

Reusable Cyclodextrin-Based Electrochemical Platform for Detection of *trans*-Resveratrol

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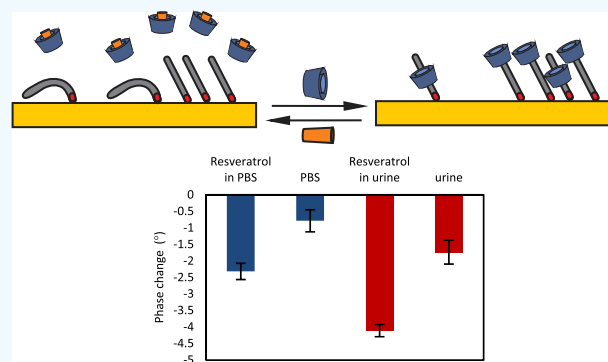
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ABSTRACT: A reusable sensor architecture, through the combination of self-assembled monolayers and cyclodextrin supramolecular interactions, is demonstrated for class recognition of hydrophobic analytes demonstrated with *trans*-resveratrol. The reloadable sensor is based on the reversible immobilization of α -cyclodextrin on the polyethylene glycol surface. α -Cyclodextrin complexes with polyethylene glycols and causes the polymer chains to change their surface configuration. The reproducibility and stability of the surface, in the detection of nanomolar concentrations of *trans*-resveratrol, can be demonstrated by electrochemical impedance spectroscopy, X-ray photoelectron spectroscopy, and attenuated total reflectance–Fourier transform infrared spectroscopy. We propose that during sensor operation, α -cyclodextrin decouples from the poly-ethylene glycol surface to complex with *trans*-resveratrol in solution, and after use, the surface regeneration is conducted with a simple α -cyclodextrin soak. To test the nonspecific response, the sensor was also tested with *trans*-resveratrol-spiked human urine.

KEYWORDS: biosensor, cyclodextrin (CD), electrochemical impedance spectroscopy (EIS), hydrophobic analytes, resveratrol



1. INTRODUCTION

Reusable sensors are critical in applications where automated in-process analyte sensing is essential, as in environmental screening,¹ cellular monitoring,² food monitoring,³ and biopharmaceutical applications.^{4,5} A reusable sensor surface would reduce material and reagent costs, and, once an appropriate calibration curve is obtained, it can be applied for subsequent sample screenings.^{6,7} In recent years, different strategies have been directed toward the development of reusable aptamer-based sensors and immunosorbent surfaces, although the restoration to the appropriate original antibody orientation and function is difficult after multiple uses.⁸

In engineering processes, hydrophobic content can indicate process efficiency or disruptions in the purity of the final product that are of interest for real-time monitoring. Water purification processes remove organic or inorganic chemical impurities and endotoxins with a roughly hydrophobic lipopolysaccharide constituent.^{9–11} Cellular and metabolic engineering processes monitor proteins and cellular secretions; most cell secretions are soluble, but some proteins exhibit hydrophobic functionalities. Moreover, pharmaceutical processes optimize drug-loading processes based on active pharmaceutical ingredient chemical and physical properties (*i.e.*, hydrophobicity and solubility) and drug dissolution.^{12,13} Thus, real-time monitoring of hydrophobic content would contribute to an increase in process efficiency and final product quality. Among hydrophobic molecules of interest, *trans*-

resveratrol offers ideal characteristics for a model analyte to evaluate the sensitivity and selectivity of the proposed sensor; *trans*-resveratrol is largely hydrophobic with a strong association to α -cyclodextrin (α CD), being the functional component of the proposed class recognition hydrophobic analyte sensor.

Animal studies and preliminary clinical trials have shown the effect of *trans*-resveratrol on general health maintenance and prevention of various diseases and disorders.^{14–16} Although, because of rapid metabolism and poor bioavailability many of the promising health-promoting effects of *trans*-resveratrol in animal models have not yet been confirmed in humans, and *trans*-resveratrol is currently not prescribed for the treatment of any human disease.^{15,16} Previous clinical studies indicate that nanomolar range of *trans*-resveratrol sensing is necessary for pharmacokinetics, bioavailability, and metabolite studies of *trans*-resveratrol in humans.^{15,17}

CDs are cyclic compounds composed of a hydrophobic inner cavity and a hydrophilic surface, and they are used in various applications including drug delivery and sensors.^{18–20}

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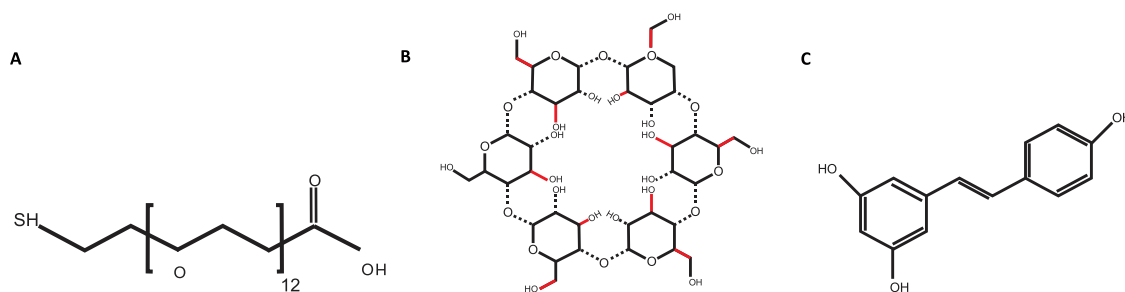


Figure 1. Chemical structures of the reusable sensor compounds and *trans*-resveratrol, the model hydrophobic analyte. (A) Carboxy-PEG₁₂-thiol [CT(PEG)₁₂] (B) α CD (C) *trans*-resveratrol.

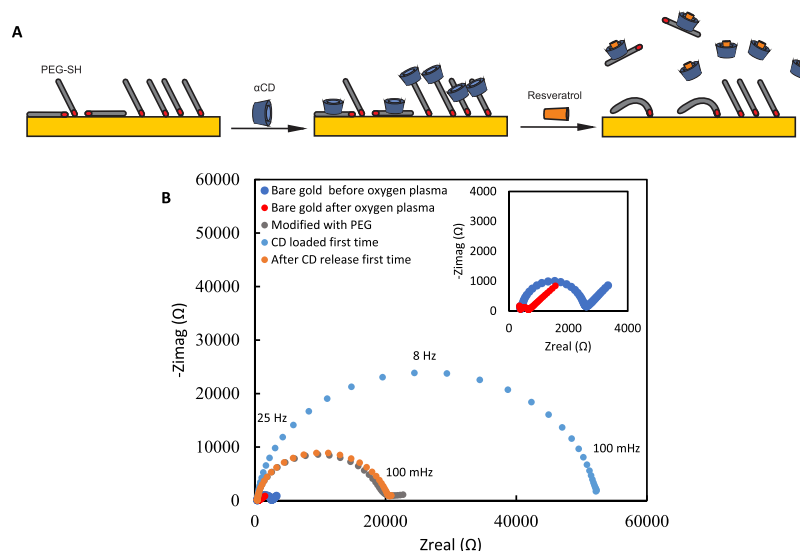


Figure 2. Developing a sensor for *trans*-resveratrol detection: (left) schematic representation of surface PEG modification, (middle) the first α CD loading, and (right) the first α CD release by *trans*-resveratrol. (B) EIS Nyquist plots in 20 mM ferri/ferrocyanide in deionized water after each modification step. After α CD loading, the impedance increased due to the formation of an α CD layer on physisorbed PEG. α CD release was after exposure to 160 nM *trans*-resveratrol in PBS.

CDs can capture various organic and inorganic hydrophobic molecules into their cavity by reversible binding, which makes them promising candidates for use as hydrophobic recognition elements in our sensor development. α CD is the most appropriate receptor for the determination of *trans*-resveratrol.²¹ A CD-modified glassy carbon electrode for *trans*-resveratrol detection has been engineered for single-use applications; *trans*-resveratrol adsorbed strongly to the surface and could not be removed by polishing or cleaning the electrode.²¹ Other CD–metal surfaces, such as CD self-assembled monolayers with thiolated CDs or CD surface free-radical polymerization, are also single-use due to strong analyte complexation, and the surface needs to be abated or polished for reuse applications.^{22–25}

Reusable CD surfaces will enable future scientists to work on commercial sensors capable of continuous class-recognition detection of various hydrophobic analytes in aqueous solutions for point-of-need applications. To improve the reusability of the sensor, we propose to use a weak surface CD mediator: surface-bound polyethylene glycol (PEG). A gold surface can be modified with carboxy-PEG₁₂-thiol (PEG-SH) via thiol chemistry. After PEG modification, the surface is thoroughly washed with water to remove any nonspecific bindings, leaving adsorbed and covalently bound PEG. α CD forms inclusion complexes with PEG if the molecular weight is higher than 200.^{26,27} A single α CD molecule is estimated for every two

CH₂–O–CH₂ PEG groups, indicating that a surface-based rotaxane can be created.^{26,27} Surface PEG will be complexed with α CD; the carboxyl end-group of PEG allows for an additional CD to potentially hydrogen bond with COOH. To demonstrate the reusability of α CD–PEG surface, we performed consecutive *trans*-resveratrol serial dilutions using a single surface. Chemical structures of the sensor compounds and *trans*-resveratrol are demonstrated in Figure 1.

2. RESULTS AND DISCUSSION

2.1. Modification of a Reusable PEG– α CD Surface.

Faradaic electrochemical impedance spectroscopy (EIS), in the presence of ferri/ferrocyanide, was used for surface monitoring during modification stages by tracking charge-transfer resistance. To construct a reusable CD sensor, a gold surface was modified with PEG-SH and then the PEG surface was complexed with α CD. Finally, the α CD–PEG surface was exposed to *trans*-resveratrol in phosphate-buffered solution (PBS), pH = 7.4 (Figure 2A). A measurable amount of α CD decouples from the surface to form a complex in solution with *trans*-resveratrol because *trans*-resveratrol has a greater affinity with α CD compared to PEG. The initial PEG-modified surface had an increase in charge-transfer resistance following α CD loading on the surface (Figure 2B). These results indicate that during the first α CD loading, α CD molecules complexed with

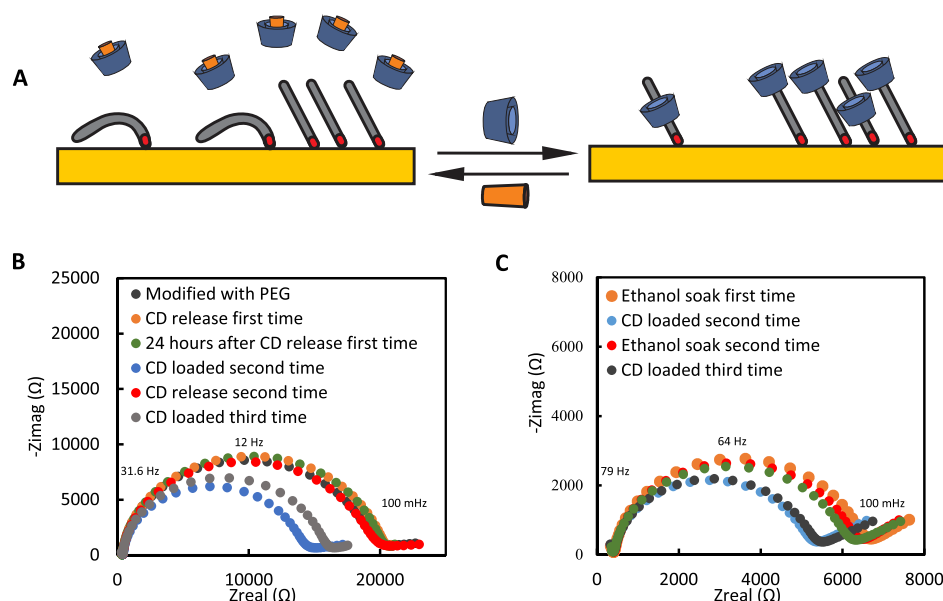


Figure 3. Reversible binding of α CD on PEG: (left) α CD release by *trans*-resveratrol (same as Figure 2A, right), (right) regeneration of surface by α CD loading. (B) Nyquist plots of reloading and release of α CD by 160 nM *trans*-resveratrol in PBS. EIS measurements were done in 20 mM ferri/ferrocyanide in deionized water. (C) α CD release by ethanol soaking for 45 min. (B,C) Surface is fully reloadable and reusable showing that it can return to the original sensing state.

physisorbed PEGs, and the charge-transfer resistance increased because a layer of α CD was formed on the surface. Thus, for the first α CD loading, α CD favorably bound to physisorbed PEG, compromising hydrogen bonding between the $-\text{OH}$ of CD to the COOH end groups or the $\text{C}-\text{O}-\text{C}$ chain groups of PEG. By exposing the PEG- α CD-modified surface to *trans*-resveratrol solution, α CD molecules dissociated from the surface, and the charge-transfer resistance decreased. The action of α CD removal also caused the removal of physisorbed PEG, further allowing the incomplete PEG surface to form a bent-over shape keeping a consistent impedance response (Figure 2).

The surface was regenerated with a second α CD soak (Figure 3A). A decrease in charge-transfer resistance was observed following α CD reloading, and an increase was observed after the α CD was fully removed following serial dilution (Figure 3B). The α CD cavity threads the chemisorbed PEG chains to form channel-type crystalline microdomains resulting in a faster electron transfer and easier diffusion of ions through the surface.²⁸ When there is no α CD on the surface, chemisorbed PEG groups have a mushroom configuration, which resulted in the PEG layer becoming a less porous surface and a decreasing electron-transfer rate (Figure 3). Unloaded states were generated after serial dilutions with *trans*-resveratrol (Figure 3B). We were able to obtain a similar response from ethanol soaking used to remove the α CD from the surface (Figures 3C and S1). X-ray photoelectron spectroscopy (XPS) and attenuated total reflectance–Fourier transform infrared spectroscopy (ATR–FTIR) were used to further investigate both α CD-loaded and unloaded surface states as described in Figure 3.

XPS analysis (Figure 4 and Table S1) revealed that a Au–S peak was observed at 160 eV, indicating that the surface was covered by thiol groups covalently attached to the gold surface. After PEG modification, the relative intensity of Au peaks decreased with respect to carbon, indicating that PEG was on the surface. When α CD was loaded on the surface, the Au

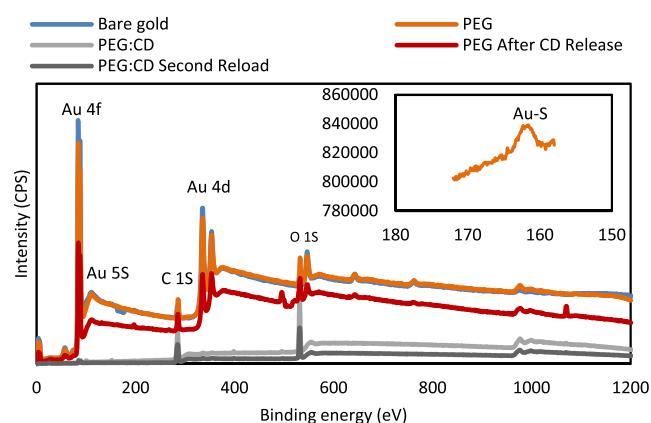


Figure 4. Characterizing the electrode after different modification steps with XPS. Intensity of Au peaks (Au 4f: 84.4 and 87.92, Au 5s: 125.4, Au 4d: 336.4 and 354.4, and Au 4p: 533 eV) decrease during different steps of surface development, i.e., PEG modification and α CD loading. Au peak intensities return after 160 nM *trans*-resveratrol soak for 10 min, which confirms the release of α CD from the surface to bind with *trans*-resveratrol. The Au–S peak at 160 eV shows the presence of covalently attached PEG on the surface. The similarity between the spectra before α CD loading and after α CD release confirms the reproducibility of the surface and reversible binding of α CD on PEG.

peaks were weaker compared to when α CD had been released from the surface indicating a surface complexation. The XPS results indicate that α CD had a strong interaction with the PEG surface, and the similarity between the ratios of Au/C and C/O after the first (0.063 and 1.306) and the second (0.087 and 1.259) CD loading confirms the reproducibility of the PEG–CD surface (Table S1).

ATR–FTIR analysis (Figure 5) showed the presence of $\text{C}=\text{O}$ bonds of the PEG end-groups at 1750 cm^{-1} and the $\text{C}-\text{O}-\text{C}$ PEG bonds at 1260 cm^{-1} . After α CD loading, $\text{C}=\text{O}$ double bonds and $\text{C}-\text{O}-\text{C}$ bonds were replaced by $\text{C}-\text{OH}$ bonds

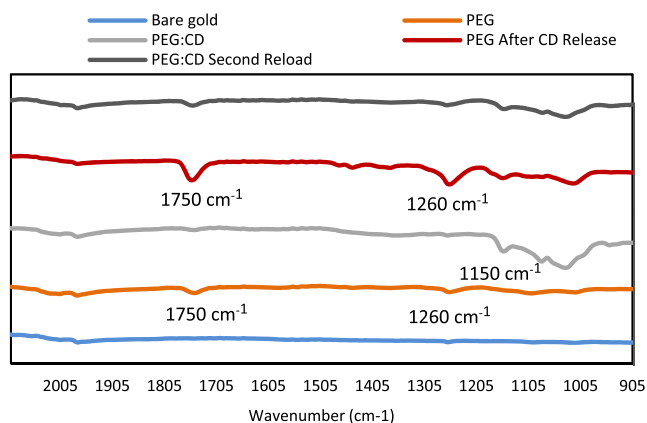


Figure 5. Characterizing the electrode after different modification steps with ATR-FTIR. After PEG-gold modification, C=O at 1750 cm^{-1} and C-O-C bindings at 1260 cm^{-1} appear. After α CD loading, COH bonds (1150 cm^{-1}) of α CD dominate the spectra, masking the PEG signal. The spectra after (1) α CD release returns in similarity to a PEG-gold modification (orange vs red) and (2) after α CD reloading, returns in similarity to the initial α CD loading (grey lines), confirming reusability of the surface.

from α CD because the α CD host is dominating the spectra of the PEG guest indicating that the α CD is forming surface rotaxane supramolecules and hydrogen bonding with the COOH end-groups. The intensity of PEG peaks at 1750 and 1260 cm^{-1} increased after the α CD was released. A similar response can be observed after α CD reloading, reconfirming the EIS and XPS results indicating the successful development of a reusable CD surface.

2.2. *trans*-Resveratrol Detection by PEG- α CD Surface. For point-of-need applications, multiple studies have shown that auxiliary redox agents are less desirable.^{29–36} In addition, non-faradaic analysis is more sensitive to changes in the interface between the electrode and the solution because the faradaic charge-transfer resistive process can mask simultaneous surface resistive and capacitive effects.²⁹ Thus, a non-faradaic approach is used for more sensitive and direct surface quantification.^{30–36} The surface's ability to monitor repeated non-faradaic impedance response to nanomolar concentrations of *trans*-resveratrol was first explored in a PBS solution. All experiments were performed in triplicate to confirm reproducibility and standard variation. Original Bode plots for four different concentrations are presented in Figure

S2 (α CD-PEG-modified surface—test) and Figure S3 (bare gold electrode—control).

The magnitude and phase of the impedance are shown for 20 nM concentration (Figure 6A), indicating the difference between the control and test cases. The capacitive behavior of the modified surface at low frequencies is indicative of the PEG coating layer which blocks the current. Based on these results, the equivalent circuit that best describes and fits our sensor is proposed as a coating with a porous structure (Figure 6B).³⁷

In parallel with the coating capacitance, a resistive path can be modeled by leakage resistance (R_L) due to the small ionic current that flows through the surface pores of the sensing layer. The serial dilution results show that leakage resistance was the main affected circuit element, and the leakage resistance provided the most detailed information about the physiochemical processes of the α CD release and PEG flattening into a mushroom configuration. The change in leakage resistance between a certain concentration and the 0 nM concentration base signal was then used for the analysis ($\Delta R_L = R_L - R_{L0}$). The sensor was first tested for concentrations in the range of 2.5–160 nM (Figures 6C and S2). As the surface was exposed to *trans*-resveratrol, α CD was released from the surface, and a decrease in leakage resistance was observed. Theoretically, for an ideal insulating layer, R_L would be infinite and the current through the leakage resistance (I_2) would equal zero (Figure 6B). However, the PEG coating layer imperfectly blocks ionic current, and R_L is finite. With a decrease in leakage resistance followed by an increase in *trans*-resveratrol concentration, the current through the leakage resistance (I_2) increases and the current through the coating capacitance (I_1) decreases. This suggests that the PEG capacitive layer becomes less porous and more capacitive due to flattening into a mushroom structure as described earlier. Figure S2 confirms the decrease in phase and increase in capacitance following the increase in the concentration of *trans*-resveratrol.

From Figure 6C, we can observe that 20 nM was the saturation concentration; the leakage resistance remained constant at concentrations higher than 20 nM because all α CD molecules were removed from the surface. In contrast, almost no response was observed by the bare gold surface (Figure S3). Likewise, a sensor employing α CD produced a weaker response to cortisol, a competing analyte that is mostly known for making complexes with β CD and γ CD (Figure S4). Two additional controls showing minimal response were (1) a

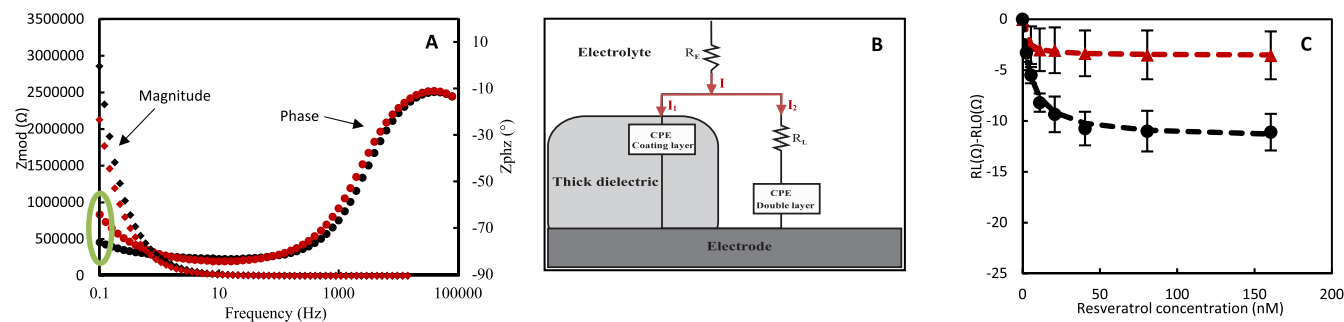


Figure 6. The developed α CD-PEG surface for *trans*-resveratrol detection: (A) magnitude and phase of the impedance for 20.8 nM concentration of (red) a bare gold surface and (black) an α CD-PEG-modified surface. The green circle shows that the phase of the modified surface is closer to -90° and is more capacitive. (B) Equivalent circuit model used to fit the data for the α CD-PEG surface. Leakage resistance (R_L) was used as the dominating element of interest. I is the total current; I_1 and I_2 are the current through the blocking PEG layer and leakage resistor, respectively. (C) Calibration curve of (red) a bare gold surface and (black) an α CD-PEG surface indicating greater sensitivity in the α CD surface.

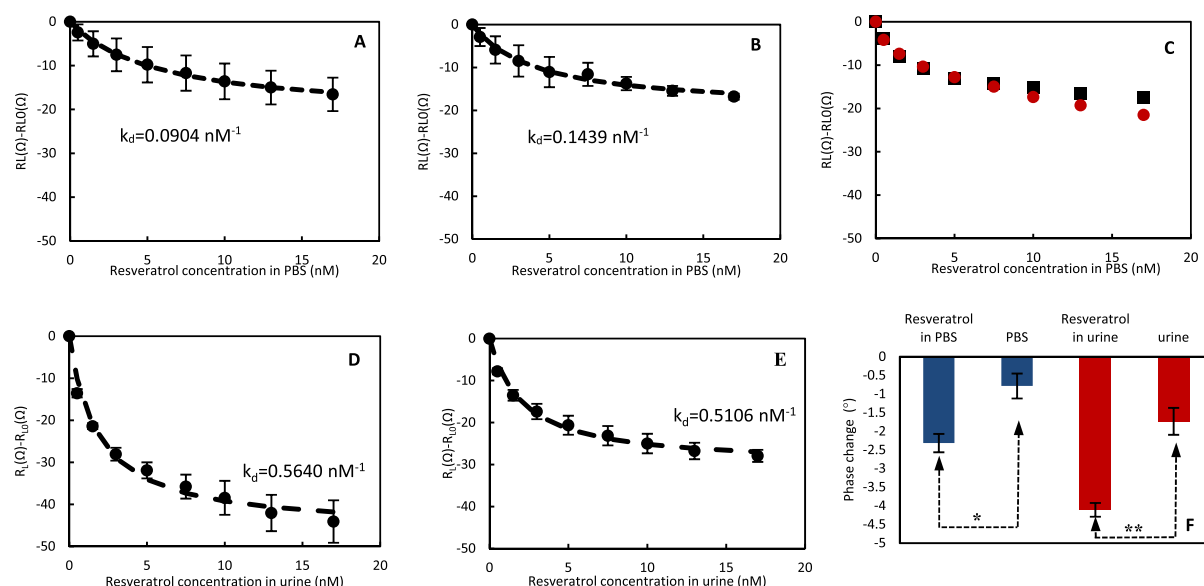


Figure 7. Calibration curve of the average of α CD–PEG surface responses to *trans*-resveratrol during (A) first usage in PBS pH = 7.4 and (B) second usage in PBS pH = 7.4. Data points (dots) and calculated Langmuir isotherm fit (dotted line) with the standard deviation error of quadruplicate data. (C) Calibration curve comparison of (black) second and (red) third usage in PBS pH = 7.4 showing minimal loss of activity from subsequent serial dilutions. Calibration curve of the average of α CD–PEG surface responses to *trans*-resveratrol during (D) first usage in urine pH = 6.3 and (E) second usage in urine pH = 6.3. Data points (dots) and calculated Langmuir isotherm fit (dotted line) with the standard deviation error of triplicate data. (F) Average phase change at 0.1 Hz comparing the baseline to 17 nM *trans*-resveratrol in PBS, PBS only (no *trans*-resveratrol), *trans*-resveratrol in urine, and urine only (no *trans*-resveratrol); * p -value < 0.05 and ** p -value < 0.01.

PEG surface not loaded with α CD to confirm that *trans*-resveratrol was not physisorbing to PEG (Figure S5) and (2) no *trans*-resveratrol in the solution to show that the α CD surface was in PBS (Figure S6). We observed Langmuir isotherm unbinding with a dissociation constant of 0.0904 nM^{-1} for the α CD–PEG surface after first modification (Figure 7A) and 0.1439 nM^{-1} after subsequent α CD loadings (Figure 7B). Finally, the third serial dilution was performed to confirm the reusability of the sensor and reproducibility of the surface (Figure 7C). To test the non-specific response of the surface in complex media, the proposed surface was tested in human urine (Figures 7D,E and S7). Langmuir dissociation constants were found to be 0.5640 and 0.5106 nM^{-1} for initial modified surface and regenerated surface, respectively. Additionally, a control experiment was performed in urine with no *trans*-resveratrol addition (Figure S8). The CD sensor in PBS and human urine showed significantly higher phase change in the presence of *trans*-resveratrol compared with controls (p -values < 0.05 and < 0.01, respectively) (Figure 7F), indicating α CD–*trans*-resveratrol binding and release occurring at the surface. The discrepancy between Langmuir dissociation constants in PBS (pH = 7.4) and urine (pH = 6.3) can be attributed to the difference in conductivity, ionic strength of the solutions, and pH of the two solutions.³⁸ This difference can be also explained by additional α CD decoupling due to unspecific bindings of α CD with other molecules in urine which are not present in PBS (Figure 7F).

After gold surface modification with PEG, the surface was rinsed with ultra-high purity (UHP) to remove excess physisorbed PEG molecules. However, the first serial dilution showed that some physisorbed PEGs still exist on the surface (Figures 2 and 7A,D). Consequently, the sensor response after the first α CD loading (Figure 7A,D) had larger error bars indicating a less precise response due to the presence of physisorbed PEG that bound with α CD (Figure 2). When

trans-resveratrol was introduced to the solution, the physisorbed PEGs decoupled from the surface with the CD–Res complexes. The second *trans*-resveratrol serial dilution, after reloading of α CD on the surface, showed a smaller error (Figure 7B,E). Figure 7C shows the consistency between the second and third serial dilution in the absence of physisorbed PEG molecules.

The resulting k_d values in PBS are different than k_d values in urine. By comparing the response of blank PBS to the response of blank urine (Figure 7F), it can be inferred that the binding of non-specified molecules within urine complex matrix to α CD also contributes to the release of physisorbed PEGs and α CD. The complex interaction of non-specified molecules with α CD within the urine complex matrix leads to differences in the reported k_d values compared to PBS and subsequent uses of the sensor.

3. CONCLUSIONS

In this work, we developed a reusable CD sensor which demonstrated excellent selectivity and sensitivity to nM ranges of hydrophobic analytes demonstrated with *trans*-resveratrol. Specifically, we modified a gold surface with PEG and then α CD was loaded on the PEG surface. Faradaic EIS was used to monitor charge-transfer resistance during sensor modification steps. ATR–FTIR and XPS techniques were further used to characterize the surface and verify the impedance response. A large conformational change takes place when α CD releases from the PEG surface to make inclusion complexes with *trans*-resveratrol in solution. In the absence of α CD, PEG flattening on the surface increases coating capacitance, allowing measurement of leakage resistance. The change in leakage resistance is further proportional to *trans*-resveratrol concentration in PBS or urine. These findings were in line with faradaic EIS results in the presence of ferri/ferrocyanide and can substantially affect the ability to improve the performance of non-faradaic sensors.

In addition, reusable CD sensors are significant for point-of-need applications due to the ubiquitous presence of hydrophobic molecules.

4. EXPERIMENTAL SECTION

4.1. Chemicals and Reagents. All chemicals were used without additional purification. Carboxy-PEG₁₂-thiol, methanol (ACS Reagent), and ethanol (ACS Reagent) were purchased from Thermo Fisher Scientific. *trans*-Resveratrol (99%) was purchased from Sigma-Aldrich. α CD (98%) was purchased from Tokyo Chemical Industry Co. Both potassium ferrocyanide (ACS Reagent) and potassium ferricyanide (98%) were purchased from Acros Organics. PBS was prepared using a standard protocol from chemicals purchased from Thermo Fisher Scientific (pH 7.4 and conductivity 14 mS/cm). Raw, unprocessed pooled human urine from 12 donors was provided by Lee BioSolutions (pH 6.3 and conductivity 12.12 mS/cm).

4.2. Preparation of α CD–PEG Surface. A gold electrode was polished in a figure-eight by 3 μ m diamond for 1 min followed by a 1 μ m diamond for 1 min. After each polishing step, the electrode was rinsed with methanol and UHP water for 1 min. The electrode was then polished with 0.55 μ m alumina for 1 min. The electrode was rinsed with UHP and dried with nitrogen. Oxygen plasma was used to remove any remaining surface organic impurities. The gold surface was modified by carboxy-PEG₁₂-thiol. 5 mg of PEG-SH was added to 10 mL of PBS and stirred by sonication for 10 min at room temperature. The gold surface was incubated in the solution for 30 min to allow the –SH groups to covalently bond with the gold surface.³⁹ Excess and weakly adsorbed carboxy-PEG₁₂-thiol were removed by rinsing with UHP for 90 s. The third step consisted of immobilizing α CD on the PEG-modified surface via incubation in a 5 mM α CD solution for 45 min at room temperature.

4.3. *trans*-Resveratrol Serial Dilution in PBS. All *trans*-resveratrol stock solutions were stored in a dark fridge to prevent *trans*-resveratrol from changing to its *cis* isomer conformation. 1.08 mg of *trans*-resveratrol was added to 50 mL of PBS to make a concentrated *trans*-resveratrol solution. Then the solution was sonicated for 10 min. Serial dilutions of the *trans*-resveratrol solutions were done in a beaker containing PBS (pH 7.4) by adding the concentrated solution to 15 mL of PBS solution to get 2.5, 5.4, 11.1, 20.8, 40.35, 80.6, and 160.5 nM concentrations. For lower concentrations, concentrations of 0, 0.5, 1.5, 3, 5, 7.5, 10, 13, and 17 nM were used. The modified surface was incubated in the *trans*-resveratrol solution, with the desired concentration, for 5 min prior to running EIS.

4.4. *trans*-Resveratrol Serial Dilution in Urine. Received pooled urine was filtered through 0.2 μ m polyethersulfone membrane filter, and it was stored in a –20 °C freezer. A stock solution was prepared by adding 0.447 mg of *trans*-resveratrol to 100 mL of urine prior to filtering. The concentrated *trans*-resveratrol solution in urine was serially diluted in 20 mL of filtered urine.

4.5. Surface Regeneration. The surface was washed thoroughly with UHP after each serial dilution. The surface was reloaded with a 45 min soak in 5 mM α CD deionized water solution at room temperature.

4.6. EIS Measurements. The electrodes were carefully rinsed with UHP thoroughly before and after each EIS experiment to remove any excess and weakly adsorbed chemicals. The electrochemical experiments were performed with Gamry Instruments Reference 600+ potentiostat in a VISTA shield faradaic cage at room temperature. The results were analyzed by Gamry Echem Analyst. A platinum wire auxiliary electrode, Ag/AgCl/3 M NaCl reference electrode, and a gold disc electrode (BASi, area = 0.0201 cm²) working electrode were used. These measurements were performed by scanning the frequency from 100 kHz to 0.1 Hz, acquiring 10 points per decade, unless stated otherwise. DC voltage was 0 V versus open-circuit potential, and the AC voltage was 10 mV. The faradaic EIS measurements for monitoring surface modification were carried out in 20 mL of 20 mM ferri/ferrocyanide in UHP. For non-faradaic analysis, EIS was

performed in PBS or urine without added redox active molecules. All other parameters were kept the same.

4.7. Surface Characterization. Gold-coated silicon wafers were used for ATR–FTIR and XPS analysis for better contact with the analytical equipment; the gold-coated silicon wafer was prepared the same way as the gold disc electrodes. ATR–FTIR data collection was conducted with Thermo Nicolet iS10 equipped with air purge with a dew point of –95 °F. Spectra were the results of 128 scans. XPS analyses were performed using Kratos AXIS Supra XPS.

4.8. Data Fitting. Previous studies have shown that a surface covered by self-assembled monolayers acts as an insulator at low frequencies.⁴⁰ Thus, we assumed the PEG– α CD layer to be an inert porous layer, and we used the corresponding circuit model, Figure S5B, to explain our serial dilution data. Also, since the impedance of solid electrodes deviates from the ideal capacitive behavior, a constant phase element was used in the circuit instead of the ideal capacitance. The changes in leakage resistance by serial dilutions are proportional to the amount of α CD molecules released by *trans*-resveratrol from the PEG surface. The amount of α CD released from self-assembled monolayers of PEG, that is, changes in leakage resistance, is dependent on the *trans*-resveratrol concentration. All experiments were repeated in triplicate or quadruplicate, and the mean value data fitted with a Langmuir model of desorption (eq 1).

$$R_L - R_{L0} = \frac{-Nk_d C}{1 + k_d C} \quad (1)$$

C is *trans*-resveratrol concentration (nM), N is desorption capacity, and k_d is the Langmuir (dissociation) constant (nM^{–1}).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsapm.0c00866>.

Reversible binding of α CD confirmed by ethanol soak; resveratrol serial dilutions by α CD–PEG surfaces in PBS; resveratrol serial dilutions by bare gold surfaces; cortisol serial dilution with α CD–PEG surfaces; resveratrol serial dilution with PEG-modified surfaces without α CD immobilization; multiple EIS scans of α CD–PEG surfaces in PBS with no addition of resveratrol; resveratrol serial dilutions by α CD–PEG surfaces in urine; multiple EIS scans of α CD–PEG surfaces in urine with no addition of resveratrol; and quantification of Au 4f, C 1s, and O 1s with XPS (PDF)

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Notes

The authors declare no competing financial interest.

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