Cyclodextrin Liquid Crystals: Synthesis and Self-organisation of Amphiphilic Thio-β-cyclodextrins

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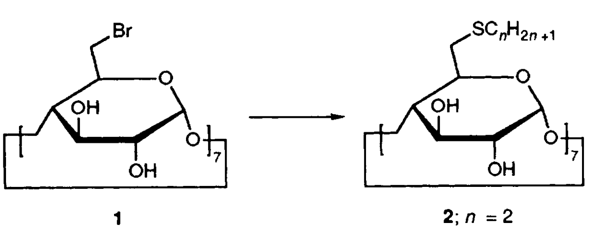
Heptakis(6-*S*-alkyl-6-thio)-cyclomaltoheptaoses (where alkyl is a C_2, C_4, C_{10}, C_{16} and C_{18} unit) have been synthesised *via* heptakis(6-bromo-6-deoxy)-cyclomaltoheptaose and shown to form thermotropic liquid crystals.

The design and synthesis of amphiphilic compounds of cyclodextrins (cyclomaltooses) have interested chemists for almost a decade. There are published references to derivatives of cyclodextrins bearing multiple hydrophobic chain groups either by 6-deoxy-6-amino,[1–3] -6-sulfide or -sulfonyl linkage,[4–5] or on the opposite side of the macrocycle by ether or ester linkage.[6–8] However, most of the results concerning modifications at the 6-position are based on a single reaction, tosylation,[9] claimed by many research workers to give the pure activated 6-persulfonyl esters in good yield by crystallisa-



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2; n = 2
3; n = 4
4; n = 10
5; n = 16
6; n = 18

Scheme 1

tion. The recent work by Stoddart's group[10,11] has demonstrated clearly that these compounds can be obtained pure only by repeated HPLC under reversed-phase conditions. Considering that the purity of amphiphiles prepared from these intermediates is therefore in doubt, we have investigated the synthesis of amphiphilic heptakis(6-*S*-alkyl-6-thio)-β-cyclodextrins by an alternative route which uses heptakis-(6-bromo-6-deoxy)-β-cyclodextrin as intermediate. We have also investigated the self-organisation properties of the products, and in particular, for the first time, their ability to form thermotropic mesophases.

The bromomethylenedimethylammonium bromide reagent, used by Takeo[12] for partial 6-bromination of cyclodextrins, has already been applied by us to introduce multiple 6-propylthio groups.[13] More recently the halogenation, with bromine and iodine, has been developed by Gadelle and Defaye[14] as the most successful route to 6-perfunctionalisation of cyclodextrins, and has been used in the synthesis of 6-*S*-glycosyl- and 6-*S*-hydroxyethyl-6-deoxy-cyclodextrins.[15]

Compounds **2**–**6** are synthesised by bromide displacement from heptakis(6-bromo-6-deoxy)-β-cyclodextrin **1** by alkylthiolate, as potassium salt, with excellent yields (>90%) (Scheme 1). The persubstitution is confirmed by the simple high-resolution ^1H and ^{13}C NMR spectra. As an example, Fig. 1 shows the ^1H NMR spectrum of compound **5** in deuteriated pyridine. 1-H resonates at δ 5.58 as a clear doublet with $J_{1,2}$ 3.06 Hz; ^1H–^1H COSY allows the complete assignment of peaks, with those of 3- and 5-H partly overlapped at δ 4.46, 2- and 4-H partly overlapped at δ 4.15, 6-H as a quartet at δ 3.41 ($J_{6,6'}$ 13.10 Hz, $J_{5,6}$ 6.45 Hz), and 6'-H as a doublet at δ 3.69. Two kinds of secondary hydroxy appear clearly as a singlet at δ 7.64 (3-OH) and a doublet at δ 8.10 (2-OH, $J_{2,OH}$ 6.39 Hz). The chain signals appear as equally simple patterns, the ω-methyl groups as a triplet at δ 0.91; however, the α-methylene groups appear as a complex set at δ 2.97, indicating magnetic inequivalence which may result from the partial hindrance to free rotation of this part of the chains and a consequent $SCH_aH_bCH_2$ system. The purity of the compounds is also verified by elemental analysis.

Langmuir balance measurements show that all the compounds **2**–**6** are capable of forming stable monolayers at the air–water interface. Except for compound **2**, the π–*A* curves have one collapse with extrapolated molecular areas from 174 to 191 Å^2 at zero pressure. Allowing for experimental error, these values correspond well to the molecular area (186 Å^2)[16] of the secondary face of β-cyclodextrin. The results indicate that at collapse, the chains of the molecules are orientated vertically to the air–water interface. The pressure at collapse varies from 45 to 65 mN m^{-1}. Compound **2** possesses very short alkylthio chains; however, a stable monolayer is formed, though a double collapse is observed which indicates formation of multilayers during compression. The extrapolated molecular areas are 224 Å^2 (first collapse, at a pressure of 28 mN m^{-1}), and 141 Å^2 (second collapse, at 65 mN m^{-1}). All the molecular area values reported in previous work[4,5] are larger than those observed by us, for example, a molecular area of 210 Å was reported for compound **6**, for which we obtained 191 Å^2. We consider these differences to be due to impurities in the earlier samples.

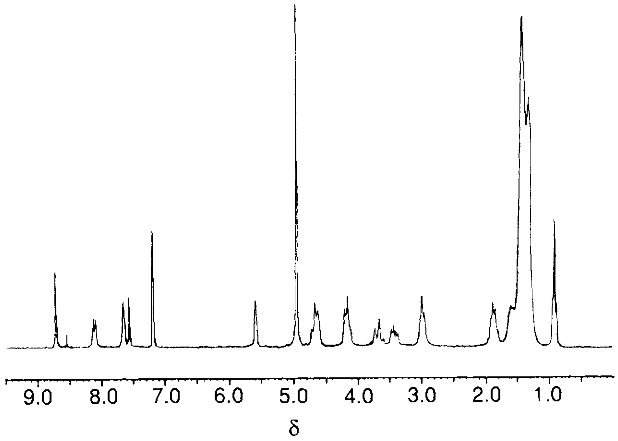

Fig. 1 200 MHz ^1H NMR spectrum of compound **5** in [$^2H_6$]pyridine

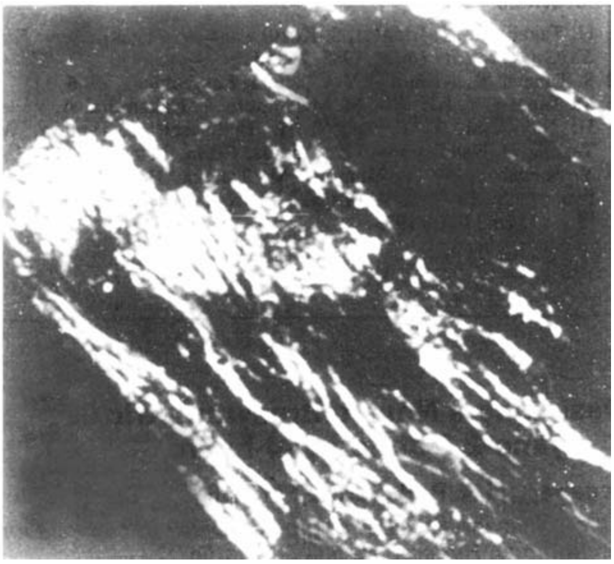

Fig. 2 Liquid crystalline compound **6** (bright area), in cross-polarised transmitted light, on cooling to room temperature

Although physical properties for different classes of amphiphilic cyclodextrin derivatives have been recorded, no one has yet reported the thermal properties of such compounds, in particular the capacity to form thermotropic liquid crystals. Using differential scanning calorimetry (DSC) and cross-polarised optical microscopy, we observed that all our compounds show thermotropic liquid crystal properties (Fig. 2). Compounds **5** and **6** strongly show liquid crystalline phases above 215 °C, and clear at 280 °C with onset of decomposition. On cooling, the crystalline phase is retained. Weakly liquid crystalline behaviour is observed for the other compounds, even for compounds **2** and **3**, which is unusual for compounds possessing such short hydrophobic chains. In comparison with analogous monosaccharide mesogens,[17] which require longer chains, the stabilising influence on mesophases of the joined sugar rings is evident. This has also been seen with per-(2,3-di-*O*-acetyl)-β-cyclodextrin, which has the capacity to form monolayers at an air–water interface.

By DSC we also detected, for compounds **5** and **6**, the alkyl chain transition temperatures (melting point at 46 °C for **5**, 54 °C for **6**, crystallisation temperature at 35 °C for **5** and 43 °C for **6**); however no chain transitions were observed for the other compounds.

Since the microscopic textures of the liquid crystals are reminiscent of monosaccharide mesogens bearing single chains,[17] we consider that the cyclodextrin liquid crystals also belong to the smectic, rather than discotic, family. X-Ray powder diffraction measurements on **5** showed a sharp reflection in the small-angle region corresponding to a bilayer depth of 38 Å. This is less than twice the calculated molecular length of 28 Å, and suggests that the rod-like molecules are inclined at an angle in the layers.

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