Preparation and characterization of 6^A-polyamine-mono-substituted β-cyclodextrins

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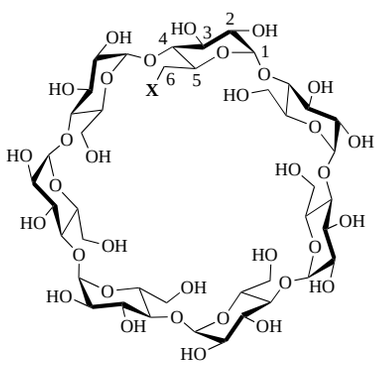
General syntheses for eleven β-cyclodextrins (cyclomaltoheptaoses) mono-substituted at the C6 position by a polyamine are described. The basis of the synthesis is the reaction of 6^A-*O*-(4-methylphenylsulfonyl)-β-cyclodextrin in the presence of KI in 1-methylpyrrolidin-2-one solution. This produces a clean product and obviates the substantial purification procedures which other preparative methods often entail. Systematic studies of the variations of the pK_as of the protonated amine groups and the ^{13}C NMR spectra of the modified β-cyclodextrins with pH are reported.

Introduction

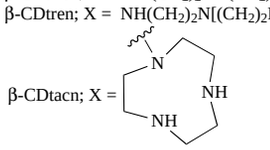
The ability of the naturally occurring cyclodextrins (cyclomaltopolyoses) to form host–guest complexes where a guest molecule enters the annulus of the host cyclodextrin is well established.[1–3] These complexing abilities may be modified by substitution at one or more of the C2, C3 and C6 sites;[1–6] the 6^A-polyamine-substituted β-cyclodextrins (β-CDX) discussed below and shown in Fig. 1 exemplify such substitutions at C6. Some of these β-CDXs have been studied because of their ability to form host–guest complexes,[2,7–10] and also because they coordinate metal ions to form binary metallocyclodextrins which sometimes show enantioselective and biomimetic characteristics in their interaction with guests in ternary metallocyclodextrins.[3,5–19]

We require a range of β-CDXs which can be produced in reasonable yield and high purity for our host–guest complex and metallocyclodextrin studies. Some of these β-CDXs have been reported previously. However, in our hands, the products obtained through these preparations usually required lengthy purification and this provided the impetus for our quest for an improved general synthetic method. Two major routes have been previously reported for the syntheses of the required β-CDXs. For the liquid polyamines, heating either β-cyclodextrin (β-CD),[18] 6^A-*O*-(4-methylphenylsulfonyl)-β-cyclodextrin (β-CDtos)[12] or 6^A-deoxy-6^A-iodo-β-cyclodextrin (β-CDI)[19] in excess polyamine in a sealed tube yields β-CDX which requires purification by lengthy chromatographic separation. For either the more expensive liquid or solid polyamines, reaction of β-CDtos[10–13,16,20] with the polyamine in *N*,*N*-dimethylformamide (DMF) under similar conditions yields β-CDX, but we found it difficult to avoid some formylation of the β-CDX which necessitated tedious separations using this method. We now report a simple general procedure for the synthesis of some reported β-CDXs where X is either the 2-aminoethylamino,[11,18] 3-aminopropylamino,[7–9] 2-(2-aminoethylamino)ethylamino,[12,14,19] 2-[2-(2-aminoethylamino)ethylamino]ethylamino,[12] 2-[bis(2-aminoethyl)amino]ethylamino[10] or 1,4,7,10-tetraazacyclododecan-1-yl[13,15] group bonded through nitrogen to the β-CD C6 carbon which in most cases have not been fully characterised, and some new β-CDXs that yield clean products under mild conditions.

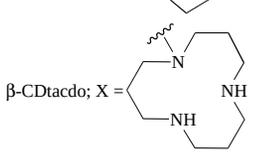
The β-CDX's protonated amine groups exhibit a wide range of pK_as which are likely to have a major influence on host–guest complexation and metal ion coordination reactions. Accordingly, a systematic study of pK_a variation with the nature of X has been carried out in parallel with a study of the ^{13}C NMR spectral variation of β-CDXs with pH to gain an insight into the factors influencing these characteristics.



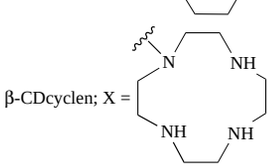
β-CDen; X = $NH(CH_2)_2NH_2$
β-CDpn; X = $NH(CH_2)_3NH_2$
β-CDbn; X = $NH(CH_2)_4NH_2$
β-CDhn; X = $NH(CH_2)_6NH_2$
β-CDdien; X = $NH(CH_2)_2NH(CH_2)_2NH_2$
β-CDdipn; X = $NH(CH_2)_3NH(CH_2)_3NH_2$
β-CDtrien; X = $NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$
β-CDtren; X = $NH(CH_2)_2N[(CH_2)_2NH_2]_2$



β-CDtacn; X =



β-CDtacdo; X =



β-CDcyclen; X =

Fig. 1 Schematic representations of the β-CDXs prepared. The individual C and H atoms of the polyamino substituent are labelled 1, 2, . . . *n* as distance from the β-CD moiety increases.

Results and discussion

Preparative aspects

The synthesis of 6^A-{2-[bis(2-aminoethyl)amino]ethylamino}-6^A-deoxy-β-cyclodextrin (β-CDtren) serves to illustrate pre-

Table 1 Reaction times, yields and analytical data for the preparation of β-CDXs

β-CDX	Reaction time *t*/h	Yield (%)	Elemental analyses (%)			
				C	H	N
β-CDen·3H_2O	6	55	Found:	42.70	6.67	2.18
			Calc.:	42.92	6.71	2.27
β-CDpn·3H_2O	4.5	42	Found:	43.65	6.85	2.39
			Calc.:	43.40	6.80	2.24
β-CDbn·2H_2O	4.5	52	Found:	44.88	7.17	2.17
			Calc.:	44.51	6.82	2.25
β-CDhn·3H_2O	5	51	Found:	44.95	7.27	1.88
			Calc.:	44.79	7.04	2.17
β-CDtrien·H_2O	7	40	Found:	44.83	6.89	4.42
			Calc.:	44.99	6.92	4.37
β-CDtren·3H_2O	4	57	Found:	43.84	7.58	4.40
			Calc.:	43.76	7.04	4.25
β-CDdien·H_2O	4.5	54	Found:	44.88	6.75	4.05
			Calc.:	44.62	6.75	3.39
β-CDdipn·2H_2O	6	50	Found:	45.17	6.52	3.12
			Calc.:	44.89	6.98	3.27
β-CDtacn·3H_2O	5	33	Found:	44.59	6.83	3.30
			Calc.:	44.34	6.90	3.23
β-CDtacdo·4H_2O	7	34	Found:	45.28	7.34	3.15
			Calc.:	45.03	7.18	3.08
β-CDcyclen·3H_2O	14	35	Found:	44.76	7.10	4.36
			Calc.:	44.71	7.05	4.17

parative aspects which generally apply to the other β-CDX considered. Heating a mixture of β-CDtos and one equivalent of tris(2-aminoethyl)amine in DMF at 70 °C in a loosely stoppered flask for 24 h gave the expected β-CDtren in low yield. This product was contaminated with *N*-formylated material formed by transacylation between primary amino groups and the DMF solvent. Reaction of 6^A-deoxy-6^A-iodo-β-cyclodextrin (β-CDI) under the same conditions gave a more rapid conversion to the product but again there was a significant amount of the formylated product formed. When pyridine was used as the solvent in place of DMF, a much cleaner β-CDtren product was obtained, but it was isolated largely as a very stable host–guest complex of pyridine with β-CDtren. Pure β-CDtren was obtained from all three of the above preparative routes, but only after lengthy purification.

NMP is a dipolar aprotic solvent that has been shown to be superior to DMF for nucleophilic substitutions of toluene-*p*-sulfonates[25] but is more stable than DMF under either acid or base conditions.[26] When β-CDtos was heated at 70 °C for 4 h with 3.3 equiv. of tris(2-aminoethyl)amine and 0.1 equiv. of KI (to generate β-CDI *in situ*) in NMP, pure β-CDtren was obtained in 60% yield following a single precipitation with ethanol and product separation through ion exchange chromatography. There was no evidence for reaction between tris(2-aminoethyl)amine or β-CDtren and NMP. The formation of β-CDI in the reaction was shown by TLC of the reaction mixture during the course of the reaction. A series of β-CDXs, having either linear, branched or cyclic polyamine substituents, was prepared under the same conditions (Table 1). All of the β-CDXs prepared by this procedure were shown to be pure by TLC, ^{1}H and ^{13}C NMR spectroscopy and microanalysis. (A referee has pointed out that the cyclic solvent, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, has been employed in the nucleophilic substitution of a modified cyclodextrin.[27])

pK_a Variations

The two pK_as of β-CDXs increase as X is systematically changed from 1,2-diaminoethane (en) to 1,6-diaminohexane (hn) while the difference between the two pK_as decreases, and a similar trend is seen for the free diamine analogues (Table 2). The latter observation is attributable to increases in charge separation in the diprotonated species decreasing electrostatic repulsion as the diamine increases in size. The increase in pK_a magnitude coincides with increases in hydrophobicity as the aliphatic chain lengthens and indicates a decrease in the ability of surrounding water to accept a proton from the protonated amine as overall hydration decreases. The two pK_as of β-CDXs are less than those of the analogous free diamine.

Table 2 pK_as[a] for some protonated 6^A-polyamine-substituted β-cyclodextrins and the corresponding free polyamines in aqueous $NaClO_4$ (I = 0.10 mol dm^{-3}) at 298.2 K

Species	pK_a	Species	pK_a
β-CDenH_2^{2+}	9.42 ± 0.01	enH_2^{2+}	9.97 ± 0.03
	5.70 ± 0.02		7.16 ± 0.02
β-CDpnH_2^{2+} [b]	9.90 ± 0.1	pnH_2^{2+}	10.56 ± 0.02
	7.39 ± 0.04		8.97 ± 0.01
β-CDbnH_2^{2+}	10.26 ± 0.02	bnH_2^{2+}	10.91 ± 0.02
	8.06 ± 0.01		9.49 ± 0.01
β-CDhnH_2^{2+}	10.27 ± 0.03	hnH_2^{2+}	11.01 ± 0.06
	8.72 ± 0.01		10.04 ± 0.03
β-CDdienH_3^{3+}	9.52 ± 0.02	dienH_3^{3+}	9.78 ± 0.01
	7.63 ± 0.03		8.99 ± 0.03
	3.88 ± 0.07		4.32 ± 0.03
β-CDdipnH_3^{3+}	10.06 ± 0.02	dipnH_3^{3+}	10.56 ± 0.05
	8.44 ± 0.03		9.44 ± 0.06
	6.72 ± 0.03		7.54 ± 0.06
β-CDtrienH_4^{4+}	9.33 ± 0.02	trienH_4^{4+}	9.83 ± 0.04
	8.22 ± 0.03		8.93 ± 0.05
	5.61 ± 0.03		5.40 ± 0.05
	3.13 ± 0.07		3.0 ± 0.1
β-CDtrenH_4^{4+} [c]	9.85 ± 0.02	trenH_4^{4+} [d]	10.14
	8.99 ± 0.09		9.43
	6.89 ± 0.05		8.41
	2.6 ± 0.3		
β-CDtacnH_3^{3+}	10.0 ± 0.1	tacnH_3^{3+}	10.69 ± 0.02
	5.89 ± 0.07		7.01 ± 0.01
	2.4 ± 0.2		
β-CDtacdoH_3^{3+}	11.24 ± 0.04	tacdoH_3^{3+} [e]	12.60
	5.85 ± 0.03		7.57
	2.8 ± 0.1		2.41
β-CDcyclenH_4^{4+}	10.40 ± 0.01	cyclenH_4^{4+} [f]	10.6
	8.62 ± 0.02		9.6

[a] Errors represent one standard deviation. [b] Ref. 7. [c] Ref. 10. [d] Ref. 28. [e] Ref. 29. [f] Ref. 30.

The increased acidity of the protonated diamine moiety of β-CDX, by comparison with that of the free diamine analogue (Table 2), may partially arise from either the electronic and steric effects of the substitution of an amine nitrogen by β-CD or the difference in solvation experienced by the protonation sites in β-CDX and the free diamine or a combination of both. In addition, the diamine moiety in β-CDX is bound adjacent to the ring of six primary hydroxy groups delineating the narrow end of the cyclodextrin annulus such that hydrogen bonding between them and the amine nitrogens may decrease the basicity of the latter. This is supported to some extent through the observation that in basic solution more fine structure is seen in the ^{13}C NMR spectra of β-CDX (see Experimental) than is seen in acidic solution, consistent with the unprotonated diamine moiety hydrogen-bonding to the β-CD hydroxy groups more effectively than does its protonated analogue. (This is illustrated by the spectra of β-CDtacdo and β-CDcyclen in Figs. 2 and 3.) A similar interpretation has been presented for β-CDdien (where pK_a magnitude increases in the sequence -NH_3^+ < β-CD-NH_2^+- < -$(CH_2)_2$-$NH_2^+$$(CH_2)_2$- as identified by ^{13}C NMR spectroscopy[19]) which together with its β-CDdipn homologue shows similar trends (Table 2) to those discussed above. Generally, similar trends in pK_a magnitudes are observed for the polyamine β-CDX as for their diamine analogues and their origins are probably similar.

^{13}C NMR Spectra

The substituent X on the β-CDX C6 carbon of the A glucopyranose unit renders it and the other six glucopyranoses (often labelled B–G) inequivalent, and as a result they may each exhibit six ^{13}C unique resonances to give a total of 42 resonances when the magnetic inequivalence is sufficiently large.

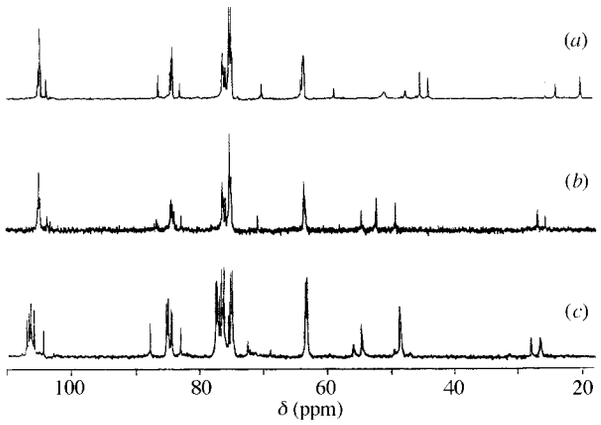


Fig. 2 75.47 MHz ^{13}C NMR spectra of β-CDtacdo in (*a*) 0.1 mol dm^{-3} HCl–D_2O, (*b*) HCl–D_2O, pH ~8.5 and (*c*) 0.1 mol dm^{-3} NaOH–D_2O ‡

‡ δ_C(0.1 mol dm^{-3} HCl–D_2O) 104.9, 104.7, 104.6, 103.7 (C1), 86.3 (C4^A), 84.3, 84.0, 82.8 (C4), 76.1, 76.0, 75.9, 75.6, 75.2, 75.0, 74.7, 74.6 (C2, C3, C5), 70.0 (C5^A), 63.8, 63.3 (C6), 58.6, 50.9 (broad), 47.5, 45.2, 43.9 (C6^A, tacdoC1, tacdoC3, tacdoC4), (25.4), 23.7, 19.9 (tacdoC2, tacdoC5); δ_C(HCl–D_2O, pH ~8.5) 104.8, 104.5, 103.4, 103.0 (C1), 86.4 (C4^A), 84.1, 83.9, 83.7, 83.6, 82.5 (C4), 76.1, 76.0, 75.9, 75.6, 74.9, 74.7 (C2, C3, C5), 70.5 (C5^A), 63.3, 63.2 (C6), 54.3 (C6^A), 51.9, 49.0 (tacdoC1, tacdoC3, tadcoC4), 26.6, 25.4 (tacdoC2, tacdoC5); δ_C(0.1 mol dm^{-3} NaOH–D_2O) 106.9, 106.6, 106.4, 106.3, 105.8, 105.7, 104.3 (C1), 87.7 (C4^A), 85.2, 85.1, 85.0, 84.9, 84.5, 84.3, 82.9 (C4), 77.4, 77.2, 77.1, 77.0, 76.9, 76.8, 76.7, 76.5, 76.3, 76.1, 75.4, 75.1, 74.9 (C2, C3, C5), 72.5 (C5^A), 63.4, 63.1 (C6), 55.9 (C6^A), 54.6 (tacdoC1), 48.7, 48.6 (tacdoC3, tacdoC4), 28.0, 26.5 (tacdoC2, tacdoC5).

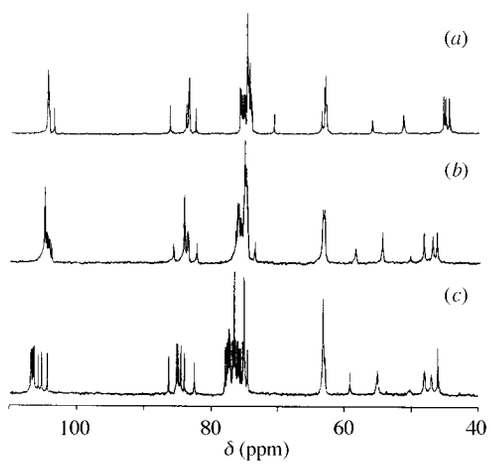


Fig. 3 75.47 MHz ^{13}C NMR spectra of β-CDcyclen in (*a*) 0.1 mol dm^{-3} HCl–D_2O, (*b*) HCl–D_2O, pH ~9 and (*c*) 0.1 mol dm^{-3} NaOH–D_2O §

§ δ_C(0.1 mol dm^{-3} HCl–D_2O) 104.5, 104.4, 104.3, 103.6 (C1), 86.4 (C4^A), 84.0, 83.7, 83.6, 82.6 (C4), 75.9, 75.8, 75.6, 75.5, 75.3, 75.2, 74.9, 74.8, 74.7, 74.6, 74.4, 74.3, 74.2 (C2, C3, C5), 70.9 (C5^A), 63.6, 63.2, 63.0 (C6), 56.2 (C6^A), 51.5 (cyclenC1), 45.7, 45.4, 44.9 (cyclenC2-4); δ_C(HCl–D_2O, pH ~9) 104.9, 104.6, 104.3, 104.2, 103.8 (C1), 85.6 (C4^A), 84.1, 83.6, 83.5, 82.2 (C4), 76.4, 76.1, 76.0, 75.8, 75.5, 75.4, 75.2, 75.1, 74.9, 74.6, 74.5, 73.5 (C2, C3, C5), 63.1, 63.0, 62.8 (C6), 58.3 (C6^A), 54.3, (50.2), 48.2, 46.9, 46.2 (cyclenC); δ_C(0.1 mol dm^{-3} NaOH–D_2O) 106.9, 106.8, 106.6, 106.4, 105.7, 105.3, 104.4 (C1), 86.35 (C4^A), 85.2, 85.0, 84.7, 84.6, 84.0, 82.6 (C4), 77.9, 77.7, 77.5, 77.4, 77.2, 77.1, 76.8, 76.6, 76.4, 76.1, 76.0, 75.8, 75.6, 75.2, 75.1, 74.6 (C2, C3, C5), 63.1, 62.9, 62.8 (C6), 59.0 (C6^A), 55.0, (50.2), 48.0, 47.1, 46.1 (cyclenC).

Usually the ^{13}C NMR chemical shift differences between the seven glucopyranose units are insufficient for all 42 ^{13}C resonances to be separately observed. As the polyamine nitrogens of β-CDX protonate as the solution pH decreases, concomitant changes in the β-CDX ^{13}C NMR spectrum occur as has been briefly discussed above and as shown in the Experimental.

The ^{13}C NMR spectra of β-CDtacdo and β-CDcyclen at different pHs appear in Figs. 2 and 3, respectively, and illustrate the substantial spectral changes which occur with change in pH. At pH 1 resolution of the ^{13}C resonances of fully protonated β-CDtacdoH_3^{3+} and β-CDcyclenH_4^{4+} is relatively small consistent with the polyamine substituent swinging out from the β-CD moiety so that it interacts weakly if at all with the primary hydroxy groups and the differentiation of the seven glucopyranose units is minimised. At the highest pH, where β-CDtacdo and β-CDcyclen exist as the deprotonated neutral species, all seven C1 and C4 resonances are observed consistent with the polyamine substituents hydrogen bonding with the primary hydroxy groups of β-CD and maximising the differentiation between the seven glucopyranose units. This interpretation is in agreement with that presented for the similarly pH dependent ^{13}C NMR spectra of β-CDdien.[19]

Experimental

Materials and instrumental methods

The polyamines 1,2-diaminoethane (en), 1,3-diaminopropane (pn), 1,4-diaminobutane (bn), 1,6-diaminohexane (hn), 2-(2-aminoethylamino)ethylamine (dien), 3-(3-aminopropylamino)-propylamine (dipn), tris(2-aminoethyl)amine (tren) and 1,4,7,10-tetraazacyclododecane bis(dihydrogen sulfate) (cyclen·2H_2SO_4) were purchased from Aldrich and used without further purification. 2-[2-(2-Aminoethylamino)ethylamino]ethylamine tetrahydrochloride (trien·4HCl, Aldrich) was purified by two recrystallisations from ethanol–water.[21] 1,4,7-Triazacyclononane·3HCl and 1,5,9-triazacyclododecane·3HCl were prepared as in the literature.[22,23] HPLC grade 1-methylpyrrolidin-2-one (NMP, Aldrich) was dried by distillation from CaH_2 at reduced pressure. β-Cyclodextrin was a gift from Nihon Shokhuin Kako Co. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} silica on aluminium sheets and samples were eluted using a mixture of propan-2-ol–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. Cyclodextrins were detected by dipping the developed plate into a solution of 1.5% H_2SO_4 in ethanol and heating the plate. R_f values are reported as R_c (retention relative to β-CD).

Titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer, and an Orion 8172 Ross Sureflow combination pH electrode which was filled with 0.10 mol dm^{-3} $NaClO_4$. During all titrations a stream of fine nitrogen bubbles (previously passed through aqueous 0.10 mol dm^{-3} NaOH to remove any last traces of CO_2 and then 0.10 mol dm^{-3} $NaClO_4$ to ensure a constant water vapour pressure) was passed through the titration solution which was magnetically stirred and thermostatted at 298.2 ± 0.1 K in a water-jacketted 20 cm^3 titration vessel which was closed to the atmosphere with the exception of a small exit for the nitrogen stream. Deionised water, purified with a MilliQ-Reagent system to produce water with a specific resistance of >15 MΩ cm, was used in the preparation of all solutions after boiling to remove CO_2. Standardised 0.100 mol dm^{-3} NaOH was titrated against 10.00 cm^3 aliquots of solutions (0.002 mol dm^{-3} in the species of interest, 0.005 mol dm^{-3} in $HClO_4$ and 0.095 mol dm^{-3} in $NaClO_4$ in all titrations). The pK_as were determined using the programme SUPERQUAD[24] on a Digital Venturis 575 computer.

NMR spectra were recorded on a Bruker ACP300 spectrometer operating at 300 (^{1}H) and 75.47 MHz (^{13}C) for all β-CDXs except for 6^A-{2-[bis(2-aminoethyl)amino]-ethylamino}-6^A-deoxy-β-cyclodextrin (β-CDtren) where a Varian Gemini 200 spectrometer operating at 200 (^{1}H) and 50.29 MHz (^{13}C) was used.

General procedure for preparation of amino-substituted β-cyclodextrins

A solution of β-CDtos[11] (2.0 g, 1.55 × 10^{-3} mol), KI (0.025 g, 0.15 × 10^{-3} mol) and the amine (5 × 10^{-3} mol) in dry NMP (5

cm^3) was stirred at 70 °C in a lightly stoppered flask for 4–8 h. The resultant light yellow solution was cooled to room temperature and diluted with ethanol (100 cm^3). The resulting precipitate was collected by vacuum filtration, washed successively with ethanol (100 cm^3) and diethyl ether (50 cm^3) and dried under vacuum to give the crude product. This material was dissolved in water (10 cm^3) and loaded onto a column (4.5 × 4.5 cm) of H^+ form BioRex 70, 100–200 mesh (Biorad). The column was washed with water (400 cm^3) and β-CDX was eluted with 1 mol dm^{-3} NH_4OH. Fractions containing β-CDX were combined and evaporated to dryness under vacuum. The residue was dissolved in water and the solution evaporated under reduced pressure to remove excess ammonia (this procedure was repeated several times). The product was dried under vacuum over P_2O_5 to give β-CDX in yields of 25–60%. Specific preparative descriptions and characterisation data of β-CDtren, previously prepared by other methods,[10] and previously unreported β-CDtacdo are provided below. Similarly detailed preparative and characterisation data for the remaining β-CDXs shown in Fig. 1 are provided as supplementary data.†

6^A-{2-[Bis(2-aminoethyl)amino]ethylamino}-6^A-deoxy-β-cyclodextrin (β-CDtren)

A mixture of β-CDtos (2.048 g, 1.59×10^{-3} mol), tris(2-aminoethyl)amine (0.74 g, 5.07×10^{-3} mol) and KI (0.024 g) in NMP (5 cm^3) was treated according to the general procedure to give β-CDtren as a white powder (1.192 g, 59%). R_c 0.31; Electrospray-MS *m/z* 1263 (M^+) [Found: C, 43.84; H, 7.58; N, 4.40. Calc. for β-CDtren·3H_2O ($C_{48}H_{92}N_4O_{34}$): C, 43.76; H, 7.04; N, 4.25%]; δ_H(D_2O–NaOH, pH ~14) 5.00 (br s, 7H + solvent, H1), 3.5–3.8 (m, 26H, H3, H5, H6), 3.1–3.4 (m, 13H, H2, H4), 3.02 (t, *J* 9.0, 1H, $H4^A$), 2.85 (d, *J* 12.0, 1H, $H6^A$), 2.2–2.7 (m, 13H, $H6^{A'}$, trenH); δ_H(D_2O, pH ~9) 5.05 (br s, 7H, H1), 3.8–4.0 (m, 26H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.41 (t, *J* 9.0, 1H, $H4^A$), 3.05 (d, *J* 11.4, 1H, $H6^A$), 2.4–2.9 (m, 13H, $H6^{A'}$, trenH); δ_H(D_2O–HCl, pH ~1) 5.00 (s, 7H, H1), 4.10 (t, *J* 9.0, 1H, $H5^A$), 3.6–4.0 (m, 25H, H3, H5, H6), 3.4–3.6 (m, 14H, H2, H4), 2.9–3.4 (m, 14H, $H6^A$, trenH); δ_C(D_2O–NaOH, pH ~14), 107.0, 106.6, 106.4, 105.2 (C1), 87.6 ($C4^A$), 85.0, 84.8, 84.5, 83.9 (C4), 77.3, 76.4, 76.3, 75.2, 74.9 (C2, C3, C5), 70.9 ($C5^A$), 63.0 (C6), 59.8 (trenC3,3′), (56.9), 55.1 ($C6^A$), 50.5 (trenC2), 46.2 (trenC1), 41.0 (trenC4,4′); δ_C(D_2O, pH ~9) 104.7, 104.3 (C1), 86.4 ($C4^A$), 84.0, 83.6 (C4), 75.9 (C2), 74.9 (C3), 74.7 (C5), 73.3 ($C5^A$), 63.1 (C6), 58.7 (trenC3,3′), 55.7 (trenC2), 52.0 ($C6^A$), 48.7 (trenC1), 40.7 (trenC4,4′); δ_C(D_2O–HCl, pH ~1) 104.5, 103.8 (C1), 85.8 ($C4^A$), 84.2, 83.8, 83.4 (C4), 75.8, 75.5, 75.0, 74.8, 74.5 (C2, C3, C5), 70.2 ($C5^A$), 63.6, 63.1 (C6), 52.8 (trenC3,3′), 51.5 ($C6^A$), 51.3 (trenC2), 47.0 (trenC1), 38.6 (trenC4,4′).

6^A-(1,5,9-Triazacyclododecan-1-yl)-6^A-deoxy-β-cyclodextrin (β-CDtacdo)

A mixture of 1,5,9-triazacyclododecane·3HCl[23] (1.451 g, 5.18×10^{-3} mol) and sodium hydroxide (0.625 g, 15.62×10^{-3} mol) in ethanol (30 cm^3) was stirred at room temp. for 90 min. The mixture was filtered and the collected solid was washed with ethanol (10 cm^3). The combined filtrates were evaporated under reduced pressure to give the free amine as a yellow oil. This was dissolved in NMP (5 cm^3) and β-CDtos (2.081 g, 1.61×10^{-3} mol) and KI (0.030 g) were added to the solution. The resultant mixture was treated according to the general procedure to give β-CDtacdo as a white powder (0.709 g, 34%). R_c 0.75; Electrospray-MS *m/z* 1288 (M^+) [Found: C, 45.28; H, 7.34; N, 3.15. Calc. for β-CDtacdo·4H_2O ($C_{51}H_{97}N_3O_{38}$): C, 45.03; H, 7.18; N, 3.08%]; δ_H(D_2O–NaOH, pH ~14) 4.9 (br s, 7H + solvent, H1), 4.14 (t, *J* 6.0, 1H, $H5^A$), 3.7–4.0 (m, 25H, H3, H5, H6), 3.17 (t, *J* 6.0, 1H, $H4^A$), 2.88 (d, *J* 15, 1H, $H6^A$), 2.64 (m, 13H, $H6^{A'}$, tacdoH1, tacdoH3, tacdoH4), 1.66 (m, 6H, tacdoH2, tacdoH5); δ_H[D_2O–HCl (1:1), pH ~8.5] 5.09 (s, 7H + solvent, H1), 4.26 (t, *J* 9.0, 1H, $H5^A$), 3.8–4.2 (m, 25H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.39 (t, *J* 9.0, 1H, $H4^A$), 2.5–3.2 (m, 14H, $H6^A$, tacdoH1, tacdoH3, tacdoH4), 1.6–2.0 (m, 6H, tacdoH2, tacdoH5); δ_H[D_2O–HCl (1:2), pH ~6.0] 5.07 (br s, 7H, H1), 4.25 (t, *J* 9.0, 1H, $H5^A$), 3.8–4.1 (m, 25H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.43 (t, *J* 9.0, 1H, $H4^A$), 2.7–3.3 (m, 14H, $H6^A$, tacdoH1, tacdoH3, tacdoH4), 1.7–2.2 (m, 6H, tacdoH2, tacdoH5); δ_H(D_2O–HCl, pH ~1) 5.0 (br s, 7H + solvent, H1), 4.33 (br t, 1H, $H5^A$), 3.7–4.0 (m, 25H, H3, H5, H6), 3.2–3.6 (m, 27H, H2, H4, $H6^A$, tacdoH1, tacdoH3, tacdoH4), 2.2 (br, 6H, tacdoH2, tacdoH5).

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