Proton switch for modulating oxygen reduction by a copper electrocatalyst embedded in a hybrid bilayer membrane

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1. Synthetic Procedures

General Methods

All reactions were carried out under a dry nitrogen atmosphere. Chemicals were purchased from Sigma-Aldrich and used without further purification. Dry dichloromethane (DCM), and dimethyl sulfoxide (DMSO) were used directly from a solvent delivery system just prior to use. Freshly purchased triethylamine (TEA) was dried and stored over 4 Å molecular sieves. All other solvents were of reagent grade and used without further purification. Reported reaction temperatures refer to the temperature of the heating medium. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) using 0.2 mm silica 60 coated, plastic plates with F254 indicator purchased from EM Science. Flash and gravity chromatography was performed using either Ultra PureSiliaFlash® P60 230-400 mesh (40-63 μm) silica gel (SiO2).

NMR spectra were performed in chloroform-d and acquired using a Varian Unity 500 MHz instrument in the VOICE laboratory, University of Illinois at Urbana-Champaign. Chemical shifts (δ) and coupling constants (J) are reported in parts per million (ppm) and hertz (Hz), respectively. For 1H spectra, chemical shifts are referenced to the residual proton solvent peak: 7.26 ppm for chloroform-d. For 13C spectra, chemical shifts are referenced to the solvent peak at 77.5 ppm in chloroform-d. Electrospray ionization mass spectrometry (ESI-MS) data were collected with a Quattro II instrument (Waters) at the University of Illinois at Urbana-Champaign.
Synthetic procedures are shown schematically in Fig. S1.

6-(Tritylthio)hexan-1-ol (1) was prepared using a literature procedure. Trityl chloride (2.78 g, 10 mmol) in DCM (50 mL) was added dropwise to a stirred solution of 6-mercapto-hexan-1-ol (2 mL, 15 mmol) in DCM (20 mL) over 30 min at room temperature. The mixture was stirred for 30 min and washed with an aqueous solution of NaOH (0.1 M). The organic layer was dried over anhydrous Na₂SO₄, gravity filtered, and concentrated in vacuo. Flash chromatography with a step gradient from 9:1 (v:v) to 3:1 (v:v) hexane:EtOAc afforded 3.2 g (85%) of 1 as a white solid. \( \delta \) 7.45 – 7.15 (m, 15H), 3.58 (t, \( J = 6.6 \), 2H), 2.15 (t, \( J = 7.3 \), 2H), 1.48 (m, 2H), 1.40 (m, 2H), 1.26 (m, 5H); ESI-LRMS calcd. for \((C_{25}H_{28}OS·H)^+\) 377.2, found 377.2.

6-(Tritylthio)hexanal (2) was prepared according to a previously reported procedure for a similar compound. A solution of oxalyl chloride (350 mg, 2.8 mmol) in DCM (6 mL) was cooled to –78 °C. A mixture of DMSO (430 mg, 5.5 mmol) and DCM (2.5 mL) was added dropwise. The resulting mixture was stirred for 5 min, and 6-(tritylthio)hexan-1-ol (1) (940 mg, 2.5 mmol) dissolved in DCM (1 mL) was added dropwise. The solution was stirred for 15 min, and TEA (1.27 g, 12.5 mmol) was added. The mixture was allowed to warm to room temperature and washed with an aqueous solution of HCl (1 M, 10 mL). The aqueous layer was extracted with DCM (3×10 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, gravity filtered, and concentrated in vacuo to yield 908 mg (97%) of 2 as a colorless oil. \( \delta \) 9.71 (s, 1H), 7.45 – 7.15 (m, 15H), 2.34 (t, \( J = 7.5 \), 2H), 2.15 (t, \( J = 7.5 \), 2H), 1.49 (m, 2H), 1.39 (m, 2H), 1.27 (m, 2H); ESI-LRMS calcd. for \((C_{25}H_{26}OS·H)^+\) 375.2, found 375.2.
**N^3-(6-(Tritylthio)hexyl)-4H-1,2,4-triazole-3,5-diamine (3).** A mixture of 6-(tritylthio)hexanal (2) (600 mg, 1.6 mmol) and 1,2,4-triazole-3,5-diamine (300 mg, 3.3 mmol) in EtOH (10 mL) was stirred at room temperature for 5 h. Sodium borohydride (100 mg, 2.6 mmol) was added, and the resulting suspension was stirred for an 1 h at room temperature. The reaction was quenched by adding water (0.5 mL) and concentrated under vacuum to yield a white solid. The solid was dissolved in DCM (10 mL) and washed with brine (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, gravity filtered, and concentrated in vacuo. Gravity chromatography with a step gradient from 19:1 (v:v) to 9:1 (v:v) DCM:MeOH afforded 124 mg (17%) of 3 as a white solid estimated by NMR to be ~90% pure. ¹H NMR: δ 7.45 – 7.15 (m, 15H), 3.10 (t, J = 7.0, 2H), 2.13 (t, J = 7.0, 2H), 1.47 (m, 2H), 1.37 (m, 2H), 1.22 (m, 4H); ESI-LRMS calcd. for (C₂₇H₃₂N₅S·H)+ 458.2, found 458.2.

**N^3-Benzyl-N^5-(6-(tritylthio)hexyl)-4H-1,2,4-triazole-3,5-diamine (4).** A mixture of N^3-(6-(tritylthio)hexyl)-4H-1,2,4-triazole-3,5-diamine (120 mg, 0.26 mmol) and benzaldehyde (60 mg, 0.57 mmol) in 3:1 (v:v) EtOH:DCM (4 mL) was stirred at 40 °C for 12 h. Sodium borohydride (50 mg, 1.3 mmol) was then added, and the suspension was stirred for 1 h at room temperature. The reaction was quenched by adding water (0.3 mL) and concentrated under vacuum to yield a white solid. The solid was dissolved in DCM (10 mL) and washed with brine (2 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄, gravity filtered, and concentrated in vacuo. Gravity chromatography with a step gradient from 49:1 (v:v) to 19:1 (v:v) DCM:MeOH afforded 20 mg (14%) of 4 as a white solid. ¹H NMR: δ 7.45 – 7.15 (m, 20H), 4.67 (b, 1H), 4.37 (d, J = 5.5, 2H), 4.19 (b, 1H), 3.07 (m, 3H), 2.12 (t, J = 7.5, 2H), 1.46 (m, 2H), 1.37 (m, 2H), 1.22 (m,
$^1$H; $^13$C NMR: δ 145.2, 129.8, 128.9, 128.0, 127.7, 127.5, 126.8, 66.6, 47.7, 43.6, 32.1, 29.7, 28.7, 26.6; ESI-HRMS calcd. for (C$_{34}$H$_{37}$N$_5$S·H)$^+$ 548.2848, found 548.2842.
2. NMR Spectra

$^1$H NMR of 1:

$^1$H NMR of 2:
$^1$H NMR of 3:

![NMR spectrum of 3](image)

$^1$H NMR of 4:

![NMR spectrum of 4](image)
$^{13}$C NMR of 4:
3. STM Procedures

STM measurements were carried out using a Nanoscope III E (Digital Instrument Corporation) system under ambient conditions. STM tips were prepared by electrochemical etching of tungsten wire (0.25 mm in diameter) in 2.0 M NaOH. The tips were then rinsed with water and dried under a gentle stream of Ar. STM images were acquired using constant current mode with a tunneling current of 3.0 nA and a tip bias of 50 mV. Mean roughness values were calculated using WSxM 5.0 Develop 6.4 software.
4. Ellipsometric Procedures

Ellipsometry was performed using a Gaertner Ellipsometer L116C equipped with a He-Ne laser (632.8 nm) set at an incidence angle of 70°. An average of four measurements was used, each of which was taken at a different spot on the Au electrodes. A two-layer transparent film model was used for the thickness calculations based on pseudosubstrate constants measured on clean Au substrates. The refractive index of the organic SAM film was fixed at 1.5.
5. Cu Coverage Calculations

The cross-sectional area calculated with Spartan ’08 (Wavefunction, Inc.) v. 1.2.0 of a Cu complex of BTT with coordinated EtOH molecules is 350 Å². Assuming a smooth Au surface, the surface coverage based upon this area is $4.7 \times 10^{-11}$ mol cm$^{-2}$, which is comparable to the experimentally observed Cu coverage.
6. O₂ Diffusion Calculations

O₂ has a partition coefficient of greater than 2 in DMPC relative to water at 25 °C.³ The diffusion coefficient of O₂ at 25 °C in a DMPC bilayer is $1.8 \times 10^{-5}$ cm²/s,⁴ which is comparable to that of water ($1.9 \times 10^{-5}$ cm²/s).⁵ The time required for a molecule of O₂ to diffuse through 21 Å (the experimental length of the lipid layer as determined by ellipsometry) of the HBM can be calculated using equation (1) and is less than 2 ns.⁶ The experimental time scales are in the range of 1 s.

$$t = \frac{\langle x \rangle^2 \pi}{4D} \quad (1)$$

where $D$ is the diffusion coefficient of O₂ in DMPC, $\langle x \rangle$ is the average distance traveled by an O₂ molecule, and $t$ is the time elapsed.

O₂ has a partition coefficient of 0.4 in DMPC relative to water at 10 °C.³ Using this partition coefficient, the diffusion coefficient of O₂ at 10 °C in a DMPC bilayer is calculated to be $2.5 \times 10^{-5}$ cm²/s using the method described by Hyde and Subczynski.⁷

Given the partition coefficient of O₂ between DMPC and water and that the solubility of O₂ in water is 0.24 mM at 25 °C,⁸ the concentration of O₂ in the HBM is estimated to be 0.48 mM. The cross-sectional area calculated with Spartan ’08 of a DMPC and a MDP molecule is 65 Å². The experimental length of the HBM as determined by ellipsometry is 42 Å. Assuming 1 equivalent of MDP relative to DMPC and using the Henderson-Hasselbalch equation, the equilibrium concentration of MDP existing as RH₂PO₄ inside the HBM is 3.8 mM at pH 5 and 0.038 mM at pH 7. We note that these calculated values are equilibrium values describing how MDP exists at the lipid-water interface in the absence of catalysis, and do not take into account the rate of flip-flop diffusion of MDP through the DMPC layer.
7. Figures

Figure S1. Synthesis of BTT.

![Chemical diagram of BTT synthesis](image)

**Figure S2.** Linear sweep voltammograms of O₂ reduction by a bare Au surface (orange) and a BTT SAM on Au (black) in pH 7 buffer solution at a scan rate of 10 mV/s at 26 °C.
Figure S3. Representative scanning tunneling microscopy images of surfaces of bare Au (a), BTT on Au (b), and the Cu complex of BTT on Au (c). The average roughness across five images was (1.50 ± 0.41) nm for bare Au, (1.74 ± 0.86) nm for BTT on Au, and (1.43 ± 0.51) nm for the Cu complex of BTT on Au.
Figure S4. Modeling of ellipsometric measurements of a BTT SAM, a SAM of the Cu complex, and the HBM containing the Cu complex on Au. The film thicknesses obtained match with theoretical modeling and literature values. Theoretical modeling was accomplished using Spartan '08 v. 1.2.0 (Wavefunction, Inc.). We hypothesize that the BTT SAM is not fully extended so that the phenyl rings can participate in favorable π-π stacking interactions. Upon addition of Cu, the complex is more rigid, and the phenyl rings are fully extended.
Figure S5. Rotating ring-disk linear sweep voltammograms (solid) and ring currents (dash) of the Cu complex of BTT on Au (blue) and a bare Au surface (orange) in pH 5 buffer solution sparged with O₂ at a scan rate of 10 mV/s at 26 °C.

Figure S6. Cyclic voltammograms at 26 °C of a BTT SAM (a, black) and a SAM of the Cu complex (a, blue) in pH 7 buffer solution sparged with Ar at a scan rate of 100 mV/s and the Cu complex of BTT (b) in KCl (100 mM) solution sparged with Ar at a scan rate of 10 mV/s.
Supplementary Information

**Figure S7.** Cyclic voltammograms of a bare glassy carbon electrode (black), DAT (orange), and protected BTT (4, purple) in an ethanolic solution containing LiClO₄ (100 mM) at a scan rate of 100 mV/s at 26 °C.

**Figure S8.** Cyclic voltammograms of a SAM of the Cu complex (blue), the HBM containing the Cu complex (red), and the HBM containing the Cu complex with 1 equivalent of MDP incorporated in the lipid layer (green) in pH 7 buffer solution sparged with Ar at a scan rate of 100 mV/s at 26 °C.
Figure S9. Electrospray ionization-mass spectrometry of DMPC and MDP extracted with EtOH and CHCl₃ from a HBM after O₂ reduction.
**Figure S10.** Linear sweep voltammograms of O₂ reduction by a SAM of the Cu complex at 10 °C (blue), the HBM containing the Cu complex with DMPC only in the lipid layer at 10 °C (red), and the HBM containing the Cu complex with 1 equivalent of MDP incorporated in the lipid layer kept at 10 °C for 30 min and then ran at 26 °C (green) on Au in pH 5 buffer solution at a scan rate of 10 mV/s.

**Figure S11.** Cyclic voltammograms of a SAM of the Cu complex (blue), the HBM containing the Cu complex (red), and the HBM containing the Cu complex with 1 equivalent of MDP incorporated in the lipid layer (green) in a solution of K₃Fe(CN)₆ (1 mM) with KCl (100 mM) at a scan rate of 50 mV/s at 26 °C.
Figure S12. Chronoamperometry at 26 °C of the Cu complex of BTT on Au with lipid (black) and lipid with MDP (red) at −0.5 V starting in pH 7 buffer solution sparged with O₂. For Figure S12a, pH 7 buffer solution (1), acid (2), and base (3) were added after 30, 60, and 90 s respectively. For Figure S12b, pH 7 buffer solution (1), pH 7 buffer solution (2), and acid (3) were added after 30, 60, and 90 s respectively.
8. References


