FULL PAPER

ADVANCED FUNCTIONAL MATERIALS

Self-Assembled Monolayers on Gold for the Fabrication of Radioactive Stents

By *Kjeld J. C. van Bommel*, *Arianna Friggeri*, *Dorine Mateman*, *Frank A. J. Geurts*, *Kees G. C. van Leerdam*, *Willem Verboom*, *Frank C. J. M. van Veggel*, and *David N. Reinhoudt**

An innovative and easily applicable method for the fabrication of radioactive stents, to be used for the treatment of restenosis, is presented. By incorporating the β-emitting radioisotopes ^{186}Re, ^{188}Re, ^{90}Y, or ^{32}P into sulfur-containing adsorbates, it becomes possible to cover a gold surface with a radioactive self-assembled monolayer (SAM). Two methods have been investigated. In the first, SAMs consisting of potentially radioactive rhenium-, yttrium-, and phosphorus-containing adsorbates have been assembled on 2D gold substrates, after which they have been studied by wettability measurements, electrochemistry, and X-ray photoelectron spectroscopy (XPS). The stability of these SAMs under simulated physiological conditions (phosphate buffered saline, PBS solution) for periods up to two months has been demonstrated. Alternatively, potentially radioactive monolayers have been prepared by exposure of SAMs of mono-, bi-, and tridentate ligands to a solution containing a radiometal (rhenium) in order to bind the metal to the monolayer. The polydentate ligands exhibit excellent binding capacity, leading to SAMs containing over 10^{-10} mol/cm^2 of the radiometal, which is more than sufficient to make this system viable for the delivery of therapeutical dosages of radiation.

1. Introduction

Balloon angioplasty[1,2] is a non-surgical method used for clearing arteries blocked by the deposition of lipids: the cause of atherosclerosis.[3] The procedure involves the introduction of a catheter with a small inflatable tip into the concerned artery. The balloon is then inflated to widen the artery by flattening the lipid deposit, subsequently deflated, and removed.[4] In spite of this effective treatment, restenosis (i.e., re-narrowing) of the arteries recurs within six months in up to 60 % of those treated.[5,6] Given the magnitude of the problem, a large number of therapeutic approaches have been tried to modify the restenosis process.[7] One of the methods currently employed for the prevention of restenosis makes use of small, metallic mesh tubes (i.e., stents).[2] A stent is introduced into the concerned artery by placing it around the balloon-like tip of the catheter. After the balloon is deflated, the stent remains in place in the artery as a permanent implant, providing support and preventing arterial remodeling. However, due to growth of the internal artery wall, reclusion continues to occur. This problem can be solved by making the stent radioactive, as radiation can stop cell division (one of the causes of restenosis).[8] Experimental studies[9] have shown that radioactive stents can effectively prevent restenosis, and different methods of producing radioactive stents are currently being employed.[10] The main disadvantage of these fabrication methods, however, is that they generally make use of irradiation with neutrons or protons. This will nearly always result in stents containing a mixture of radioisotopes with (large) differences in half-life, the type of emission (e.g., β, γ) and the energy of the emitted particle, making it difficult to obtain stents with the desired dosimetry. Furthermore, the mixture of isotopes present in the stents will complicate the assignment of the observed therapeutic effect to a specific isotope. The fact that all these methods require the use of a nuclear reactor, cyclotron, or at least a mass separator, may also make routine hospital use of radioactive stents, produced via these methods, either unpractical or too costly.[11]

Here, an innovative and easily applicable method for the fabrication of radioactive stents, involving self-assembled monolayers (SAMs) of sulfur-containing adsorbates on gold surfaces,[12–15] is presented.[16] By incorporating the radioisotopes ^{186}Re, ^{188}Re, ^{90}Y, or ^{32}P (all pure, or nearly pure, β-emitters) into the structure of the adsorbates, it becomes possible to cover a gold surface with a radioactive monolayer.[17] Two methods have been investigated. In the first, SAMs consisting of potentially radioactive rhenium-, yttrium-, and phosphorus-containing adsorbates have been assembled on 2D gold substrates, after which they have been studied by wettability measurements (Table 1), electrochemistry (Table 1), and X-ray photoelectron spectroscopy (XPS). Moreover, the in vitro stability of these SAMs under simulated physiological conditions (phosphate buffered saline [PBS] solution) has been investigated. Alternatively, potentially radioactive monolayers have been prepared by exposure of SAMs of mono-, bi-, and tridentate ligands to a solution containing a radiometal (rhenium) in order to bind the radiometal to the monolayer.

[*] Prof. D. N. Reinhoudt, Dr. K. J. C. van Bommel,[+] Dr. A. Friggeri, D. Mateman, Dr. W. Verboom, Dr. F. C. J. M. van Veggel
Laboratory of Supramolecular Chemistry and Technology
MESA$^+$ Research Institute, University of Twente
PO Box 217, NL-7500 AE Enschede (The Netherlands)
E-mail: d.n.reinhoudt@ct.utwente.nl

Dr. F. A. J. Geurts, Dr. K. G. C. van Leerdam
Akzo Nobel Cent Res, Dept RGL
NL-6800 SB Arnhem (The Netherlands)

[+] Second address: NRG, PO Box 25, NL-1755 ZG Petten, The Netherlands.
E-mail: K.J.C.vanBommel@ct.utwente.nl

  1616-301X/01/0204-0140 $ 17.50+.50/0

Table 1. Advancing CAs (θ_a), hysteresis ($\Delta\theta$), electrochemical capacitance (C_{ML}), and charge transfer resistance (R_{CT}) of SAMs of adsorbates **1** to **8**.

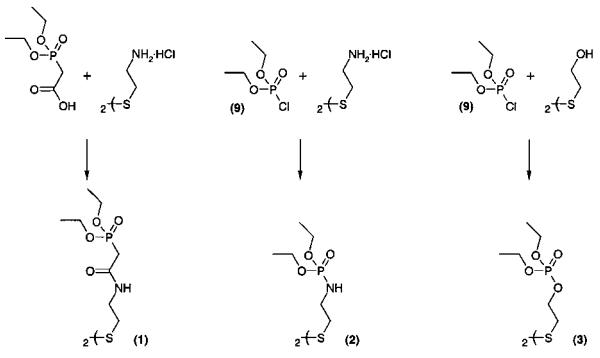
Adsorbate	θ_a [°]	$\Delta\theta$ [°]	C_{ML} [μF cm^{-2}][a]	R_{CT} [kΩ][b]
1	68 ± 3	19	11.28	15.0
2	68 ± 3	27	9.31	80.7
3	62 ± 1	23	8.65	36.2
4	96 ± 3	17	2.70	5.5
5	58 ± 1	46	9.79	2.0
6	86 ± 3	21	4.85	< 1.0
6 + Re	80 ± 3	41	–[d]	–[d]
7	90 ± 1	32	8.25	20.7
7 + Re	78 ± 3	49	–[d]	–[d]
8	51 ± 2	35	10.26	< 0.1
8 + Re	< 20	–[c]	–[d]	–[d]

[a] All capacitance values are the average of three measurements on three individual layers. The error on the values is within 10 %. [b] Error: ±15 %. [c] No hysteresis was determined due to the low CAs. [d] Not determined due to the interfering presence of the rhenium in the layer.

Alkanethiol monolayers on gold are known to contain about 10^{14} molecules per cm^2,[18] which is more than sufficient to make them suitable for the delivery of therapeutical dosages of radiation, which are in the range of 0.05 to 3.0 μCi for β-particle emitting stents.[5c] This corresponds to ca. 10^8–10^{11} atoms of ^{186}Re, ^{188}Re, or ^{90}Y, and ca. 10^9–10^{11} atoms of ^{32}P.[19]

2. Results and Discussion

In the first approach to obtain SAMs of β-emitters on gold, the adsorbates, containing both the sulfur moiety as well as the (potential) radioisotope are synthesized and subsequently adsorbed to the gold. This method holds several advantages over currently used methods for the fabrication of radioactive stents. Firstly, the knowledge about the synthesis of radiopharmaceuticals can be exploited to synthesize a variety of sulfur-containing adsorbates that may subsequently be used for the formation of radioactive SAMs. Secondly, the actual fabrication of the radioactive stent would only require formation of the radioactive compound (presently already carried out in the hospital) followed by exposure of the stent to a solution of this compound. Three potential radioisotopes (Re, Y, and P) have been incorporated (Scheme 1) into adsorbates that can be used to form SAMs on gold (compounds **1**–**5** in Fig. 1).[20] Whereas normally the presence of well-defined, densely packed monolayers is desired, in this case the only requirement is the formation of SAMs that are stable under physiological conditions.



Scheme 1. Synthesis of the phosphorus adsorbates **1**, **2**, and **3**.

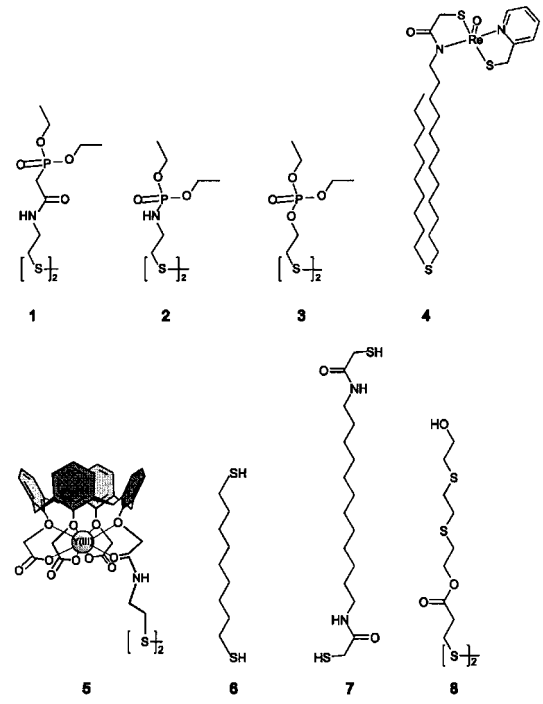
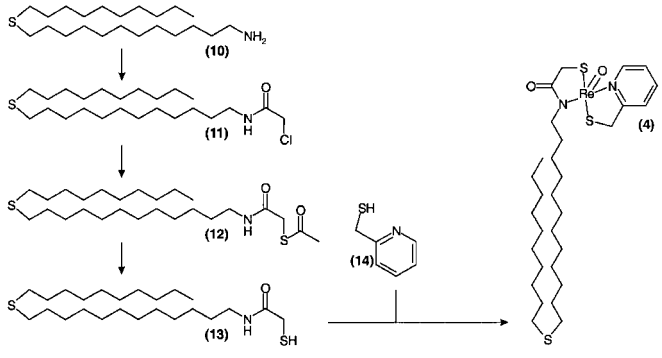


Fig. 1. Structures of the adsorbates **1**–**8**.

Contact angle (CA) measurements of SAMs of the rhenium-based adsorbate **4** (Scheme 2) showed that these layers are quite hydrophobic ($\theta_a = 96 \pm 3°$) and well-ordered ($\Delta\theta = 17°$). The capacitance of these SAMs ($C_{ML} = 2.70$ μF cm^{-2}) is higher than expected,[21] suggesting that rather than adsorbing perpendicularly to the gold surface, the molecules are adsorbed in a tilted fashion, resulting in a lower layer thickness. The low resistance ($R_{CT} = 5.5$ kΩ) is indicative of the presence of many small defects in the monolayer. Cyclic voltammetry measurements performed on SAMs of **4** in the potential range –0.8 to +0.4 V_{MSE} (MSE = mercury sulfate electrode, +0.61 V vs. normal hydrogen electrode (NHE)). In this range monolayers of sulfur-containing compounds are known to be electrochemically stable[22] and the voltammograms did not show the presence of redox processes.[23] XPS spectra of a SAM of adsorbate **4** show the presence of all the elements in the molecule (Table 2). The observed discrepancy in the oxygen percentage might be due to the presence of water, either physisorbed to the layer or coordinated to the rhenium.[24] The intensity of the Re(4f) signals is very low, which can be attributed to the low



Scheme 2. Synthesis of the rhenium adsorbate **4**.

1616-301X/01/0204-0141 $ 17.50+.50/0

Table 2. XPS data of rhenium adsorbate **4**. Values are percentages corrected for Au.

	S	C	O	N	Re
Experimental (layer, t = 0)	5.6	79.0	11.0	3.9	< 1.0 [a]
Experimental (layer, t = 1 month)	5.4	81.0	8.3	5.3	< 1.0 [a]
Calculated	7.9	78.9	5.3	5.3	2.6
Calculated ·1 H_2O	7.7	76.9	7.7	5.1	2.5
Experimental (bulk) [b]	4.7	87.6	3.6	3.4	0.7

[a] Due to the signal to noise ratio no accurate value could be determined. [b] All signals in the bulk XPS spectra of **4** have been corrected for sample charging (5 eV).

atomic sensitivity factor of Re.[25] To ascertain the presence of the rhenium, XPS was also carried out on a bulk sample of **4** and it clearly showed the presence of the metal (Table 2 and Fig. 2).[26] Since N_2S_2 rhenium complexes like **4** are very stable,[27] it is unlikely that **4** would decompose upon coordination to the gold. Furthermore, such a decomposition would result in large differences in the nitrogen and sulfur percentages in the XPS spectra, which do not occur. Therefore, it can be concluded that adsorbate **4** remains intact upon SAM formation.

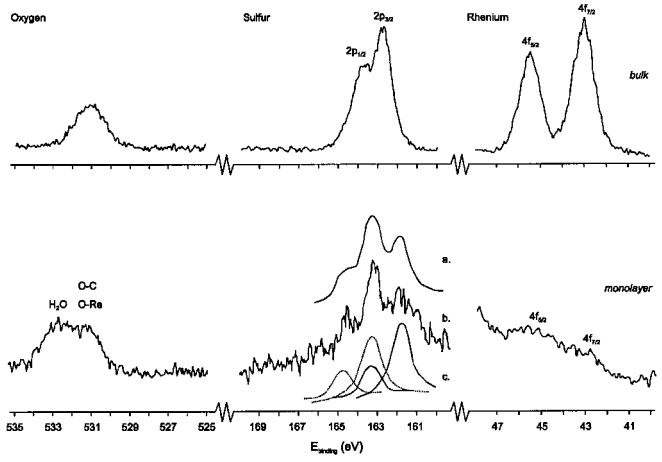
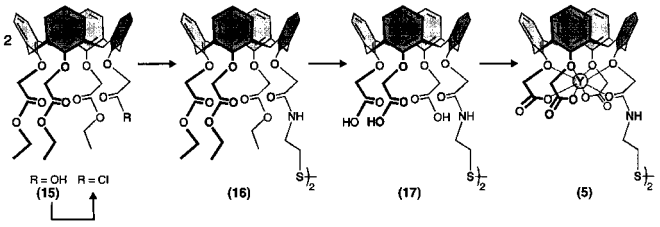


Fig. 2. XPS spectra of the Re(4f), O(1s), and S(2p) signals in bulk [26] and monolayer samples of adsorbate **4**. Line b shows the S(2p) monolayer signal. The deconvoluted S(2p) signal from the monolayer spectrum (line c) shows two sets of two peaks each for S–Au, at 161.9 eV (continuous line), and S–Re, at 162.7 eV (dotted line). The sum of these is depicted by line a.

After exposure of SAMs of **4** to a PBS solution at 37 °C for a period of one month, wettability studies showed that the layers had become slightly less hydrophobic (θ_a = 87 ± 2°) and somewhat more disordered ($\Delta\theta$ = 33°). Minor changes were observed in the values for the electrochemical capacitance (3.60 vs. 2.70 μF cm^{-2}) and charge transfer resistance (7.1 vs. 5.5 kΩ). These relatively small changes, combined with the fact that XPS measurements of the SAMs of **4**, after exposure to the PBS solution for one month, showed that the atomic percentages remained virtually unchanged (Table 2), prove the in vitro stability of the SAMs of adsorbate **4** and hence the potential of this method for the fabrication of stents coated with radioactive monolayers. Similar experiments, using the Y-containing adsorbate **5** (Scheme 3), clearly demonstrated the need for a kinetically stable complex in the SAM. After a one-month exposure of SAMs of **5** to a PBS solution at 37 °C, XPS measurements showed that all Y^{3+} had been replaced by Na^+ (present in a large excess in the PBS solution).



Scheme 3. Synthesis of the yttrium adsorbate **5**.

Using the P-containing adsorbates **1** to **3**, it was demonstrated that SAMs of adsorbates **1** and **2**, both containing amide bonds in the linker connecting P to S, displayed excellent stability for periods up to two months. However, adsorbate **3**, containing an ester bond in the linker, displayed poor stability. Whether this difference is caused by the formation of stabilizing intermolecular hydrogen bonds in SAMs of **1** and **2**, or simply by the higher chemical stability of the amide over the ester bond is unclear. Nevertheless, the in vitro stability of SAMs of adsorbates **1** and **2** shows that this method for the fabrication of radioactive stents is not limited to the use of radiometals, but may also involve non-metallic radioisotopes, which can be attached covalently to an adsorbate.

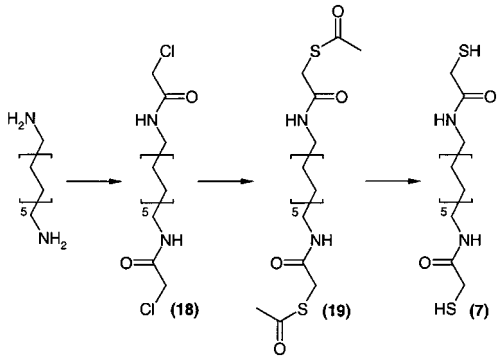
In the second approach to obtain (potentially) radioactive monolayers, SAMs have been prepared of molecules that, after coordination to the gold surface, are still able to bind a radioisotope (compounds **6**–**8** in Fig. 1). Similar to the first approach, this method would hold several advantages over currently used procedures for the fabrication of radioactive stents. Besides the previously mentioned advantage of not requiring the proximity of a nuclear reactor, cyclotron, or mass separator, this approach would furthermore considerably simplify and shorten the preparation procedure carried out by the hospital staff. Stents, coated in gold and equipped with a SAM, may be prepared outside the operating room or even hospital, long before the stent-placement procedure. The labeling procedure would be limited to an exposure of the stent to a solution of the radioisotope, after which the now labeled stent would be ready for implantation. To explore the possibilities of this approach, SAMs of mono-, bi-, and tridentate ligands **6**–**8** were used. After characterization, these monolayers were exposed to a rhenium gluconate solution[28] for a period of 3 h, rinsed, and characterized again in order to determine their capability to bind rhenium.

CA measurements revealed that SAMs of the NS-adsorbate **7** (Scheme 4) possess hydrophobic surfaces (θ_a = 90 ± 1°) and are quite disordered ($\Delta\theta$ = 32°). The electrochemical quality of the layer was poor, as demonstrated by the rather low resistance (R_{CT} = 20.7 kΩ) and high capacitance (C_{ML} = 8.25 μF cm^{-2}), indicating the presence of relatively thin layers with many defects. XPS data (Table 3) generally show a good agreement between calculated and observed atomic percentages. The relatively high oxygen percentage (before labeling) might be due to the presence of water in the monolayer, owing to the hygroscopic character of **7**.

In contrast to what was observed for SAMs of 1,9-nonanedithiol (**6**),[29] adsorbate **7**, which also contains two thiol moieties, preferentially binds to gold with only one of its thiol moi-

  1616-301X/01/0204-0142 $ 17.50+.50/0

ADVANCED FUNCTIONAL MATERIALS



Scheme 4. Synthesis of the bidentate adsorbate **7**.

Table 3. XPS data of adsorbate **7**. Values are percentages corrected for Au.

	C(1s) [%] Calc./Exp.	N(1s) [%] Calc./Exp.	O(1s) [%] Calc./Exp.	S(2p) [%] Calc./Exp.	Re(4f) [%] Calc./Exp.
7	72.7 / 68.1	9.1 / 8.0	9.1 / 17.3	9.1 / 6.6	— [a]
7 + ½ ReO	69.6 / 70.2	8.7 / 8.0	10.9 / 15.7	8.7 / 4.8	2.2 / 0.2
7 + ½ ReO ½ H_2O	68.1 / 70.2	8.5 / 8.0	12.8 / 15.7	8.5 / 4.8	2.1 / 0.2

[a] Does not contain rhenium.

eties. XPS spectra, after deconvolution of the sulfur signal, show that nearly equal amounts of bound sulfur and unbound sulfur could be found in SAMs of **7**.[30] This particular orientation of the adsorbate molecules might be aided by the amide–amide interactions that are known to help in the lateral stabilization of monolayer structures.[31]

After having been exposed to a basic solution of rhenium gluconate for a period of 3 h, the layers of adsorbate **7** were characterized again. CA measurements showed that the surface had become more hydrophilic ($\theta_a = 78 \pm 3°$), when compared to the original layer of **7**, and an increase in hysteresis ($\Delta\theta = 49°$) indicates an increased disorder. Before exposure to a rhenium gluconate solution, featureless cyclic voltammetry spectra were obtained. However, after exposure to the rhenium gluconate solution for 3 h, cyclic voltammetry measurements showed the presence of an oxidation peak at –0.14 V_{MSE}, indicating the presence of the rhenium in the layer (Fig. 3). The absence of the corresponding reduction peak indicates that the oxidative process is irreversible. Furthermore, the oxidation peak disappeared almost completely after repetitive scanning (20–30 scans at a scan rate of 0.1 V/s), indicative of the presence of a surface confined electrochemically active species. Similar electrochemical behavior has been observed for many

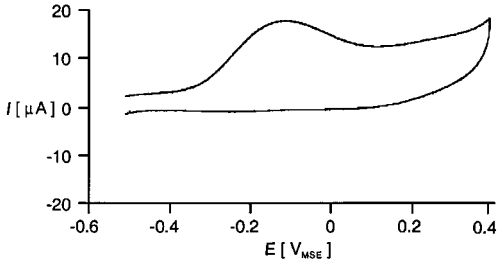
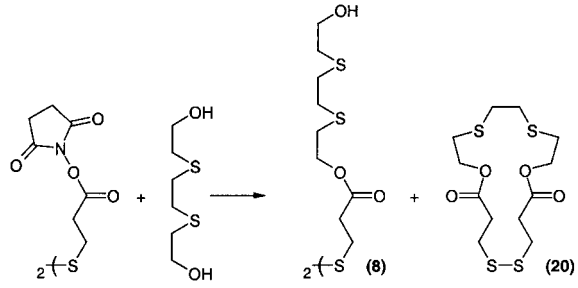


Fig. 3. Cyclic voltammogram of a monolayer of adsorbate **7** after immersion in Re^V–glu solution for 3 h. Only one oxidation peak at –0.14 V_{MSE} is present, but it disappears producing a featureless spectrum after 20–30 scans. Scan rate: 0.1 V/s. Electrolyte: 0.1 M K_2SO_4.

Re^V complexes in solution by Bottomley et al.[32] and by Chiotellis et al.[33] The disappearance of the oxidation peak is attributed to the oxidation of Re^V followed by a chemical reaction, which gives rise to species that are either unstable or redox inactive within the applied potential window. By determining the area underneath the oxidation peak in the cyclic voltammogram, the total number of redox active atoms (= Re-atoms) per cm^2 was calculated. The values obtained were 5.0×10^{-10} (assuming a one-electron process)[34] and 2.5×10^{-10} mol/cm^2 (assuming a two-electron process),[34] and are in good agreement with monolayer coverages in the range of 10^{-10} mol/cm^2 as reported in the literature.[18] XPS measurements performed after labeling, provided additional evidence for the presence of the rhenium in the SAM, as can be concluded from the data shown in Table 3. Since in solution thiol-amide bidentate ligands usually coordinate in a bisbidentate fashion,[35] atomic percentages have been calculated for **7** + 1/2 ReO and **7** + 1/2 ReO + 1/2 H_2O (i.e., again assuming the presence of water in the SAM),[24] the latter showing only a slightly better agreement with the experimental values. The characterization data presented here, clearly proves that SAMs of the bidentate NS adsorbate **7** are capable of binding rhenium and can thus lead to the formation of radioactive SAMs. Similar results were obtained using the tridentate adsorbate **8** (Scheme 5),[36] clearly proving the potential of this method for the fabrication of radioactive stents. The superior metal binding capacity of SAMs of polydentate ligands over monodentate ligands was proven by performing labeling experiments using SAMs of the monodentate ligand 1,9-nonanedithiol (**6**), which resulted in the binding of only very low amounts of rhenium.



Scheme 5. Synthesis of the tridentate adsorbate **8**.

3. Conclusions

In conclusion, it is clear that both approaches presented here can lead to the formation of (potentially) radioactive SAMs, thus bringing the facile fabrication of radioactive stents for the treatment of restenosis within reach. Prolonged in vitro stability of the SAMs in PBS solution has been proven; however, the effects of human blood with its variety of proteins and cells on these monolayers remain to be investigated. Future research will be aimed at the integration of polyethylene glycol (PEG) units into the radioactive SAMs in order to prevent protein and cell binding,[37–40] as well as the expansion of the range of radioisotopes that can be utilized.

  1616-301X/01/0204-0143 $ 17.50+.50/0

4. Experimental

General: Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova NMR spectrometer operating at 300, 121.4, and 75.5 MHz for ^{1}H, ^{31}P, and ^{13}C, respectively. All spectra were recorded in $CDCl_3$ unless otherwise stated. Residual solvent protons were used as internal standard and chemical shifts are given in ppm relative to tetramethylsilane (TMS). Fast atom bombardment (FAB) mass spectra were measured on a Finnigan MAT 90 spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. All solvents were purified by standard procedures. All other chemicals were analytically pure and were used without further purification. All reactions were carried out under an inert argon atmosphere. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Melting points (uncorrected) of all compounds were obtained on a Reichert melting point apparatus. The name calix[4]arene is used instead of the official CA name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol. Compound **6** was purchased from Aldrich. Compounds **9** [41], **14** [42], and **15** [43] were synthesized according to literature procedures. Compound **10** was a generous gift from Dr. S. Flink, University of Twente.

Gold Substrates: Gold substrates were prepared on glass slides (25 mm in diameter) by evaporation of an adhesion layer of chromium (2 nm) followed by evaporation of gold (200 nm). Immediately before use, the substrate was cleaned with an oxygen plasma (10 min) and subsequently rinsed with copious amounts of ethanol [44].

Monolayer Preparation: All glassware used to prepare monolayers was immersed in piraña solution. Warning: piraña solution should be handled with caution; it has been reported to detonate unexpectedly [45]. Next, the glassware was rinsed with large amounts of high-purity water (Millipore). Monolayers of compounds **1** and **6** were prepared by immersing freshly cleaned gold substrates in the respective 1 mM ethanolic solutions for 16 h. Monolayers of **2**, **3**, **4**, **7**, and **8** were prepared by immersing freshly cleaned gold substrates in the respective 1 mM dichloromethane solutions for 16 h. Monolayers of **5** were prepared by immersing freshly cleaned gold substrates in a 0.05 mM dimethylformamide (DMF) (5 mL)/dimethyl sulfoxide (DMSO) (5 mL) solution for 16 h. All layers were subsequently rinsed thoroughly with dichloromethane, ethanol, and water (Millipore). Layers of **5** were also rinsed with DMF and DMSO. For the in-situ Re complex-formation experiments, SAMs of **6** and **7** were immersed in a 0.1 N NaOH solution (20 mL) for 30 min, which had previously been deoxygenated by bubbling N_2 through it for 30 min. 1 mL of Re-gluconate complex solution, $[ReO(gluc)_2]^-$, was then added to the NaOH solution, and the layers were left standing for 3 h, after which they were taken out and rinsed extensively with 0.1 N NaOH, water (Millipore), ethanol, and dichloromethane. SAMs of **8** were immersed in 20 mL of water (Millipore) to which 1 mL of Re-gluconate complex had been added for 3 h, and subsequently rinsed with water, ethanol, and dichloromethane.

Instrumentation: CA measurements were carried out on a KRÜSS CA measuring system G10. Measurements for a drop of water whose volume was gradually increased (advancing CA) and then decreased (receding CA) were repeated on three sites of the same sample. For each adsorbate, four samples were measured for a total of 12 drops, of which the average values are reported. XPS was performed on a VG Escalab 220i-XL with monochromatic Al Kα X-ray source. Electrochemical measurements were performed with an AUTOLAB PGSTAT10, in a home-made electrochemical cell equipped with a platinum counter electrode, a mercury sulfate reference electrode (+0.61 V_{NHE}), and a screw cap to position the gold electrode (area exposed to electrolyte: 0.44 cm^2). For capacitance measurements, the cell was filled with 50 mL of a 0.1 M K_2SO_4 electrolyte solution. Nitrogen was bubbled through the cell for at least 5 min before each measurement. Cyclic voltammograms were recorded between –0.3 and –0.1 mV at scan rates of 0.1, 0.2, and 0.5 V/s, and the capacitance was calculated from the voltammograms recorded at 0.2 V/s, at –0.2 V_{MSE}. The values reported are the average of measurements on three separate samples. Heterogeneous electron transfer (HET) and impedance measurements were carried out in the presence of 50 mL of 0.1 M K_2SO_4, 1 mM $K_3[Fe(CN)_6]$, and 1 mM $K_4[Fe(CN)_6]$ electrolyte solution. HET cyclic voltammograms were recorded between 0.4 and –0.5 mV_{MSE} with a scan rate of 0.1 V/s. Resistance values were obtained by analyzing the impedance spectra measured at –0.2 mV, between 0.1 Hz and 10 kHz, with the equivalent circuit method of Boukamp [46–48]. The system can be described by a circuit consisting of a parallel resistance (R_{CT}) and capacitance (C_{ML}), in series with a second resistance (R_{EL}). Where R_{EL} is the resistance of the electrolyte, R_{CT} is the resistance of the monolayer and C_{ML} is the capacitance of the monolayer [49,50].

Stability Studies: Freshly prepared SAMs on gold of compounds **1**–**5** were immersed in 50 mL of PBS solution (1 M K_2HPO_4, 1 M KH_2PO_4, 5 M NaCl in 7.6:42.4:30 mL ratio, respectively, diluted to 1 L) and placed in a thermostat at 37 °C for 0.5, 1, 24, 48, 120 h, 1 month, and 2 months in the case of SAMs of **1**, and for 1 month for SAMs of **2**–**5**. Subsequently, they were removed from the PBS solution, rinsed extensively with water (Millipore), and characterized by wettability measurements with water, cyclic voltammetry, impedance spectroscopy, and XPS.

Bis(diethylphosphonate)disulfide (**1**): HOBT (1-hydroxybenzotriazole) (0.28 g, 2.10 mmol) and EDC (*N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride) (0.40 g, 2.10 mmol) were added to a cooled (0 °C) solution of diethylphosphonoacetic acid (0.41 g, 2.10 mmol) in DMF (5 mL). The solution was stirred for 1 h at 0 °C, followed by 1 h at room temperature (RT). To the mixture was added dropwise a solution of cystamine·2HCl (0.23 g, 1.00 mmol) and *N*-ethylmorpholine (0.1 mL) in a mixture of DMF (50 mL) and tetrahydrofuran (THF) (15 mL). After the mixture was stirred at RT for 24 h, 1 N HCl (250 mL) was added, whereupon it was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with 1 N HCl (5 × 250 mL), water (250 mL), and brine (250 mL), after which they were dried with $MgSO_4$. Removal of the solvent in vacuo gave a yellow oil, which was purified using *p*-TLC (preparative thin layer chromatography) (SiO_2, 2 mm, CH_2Cl_2/MeOH = 98:2) to give **1** as a light yellow oil. Yield: 18 % [51]. ^{1}H NMR ($CDCl_3$): δ 7.45 (t, 2H, J = 5.5 Hz, NH), 4.10 (m, 8H, OCH_2), 3.52 (m, 4H, CH_2N), 2.85 (d, 4H, J = 20.9 Hz, CH_2P), 2.77 (t, 4H, J = 6.2 Hz, CH_2S), 1.29 (t, 12H, J = 7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 164.4, 62.6, 38.6, 37.3, 35.8, 34.1, 16.4. ^{31}P NMR: δ 22.40. Fast atom bombardment mass spectrometry (FABMS) m/z 509.7 $[M + H]^+$, calcd. for ($C_{16}H_{34}N_2O_8P_2S_2$) 508.1.

Bis(diethylphosphonamide)disulfide (**2**): A solution of **9** (0.82 g, 4.75 mmol) in THF (5 mL) was added dropwise to a cooled (0 °C) suspension of cysteamine·2HCl (0.51 g, 2.26 mmol) and Et_3N (1.0 g, 10.0 mmol) in THF (10 mL). After the addition was complete, the mixture was allowed to come to RT and stirring was continued overnight, after which the mixture was filtered to remove unreacted cystamine. The filtrate was evaporated to dryness and subsequently purified by flash column chromatography (SiO_2, EtOAc slowly increasing to EtOAc/MeOH = 9:1) to give **2** as a colorless solid. Yield: 52 %; melting point (m.p.) 53–55 °C. ^{1}H NMR (CD_3OD): δ 4.05 (m, 8H, OCH_2CH_3), 3.22 (m, 4H, CH_2N), 2.97 (t, 4H, J = 6.6 Hz, SCH_2), 1.32 (t, 12H, J = 6.9 Hz, CH_3). ^{13}C NMR (CD_3OD): δ 65.8, 65.7, 43.5, 42.8, 42.7, 18.6, 18.5. ^{31}P NMR (CD_3OD): δ 60.2. FABMS m/z 425.1 $[M + H]^+$, 447.0 $[M + Na]^+$. Anal. calcd. for $C_{12}H_{30}N_2O_6P_2S_2$: C, 33.96; H, 7.12; N, 6.60; S, 15.11; P, 14.59. Found: C, 33.96; H, 6.90; N, 6.65; S, 15.13; P, 14.50.

Bis(diethylphosphate Ester)disulfide (**3**): A solution of **9** (1.20 g, 6.69 mmol) in THF (5 mL) was added dropwise to a cooled (0 °C) solution of 2-hydroxyethyl disulfide (0.45 g, 2.92 mmol) and Et_3N (0.72 g, 7.1 mmol) in THF (10 mL). After the addition was complete, the mixture was allowed to come to RT and stirring was continued overnight, after which it was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 1 N HCl (3 × 25 mL), water (50 mL), and brine (25 mL) after which it was dried with $MgSO_4$. The crude product was purified by flash column chromatography (SiO_2, EtOAc) to give **3** as a colorless oil. Yield: 22 %. ^{1}H NMR ($CDCl_3$): δ 4.28 (m, 4H, SCH_2CH_2O), 4.13 (m, 8H, OCH_2CH_3), 2.97 (t, 4H, J = 6.6 Hz, SCH_2), 1.35 (t, 14H, J = 6.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 64.5, 64.4, 63.5, 63.4, 38.0, 37.9, 15.6, 15.5. ^{31}P NMR: δ 49.2. FABMS m/z 427.0 $[M + H]^+$, 449.0 $[M + Na]^+$, calcd. for ($C_{12}H_{28}O_8P_2S_2$) 426.1.

11-(Chloroacetamido)dodecyldecylsulfide (**11**): A solution of chloroacetyl chloride (0.12 g, 1.10 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a cooled (0 °C) solution of aminosulfide **10** (0.36 g, 1.00 mmol) and Et_3N (0.11 g, 1.10 mmol) in a mixture of CH_2Cl_2 (30 mL) and THF (20 mL). The solution was allowed to reach RT and was stirred overnight, after which CH_2Cl_2 (100 mL) and 1 N HCl (100 mL) were added. The organic phase was washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL). After drying the solution with $MgSO_4$, the solvent was evaporated in vacuo to give **11** as a colorless oil in quantitative yield. ^{1}H NMR: δ 6.56 (bs, 1H, NH), 4.05 (s, 2H, CH_2Cl), 3.30 (m, 2H, CH_2N), 2.50 (t, 4H, J = 7.3 Hz, CH_2S), 1.60 (m, 6H, CH_2CH_2S and CH_2CH_2N), 1.6–1.25 (m, 30H, CH_2), 0.88 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR: δ 165.7, 42.7, 39.9, 32.2, 31.9, 29.7, 29.5, 29.3, 29.3, 29.2, 28.9, 26.8, 22.7, 14.1. FABMS m/z 434.3 $[M + H]^+$, calcd. for $C_{24}H_{49}ClNOS$: 434.3.

11-(Acetylthioacetamido)dodecyldecylsulfide (**12**): A solution of **11** (0.38 g, 0.86 mmol) in DMF (10 mL) was added dropwise to a solution of potassium thioacetate (0.11 g, 0.95 mmol) in DMF (15 mL) in a darkened round bottom flask. The reaction mixture was stirred overnight at RT, after which it was dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with 0.5 N HCl (3 × 50 mL), brine (50 mL) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, giving a light yellow oil. Trace amounts of DMF were removed by repeated azeotropic evaporation with toluene, to give pure **12**. Yield: 95 %. ^{1}H NMR: δ 6.21 (bs, 1H, NH), 3.51 (s, 2H, CH_2SAc), 3.19 (m, 2H, CH_2N), 2.48 (t, 4H, J = 7.3 Hz, CH_2S), 2.39 (s, 3H, $C(O)CH_3$), 1.6–1.2 (m, 36H, CH_2), 0.87 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR: δ 195.8, 168.0, 39.8, 33.0, 32.1, 31.8, 30.2, 29.7, 29.5, 29.2, 29.2, 28.9, 26.7, 22.6, 14.0. FABMS m/z 474.4 $[M + H]^+$, calcd. for $C_{26}H_{52}NO_2S_2$: 474.3.

11-(Mercaptoacetamido)dodecyldecylsulfide (**13**): An aqueous solution of K_2CO_3 (0.5 g in 20 mL of water) was added to a nitrogen-saturated solution of **12** (100 mg, 0.21 mmol) in methanol (40 mL). After the addition of THF (30 mL) for solubility reasons, the solution was refluxed for 30 min. After the solution had cooled to RT, 2 N HCl solution (50 mL) was added. The water layer was extracted with CH_2Cl_2 (3 × 50 mL), after which the combined extracts were washed with water (100 mL) and brine (100 mL) and dried with $MgSO_4$. The solvent was evap-

  1616-301X/01/0204-0144 $ 17.50+.50/0

orated under reduced pressure to give **13** as a light yellow oil in 95 % yield. ^{1}H NMR: δ 6.65 (s, 1H, NH), 3.19 (m, 2H, CH_2N), 3.17 (d, 2H, J = 9.1 Hz, CH_2SH), 2.43 (t, 4H, J = 7.3 Hz, CH_2S), 1.80 (t, 1H, J = 9.1 Hz, SH), 1.6–1.4 (m, 6H, CH_2CH_2S and CH_2CH_2N), 1.4–1.1 (m, 30H, CH_2), 0.81 (t, 3H, J = 6.7 Hz, CH_3). The crude reaction product was used directly and without further purification.

Mixed Ligand Bis(bidentate) Rhenium Complex (**4**): i) Synthesized in organic solvent: A solution of **13** (0.26 g, 0.60 mmol) and **14** (0.08 g, 0.60 mmol) in a 1 N NaOH solution in MeOH (40 mL) was refluxed for 30 min. $ReO(PPh_3)_2Cl_3$ (0.50 g, 0.60 mmol) was added, together with THF (20 mL) for solubility reasons, and refluxing was continued for another 3 h. The purple solution was evaporated to dryness, after which the remaining solid was partitioned between CH_2Cl_2 (200 mL) and 1 N HCl (200 mL). The organic layer was washed with 1 N HCl solution (200 mL), water (200 mL), and brine (200 mL) and subsequently dried with $MgSO_4$. The solvent was evaporated under reduced pressure, giving a purple oil, which was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH = 99:1) to give **4** as a purple oil. Yield: 43 %. ^{1}H NMR ($CDCl_3$): δ 9.67 (d, 1H, J = 6.5 Hz, PyrH), 8.13 (m, 1H, PyrH), 8.02 (d, 1H, J = 8.1 Hz, PyrH), 7.63 (m, 1H, PyrH), 5.30 and 4.21 (ABq, 2 × 1H, J = 19.4 Hz, PyrCH_2S), 5.27 and 4.03 (2 × m, 2 × 1H, CH_2N), 4.06 and 3.76 (ABq, 2 × 1H, J = 17.6 Hz, C(O)CH_2S), 2.50 (t, 4H, J = 6.9 Hz, CH_2S), 1.8–1.5 (m, 6H, CH_2CH_2S and CH_2CH_2N), 1.5–1.2 (m, 30H, CH_2), 0.88 (t, 3H, J = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 195.3, 155.7, 141.7, 124.5, 121.8, 58.8, 57.7, 53.3, 39.2, 32.2, 31.8, 30.1, 29.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 28.9, 27.3, 24.0, 22.7, 19.9, 14.2, 13.6. FABMS m/z, correct rhenium isotope pattern = 757.2 $[M + H]^+$ calcd. for $(C_{30}H_{53}N_2O_2ReS_2)$ 724.3.

ii) Synthesized in water: A solution of **13** (180 mg, 0.40 mmol) and **14** (50 mg, 0.40 mmol) dissolved in degassed THF (40 mL) was added to a nitrogen-flushed (1 h) solution of α-cyclodextrin (2.88 g, 4.00 mmol) in water (100 mL). A freshly prepared $NaRe(gluc)_2$ solution (5.00 mL, 0.40 mmol), adjusted to pH = 10 by the addition of 1 N NaOH solution, was added and the resulting mixture was flushed with nitrogen for an additional 15 min. After stirring for 5 h at 55 °C, the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water (200 mL) and brine (200 mL) and subsequently dried with $MgSO_4$. The solvent was removed under reduced pressure, giving a purple oil, which was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH = 99:1) to give **4** as a purple oil. Yield: 82 %.

Bis(triester Monoamide Calix[4]arene) (**16**): A solution of calix[4]arene monocarboxylic acid (**15**) (1.00 g, 1.35 mmol) in oxalyl chloride (20 mL) was refluxed for 1.5 h, after which the excess oxalyl chloride was removed in vacuo. The remaining white solid was dissolved in CH_2Cl_2 (40 mL) and this solution was added dropwise to a cooled (0 °C) suspension of cystamine·2HCl (0.14 g, 0.61 mmol) and Et_3N (0.68 g, 6.76 mmol) in CH_2Cl_2 (40 mL). The mixture was allowed to reach RT and was stirred overnight to give a clear light yellow solution, which was subsequently washed with 2 N HCl (100 mL), water (2 × 100 mL), and brine (100 mL), whereupon the solvent was removed in vacuo. The resulting solid was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH = 95:5) to give **16** as a white solid. Yield: 83 %; m.p. 61–62 °C. ^{1}H NMR: δ 8.59 (t, 2H, J = 6.2 Hz, NH), 6.95–6.8 (m, 12H, ArH), 6.52 (m, 2H, ArH), 6.43 (m, 6H, ArH), 6.28 (d, 4H, J = 7.3 Hz, ArH), 5.00 and 4.64 (ABq, 2 × 4H, J = 16.3 Hz, ArOCH_2), 4.75, 4.74, and 3.28 (ABq, 2H, 2H, and 4H, J = 13.9 Hz, ArCH_2Ar), 4.55 (s, 2H, ArOCH_2), 4.40 (s, 2H, ArOCH_2), 4.25 (m, 12H, OCH_2CH$_3$), 3.76 (m, 4H, CH_2N), 3.03 (m, 4H, CH_2S), 1.33 (t, 6H, J = 7.3 Hz, CH_3), 1.30 (t, 6H, J = 7.3 Hz, CH_3). ^{13}C NMR: δ 170.6, 169.6, 169.4, 156.7, 155.0, 154.8, 135.3, 135.0, 133.5, 133.2, 129.2, 129.1, 128.2, 128.2, 123.2, 123.1, 122.8, 73.9, 71.4, 71.3, 60.8, 39.0, 37.5, 31.4, 31.2, 30.8, 14.1. FABMS m/z 1598.0 $[M + H]^+$, 1620.1 $[M + Na]^+$. Anal. calcd, for $C_{88}H_{96}N_2O_{22}S_2$·0.25NaCl: C, 65.55; H, 6.00; N, 1.74; S, 3.98. Found: C, 65.30; H, 5.86; N, 1.80; S, 3.93.

Bis(tricarboxylic Acid Monoamide Calix[4]arene) (**17**): A suspension of **16** (0.23 g, 0.144 mmol) and K_2CO_3 (0.40 g, 2.88 mmol) in MeOH/H_2O = 9:1 (50 mL) was refluxed for 2 h, after which the solvents were removed in vacuo. A 2N HCl (200 mL) solution was added to the remaining solid, after which the resulting suspension was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 1 N HCl (2 × 100 mL) and water (100 mL) and dried with $MgSO_4$. Evaporation of the solvent in vacuo gave pure **17**. Yield: 73 %; m.p. 170–172 °C. ^{1}H NMR (CD_3OD): δ 6.8–6.55 (m, 24H, ArH), 4.85–4.65 (m, 12H, ArCH_2Ar and ArOCH_2), 4.60 (s, 4H, ArOCH_2), 4.55 (half ABq, 4H, J = 16.5 Hz, ArOCH_2), 4.49 (s, 4H, ArOCH_2), 3.73 (m, 4H, CH_2N), 3.02 (t, 4H, J = 6.6 Hz, CH_2S). ^{13}C NMR (CD_3OD): δ 171.4, 171.2, 170.1, 154.9, 154.5, 154.4, 134.1, 134.1, 133.7, 133.4, 128.3, 128.1, 128.0, 122.8, 73.4, 71.1, 70.8, 38.0, 36.2, 30.0, 29.7. FABMS m/z 1430.0 $[M + H]^+$. Anal. calcd. for $C_{76}H_{72}N_2O_{22}S_2$·H_2O: C, 63.06; H, 5.15; N, 1.94; S, 4.43. Found: C, 62.80; H, 4.97; N, 1.82; S, 4.50. Infrared (IR) (KBr): 1744 (ν_{COO}), 1640 (ν_{NCO}) cm^{-1}.

Bis(calix[4]arene Y Complex) (**5**) [52]: A solution of $Y(NO_3)_3$·$6H_2O$ (75 mg, 196 μmol) in MeOH (10 mL) was added to a solution of **17** (70 mg, 49 μmol) and Et_3N (30 mg, 294 μmol) in MeOH (10 mL). The mixture was refluxed for 1 h, after which it was allowed to come to RT. The resulting precipitate was filtered off, washed with water (3 × 50 mL) and acetonitrile (3 × 50 mL) and dried in vacuo. Yield: 93 %; m.p. >300 °C. FABMS m/z 1623 $[M + Na]^+$. IR (KBr): 1596 cm^{-1} (br, ν_{COO}, ν_{NCO}) [53].

1,12-Bis(2-chloroacetamido)dodecane (**18**): A solution of chloroacetyl chloride (5.60 g, 50.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a cooled (0 °C) solution of 1,12-diaminododecane (4.00 g, 20.0 mmol) and Et_3N (6.06 g, 60 mmol) in a mixture of CH_2Cl_2 (200 mL) and THF (100 mL). After the mixture was stirred overnight at RT, CH_2Cl_2 (200 mL) was added. The organic layer was washed with 1 N HCl (3 × 200 mL), water (200 mL), and brine (200 mL) after which it was dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave a brown solid that was triturated with cold CH_2Cl_2 (2 × 50 mL) to give pure **18** as a light gray solid. Yield: 95 %; m.p. 120–122 °C; ^{1}H NMR: δ 7.29 (bs, 2H, NH), 4.07 (s, 4H, CH_2Cl), 3.32 (m, 4H, CH_2N), 1.56 (m, 4H, CH_2CH$_2$N), 1.4–1.2 (m, 16H, CH_2). ^{13}C NMR: δ 165.2, 42.2, 39.4, 28.9, 28.8, 28.7, 26.3. FABMS m/z 353.2 $[M + H]^+$. Anal. calcd. for $C_{16}H_{30}Cl_2N_2O_2$: C, 54.39; H, 8.56; N, 7.93. Found: C, 54.50; H, 8.60; N, 7.86.

1,12-Bis((2-acetylmercapto)acetamido)dodecane (**19**): A solution of **18** (1.00 g, 2.83 mmol) in DMF (25 mL) was added dropwise to a suspension of potassium thioacetate (0.81 g, 7.08 mmol) in DMF (25 mL). The solution was stirred overnight in the dark, after which it was poured into water (250 mL). The resulting precipitate was filtered off, washed with water (50 mL), acetonitrile (25 mL), and acetone (25 mL) and was subsequently dried to afford analytically pure **19** as a light gray solid. Yield: 96 %; m.p. 135–137 °C; ^{1}H NMR: δ 6.20 (bs, 2H, NH), 3.54 (s, 4H, CH_2S), 3.23 (m, 4H, CH_2N), 2.43 (s, 6H, CH_3), 1.50 (m, 4H, CH_2CH$_2$N), 1.4–1.2 (m, 16H, CH_2). ^{13}C NMR: δ 197.9, 170.0, 41.9, 35.1, 32.3, 31.5, 31.3, 31.2, 28.8. FABMS m/z 433.2 $[M+H]^+$. Anal. calcd. for $C_{20}H_{36}N_2O_4S_2$·0.1H_2O: C, 55.29; H, 8.40; N, 6.45; S, 14.76. Found: C, 54.99; H, 8.27; N, 6.62; S, 14.98.

1,12-Bis(2-mercaptoacetamido)dodecane (**7**): A solution of **19** (0.43 g, 1.00 mmol) in MeOH (60 mL) was added to a solution of potassium carbonate (1.38 g, 10 mmol) in water (30 mL). N_2 gas was bubbled through the mixture for 20 min, after which it was refluxed for 30 min. After the solution had cooled down to RT, 2 N HCl solution (300 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 100 mL). After washing the combined organic layers with water (200 mL) and brine (200 mL), they were dried with $MgSO_4$ and evaporated in vacuo, to give **7** as white solid, which was used immediately, without any further purification. Yield: 97 %. ^{1}H NMR ($CDCl_3$): δ 6.60 (bs, 2H, NH), 3.19 (m, 4H, CH_2N), 3.17 (d, 4H, J = 9.1 Hz, CH_2S), 1.78 (t, 2H, J = 9.1 Hz, SH), 1.46 (m, 4H, CH_2CH$_2$N), 1.4–1.1 (m, 16H, CH_2). ^{13}C NMR ($CDCl_3$): δ 168.9, 39.9, 29.4, 22.2, 28.3, 26.8. FABMS m/z 349.2 $[M+H]^+$.

Tridentate Dithiaoctane-Based Ligand (**8**): A solution of 3,3′-dithiopropionic acid di(*N*-succinimidyl ester) (0.15 g, 0.37 mmol), 1,8-dihydroxy-3,6-dithiaoctane (0.41 g, 2.22 mmol), and Et_3N (0.5 mL) in THF (40 mL) was stirred for 3 days at RT. After evaporating the solvent and the Et_3N, the crude reaction product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH = 97:3) to first give **20**, followed by **8** both as highly viscous oils. Yields: 38 % and 46 %, respectively (both calculated from the activated ester). **8**: ^{1}H NMR ($CDCl_3$): δ 4.27 (t, 4H, J = 7.0 Hz, C(O)OCH_2), 3.75 (t, 4H, J = 6.1 Hz, CH_2OH), 2.95 (t, 4H, J = 7.0 Hz, CH_2SS), 2.8–2.75 (m, 20H, CH_2), 2.38 (s, 2H, OH). ^{13}C NMR ($CDCl_3$): δ 173.5, 65.7, 62.8, 37.4, 36.0, 35.1, 34.4, 33.9, 32.5. FABMS m/z 539.9 $[M + H]^+$, calcd. for $(C_{18}H_{34}O_6S_6)$ 538.1. **20**: ^{1}H NMR: δ 4.34 (t, 4H, J = 6.5 Hz, OCH_2), 3.03 (t, 4H, J = 7.1 Hz, CH_2SS), 2.88 (s, 4H, SCH_2CH_2S), 2.85 (t, 4H, J = 6.6 Hz, OCH_2CH_2S), 2.78 (t, 4H, J = 6.8 Hz, OCH_2CH$_2$S). ^{13}C NMR: δ 173.4, 66.6, 36.1, 35.9, 34.2, 32.2. FABMS m/z 356.2 $[M]^+$, calcd. for $C_{12}H_{20}O_4S_4$: 356.0.

Received: October 30, 2000
Final version: December 13, 2000

[1] Also known as percutaneous transluminal angioplasty = PTA or in the case of coronary arteries, PTCA.
[2] C. T. Dotter, M. P. Judkins, *Circulation* **1964**, *30*, 654.
[3] a) U. Quast, D. Flühs, M. Bambynek, *Herz* **1998**, *23*, 337. b) J. Kotzerke, H. Hanke, M. Höher, *Eur. J. Nucl. Med.* **2000**, *27*, 223.
[4] From the online Medical Encyclopedia of drkoop.com: http://www.drkoop.com/conditions/encyclopedia/.
[5] a) R. M. Califf, D. F. Fortin, D. J. Frid, W. R. Harlan, E. M. Ohman, J. R. Bengtson, C. L. Nelson, J. E. Tcheng, D. B. Mark, R. S. Stack, *J. Am. Coll. Cardiol.* **1991**, *17*, 2B. b) D. L. Fischman, M. B. Leon, D. S. Baim, R. A. Schatz, M. P. Savage, I. Penn, K. Detre, L. Veltri, D. Ricci, M. Nobuyoshi, M. Cleman, R. Heuser, D. Almond, P. S. Teirstein, R. D. Fish, A. Colombo, J. Brinker, J. Moses, A. Shaknovich, J. Hirshfeld, S. Bailey, S. Ellis, R. Rake, S. Goldberg, *N. Engl. J. Med.* **1994**, *331*, 496. c) T. A. Fischell, C. Hehrleir, *Herz* **1998**, *23*, 373.
[6] D. P. Lee, S. Lo, K. Forster, A. C. Yeung, S. N. Oesterle, *Vasc. Med.* **1999**, *4*, 257.
[7] a) D. Nori, S. Parikh, J. Moni, *Int. J. Radiat. Onc. Biol. Phys.* **1996**, *36*, 847. b) M. Mosseri, H. Schwabl, Z. Weshler, *J. Interv. Cardiol.* **1999**, *12*, 283. c) W.-J. Koh, M. R. Mayberg, J. Chambers, K. L. Lindsey, A. Tran, J. S. Rasey, T. W. Griffin, *Int. J. Radiat. Onc. Biol. Phys.* **1996**, *36*, 829.
[8] A. Gassmann, *Fortschr. Roentgenstr.* **1899**, *2*, 199.

  1616-301X/01/0204-0145 $ 17.50+.50/0

[9] A. J. Carter, J. R. Laird, L. R. Bailey, T. G. Hoopes, A. Farb, D. R. Fischell, R. E. Fischell, T. A. Fischel, R. Virmani, *Circulation* **1996**, *94*, 2364.
[10] a) A. J. Carter, J. R. Laird, *J. Radiat. Onc. Biol. Phys.* **1996**, *36*, 797. b) C. Hehrlein, M. Stintz, R. Kinscherf, K. Schlosser, E. Huttel, L. Friedrich, P. Fehsenfeld, W. Kubler, *Circulation* **1996**, *93*, 641. c) C. Hehrlein, C. Gollan, K. Donges, J. Metz, R. Riessen, P. Fehsenfeld, E. Vonhodenberg, W. Kubler, *Circulation* **1995**, *92*, 1570. d) J. R. Laird, A. J. Carter, W. Kufs, T. G. Hoopes, A. Farb, S. H. Nott, R. E. Fischell, D. R. Fischell, R. Virmani, T. A. Fischell, *Circulation* **1996**, *93*, 529. e) U. O. Hafeli, M. C. Warburton, U. Landau, *Biomaterials* **1998**, *19*, 925.
[11] Radioactive stents have also been produced by electroplating the stent with radioactive rhenium [10e]. However, this method is restricted to a small number of metals, thus limiting the range of isotopes that can be used for restenosis treatment.
[12] C. D. Bain, E. B. Troughton, Y.-T. Tao, J. Evall, G. M. Whitesides, R. G. Nuzzo, *J. Am. Chem. Soc.* **1989**, *111*, 321.
[13] L. H. Dubois, R. G. Nuzzo, *Annu. Rev. Phys. Chem.* **1992**, *43*, 437.
[14] K. D. Schierbaum, T. Weiss, E. U. Thoden van Velzen, J. F. J. Engbersen, D. N. Reinhoudt, W. Göpel, *Science* **1994**, *265*, 1413.
[15] S. Flink, F. C. J. M. van Veggel, D. N. Reinhoudt, *Adv. Mater.* **2000**, *12*, 1315.
[16] In the course of the research described in this article, we became aware of a patent describing the use of the S–Au interaction for the fabrication of radioactive stents. However, in the patent no characterization and stability studies were performed on these thin films. *PCT Int. Appl. WO 98 48,851*. L. Dinkelborg, F. Blume, C.-S. Hilger, D. Heldmann, J. Platzek, U. Niedballa, H. Miklautz, U. Speck, S. Duda, G. Tepe, B. Noll, H. Goerner, *Chem. Abstr.* **1999**, *130*, 7446m.
[17] In the work described here, the non-radioactive isotopes of Re, Y, and P are used. Naturally, the chemistry would be identical when using their radioactive counterparts. For the ease of discussion, however, these non-radioactive elements will be called (potential) radioisotopes.
[18] Determined for alkanethiol layers: J. B. Schlenoff, M. Li, H. Ly, *J. Am. Chem. Soc.* **1995**, *117*, 12 528.
[19] Calculated for carrier-free materials.
[20] All synthesis routes have been designed so as to minimize the number of steps (i.e., time) in which the radioisotope is present. For the ease of synthesis and characterization, the non-radioactive isotopes have been used here.
[21] Corey—Pauling—Kolton (CPK) modeling shows that the C12 chain of **4** can have a maximum length of ca. 13.8 Å, however, this should correspond to a $C_{ML} = 1.50\ \mu F\,cm^{-2}$. (Utilizing the formula that relates capacitance to thickness: H. O. Finklea, in *Electroanalytical Chemistry*, Vol. 19 (Eds: A. J. Bard, I. Rubinstein), Marcel Dekker, New York **1996**, pp. 109–335.)
[22] M. W. J. Beulen, M. I. Kastenberg, F. C. J. M. van Veggel, D. N. Reinhoudt, *Langmuir* **1998**, *14*, 7463.
[23] Redox processes due to the presence of Re in the SAM might, however, occur outside the potential window used for this experiment.
[24] Coordination of a water molecule *trans* to the doubly bound oxygen in N_2S_2 rhenium(v) complexes has been reported: a) E. Wong, T. Fauconnier, S. Bennett, J. Valliant, T. Nguyen, F. Lau, L. F. L. Lu, A. Pollak, R. A. Bell, J. R. Thornback, *Inorg. Chem.* **1997**, *36*, 5799. b) L. Hansen, M. Lipowska, E. Meléndez, X. Xu, S. Hirota, A. T. Taylor, L. G. Marzilli, *Inorg. Chem.* **1999**, *38*, 5351.
[25] C. D. Wagner, W. M. Riggs, L. E. Davis, J. F. Moulder, G. E. Muilenberg, *Handbook of X-ray Photoelectron Spectroscopy*, Perkin-Elmer Corporation, Eden Prairie, MN **1979**.
[26] All signals in the bulk XPS spectra have been corrected for sample charging (5 eV).
[27] J. R. Dilworth, S. J. Parrott, *Chem. Soc. Rev.* **1998**, *27*, 43.
[28] Rhenium(v) gluconate was synthesized according to an adapted literature procedure, using $NaReO_4$ instead of NBu_4ReO_4. B. Noll, T. Kniess, M. Freibe, H. Spies, B. Johannsen, *Isotopes Environ. Health Stud.* **1996**, *32*, 21.
[29] XPS spectra of SAMs of adsorbate **6** combined with CA measurements strongly suggest that a substantial part of the dithiols binds to the gold with both sulfurs, contrary to reported SAMs of "upright aligned dithiols": H. Rieley, G. K. Kendall, F. W. Zemicael, T. L. Smith, S. Yang, *Langmuir* **1998**, *14*, 5147.
[30] The calculated percentages of sulfur bound and unbound to gold are 35 % and 65 % respectively, however, with an error margin of 20 to 30 %.
[31] R. S. Clegg, S. M. Reed, R. K. Smith, B. L. Barron, J. A. Rear, J. E. Hutchinson, *Langmuir* **1999**, *15*, 8876.
[32] L. A. Bottomley, P. E. Wojciechowski, G. N. Holder, *Inorg. Chim. Acta* **1997**, *255*, 149.
[33] M. Pelecanou, I. C. Pirmettis, M. S. Papadopoulos, C. P. Raptopoulou, A. Terzis, E. Chiotellis, C. I. Stassinopoulou, *Inorg. Chim. Acta* **1999**, *287*, 142.
[34] Starting from Re^{V}, oxidation can only lead to Re^{VI} or Re^{VII} species.
[35] K. J. C. van Bommel, W. Verboom, R. Hulst, H. Kooijman, A. L. Spek, D. N. Reinhoudt, *Inorg. Chem.* **2000**, *39*, 4099.
[36] Besides proving the presence of the expected elements, XPS spectra also show the presence of tin. Sn^{IV} is present in the Re^{V}–glu solution as a product of the redox reaction between $NaReO_4$ and $SnCl_2$.
[37] R. L. C. Wang, H. J. Kreuzer, M. Grunze, *J. Phys. Chem. B* **1997**, *101*, 9767.
[38] P. Harder, M. Grunze, R. Dahint, G. M. Whitesides, P. E. Laibinis, *J. Phys. Chem. B* **1998**, *102*, 426.
[39] G. B. Sigal, M. Mrksich, G. M. Whitesides, *J. Am. Chem. Soc.* **1998**, *120*, 3464.
[40] K. Feldman, G. Hähner, N. D. Spencer, P. Harder, M. Grunze, *J. Am. Chem. Soc.* **1999**, *121*, 10 134.
[41] K. Sasse, in *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed., Vol. XII, Part 2.
[42] J.-C. Aloup, J. Bouchaudon, D. Farge, C. James, J. Deregnaucourt, M. Hardy-Houis, *J. Med. Chem.* **1987**, *30*, 24.
[43] Y. Morzherin, D. M. Rudkevich, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1993**, *58*, 7602. This is an adaptation of a literature procedure for the monohydrolysis of *tert*-butyl calix[4]arene tetraethyl ester: V. Böhmer, W. Vogt, S. J. Harris, G. L. Raymond, E. M. Collins, M. Deasy, M. A. McKervey, M. Owens, *J. Chem. Soc., Perkin Trans. 1* **1990**, 431.
[44] H. Ron, I. Rubinstein, *Langmuir* **1994**, *10*, 4566.
[45] a) D. A. Dobbs, R. G. Bergman, K. H. Theopold, *Chem. Eng. News* **1990**, *68(17)*, 2. b) T. Wnuk, *Chem. Eng. News* **1990**, *68(26)*, 2. c) S. L. Matlow, *Chem. Eng. News* **1990**, *68(30)*, 2.
[46] B. A. Boukamp, *Equivalent Circuit Version 4.55*, University of Twente, Dept. Chemical Technology **1996**, Enschede, The Netherlands.
[47] B. A. Boukamp, *Solid State Ionics* **1986**, *18*, 136.
[48] B. A. Boukamp, *Solid State Ionics* **1986**, *20*, 31.
[49] B. Lindholm-Sethson, *Langmuir* **1996**, *12*, 3305.
[50] T. M. Nahir, E. F. Bowden, *Electrochim. Acta* **1994**, *39*, 2347.
[51] The rather low yield is most likely due to the extensive washing steps that were necessary to remove the DMF. However, removal of the DMF in vacuo (80 °C), prior to further work-up, resulted in the appearance of extra spots on TLC, which made subsequent purification by *p*-TLC impossible. No further attempts were made to optimize this yield.
[52] The ^1H NMR spectrum of **5** only showed very broad signals and therefore did not provide any useful information.
[53] The precursor of **5** (the calix[4]arene ligand) has a m.p. of 170–172 °C. The IR spectrum of this precursor displays two separate peaks: 1744 (ν_{COO}), 1640 (ν_{NCO}) cm^{-1}. Both changes are indicative of complex formation. M. P. Oude Wolbers, F. C. J. M. van Veggel, R. H. M. Heeringa, J. W. Hofstraat, F. A. J. Geurts, G. J. van Hummel, S. Harkema, D. N. Reinhoudt, *Liebigs Ann./Recueil* **1997**, 2587.

  1616-301X/01/0204-0146 $ 17.50+.50/0