Highly fluorinated cyclodextrins and their host–guest interactions†

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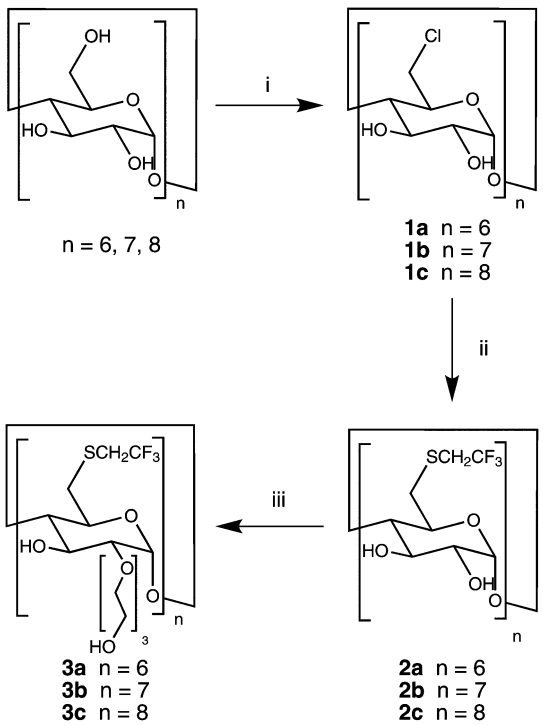
Highly fluorinated, water soluble cyclodextrins were synthesized by substitution with trifluoroethylthiol at the primary face and triethyleneglycol at the secondary face. The fluorinated cyclodextrins interact preferentially with fluorinated guest molecules.

Cyclodextrins are among the most studied host molecules available to the supramolecular chemist.[1,2] The primary driving force for the inclusion of guests into cyclodextrin hosts is the hydrophobic effect. However, it is widely accepted that secondary interactions between hosts and guests can play an important role in the thermodynamic stability as well as the structure and dynamics of the host–guest complex.[3] Secondary interactions include electrostatic interactions, hydrogen bonding, and metal–ligand coordination. Secondary interactions are of particular relevance to understand the interaction between modified cyclodextrins and guests, since they may either stabilize or destabilize the host–guest complex.

In solution, fluorinated molecules tend to cluster due to the so-called fluorophobic effect.[4] The fluorophobic effect operates in water, and also in apolar environment, *i.e.* in hydrocarbon solvents. Amongst others, the fluorophobic effect has been exploited in the aggregation of fluorinated surfactants and lipids,[5] the self-assembly of fluorinated polymers,[6] liquid crystals[7] and metal–organic nanocapsules,[8] and fluorinated tags for organic synthesis.[9] In this communication, we demonstrate that cyclodextrin host–guest complexes can be significantly stabilized by the fluorophobic effect. To this end, we synthesized highly fluorinated, yet water-soluble cyclodextrins. Their interaction with fluorinated and non-fluorinated guests was investigated with isothermal titration calorimetry (ITC) and NMR.

Cyclodextrins substituted with one or more fluoro,[10] trifluoromethylthio,[11] trifluoroethylthio,[10b] 3-perfluorohexylpropanethio[12] and perfluorobutanoyl groups[13] have been previously reported, but the water solubility of the persubstituted cyclodextrins is negligible. Furthermore, there are a number of studies that show that fluorinated guests typically bind *weaker* to cyclodextrins than non-fluorinated guests.[14] Here we show that water soluble fluorinated hosts interact preferentially with fluorinated guests.

Fluorinated α, β and γ-cyclodextrins were synthesized in a straightforward three-step synthesis (Scheme 1). First, the cyclodextrins were perchlorinated at C6 using methylsulfonylchloride



Scheme 1 Synthesis of water-soluble fluorinated cyclodextrins. (i) CH_3SO_2Cl, DMF, 65 °C. (ii) CF_3CH_2SH, NaH, DMF, 75 °C. (iii) $HO(C_2H_4O)_3Tos$, NaH, DMF, rt.

to give chlorocyclodextrins **1a–1c** in 80–90% yield.[15] Second, each C6 was functionalized in a nucleophilic substitution with trifluoroethylthiol in the presence of NaH to give trifluoroethylthio-modified cyclodextrins **2a–2c** in 60–85% yield. In accordance with their high degree of fluorination, cyclodextrins **2a–2c** are insoluble in water.

Finally, trifluoroethylthio-modified cyclodextrins **2a–2c** were reacted with triethyleneglycol *p*-toluenesulfonate ester in the presence of NaH to give cyclodextrins **3a–3c**. The reaction of **2a–2c** with the *p*-toluenesulfonate ester proceeded in high yield (80–100%) under mild conditions. We assume that the electron withdrawing substituents at C6 increase the acidity of the secondary hydroxyl group at C2 (and C3).

The spectroscopic and analytical data of cyclodextrins **2a–2c** and **3a–3c** are consistent with the molecular structure shown in Scheme 1. Alkylation occurs primarily at the hydroxyl group at C2, with some additional reaction at C3. Selected NMR and MS data of cyclodextrins **2b** and **3b** are shown in Fig. 1. Further details regarding the synthesis and characterization of **2a–2c** and **3a–3c** are provided as electronic supplementary information.† The water solubility of **3a–3c** is higher than 50 mM.

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† Electronic supplementary information (ESI) available: Synthesis and characterization of cyclodextrins. ITC and NMR titrations. See DOI: 10.1039/c0cc00616e

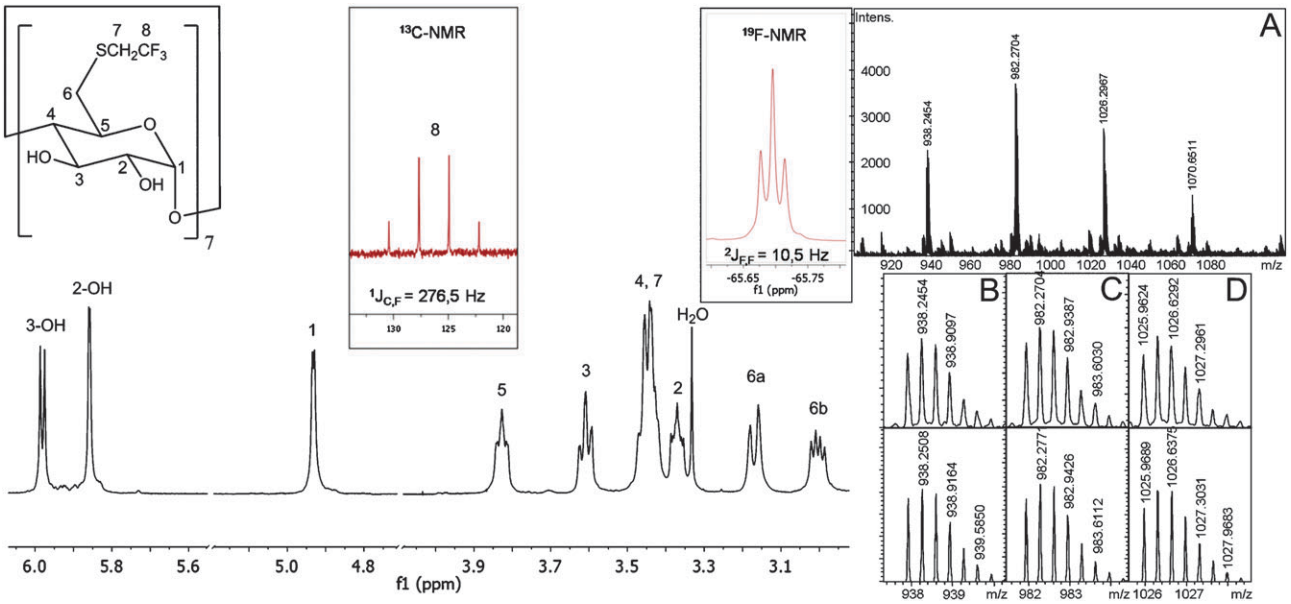

Fig. 1 Left: ^{1}H, ^{13}C and ^{19}F-NMR of **2b** in DMSO-D_6. Right: MS and isotope distribution of **3b**; (A) measured positive ion MS; (B) measured (top) and calculated (bottom) positive ion MS $[M_{EO21} + 3Na]^{3+}$, (C) $[M_{EO24} + 3Na]^{3+}$, and (D) $[M_{EO27} + 3Na]^{3+}$.

The interaction between cyclodextrins **3a** and **3b** and a range of fluorinated and non-fluorinated guest molecules in water was determined by ITC (Tables 1 and 2). ITC provides the binding constant K_a, thermodynamic parameters (ΔH, ΔG and ΔS) and stoichiometry in one experiment. The ITC data could be accurately fitted to a 1 : 1 model for all host–guest complexes investigated. ΔH was negative for each complex, while ΔS was generally positive (with some exceptions for **3a**). Binding constants K_a for β-cyclodextrin **3b** are larger than K_a for α-cyclodextrin **3a**.

Invariably, the binding constant K_a was *larger* for the fluorinated than for the non-fluorinated guests, typically by a factor of 3–5, but in several cases by an order of magnitude. The larger K_a values observed for fluorinated guests compared to non-fluorinated guests indicate a stronger host–guest complexation due to the fluorophobic effect.

The host–guest complex of cyclodextrin **3b** with *p*-trifluoromethylphenol was also investigated with ^{19}F and ^{1}H-NMR. *p*-Trifluoromethylphenol (5 mM) was titrated into cyclodextrin **3b** (5 mM) in D_2O. Fig. 2 shows the ^{19}F-NMR spectra of the titration. The guest signal shifts downfield upon complexation because of the less polar surrounding of the cyclodextrin cavity. In contrast, the host signal shifts upfield at higher guest concentration. To explain this observation, we propose that, in the absence of guest, one of the fluorinated substituents of the cyclodextrin folds into the cavity of the cyclodextrin, while in the presence of guest it is displaced.

The ^{19}F-NMR data in Fig. 2 were used to determine the complex stoichiometry as well as the binding constant K_a. According to a Job's plot (Fig. 3), the stoichiometry of the complex is 1 : 1, which is consistent with the ITC data shown

Table 1 ITC of fluorinated and non-fluorinated guests with **3a**

Guest	K_a/ L mol^{-1}	ΔG/ kJ mol^{-1}	ΔH/ kJ mol^{-1}	ΔS/ J K^{-1} mol^{-1}
Fluorophenol	138	−12.1	−9.4	9.3
p-Trifluoromethylphenol	383	−14.6	−16.5	−6.3
m-Trifluoromethylphenol	361	−14.5	−16.4	−6.5
Phenol	72	−10.5	−15.9	−17.9
p-Cresol	50	−9.6	−0.7	30.2

Table 2 ITC of fluorinated and non-fluorinated guests with **3b**

Guest	K_a/ L mol^{-1}	ΔG/ kJ mol^{-1}	ΔH/ kJ mol^{-1}	ΔS/ J K^{-1} mol^{-1}
Fluorophenol	146	−12.3	−6.5	19.3
p-Trifluoromethylphenol	1050	−17.1	−4.0	44.2
m-Trifluoromethylphenol	705	−16.1	−1.5	49.3
4-Trifluoromethyl CCA	1460	−17.9	−3.2	49.7
Diflunisal	2150	−18.9	−10.7	27.7
Phenol	121	−11.8	−9.7	7.0
p-Cresol	136	−12.1	−4.0	27.4
4-Methyl CCA	203	−13.1	−4.1	30.3

CCA: cyclohexane carboxylic acid.

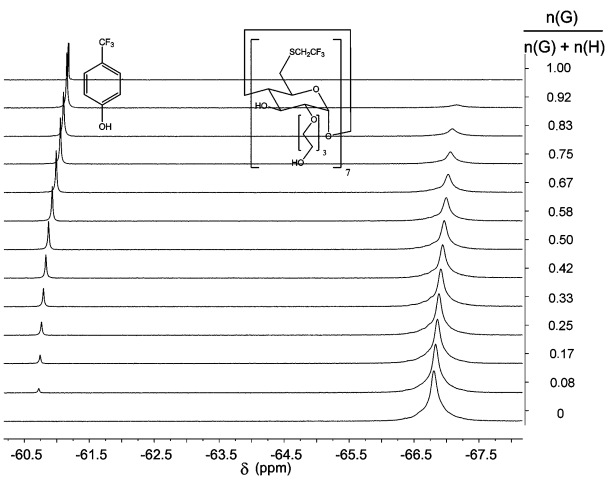

Fig. 2 ^{19}F-NMR titration of cyclodextrin **3b** with *p*-trifluoromethylphenol.

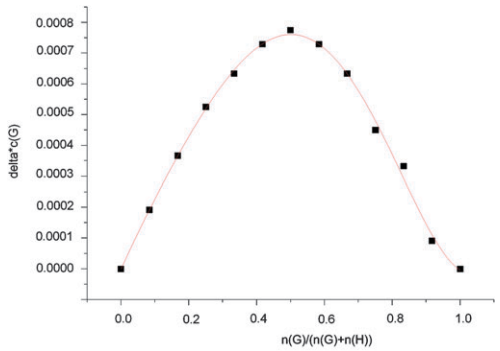

Fig. 3 Job's plot based on the ^{19}F-NMR titration of cyclodextrin **3b** with *p*-trifluoromethylphenol.

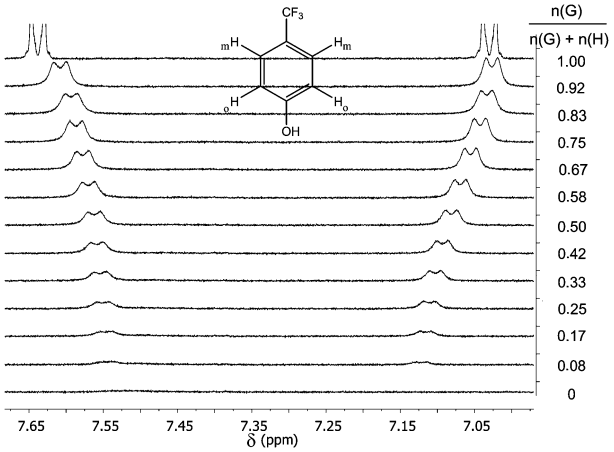

Fig. 4 ^{1}H-NMR titration of cyclodextrin **3b** with *p*-trifluoromethylphenol.

in Table 1. According to a 1 : 1 fit, the binding constant $K_a = 2.06 \times 10^3$ M^{-1}, which is also consistent with the ITC data.

^{1}H-NMR spectra for the complexation of cyclodextrin **3b** and *p*-trifluoromethylphenol (Fig. 4) show the expected downfield shift of the guest proton (H_o) in *ortho* position to the hydroxyl group. Just like the trifluoromethyl group, H_o is deshielded by the less polar surrounding of the cyclodextrin cavity. However, the guest proton (H_m) in *meta* position is shifted upfield. The upfield shift of H_m is diagnostic of a significant fluorine–fluorine interaction, which increases the electron density of the trifluoromethyl group and shields nearby H_m (*ortho* to CF_3). Obviously, the deshielding effect of the less polar surrounding of the cyclodextrin cavity is more than compensated by the shielding effect due to the fluorine–fluorine interaction. These data show that the trifluoromethylphenol penetrates deeply into the cyclodextrin cavity with the trifluoromethyl group of the guest in close proximity to the trifluoroethyl group of the host.

NMR titration of cyclodextrin **3a** with *p*-trifluoromethylphenol under the same conditions gave similar results. Using ^{19}F-NMR data a 1 : 1 complex stoichiometry and a binding constant $K_a = 1.37 \times 10^2$ M^{-1} were found. Unlike **3b**, ^{19}F-NMR data of **3a** show hardly any shift of the host signal. We propose that due to the smaller cavity of **3a**, none of the fluorinated substituents reaches into the cavity. Accordingly, H_m shows only a small upfield shift.

Finally, we measured the interaction of the fluorinated anti-inflammatory drug diflunisal (2′,4′-difluoro-4-hydroxy-biphenyl-3-carboxylic acid) with cyclodextrins **3b** and **3c**. It was found by ITC that diflunisal binds to **3b** in a 1 : 1 complex with $K_a = 2.15 \times 10^3$ M^{-1} and $\Delta H = -10.7$ kJ mol^{-1} and to **3c** in a 2 : 1 complex with $K_a = 1.46 \times 10^3$ M^{-1} and $\Delta H = -8.5$ kJ mol^{-1}.

We conclude that the fluorophobic effect can contribute significantly to the stability of cyclodextrin host–guest complexes in water and we anticipate that the water-soluble fluorinated cyclodextrins described in this communication may be of particular use for the selective solubilization of fluorinated compounds.

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