Electrochemistry of Guest Molecules in Thiolated Cyclodextrin Self-Assembled Monolayers: An Implication for Size-Selective Sensors

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The electrochemistry of a few guest molecules captured in cavities of self-assembled monolayers of thiolated cyclodextrins on gold electrodes has been examined. When electroactive molecules with different molecular dimensions such as *p*-benzoquinone, 2-methyl-1,4-naphthoquinone, and anthraquinone were used as guest molecules, only those with molecular dimensions smaller than the cyclodextrin cavity sizes were shown to be included by both cyclic voltammetric and electrochemical quartz crystal microbalance experiments. These results lead to the possibility that the self-assembled monolayers prepared from properly shaped compounds can be used as molecular size selective sensors. The molecules captured in the cavities were detected by linear sweep voltammetry with a detection limit of about 10^{-8} M.

Introduction

Cyclodextrins (CDs) have drawn much attention due to their capability of molecular recognition[1,2] owing to their well-defined cavities,[3] whose sizes are different depending on the number of amylose units in cyclic oligomers, i.e., CDs. The cavity diameters of α- and β-cyclodextrin are about 4.7−5.3[4a] and 6.6−7.8 Å,[4b] respectivley. Host−guest interactions[5] through these cavities lead to the formation of inclusion complexes within the cavities with guest molecules smaller than the cavity size. Driving forces for the formation of the CD inclusion complex arise from apolar−apolar interactions between guest molecules and host cavities, the CD ring strain release on complexation, and van der Waals interactions.[6] A few requirements must be met for the host−guest complexes to form, one being that the binding sites of the host and guest molecules should be stereoelectronically complementary. The multiple stoichiometric ratios of 1:1 and 1:2 or even more complicated complexes are also possible.[6]

Immobilized CDs on the surface have been described in a few studies reported[7] in which self-assembled monolayer (SAM) coated electrodes have been used. Rubinstein et al.[8a,b] and later Turyan and Mandler[8c] reported selective binding of metal ions to SAMs composed of alkanethiols with an electroactive group. Also, electrochemical quartz crystal microbalance (EQCM) experiments have been employed for sensing target molecules[9] and monitoring ionic or redox interactions in SAMs to study their chemical dynamics.[10]

In our current study, the SAMs of thiolated α- and β-cyclodextrins (β-CD) were prepared on the gold electrode surface with pentanethiols or hexanethiols filling up the exposed surfaces between CD molecules,[1,8a] and the electrochemistry of guest molecules captured in their cavities has been examined. To test these cavities as size-selective sensors, guest molecules of different sizes with reduction potentials less negative than the reductive stripping potentials of the CDs were used. Some inorganic salts have been reported as probe molecules in the
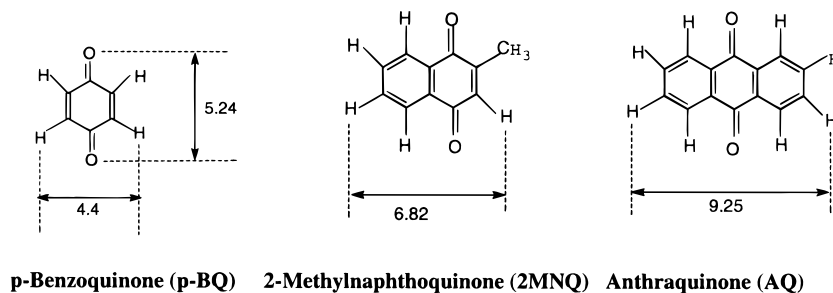
literature;[11] however, since their sizes are difficult to vary, a series of aromatic quinones of different molecular sizes (Figure 1) was used in this study. Cyclic voltammetric experiments were used as a detection tool for guest molecules. In addition, the EQCM was also used to determine the amount of thiolated CDs on the electrode surface as well as the amount of guest molecules captured in the cavities. The results obtained indicate that size-selective sensors can be constructed based on the concept developed here.

Experimental Section

Thiolated β-CD was prepared according to the procedure reported by Stoddart et al.[1] A similar procedure to the one published by these investigators was employed for the synthesis of thiolated α-CD. The synthesis consisted of two steps. The first was the preparation of per-6-iodo-α-CD, which was confirmed by ^{13}C NMR signals (10.6 (C-6), 71.5 (C-2), 72.5 (C-3), 73.0 (C-5), 87.1 (C-4), 102.6 (C-1)) and then thiolated-α-cyclodextrin (26.9 (C-6), 72.7 (C-2, C-3), 73.6 (C-5), 85.9 (C-4), 102.6 (C-1)), both with CD_3SOCD_3 used as a solvent. An infrared absorption band at 2565.4 cm^{-1} due to the S−H group was observed in its FTIR spectrum recorded using a KBr pellet, consistent with previous reports on thiolated β-CD.[7d] The S−H stretching band disappeared in the spectrum obtained with the compound adsorbed on the gold surface, indicating the formation of the Au−S bond on the gold surface. Also, a mass peak of 1052.04, which corresponds to the parent peak of thiolated α-CD with its five primary alcohol groups replaced by SH, as well as various fragmentation peaks, was detected in a FAB (fast atomic bombardment) mass spectrum obtained with triethanolamine as a matrix. Only five alcohol groups of six possible primary alcohols might have been thiolated. Other chemicals were used as received. Doubly distilled water was used for the preparation of solutions.

NMR spectra were recorded with a Bruker DPX300 NMR spectrometer. An EG&G model 283 potentiostat/galvanostat was used to record cyclic voltammograms at a polycrystalline gold electrode, which was prepared by sealing a gold wire (Johnson Matthey, 99.999%, area = 0.02 cm^2) into a Teflon

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p-Benzoquinone (p-BQ)   2-Methylnaphthoquinone (2MNQ)   Anthraquinone (AQ)

Figure 1. Quinones used as guest molecules with their dimensions: (a) 1,4-benzoquinone; (b) 2-methyl-1,4-naphthoquinone; and (c) 9,10-anthraquinone. The molecular dimensions were obtained using the Hyperchem program.

rod. An AT cut quartz crystal coated with gold possessing a base frequency of 9 MHz was used for the EQCM measurements. The EQCM measurements were made by employing an EG&G-Seiko model 917 quartz crystal analyzer (QCA) along with an EG&G model 273A potentiostat/galvanostat. Frequency responses were recorded through an RS-232 interface controlled by a BASIC program. Gold-plated quartz crystals provided by EG&G were used as a working electrode. A platinum wire spiral and Ag/AgCl (in saturated KCl) electrodes were used as counter and reference electrodes, respectively.

The polycrystaline gold electrode was sonicated in a pirahna solution for an hour before used. After being washed extensively with water, it was annealed in an oven at 200 °C. Then, the electrode was polished with moistened alumina powder (1 and 0.05 μm) on microcloth pads (Buehler), followed by rinsing with doubly distilled water and cleansing in an ultrasonic bath. A SAM was prepared on it with a thiolated CD. A gold electrode was dipped into a 1.0 mM CD solution in a 3:2 (v/v) DMSO/water mixed solvent for over 12 h. The electrode was then washed thoroughly with water and dried by purging with dry nitrogen. The surface uncovered by thiolated CDs was then sealed with pentanethiol by dipping the CD-coated electrode into a 0.75 mM thiol solution in a 1:1 (v/v) ethanol/water mixed solvent after the β-CD cavities had been masked by ferrocene molecules. The CD-coated, thiol-masked electrodes were then demasked according to the reported procedure.[1] In the case of thiolated α-CD, p-benzoquinone (p-BQ) was used for masking the cavities. The CD-coated, thiol-masked (i.e., pentanethiol sealed) electrodes were used in all cases but the kinetic experiments for the thiolated CD adsorption.

For EQCM measurements, the gold-plated quartz crystal was exposed overnight to a deaerated solution of 1.0 mM thiolated CD in the 3:2 DMSO/water mixed solvent. Then, information related to desorption of immobilized CD on the gold surface was obtained by EQCM experiments.

An increase in mass corresponds to a decrease in frequency according to the Sauerbrey eq 1[12]

$$\Delta f = -C_f \Delta m \tag{1}$$

where Δf is the change in frequency, Δm is the mass change, and C_f is the sensitivity constant. We obtained relation 2 from calibration data obtained by electrochemically depositing silver from a silver nitrate solution.

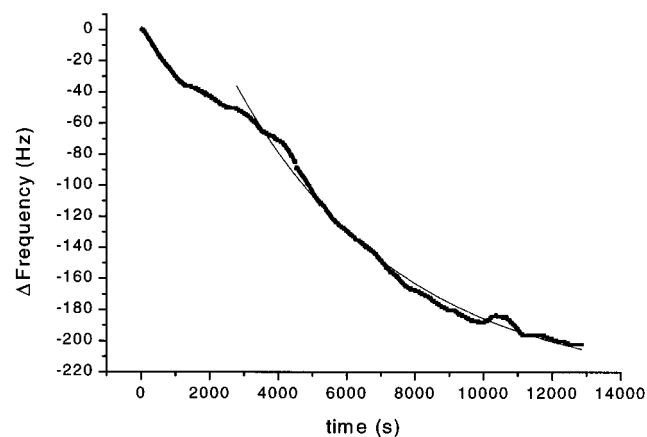$$\Delta m = -(6.68 \text{ ng/(Hz/cm}^2)) \, \Delta f \tag{2}$$

Derivative signals of the frequency shifts are related to voltammetric currents as in

$$i = n v F M_w C_f \, d(\Delta f)/dE \tag{3}$$

if the Coulombic efficiency is 100%. Here, n is the number of
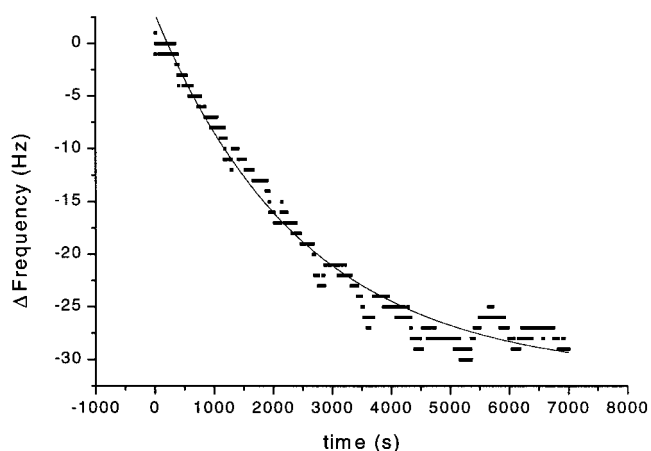
Figure 2. Decrease in frequency recorded during adsorption of thiolated β-CD in DMSO/H$_2$O (1:5 v/v) containing 7.6 μM β-CD. The solid line is for an ideal Langmuirian behavior.

Figure 3. Decrease in frequency recorded during adsorption of thiolated α-CD in DMSO/H$_2$O (1:5 v/v) containing 5.0×10^{-5} M α-CD. The thin solid line is for an ideal Langmuirian behavior during the second stage of adsorption (see text), while the thick line represents the data points.

electrons transferred, v is the scan rate, M_w is the molecular weight, F is the Faraday constant, and d(Δf)/dE is the derivative of the frequency shift with respect to potential.

Results and Discussion

EQCM Study of SAMs of Thiolated CDs. The adsorption kinetics of thiolated α- and β-cyclodextrins have been studied. The decreases in frequency observed for the adsorption of thiolated α- and β-CDs are shown in Figures 2 and 3, respectively. Fitting the data according to the Langmuirian adsorption isotherm gave an adsorption rate constant of 52.5 M^{-1} s^{-1} for β-CD. For thiolated α-CD, the decay curve is made

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of two components, a fast component of 20.5 M^{-1} s^{-1} before about 2700 s and a slow one of 5.9 M^{-1} s^{-1} after that. β-CD is seen to form a well-defined self-assembled monolayer, as the decay curve for the frequency follows the Langmuir adsorption isotherm rather smoothly with a relatively large adsorption rate, while that for α-CD is not as straightforward. The coverage on the electrode surface is estimated to be 8.3 $\times$ 10^{13} molecules/cm^2 for β-CD, while it is 19.6 $\times$ 10^{13} molecules/ cm^2 for α-CD, from the decrease in frequency. The theoretically calculated values for the coverage of a flat surface for single-crystal gold are 6.8 $\times$ 10^{13} and 5.6 $\times$ 10^{13}, respectively, for α- and β-CDs.[13] From the fact that the decay curve for the β-CD is described satisfacrorily by the Langmuirian kinetics, we believe that β-CD forms a rather well-defined monolayer. The difference between the calculated and observed amounts of adsorbed molecules may reflect the difference between the surfaces of the single-crystal and polycrystalline electrodes. However, the observed amount of adsorbed molecules for the case of α-CD, which is nearly 3 times the expected amount, indicates that α-CD deposits as a multilayer, not a monolayer, under the experimental conditions used here. This is probably because α-CD is smaller than β-CD and, thus, does not form a very rigid layer due to its more flexible shape, which results in molecular motions. This may also lead to the formation of oligomers with adsorbed molecules rather than a well-defined multilayer structure on the surface. Multilayer formation has been reported by Schneider and Buttry for alkanethiols in some organic solvents.[14,15a] Recently, Maeda et al.[7a] reported that 6-(2-mercaptoethylamino)-6-deoxy-α-cyclodextrin, which has an $-NH(CH_2)_2-$ group between SH and α-CD-CH$_2-$ in thiolated α-CD, is estimated to have a 97% surface coverage from the integration of the reductive desorption current. In this case, a better defined SAM might have been formed because of a longer chain bearing the $-SH$ group at end.

The amount of CDs adsorbed on the surface was also determined by their reductive stripping. Porter and co-workers reported that thiols attached on gold surfaces undergo reductive desorption by breaking the Au$-$S bond in KOH solutions.[15b] The reductive desorption of SAMs on gold can also be monitored with EQCM experiments.[15a]

Figure 4 shows the results of reductive desorption monitored employing an EQCM experiment in a 0.5 M KOH solution according to the following reaction:

$$R-S-Au + e^- \rightarrow R-S^- + Au \qquad (4)$$
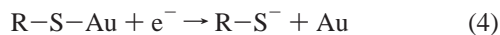
The sudden increase in frequency at around -0.92 V is attributed to the reductive desorption of the β-CD SAM from the surface. The initial slow decrease in frequency starting at about -700 mV may result from adsorption of water dipoles with protons facing the gold surface. From the derivative frequency signals shown in Figure 4b, the faradaic current taken to cause the weight change can be calculated for the desorption process according to eq 3; the calculated peak current for desoprtion was 16.2 μA. The observed peak current was 13.4 μA (not shown), which is lower than that calculated from the frequency decrease by about 20%. This is a reasonable agreement considering that the reaction used for the calibration is different from the reaction studied. The surface coverage was calculated to be 6.0 $\times$ 10^{13} molecules/cm^2 from the frequency decrease observed during the reductive stripping. This value is very close to that estimated for the maximum β-CD surface coverage of 5.8 $\times$ 10^{13} molecules/cm^2. The roughness factor of the commercial gold electrode for the EQCM might
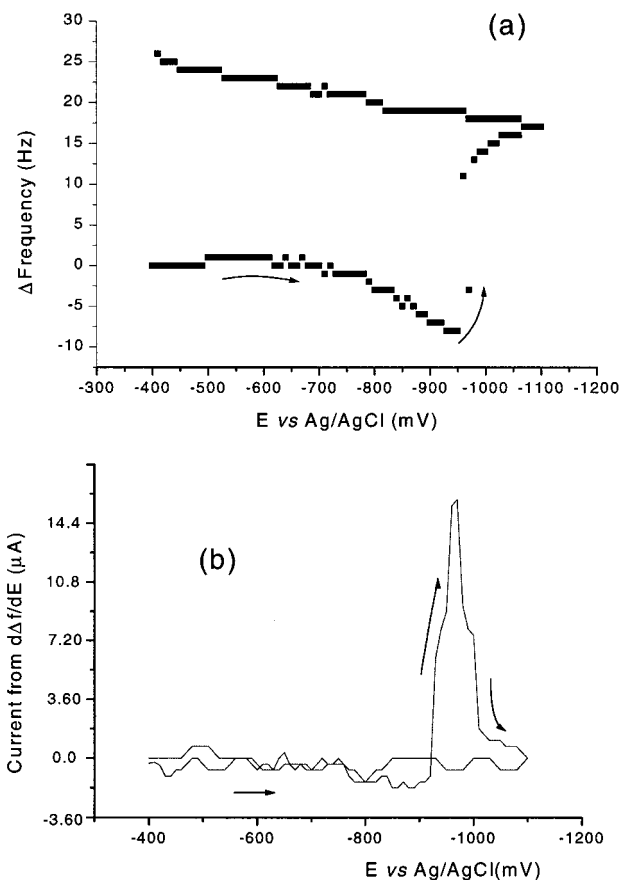
Figure 4. (a) Change in frequency recorded in 0.5 M KOH during reductive stripping of β-CD SAM at a gold electrode (0.19 cm^2) prepared by overnight exposure to a 1.0 mM solution of thiolated β-CD in DMSO/H$_2$O (60:40 v/v). (b) Voltammetric response converted from d(Δf)/dE signals using eq 3 in the text. The scan rate was 50 mV/s.
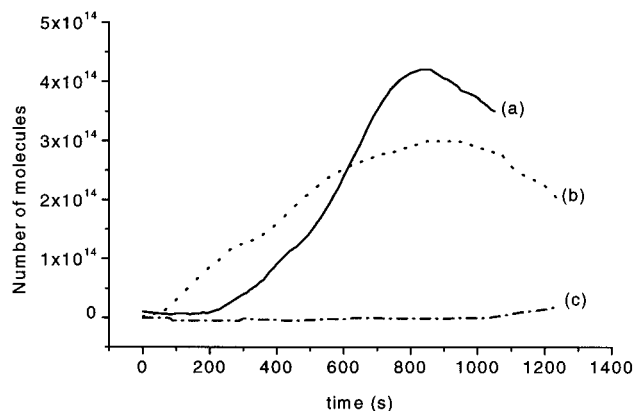
Figure 5. The number of molecules taken up by β-CD cavities monitored by EQCM experiments for *p*-benzoquinone (a), ferrocene (b), and anthraquinone (c) from separate solutions containing 8.0 $\times$ 10^{-7}, 7.0 $\times$ 10^{-7}, and 1.7 $\times$ 10^{-6} M *p*-benzoquinone, ferrocene, and anthraquinone in a methanol/water mixed solvent (1:1 by volume), respectively.

have contributed to the slightly larger number than that calculated for an atomically flat surface.

Electrochemistry of Guest Molecules. The amounts of guest molecules captured inside, or rather in equilibrium with, cavities of CD molecules were first determined using QCM and cyclic voltammetry experiments. Examples of these experiments are shown in Figures 5 and 6. In Figure 5, the numbers of *p*-benzoquinone, ferrocene, and anthraquinone (AQ) molecules captured in the β-CD cavities determined by QCM

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SCHEME 1
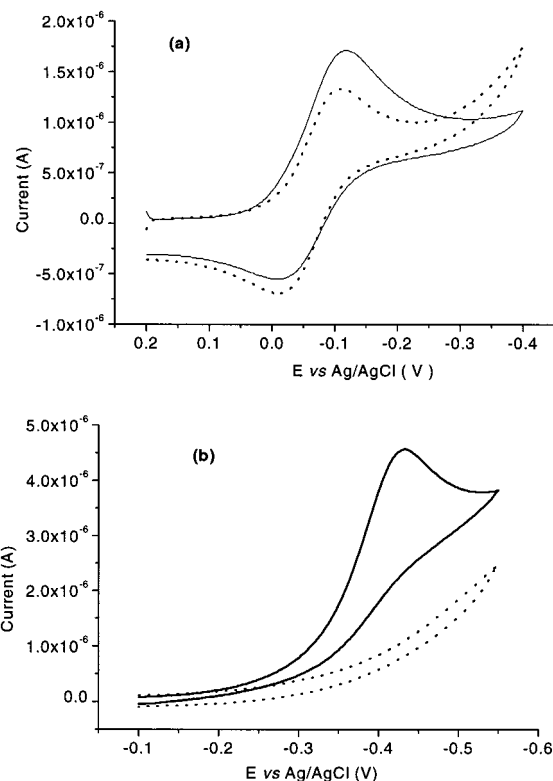
Figure 6. Voltammetric responses at α-CD- (···) and β-CD-modified (—) gold electrodes for (a) 0.12 mM 1,4-benzoquinone and (b) 23 μM 2-methyl-1,4-naphthoquinone. The scan rate was 100 mV/s in 0.2 M Na$_2$SO$_4$.

experiments are plotted as a function of the exposure time. It is seen from this figure that AQ is not forming a complex with β-CD, while two other molecules are being captured. When the system was fully equilibrated, the number of *p*-benzoquinone molecules captured was estimated at 3.5×10^{14} molecules/cm^2 (5.0 molecules/cavity) from the integration of the reductive desorption current and 8.3×10^{13} molecues/cm^2 (3.7 molecules/cavity) from QCA measurements for each β-CD cavity. The reason the number of *p*-BQ molecules estimated from desorption currents is larger than that obtained from QCA experiments is probably because it contains a small fraction of capacitive currents and a good fraction of faradaic currents resulting from reduction of the molecules that are diffusing in from the bulk. In other words, the current observed for *p*-BQ reduction is primarily from the reduction of molecules captured in the β-CD cavities, but we believe there are molecules that are diffusing in from the bulk solution. A similar number of ferrocene molecules are shown to be captured in β-CD cavities. For 2MNQ, approximately 1.2 molecules were captured for each cavity (not shown; see below). Results of cyclic voltammetric experiments are shown in Figure 6, where the currents obtained from reduction of *p*-BQ and 2MNQ with α- and β-CD SAMs present are being compared. As can be seen, slightly lower currents are observed for α-CD than for β-CD, even though the number of cavities should be larger for α-CD than for β-CD, as noted above. This observation suggests that the average number of molecules accessible to the α-CD cavities must be fewer than that available to β-CD, resulting in lower cathodic currents for reducing these guest molecules. It also indicates that only the guest molecules accessible to the cavities of CD molecules give electrochemical responses. Note also that 2MNQ forms an inclusion complex in the β-CD cavities, but not in α-CD (Figure 6b). However, it is noticed that some currents flow with 2MNQ present in the α-cavities, suggesting
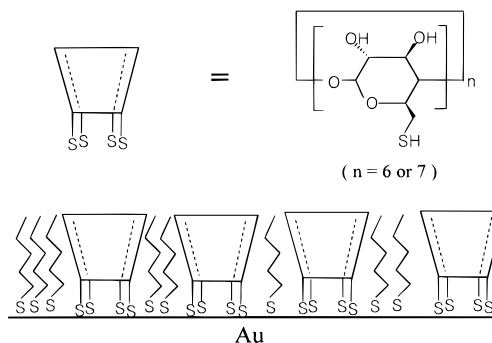
that the currents flowing with CD layers present may contain some contribution from another source, e.g., reduction of molecules penetrating the cavities. In this case, cavities are regarded as defects on the monolayer-covered electrode.[11]

To examine the molecular size selectivities of the cavities of the thiolated CDs, we used quinones of different sizes, as these compounds have reduction potentials less negative than that for stripping thiolated CDs from the surface. The diameters of these molecules shown in Figure 1 were estimated using the Hyper-chem program. Thus, the cavity of β-CD attached on the gold surface should be large enough to capture 2MNQ, while AQ would be too large to fit in its cavity. The SAM formed upon adsorption of thiolated β-CD with its open surfaces blocked by adsorbed pentanethiol is shown in Scheme 1. Pentanethiol was proposed to be a good sealing agent for the unoccupied spaces, which creates an uneven monolayer interface with multiple steps.[1] Thus, only electrochemically active guest molecules accessible to cavities of thiolated β-CDs would give voltam-metric responses. The height of CD molecules is about 8 Å from the S atom,[1] which is approximately the same as that of the pentanethiol molecule. It is well documented that the self-assembled monolayers of pentanethiol block electron transfer to and from the solutions species,[16] unless an electroactive group is attached to the other end of the alkyl group.[17] Thus, it is unlikely that the electron transfer would take place to and from the electroactive molecules present in the bulk solution via tunneling through the CD molecular pilars.
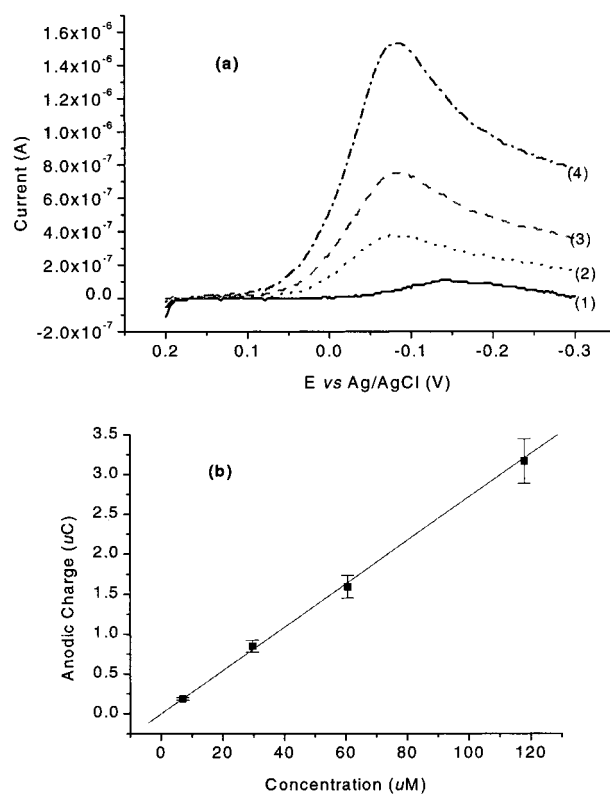
Figure 7 shows the cyclic voltammograms (CVs) for reduction of (a) 1.0 mM *p*-BQ, (b) 0.23 mM 2MNQ, and (c) 0.14 mM AQ in 0.2 M Na$_2$SO$_4$ at bare (solid lines) and thiolated β-CD SAM-covered (broken lines) electrodes, respectively. There are a few points to be noticed from the figure. First, it is seen from Figure 7c that AQ is completely discriminated against when the elctrode is covered with the β-CD SAM, while the reduction current is observed for *p*-BQ and 2MNQ regardless of whether the SAM is present or not. This is consistent with the EQCM results described above. The second point is that the peak potential for 2MNQ is significantly shifted in a more negative direction, indicating that the inclusion complex formation took place. This is not very apparent for *p*-BQ, although a slight shift in potential is noted. From the shift in potential of -71 mV, the formation constant is estimated to be about 16 L mole^{-1} for the 2MNQ$-$β-CD complex. This observation indicates that 2MNQ interacts relatively strongly with CD cavities while BQ molecules may just get into, i.e., penetrate, the cavities. Third, the 2MNQ CV for reduction is better resolved for two peaks and more reversible when the electrode is covered with the β-CD SAM, as the current rise is faster requiring a smaller over-potential at the SAM-covered electrode than at the bare electrode. This result may be interpreted as (1) the 2MNQ molecules accept electrons from the electrode surface in the
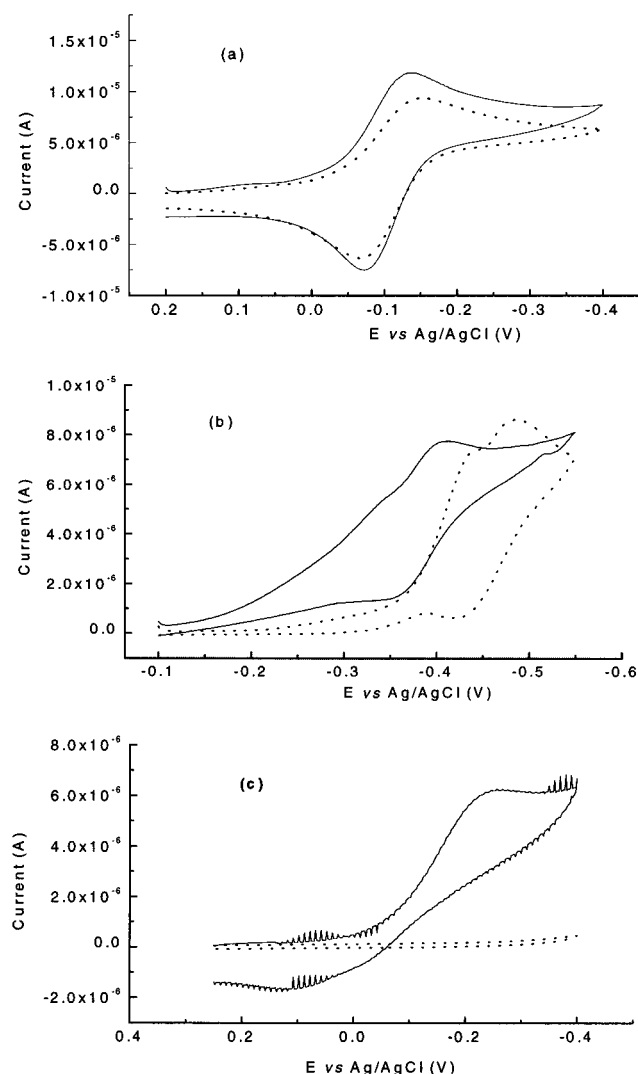
Figure 7. Voltammetric response for (a) 1.0 mM *p*-benzoquinone, (b) 0.23 mM 2MNQ, and (c) 0.20 mM anthraquinone in 0.20 M Na₂SO₄ solution at bare (—) and *β*-CD-modified (- - -) gold electrodes. The scan rate was 100 mV/s.

Figure 8. (a) Linear sweep voltammograms of p-benzoquinone with concentrations of 7.0 (trace 1), 29.6 (trace 2), 60.6 (trace 3), 118 (trace 4) μM in 0.20 M Na₂SO₄ at 100 mV/s. (b) Anodic charge integrated from the above voltammograms plotted vs the concentrations of *p*-BQ in solution.

solvated state in the bulk solution while the solvent sheath may be thinner when inside the cavity and (2) the prewaves in the bulk solution may result from underpotential reduction of adsorbed 2MNQ. The current is approximately the same in the presence and absence of the thiolated *β*-CD SAMs, indicating that the current for reduction of molecules in the bulk solution is not higher than that for molecules in the cavities for 2MNQ. This is explained by the semiinfinite diffusion behavior observed at a microelectrode array in which microelectrodes are located very close to each other. This behavior would be observed when the diffusion layer thickness becomes larger than the distance between microelectrodes so that the diffusion layers overlap each other. This behavior suggests that CD cavities may make a microelectrode array where the interelectrode distance is small in relation to the diffusion layer thickness. A similar observation was reported by Sabatani and Rubinstein at the microelectrode array prepared by making fractional coverage of SAM-coated electrodes of nearly 1.0.[19] Thus, what we have assembled here might be the smallest microelectrodes with their diameters smaller than 1 nm. Thus, the cavities play a role as a channel for electron transfer for 2MNQ molecules. It is clearly seen from Figure 7c that AQ is too large to fit in cavities of *β*-CDs.[6] From the behavior shown here, we surmise that these molecules accept elecrons from the electrode in a horizontal position with

respect to the electrode surface, as an AQ molecule would also accept the electron had it stood vertically inside the cavities. Recently, AQ was also reported to form an inclusion complex with the *β*-CD,[18] but our results indicate that this is not the case. We believe that AQ may form an adduct with *β*-CD, not necessarily the inclusion complex.

The size selectivity of the thiolated *β*-CD SAM-covered gold electrode was also confirmed by the frequency response using EQCM experiments. Before the potential was applied, 2MNQ was allowed to form complexes inside cavities. When a negative potential was applied to the inclusion complex, the dissociation of the complex took place and the 2MNQ molecules were rejected from the cavities due to the negative charge of the radical anion and the electrode. These molecules were reinserted upon potential reversal. The difference in frequency between the two states corresponds to about 1.2 molecules for each cavity. The agreement between the number of cavities and the molecules captured is very good. No frequency change is observed in the presence of AQ, indicating that it does not form an inclusion complex with *β*-CD. This is further evidence for the size selectivity of the thiolated *β*-CD SAM.

To see whether *p*-BQ and 2MNQ concentrations can be assayed selectively in the presence of AQ, we ran linear sweep voltammetry experiments after the thiolated *β*-CD SAM is allowed to form an inclusion complex with BQ or 2MNQ. After the SAM was dipped in the solution containing a certain concentration of BQ or 2MNQ for 3 min while the solution was being stirred, the linear sweep voltammetric experiment was run. The result is shown in Figure 8 in which the cathodic charge for reduction of BQ captured in the *β*-CD cavities is plotted against the concentration of BQ. The current observed here results from reduction of *p*-BQ molecules that are in

equilibrium with the β-CD cavities rather than those captured and firmly fixed inside the cavities. That is, only molecules capable of diffusing into the cavities show voltammetric responses. The linearity of the calibration curve is excellent with a correlation coefficient of 0.999. This demonstrates that a molecular size selective sensor can be constructed based on the self-assembled monolayer with an appropriate cavity size. The sensor, however, cannot discriminate against molecules of smaller sizes than that of the cavity.

Conclusion

Self-assembled monolayers of thiolated α- and β-CDs have been studied on the gold electrode by employing EQCM and cyclic voltammetric experiments. α-CD shows slower adsorption kinetics compared to that of β-CD. β-CD appears to form a rather well-defined monolayer, whereas α-CD deposits as a multilayer. This might be due to their relative molecular weights and the relative energy of the S−Au bonding. It appears that α-CD molecules in the bulk solutions form oligomers with a molecule on the surface.

Guest molecules smaller than the cavity sizes of CDs were shown to undergo reduction at the SAM-covered electrode. When reduced, the inclusion complex becomes dissociated, but the process was reversed when the reduced product was reoxidized. While only one molecule of 2 MNQ was shown to have been complexed into the cavity of β-CD, approximately three to four p-BQ molecules were captured. However, molecules such as anthraquinone bulkier than the cavity size of immobilized β-CD did not form a complex. This demonstrates that self-assembled monolayers of properly shaped molecules can be used as molecular size-selective sensors. More extensive studies along this line are in progress in our laboratory.

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