Synthesis and Spectroscopic Characterisation of Lipophilic Octylated α-, β- and γ-Cyclodextrin Derivatives

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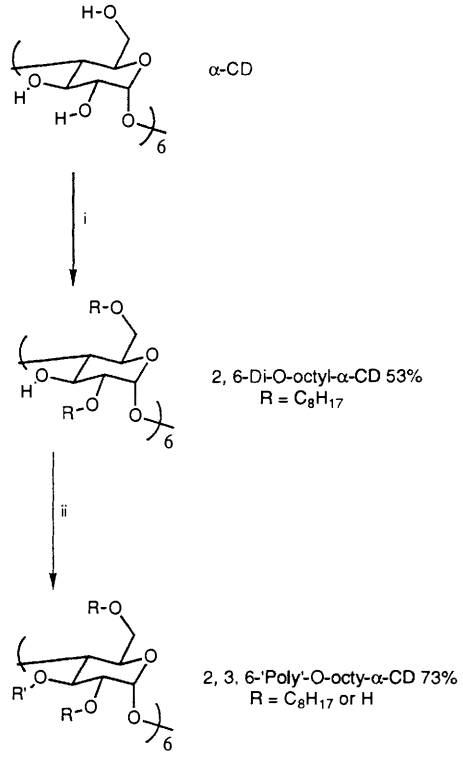
The octylation of α-, β- and γ-cyclodextrin may be undertaken in two steps: reaction with octyl bromide (NaOH–Me_2SO) gives relatively monodisperse 2,6-di-*O*-alkylated material and further reaction (NaH–THF) with octyl bromide yields incompletely octylated products. Complete alkylation may be achieved with KH–18-crown-6–THF. Quantification of the degree of octylation was achieved directly by electrospray mass spectrometry and ^{13}C NMR analysis of methylated analogues and also by GC–MS analysis of reductively depolymerised samples. Assignment of the ^{1}H and ^{13}C NMR spectra of selected derivatives has been carried out.

Cyclodextrins and their simple derivatives are attractive and versatile receptors for the chemoselective and enantioselective complexation of certain cations and neutral molecules.[1,2] Recent work with per-*O*-pentylated derivatives has been focused on their use in chiral stationary phases for chiral GC and HPLC analyses.[3,4] A GC column incorporating per-*O*-pentyl-β-cyclodextrin, for example, was found effectively to separate the enantiomers of acyclic, monocyclic and bicyclic alkenes while 3-*O*-acetyl-2,6-di-*O*-pentyl-β-cyclodextrin effected the separation of more polar chiral compounds such as β-amino acids and chiral α- and β-arylamines.[5]

Such lipophilic cyclodextrins were therefore considered to be ideal candidates as ionophores in a potentiometric ion-selective electrode, for the chemoselective and enantioselective inclusion of chiral arylammonium ions.[6,7] The ionophore for such an application needs to be sufficiently lipophilic so as not to leach out into an aqueous analyte, should also be charge neutral and stable over a wide pH range and ideally it should respond selectively to the target ion with a Nernstian response down to at least micromolar concentrations with a free energy for exchange (free/bound) of less than *ca.* 65 kJ mol^{-1} in order to allow good response times. Accordingly per-octyl-α-, β- and γ-cyclodextrins were sought. The alkylation reaction used followed the method of Ciucanu,[8] developed for the permethylation of monosaccharides, involving reaction with MeI–NaOH in dimethyl sulfoxide (DMSO). This method has been shown to lead to formation of 2,6-di-*O*-alkyl cyclodextrin derivatives,[9] with the more hindered (and less reactive) 3-hydroxy group left intact under these conditions.



Scheme 1 *Reagents and conditions:* i, NaOH–DMSO, $C_8H_{17}Br$, 20 °C; ii, NaH–THF, $C_8H_{17}Br$, 60 °C, 96 h

Results and Discussion

Formation of the 2,6-di-*O*-octyl-α-, β- and γ-cyclodextrins was achieved using a 3:3:1 ratio of NaOH–octyl bromide–each cyclodextrin hydroxy group, at a concentration of approximately 1 g of cyclodextrin per 20 cm^3 of DMSO. Under these conditions reasonable yields of the dialkylated materials **1, 5** and **8** were achieved (Scheme 1), although the γ-cyclodextrin consistently gave lower yields. Purification by silica-gel chromatography afforded homogeneous (by TLC analysis) materials. In the case of 2,6-di-*O*-octyl-β-cyclodextrin, field desorption mass spectral analysis revealed that the isolated product **5** was relatively monodisperse, with 85% of the product containing 14 octyl groups (*m/z* 2760, M^+) and with 5% of 13-octylated (2594) and 10% of 15-octylated (2818) material also identified.‡ In order further to alkylate these 2,6-dioctylated derivatives more forcing conditions were required to overcome the lack of reactivity of the 3-hydroxy group which may be related to intramolecular OH(3)···O(2) hydrogen bonding.

Using NaH as a base in tetrahydrofuran (THF) (Scheme 1), reaction of **1, 5** and **8** gave compounds **2, 6a** and **9**, for which ^{1}H and ^{13}C analyses confirmed that further reaction had occurred. However the lack of time-averaged C_n symmetry (n = 6, 7, 8) suggested by the NMR spectra of **2, 6** and **9** and the presence of a clear OH stretch in the infrared spectrum, indicated that

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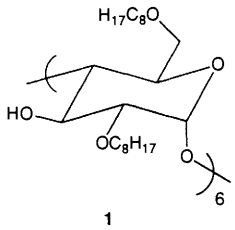
‡ Mass spectral compositions are based on relative peak intensities and assume that in this case the 13-, 14- and 15-octylated compounds have similar ionisation potentials. ^{1}H and ^{13}C NMR analysis did not allow a clear distinction to be made of the relative amounts present of these compounds.



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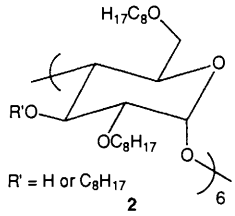
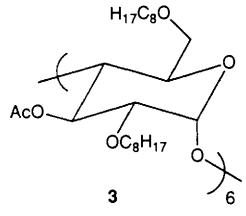


R' = H or C_8H_{17}

2



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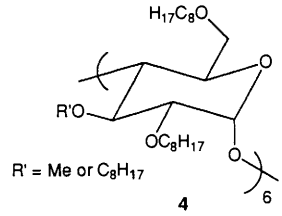

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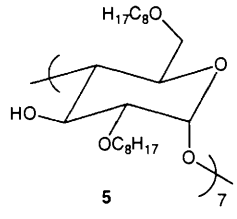

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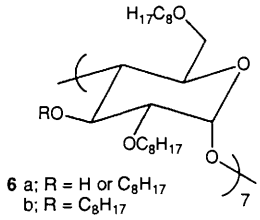
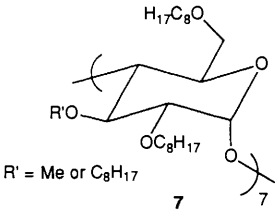


6 a; R = H or C_8H_{17}
b; R = C_8H_{17}



R' = Me or C_8H_{17}

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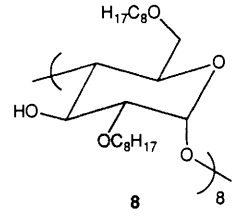

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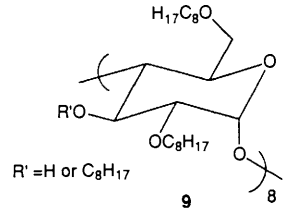

R' =H or C_8H_{17}

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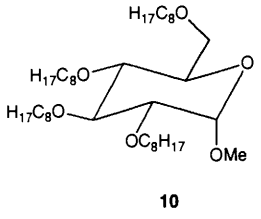

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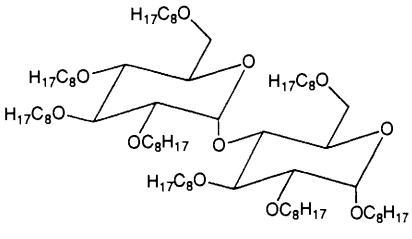

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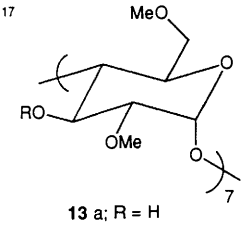
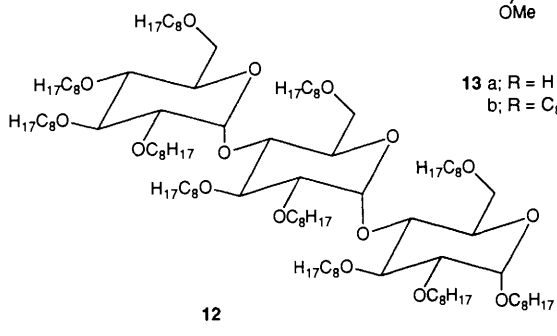


13 a; R = H
b; R = C_8H_{17}



12

incomplete alkylation had occurred. (Similarly, attempted alkylation of 2,6-di-*O*-methyl-β-cyclodextrin under the same reaction conditions yielded only partially octylated product, with a strong OH stretch present in the infrared spectrum.) Under these reaction conditions, residual OH groups are present in the 3-position. It should be noted that peralkylation (alkyl = C_{12} and C_{18}) of cyclodextrins has been reported[10] to occur using different conditions (PhMe, RBr, KOBu^t under phase-transfer catalysis) although no supporting evidence for complete reaction has been presented.

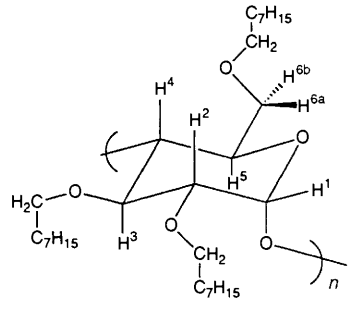
When 2,6-di-*O*-octyl-β-cyclodextrin, **5**, was reacted with 1-bromooctane in the presence of KOBu^t and Aliquat 336 in toluene at 60 °C, no fully alkylated product could be isolated, even with extended reaction times (14 days). Complete octylation to form **6b** was successful, however, using potassium hydride in the presence of 18-crown-6 in boiling THF. The isolated product lacked an OH stretch in the IR spectrum and the ^{13}C and ^1H NMR spectra were consistent with time-averaged C_7-symmetry (see below for spectral assignments). Moreover 2,6-di-*O*-methyl-β-cyclodextrin could also be converted into the 2,6-di-*O*-methyl-3-*O*-octyl derivative **13b** under these conditions.

Complete transformation of the 3-hydroxy group in these dioctylated derivatives may also be achieved using different electrophiles. Reaction of **1** with acetic anhydride in the presence of triethylamine yielded **3**, with no OH-stretch present in the infrared spectrum. In general, residual hydroxy groups in *all* of the derivatives studied could be capped with methyls under relatively forcing conditions (NaH–THF–MeI–reflux), allowing for example, the preparation of **4** from **2** and of **7** from **6**, in 87% yield.

For purposes of comparison, the sugars methyl α-D-glucose, maltose and maltotriose were octylated in a similar manner. Methyl per-*O*-octyl-α-D-glucopyranoside, **10**, was prepared in one step using fused NaOH–DMSO–$C_8H_{17}Br$, while the peroctylated di- and tri-saccharides **11** and **12**, required the two-step alkylation procedure for complete alkylation to occur.

Characterisation of Octylated Cyclodextrins.—Several methods of analysis were used in order to assess the extent of derivatisation and the homogeneity of the products. In native cyclodextrins and symmetrically substituted derivatives (where all the glucopyranose sub-units have the same substitution pattern at O(2), O(3) and O(6) *and* each ring adopts a chair conformation), the glucopyranose sub-units are magnetically equivalent because of the presence of an effective C_n (n = 6, 7, 8 for α-, β- and γ-cyclodextrin, respectively) axis in solution and a single set of NMR resonances is observed.[11]

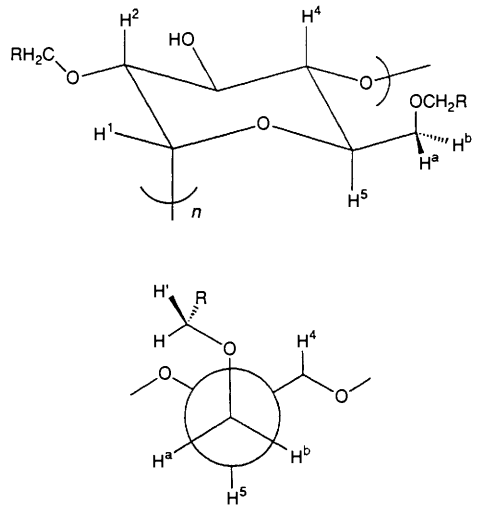
In the ^1H NMR spectrum of 2,6-di-*O*-octyl-α-cyclodextrin the acetal hydrogen H^1 (see the proton-numbering scheme) appeared as a single resonance at 4.90 ppm and C^1 also resonated as a singlet (at 101.4 ppm) in the ^{13}C NMR spectrum. Using this as a starting point, the remaining ring CHO and



Proton numbering scheme

CH_2O resonances were assigned from the ^1H–^1H COSY spectrum. The well resolved multiplets at 3.35 and 4.07 ppm (due to H^2 and H^3, respectively) are distinct and indicative of a symmetrically substituted cyclodextrin with near C_6 symmetry. The chemical shift non-equivalence of the diastereotopic methylenes. H^{6a} and H^{6b} is modest (0.04 ppm) and was confirmed by coupling to H^5 and from the ^{13}C–^1H HETCOR spectrum which pinpointed the relationship of each to C^6. The coupling constant $J_{H^1H^2}$ was observed to be 3.6 Hz, a similar value to those noted for related methylated α-cyclodextrins.[12]

The diastereotopic methylene CH_2O resonances of the octyl chains of **1** (attached to the oxygens at C^2 and C^6) were shift non-equivalent in the ^1H NMR spectrum (0.3 ppm in one case) which hinted that there might be a preferential orientation of the octyl chains with respect to the cyclodextrin cavity. Indeed it has been reported that in 2,6-di-*O*-pentyl-α-cyclodextrin,[13] the pentyl chain attached to the primary ether oxygen (in the 6-position) was preferentially oriented across the cavity with a *gauche–trans* conformation (illustrated below). Both '*gauche–trans*' and '*gauche–gauche*' conformations are evident in the crystal structure of per-*O*-methyl-β-cyclodextrin.[14]



gauche–trans conformation at C_6 of a glucopyranosyl unit

The ^1H and ^{13}C NMR spectra of the 'poly'-octylated* α-cyclodextrin derivative, **2**, indicated a sharp increase in complexity, compared with **1**, indicative of a loss of C_6-symmetry and suggestive of incomplete 3-*O*-alkylation as defined by IR analysis, and subsequent mass spectral studies. No attempt was made fully to assign these spectra as they were representative of a material that is composed of homologous octylated compounds and their constitutional isomers. A summary of partial ^{13}C NMR assignments of the α-cyclodextrin derivatives, and the β- and γ-analogues (Tables 1, 2 and 3) show how the C^2 and C^6 ring carbons show the strongest changes in chemical shift induced by *O*-octylation, in each case the resonance moving to higher frequency.

The ^1H NMR spectrum of 2,3,6-tri-*O*-octyl-β-cyclodextrin, **6b**, showed a well resolved doublet at 5.20 ppm (H^1), and a doublet of doublets at 3.20 (H^2) and 3.78 (H^4) ppm, respectively (for H^4 the doublets overlap to give an apparent triplet). Assignments were made with the aid of a ^1H–^1H COSY spectrum (Fig. 1), and were confirmed by analysis of the ^1H–^{13}C HETCOR spectrum.

* Multiplying prefixes enclosed within quotation marks indicate incompletely and irregularly alkylated products.

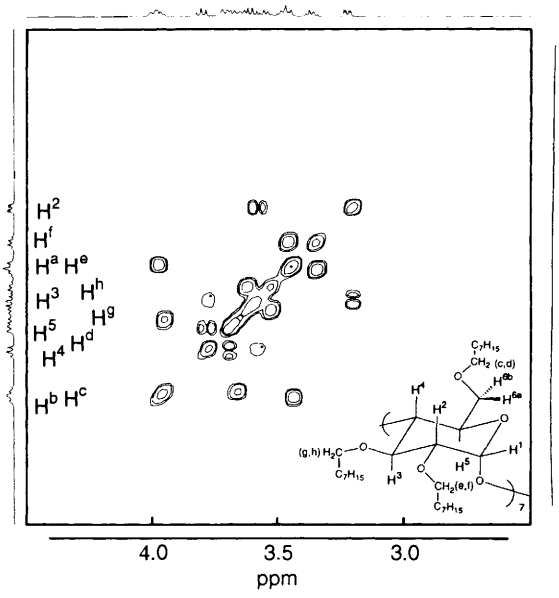


Fig. 1 Partial proton–proton COSY NMR spectrum of 'tri'-*O*-octyl-β-cyclodextrin **6b** ($CDCl_3$; 500 MHz; 298 K)

The 'poly'-*O*-octyl α- and β-cyclodextrins in which residual OH groups had been methylated, **4** and **7**, were examined in detail by ^{13}C NMR spectroscopy in order to determine precisely the degree of methylation, and hence the number of octyl groups in them and their precursors **1** and **5**. The methoxy carbon resonance at 61.8 ppm was well resolved at 100 MHz and was integrated against other resonances (*e.g.*, octyl CH_2O, CH_2CH_2O and ring OCHO) to measure the number of methyls present.

This analysis was carried out in the presence of 0.5 mol% of the paramagnetic relaxation agent $Cr(acac)_3$ with a ten second pulse delay using gated ^1H-decoupling so that nuclear Overhauser effects on peak intensities were eliminated. With **4**, 2.5 methyl groups per α-cyclodextrin were measured and with **7**, 3.7 methyl groups per β-cyclodextrin were found. These values agreed (±0.2) with values estimated from ^1H NMR integrations of the methoxy resonances at *ca.* 3.56 ppm.

The technique of reductive depolymerisation is well known in the analysis of polysaccharides, being a relatively recent development of the classical methylation analysis.[15] It results in the formation of reduced monosaccharides which are amenable to direct methods of analysis, *e.g.*, by GC–MS. Using a modification[16] of the original method,[17] the alkylated cyclodextrins were treated with Et_3SiH in the presence of BF_3 followed by methanolysis. Under these conditions selective cleavage at the glycosidic carbon occurs *via* the intermediacy (and subsequent reduction) of cyclic oxonium ions (Scheme 2). This yields the corresponding alkylated 1,5-anhydro-D-glucitols which after acetylation may be analysed by GC–MS, permitting separation and quantification of the variously alkylated compounds. The percentage of the di- and tri-octylated compounds determined in this way allows an estimate to be made of the mean number of octyl groups in the parent cyclodextrin (Table 4). All of the cyclodextrin derivatives prepared, except **6b** and **13b** constitute several homologues with different degrees of octylation. Using NaH as a base (in the absence of 18-crown-6), complete alkylation of the 3-hydroxy group does not occur. Given that per-*O*-pentylation does occur completely under the same conditions,[16] it is possible that one of the octyl groups already linked to O(2) or O(6) (or from another molecule of octyl bromide) is included *inside* the cyclodextrin core in THF,

Table 1 Selected ^{13}C resonances of α-cyclodextrin derivatives (100 MHz; $CDCl_3$; 25 °C)

Derivative	^{13}C Resonance of carbon number						
	1	2	3	4	5	6	CH_2O
α-Cyclodextrin[a]	102.2	72.4	74.1	82.1	72.8	61.1	—
2,6-di-*O*-*octyl*-α-*cyclodextrin*	101.4	79.9	73.7	83.5	70.4	69.3	72.7 71.8
'Poly'-*O*-octyl-α-cyclodextrin	101.7 98*	79.8	73.8	83.3*	70.5	69.8	71.8 72.8 70.9
Methylated[b] 'poly'-*O*-octyl-α-cyclodextrin	99.2*	80.3*	80.5	82.9*	70.7	69.8	71.8 72.7 71.1
3-*O*-Acetyl-2,6-di-*O*-octyl-α-cyclodextrin[c]	100.8	78.6	77.3	80.4	71.3	69.1	71.8 71.5

[a] In D_2O. [b] $\delta_C(OMe) = 61.8$. [c] $\delta_C(C{=}O) = 170.5$. * Indicates that the resonance could not be assigned with absolute certainty because of the complexity of the spectrum and should be taken to be ±0.2 ppm.

Table 2 Selected ^{13}C resonances of β-cyclodextrin derivatives (100 MHz; $CDCl_3$; 25 °C)

Derivative	^{13}C Resonance of carbon number						
	1	2	3	4	5	6	CH_2O
β-Cyclodextrin[a]	102.8	72.9	74.1	82.0	72.9	61.0	—
2,6-Di-*O*-octyl-β-cyclodextrin	101.8	80.3	74.2	82.9	71.1	69.4	72.9 71.8
'Poly'-O-octyl-β-cyclodextrin	101.4* and 99.1*	80.5*	74.1	83.1*	70.9	69.5	71.7 72.9 71.1
Methylated[b] 'poly'-*O*-octyl-β-cyclodextrin	99.2	80.9*	82.3	82.9*	71.0	69.4	71.8 72.8 71.1

[a] In D_2O. [b] $\delta_C(OMe) = 61.8$. * Indicates that the resonance could not be assigned with absolute certainty because of the complexity of the spectrum and should be taken to be ±0.2 ppm.

Table 3 Selected ^{13}C resonances of γ-cyclodextrin derivatives (100 MHz; $CDCl_3$; 25 °C)

Derivative	^{13}C Resonance of carbon number						
	1	2	3	4	5	6	CH_2O
γ-Cyclodextrin	103.1	72.7	74.2	82.0	72.9	61.1	—
2,6-Di-*O*-octyl-γ-cyclodextrin	101.8	80.8	73.3	83.2	70.4	69.1	73.1 71.6
'Poly'-*O*-octyl-γ-cyclodextrin	102.3*	80.1*	74.1	82.1*	70.8	70.3	71.8 72.7 71.2

* Indicates that the resonance could not be assigned with absolute certainty because of the complexity of the spectrum and should be taken to be ±0.2 ppm.

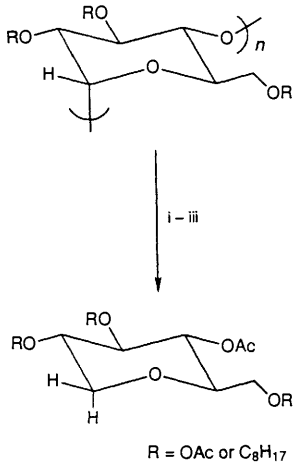
and is aligned such that the approach of another molecule of octyl bromide for the S_N2 reaction at the 3-OH group is inhibited. Certainly it is well known that the stability of the 1:1 complexes of long-chain alkyl derivatives with cyclodextrins increases with alkyl chain length.[1] Of course this effect is likely to be strongly solvent-dependent, and we have demonstrated ourselves that complete octylation is feasible under more forcing reaction conditions (KH–18-crown-6).

Direct mass spectroscopic analysis of the octylated cyclodextrins was studied comparatively using positive ion field desorption (FD), fast atom bombardment (FAB) and electrospray ionisation (ES) modes. The FAB mass spectra obtained with a glycerol matrix were rather weak and irreproducible and although FAB has been used to characterise the parent cyclodextrins[18] and their adducts[19] it was not suited to the analysis of these less polar molecules. The FD spectra gave

Table 4 Reductive depolymerisation of octylated α-, β- and γ-cyclodextrins

Cyclodextrin derivative	% Disubstituted[a]	% Trisubstituted[a]	Mean no. of octyl groups
2,6-Di-*O*-octyl-α-cyclodextrin	88	12	12.7
'Poly'-*O*-octyl-α-cyclodextrin	43	57	15.4
Methylated 'poly'-*O*-octyl-α-cyclodextrin	< 1	58[b]	15.4
2,6-Di-*O*-octyl-β-cyclodextrin	95	5	14.3
'Poly'-*O*-octyl-β-cyclodextrin	51	49	17.4
'Poly'-*O*-octyl-γ-cyclodextrin	45	55	20.4

[a] As % areas from GC–MS. [b] 42% 3-*O*-methylated.



Scheme 2 Reductive depolymerisation of alkylated cyclodextrins. *Reagents:* i, Et_3SiH–BF_3; ii, MeOH; iii, Ac_2O–Et_3N.

better signal-to-noise than the corresponding FAB spectra but the relative peak intensities for derivatives with different degrees of octylation (*e.g.*, 14, 15, 16 and 17 octyl groups with **2**) were somewhat variable between different runs and scans. The best data were obtained using electrospray ionisation. Using isopropyl alcohol solutions of the alkylated cyclodextrins in the presence of a large excess of ammonium acetate, spectra with excellent signal-to-noise and consistent peak intensities were obtained.[20] Representative spectra for 3-*O*-acetyl-2,6-di-*O*-octyl-α-cyclodextrin, **3** (Fig. 2) and for the 'poly'-*O*-octyl α- and β-cyclodextrins **2** and **6** and their 'methyl-capped' derivatives **4** and **7** (Figs. 3 and 4) highlight the good signal-to-noise obtained. Doubly charged ions of composition ($M + 2NH_4^+$) were also produced from each sample at the expected *m*/*z* ratio (*e.g.*, Figs. 2 and 4). The relative peak intensities due to the different octylated species were measured and allowed the mean number of octyl groups per cyclodextrin to be accurately measured (Table 5). In addition, the spectra of the methylated and acetylated derivatives showed clearly that functionalisation of the 3-OH group was complete, as had been indicated by the complete disappearance of the OH-stretch in their infrared spectra.

The agreement between the values obtained by the different NMR, GC–MS and ES–MS methods for the degree of octylation of the cyclodextrin derivatives is very good (Table 6) and is indicative of the accuracy of each independent method.

In summary, the octylation of α-, β- and γ-cyclodextrin with fused NaOH in DMSO gives relatively monodisperse 2,6-di-octylated material. Further reaction (NaH–THF–C_8-bromide) yields incompletely alkylated material with residual hydroxy groups in the 3-position. Using potassium hydride as the base, in the presence of 18-crown-6, complete alkylation of the hindered 3-oxygen may be achieved. These partially octylated materials function as very good ionophores in the enantioselective detection of chiral β-arylamino alcohols,[6] and the completely alkylated compounds work best in the selective detection of onium ions.[21] The presence of residual OH groups in the 3-position is essential for the discriminating behaviour of these ionophores in enantioselective analysis (see the following paper).

Experimental

Gas chromatography was carried out with a Hewlett Packard HP 5890 using an SE-30 capillary column with heating from 100 to 240 °C at 10 °C min^{-1}. Column chromatography on silica was effected using Merck 60 7354 (or 9385 for flash chromatography) and on neutral alumina using Merck alumina treated with ethyl acetate. Field desorption and fast atom bombardment mass spectra were recorded on a VG ZAB-2VSE instrument operating in the positive ionisation mode (matrix *m*-nitrobenzyl alcohol with added trifluoroacetic acid for FAB analyses). Electrospray ionisation mass spectra were recorded by Dr. B. N. Green (Fisons Instruments, Altrincham) with a VG Quattro-BQ operating with an atmospheric pressure electrospray source. Samples were presented as solutions in isopropyl alcohol (typically 35 pmol μl^{-1}) at a rate of 5 μl min^{-1}. Mass scale calibrations employed the ammonium adducts from polypropylene glycols 2000 and 3000 (1 μg μl^{-1}), introduced into the source at 5 μl min^{-1} in 50:50 acetonitrile water containing 1.0 mmol dm^{-3} NH_4OAc. Ammonium acetate (10 mmol dm^{-3}), tetramethylammonium trifluoroacetate (0.2 to 2 mmol dm^{-3}), ephedrinium trifluoroacetate (0.2 mmol dm^{-3}) solutions in isopropyl alcohol were added, as required, to the cyclodextrin samples. Agreement between observed and calculated *m*/*z* values were typically within 0.5 mass units. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 400, a Bruker AC250 or a Bruker AMX 500 spectrometer. T_1 values (mean of 10 calculations is given) were recorded on degassed samples using the inversion–recovery sequence. Chemical shifts are given in ppm to higher frequency of tetramethylsilane with coupling constants in Hz. Rotating Frame Overhauser Effect Spectra (ROESY) were recorded on a Bruker AMX 500 using the sequence (π/2, ^1H)–10^{-5} s-(spin lock ^1H)–(FID, t_2)–(^1H by decoupler). 512 transients were recorded and the data were multiplied by cosine bell squared in each dimension prior to Fourier transformation and phase-sensitive treatment. As a result of the low symmetry of some of the products, several of the proton assignments are only tentatively reported (indicated by *). Such assignments were made through the use of ^1H–^{13}C heteronuclear correlation spectroscopy. Integrals for CHO and

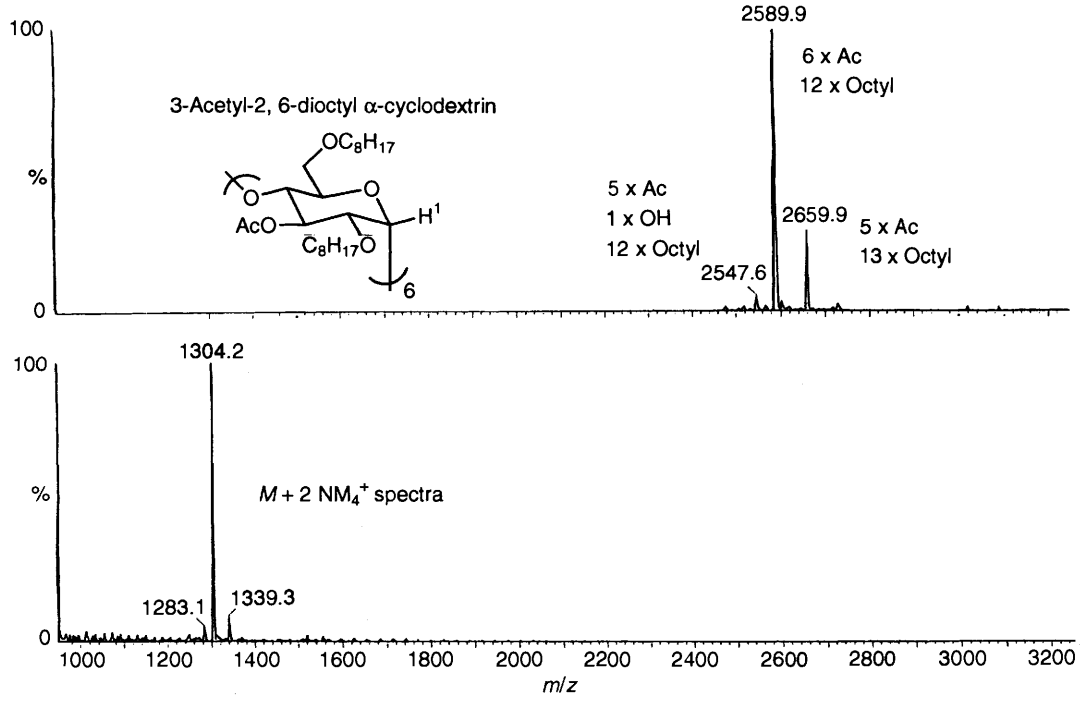


Fig. 2 Electrospray-ionisation mass spectrum of 3-*O*-acetyl-2,6-di-*O*-octyl-α-cyclodextrin **3**, showing singly and doubly charged ions. Calculated masses: (*a*) 2589.7 (12 octyl, 6 acetyl, M + NH_4^+); (*b*) 1303.9 (M + $2NH_4^+$).

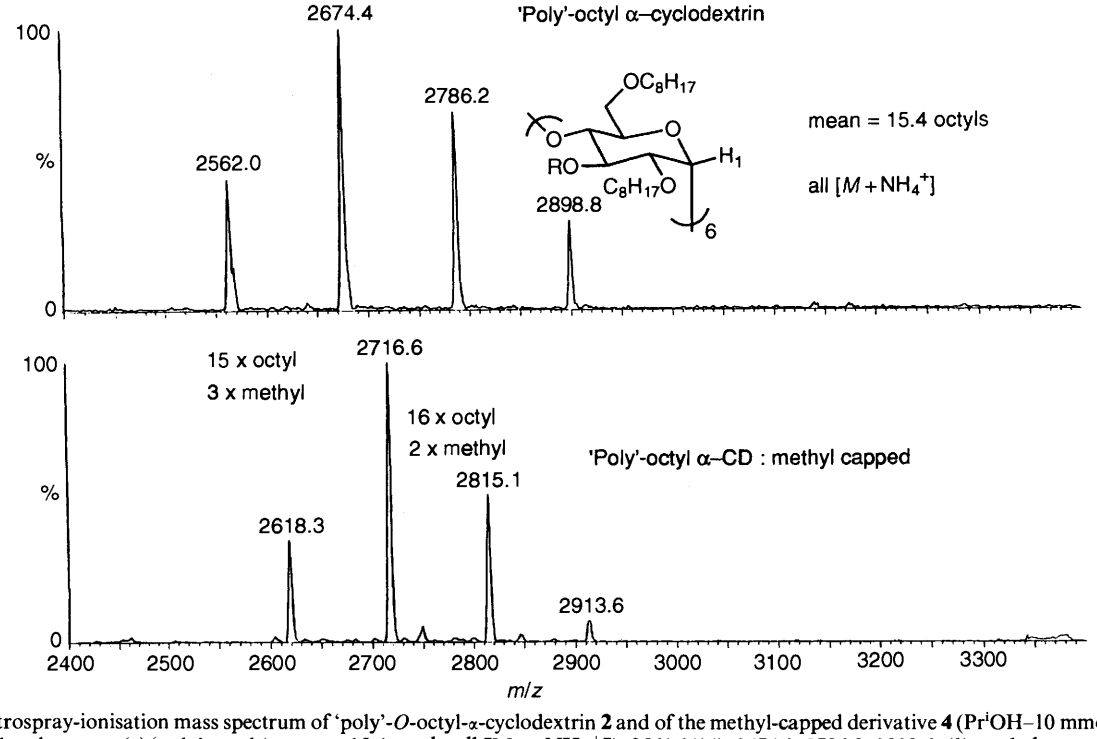


Fig. 3 Electrospray-ionisation mass spectrum of 'poly'-*O*-octyl-α-cyclodextrin **2** and of the methyl-capped derivative **4** (Pr^iOH–10 mmol dm^{-3} NH_4 OAc). Calculated masses: (*a*) 'poly'-octyl (mean = 15.4 octyls; all [M + NH_4^+]), 2561.9(14), 2674.1, 2786.3, 2898.6; (*b*) methyl capped, 2618.0 (14 octyls, 4 methyls), 2716.2 (15 octyls, 3 methyls), 2814.4 (16 octyls, 2 methyls), 2912.6.

CH_2O are only approximate and are such that the total is equal to that observed experimentally. In the ^{13}C NMR spectrum resonances indicated by ‡ were not resolved at 100 MHz: H^c, H^d, H^e and H^f refer to the diastereotopic methylene protons of the octyl OCH_2 moieties—H^d/H^c are geminally related as are H^e, H^f.

Synthesis of Cyclodextrin Derivatives

Hexakis(2,6-*di*-O-*octyl*)-α-*cyclodextrin*, **1** [*Hexakis*-(2,6-*di*-O-*octyl*)*cyclomaltohexaose*].—Powdered α-cyclodextrin hydrate (1 g, 0.97 mmol) was dried overnight under reduced pressure. Anhydrous DMSO (20 cm^3) and fused, dried, powdered sodium hydroxide (2.2 g, 55 mmol) were added sequentially and the mixture stirred at room temperature for 1 h. 1-Bromooctane (14.1 g, 73 mmol) was then added slowly to the vigorously stirred solution. The complete mixture was stirred at room temperature and the reaction monitored by TLC [20% methanol–80% dichloromethane; silica; R_f(α-cyclodextrin) = 0.25]. After one week solvents were removed under reduced pressure. The resulting yellow solid was taken up in

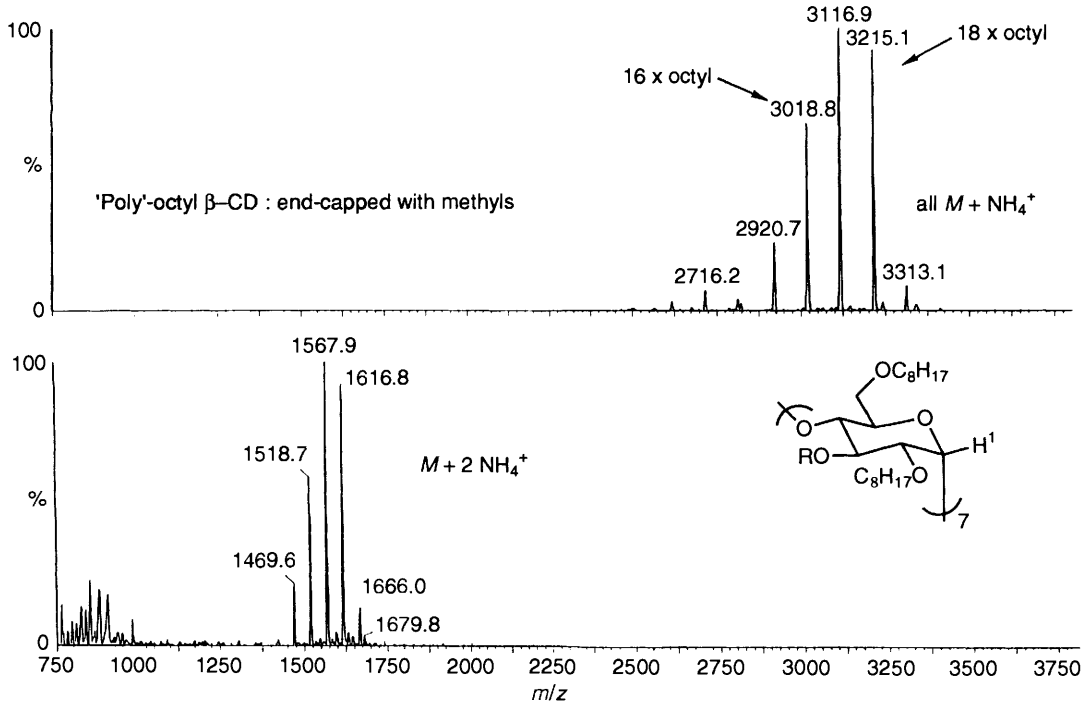


Fig. 4 Electrospray-ionisation mass spectrum of the methyl-capped 'poly'-*O*-octyl-β-cyclodextrin derivative, **7**, showing adducts with one (*a*) and two (*b*) ammonium cations (Pr^iOH-NH_4 OAc). Calculated masses: (methyl capped) 2920.4 (15 octyls), 3018.6 (16 octyls), 3116.8, 3215.0 (18 octyls), 3313.2.

Table 5 Degree of cyclodextrin functionalisation determined by ES–MS

Cyclodextrin derivative	No. of 'molecular ions' present	Mean. no. of octyl groups
'Poly'-*O*-octyl-α-cyclodextrin **2**	4	15.4
Methylated 'poly'-*O*-octyl-α-cyclodextrin **4**	4	15.4
3-*O*-Acetyl-α-cyclodextrin **3**	3	12.2
'Poly'-*O*-octyl-β-cyclodextrin **6**	4	17.4
Methylated 'poly'-*O*-octyl-β-cyclodextrin **7**	4	17.4
'Poly'-*O*-octyl-γ-cyclodextrin **9**	5	20.7

Table 6 Degree of octylation for 'poly'-*O*-octyl α-, β- and γ-cyclodextrin

'Poly'-*O*-octyl-cyclodextrin	Degree of octylation determined by		
	^{13}C NMR	ES–MS	Reductive depolymerisation
α	15.5	15.4	15.4
β	17.3	17.5	17.4
γ	20.5	20.7	20.4

dichloromethane (40 cm^3) and the solution filtered. The organic phase was washed with distilled water (2 × 30 cm^3), dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to give the crude product as a viscous yellow oil. Column chromatography (0→1% methanol–dichloromethane, R_f(product) = 0.3 in 0.5% CH_3OH–CH_2Cl_2) then gave the required product as a clear viscous oil (1.7 g, 76%); *m/z*(+FD) 2320 $(M + 1)^+$ for 12 octyl groups, 2432 $(M + 1)^+$ for 13 octyl groups and 2545 $(M + 1)^+$ for 14 octyl groups; $\delta_H(CDCl_3)$ 4.90 [12 H, s, H^1 and OH(3)], 4.07 (6 H, dd, *J* 9.4 Hz, 9.0 Hz part of an A'M'N' system, H^3), 3.93 (6 H, m, H^c), 3.86 (6 H, m, H^5), 3.66 (6 H, m, H^{6a}), 3.63 (6 H, m, H^d), 3.62 (6 H, m, H^{6b}), 3.50 (6 H, m, H^4), 3.44 (6 H, m, H^e), 3.41 (6 H, m, H^f), 3.35 (6 H, dd, *J* 3.6, 9.4 Hz, part of an A'M'N' system, H^2), 1.52 (12 H, m, CH_2CH_2O) and 1.26 (120 H, m, CH_2O); $\delta_C(CDCl_3)$ 101.4 (C^1), 83.5 (C^4), 79.9 (C^2), 73.7 (C^3), 72.7 (CH_2O), 71.8 (CH_2O'), 70.4 (C^5), 69.3 (C^6), 31.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.25 (CH_2CH_2O) and 14.1 (CH_3), (see the proton numbering scheme for designation of resonances).

Hexakis(2,3,6-*'poly'*-O-*octyl*)-α-*cyclodextrin* **2** [*Hexakis*-2,3,6-*'poly'*-O-*octyl*]*cyclomaltohexaose*.—1-Bromooctane (347 mg, 1.8 mmol) was added to a stirred solution of sodium hydride (430 mg, 18 mmol) and the dialkylated α-cyclodextrin **1** (1.39 g, 0.6 mmol) in anhydrous tetrahydrofuran (35 cm^3). The complete mixture was heated to reflux for 4 days. Filtration, followed by removal of the solvents under reduced pressure, gave the crude product. Column chromatography (1% methanol–99% dichloromethane; silica) then gave the required product as a highly

viscous oil (1.3 g, 73%); *m/z* (ES+, 50 ng μl^{-1} isopropyl alcohol, 10 mmol dm^{-3} ammonium acetate) 2561.9 $(M + 18)^+$ for 14 octyl groups, 2674.3 $(M + 18)^+$ for 15 octyl groups, 2786.6 $(M + 18)^+$ for 16 octyl groups, 2898.0 $(M + 18)^+$ for 17 octyl groups, 1346.2 $(M + 2NH_4)^{2}$ for 15 octyl groups, 1402.5 $(M + 2NH_4)^{2+}$ for 16 octyl groups and 1459 $(M + 2NH_4)^{2+}$ for 17 octyl groups; $\delta_H(CDCl_3)$ 4.92* (6 H, s, H^1), 4.08* (6 H, m, H^3), 3.94 (6 H, m, H^c), 3.88 (6 H, m, H^e), 3.86* (6 H, m, H5), 3.67 (6 H, m, H^{6a}), 3.61 (6 H, m, H^d), 3.62 (6 H, m, H^{6b}), 3.50* (6 H, m, H^4), 3.48 (6 H, m, H^f), 3.45* (6 H, m, H^g), 3.41 (6 H, m, H^f), 3.352 (6 H, m, H^2), 1.52 (36 H, m, CH_2CH_2O), 1.24 (180 H, m, CH_2) and 0.88 (54 H, t, CH_3); $\delta_C(CDCl_3)$ 101.7 and 98 (C^1), 83.3 (C^4), 79.8 (C^2), 73.8 (C^3), 72.8 (CH_2O), 71.8 (CH_2O'), 70.9 (CH_2O), 70.5 (C^5), 69.8 (C^6), 31.8 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 29.8–28.9‡ (CH_2 and CH_2CH_2O), 26.1–26.0‡ (CH_2), 25.8–25.9‡ (CH_2, 14.1 (CH_3).

Attempted further Octylation of Hexakis(2,3,6-*'poly'*-O-*octyl*)-α-*cyclodextrin*, **2**.—Reductive depolymerisation and ES–MS analyses showed that a mean of 15.4 octyl groups for each cyclodextrin core were present in 'poly'-*O*-octyl-α-cyclodextrin. This mean value is used in mole equivalence calculations in the reaction below, where an attempt was made to introduce further octyl groups into the 3-position.

'Poly'-*O*-octyl-α-cyclodextrin **2** (500 mg, 0.18 mmol) was dried overnight under reduced pressure at 50 °C. Anhydrous tetrahydrofuran (10 cm^3) and sodium hydride (40 mg, 1.67 mmol) were added sequentially under an atmosphere of nitrogen and the mixture stirred at room temperature for 1 h. 1-Bromooctane (500 mg, 2.6 mmol) was added and the reaction mixture was heated to reflux. After 3 days further sodium hydride (15 mg, 0.6 mmol) was added and the solution was maintained under reflux for a further 4 days. After cooling, solid material was removed by filtration and the solvent was removed under reduced pressure. Column chromatography (0→1% methanol–dichloromethane; silica) gave a clear colourless oil (410 mg, 82%). NMR, mass spectral analysis and infrared spectroscopy showed this product to be indistinguishable from the 'poly'-*O*-octyl-α-cyclodextrin starting material, **2**.

Hexakis(3-O-*acetyl*-2,6-*di*-O-*octyl*)-α-*cyclodextrin*, **3** [*Hexakis*(3-O-*acetyl*-2,6-*di*-O-*octyl*)*cyclomaltohexaose*.—Hexakis-(2,6-di-*O*-octyl)-α-cyclodextrin (**2**, R′ = H) (2.2 g, 0.95 mmol) was dried overnight under reduced pressure. Anhydrous acetic anhydride (10 cm^3) and anhydrous triethylamine (3.0 cm^3, 4.1 g, 41 mmol) were added and the complete reaction mixture heated to 60 °C under reflux and under a nitrogen atmosphere. After 4 days, the solvents were removed under reduced pressure to give a pale brown oil.

Column chromatography (2% methanol–98% dichloromethane; silica) yielded a colourless oil (1.67 g, 66%); *m/z* (ES, ammonia) 2589.8 $(M + 18)^+$, 100%, 2659.9 $(M + 18)^+$, 20% for 13 octyl groups/5 acetyl groups, 1304.2 $(M + 2NH_4)^{++}$, 100% and 1339.3 $(M + 2NH_4)^{++}$, 10%, for 13 octyl groups/5 acetyl groups; ν/cm^{-1} 1735 (C=O); $\delta_H(CDCl_3)$ 5.18 (6 H, br s, H^3), 4.91 (6 H, d, *J* 2.4, part of an A′M′ system, H^1), 3.97 (6 H, m, H^c of CH_2O), 3.89 (6 H, m, H^{6a}), 3.76 (6 H, m, H^d of CH_2O), 3.61 (6 H, m, H^{6b}), 3.57 (6 H, m, H^e of CH_2O'), 3.47 (6 H, m, H^5), 3.44 (6 H, m, H^4), 3.37 (6 H, m, H^f of CH_2O'), 3.24 (6 H, m, H^2), 2.08 [18 H, s, $CH_3C(O)O$], 1.58 (12 H, m, CH_2CH_2O), 1.50 (12 H, m, CH_2CH_2O'), 1.26 (120 H, m, CH_2) and 0.88 (32 H, m, CH_3); $\delta_C(CDCl_3)$ 170.5 (C=O), 100.8 (C^1), 80.4 (C^4), 78.6 (C^2), 77.3 (C^3), 71.8 (CH_2O), 71.5 (CH_2O'), 71.3 (C^5), 69.1 (C^6), 31.8 (CH_2), 29.8–29.7 (CH_2 and CH_2O, 26.1 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 21.8 (CH_2) and 14.1 (CH_3).

Tris(3-O-*methyl*)-*tris*-(3-O-*octyl*)*hexakis*(2,6-*di*-O-*octyl*)-α-*cyclodextrin* **4** [*Tris*(3-O-*methyl*)*tris*(3-O-*octyl*)*hexakis*(2,6-*di*-O-*octyl*)*cyclomaltohexaose*].—A mean value of 15 octyl groups for each cyclodextrin core in 'poly'-*O*-octyl-α-cyclodextrin, **2**, was assumed in calculating the molar quantities for this methylation.

'Poly'-*O*-octyl-α-cyclodextrin **2** (450 mg, 0.17 mmol) was dried overnight under reduced pressure. Anhydrous tetrahydrofuran (10 cm^3) and sodium hydride (80 mg, 3.3 mmol) were added sequentially and the mixture stirred under a nitrogen atmosphere for 1 h. Iodomethane (568 mg, 249 mm^3, 4.0 mmol) was added and the complete reaction mixture heated to 35 °C under conditions of gentle reflux. After 3 days, further sodium hydride (20 mg, 0.83 mmol) and iodomethane (568 mg, 294 mm^3, 4.0 mmol) were added and stirring was continued for a further 4 days at 35 °C. Solid material was removed by filtration under a nitrogen atmosphere and the solvents were then removed under reduced pressure. The resulting yellow oil was taken up in dichloromethane (25 cm^3) filtered, washed with distilled water (2 × 10 cm^3) and dried over sodium hydroxide pellets (about 3 g).

Removal of the solvent under reduced pressure gave the product as a clear viscous oil (398 mg, 87%); *m/z* (CI, ammonia) 2618.3 (29%, $([M + 18]^+)$ for 14 octyl groups/4 methyl groups, 2716.6 (100%, $[M + 18]^+$) for 15 octyl groups/3 methyl groups, 2815.1 (56%, $[M + 18]^+$) for 16 octyl groups/2 methyl groups and 2913.6 (16%, $[M + 18]^+$) for 17 octyl groups/1 methyl group. Assuming equal ionisation efficiencies for each homologue, the mean number of methyl groups for each cyclodextrin core can be calculated, as a weighted mean, to be 2.7; $\delta_H(CDCl_3)$ 5.04 (6 H, m, H^1), 3.96* (6 H, m, H^3), 3.95 (6 H, m, H^c of CH_2O), 3.78* (6 H, m, H^5), 3.71 (6 H, m, H^{6a}), 3.70 (3 H, m, H^g of CH_2O''), 3.69* (6 H, m, H^e of CH_2O'), 3.64* (6 H, m, H^d of CH_2O), 3.59* (6 H, m, H^{6b}), 3.565 (5 H, m, OCH_3), 3.56 (4 H, m, OCH_3), 3.47 (6 H, m, H^f of CH_2O'), 3.44 (3 H, m, H^h of CH_2O''), 3.36* (6 H, m, H^4), 3.17 (6 H, m, H^2), 1.57 (30 H, m, CH_2CH_2O), 1.32 (150 H, m, CH_2) and 0.82 (45 H, m, CH_3); $\delta_C(CDCl_3)$ 99‡ (C^1), 82‡ (C^4), 80.5 (C^3), 72.7 (CH_2O), 71.1 (CH_2O''), 70.7 (C^5), 69.8 (C^6), 61.8 (OCH_3), 31.9 (CH_2), 31.6–28.9‡ (CH_2), 25.8–25.9‡ (CH_2 and CH_2CH_2O), 26.1–26.0‡ (CH_2), 25.8–25.9‡ (CH_2), 22.4 (CH_2) and 14.1 (CH_3).

Heptakis(2,6-*di*-O-*octyl*)-β-*cyclodextrin*, **5** [*Heptakis*(2,6-*di*-O-*octyl*)*cyclomaltoheptaose*.—1-Bromooctane (16.3 g, 84 mmol) was added to a stirred solution of fused, dried, powdered sodium hydroxide (2.65 g, 63 mmol) and anhydrous β-cyclodextrin (1.2 g, 1.05 mmol) in DMSO (25 cm^3). After one week, TLC analysis [silica; 20% methanol–80% dichloromethane, R_f(β-cyclodextrin) = 0.23] indicated complete reaction. The solvent was removed under reduced pressure to yield a pale yellow solid which was extracted into dichloromethane (35 cm^3).

The organic phase was washed with distilled water (2 × 25 cm^3), dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to give the crude product as a yellow oil (1.9 g). Column chromatography (silica; 0→1% methanol–dichloromethane) then gave two products (R_f = 0.33 and 0.25 in 0.5% CH_3OH–CH_2Cl_2) which could only be distinguished by mass spectral analysis; *m/z* (+FD) for R_f = 0.25:2594 (M^+ for 13 octyl groups), 6%, 2706 (M^+ for 14 octyl groups), 100%, 2817 (M^+ for 15 octyl groups), 13%; R_f = 0.33:2706 (M^+ for 14 octyl groups), 10%, 2818 (M^+ for 15 octyl groups), 40% and 2930 (M^+ for 16 octyl groups), 27%; $\delta_H(CDCl_3)$ 5.05 (7 H, br s, OH), 4.87 (7 H, s, H^1, *J* 3.6 Hz part of an A′M′ system), 3.89 (7 H, t, *J* 9.5 Hz, part of a A′M′N′ system, H^3), 3.84 (7 H, m, H^c), 3.70 (7 H, m, H^5), 3.63 (7 H, m, H^d), 3.61 (7 H, m, H^{6a}), 3.56 (7 H, m, H^{6b}), 3.47 (7 H, m, H^e), 3.43 (7 H, m, H^f), 3.40 (7 H, m, H^4), 3.31 (7 H, dd, *J* 3.6, 9.6 Hz, part of an A′M′X′ system, H^2), 1.52 (14 H, m, CH_2CH_2O), 1.24 (140 H, m, CH_2) and 0.88 (42 H, t, CH_3); $\delta_C(CDCl_3)$ 101.8

(C^1), 82.9 (C^4), 80.3 (C^2), 74.2 (C^3), 72.9 (CH_2O), 71.8 (CH_2O'), 71.1 (C^5), 69.4 (C^6), 31.8 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.25 (CH_2CH_2O), 29.2 (CH_2CH_2O) and 14.0 (CH_3).

Heptakis(2,3,6-*'poly'*-O-*octyl*-β-*cyclodextrin*, **6a** [*Heptakis*(2,3,6-*'poly'*-O-*octyl*)*cyclomaltoheptaose*.—1-Bromooctane (347 mg, 1.8 mmol) was added to a stirred solution of sodium hydride (430 mg, 18 mmol) and the di-*O*-octylated-β-cyclodextrin **5** (1.39 g, 0.6 mmol) in anhydrous tetrahydrofuran (35 cm^3). The mixture was heated to reflux for 4 days. Filtration, followed by removal of the solvents under reduced pressure gave the crude product. Column chromatography (1% methanol–99% dichloromethane; silica) then gave the required product as a highly viscous oil (1.3 g, 73%); *m*/*z* (ES+, 50 ng μl^{-1} isopropyl alcohol, 10 mmol dm^{-3} ammonium acetate) 2948.7 $(M + 18)^+$, 24%, for 16 octyl groups, 3060.8 $(M + 18)^+$ 100% for 18 octyl groups, 3285.3 $(M + 18)^+$ 100%, for 19 octyl groups; 1483.5 $(M + 2NH_4)^{2+}$ for 16 octyl groups, 1539.9 $(M + 2NH_4)^{2+}$ for 17 octyl groups, 1595.9 $(M + 2NH_4)^{2+}$ for 18 octyl groups and 1651.8 $(M + 2NH_4)^{2+}$ for 19 octyl groups; $\delta_H(CDCl_3)$ 4.86 (7 H, s, H^1), 3.91* (7 H, m, H^3), 3.90 (7 H, m, H^c), 3.86 (7 H, m, H^d), 3.71 (7 H, m, H^5), 3.69 (7 H, m, H^{6a}), 3.61 (7 H, m, H^e), 3.62* (7 H, m, H^{6b}), 3.58 (7 H, m, H^f), 3.48 (7 H, m, H^g), 3.44 (7 H, m, H^4), 3.33 (7 H, m, H^2), 1.51 (36 H, m, CH_2CH_2O), 1.26 (210 H, m, CH_2) and 0.88 (63 H, t, CH_3); $\delta(CDCl_3)$ 101.4 and 99.1‡ (C^1), 83.1‡ (C^4), 80.5‡ (C^2), 74.1 (C^3), 72.9 (CH_2O), 71.7 (CH_2O'), 71.1 (CH_2O''), 70.9 (C^5), 69.5 (C^6), 32.1 (CH_2), 31.5–29.0‡ (CH_2 and CH_2CH_2O), 26.3–26.1‡ (CH_2), 25.9–25.8‡ (CH_2), 22.1 (CH_2) and 14.1 (CH_3).

Heptakis(2,3,6-*tri*-O-*octyl*)-β-*cyclodextrin* (**6b**) [*Heptakis*-(2,3,6-*tri*-O-*octyl*)*cyclomaltoheptaose*].—Potassium hydride (0.53 g) was added to a stirred solution of heptakis(2,6-di-*O*-octyl)-β-cyclodextrin **5** (1.0 g, 0.43 mmol) and 18-crown-6 (50 mg) in anhydrous tetrahydrofuran (40 cm^3) under a nitrogen atmosphere. The mixture was heated under reflux for 1 h after which 1-bromooctane (1.5 g, 7.7 mmol) was added and reflux continued for 4 days. After 2 days, further potassium hydride (0.175 g) and 1-bromooctane (0.5 g) were added to the reaction mixture. After being cooled, the reaction mixture was treated with ethyl acetate (5 cm^3) and the solvent removed under reduced pressure. The semi-solid residue was suspended in dichloromethane (120 cm^3), washed with distilled water (3 × 40 cm^3), dried over anhydrous sodium sulfate and filtered. After solvent removal under reduced pressure, the resulting oil was further treated under high vacuum (0.5 mmHg) at 100 °C for 6 h (Kugelrohr) to remove residual 1-bromooctane.

Column chromatography (silica, 100% *n*-hexane) gave the required product as a colourless oil (0.83 g, 55%), R_f(*n*-hexane) = 0.8 (SiO_2); ν_{max}(thin film)/cm^{-1} 2954s, 2929s, 1467m, 1378m, 1099vs m, 1041s, 723w (*n.b.* OH absent) (Found: C, 72.4; H, 11.9. $C_{210}H_{406}O_{35}$ requires: C, 72.2; H, 11.7%); $\delta_H(CDCl_3)$ 5.20 (7 H, d, *J* 2.8 Hz, H^1), 3.96 (14 H, m, H^{6b} + 6-OCH^cCH_2), 3.78 (7 H, dd, *J* 9.2 Hz, H^4), 3.70 (7 H, m, H^5), 3.65 (7 H, m, 6-O-CH^dCH_2), 3.63 (7 H, m, 3-OCH^h), 3.60 (7 H, m, H^3), 3.56 (7 H, m, 3-O-CH^g), 3.45 (7 H, m, 2-OCH^eCH_2), 3.44 (7 H, m, H^{6a}), 3.34 (7 H, m, 2-OCH^fCH_2), 3.20 (7 H, dd, *J* 9.6, 2.8 Hz, H^2) 1.58 (42 H, m, OCH_2CH_2), 1.27 (210 H, br s, CH_2O) and 0.89 (63 H, br t, CH_3); $\delta_C(CDCl_3)$ 97.9 (C^1), 80.4 (C^3), 80.3 (C^2), 78.0 (C^4), 74.2 (CH_2O), 71.6 (CH_2O'), 71.5 (CH_2O''), 71.2 (C^5), 69.4 (C^6), 32.0 (OCH_2CH_2), 31.9 ($O'CH_2CH_2$), 30.7 ($O''CH_2CH_2$), 30.3, 30.0 (OCH_2CH_2), 29.80, 29.71, 29.60, 29.52, 29.43, 29.42 (CH_2), 26.37, 26.35, 26.1 (CH_2), 22.71, 22.69 and 22.68 (CH_3).

'Tetrakis'(3-O-*methyl*)*'tris'*(3-O-*octyl*)*'hexakis'*(2,6-*di*-O-*octyl*)-β-*cyclodextrin* **7** [*Tetrakis*(3-O-*methyl*)*tris*(3-O-*octyl*)-*hexakis*(2,6-*di*-O-*octyl*)*cyclomaltoheptaose*.—A mean value of 17 octyl groups for each cyclodextrin core in 'poly'-*O*-octyl-β-cyclodextrin, **6**, was assumed in calculating the molar quantities for this methylation.

'Poly'-*O*-octyl-β-cyclodextrin, **6** (500 mg, 0.16 mmol) was dried overnight under reduced pressure. Anhydrous tetrahydrofuran (10 cm^3) and sodium hydride (90 mg, 3.7 mmol) were added sequentially and the mixture stirred under a nitrogen atmosphere for 1 h. Iodomethane (568 mg, 249 mm^3, 4.0 mmol) was added and the complete reaction mixture heated to 35 °C under conditions of reflux. After 3 days, further sodium hydride (20 mg, 0.83 mmol) and iodomethane (568 mg, 249 mm^3, 4.0 mmol) were added and stirring was continued at 35 °C for 4 more days. Solid material was removed by filtration under a nitrogen atmosphere and the solvents were then removed under reduced pressure. The resulting yellow oil was taken up in dichloromethane (25 cm^3) filtered, washed with distilled water (2 × 10 cm^3) and dried over sodium hydroxide pellets (about 3 g). Removal of the solvent under reduced pressure gave the product as a clear viscous oil (398 mg, 87%); *m*/*z* (CI, ammonia) 2920.7 (25%, $[M + 18]^+$ for 15 octyl groups/6 methyl groups, 3018.8 (68%, $[M + 18]^+$) for 15 octyl groups/6 methyl groups, 3018.8 (68%, $[M + 18]^+$ for 16 octyl groups/5 methyl groups, 3116.9 (100%, $[M + 18^+$) for 17 octyl groups/4 methyl groups, 3215.1 (91%, $[M + 18]^+$) for 18 octyl groups/3 methyl groups and 3313.1 (8%, $[M + 18]^+$) for 19 octyl groups/2 methyl groups. Assuming equal ionisation potentials for each homologue, the mean number of methyl groups for each cyclodextrin core can be calculated, as a weighted mean, to be 3.5; $\delta_H(CDCl_3)$ 4.93 (7 H, m, H^1), 3.91 (7 H, m, H^c of CH_2O), 3.87* (7 H, m, H^3), 3.81* (7 H, m, H^5), 3.73 (7 H, m, H^{6a}), 3.70 (3 H, m, H^g of CH_2O''), 3.67* (7 H, m, H^e of CH_2O'), 3.66* (7 H, m, H^d of CH_2O), 3.56* (7 H, m, H^{6b}), 3.565 (5 H, m, OCH_3), 3.51 (7 H, m, OCH_3), 3.48 (7 H, m, H^f of CH_2O'), 3.44 (3 H, m, H^h of CH_2O''), 3.41* (7 H, m, H^4), 3.33 (7 H, m, H^2), 1.56 (30 *H*, m, CH_2CH_2O), 1.25 (170 H, m, CH_2) and 0.88 (51 H, m, CH_3); $\delta_C(CDCl_3)$ 99‡ (C^1), 82‡ (C^4), 80‡ (C^2), 80.4 (C^3), 72.7 (CH_2O), 71.8 (CH_2O'), 71.3 (CH_2O''), 70.6 (C^5), 69.8 (C^6), 61.8 (OCH_3), 31.9 (CH_2), 31.6–28.9‡ (CH_2) and CH_2CH_2O), 26.2–26.0‡ (CH_2), 25.8–25.9‡ (CH_2), 22.4 (CH_2) and 14.0 (CH_3).

Octakis(2,6-*di*-O-*octyl*)-γ-*cyclodextrin*, **8** [*Octakis*(2,6-*di*-O-*octyl*)*cyclomaltooctaose*].—Powdered γ-cyclodextrin hydrate (1.0 g, 0.77 mmol) was dried overnight under reduced pressure. Anhydrous DMSO (20 cm^3) and fused, dried, powdered sodium hydroxide (2.2 g, 55.5 mmol) were added sequentially under a nitrogen atmosphere and the mixture vigorously stirred for 1 h. 1-Bromooctane (9.6 cm^3, 10.7 g, 55.7 mmol) was added and the complete reaction mixture stirred at room temperature. The reaction was continued until TLC analysis (20% methanol–80% dichloromethane; silica) showed complete consumption of the γ-cyclodextrin (R_f = 0.26). After 7 days solvents were removed under reduced pressure. Dichloromethane (50 cm^3) and distilled water (30 cm^3) were added. The lower organic layer was separated, washed with distilled water (2 × 25 cm^3) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a yellow oil. Column chromatography (0→2% methanol–dichloromethane; silica) gave the required product (R_f = 0.32, 2% methanol) as a viscous pale yellow oil (1.1 g, 47%); $\delta_H(CDCl_3)$ 4.96 (8 H, d, *J* 3.6, part of an A'M' system, H^1), 3.96 (8 H, m, H^3), 3.75 (8 H, m, H^5), 3.68 (8 H, m, H^{6b}), 3.63 (16 H, m, CH_2O), 3.59 (8 H, m, H^{6a}), 3.44 (16 H, m, CH_2O), 3.40 (8 H, m, H^4), 3.36 (8 H, dd, *J* 3.5, 9.6 Hz, part of an A'M'X' system, H^2), 1.58 (32 H, m, CH_2CH_2O), 1.27 (160 H, m, CH_2) and 0.88 (48 H, t, CH_3). Integration ratios quoted are such that Σ_H = 80 for all the CHO and CH_2O resonances; $\delta_C(CDCl_3)$ 101.8 (C^1), 83.2 (C^4), 80.8 (C^2), 73.3 (C^3), 73.1 (CH_2O), 71.6 (CH_2O), 70.4 (C^5),

Results from GC–MS analysis of reductively depolymerized cyclodextrin derivatives[a]

Cyclodextrin derivative	% Dioctylated, (k')[b]	% Trioctylated, (k')	Mean no. of octyl groups
2,6-Di-*O*-octyl-α-cyclodextrin	88 (12.45)	12 (11.34)	12.7
'Poly'-*O*-octyl-α-cyclodextrin	43 (12.43)	57 (11.35)	15.4
Methylated 'poly'-*O*-octyl-α-cyclodextrin ‡	< 1 (12.45)	58 (11)35	15.4
2,6-Di-*O*-octyl-β-cyclodextrin	95 (12.45)	5 (11.41)	14.3
'Poly'-*O*-octyl-β-cyclodextrin	51 (12.51)	49 (11.31)	17.4
'Poly'-*O*-octyl-γ-cyclodextrin	45 (12.45)	55 (11.31)	20.4

[a] Numbers in parentheses refer to t_R/min. [b] $k' = t_R$/min 100–240 °C at 10 °C min^{-1} on a capillary SE-30 column. ‡ 48% 3-*O*-methylated, $k' = 14.79$ min.

69.1 (C^6), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2CH_2O) and 14.1 (CH_3).

Octakis(2,3,6-*'poly'*-O-*octyl*)-γ-*cyclodextrin*, **9** [*Octakis*-(2,3,6-*'poly'*-O-*octyl*)*cyclomaltooctaose*.—1-Bromooctane (1.38 g, 7.2 mmol) was added to a stirred solution of sodium hydride (172 mg, 7.2 mmol) and the dioctylated γ-cyclodextrin, **8** (1.1 g, 0.3 mmol) in anhydrous tetrahydrofuran (35 cm^3). The mixture was heated to reflux for 4 days. Filtration, followed by removal of the solvents under reduced pressure gave the crude product. Column chromatography (1% methanol–99% dichloromethane; silica) yielded a highly viscous oil (0.49 g, 46%); *m/z* (ES+, 50 ng μl^{-1} isopropyl alcohol, 10 mmol dm^{-3} ammonium acetate) 3222.8 $(M + 18)^+$ for 17 octyl groups, 3335.0 $(M + 18)^+$ for 18 octyl groups, 3447.3 $(M + 18)^+$ for 19 octyl groups, 3559.7 $(M + 18)^+$ for 20 octyl groups, 3672.1 $(M + 18)^+$ for 21 octyl groups, 3784.1 $(M + 18)^+$ for 22 octyl groups, 1718.7 $(M + 2NH_4)^{2+}$ for 18 octyl groups, 1767.6 $(M + 2NH_4)^{2+}$ for 19 octyl groups, 1816.9 $(M + 2NH_4)^{2+}$ for 20 octyl groups, 1402.5 $(M + 2NH_4)^{2+}$ for 21 octyl groups and 1866.2 $(M + 2NH_4)^{2+}$ for 22 octyl groups; $\delta_H(CDCl_3)$ 4.96* (8 H, s, H^1), 4.01* (8 H, m, H^3), 3.94 (8 H, m, H^c), 3.88 (8 H, m, H^d), 3.79 (8 H, m, H^5), 3.67 (8 H, m, H^{6a}), 3.61 (8 H, m, H^e), 3.60 (8 H, m, H^{6b}), 3.42 (8 H, m, H^4), 3.48 (8 H, m, H^f), 3.45 (8 H, m, H^g), 3.41 (8 H, m, H^f), 3.34 (8 H, m, H^2), 1.57 (48 H, m, CH_2CH_2O), 1.26 (240 H, m, CH_2) and 0.88 (72 H; t, CH_3); $\delta_C(CDCl_3)$ 102.3 (C^1), 82.1 (C^4), 80.1 (C^2), 74.1 (C^3), 72.7 (CH_2O), 71.8 (CH_2O'), 71.2 (CH_2O''), 70.8 (C^5), 70.3 (C^6), 31.8 (CH_2), 30.5 (CH_2), 30.1 (CH_2), 30.0–28.9‡ (CH_2 and CH_2CH_2O), 26.3–26.1‡ (CH_2), 25.8–25.9‡ (CH_2) and 14.2 (CH_3).

Analysis of Degree of Octylation using Reductive Depolymerisation.—Several cyclodextrin derivatives were reductively depolymerised by a method similar to that described by Mishnick-Lubbecke.[16]

The modified cyclodextrin (17 mg, 0.006 mmol) was dried overnight under reduced pressure. The flask was cooled to 0 °C and anhydrous dichloromethane (80 mm^3) added under a nitrogen atmosphere. The mixture was stirred until dissolution was complete. Triethylsilane (54 mm^3, 0.34 mmol) and boron trifluoride–dimethyl ether (33 mm^3) were added sequentially and the complete mixture was stirred under an atmosphere of nitrogen for 16 h. The reaction was quenched with methanol (1.5 cm^3) and the reddish brown solution was passed through a cation-exchange column (2 cm^3 of Dowex-50X4-400 ion-exchange resin) contained inside a pipette. A further 6 cm^3 of methanol were used to elute the column. The resulting solution was dried overnight under reduced pressure to give a brown oil (16 mg). Acetic anhydride (10 cm^3) and anhydrous triethylamine (2 cm^3) were added to this oil under a nitrogen atmosphere. The mixture was heated to 75 °C with stirring and the temperature maintained for 4 h. Solvents were removed under reduced pressure. The resulting oil was taken up in dichloromethane (10 cm^3), washed with distilled water (2 × 5 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a viscous brown oil containing a mixture of alkylated 1,5-anhydro-D-glucitols. This mixture was analysed by GC–MS directly (using desorption chemical ionisation with ammonia gas). The results obtained from GC–MS analysis of the cyclodextrin derivatives investigated by this method are detailed above.

Octylation of Oligosaccharides

Methyl Tetrakis(2,3,4,6-O-*octyl*)-α-D-*glucopyranoside*.—To a stirred solution of anhydrous methyl α-D-glucopyranoside (1.0 g, 5.2 mmol) in DMSO (20 cm^3) was added fused, dried, powdered sodium hydroxide (2.5 g, 62 mmol). This mixture was stirred at room temperature for 1 h after which time 1-bromooctane (11.9 mg, 10.7 cm^3, 62 mmol) was added. The solution was stirred under a nitrogen atmosphere until TLC analysis showed complete disappearance of glucose ($R_f = 0.3$, 10% methanol–90% dichloromethane; silica). After five days all volatile material was removed under reduced pressure. The residue was extracted into dichloromethane (40 cm^3) and the organic phase washed with distilled water (3 × 20 cm^3) and dried over anhydrous magnesium sulfate to give a yellow oil. Column chromatography (100% dichloromethane; silica) then gave the required product ($R_f = 0.6$) as a colourless oil (1.9 g, 58%); *m/z* (CI, ammonia): 660 $(M + 18)^+$, 628 $(M - Me)^+$, 611 $(M - MeO)^+$, 481 and 351; $\delta_H(CDCl_3)$ 4.775 (1 H, d, J 3.6, H^1), 3.85 (1 H, m, H^3), 3.79 (2 H, m, CH_2O), 3.77 (1 H, m, H^{6a}), 3.68 (1 H, m, H^{6b}), 3.60 (2 H, m, CH_2O), 3.54 (2 H, m, CH_2O), 3.52 (1 H, m, H^5), 3.42 (2 H, m, CH_2O), 3.38 (3 H, m, OCH_3), 3.34 (1 H, m, H^4), 3.273 (1 H, dd, J 3.6, 10 Hz, H^2), 1.57 (8 H, m, CH_2CH_2O), 1.27 (40 H, m, CH_2), 0.88 (12 H, m, CH_3); $\delta_C(CDCl_3)$ 98.1 (C^1), 81.6 (C^3), 80.6 (C^2), 77.7 (C^4), 73.6 (C^6), 73.1 (CH_2O), 71.7 (C^5), 71.6 (CH_2O), 70.1 (CH_2O), 69.2 (CH_2O), 54.9 (OCH_3), 31.83 (CH_2), 31.82 (CH_2), 31.80 (CH_2), 31.7 (CH_2), 30.5 (CH_2CH_2O), 30.4 (CH_2CH_2O), 30.0 (CH_2CH_2O), 29.6 (CH_2), 29.54 (CH_2), 29.51 (CH_2), 29.45

(CH_2), 29.37 (CH_2), 29.30 (CH_2), 29.28 (CH_2), 29.24 (CH_2), 29.23 (CH_2), 26.24 (CH_2), 26.20 (CH_2), 26.18 (CH_2), 25.9 (CH_2), 22.6 (CH_2) and 14.0 (CH_3).

Per-O-*octylmaltose*, **11**.—D-Maltose monohydrate (1.0 g, 2.78 mmol) was dried under reduced pressure overnight. DMSO (20 cm^3) and fused, dried, powdered sodium hydroxide (2.67 g, 66.7 mmol) were added sequentially and the mixture was stirred at room temperature under nitrogen for 1 h. 1-Bromooctane (13.07 g, 66.7 mmol) was added and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 7 days. Solvents were removed under reduced pressure and the crude product purified by column chromatography (2% methanol–98% dichloromethane; silica) to give a mixture of partially alkylated homologues (R_f = 0.25–0.40). The partially alkylated homologues were combined and the solvent was removed under reduced pressure to give a yellow oil (2.1 g). The yellow oil was dried under reduced pressure overnight. Anhydrous tetrahydrofuran (35 cm^3) and sodium hydride (400 mg, 16.7 mmol) were added under a nitrogen atmosphere and the mixture was stirred at room temperature for 1 h. 1-Bromooctane (3.27 g, 16.7 mmol) was added and the mixture heated to reflux under a nitrogen atmosphere for 4 days. TLC analysis (100% dichloromethane; silica) indicated complete reaction (R^f = 0.7). Solvents were removed under reduced pressure and column chromatography (100% dichloromethane; silica) gave a very pale yellow oil (R^f = 0.70), (2.1 g, 61%); *m/z* (CI, ammonia) 1240 $(M + 18)^+$ 100% and 1223 $(M + 1)^+$ 56%; $\delta_H(CDCl_3)$ 4.84 (1 H, d, H^{1A}), 4.17 (1 H, d, H^{1B}), 3.82–3.14¶ (26 H, m, CHO and CH_2O), 3.05 (2 H, m, H^2), 1.49 (16 H, m, CH_2CH_2O), 1.18 (80 H, m, CH_2) and 0.81 (24 H, m, CH_3); $\delta_C(CDCl_3)$ 103.4 (C^{1A}), 96.3 (C^{1B}), 31.6 (CH_2), 31.3 (CH_2), 22.8 (CH_2), 14.4 (CH_3) and 84.9, 81.7, 80.4, 77.8, 74.2, 73.6, 73.1, 72.9, 72.6, 72.5, 71.9, 71.8, 71.7, 71.0, 70.0, 69.9, 69.1, 30.6–30.2¶, 29.8–29.5¶, 26.4–26.2¶ (¶ indicates several resonances which could not be distinguished from the complex spectrum). Attempts were made to assign all the resonances for per-*O*-octylmaltose through the use of ^1H–^1H COSY and ^1H–^1C HETCOR analyses. However, the spectra were still too complex for a complete assignment.

Per-O-*octylmaltotriose*, **12**.—Maltotriose hydrate (1.0 g, 2.00 mmol) was dried overnight at 50 °C under reduced pressure. Anhydrous DMSO (20 cm^3) and fused, dried, powdered sodium hydroxide (2.70 g, 67.6 mmol) were added sequentially under an atmosphere of dry nitrogen. The mixture was stirred at room temperature for 1 h and 1-bromooctane (13.25 g, 67.6 mmol) was added. The reaction mixture was stirred at room temperature for 6 days after which time TLC analysis (15% methanol–85% dichloromethane; silica) revealed the total consumption of the maltotriose (R_f = 0.36). Solvents were removed under reduced pressure and the crude mixture purified by column chromatography (100% dichloromethane; silica) to give a mixture of several partially alkylated homologues (R_f = 0.4–0.6) which were recombined for further alkylation. Removal of the solvent under reduced pressure gave a pale yellow oil (2.23 g). The pale yellow oil was dried overnight under reduced pressure. Anhydrous tetrahydrofuran (40 cm^3) and sodium hydride (400 mg, 16.7 mmol) were added under a nitrogen atmosphere and the mixture stirred at room temperature for 1 h. 1-Bromooctane (3.27 g), 16.7 mmol) was added and the mixture was heated to reflux for 4 days. After cooling, solid material was removed by filtration under an atmosphere of dry nitrogen. The solvent was removed under reduced pressure and column chromatography (10% ethyl acetate–90% hexanes; silica) gave a slightly yellow, clear oil (R_f = 0.6) (1.93 g, 56%); *m/z* (CI, ammonia) 1738 $(M + 18)^+$, 100% and 1721 $(M + 1')^+$ 41%; $\delta_H(CDCl_3)$ 4.22 (3 H, m, H^1), 3.86–3.16 (40 H, m, CHO and CH_2O), 3.37 and 3.55 (CH_2O of OC_8H_{17}), 1.56 (22 H, m, CH_2CH_2O), 1.27 (110 H, m, CH_2) and 0.88 (33 H, t, CH_3); $\delta_C(CDCl_3)$ 103.6 (C^{1A}), 103.4 (C^{1B}), 96.3 (C^{1C}), 82.6 (C^{2A}), 82.4 (C^{2B}), 82.3 (C^{2C}), 31.9 (CH_2), 31.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3) and 84.9 84.8, 81.7, 80.4, 78.3, 77.7, 77.3, 74.8, 74.2, 73.8, 73.6, 73.2–72.87¶, 72.6, 72.5, 71.9–71.7¶, 70.9, 70.1–69.8¶, 69.1, 30.7–30.2¶, 29.8–29.3¶ and 26.3–26.1¶. Resonance indicated by ¶ as described above.

Heptakis(2,6-*di*-O-*methyl*-3-O-*octyl*)-β-*cyclodextrin*, **13b** [*Heptakis*(2,6-*di*-O-*methyl*-3-O-*octyl*)*cyclomaltoheptaose*.—Potassium hydride (600 mg) was added to a stirred solution of 18-crown-6 (50 mg) and heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (1.0 g, 0.8 mmol, dried overnight under vacuum) in anhydrous tetrahydrofuran (40 cm^3) under a nitrogen atmosphere. The mixture was heated at reflux (50 °C) for 1 h, following which a bromooctane (2.5 g, 13 mmol) was added and boiling was continued for 3 days. The reaction mixture was then cooled, treated with ethyl acetate (5 cm^3) and the solvent removed under reduced pressure. The residue was suspended in dichloromethane (120 cm^3), washed with distilled water (3 × 40 cm^3), dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure, leaving a yellow oil which was further heated under vacuum (0.5 mmHg) at 100 °C for 6 h to remove 1-bromooctane. Column chromatography (silica; ethyl acetate) of the remaining yellow oil gave a colourless oil (1.1 g) which showed three major components on thin-layer chromatography (R_f = 0.43, 0.35, 0.25).

Further column chromatography (silica gel; ethyl acetate) of the oily mixture gave a colourless oil (400 mg, 24%), R_f = 0.5; SiO_2, EtOAc); ν_{max}(thin film)/cm^{-1} 2925s, 2855s, 1459m, 1357w, 1095s and 1038s (Found: C, 63.2; H, 10.2. Calc. for $C_{112}H_{210}O_{35}$. C, 63.54%; H, 10.0%); $\delta_H(CDCl_3)$ 5.19 (7 H, d, *J* 3.6, H^1), 3.87–3.98 (14 H, m, H^5 or H^3, H^{6a}), 3.56–3.77 (28 H, m, H^4, H^5 or H^3, 3-OCH_2), 3.48–3.53 (28 H, m, 2-OCH_3, H^{6b}), 3.34 (21 H, s, 6-OCH_3), 3.18 (7 H, dd, *J* 9.6, H^z, *J* 3.6 H^3, H^2), 1.55–1.66 (14 H, m, OCH_2CH_2), 1.22–1.38 (84 H, m, CH_2) and 0.88 (21 H, t, *J* 6.8 H^z, CH_3); $\delta_C(CHCl_3)$ 98.4 (C^1), 81.7 (C^4), 80.5 (C^2), 79.1 (C^3), 74.2 (C^5), 71.4 (OCH_2), 71.0 (C^6), 59.4 (OCH_3), 59.0 (OCH_3), 31.9 (OCH_2CH_2), 30.5 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 22.7 (CH_2) and 14.1 (CH_3).

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