 isovalue].

4. Virtual screening of copper complex

The Three-Dimensional (3D) structure of Fungus *Trametes versicolor* laccase (PDB id: 1GYC) was obtained from RCSB database.^[23] The structure of the ligand (copper complex) was obtained from CSD. 3D optimization was carried out using density functional theory (DFT) with the help of Gaussian 16 and Gauss View 6.0 packages.^[15] The 3D optimized (Fig. 2) structure was acquired for docking by adding Gasteiger charge, detecting routes and selecting torsion from the torsion tree of

the Autodock Tools panel.^[24-27] Water from Laccase protein file has been removed, bound ligand to the protein structure has been deleted and hydrogens added to the protein structure in order to make Laccase structure compatible for docking with help of Autodock Tools. Center Grid box x: 27.338, y:14.893 9.456, z:36.161 and number of points in x,y,z dimensions are measured as $30 \times 30 \times 30 \text{ \AA}^3$ respectively and grid spacing has been taken as 0.3750 \AA . Docking process has been executed by using Lamarckian genetic algorithm.^[28]

5. Result & discussion

Experimental data obtained can be explained as follows. The crystal structure of the trinuclear Cu-Ag complex revealed the size of the mediator, which may be possible to fit so-called "Hydrophobic pocket" on the surface around the T1 copper site of the laccase. Therefore, "mediated electron transfer" mechanism may be possible according to steric factors. In addition, steric factor, namely approaching mediator and laccase, is also supported by clear quenching of fluorescence spectra (Fig. 1c) and the corresponding UV-vis spectra (Fig. 1d). Although Ag(I) is not redox active in general, at least Cu(II) ion of the Cu-Ag complex play an important role of the redox reaction to give electrons to the T1 copper site of the laccase. Such redox behaviour can be expected according to CV data (Fig. 1e). Initial electronic states of Cu(II) of d^9 configuration was also elucidated by ESR and UV-vis spectra (Fig. 1d). In this way, such systems should be discussed by using computational methods furthermore in the following part of this section. From Table 1, it is shown that the dual descriptor (Δf_k) of metal centre Cu is positive, which indicates that the centre is electrophilic in nature and it is favourable for nucleophilic attack. However, this value is almost zero. Further, to confirm the reactivity of the metal centre in Cu-complex, we have employed dual descriptor $\Delta f(r)$ from FMOs (Frontier molecular orbitals) approach.^[13,14] It can be calculated from the densities of frontier molecular orbitals as:

$$\Delta f(r) = \rho_{Lumo(r)} - \rho_{Homo(r)} \quad (4)$$

From Fig. 3, it has been proved that the metal center of the complex shows both nucleophilic as well as electrophilic characters.

Docking of metal complexes has been performed out with AutoDock 4.2.6 on the windows platform. Copper complex showed the docking score of -8.5 kcal/mol when bind with laccase. Fig. 4a shows that amino acids surround copper complex and it can be assured that the complex was bound to domain three, near T1 site [type-1 (T1) copper], of the *T. versicolor* laccase.^[29] The seven hydrogen bonds and twelve hydrophobic bonds (Table 2) between laccase and copper

Table 1. Calculated f_k^+ , f_k^- , Δf_k of site atom (k) in the Cu-complex.

Site atom (k)	Cu-1	N-15	N-16	N-21	N-36	N-37	N-42
f_k^+ (au)	0.019	-0.046	-0.089	0.023	-0.025	-0.305	0.013
f_k^- (au)	-0.011	-0.072	-0.064	-0.028	-0.093	0.152	-0.017
Δf_k (au)	0.03	0.026	-0.025	0.051	0.068	-0.457	0.03

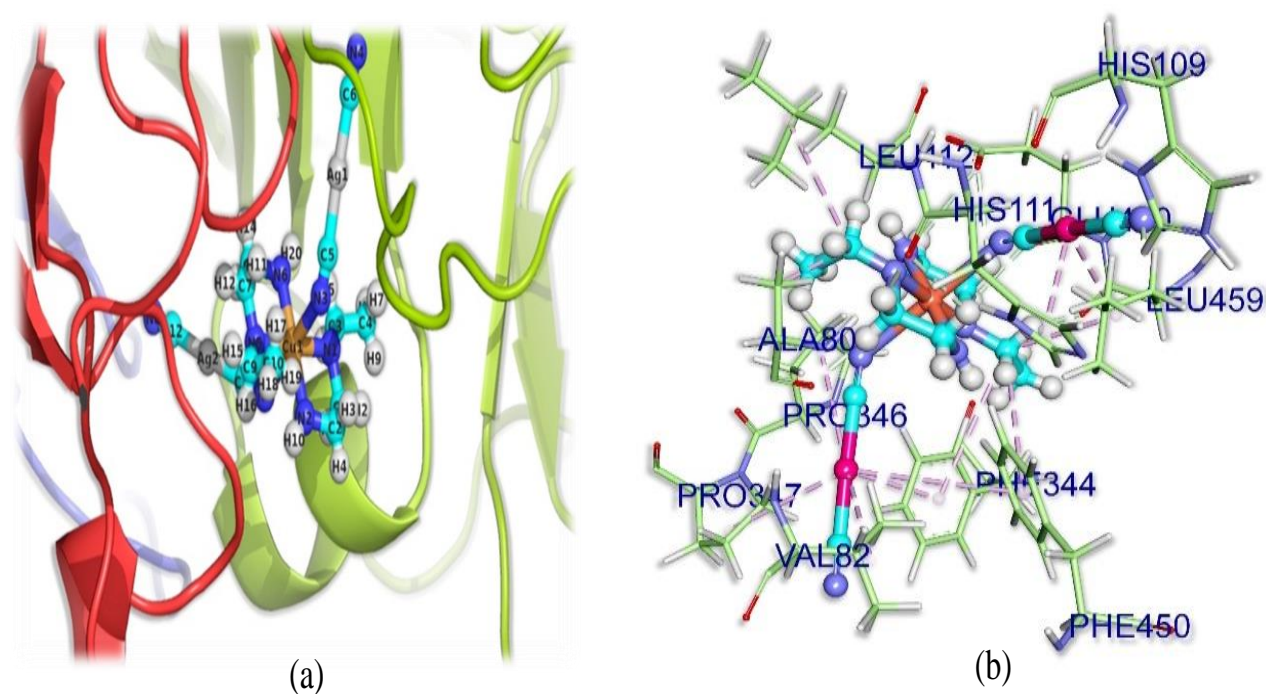


Fig. 4 Comprehensive perception of laccase (receptor) and copper complex (ligand) interaction after docking. (a) The copper complex was docked in the active site of the laccase receptor. The ribbon model represents the laccase receptor's ribbon structure, and The arrangement of the domain structure is depicted in different colour coding (D1–D3), blue represents D1 red represents D2 and green represents D3; (b) Interactions of ligand with laccase receptor amino acids omitting laccase receptor, with ligand surrounding amino acids in three-letter-code represented.

complex confirm that the copper complex has a strong affinity toward laccase. **Fig. 4b** shows the interactions of ligand with laccase receptor amino acids omitting laccase receptor, with

ligand surrounding amino acids in three-letter-code represented.

Table 2. Bond distances and type between laccase receptor and copper complex.

Bond Name	Distance (Å)	Bond category	Bond type
P:CU-COMPLEX :H12 - A:HIS111:O	1.91019	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H11 - A:ALA80:O	1.94504	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H6 - A:LEU459:O	2.3027	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H1 - A:GLU460:OE1	2.84563	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H4 - A:GLU460:OE1	2.85674	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H13 - A:HIS111:O	2.88832	Hydrogen Bond	Carbon Hydrogen Bond
P:CU-COMPLEX :H2 - A:GLU460:O	2.95319	Hydrogen Bond	Carbon Hydrogen Bond
A:ALA80 - P:CU-COMPLEX :C9	3.1420	Hydrophobic	Alkyl
A:PHE344 - P:CU-COMPLEX	3.49947	Hydrophobic	Pi-Alkyl
P:CU-COMPLEX :C3 - A:LEU459	3.72380	Hydrophobic	Alkyl
A:HIS111 - P:CU-COMPLEX	3.88691	Hydrophobic	Pi-Alkyl
P:CU-COMPLEX - A:LEU459	3.95107	Hydrophobic	Alkyl
P:CU-COMPLEX :C9 - A:LEU112	4.08295	Hydrophobic	Alkyl
A:PRO347 - P:CU-COMPLEX	4.34041	Hydrophobic	Alkyl
A:VAL82 - P:CU-COMPLEX	4.43211	Hydrophobic	Alkyl
A:PRO346 - P:CU-COMPLEX	4.46944	Hydrophobic	Alkyl
A:PHE344 - P:CU-COMPLEX :C3	4.71718	Hydrophobic	Pi-Alkyl
A:PHE450 - P:CU-COMPLEX	5.36629	Hydrophobic	Pi-Alkyl
A:PHE450 - P:CU-COMPLEX :C3	5.47244	Hydrophobic	Pi-Alkyl

6. Conclusion

In the previous summary,^[1] we measured the fluorescence, ESR, and CV of the complex alone and with laccase from *C. versicolor* before and after docking and correlated with the observed data to confirm whether the enzyme can function as an oxygen reduction catalyst. In fluorescence study, four different concentration solutions of the Ag-Cu complex were used and fluorescence quenching was observed reasonably. There was no noticeable difference in the three-dimensional structure of Alpha Fold and PDB. Furthermore, DFT calculation using the Fukui function shows that the metal centre of the complex shows both nucleophilic as well as electrophilic character and docking studies provides good results which support the previous experimental findings. The copper complex has a strong affinity towards laccase and so form a strong binding, it can act as a good redox complex, and as mediator to improve electron transfer between cathode and laccase enzyme, and can be useful to configure biofuel cells. It is still difficult to reproduce and interpret the simple combination of individual elements and the effects to the interaction by the theoretical calculation; however we have tried to correlate the experimental findings by computational data beyond the accuracy of each individual; however, the newly synthesized material (laccase and cyanide-bridged Ag-Cu complex) can be widely used as electron-transfer improved biofuel cell cathode with a mediator.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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