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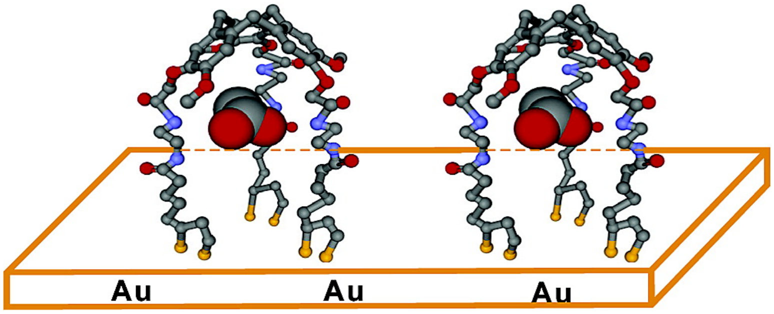

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Selective Anion Sensing by a Tris-Amide CTV Derivative: ^{1}H NMR Titration, Self-Assembled Monolayers, and Impedance Spectroscopy

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Abstract: A hydrogen-bond forming tris(amide) receptor based on cyclotriveratrylene (CTV) was prepared. Self-assembled monolayers (SAMs) of the receptor were formed on gold surfaces. Desorption experiments show a surface coverage of 2.26×10^{-10} mol/cm^2. ^{1}H NMR and UV measurements confirm that the receptor exhibits the highest affinity for acetate ions among the anions studied. Electrochemical impedance was used to investigate anion sensing by the SAMs and proved to be an efficient and convenient technique for detecting anions in aqueous solutions. Upon binding acetate anions, the monolayer-modified gold electrodes show a drastic increase of the R_{ct} values when $Fe(CN)_6^{3-/4-}$ is used as the redox probe. When the probe was changed to a positively charged one, $Ru(NH_3)_6^{3+/2+}$, the R_{ct} values decreased monotonically as the acetate concentration was increased, thus confirming the accumulation of negative surface charge upon anion binding. $H_2PO_4^-$ shows some interference when sensing AcO^-. Other monovalent anions such as Cl^-, Br^-, NO_3^-, and HSO_4^- do not bind to the CTV receptor either in solution or on the surfaces.

Introduction

As compared to the well-developed field of cation binding and sensing, anion recognition is a more challenging field due to the variable size, shape, and strong solvation of the species.[1] The recognition and sensing of anionic species has recently gained more attention and has emerged as a promising research area for the development of environmentally and biologically related anion sensors.[2−4] Generally, anion sensors are based either on electrochemical or on fluorescent properties, where electrochemically active groups or fluorophores have to be incorporated into the receptors to signal the anion complexation phenomena. On the other hand, a few colorimetric anion sensors have also been reported which allow "naked-eye" detection of anion species.[5−7] However, such chemosensors usually require intricate chemical design and laborious synthetic construction.

Most anion sensors reported thus far have been investigated in solution, especially in organic media. Anion recognition in aqueous media remains a challenging task. Receptors for anions that are based solely on hydrogen-bonding interactions cannot serve as efficient sensors in aqueous media due to the strong solvent competition. Another limitation usually encountered is that neutral receptors for anions are typically soluble in organic solvents instead of water. However, specific sensors for small inorganic anions that exist in natural aqueous environments are needed. Although the use of positively charged anion receptors exhibiting strong electrostatic interactions can overcome competing solvation effects and improve the solubility in aqueous systems, their counteranions can interfere with the anion sensing process.[1,8] Because of this, anion binding using hydrogen bonding is normally preferred over the use of electrostatic interactions.[9] For example, anion binding by polyanionic DNA is basically controlled by hydrogen bonding with the amide NH groups. Yet anion sensing using these receptors in aqueous media remains a problem. Incorporation of these molecular recognition properties into self-assembled monolayers (SAMs) offers a possible solution. By attaching sensing groups to the electrodes, the anion recognition event can be detected at the interface between the electrode and the anion-containing aqueous solution. Thus far, anion sensing using SAMs remains largely unexplored. Some of the few examples that have been reported include a dihydrogenphosphate anion sensor derived from a SAM-modified gold electrode by an amidoferrocene derivative.[10] Ohsaka et al. also investigated anion recognition by SAMs modified with a nickel azamacrocycle complex.[11] Beer et al. studied the anion recognition properties of ferrocene SAMs on gold surfaces[12] and metalloporphyrin-functionalized gold nanoparticles.[13] In addition, the anion sensing properties of gold nanoparticles modified by ferrocene derivatives were investi-

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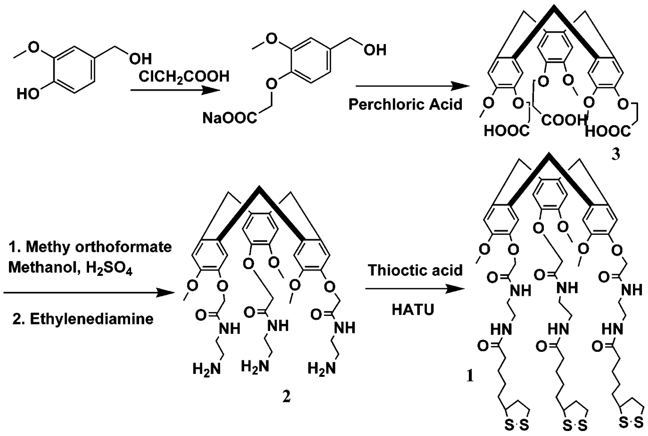
Scheme 1. Synthesis of CTV Thioctic Ester Derivative **1**



gated in organic solution by Astruc et al.[14,15] In all of those cases, electrochemically active groups were included to monitor the anion sensing processes.

Impedance spectroscopy is a powerful technique for studying the recognition properties of electrochemically inactive SAMs with guest species.[16] The cation recognition properties of some SAMs have been investigated by impedance spectroscopy.[17] We have recently studied the selective K^+ recognition by SAMs of oligoethylene glycol derivatives[18] and the metal cation sensing properties of self-assembled monolayers of calix[4]crown-6 derivatives.[19,20] We also developed a remarkably selective anilinium cation sensor using SAMs of a calix[6]crown-4 derivative.[21] As far as we know, impedance spectroscopy has never been employed to investigate anion sensing at the interface of SAM-modified electrodes and aqueous electrolyte solutions. Here, we report the preparation of SAMs containing a rigid and electrochemically inactive CTV derivative and the use of impedance spectroscopy to study its anion sensing properties. Anion recognition on the surfaces was demonstrated by using both positively and negatively charged redox probes.

Results and Discussion

Synthesis of the Thioctic Ester Derivative of Cyclotriveratrylene (CTV). The synthetic procedure for preparing target compound **1** is depicted in Scheme 1. CTV−tris-amine compound **2** was obtained following a published procedure with small modifications.[22] CTV−tris(methyl ester) **4** was prepared by treatment of tris-acid **3** with trimethyl orthoformate and methanol. We do not get a satisfactory yield of **4** following this procedure. However, addition of sulfuric acid to the reaction mixture makes the esterification reaction more efficient. Coupling of the CTV−tris-amine compound with thioctic acid in the presence of HATU and triethylamine afforded the target compound in 67% yield.[23,24] We also tried DIC and HOBt as the coupling reagents, but the reaction gave worse yields. The structure and conformation of **1** were confirmed by ^{1}H and ^{13}C NMR, MS, and elemental analysis.

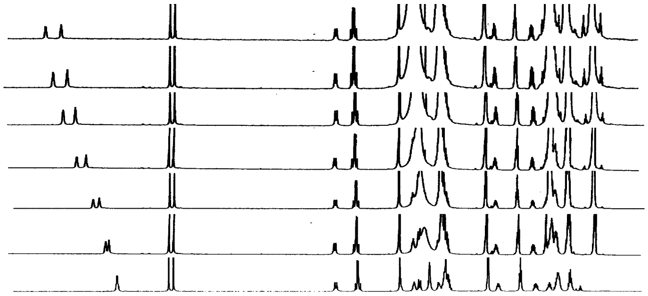


Figure 1. 500 ^{1}H NMR spectra of compound **1** in DMSO-d_6 at room temperature. From bottom to top: **1** only; **1** + 1.35 equiv of tetrabutylammonium acetate; **1** + 3 equiv; **1** + 6 equiv; **1** + 11 equiv; **1** + 18 equiv; **1** + 33 equiv.

^{1}H NMR Titration of 1 with Different Anions. Because of the low solubility of compound **1** in $CDCl_3$, the NMR titration experiments were carried out in DMSO-d_6. We studied the binding ability of the target ligand with the monovalent anions Cl^-, Br^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, and AcO^- as their tetrabutylammonium salts. The NH protons of the unequivalent amide groups in the compound were monitored, and they were found to exhibit one broad single peak around 7.86 ppm. The NH signals were not affected upon addition of Cl^-, Br^-, NO_3^-, or HSO_4^-, suggesting that compound **1** does not interact significantly with these anions. Upon addition of $H_2PO_4^-$, a small downfield shift was observed for the NH protons and the single peak was split into two peaks at 7.98 and 8.01 ppm, respectively. In the case of AcO^- addition, significant downfield shifts of the NH peaks were observed. Figure 1 shows the ^{1}H NMR spectra for the titration of receptor **1** with tetrabutylammonium acetate. The broad single peak at 7.86 ppm shifts downfield and splits upon the addition of acetate salts and eventually results in two well-defined single peaks at 8.69 and 8.92 ppm in the presence of 34 equiv of AcO^-. As expected, the signals for other protons in compound **1** exhibit essentially no shift upon AcO^- addition. These observations indicate that the host **1** can bind weakly with $H_2PO_4^-$ but much more strongly with AcO^- through hydrogen bonds. Two different kinds of amide NH groups contribute to the formation of the complex but to a different extent. Figure 2 shows the plot of the chemical shift versus the number of equivalents of acetate anion. A nonlinear least-squares fit was consistent with a 1:1 receptor/anion stoichiometry. Binding constants of compound **1** with AcO^- and $H_2PO_4^-$ are 57 (±0.9) and 14 (±1.3) M^{-1}, respectively, by fitting the NMR titration data with a program developed by Diederich et al.[25] The complexation and electrochemical sensing of $H_2PO_4^-$ by CTV-based receptors has been reported,[26] but not with acetate.

Anion Sensing Detected by UV−Vis Spectroscopy. The binding properties of **1** with different anions were also assessed via UV−vis spectroscopy. Figure 3 shows the changes in the

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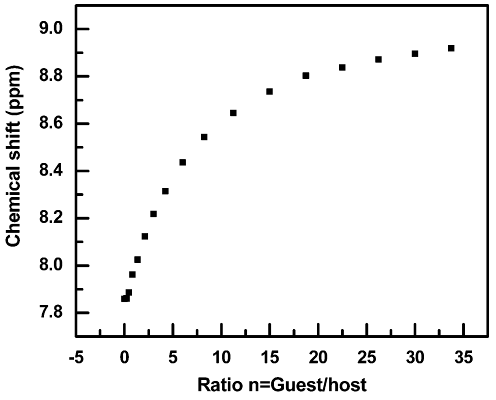

Figure 2. Titration binding curves for receptor **1** with acetate.

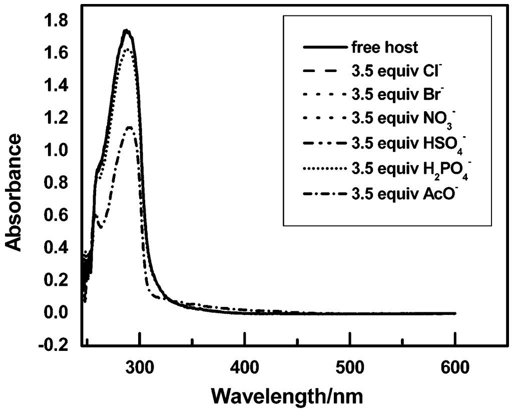

Figure 3. UV spectra of **1** upon the addition of 3.5 equiv of tetrabutylammonium chloride, bromide, nitrate, bisulfate, dihydrogen phosphate, and acetate in DMSO.

UV spectra of **1** at a concentration of 1.11×10^{-4} M in DMSO upon the addition of different anions. The absorption band for the free receptor appears at 288 nm with a shoulder around 260 nm. When 3.5 equiv of Cl^-, Br^-, NO_3^-, or HSO_4^- was introduced to the solution of **1**, the absorbance remained unchanged, again indicating no significant interaction between these anions and the receptor. Addition of the same equivalent amount of $H_2PO_4^-$ leads to a slight decrease of the intensity of the absorption band at 288 nm. However, the intensity of the absorbance decreased drastically when 3.5 equiv of AcO^- was added to the solution of **1**. Further addition of AcO^- to the solution did not decrease the intensity any more. These observations demonstrate that receptor **1** cannot bind appreciably with Cl^-, Br^-, NO_3^-, or HSO_4^-, that it binds weakly with $H_2PO_4^-$, but binds more strongly with AcO^-.

Preparation and Characterization of SAMs. Gold bead electrodes were prepared as described earlier from gold wire with a 99.999% purity.[19–21,27] SAMs of **1** were obtained by dipping the gold beads into 20% $MeOH/CH_2Cl_2$ solutions of **1** for 48 h. After being rinsed with copious amounts of these solvents and dried under a stream of Ar, the SAM-modified gold beads were used as working electrodes to investigate the anion sensing properties in an electrolyte solution containing 1 mM of $Ru(NH_3)_6Cl_3$ or $K_3Fe(CN)_6$. The SAMs of **1** were characterized by observing their CV blocking effect on the $Fe(CN)_6^{3-/4-}$ redox couple as shown in Figure 4 (solid line). A complete absence of the redox current reveals that densely packed SAMs are formed on gold surfaces that block the redox processes very well. Electrochemical desorption experiments were performed by immersing the SAM-modified gold beads into thoroughly degassed 0.5 M KOH by high-purity Ar for 25 min. The scans were initiated at a potential of 0.00 V and swept cathodically to a potential of −1.35 V at a scan rate of 0.1 V/s. As shown in Figure 5, the modified gold electrodes exhibit a cyclic voltammetric response with an irreversible cathodic wave at ca. −1.0 V, which is due to the reductive desorption of the surface-attached thiolates. The shape and position of the desorption peak are similar to those previously reported for SAMs of thioctic acid.[28,29] By integrating the current under the cathodic wave, the estimated surface coverage for the CTV thioctic ester was 2.26×10^{-10} mol/cm^2. After desorption, the CV was recorded again, and a nearly reversible cyclic voltammetric response was observed (Figure 4, dashed line), as expected.

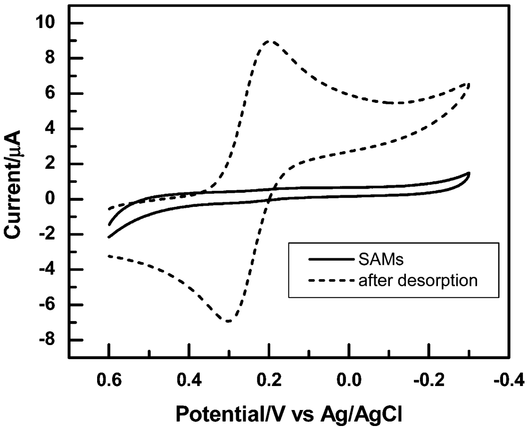

Figure 4. CV of $Fe(CN)_6^{3-/4-}$ in 0.1 M aqueous $NaPF_6$ at SAM-modified gold electrodes with **1** before (−) and after (- - - -) electrochemical desorption of **1**.

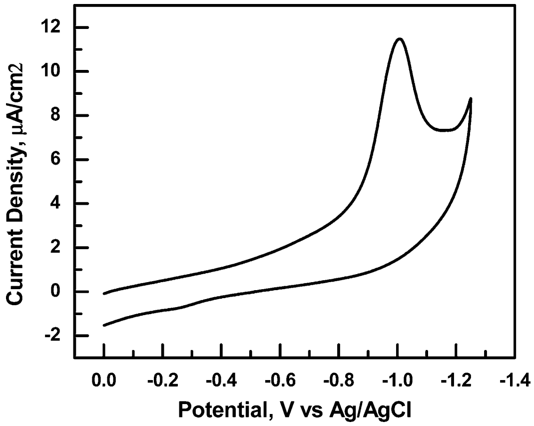

Figure 5. Electrochemical desorption of SAMs of **1** on Au in 0.5 M KOH.

Anion Sensing Properties of the Monolayers by Impedance Spectroscopy Using $Fe(CN)_6^{3-/4-}$ as the Redox Probe. Impedance spectroscopy was also employed to investigate the interfacial anion sensing process using an electrochemically active redox probe. Electrochemical impedance is based upon measurement of the response of the electrochemical cell to an alternating potential. Binding of charged analytes to the receptors immobilized on the electrode surfaces can affect the electron-

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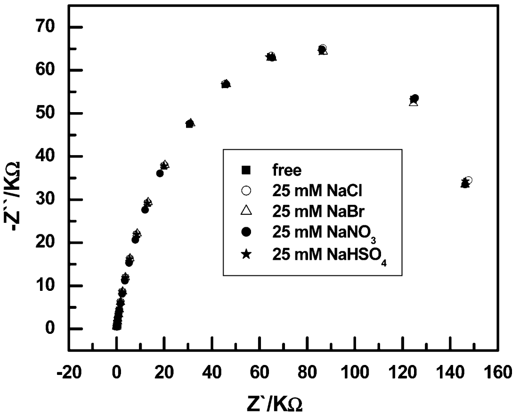

Figure 6. Impedance response of $Fe(CN)_6^{3-/4-}$ at the monolayer-modified gold electrodes in the absence and presence of 25 mM of Cl^-, Br^-, NO_3^-, and HSO_4^-.

transfer process between the electrodes and the charged redox probes in solutions due to the electrostatic attraction or repulsion between the SAM surface and the redox couple in the electrolyte solutions. The AC response can be analyzed using a simple Randles equivalent circuit,[30] which consists of a charge-transfer resistance across the SAMs, R_{ct}, in series with a Warburg impedance and in parallel with a total interfacial capacitance. The R_{ct} will reflect the charge-transfer resistance across the SAMs and thus can be used to detect the binding events that occur at the interface between the electrodes and the analyte-containing electrolytes. Figure 6 shows the complex impedance responses of 1 mM $Fe(CN)_6^{3-/4-}$ at a SAM-modified gold electrode in the absence and presence of different anions. The monolayer-modified gold electrodes exhibit a value of 162 kΩ for R_{ct}, suggesting very densely packed SAMs which effectively block electron transfer to the redox probe at the monolayer/solution interfaces. The complex impedance obtained at a bare gold electrode exhibits mainly a linear part (Warburg impedance) due to a fast electrode reaction. Upon the addition of 25 mM of Cl^-, Br^-, NO_3^-, and HSO_4^- to the electrolytes, no effect on the charge-transfer resistance was observed, indicating that the SAM receptors cannot bind with these anions, and the surface charge is unchanged.

In contrast, the impedance response of the same monolayers upon AcO^- additions is very dramatic. As shown in Figure 7, addition of AcO^- to the electrolyte results in a pronounced increase in the value of R_{ct}, from 162 kΩ in the absence of AcO^- to a limiting value of 329 kΩ in the presence of ≥ 15 mM AcO^-. These results indicate substantial negative charge buildup on the surface due to anion binding. The electrostatic repulsion between the negatively charged redox probe and the negatively charged SAM surface gives rise to the increase of R_{ct}. Also, addition of 10 mM of AcO^- to the electrolytes containing 25 mM of the other anions (Cl^-, Br^-, NO_3^-, and HSO_4^-) results in a similar increase of R_{ct}. At $[AcO^-] = 15$ mM, the R_{ct} approaches a limiting value, indicative of surface binding site saturation. The same monolayer responds weakly to the presence of $H_2PO_4^-$ as demonstrated in Figure 8. The R_{ct} value increased to 183 kΩ upon the addition of 25 mM of $H_2PO_4^-$. Further addition of $H_2PO_4^-$ to the electrolyte does not change the R_{ct} value. These observations are in perfect agreement with those obtained in bulk solution via ^1H NMR and UV−vis measurements. Experiments conducted both on the surface and in solution confirm that the CTV receptor **1** has a higher affinity for AcO^- than for all other anions investigated. Sensing of AcO^-, an important anion in fermentation processes and food science,[31] is done using techniques such as high-pressure liquid chromotagraphy,[32] capillary isotachophoresis,[33] ion selective electrode,[34] and gas permeable membranes.[35] However, there is still a need for simple and selective determination of acetate.

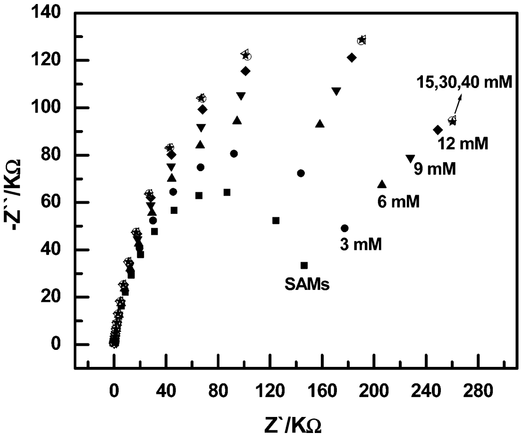

Figure 7. Impedance response of $Fe(CN)_6^{3-/4-}$ at the electrode modified by SAMs of **1** in the absence and presence of increasing $[AcO^-]$.

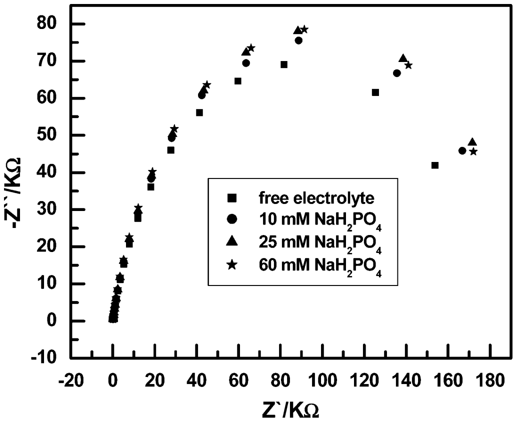

Figure 8. Impedance response of $Fe(CN)_6^{3-/4-}$ at the electrode modified by SAMs of **1** in the absence and presence of increasing $[H_2PO_4^-]$.

Anion Sensing Properties of the Monolayers by Impedance Spectroscopy Using $Ru(NH_3)_6^{3+/2+}$ as the Redox Probe. To further prove the anion recognition properties of the receptor on the surfaces, the positively charged redox probe $Ru(NH_3)_6^{3+/2+}$ was employed. While anion complexation at the electrode surfaces hinders the approach of the negatively charged redox probe, $Fe(CN)_6^{3-/4-}$, it should facilitate the access of the cationic redox probe, $Ru(NH_3)_6^{3+/2+}$, due to electrostatic attraction. Both CV and impedance experiments show that the same SAM-modified electrodes exhibit a better blocking effect for the negatively charged redox probe, $Fe(CN)_6^{3-/4-}$, than for the positively charged redox couple, $Ru(NH_3)_6^{3+/2+}$. Creager et al.

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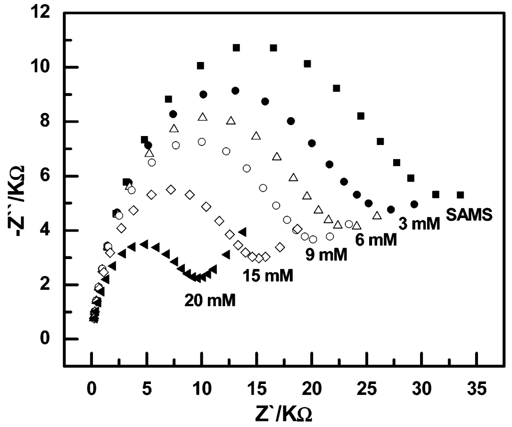

Figure 9. Impedance response of $Ru(NH_3)_6^{3+/2+}$ at the electrode modified by SAMs of **1** in the absence and presence of increasing [AcO^-].

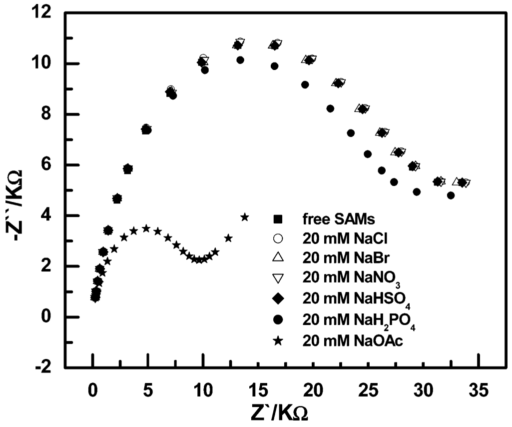

Figure 10. Impedance response of $Ru(NH_3)_6^{3+/2+}$ at the monolayer-modified gold electrode in the absence and presence of 20 mM of Br^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, and AcO^-.

found that redox probe molecules which exhibit fast homogeneous electron self-exchange kinetics also exhibit relatively rapid interfacial electron-transfer kinetics at a SAM-modified electrode.[36] The electron-transfer rate for $Fe(CN)_6^{3-/4-}$ is slower than that for $Ru(NH_3)_6^{3+/2+}$ because $Fe(CN)_6^{3-/4-}$ is more highly charged. Figure 9 shows the impedance spectroscopy of a SAM-modified gold electrode using 1 mM of $Ru(NH_3)_6^{3+/2+}$ as the redox probe in the presence of different concentrations of AcO^-. As expected, addition of AcO^- to the electrolyte leads to a decrease in the value of R_{ct}, from 33.9 kΩ in the absence of AcO^- to 10.9 kΩ in the presence of 20 mM of AcO^-. The electrostatic attraction between the positively charged probes and the increasingly negative SAM surfaces, due to anion binding, increases the local concentrations of the redox probe and facilitates the electron transfer to/from $Ru(NH_3)_6^{3+/2+}$. Anion binding to these SAMs was found to be reversible, as was the case when $Fe(CN)_6^{3-/4-}$ was used. When the sodium acetate containing solution was replaced with simple electrolyte, R_{ct} returned to its original value.

The sensing properties of the monolayer of **1** to other anions were also monitored by impedance spectroscopy using $Ru(NH_3)_6^{3+/2+}$ as the redox probe. As shown in Figure 10, addition of 20 mM of Cl^-, Br^-, NO_3^-, and HSO_4^- does not change the R_{ct} value, indicating that these anions are not bound by the receptor monolayer. Addition of $H_2PO_4^-$ decreases the R_{ct} value somewhat from 33.9 kΩ in the absence of $H_2PO_4^-$ to 31.2 kΩ in the presence of 20 mM of sodium dihydrogenphosphate. However, addition of 20 mM of AcO^- lowers the value of R_{ct} to 10.9 kΩ. It should be noted that we have used, for the first time, both positively and negatively charged redox couples to probe the anion sensing properties of SAM-modified electrodes by impedance spectroscopy. Even in the presence of an aqueous environment, anion recognition by hydrogen bonding is easy to detect in this manner. This is attributed to the hydrogen bonds at the monolayer/water interface being stronger than those in bulk water solution.[37] The high stability of the interfacial complexes may be due to the low dielectric constant of the monolayer phase.[38]

Conclusions

A tripodal CTV anion receptor was prepared. The anion recognition properties of the receptor were evaluated via ^1H NMR and UV−vis spectroscopy in solution and exhibit selective binding with AcO^-. After immobilizing the CTV thioctic ester derivative on gold surfaces, impedance spectroscopy was used to detect the anion sensing properties of the resulting SAMs. Impedance responses obtained by employing both negatively and positively charged redox couples confirmed that selective acetate anion binding occurred on the surfaces, consistent with the results obtained in bulk solution. The use of impedance spectroscopy measurements on SAMs provides several advantages for anion sensing: (a) anion sensing can be easily conducted in aqueous systems, (b) practical anion sensors are possible by assembling receptor on surfaces, and (c) any suitable receptors can be used even in the absence of electrochemical or fluorescent active centers, thus broadening the options for the development of more selective and sensitive anion sensors.

Experimental Section

General. The syntheses of **2**−**4** have been reported before.[22] NMR spectra were recorded on a Bruker Ac 300 spectrometer, and the NMR titration experiments were recorded on a Eclipse$^+$ 500 spectrometer. The transmission infrared spectra of the compounds were recorded on a Perkin-Elmer 2000 FT-IR spectrophotometer. UV−vis spectroscopy was recorded on a Shimadzu 2101PC spectrophotometer. Mass spectroscopy was recorded with an Omni Flex Maldi TOF spectrometer. Elemental analyses were performed using a Carlo Erba EA 1106. Deionized water was prepared with a Nanopure infinity ultrapure water system. All anions studied here were used as their corresponding sodium salts.

Electrochemical Measurements. All electrolyte solutions for electrochemical measurements were prepared with Nanopure water and purged with Ar before measuring. Impedance and cyclic voltammetric measurements were conducted in a three-electrode glass cell at room temperature. A coiled platinum mesh, a Ag/AgCl aqueous solution, and a monolayer-modified gold bead were used as counter, reference, and working electrodes, respectively. All electrode potentials are referenced to Ag/AgCl electrode. Electrochemical experiments were performed with a CHI-660 electrochemical workstation. Impedance measurements were performed in a 0.1 M $NaPF_6$ solution containing equal concentrations of oxidized and reduced forms of the $Ru(NH_3)_6^{3+/2+}$ and $Fe(CN)_6^{3-/4-}$ redox couples. The frequency range used was 1 kHz to 0.1 Hz with an ac amplitude of 5 mV. The formal redox potential was determined by cyclic voltammetry. Impedance data were analyzed by the program EQUIVALENT CIRCUIT. The electrochemical de-

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sorption experiments were conducted in a 0.5 M KOH solution purged by Ar for 25 min.

Monolayer Preparation. The gold beads were cleaned by electrolysis in 0.1 M $HClO_4$ at a potential of 2.3 V for 5 min and dipped into 0.1 M HCl for 20 min. The gold beads were then washed with water and methanol. The surface areas of the gold beads were calculated from the slopes of the linear plots of the cathodic peak current obtained for the reduction of $Ru(NH_3)_6^{3+/2+}$ versus the square root of the scan rates. Monolayers of **1** were self-assembled by immersing the gold beads into a deaerated 20% $MeOH/CH_2Cl_2$ mixed solution for 48 h. The SAM-modified gold beads were rinsed with suitable solvents and dried in a stream of Ar.

Synthesis of 1. Thioctic acid (0.146 g, 0.71 mmol) was dissolved in 2 mL of anhydrous DMF and cooled to 0 °C under argon. Triethylamine (0.172 g, 1.69 mmol) and HATU (0.269 g, 0.71 mmol) were added. The mixture was allowed to stir at room temperature for 10 min and cooled to 0 °C again. Compound **2** (0.1 g, 0.14 mmol) dissolved in 4 mL of anhydrous DMF was added, and the mixture was stirred for another 50 min at 0 °C. The cooling bath was then removed, and the solution was stirred for 48 h at room temperature. The solvent was removed, and the residue was subjected to column chromatography (SiO_2, 5% $MeOH/CH_2Cl_2$) to give a pale yellow solid **1** (120 mg, 67%). mp 138.6−141.4. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88 (s, broad, 6H), 7.11 (s, 6H), 7.04 (s, 6H), 4.72−4.68 (d, 3H, J = 13.2 Hz), 4.38 (s, 6H), 3.77 (s, 9H), 3.59−3.55 (m, 3H), 3.52−3.47 (d, 3H, = 13.2 Hz), 3.23−3.04 (m, 18H), 2.39−2.33 (m, 6H), 2.07−2.02 (t, 6H), 1.86−1.65 (m, 18H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.7, 168.7, 148.3, 146.3, 134.0, 132.3, 117.2, 114.5, 69.5, 56.6, 56.4, 38.8, 38.6, 38.5, 35.5, 34.6, 28.8, 25.4. MS (MALDI): m/z 1274 [M^+ + H], 1296 [M^+ + Na]. IR (KBr): 3442, 3290, 2921, 2858, 1656, 1509, 1442, 1261, 1145, 1088, 1048, 844. Anal. Calcd for $C_{60}H_{84}N_6O_{12}S_6 \cdot H_2O$: C, 55.79; H, 6.71. Found: C, 55.75; H, 6.78.

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