Host–Guest Interactions at Self-Assembled Monolayers of Cyclodextrins on Gold

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Abstract: We have developed synthesis routes for the introduction of short and long dialkylsulfides onto the primary side of α-, β-, and γ-cyclodextrins. Monolayers of these cyclodextrin adsorbates were characterized by electrochemistry, wettability studies, X-ray photoelectron spectroscopy (XPS), time-of-flight secondary ion mass spectrometry (TOF-SIMS), and atomic force microscopy (AFM). The differences in thickness and polarity of the outerface of the monolayers were measured by electrochemistry and wettability studies. On average about 70% of the sulfide moieties were used for binding to the gold, as measured by XPS. Tof-SIMS measurements showed that the cyclodextrin adsorbates adsorb without any bond breakage. AFM measurements revealed for β-cyclodextrin monolayers a quasi-hexagonal lattice with a lattice constant of 20.6 Å, which matches the geometrical size of the adsorbate. The α-cyclodextrin and γ-cyclodextrin monolayers are less ordered. Interactions of the anionic guests 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS) and 2-(*p*-toluidinyl)naphthalene-6-sulfonic acid (2,6-TNS) and the highly ordered monolayers of heptapodant β-cyclodextrin adsorbates were studied by surface plasmon resonance (SPR) and electrochemical impedance spectroscopy. The SPR measurements clearly showed interactions between a β-cyclodextrin monolayer and 1,8-ANS. Electrochemical impedance spectroscopy measurements gave high responses even at low guest concentrations ($\leq 5\,\mu$M). The association constant for the binding of 1,8-ANS ($K = 289\,000 \pm 13\,000\,\text{M}^{-1}$) is considerably higher than the corresponding value in solution. (Partial) methylation of the secondary side of the β-cyclodextrin strongly decreases the binding.

Keywords: cyclodextrins · electrochemistry · host–guest chemistry · monolayers · supramolecular chemistry

Introduction

The use of self-assembled monolayers[1] of receptor adsorbates in sensor applications requires a high degree of order and packing of the monolayer. The order renders the cavities of the receptors more or less identical for complexation, whereas the packing of the monolayer minimizes nonspecific adsorption. Self-assembly on gold is attractive for a number of reasons. First, clean gold is relatively easy to prepare, because gold oxide is thermodynamically less stable than metallic gold. Second, large, flat Au(111) surfaces can be easily prepared. Third, the gold layer also serves as the working electrode in electrochemical techniques, such as cyclic voltammetry and impedance spectroscopy, is used in surface plasmon resonance measurements, and is compatible with quartz crystal microbalance and surface acoustic wave set-ups. To obtain devices for the transduction of molecular recognition into macroscopic properties, our group has previously reported the self-assembly of receptor molecules such as resorcin[4]arene[2] and crown ether derivatives[3] on gold. Interactions of the resorcin[4]arene monolayer with volatile gases like perchloroethylene were monitored by quartz crystal microbalance (QCM)[2d] or surface plasmon resonance (SPR).[2e] Self-assembled monolayers (SAMs) of crown ether adsorbates on gold bind metal ions reversibly from aqueous

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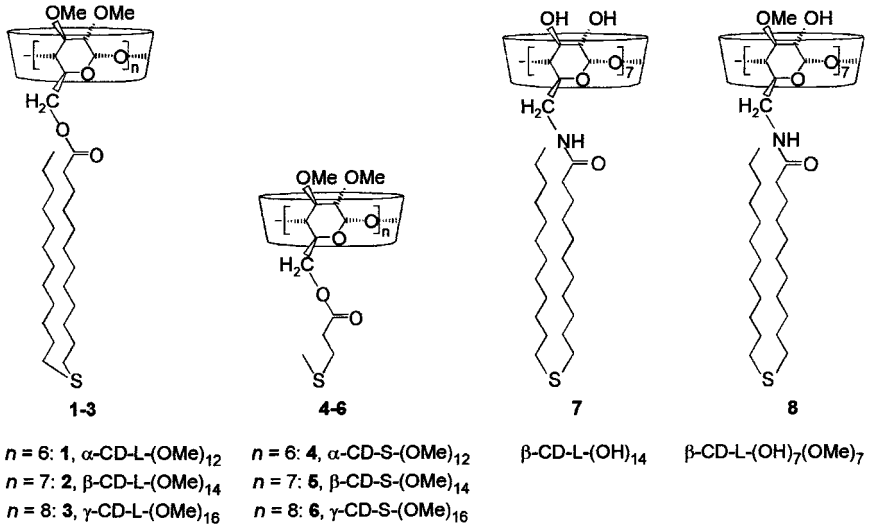
solution with a high selectivity, as was shown by electrochemical impedance spectroscopy measurements.[3]

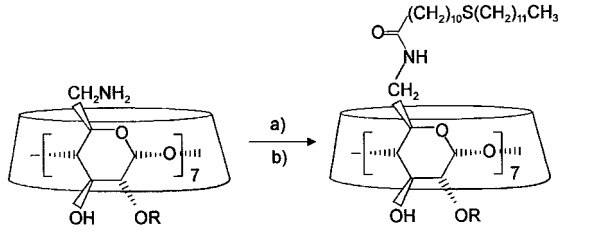
Cyclodextrins are cyclic oligosaccharides which are formed by a degradation of starch by *Bacillus Macerans*.[4] Cyclodextrins consist of α-D-glucose units and these molecules contain a hydrophobic cavity. They are attractive host molecules for sensing purposes, as they can accommodate a variety of organic guest molecules.[5] Sulfur-modified cyclodextrin derivatives have been used previously for the preparation of monolayers on gold by others[6, 7] and our group.[8] Although there are some reports on α-cyclodextrin monolayers,[6] most work has been performed on β-cyclodextrin monolayers.[7, 8] So far there are to our knowledge no reports of monolayers of higher cyclodextrins (γ- or δ-cyclodextrin). For example, Kaifer et al. reported a per-6-deoxy-(6-thio)-β-cyclodextrin monolayer which can use seven thiol moieties for binding to the gold surface.[7a] Galla et al. synthesized a β-cyclodextrin adsorbate with only one thiol moiety as attachment point.[7e] However, recent molecular dynamic calculations indicated that cyclodextrin monolayers with only one attachment point are assembled into a random, quasi-two-layer system rendering only half of the β-cyclodextrins available as hosts.[7i] Previously we have shown that the use of sulfides instead of thiols for attachment to a gold surface was more effective for the preparation of self-assembled β-cyclodextrin monolayers.[8] XPS-S_{2p} measurements showed that for sulfide-based β-cyclodextrins on average 4.5 out of 7 sulfur moieties are used for binding to the gold surface, whereas a thiol-based β-cyclodextrin adsorbate only utilizes 3.2 out of 7 sulfur moieties. There are only a few reports on the complexation behavior of such β-cyclodextrin monolayers. Kaifer et al. described the detection of ferrocene at a β-cyclodextrin monolayer by cyclic voltammetry.[7a] The complexation of ferrocene in the β-cyclodextrin cavities was proven by the linear scaling of the redox current with the scan rate, characteristic of a surface-confined redox center. Galla et al. reported the interaction of 1-adamantanecarboxylic acid (1-ADC) and 2-(*p*-toluidinyl)naphthalene-6-sulfonic acid (2,6-TNS) with a β-cyclodextrin monolayer monitored by electrochemical impedance spectroscopy measurements. The disorder in the monolayer resulted in a two-step adsorption process which was attributed to the presence of two energetically different binding sites at the surface.[7f]

Here we report the synthesis of several α-, β-, and γ-cyclodextrin adsorbates modified with sulfide moieties of different lengths and with different substitution patterns at the secondary side, in addition to the full characterization of the monolayers by various techniques, and host–guest interactions at these cyclodextrin monolayers monitored by SPR and electrochemistry. Our goal is to obtain highly ordered self-assembled monolayers with recognition sites all exposed to the outer interface.

Results and Discussion

Synthesis of the cyclodextrin adsorbates: Our strategy to obtain dense, well-packed monolayers of receptor molecules consists of filling the space underneath the headgroup by alkyl chains using multiple attachment points.[9] For example, we equipped a resorcin[4]arene with four sulfide[10] units (4×40 Å^2) to match the size of the cavity headgroup (160 Å^2).[2] The calculated cross sections (A) of cyclodextrin molecules are approximately 165, 185, and 240 Å^2 for α, β, and γ-cyclodextrin respectively and therefore we have used six (α), seven (β), and eight (γ) dialkyl sulfide moieties for each cyclodextrin to obtain highly ordered monolayers. Previously we have reported the synthesis and monolayer characterization of the β-cyclodextrins **2** and **5**.[8] It is known that the complexation behavior of cyclodextrins strongly depends on the substitution pattern and that permethylation, as in the β-cyclodextrins **2** and **5**, prevents complexation.[11] Therefore, β-cyclodextrin adsorbates with free hydroxy groups at the 2- and 3-positions (**7**) and with a free hydroxy group at the 2-positions (**8**) have been synthesized. The dialkyl sulfide moiety can be coupled to the cyclodextrin core in a very efficient way by an amide linkage. The β-cyclodextrins **7** and **8** were synthesized starting from the corresponding amino derivatives[12] in a coupling reaction using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-ethylmorpholine (Scheme 1). Furthermore, to study the effect of the size of the cyclodextrin cavity on the properties of the monolayers, the α-cyclodextrins **1** and **4** and γ-cyclodextrins **3** and **6** were prepared. They are equipped with multiple attachment points by a six- (α) or eightfold (γ) 1-(3-dimethylamino)-3-ethylcarbodiimide hydrochloride (EDC) coupling of the permethylated cyclodextrin with a dialkyl sulfide carboxylic acid. The cyclodextrin adsorbates **1**–**8** were obtained in good yields after chromato-





Scheme 1. Synthesis of cyclodextrin adsorbates. $CH_3(CH_2)_{11}S(CH_2)_{10}$-COOH (**14**), DCC, *N*-ethylmorpholine, DMF; a) $Y=45\,\%$ (**7**), b) $Y=54\,\%$ (**8**).

graphic purification, and all compounds were fully characterized. For example, the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum of β-cyclodextrin **7** showed a clear peak for $[M+Na]^+$.[13] In contrast to compounds **2**, **5**, **7**, and **8**, for which fragments were only detected by FAB mass spectrometry, this method gave one peak for the other cyclodextrins with *m/z* matching the $[M+Na]^+$ or $[M]^+$ ions.

Monolayer characterization: The monolayers of the cyclodextrin adsorbates **1**–**8** were fully characterized by electrochemistry, wettability studies, X-ray photoelectron spectroscopy (XPS), time-of-flight secondary ion mass spectrometry (TOF-SIMS), and atomic force microscopy (AFM). Typical results are summarized in Table 1. The thickness and capacitance of a monolayer have a reciprocal linear relationship.[1b] As expected, the capacitance measurements performed by cyclic voltammetry show a large difference in thickness of the monolayers with short (**4**–**6**) and long sulfide units (**1**–**3**, **7**, **8**). Furthermore, the long alkyl chains in the β-cyclodextrin monolayer **2**, **7**, and **8** result in a much higher charge-transfer resistance (R_{CT}) towards the $K_3Fe(CN)_6/K_4Fe(CN)_6$ external redox couple in comparison with the short alkyl chain β-cyclodextrin **5** monolayer, and this also reflects the differences in thickness and in order between the monolayers. Wettability studies can be used to study the outerface of a monolayer and provide information on the polarity. The contact angles with water for the methylated monolayers (**1**–**6**) are not very different (Table 1), and indicate layers of moderate polarity. The monolayers of the β-cyclodextrins with free hydroxy groups at the interface (**7** and **8**) are hydrophilic and therefore wetted by water (contact angles $\leq 20^o$). XPS measurements were used to study the atomic composition of the monolayers and showed the presence of all elements (C, S, N, O) in fairly good ratios (Table 1). XPS can also be used to determine the number of sulfur moieties actually used for binding to the gold surface. For sulfur adsorbates (thiols and sulfides) 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 $sulfur_{2p3/2}$ 161.9 eV, unbound $sulfur_{2p3/2}$ 163.4 eV).[8, 14] These monolayers use 60–75 % of their sulfur moieties. The low value of bound sulfur of 39 % obtained for the γ-CD-S-$(OMe)_{16}$ monolayer may result from the rotational freedom of this large cyclodextrin adsorbate. TOF-SIMS is a mass spectrometry technique that uses mild ionization and therefore mainly detects unfragmented species. As an example the positive SIMS spectrum of α-CD-S-$(OMe)_{12}$ is shown in Figure 1. The presence of clear peaks at 1945–1952 $[M+Au]^+$ and 1898–1903 $[M+Au-SMe]^+$ proves the surface confinement of this adsorbate.[15]

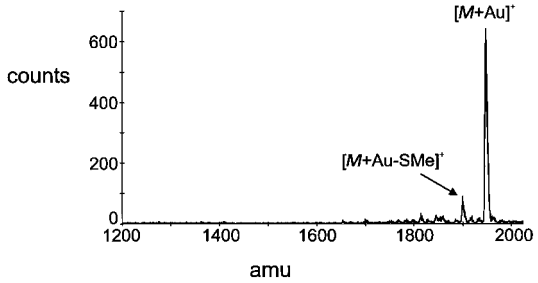


Figure 1. Positive SIMS spectra for α-CD-S-$(OMe)_{12}$ monolayer.

The characterization of the cyclodextrin monolayers with the techniques described above provides a wealth of information about the structure and properties of these monolayers. In addition, we investigated the monolayers at the level of molecular resolution by AFM.[16] AFM measurements can provide information on the packing of the molecules.[17] For monolayers of the cyclodextrins **1**–**3**, patterns which consisted of parallel lines were observed in the AFM images. The spacing was found to be 17.5 ± 1.2 Å, 18.4 ± 1.8 Å, and 23.4 ± 1.3 Å, for α-CD-L-$(OMe)_{12}$, β-CD-L-$(OMe)_{14}$, and γ-CD-L-$(OMe)_{16}$, respectively (histograms, see Figure 2a–c). The parallel lines are assigned to rows of unresolved adsorbate molecules. The values for the repeat distances are quantitatively in accordance with the differences in size between the adsorbates. As an example, a friction mode AFM image of the β-

Table 1. Properties of the self-assembled cyclodextrin monolayers.

SAM	θ_a/θ_r [H_2O, °][a]	C_{ML} ($\mu F\,cm^{-2}$)[b]	R_{CT} [kΩ][c]	XPS-C/S [found/calcd]	XPS-S_{2p} [%S bound][e]
α-CD-L-$(OMe)_{12}$ **1**	87/62	4.1	n. d.[d]	34/32	70
β-CD-L-$(OMe)_{14}$ **2**	81/58	2.5	48	34/32	66
γ-CD-L-$(OMe)_{16}$ **3**	85/58	3.3	n. d.[d]	24/32	60
α-CD-S-$(OMe)_{12}$ **4**	79/48	9.1	n. d.[d]	8/12	58
β-CD-S-$(OMe)_{14}$ **5**	78/55	9.6	5	14/12	64
γ-CD-S-$(OMe)_{16}$ **6**	76/45	8.5	n. d.[d]	17/12	39
β-CD-L-$(OH)_{14}$ **7**	<20	2.6	49	30/30	67
β-CD-L-$(OH)_7(OMe)_7$ **8**	<20	2.7	67	15/31	73

[a] Advancing (θ_a) and receding (θ_r) contact angles of the monolayer with water. [b] Capacitance of the monolayer determined by cyclic voltammetry at a scan rate of $0.1\,V\,s^{-1}$. [c] Charge-transfer resistance of the monolayer determined by fitting the impedance data to an equivalent circuit (see Experimental Section). [d] Not determined. [e] Percentage of sulfurs used by the adsorbates for binding to the gold surface. The experimental XPS-(S_{2p}) curves were fitted to four peaks (both $S_{2p3/2}$ and $S_{2p1/2}$, bound and unbound).

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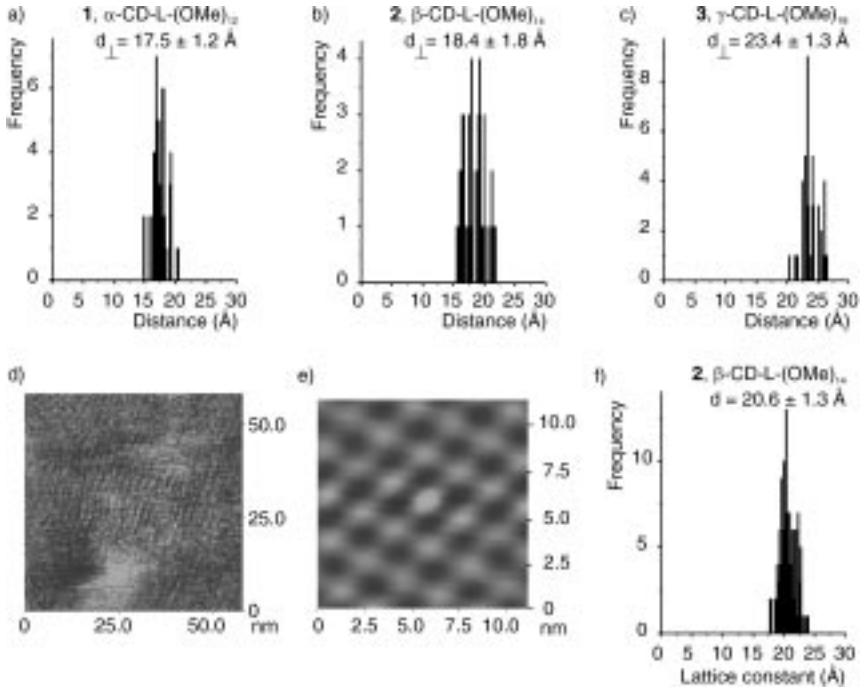

Figure 2. AFM data of cyclodextrin self-assembled monolayers. (a–c) Histograms of the distances of parallel lines in the AFM images of α-CD-L-$(OMe)_{12}$, β-CD-L-$(OMe)_{14}$, and γ-CD-L-$(OMe)_{16}$ monolayers. d) AFM image of the β-CD-L-$(OMe)_{14}$ monolayer in the contact mode. e) Autocorrelation-filtered AFM image of the β-CD-L-$(OMe)_{14}$ monolayer, taken form an ordered area. f) Histogram of the repeat distances observed for the β-CD-L-$(OMe)_{14}$ monolayer.

CD-L-$(OMe)_{14}$ monolayer is shown in Figure 2d. Parallel lines are clearly resolved in the center of the image. Only for SAMs of β-CD-L-$(OMe)_{14}$ could the lattice be resolved. An autocorrelation filtered AFM height image of a β-CD-L-$(OMe)_{14}$ monolayer reveals a quasihexagonal lattice (Figure 2e). A lattice constant of 20.6 ± 1.3 Å was obtained by averaging the constants in the three directions of symmetry (Figure 2f). This distance matches the geometric size of the adsorbate. In addition, the corresponding angle of this hexagonal lattice is $60.6 \pm 3.6^{\circ}$, in accordance with the theoretical value of 60° for this lattice. For monolayers of α-CD-L-$(OMe)_{12}$ and γ-CD-L-$(OMe)_{16}$ less order in the monolayer was observed by AFM (vide supra), and therefore no lattice constants could be determined. However, the parallel lines can be tentatively interpreted as rows of adsorbate molecules.

The characterization of the cyclodextrin monolayers described above shows that highly ordered monolayers were formed which expose their cavities to the outerface of the monolayer. In the next paragraph interactions of the β-cyclodextrin cavities with guests from solution will be described.

Interactions at self-assembled β-cyclodextrin monolayers:

SPR and electrochemical impedance spectroscopy were used to monitor host–guest interactions at self-assembled monolayers of the β-cyclodextrin derivatives **2**, **7**, and **8**.

The complexation at the β-cyclodextrin monolayers **2** and **7** of a guest **11** (1-anilinonaphthalene-8-sulfonic acid: 1,8-ANS; see Figure 4 for chemical structures)[18] that is known to form a complex with β-cyclodextrin was investigated by SPR. This is a technique where changes in the refractive index and thickness near an interface can readily be detected. Experimentally, the 'plasmon resonance angle' is determined, which is the angle under which light, reflected at a prism/metal interface in the so-called Kretschmann configuration, exhibits a minimum in the reflectance. The change of the plasmon angle during a surface binding experiment is proportional to the amount of material bound to the surface.[19] The SPR-curve of the β-CD-L-$(OH)_{14}$ monolayer is shown in Figure 3a. After addition of 1,8-ANS (200 μM) the angle at the minimum in reflection shifted to a slightly higher value ($\theta_{H_2O} = 57.01^{\circ}$ to $\theta_{1,8\text{-ANS}} = 57.08^{\circ}$; see Figure 3b), in correspondence with a thicker monolayer as a result of complexation. The addition of the guest 1,8-ANS (200 μM) to the β-CD-L-$(OMe)_{14}$ monolayer resulted in no observable shift of the plasmon angle. Kinetic SPR measurements were performed at a fixed angle of $\theta = 55.85^{\circ}$. In this part of the SPR-curve the reflectance changes linearly with the angle of incidence (Figure 3a).[20] The change in reflectance for the β-CD-L-$(OH)_{14}$ monolayer upon the addition of the guest 1,8-ANS (200 μM) is about 1.5–2%, and reversible (Figure 3c). It is obvious from Figure 3c that there was some baseline drift

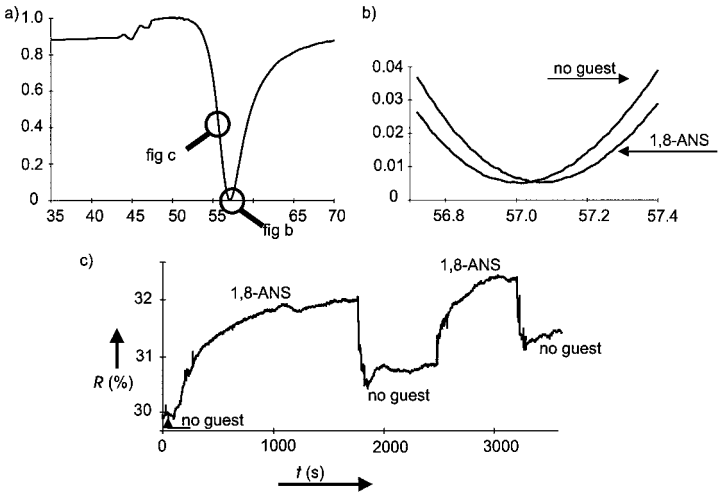

Figure 3. SPR measurements on the β-CD-L-$(OH)_{14}$ (**7**) monolayer. a) Total SPR curve. b) Shift in minimum of reflectance upon the addition of 1,8-ANS (200 μM). c) Change in reflectance at $\theta = 55.85^{\circ}$ monitored by kinetic SPR measurements by adding and washing away the guest 1,8-ANS.

during the measurements. On the contrary, addition of the guest 1,8-ANS to the β-CD-L-$(OEM)_{14}$ monolayer resulted in changes in reflectivity which are smaller than 0.5%. These SPR measurements show that the guest 1,8-ANS interacts with the β-CD-L-$(OH)_{14}$ monolayer, but the measured changes are quite small. Therefore, we used electrochemical impedance measurements (EIS) to monitor the complexation more quantitatively.

The complexation at the β-cyclodextrin monolayers **2**, **7**, and **8** of the guests 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS, **11**) and 2-(*p*-toluidinyl)naphthalene-6-sulfonic acid (2,6-TNS, **12**)[18] was studied by EIS with the negatively charged $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ as the reporter redox couple.[21] The response curves of the β-CD-L-$(OH)_{14}$ monolayer for these guests are shown in Figure 4. The initial value of the

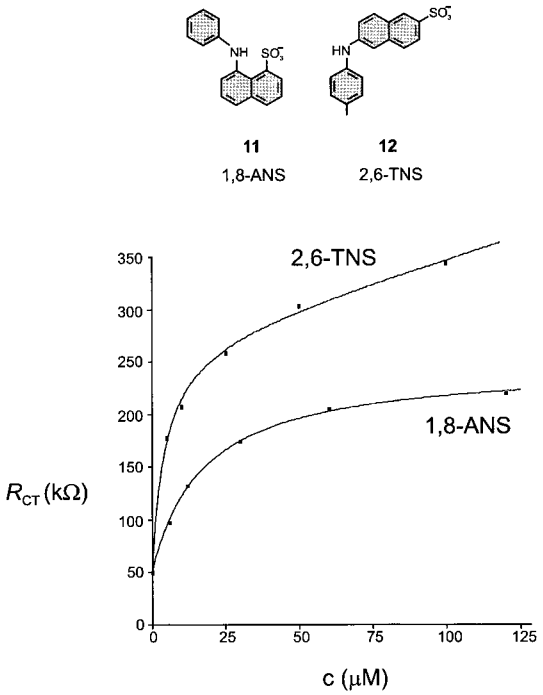

Figure 4. Dependence of the R_{CT} of the β-CD-L-$(OH)_{14}$ monolayer on the concentration of anionic guests obtained by electrochemical impedance spectroscopy measurements. The solid line for 1,8-ANS is a fitted Langmuir isotherm, whereas the solid line shown for 2,6-TNS is merely added to guide the eye.

charge-transfer resistance (R_{CT}) of the β-CD-L-$(OH)_{14}$ monolayer of 49.2 kΩ is high, indicating a highly ordered monolayer, that blocks the redox current effectively.[9a] Binding of the anionic guests to the β-cyclodextrin monolayer results in an increase of R_{CT} by electrostatic repulsion between the sulfonic anions and the $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ redox couple. Even at very low concentrations of guests, for example addition of 5 μM of 1,8-ANS or 2,6-TNS, the R_{CT} more than doubled. Furthermore, the titration curve of 1,8-ANS levels off at a concentration of about 120 μM, as a result of saturation of the monolayer. The cavities of the β-cyclodextrin monolayer can be modeled as a set of parallel resistances as shown in Equation (1), in which R_{CT} = measured charge-transfer resistance; R_0 = charge-transfer resistance of a 'bare' β-cyclodextrin monolayer; R_{max} = charge-transfer resistance of a β-cyclodextrin monolayer with all cavities filled by a guest and θ = the fraction of the cavities which are filled with a guest molecule.

$$R_{CT} = \left(\frac{1-\theta}{R_0} + \frac{\theta}{R_{max}}\right)^{-1} \quad (1)$$

The experimental R_{CT} data of 1,8-ANS were fitted to a Langmuir isotherm [Eq. (2)] using Equation (3).[22, 23] Where R_0 was experimentally determined as 49.2 kΩ, c is the

$$\theta = \frac{K_c}{1+K_c} \quad (2)$$

$$R_{CT} = \left(\frac{1-\left(\frac{K_c}{1+K_c}\right)}{R_0} + \frac{\left(\frac{K_c}{1+K_c}\right)}{R_{max}}\right)^{-1} \quad (3)$$

concentration of guest in solution (M), and parameters K_c (association constant) and R_{max} are obtained from the non-linear least squares fit.

This fitted Langmuir isotherm (Figure 4; $r^2 = 0.9989$, $R_{max} = 246.3 \pm 3.0\ \Omega$) gave for 1,8-ANS at the β-CD-L-$(OH)_{14}$ monolayer an association constant K_c of $289\,000 \pm 13\,000\ M^{-1}$, which corresponds to a complexation energy of -7.4 kcal mol^{-1}. This free energy of binding is considerably higher than measured in solution for β-CD (-2.7 kcal mol^{-1}).[18] This might be caused by a different microenvironment of the receptor at the interface and a different diffusional freedom of the cavities.

Studies on the complexation of 2,6-TNS at the β-CD-L-$(OH)_{14}$ monolayer were obscured by the low solubility of this guest in water. Therefore the measurements were performed in the presence of small amounts of ethanol in the aqueous electrolyte solution (e.g. 2% at 100 μM 2,6-TNS). We experimentally determined that ethanol already has a slight, increasing effect on the R_{CT} of a β-cyclodextrin monolayer. The association constant of the host–guest complex will also be influenced, rendering the extraction of thermodynamic data from the 2,6-TNS curve in Figure 4 virtually impossible.[24]

Permethylation at the secondary side of β-cyclodextrin breaks the hydrogen-bond arrays, reduces rigidity, and therefore leads to partial collapse of the cavity. Methylation at only the 2-position significantly influences the complexation properties of β-cyclodextrin.[11] The influence of partial methylation and permethylation on the response towards 1,8-ANS was studied with the β-cyclodextrin monolayers **2**, **7**, and **8** (bar graph of Figure 5). For the partially methylated β-CD-L-$(OH)_7(OMe)_7$ monolayer a fairly high response with 1,8-ANS (5 μM) was also measured. The permethylated β-CD-L-$(OMe)_{14}$ monolayer does not complex 1,8-ANS at all. These impedance measurements show that the influence of methylation on complexation is the same on a monolayer as in solution. A reference monolayer of 11-hydroxyundecanethiol (**13**) has hardly any interactions with 1,8-ANS, which is a strong indication that the guests complex in the β-cyclodextrin cavities.[25]

The electrochemical measurements show that these β-cyclodextrin monolayers can detect low concentrations of guests and that there is a large influence of the substitution pattern at the secondary side of the β-cyclodextrin adsorbates on this complexation behavior.

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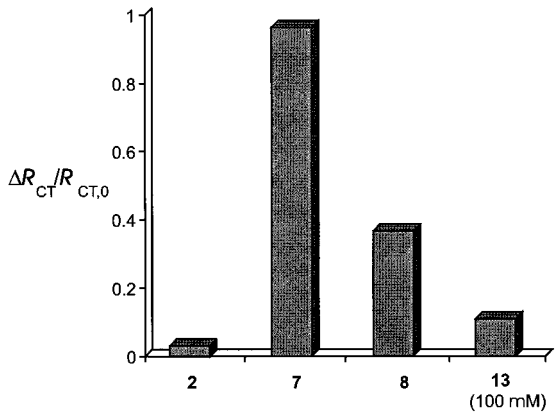

Figure 5. Relative change in R_{CT} for monolayers of β-CD-L-$(OMe)_{14}$ (**2**), β-CD-L-$(OH)_{14}$ (**7**), β-CD-L-$(OH)_7(OMe)_7$ (**8**), and 11-hydroxy-undecanethiol (**13**) upon the addition of 5 μM (**2**, **7**, and **8**) and 100 μM (**13**) of 1,8-ANS.

Conclusion

Highly ordered self-assembled monolayers with recognition properties can be achieved by molecular design. Our strategy uses adsorbates with multiple attachment points to fill the space underneath the headgroup. This strategy resulted in highly ordered α-, β-, and γ-cyclodextrin self-assembled monolayers. This order minimizes nonspecific interactions and leads to well-defined host–guest interactions, as shown for 1,8-ANS with a very high binding constant.

Experimental Section

Materials: α-Cyclodextrin, β-cyclodextrin, and γ-cyclodextrin were a generous gift of Wacker-Chemie GmbH, München, Germany and were dried prior to use. All other chemicals were used as received, unless otherwise stated. Solvents were purified according to standard laboratory methods.[26] All reactions were carried out in an inert atmosphere. NMR spectra were taken on a 300 MHz spectrometer, using residual solvent protons or TMS as internal standard. 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 were uncorrected. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry was carried out using a perseptive biosystems voyager-de-rp MALDI-TOF mass spectrometer. FAB mass spectra were obtained with a Finnigan MAT 90 spectrometer. For MALDI-TOF mass spectrometry α-cyano-4-hydroxycinnamic acid and for FAB mass spectrometry *m*-nitrobenzyl alcohol were used as the matrix. We have previously described the synthesis of heptakis{6-*O*-[12-(thiododecyl)dodecanoyl]-2,3-di-*O*-methyl}-β-cyclodextrin (**2**) and heptakis{6-*O*-[3-(thiomethyl)propionyl]-2,3-di-*O*-methyl}-β-cyclodextrin (**5**).[8] Heptakis(6-deoxy-6-amino)-β-cyclodextrin (**9**) and heptakis(2-*O*-methyl-6-deoxy-6-amino)-β-cyclodextrin (**10**), were prepared according to literature procedures[12] and were vacuum-dried over P_2O_5 at 80 °C for 1 d before use. The dialkyl sulfide carboxylic acid **14**, $CH_3(CH_2)_{11}S(CH_2)_{10}COOH$, was synthesized according to literature procedures.[27]

The α-cyclodextrins **1** and **4**, and γ-cyclodextrins **3** and **6** were prepared analogously to the synthesis described for the β-cyclodextrins **2** and **5**.[8] Selected spectral data:

Hexakis{6-*O*-[12-(thiododecyl)dodecanoyl]-2,3-di-*O*-methyl}-α-cyclodextrin (1): Yield = 20%; ^{1}H NMR ($CDCl_3$): δ = 4.96 (s, 6H), 4.41–4.28 (m, 12H), 3.94–3.88 (m, 6H), 3.63–3.49 (m, 48H), 3.14–3.09 (m, 6H), 2.47 (t, ^3J(H,H) = 7.3 Hz, 24H), 2.31–2.26 (m, 12H), 1.58–1.49 (m, 42H), 1.35–1.19 (m, 186H), 0.86 (t, ^3J(H,H) = 6.6 Hz, 18H); ^{13}C NMR ($CDCl_3$): δ = 173.0, 99.8, 82.3, 82.0, 81.3, 70.0, 62.9, 61.8, 58.2, 34.1, 32.2, 31.9, 29.8–29.0, 25.0, 22.7, 14.1; MS (FAB): *m/z*: 3458.6 ($[M+Na]^+$, calcd: 3458.5).

Octakis{6-*O*-[12-(thiododecyl)dodecanoyl]-2,3-di-*O*-methyl}-γ-cyclodextrin (3): Yield = 66%; ^{1}H NMR ($CDCl_3$): δ = 5.15 (s, 8H), 4.41–4.25 (m, 16H), 3.85–3.83 (m, 8H), 3.64–3.52 (m, 64H), 3.17–3.14 (m, 8H), 2.48 (t, ^3J(H,H) = 7.3 Hz, 32H), 2.34–2.27 (m, 16H), 1.69–1.53 (m, 56H), 1.35–1.19 (m, 248H), 0.86 (t, ^3J(H,H) = 6.6 Hz, 28H); ^{13}C NMR ($CDCl_3$): δ = 172.9, 97.9, 82.0, 81.7, 78.7, 69.6, 62.7, 61.1, 59.0, 34.1, 32.2, 31.9, 29.8–29.0, 25.0, 22.7, 14.1; MS (FAB): *m/z*: 4582.4 ($[M]^+$, calcd: 4582.3).

Hexakis{6-*O*-[3-(thiomethyl)propionyl]-2,3-di-*O*-methyl}-α-cyclodextrin (4): Yield = 93%; ^{1}H NMR ($CDCl_3$): δ = 5.00 (d, ^3J(H,H) = 3.1 Hz, 6H), 4.44–4.32 (m, 12H), 3.94–3.93 (m, 6H), 3.63–3.50 (m, 48H), 3.17–3.11 (m, 6H), 2.74–2.65 (m, 24H), 2.10 (s, 18H); ^{13}C NMR ($CDCl_3$): δ = 171.4, 99.9, 82.4, 81.9, 81.2, 69.9, 63.5, 61.8, 58.2, 34.3, 29.0, 15.5; MS (FAB): *m/z*: 1775.8 ($[M+Na]^+$, calcd: 1775.6).

Octakis{6-*O*-[3-(thiomethyl)propionyl]-2,3-di-*O*-methyl}-γ-cyclodextrin (6): Yield = 85%; ^{1}H NMR ($CDCl_3$): δ = 5.13 (d, ^3J(H,H) = 3.4 Hz, 8H), 4.46–4.27 (m, 16H), 3.87–3.85 (m, 8H), 3.64–3.52 (m, 64H), 3.19–3.14 (m, 8H), 2.75–2.66 (m, 32H), 2.10 (s, 24H); ^{13}C NMR ($CDCl_3$): δ = 171.4, 98.4, 81.8, 79.3, 69.6, 63.3, 61.3, 59.1, 34.4, 28.9, 15.5; MS (FAB): *m/z*: 2337.9 ($[M]^+$, calcd: 2337.8); 2361.3 ($[M+Na]^+$, calcd: 2360.8).

Heptakis{6-deoxy-6-[12-(thiododecyl)undecanamido]}-β-cyclodextrin (7): A solution of 12-(thiododecyl)undecanoic acid (**14**, 0.63 g, 1.56 mmol) and 1-hydroxybenzotriazol monohydrate (0.23 g, 1.67 mmol) in DMF (10 mL) was cooled to 0 °C and *N*,*N*′-dicyclohexylcarbodiimide (0.32 g, 1.57 mmol) was added. Stirring was continued for 1 h at 0 °C and 1 h at room temperature. Subsequently, a slurry of heptakis(6-deoxy-6-amino)-β-cyclodextrin (**9**, 0.25 g, 0.22 mmol) and *N*-ethylmorpholine (0.20 mL, 1.56 mmol) in DMF (10 mL) was added and stirring was continued for two days at room temperature. The solvent was removed in vacuo and the residue was partitioned in water/brine (50 mL; 1/1 *v*/*v*) and petroleum ether 60/80 (50 mL). The aqueous layer was extracted with petroleum ether 60/80 ((3 × 50 mL). After drying the combined organic layers ($MgSO_4$) and filtration, the solvent was evaporated to give an off-white powder. The crude product was purified twice by flash chromatography (eluent: CH_2Cl_2/methanol, gradient 0–5% *v*/*v*%) to give cyclodextrin **7** as a colorless solid (0.38 g, 0.10 mmol, 45%). TLC: R_f = 0.56 (CH_2Cl_2/MeOH 30% *v*/*v*); ^{1}H NMR ($CDCl_3$): δ = 7.09 (s, 7H), 6.57 (s, 7H), 5.13 (s, 7H), 4.80 (s, 7H), 3.92–3.11 (m, 42H), 2.42 (t, ^3J(H,H) = 7.5 Hz, 28H), 2.13 (m, 14H), 1.52–1.47 (m, 42H), 1.41–1.11 (m, 224H), 0.81 (t, ^3J(H,H) = 6.5 Hz, 21H); ^{13}C NMR ($CDCl_3$): δ = 174.2, 102.5, 84.3, 73.4, 71.1, 54.3, 43.1, 37.2, 36.4, 32.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.0, 26.0, 22.7, 14.2; MS (MALDI-TOF) *m/z*: 3732 ($[M+Na]^+$, calcd: 3732); elemental analysis calcd. for $C_{203}H_{385}N_7O_{35}S_7 \cdot 5H_2O$ (%): C 64.18, H 10.48, N 2.58, S 5.91; found: C 64.54, H 10.23, N 2.67, S 5.70.

Heptakis{2-*O*-methyl-6-deoxy-6-[12-(thiododecyl)undecanamido]}-β-cyclodextrin (8): Analogously to the preparation of β-cyclodextrin **7**, heptakis(2-*O*-methyl-6-deoxy-6-amino)-β-cyclodextrin (**10**, 0.25 g, 0.20 mmol), *N*-ethylmorpholine (0.18 mL, 1.41 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.30 g, 1.43 mmol), 12-(thiododecyl)undecanoic acid (**14**, 0.57 g, 1.41 mmol), and 1-hydroxybenzotriazol monohydrate (0.21 g, 1.52 mmol) yielded cyclodextrin **8** as a colorless solid (0.42 g, 0.11 mmol, 54%). TLC: R_f = 0.27 (CH_2Cl_2/MeOH 10% *v*/*v*); ^{1}H NMR ($CDCl_3$): δ = 5.09–5.05 (m, 7H), 4.83 (m, 7H), 3.87–3.06 (m, 35H), 3.59 (s, 21H), 3.18 (d, ^3J(H,H) = 9.3 Hz, 7H), 2.42 (t, ^3J(H,H) = 7.2 Hz, 28H), 2.11 (m, 14H), 1.90–1.87 (m, 14H), 1.69–1.45 (m, 56H), 1.29–1.13 (m, 234H), 0.81 (t, ^3J(H,H) = 6.9 Hz, 21H); ^{13}C NMR ($CDCl_3$) δ = 173.5, 100.6, 81.5, 72.4, 60.0, 35.9, 31,7, 31.4, 29.2, 29.1, 28.8, 28.5, 25.4, 22.2, 13.6.

Monolayers: **Gold substrates**: Gold substrates were prepared by evaporating 200 nm 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.[28] For AFM measurements, gold substrates were purchased from Metallhandel Schröer GmbH, Lienen, Germany (200 nm gold on 5 nm chromium on glass substrates [11 × 11 mm^2]). These samples were stored under nitrogen. Prior to use, substrates were flame annealed with a H_2 flame (quality 6). The annealing yielded reproducibly large Au(111) terraces of a few micrometers in size.

After annealing, the substrates were allowed to cool to room temperature and transferred with minimal delay to the adsorption solution. For SPR measurements 50 nm thick gold-coated glass substrates were used.

Monolayer preparation: All glassware used to prepare monolayers was immersed in *piraña* at 70 °C for 1 h. **Warning**: *piraña* solution should be handled with caution; it can detonate unexpectedly. Next, the glassware was rinsed with large amounts of high purity water (Millipore). 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. The sulfide monolayers were prepared at 60 °C for 16 h. Subsequently, the substrates were removed from the solution and rinsed with dichloromethane, ethanol, and water to remove any physisorbed material.

Monolayer characterization: The advancing and receding contact angles with water were measured on a Krüss G10 Contact Angle Measuring Instrument, equipped with a CCd camera. The contact angle measurements were measured during the growth and shrinkage of a droplet. 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. For X-ray photoelectron spectroscopy (XPS) a VG Escalab 220i-XL instrument was used with a monochromatic $Al_{K\alpha}$ X-ray source. XPS-data were collected from a surface area of 150 mm × 150 mm with a pass energy window of 20 eV using 10, 20, and 10 scans for carbon, sulfur, and oxygen, respectively.[29] Electrochemical measurements (cyclic voltammetry and impedance spectroscopy) were performed on a 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 K_2SO_4 (0.1 M) between −0.4 V_{MSE} and −0.3 V_{MSE} at scan rates ranging from 0.1 $V s^{-1}$ to 2.0 $V s^{-1}$. Impedance spectroscopy measurements were performed in 1 mM $K_3Fe(CN)_6/K_4Fe(CN)_6$ and 0.1 M K_2SO_4 at −0.2 V_{MSE} with an amplitude of 5 mV using a frequency range from 50 kHz to 0.1 Hz. The charge-transfer resistance of the monolayer was obtained by fitting the experimental data to an equivalent circuit consisting of the monolayer resistance parallel with the monolayer capacitance, in series with the solution resistance.[30] Good fits were obtained.[21b] The starting volume of the electrolyte solution in the electrochemical cell was 60 mL. Guests were titrated from stock solutions: 1,8-ANS (3.5 mM) in an aqueous solution of K_2SO_4 (0.1 M) and $K_3Fe(CN)_6/K_4Fe(CN)_6$ (1 mM), and 2,6-TNS (3.0 mM) in a 60% EtOH solution. The experimental titration curve of the β-CD-L-$(OH)_{14}$ monolayer was fitted with the program Table Curve V 1.0 by Jandel Scientific. The AFM measurements were carried out with a Nanoscope II and a Nanoscope III AFM (Digital Instruments, Santa Barbara, California, USA) in the contact mode. AFM scans were performed in water using a liquid cell. Silicon nitride cantilevers with nominal spring constants of 0.38 $N m^{-1}$ and 0.06 $N m^{-1}$ were used. The system was allowed to equilibrate prior to measurements until no drift was observed, which could last up to 24 hours. For a quantitative analysis of the lattices, 'up' and 'down' scans were averaged in order to eliminate thermal drift. The images were analyzed as reported previously.[31] After multiplication with a calibration factor,[32] which takes into account the influence of the sample height on the measured distances, the observed values were plotted in histograms, and the average for each of the three directions was calculated. SPR measurements were performed in a so-called Kretschmann configuration by optically matching the gold substrate with the monolayer to the base of a 90° LaSFN9 glass prism ($n = 1.85$ at $\lambda = 632.8$ nm) using an index matching oil. The plasmon polaritons were excited at the metal/dielectric interface, upon total internal reflection of the laser beam (HeNe, $\lambda = 632.8$ nm, power 5 mW) at the prism base. By varying the angles of incidence of the laser beam, a plot of reflected intensity as a function of the angle of incidence was obtained.[7b]

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[24] The line for the titration curve of 2,6-TNS shown in Figure 4 is a superposition of a Langmuir isotherm and a straight line, as a representation of the contribution of the complexation in the β-cyclodextrin cavities and the influence of the amount of ethanol present, respectively. A tentative fit on a superposition of these two components resulted in an association constant of $1250000\,\text{M}^{-1}$ (ΔG° of $-8.3\,\text{kcal mol}^{-1}$; $r^2 = 0.9980$). The complexation constant of 2,6-TNS to β-CD in solution is also higher than of 1,8-ANS.
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