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pH-dependent voltammetric responses of microdisc gold electrodes modified with thiotic acid self-assembled monolayers

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This paper describes the pH dependence of cyclic voltammograms (CVs) of hexacyanoferrate(III) ($Fe(CN)_6^{3-}$) on microdisc gold electrodes (25 μm in diameter) modified with thioctic acid (TA) monolayers. The use of a microdisc electrode made it possible to directly compare the experimental CV data with theoretical simulation, and thus to discuss the main factors affecting voltammetric responses in ion-channel sensors (ICSs) based on electrostatic repulsion. Whereas unmodified gold microdisc electrodes gave very similar sigmoidal CVs at pH 2.5–7.5, TA-modified microdisc electrodes exhibited gradual decrease in the reduction current of $Fe(CN)_6^{3-}$ from pH 2.5 to 5.5 due to the deprotonation of the terminal —COOH groups of TA monolayers. The experimental pH dependence was consistent with theoretical quasi-reversible steady-state voltammograms reflecting the Frumkin effect, suggesting that the changes in the electrode reaction kinetics affected by electrode surface charge would be one of the major factors that offer voltammetric response in such ICSs.

Keywords: ion-channel sensor; microdisc electrode; self-assembled monolayer; Frumkin effect

Introduction

Ion-channel sensors (ICSs) are electrochemical sensors that can determine the concentration of a redox-inactive analyte in an aqueous solution (*1*). ICSs employ electrodes modified with thin films containing analyte-selective binding moieties (e.g. thiolate self-assembled monolayers). If the analytes bound to the thin films change the surface charge (*2*) and/or porosity of the films (*3*), they can be measured as the changes in the redox current of the electroactive markers added to the solution (e.g. $Fe(CN)_6^{3-}$). The sensitivity and selectivity of the ICSs can be regulated by controlling the affinity of binding moieties in the thin films. In addition, ICSs inherently involves signal amplification, as a small number of analytes give an electrochemical response caused by a larger number of electroactive species. As a result, the detection principle can be generally applied for designing electrochemical sensors for redox-inactive analytes, ranging from small ions and molecules (*2–10*) to relatively large bioactive molecules (*11–14*). In particular, charge-based ICSs (CB-ICSs), which exhibit voltammetric responses based on electrode surface charge changes induced by analyte complexation, will be unique tools for detecting highly charged analytes: binding of such analytes to sensor surface induces large changes in the surface charge of the thin films, leading to large voltammetric responses for charged electroactive markers (*7*, *11*, *12*).

This paper reports our attempt to experimentally and theoretically investigate the voltammetric responses of CB-ICSs based on microdisc electrodes. Understanding the response behaviour of microelectrode-based ICSs is important for their future applications in *in vivo* biological research (*15*), array-based sensor chips (*16*) and detectors in microfluidic devices (*17*). More importantly, voltammograms at a microdisc electrode can be theoretically described using closed-form equations (*18–20*), making it possible to analyse the experimental data quantitatively. Quantitative analysis based on a simple model will permit us to recognise chemical processes that play essential roles in the voltammetric response of ICSs. Although it was reported that multiple processes could be involved in the responses of ICSs (*21*, *22*), this study focused only on investigating the simplest case of voltammetric response of a CB-ICS, i.e. an ICS based on electrostatic repulsion. The voltammetric responses of such ICSs were considered on the basis of the effects of electrode surface charge on electrode reaction kinetics, the Frumkin effect (*23*, *24*).

In this study, we investigated the pH dependence of cyclic voltammograms (CVs) of $Fe(CN)_6^{3-}$ on microdisc gold electrodes modified with thioctic acid (TA) monolayers. A TA-modified microelectrode is a simple model system of an ICS based on electrostatic repulsion. The terminal —COOH groups of a TA monolayer offer a negative surface charge upon their deprotonation at higher pH, which can be recognised by measuring the redox current of charged electroactive markers (*24–26*). The use of a negatively charged marker ($Fe(CN)_6^{3-}$) will simplify our theoretical simulation, because the voltammetric

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responses originate from the marker molecules diffusing from the solution, rather than those adsorbed onto the electrode (*21*). The CVs of $Fe(CN)_6^{3-}$ on a TA-modified microelectrode at pH 1.5 and 7.4 were previously reported (*26*), but were not discussed quantitatively using theoretical equations.

Experimental section

Chemicals

All the solutions were prepared with ultra-pure water with a specific resistance greater than 18.0 MΩ cm (Barnstead Nanopure Systems, Dubuque, IA, USA). Potassium chloride (KCl; Fisher, Fair Lawn, NJ, USA), potassium hydroxide (KOH; Fisher), hydrochloric acid (HCl; Fisher), potassium dihydrogen phosphate (KH_2PO_4; Fisher), potassium hydrogen phosphate (K_2HPO_4, Fisher), potassium hexacyanoferrate(III) ($K_3Fe(CN)_6$; Acros Organics, Geel, Belgium) and TA (TCI, Tokyo, Japan) were of analytical grade and used as received.

Electrode preparation and electrochemical measurements

A gold microdisc electrode (25 μm in diameter; CH Instruments, Austin, TX, USA) was polished with wet alumina slurry (0.05 μm; Buehler, Lake Bluff, IL, USA). The polished electrode was dipped in an ethanolic solution of 5 mM TA overnight, and then washed with ethanol and subsequently with ultra-pure water prior to use. Electrochemical measurements were performed in a three-electrode set-up containing an Ag–AgCl (3 M KCl) reference electrode and a Pt counter electrode with a CH Instrument 720C electrochemical analyser. The CVs of gold microdisc electrodes before and after TA modification were measured in 3.0 mM $K_3Fe(CN)_6$ solutions containing 0.1 M KCl and 10 mM phosphate (pH 2.5, 3.5, 4.5, 5.5, 6.5 and 7.5) at room temperature (ca. 25°C). The relative standard deviation of the reduction current of ($Fe(CN)_6^{3-}$) obtained at 3–6 separate TA-modified electrodes was ca. 20%, probably due to the variation in the molecular packing of the TA monolayers. The reproducibility of the CV data was not improved by increasing the TA modification time or by electrochemically cleaning a microdisc gold electrode in an aqueous KOH or H_2SO_4 solution prior to TA modification. Theoretical voltammograms for the reduction of $Fe(CN)_6^{3-}$ on microelectrodes under the influence of the Frumkin effect were obtained using MS-Excel.

Results and discussion

Stability of the TA monolayer on a microdisc gold electrode

First, we examined the stability of a TA-modified microdisc gold electrode during multiple CV measurements in 3.0 mM ($Fe(CN)_6^{3-}$) solutions. Figure 1 shows the voltammetric response of a TA-modified microelectrode for $Fe(CN)_6^{3-}$ as a function of pH. The CV measurements were performed in seven separate solutions with different pH, from acidic (2.5) to neutral pH (7.5) and then a pH of 2.5. The reduction current of $Fe(CN)_6^{3-}$ was smaller at higher pH, reflecting deprotonation of the terminal —COOH groups of the TA monolayer (*26*). However, the second measurement at pH 2.5 exhibited a larger reduction current as compared with the first measurement at pH 2.5, suggesting desorption of TA from the gold surface during the CV measurements, probably due to the etching of gold by $Fe(CN)_6^{3-}$ (*27*). The etching may have occurred at the defects in the loosely packed TA monolayer: its surface coverage (3.1×10^{-10} mol/cm^2) (*28*) was much lower than that of densely packed alkanethiol monolayers (2.5×10^{-9} mol/cm^2) (*18*). Because of the relatively low stability of the TA monolayer in $Fe(CN)_6^{3-}$ solutions, each freshly prepared TA-modified microelectrode was used to measure one CV datum at a certain pH condition.

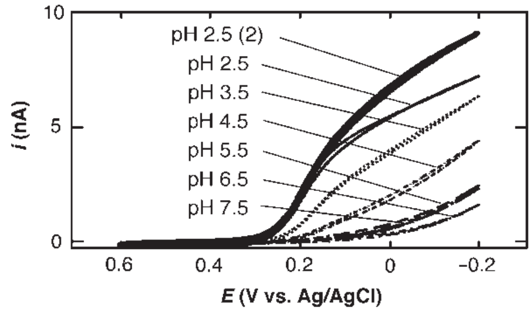

Figure 1. Typical voltammetric response (scan rate: 10 mV/s) of a TA-modified microdisc gold electrode (25 μm in diameter) for $Fe(CN)_6^{3-}$ as a function of pH. CV measurements were taken at pH 2.5–7.5 and then at pH 2.5 (pH 2.5 (2)) in 3.0 mM $Fe(CN)_6^{3-}$ solutions containing 0.1 M KCl and 10 mM phosphate at room temperature (ca. 25°C).

pH dependence of the CVs of $Fe(CN)_6^{3-}$ on freshly prepared TA-modified microdisc gold electrodes

Figure 2 shows the typical CVs of $Fe(CN)_6^{3-}$ on microdisc gold electrodes before and after TA modification at different pH. Bare microdisc gold electrodes exhibited very similar sigmoidal CVs at all the pH conditions examined. The similarity in limiting currents (i_{lim}) and CV shapes indicates that the solution pH did not affect the diffusion coefficient (D) and electron-transfer rate constant (k^0) of $Fe(CN)_6^{3-}$. These parameters were calculated from the CV data using the following equations (*18*, *19*):

$$i_{\mathrm{lim}} = 4nFDCr \tag{1}$$

$$\frac{i}{i_{\mathrm{lim}}} = \frac{1}{\frac{D}{rk}\exp\left[\frac{\alpha F}{RT}(E - E^{0\prime})\right] + 1 + \exp\left[\frac{F}{RT}(E - E^{0\prime})\right]} \tag{2}$$

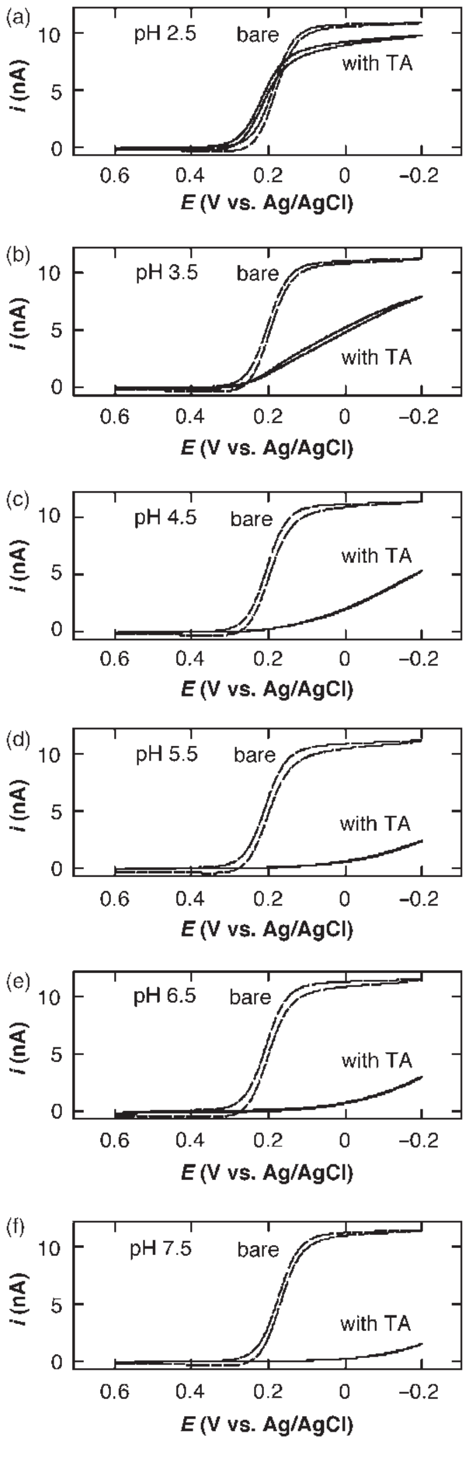

Figure 2. CVs (scan rate: 10 mV/s) of $Fe(CN)_6^{3-}$ on microdisc gold electrodes (25 μm in diameter) before (dashed lines) and after (solid lines) TA modification in solutions of different pH. Each CV was measured at a freshly prepared electrode. Measurements were taken in 3.0 mM $Fe(CN)_6^{3-}$ solutions containing 0.1 M KCl and 10 mM phosphate at room temperature (ca. 25°C).

where n is the number of electrons ($n = 1$ for $Fe(CN)_6^{3-}$), F is Faraday's constant ($= 96{,}485$ C/mol), C is the concentration of $Fe(CN)_6^{3-}$ ($= 3.0$ mM), r is the radius of the disc electrode ($= 12.5$ μm), R is the gas constant ($= 8.31$ J/K mol), T is the temperature ($= 298$ K for 25°C), k is the electron-transfer rate constant ($= k^0$ at an unmodified gold electrode), α is the transfer coefficient (≈ 0.5), E is the applied potential and $E^{0'}$ is the formal potential of $Fe(CN)_6^{3-/4-}$. Regardless of the solution pH, D and k^0 of $Fe(CN)_6^{3-}$ were similar (Figure 3), with values of ca. 7.7×10^{-6} cm^2/s and 2.5×10^{-2} cm/s, respectively, which were very close to literature values (*18*, *29*).

In contrast, the reduction current of $Fe(CN)_6^{3-}$ on TA-modified microelectrodes gradually decreased from pH 2.5 to 5.5, and then was similar at higher pH. At pH 2.5, a quasi-reversible CV was observed, although the limiting current was slightly smaller than that at the microelectrode prior to TA modification. At a higher pH, the CVs were less reversible, suggesting a decrease in the rate constant of the electrode reaction. These observations could be related to the deprotonation of the —COOH groups of the TA monolayer covalently immobilised onto the electrode surface, as described in 'Stability of the TA monolayer on a microdisc gold electrode' section (*26*). In contrast, electrodes coated with insulator-based nanopores having ionisable surface functional groups exhibited pH-dependent CV changes with similar reversibility, which could be explained by the changes in the effective pore size due to the electrical double layer extending from the pore surface (*30–34*). The CV data of TA-modified microdisc electrodes were compared to the theoretical voltammograms in 'Theoretical voltammetric responses of TA-modified microdisc electrodes' section.

Theoretical voltammetric responses of TA-modified microdisc electrodes

As discussed above, the pH-dependent changes in voltammetric reversibility at TA-modified electrodes could reflect electrode reaction kinetics on charged electrodes that can be interpreted based on the Frumkin effect (*18*). In the Frumkin effect, electrode reaction

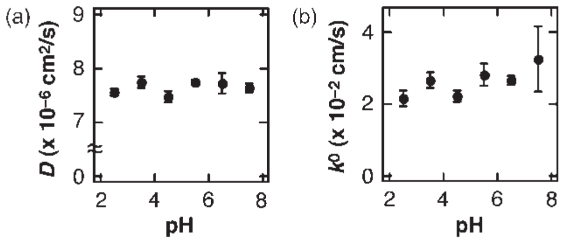

Figure 3. (a) D and (b) k^0 values of $Fe(CN)_6^{3-}$ measured at bare microdisc gold electrodes (25 μm in diameter) in 3.0 mM $Fe(CN)_6^{3-}$ solutions containing 0.1 M KCl and 10 mM phosphate at room temperature (ca. 25°C). The plots and error bars indicate the averages and standard deviations obtained from three separate electrodes.

kinetics is affected by the changes in the (i) distribution of ionic electroactive species at a charged electrode surface due to electrostatic interactions and (ii) effective potential driving the redox reaction at a charged electrode. The rate constant at a charged electrode (k^0_{eff}) can be related to the rate constant at a bare electrode (k^0) using the following equation (*18*, *20*, *35*):

$$k^0_{\mathrm{eff}} = k^0 \exp\left[\frac{(\alpha - z_{\mathrm{red}})F\phi_2}{RT}\right] \tag{3}$$

where z_{red} is the charge of the electroactive species ($z_{\mathrm{red}} = -3$ for $\mathrm{Fe(CN)}_6^{3-}$) and ϕ_2 (V) is the potential at the outer Helmholtz plane. In a 1:1 electrolyte, ϕ_2 is described using the electrode surface charge density, σ (C/cm^2), according to the Gouy–Chapman theory (*18*):

$$\sigma = (8RT\varepsilon\varepsilon_0 C_{\mathrm{elec}})^{1/2} \sinh\left(\frac{zF\phi_2}{2RT}\right) \tag{4}$$

where z is the charge of the supporting electrolyte ions (here, $z = 1$), ε is the dielectric constant of the solution ($\sim$78.35), ε_0 is the permittivity of free space ($= 8.85 \times 10^{-12}$ F/m) and C_{elec} is the supporting electrolyte concentration ($\sim$0.1 M). Assuming that the electrode surface density is determined by the charge of a TA monolayer, σ can be described using the following equation regarding the protonation/deprotonation of the surface —COOH groups (*36*):

$$\sigma = -\frac{FK_{\mathrm{a}}\Gamma_{\mathrm{COOH,total}}}{[\mathrm{H}^+] + K_{\mathrm{a}}} \tag{5}$$

where K_{a} is the apparent acid dissociation constant of the surface $-$COOH groups, $\Gamma_{\mathrm{COOH,total}}$ is the TA density on the electrode surface ($= 3.1 \times 10^{-10}$ mol/cm^2) (*28*) and [H$^+$] is the proton concentration in the solution. A solid-form equation describing the relationship between i/i_{lim} and $E - E^0$ could be obtained from Equations (2)–(5) ($k = k^0_{\mathrm{eff}}$ in Equation (2)), and was used to simulate the pH dependence of voltammetric response of a TA-modified microdisc electrode.

Figure 4 shows the theoretical voltammetric pH responses for the reduction of a trivalent redox-active anion at microdisc electrodes coated with monolayers having acidic functional groups. The pH dependences were simulated by varying the apparent surface pK_{a} of the acidic groups. In all the cases, more reversible voltammograms could be obtained at lower pH, reflecting larger k^0_{eff} value due to smaller negative surface charge, as suggested by Equation (3). In addition, the trivalent redox-active anion could be reduced at higher pH, for surface acidic groups having higher apparent surface pK_{a}, i.e. higher affinity to H$^+$. Importantly, the pH dependence measured experimentally (Figure 2) was close to the one theoretically obtained with the apparent surface pK_{a} of 5.5 (Figure 4(c)), which was consistent with that of surface —COOH groups in loosely packed monolayers (*37*). Indeed, the apparent surface pK_{a} estimated using the least-squares fitting of the theoretical curves to the CV data was 5.42. Using the pK_{a} value, k^0_{eff} values (cm/s) for the trivalent redox-active anion were calculated as 1.1×10^{-2} (pH 2.5), 5.5×10^{-5} (pH 3.5), 3.5×10^{-11} (pH 4.5), 5.9×10^{-16} (pH 5.5), 1.6×10^{-17} (pH 6.5) and 1.2×10^{-17} (pH 7.5). The decrease in the k^0_{eff} values from pH 2.5 to 5.5 originates from an increase in the surface

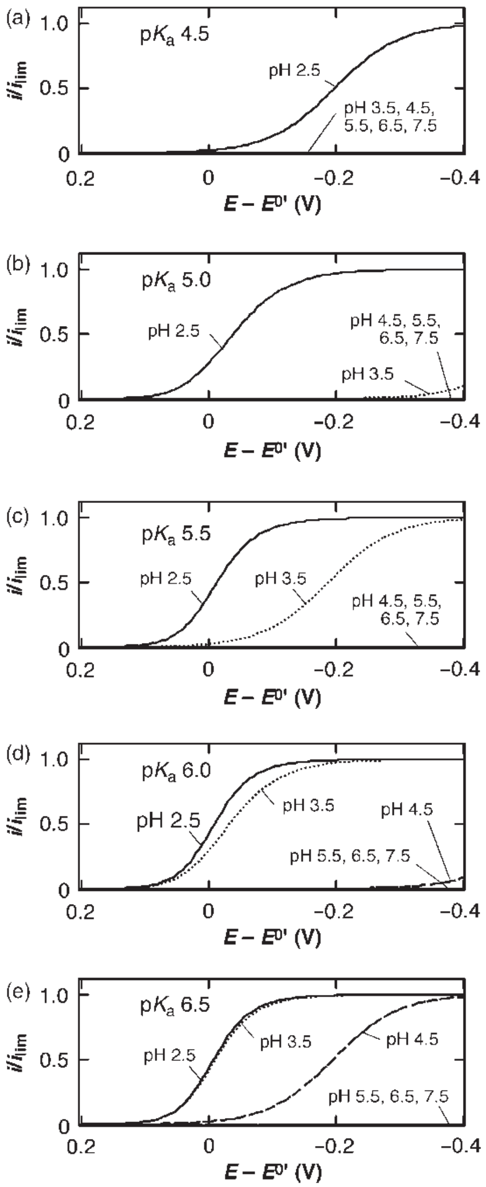

Figure 4. Theoretical voltammetric pH responses for the reduction of a redox-active trivalent anion at microdisc electrodes coated with acidic functional groups having different apparent surface pK_{a} values: (a) pK_{a} 4.5, (b) pK_{a} 5.0, (c) pK_{a} 5.5, (d) pK_{a} 6.0 and (e) pK_{a} 6.5. The k^0 and D values employed for the simulation were obtained from Figure 3. The currents were normalised by the transport-limited current value (i_{lim}).

negative charge due to the deprotonation of the surface acidic groups, leading to voltammetric response. The similarity between the experimental and theoretical data suggests that the voltammetric response of a TA-modified electrode to pH can be primarily explained on the basis of the variation in the electrode reaction kinetics of $Fe(CN)_6^{3-}$ due to the charge of the COOH-terminated surface. On the other hand, experimental reduction currents at pH higher than 4.5 were greater than the theoretical currents (Figure 2(c)–(f) vs. Figure 4(c)), probably reflecting the presence of defects in the TA monolayers. It should be noted that the theoretical equations could be used for predicting the effects of different parameters, including the density and affinity of surface-binding moieties as well as the charges of the analytes and electroactive markers on the voltammetric responses of microelectrode-based CB-ICSs.

Conclusions

This paper reported our experimental and theoretical investigations on the pH dependence of the CVs of $Fe(CN)_6^{3-}$ on TA-modified microdisc electrodes. Although the defects of a monolayer significantly influenced the experimental CV data, the voltammetric pH responses measured experimentally were similar to quasi-reversible steady-state voltammograms simulated in consideration of the Frumkin effect. The similarity suggests that changes in electrode reaction kinetics reflecting the distribution of $Fe(CN)_6^{3-}$ and the effective potential at the charged electrode surface would be one of the major factors offering voltammetric responses of ICSs based on electrostatic repulsion.

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