Novel Amphiphilic Cyclodextrins: Graft-Synthesis of Heptakis(6-alkylthio-6-deoxy)-β-cyclodextrin 2-Oligo(ethylene glycol) Conjugates and Their ω-Halo Derivatives

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Novel amphiphilic cyclodextrins were synthesised by grafting oligo(ethylene glycol) units onto the secondary side of heptakis(6-alkylthio-6-deoxy)-β-cyclodextrins (alkyl = ethyl, hexyl, dodecyl and hexadecyl). The oligo(ethylene glycol) substituents were introduced by reaction of heptakis(6-alkylthio-6-deoxy)-β-cyclodextrins with ethylene carbonate in the presence of potassium carbonate at elevated temperatures. The resulting oligo(ethylene glycol)-cyclodextrin conjugates were characterised by ^{1}H NMR and ^{13}C NMR, COSY and HSQC spectroscopy, and mass spectrometry. Addition of ethylene carbonate occurs exclusively at OH2 and results in a degree of substitution of 8–22 ethylene glycol units per cyclodextrin. Also, the ω-bromo and ω-iodo derivatives of heptakis[6-deoxy-6-hexylthio-2-oligo(ethylene glycol)]-β-cyclodextrin were prepared as strategic synthetic intermediates. The observation that seven halogen atoms are introduced per cyclodextrin provides strong evidence for the grafting of oligo(ethylene glycol) to each of the seven glucose units in the cyclodextrin ring.

Introduction

Cyclodextrins are cyclic α(1−4)oligoglucopyranosides that have extensive potential for use as efficient molecular encapsulators and solubilisers for valuable hydrophobic additives such as fragrances, flavours, preservatives etc.[1] However, the potential of most cyclodextrins in pharmaceutics is restricted by their poor in vivo drug complexation and delivery capacity.[2] Polymeric cyclodextrins and/or supramolecular aggregates of cyclodextrins may provide more versatile carrier and delivery systems for a variety of drug molecules. Amphiphilic cyclodextrins are potentially useful building blocks for such aggregates.

Over the past decade, several groups have reported amphiphilic cyclodextrin derivatives that display a wide range of lyotropic and thermotropic mesophases. Amphiphilic cyclodextrins have been shown to form monolayers at the air-water interface,[3] and micelles.[4] Thermotropic liquid crystals of cyclodextrins have also been described.[5] Furthermore, amphiphilic cyclodextrins can be admixed to phospholipid monolayers[6] as well as liposomes,[7] and they can be dispersed into ''nanoparticles'' of pharmaceutical interest.[8] However, with few exceptions, these materials have poor water solubility.

Heptakis(6-alkylthio-6-deoxy)-β-cyclodextrins, which are accessible in an efficient two-step synthesis,[5] display thermotropic mesophases and form monolayers at the air-water interface,[3f,3g,5] but are insoluble in water. The poor water solubility of these and other β-cyclodextrins probably results from strong intramolecular hydrogen bonding of the secondary hydroxyl groups, as in native β-cyclodextrin. In the case of native β-cyclodextrin, even a random and low degree of substitution with hydrophilic hydroxyethyl or oligo(ethylene glycol) groups disrupts the hydrogen bond network and dramatically improves water solubility. This solubilising effect was observed upon reaction of β-cyclodextrin with ethylene carbonate[9] or with ethylene oxide.[10] In our case, substitution on the secondary side of heptakis(6-alkylthio-6-deoxy)-β-cyclodextrins provides cyclodextrins with a pronounced amphiphilic character. We recently reported ethylene glycol conjugates of cyclodextrins which result from extensive hydroxyethylation of the secondary side of heptakis(6-deoxy-6-dodecylthio)-β-cyclodextrin and (6-deoxy-6-hexadecylthio)-β-cyclodextrin using ethylene carbonate under mildly alkaline conditions.[11] The introduction of hydrophilic oligo(ethylene glycol) units significantly increases the water solubility of these molecules. Depending on the length of the alkyl substituents, the new cyclodextrins form different lyotropic phases in aqueous solution, and we have already reported the first examples of bilayer vesicles composed entirely of cyclodextrins.[11] In view of the remarkable properties of ''stealth'' liposomes that are effectively coated with a poly(ethylene glycol) layer,[12] it is possible that the presence of oligo(ethylene glycol) units will decrease the immunogenicity and increase the colloidal stability of these novel cyclodextrin vesicles, which would offer significant new possibilities for their application as drug delivery systems.

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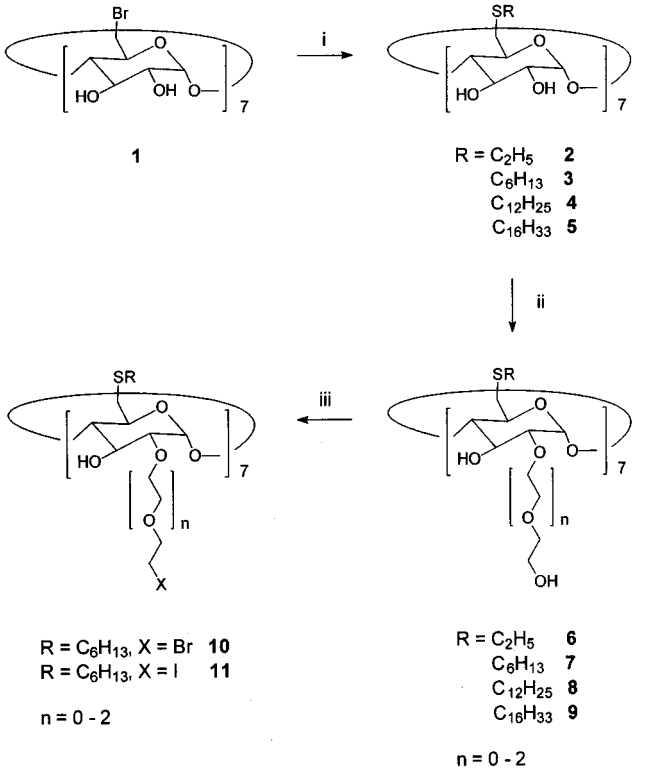
This paper describes in detail the synthesis and structural characterisation of oligo(ethylene glycol)-conjugated amphiphilic cyclodextrins prepared from heptakis(6-alkylthio-6-deoxy)-β-cyclodextrins (alkyl = ethyl, hexyl, dodecyl or hexadecyl). Furthermore, we prepared the ω-bromo and ω-iodo derivatives of heptakis[6-deoxy-6-hexylthio-2-oligo-(ethylene glycol)]-β-cyclodextrin. This modification assisted in elucidation of the substitution pattern of the oligo(ethylene glycol) cyclodextrins and opens up routes for further elaboration of the amphiphilic cyclodextrins.[13]

Results and Discussion

The novel amphiphilic cyclodextrins were obtained in a three-step synthesis from β-cyclodextrin (Scheme 1). β-cyclodextrin was perbrominated at C6 to yield **1**.[14] Next, the thioethers **2**−**5** were prepared by reaction of **1** with linear thiols $C_nH_{2n+1}SH$ (n = 2, 6, 12, 16) by nucleophilic displacement reactions.[5] We then developed an efficient modification of the hydroxyethylation protocol reported for β-cyclodextrin using ethylene carbonate as the alkylating agent.[9,11] Cyclodextrins **2**−**5** can be efficiently substituted with hydroxyethyl groups at C2 in tetra-*N*-methylurea at 150 °C, using an excess of ethylene carbonate and adding K_2CO_3 as base. The elevated temperature is essential for rapid and full substitution. The reaction can be monitored by TLC. Also, completion of the reaction is indicated by cessation of CO_2 evolution. Cyclodextrins **6**−**8** were purified by size-exclusion chromatography and product **9** was purified by crystallisation.



Scheme 1. Synthesis and molecular structures of cyclodextrins **1**−**11**; i: RSH, *t*BuOK, DMF, 80 °C, 4 days; ii: K_2CO_3, ethylene carbonate, tetra-*N*-methylurea, 150 °C, 4 h; iii: NBS or NIS, PPh_3, DMF, 70−80 °C, 4 h

New compounds were characterised by microanalysis, electrospray mass spectrometry and NMR spectroscopy. The positive-ion-mode electrospray mass spectrum of **8** (Figure 1) shows two groups of signals for singly charged and doubly charged compounds. The peaks for the singly charged compounds are separated by 44 mass units (which corresponds to the molecular mass of one ethylene glycol repeating unit) indicating a variable degree of substitution. The *m*/*z* ratios in the spectrum of **8** show that **4** has been substituted with 9 to 14 ethylene glycol units. The most abundant species has a *m*/*z* ratio of 3023, which is **4** with a degree of substitution of 13, plus one sodium ion. Correspondingly, the peaks for the doubly charged compounds are separated by 22 mass units, and the most abundant species has a *m*/*z* ratio of 1500, which is **4** with a degree of substitution of 12, plus two sodium ions. This conclusion was confirmed by microanalysis and by integration of the ^{1}H NMR spectrum. Comparable results were obtained for **9** (with a degree of substitution of 8−12 per cyclodextrin), while a significantly higher degree of substitution was observed for **6** (12−19 units per cyclodextrin) and for **7** (16−22 units per cyclodextrin).

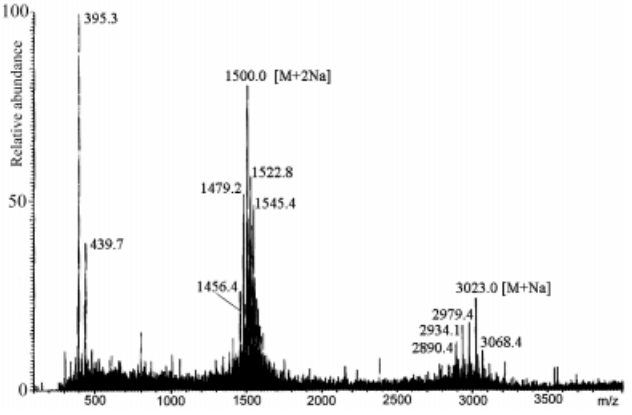


Figure 1. Positive-ion-mode electrospray mass spectrum of cyclodextrin **8**

The ^{1}H NMR and ^{13}C NMR spectra of oligo(ethylene glycol) conjugates **6**−**9** were recorded in $CDCl_3$ at ambient temperature and were assigned by comparison with the corresponding spectra of precursors **2**−**5**. The assignment was assisted by COSY, DEPT and HSQC spectra. The ^{1}H, ^{13}C and HSQC spectrum of **7** is shown in Figure 2. It is evident from significant line broadening of critical signals such as the anomeric proton in the ^{1}H NMR spectrum (Figure 2A) and both C1 and C4 in the ^{13}C NMR spectrum (Figure 2B)

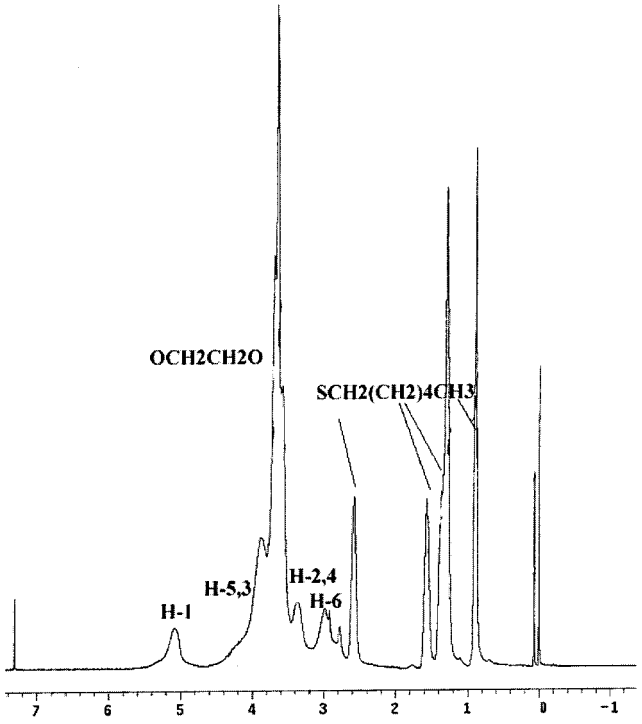


Figure 2A. ^{1}H NMR spectrum of cyclodextrin **7**

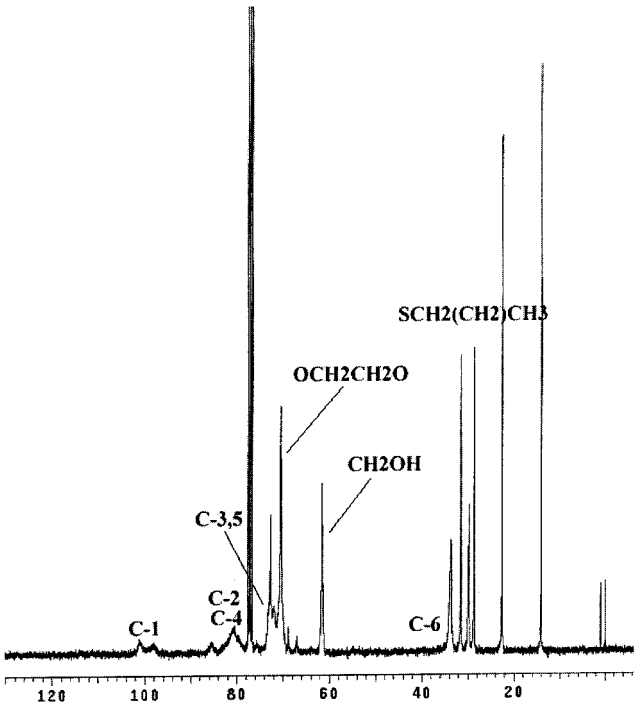


Figure 2B. ^{13}C NMR spectrum of cyclodextrin **7**

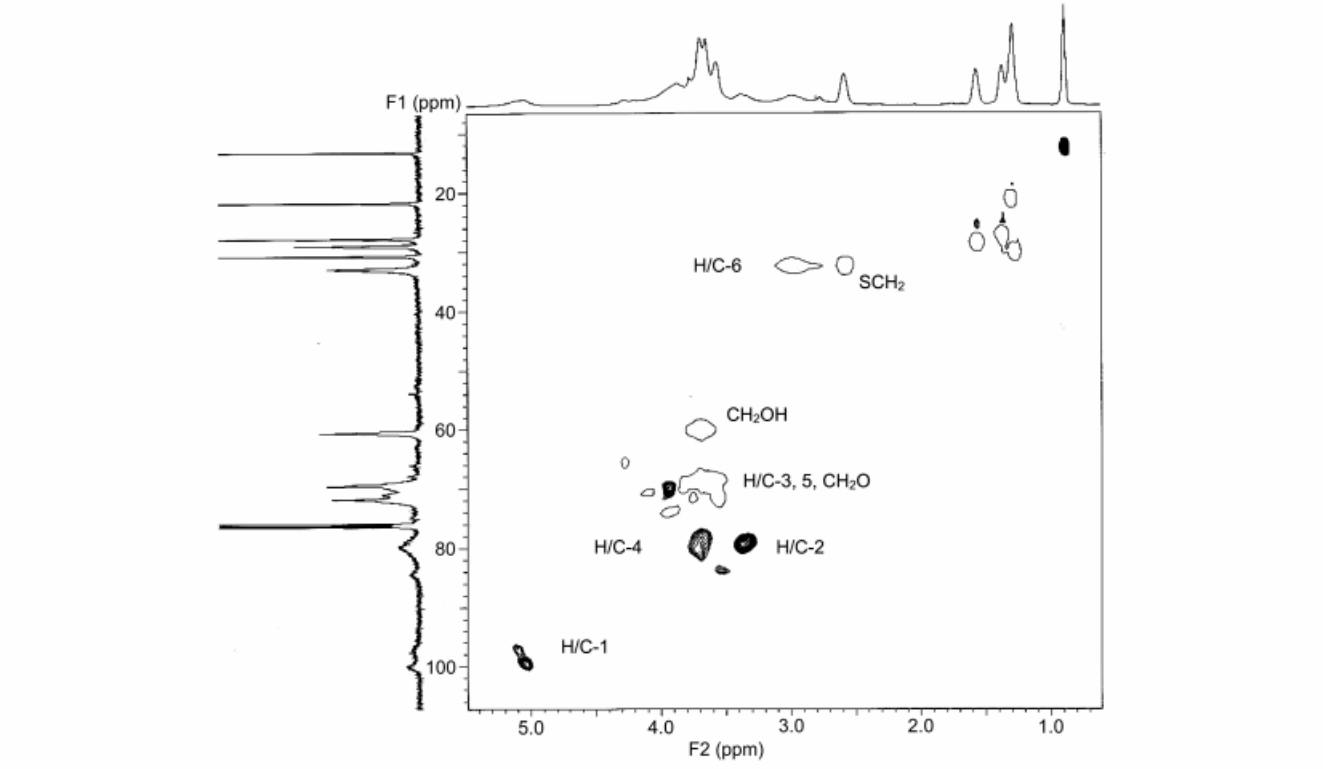
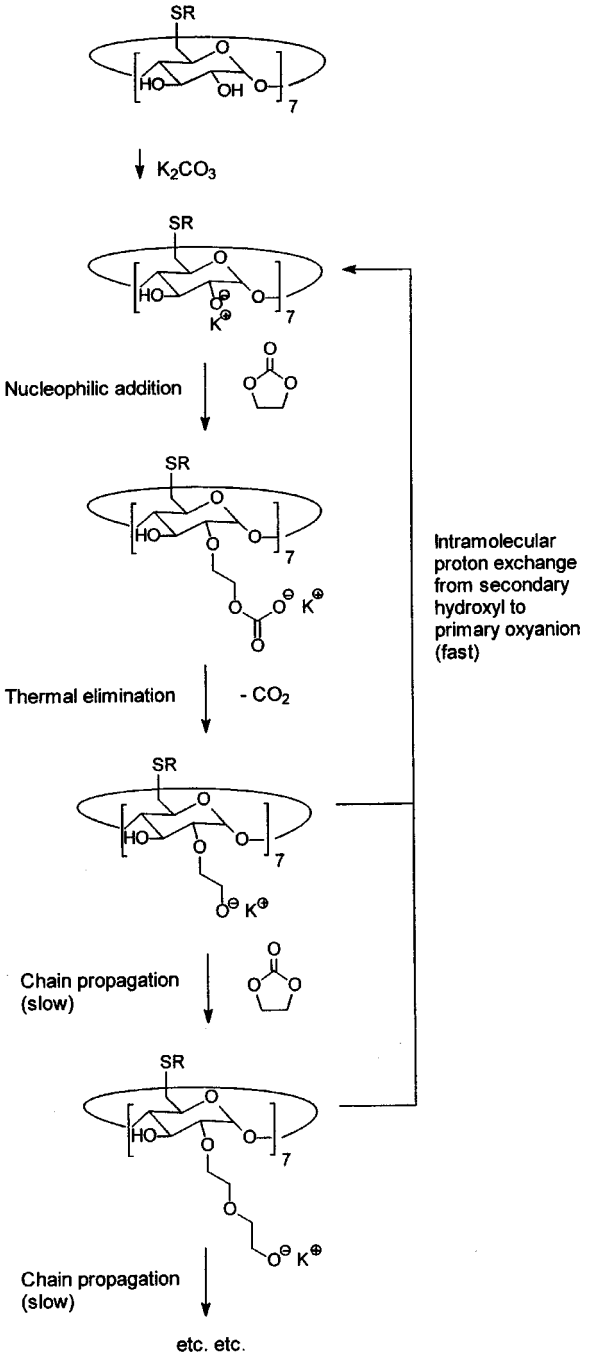


Figure 2C. HSQC NMR spectrum of cyclodextrin **7**

that the cyclodextrin molecules **6**−**9** have reduced symmetry as a result of the introduction of ethylene glycol substituents. The ^{13}C NMR spectrum shows two populations of C1 at δ = 101 and 98, and of C4 at δ = 84 and 81. Possibly, this is the result of rotational distortion of the symmetry of the cyclodextrin molecule due to substitution at C6 and C2.[15] Furthermore, we attribute a certain degree of line broadening to anisotropy as a result of the formation of inverted micellar aggregates of **6**−**9** in chloroform (compare results for **2**−**5**).[5b] The ethylene glycol substituents appear in the δ = 3.3−4.0 region of the ^1H NMR spectrum. In the ^{13}C NMR spectrum, signals corresponding to the ether carbons in the ethylene glycol substituents are observed near δ = 72, and the terminal alcohol carbons are observed near δ = 61.[9,10] The HSQC spectrum of **7** (Figure 2C) shows correlation between the resonance peaks of H2 and C2, which is shifted downfield from δ = 73 in precursor **3** to δ = 81 in **7** and confirms the formation of a product substituted at C2.[16]

In summary, on the basis of mass spectrometry, NMR spectroscopy, and microanalysis, we suggest the molecular formulas of Scheme 1 for products **6**−**9**, which are polydisperse materials with an average of about two units of ethylene glycol per glucose. The NMR chemical shifts of H2 and C2 indicate that the substitution occurs principally at OH2, and not at OH3, of cyclodextrins **2**−**5**. Thus, we propose the reaction mechanism of Scheme 2, consisting of: (1) deprotonation of the most acidic protons (of OH2) by the weak base potassium carbonate; (2) attack by the most accessible cyclodextrin oxyanion (of OH2) at the ethylene carbonate ring; (3) ethylene carbonate ring opening and thermal elimination of CO_2; (4) intramolecular proton exchange between the terminal primary oxyanion and a hydroxyl at an adjacent C2. Substitution does not occur at OH3 because of steric hindrance upon substitution at OH2. A certain degree of oligomerisation by substitution at the terminal hydroxyl of the initial hydroxyethyl substituents occurs, but extensive polymerisation does not occur due to the low acidity of this proton. In support of this reaction mechanism, it was observed that an appreciable amount of oligo(ethylene glycol-*co*-ethylene carbonate) instead of oligo(ethylene glycol) was grafted to the cyclodextrin when the synthesis is carried out on a larger scale (3 g of cyclodextrin). We propose that this minor product results from nucleophilic attack of a grafted ethylene carbonate (Scheme 2) at a second molecule of ethylene carbonate prior to elimination of CO_2 from the grafted carbonate. The grafted oligo(ethylene carbonate) is detected in the ^1H NMR at δ = 4.25 and in the ^{13}C NMR at δ = 156, and it is readily removed by treatment with sodium methoxide in methanol.



Scheme 2. Mechanism of grafting of oligo(ethylene glycol) to cyclodextrins **2**−**5** by ethylene carbonate

We note that the analysis presented above gives a structure which differs from that proposed for **8** and **9** in our first report on these molecules: initially, we assumed that grafting of ethylene glycol would occur at OH3 as well as OH2.[11]

The synthesis of halo derivatives **10** and **11** was carried out according to the procedure reported for the preparation of per(6-deoxy-6-halo) cyclodextrins.[14,17] Product **10** is more soluble in methanol than **1**. However, upon treatment of the reaction mixture with sodium methoxide in methanol and water (in order to destroy excess bromination reagent), **10** precipitated and was purified by chromatography. The iodo derivative **11** did not precipitate in this way and was

obtained by pouring the reaction mixture into ethanol and water, followed by chromatography. Compounds **10** and **11** were dried under vacuum at room temperature — not at elevated temperature — to avoid formation of resinous, completely desolvated solids, which are extremely difficult to dissolve even in DMSO.

The ^{1}H NMR spectra of **10** and **11** in $CDCl_3$ at ambient temperature display sharper peaks than the spectrum of **7**, particularly in the region of the ethylene glycol resonances. We suggest that whereas the oligo(ethylene glycol) conjugates may form inverted micellar aggregates in $CDCl_3$, resulting in anisotropy and line broadening, the less polar derivatives **10** and **11** do not aggregate. The ^{13}C NMR spectrum of **10** in $CDCl_3$ shows the disappearance of the peak for terminal alcohol carbons at $\delta = 61$, and the signal for terminal bromide carbons at $\delta = 29.8$. The ^{13}C NMR spectrum of **11** in $CDCl_3$ shows disappearance of the peak for terminal alcohol carbons at $\delta = 61$, and the signal for terminal iodide carbons at $\delta = 3.0$. Assignment was assisted by DEPT and HSQC spectra. Microanalysis confirms the introduction of exactly seven bromine atoms per cyclodextrin for **10** and seven iodine atoms for **11**, and, in retrospect, supports the molecular formulas of the heptakis[2-oligo-(ethylene glycol)] conjugates shown in Scheme 1.

Conclusion

A series of novel conjugates of oligo(ethylene glycol) and (6-alkylthio-6-deoxy)-β-cyclodextrins was synthesised by grafting and characterised by NMR spectroscopy and mass spectrometry. The reaction of (6-alkylthio-6-deoxy)-β-cyclodextrins with ethylene carbonate under mildly alkaline conditions results in selective substitution at the C2 position, with a degree of substitution of 8−22 ethylene glycol units per cyclodextrin. In addition, the ω-bromo and ω-iodo-derivatives of heptakis[6-deoxy-6-hexylthio-*2*-oligo-(ethylene glycol)]-β-cyclodextrin have been prepared. The introduction of seven halogen atoms per cyclodextrin gives strong evidence for the grafting of oligo(ethylene glycol) to each of the seven glucose units in the cyclodextrin ring.

Experimental Section

General Remarks: β-Cyclodextrin (Wacker) was crystallised from distilled water and dried under vacuum (0.1 mm, 80 °C) for 4 h. Anhydrous *N*,*N*-dimethylformamide (DMF) was taken under N_2 from sealed bottles. Triphenylphosphane was crystallised from methanol and dried overnight under vacuum (0.1 mm, 55 °C). TLC was carried out on Merck Kieselgel 60 analytical plates with the specified solvent system. Cyclodextrin derivatives were detected with UV light or by dipping in 5% sulfuric acid/ethanol and heating. Lipophilic Sephadex LH-20−100 (25−100 μm) from Sigma and Silica Gel (Kieselgel 60, 0.040−0.063 mm) from Merck were used for chromatography. NMR analysis was performed on 300 and 500 MHz Varian Unity spectrometers in $CDCl_3$ and in [D_6]DMSO solutions. Electrospray mass spectrometry was performed at the Mass Spectrometry Laboratory, University of Edinburgh, UK and microanalysis was carried out at the analytical services unit, University College Dublin.

General Procedure for the Synthesis of the 2-Oligo(ethylene glycol) Conjugates (6−9): Heptakis(6-alkylthio-6-deoxy)-β-cyclodextrin (ca. 1 mmol), K_2CO_3 (10% by weight relative to cyclodextrin) and ethylene carbonate (50 molar equiv.) were dissolved in 10 mL of tetra-*N*-methylurea. The mixture was stirred at 150 °C under N_2 for 4 h, after which time TLC analysis ($CHCl_3/CH_3OH/H_2O$ = 50:10:1) indicated complete conversion of compounds **2−5** (R_f = 0) into **6−9** ($R_f = 0.55$), respectively. Furthermore, after this period CO_2 evolution had ceased. The solvent was removed at 100 °C under reduced pressure. The crude product was dissolved in the minimum quantity of methanol and was purified by size-exclusion chromatography with methanol as eluent. Alternatively, the product was purified by crystallisation as indicated. When the reaction was carried out on a larger scale, the crude product was treated with 0.1 M sodium methoxide in methanol for 24 h prior to purification (see text).

Heptakis[6-deoxy-6-ethylthio-2-oligo(ethylene glycol)]-β-cyclodextrin (6): Product **6** (79% yield) was isolated as a viscous oil which solidified upon standing. It was further purified by crystallisation from diethyl ether containing 10% methanol at 0 °C. − ^{1}H NMR ($CDCl_3$): $\delta = 1.27$ (t, 21 H, CH_3), 1.79 (br, OH), 2.64 (m, 14 H, SCH_2), 3.05 (m, 14 H, H6), 3.3−4.0 (m, ca. 84 H, H2−5 and OCH_2CH_2O), 5.08 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): $\delta = 14.9$ (CH_3), 27.4 (CH_2S), 33.3 (C6), 61.5 (CH_2OH), 71.0−72.0 (C3, C5, CH_2O), 80.5 (C2, C4), 101.4 (C1). − $(C_{12}H_{22}O_6S)_7$: calcd. C 48.98, H 7.48, S 10.88; found C 48.41, H 7.18, S 9.60. − ESI-MS: *m*/*z* (%) = 1996 (64) [M^+_{12EO} − Na], 2042 (68) [M^+_{13EO} − Na], 2084 (100) [M^+_{14EO} − Na], 2129 (100) [M^+_{15EO} − Na], 2173 (91) [M^+_{16EO} − Na], 2216 (85) [M^+_{17EO} − Na], 2260 (61) [M^+_{18EO} − Na], 2303 (47) [M^+_{19EO} − Na].

Heptakis[6-deoxy-6-hexylthio-2-oligo(ethylene glycol)]-β-cyclodextrin (7): Product **7** was isolated in 74% yield as a viscous yellow oil which solidified upon drying. − ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, 21 H, CH_3), 1.30 (br s, 42 H, CH_2), 1.57 (m, 14 H, CH_2), 2.60 (m, 14 H, SCH_2), 2.95 (m, 14 H, H6), 3.35 (m, 7 H, H4), 3.70 (m, 21 H, H2 and CH_2O), 3.5−4.0 (m, ca. 56 H, H3, H5, and OCH_2-CH_2O), 5.05 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): $\delta = 14.1$ (CH_3), 22.6 (CH_2), 28.7 (CH_2), 29.8 (CH_2), 31.6 (CH_2), 33.7 (CH_2S), 33.7 (C6), 61.6 (CH_2OH), 71.0−72.5 (C3, C5, CH_2O), 80.8 (C2, C4), 101.0 (C1). − $(C_{16}H_{30}O_6S)_7$: calcd. C 54.86, H 8.57, S 9.14; found C 54.28, H 8.85, S 8.88. − ESI-MS: *m*/*z* (%) = 2543 (45) [M^-_{16EO}], 2587 (45) [M^-_{17EO}], 2631 (65) [M^-_{18EO}], 2675 (87) [M^-_{19EO}], 2719 (95) [M^-_{20EO}], 2763 (100) [M^-_{21EO}], 2807 (85) [M^-_{22EO}].

Heptakis[6-deoxy-6-dodecylthio-2-oligo(ethylene glycol)]-β-cyclodextrin (8): Product **8** was isolated in 89% yield as a wax. − ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, 21 H, CH_3), 1.27 (br s, 126 H, CH_2), 1.60 (m, 14 H, CH_2), 2.60 (m, 14 H, SCH_2), 3.00 (m, 14 H, H6), 3.3−4.0 (m, ca. 84 H, H2−5 and OCH_2CH_2O), 5.05 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (CH_3), 22.4 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 29.5 [$(CH_2)_n$], 31.7 (CH_2), 33.4 (CH_2S), 33.4 (C6), 61.2 (CH_2OH), 71.0−72.0 (C3, C5, CH_2O), 81.0 (C2, C4), 100.7 (C1). − $(C_{22}H_{42}O_6S)_7$: calcd. C 60.83, H 9.68, S 7.37; found C 60.12, H

9.38, S 7.62. − ESI-MS: *m/z* (%) = 2890 (50) [M^+_{10EO} − Na], 2934 (69) [M^+_{11EO} − Na], 2979 (74) [M^+_{12EO} − Na], 3023 (100) [M^+_{13EO} − Na], 3067 (42) [M^+_{14EO} − Na].

Heptakis[6-deoxy-6-hexadecylthio-2-oligo(ethylene glycol)]-β-cyclodextrin (9): The crude product was purified by crystallisation from 25 mL of methanol containing 20% acetone to give product **9** (71%) as a powder. − ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 21 H, CH_3), 1.30 (br s, 182 H, CH_2), 1.57 (m, 14 H, CH_2), 2.00 (br, OH), 2.60 (m, 14 H, SCH_2), 3.00 (m, 14 H, H6), 3.3−4.0 (m, ca. 84 H, H2−5 and OCH_2CH_2O), 5.05 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.8 [$(CH_2)_n$], 32.0 (CH_2), 33.7 (CH_2S), 34.1 (C6), 61.2 (CH_2OH), 71.0−72.5 (C3, C5, CH_2O), 81.2 (C2, C4), 100.9 (C1). − $(C_{24}H_{50}O_6S)_7$: calcd. C 63.67, H 10.20, S 6.53; found C 62.90, H 9.47, S 6.77. − ESI-MS: *m/z* (%) = 3196 (43) [M^+_{8EO} − Na], 3239 (100) [M^+_{9EO} − Na], 3284 (94) [M^+_{10EO} − Na], 3327 (72) [M^+_{11EO} − Na], 3372 (40) [M^+_{12EO} − Na].

Heptakis[2-ω-bromo-6-deoxy-6-hexylthio-oligo(ethylene glycol)]-β-cyclodextrin (10): Vacuum-dried **7** (400 mg, 0.16 mmol) in anhydrous DMF (6 mL) was stirred for 15 min. at room temperature with molecular sieves, filtered and diluted with anhydrous DMF (12 mL). PPh_3 (840 mg, 3.2 mmol) was added and the solution was heated at 80 °C. After addition of *N*-bromosuccinimide (NBS; 570 mg, 3.2 mmol), the reaction mixture was stirred for 3−4 h at 80 °C. Upon completion of the reaction (TLC, $CHCl_3/CH_3OH$ = 8:1, R_f = 0.85) the pH was adjusted to 9−10 with 3 M sodium methoxide in methanol and the mixture was stirred for 30 min., then poured into ice-water (100 mL) resulting in the formation of a precipitate which was filtered off and washed with water. TLC ($CHCl_3/CH_3OH$ 8:1) showed more than one spot and **10** was purified using silica gel chromatography (column 15×190 mm). Elution with chloroform removed undesired side-products and excess Ph_3PO, and **10** was obtained by elution with 5% methanol in $CHCl_3$. Under these conditions, **10** was isolated as an oil (150 mg, yield 32%, R_f = 0.85 in $CHCl_3/CH_3OH$ = 8:1). − ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 21 H, CH_3), 1.30 (br s, 42 H, CH_2), 1.57 (m, 14 H, CH_2), 2.60 (m, 14 H, SCH_2), 2.95 (m, 14 H, H6), 3.40 (m, 14 H, H2, H4), 3.55 (m, 14 H, CH_2Br), 3.4−4.0 (m, ca. 56 H, H3, H5, and OCH_2), 5.05 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 22.7 (CH_2), 28.8 (CH_2), 29.8 (CH_2Br) 31.6 (CH_2), 33.8 (CH_2S), 33.8 (C6), 71.0−72.0 (C3, C5, CH_2O), 80.8 (C2, C4), 101.0 (C1). − $(C_{16}H_{29}O_5SBr)_7$: calcd. C 46.50, H 7.0, S 7.73, Br 19.37; found C 46.69, H 6.66, S 6.60, Br 20.31.

Heptakis[6-deoxy-6-hexylthio-2-ω-iodo-oligo(ethylene glycol)]-β-cyclodextrin (11): Product **11** was obtained from 300 mg of **7** (0.112 mmol), 440 mg of Ph_3P (1.68 mmol) and 378 mg (1.68 mmol) of *N*-iodosuccinimide (NIS) as described for the synthesis of **10**. Upon completion of the reaction (after 4 h, TLC R_f = 0.85 in $CHCl_3/CH_3OH$ = 8:1), the product was isolated by precipitation in water/ethanol (1:1) to give a creamy precipitate, which was washed repeatedly with hexane to remove remaining Ph_3PO. The oily residue was taken up in chloroform and **11** was isolated in 46% yield by silica gel chromatography (column 15 × 190 mm, elution with 5% methanol in $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 21 H, CH_3), 1.30 (br s, 42 H, CH_2), 1.57 (m, 14 H, CH_2), 2.60 (m, 14 H, SCH_2), 2.95 (m, 14 H, H6), 3.2−3.5 (m, ca 21 H, H4, CH_2I), 3.5−4.2 (m, ca. 63 H, H2, H3, H5, OCH_2), 5.07 (br, 7 H, H1). − ^{13}C NMR ($CDCl_3$): δ = 3.0 (CH_2I), 14.2 (CH_3), 22.7 (CH_2), 28.8 (CH_2), 29.8 (CH_2) 31.6 (CH_2), 33.8 (CH_2S), 33.8 (C6), 71.0−72.0 (C3, C5, CH_2O), 80.8 (C2, C4), 101.0 (C1). − $(C_{16}H_{29}O_5SI)_7$: calcd. C 41.71, H 6.34, S 6.96, I 27.6; found C 40.14, H 5.67, S 6.45, I 28.8.

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