Intramolecular complexation in modified β-cyclodextrins:† a preparative, nuclear magnetic resonance and pH titration study

Michael J. Field,[a] Bruce L. May,[a] Philip Clements,[a] John Tsanaktsidis,[b] Christopher J. Easton[c] and Stephen F. Lincoln[a]*

[a] *Department of Chemistry, University of Adelaide, Adelaide, SA 5005, Australia*
[b] *CSIRO Molecular Science, Private Bag 10, Clayton South MDC, Vic 3169, Australia*
[c] *Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia*

Received (in Cambridge, UK) 13th December 1999, Accepted 28th February 2000
Published on the Web 31st March 2000

The reactions of 4-nitrophenyl trinorbornane-2-acetate and 4-nitrophenyl noradamantane-1-carboxylate with 6^A-(6-aminohexylamino)-6^A-deoxy-β-cyclodextrin **1** produce 6^A-{6-(bicyclo[2.2.1]heptan-2-ylacetylamino)hexylamino}-6^A-deoxy-β-cyclodextrin **2** (pK_a = 8.98) and 6^A-deoxy-6^A-{6-(tricyclo[3.3.1.0^{3,7}]nonan-3-ylcarbonylamino)-hexylamino}-β-cyclodextrin **4** (pK_a = 8.47), respectively, in good yield together with 4-nitrophenolate. The reaction of 2,3-dimethyl-1,8-bis-(4-nitrophenoxycarbonyl)cubane with two moles of **1** produces dimeric 1,8-bis-[6-(6^A-deoxy-β-cyclodextrin-6^A-ylamino)hexylaminocarbonyl]-2,3-dimethylcubane **7** (pK_a = 8.80) in good yield together with two moles of 4-nitrophenolate. The pK_as in brackets are those of the single protonated amine functions of **2** and **4**, and of both protonated amine functions of **7** which have identical pK_as [in each case at 298.2 K and I = 0.10 mol dm^{-3} ($NaClO_4$)]. ^{1}H NMR ROESY studies are consistent with the trinorbornyl, noradamantyl and dimethylcubyl entities of **2**, **4** and **7** complexing inside the βCD annuli in D_2O at pD ≥ 11. Under the same conditions, adamantane-1-carboxylate forms intermolecular complexes with **2**, **4** and **7** and displaces their trinorbornyl, noradamantyl and the dimethylcubyl entities from the β-cyclodextrin annulus to varying degrees depending on the relative size, shape and hydrophobicity of these groups. These data are compared with those for analogous modified β-cyclodextrins.

Introduction

The intramolecular complexation of the 6-aminohexylamino substituent in the β-cyclodextrin (βCD) annulus of 6^A-(6-aminohexylamino)-6^A-deoxy-β-cyclodextrin (**1**, Fig. 1)[1] provides the possibility of generating a range of intramolecularly complexing modified βCDs through substitution of the primary nitrogen of **1** with a variety of entities, X.[2,3] When the precursor of the X substituent has either one or two groups participating in this substitution, a modified βCD monomer and a linked βCD dimer are obtained, respectively (Schemes 1 and 2, where 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). We have previously prepared such monomers where X is either a cubyl, a dimethylcubyl or an adamantyl entity and a dimer where X incorporates a cubyl entity (**3** and its dimethylcubyl analogue, **5** and **6** in Fig. 1).[2] We now report preparations where X incorporates trinorbornyl and noradamantyl entities into the modified βCD monomers (**2** and **4** in Fig. 1 and Scheme 1), and the dimethylcubyl entity into the βCD dimer (**7** in Fig. 1 and Scheme 2). The X entities of **2**, **4** and **7** were selected on the basis that they are hydrophobic and likely to enter the largely hydrophobic βCD annulus to form intramolecular complexes stabilised by a combination of secondary forces in aqueous solution.[4–10] The modified βCDs incorporating these X entities, together with analogous species reported earlier, facilitate an experimental assessment of the extent to which the size of X places a mechanical constraint on its occupancy of the annuli of the modified βCD monomers and dimers. Also shown in Fig. 1 is adamantane-1-carboxylate, **8**, which competes with the substituents for intramolecular complexation in the βCD annulus as is discussed below. The ability of the guest **8** to displace the X entity from the annulus is dependent on the relative size, shape and hydrophobicity of the polycyclic entity X.

† β-Cyclodextrin = cycloheptamaltose.

Results and discussion

The reaction of 4-nitrophenyl trinorbornane-2-acetate **9** and 4-nitrophenyl noradamantane-1-carboxylate **10** with **1** produced 6^A-{6-(bicyclo[2.2.1]heptan-2-ylacetylamino)hexylamino}-6^A-deoxy-β-cyclodextrin **2** and 6^A-deoxy-6^A-{6-(tricyclo[3.3.1.0^{3,7}]nonan-3-ylcarbonylamino)hexylamino}-β-cyclodextrin **4** (Scheme 1), respectively, in good yield together with 4-nitrophenolate **11**. The reaction of 1,2-dimethyl-3,8-bis (4-nitrophenoxycarbonyl)cubane **14** with two mole equiv. of **1** produced 1,8-bis[6-(6^A-deoxy-β-cyclodextrin-6^A-ylamino)-hexylaminocarbonyl]-2,3-dimethylcubane **7** in good yield together with two moles of **11** (Scheme 2). These new modified βCDs may either exist as **2**, **4** and **7** with their substituents outside the βCD annulus or as **2′**, **4′** and **7′** where the substituents are intramolecularly complexed inside the βCD annulus.

The experimental evidence for the equilibria shown in Schemes 1 and 2 depends on solution ^{1}H and ^{13}C NMR spectroscopy, of which the major aspects are presented below. Detailed resonance assignments based on the COSY and HSQC spectra of the new derivatives appear at the conclusion of each of the preparative sections for **2**, **4** and **7** in the Experimental section.

6^A-{6-(Bicyclo[2.2.1]heptan-2-ylacetylamino)hexylamino}-6^A-deoxy-β-cyclodextrin 2 and 6^A-deoxy-6^A-{6-(tricyclo[3.3.1.0^{3,7}]-nonan-3-ylcarbonylamino)hexylamino}-β-cyclodextrin 4

The ^{1}H ROESY NMR spectrum of **2**/**2′** showed significant cross-peaks arising from NOE interactions between the tri-

DOI: 10.1039/a909766j

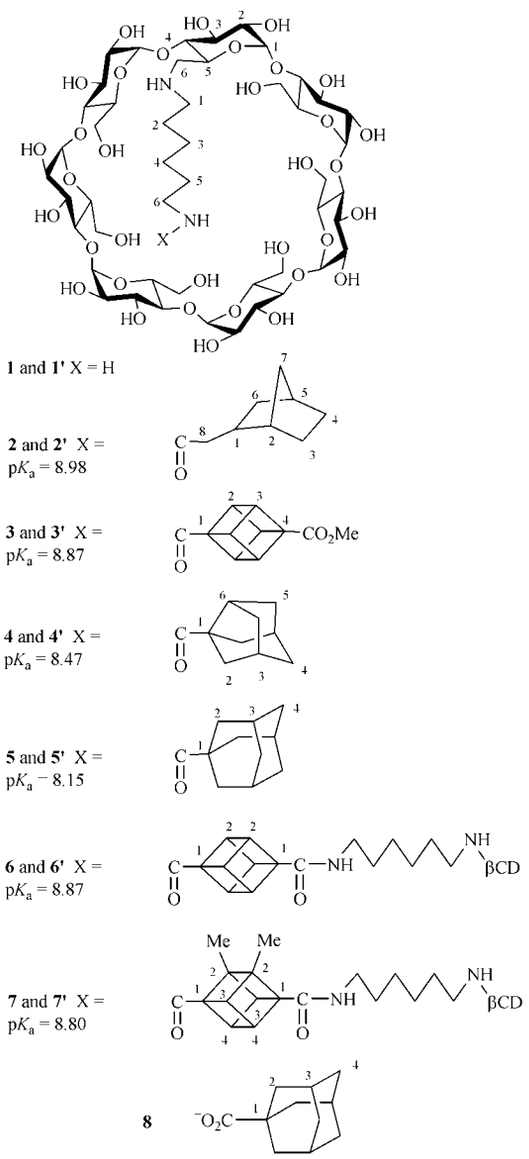
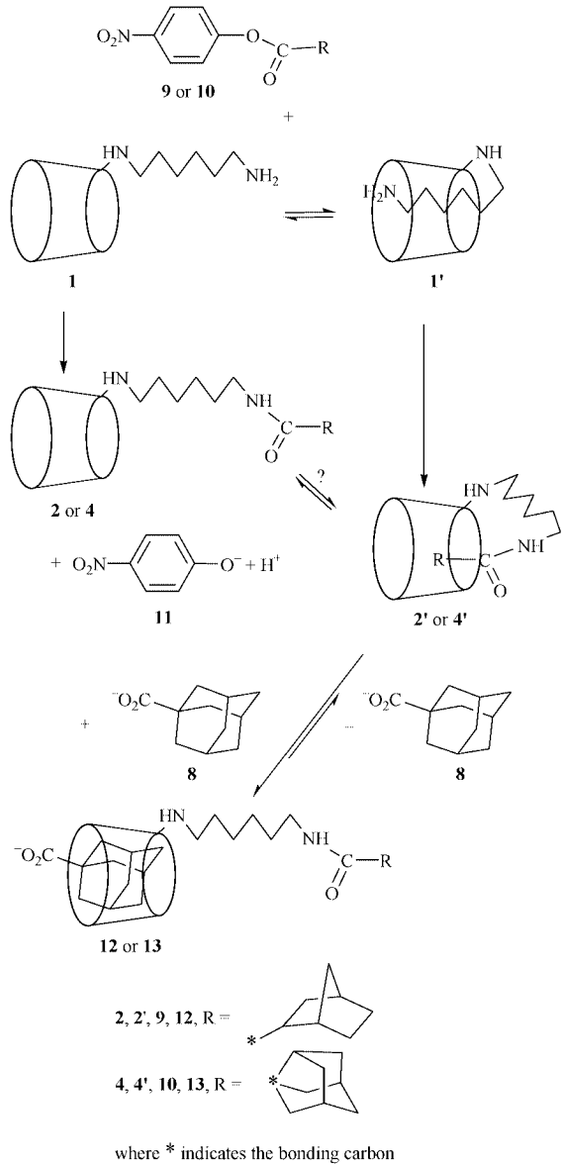


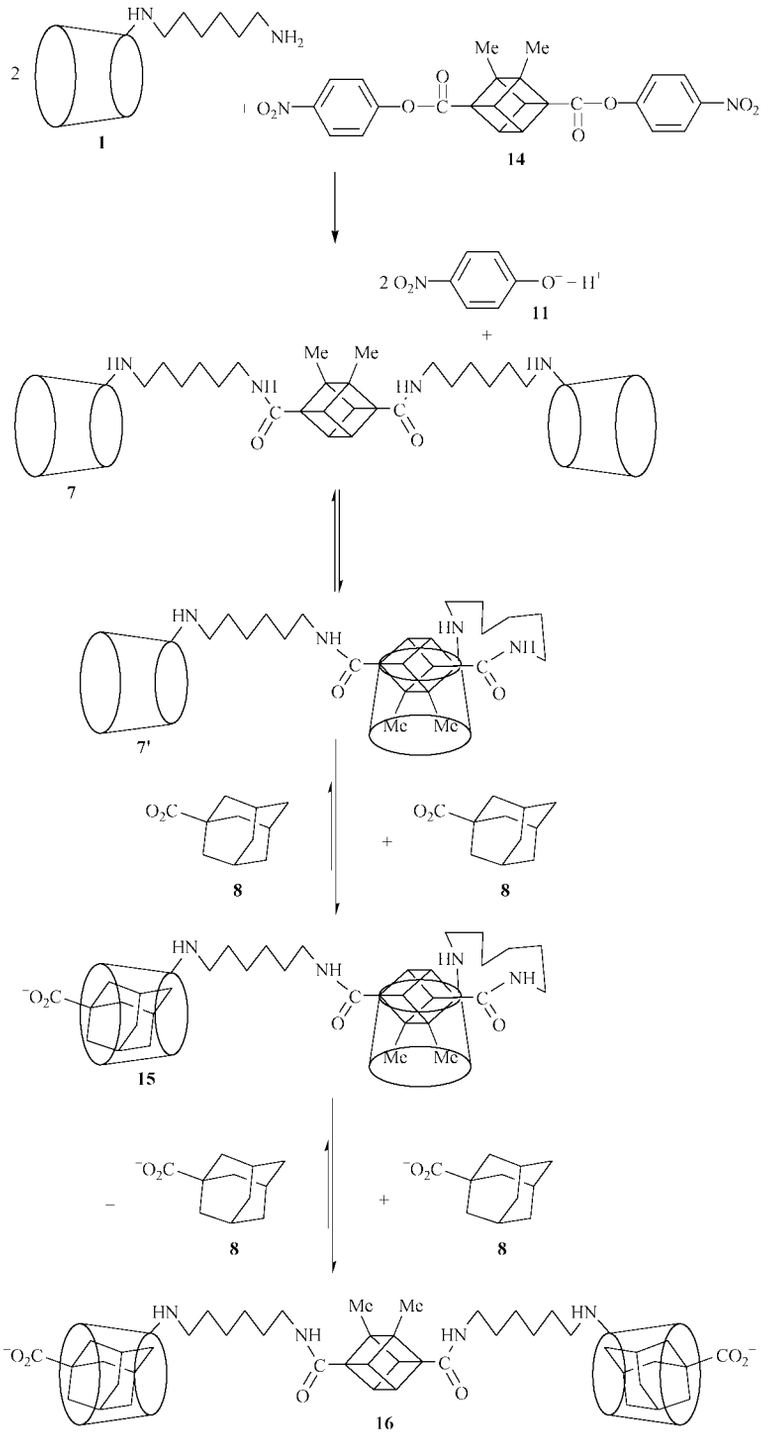
Fig. 1 Structures of C-6-substituted βCDs, **1/1′**–**7/7′**, where the substituent is intramolecularly complexed in the primed species, adamantane-1-carboxylate **8**, showing the (mostly arbitrary) atom-labelling schemes. The prefixes annular, hexyl, trinorbornyl, cubyl, noradamantyl and adamantyl are used as appropriate in referring to ^{1}H and ^{13}C resonances in the NMR spectra. The pK_as (± 0.02) are those of the protonated secondary amine function in each case at 298.2 K and $I = 0.10$ mol dm^{-3} ($NaClO_4$). In each case the amine groups of **6** and **7** have identical pK_as.



Scheme 1

norbornyl protons and the annular H-3 and H-5 protons which line the interior of the βCD annulus (Table 1). The analogous spectrum of **4/4′** showed cross-peaks between the noradamantyl protons and the annular H-3 and H-5 protons (Fig. 2 and Table 1). This is consistent with intramolecular complexation of the trinorbornyl and noradamantyl substituent in the annulus of **2′** and **4′** as shown in Scheme 1. Usually, the annular H-3 and H-5 resonances occur at δ ≈3.8 and ≈3.5, respectively, but in Fig. 2 they can neither be separately distinguished from each other nor from the resonance of H-6 which lies on the outside of the annulus. Hence the separate assignment of cross-peaks arising from the annular H-3 and H-5 is not possible. However, as the variations in the ROESY spectra discussed herein are consistent with intra- and intermolecular complexation in the βCD annulus, it seems unlikely that any of the cross-peaks arise from NOE interactions of the protons of complexed entities with H-6 on the outside of the βCD annulus. (Cross-peaks also arise from interactions between protons which are at small through-bond separations from each other, but these provide little information on complexation and are not further considered.)

On addition of **8**, new cross-peaks (Table 1) arising from the NOE interactions of the adamantyl H-1- H-4 protons with the annular H-3 and H-5 protons appeared, consistent with **8** competing with the intramolecularly complexed trinorbornyl and noradamantyl entities to form the intermolecular complexes **12** and **13** in Scheme 1. (The orientation of the carboxylate group of **8** towards the secondary face of the βCD annuli of **12** and **13** shown in Scheme 1 is consistent with modelling studies of intermolecular complexes formed by **8** with βCD and **1**.[2,11,12]) However, the cross-peaks arising from the protons of the trinorbornyl and noradamantyl entities remained, at a lower intensity, consistent with the intramolecular complexes **2′** an **4′** coexisting in solution with the intermolecular complexes **12** and **13**, respectively. The complexation of the adamantyl group within the annuli of **2** and **4** in competition with the trinorbornyl and noradamantyl groups, respectively, is consistent with the measured values of the formation constants for complexation of adamantane-1-carboxylate, noradamantane-1-carboxylate and trinorbornane-2-acetate within β-cyclodextrin ($K = 4.2 \times 10^4$, 8.2×10^3 and 4.3×10^3 dm^3 mol^{-1} at pH 7.2, respectively).[12] The stability of the intramolecular complexes **2′** and **4′** is probably enhanced by the favourable entropy contribution arising from the tether-



Scheme 2 A form of **7′** where the hexyl entity is complexed in the second βCD annulus probably also exists but this is not shown in the Scheme.

ing of the trinorbornyl and noradamantyl groups to the βCD entity.

Similar intramolecular complexation of the cubyl and adamantyl entities of **3** and **5** to form **3′** and **5′**, respectively, has been reported.[3] However, while **8** displaced the cubyl entity from the annulus of **3′**, it did not displace the adamantyl entity from the annulus of **5′** possibly because the intramolecularly complexed adamantyl substituent of **5′** has an entropic advantage in competing with **8** for occupancy of the βCD annulus. Alternatively, it may be that substitution of **1′** through the secondary face of the βCD annulus produces **5′** and the adamantyl entity is too large to pass through the primary face. In the latter case, **5′** is a mechanically constrained molecular slip-knot. Despite uncertainty as to whether the entropic or the mechanical constraint rationale is correct, the ability of the trinorbornyl and noradamantyl entities of **2′** and **4′** to compete with **8** for occupancy of the βCD annulus, whereas the cubyl and dimethylcubyl entities of **3′** and its dimethylcubyl analogue **7′** appear to be less effective,[3] is consistent with a decreasing strength of intramolecular retention in the βCD annulus in the sequence: adamantyl > noradamantyl ≈ trinorbornyl > dimethylcubyl ≈ cubyl. This suggests that a combination of closeness of fit and degree of hydrophobicity of the substituent determines the relative stabilities of the modified βCD intramolecular complexes. It is also consistent with the closer fit of the adamantyl entity of **8**, in combination with its hydrophobicity, stabilising its intermolecular complex with **3** by comparison with the intramolecular cubyl complex **3′**. This interpretation is in accord with adamantan-1-ol, adamantan-2-ol and adamantane-1-carboxylate competing

Table 1 600 MHz ^{1}H NMR ROESY cross-peaks observed in D_2O solution at pD ≥ 10 and identified as arising from intra- and intermolecular complexation

	System **2/2′**								
Annular protons	Trinorbornyl protons								
	Nor H-2	Nor H-5	Nor H-8	Nor H-8′	Nor H[a]				
H-3	+	+	+	+	+				
H-5	+	+	+	+	+				
	System **2/2′** + **8**								
Annular protons	Trinorbornyl and adamantyl protons								
	Nor H-2	Nor H-5	Nor H-8	Not H-8′	Nor H[a]	Adam 2	Adam 3	Adam 4	Adam 4′
H-3	+	+	+	+	+	+	+	+	+
H-5	+	+	+	+	+	+	+	+	+
	System **4/4′**								
Annular protons	Noradamantyl protons								
	Norad H-3	Norad H-6	Norad H[a]						
H-3	+	+	+						
H-5	+	+	+						
	System **4/4′** + **8**								
Annular protons	Noradamantyl and adamantyl protons								
	Norad H-3	Norad H-6	Norad H[a]	Adam 2	Adam 3	Adam 4			
H-3	+	+	+	+	+	+			
H-5	+	+	+	+	+	+			
	System **7/7′**								
Annular protons	Hexyl and dimethylcubyl protons								
	Hexyl H-2–H-5	Cubyl H[a]	Cubyl Me						
H-3	+	+	+						
H-5	+	+	+						
	System **7/7′** + **8**								
Annular protons	Dimethylcubyl and adamantyl protons								
	Cubyl Me	Adam 2	Adam 3	Adam 4	Adam 4′				
H-3	+	+	+	+	+				
H-5	+	+	+	+	+				

[a] Identification of individual resonances uncertain. Crosses indicate the presence of a cross-peak.

more effectively with the dansyl entity for occupancy of the βCD annulus of N^{α}-dansyl-L-lysine-β-cyclodextrin than do (−)-borneol, (+)- and (−)-camphor and (+) and (−)-fenchone which are smaller.[5] Intramolecular complexation of aromatic substituents of modified βCDs is well established, particularly in the case of those incorporating the dansyl entity.[4–8]

1,8-Bis[6-(6^{A}-deoxy-β-cyclodextrin-6^{A}-ylamino)hexylamino-carbonyl]-2,3-dimethylcubane 7

The substituted βCD **7**, prepared from the racemic diester **14** and homochiral **1**, was a 1 : 1 mixture of diastereomers. The 1D ^{1}H NMR spectrum of **7/7′** showed three multiplet resonances for the dimethylcubyl methine protons and a single resonance for the methyl protons. The ^{1}H ROESY NMR spectrum showed cross-peaks arising from NOE interactions between the dimethylcubyl methine and methyl protons and the annular H-3 and H-5 protons (Fig. 3 and Table 1). Cross-peaks also arise from the interaction of the hexyl H-2–H-5 protons with the annular H-3 and H-5 protons, which is consistent with complexation of a hexyl entity in the second βCD annulus. These observations are consistent with exchange of the dimethylcubyl entity between the two equivalent annular intramolecular complexation sites of **7′** (Scheme 2) occurring slowly on the ^{1}H NMR timescale and resulting in an inequivalence of the βCD entities. There was no detectable spectral differentiation of the diastereomers of **7/7′** in the ^{1}H NMR spectra.

On addition of two mol equiv. of **8**, ^{1}H NMR spectral changes occurred consistent with step-wise intermolecular complexation of **8** to give a symmetric 2 : 1 guest : host complex, **16**, through the 1 : 1 intermediate complex **15**. New cross-peaks arose from the NOE interaction of the adamantyl protons H-1–H-4 with the annular H-3 and H-5 protons of the intermolecular complex **16** (Scheme 2 and Table 1). The cross-peaks from the hexyl H-2–H-5 protons disappeared, consistent with **8** displacing the hexyl entity from a βCD annulus. While the

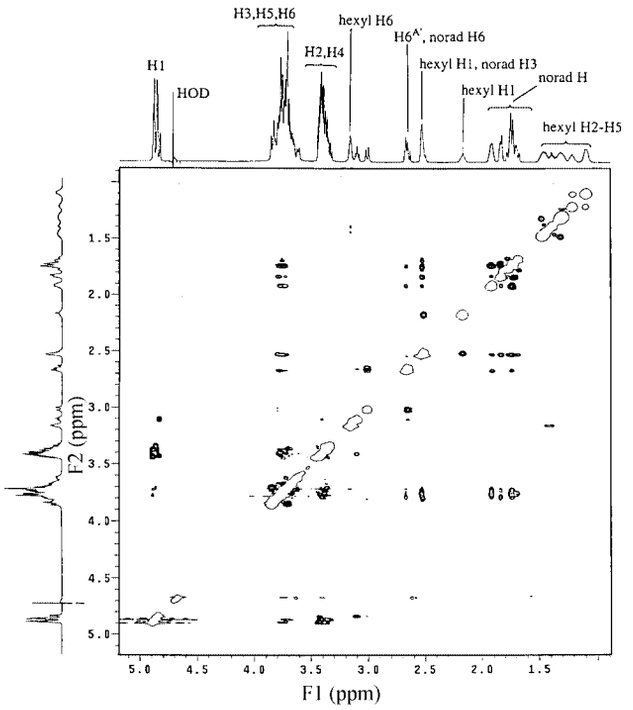


Fig. 2 600 MHz ^{1}H NMR ROESY spectrum of **4**/**4′** in D_2O at pH ≥ 11.

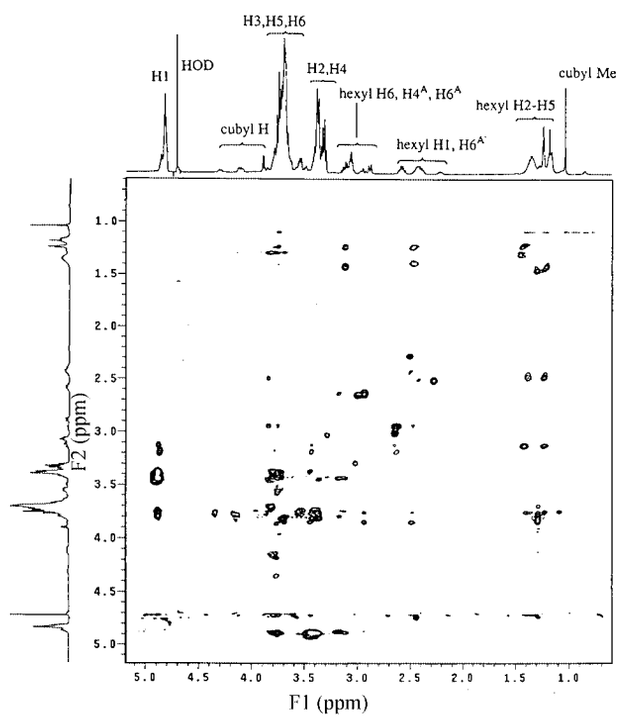


Fig. 3 600 MHz ^{1}H NMR ROESY spectrum of **7**/**7′** in D_2O at pH ≥ 11.

observed changes in chemical shift rendered any change in the cross-peaks arising from the dimethylcubyl methine protons difficult to detect because of other overlapping cross-peaks, a cross-peak arising from the methyl protons interacting with the annular H-3 or H-5 protons remained. This is consistent with the dimethylcubyl entity competing with **8** for occupancy of a βCD annulus through the equilibria between **7′**, **15** and **16** shown in Scheme 2. In the 1D ^{1}H NMR spectrum, only a single resonance was observed for the cubyl protons, consistent with both βCD entities becoming equivalent and complexed by **8** in **16**, the dominant species in solution. (Similar equilibria have previously been reported for **6** and **6′**.[3])

These interpretations are supported by ^{13}C NMR studies. In D_2O solution, three carbonyl and five methyl ^{13}C resonances were observed, arising from both the asymmetry of **7′** and some spectral differentiation of the diastereomers of **7**/**7′**. On addition of two mol equiv. of **8**, only single carbonyl and methyl ^{13}C resonances were observed, consistent with the dominant formation of the symmetric 2:1 guest:host complex **16** (Scheme 2). In **7′**, the distereomeric dimethylcubyl entities were distinguished by two distinct pairs of methyl ^{13}C resonances arising from differing interactions of the methyl groups with the homochiral βCD annulus. It appears that a combination of the deep penetration of the methyl groups into the βCD annulus of **7′** and the large chemical-shift scale for ^{13}C was responsible for this detection of chiral discrimination but no other evidence for it was provided by either the ^{13}C or ^{1}H spectra.

pK_a Studies

The pK_as of the new modified βCDs **2**, **4** and **7**, and those of their earlier reported analogues **3**, **5** and **6**, were determined by pH titration (Fig. 1). The increased acidity of the protonated amine group of the modified βCDs, by comparison with that expected for simple aliphatic diamines, was similar to that observed in other amino-substituted βCDs.[13] This may partially have arisen from either the electronic and steric effects of the βCD entity, or a change in solvation experienced by a protonated amine adjacent to the βCD annulus, or combination of these factors. The pK_a of the protonated amine decreased as the size and hydrophobicity of the X entity increased, consistent with an increasingly hydrophobic environment destabilising the protonated amine. The βCD dimers **6** and **7** were each characterised by identical pK_as for the two protonated amines, consistent with each amine being sufficiently insulated from a change in the protonation state of its twin to behave independently. This may also be reflected through the identical pK_as of **3** and **6**. The protonated amine groups of the modified βCDs experienced different environments in their uncomplexed and intramolecularly complexed forms. However, two distinct pK_as were not observed, consistent with either the intramolecular complex being greatly dominant, or for exchange between it and its uncomplexed analogue being sufficiently rapid to yield an averaged pK_a, or a combination of these effects. (Above pH 10 a time-dependent pH change occurred for **3**, which is thought to arise from hydrolysis of the methyl ester.)

Experimental

Physical methods

Elemental analyses were carried out by the Microanalytical Service of the University of Otago. Modified βCDs were characterised as the hydrates by adding whole molecules of water to the molecular formula to give the best fit to the microanalytical data. Mps were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. As βCD derivatives generally decompose without melting above 180 °C, mps were not determined for these compounds. TLC was carried out on Kieselgel 60 F_{254} (Merck) on aluminium backed plates. Unless otherwise stated, plates were developed with 7:7:5:4 *v*/*v* ethyl acetate–propan-2-ol–ammonium hydroxide–water for the analysis of all cyclodextrin samples. Compounds bearing amino groups were visualised by drying the plate then dipping it into a solution of 0.5% ninhydrin in ethanol and heating it with a heat-gun. Modified βCDs were further visualised by dipping the plate into a solution of 1% sulfuric acid in ethanol and heating it with a heat-gun. Iodine vapour was also used to visualise cyclodextrins. The value R_c represents the R_f of a modified βCD relative to the R_f of βCD. Squat-column chromatography was carried out using Kieselgel 60 F_{254} TLC-grade silica.[14]

IR spectra were recorded on an ATI Mattson Genesis FT-IR. The abbreviations strong (s), medium (m), weak (w) and broad (b) are used in reporting the IR data. Electrospray mass spectroscopy (ESMS) was carried out at the Australian National University. Samples were dissolved in 10% acetonitrile for injection and the cone voltage was set to 120 V.

All ^{1}H and ^{13}C NMR spectra were run on solutions 0.10 mol dm^{-3} in the cyclodextrin of interest using Varian Gemini 200 and 300 spectrometers except for the ROESY ^{1}H NMR spectra which were run on a Varian Inova 600 using a standard sequence with a mixing time of 0.3 s.[15] The modified βCDs **2**, **4** and **7** (and **8** when present) were dissolved in D_2O to give final concentrations of 0.06 mol dm^{-3} of each component and a final pH ≥ 11 adjusted with NaOD. The resultant solutions were filtered (0.22 μm) and degassed by freeze–thawing before the spectra were recorded. Resonances were assigned on the basis of COSY and HSQC spectra. The spectral assignments presented below with the preparative details of each modified βCD are listed according to the (mostly arbitrary) atom labelling in Fig. 1. All chemical shifts are referenced to aq. 3-(trimethylsilyl)propanesulfonic acid as external standard.

pH Titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer and an Orion 8172 Ross Sureflow combination pH electrode filled with 0.10 mol dm^{-3} $NaClO_4$. Titration solutions were saturated with nitrogen by passing a fine stream of bubbles (previously passed through aqueous 0.10 mol dm^{-3} NaOH followed by 0.10 mol dm^{-3} $NaClO_4$) through them for at least 15 min before the commencement of the titration. During the titrations a similar stream of nitrogen bubbles was passed through the titration solution which was magnetically stirred and held at 298.2 ± 0.1 K in a water-jacketed 20 cm^3 titration vessel which was closed to the atmosphere except for a small exit for nitrogen. In all titrations, standardised 0.100 mol dm^{-3} NaOH was titrated against solutions which were 1×10^{-3} mol dm^{-3} in the species of interest, 5×10^{-3} mol dm^{-3} in $HClO_4$ and 9.5×10^{-2} mol dm^{-3} in $NaClO_4$ ($I = 0.10$). Values of E_o and pK_w were determined by titration of a solution which was 1×10^{-4} mol dm^{-3} in $HClO_4$ and 9×10^{-4} mol dm^{-3} in $NaClO_4$ against 0.100 mol dm^{-3} NaOH. Values of pK_a were determined using the program SUPERQUAD.[16] At least three runs were performed for each system and at least two of these runs were averaged, the criterion for selection for this averaging being that χ^2 for each run was <12.6 at the 95% confidence level.

Preparations of modified β-cyclodextrins and their precursors

Literature methods were used to prepare 6^A-(6-aminohexylamino)-6^A-deoxy-β-cyclodextrin[13] and dimethyl 2,3-dimethylcubane-1,8-dicarboxyate.[17] 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.

4-Nitrophenyl trinorbornane-2-acetate 9

A mixture of trinorbornane-2-acetic acid (0.571 g, 3.70×10^{-3} mol), 4-nitrophenol (0.516 g, 3.71×10^{-3} mol) and dicyclohexylcarbodiimide (DCC) (0.748 g, 3.63×10^{-3} mol) in dichloromethane (10 cm^3) was stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure to give the crude ester as a yellow oil. This material was further purified by passage through a squat column eluted with dichloromethane. Fractions containing the ester were combined and evaporated to give the product as a colourless oil (0.830 g, 83%). An attempt to further purify the ester by bulb-to-bulb distillation (150 °C/0.05 mmHg) resulted in some decomposition. Accurate mass data: calculated for **9** ($C_{15}H_{18}NO_4$) $(M + H)^+$, 276.1236. Found: *m*/*z*, 276.1249; δ_H (200 MHz; $CDCl_3$) 8.27 (d, *J* 9.2 Hz, 2H, ArH), 7.28 (d, *J* 9.2 Hz, 2H, ArH), 2.0–2.5 (m, 5H), 1.0–1.6 (m, 8H); δ_C (50.4 MHz; $CDCl_3$) 170.6 (C=O), 155.5, 145.1, 125.0, 122.4 (ArC), 41.1, 38.3, 38.1, 37.6, 36.7, 35.2, 29.6, 28.4; ν_{max} (film)/cm^{-1} 3115w, 3088w, 2951s, 2871s, 1768s, 1706m, 1615m, 1593m, 1525s, 1490m, 1455w, 1347s, 1208s, 1162s, 1106s, 915m, 864m, 749w, 716w.

6^A-{6-(2-Bicyclo[2.2.1]heptan-2-ylacetylamino)hexylamino}-6^A-deoxy-β-cyclodextrin 2

A mixture of **1** (0.565 g, 4.58×10^{-4} mol) and **9** (0.131 g, 4.76×10^{-4} mol) in DMF (5 cm^3) was stirred at room temperature for 3 h and then diluted with diethyl ether (100 cm^3). The resultant yellow precipitate was collected by vacuum filtration and washed with diethyl ether (100 cm^3). The solid was dissolved in water (20 cm^3) and the solution was acidified by the addition of 3 mol dm^{-3} HCl (1 cm^3). The solution was washed with dichloromethane (3 × 20 cm^3) and then treated with AG 4-X4-anion-exchange resin (free-base-form, 10 g). The filtered solution was evaporated and the residue was dissolved in water (10 cm^3) and loaded on to a BioRex 70 cation-exchange column (NH_4^+-form, 4.5 × 4.5 cm). The column was eluted with water (100 cm^3) and fractions containing the product were combined, and evaporated under reduced pressure to give **2** as a white powder (0.320 g, 51%), $R_c = 1.4$; ESMS *m*/*z* 1370 $(M + H)^+$ [Found: C, 46.65; H, 7.22; N, 1.83. Calc. for M·**2**.5H_2O ($C_{57}H_{106}N_2O_{40}$): C, 46.91; H, 7.32; N, 1.92%]; δ_H (**2**/**2′**; 600 MHz; D_2O; pH ≥ 11) 4.89 (br s, 7H, H-1), 3.6–3.9 (m, 26H, H-3, -5, -6), 3.2–3.5 (m, 14H, H-2, -4, hexyl H-6), 2.9–3.2 (m, 3H, H-4^A, -6^A, hexyl H-6′), 2.67 (t, *J* 12.0 Hz, 1H, H-6$^{A'}$), 2.51 (m, 1H, hexyl H-1), 2.35 (br s, 1H, H-1), 2.24 (m, 1H, hexyl H-1′), 2.06 (m, 1H, trinorbornyl H-8), 1.95 (br s, 1H, trinorbornyl H-2), 1.74 (m, 1H, trinorbornyl H-8′), 0.9–1.7 (m, 17H, hexyl H-2–H-5 + trinorbornyl H); δ_C (**2**/**2′**; 75.4 MHz; D_2O; pH ≥ 11) 176.7 (C=O), 105.9, 105.6 (C-1), 87.45 (C-4^A), 85.1, 84.4 (C-4), 76.8, 76.6, 76.2, 75.9, 75.3, 74.8 (C-2, -3, -5), 70.3 (C-5^A), 63.0 (C-6), 52.2 (C-6^A), 49.4 (hexyl C-1), 46.4 (trinorbornyl C-8), 44.3, 42.2, 40.4, 39.3, 38.3, 38.2, 32.7, 31.4, 31.1, 30.7, 28.8, 27.3; δ_H (**2**/**2′** + 1 mol equiv. **8**; 600 MHz; D_2O; pH ≥ 11) 4.89 (br s, 7H, H-1), 3.6–3.9 (m, 26H, H-3, -5, -6), 3.2 (br s, 13H, H-2, -4), 2.9–3.2 (m, 4H, H-4^A, -6^A, hexyl H-6), 2.70 (m, 1H, H-6$^{A'}$), 2.50 (m, 1H, hexyl H-1), 2.30 (m, 1H, hexyl H-1′), 2.20 (br s, 1H, trinorbornyl H-5), 1.8–2.1 (m, 6H, trinorbornyl H-2 and -8, adamantyl H-3), 1.76 (s, 6H, adamantyl H-2), 0.8–1.7 (m, 23 H, adamantyl H-4, trinorbornyl H, hexyl H-2–H-5).

4-Nitrophenyl noradamantane-1-carboxylate 10

A solution of noradamantane-1-carboxylic acid (0.505 g, 3.04×10^{-3} mol), 4-nitrophenol (0.430 g, 3.09×10^{-3} mol) and DCC (0.624 g, 3.03×10^{-3} mol) was stirred at room temperature for 3 h. The reaction mixture was filtered and the filtrate was washed successively with 5% aq. sodium hydrogen carbonate (3 × 20 cm^3) and brine (20 cm^3) and dried over sodium sulfate. The filtered solution was evaporated under reduced pressure and the oily residue was suspended in 1 : 1 dichloromethane–hexane and loaded onto a squat column (4.5 cm i.d.; 30 g silica gel). Elution of the column was commenced with 1 : 1 dichloromethane–hexane and the proportion of dichloromethane was progressively increased. Fractions containing the product were combined, and evaporated under reduced pressure to give the product as a colourless oil which solidified on storage (0.812 g, 93%), mp 82–83 °C; EI-MS *m*/*z* 287 ($M^{+\bullet}$) [Found: C, 66.81; H, 5.91; N, 4.99. Calculated for **10** ($C_{16}H_{17}NO_4$): C, 66.89; H, 5.96; N, 4.87%]; δ_H (200 MHz; $CDCl_3$) 8.26 (d, *J* 9.2 Hz, 2H, ArH), 7.28 (d, *J* 9.2 Hz, 2H, ArH), 2.86 (t, *J* 6.6 Hz, 1H, H-7), 2.24 (m, 4H), 1.91 (m, 4H), 1.73 (m, 4H); δ_C (50.4 MHz; $CDCl_3$) 175.0 (C=O), 156.0, 145.1, 125.1, 122.4 (ArC), 54.1 (C-3), 46.8 (C-7), 44.5 (C-9), 43.5 (C-6), 37.4 (C-1),

34.5 (C-2); ν_{max} (Nujol)/cm^{-1} 1747s, 1614m, 1591m, 1521s, 1346s, 1305m, 1274m, 1209m, 1182s, 1097m, 1074m, 1020m, 997m, 873m, 862m, 742m.

6^{A}-Deoxy-6^{A}-{6-(tricyclo[3.3.1.0^{3,7}]nonan-3-ylcarbonylamino)-hexylamino}-β-cyclodextrin 4

A mixture of **1** (0.504 g, 4.09×10^{-4} mol) and 4-nitrophenyl noradamantane-1-carboxylate (0.125 g, 4.36×10^{-4} mol) in DMF (7 cm^3) was stirred at room temperature for 3 h and then diluted with diethyl ether (100 cm^3). The resultant yellow precipitate was collected by vacuum filtration and washed with diethyl ether (100 cm^3). The solid was dissolved in water (20 cm^3) and the solution was acidified by the addition of 3 mol dm^{-3} HCl (1 cm^3). The solution was washed with dichloromethane (3 × 20 cm^3) and then treated with AG 4-X4 anion-exchange resin (free-base-form, 10 g). The filtered solution was evaporated and the residue was dissolved in water (10 cm^3) and loaded on to a BioRex 70 cation-exchange column (NH_4^+-form, 4.5 × 4.5 cm). The column was eluted with water (100 cm^3) and fractions containing the product were combined, and evaporated under reduced pressure to give **4** as a white powder (0.307 g, 54%), R_c = 1.4; ESMS *m*/*z* 1382 (M + H)$^+$ [Found: C, 46.46; H, 7.30; N, 1.83. Calc. for M·**4**·7H$_2$O ($C_{58}H_{110}N_2O_{42}$): C, 46.21; H, 7.35; N, 1.86%]; δ_H (**4**/**4**′; 600 MHz; D_2O; pH ≥ 11) 4.8 (m, 7H, H-1), 3.6–3.9 (m, 26H, H-3, -5, -6), 3.3–3.5 (m, 13H, H-2, -4), 3.16 (br s, 2H, hexyl H-6), 3.10 (t, *J* 9.0 Hz, 1H, H-4^{A}), 3.01 (d, *J* 13.0 Hz, 1H, H-6^{A}), 2.67 (m, 2H, H-6$^{A'}$, noradamantyl H-6), 2.53 (m, 3H, hexyl H-1, noradamantyl H-3), 2.17 (m, 1H, hexyl H-1′), 1.7–2.0 (m, 10H, noradamantyl H), 0.9–1.5 (m, 8H, hexyl H-2–H-5); δ_C (**4**/**4**′; 75.4 MHz; D_2O; pH ≥ 11) 181.6 (C=O), 106.1, 106.0, 105.9 (C-1), 88.0 (C-4^{A}), 85.1, 85.0, 84.9, 84.8, 84.7 (C-4), 76.7, 76.5, 76.4, 76.1, 75.9, 75.1, 75.0, 74.9, 74.8, 74.7 (C-2, -3, -5), 70.5 (C-5^{A}), 63.4, 63.3, 63.0, 62.9, 62.8 (C-6), 57.9 (noradamantyl C-1), 52.4 (C-6^{A}), 51.4, 50.8, 49.6 (hexyl C-1), 46.7, 46.5, 45.4 (noradamantyl C-6), 40.1, 39.9 (hexyl C-6, noradamantyl C-5), 36.7, 31.0, 30.8, 28.2, 26.1 (hexyl C-2–C-5); δ_H (**4**/**4**′ + 1 mol equiv. **8**; 600 MHz; D_2O; pH ≥ 11) 4.8 (m, 7H, H-1), 3.6–3.9 (m, 26H, H-3, -5, -6), 3.3–3.5 (m, 13H, H-2, -4), 3.15 (m, 3H, H-4^{A}, hexyl H-6), 2.96 (d, *J* 13.0 Hz, 1H, H-6^{A}), 2.70 (dd, *J* 9.0, 13.0 Hz, 1H, H-6$^{A'}$), 2.60 (m, 1H, noradamantyl H-6), 2.50 (m, 1H, hexyl H-1), 2.28 (br s, 2H, noradamantyl H-5), 2.26 (m, 1H, hexyl H-1′), 1.95 (s, 3H, adamantyl H-3), 1.5–1.9 (m, 22H, adamantyl H, noradamantyl H), 1.0–1.5 (m, 8H, hexyl H-2–H-5).

2,3-Dimethyl-1,8-bis(4-nitrophenoxycarbonyl)cubane 14

A mixture of 2,3-dimethylcubane-1,8-dicarboxylic acid (0.320 g, 1.45×10^{-3} mol), 4-nitrophenol (0.409 g, 2.94×10^{-3} mol) and DCC (0.613 g, 2.98×10^{-3} mol) in dichloromethane (8 cm^3) was stirred at room temperature for 18 h. The reaction mixture was filtered and the collected solid was washed with dichloromethane (3 × 10 cm^3). The combined filtrate was washed with 5% aq. sodium hydrogen carbonate (3 × 20 cm^3) and dried over sodium sulfate. The solution was concentrated to approx. 20 cm^3 and loaded onto a squat column (30 g silica gel; 4.5 cm i.d.) and the column was eluted successively with dichloromethane (3 × 25 cm^3) and chloroform (3 × 25 cm^3). Fractions containing the product were combined and evaporated to give the diester as a white powder (0.451 g, 67%). A portion of this material was recrystallised from dichloromethane–hexane, mp 202–204 °C [Found: C, 62.32; H, 3.90; N, 6.08. Calc. for **14** ($C_{24}H_{18}N_2O_8$): C, 62.34; H, 3.92; N, 6.06%]; δ_H (200 MHz; $CDCl_3$) 8.31 (d, *J* 8.4 Hz, 4H, ArH), 7.29 (d, *J* 8.4 Hz, 4H, ArH), 4.38 (t, *J* 4.0 Hz, 2H, cubyl H), 4.12 (t, *J* 4.0 Hz, 2H, cubyl H), 1.46 (s, 6H, Me); δ_C (50.4 MHz; $CDCl_3$) 167.9 (C=O), 155.3, 145.4, 125.2, 122.4 (ArC), 57.8, 55.3, 48.3, 45.0 (cubyl C), 12.4 (Me); ν_{max} (Nujol)/cm^{-1} 1731s, 1614m, 1591m, 1519s, 1319s, 1203s, 1187s, 1155s, 1108s, 1095s, 995s, 873m, 860m, 740m.

1,8-Bis[6-(6^{A}-deoxy-β-cyclodextrin-6^{A}-ylamino)hexylamino-carbonyl]-2,3-dimethylcubane 7

A mixture of **1** (0.550 g, 4.46×10^{-4} mol) and **13** (0.098 g, 2.21×10^{-4} mol) in dry DMF (5 cm^3) was stirred at room temperature for 18 h. The yellow reaction mixture was diluted with diethyl ether (100 cm^3) and the resultant precipitate was collected by vacuum filtration and washed with diethyl ether (100 cm^3 in portions). The crude product was dissolved in water (20 cm^3) and passed through an AG 4-X4 anion-exchange column (free-base-form, 4.5 × 4.5 cm) and was further eluted with water (150 cm^3). The eluent was concentrated under reduced pressure to ≈15 cm^3 and this solution was loaded on to a BioRex 70 cation-exchange column (NH_4^+-form, 4.5 × 4.5 cm) which was then eluted sequentially with water (150 cm^3) and 0.05 mol dm^{-3} aq. ammonium hydrogen carbonate (200 cm^3). Fractions containing the product were combined and evaporated under reduced pressure to give **7** as a white powder (0.340 g, 60%), R_c = 0.76; ESMS *m*/*z* 2651 (M + H$^+$) [Found: C, 45.83; H, 6.96; N, 2.06. Calc. for **7**·10H$_2$O ($C_{198}H_{196}N_4O_{80}$): C, 45.83; H, 6.98; N, 1.98%]; δ_H (**7**/**7**′; 600 MHz; D_2O; pH ≥ 11) 4.88 (br s, 14H, H-1), 4.30 (m, 1H, cubyl H), 4.10 (m, 2H, cubyl H), 3.80 (m, 1H, cubyl H), 3.5–3.8 (m, 52H, H-3, -5, -6), 3.3–3.5 (m, 26H, H-2, -4), 2.8–3.2 (m, 8H, hexyl H-6, H-4^{A}, H-6^{A}), 2.2–2.7 (m, 6H, H-6$^{A'}$, hexyl H-1), 1.0–1.5 (m, 22H, hexyl H-2–H-5, Me); δ_C (**7**/**7**′; 75.4 MHz; D_2O; pH ≥ 11) 176.1, 175.7, 174.4 (C=O), 106.0, 105.7, 105.5, 105.2 (C-1), 87.3 (C-4^{A}), 84.8, 84.7, 84.4 (C-4), 76.6, 75.8, 74.9, 74.8, 74.6 (C-2, -3, -5), 72.8, 72.5, 72.3, 69.9 (C-5^{A}?), 63.1 (C-6), 59.6, 59.5, 58.8, 58.7, 58.5, 52.1, 51.3, 51.0, 49.5, 48.6, 46.3, 46.1, 41.9, 41.7, 40.3, 35.4, 33.5, 32.1, 31.5, 31.2, 31.1, 30.2, 30.1, 28.9, 28.8, 28.6, 28.1, 27.0 (C-6^{A}, hexyl C-1–C-6, cubyl C), 16.0, 15.8, 14.7, 14.4, 13.7 (Me); δ_H (**7**/**7**′ + 2 mol equiv. **8**; 600 MHz; D_2O; pH ≥ 11 + 2 equiv. **8**) 4.86 (m, 14H, H-1), 3.86 (m, 2H, cubyl H), 3.84 (t, *J* 10.0 Hz, 2H, H-5^{A}), 3.5–3.8 (m, 52H, H-3, -5, -6, cubyl H), 3.4 (m, 26H, H-2, -4), 3.1 (m, 6H, hexyl H-6, H-4^{A}), 2.94 (d, *J* 13.2 Hz, 2H, H-6^{A}), 2.63 (m, 2H, H-6$^{A'}$), 2.46 (m, 2H, hexyl H-1), 2.27 (m, 2H, hexyl H-1′), 2.01 (br s, 6H, adamantyl H-3), 1.79 (br s, 12H, adamantyl H-2), 1.72 (d, *J* 11.4 Hz, 6H, adamantyl H-4), 1.47 (d, *J* 11.4 Hz, 6H, adamantyl H-4′), 1.0–1.4 (m, 22H, hexyl H-2–H-5, Me); δ_C (**7**/**7**′ + 2 mol equiv. **8** 75.4 MHz; D_2O; pH ≥ 11) 189.9 (CO_2^-), 176.0 (CONHR), 106.3, 106.0, 105.9, 105.3 (C-1), 87.7 (C-4^{A}), 84.6, 84.5, 84.4, 84.1 (C-4), 76.8, 76.5, 76.4, 76.0, 75.0, 74.9, 74.7 (C-2, -3, -5), 72.3, 69.8 (C-5^{A}?), 62.7 (C-6), 59.6, 58.8, 50.7, 49.5, 49.2, 46.1, 44.8, 42.4, 41.3, 39.8, 34.6, 31.3, 31.0, 30.6, 29.1, 28.5 (C-6^{A}, hexyl C-1–C6, adamantyl C, cubyl C), 13.7 (Me).

References

1 S. D. Kean, B. L. May, P. Clements, S. F. Lincoln and C. J. Easton, *J. Chem. Soc.*, *Perkin Trans. 2*, 1999, 1257, 2231.
2 K. Redman, B. L. May, S. D. Kean, P. Clements, C. J. Easton and S. F. Lincoln, *J. Chem. Soc.*, *Perkin Trans. 2*, 1999, 1711.
3 B. L. May, P. Clements, J. Tsanaktsidis, C. J. Easton and S. F. Lincoln, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, 463.
4 H. Ikeda, M. Nakamura, N. Ise, N. Oguma, A. Nakamura, T. Ikeda, F. Toda and A. Ueno, *J. Am. Chem. Soc.*, 1996, **118**, 10980.
5 H. Ikeda, M. Nakamura, N. Ise, F. Toda and A. Ueno, *J. Org. Chem.*, 1997, **62**, 1411.
6 R. Corradini, A. Dossena, G. Galaverna, R. Marchelli, A. Panagia and G. Sartor, *J. Org. Chem.*, 1997, **62**, 6283.
7 A. Ueno, A. Ikeda, H. Ikeda, T. Ikeda and F. Toda, *J. Org. Chem.*, 1999, **64**, 382.
8 C. J. Easton and S. F. Lincoln, *Modified Cyclodextrins*, *Scaffolds and Templates for Supramolecular Chemistry*, Imperial College Press, London, 1999.
9 K. A. Connors, *Chem. Rev.*, 1997, **97**, 1325.
10 M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875.
11 V. Rüdiger, A. Eliseev, S. Simonova, H.-J. Schneider, M. J. Blandamer, P. Cullis andA. J. Meyer, *J. Chem. Soc.*, *Perkin Trans. 2*, 1996, 2119.

12 M. R. Eftink, M. L. Landy, K. Bystrom, H. D. Perlmutter and D. S. Kristof, *J. Am. Chem. Soc.*, 1989, **111**, 6765.
13 B. L. May, S. D. Kean, C. J. Easton and S. F. Lincoln, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3157.
14 L. M. Harwood, *Aldrichimica Acta*, 1985, **18**, 25; A. J. Shusterman, P. J. McDougal and A. Glasfeld, *J. Chem. Educ.*, 1997, **74**, 1222.
15 J. N. S. Evans, *Biomolecular NMR Spectroscopy*, Oxford University Press, Oxford, 1995.
16 P. Gans, A. Sabatini and A. Vacca, *J. Chem. Soc.*, *Dalton Trans.*, 1985, 1195.
17 M. Bliese, D. Cristiano and J. Tsanaktsidis, *Aust. J. Chem.*, 1997, **50**, 1043.