Complexation by α- and β-cyclodextrin† C(6) linked homo- and hetero-dimers of Brilliant Yellow tetraanion: a study of host–guest size relationships‡

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Complexation by α- and β-cyclodextrin (αCD and βCD) homo- and heterodimers linked at C(6) by a urea linker (*N*,*N*′-bis(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl)urea, *N*-(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl)-*N*′-(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea and *N*,*N*′-bis(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea **1**–**3**) of the tetraanion of the dye Brilliant Yellow (**4**) has been studied. In aqueous solution at 298.2 K, pH 10.0 (borate) and $I = 0.10$ mol dm^{-3} ($NaClO_4$) the spectrophotometrically determined complexation constants $K = (1.40 \pm 0.08) \times 10^4$, $(9.05 \pm 0.16) \times 10^4$ and $(3.92 \pm 0.06) \times 10^4$ dm^3 mol^{-1}, for the complexes **1**·**4**, **2**·**4** and **3**·**4**, respectively, that compare with $K = (1.05 \pm 0.08) \times 10^4$ and $(2.20 \pm 0.05) \times 10^3$ dm^3 mol^{-1} for the αCD·**4** and βCD·**4** complexes, respectively. Thus, the complexation of **4** in **1**·**4** shows little cooperativity consistent with the annulus of each αCD component of **1** being too small to pass over the phenylsulfonate component of **4**. It is probable that two complexes are formed when **2** complexes **4**: one in which **4** is complexed by the αCD component alone and which has a similar stability to **1**·**4** and a second complex where **4** is complexed by both the αCD and βCD components of **2** to form a complex 8.6 and 41 times more stable than αCD·**4** and βCD·**4**, respectively. The cooperativity between the two βCD components of **3** causes **3**·**4** to be 18 times more stable than βCD·**4**. These conclusions are supported by ^{1}H NMR spectroscopic studies.

Introduction

The complexation by native and modified cyclodextrin hosts of guest species is a much explored area of chemistry.[1,2] It has recently assumed increased importance with the realisation that supramolecular assemblies may either be prototypes for, or components of, molecular devices with potential uses in nanotechnology.[3,4] As a contribution to the understanding of the host–guest relationships governing the formation of supramolecular assemblies we have studied the α- and β-cyclodextrin (αCD and βCD) homo- and hetero-dimer (**1**–**3**) complexation of the Brilliant Yellow tetraanion, **4**. The dimers, *N*,*N*′-bis(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl)urea, **1**, *N*-(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl)-*N*′-(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea, **2**, and *N*,*N*′-bis(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea,[5] **3**, are joined at C(6) of their αCD and βCD components by a urea linker. These systems were selected because the tetranegative charge of **4** minimises the likelihood of aggregation that characterises some extended aromatic systems in water, and because **4** has a linear structure that is long relative to the length of the axes passing through both cyclodextrin annuli of **1**–**3** that contain one of the shortest reported linkages between two cyclodextrins. Thus, the simultaneous complexation of **4** by both CD components of **2** and **3** may be also viewed as formation of pseudo [2]-rotaxane, one of a class of molecular assemblies under active study as molecular devices.[3,4]

† α- and β-cyclodextrin = cyclomaltohexaose and cyclomaltoheptaose, respectively.
‡ Electronic supplementary information (ESI) available: Figs. S1–S4 with spectra. See http://www.rsc.org/suppdata/p2/b2/b200026c/

Results and discussion

Spectrophotometric equilibrium studies

The complexation of **4** by αCD and **1**–**3** was studied spectrophotometrically at $[\mathbf{4}]_{total} = 8.76 \times 10^{-6}$ mol dm^{-3} and $[\alpha CD]_{total} = 1.00 \times 10^{-6}$–$1.00 \times 10^{-2}$ mol dm^{-3} and $[\mathbf{1}–\mathbf{3}]_{total} = 1.00 \times 10^{-6}$–$1.00 \times 10^{-3}$ mol dm^{-3} in borate buffer at pH 10.00 ($I = 0.10$ mol dm^{-3}) at 298.2 K. (The complexation of **4** by βCD under the same conditions has been previously studied.[6]) In all cases the absorption maximum of **4** showed a small shift to longer wavelengths over most of the range 350 to 600 nm on complexation as exemplified by the absorbance variations shown with increasing [αCD or $\mathbf{1}–\mathbf{3}]_{total}$ in Fig. 1 and Supplementary Fig. S1. The **1/4** system showed isosbestic points at 515 and 553 nm, and the **3/4** system at 520 nm consistent with uncomplexed **4** and one complex being dominant in each system. The αCD/**4** and **2**/**4** systems showed systematic decreases in absorbance of **4** with increasing [αCD or $\mathbf{3}]_{total}$. The spectral variations of **4** in each system were analysed by attempting to fit algorithms for the formation of 1 : 1, 1 : 1 and 2 : 1, 1 : 2, and 2 : 1 complexes to the absorbance data at 1 nm intervals simultaneously over wavelength ranges that varied with the system as described in the Experimental section. In each case the best fit was obtained with the 1 : 1 model except in the case of the **2**–**4** system where similarly good fits were obtained for the 1 : 1 and the 1 : 1 and 2 : 1 model. (For the latter system both models include the **2**·**4** complex but the second model also includes the $\mathbf{2}_2$·**4** complex that appears entropically less favoured than the **2**·**4** complex. Therefore, the first model involving only the **2**·**4** complex was analysed in detail.) Two typical fits at single

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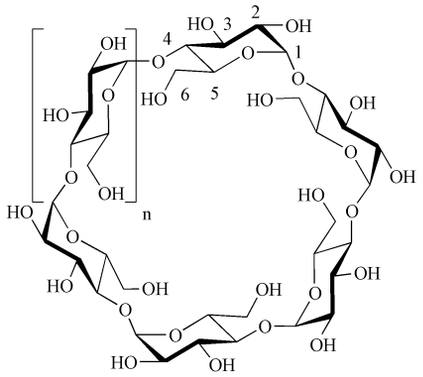
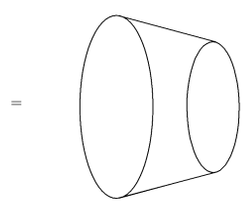
Table 1 Complexation constants for cyclodextrin/Brilliant Yellow tetraanion complexes in water at 298.2 K, pH = 10.0 and I = 0.10 mol dm^{-3}

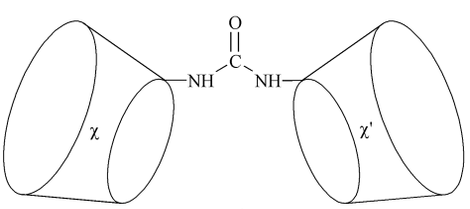
Cyclodextrin	10^{-4} K/dm^3 mol^{-1}
αCD	1.05 ± 0.01
βCD[a]	0.220 ± 0.005
1	1.40 ± 0.08
2[b]	9.05 ± 0.16
3	3.92 ± 0.06

[a] Ref. 6. [b] A fit for the model involving the formation of **2·4** (K_1) and **2_2·4** (K_2) gave sequential complexation constants of $K_1 = (5.72 \pm 0.09) \times 10^{-4}$ dm^3 mol^{-1} and $K_2 = (1.01 \pm 0.09) \times 10^{-4}$ dm^3 mol^{-1}.

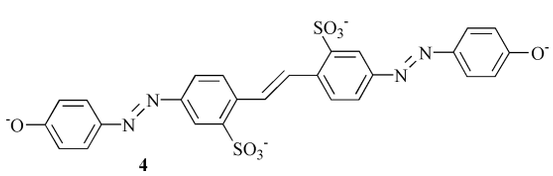


αCD, n = 1; βCD, n = 2





χ χ'
1 α α
2 α β
3 β β

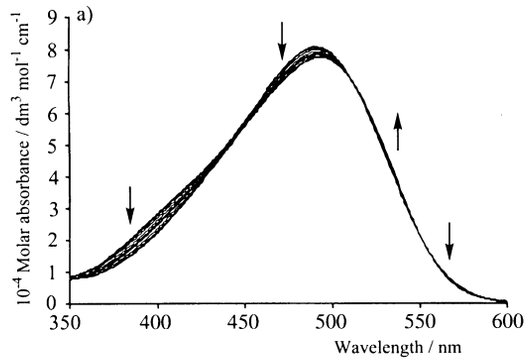


4

wavelengths are shown for **1·4** and **2·4** in Fig. 2. The derived complexation constants appear in Table 1.

Under the same conditions as those for the complexation studies, the absorbance of solutions of **4** alone increased linearly over the concentration range 7.00×10^{-7}–1.76×10^{-5} mol dm^{-3} consistent with no significant aggregation occurring.

Simultaneous complexation of a guest species by both αCD components of **1** should result in the complexation constant, K, for **1** being twice that for αCD on the basis of a simple collision model. In the event that cooperative complexation occurs, K for **1** should be significantly greater than twice that for αCD. It is seen from Table 1 that this is not the case. This is consistent with



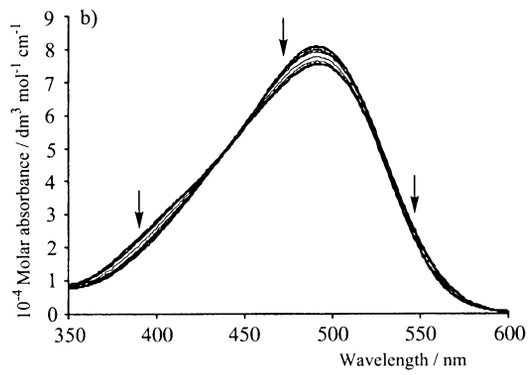


Fig. 1 a) The variation of the molar absorbance of **4** (8.78×10^{-6} mol dm^{-3}) as $[\mathbf{1}]_{total}$ increases in the range 1.00×10^{-6}–1.00×10^{-3} mol dm^{-3} at pH 10.00, I = 0.10 mol dm^{-3} and 298.2 K. b) The variation of the molar absorbance of **4** (8.78×10^{-6} mol dm^{-3}) as $[\mathbf{2}]_{total}$ increases in the range 1.00×10^{-6}–1.00×10^{-3} mol dm^{-3}. In both cases the arrows indicate the direction of absorbance change with increase in $[\mathbf{1}]_{total}$ and $[\mathbf{2}]_{total}$.

the annulus of the αCD component of **1** being too small to pass over the phenylsulfonate component of **4**, and both **1** and **4** being insufficiently flexible to allow complexation by a process obviating this spatial mismatch. Thus, **1·4** is dominantly a complex in which one end of **4** is complexed by only one αCD component of **1** consistent with the ^{1}H NMR data discussed below. The slightly greater value of K for **1·4** by comparison with K for αCD·**4** may arise from protrusion of the phenyl group of the complexed end of **4** into the space between the two αCD components of **1**.

The K for the complexation of **4** by **2** is 8.6 and 41 times greater than those for the complexation of **4** by αCD and βCD, respectively, and the complexation of **4** by **3** is 18 times that for the complexation of **4** by βCD consistent with cooperativity occurring between the CD components in the complexing of **4** in both systems. The complexation of **4** by **2** most probably involves the formation of three complexes as shown in Fig. 3. In the first, **2·4′**, one end of **4** is complexed by the αCD component of **2** and it is assumed to be characterised by $K' \approx 1.4 \times 10^4$ dm^3 mol^{-1} by analogy to the **1·4** complex. The second complex, **2·4″**, is formed by **2** complexing **4** through the βCD component to initially form a complex similar to **1·4**, but of lower stability because of the looser fit of the βCD component of **2**. While the stability of **2·4″** is unknown, by analogy it is assigned $K'' \approx 2.9 \times 10^3$ dm^3 mol^{-1} which is larger than the K for the βCD·**4** complex to the same extent as **1·4** is more stable than is αCD·**4**. Subsequently, **4** becomes simultaneously complexed by both the αCD and βCD components of **2** to form a third complex, **2·4‴**, for which $K''' \approx 26.4$ on the basis that $K = K' + K'' K''' \approx 9.05 \times 10^4$ dm^3 mol^{-1} (Table 1). (This assumes that **2·4″** is predominantly converted to **2·4‴** so that [**2·4″**] is negligible at equilibrium in accord with Fig. 3.) This is as anticipated from the K values for αCD·**4** and βCD·**4** (Table 1) and is reflected in $K = 9.05 \times 10^4$ dm^3 mol^{-1} for the **2**–**4** system which is consistent

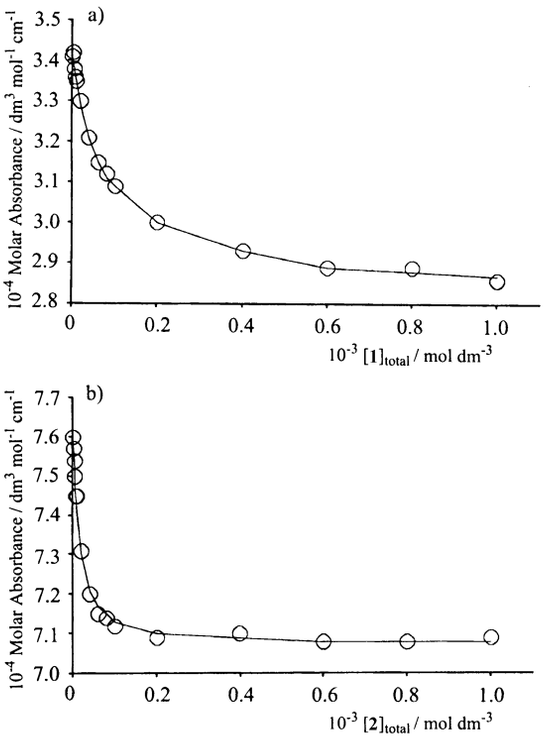


Fig. 2 a) The variation of molar absorbance of **4** at 410 nm with increasing concentration of $[\mathbf{1}]_{total}$. The curve represents the best fit of the algorithm for the formation of **1·4** to molar absorbance data at 1 nm intervals over the range 380–420 nm. b) The variation of molar absorbance of **4** at 475 nm with increasing concentration of $[\mathbf{3}]_{total}$. The curve represents the best fit of the algorithm for the formation of **2·4** to molar absorbance data at 1 nm intervals over the range 450–510 nm. The curve obtained for the best fit of the algorithm for the sequential formation of **2·4** and $\mathbf{2}_2$**·4** to the molar absorbance data is visually very similar.

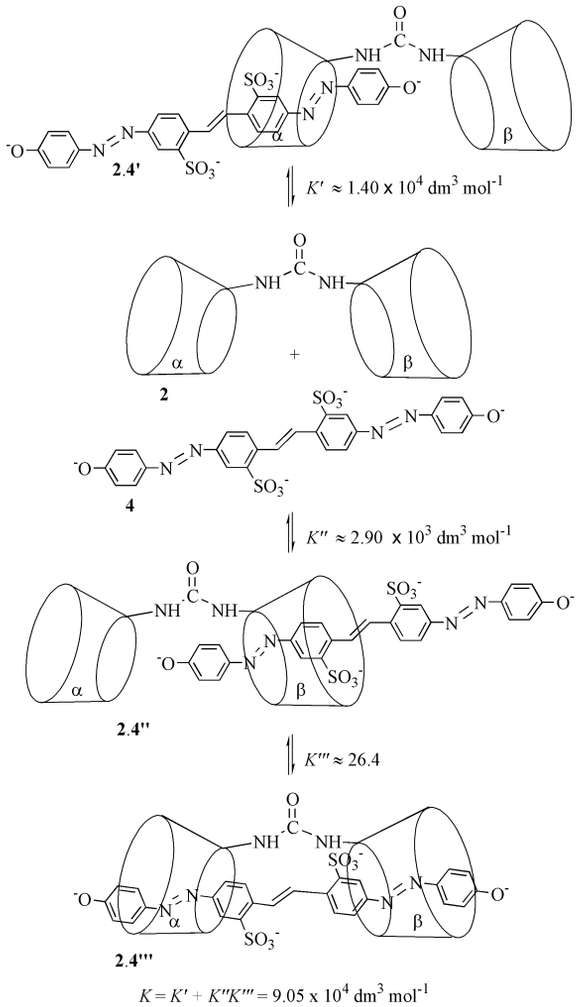


Fig. 3 Pathways for the complexation of **4** by **2** showing the derived complexation constant magnitudes.

with the ratio [**2·4**′]/[**2·4**‴] ≈ 0.18. A similar analysis of the complexation of **4** by **3** (where **3·4**′ and **3·4**″ are equivalent as are K' and K'') where one end of **4** enters one of the βCD components of **3** and is assigned $K'' \approx 0.29 \times 10^4$ dm^3 mol^{-1} is consistent with $K''' \approx 13.5$ for **3·4**‴ where **4** is complexed by both βCD components of **3** ($K = K''\ K''' = 3.92 \times 10^4$ dm^3 mol^{-1}). The larger value of $K''' \approx 26.4$ for **2·4**‴ by comparison with $K''' \approx 13.5$ for **3·4**‴ reflects the tighter fit of the αCD component of **2** to **4** by comparison with that of the βCD component of **3**.

^{1}H NMR spectroscopic studies

The ^{1}H (599.957 MHz) spectra of solutions of **4** alone and in the presence of equimolar **1**–**3** are shown in Fig. 4. While **4** alone is characterised by well resolved resonances (identified from COSY and TOCSY spectra), in the presence of **1**–**3**, the resonances of **4** exhibit chemical shift changes consistent with complexation, and broadening consistent with chemical exchange occurring in the intermediate timescale. In the presence of **1** and **2**, some of the resonances of **4** are duplicated consistent with each end of **4** experiencing different magnetic environments as seen most clearly for the H1 resonance of **4**. This is expected for the **1·4**, **2·4**′, **2·4**″ and **2·4**‴ complexes, but **4** does not show this duplication in **3·4**‴ as both ends of **4** are equivalent in the complex (Fig. 4). The concentration of uncomplexed **4** in the presence of **1**–**3** is insufficient to be detected in the solutions studied by ^{1}H NMR as expected from the K values in Table 1. (The tetraethylammonium salt of **4** is the origin of the tetraethylammonium resonances seen in all spectra.)

In equimolar D_2O solutions of αCD and **4** at 278.2 K the H1 resonance of **4** splits into two doublets at 6.50 and 6.49 ppm and 6.23 and 6.22 ppm assigned to the inequivalent **4** H1 in αCD**·4** and the less intense and broadened resonance at 6.37 ppm assigned to H1 in uncomplexed **4** (Fig. 5). The splitting of the **4** resonances H2–H6 arises from the same source but their resolution is insufficient for unequivocal assignment. Resonance broadening occurs at 298.2 K followed by coalescence and narrowing at 323.2 K consistent with **4** exchanging between complexed and uncomplexed environments. (The 2D ^{1}H ROESY NMR spectrum of the equimolar αCD/**4** system at 298.2 K shows ROE cross-peaks between both of the broadened H1 resonances of **4** and αCD H3, H5 and H6 as anticipated for chemical exchange at an intermediate rate (Supplementary Fig. S2).

The 2D ^{1}H (599.957 MHz) ROESY NMR spectra of solutions that are equimolar in either **1**, **2** or **3** and **4**, show cross-peaks arising from ROE interactions between H1–H6 of **4** and the αCD and βCD H3, H5 and H6, consistent with **4** complexing in the αCD and βCD component annuli as shown for **2/4** in Fig. 6. In the **1/4** system the **4** H1 is characterised by a well resolved doublet (Fig. 4b) that is assigned to the complexed end of **4** on the basis that it generates cross-peaks through interaction with αCD H3, H5 of **1** (Supplementary Fig. S3). The other H1 of **4** is broadened, generates no cross-peaks and is assigned to the free end of **4**. The broadening of the latter H1 is attributable to a chemical exchange that cannot be between the complexed and free ends of complexed **4**, as the broadening would be similar for each H1 environment. The greater **4** H1 broadening seen for the free end suggests that a faster exchange process is occurring than for the complexed end. The free end of **4** may experience a shallow and short-lived complexation by a second **1** that could generate the observed broadening. This

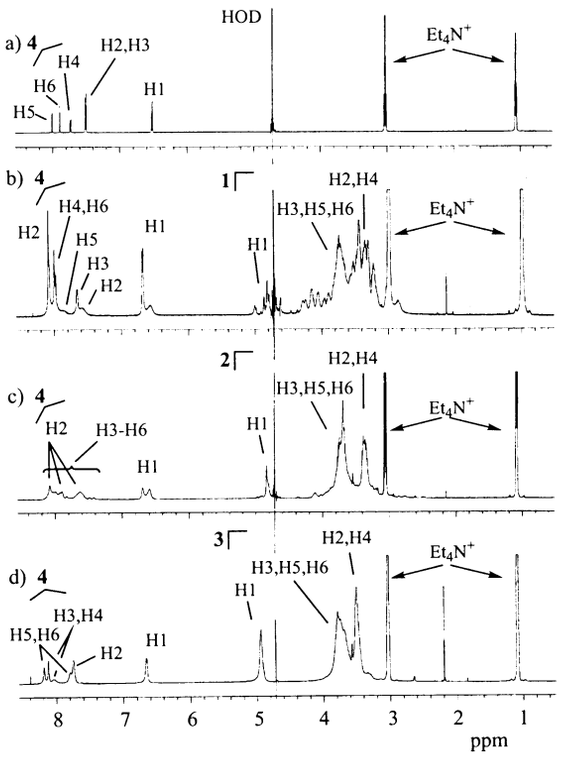


Fig. 4 ^{1}H NMR (599.957 MHz) spectra of D_2O solutions at pD ≥ 11 and 298.2 K of a) **4** (0.015 mol dm^{-3}), b) **1** and **4** (both 0.015 mol dm^{-3}), c) **2** and **4** (both 0.013 mol dm^{-3}), and d) **3** and **4** (both 0.014 mol dm^{-3}), where the assignments of H5 and H6 of **4** in the latter case are alternative assignments that cannot be distinguished between with certainty.

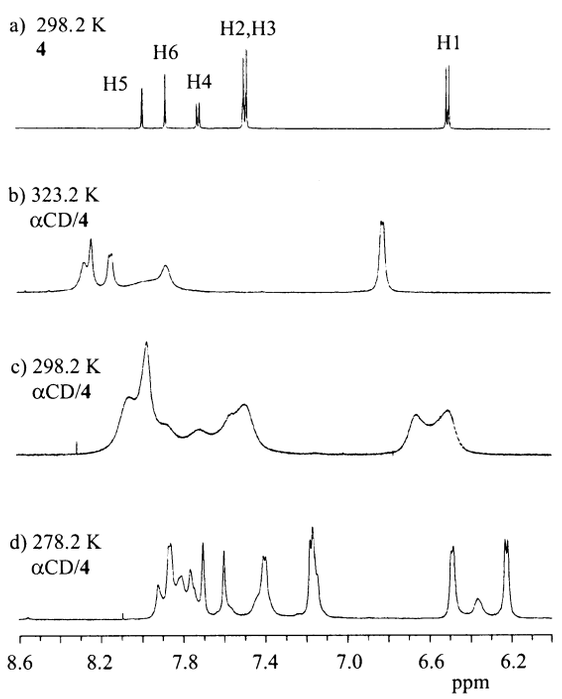


Fig. 5 ^{1}H NMR (599.957 MHz) spectra of D_2O solutions at pD ≥ 11 of a) **4** at 298.2 K and b)–d) a solution of αCD and **4** at 323.2, 298.2 and 278.2 K, respectively. The total concentration of each species is 0.015 mol dm^{-3}.

may be the preliminary stage in a pathway where the first **1** is displaced by a second **1** to exchange the complexed and free ends of **4**. The probability of this preliminary stage proceeding through to the complete displacement of the first complexed **1** is small, otherwise significant broadening of the doublet 1H

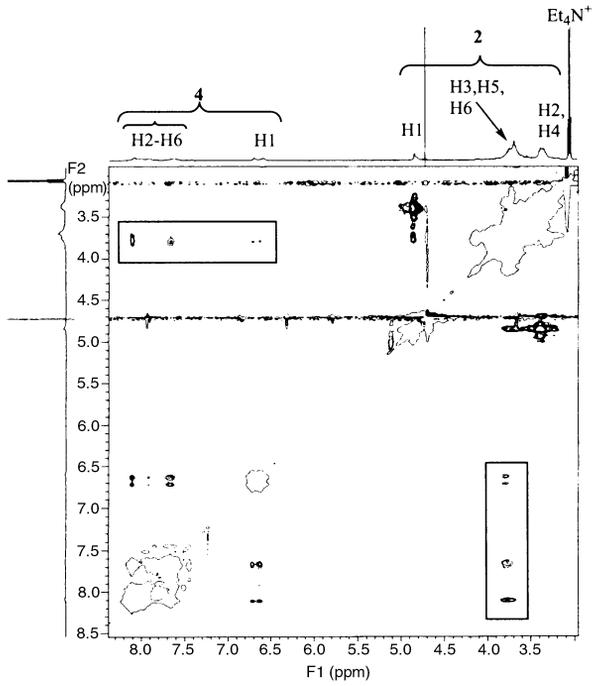


Fig. 6 The 2D ^{1}H ROESY NMR (599.957 MHz) spectum of a D_2O solution 0.014 mol dm^{-3} in **2** and 0.015 mol dm^{-3} in **4** at pD ≥ 11 and 298.2 K. The rectangles enclose the cross-peaks arising from ROE interactions between the protons of **4** and the βCD component protons of **2**, H3, H5 and H6.

resonance of the complexed end of **4** in αCD would occur. The alternative pathway involving complete decomplexation of **4** before a second **4** is complexed may also operate, but only a full kinetic analysis could determine this. Cross-peaks arising from ROE interactions between the protons of **4** and the βCD H3, H5 and H6 are also seen in the 2D ^{1}H ROESY NMR spectrum of the **3**/**4** system consistent with the formation of **3**·**4**‴ (Supplementary Fig. S4). (The spectra were obtained at pD ≥ 11 under which circumstances some deprotonation may have occurred in **1**–**3** as the pK_a of OH(2) is 12.33 for native αCD and βCD.[3])

Conclusion

The complexation of the Brilliant Yellow tetraanion, **4**, by the C(6) urea-linked αCD and βCD dimers **1**–**3** shows the importance of spatial relationships in host–guest complexation through the inability of the two αCD components of **1** to simultaneously complex **4** while the αCD and βCD components of **2** and the two βCD components of **3** complex **4** simultaneously. It is estimated that the stability of the complex **2**·**4**″ where one end first enters the βCD component of **2** increases by a factor of ≈ 26.4 as **4** subsequently enters the αCD component of **2** to give the final complex, **2**·**4**‴. The analogous enhancement for the sequential complexation of **4** by both βCD components of **3** to form **3**·**4**‴ is ≈ 13.5 reflecting the looser fit to, and the weaker complexation of, **4** by the second βCD component of **3** by comparison with the αCD component of **2** that is entered second by **4**.

Previous studies of βCD dimers exemplified by those linked through C(6) by disulfide,[7] diamide and urea[8] linkers have shown substantial enhancement of complexation of a variety of guests by comparison with the complexation by βCD alone. However, in the case of an αCD disulfide (C6) linked dimer insignificant enhancement of complexation of ethyl orange occurs in contrast to the analogous βCD disulfide system where a 224 times complexation enhancement occurs. This is attributed to the critical nature of the relative size of the host and

guest entities as is the similar observation in the present study, which for the first time presents a plausible analysis of the sequential dimer host–guest complexation events made possible by study of the hetero dimer *N*-(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl),*N*′-(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea, **2**.

Experimental

General

All aqueous solutions were prepared with water purified with a Waters Milli-Q system to give a specific resistance of >15 MΩ cm that was then boiled for 30 min to remove CO_2 and allowed to cool in containers fitted with a soda lime drying tube. The disodium salt of Brilliant Yellow (Aldrich 70%) was twice recrystallised from methanol. A hot aqueous solution of Brilliant Yellow was prepared and filtered (150 cm^3). Hot aqueous tetraethylammonium perchlorate (100 cm^3, 0.1 mol dm^{-3}) was slowly added with stirring and the rapidly formed orange precipitate was filtered off, washed with distilled water and dried over P_2O_5 in a darkened vacuum desiccator (Found: C, 55.56; H, 7.13; N, 9.27%. The tetrahydrated di-tetraethylammonium salt of Brilliant Yellow ($C_{42}H_{66}N_6O_{12}S_2$): C, 55.37; H, 7.02; N, 9.23%). Uv–visible spectra of **4** alone or in the presence of either αCD or **1**–**3** in aqueous 0.05 mol dm^{-3} borate buffer at pH 10.00 and I = 0.10 mol dm^{-3} ($NaClO_4$) were run at 298.2 ± 0.1 K in matched quartz cuvettes of 1 cm path length against a reference containing the same buffer and supporting electrolyte. Absorbance data were collected at 1 nm intervals with a Cary 300 Bio double beam spectrophotometer. Wavelength ranges where the greatest absorbance change occurred were selected for analysis. These ranges were: 380–420 nm and 480–510 nm for αCD/**4**, 380–430 nm for **1**/**4**, 450–510 nm for **2**/**4** and 380–420 nm and 480–510 nm for **3**/**4**.

Complex stoichiometry and complexation constants were determined through non-linear least squares fitting of algorithms for the formation of 1 : 1, 1 : 1 and 2 : 1, 1 : 2, and 2 : 1 complexes to the absorbance variation of **4** with concentration of αCD, **1**, **2** or **3** at 1 nm intervals by using Method 5 of Pitha and Jones,[9] through an in-house least squares regression routine DATAFIT[10] using the MATLAB formalism.[11] Taking the **2**/**4** system as an example, the observed absorbance, A, is related to the molar absorbances of the species in solution, ε, and their concentrations through:

$$A = \varepsilon_2[\mathbf{2}] + \varepsilon_4[\mathbf{4}] + \varepsilon_{2.4}[\mathbf{2{\cdot}4}] \quad (1)$$

where ε_2 = 0 and species concentrations are related through the complexation constant K = [**2**·**4**]/([**2**][**4**]) where [**2**·**4**] = [**2**·**4**′] + [**2**·**4**‴] which are related through the equality: $K = K' + K'' K'''$ as shown in Fig. 3 and discussed in the text.

^{1}H (300.145 MHz) and ^{13}C (75.479 MHz) NMR spectra were run on a Varian Gemini 300 spectrometer, and ^{1}H (599.957 MHz) NMR spectra were run on an Inova 600 spectrometer. Solutions of **4** alone or in the presence of either αCD or **1**–**3** were prepared in 0.10 mol dm^{-3} NaOH in D_2O to give concentrations of 0.013–0.015 mol dm^{-3} in each constituent and pD ≥ 11. Chemical shifts were determined against external trimethylsilylpropanesulfonic acid. ESI mass spectrometric studies were made in positive ion mode with a Finnigan MAT ion trap LC-Q mass spectrometer fitted with an electrospray ionisation source. Accurate mass spectrometry was carried out at the University of Tasmania, Hobart. 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. Thin layer chromatography (TLC) was carried out on Kieselgel 60 F254 (Merck) on aluminium backed sheets. Plates were developed with 7 : 7 : 5 : 4 v/v ethyl acetate–propan-2-ol–ammonium hydroxide–water. Modified and native CDs 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 αCDs bearing amino groups, 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 ethanolic acid solution. The modified CDs decomposed upon heating which precluded the determination of melting points. All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. α-CD (Nihon Shokuhin Kako Co.) was dried by heating at 100 °C under vacuum for 18 hours. All solvents used in syntheses were redistilled and dried by standard methods.

Syntheses

6^{A}-*O*-*p*-Tolylsulfonyl-α- and 6^{A}-*O*-*p*-tolylsulfonyl-β-cyclodextrin,[12] 6^{A}-azido-6^{A}-deoxy-α- and 6^{A}-azido-6^{A}-deoxy-β-cyclodextrin[13] and 6^{A}-amino-6^{A}-deoxy-β-cyclodextrin[14] were prepared by literature methods and gave good elemental analysis results and ^{1}H NMR spectra consistent with those in the literature.

***N*,*N*′-Bis(6^{A}-deoxy-α-cyclodextrin-6^{A}-yl)urea 1 and its β-cyclodextrin analogue 3.** A solution of 6^{A}-azido-6^{A}-deoxy-α-cyclodextrin (302 mg, 0.30 mmol) in DMF (6 cm^3) was saturated with dry CO_2; triphenylphosphine (132 mg, 0.50 mmol) in DMF (3 cm^3) was added dropwise to the solution of 6^{A}-azido-6^{A}-deoxy-α-cyclodextrin through which CO_2 was bubbled until no starting material was detected (27 hours). The DMF was removed and the resulting solid washed with acetone (10 cm^3). After filtration, this product was dissolved in water (45 cm^3), precipitated by addition of acetone (350 cm^3) and gravity filtered. The product was dissolved in water (3 cm^3) and passed through a Sephadex G25 size exclusion column to remove an unidentified impurity. The white solid product, **1**, was obtained after freeze drying (174 mg, 58%), ESI-MS (M + Na) 1993.0; (M + H) 1971.0. Elemental analysis for $C_{73}H_{120}N_2O_{59}$·$11H_2O$: C, 40.45; H, 6.60; N, 1.29. Found: C, 40.32; H, 6.25; N, 1.21%. $\delta_H(D_2O)$ 5.04 (s, 12H, H1), 3.70–3.51 (m, 72H, H3, H5, H6, H2, H4). $\delta_C(D_2O)$ 163.0 (NH–CO–NH), 104.2 (C1), 83.3–86.3 (C4), 73.5–77.0 (C2, C3, C5), 63.5 (C6$^{B–F}$), 43.5 (C6^{A}). Previously reported *N*,*N*′-bis(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea **3** was prepared from 6^{A}-azido-6^{A}-deoxy-β-cyclodextrin prepared in 67% yield in a similar manner.[5] ESI-MS (M + Na) 2316.8; (M + H) 2294.8. Elemental analysis for $C_{85}H_{140}N_2O_{69}$·$10H_2O$: C, 41.26; H, 6.52; N, 1.13. Found: C, 39.63; H, 6.13; N, 1.37%. $\delta_H(D_2O)$ 5.03 (s, 14H, H1), 3.71–3.50 (m, 84H, H3, H5, H6, H2, H4). $\delta_C(D_2O)$ 163.2 (NH–CO–NH), 104.5 (C1), 83.0–85.9 (C4), 72.4–76.4 (C2, C3, C5), 63.0 (C6$^{B–G}$), 43.2 (C6^{A}). The ^{1}H NMR data were consistent with those reported in the literature.

***N*-(6^{A}-Deoxy-α-cyclodextrin-6^{A}-yl)-*N*′-(6^{A}-deoxy-β-cyclodextrin-6^{A}-yl)urea 2.** Dry CO_2 was bubbled through a solution of 6^{A}-amino-6^{A}-deoxy-α-cyclodextrin (403 mg, 0.42 mmol) in DMF (6 cm^3) at room temperature for 20 h after which 6^{A}-azido-6^{A}-deoxy-α-cyclodextrin (310 mg, 0.32 mmol) was added followed by dropwise addition of triphenylphosphine (100 mg, 0.38 mmol) over 6 h. After stirring for 40 h, DMF was removed under reduced pressure. The residue was triturated with acetone (30 cm^3) and collected by vacuum filtration, before dissolution in water (50 cm^3) and precipitation by addition of acetone (500 cm^3). The collected product was dissolved in water (100 cm^3) and run down a BioRex 70 (H^+) column. Water was removed under reduced pressure at 398.2 K to give **3** as a white solid (352 mg, 52%). ESI-MS (M + Na) 2155.0; (M + H) 2132.1. Elemental analysis for: $C_{79}H_{130}N_2O_{64}$·$6H_2O$: C, 42.36; H, 6.39; N, 1.25. Found: C, 42.50; H, 6.40; N, 1.25%. $\delta_H(D_2O)$ 5.05 (m, 13H, 1H), 3.70–3.50 (m, 78H, H3, H5, H6, H2, H4). $\delta_C(D_2O)$ 163 (NH–CO–NH), 104.5 (C1), 83.9–85.5 (C4), 73.0–76.3 (C2, C3, C5), 63.2 (C6$^{B–G}$), 43.4 (C6^{A}).

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