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Fluorine containing β-cyclodextrin: a new class of amphiphilic carriers

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Abstract

β-cyclodextrins (β-CD), functionalised at the 6-position with trifluoromethylthio groups, are obtained in five steps from the native β-CD. The fluorinated cyclodextrin derivatives exhibit an amphiphilic behaviour at the air–water interface and thus are good candidates for a new class of amphiphilic carriers.

Keywords: fluorine containing β-cyclodextrins; amphiphilic; synthesis; Langmuir isotherms.

For many years, modifications of cyclodextrins provide interesting organic host molecules for the encapsulation, solubilisation and transport of drugs.[1] The resulting cyclodextrin derivatives are known to increase the bioavailability of pharmaceuticals.[2] However, their use in biological systems requires amphiphilic properties. In order to obtain amphiphilic cyclodextrins, one of the two hydrophilic rims has to be modified by the introduction of lipophilic groups. A large variety of amphiphilic β-cyclodextrins is described in the literature,[3–6] especially with a wide range of long alkyl chains as hydrophobic substituents.

On the other hand, much attention has been focused on the development of fluorine-containing organic compounds, owing to their potential importance in the biological field.[7–9] It is noteworthy that a fluorinated molecule can take place in the same biological receptor as its hydrogenated counterpart, but then exhibits a very different behaviour owing to the high electronegativity and the low polarisability of the fluorine atom. Another point is the important lipophilicity imported by polyfluorinated moieties to the molecules which carry them. So, bearing in mind the very high lipophilicity of the SCF_3 group (Hansch parameter $\Pi_R = 1.44$) versus the CH_3 group ($\Pi_R = 0.61$),[7] we attempted to link it to the β-cyclodextrin. The SCF_3

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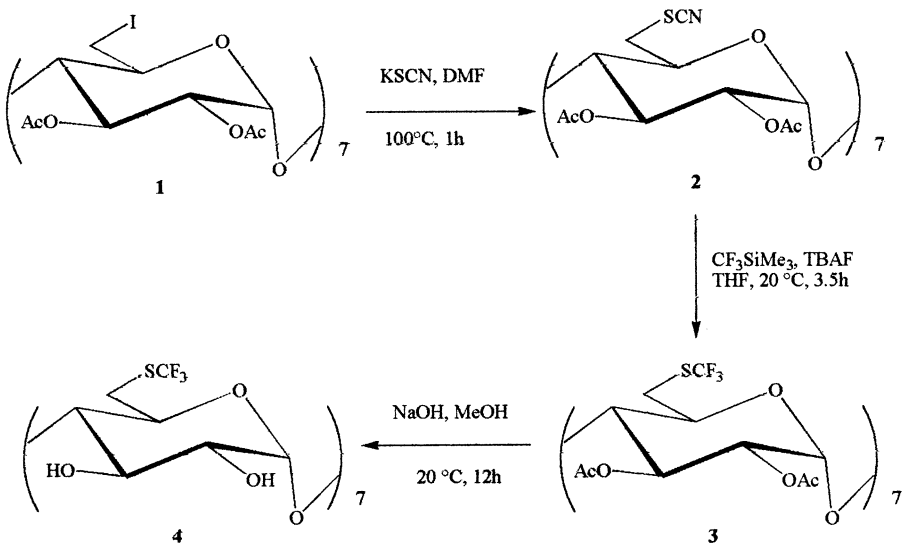
group seems to be a good candidate to induce lipophilicity in β-cyclodextrins with short side chains as indicated from the recent synthesis of a monotrifluoroethylthio-β-cyclodextrin.[10] This compound displays suitable ability for drug delivery of hydrophobic drug molecules.

The preparation of trifluoromethyl sulphides from trifluoromethyl trimethylsilane and thiocyanates in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF) has been described by some of us[11,12] and recently applied to protected sugar thiocyanates to yield trifluoromethylthio-substituted carbohydrates.[13]

In this paper, we describe an efficient route to an amphiphilic β-cyclodextrin derivative substituted at the primary face by the SCF_3 group. We have also investigated the self-organisation properties of the heptakis-(6-deoxy-6-trifluoromethylthio)-β-cyclodextrin and in particular its ability to form monolayers at the air–water interface.

The starting material was the heptakis (6-deoxy-6-iodo-2,3-di-*O*-acetyl)-β-cyclodextrin **1** obtained in two steps from native β-cyclodextrin,[14] which was modified as indicated in Scheme 1.



Scheme 1. Synthesis of trifluoromethylthio-β-cyclodextrin derivatives

The thiocyanato-derivative **2** was prepared with an excess of potassium thiocyanate in DMF at 100°C[15] (83%).[16] The introduction of the trifluoromethyl group is achieved by treatment of **2** with a large excess of CF_3SiMe_3 in the presence of TBAF (Table 1, entry 3).

Table 1
Formation of the trifluoromethylthio derivative **3**

Entry	**2** (equiv.)	CF_3SiMe_3 (equiv.)	TBAF (equiv.)	Reaction time (h)	Yield (%)[a]
1	1	2	Cat.	2.5	35
2	1	2	Cat.	24	42
3	1	4	Cat.	3.5	72
4	1	4	4	3.5	44

[a] Of isolated product.

The conversion of the thiocyanato-derivative **2** into the trifluoromethylthio-derivative is not complete. We obtained a mixture of isomers with different degrees of substitution at the C-6 position (the isomers could not be completely separated by column chromatography, however we obtained a fraction of the persubstituted cyclodextrin derivative **3** with a satisfactory purity). Unfortunately, we failed in our attempt to improve this reaction. The fully unprotected trifluoromethylthio-β-cyclodextrin **4** is obtained after treatment of **3** with sodium hydroxide in methanol, followed by the action of an Amberlite resin (IRN 77)[17].

Mass and NMR spectra confirmed the identification of the new cyclodextrin derivatives.

The compression isotherm of **4** at the air–water interface is given in Fig. 1.[18] The characteristics of the isotherm are given in Table 2 and are compared to the literature.[19] The curve shows a collapse at $A = 280$ Å, $\Pi = 25.1$ mN m^{-1} and is typical for cyclodextrin systems. The Langmuir balance measurements show that the cyclodextrin derivative **4** is capable of forming stable monolayers at the air–water interface although it possesses very short hydrophobic chains. The increase of the area A_0 for the trifluoromethylthio derivative indicates that the CF_3 group seems to be bulkier than the phenyl one.

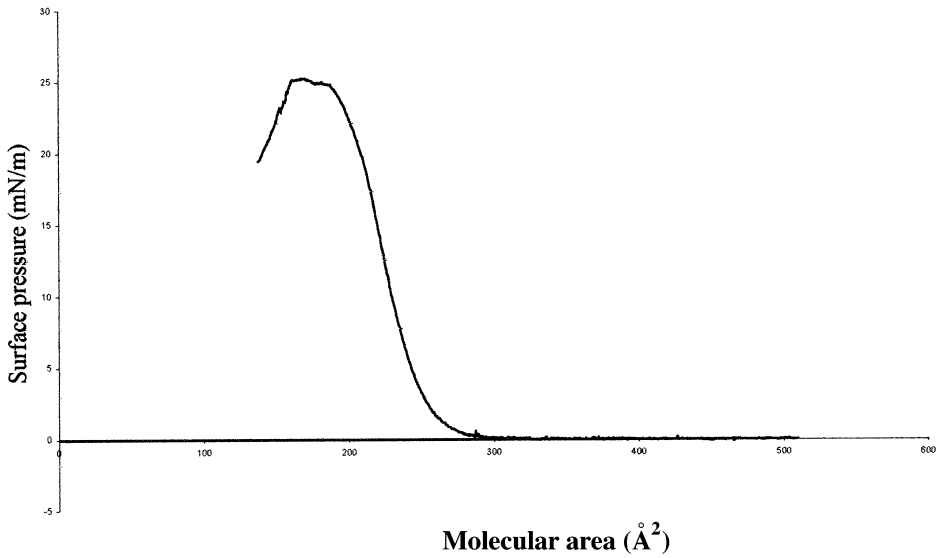


Figure 1. Surface pressure-molecular area isotherm of **4**

Table 2
Comparison of parameters of the isotherm for the derivative **4** with *S*-aryl substituents

Compound	Substituent	Πcoll. (mN/m)	A_0 (Å^2)
4	SCF_3	25.1	280
Lit.[19]	SPh	34.1	228

In conclusion, treatment of protected β-cyclodextrin thiocyanate with an excess of trifluoromethyl trimethylsilane, followed by a deprotection sequence, offers a direct route to a new and attractive class of amphiphilic β-cyclodextrins substituted at the primary face by trifluoromethylthio substituents. This group allows the self-organisation of the molecules into stable

monolayers at the air–water interface. This fluorinated amphiphilic β-cyclodextrin could be associated in supramolecular assemblies such as nanospheres and might have interesting properties for drug encapsulation.

Acknowledgements

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16. Selected spectral data for **2**: mp 212–220°C; IR (KBr) 2518 cm^{-1}; ^1H NMR ($CDCl_3$-300 MHz) δ (ppm) 5.3 (dd, 7 H, $^3J=9.3$ Hz, $^3J=7.6$ Hz), 5.13 (d, 7 H, $^3J=3.9$ Hz), 4.89 (dd, 7H, $^3J=9.4$ Hz, $^3J=3.5$ Hz), 4.34–4.28 (m, 7H), 3.81 (dd, 7H, $^3J=2.5$ Hz, $^3J=14.1$ Hz), 3.68 (dd, 7H, $^3J=^3J=7.7$ Hz), 3.25 (dd, 7H, $^3J=7.9$ Hz, $^3J=14.0$ Hz), 2.12 (s, 21H), 2.07 (s, 21H); ^{13}C NMR (HSQC–$CDCl_3$) δ (ppm) 170.4–169.3 (2 peaks CO), 112.3 (CN), 97.3 (C-1), 80.1 (C-4), 70.6 (C-5), 69.9 (C-3), 69.6 (C-2), 35.9 (C-6), 20.7 (CH_3); ES-MS (m/z) 1745 for $[M+H]^+$.
17. Selected spectral data for **4**: ^1H NMR (Pyr-d_5-300 MHz) δ (ppm) 5.51 (s, 7 H), 4.75–3.86 (m, 42 H), 1.57(s, 6 H); ^{13}C NMR (Pyr d_5) δ (ppm) 130.5 (q, $^1J_{CF}=300$ Hz, CF_3), 102.3 (C-1), 84.7 (C-4), 72.2, 72.6, 72.7 (C-2, C-3, C-5), 31.0 (C-6); ^{19}F NMR (Pyr d_5) δ (ppm) −42.8 (s, CF_3);ES-MS (m/z) 1745 for $[M+Na]^+$.
18. Compression isotherms of **4** were obtained at 290 K with distilled water as subphase, using a Lauda film balance: 0.33×10^{15} molecules μL^{-1} of **4** in $CHCl_3$; 30 μL was spread on the aqueous surface; a compression rate 18 cm^2 mn^{-1} was used. The isotherms were recorded three times and are reproducible.
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