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Chiral discrimination of enantiomers with a self-assembled monolayer of functionalized β-cyclodextrins on Au surfaces

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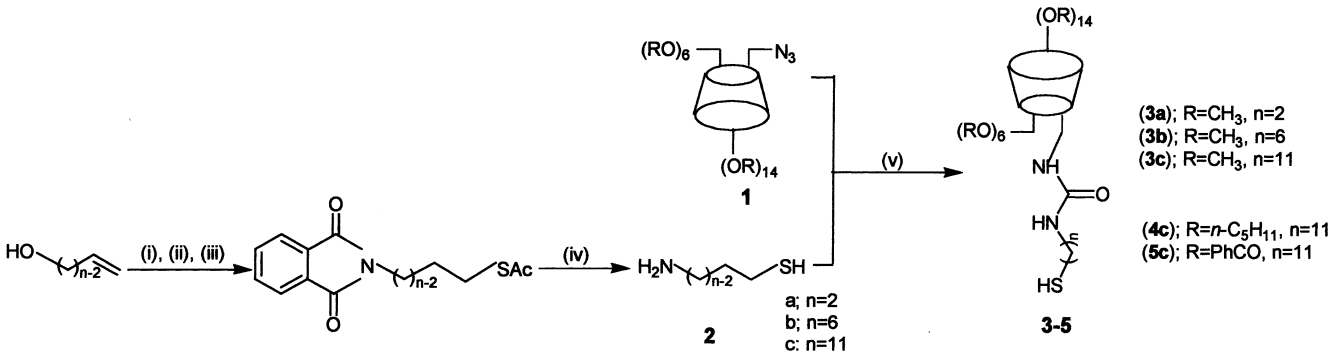
Abstract—A facile synthetic route to mercaptyl functionalized β-cyclodextrins was devised and self-assembled onto the gold electrodes of a quartz crystal microbalance (QCM) to afford a durable sensor capable of chiral discrimination of enantiomers.

Molecular host–guest recognition systems have attracted significant attention in recent years.[1] It becomes evident that researchers in this area are increasingly interested in the potential applications of these systems in chemical sensors and molecular electronics.[2] Among synthetic host molecules, cyclodextrin (CD) has emerged as an ideal candidate for this pursuit due to its well-defined molecular cavity and its ability to accommodate a variety of guest molecules.[3] It is necessary for cyclodextrin to be confined or immobilized on the surface of a substrate such as the Au surface at the device level. Therefore, several routes for the synthesis of dialkyl sulfide- and alkanethiol-substituted cyclodextrins forming self-assembled monolayers (SAMs) on Au and Ag have been reported. Rojas et al.[1] immobilized native β-CD molecules on a gold surface through thiol moieties directly linked to the β-CD molecule. Nelles et al.[4] reported the immobilization kinetics of β-CD through mono- or multithiol linkers. More recently, Beulen et al.[5] developed synthetic routes to introduce short and long dialkyl sulfides onto the primary side of α-, β-, and γ-CDs. However, it is apparent that these synthetic routes were invariably applied to native CDs whilst a systematic approach towards dialkyl sulfide- or thiol-modified functionalized CDs was not reported.

The present work reports on a facile synthetic approach to structurally well-defined mercaptyl functionalized β-CDs. Subsequently, self assembly onto an Au surface of a quartz crystal microbalance (QCM) afforded a durable enantioselective coating which was applicable for the chiral discrimination of enantiomers.

Scheme 1 depicts the synthetic route to mercaptyl functionalized β-CD from (6^A-azido-6^A-deoxy)heptakis(2,3-



Scheme 1. *Reagents and conditions*: (i) imidazole/Ph_3P/I_2/DCM (dry); (ii) potassium phathalimide/DMF (dry)/Δ; (iii) CH_3COSH/hexane (dry)/UV; (iv) $NH_2NH_2{\cdot}H_2O$/MeOH/reflux; (v) PPh_3/CO_2/THF (dry).

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di-*O*-functionalized)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-functionalized-β-CD (**1**). The synthesis of (**1**) has been reported previously,[6] thus the crucial part of the whole scheme relies on the availability of mercaptyl-alkylamines of different lengths, $NH_2(CH_2)_nSH$ (**2**). With $n=2$, commercially available cysteamine was used directly. For $n>2$, a facile route was derived for the synthesis of 6-(ω-mercaptyl)-hexanamine (**2b**) and 11-(ω-mercaptyl)-undecanylamine (**2c**) using a modified Gabriel reaction[7] followed by a photoaddition reaction[8] and then a deprotection step which conveniently cleaved both protective groups in one step (step iv). Coupling of (**1**) and the thiol linker (**2**) was accomplished using a Staudinger reaction under mild conditions and the expected products (**3**) were obtained.[9] Table 1 summarizes the respective yields of these mercaptyl β-CD derivatives, in which R = methyl, pentyl, and benzoyl, respectively. The formation of the carbamido moiety in these compounds was evident from the ^{13}C NMR resonance at ca. δ 159 ppm.

Immobilization of mercaptyl β-CDs (**3a**)–(**5c**) on the Au surface was achieved using established procedures.[10] Subsequently, XPS studies of the Au surface revealed the presence of the elements C, N, O and S. Moreover, the presence of a broad peak with binding energy at ca. 162 eV for the S_{2p} environment is consistent with the presence of an Au–S moiety due to self-assembly of the thiols on the Au surface.[4] Further corroborative evidence of the successful immobilization of these β-CD derivatives on the Au surface was obtained from positive 10 KeV Ar TOF-SIMS spectra (Table 2). The presence of two distinct groups of fragments at molecular mass $[M+Au]^+$ and $[M+Au–S]^+$, where M is the molecular mass of the mercaptyl β-CD molecule (i.e. $M_{\mathbf{3a}}=1517.2$ g/mol) confirms the formation of the Au–S covalent bond between the mercaptyl β-CD molecule and the Au substrate.[11]

Table 1. Yields of mercaptyl functionalized persubstituted β-CD derivatives

Compd	*n*	Yield (%)
2a	2	–
2b	6	82
2c	11	87
3a	2	19
3b	6	25
3c	11	34
4c	11	29
5c	11	30

A study of the gas phase chiral discrimination of enantiomers by immobilized β-CD monolayers was carried out using an AT-cut 10 MHz quartz crystal microbalance (QCM). Compounds (**3a**)–(**5c**) were immobilized on the surface of the Au electrodes of a QCM, and the surface concentration of the immobilized β-CD host molecules was calculated according to the equation:[12] $\Delta f=(2.26\times 10^{-6}) f_0^2 (\Delta m/A)$ and summarized in Table 2.

The influence of the thiol linker length (n) on the surface concentration of immobilized β-CD monolayers was well reflected in SAM (**3a**) and (**3c**), where the longer thiol linker ($n=11$) affords compound (**3c**) which is more densely packed in the monolayer.

The chiral discrimination experiment was carried out in a home-made pulse measuring system using pre-dried N_2 as carrier gas, at 200 ml/min.[13] The coated QCM sensors were exposed to the same concentration of (+)-methyl lactate and (−)-methyl lactate analytes at 25±0.1°C. Their respective time-course signals were recorded and are plotted in Fig. 1.[†]

As can be seen, the responses of the QCM sensors due to the inclusion complexation of the analyte molecule by the β-CD monolayer are reproducible. Moreover, the responses towards the respective chiral forms of methyl lactate are similar but differ in the extent of frequency reductions (Δf), reflecting the differences in the binding affinity of the β-CD monolayers towards the respective enantiomer.[14] All four β-CD monolayers depict higher binding affinity towards the (+)-methyl lactate than the (−)-form.

Amongst the β-CD SAMs, (**3c**) depicts better chiral discrimination as measured by the chiral discrimination factor, $\alpha_{R/S}$,[‡] than (**3a**) corresponding to the increase in the surface concentration of the immobilized permethylated β-CD molecules on the Au surface.

The more crowded β-CD cavity in the molecular structures of (**4c**) and (**5c**) probably enhances the non-covalent interactions between the interior cavity and the

Table 2. Immobilization of mercaptyl functionalized β-CD derivatives on the Au electrodes of a QCM

SAMs		**3a**	**3c**	**4c**	**5c**
Surface concentration ($\times 10^{11}$ mol/cm^2)		6.90	8.98	4.91	3.44
TOF-SIMS	$[M+Au–S]^{+a}$	1679	1807	2931	3609
	$[M+Au]^+$	1713	1839	2963	3641
	$[M+Au_2]^+$	1910		3160	3840
$\alpha_{R/S}$		1.114	1.125	1.145	1.178

[a] m/z, M is the molecular mass of the mercaptyl functionalized β-CD molecule, e.g. $M_{\mathbf{3a}}=1517.2$ g/mol.

[†] Lab Crystal Oscillator and AT-cut 10 MHz quartz plates were purchased from International Crystal Manufacturer Inc., Oklahoma City, OK. The time-course frequency signals were monitored by TF830 universal frequency counter and recorded by PC.

[‡] $\alpha_{R/S}=\Delta f_{max\text{-}R}/\Delta f_{max\text{-}S}$. $\Delta f_{max\text{-}R}$, $\Delta f_{max\text{-}S}$ standing for the maximum frequency reductions of a QCM while exposed to the respective enantiomeric analyte.[15]

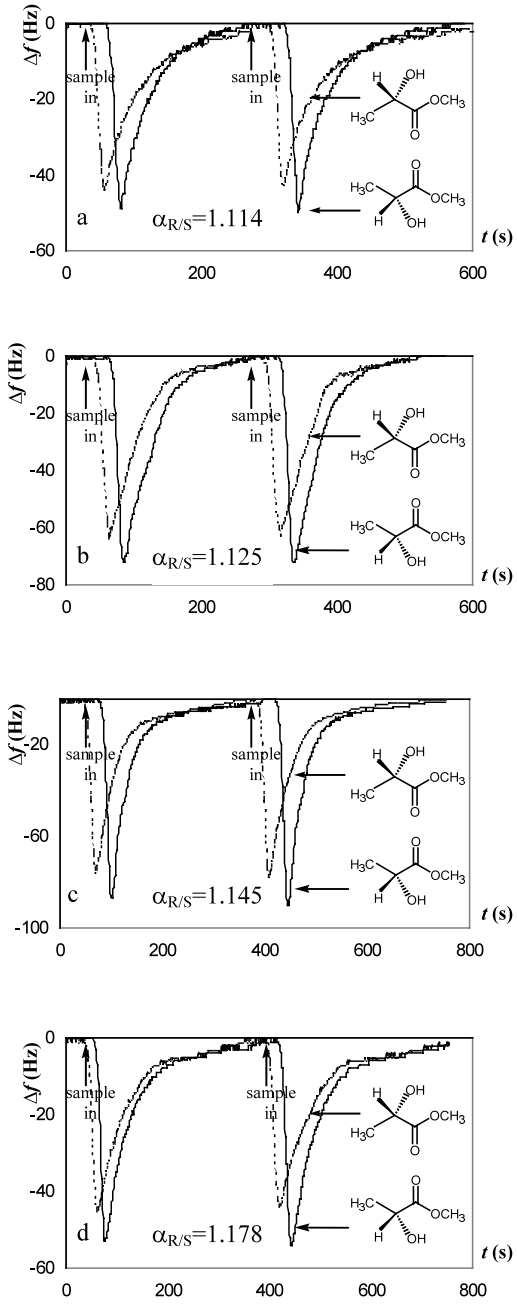

Figure 1. Chiral discrimination of four QCM sensors towards (+)-methyl lactate and (−)-methyl lactate. (a) **3a**; (b) **3c**; (c) **4c**; (d), **5c**. Temp. 25±0.1°C; carrier gas N_2, 200 ml/min; sample injection, 2.0 μl.

included methyl lactate molecules, thus affording improved chiral discrimination: $\alpha_{R/S\text{-}\mathbf{5c}}>\alpha_{R/S\text{-}\mathbf{4c}}>\alpha_{R/S\text{-}\mathbf{3c}}$ despite the decreased surface concentration of the immobilized derived β-CD molecules.

In summary, Scheme 1 depicts a facile synthetic route for the synthesis of mercaptyl functionalized β-CD derivatives. Analytical data for compounds (**2**)–(**5**) is detailed in Ref. 16. These can be self-assembled onto the Au electrodes of a QCM. The application of these structurally defined β-CD monolayers for the study of gas phase chiral discrimination of enantiomers of methyl lactate were successful. It was found that the perbenzoylated β-CD monolayer depicted the best enantiomeric discriminatory ability towards methyl lactate. Further investigations on the host–guest interactions between chiral ligands and the monolayers are currently underway.

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16. Analytical data for compounds **2**–**5**:

6-(ω-Mercapto)-hexanamine (2b): IR (cm^{-1}) 3382 (N–H str), 2940 (C–H str), 2502 (S–H str), 1595 (–NH_2 def), 1065 (C–NH_2 str); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.66 (m, 2H, C$\underline{H}_2$–SH), 2.49 (t, $J=7.2$ Hz, 2H, C$\underline{H}_2$–NH_2), 1.67 (m, 2H, C$\underline{H}_2$–CH_2–NH_2), 1.41 (m, 6H), 0.96 (t, $J=7.2$ Hz, 1H, S$\underline{H}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 41.9 ($NH_2\underline{C}H_2$–), 38.9, 33.4, 29.0, 28.2 (–($\underline{C}H_2)_4$–), 26.3 (–$\underline{C}H_2$–SH); accurate MS m/z calcd 133.0925, found 133.0921.

11-(ω-Mercapto)-undecanylamine (2c): IR (cm^{-1}) 3372 (N–H str), 2920 (C–H str), 2510 (S–H str), 1595 (–NH_2 def.), 1065 (C–NH_2 str); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.66 (t, $J=7.2$ Hz, 2H, C$\underline{H}_2$–SH), 2.50 (t, $J=7.2$ Hz, 2H, C$\underline{H}_2$–NH_2), 1.59 (m, 2H, C$\underline{H}_2$–CH_2–NH_2), 1.26–1.40 (m, 17H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 42.0 ($NH_2\underline{C}H_2$–), 39.1, 33.9, 33.6, 29.3, 29.1, 28.9, 28.4, 28.2, 26.8 (–($\underline{C}H_2)_9$–), 24.5 (–$\underline{C}H_2$–SH); accurate MS m/z calcd 203.1708, found 203.1705.

6^A-ω-Mercapto-ethylureado-6^A-deoxy)heptakis(2,3-di-*O*-methyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-methyl-β-cyclodextrin (3a): IR (cm^{-1}) 3396 (N–H str), 2931 (C–H str), 1668 (C=O str, urea), 1040 (C–O–C str); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 158.72 (–NH–$\underline{C}$O–NH–), 98.73 (C–1), 81.66 (C-2), 80.24 (C-3), 80.02 (C-4), 71.16 (C-6b), 70.83 (C-5), 67.73 (C-6a), 61.11 ($H_3\underline{C}$O-C3), 58.81 ($H_3\underline{C}$O–C6), 58.28 ($H_3\underline{C}$O–C2), 40.82 (–NH$\underline{C}H_2$–), 25.43 (–$\underline{C}H_2$–SH); ESI-MS m/z Calcd 1517.4, found 1517.2; elemental analysis calcd: C, 51.45; H, 7.70; N, 1.84; S, 2.11; found: C, 51.54; H, 7.51; N, 1.93; S, 1.95%.

(6^A-ω-Mercapto-hexanureado-6^A-deoxy)heptakis(2,3-di-*O*-methyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-methyl-β-cyclodextrin (3b): IR (cm^{-1}) 3399 (N–H str), 2930 (C–H str), 1657 (C=O str, urea), 1037 (C–O–C str); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.00 (NH–$\underline{C}$O–NH), 98.76 (C-1), 81.66 (C-2), 81.32 (C-3), 80.22 (C-4), 71.40 (C-6b), 70.84 (C-5), 67.54 (C-6a), 61.18 ($H_3\underline{C}$O-C3), 58.90 ($H_3\underline{C}$O–C6), 58.47 ($H_3\underline{C}$O–C2), 41.22 (–NH$\underline{C}H_2$–), 38.67, 30.07, 28.99, 28.14 (–($\underline{C}H_2)_4$–), 26.44 (–$\underline{C}H_2$–SH); ESI-MS m/z calcd 1573.5; found: 1596.5 for $[M+Na]^+$; elemental analysis calcd C, 52.67; H, 7.94; N, 1.78; S, 2.03; found: C, 52.71; H, 7.79; N, 1.76; S, 1.92%.

(6^A-ω-Mercapto-undecanylureado-6^A-deoxy)heptakis(2,3-di-*O*-methyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-methyl-β-cyclodextrin (3c): IR (cm^{-1}) 3396 (N–H str), 2928 (C–H str), 1659 (C=O str, urea), 1039 (C–O–C str). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.02 (NH–$\underline{C}$O–NH), 98.70 (C-1), 81.64 (C-2), 81.35 (C-3), 80.26 (C-4), 71.85 (C-6b), 70.97 (C-5), 67.68 (C-6a), 61.14 ($H_3\underline{C}$O–C3), 58.83 ($H_3\underline{C}$O–C6), 58.36 ($H_3\underline{C}$O–C2), 41.27 (–NH$\underline{C}H_2$–), 40.36–26.80 (–($\underline{C}H_2)_9$–), 24.44 (–$\underline{C}H_2$–SH); ESI-MS m/z calcd 1643.6, found 1666.1 for $[M+Na]^+$; elemental analysis calcd C, 54.05; H, 8.22; N, 1.70; S, 1.95; found: C, 54.4; H, 7.82; N, 1.29%; S, 1.70%.

(6^A-ω-Mercapto-undecanylureado-6^A-deoxy)heptakis(2,3-di-*O*-pentyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-pentyl-β-cyclodextrin (4c): IR (cm^{-1}) 3409 (N–H str), 2933 (C–H str), 1670 (C=O str, urea), 1043 (C–O–C str); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.03 (NH–$\underline{C}$O–NH), 98.76 (C–1), 81.39 (C-2), 81.19 (C-3), 78.94 (C-4), 74.94 (C-5), 71.79 (C-6b), 67.48 (C-6a), 72.42–72.18 (C-1′), 30.78–29.93 (C–2′), 29.31–29.06 (C-3′), 23.67–23.42 (C-4′), 14.87 (C-5′), 39.64 (–NH$\underline{C}H_2$–), 35.51–24.38 (–($\underline{C}H_2)_9$–), 21.50 (–$\underline{C}H_2$–SH); ESI-MS m/z calcd 2788.7, found 2789.1; elemental analysis calcd C, 66.82; H, 10.82; N, 0.72; S, 1.16; found: C, 66.49; H, 11.21; N, 1.17; S, 1.02%.

(6^A-ω-Mercapto-undecanylureado-6^A-deoxy)heptakis(2,3-di-*O*-benzoyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-benzoyl-β-cyclodextrin (5c): IR (cm^{-1}) 3412 (N–H str), 3069 (Ar–H str), 2922 (C–H str), 1732 (C=O str, urea), 1610, 1449 (Ar-ring), 1043 (C–O str); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 166.15, 165.88, 164.82 (Ar–$\underline{C}$O–), 158.47 (NH–$\underline{C}$O–NH), 127.58, 127.72, 129.43, 129.61, 129.97, 132.16, 132.50 (H-bearing aromatic carbon atoms), 128.21, 128.50, 128.64 (quaternary aromatic carbon atoms) 97.57 (C-1), 77.4 (C-4), 71.33 (C-2 and C-3), 69.99 (C-5), 63.49 (C-6b), 63.39 (C-6a), 40.63 (–NH$\underline{C}H_2$–), 34.01–26.94 (–($\underline{C}H_2)_9$–), 24.57 (–$\underline{C}H_2$–SH); ESI-MS m/z calcd 3445.2, found 3468.1 for $(M+Na^+)$; elemental analysis calcd: C, 67.61; H, 5.09; N, 0.81; S, 0.93; found: C, 68.04; H, 4.88; N, 0.74; S, 0.82%.