Electrochemical Detection of Electrochemically Inactive Cations by Self-Assembled Monolayers of Crown Ethers

**Simon Flink,[†] Bernard A. Boukamp,[‡] Albert van den Berg,[§]
Frank C. J. M. van Veggel,*[,†] and David N. Reinhoudt*[,†]**

*Contribution from the Department of Supramolecular Chemistry and Technology, MESA Research
Institute, and Department of Inorganic Materials Science, University of Twente, P.O. Box 217,
7500 AE Enschede, The Netherlands*

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Abstract: Self-assembled monolayers (SAMs) of 2-[(6-mercaptohexyl)oxy]methyl-12-crown-4 (**1**) and 2-[(6-mercaptohexyl)oxy]methyl-15-crown-5 (**2**) on gold are able to bind cations reversibly from aqueous solutions. This binding of the electrochemically inactive cations is monitored by cyclic voltammetry and impedance spectroscopy using the redox couple $Ru(NH_3)_6^{2+/3+}$ as "reporter ion". Gold electrodes modified with **1** detect Na^+ even in the presence of a 100-fold excess of K^+; SAMs of **2** are K^+ selective. As a result of the high surface density of crown ethers, sandwich complexes are formed. Reduced surface concentrations of receptors in mixed monolayers of **2** with heptanethiol prevent the sandwich complexation and decreases the K^+/Na^+ selectivity of the SAM.

Introduction

Modification of surfaces by self-assembled monolayers (SAMs) is currently under extensive investigation.[1] The ease of their preparation, their stability, and the possibility to introduce different functional groups provide facile means to prepare surfaces with tailor-made properties.[2−4] Our interest in using these modified surfaces in sensing devices has led to the development of resorcin[4]arene SAMs which are able to detect organic compounds from the gas phase.[5] Monolayers of synthetic receptors have also been used to detect the binding of guests from aqueous solutions. Mass sensitive devices (QCM) have been especially successfully applied.[6] The very attractive option of using electrochemical detection has thus far mainly been focused on the voltammetric detection of electrochemically active metal ions as shown by Rubinstein et al.[7] and Mandler et al.[8] Recently, impedance spectroscopy was also used to detect the binding of charged guests to self-assembled monolayers. This technique enables the determination of the electrochemical properties of a system, while minimizing the amplitude of the applied electric potential to a few millivolts.[9] A decrease of the monolayer capacitance by ~20% of the initial value was observed by Rubinstein et al.,[10] and Vogel et al.[11] Henke et al.[12] reported a change of their cyclodextrin monolayer resistance after the binding of organic sulfonic acids.

In this paper we describe the *reversible* and *selective* complexation of electrochemically inactive metal ions from aqueous solutions to self-assembled monolayers of 12-crown-4 and 15-crown-5 adsorbates as monitored both by cyclic voltammetry and impedance spectroscopy. The selectivity of the complexation is a result of the formation of sandwich complexes and can be altered by changing the concentration of crown ether ligands in the monolayer.

* To whom correspondence should be addressed. Fax: +31 53 4894645. Phone: +31 53 4892980. E-mail: D.N.Reinhoudt@ct.utwente.nl.

† Supramolecular Chemistry and Technology, and MESA Research Institute.

‡ Inorganic Materials Science.

§ MESA Research Institute.

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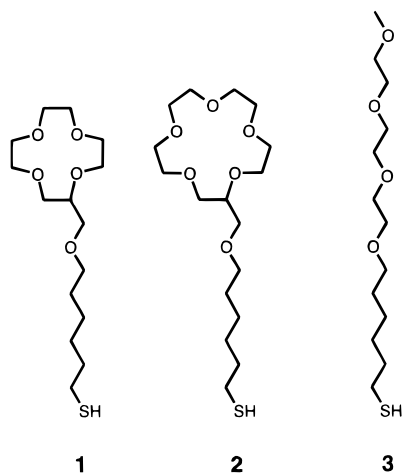
Experimental Section

Chemicals. All chemicals used for synthesis were obtained from Aldrich and used as received. All reactions were conducted under an argon atmosphere. Electrolyte solutions were freshly prepared from nitrogen-purged, high purity water (Millipore). The salts were obtained from Merck and were of "pro analysis" purity. $Ru(NH_3)_6Cl_3$ was purchased from Alfa Products.

2-[(6-Bromohexyl)oxy]methyl-12-crown-4 (4). A suspension of 2-(hydroxymethyl)-12-crown-4 (0.80 g, 3.88 mmol) and sodium hydride (55% in mineral oil; 0.4 g, 9 mmol) in DMF was stirred at room temperature. After 30 min, 1,6-dibromohexane (3.1 mL, 20.2 mmol) was added, and the reaction mixture was stirred overnight. Subsequently, the reaction was quenched with methanol and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL) and washed with water (3×100 mL). After the mixture was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to yield **4** as a colorless oil (0.80 g, 56%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28−1.50 (m, 4H), 1.50−1.65 (m, 2H), 1.80−1.92 (m, 2H), 3.32−3.57 (m, 7H), 3.57−3.92 (m, 14H).

2-[(6-Mercaptohexyl)oxy]methyl-12-crown-4 (1). A solution of **4** (0.80 g, 2.17 mmol) and thiourea (0.8 g, 11 mmol) in ethanol (50 mL) was heated under reflux for 16 h. The solvent was evaporated under reduced pressure. Potassium hydroxide (0.8 g, 14 mmol) and nitrogen-purged water were added to the residue, and the reaction mixture was heated under reflux for 2 h. After acidifying with 1 M HCl, CH_2Cl_2 (100 mL) was added and the organic layer was washed with water (3×100 mL). The solution was dried over $MgSO_4$, filtered and the solvent was evaporated to give the crude product which was purified by column chromatography (SiO_2, hexane/EtOAc 1:3) to yield **1** as a colorless oil (0.25 g, 36%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25−1.50 (m, 4H), 1.50−1.70 (m, 4H), 2.51 (q, 2H), 3.33−3.56 (m, 5H), 3.56−3.90 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 24.56, 25.58, 28.15, 29.49, 33.94, 70.25, 70.40, 70.70, 70.89, 70.98, 71.52, 71.83, 78.66; EI MS m/z 322.1 (M^+, calcd 322.18); IR (CCl_4) 2934, 2909 (shoulder), 2859 (C−H), 1127 (C−O) cm^{-1}.

2-[(6-Mercaptohexyl)oxy]methyl-15-crown-5 (2). This compound was synthesized from 2-(hydroxymethyl)-15-crown-5 by alkylation with 1,6-dibromohexane (analogous to the synthesis of **4**), followed by conversion of the bromide into the thiol (analogous to the synthesis of **1**). The crude product was purified by column chromatography (Al_2O_3, EtOAc) to give **2** as a colorless oil (25% from 2-(hydroxymethyl)-15-crown-5): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25−1.47 (m, 4H), 1.47−1.68 (m, 4H), 2.51 (q, 2H), 3.35−3.50 (m, 19H), 3.50−3.88 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 24.56, 25.58, 28.15, 29.49, 33.95, 70.25, 70.54, 70.58, 70.77, 70.92, 71.04, 71.05, 71.43, 71.58, 78.72; FAB MS m/z 389.2 ($[M + Na]^+$, calcd 389.2); IR (CCl_4) 2934, 2909, 2861 (C−H), 1129 (C−O) cm^{-1}.

7,10,13,17-Tetraoxaheptadecanethiol (3). This compound was synthesized from triethylene glycol monomethyl ether by alkylation with 1,6-dibromohexane (analogous to the synthesis of **4**), followed

by conversion of the bromide into the thiol (analogous to the synthesis of **1**). The crude product was purified by column chromatography (SiO_2, EtOAc) to give **3** as a colorless oil (50% from triethylene glycol monomethyl ether): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25−1.50 (m, 4H), 1.50−1.68 (m, 4H), 2.51 (q, 2H), 3.36 (s, 3H), 3.43 (t, 2H), 3.50−3.60 (m, 4H), 3.60−3.70 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 24.55, 25.57, 28.16, 29.49, 33.94, 59.03, 70.07, 70.51, 70.58, 70.62, 71.30, 71.93; EI MS m/z 281.2 ($[M + H]^+$, calcd 281.17); IR (CCl_4) 2932, 2864 (C−H), 1113 (C−O) cm^{-1}.

Gold substrates were prepared by resistive evaporation of gold (200 nm) on glass slides of 25 mm diameter. A layer of 2 nm of chromium was evaporated onto the glass prior to the deposition of the gold layer in order to improve the adhesion of the gold to the substrate.

Monolayer Preparation. All glassware used to prepare monolayers was cleaned in boiling *piraña* (solution of 1:4 30% H_2O_2 and concentrated H_2SO_4) and rinsed several times with high purity water. **Caution**: *Piraña* is a very strong oxidant and reacts violently with many organic materials. The gold substrates were cleaned in an oxygen plasma (5 min) and subsequently immersed in ethanol for 10 min to remove the oxide layer.[13] Formation of the self-assembled monolayer was achieved by immersion of the gold substrate into a 1 mM solution of the adsorbate(s) in ethanol for 18 h. After the substrate was taken from the solution it was rinsed with ethanol (3 times) and water (2 times) to remove any physisorbed material.

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Brucker AC 250 spectrometer in $CDCl_3$ using the traces of nondeuterated solvent as an internal standard. FAB-mass spectra were obtained with a Finnigan MAT90 mass spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. Bulk IR spectra were recorded in CCl_4 with a Biorad FTS 60 spectrophotometer (256 scans with 4 cm^{-1} resolution). Grazing incidence FT-IR spectra were obtained with a Biorad FTS 60 A spectrophotometer at an angle of incidence of 84°. For each spectrum 512 scans were recorded with 2 cm^{-1} resolution. A background spectrum was recorded using a freshly cleaned gold substrate. Contact angles were measured on a Krüss G10 Contact Angle Measuring Instrument, equipped with a CCD camera. Advancing and receding contact angles were determined automatically during growth and shrinkage of the droplet by the drop shape analysis routine.

Electrochemical measurements were performed in a three-electrode cell containing a monolayer-covered gold working electrode (clamped to the bottom of the cell exposing a geometric area of 0.44 cm^2 to the electrolyte), a platinum counter electrode, and a mercurous sulfate reference electrode (0.61 V_{SHE}). After the cell was filled with the electrolyte (0.1 M Et_4NCl and 1 mM $Ru(NH_3)_6Cl_3$), nitrogen was bubbled through the solution for at least 3 min. During the measurements, a constant flow of nitrogen was maintained over the solution. Titration of the electrolyte with metal chlorides (MCl_x) was performed with solutions of 1 mM $Ru(NH_3)_6Cl_3$ and $[MCl_x] + [Et_4NCl] = 0.1$ M to ensure a constant concentration of the background electrolyte and the redox couple. Cyclic voltammetry and impedance spectroscopy were performed with an Autolab PGSTAT10. The cyclic voltammograms were recorded with a scan rate of 100 mV/s between −0.3 and −0.9 V_{MSE} (starting from −0.3 V_{MSE}). Impedance spectroscopic experiments were conducted at the formal redox potential of $Ru(NH_3)_6^{2+/3+}$, in a frequency range of 10 kHz to 0.1 Hz, with an ac amplitude of 5 mV. The formal redox potential ($E_{1/2} = \frac{1}{2}(E_p^c + E_p^a)$), where $[Ru(NH_3)_6^{2+}] = [Ru(NH_3)_6^{3+}]$ near the working electrode, was determined from the cyclic voltammogram. The spectra were analyzed using the software package "Equivalent Circuit".[14]

Results and Discussion

Monolayer Characterization. Grazing-incidence infrared spectroscopy was used as a convenient method to identify the functional groups of the adsorbates which had self-assembled onto the gold surface. The SAMs of both crown ether

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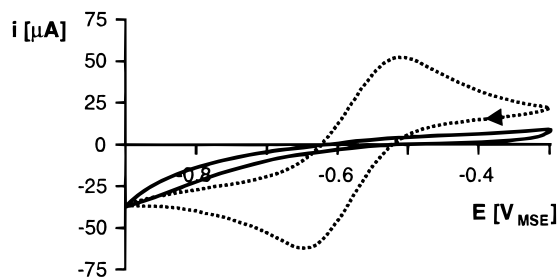
Figure 1. Cyclic voltammograms of a 12-crown-4 derivative **1** modified gold electrode in aqueous solutions. The dotted CV is recorded in 100 mM Et_4NCl + 1 mM $Ru(NH_3)_6Cl_3$; the solid CV is recorded in 14 mM NaCl + 86 mM Et_4NCl + 1 mM $Ru(NH_3)_6Cl_3$.

adsorbates **1** and **2** showed methylene C−H stretching vibrations at 2930, 2904, and 2859 cm^{-1}, in accordance with the bulk spectra. The fact that three methylene stretching vibrations are observed can be explained by the presence of chemically different methylene groups. The oxygen-bound methylene groups have absorptions at 2905 and 2859 cm^{-1}, as it was found for 12-crown-4 and 15-crown-5 in solution. The asymmetric and symmetric C−H stretching vibrations of the hexyl chains of compounds **1** and **2** give rise to peaks at 2930 cm^{-1} and a part of the peak at 2859 cm^{-1}, respectively. The position of these peaks indicates that the alkyl chains are in a liquidlike, disordered conformation.[15] Furthermore, in both cases a strong absorption was found at 1138 cm^{-1}, which is assigned to the C−O stretching mode of the ether groups.[16] The monolayer of the triethylene glycol adsorbate **3** showed a broad absorption centered around 2870 cm^{-1}, which is assigned to the various stretching modes of the methyl and methylene groups. In addition, a peak of the C−O stretching vibration was present at 1115 cm^{-1}.

Wettability studies of the three SAMs with water showed contact angles that are characteristic for a surface of low hydrophobicity. The self-assembled monolayers of 12-crown-4 derivative **1**, 15-crown-5 derivative **2**, and the triethylene glycol adsorbate **3** had advancing contact angles of 59, 55, and 58 ± 1°, respectively. In the case of both crown ether monolayers **1** and **2**, the hysteresis between the advancing and receding contact angle was 20°. SAMs of **3** showed a hysteresis of 15°, which might indicate a slightly more ordered layer.
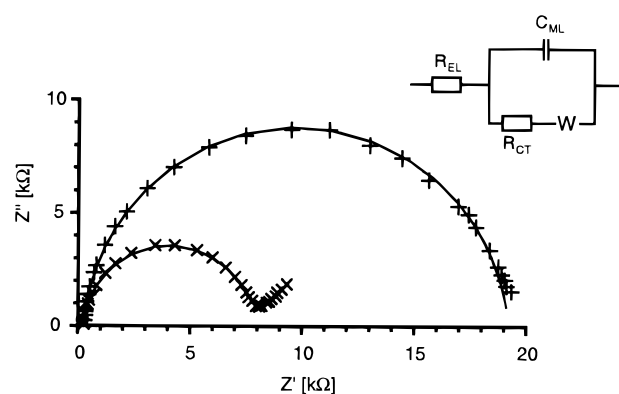
Characterization of the crown ether monolayers by cyclic voltammetry in the presence of $Ru(NH_3)_6Cl_3$ showed that the heterogeneous electron transfer from the gold electrode to the redox couple in aqueous solution was hardly influenced by the presence of the SAM. The large current density of the redox waves around −0.56 V$_{MSE}$ indicates that the redox couple can easily access the electrode surface. Addition of NaCl to the electrolyte leads to a drastic decrease of the faradaic current for the 12-crown-4 derivative **1** modified electrode as shown in Figure 1. Similarly, a 15-crown-5 derivative **2** modified gold electrode showed a large attenuation of the redox current when KCl was added to the electrolyte (data not shown).

Similar effects have previously been reported by Cheng et al. and Takehara et al., who have studied self-assembled monolayers with amine or carboxylic acid headgroups.[17] Charging of the monolayers by protonation or deprotonation

could be detected with cyclic voltammetry. The influence of a charged monolayer on the electron transfer to a charged redox couple has been attributed to the electrostatic forces acting between them, and the shift of the potential drop across the diffuse layer. Hence, complexation of metal cations by the SAM generates a repulsion toward the positively charged redox couple which attenuates its redox current.[17b] This means that cyclic voltammetry allows the detection of metal cation complexation by the monolayer.

Impedance Spectroscopy. The application of large potential sweeps (in the range of several hundreds of millivolts) as used in cyclic voltammetry can have an influence on the monolayer structure.[18] Impedance spectroscopy uses potential sweeps in the range of 5−10 mV and is therefore a less interfering technique. Furthermore, it enables the simultaneous determination of the electrochemical properties of the monolayer by using a wide frequency range.[19] The impedance spectra of the crown ether SAMs **1** and **2** are best described by the Randles equivalent circuit (Figure 2).[20] However, at high metal ion concentrations the diffusion-limited part of the impedance spectra could not be recorded within the frequency domain used due to the high charge-transfer resistance (R_{CT}). In these cases the Warburg element (W) of the equivalent circuit was neglected.

The dependence of R_{CT} on the concentration of sodium ions demonstrates that binding of the metal ions to the monolayer of 12-crown-4 increases its resistance from 0.25 kΩ to a limiting value of 145 kΩ at concentrations above 23 mM (see Figure 3). Measurements were carried out with at least three modified electrodes and the variations of the responses for different electrodes were within 15%. However, all modified electrodes showed the same characteristics in their response curve: an initially linear increase of R_{CT} at low concentrations of Na$^+$ that levels off at concentrations above 10 mM, and finally reaches a plateau value. The latter observation indicates that the binding sites become saturated at high guest concentrations. The fact that the observed response curve could not be fitted to

Figure 2. Impedance spectra of a 12-crown-4 derivative **1** modified gold electrode in solutions containing 1 mM NaCl (×) and 2.5 mM NaCl (+). Fits to the spectra are indicated by the solid lines. Inset shows the Randles equivalent circuit, used to fit the spectra, consisting of an electrolyte resistance (R_{EL}), a monolayer capacitance (C_{ML}), a charge-transfer resistance (R_{CT}), and a diffusion element (W).

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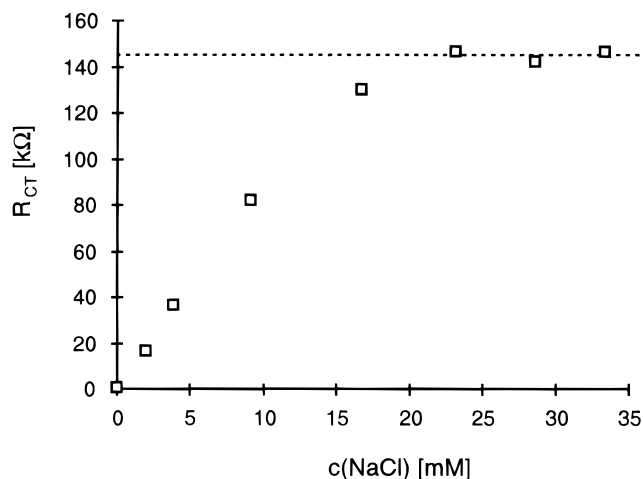
Figure 3. A representative plot of the charge-transfer resistance (R_{CT}) of a 12-crown-4 monolayer as a function of the sodium concentration. Errors in the values are 15%, determined from triplos on different electrodes.

any of the familiar isotherms (Langmuir, Temkin, Freundlich),[21] suggests that the change in the response is the result of several factors that influence the charge transfer resistance. This is currently under investigation.

The system was found to be reversible in the way that replacement of the sodium chloride containing solution by a Na^+ free electrolyte resulted in the initially determined charge transfer resistance of 0.25 kΩ. Addition of sodium salts resulted in the above-described changes of R_{CT}. The monolayer capacitance (C_{ML}), determined simultaneously from the impedance spectra, hardly responds to the binding of sodium (6.4 μF/cm^2 at $[Na^+] = 0$ mM and 6.8 μF/cm^2 at $[Na^+] > 15$ mM). The slight increase of C_{ML} is probably due to a small change of the relative permittivity ϵ_r of the monolayer upon binding of cations.[10,11,22] The response of the monolayer of **1** (ΔR_{CT}[23] vs salt concentration) was also determined for several other alkali and alkaline earth salts. Figure 4a shows the change of the resistance of the 12-crown-4 SAM at two guest concentrations (3.8 and 9.1 mM). It is clear that sodium gives the largest response. Also potassium salts affect ΔR_{CT}, but the increase of the resistance is roughly 100 times smaller than for the same concentrations of sodium. Other ions had even smaller effects on ΔR_{CT}. The fact that sodium gives rise to a response that is 100 times larger than for potassium is also found in selectivity measurements. In the presence of 10 mM of interfering potassium cations it is still possible to detect sodium concentrations down to 0.1 mM (Figure 5).

A self-assembled monolayer of the 15-crown-5 derivative **2** showed a completely different response pattern toward alkali and alkaline earth cations (Figure 4b). This larger crown ether shows the highest response for potassium. Besides potassium, cesium cations also cause a significant increase of the charge-transfer resistance. It is remarkable that sodium gives rise to a signal which is less than 1% of that observed for the same concentration of potassium.

Monolayers of the triethylene glycol adsorbate **3** showed no detectable change in both parameters (R_{CT} and C_{ML}) upon addition of alkali metals. Hence, the binding of metal ions to

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(23) ΔR_{CT} is defined as the difference of R_{CT} at a given metal concentration and R_{CT} at zero metal concentration.
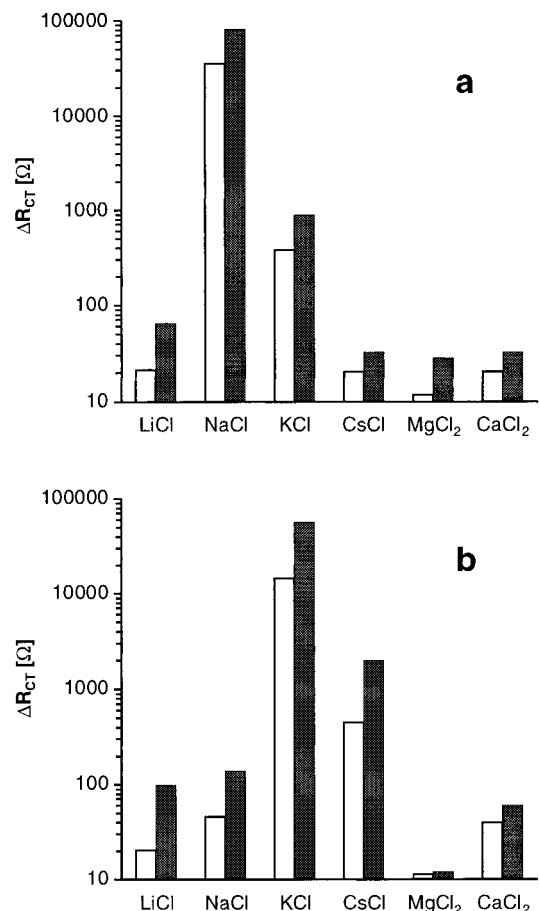

Figure 4. (a) ΔR_{CT} of a 12-crown-4 monolayer in the presence of different salts (the white and the black columns represent concentrations of 3.8 and 9.1 mM, respectively). (b) ΔR_{CT} of a 15-crown-5 monolayer in the presence of different salts (the white and the black columns represent concentrations of 2.0 and 9.1 mM, respectively). Errors in the values are 15%, determined from triplos on different electrodes.
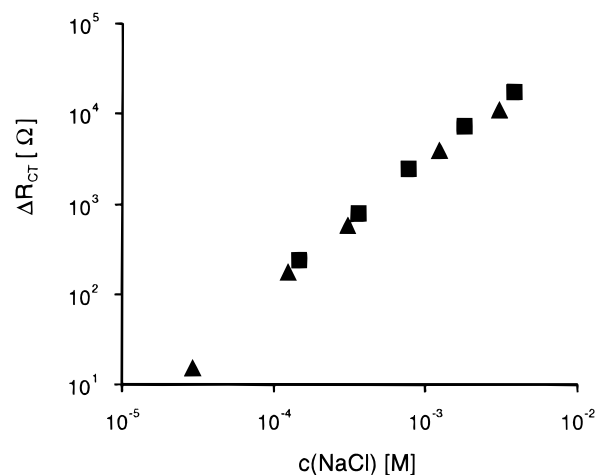
Figure 5. Changes of the charge-transfer resistance of a 12-crown-4 monolayer as a function of the sodium concentration in a background electrolyte of 100 mM Et_4NCl + 1 mM $Ru(NH_3)_6Cl_3$ (triangles) and 90 mM Et_4NCl + 10 mM KCl + 1 mM $Ru(NH_3)_6Cl_3$ (squares).

the crown ether SAMs is a result of the macrocyclic structure of the receptor adsorbates. On the basis of the association constants determined for the 1:1 complexes of 12-crown-4 and 15-crown-5 with metal ions in aqueous solutions, preferential binding of sodium and potassium to monolayers of 12-crown-4 (**1**) and 15-crown-5 (**2**) would not be expected.[24] The fact that
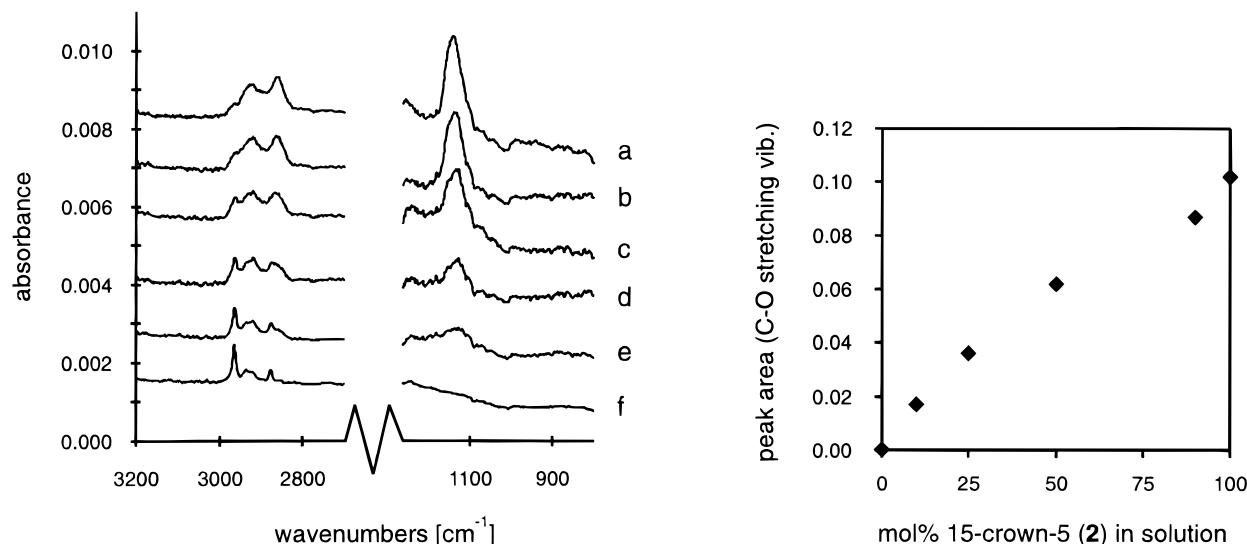
Figure 6. (Left) Grazing incidence infrared spectra of SAMs prepared from solutions containing 1 mM 15-crown-5 adsorbate **2** (a), 0.9 mM **2** + 0.1 mM heptanethiol (b), 0.5 mM **2** + 0.5 mM heptanethiol (c), 0.25 mM **2** + 0.75 mM heptanethiol (d), 0.1 mM **2** + 0.9 mM heptanethiol (e), and 1 mM heptanethiol (f). (Right) Absorbance of the SAM (C−O) vs solution concentration.

the metal ions are bound to a monolayer with its high surface concentration of crown ethers makes the formation of sandwich complexes, in which one metal ion is complexed by two crown ethers, very likely. The influence of sandwich complexation on the selectivity has been studied by incorporating (bis-)crown ethers into the membrane of ion-selective electrodes.[25] A bis-(12-crown-4) ligand, with a seven-atom spacer between both crown ethers, exhibits a much larger Na^+/K^+ selectivity ($k_{Na,K}$ = 1×10^{-2}) than monomeric 12-crown-4 ($k_{Na,K}$ = 4×10^{-1}). Similarly, an analogous bis(15-crown-5) ligand has a higher K^+/Na^+ selectivity ($k_{K,Na}$ = 3×10^{-4}) than 15-crown-5 ($k_{K,Na}$ = 2×10^{-3}). The high resemblance of the selectivity reported for these ion-selective electrodes with the responses of the crown ether SAMs **1** and **2** strongly suggests that sandwich complexation in the monolayer occurs.

Mixed SAMs. The formation of sandwich complexes should be prevented when the average distance between the ligands in the monolayer is increased. We have achieved this by the preparation of mixed monolayers of the 15-crown-5 adsorbate **2** and heptanethiol from solutions with various concentrations of both thiols. An estimate of the relative amount of **2** in the mixed monolayers with respect to the pure SAM was made by IR spectroscopy (Figure 6). Assuming that the intensity of the C−O absorption at 1138 cm^{-1} is directly proportional to the amount of 15-crown-5, the surface concentration of **2** scales linearly with its relative concentration in solution.

Impedance spectroscopic analysis of the monolayers revealed that the resistances (R_{CT}) increased from 0.5 kΩ for SAMs of pure **2**, to values above 5 kΩ for mixed monolayers of heptanethiol and **2**. This indicates that heptanethiol is able to fill monolayer defects which are present in the case of a 15-crown-5 derivative **2** SAM.[26] The addition of sodium and potassium salts to the electrolyte leads to an increase of the charge-transfer resistance. However, the maximal increase of R_{CT} for monolayers prepared from solutions containing 10, 25, or 50 mol % **2**, is reduced considerably compared to a 100%
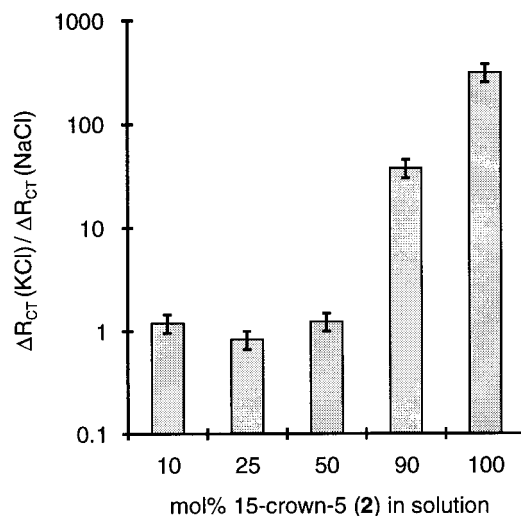
Figure 7. Change of R_{CT} at potassium concentrations of 2 mM relative to the change of R_{CT} at sodium concentrations of 2 mM for several mixed monolayers of **2** and heptanethiol.

15-crown-5 monolayer. The charge-transfer resistances of the mixed SAMs reach plateau values after an increase of 4, 5, and 10 kΩ for 10%, 25%, and 50% of **2**, respectively. The most striking feature is that the mixed monolayers, prepared from solutions with 50% or less 15-crown-5 adsorbate, no longer show selectivity for potassium. The responses at a metal ion concentration of 2 mM (which is well below the concentration where the maximal change of R_{CT} is observed) are equal for sodium and potassium (Figure 7). Mixed monolayers prepared from solutions with 90 mol % **2** do show a much larger response for potassium than for sodium salts, but it has a K^+/Na^+ selectivity which is still 10 times lower than a SAM of pure **2**.

These results confirm that the observed selectivities of the monolayers of 12-crown-4 derivative **1** and 15-crown-5 derivative **2** are indeed the result of sandwich complex formation. Diluting the receptor monolayer of **2** with heptanethiol prevents the formation of 2:1 complexes. Moreover, the fact that the preparation of mixed SAMs is accompanied by a selectivity change, simultaneously proves that homogeneous monolayers were formed. If, however, domains of **2** and heptanethiol had

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been formed, the selectivity of the monolayer should have remained unaffected.

Conclusions

Modification of a gold electrode with self-assembled monolayers of crown ethers enables the reversible binding of metal ions from aqueous solutions. The use of a positively charged redox couple in the electrolyte transduces the binding event into an electrochemically detectable signal. The remarkable selec-tivities of the crown ether SAMs is caused by the cooperative binding of one metal ion by two crown ether moieties. Dilution of the 15-crown-5 monolayer with heptanethiol prevents the formation of sandwich complexes and it changes the selectivity. This result also proves that homogeneously mixed self-assembled monolayers are formed and phase separation of both adsorbates does not occur.