Square pegs in round holes. Preparation and intramolecular complexation of cubyl substituted β-cyclodextrins† and of an adamantane analogue

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Received (in Cambridge, UK) 5th July 1999, Accepted 8th November 1999

The reaction of either 1-methoxycarbonyl-4-(4-nitrophenoxycarbonyl)cubane or its dimethyl analogue, 2,3-dimethyl-1-methoxycarbonyl-4-(4-nitrophenoxycarbonyl)cubane, with the primary amine of 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin produces the first cubyl substituted β-cyclodextrins, 6^A-deoxy-6^A-{6-[*N*-(4-methoxycarbonylcuban-1-ylcarbonyl)amino]hexylamino}-β-cyclodextrin and its dimethyl analogue, respectively, and 4-nitrophenolate. The reaction of 1,4-bis(4-nitrophenoxycarbonyl)cubane with 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin produces the dimer 1,4-bis{6-[*N*-(6^A-deoxy-β-cyclodextrin-6^A-yl)amino]-hexylaminocarbonyl}cubane. ^{1}H NMR ROESY studies are consistent with the cubyl moiety of each of the above three cubyl-substituted β-cyclodextrins complexing in the β-cyclodextrin annuli in D_2O. The reaction of 1-(4-nitrophenoxycarbonyl)adamantane with β-cyclodextrin produces 6^A-{6-[*N*-(1-adamantylcarbonyl)amino]-hexylamino}-6^A-deoxy-β-cyclodextrin which shows a strong intramolecular complexation of its adamantyl moiety. Adamantane-1-carboxylate forms intermolecular complexes with the above three cubyl-substituted β-cyclodextrins in D_2O solution and excludes the cubyl moiety from the β-cyclodextrin annulus. However, this does not occur for 6^A-{6-[*N*-(1-adamantylcarbonyl)amino]hexylamino}-6^A-deoxy-β-cyclodextrin where intramolecular complexation appears to be sufficiently strong to prevent intermolecular complexation of adamantane-1-carboxylate.

Introduction

We recently reported the intramolecular complexation of the (6-aminohexyl)amino substituent in the β-cyclodextrin (βCD) annulus of 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin (**1**) shown in Fig. 1.[1] Similar intramolecular complexation of aromatic substituents of modified βCDs is well established, particularly in the case of those incorporating the dansyl (dansyl = 5-dimethylaminonaphthalene-1-sulfonyl) moiety.[2–6] In principle, such complexation offers the opportunity to generate unusual molecular architectures in modified βCDs, an aspect which is explored in this study. The driving force for intramolecular complexation is probably similar to that for the intermolecular complexation of guest species by CDs and appears to arise from the summation of weak secondary forces to give complexes of moderate stability.[6–8] Commonly, intramolecular complexing substituents and intermolecular guests possess hydrophobic character, a feature which is present in the substituents of the new modified βCDs discussed here. We selected cubyl and adamantyl substituents because they are strongly hydrophobic and models show that their three dimensional polycyclic structures fit into the βCD annulus. The cubyl substituents appear to be of a size which permits their passage through the primary and the secondary faces of βCD while there is the possibility of some mechanical constraint applying to the passage of the larger adamantyl substituent through the primary face. Substitution at the primary amine of **1** produces 6^A-deoxy-6^A-{6-[*N*-(4-methoxycarbonylcuban-1-ylcarbonyl)-amino]hexylamino}-β-cyclodextrin (**2**), 6^A-deoxy-6^A-{6-[*N*-(2,3-dimethyl-4-methoxycarbonylcuban-1-ylcarbonyl)amino]-hexylamino}-β-cyclodextrin (**3**), dimeric 1,4-bis{6-[*N*-(6^A-deoxy-β-cyclodextrin-6^A-yl)amino]hexylaminocarbonyl}-cubane (**4**) and 6^A-{6-[*N*-(1-adamantylcarbonyl)amino]hexylamino}-6^A-deoxy-β-cyclodextrin (**5**) (Fig. 1), which appear to be the first reported modified βCDs with substituents incorporating cubyl and adamantyl moieties. In D_2O **2**–**5** adopt structures **2′**–**5′** where the substituent intramolecularly complexes inside the βCD annulus to a significant extent as shown in Schemes 1–3.

† β-Cyclodextrin = cycloheptamaltose.

Results and discussion

The major products arising from the deacylation of 4-nitrophenyl acetate by 6^A-(6-aminohexylamino)-6^A-deoxy-β-cyclodextrin (**1**) are 6^A-deoxy-6^A-{6-[*N*-(methoxycarbonyl)amino]-hexylamino}-β-cyclodextrin and 4-nitrophenolate.[9] We have adapted this reaction to produce the C6 substituted CDs, **2**, **3**, **4** and **5** (Fig. 1) which in principle may either exist with the substituent outside the βCD annulus or intramolecularly complexed in it as shown for **2′**, **3′**, **4′** and **5′** in Schemes 1–3. (The truncated cones represent the βCD annuli where the secondary faces are delineated by 14 secondary hydroxy groups and the primary faces are delineated by 6 primary hydroxy groups and a secondary amine group.) Also shown in Fig. 1 is adamantane-1-carboxylate (**6**) which competes with the cubyl substituents for complexation in the βCD annulus as is discussed below. The preparations of the modified CDs in Fig. 1 and their complexing characteristics are now considered in more detail.

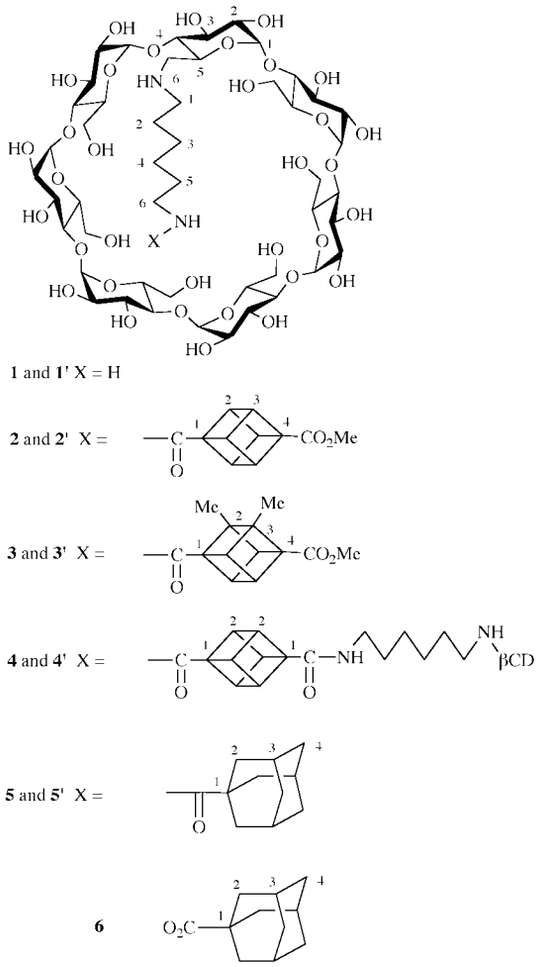


Fig. 1 Structures of C6 substituted βCDs, **1/1′**–**5/5′** where the substituent is intramolecularly complexed in the primed species and adamantane-1-carboxylate (**6**) showing the atom labelling scheme. The prefixes, hexyl, cubyl and adamantyl are used as appropriate in referring to ^{1}H and ^{13}C resonances in the NMR spectra.

6^{A}-Deoxy-6^{A}-{6-[*N*-(4-methoxycarbonylcuban-1-ylcarbonyl)-amino]hexylamino}-β-cyclodextrin (2) and 6^{A}-deoxy-6^{A}-{6-[*N*-(4-methoxycarbonyl-2,3-dimethylcuban-1-ylcarbonyl)amino]hexyl-amino}-β-cyclodextrin (3)

The reaction of **1** with either 1-methoxycarbonyl-4-(4-nitrophenoxycarbonyl)cubane (**7**) or racemic 1-methoxycarbonyl-2,3-dimethyl-4-(4-nitrophenoxycarbonyl)cubane (**8**) produces **2** and **3**, respectively, and 4-nitrophenolate (**9**) as shown in Scheme 1. The ^{1}H ROESY NMR spectrum of **3** shows significant cross-peaks arising from NOE interactions between the cubyl methine and methyl protons and the H3 and H5 protons which line the βCD annulus (Fig. 2 and Table 1). This is consistent with the complexation of the cubyl substituent in the annulus of **3′** as shown in Scheme 1. (Usually, the H3 and H5 resonances occur at δ ~3.8 and ~3.5 ppm, respectively, but in Fig. 2 they cannot be separately distinguished from the H6 resonances.) On addition of **6**, these interactions and cross-peaks are replaced by those arising from the NOE interactions of the adamantyl protons H1–H4 with the H3 and H5 annular protons of the intermolecular complex, **11**, consistent with the displacement of the cubyl moiety from the annulus by **6** (Fig. 3, Scheme 1 and Table 1). The orientation of **6** in **11** with the carboxylate function of **6** towards the secondary face of the βCD annulus, shown in Scheme 1, is consistent with modelling studies of intermolecular complexes formed by **6** with βCD and **1**.[9,10] Because of the homochirality of **1** its reaction with racemic **8** produces diastereomeric **3** and **3′**. In the latter case it is expected that the homochiral βCD

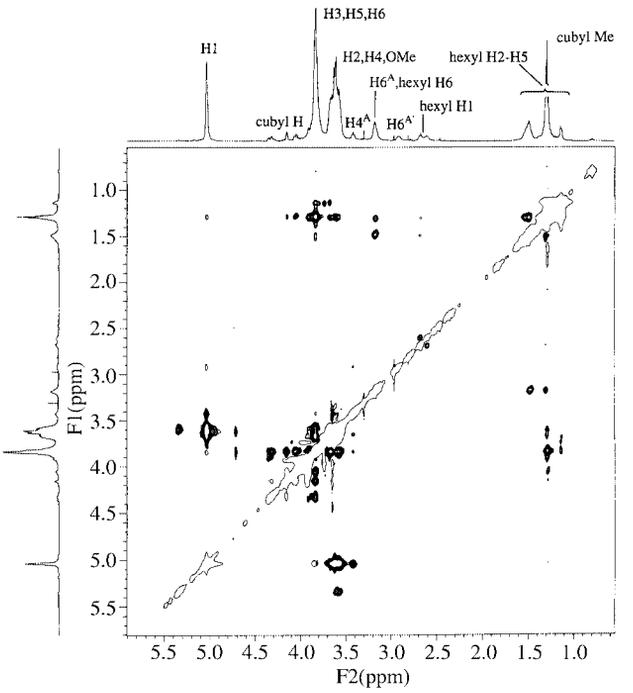


Fig. 2 600 MHz ^{1}H NMR ROESY spectrum of **3/3′** in D_2O at pD ≥ 11.

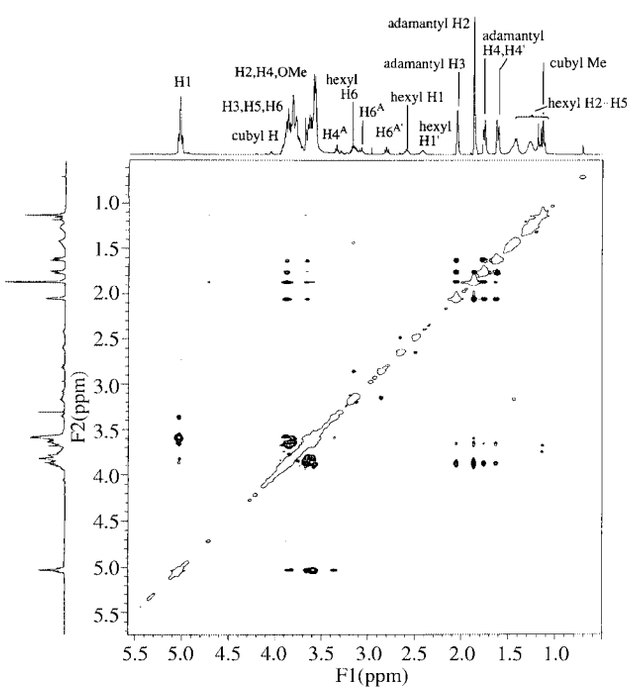


Fig. 3 600 MHz ^{1}H NMR ROESY spectrum of **3/3′** and **6** in D_2O at pD ≥ 11.

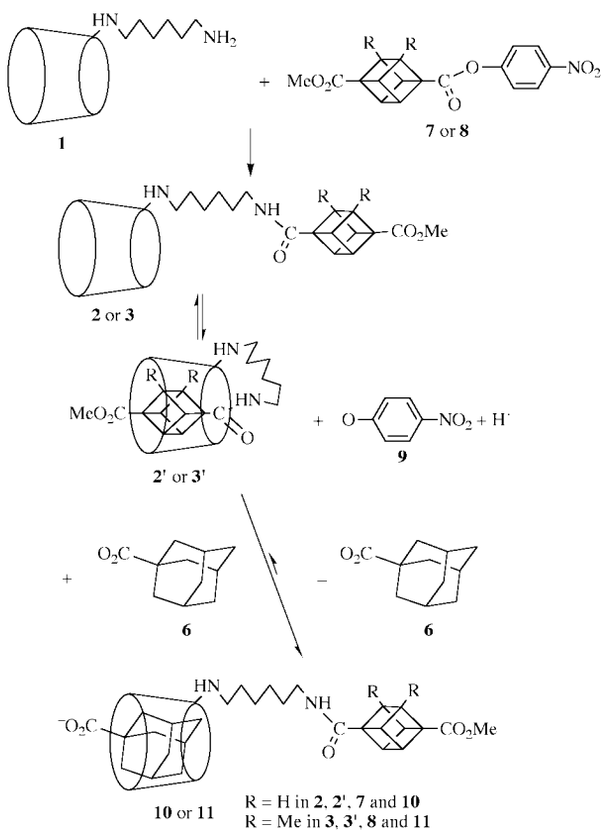
annulus could induce different ^{1}H NMR chemical shifts for the two enantiomers of the 2,3-dimethylcubyl moiety but this was not discerned.

The ^{1}H ROESY NMR spectrum of **2** shows cross-peaks consistent with NOE interactions occurring between the cubyl methine protons and the annular protons H3 and H5 (Table 1) consistent with the complexation of the cubyl moiety in the annulus of **2′** as shown in Scheme 1. On addition of **6**, these interactions and cross-peaks are replaced by those arising from the NOE interaction of the adamantyl protons H1–H4 with the H3 and H5 annular protons of the intermolecular complex, **10**, consistent with the displacement of the cubyl moiety from the annulus by **6** (Table 1 and Scheme 1).

Table 1 600 Mz ^{1}H NOE cross-peaks observed in ROESY NMR spectra of solutions of cubyl and adamantyl substituted βCDs[a]

Solution/Species	Annular protons	Cubyl protons		Adamantyl protons			
		Methine	Methyl	H2	H3	H4	H4′
Solution A **2**/**2**′	H3	+					
	H5	+					
Solution B **2**/**2**′ + **6**	H3			++	++	++	
	H5			+	+	+	
Solution C **3**/**3**′	H3	++	++				
	H5	+	++				
Solution D **3**/**3**′ + **6**	H3			++	++	++	
	H5		+	+	+	+	
Solution E **4**/**4**′	H3	+					
	H5	+					
Solution F **4**/**4**′ + **6**	H3			++	++	++	
	H5			++	+	+	
Solution G **5**/**5**′	H3			+++	+++	+	+
	H5			++	++		

[a] The spectra were run in D_2O at pD ≥ 11 at 298.2 K. The concentrations of the solutions of **2**, **2** + **6**, **3**, **3** + **6**, **4** and **5** were 0.06 mol dm^{-3} in each species, and in the solution of **4** + **6** the species concentrations were 0.06 and 0.12 mol dm^{-3}, respectively. The intensity of the cross peaks increases from + to +++.



Scheme 1

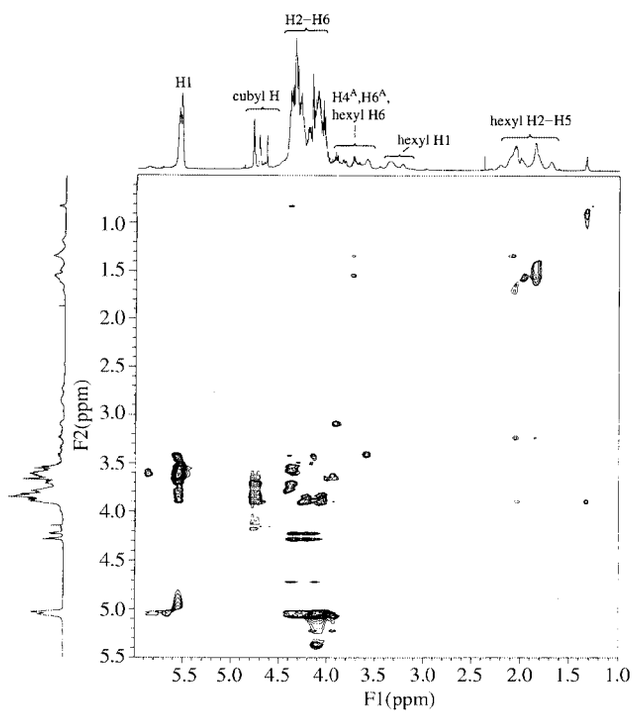


Fig. 4 600 MHz ^{1}H NMR ROESY spectrum of **4**/**4**′ in D_2O at pD ≥ 11.

1,4-Bis{6-[*N*-(6^A-deoxy-β-cyclodextrin-6^A-yl)amino]hexylaminocarbonyl}cubane (4)

The reaction of 2 moles of **1** with 1,4-bis(4-nitrophenoxycarbonyl)cubane (**12**) produces the dimer 1,4-bis{6-[*N*-(6^A-deoxy-β-cyclodextrin-6^A-yl)amino]hexylaminocarbonyl}cubane (**4**) together with two moles of **9** (Scheme 2). The 1D ^{1}H NMR spectrum shows at least three resonances for the non-equivalent cubyl protons and the ^{1}H ROESY NMR spectrum of **4** shows significant cross-peaks arising from NOE interactions between the cubyl methine protons and the H3 and H5 annular protons (Fig. 4 and Table 1). This is consistent with the intramolecular complexation of the cubyl moiety in one of the annuli of **4**′ (Scheme 2). On addition of two moles of **6** these cross-peaks are replaced by those arising from the NOE interaction of the adamantyl protons H1–H4 with the H3 and H5 annular protons of the intermolecular complex **13** consistent with the displacement of the cubyl moiety from the βCD annulus of **4**′ (Fig. 5, Table 1 and Scheme 2). Simultaneously, the 1D ^{1}H NMR spectrum (Fig. 5) simplifies to give a single resonance for the cubyl protons consistent with both the βCD moieties becoming equivalent and complexed by **6** in **13**.

6^A-{6-[*N*-(Adamant-1-ylcarbonyl)amino]hexylamino}-6^A-deoxy-β-cyclodextrin (5)

Our earlier studies showed that **1** exists predominantly in the intramolecular complexed form **1**′ in D_2O (Scheme 3).[1] In principle 1-(4-nitrophenoxycarbonyl)adamantane (**14**) may react with either **1** or **1**′ to give **5** and **5**′ (and **9**) which may exist in a dynamic equilibrium if the adamantyl moiety passes through the primary face of the βCD annulus. The NOE cross-peaks between the annular H3 and H5 protons and the adamantyl

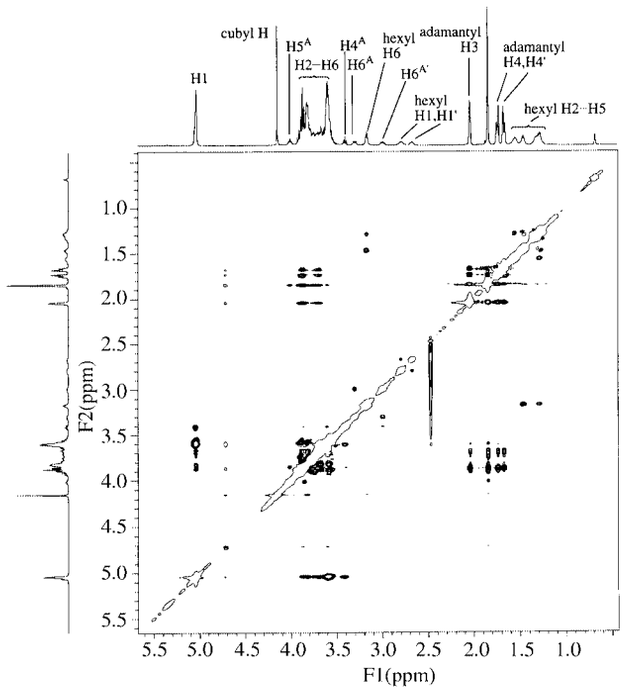
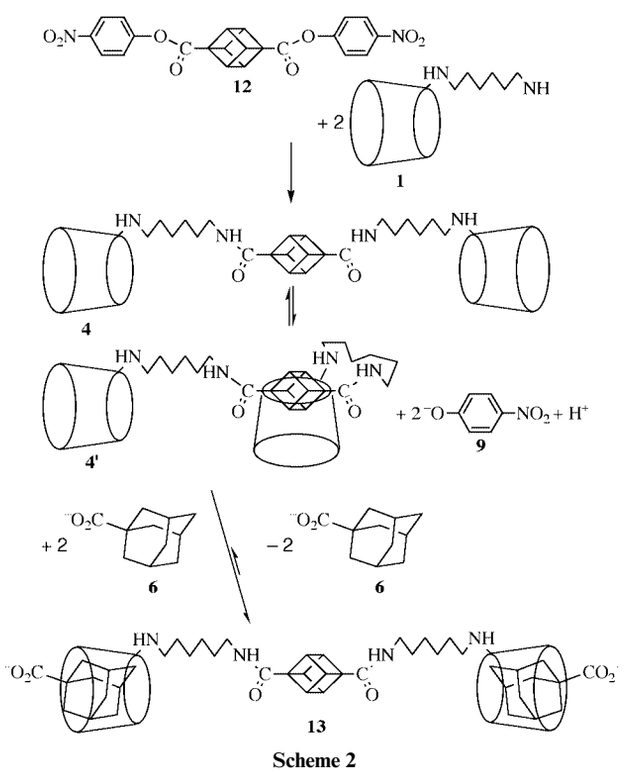
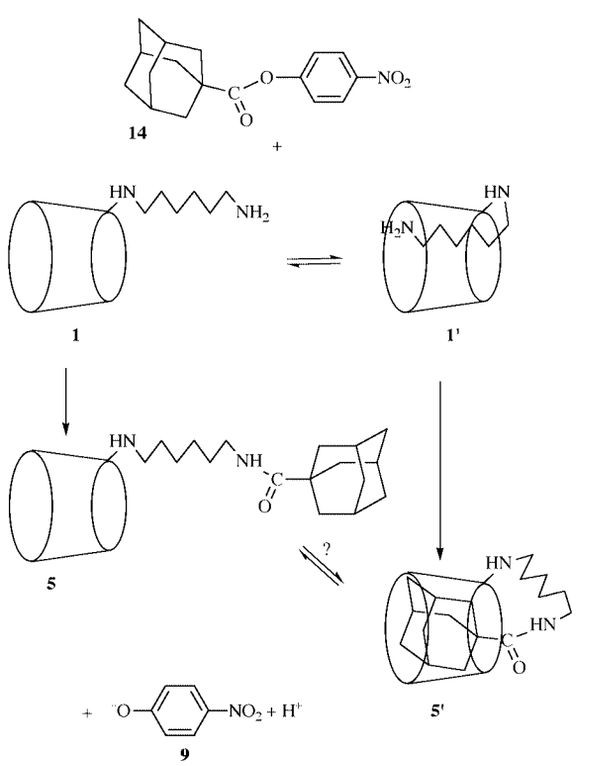


Fig. 5 600 MHz ^{1}H NMR ROESY spectrum of **4**/**4′** and **6** in D_2O at pD ≥ 11.

Fig. 6 600 MHz ^{1}H NMR ROESY spectrum of **5**/**5′** in D_2O at pD ≥; 11.



Scheme 2



Scheme 3

methine protons in the ^{1}H ROESY NMR spectrum of **5** (Table 1 and Fig. 6) are consistent with the adamantyl moiety residing in the annulus of the intramolecular complex **5′** to a significant extent. No change in the cross-peaks occurs on addition of two equivalents of **6**, although distinctive resonances of **6** appear in the 1D ^{1}H NMR spectrum. It appears that **6** is unable to compete with the intramolecularly complexed adamantyl substituent of **5′** to form an intermolecular complex. This may be because either the adamantyl substituent of **5′** has an entropic advantage in competing with **6**, or because substitution of **1′** by **14** through the secondary face of the βCD annulus produces **5′** where the adamantyl moiety is too large to pass through the primary face. In the latter case **5′** would constitute a mechanically constrained molecular slip-knot. Irrespective of whether the entropic or the mechanical constraint rationale is correct, it is apparent that **5′** has an unusually low capacity to form intermolecular complexes.

Conclusions

The intramolecular complexation of the cubyl moiety in the annuli of modified βCDs in preference to the hexyl chain, which links it to the amine group at C6, is consistent with the more spatially restricted fit of cubane producing a greater

thermodynamic stability in the intramolecular complex than that of the alternative complex where the flexible hexyl moiety intramolecularly complexes and excludes the cubyl moiety. However, despite the entropic advantage that the cubyl substituent might be expected to have in competition for occupancy of the βCD annulus in the formation of intramolecular complexes, it is excluded by **6** which forms intermolecular complexes. This is consistent with the closer fit of the adamantyl moiety in combination with its hydrophobicity stabilising its intermolecular complex by comparison with the intramolecular cubyl complex. This interpretation is also in accord with adamantan-1-ol, adamantan-2-ol and adamantane-1-carboxylic acid forming significantly more stable intermolecular complexes with N^{α}-dansyl-L-lysine-β-cyclodextrin than the smaller cage species (−)-borneol, (+)- and (−)-camphor and (+)- and (−)-fenchone.[5]

The intramolecular complexation of the reactive substituents of modified βCDs, exemplified by the aminohexyl substituent of 6^{A}-(6-aminohexylamino)-6^{A}-deoxy-β-cyclodextrin (**1**), offers the opportunity for a substituent bound at C6 to form an intramolecular complex (**1′**) and subsequently react at the secondary face with a reactive molecule which is too large to pass through the βCD annulus and form a mechanically constrained molecular slip-knot. Similarly, a substituent bound at either C2 or C3 might react at the primary face to form a molecular slip-knot. We are studying these possibilities.

Experimental

Physical methods

The ^{1}H NMR (300 MHz) and ^{13}C NMR (74.57 MHz) spectra were run on a Varian Gemini 300 spectrometer, except for the spectra of solutions A–G where ^{1}H ROESY NMR (600 MHz) spectra (mixing time of 0.35 s)[11] were run on a Varian Inova 600 spectrometer. The spectral assignments below are listed according to the atom labelling in Fig. 1. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} silica on aluminium sheets. Samples were eluted using a mixture of isopropanol–ethyl acetate–water–ammonium hydroxide (7 : 7 : 5 : 4). Compounds containing amino groups were detected by dipping the developed plate into a solution of 1% ninhydrin in ethanol and heating the plate. CDs were detected by dipping the developed plate into a solution of 1.5% H_2SO_4 in ethanol and heating the plate. Values of R_f are reported as R_c (retention relative to βCD).

Preparation of cubyl and adamantyl substituted β-cyclodextrins

Literature methods were used to prepare 6^{A}-(6-aminohexylamino)-6^{A}-deoxy-β-cyclodextrin,[12] 1-methoxycarbonylcubane-4-carboxylic acid, cubane-1,4-dicarboxylic acid and dimethyl 2,3-dimethylcubane-1,4-dicarboxylate.[13–16] Either standard procedures were employed in the preparation of the other compounds used in the preparations described below, or they were of good commercial grade. **CAUTION**: While no instability was noted in the cubyl-substituted βCDs prepared in this study, it should be noted that cubanes are high energy materials and should be handled accordingly.

1-Methoxycarbonyl-2,3-dimethylcubane-4-carboxylic acid

A 2 dm^3 mol^{-1} solution of sodium hydroxide in methanol (100 cm^3, 200 mmol) was added dropwise over 15 min, with stirring, to a solution of dimethyl 2,3-dimethylcubane-1,4-dicarboxylate (50 g, 201.4 mmol) in tetrahydrofuran (400 cm^3) at ~0 °C, under nitrogen. The cooling bath was then removed and the reaction mixture stirred for 16 h before being concentrated to dryness under reduced pressure. The resulting solid was partitioned between water (400 cm^3) and dichloromethane (250 cm^3). Desiccation ($MgSO_4$) and concentration of the CH_2Cl_2 extracts led to the recovery of 5.97 g (8.4%) of dimethyl 2,3-dimethylcubane-1,4-dicarboxylate. The aqueous solution was then acidified with conc. HCl to pH 3 and extracted with carbon tetrachloride (3 × 150 cm^3). These extracts upon desiccation ($MgSO_4$) and concentration furnished **2** as a colourless solid (38.9 g, 82.5%). Accurate mass 234.090 $[M]^+$. Calculated for $C_{13}H_{14}O_4$ $[M]^+$ 234.089. δ_H ($CDCl_3$) 1.24 (s, 3H), 1.28 (s, 3H), 3.70 (s, 3H), 3.81–3.91 (m, 3H), 4.06–4.17 (m, 3H); δ_C ($CDCl_3$) 12.18, 44.56, 44.67, 47.88, 47.95, 51.40, 55.11, 55.31, 56.70, 56.86, 171.47, 177.22.

1-Methoxycarbonyl-4-(4-nitrophenoxycarbonyl)cubane (7)

A mixture of 4-nitrophenol (0.139 g, 1 × 10^{-3} mol), 1-methoxycarbonylcubane-4-carboxylic acid (0.207 g, 1 × 10^{-3} mol) and dicyclohexylcarbodiimide (0.216 g, 1.02 × 10^{-3} mol) in dry CH_2Cl_2 (5 cm^3) was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite which was washed with CH_2Cl_2 (3 × 5 cm^3) and the combined filtrate was washed successively with 5% sodium bicarbonate solution (3 × 25 cm^3) and brine (25 cm^3) and dried over sodium sulfate. The filtered solution was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (2 cm^3) and subjected to flash chromatography (column 1.5 cm id, eluted with dichloromethane).[17] Fractions containing the product were combined and evaporated under reduced pressure to give the diester as colourless needles (0.163 g, 50%). This material was used in later steps without further purification. A small portion of this material was recrystallised from dichloromethane–hexane, mp 150–151 °C. Accurate mass 327.075 $[M]^+$. Calculated for $C_{17}H_{13}NO_6$ $[M]^+$ 327.074. δ_H ($CDCl_3$; 300 MHz) 8.27 (d, J = 6.8 Hz, 2H, ArH), 7.33 (d, J = 6.8 Hz, 2H, ArH), 4.4 (m, 6H, cubyl H), 3.75 (s, 3H, MeO); δ_C ($CDCl_3$) 171.6, 168.7, 155.3, 145.2, 125.1, 122.3, 55.7, 55.4, 51.5, 47.1, 47.0; IR ($CDCl_3$) 3114 (w), 3083 (w), 3019 (w), 2996 (m), 2948 (w), 1735 (s), 1722 (s), 1589 (m), 1521 (m), 1490 (s), 1430 (s), 1342 (s), 1305 (s), 1222 (m), 1199 (s), 1052 (s), 863 (m), 844 (m), 736 (m) cm^{-1}.

1-Methoxycarbonyl-4-(4-nitrophenoxycarbonyl)-2,3-dimethylcubane (8)

A mixture of 4-nitrophenol (0.142 g, 1.02 × 10^{-3} mol), 1-methoxycarbonyl-2,3-dimethylcubane-4-carboxylic acid (0.245 g, 1.05 × 10^{-3} mol) and dicyclohexylcarbodiimide (0.220 g, 1.07 × 10^{-3} mol) in dry CH_2Cl_2 (5 cm^3) was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite which was washed with CH_2Cl_2 (3 × 5 cm^3) and the combined filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform (2 cm^3) and subjected to flash chromatography (column 1.5 cm id, eluted with chloroform).[17] Fractions containing the product were combined and evaporated under reduced pressure to give a viscous oil (0.417 g) which solidified on standing. This material was used in later steps without further purification. A small portion of this material was recrystallised from dichloromethane–hexane, mp 79–80 °C. Accurate mass 355.104 $[M]^+$. Calculated for $C_{19}H_{17}NO_6$ $[M]^+$ 355.106. δ_H ($CDCl_3$; 300 MHz) 8.29 (d, J = 6.7 Hz, 2H, ArH), 7.31 (d, J = 6.7 Hz, 2H, ArH), 4.25 (m, 2H, cubyl H), 4.17 (m, 2H, cubyl H), 3.73 (s, 3H, MeO), 1.32 (s, 3H, Me), 1.31 (s, 3H, Me); δ_C ($CDCl_3$) 171.0, 168.3, 155.4, 145.3, 125.1, 122.4, 57.4, 56.8, 55.9, 55.3, 55.1, 51.25, 48.2, 44.9, 12.2, 12.0. IR (film) 3116 (w), 3085 (w), 2996 (m), 2915 (m), 2856 (m), 1745 (s), 1722 (s), 1614 (m), 1592 (m), 1525 (s), 1490 (m), 1436 (m), 1348 (s), 1324 (s), 1203 (s), 1160 (s), 1110 (s), 1091 (s), 1002 (m), 862 (m), 756 (m) cm^{-1}.

1,4-Bis(4-nitrophenoxycarbonyl)cubane (12)

A mixture of 4-nitrophenol (0.282 g, 2.00 × 10^{-3} mol), cubane-1,4-dicarboxylic acid (0.193 g, 1.00 × 10^{-3} mol) and dicyclohexylcarbodiimide (0.411 g, 2.0 × 10^{-3} mol) in CH_2Cl_2 (10 cm^3)

was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (30 cm^3). The combined filtrates were washed with 5% sodium bicarbonate (3 × 20 cm^3), water (20 cm^3) and brine (20 cm^3) and dried over sodium sulfate. The filtered solution was evaporated to about 20 cm^3 and loaded onto a squat column (30 g, 4.5 cm id) which was eluted with CH_2Cl_2.[18,19] Fractions containing the product were combined and evaporated under reduced pressure to give the diester as a white powder (0.263 g, 60%). A small portion of this material was recrystallised from dichloromethane–hexane, mp 215–217 °C. Accurate mass 434.074 $[M]^+$. Calculated for $C_{22}H_{14}N_2O_8$ $[M]^+$ 434.075. δ_H ($CDCl_3$; 300 MHz) 8.30 (d, J = 9.2 Hz, 4H, ArH2), 7.33 (d, J = 9.2 Hz, 4H, ArH3), 4.53 (s, 6H, cubyl H); δ_H($CDCl_3$) 168.5, 155.3, 145.5, 125.3, 122.4, 47.4. IR (Nujol) 1741 (s), 1612 (m), 1589 (m), 1521 (s), 1488 (m), 1339 (s), 1199 (s), 1049 (s) cm^{-1}.

1-(4-Nitrophenyloxycarbonyl)adamantane (14)

A mixture of 4-nitrophenol (0.139 g, 1.0×10^{-3} mol), adamantane-1-carboxylic acid (0.182 g, 1.0×10^{-3} mol) and dicyclohexylcarbodiimide (0.218 g, 1.1×10^{-3} mol) in CH_2Cl_2 (5 cm^3) was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (10 cm^3). The filtrate was loaded onto a squat column (30 g, 4.5 cm id)[18,19] and eluted with CH_2Cl_2 (100 cm^3). Fractions containing the ester were combined and evaporated under reduced pressure to give an off-white powder (0.270 g, 90%). This material was used in later steps without further purification. A small portion of this material was recrystallised from dichloromethane–hexane, mp 130–132 °C. Accurate mass 302.139 $[M + H]^+$. Calculated for $C_{17}H_{20}NO_4$ $[M + H]^+$ 302.139. δ_H ($CDCl_3$; 300 MHz) 8.21 (d, J = 9.0 Hz, 2H, ArH), 7.22 (d, J = 9.0 Hz, 2H, ArH), 2.04 (br s, 10H), 1.91 (br s, 2H), 1.70 (br s, 3H); δ_C ($CDCl_3$) 175.1, 156.0, 145.1, 124.9, 122.3, 41.0, 38.4, 38.1, 27.5. IR (Nujol) 1747 (s), 1614 (m), 1589 (m), 1519 (s), 1488 (m), 1342 (s), 1199 (s), 1049 (s) cm^{-1}.

6^A-Deoxy-6^A-{6-[*N*-(4-methoxycarbonylcuban-1-ylcarbonyl)-amino]hexylamino}-β-cyclodextrin (2)

A solution of **1** (0.128 g, 1.0×10^{-4} mol) and **7** (0.036 g, 1.1×10^{-4} mol) in dry DMF (2 cm^3) was stirred at room temperature for 20 h. The resultant yellow solution was added dropwise with stirring to 1 : 1 ether–ethanol (50 cm^3) cooled to 0 °C and the resultant fine yellow precipitate was collected by vacuum filtration on a Celite pad. The product was dissolved in water (5 cm^3) and the Celite was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and washed with CH_2Cl_2 (3 × 20 cm^3). The aqueous layer was treated with AG 4-X4 weak anion exchanger (5 g, Bio Rad Laboratories, 100–200 Mesh, free base form) for 1 h. The resin was removed by filtration and the filtrate was freeze-dried to give a colourless powder (0.072 g, 51%), R_c = 1.11; Electrospray-MS *m*/*z* 1421 (M^+) (Found: C, 45.71; H, 6.79; N, 1.75%. Calculated for **2**·HCl·5H_2O ($C_{59}H_{103}ClN_2O_{42}$) C, 45.77; H, 6.70; N, 1.80%); δ_C (D_2O) 176.5, 175.6 (C=O), 105.0 (C1), 87.3 ($C4^A$), 83.9 (C4), 76.0, 74.9, 72.4, 70.6 (C2, C3, C5), 63.0 (C6), 60.6, 58.7, 55.3, 52.3, 51.6, 49.5, 49.1, 40.3 ($C6^A$, cubyl C, hexyl C1, hexyl C6, MeO), 25–31 (broad band, hexyl C2–5).

6^A-Deoxy-6^A-{6-[*N*-(4-methoxycarbonyl-2,3-dimethylcuban-1-ylcarbonyl)amino]hexylamino}-β-cyclodextrin (3)

A solution of **1** (0.123 g, 1.0×10^{-4} mol) and **8** (0.058 g, 1.6×10^{-4} mol) in dry DMF (2 cm^3) was stirred at room temperature for 20 h. This solution was diluted with ether (50 cm^3) and the resultant precipitate was collected on a pad of Celite. The pad was washed with ether (3 × 10 cm^3) and then suspended in water (25 cm^3) to dissolve cyclodextrins. The Celite was filtered off and the filtrate was acidified with dilute hydrochloric acid and washed with CH_2Cl_2 (3 × 20 cm^3). The aqueous layer was treated with AG 4-X4 weak anion exchanger (5 g) for 1 h and the resin was removed by vacuum filtration. The colourless filtrate was freeze-dried to give the product as a white powder (0.092 g, 63%), R_c = 1.11; Electrospray-MS *m*/*z* 1449 (M^+) (Found: C, 46.94; H, 6.68; N, 1.79%. Calculated for **3**·HCl·4H_2O ($C_{61}H_{105}ClN_2O_{41}$) C, 47.03; H, 6.79; N, 1.80%); δ_C (D_2O) 175.8, 175.5 (C=O), 105.1 (C1), 86.7 ($C4^A$), 84.2 (C4), 76.0, 74.8, 72.3 (C2, C3, C5), 62.8 (C6), 60.9, 59.9, 59.7, 59.1, 57.5, 57.4, 54.5, 51.5, 49.6, 46.9, 46.1, 45.6, 41.7 ($C6^A$, cubyl C, hexyl C1, hexyl C6, MeO), 28.5–31.4 (broad band, hexyl C2–C5), 15.4, 14.5, 14.2 (cubyl Me).

1,4-Bis{6-[*N*-(6^A-deoxy-β-cyclodextrin-6^A-yl)amino]hexylamino-carbonyl}cubane (4)

A solution of **1** (0.128 g, 1.0×10^{-4} mol) and **12** (0.020 g, 4.61×10^{-5} mol) in dry DMF (2 cm^3) was stirred at room temperature for 20 h. The reaction mixture was diluted with ether (40 cm^3) and the resultant precipitate was collected by vacuum filtration and washed with ether (3 × 10 cm^3). The crude product was dissolved in water (20 cm^3) and the solution was acidified with dilute hydrochloric acid and extracted with CH_2Cl_2 (3 × 15 cm^3). The aqueous layer was treated with AG 4-X4 weak anion exchanger (5 g) for 1 h and the resin was removed by filtration and the colourless filtrate was diluted with acetic acid (1 cm^3) to increase solubility, and was freeze-dried to give the product as a white powder (0.046 g, 38%), R_c = 0.71; Electrospray-MS *m*/*z* 2622 (M^+) (Found: C, 45.33; H, 6.75; N, 2.21%. Calculated for **4**·2AcOH·9H_2O ($C_{110}H_{198}N_4O_{83}$) C, 45.48; H, 6.87; N, 1.93%); δ_C (D_2O) 175.9, 175.6 (C=O), 105.1, 104.6, 104.1 (C1), 87.8, 86.9, 85.8, 84.4, 84.3, 84.0, 83.8, 83.3, 83.1 (C4), 75.8, 75.6, 75.3, 75.2, 74.9, 74.7, 74.5, 72.3, 72.2, 72.1, 70.4, 69.6 (C2, C3, C5), 63.2, 63.0, 60.5, 60.1 (C6), 51.5, 51.0, 50.8, 49.4, 49.1, 49.0, 48.8, 42.0, 41.9, 39.7 ($C6^A$, cubyl C, hexyl C1, hexyl C6), 34.7, 34.0, 31.8, 31.4, 31.1, 30.8, 29.6, 29.5, 29.2, 28.6, 28.3, 28.2, 27.9, 27.5, 25.6, 25.0 (broad band, hexyl C2–C5).

6^A-Deoxy-6^A-{6-[*N*-(1-adamantylcarbonyl)amino]hexylamino}-β-cyclodextrin (5)

A solution of **1** (0.130 g, 1.05×10^{-4} mol) and **14** (0.037 g, 1.22×10^{-4} mol) in dry DMF (4 cm^3) was stirred at room temperature for 20 h. TLC showed two new spots at R_c 1.2 and 1.0. The reaction mixture was diluted with ether (40 cm^3) and the resultant precipitate was collected by vacuum filtration and washed with ether (3 × 10 cm^3). The crude product was dissolved in water (20 cm^3) and the solution was acidified with dilute hydrochloric acid and extracted with CH_2Cl_2 (3 × 15 cm^3). The aqueous layer was treated with AG 4-X4 weak anion exchanger (5 g) for 1 h and the resin was removed by filtration and the colourless filtrate was freeze-dried to give the product as a white powder (0.103 g, 70%). R_c = 1.2, 1.0; Electrospray-MS *m*/*z* 1395 (M^+) (Found: C, 45.98; H, 7.07; N, 1.86%. Calculated for **5**·HCl·7H_2O ($C_{59}H_{111}ClN_2O_{41}$) C, 46.02; H, 7.27; N, 1.82%); δ_C (D_2O) 182.4 (177.1) (C=O), 105.2, 105.0, 104.8, 102.3 (C1), 87.85, 86.7, 86.0, 84.5, 84.3, 84.2, 84.1, 83.8 (C4), 79.5, 76.0, 75.9, 75.8, 75.5, 75.2, 75.1, 75.0, 74.8, 74.7, 74.6, 74.5, 73.9, 72.3, 72.2, 72.1, 70.2, 69.6 (C2, C3, C5), 63.2, 63.0, 62.8, 62.7 (C6), 57.1, 51.1, 50.6, 48.8, 45.5, 43.3, 43.2, 42.0, 41.5, 39.4, 39.2, 38.6 ($C6^A$, hexyl C1, hexyl C6, adamantyl C1–C3), 34.9, 33.9, 31.8, 31.3, 30.7, 30.3, 30.0, 29.4, 28.5, 28.0, 27.8, 27.4, 26.0, 25.0 (hexyl C2–C5, adamantyl C4).

600 MHz 1D ^1H and ^1H ROESY NMR spectra of D_2O solutions A–G

Solution A containing 2/2′. 1D ^1H NMR data: δ_H 4.76 (br s, 7H, H1), 4.30 (m, 3H, cubyl H), 4.16 (m, 3H, cubyl H′), 3.4–4.0

(m, 42H, βCD H, MeO), 3.33 (m, 2H, C4^{A}, hexyl H6), 3.06 (m, 2H, H6^{A}, hexyl H6′), 2.8 (m, 1H, C6$^{A'}$), 2.55 (m, 1H, hexyl H1), 2.40 (m, 1H, hexyl H1′), 1.1–1.5 (m, 8H, hexyl H2–5); ^{1}H ROESY NMR data: δ_H 3.4–4.0 (βCD H) shows cross-peaks with 4.16 (cubyl H′), 4.30 (cubyl H), 4.16 shows cross-peaks with 3.4–4.0 (βCD H), 4.30 (cubyl H) shows cross-peaks with 3.4–4.0 (βCD H).

Solution B containing 2/2′ and 6. 1D ^{1}H NMR data: δ_H 5.04 (br s, 7H, H1), 4.20 (m, 2H, cubyl H), 4.12 (m, 4H, cubyl H′), 3.5–4.0 (m, 42H, βCD H, MeO), 3.37 (t, J = 9.6 Hz, 1H, H4^{A}), 3.17 (m, 3H, H6^{A}, hexyl H6), 2.87 (m, 1H, H6$^{A'}$), 2.67 (m, 1H, hexyl H1), 2.47 (m, 1H, hexyl H1′), 2.04 (br s, 3H, adamantyl H3), 1.86 (br s, 6H, adamantyl H2), 1.75 (d, J = 12.0 Hz, 3H, adamantyl H4), 1.64 (d, J = 12.0 Hz, 3H, adamantyl H4′), 1.2–1.5 (m, 8H, hexyl H2–H5); ^{1}H ROESY NMR data: δ_H 1.64 (adamantyl H4′) shows cross-peaks with 3.5–4.0 (βCD H), 1.75 (adamantyl H4) shows cross-peaks with 3.5–4.0 (βCD H), 1.86 (adamantyl H2) shows cross-peaks with 3.5–4.0 (βCD H), 2.04 (adamantyl H3) shows cross-peaks with 3.5–4.0 (βCD H), 3.54 (βCD H) shows cross-peaks with 1.64 (adamantyl H4′), 1.75 (adamantyl H4), 1.86 (adamantyl H2), 2.04 (adamantyl H3).

Solution C containing 3/3′. 1D ^{1}H NMR data: δ_H 5.04 (br s, 7H, H1), 3.5–4.4 (m, 46H, cubyl H, βCD H, MeO), 3.42 (t, J = 9.0 Hz, 1H, H4^{A}), 3.19 (m, 3H, H6^{A}, hexyl H6), 2.92 (m, 1H, H6$^{A'}$), 2.64 (m, 2H, hexyl H1), 1.1–1.5 (m, 14H, hexyl H2–H5, Me); ^{1}H ROESY NMR data: δ_H 1.3 (Me) shows cross-peaks with 3.5–4.0 (βCD H), 4.0–4.2 (cubyl H), 3.5–4.0 (βCD H) shows cross-peaks with 1.3 (Me), 4.0–4.2 (cubyl H), 4.0–4.2 (cubyl H) shows cross-peaks with 1.3 (Me), 3.5–4.0 (βCD H).

Solution D containing 3/3′ and 6. 1D ^{1}H NMR data: δ_H 5.05 (br s, 7H, H1), 3.5–4.2 (m, 46H, cubyl H, βCD H, MeO), 3.36 (t, J = 9.0 Hz, 1H, H4^{A}), 3.10 (m, 3H, H6^{A}, hexyl H6), 2.81 (dd, J = 7.2, 14.3 Hz, 1H, H6$^{A'}$), 2.59 (m, 1H, hexyl H1), 2.42 (m, 1H, hexyl H1′), 2.05 (br s, 3H, adamantyl H3), 1.87 (br s, 6H, adamantyl H2), 1.76 (d, J = 12 Hz, 3H, adamantyl H4), 1.61 (d, J = 12 Hz, 3H, adamantyl H4′), 1.1–1.4 (m, 14H, hexyl H2–H5, Me); ^{1}H ROESY NMR data: δ_H 1.61 (adamantyl H4′) shows cross-peaks with 3.8 (H3), 1.76 (adamantyl H4) shows cross-peaks with 3.8 (H3), 1.87 (adamantyl H2) shows cross-peaks with 3.8 (H3), 2.05 (adamantyl H3) shows cross-peaks with 3.8 (H3), 3.8 (H3) shows cross-peaks with 1.61 (adamantyl H4′), 1.76 (adamantyl H4), 1.87 (adamantyl H2), 2.05 (adamantyl H3).

Solution E containing 4/4′. 1D 1H NMR data: δ_H (D_2O) 5.00 (br s, 14H, H1), 2.5–4.4 (m, 142H, cubyl H, βCD H, hexyl H1, hexyl H6), 1.1–1.8 (m, 16H, hexyl H2–H5); ^{1}H ROESY NMR data: δ_H 4.1–4.4 (cubyl H) shows cross-peaks with 3.5–4.0 (βCD H) and *vice versa*.

Solution F containing 4/4′ and 6. 1D 1H NMR data: δ_H 5.06 (s, 14H, H1), 4.16 (s, 6H, cubyl H), 4.01 (t, J = 9.2 Hz, 2H, H5^{A}), 3.9–3.5 (m, 76H, H2–H6), 3.40 (t, J = 9.2 Hz, 2H, H4^{A}), 3.30 (d, J = 13.2 Hz, 2H, H6^{A}), 3.18 (m, 4H, hexyl H6), 3.01 (m, 2H, H6$^{A'}$), 2.80 (m, 2H, hexyl H1), 2.68 (m, 2H, hexyl H1′), 2.04 (s, 6H, adamantyl H3), 1.84 (s, 12H, adamantyl H2), 1.74 (d, J = 11 Hz, 6H, adamantyl H4), 1.67 (d, J = 11 Hz, 6H, adamantyl H4′), 1.2–1.6 (m, 16H, hexyl H2–H5); ^{1}H ROESY NMR data: δ_H 1.2–1.6 (hexyl H2–H5) shows cross-peaks with 3.18 (hexyl H6), 1.67 (adamantyl H4′) shows cross-peaks with 3.6–3.9 (H3, H5), 1.74 (adamantyl H4) shows cross-peaks with 3.6–3.9 (H3, H5), 1.84 (adamantyl H2) shows cross-peaks with 3.6–3.9 (H3, H5), 2.04 (adamantyl H3) shows cross-peaks with 3.6–3.9 (H3, H5), 3.18 (hexyl H6) shows cross-peaks with 1.2–1.6 (hexyl H2–H5), 3.6–3.9 (H3, H5) shows cross-peaks with 1.67 (adamantyl H4′), 1.74 (adamantyl H4), 1.84 (adamantyl H2), 2.04 (adamantyl H3).

Solution G containing 5/5′. 1D ^{1}H NMR data: δ_H 5.1 (br s, 7H, H1), 3.5–4.0 (m, 39H, βCD H), 3.32 (t, J = 9.0 Hz, 1H, H4^{A}), 3.25 (m, 1H, hexyl H6), 3.0 (m, 2H, hexyl H6′, H6^{A}), 2.79 (dd, J = 9.0, 12.0 Hz, 1H, H6^{A}), 2.56 (m, 1H, hexyl H1), 2.28 (m, 4H, hexyl H1′, adamantyl H3), 1.94 (d, J = 12.6 Hz, 3H, adamantyl 4), 1.84 (s, 6H, adamantyl H2), 1.79 (d, J = 12.6 Hz, 3H, adamantyl H4′), 1.0–1.8 (m, 8H, hexyl H2–H5); ^{1}H ROESY NMR data: δ_H 1.79 (adamantyl H4′) shows cross-peaks with 3.7–4.0 (βCD H), 1.84 (adamantyl H2) shows cross-peaks with 3.5–4.0 (βCD H), 2.28 (adamantyl H3) shows cross-peaks with 3.7–4.0 (βCD H).

Solution H containing 5/5′ and 6. 1D ^{1}H NMR data: δ_H 5.1 (br s, 7H, H1), 3.5–4.0 (m, 39H, βCD H), 3.37 (t, J = 9.0 Hz, 1H, H4^{A}), 3.23 (m, 1H, hexyl H6), 3.16 (m, 1H, hexyl H6′), 3.07 (d, J = 12.0 Hz, 1H, H6^{A}), 2.80 (dd, J = 9.0, 12.0 Hz, 1H, H6^{A}), 2.57 (m, 1H, hexyl H1), 2.29 (m, 1H, hexyl H1′), 2.17 (br s, 3H, adamantyl H3), 1.95 (br s, 6H, adamantyl H3 of **6**), 1.84 (m, 9H, adamantyl H4, adamantyl H2), 1.79 (m, 15H, adamantyl H2 of **6**, adamantyl H4′), 1.67 (br s, 6H, adamantyl H4 of **6**), 1.0–1.8 (m, 8H, hexyl H2–5); ^{1}H ROESY NMR data: δ_H 1.67 (adamantyl H4 of **6**) shows cross-peaks with 3.8–4.0 (βCD H), 1.8 (adamantyl H4′) shows cross-peaks with 3.8–4.0 (βCD H), 1.84 (adamantyl H2) shows cross-peaks with 3.5–4.0 (βCD H), 2.17 (adamantyl H3) shows cross-peaks with 3.8–4.0 (βCD H).

Acknowledgements

We are grateful to the Australian Research Council and the University of Adelaide for supporting this research. We thank Nihon Shokuhin Kako Co. for a gift of βCD.

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Paper a905390e