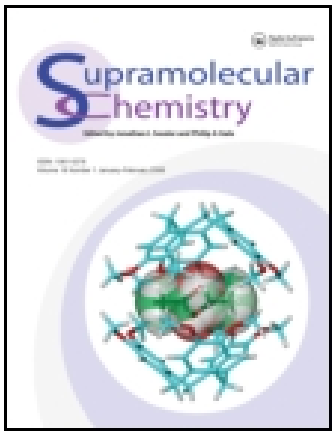

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Molecular interactions of β-cyclodextrins with monolayers containing adamantane and anthraquinone guest groups

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Molecular interactions of β-cyclodextrins with monolayers containing adamantane and anthraquinone guest groups

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Complexing abilities of β-cyclodextrin (β-CD) towards anthraquinone derivatives in solution and immobilised on gold surfaces were studied by voltammetry. The association constant of β-CD with 1-aminoanthraquinone in solution was found to be $1.03 \pm 0.05 \times 10^3\,M^{-1}$; hence, smaller than that with anthraquinone. Capping the surface-immobilised *N*-(1-anthraquinone) lipoamide with β-CD led to decrease in the heterogeneous electron transfer rate constant due to the change in the immediate environment around the electroactive group. To detect the interactions of β-CD with a non-electroactive guest, *N*-(1-adamantane) lipoamide (AD-Lip), the CD was modified by the attachment of an anthraquinone group as the electroactive marker. The appearance of the voltammetric peak corresponding to the reduction of the anthraquinone side-group indicated the binding of β-CD to the AD-Lip self-assembled in a monolayer on the gold electrode.

Keywords: cyclodextrin; adamantane; anthraquinone; self-assembled monolayer; association constant

1. Introduction

Cyclodextrins (CDs), cyclic organic compounds obtained by the enzymatic transformation of starch, belong to one of the most intensively investigated classes of 'host' molecules in supramolecular chemistry. β-CD is one of the most abundant natural oligomers, and corresponds to the association of seven glucose units. The hydrophobic cavity and hydrophilic exterior makes the molecule an appropriate host for various guest molecules bound via non-covalent bonds to form inclusion complexes (*1*, *2*). This inclusion ability of CDs has attracted considerable attention due to the applications in drug delivery systems, sensing devices and for the construction of molecular machines designed to perform tailored mechanical tasks (*3–6*).

Adamantane, an apolar cage hydrocarbon, is one of the guest molecules forming strong inclusion complexes with β-CD, with equilibrium constant above $10^4\,M^{-1}$ (*7*). Complexation between β-CD and adamantane and its derivatives has been exploited for molecular linking, gene delivery and sensor applications (*8*, *9*).

Anthraquinone derivatives are the largest group of naturally occurring quinones. Redox cycling of anthraquinone is supposed to play an important role in the activation of many anthraquinone-based drugs under aerobic conditions (*10*). The inclusion complex between anthraquinone and β-CD in aqueous solution was reported by Jiang et al. (*11*). To our knowledge, there are only a few reports on the complexes of amino derivatives of anthraquinone with β-CD, and weaker interactions due to the presence of amino group were shown (*12*, *13*).

In the present study, the complexation of β-CD with 1-aminoanthraquinone (AAQ) in solution and with surface-immobilised *N*-(1-anthraquinone) lipoamide (AQ-Lip), were investigated (Figure 1(a)). Since the anthraquinone group is electroactive, voltammetry can be used to follow the complexation reactions. The electrochemical behaviour of a non-electroactive guest, *N*-(1-adamantane) lipoamide (AD-Lip), self-assembled in a monolayer on the gold electrode was also studied (Figure 1(b)). The monolayer-covered electrode was exposed to the solution of electroactive derivative of β-CD, mono(6-deoxy-6-thio-ureido(1-anthraquinone))-per(2,3,6-*O*-methyl)-β-CD (AQ-β-CD), and the changes in the voltammograms were discussed in terms of the interaction between the β-CD and adamantane moiety.

2. Experimental

2.1 Chemicals

All compounds used in this work for the syntheses were purchased from Aldrich and Fluka (Karlsruhe and Steinheim, Germany).

2.1.1 N-(1-anthraquinone) lipoamide

Seven hundred and seventy milligrams (3.73 mM) of lipoic acid were mixed with 30 ml of dichloromethane in the reaction vessel. The solution was protected from light, cooled to $-1^\circ C$ and kept under argon atmosphere. 1.1 equiv. (4.11 mM of 521 mg) of oxalyl chloride was added followed

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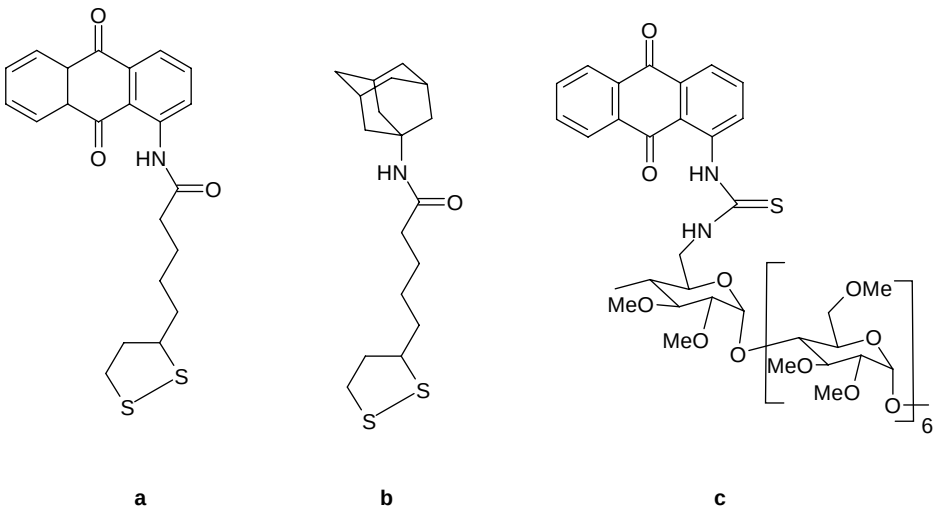

Figure 1. Structures of (a) AQ-Lip, (b) AD-Lip and (c) AQ-β-CD.

by the addition of 1 ml of DMF. The reaction mixture was stirred for 3 h. AAQ (3.8 mM of 899 mg) in 50 ml of dichloromethane was dropped into this mixture and the reaction was continued overnight, and a grey-green precipitate was formed. The latter was filtered and the mixture was evaporated to dryness by means of rotary evaporator. The title compound was isolated by column chromatography on silica gel with dichloromethane as eluent; $R_f = 0.14$. The yield was 342 mg (0.83 mM), obtained as orange solid, 22.3%; MS-ES+: AcONa *m/z* 434.1 [M+Na].

2.1.2 *N-(1-adamantane) lipoamide*

2.5 g of dicyclohexylocarbodiimide was dissolved in DMF (8 ml). 2.2 g (9.8 mM) of lipoic acid was added to this solution under magnetic stirring. Immediately, a white precipitate was formed. The reaction mixture was diluted with 50 ml of acetonitrile. To this suspension, 1 equiv. (1.86 g) of 1-amino adamantane hydrochloride was added followed by the addition of 1 ml of triethylamine and the reaction was continued overnight. The precipitate, *N*,*N*′-dicyclohexylurea, was filtered off and all the solvents were removed under reduced pressure. The solid residue was analysed by TLC on silica gel with 5% MeOH in dichloromethane as eluent, and a new compound was detected; $R_f = 0.16$. This product was purified by column chromatography on silica gel with 4:1 v/v chloroform: acetone system as eluent; $R_f = 0.15$. The yield was 1.6 g (4.7 mM) obtained as yellow solid, 48%; MS-ES+: *m/z* 362.1 [M+Na].

2.1.3 *Mono(6-deoxy-6-thioureido(1-anthraquinone))-per(2,3,6-O-methyl)-β-CD*

Two hundred and fifty-seven milligrams (0.246 mM) of mono(6-amino-6-deoxy)-per(2,3,6-*O*-methyl) β-CD were dissolved in dry pyridine (5 ml) and 1 equiv. of 1-isothiocynatoanthraquinone dissolved in the same solvent was added to this solution at room temperature. After 16 h, pyridine was evaporated using a rotary evaporator. The remaining traces of pyridine were removed by co-evaporation with toluene. Solid residue was dissolved in dichloromethane and purified by column chromatography on silica gel with 5% MeOH in dichloromethane as eluent; $R_f = 0.2$. Orange amorphous solid was obtained with a yield of 300 mg (0.229 mM), 92.9%; MS-TOF-ES+: *m/z* 1719 [M+Na]. NMR revealed loss of symmetry of the macrocycle resulting in signal-broadening ^{1}H NMR (200 MHz, CD_2Cl_2); $\delta = 8.5–7.56$ (5m, 7H) anthraquinone, 5.33–5.51 (m, d × d, m, 7H) $H1^{I}$, $H1^{II-VII}$), 4–3 (m remaining H): ^{13}C (50.28 MHz CD_2Cl_2) $\delta = 185.88$ C═O, 183.03 CS, 134–120 anthraquinone aromatic C, 99.48–99.075 C-1, 82.9–78.72 C-4, 72.39–70.68 C-2, C-3, C-5, 60.03–58.31 C3—OMe, 54.92–52.76 C2—OMe and C6—OMe.

2.2 *Electrochemistry*

Electrochemical measurements were performed using a PGSTAT Autolab (Eco Chemie BV, Utrecht, The Netherlands). All the electrochemical experiments were done in a three-electrode arrangement with silver/silver chloride (Ag/AgCl) electrode (saturated solution of KCl) as the reference, platinum foil as the counter and Au electrode (Bioanalytical Systems, 2 mm of diameter) as the working electrode. The working electrode was polished mechanically with 1.0, 0.3 and 0.05 μm alumina powder on a Buehler polishing cloth. Prior to measurements, the buffer solutions were purged with purified nitrogen for 30 min and all the experiments were performed at room temperature. For all the experiments, Milli-Q ultra-pure water (resistivity 18.2 MΩ/cm) was used.

2.3 Preparation of the modified gold electrodes

The gold electrode was polished to a mirror finish with 0.05 μm alumina powder and electrochemically cleaned by cycling in the range of potentials from −0.2 to 1.6 V in 0.5 M H_2SO_4 solution until the typical cyclic voltammogram of a clean gold surface was obtained (*14*). Modification of the gold electrodes was carried out by self-assembly from oxygen-free 0.1 mM solutions of AQ-Lip and AD-Lip in DMF for 25 min. Next, the electrodes were immersed in 0.1 mM solution of hexanethiol in DMF for 24 h. The modified electrode was then washed with Milli-Q ultra-pure water.

3. Results and discussion

3.1 β-CD complex formation with AAQ in solution

In the phosphate buffer with 40% DMF (pH 9.1), the decrease in anodic and cathodic peaks of AAQ was observed upon the addition of β-CD to the AAQ solution, due to the smaller diffusion coefficient of the β-CD complex formed, compared to the diffusion coefficient of free guest. The dependence of reduction peak current of AAQ on the ratio of β-CD to AAQ concentrations is shown in Figure 2.

The formation constant of 1:1 CD complex was calculated using the Osa equation (*15*):

$$D_{\text{obs}} = \frac{(D_{\text{f}} - D_{\text{obs}})}{K_{\text{s}} \cdot (L)} + D_{\text{c}},$$

where D_{obs} is the observed diffusion coefficient, and D_{f} and D_{c} are the diffusion coefficients of free guest and inclusion complex, respectively. K_{s} is the formation constant and $[L]$ is the concentration of the ligand. D_{obs} and D_{f} can be calculated from the experiments. The value of K_{s} can be obtained from the slope of the linear plot of D_{obs} vs. $(D_{\text{f}} - D_{\text{obs}})/[L]$. The formation constant was $1.03 \pm 0.05 \times 10^3\ \text{M}^{-1}$.

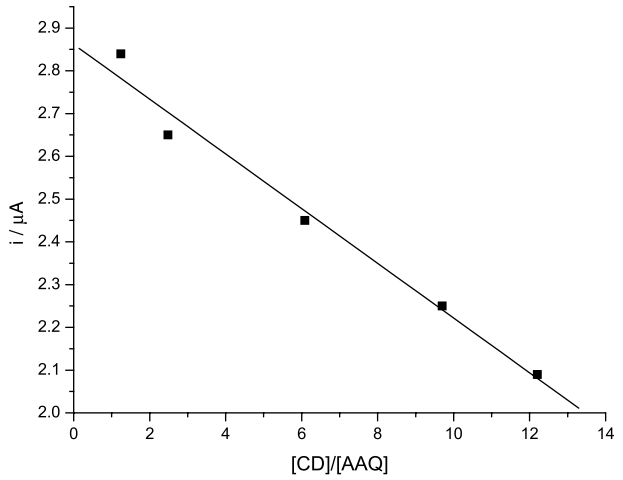

Figure 2. Dependence of reduction peak current of AAQ on the ratio of the concentrations of CD to AAQ.

The ratio of the association constants of the reduced and oxidised forms of AAQ are described by the equation (*3*):

$$K_{S1}/K_{S2} = e^{\left[-F\left(E'_{\text{F}} - E'_{\text{c}}\right)/RT\right]},$$

where K_{S1} and K_{S2} are the association constants of the oxidised and reduced forms, respectively, and E_{F} and E_{C} are the formal potentials of free and complexed forms, respectively. While the peak-to-peak separation increased upon addition of β-CD, the formal potential did not change. In a 1:1 complex, this indicated similar binding strength of β-CD with the oxidised and reduced forms of AAQ.

The heterogeneous standard rate constant was calculated from the equation (*16*):

$$\Psi = \left(\frac{D_{\text{ox}}}{D_{\text{red}}}\right)^{(\alpha/2)} \frac{k_s (RT)^{(1/2)}}{(\pi n F v D_{\text{ox}})^{(1/2)}},$$

where Ψ is a function fixed from the product of electron number *(n)* and the difference between the anodic and cathodic peaks potential $(E_{\text{ox}} - E_{\text{red}})$. The dependence, $\Psi = n(E_{\text{ox}} - E_{\text{red}})$, is tabulated. D_{ox} and D_{red} are the diffusion coefficients of anodic and cathodic processes, α is the transfer coefficient, k_s is the heterogeneous rate constant and v, R, T, F and π denote their usual meanings.

The rate constant of the AAQ electrode process decreases upon the addition of β-CD. The values of the standard rate constants are 2.5×10^{-3} and 0.5×10^{-3} cm/s for AAQ and AAQ:β-CD system, respectively.

The complexation of AAQ by β-CD was confirmed using UV-vis spectrometry. The addition of β-CD to the solution of AAQ resulted in the increase in AAQ absorbance.

3.2 β-CD complex formation with AQ-Lip immobilised in a mixed monolayer at gold electrode

Two-component monolayers containing AQ-Lip and hexanethiol showed a pair of reversible redox peaks; its anodic and cathodic peak potentials were −0.637 and −0.654 V at 0.05 V/s scan rate, respectively. The cathodic and anodic peaks were almost symmetric and the formal potential is −0.645 V (Figure 3). The dependence of peak current, i_{p} on the scan rate, v, is linear and i_{p} is related to the surface concentration of the electroactive component of the monolayer, Γ, according to the equation (*17*):

$$i_{\text{p}} = \frac{n^2 \cdot F^2 \cdot \nu \cdot A \cdot \Gamma}{4 \cdot R \cdot T}.$$

The surface concentration and molecular area of AQ-Lip-modified electrodes calculated based on this equation were $7.73 \pm 0.39 \times 10^{-11}$ mol/cm^2 and 217 ± 13 Å^2, respectively.

Electrochemical desorption experiments were performed in 0.1 M NaOH aqueous solution, and the surface concentration of the thiolated molecules (both the

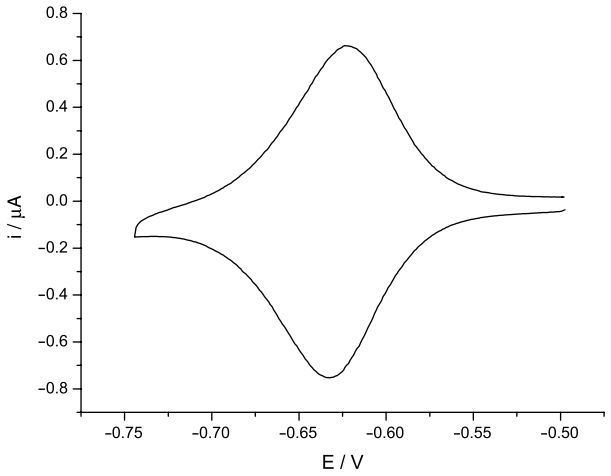

Figure 3. Cyclic voltammogram of mixed AQ-Lip–hexanethiol-modified gold electrode performed in phosphate buffer with 40% addition of DMF. Scan rate: 50 mV/s.

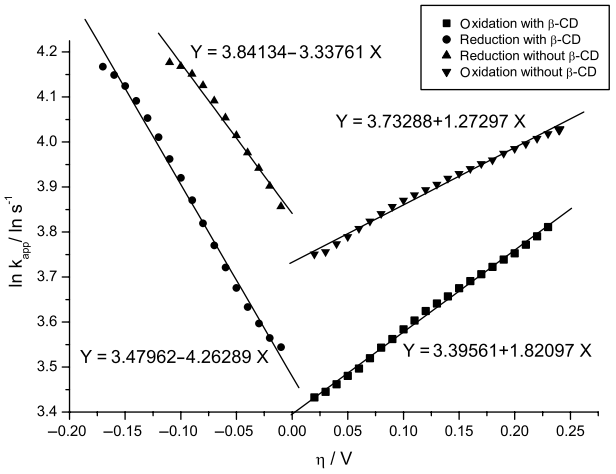

Figure 4. The Tafel plot for mixed AQ-Lip–hexanethiol monolayer in the presence and absence of β-CD recorded in 0.1 M phosphate buffer without DMF; pH 9.1.

components of the monolayer) was found to be $3.50 \pm 0.17 \times 10^{-10}$ mol/cm^2. The ratio of the surface concentrations can be calculated based on these two measurements. For the two-component monolayer, the ratio of AQ-Lip:hexanethiol was 1:4.

The apparent rate constant, k_{app}, was obtained using the equation (*18*):

$$i = k_{app} Q \exp(-k_{app} t),$$

where Q is the charge associated with converting the redox centres from one oxidation state to another.

The plot of ln(i) vs. time is linear. The experimental Tafel plot was fitted to the theoretical line of the Butler–Volmer equations for low overpotential region (*19*):

$$k_{ox} = k_{ET} \exp\left[-\frac{\lambda - 2e_0\eta}{4k_B T}\right],$$

$$k_{red} = k_{ET} \exp\left[-\frac{\lambda + 2e_0\eta}{4k_B T}\right],$$

where k_{ET} is the electron transfer rate at zero overpotential, k_{ox} and k_{red} are the apparent rate constants for anodic and cathodic processes, respectively, λ is the reorganisation energy, e_0 and k_B are the static dielectric and Boltzmann constants, respectively and η is the applied overpotential.

The dependencies of ln k_{app} vs. η for mixed AQ-Lip–hexanethiol monolayer in the presence and absence of β-CD are shown in Figure 4. The value of the standard rate constant was found to be $44.1 \pm 1.7\,s^{-1}$ without β-CD, while in solutions containing 0.1 mM β-CD, it decreased to $31.2 \pm 0.8\,s^{-1}$. In the presence of larger amounts of DMF, the rate constants decreased, probably reflecting the interaction with the solvent and a more complicated mechanism. Practically, the lack of differences upon addition of β-CD to solutions containing DMF may reflect weaker affinity of the β-CD cavity to AQ-Lip in solutions containing DMF.

In the case of adamantane–β-CD complexes, both the host and the guest are non-electroactive and a different method should be used for monitoring the complexation reaction. Our approach was to 'decorate' β-CD with a side group that is electroactive. Therefore, β-CD with an anthraquinone side group was synthesised, and its electrochemical properties were studied in the solution (Figure 5). The voltammogram showed a cathodic peak at −0.617 V. The plot of the reduction peak current vs. square root of the scan rate is shown in Figure 6. Positive deviations from linearity at larger scan rates can be explained by the contribution of adsorption of AQ-β-CD molecules on the electrode surface.

Since AD-Lip is non-electroactive, the surface concentration of modified electrodes was calculated from

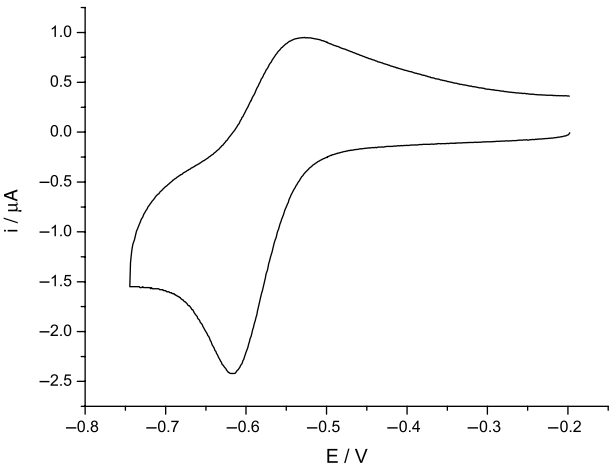

Figure 5. Cyclic voltammogram of AQ-β-CD in phosphate buffer solution with 25% DMF. Scan rate: 50 mV/s.

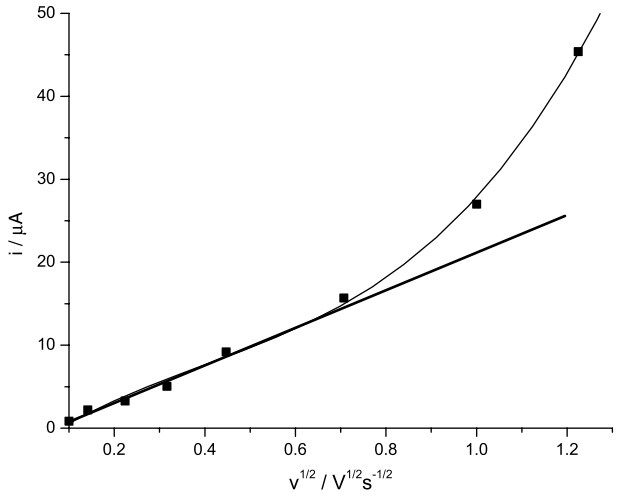

Figure 6. The dependence of cathodic peak current on the scan rate for AQ-β-CD solution. Supporting electrolyte: 0.1 M phosphate buffer+25% DMF; pH 8.9.

the electrochemical desorption of mixed AD-Lip–hexanethiol monolayer in 0.1 M NaOH. The surface concentration of the thiolated molecules in the mixed monolayer was $4.55 \pm 0.9 \times 10^{-10}$ mol/cm^2.

In phosphate buffer solution containing 25% DMF (pH 8.9), the interaction between mixed AD-Lip–hexanethiol monolayer modified electrode and AQ-β-CD could be easily detected. Figure 7(a) shows the cyclic voltammetry curves of the bare gold electrode. Curve (b) was recorded using the electrode covered with mixed AD-Lip–hexanethiol-modified gold electrode, and curve (c) shows, for comparison, the behaviour of the AQ-β-CD system in the single-component hexanethiol monolayer. The interaction between bare gold electrode and AQ-β-CD led to the appearance of a cathodic peak at −0.777 V. The hexanethiol-modified gold electrode exposed to AQ-β-CD showed a cathodic peak at a potential of 0.628 V. Finally, the two-component monolayer containing both hexanethiol and AD-Lip immersed in the AQ-β-CD solution led to the appearance of two peaks. Thus, AQ-β-CD can affect AD-Lip monolayer in two ways. First, the molecule can be incorporated between other molecules of the monolayer and interact with the electrode surface. This results in the formation of a peak at a potential of ca. −0.628 V. In addition, the molecule interacts directly with the AD-Lip component of the monolayer giving the other peak at ca. −0.735 V.

The peak at −0.735 V remains when the electrode is replaced by a clean supporting electrolyte solution, which proves the specific interaction of CD with the AD-Lip component of the monolayer.

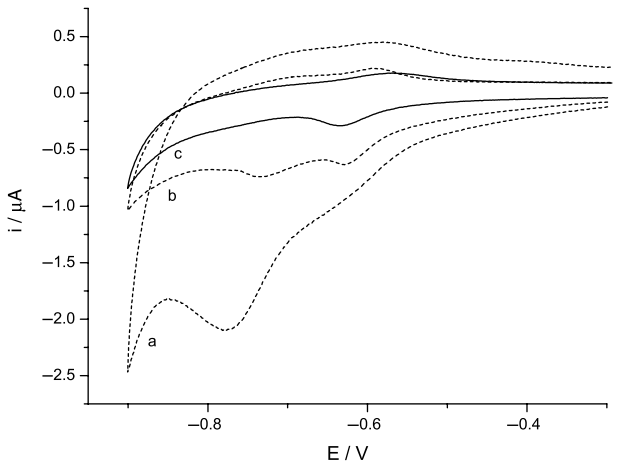

Figure 7. Cyclic voltammograms recorded using a (a) gold electrode and electrode modified by (b) a mixture of AD-Lip and hexanethiol and (c) hexanethiol in phosphate buffer containing 25% DMF; pH 8.9. All the electrodes were kept in 0.1 mM solution of AQ-β-CD for 2 h.

4. Conclusion

Interaction of β-CD with AAQ in the solution and with the surface-immobilised AQ-Lip slows down the rate of anthraquinone group reduction. In the case of solution-resident complex, the association constant can be easily evaluated based on the decrease in the diffusion coefficient of the electroactive guest due to complexation. The association constant with AAQ was $1.03 \pm 0.05 \times 10^3$ M^{-1}; hence, smaller than that of anthraquinone, which was equal to 2.86×10^3 M^{-1} (*20*).

The decrease in the electron transfer rate constants of the electroactive anthraquinone moiety upon complexation can be ascribed to the change in its immediate environment caused by the hydrophobicity of the β-CD cavity.

Surface-immobilised non-electroactive guest, AD-Lip, was also found to bind β-CD from the solution. The monolayer-covered electrode was exposed to the solution of the electroactive derivative of β-CD, AQ-β-CD, and then transferred to a pure supporting electrolyte solution. The CD was modified by the attachment of the anthraquinone group as the electroactive marker. The appearance of the voltammetric peak corresponding to the reduction of the anthraquinone side group indicated binding of β-CD to the AD-Lip monolayer, since it remained upon replacing the modified electrode to the solution of pure supporting electrolyte.

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