Synthesis and characterisation of *O*-6-alkylthio- and perfluoroalkylpropanethio-α-cyclodextrins and their *O*-2-, *O*-3-methylated analogues

Bernard Bertino Ghera,[a] Florent Perret,[a] Anne Baudouin,[b] Anthony W. Coleman[c] and Hélène Parrot-Lopez*[a]

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The synthesis of twelve alkylthio- or perfluoroalkylpropanethio-α-cyclodextrin derivatives and their *O*-2-, *O*-3-methylated analogues are described. The coupling reaction involves firstly the basic *in situ* hydrolysis of alkylperfluoropropane isothiouronium iodide or alkylisothiouronium bromide, then reaction with an α-cyclodextrin modified at the C-6 position by an iodine or methylsulfonyl group. The interfacial properties of these new compounds have been determined by the studies of their mono-molecular layer at the air–water interface.

Introduction

Cyclodextrins are a class of macrocyclic host compounds formed from α-1,4-glucopyranose units and are widely studied for their inclusion properties. Amphiphilic cyclodextrin derivatives are of considerable interest for pharmaceutical applications in view of their capacity for self-organisation in water.[1] Amphiphilic α-, β- or γ-cyclodextrins can be obtained by the introduction of lipophilic groups at the primary face[2] or at the secondary face.[3] Such molecules have allowed the preparation of various self-assembled structures including nanospheres,[4] solid-lipid nanoparticles,[5] liquid crystals[6] and vesicles.[7]

Fluorine-containing organic compounds have attracted scientific attention due to their potential activity in biomedical research.[8] Vesicles and nanocapsules made from fluorinated surfactants are usually more stable and less permeable than those made from non-fluorinated surfactants.[9] Recently, fluorinated vesicles were obtained from combinations of phospholipids and semi-fluorinated alkanes.[10]

In previous studies, we have functionalised β-cyclodextrin at the 6-position with trifluoromethylthio groups and we have shown that this derivative exhibits amphiphilic properties at the air–water interface.[11] However, self-assembled structures in water (nanospheres) derived from these molecules show poor temporal stability. More recently, the association properties of amphiphilic β-cyclodextrins and fluorocarbon chains have been studied by Skiba *et al.*[12] Nanocapsules obtained from the 2,3-di-*O*-decafluorooctanoyl-β-cyclodextrin are suitable vehicles for oxygen solubilisation. In our research group, we have synthesised mono-, bis- and heptakis(β-cyclodextrin) derivatives substituted at the C-6 position by a perfluorohexylpropanethiol chain.[13] The stability of nanoparticles prepared using the nanoprecipitation method,[14] with regard to the number and the length of the hydrophobic chains, has been demonstrated.[15] For β-cyclodextrin derivatives, the lipophilic–hydrophilic balance is very strongly shifted towards lipophilicity with critical micellar concentration (CMC) values up to 10^{-6} M^{-1}; this may reflect the non-compatibility of the seven-fold symmetry of β-cyclodextrin towards water[16] and also towards chain organisation in the assemblies. Use of α-cyclodextrin derivatives may favour both interactions with water and also organisation in molecular assemblies.[17]

In this paper, we describe an efficient synthesis of amphiphilic α-cyclodextrin derivatives substituted at the primary face by alkylthio- and perfluoroalkylpropanethio-groups and their analogues substituted at the secondary face by methyl groups. In the case of highly insoluble non-methylated derivatives, ^{19}F and ^{13}C solid state NMR spectroscopies were used to demonstrate achievement of full substitution at the primary face. The assembly properties of the molecules at the air–water interface show clear difference between alkylthio- and perfluoroalkylpropanethio-derivatives, with higher molecular areas and collapse pressures observed for the latter.

Results and discussion

Synthesis

Perfluoroalkyl chains are commonly introduced onto organic compounds *via* a radical reaction, involving an iodoperfluoroalkane and an ethylenic derivative with a radical activator, such as AIBN,[18] Cu[19] or $Na_2S_2O_4$.[20] This method is not suitable for the cyclodextrins: previous experiments undertaken using Hein and Meintchen's method[20] led to mixtures of multisubstituted cyclodextrins.[21] A new strategy has thus been developed using a polar reaction between a perfluoroalkylpropanethiol and a cyclodextrin bearing a suitable leaving

[a] *Laboratoire de Chimie Organique 2, LCO2, ICBMS, CNRS UMR 5246, Université Lyon 1, 43, bd du 11 novembre 1918, 69622 Villeurbanne cedex, France. E-mail: helene.parrot@univ-lyon1.fr,; Fax: +33 4 72 44 84 38; Tel: +33 4 72 43 15 32*
[b] *Laboratoire de Chimie Organométallique de Surface, LCOMS, CNRS UMR 9986, CPE Lyon, 43, bd du 11 novembre 1918, 69622 Villeurbanne cedex, France. E-mail: baudouin@cpe.fr; Fax: +33 4 72 43 17 95; Tel: +33 4 72 43 18 20*
[c] *Institut de Biologie et Chimie des Protéines, CNRS UMR 5086, Université Lyon 1, 7, passage du Vercors, 69367 Lyon cedex 07, France. E-mail: aw.coleman@ibcp.fr; Fax: +33 4 72 72 26 90; Tel: +33 4 72 72 26 95*

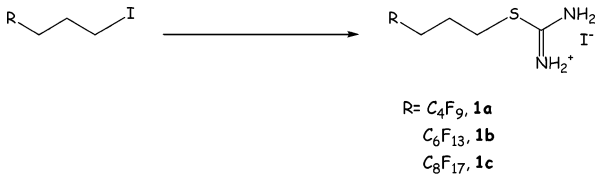

Fig. 1 Reagents and conditions: thiourea, acetone, 60 °C.

group.[13] The use of a precursor to generate this thiol *in situ* would be preferred because of the facile oxidative dimerisation of the perfluoropropanethiol. The procedure for the synthesis of the perfluoroalkylated isothiouronium salts, is shown in Fig. 1.

The isothiouronium salt derivatives, **1a–c**, are obtained in moderate yields (57–67%), using the corresponding 1-iodo-3-perfluoroalkylpropane, available *via* a literature method,[19,22,23] and thiourea in acetone.

The synthetic route to the thioalkylated and perfluoroalkylpropanethio-α-cyclodextrins, **3a–c** and **4a–c**, is given in Fig. 2. The corresponding synthetic route to the thioalkylated and perfluoroalkylpropanethio-*O*-2-, -*O*-3-methylated analogues, **8a–c** and **9a–c**, is given in Fig. 3. The hexakis(6-deoxy-6-iodo)-α-cyclodextrin, **2**, is obtained *via* the procedure described by Gadelle and Defaye,[24] and improved by Stoddart *et al.*[25] The synthesis of the hexakis(2,3-di-*O*-methyl)-α-cyclodextrin, **5**, was based on a synthetic route in 3 steps as described by Mitoh *et al.*[26] Iodine was chosen first as the leaving group. The hexakis(6-deoxy-6-iodo-2,3-di-*O*-methyl)-α-cyclodextrin, **6**, was prepared using triphenylphosphine and iodine in DMF. Difficulties in the removal of the triphenylphosphine oxide product led us to change to the use of a mesityl group. Hexakis(2,3-di-*O*-methyl)-α-cyclodextrin, **5**, reacts with mesityl chloride in pyridine at 5 °C to give hexakis-(6-*O*-methylsulfonyl-2,3-di-*O*-methyl)-α-cyclodextrin **7**, in quantitative yield. It is worth noting that incomplete substitution was obtained if mesityl anhydride was used.

The coupling reaction of the thioalkyl chain and thioperfluoropropyl chain was achieved using 18 equiv. of Cs_2CO_3 and 12 equiv. of the corresponding isothiouronium salt in dry DMF. The desired product was obtained in good yield: 59% to quantitative for the *S*-6-α-cyclodextrin derivatives and 50–62% for the methylated analogues. The highly insoluble perfluoroalkylpropanethio-α-cyclodextrin and the very poorly soluble hydrocarbon analogues, both with regard to aqueous or organic solvent, led us to characterise them by solid state NMR spectroscopy. Fig. 4 shows the strength of this technique, especially in the case of insoluble macrocyclic compounds containing a high number of carbon atoms.

The success of the coupling reaction in this series was confirmed by ^{13}C solid state NMR spectroscopy (125 MHz), with a clear change in the chemical shifts of C-6, which is displaced from 10.6 ppm in the hexakis(6-deoxy-6-iodo)-α-cyclodextrin, **2**, to 33.4 ppm in the desired product.

The *O*-2-, *O*-3-methylated analogues have higher solubilities in organic solvents and NMR spectroscopy in the liquid state was then possible. Fig. 5 shows partial ^1H NMR spectra at 300 MHz of compounds **8a** and **9a** in $CDCl_3$.

Full substitution at the primary rim was confirmed by the presence of a doublet for the anomeric proton at $\delta = 5.04$ or 5.08 ppm with $J_{H1/H2} = 3.0$–3.3 Hz. It is worth noting that the α-methylene groups appeared as a triplet at $\delta = 2.57$ ppm with $J = 7.2$ Hz for the thioalkylated compounds, whereas for the perfluoroalkylpropanethio-compounds, a complex symmetrical signal at $\delta = 2.57$–2.87 ppm is present. This result indicates magnetic inequivalence between these two protons, which may result from greater steric hindrance with regard to free rotation of the perfluoroalkylpropanethio- *versus* the thioalkylated analogues.

All products were also characterised either by electrospray mass spectroscopy or by Maldi mass spectroscopy to confirm full substitution.

Interfacial properties

The compression isotherms for **8a–c** and **9a–c**, on a pure water surface, are presented in Fig. 6 and the characteristic values summarised in Table 1.

From the external cavity diameter of unsubstituted α-cyclodextrin, Taneva *et al.* calculated the area of the secondary rim

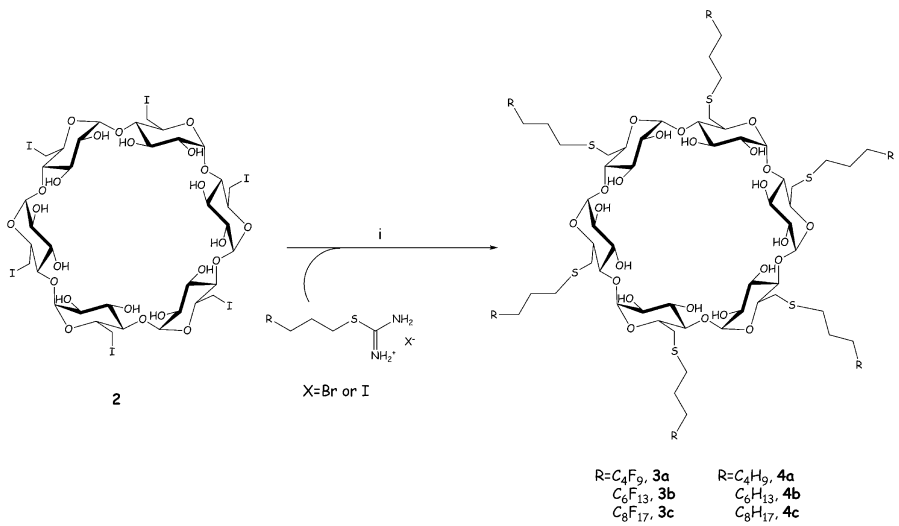

Fig. 2 Reagents and conditions: (i) Cs_2CO_3, DMF, 60 °C.

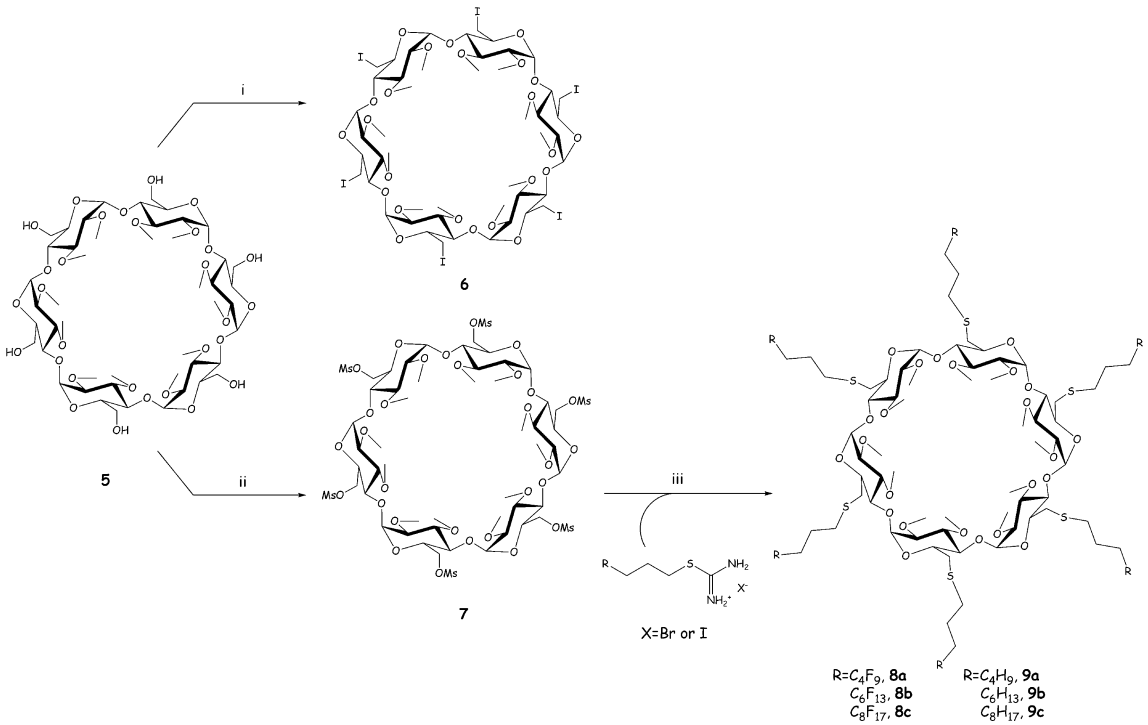

Fig. 3 Reagents and conditions: (i) PPh_3, I_2, DMF, 80 °C; (ii) MsCl, pyridine, 5 °C; (iii) Cs_2CO_3, DMF, 60 °C.

in the range of 158–177 Å^2 per molecule.[27] The observed collapse areas for **9a–c** are in the range of 166 Å^2 per molecule for **9a** and **9b** and 170 Å^2 per molecule for **9c**. This result clearly indicates that the thioalkyl chains are aligned perpendicular to the air–water interface. The stability of these monolayers, as determined by the collapse pressure (π_c), is in the range of 27–29 mN m^{-1} and increases very slightly with the chain length (1 mN m^{-1} per –CH_2–CH_2). The above results can be compared to the values found for hexakis[6-deoxy-6-(*S*-hexadecanethio)]-α-cyclodextrin,[28] which are 173 Å^2 per molecule for the A_0 value and 60 mN m^{-1} for π_c. The decrease of π_c can be explained by weaker interactions between **9a**, **9b** and **9c** and the aqueous subphase, due to the higher polarity of the hydroxyl group as compared to the methoxy group. Nicolis *et al.* described a similar phenomenon for the monolayer stability of hexakis[6-deoxy-6-bromo]-α-, -β-, -γ-cyclodextrins.[29] The author postulated that π_c increases with larger numbers of hydroxyl groups adhering to the water surface.

The observed compression isotherms for **8a**, **8b** and **8c** differ clearly from those observed for **9a–c**, except for the observed collapse area, which is, again, in the range of 160–163 Å^2 per molecule. Thus, these chains are perpendicular to the air–water interface. The stabilities of the monolayers are higher in comparison with the hydrocarbon analogues. π_c values increase with the chain length, from 36 mN m^{-1} for **8a** to 59 mN m^{-1} for **8c**. This result is in agreement with Rogalska *et al.*, who studied hydrocarbon and partially fluorinated amphiphilic derivatives of mannitol.[30] The authors observed an increase in the collapse pressure that was dependent on the fluorous chain length.

The compressibility moduli Cs^{-1} [eqn (1)][31] reflect the behaviour of the state of the monolayer at the air–water interface.

$$Cs^{-1} = -A(\delta\pi/\delta A) \quad (1)$$

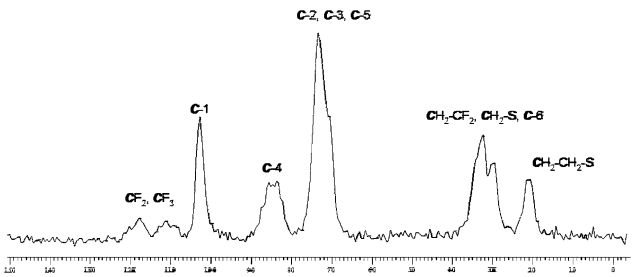

Fig. 4 125 MHz ^{13}C CP MAS experiment (τ_c = 2 ms, RD = 4 s, ω_R = 10 kHz) of compound **3b**.

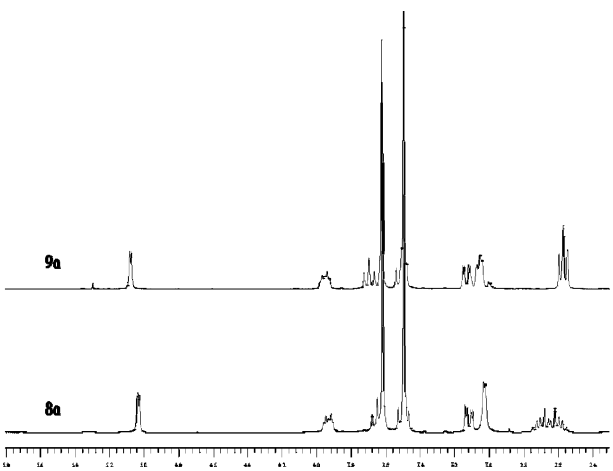

Fig. 5 300 MHz ^{1}H NMR partial spectra of compound **8a** and **9a** in $CDCl_3$.

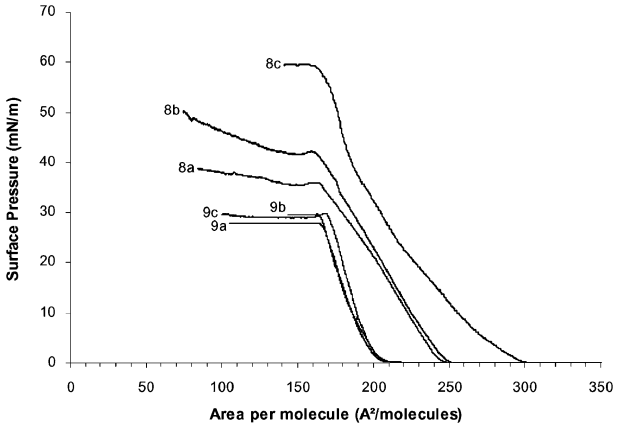

Fig. 6 Compression isotherms of **8a–c** and **9a–c**.

Cs^{-1} vary from 139 mN m^{-1} to 179 mN m^{-1} for **9a–c**; these values are typical of condensed liquid phase monolayers.[31] In the case of the fluorinated analogues, these values decrease to 75 and 83 mN m^{-1} for **8a** and **8b**, values that are in the range typical of an expanded liquid phase monolayer. Similarly, there are increases in the A_0 and A_1 values, being around 210 $Å^2$ per molecule for alkylthio-α-cyclodextrin and around 250 $Å^2$ per molecule for perfluoroalkylpropanethio-derivatives. These observations would seem to imply that these latter fluorinated amphiphilic molecules may interact to form weaker organised structures at the air–water interface, and then that the perfluoroalkylpropanethio-chains have a strong geometric influence. These effects are much more notable for **8c**; here A_0 and A_1 are displaced to up to 300 $Å^2$ per molecule, the Cs^{-1} decreases to 59 mN m^{-1} until an apparent molecular area of 200 $Å^2$ per molecule and then increases to 171 mN m^{-1} until the observed collapse. This result may be explained by a change of the state of the monolayer, from an expanded liquid phase to a condensed liquid phase.

Experimental

General

α-Cyclodextrin was generously provided by Wacker (France). The 1-iodo-3-perfluoroalkylpropanes and alkylisothiouronium bromides were synthesised according to literature procedures,[19,22,23,32] and analytical data were in good agreement with these references. Thiourea, iodine and caesium carbonate were purchased from Sigma-Aldrich and mesityl chloride, anhydrous DMF with molecular sieves and anhydrous pyridine with molecular sieves from Acros Organics. All these compounds were used without further purification, except for Cs_2CO_3 which was dried at low pressure at 120 °C overnight before use. Other solvents were of chemical grade and were used as received. All reactions were carried out under an argon atmosphere.

Table 1 Isotherm data for **8a–c** and **9a–c** on pure water[a]

Compound	A_0	A_1	A_m	A_c	π_c	Cs^{-1}
8a	255	242	228	163	36	75
8b	264	247	246	160	42	83
8c	302	293	270	162	59	59/171
9a	213	202	195	166	27	146
9b	212	204	194	166	28	139
9c	220	205	199	170	29	179

[a] A_0 is the apparent molecular area at $\pi = 0$; A_1 is the apparent molecular area at $\pi = 1$ mN m^{-1}; A_m is the extrapolated molecular area; A_c is the apparent molecular area at the collapse point; and π_c is the collapse pressure. Cs^{-1} is the compressibility modulus. Areas A have units $Å^2$ per molecule; pressures π have units mN m^{-1}; Cs^{-1} has units mN m^{-1}.

^1H, ^{13}C and ^{19}F COSY, HSQC and HMBC NMR experiments were performed at 300 MHz, 75 MHz and 280 MHz, respectively using a Bruker DRX 300 spectrometer or a Bruker ALS 300 spectrometer. Chemical shifts are reported from internal tetramethylsilane standards for ^1H and ^{13}C and from internal $CFCl_3$ for ^{19}F.

^{19}F and ^{13}C solid state NMR experiments were performed at 480 MHz and 125 MHz using a Bruker Avance 500 equipped with a Bruker 4 mm CP MAS probe. External tetramethylsilane and $PhCF_3$ were used as standards for chemical shifts in ^{13}C and ^{19}F experiments, respectively.

Electrospray mass spectra were measured using a Perkin-Elmer Sciex spectrometer and MALDI-TOF mass spectra using an Applied Biosystems Voyager-DE Pro.

IR spectra were recorded on a FT-Perkin-Elmer Spectrum One instrument. Optical rotations were tested on a Perkin-Elmer 241 polarimeter.

Melting point determinations were performed on an Electrothermal-9100 apparatus and are uncorrected.

Preparation of perfluoroalkylpropane isothiouronium iodides 1a–c

1a. 3-Perfluorobutylpropane isothiouronium iodide. To a solution of 1-iodo-3-perfluorobutylpropane (3.70 g, 9.50 mmol) in acetone (110 ml) was added thiourea (1.09 g, 14.31 mmol, 1.5 equiv.). The mixture was stirred for 26 h at reflux and the reaction monitored by TLC (AcOEt–CH_3CN, 9 : 1). The solvent was evaporated and the product was purified by several recrystallisations in acetone–$CHCl_3$ to obtain **1a** as a white powder. Yield: 65% (2.86 g). R_f (AcOEt–CH_3CN, 9 : 1) = 0.22. Mp (dec.): 134 °C. ^1H NMR (DMSO-d_6, 300 MHz, assignments by COSY): δ (ppm): 1.87 (qi, 2H, SCH_2CH_2, J = 7.4 Hz), 2.37 (tt, 2H, CH_2CF_2, J = 19.5 Hz, 7.8 Hz), 3.22 (t, 2H, SCH_2, J = 7.4 Hz), 8.96 (s, 4H, $C(NH_2)_2$). ^{13}C NMR (DMSO-d_6, 75 MHz, assignments by HSQC): δ (ppm): 20.3 (SCH_2CH_2), 28.3 (t, CH_2CF_2, J = 22.6 Hz), 28.9 (SCH_2), 169.2 ($C(NH_2)_2$). ^{19}F NMR (DMSO-d_6, 280 MHz, $CFCl_3$): δ (ppm): −81.2 (t, 3F, CF_3, J = 9.1 Hz), −114.3 (qi, 2F, CH_2CF_2, J = 15.0 Hz), −124.8 (d, 2F, CF_2, J = 7.6 Hz), −126.7 (t, 2F, CF_2CF_3, J = 11.2 Hz). ES MS (m/z): $[M - I]^+$ 336.9. IR υ (cm^{-1}): 3261 (N–H), 2971 (C–H), 1651 (C=N), 1229–1132 (C–F).

1b. 3-Perfluorohexylpropane isothiouronium iodide. To a solution of 1-iodo-3-perfluorohexylpropane (5.10 g, 10.50 mmol) in acetone (125 ml) was added thiourea (1.20 g, 15.75 mmol, 1.5 equiv.). The mixture was stirred for 27 h at reflux and the reaction monitored by TLC (AcOEt–CH_3CN, 9 : 1). The solvent was evaporated and the product was precipitated from $CHCl_3$. The precipitate was filtered off, washed with

tepid water (40 °C) and dried over P_2O_5 overnight to afford **1b** as a white powder. Yield: 57% (3.19 g). R_f (AcOEt–CH_3CN, 9 : 1) = 0.24. Mp (dec.): 148 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, assignments by COSY): δ (ppm): 1.86 (qi, 2H, SCH_2CH_2, J = 7.4 Hz), 2.38 (tt, 2H, CH_2CF_2, J = 19.8 Hz, 8.0 Hz), 3.23 (t, 2H, SCH_2, J = 7.2 Hz), 9.01 (s, 4H, $C(NH_2)_2$). ^{13}C NMR (DMSO-d_6, 75 MHz, assignments by HSQC): δ (ppm): 20.2 (SCH_2CH_2), 28.2 (t, CH_2CF_2, J = 21.6 Hz), 28.8 (SCH_2), 169.2 ($C(NH_2)_2$). ^{19}F NMR (DMSO-d_6, 280 MHz, $CFCl_3$): δ (ppm): −81.2 (t, 3F, CF_3, J = 9.8 Hz), −114.2 (qi, 2F, CH_2CF_2, J = 15.8 Hz), −122.7 (m, 2F, CF_2), −123.6 (m, 2F, CF_2), −124.1 (m, 2F, CF_2), −126.7 (m, 2F, CF_2CF_3). ES MS (m/z): $[M - I]^+$ 437.0. IR υ (cm^{-1}): 3310 (N–H), 2969 (C–H), 1648 (C═N), 1232–1122 (C–F).

1c. 3-Perfluorooctylpropane isothiouronium iodide. To a solution of 1-iodo-3-perfluorooctylpropane (2.85 g, 4.85 mmol) in acetone (70 ml) was added thiourea (0.74 g, 9.70 mmol, 2.0 equiv.). The mixture was stirred for 27 h at reflux and the reaction monitored by TLC (AcOEt–CH_3CN, 9 : 1). The solvent was evaporated and the product was precipitated from $CHCl_3$. The precipitate was centrifuged with water several times to eliminate thiourea and dried over P_2O_5 overnight to afford **1c** as a white powder. Yield: 67% (2.14 g). R_f (AcOEt–CH_3CN, 9 : 1) = 0.2. Mp (dec.): 162 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, assignments by COSY): δ (ppm): 1.86 (qi, 2H, SCH_2CH_2, J = 7.5 Hz), 2.36 (tt, 2H, CH_2CF_2, J = 19.5 Hz, 8.2 Hz), 3.24 (t, 2H, SCH_2, J = 7.5 Hz), 9.01 (s, 4H, $C(NH_2)_2$). ^{13}C NMR (DMSO-d_6, 75 MHz, assignments by HSQC): δ (ppm): 20.2 (SCH_2CH_2), 28.4 (t, CH_2CF_2, J = 22.6 Hz), 28.8 (SCH_2), 169.1 ($C(NH_2)_2$). ^{19}F NMR (DMSO-d_6, 280 MHz, $CFCl_3$): δ (ppm): −81.3 (t, 3F, CF_3, J = 9.8 Hz), −114.2 (qi, 2F, CH_2CF_2, J = 16.1 Hz), −122.5 (m, 6F, CF_2), −123.4 (m, 2F, CF_2), −123.9 (m, 2F, CF_2), −126.7 (m, 2F, CF_2CF_3). ES MS (m/z): $[M - I]^+$ 537.0. IR υ (cm^{-1}): 3320 (N–H), 2962 (C–H), 1621 (C═N), 1255–1149 (C–F).

General procedure for the preparation of alkylthio- and perfluoroalkylpropanethio-α-cyclodextrin 3a–c and 4a–c

Dry Cs_2CO_3 (18 equiv., 3 equiv. per OH) was added to a solution of **1a–c** or alkylisothiouronium bromide (12 equiv., 2 equiv. per OH) in DMF (5 ml). The mixture was stirred for 2 h, then a solution of **2** (1 equiv.) in DMF (5 ml) was added dropwise to the suspension. The solution was stirred at 60 °C and the reaction monitored by TLC (*n*BuOH–EtOH–water, 5 : 4 : 3). After stirring for 4 days, the product was precipitated from cold acetone (500 ml). The precipitate was filtered off, washed with acetone (50 ml) and with water (2 × 10 ml) and re-precipitated from hot EtOH (20 ml) to afford the pure product.

3a: Hexakis[6-deoxy-6-(3-perfluorobutylpropanethio)]-α-cyclodextrin. Yield: 59% (280 mg). Mp (dec.): 190 °C. ^{13}C NMR (125 MHz, CP MAS 10 kHz, RD = 4 s): δ (ppm): 20.6 (CH_2CH_2S), 29.7–32.2 (CH_2CF_2, CH_2S, C-6), 70.2–73.2 (C-2, C-3, C-5), 84.5 (C-4), 102.9 (C-1), 108.7–120.6 (CF_2, CF_3). ^{19}F NMR (pyridine-d_5, 280 MHz, $CFCl_3$): δ (ppm): −82.5 (m, 3F, CF_3), −115.3 (m, 2F, CH_2CF_2), −125.5 (m, 2F, CF_2), −127.2 (m, 2F, CF_2CF_3). ES MS (m/z): $[M + H]^+$ 2629.3, $[M + Na]^+$ 2651.2. IR υ (cm^{-1}): 3400 (O–H), 2910 (C–H), 1227–1134 (C–F). $C_{78}H_{90}O_{24}S_6F_{54}$.

3b: Hexakis[6-deoxy-6-(3-perfluorohexylpropanethio)]-α-cyclodextrin. Yield: 93% (450 mg). Mp (dec.): 205 °C. ^{13}C NMR (125 MHz, CP MAS 10 kHz, RD = 4 s): δ (ppm): 20.4 (CH_2CH_2S), 29.1–32.2 (CH_2CF_2, CH_2S, C-6), 70.4–73.2 (C-2, C-3, C-5), 84.5 (C-4), 102.6 (C-1), 108.3–119.7 (CF_2, CF_3). ^{19}F NMR (470 MHz, MAS 10 kHz and 12 kHz, RD = 4 s, $PhCF_3$): δ (ppm): −75.2 (s, 3F, CF_3), −107.0 (br s, 2F, CH_2CF_2), −115.8 (br s, 6F, CF_2), −120.0 (s, 2F, CF_2CF_3). MALDI mass (m/z): $[M + Na]^+$ 3252.4. IR υ (cm^{-1}): 3399 (O–H), 2964 (C–H), 1239–1146 (C–F). $C_{90}H_{90}O_{24}S_6F_{78}$.

3c: Hexakis[6-deoxy-6-(3-perfluorooctylpropanethio)]-α-cyclodextrin. Yield: 98%. Mp (dec.): 220 °C. ^{13}C NMR (125 MHz, CP MAS 10 kHz, RD = 4 s): δ (ppm): 20.4 (CH_2CH_2S), 29.6–32.1 (CH_2CF_2, CH_2S, C-6), 70.8–73.2 (C-2, C-3, C-5), 84.7 (C-4), 102.0 (C-1), 108.1–119.7 (CF_2, CF_3). ^{19}F NMR (470 MHz, MAS 10 kHz and 12 kHz, RD = 4 s, $PhCF_3$): δ (ppm): −75.2 (s, 3F, CF_3), −106.,7 (br s, 2F, CH_2CF_2), −114.8 (br s, 10F, CF_2), −119.7 (s 2F, CF_2CF_3). MALDI mass (m/z): $[M + Na]^+$ 3855.8. IR υ (cm^{-1}): 3434 (O–H), 2969 (C–H), 1245–1149 (C–F). $C_{102}H_{90}O_{24}S_6F_{102}$.

4a: Hexakis(6-deoxy-6-heptanethio)-α-cyclodextrin. Yield: 69% (350 mg). Mp (dec.): 195 °C. ^{1}H NMR (pyridine-d_5, 300 MHz): δ (ppm): 0.91 (s, 18H, CH_3), 1.39–1.60 (m, 48H, CH_2), 1.88 (s, 12H, CH_2), 2.99 (t, 12H, CH_2S, J = 6.5 Hz), 3.36–3.43 (m, 6H, H-6a), 3.62–3.67 (m, 6H, H-6b), 4.12–4.15 (m, 12H, H-2, H-4), 4.66 (s, 12H, H-3, H-5), 5.51 (d, 6H, H-1, J = 2.2 Hz), 7.49 (s, 6H, OH-3), 8.01 (s, 6H, OH-2). ^{13}C NMR (125 MHz, CP MAS 10 kHz, RD = 4 s): δ (ppm): 13.6 (CH_3), 22.5 (CH_2CH_3), 29.3–32.2 (CH_2, C-6), 70.8–73.8 (C-2, C-3, C-5), 84.9 (C-4), 102.5 (C-1). MALDI mass (m/z): $[M + Na]^+$ 1680.0. IR υ (cm^{-1}): 3368 (O–H), 2924–2854 (C–H). $C_{78}H_{144}O_{24}S_6$.

4b: Hexakis(6-deoxy-6-nonanethio)-α-cyclodextrin. Yield: 90% (504 mg). Mp (dec.): 225 °C. ^{1}H NMR (pyridine-d_5, 300 MHz): δ (ppm): 0.90 (s, 18H, CH_3), 1.35–1.65 (m, 72H, CH_2), 1.90 (m, 12H, CH_2), 3.01 (t, 12H, CH_2S, J = 6.8 Hz), 3.39–3.46 (m, 6H, H-6a), 3.65–3.70 (m, 6H, H-6b), 4.13–4.16 (m, 12H, H-2, H-4), 4.67–4.70 (m, 12H, H-3, H-5), 5.51 (d, 6H, H-1, J = 2.1 Hz), 7.49 (s, 6H, OH-3), 7.95 (d, 6H, OH-2, J = 5.6 Hz). ^{13}C NMR (pyridine-d_5, 75 MHz, assignments by DEPT and HSQC): δ (ppm): 14.5 (CH_3), 23.2 (CH_2CH_3), 29.4, 29.9, 30.6, 31.9, 32.3, 32.5 (CH_2), 34.3 (CH_2S), 34.7 (SC-6), 73.2, 74.2, 74.5 (C-2, C-3, C-5), 86.8 (C-4), 103.8 (C-1). MALDI mass (m/z): $[M + Na]^+$ 1848.9. IR υ (cm^{-1}): 3340 (O–H), 2923–2853 (C–H). $C_{90}H_{168}O_{24}S_6$.

4c: Hexakis(6-deoxy-6-undecanethio)-α-cyclodextrin. Yield: 68% (417 mg). Mp (dec.): 235 °C. ^{1}H NMR (pyridine-d_5, 300 MHz): δ (ppm): 0.89 (s, 18H, CH_3), 1.33–1.66 (m, 96H, CH_2), 1.87–1.92 (m, 12H, CH_2), 3.02 (t, 12H, CH_2S, J = 6.8 Hz), 3.40–3.46 (m, 6H, H-6a), 3.65–3.69 (m, 6H, H-6b), 4.14–4.16 (m, 12H, H-2, H-4), 4.68–4.74 (m, 12H, H-3, H-5), 5.52 (d, 6H, H-1, J = 2.3 Hz), 7.48 (d, 6H, OH-3, J = 4.8 Hz), 7.99 (d, 6H, OH-2, J = 6.0 Hz). ^{13}C NMR (125 MHz, CP MAS 10 kHz, RD = 4 s): δ (ppm): 13.7 (CH_3), 22.4 (CH_2CH_3), 29.8–33.8

(CH_2, C-6), 70.4–73.8 (C-2, C-3, C-5), 84.1 (C-4), 102.5 (C-1). MALDI mass (m/z): $[M + Na]^+$ 2017.5. IR υ (cm^{-1}): 3367 (O–H), 2923–2853 (C–H). $C_{102}H_{192}O_{24}S_6$.

6: Hexakis(6-deoxy-6-iodo-2,3-di-*O*-methyl)-α-cyclodextrin. To a solution of triphenylphosphine (415 mg, 1.58 mmol, 18 equiv., 3 equiv. per OH) and iodine (401 mg, 1.58 mmol, 18 equiv., 3 equiv. per OH) in DMF (5 ml) was added a solution of **5** (100 mg, 88 μmol) in DMF (5 ml). The resulting solution was stirred for 19 h at 80 °C. After cooling the reaction mixture, a saturated solution of $NaHCO_3$ was added (15 ml). The organic layer was extracted with diethyl ether (3 × 20 ml). The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was evaporated and the solid was subjected to column chromatography (SiO_2, CH_2Cl_2–AcOEt, 4 : 6) to afford **6** as a yellow powder. Yield: 32% (50 mg). R_f (CH_2Cl_2–AcOEt, 4 : 6) = 0.47. Mp (dec.): 200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 3.11 (dd, 6H, H-2, J = 3.3 Hz, 9.2 Hz), 3.34 (t, 6H, H-4, J = 9.2 Hz), 3.45 (s, 18H, 2-OCH_3), 3.47–3.53 (m, 12H, H-3, H-5), 3.57–3.69 (m, 30H, H-6a, H-6b, 3-OCH_3), 5.06 (d, 6H, H-1, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 9.8 (C-6), 58.7 (2-OCH_3), 62.1 (3-OCH_3), 71.1 (C-5), 81.1 (C-3), 82.2 (C-2), 86.7 (C-4), 99.9 (C-1). ES MS (m/z): $[M + NH_4]^+$ 1818.2, $[M + Na]^+$ 1823.1, $[M + K]^+$ 1839.0. IR υ (cm^{-1}): 2926 (C–H), 1163 (C–O–C). $C_{48}H_{78}O_{24}I_6$.

7: Hexakis(6-*O*-methylsulfonyl-2,3-di-*O*-methyl)-α-cyclodextrin. To a solution of **5** (40 mg, 35 μmol) in pyridine (5 ml) was added mesityl chloride (100 μl, 1.29 mmol, 36 equiv., 6 equiv. per OH) at −10 °C. The solution was stirred at 5 °C overnight and the reaction monitored by TLC (Et_2O–MeOH, 90 : 10). A saturated solution of $NaHCO_3$ was added (10 ml). The organic layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was evaporated and the resulting solution was co-evaporated three times with toluene to afford **7** as a red-brown powder. Yield: 99%. R_f (Et_2O–MeOH, 9 : 1) = 0.36. Mp (dec.): 118 °C. $[\alpha]_D$ +97 (c 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 3.02 (s, 18H, –SO_2CH_3), 3.09 (dd, 6H, H-2, J = 3.2 Hz, 9.4 Hz), 3.39–3.51 (m, 30H, H-3, H-4, 2-OCH_3), 3.57 (s, 18H, 3-OCH_3), 3.96–3.98 (m, 6H, H-5), 4.40–4.53 (m, 12H, H-6a, H-6b), 4.98 (d, 6H, H-1, J = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 37.7 (–SO_2CH_3), 58.4 (2-OCH_3), 62.3 (3-OCH_3), 70.1 (C-6), 71.2 (C-5), 81.0 (C-3), 82.1 (C-2), 82.4 (C-4), 100.1 (C-1). ES MS (m/z): $[M + Cl]^-$ 1643.6, $[M + HCOO]^-$ 1653.2. IR υ (cm^{-1}): 2930 (C–H), 1356 (C–SO_2–OC). $C_{54}H_{96}O_{42}S_6$.

General procedure for the preparation of perfluoroalkylpropanethio- and alkylthio(2,3-di-*O*-methyl)-α-cyclodextrin 8a–c and 9a–c

Dry Cs_2CO_3 (18 equiv., 3 equiv. per OH) was added to a solution of **1a–c** or alkylisothiouronium bromide (12 equiv., 2 equiv. per OH) in DMF (5 ml) and the mixture was stirred for 2 h. A solution of **7** (1 equiv.) in DMF (5 ml) was added dropwise to the suspension. The solution was stirred at 60 °C and the reaction monitored by TLC (petroleum ether–AcOEt, 65 : 35 or 60 : 40). After stirring for 4 days, the product was precipitated from cold acetone (500 ml). The precipitate was filtered off and washed with acetone (50 ml) and with water (2 × 10 ml). The crude product was subjected to column chromatography (SiO_2, petroleum ether–AcOEt, step gradient: 100 : 0 to 60 : 40) to afford the product as a yellow oil or solid.

8a: Hexakis[6-deoxy-6-(3-perfluorobutylpropanethio)-2,3-di-*O*-methyl]-α-cyclodextrin. Yield: 63% (547 mg). R_f (petroleum ether–AcOEt, 65 : 35) = 0.61. Mp (dec.): 75 °C. $[\alpha]_D$ +70 (c 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 1.83–1.93 (m, 12H, C$H_2$$CH_2$S), 2.07–2.25 (m, 12H, CH_2CF_2), 2.56–2.76 (m, 12H, CH_2S), 3.04 (br s, 12H, H6a, H-6b), 3.13 (dd, 6H, H-2, J = 3.2 Hz, 9.4 Hz), 3.51 (s, 18H, 2-OCH_3), 3.51 (t, 6H, H-3, J = 9.4 Hz), 3.63 (s, 18H, 3-OCH_3), 3.66 (t, 6H, H-4, J = 9.4 Hz), 3.93–3.96 (m, 6H, H-5), 5.04 (d, 6H, H-1, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 20.7 (CH_2CH_2S), 30.0 (CH_2CF_2, J = 22.0 Hz), 33.2 (CH_2S), 34.1 (C-6), 58.4 (2-OCH_3), 62.2 (3-OCH_3), 72.4 (C-5), 81.4 (C-3), 82.5 (C-2), 84.8 (C-4), 100.0 (C-1), 105.8–122.4 (CF_2, CF_3). ^{19}F NMR ($CDCl_3$, 280 MHz, $CFCl_3$): δ (ppm): −81.4 (t, 3F, CF_3, J = 9.7 Hz), −114.7 (m, 2F, CH_2CF_2), −124.7 (m, 2F, CF_2), −126.4 (m, 2F, CF_2CF_3). ES MS (m/z): $[M + H]^+$ 2798.6, $[M + NH_4]^+$ 2814.7, $[M + Na]^+$ 2820.3. IR υ (cm^{-1}): 2930 (C–H), 1224–1134 (C–F). $C_{90}H_{114}F_{54}O_{24}S_6$.

8b: Hexakis[6-deoxy-6-(3-perfluorohexylpropanethio)-2,3-di-*O*-methyl]-α-cyclodextrin. Yield: 53% (785 mg). R_f (petroleum ether–AcOEt, 6 : 4) = 0.65. Mp (dec.): 91 °C. $[\alpha]_D$ +52 (c 0.56, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 1.83–1.93 (m, 12H, C$H_2$$CH_2$S), 2.04–2.25 (m, 12H, CH_2CF_2), 2.56–2.76 (m, 12H, CH_2S), 3.05 (br s, 12H, H6a, H-6b), 3.13 (dd, 6H, H-2, J = 3.2 Hz, 9.4 Hz), 3.50 (s, 18H, 2-OCH_3), 3.50 (t, 6H, H-3, J = 9.4 Hz), 3.66 (s, 18H, 3-OCH_3), 3.67 (t, 6H, H-4, J = 9.4 Hz), 3.93–3.96 (m, 6H, H-5), 5.04 (d, 6H, H-1, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 20.4 (CH_2CH_2S), 29.7 (CH_2CF_2, J = 22.0 Hz), 32.8 (CH_2S), 33.7 (C-6), 58.1 (2-OCH_3), 61.9 (3-OCH_3), 72.1 (C-5), 81.2 (C-3), 82.2 (C-2), 84.6 (C-4), 99.7 (C-1), 105.8–122.4 (CF_2, CF_3). ^{19}F NMR ($CDCl_3$, 280 MHz, $CFCl_3$): δ (ppm): −81.3 (t, 3F, CF_3, J = 9.8 Hz), −114.7––114.8 (m, 2F, CH_2CF_2), −122.4 (m, 2F, CF_2), −123.4 (m, 2F, CF_2), −123.8 (m, 2F, CF_2), −124.0 (m, 2F, CF_2), −126.6 (m, 2F, CF_2CF_3). MALDI mass (m/z): $[M + Na]^+$ 3420.1, $[M + K]^+$ 3436.1. IR υ (cm^{-1}): 2933 (C–H), 1240–1144 (C–F). $C_{102}H_{114}F_{78}O_{24}S_6$.

8c: Hexakis[6-deoxy-6-(3-perfluorooctylpropanethio)-2,3-di-*O*-methyl]-α-cyclodextrin. Yield: 57% (0.243 mg). R_f (petroleum ether–AcOEt, 6 : 4) = 0.65. Mp (dec.): 106 °C. $[\alpha]_D$ +50 (c 0.49, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 1.81–1.90 (m, 12H, C$H_2$$CH_2$S), 2.07–2.24 (m, 12H, CH_2CF_2), 2.58–2.76 (m, 12H, CH_2S), 3.04 (dd, 12H, H6a, H-6b, J = 3.3 Hz, 11.4 Hz), 3.13 (dd, 6H, H-2, J = 3.0 Hz, 9.2 Hz), 3.51 (s, 18H, 2-OCH_3), 3.51

(t, 6H, H-3, J = 9.2 Hz), 3.63 (s, 18H, 3-OCH_3), 3.67 (t, 6H, H-4, J = 9.2 Hz), 3.93–3.96 (m, 6H, H-5), 5.05 (d, 6H, H-1, J = 3.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 20.4 (CH_2CH_2S), 29.7 (CH_2CF_2, J = 22.0 Hz), 32.8 (CH_2S), 33.6 (C-6), 58.1 (2-OCH_3), 61.9 (3-OCH_3), 72.1 (C-5), 81.2 (C-3), 82.2 (C-2), 84.6 (C-4), 99.7 (C-1), 105.8–122.4 (CF_2, CF_3). ^{19}F NMR ($CDCl_3$, 280 MHz, $CFCl_3$): δ (ppm): −81.3 (t, 3F, CF_3, J = 9.8 Hz), −114.5––114.6 (m, 2F, CH_2CF_2), −122.0–– 122.3 (m, 6F, CF_2), −123.1 (m, 2F, CF_2), −123.5 (m, 2F, CF_2), −126.6 (m, 2F, CF_2CF_3). MALDI mass (m/z): $[M + Na]^+$ 4021.0, $[M + K]^+$ 4037.6, $[M + 2Na - H]^+$ 4053.7. IR υ (cm^{-1}): 2930 (C–H), 1240–1148 (C–F). $C_{114}H_{114}F_{102}O_{24}S_6$.

9a: Hexakis(6-deoxy-6-heptanethio-2,3-di-*O*-methyl)-α-cyclodextrin. Yield: 69% (350 mg). R_f (petroleum ether–AcOEt, 65 : 35) = 0.83. $[\alpha]_D$ +121 (c 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 0.88 (t, 18H, CH_3, J = 6.6 Hz), 1.27–1.35 (m, 48H, CH_2), 1.52–1.59 (m, 12H, CH_2CH_2S), 2.57 (t, 12H, CH_2S, J = 7.4 Hz), 2.99–3.07 (m, 12H, H6a, H-6b), 3.13 (dd, 6H, H-2, J = 3.3 Hz, 9.2 Hz), 3.49 (s, 18H, 2-OCH_3), 3.51 (t, 6H, H-3, J = 9.2 Hz), 3.62 (s, 18H, 3-OCH_3), 3.70 (t, 6H, H-4, J = 9.2 Hz), 3.94–3.97 (m, 6H, H-5), 5.08 (d, 6H, H-1, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 14.2 (CH_3), 22.8 (CH_2CH_3), 29.1, 29.2, 30.1, 31.9 (CH_2), 33.8 (CH_2S), 34.3 (C-6), 58.0 (2-OCH_3), 61.8 (3-OCH_3), 71.6 (C-5), 81.2 (C-3), 82.2 (C-2), 84.2 (C-4), 99.5 (C-1). ES MS (m/z): $[M + NH_4]^+$ 1844.2, $[M + NH_4]^+$ 1848.1. IR υ (cm^{-1}): 2926 (C–H). $C_{90}H_{168}O_{24}S_6$.

9b. Hexakis(6-deoxy-6-nonanethio-2,3-di-*O*-methyl)-α-cyclodextrin. Yield: 50% (413 mg). R_f (petroleum ether–AcOEt, 65 : 35) = 0.53. $[\alpha]_D$ +105 (c 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 0.88 (t, 18H, CH_3, J = 6.5 Hz), 1.26–1.35 (m, 72H, CH_2), 1.52–1.58 (m, 12H, CH_2CH_2S), 2.57 (t, 12H, CH_2S, J = 7.2 Hz), 3.00–3.07 (m, 12H, H6a, H-6b), 3.13 (dd, 6H, H-2, J = 3.0 Hz, 9.5 Hz), 3.50 (s, 18H, 2-OCH_3), 3.51 (t, 6H, H-3, J = 9.5 Hz), 3.62 (s, 18H, 3-OCH_3), 3.69 (t, 6H, H-4, J = 9.5 Hz), 3.94–3.97 (m, 6H, H-5), 5.08 (d, 6H, H-1, J = 3.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 14.2 (CH_3), 22.8 (CH_2CH_3), 29.2, 29.5, 29.6, 29.7, 30.1, 32.0 (CH_2), 33.8 (CH_2S), 34.3 (C-6), 58.0 (2-OCH_3), 61.9 (3-OCH_3), 71.6 (C-5), 81.3 (C-3), 82.2 (C-2), 84.2 (C-4), 99.5 (C-1). ES MS (m/z): $[M + H]^+$ 1995.3, $[M + NH_4]^+$ 2012.3, $[M + NH_4]^+$ 2017.2. IR υ (cm^{-1}): 2926 (C–H). $C_{102}H_{192}O_{24}S_6$.

9c. Hexakis(6-deoxy-6-undecanethio-2,3-di-*O*-methyl)-α-cyclodextrin. Yield: 51% (613 mg). R_f (petroleum ether–AcOEt, 8 : 2) = 0.30. $[\alpha]_D$ +101 (c 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 0.88 (t, 18H, CH_3, J = 6.6 Hz), 1.25–1.35 (m, 96H, CH_2), 1.52–1.59 (m, 12H, CH_2CH_2S), 2.57 (t, 12H, CH_2S, J = 7.2 Hz), 3.00–3.07 (m, 12H, H6a, H-6b), 3.13 (dd, 6H, H-2, J = 3.2 Hz, 9.3 Hz), 3.50 (s, 18H, 2-OCH_3), 3.51 (t, 6H, H-3, J = 9.3 Hz), 3.66 (s, 18H, 3-OCH_3), 3.70 (t, 6H, H-4, J = 9.3 Hz), 3.94–3.97 (m, 6H, H-5), 5.08 (d, 6H, H-1, J = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by COSY, DEPT, HSQC, HMBC): δ (ppm): 14.5 (CH_3), 23.1 (CH_2CH_3), 29.5, 29.8, 29.9, 30.1, 30.2, 30.2, 30.4, 32.3 (CH_2), 34.1 (CH_2S), 34.6 (C-6), 58.3 (2-OCH_3), 62.2 (3-OCH_3), 71.9 (C-5), 81.5 (C-3), 82.1 (C-2), 82.5 (C-4), 99.8 (C-1). ES MS (m/z): $[M + H]^+$ 2163.5, $[M + NH_4]^+$ 2180.8, $[M + NH_4]^+$ 2184.8. IR υ (cm^{-1}): 2924 (C–H). $C_{114}H_{216}O_{24}S_6$.

Langmuir experiments

Langmuir film measurements were carried out in a Teflon trough of 400 ml. 3 mg ml^{-1} α-cyclodextrin derivative solutions in $CHCl_3$ were spread at appropriate volumes with a micropipetman (Gilson) at the air–water interface. 30 min were allowed for solvent evaporation and equilibration, except for **8c**, where 1 h is needed. Isotherms were carried out on a Langmuir type balance (NIMA technology). Compressions were performed continuously at a rate of 20 cm^2 min^{-1} (50 cm^2 min^{-1} for **8c**, speed rate allowing a better reproducibility) from 510 to 50 cm^2. Each sample was run at least three times to ensure reproducibility of results (deviation of area and pressure were less than 3%).

Conclusions

The synthesis of a series of *O*-6-alkylthio- and *O*-6-perfluoroalkylpropanethio-α-cyclodextrins and their *O*-2-, *O*-3-methylated analogues has been achieved in reasonable overall yields. Solid state ^{13}C and ^{19}F NMR spectroscopies allowed confirmation of the success of the coupling reaction as the very poor solubility of the perfluoroalkylpropanethio-α-cyclodextrins excluded the use of solution NMR spectroscopy. For the hexakis(6-deoxy-6-alkylthio-2,3-di-*O*-methyl)-α-cyclodextrin derivatives the formation of stable monolayers at the air–water interface was observed with no significant influence of the chain length. In the case of the corresponding perfluoroalkylpropanethio-compounds, the stabilities of the monolayers were higher and increased with the fluorous chain length. Work is currently underway to prepare nanoparticles from these molecules.

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