Synthesis of a cyclodextrin azo dye [3]rotaxane as a single isomer

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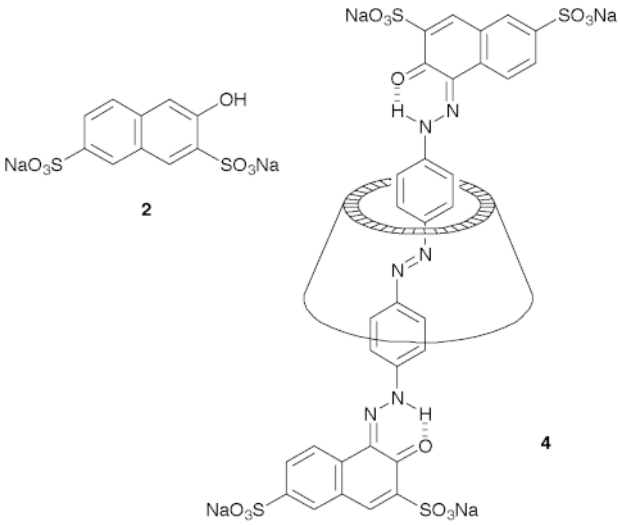
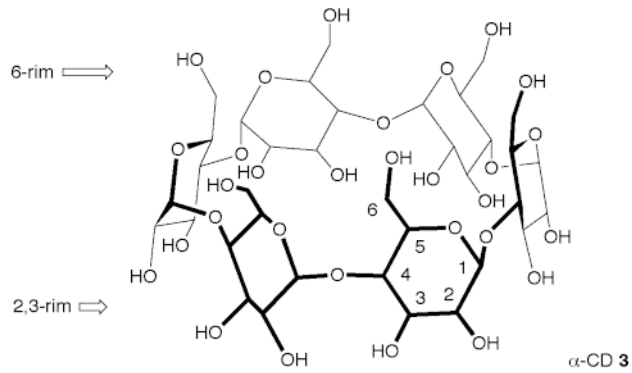
Azo coupling between 2,6-dimethylphenol and aqueous 4,4′-bis(diazonio)azobenzene chloride in the presence of α-cyclodextrin yields an azo dye [3]rotaxane as a single stereoisomer, with the 2,3-rims of both cyclodextrins pointing outwards.

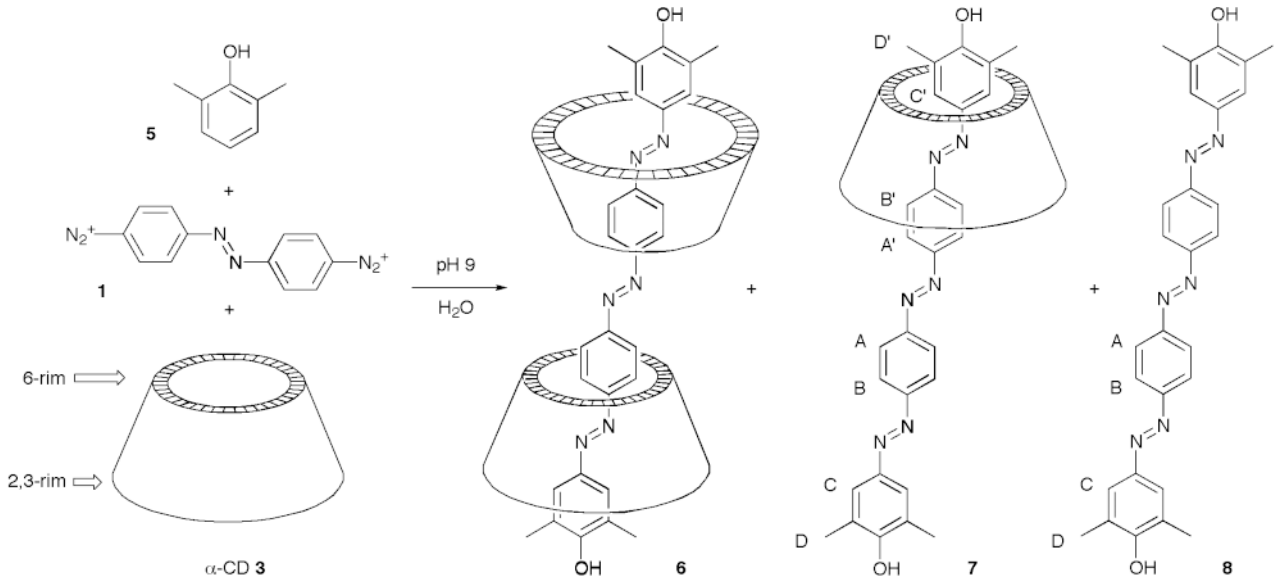
As part of a project on the encapsulation of chromophores,[1] we recently reported[1b] that reaction of 4,4′-bis(diazonio)azobenzene chloride **1** with aqueous β-naphthol **2** in the presence of



α-cyclodextrin (α-CD) **3** yields the azo dye [2]rotaxane **4**. Here we present the unexpected discovery that, when this reaction is carried out using 2,6-dimethylphenol **5** instead of β-naphthol **2**, the main product is the [3]rotaxane **6** (Scheme 1). The [2]rotaxane **7** and the unencapsulated dye **8** are also formed. To the best of our knowledge this is the first report of a cyclodextrin [3]rotaxane[2] (previous [3]rotaxanes have been made from crown ethers[3] and cyclophanes;[1a,c,4] polyrotaxanes have also been prepared using cyclodextrins[5]). α-Cyclodextrin has a narrow 6-rim (with primary OH groups) and a wider 2,3-rim (with secondary OH groups). There are three possible relative orientations of the cyclodextrin units in **6**, but, remarkably, this [3]rotaxane is formed as a single stereoisomer.



The three products of the reaction shown in Scheme 1 were separated by column chromatography on silica, eluting with 25% aqueous ammonia–butanone–*n*-propanol (1:1:1). Traces of [2]rotaxane **7**, dumbbell **8** and free α-CD **3** can be removed from the [3]rotaxane **6** by ultrafiltration; **6** is retained by a cellulose ultrafiltration membrane (1000 nominal molecular weight limit†), whereas the other components wash through.



Scheme 1

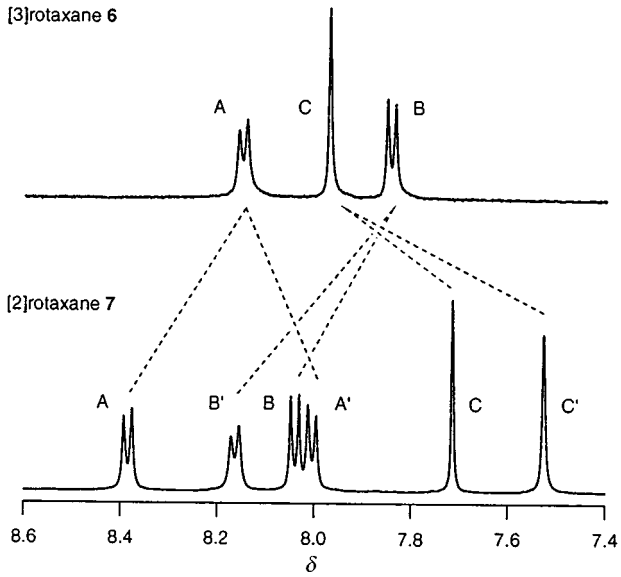


Fig. 1 Aromatic regions of the ^{1}H NMR spectra (DMSO-d_6, 340 K, 500 MHz) of [2]rotaxane **7** and [3]rotaxane **6**.

The isolated yields of **6** and **7** are 12 and 9%, respectively, and the [3]rotaxane can be prepared on a 0.5 g scale using this technique.

The [2]rotaxane and [3]rotaxane were thoroughly authenticated by ^{1}H and ^{13}C NMR, and mass spectrometry.‡ Their ^{1}H NMR spectra were assigned using 2D techniques. The aromatic regions of these spectra are shown in Fig. 1. In the [2]rotaxane, all the resonances of the azo dye dumbbell are split, as expected, due to the inequivalence of the rims of the cyclodextrin, leading to six aromatic signals (H_A–H_C are nearer the 2,3-rim and H_A–$H_{C'}$ are nearer the 6-rim). This type of splitting is not observed in the spectra of the [3]rotaxane, which has only three aromatic resonances (H_A–H_C). This shows that the two α-CD units are either 6-rim-to-6-rim or 2,3-rim-to-2,3-rim; these possibilities were distinguished using 1D gradient NOESY experiments. Strong NOEs are observed from the methyl protons (H_D) to positions on the 2,3-rim of the α-CD (H-3, OH-3 and OH-2), proving that it is the 6-rim-to-6-rim isomer, as depicted in Scheme 1. The reasons for exclusive formation of this isomer are being investigated. Surprisingly, NOE experiments on the [2]rotaxane, in DMSO-d_6, show that it prefers the conformation shown in Scheme 1, with the 6-rim near the end of the chromophore. The two methyl signals, H_D and $H_{D'}$, are almost coincident, and cannot be selectively inverted, however when both methyl resonances are inverted, the dominant NOEs are to H-6, H-6′ and H-5; an NOE is also observed to H-3, but it is about half as large as those to H-6, H-6′ and H-5. Strong NOEs are also observed from $H_{C'}$ to H-6, H-6′ and H-5, whereas H_C shows only a weak NOE to H-3 (about four times smaller than those from $H_{C'}$ to H-6, H-6′ and H-5). The cyclodextrin shuttles rapidly along the dumbbell on the NMR timescale at room temperature, but it shows a distinct preference for the A′–D′ end near the 6-rim.

Yoshida has shown that azo dyes derived from 2,6-dimethylphenol do not easily slip through the cavity of α-CD,[6] but we were initially uncertain as to whether this end-group would be large enough to yield a stable rotaxane. No unthreading[3f,7] of **6** and **7** has been observed in solution at temperatures up to 100 °C, but when **6** was heated to 120 °C in DMSO-d_6 for a week, ^{1}H NMR showed about 15% of the material unthreaded to give **7** and α-CD **3**. This corresponds to a unimolecular rate constant for unthreading of about 10^{-7} s^{-1} and a free energy barrier ($\Delta G^{\ddagger}$) of 147 kJ mol^{-1} at 120 °C, which indicates that the half-life for unthreading at room temperature is probably more than 10^5 years.

This direct route to a [3]rotaxane encapsulated azo dye, in one step from readily available materials, will facilitate investigations into the consequences of chromophore encapsulation, and into the photochemistry of these rotaxanes.[8]

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Notes and references

† Amicon YM1 membrane, from Millipore Ltd.

‡ *Selected data* for **6**: δ_H(330 K, DMSO-d_6) 2.39 (12H, s, H_D), 3.27 (12H, d, H-2), 3.44 (12H, t, H-6′), 3.47 (12H, t, H-4), 3.65 (12H, t, H-3), 3.73 (24H, m, H-5 and H-6), 4.21 (12H, t, OH-6), 4.75 (12H, d, H-1), 5.00 (12H, d, OH-3), 5.14 (12H, d, OH-2), 7.83 (4H, d, H_B), 7.96 (4H, s, H_C), 8.14 (4H, d, H_A); δ_C(330 K, DMSO-d_6) 15.93, 59.77, 70.94, 72.08, 72.87, 81.48, 101.93, 122.05, 123.81, 124.18, 124.47, 145.20, 151.73, 153.79, 157.44; λ_{max}/nm (log ε) (DMSO) 454 (4.8); *m*/*z* (MALDI TOF) 2446.3 (M + Na)$^+$ (Calc. for $C_{100}H_{146}N_6O_{62}\cdot 12H_2O$: C, 45.5; H, 6.5; N, 3.2. Found C, 45.6; H, 6.8; N, 3.2%). For **7**: δ_H(300 K, DMSO-d_6) 2.28 (6H, s, H_D or $H_{D'}$), 2.29 (6H, s, H_D or $H_{D'}$), 3.15 (6H, m, H-2), 3.26 (6H, m, H-6′), 3.36 (6H, t, H-4), 3.52 (12H, m, H-6 and H-3), 3.61 (6H, d, H-5), 4.34 (6H, t, OH-6), 4.67 (6H, d, H-1), 5.23 (6H, d, OH-3), 5.28 (6H, d, OH-2), 7.48 (2H, s, $H_{C'}$), 7.76 (2H, s, H_C), 7.96 (2H, d, $H_{A'}$), 8.00 (2H, d, H_B), 8.12 (2H, d, $H_{B'}$), 8.34 (2H, d, H_A); δ_C(300 K, DMSO-d_6) 16.50, 16.53, 59.92, 71.63, 72.45, 73.32, 82.09, 102.30, 122.54, 123.48, 123.60, 123.64, 123.95, 125.00, 125.24, 125.41, 145.34 (2C), 152.39, 152.67, 153.55, 153.95, 158.12 (2C); λ_{max}/nm (log ε) (DMSO) 439 (4.8); *m*/*z* (MALDI TOF) 1473.5 (M + Na)$^+$.

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