Self-Assembled Monolayers of Heptapodant *β*-Cyclodextrins on Gold

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A route was developed for the synthesis of three different cyclodextrin adsorbates: heptakis{6-*O*-[3-(thiomethyl)propionyl)]-2,3-di-*O*-methyl}-*β*-cyclodextrin, heptakis{6-*O*-[12-(thiododecyl)dodecanoyl)]-2,3-di-*O*-methyl}-*β*-cyclodextrin (a short and long alkyl chain sulfide cyclodextrin adsorbate, respectively), and heptakis[6-deoxy-6-(3-mercaptopropionamidyl)-2,3-di-*O*-methyl]-*β*-cyclodextrin (a short alkyl chain thiol adsorbate). Self-assembled monolayers on gold of these three cyclodextrin adsorbates with seven sulfur moieties were fully characterized by electrochemistry, wettability studies, X-ray photoelectron spectroscopy (XPS), and time-of-flight secondary ion mass spectrometry (TOF-SIMS). The electrochemical capacitance measurements show the differences between the thicknesses of the *β*-cyclodextrin monolayers, and the XPS-(S_{2p}) measurements show the different effectivenesses of the sulfur moieties of the three monolayers in their binding to the gold surface. Sulfide-based *β*-cyclodextrin monolayers use on average 4.5 of the 7 attachment points whereas the thiol-based cyclodextrin monolayer only uses 3.2 of the 7 sulfurs. These experiments show that, for adsorbates with multiple attachment points, *sulfides* may be more effective than *thiols*. TOF-SIMS measurements confirm the robust attachment of these adsorbates on gold obtained by XPS.

Introduction

Molecular recognition by synthetic receptors in solution has reached a high degree of sophistication.[1] However, for possible applications at the device level, such receptors should be confined in space. Self-assembled monolayers of such receptor molecules on gold have the advantage of a high degree of molecular organization.[2] The most studied monolayers are based on thiols as the anchoring group, although stable monolayers of dialkyl sulfides have also been reported.[3] To obtain devices for the transduction of molecular recognition into macroscopic properties, we have previously reported the self-assembly of receptor molecules such as resorcin[4]arene,[4] calix[4]arene,[5] and carceplex[6] derivatives, on gold. We have attached to these molecules 4 dialkyl sulfide tails for coordination to the gold surface. In these studies it appeared that multiple points of attachment can be advantageous for the quality and stability[7] of self-assembled monolayers. Four dialkyl sulfide units (4×40 Å^2) are necessary to fill the space underneath the cavity head group (160 Å^2) of, for example, a resorcin[4]arene in order to obtain dense, well-packed monolayers (a schematic picture is given in Chart 1).[4] A resorcin[4]arene monolayer binds, for example, perchloroethylene, as was proven by quartz crystal micro balance[8a] and surface plasmon resonance measurements.[8b] As an extension of our work on the assembly of large receptor molecules on gold, we report in this paper the functionalization of the natural host molecule *β*-cyclodextrin with seven dialkyl sulfide or seven alkylthiol chains and the characterization of the self-assembled monolayers on gold surfaces. Our XPS measurements of *β*-cyclodextrin adsorbates with multiple points of attachement indicate that *sulfides* may form more regular layers than *thiols*.

β-Cyclodextrins are attractive host molecules for sensing purposes, as they can accommodate a variety of organic guest molecules.[9] Sulfur-modified cyclodextrin derivatives have been used previously for the preparation of monolayers on gold.[10] Kaifer et al. used monolayers of per-6-deoxy-(6-thio)-*β*-cyclodextrin with seven thiol attachment

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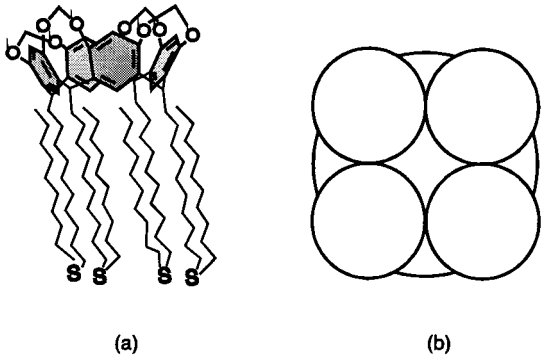
Chart 1. Schematic Side (a) and Top View (b) of a Cavitand Adsorbate Showing the Match between the Headgroup and Supporting Alkyl Chains (for Simplicity Reasons the Sulfide Group Is Depicted as a Circle



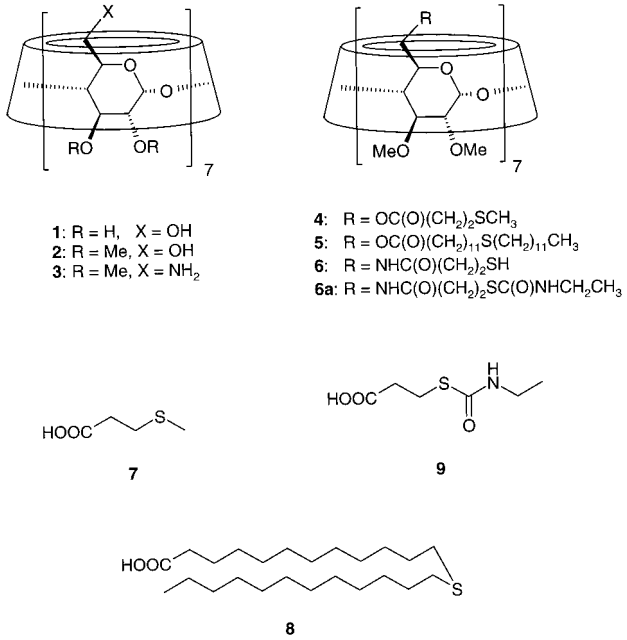
units directly linked to the cyclodextrin, for the complexation of ferrocene.[10a] Wenz et al. have thoroughly studied monolayers of β-cyclodextrins substituted with 1 or with a mixture of 2−4 thiol units.[10b−d] Moreover, several groups focused more on possible applications rather than characterization and used β-cyclodextrins with only 1 thiol group for attachment to the gold surface.[10e−g] However, recent molecular dynamic calculations indicated that cyclodextrin monolayers with only 1 attachment point are assembled into a random, quasi-two-layer system.[10h] This imperfect structure renders only half of the β-cyclodextrins available as hosts.

In this study we have prepared β-cyclodextrins with 7 dialkyl sulfide or alkanethiol units at the primary side of the cavities, to study the influence of chain length on the way of binding on the surface and on the monolayer properties. The calculated surface area (*A*) of a β-cyclodextrin molecule is approximately 185 Å^2, whereas the cross section of the support structure ranges from 140 Å^2 (7 alkanethiols) to 280 Å^2 (7 dialkyl sulfides). Our hypothesis was that multiple points of attachment will result in robust layers in which the space underneath the β-cyclodextrin head group is completely filled. This could prevent intercalation in the monolayer and render all cavities available for molecular recognition.

Experimental Section

Materials. β-Cyclodextrin was a generous gift from Wacker-Chemie GmbH, München, Germany. All other chemicals were used as received, unless otherwise stated. Solvents were purified according to standard laboratory methods.[11] All reactions were carried out in an inert atmosphere. TLC was performed on aluminum sheets precoated with silica gel 60 F_{254} (E. Merck). The cyclodextrin spots were visualized by dipping the sheets in 5% sulfuric acid in ethanol followed by heating. Chromatographic separations were performed on silica gel 60 (E. Merck, 0.040−0.063 mm, 230−240 mesh). Melting points are uncorrected. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry was carried out using a perceptive biosystems voyager-de-rp MALDI-TOF mass spectrometer. FAB-mass spectra were obtained with a Finnigan MAT 90 spectrometer. For MALDI-TOF mass spectroscopy α-cyano-4-hydroxycinnamic acid and for FAB-mass spectroscopy *m*-nitrobenzyl alcohol were used as the matrix. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 63 MHz, respectively, using residual solvent protons as the internal standard. Heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**2**) and heptakis(2,3-di-*O*-methyl-6-deoxy-6-amino)-β-cyclodextrin (**3**) (Chart 2) were prepared according to literature procedures and were vacuum-dried over P_2O_5 at 80 °C for 1 day before use.[12,13] The protected mercapto acid **9** was prepared from commercially available 3-mercaptopropionic acid and ethyl isocyanate.[14]

Chart 2. Compounds Used in This Study



Heptakis{6-*O*-[3-(thiomethyl)propionyl)]-2,3-di-*O*-methyl}-β-cyclodextrin (4). A solution of heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**2**, 0.20 g, 0.15 mmol), 3-(thiomethyl)propionic acid (**7**, 0.25 g, 2.1 mmol), and DMAP (4-(dimethylamino)pyridine) (0.42 g, 3.5 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and EDC·HCl (1-(3-dimethylamino)-3-ethylcarbodiimide hydrochloride) (0.55 g, 2.85 mmol) was added. The solution was stirred for 1 h at 0 °C and then stirred for 1 day at room temperature. Subsequently, CH_2Cl_2 was added (100 mL) and the solution was washed with 1 N HCl (3 × 50 mL) and brine (50 mL). After the solution was dried over $MgSO_4$, the solvent was removed and the oily residue purified by flash chromatography (eluent, ethyl acetate) to give cyclodextrin **4** as a sticky, white solid (0.20 g, 65%): TLC $R_f = 0.31$ (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 5.04 (d, 7H, $J = 4.0$ Hz), 4.47−4.29 (m, 14H), 3.91 (d, 7H, $J = 4.0$ Hz), 3.64−3.45 (m, 56H), 3.17 (dd, 7H, $J = 9.8$ Hz, $J = 4.8$ Hz), 2.80−2.62 (m, 28H), 2.13 (s, 21H). ^{13}C NMR ($CDCl_3$) δ: 171.5, 99.1, 81.8, 81.6, 80.6, 69.7, 63.4, 61.4, 58.8, 34.4, 29.0, 15.5. MS (MALDI-TOF) *m*/*z*: 2022 ([M − MeS + Na]$^+$, calcd., 2021.7); 1974 ([M − 2MeS + Na]$^+$, calcd., 1974.7); 1926 ([M − 3MeS + Na]$^+$, calcd., 1927.4); 1879 ([M − 4MeS + Na]$^+$, calcd., 1880.4); 1831 ([M − 5MeS + Na]$^+$, calcd., 1833.2). Anal. Calcd. for $C_{84}H_{140}O_{42}S_7$: C, 49.30; H, 6.90. Found: C, 49.40; H, 6.98.

Heptakis{6-*O*-[12-(thiododecyl)dodecanoyl)]-2,3-di-*O*-methyl}-β-cyclodextrin (5). Adsorbate **5** was prepared as described for adsorbate **4** from heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**2**, 0.10 g, 0.075 mmol), 12-(thiododecyl)dodecanoic acid (**8**, 0.42 g, 1.05 mmol), DMAP (0.21 g, 1.7 mmol), and EDC·HCl (0.27 g, 1.4 mmol) in CH_2Cl_2 (10 mL). Purification of the crude product by flash chromatography (eluent, hexanes/ethyl

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acetate gradient 5:1 to 2:1) yielded cyclodextrin **5** as a waxy solid (0.13 g, 43%): mp 45−46 °C. TLC R_f = 0.27 (hexanes/ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$) δ: 5.05 (s, 7H), 4.43−4.27 (m, 14H), 3.88 (d, 7H, J = 2.8 Hz), 3.63−3.50 (m, 56H), 3.14 (d, 7H, J = 3.0 Hz), 2.48 (t, 28H, J = 3.0 Hz), 2.34−2.27 (m, 14H), 1.63−1.50 (m, 49H), 1.35−1.19 (m, 217H), 0.89−0.84 (m, 21H). ^{13}C NMR ($CDCl_3$) δ: 172.9, 98.8, 81.8, 80.3, 69.7, 62.8, 61.4, 58.8, 34.0, 32.2, 31.9, 29.7−28.9, 25.0, 22.7, 14.1. MS (MALDI-TOF) *m*/*z*: 4042 ([M + 32]$^+$, calcd. for $C_{224}H_{420}O_{42}S_7$, 4009.9). Anal. Calcd for $C_{224}H_{420}O_{42}S_7$: C, 67.09; H, 10.56. Found: C, 67.12; H, 10.65.

Heptakis[6-deoxy-6-(3-mercaptopropionamidyl)-2,3-di-*O*-methyl]-β-cyclodextrin (6). Adsorbate **6** was prepared as described for adsorbate **4** from heptakis-(2,3-di-*O*-methyl-6-deoxy-6-amino)-β-cyclodextrin (**3,** 0.20 g, 0.15 mmol), protected mercapto acid **9** (0.37 g, 2.1 mmol), DMAP (0.42 g, 3.5 mmol), and EDC·HCl (0.55 g, 2.9 mmol) in CH_2Cl_2 (20 mL), yielding the intermediate product **6a** (0.15 g, 55%) as a colorless powder after chromatography (eluent: CH_2Cl_2/MeOH 5% v/v). MS (FAB) *m*/*z*: 2461.4 ([M + 32]$^+$, calcd. for $C_{98}H_{161}N_{14}O_{42}S_7$: 2429.8).

Intermediate **6a** (0.14 g, 0.055 mmol) was dissolved in MeOH (7 mL) and aqueous NaOH (1 N, 5 mL) and stirred until the gas evolution had ceased. The solution was neutralized (1 N HCl) and the solvents were evaporated. After the addition of 50 mL of CH_2Cl_2, the organic layer was washed with brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (eluent, CH_2Cl_2/MeOH 10% v/v) to give adsorbate **6** as a colorless powder (0.10 g, 88%): TLC R_f = 0.42 (CH_2Cl_2/MeOH 15% v/v), mp 57−58 °C. ^{1}H NMR ($CDCl_3$) δ: 7.37 (s, 7H), 4.95 (d, 7H, J = 3.5 Hz), 3.91−3.79 (m, 14H), 3.59−3.39 (m, 14H), 3.53 (s, 21H), 3.43 (s, 21H), 3.20 (t, 7H, J = 8.5 Hz), 3.09 (dd, 7H, J = 9.5 Hz, J = 3.6 Hz), 2.77−2.68 (m, 14H), 2.49−2.44 (m, 14H), 1.58 (t, 7H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 171.7, 99.5, 83.3, 81.9, 80.9, 70.7, 61.3, 58.7, 40.4, 40.0, 20.6. MS (FAB) *m*/*z*: 1963.3 ([M + Na]$^+$, calcd. for $C_{77}H_{133}N_7O_{35}S_7$: 1941.4). Anal. Calcd. for $C_{77}H_{133}N_7O_{35}S_7$: C, 47.64; H, 6.91; N, 5.05. Found: C, 47.00; H, 6.83; N, 4.96.

Monolayers. Gold Substrates. Gold substrates were prepared by evaporating 200 nm of gold on a glass slide of 25-mm diameter with a 2-nm chromium layer for adhesion. Before use, the gold substrates were cleaned in an oxygen plasma for 5 min. The resulting oxide layer was removed by leaving the substrates in EtOH for 10 min.[15]

Monolayer Preparation. All glassware used to prepare monolayers was immersed in *piraña* at 70 °C for 1h. WARNING: *piraña* solution should be handled with caution; it has detonated unexpectedly. Next, the glassware was rinsed with large amounts of high-purity water (Millipore). The cleaned gold substrates were immersed with minimal delay into a 1 mM adsorbate solution in EtOH and $CHCl_3$ (1:2, v/v) for 16 h. Sulfide monolayers were prepared at 60 °C and thiol monolayers at room temperature.[4a] Subsequently, the substrates were removed from the solution and rinsed with dichloromethane, ethanol, and water to remove any physisorbed material. The in situ preparation of the thiol-based amide β-cyclodextrin monolayer was performed according to literature procedures using Lomant's Reagent (3,3′-dithio-bis(propionic acid-*N*-hydroxysuccinimide ester), DTSP) for the formation of the activated monolayer.[16]

Instrumentation. For X-ray photoelectron spectroscopy (XPS) a VG Escalab 220i-XL instrument was used with a monochromatic Al Kα X-ray source. XPS data were collected from a surface area of (150 μm × 150 μm) with a pass energy window of 20 eV using 10 and 20 scans for carbon and sulfur, respectively. The advancing and receding contact angles with water were measured on a Krüss G10 contact angle measuring instrument, equipped with a CCd camera during the growth and shrinkage of droplets. The time-of-flight secondary ion mass spectrometry (TOF-SIMS) spectra were acquired with a VG IX23LS time-of-flight instrument with a pulsed primary beam of Ga^+ ions (30 keV) under "static" conditions. Electrochemical measurements (cyclic voltammetry and impedance spectroscopy) were performed on an Autolab PGSTAT10 (ECOCHEMIE, Utrecht, The Netherlands) in a three-electrode system consisting of a gold working electrode (clamped to the bottom of the cell, exposing a geometric area of 0.44 cm^2 to the electrolyte solution), a platinum counter electrode, and a mercurous sulfate reference electrode (+0.61 V_{NHE}). Cyclic voltammetric capacitance measurements were conducted in 0.1 M K_2SO_4 and impedance spectroscopy measurements in 1 mM $K_3Fe(CN)_6$/$K_4Fe(CN)_6$ and 0.1 M K_2SO_4. Grazing angle FT-IR was performed on a Biorad FTS 60 A spectrophotometer at an angle of 87°, with a nitrogen purge, by co-adding 512 scans with a 2-cm^{-1} resolution. Clean substrates were used as a background.

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Results and Discussion

First, the nontrivial synthesis toward the β-cyclodextrin adsorbates modified with sulfur moieties of different lengths is described. The second part describes the full characterization of the monolayers by various techniques.

Synthesis of the β-Cyclodextrin Adsorbates. Several routes for the synthesis of dialkyl sulfide- and alkanethiol-substituted β-cyclodextrins are conceivable. Direct substitution at the C6 carbon atom of the glucose units having appropriate leaving groups by a dialkyl sulfide bearing a terminal *O*- or *N*-nucleophile[17] often lead to an undesired intramolecular substitution.[18] The alternative is a reaction of a cyclodextrin with a sulfide bearing a leaving group, for example, a halogen dialkyl sulfide, which may lead to an undesired cyclic sulfonium intermediate, thus giving rise to a mixture of products.[19] Therefore, the coupling of the dialkyl sulfide to the cyclodextrin core via an ester or an amide linkage was used.[20] To attach the chains selectively to the primary hydroxyl groups, the secondary side was blocked by methylation to give heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**2**) or heptakis(2,3-di-*O*-methyl-6-deoxy-6-amino)-β-cyclodextrin (**3**).[12,13]

The dialkyl sulfide carboxylic acids **7** and **8** were synthesized according to literature procedures.[21,22] For the preparation of a heptaalkanethiol-substituted cyclodextrin, the thiol group of 3-mercapto propionic acid was protected as a thiocarbamate to give acid **9**.[14] The reactions of cyclodextrins **2** or **3** with the acids **7**, **8**, and **9**, respectively, were performed in concentrated dichloromethane solutions using 1-(3-dimethylamino)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine (DMAP) as coupling reagents.[23] Deprotection of the thiol group of β-cyclodextrin **6a** was performed under alkaline conditions. Adsorbates **4**−**6** were obtained in good yields after chromatographic purification.

All compounds were fully characterized and showed satisfactory elemental analysis. The MALDI-TOF spectrum of adsorbate **4** showed 5 equidistant peaks which can each be attributed to the loss of methyl sulfide (MeS) groups. Adsorbate **5** shows only 1 peak resembling the molecular mass plus 32 (i.e., including a sulfur atom, a known phenomenon for sulfur compounds).[24] In contrast

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Table 1. Electrochemical Data of β-$CD_{longsulfide}$, β-$CD_{shortsulfide}$, and β-$CD_{shortthiol}$ Monolayers

	β-$CD_{longsulfide}$	β-$CD_{shortsulfide}$	β-$CD_{shortthiol}$
capacitance ($\mu F \cdot cm^{-2}$)	2.5	9.6	11.9
resistance (kΩ)	48	5	39

to compounds **4** and **5** for which only fragments were detected by FAB-mass spectroscopy, the latter method gave mainly 1 peak for compound **6** with *m*/*z* matching the $[M + Na]^+$ ion.

Monolayer Characterization. *Self-Assembled Monolayers of the Cyclodextrin Adsorbates (**4**)−(**6**).* As the full characterization of a monolayer is inherently difficult, we have to rely on several complementary techniques. Monolayers of the short (**4**) or long dialkyl sulfide (**5**), and short alkanethiol β-cyclodextrin (**6**) (abbreviated as β-$CD_{shortsulfide}$, β-$CD_{longsulfide}$, and β-$CD_{shortthiol}$, respectively), were prepared by adsorption overnight from a 1 mM adsorbate solution.[25] Characterization was performed by electrochemistry, wettability studies, X-ray photoelectron spectroscopy (XPS), and time-of-flight secondary ion mass spectrometry (TOF-SIMS).

The thickness and capacitance of a monolayer have a reciprocal linear relationship.[2b] We found that the value of the capacitance for β-$CD_{longsulfide}$ (Table 1) is almost the same as that of well-packed monolayers of equal thickness such as monolayers of carceplex, cavitands, and calixarenes (all in the range of 1.5−2.5 $\mu F \cdot cm^{-2}$).[4−6] The values of the capacitance for the β-$CD_{shortsulfide}$ (9.6 $\mu F \cdot cm^{-2}$) and β-$CD_{shortthiol}$ (11.9 $\mu F \cdot cm^{-2}$) monolayers are much higher and similar to the value reported by Kaifer (10−11 $\mu F \cdot cm^{-2}$) for a monolayer of per-6-deoxy-(6-thio)-β-cyclodextrin.[10a] This indicates thinner monolayers.[2b] Impedance spectroscopy gives information about the charge-transfer resistance of the monolayer toward an external redox couple. The resistance is a measure for the quality and number of pinholes present in the monolayer. We found that the β-$CD_{longsulfide}$ monolayer has a higher resistance toward an external redox couple (ferro/ferri) than monolayers of β-$CD_{shortsulfide}$ and β-$CD_{shortthiol}$. The blocking ability of the short alkanethiol monolayer is significantly higher than that of the short dialkyl sulfide monolayer (see Table 1), but lower than that of the layer of β-$CD_{longsulfide}$.[26]

Wettability studies provide information on the polarity of the outerface of the monolayer. The contact angles with water for our monolayers are not very different (Table 2), and they point to layers of moderate polarity. The contact angle values correspond to monolayers such as $HS(CH_2)_{11}OMe$ ($\theta_a = 74°$) and $HS(CH_2)_{10}C(O)OMe$ ($\theta_a = 67°$).[27]

Table 2. Contact Angles with Water (Advancing and Receding) for β-$CD_{longsulfide}$, β-$CD_{shortsulfide}$, and β-$CD_{shortthiol}$ Monolayers

β-$CD_{longsulfide}$	β-$CD_{shortsulfide}$	β-$CD_{shortthiol}$
81−58	78−55	65−50

To the best of our knowledge, XPS measurements on cyclodextrin monolayers have not been reported previously. Our measurements proved the presence of all the elements in the monolayer (C, S, O, and N).[28] They show that the adsorbates are attached to gold by sulfur, rendering this the most interesting part of the XPS window. For thiols it is known that adsorption on gold results in a negative shift of about 1.5 eV for the XPS signal of the S_{2p} electrons (bound $S_{2p_{3/2}}$ 161.9 eV, unbound $S_{2p_{3/2}}$ 163.4 eV).[29] Spin-coated multilayers and self-assembled monolayers of dialkyl sulfides showed that also for sulfides a similar difference between bound (161.8 eV) and nonbound sulfur (163.0 eV) can be detected.[30] For monolayers with multiple points of attachment, we therefore measure the percentage of sulfur moieties bound and unbound to the gold. A theoretical example of a monolayer with multiple points of attachment containing bound and unbound sulfur in a ratio of about 3:2 is shown in Figure 1.

The XPS-(S_{2p}) spectra of all 3 cyclodextrin monolayers (Figure 2) show that not all sulfurs are attached to gold. Deconvolution of the signals depicted in Figure 2 results for the sulfide monolayers (β-$CD_{shortsulfide}$ and β-$CD_{longsulfide}$) in an average of 4.5 of 7 sulfides attached to the surface.[31] For the thiol monolayer (β-$CD_{shortthiol}$) this is 3.2 out of 7 thiol units. These XPS measurements show that adsorbates with *sulfides* are bound via more points of attachment than those with *thiols*. A possible explanation for the ratios between bound and unbound sulfur for the different SAMs might be the reversibility of the binding of sulfides to gold. Thiols are known to adsorb on gold as thiolates, while the sulfide bond to gold is more coordinative.[2] Moreover, thiols adsorb with a higher rate constant on gold than sulfides.[3a] The stronger interaction and faster adsorption may limit the possibilities for the adsorbate β-$CD_{shortthiol}$ to achieve the most ordered conformation, whereas the weaker and reversible binding of the two sulfide adsorbates does allow a rearrangement of the assembly. In an earlier investigation, Kaifer et al. determined the percentage of thiol units bound to the gold surface by reductive electrochemical desorption measurements. However, as this method is only applicable for thiol-based monolayers and has been criticized in the literature,[2b,32] we rely on our XPS-(S_{2p}) measurements for the discrimination between bound and unbound sulfur units.

(25) Sulfide monolayers were prepared at 60 °C and thiol monolayers at room temperature. In a previous paper (ref 4a) we have shown by heteregeneous electron transfer that elevated adsorption temperatures are necessary to form highly ordered sulfide monolayers.

(26) The β-$CD_{shortthiol}$ monolayer can, in principle, also be prepared via an indirect way: a chemical reaction on a monolayer. A well-known surface reaction is the amide formation at a monolayer of activated esters by an amine in solution. We tested this method by the reaction of hexylamine with a surface of an activated ester (DTSP, see Experimental Section). Infrared spectroscopy measurements showed two peaks at 1655 cm^{-1} (amide I) and 1550 cm^{-1} (amide II) and the complete disappearance of the C=O ester band, at 1750 cm^{-1} for the resulting monolayer. Thus, we decided to attach heptaamino β-cyclodextrin **3** to a surface of activated esters (DTSP). From the chemical point of view, this could yield the same monolayer as we obtained using the β-$CD_{shortthiol}$ adsorbate. Electrochemical impedance measurements indicated that the reaction leads to a monolayer of low quality (R_{CT} = 0.2 kΩ, vs R_{CT} = 39 kΩ for direct adsorption of β-$CD_{shortthiol}$). Moreover, IR measurements showed still a large signal for the nonreacted activated ester (C=O, at 1750 cm^{-1}). These measurements indicate that, for the preparation of monolayers using molecules which are attached to the surface via multiple points of attachment, the direct adsorption process is superior to an in situ preparation. The reactions of further amine functionalities of an already attached cyclodextrin molecule with the activated surface is apparently not favored, leaving a large amount of unreacted activated ester even after "completion" of the surface reaction.

(27) Laibinis, P. E.; Whitesides, G. M.; Allara, D. L.; Tao, Y.-T.; Parikh, A. N.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7152−7167.

(28) XPS-C/S ratio (calc./found) for the three different monolayers: β-$CD_{longsulfide}$ (32:1/34:1); β-$CD_{shortsulfide}$ (12:1/14:1), β-$CD_{shortthiol}$ (11:1/10:1).

(29) (a) Nuzzo, R. G.; Zegarski, B. R.; Dubois, L. H. *J. Am. Chem. Soc.* **1987**, *109*, 733−740. (b) Sun, F.; Grainger, D. W.; Castner, D. G.; Leach-Scampavia, D. K. *Macromolecules* **1994**, *27*, 3053−3062. (c) Castner, D. G.; Hinds, K.; Grainger, D. W. *Langmuir* **1996**, *12*, 5083−5086.

(30) Huisman, B.-H. Functional Monolayers; Self-Assembly of Sulfide Adsorbates on Gold. Ph.D. Thesis, University of Twente, The Netherlands, 1998.

(31) The S_{2p}-curve was fitted with four peaks (bound and unbound $S_{2p_{3/2}}$ and $S_{2p_{1/2}}$) to determine the ratio between bound and unbound sulfur.

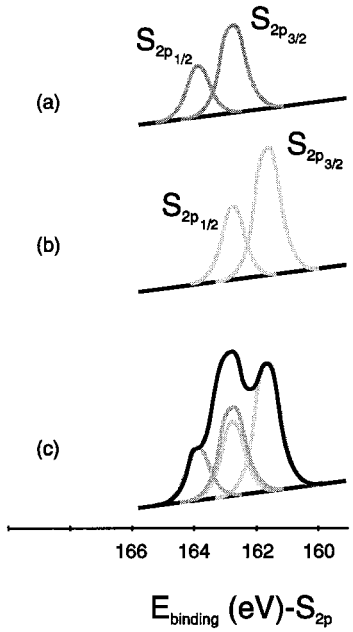

Figure 1. Theoretical XPS-(S_{2p}) signals and possible resulting XPS-(S_{2p}) signal of a monolayer of an adsorbate with multiple attachment points using about 3 of 5 sulfur units. (a) XPS-(S_{2p}), unbound sulfur; (b) XPS-(S_{2p}), bound sulfur; (c) XPS-(S_{2p}), resulting signal.

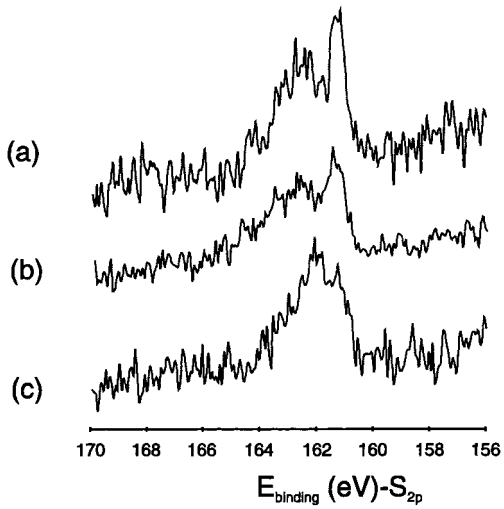

Figure 2. XPS-(S_{2p}) spectra for β-$CD_{longsulfide}$ (a), β-$CD_{shortsulfide}$ (b), and β-$CD_{shortthiol}$ (c). Deconvolution of the peaks gives 66%, 64%, and 45% bound sulfur units for β-$CD_{longsulfide}$, β-$CD_{shortsulfide}$, and β-$CD_{shortthiol}$, respectively.

The oxidation states of the carbon atoms in the monolayer can be detected by XPS-(C_{1s}). The binding energies for carbon reflect the different oxidization state as a result of different neighboring atoms (C, O, or N). Every oxygen or nitrogen binding to the carbon results in a positive shift of the C_{1s} binding energy to higher values of about 1.5 eV. Different C_{1s} peaks are clearly present in the spectrum (*x*, C−alkyl 284.7 eV; *y*, C−O 286.3 eV; *z*, O−C═O, N−C═O, and O−C−O 288.2 eV; see Figure 3). The peak at 288.2 eV is broad because it is a combination of 2 carbon atoms that could not be resolved. The composition of the monolayer for the 3 cyclodextrin monolayers is nicely reflected by the integration of the carbon peaks (see Table 3).

(32) Schneider, T. W.; Buttry, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 12391−12397.

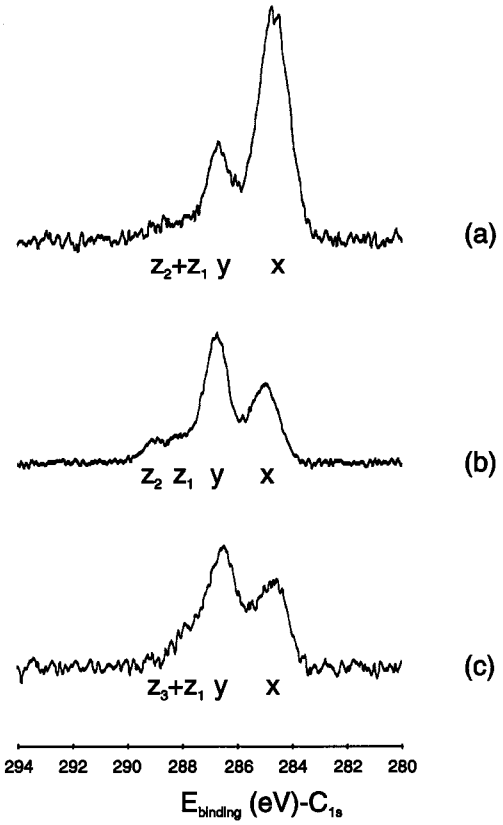

Figure 3. XPS-(C_{1s}) spectra for β-$CD_{longsulfide}$ (a), β-$CD_{shortsulfide}$ (b), and β-$CD_{shortthiol}$ (c). The letters *x*, *y*, and *z* are used for the different carbon atoms (see Table 3).

Table 3. XPS-(C_{1s}) Data for β-$CD_{longsulfide}$, β-$CD_{shortsulfide}$, and β-$CD_{shorthiol}$ Monolayers

	C−alkyl (*x*)		C−O (*y*)		O−C−O (z_1)/O−C═O(z_2)/ N−C═O (z_3)	
	exp.	calc.	exp.	calc.	exp.	calc.
β-$CD_{longsulfide}$	69.5	75.0	23.2	18.8	7.2	6.3
β-$CD_{shortsulfide}$	39.8	33.3	49.0	50.0	11.1	16.7
β-$CD_{shortthiol}$	38.4	27.3	50.4	54.5	11.2	18.2

Time-of-flight secondary ion mass spectrometry uses a mild ionization technique which mainly detects molecular peaks. Inclusion of a gold atom in the detected ionic species is a common feature. For example, the positive TOF-SIMS spectrum of didecyl sulfide ($C_{10}SC_{10}$) exhibits clear peaks at 370 (M^+) and 567 $(M + Au)^+$. The presence of these peaks gave us the unequivocal evidence for the nondestructive adsorption of sulfides on gold.[33] The positive TOF-SIMS spectra of the β-cyclodextrin monolayers show only weak peaks of the adsorbates.[34] The positive TOF-SIMS spectra of β-$CD_{longsulfide}$ is given as an example in Figure 4. The low-weight region (under 1000 amu) is not shown, as it consists of sulfur gold clusters (for example, Au at 197 amu: 20 000 counts). The inset shows two broad, very small but significant peaks (4200−4112 and 4228−4241, approximately 20−30 counts), which are tentatively attributed to $[(M + Au)^+$, 4207] and $[(M + Au + S)^+$, 4239]. The low intensity of the molecular peaks is qualitative proof for the robust attachment of the molecules on gold.

The multiple points of attachment apparently prevent desorption of the adsorbates from the gold surface by the

(33) Beulen, M. W. J.; Huisman, B.-H.; van der Heijden, P. A.; van Veggel, F. C. J. M.; Simons, M. G.; Biemond, E. M. E. F.; de Lange, P. J.; Reinhoudt, D. N. *Langmuir* **1996**, *12*, 6170−6172.

(34) Negative TOF-SIMS spectra mainly exhibit sulfur−gold clusters.

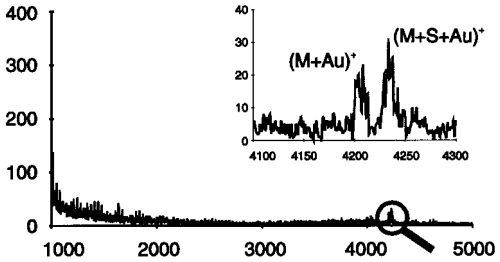

Figure 4. Positive SIMS spectra for the β-$CD_{longsulfide}$ monolayer.

mild TOF-SIMS technique. For example, removal of β-$CD_{longsulfide}$ adsorbate from the gold surface would need breakage of, on average, 4.5 Au−S bonds. Other results obtained in our group are consistent with these observations. Adsorbates with 1 or 2 attachment points show clear molecular peaks in TOF-SIMS, but adsorbates with, for example, 4 attached sulfur units such as the cavitands, show at best weak molecular peaks.[35]

Conclusions

In conclusion, we have developed a synthesis for the 7-fold introduction of dialkyl sulfides and alkanethiols on the primary side of β-cyclodextrin by ester or amide formation. Monolayers of the short- and long-chain β-cyclodextrin derivatives were characterized by XPS, TOF-SIMS, wettability studies, and electrochemistry. The effect of the length of the alkyl chains on the thickness of the monolayer was shown by cyclic voltammetric measurements. The outerface of the monolayer was studied by contact angles, which indicate a moderate polarity of the head group. XPS measurements revealed the number of attached sulfurs on gold. The *sulfide* adsorbates use their multiple attachment points in a *more efficient* way than those of the *thiol* monolayer. The robust attachment of the monolayer was proven by the weak molecular peaks in the TOF-SIMS-spectra. Moreover, XPS showed nicely the different oxidation states of the carbon atoms in the monolayer. The characterization of the β-cyclodextrin monolayers with the different techniques mentioned above supports our strategy of assembling large receptor molecules on gold. Long dialkyl sulfides and multiple points of attachment are necessary to obtain well-packed and stable monolayers. The applicability of these cyclodextrin monolayers, for example, for the selective detection of analytes, is under investigation.

Acknowledgment. The work was partly financed by a FAIR project of the EU (J.B., project PL 950300).

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(35) Thoden van Velzen, E. U. Self-Assembled Monolayers of Receptor Adsorbates on Gold. Ph.D. Thesis, University of Twente, The Netherlands, 1994.