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Intra- and intermolecular complexation in C(6) monoazacoronand substituted cyclodextrins †

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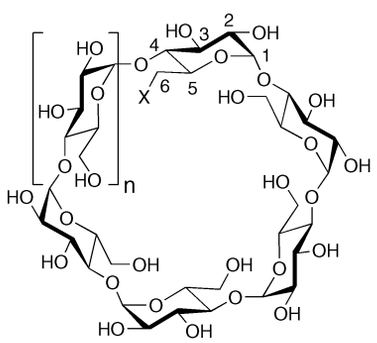
The preparation of 6^A-deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin, **3**, 6^A-deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin, **4**, and their β-cyclodextrin analogues, **5** and **6**, are described. ^{1}H (600 MHz) ROESY NMR spectra of the C(6) substituted β-cyclodextrins, **5** and **6**, are consistent with the intramolecular complexation of their azacyclopentadecanyl- and azacyclooctadecanyl(acetamido)hexylamino substituents in the β-cyclodextrin annulus in D_2O at pD = 8.5 whereas those of their α-cyclodextrin analogues, **3** and **4** are not complexed in the α-cyclodextrin annulus. This is attributed to the monoazacoronand components of the substituents being able to pass through the β-cyclodextrin annulus whereas they are too large to pass through the α-cyclodextrin annulus. However, the substituents of **3** and **4** are intermolecularly complexed by β-cyclodextrin to form pseudo [2]-rotaxanes. Metallocyclodextrins are formed by **5** through complexation by the monoazacoronand substituent component for which log (K/dm^3 mol^{-1}) = <2, 6.34 and 5.38 for Ca^{2+}, Zn^{2+} and La^{3+}, respectively, in aqueous solution at 298.2 K and I = 0.10 mol dm^{-3} (NEt_4ClO_4).

Introduction

A substantial range of modified cyclodextrins (CDs) have been prepared because of their intrinsic interest and their potential and actual use as drug delivery agents, catalysts, chromatographic materials and components of nanodevices.[1–5] Among the latter are rotaxanes and catenanes where the relative size of their components is crucial in achieving the mechanical restraints which hold such assemblies together.

As part of our studies in this area, we have reported substitution at C(6) of both α- and β-cyclodextrin (αCD and βCD) by extended substituents which complex inside the annulus of the CD to which they are attached when the spatial requirements are appropriate.[6] Such intramolecular complexation is entropically favoured over potentially competing intermolecular complexation and provides a method of experimentally calibrating the fit, or otherwise, of components of the extended substituent into the CD annulus. In this study we seek to further explore the utility of this approach in assessing the spatial aspects of intramolecular interactions. Accordingly, we have acylated 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**, and its βCD analogue, **2**, to give 6^A-deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin, **3**, 6^A-deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin, **4**, and their β-cyclodextrin analogues, **5** and **6**, (Scheme 1) through reaction with the 4-nitrophenyl esters, **7** and **8** (Scheme 2). These substituted CDs have either a 15- or 18-membered monoazacoronand attached to the C(6) position by an acetamidohexylamino tether of sufficient flexibility to allow the monoazacoronands to adapt their conformations to enter the CD annulus if it is sufficiently large and possibly pass through it. Both events provide a calibration of CD annular size with respect to the two monoazacoronands. The second event offers the opportunity to stiffen the monoazacoronand conformation in a metal complex with a molecular volume too large to pass through the CD annulus and thereby lock the substituted CD into a molecular knot structure.



Scheme 1

Results and discussion

Intramolecular complexation

The C(6) substituted CDs **3**–**6** were synthesized by the acylation of either 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**,

† Electronic supplementary information (ESI) available: ^{1}H 600 MHz 2D ROESY NMR spectra. See http://www.rsc.org/suppdata/ob/b3/b316450k/

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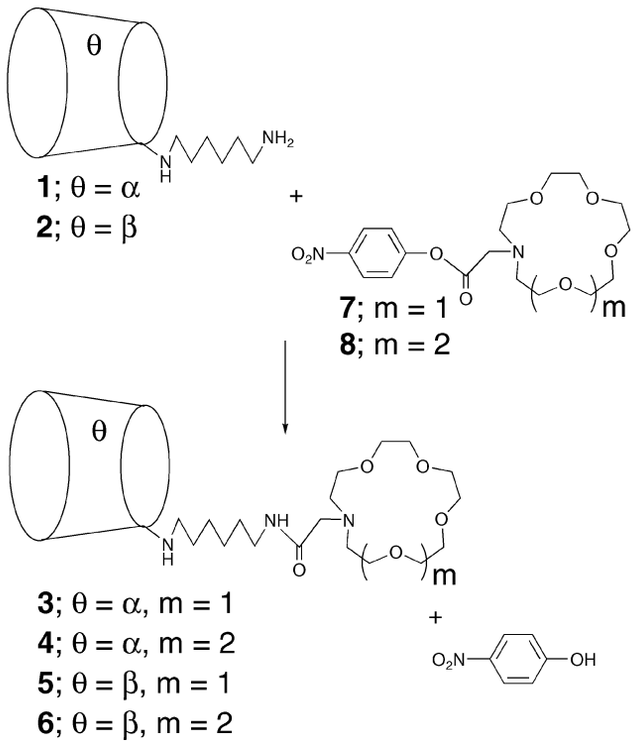


Scheme 2

or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin, **2**, by either of the 4-nitrophenyl esters **7** or **8** (Scheme 2). The secondary and tertiary amine groups of the substituents protonate and are characterised by the potentiometrically determined pK_as for $\mathbf{5}H_2^{2+}$ being 5.84 ± 0.03 and 8.49 ± 0.04 at 298.2 K and $I = 0.10$ mol dm^{-3} (NEt_4ClO_4) in aqueous solution. They are assigned to the amine of the azacoronand and the amine directly attached to β-cyclodextrin, respectively, by comparison with previous work.[7]

Dissolution of **3**–**6** in water results in a mixture of the zero- and monoprotonated species and a solution pH of ~8.5. ^{1}H ROESY NMR (600 MHz) spectra of **3** and **4** in D_2O show no cross-peaks arising from NOE interaction between the substituent at C(6) and protons H3, H5 and H6 of the interior of the CD annulus (Figs S1 and S2)† whereas such cross-peaks are observed for **5** (Fig. 1) and **6** (Fig. 2). This is consistent with the

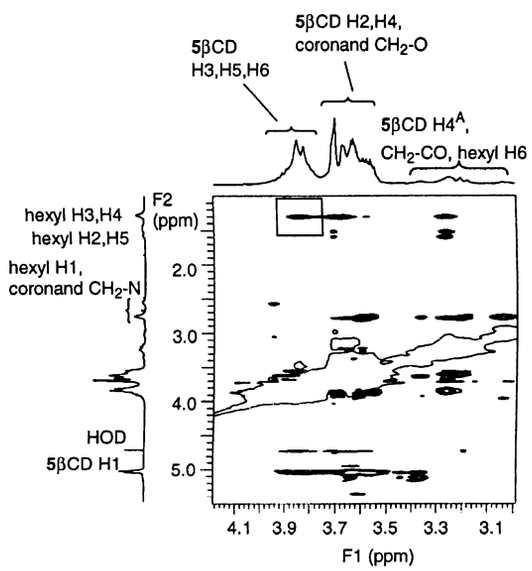


Fig. 1 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[\mathbf{5}]_{total}$ is 0.025 mol dm^{-3}. The cross-peak enclosed in the rectangle arises from dipolar interactions between the protons indicated on the F1 and F2 axes.

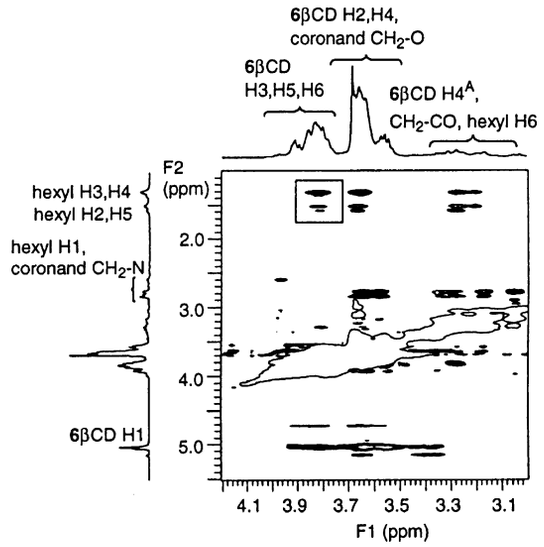
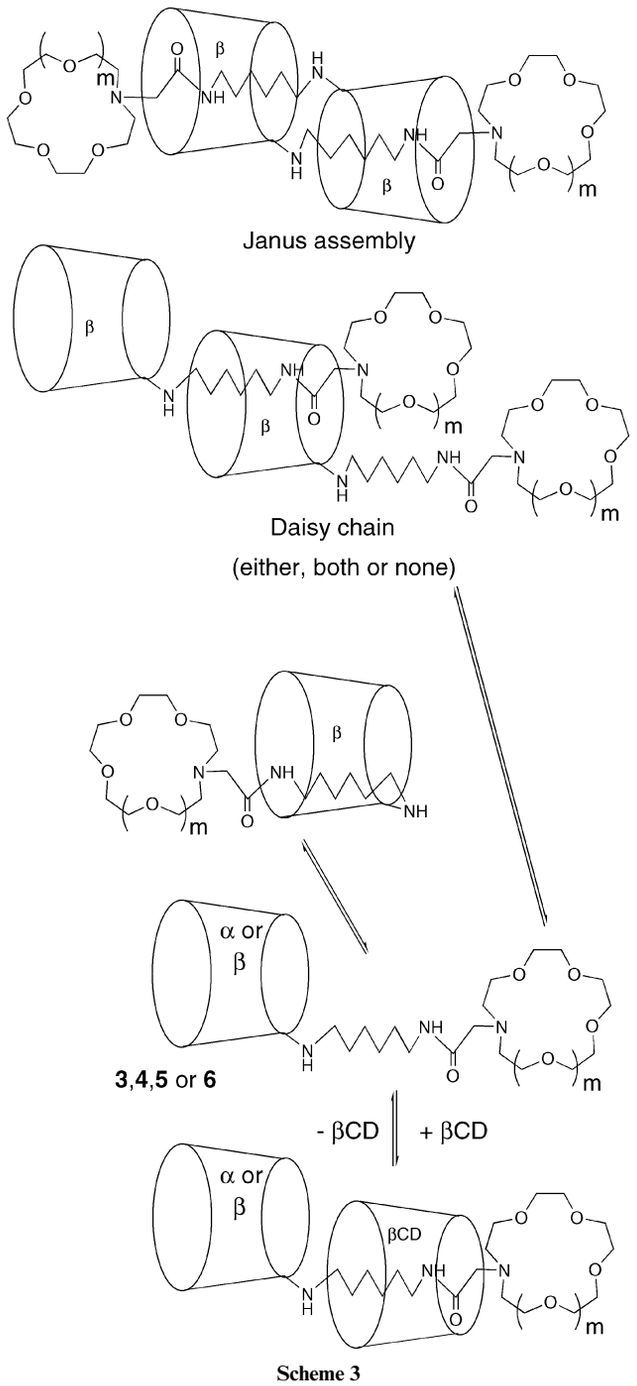


Fig. 2 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[\mathbf{6}]_{total}$ is 0.025 mol dm^{-3}. The cross peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

αCD annuli of **3** and **4** being too small to allow the intramolecular complexation of the substituent at C(6) whereas such complexation does occur for **5** and **6**, evidently because of the larger size of the βCD annulus. Strong cross-peaks are observed for NOE interactions in **5** between the hexyl H3 and H4 protons and the H3, H5 and H6 protons in the annulus of the βCD component, similar interactions with the hexyl H2 and H5 protons produce much weaker cross-peaks (which are not visible at the level of spectral presentation of Fig. 1). This is consistent with the substituent azacoronand passing into or through the βCD annulus so that the particularly hydrophobic midsection of the hexyl entity is in the βCD annulus as shown in Scheme 3, and the hexyl H3 and H4 protons are closer to the H3, H5 and H6 annular protons than are the hexyl H2 and H5 protons. (The overlap of the azacoronand resonances with the βCD H2 and H4 resonances renders it impossible to determine whether the azacoronand moieties of **3**–**6** are within the CD annuli, although it is unlikely that they would complex in preference to the hexyl component because of their lesser hydrophobicity. This aspect is further explored under "Intermolecular complexation" below.) In the case of **6** the hexyl H2–H5 protons all produce cross-peaks through NOE interactions with the H3, H5 and H6 annular protons, consistent with the interpretation presented for **5**. This also shows that the size of the azacoronand influences the orientation of the hexyl entity within the annulus as indicated by the differences in the cross-peaks of **5** and **6**.

An alternative explanation that the hexyl component folds into the annulus which the azacoronand does not enter appears to be unlikely as the analogue of both **5** and **6** in which the 1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido- and 1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido entities were replaced by a 1-amino-2,4,6-trinitrophenyl group which is too large to enter βCD through the smaller end of the annulus showed no cross-peaks arising from the substituent protons and the H3, H5 and H6 protons of the annular interior in its ^{1}H ROESY NMR spectrum in D_2O.[8] In contrast, the dodecyl analogue did show cross-peaks arising from NOE interactions between some of the dodecyl protons and the H3, H5 and H6 protons of the βCD annulus interior consistent with the longer alkyl chain being sufficiently long and flexible for part of it to be intramolecularly complexed in the βCD annulus.

The substituent and βCD resonances of **5** and **6** are broadened consistent with constrained motion bringing exchange between two or more magnetic environments into the moderate



Scheme 3

exchange rate region of the NMR timescale. Such exchange is anticipated between the intramolecular and non-complexed forms of **5** and **6**. By comparison, the resonances of **3** and **4** are narrower consistent with no intra- or intermolecular complexation. (The latter could occur through either intermolecular hermaphrodite or daisy chain complexation as observed in other CD systems.[9,10]) When the pD of the solutions of **5** and **6** is decreased to ~7, the ROESY cross-peaks become very weak consistent with protonation of the amine directly attached to βCD in H**5**$^+$ and H**6**$^+$ inhibiting intramolecular complexation.

Intermolecular complexation

When substituents are flexible, as in **5** and **6**, intramolecular complexation is entropically favoured over the formation of intermolecular Janus (hermaphrodite) and daisy chain complexes (Scheme 3).[9,10] Generally, the latter two types of complexes form when the substituent is less flexible than those of **5** and **6**. It is also significant that under the conditions of this study **5** and **6** are present as a mixture of zero- and mono-protonated species where the charge of the latter is expected to inhibit intermolecular complexation as it does intramolecular complexation. Intermolecular complexation between either neutral **3** or **4** and βCD to form the pseudo [2]-rotaxanes **3**·βCD and **4**·βCD is more likely as there is no detectable intramolecular substituent complexation (Scheme 3). Evidence for the formation of **3**·βCD and **4**·βCD is afforded by the appearance of cross-peaks from NOE interactions between the substituent H2–H5 protons of the hexyl substituent of **3** and **4** and the H3, H5 and H6 protons of βCD in the ^{1}H ROESY NMR spectra of D_2O solutions of βCD and either **3** or **4** (Figs. 3 and 4). These pseudo [2]-rotaxanes are unusual in possessing αCD as a blocking group on one end of the axle and the complexation and decomplexation of the other end of the axle being slowed by the bulk of the azacoronand as akin to a "slippage" mechanism for rotaxane formation.[11] Evidence for this slowing is adduced from the resonance broadening observed for

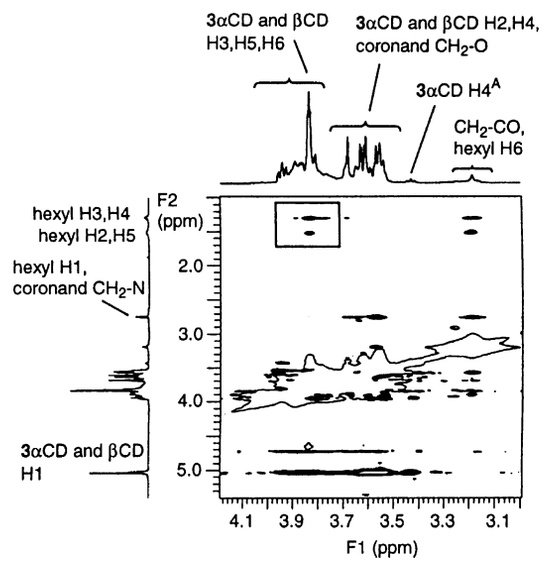


Fig. 3 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[\mathbf{3}]_{total}$ and $[\beta CD]_{total}$ are 0.023 mol dm^{-3} and 0.030 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

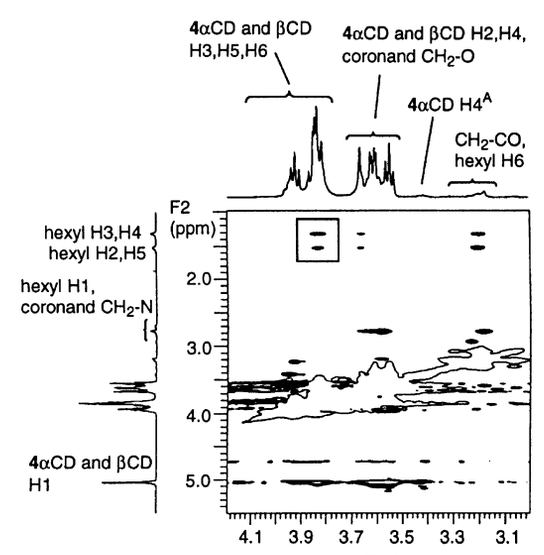


Fig. 4 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[\mathbf{4}]_{total}$ and $[\beta CD]_{total}$ are 0.014 mol dm^{-3} and 0.020 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

the **3**·βCD and **4**·βCD pseudo [2]-rotaxanes seen in Figs. 3 and 4. It is anticipated that similar **5**·βCD and **6**·βCD pseudo [2]-rotaxanes should also form in competition with intramolecular complexation, but because of the uncertainty in interpretation of the ROESY spectra resulting from the overlap of the cross-peaks arising from **5**, **6** and βCD, these systems were not studied in detail.

The ^{1}H ROESY NMR spectrum of a D_2O solution of **3** and αCD shows no cross-peaks arising from dipolar interactions between the protons of the substituent and the H3, H5 and H6 protons of αCD consistent with the αCD annulus being too small to allow passage of the 15-membered azacoronand through it to form the **3**·αCD pseudo [2]-rotaxane (Fig. S3†). This, together with the observations for **5** and **6** and βCD, demonstrates the importance of the relative size of the azacoronand and the CD annulus in intermolecular complexation and reinforces the earlier deductions made concerning intramolecular complexation in **3**–**6**.

Metal ion complexation

In principle, the intramolecular complexes of **5** and **6** could be mechanically restrained to form a molecular knot and the **3**·βCD and **4**·βCD pseudo [2]-rotaxanes to form [2]-rotaxanes by stiffening the 15- and 18-membered azacoronand components in conformations too large to pass through the βCD annuli as a consequence of complexing metal ions. Potentiometric titrations of **5** in the presence of Ca^{2+}, Zn^{2+} and La^{3+} yield log (K/dm^3 mol^{-1}) = <2, 3.93 ± 0.07, 6.34 ± 0.06, 3.06 ± 0.07 and 5.38 ± 0.05 for Ca^{2+}·**5**, Zn^{2+}·**H5**$^+$, Zn^{2+}·**5**, La^{3+}·**H5**$^+$ and La^{3+}·**5** (where K is the stepwise complexation constant) at 298.2 K and I = 0.10 mol dm^{-3} (NEt_4ClO_4) in aqueous solution.

A combination of the precipitation of the Zn^{2+} and La^{3+} hydroxides above pH 6.5 and 7.5, respectively, and the protonation of **3**–**6** inhibiting formation of **3**·βCD and **4**·βCD and the intramolecular complexation of **5** and **6** hindered significant study of [2]-rotaxanes Zn^{2+}·**3**·βCD and Zn^{2+}·**4**·βCD and their La^{3+} analogues and the intramolecular complexes Zn^{2+}·**3** and Zn^{2+}·**4** and their La^{3+} analogues in which it is anticipated that the metal ion complexation induced stiffening of extended azacoronand conformations could cause considerable mechanical restraint. Thus, the weak cross-peaks observed in the ROESY spectrum of **5** at pD = 7 were absent at pD = 6.5 after the addition of 2 equivalents of $Zn(ClO_4)_2$ to the solution consistent with none of Zn^{2+}·**5** existing in the molecular knot form.

Conclusion

The preparation of the C(6) mono-substituted αCD and βCD, **3**–**6**, has facilitated an experimental calibration of the αCD and βCD annular sizes relative to those of their 15- and 18-membered azacoronand substituent components. Thus, both azacoronands pass through the βCD annulus whereas they do not pass through the αCD annulus as demonstrated by the formation of intramolecular complexes of **5** and **6** and the formation of **3**·βCD and **4**·βCD pseudo [2]-rotaxanes. It is also found that monoprotonation of **3**–**6** inhibits the formation of both the intramolecular complexes and the pseudo [2]-rotaxanes. Metal ion complexation of the azacoronand component of the C(6) substituent of **5** is consistent with the possibility of developing molecular knots and [2]-rotaxanes in which metal ion complexation locks substituent components into mechanically restraining conformations. Several syntheses of cyclodextrin [2]-rotaxanes in water have been reported[12–15] and generally their yields are higher than those obtained in non-aqueous solution[16] probably because of the strong hydrophobic driving force for the formation of precursor pseudo [2]-rotaxanes that exists in water. Accordingly, studies of groups at the ends of the CD substituents of potential molecular knots and of potential rotaxane axles that complex metal ions more strongly than the monoazacoronands are in progress with a view to developing systems in which such groups assume mechanically restraining conformations in molecular knots and [2]-rotaxanes upon metal complexation in water.

Experimental

General

Infrared spectra were recorded on an ATI Mattson Genesis FT-IR. The abbreviations strong (s), medium (m), weak (w) and broad (b) are used for reporting the intensity of the bands observed. ^{1}H and ^{13}C NMR spectra were recorded using a Varian-300 spectrometer operating at 300.145 MHz (^{1}H) or 75.4 MHz (^{13}C), unless otherwise stated. A Varian Gemini 200 spectrometer operating at 199.953 MHz (^{1}H) and 50.4 MHz (^{13}C) was also used. The NMR spectra of cyclodextrin derivatives were recorded at approximate concentrations of 0.02–0.03 mol dm^{-3} in D_2O. Signals were referenced to an external standard, aqueous trimethylsilylpropiosulfonic acid. The 2D-ROESY NMR spectra of cyclodextrin derivatives were recorded on a Varian Inova 600 Spectrometer operating at 599.957 MHz, using a standard sequence with a mixing time of 0.3 seconds. MALDI-TOF mass spectrometry was carried out at the Research School of Chemistry at the Australian National University, Canberra, ACT. Electrospray mass spectrometry (ESMS) was carried out at the University of Adelaide. Samples were dissolved in water for injection.

Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. As cyclodextrin derivatives have water molecules associated with them, they were characterised by adding whole numbers of water molecules to the molecular formula to give the best fit to the microanalytical data.

Potentiometric titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer and an Orion 81–03 combination electrode that was filled with 0.10 mol dm^{-3} NEt_4ClO_4. The electrode was soaked in 0.10 mol dm^{-3} NEt_4ClO_4 solution for at least three days prior to use. Titrations were performed in a water-jacketed 2 cm^3 titration vessel held at 298 ± 0.1 K. A gentle stream of nitrogen was passed through the titration solutions which were magnetically stirred. The titration solutions were allowed to stand in the titration vessel for 15 minutes before the titration was begun to allow the solution to equilibrate to 298 K and become saturated with nitrogen. In titrations of **5**, 0.0975 mol dm^{-3} NEt_4OH was titrated against a solution that was 1.0×10^{-3} mol dm^{-3} in the cyclodextrin derivative, 3.2×10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in NEt_4ClO_4 (I = 0.1). The NEt_4OH solution was standardised by titrating against 0.010 mol dm^{-3} potassium hydrogen phthalate. All titrations that were performed in the presence of metal ions were carried out using 2 equivalents of the metal ion. The electrode was calibrated every 24 hours by titration of a solution that was 3.2×10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in NEt_4ClO_4. Values of pK_a (acid dissociation constant) and K (metal complex stability constant) were determined using the program SUPERQUAD. For each system, the titration was performed at least three times and at least two of the runs were averaged. Only runs for which χ^2 was < 12.6 at the 95% confidence interval were selected for averaging.

Thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) on aluminium-backed sheets. Plates were developed with 7 : 7 : 5 : 4 v/v ethyl acetate/propan-2-ol/ammonium hydroxide/water. Cyclodextrin compounds were visualised by drying the plate then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat gun. To visualise amino bearing compounds, plates were dried then dipped into a 0.5% ninhydrin in ethanol solution and heated with a heat-gun, prior to being dipped in the acid solution. The

value R_c represents the R_f of a modified cyclodextrin relative to the R_f of the parent cyclodextrin.

All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. β-Cyclodextrin was donated by Nihon Shokuhin Kako Co. Both α- and β-cyclodextrin were dried by heating at 100 °C under vacuum for 18 hours. 6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**, and 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin, **2**, were prepared by literature procedures.[6] The precursors to the 4-nitrophenyl esters **7** and **8**, 2-(1,4,7,10-tetraoxa-13-azacyclopentadecanyl)acetic acid and 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecanyl)acetic acid were prepared in a similar manner to literature procedures.[17–19] Pyridine and 1-methylpyrrolidin-2-one (NMP) were dried by distillation from calcium hydride. *N*,*N*′-dimethylformamide (DMF) was dried over molecular sieves.

4-Nitrophenyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate 7

2-(1,4,7,10-Tetraoxa-13-azacyclopentadecanyl)acetic acid (0.151 g, 0.403 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.0584 g, 0.422 mmol) and dicyclohexylcarbodiimide (0.086 g, 0.42 mmol) were added and the mixture was stirred under nitrogen for 2 hours. The solution was filtered through Celite to remove DCU. Dichloromethane was removed at reduced pressure to leave the ester **7** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (thin film) 1764 cm^{-1} (C=O), 855 cm^{-1} (Ar).

4-Nitrophenyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate 8

2-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecanyl)acetic acid (0.116 g, 0.372 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.0570 g, 0.409 mmol) and dicyclohexylcarbodiimide (0.0859 g, 0.417 mmol) were added and the mixture was stirred at room temperature for 4 hours, and then heated at reflux under nitrogen for 24 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and dichloromethane was removed at reduced pressure to leave **8** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (thin film) 1767 cm^{-1} (C=O), 856 cm^{-1} (Ar).

General procedure for the preparation of the monoazacoronand-tethered cyclodextrins 3–6

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.3 mmol) was added to a solution of the nitrophenyl ester **7** or **8** (~1.5 molar equiv.) in dry DMF (5 cm^3) and the mixture was stirred for 18–48 hours in a lightly stoppered flask at room temperature. A 1 : 1 v/v ethanol/ether solution (100 cm^3) was added with stirring to precipitate out the product. The pale yellow precipitate was collected and washed with 1 : 1 v/v ethanol/ether (60 cm^3) followed by ether (60 cm^3). The precipitate was dissolved in water (10 cm^3) and loaded onto an AG-4X4 (4.5 × 3 cm) anion exchange column (free base form). The cyclodextrin product was eluted with water (100 cm^3). The residue was dissolved in water (10 cm^3) and loaded on to a Bio-Rex 70 (NH_4^+ form) column (4.5 × 4.5 cm) and eluted with water (250 cm^3) followed by 0.05 mol dm^{-3} ammonium bicarbonate solution (250 cm^3). Fractions containing the product were combined and water was removed under reduced pressure. The residue was freeze-dried, then dried over phosphorus pentoxide to give the product as a white or pale yellow solid.

6^A-Deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin 3

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** (0.286 g, 0.267 mmol) was added to a solution of the nitrophenyl ester **7** (0.240 g, 0.478 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **3** was obtained as a white solid (0.086 g, 24%), R_c = 1.4; ES-MS *m*/*z* 1331 (M^+); [Found: C, 44.50; H, 7.20; N, 2.77%. Calc. for **3**·7H_2O ($C_{54}H_{109}N_3O_{41}$) C, 44.53; H, 7.54; N, 2.89%]; δ_H(D_2O, pD ~ 9) 4.97–5.00 (m, 6H, H1), 3.76–3.93 (m, 22H, H3, H5, H6), 3.50–3.66 (m, 27H, H2, H4, coronand CH_2-O), 3.39 (t, J = 9.0 Hz, 1H, H4^A), 3.13–3.17 (m, 5H, hexyl H6, H6^A, N-CH_2-C=O), 2.82–2.85 (m, 1H, H6$^{A'}$), 2.70 (t, J = 4.8 Hz, 4H, coronand N-CH_2), 2.62 (t, J = 7.2 Hz, 2H, hexyl H1), 1.43–1.48 (m, 4H, hexyl H2, hexyl H5), 1.25–1.29 (m, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 177.30 (C=O), 104.17, 104.07, 103.83 (C1), 86.37 (C4^A), 83.94, 83.90, 83.80 (C4), 76.43, 76.08, 76.02, 75.90, 75.76, 74.77, 74.36 (C2, C3, C5), 72.68 (C5^A), 72.43, 72.12, 71.64, 71.42 (coronand C-O), 63.14 (C6), 61.38, 56.92, 51.96, 51.49 (C6^A, hexyl C1, N-C-C=O, coronand C-N), 41.80 (hexyl C6), 31.20, 30.34, 28.69 (hexyl C2–C5).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin 4

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** (0.192 g, 0.179 mmol) was added to a solution of the nitrophenyl ester **8** (0.159 g, 0.359 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **4** was obtained as a white solid (0.082 g, 45%), R_c = 1.6; MALDI-TOF-MS *m*/*z* 1375.5 ($M + H^+$); [Found: C, 45.04; H, 7.26; N, 2.90%. Calc. for **4**·6H_2O ($C_{56}H_{111}N_3O_{41}$) C, 45.33; H, 7.55; N, 2.83%]; δ_H(D_2O, pD ~ 9) 5.02 (s, 6H, H1), 3.79–3.96 (m, 22H, H3, H5, H6), 3.53–3.66 (m, 31H, H2, H4, coronand CH_2-O), 3.41 (t, J = 8.4 Hz, 1H, H4^A), 3.17–3.21 (m, 5H, hexyl H6, N-CH_2-C=O, H6^A), 2.87–2.91 (m, 1H, H6$^{A'}$), 2.76 (t, J = 4.8 Hz, 4H, coronand N-CH_2), 2.66 (t, J = 6.6 Hz, 2H, hexyl H1), 1.47–1.52 (m, 4H, hexyl H2, hexyl H5), 1.26–1.33 (m, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 174.29 (C=O), 102.71, 102.50, 102.30 (C1), 84.72 (C4^A), 81.98, 81.85 (C4), 74.49, 72.94, 72.49, 72.40 (C2, C3, C5), 70.79 (C5^A), 69.58, 69.49, 67.99 (coronand C-O), 60.96 (C6), 57.58, 55.28, 50.16, 49.08 (C6^A, hexyl C1, N-*C*-C=O, coronand C-N), 39.46 (hexyl C6), 28.78, 28.69, 26.49, 26.36, (hexyl C2–C5).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-β-cyclodextrin 5

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.483 g, 0.392 mmol) was added to a solution of the nitrophenyl ester **7** (0.275 g, 0.549 mmol) in dry DMF (5 cm^3) and the mixture was stirred for 18 hours in a lightly stoppered flask. After the general work-up and purification procedure, the product **5** was obtained as a pale yellow solid (0.287 g, 49%), R_c = 1.4; MALDI-TOF-MS *m*/*z* 1493 ($M + H^+$); [Found: C, 43.50; H, 7.59; N, 2.54%. Calc. for **5**·9H_2O ($C_{60}H_{123}N_3O_{48}$) C, 43.55; H, 7.49; N, 2.61%]; δ_H(D_2O, pD ~ 9) 5.00–5.03 (m, 7H, H1), 3.70–3.90 (m, 26H, H3, H5, H6), 3.56–3.70 (m, 29H, H2, H4, coronand O-CH_2), 3.18–3.39 (m, 5H, H4^A, hexyl H6, N-CH_2-C=O), 3.03–3.08 (m, 1H, H6^A), 2.70–2.81 (m, 5H, H6$^{A'}$, coronand N-CH_2), 2.52–2.57 (m, 2H, hexyl H1), 1.41–1.60 (m, 4H, hexyl H2, hexyl H5), 1.24–1.31 (m, 4H, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 174.10 (C=O), 103.54, 103.39, 103.33, 103.26, 103.17 (C1), 84.76 (C4^A), 82.22, 82.08 (C4), 74.47, 74.32, 74.21, 73.53, 72.32 (C2, C3, C5), 69.23, 68.94, 68.90, 68.72, 68.35, 67.95, 67.72 (coronand C-O, C6), 60.69, 58.99, 55.57, 55.22 (C6^A, hexyl C1, N-*C*-C=O, coronand C-N), 39.50 (hexyl C6), 28.72, 26.36 (hexyl C).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-β-cyclodextrin 6

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.404 g, 0.328 mmol) was added to a solution of the nitrophenyl ester **8**

(0.210 g, 0.450 mmol) in dry DMF (5 cm^3) and the mixture was stirred for 18 hours in a lightly stoppered flask. After the general work-up and purification procedure, the product **6** was obtained as a white solid (0.249 g, 50%), R_c = 1.3; ES-MS *m*/*z* 1537 (M^+); [Found: C, 43.58; H, 6.70; N, 2.38%. Calc. for **6**.9H_2O ($C_{62}H_{127}N_3O_{49}$) C, 43.84; H, 7.54; N, 2.47%]; δ_H(D_2O, pD ~ 9) 5.02–5.05 (m, 7H, H1), 3.73–3.99 (m, 26H, H3, H5, H6), 3.53–3.69 (m, 31H, H2, H4, coronand O-CH_2, N-CH_2-C=O), 3.22–3.24 (m, 3H, $H4^A$, hexyl H6), 3.04 (d, J = 14.4 Hz, 1H, $H6^A$), 2.76–2.84 (m, 5H, $H6^{A'}$, coronand N-CH_2), 2.59–2.61 (m, 2H, hexyl H1), 1.42–1.57 (m, 4H, hexyl H2, hexyl H5), 1.25–1.38 (m, 4H, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 176.90, (C=O), 104.96, 104.60, 102.61 (C1), 85.15 ($C4^A$), 84.14, 83.86 (C4), 77.02, 76.07, 75.53, 74.78, 74.67, 73.95 (C2, C3, C5), 72.63, 72.47, 72.34, 71.43 (coronand C-O), 62.85 (C6), 60.30, 57.46, 48.40, 46.61 ($C6^A$, hexyl C1, N-C-C=O, coronand C-N), 41.53 (hexyl C6), 31.41, 29.80, 28.67, 28.26 (hexyl C).

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