Kinetic Covalent Chemistry

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Quantitative Emergence of Hetero[4]rotaxanes by Template-Directed Click Chemistry**

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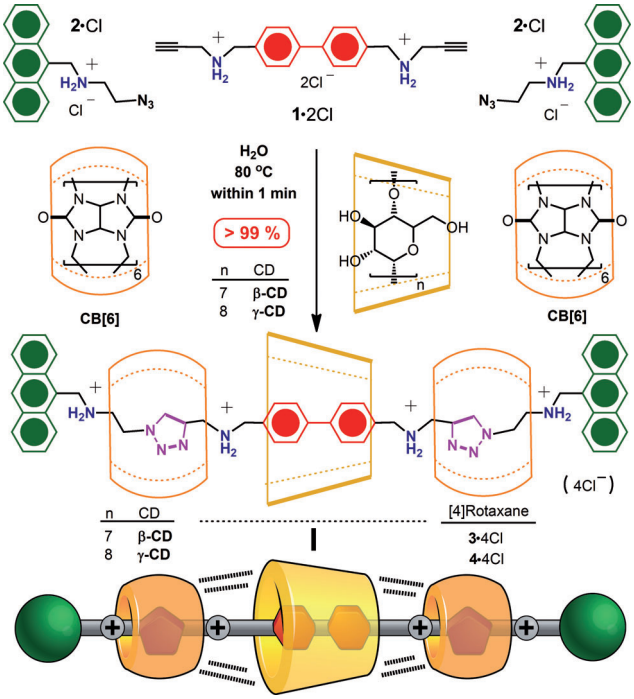
Self-assembly is a key process in biology, chemistry, and materials science, underlying DNA replication,[1] quaternary structure formation in proteins,[2] the complexation of primary alkylammonium salts by crown ethers,[3] liquid crystalline behavior,[4] to mention but a few examples. When it comes to multicomponent self-assembly[5] and the template-directed synthesis[6] of mechanically interlocked molecules[7] (MIMs), dynamic covalent chemistry[8] (DCC) provides an efficient route to supramolecular and molecular entities of considerable complexity. DCC, a process whereby covalent bonds are formed reversibly under thermodynamic control and so possesses the elements of "error-checking" and "proof-reading", has yielded oligorotaxanes[9] near quantitatively in a cooperative fashion.[10] An alternative synthetic approach, based on irreversible kinetic covalent chemistry (KCC), is more likely to require arduous purification procedures in order to remove unwanted by-products. Pre-organization[11] of the precursors, however, in the case of KCC can link the molecular building blocks efficiently in desired sequences and so minimize the errors being committed during the self-assembly process. Furthermore, these pre-organized precursors can be mechanically interlocked readily to afford MIMs. A powerful synthetic approach—the Cu^{I}-catalyzed version of the [3+2] Huisgen[12] azide–alkyne cycloaddition (CuAAC), known as click chemistry[13]—has been employed[14] extensively to good effect in the production of MIMs. Herein, we describe how we have appealed to 1) the well-known[15–17] ability of cucurbiturils[18] (CBs) to "catalyze" this 1,3-dipolar cycloaddition along with 2) the propensity of CBs to enter into cooperative binding interactions[19] with cyclodextrins[20] (CDs) to generate (Scheme 1) in one pot rapidly (within 1 min) and quantitatively (> 99 %) a hetero[4]rotaxane **3**·4Cl from a) the bispropargyl derivative **1**·2Cl of a bisammonium salt, where the two NH_2^+ recognition sites are separated by a bitolyl spacer which is capable of binding,[21] b) β-CD, and c) the stoppers' precursor, *N*-(anthracen-9-ylmethyl)-2-azidoethylammonium chloride **2**·Cl, which is predisposed towards entering, along with the bispropargyl derivative, into [3+2] azide-alkyne cycloadditions (> 100-fold rate increase) in the presence of d) cucurbit[6]uril[18] (CB[6]) when all components are present in aqueous solution at 80 °C in the molar ratio, 1:1:2:2, respectively. These results augur well for the synthesis of polyrotaxanes, incorporating upwards of 64 rings on the dumbbells.



Scheme 1. Synthesis of the hetero[4]rotaxanes **3**·4Cl and **4**·4Cl starting from **1**·2Cl and **2**·Cl in the presence of CB[6] and β-CD and γ-CD, respectively. The hatched lines in the graphical representation indicate the hydrogen bonding interactions between CB[6] and CD rings.

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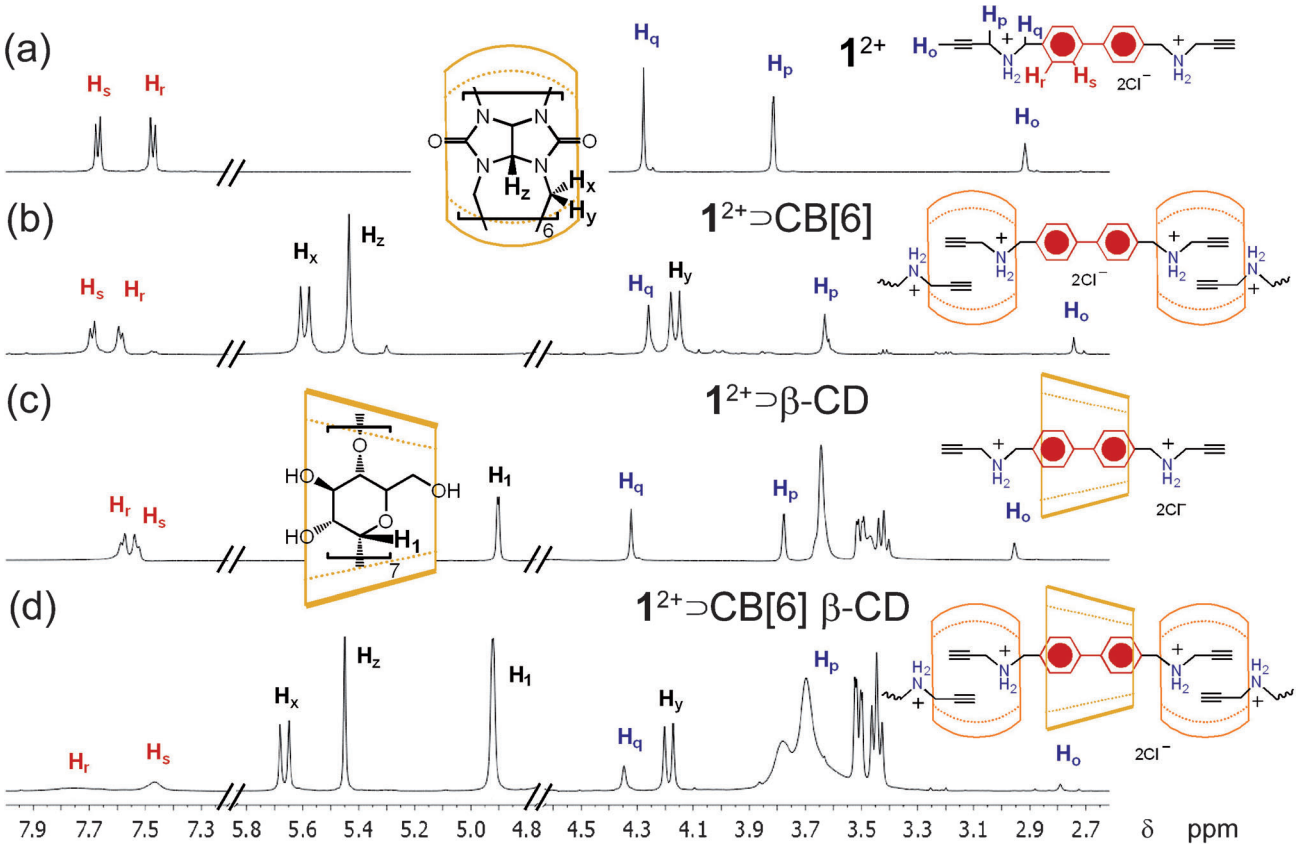

Figure 1. ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of a) **1**·2Cl (10.0 mM), b) **1**·2Cl (10.0 mM) saturated with CB[6], c) **1**·2Cl (10.0 mM) with β-CD (11.0 mM), and d) **1**·2Cl (10.0 mM) saturated with CB[6] and β-CD (11.0 mM).

At the outset, we investigated the binding of both CB[6] and β-CD with the bispropargyl derivative **1**·2Cl by ^{1}H NMR spectroscopy (Figure 1a) in D_2O. Compound **1**·2Cl was prepared by reacting 4,4′-bis(chloromethyl)-1,1′-biphenyl with propargylamine and recrystallizing the crude product from HCl (1M) in Me_2CO. Upon addition of excess of CB[6] to **1**·2Cl, the signals for H_o, H_p and H_q were shifted upfield, whereas the resonance for H_r was shifted downfield while that for H_s remained unperturbed, indicating that the CB[6] rings encircle the propargyl groups of **1**·2Cl, rather than its bitolyl spacer unit.[22] The fact that the relative intensities of these signals (Figure 1b) are 1:1 suggests that **1**·2Cl forms a complex with *n*:*n* stoichiometry, whereas the propargyl groups in **1**·2Cl half-occupy the CB[6] cavities, forming small dynamic supramolecular oligomers. These observations are in agreement with the fact that CB[6], which is very poorly soluble[18b] (18 μM) in D_2O, only dissolves as a result of its binding with the propargyl groups of **1**·2Cl. The situation is quite different when considering the binding of **1**·2Cl by β-CD in D_2O. The ^{1}H NMR spectrum (Figure 1c) of an equimolar mixture reveals that the resonances for H_o, H_p and H_q undergo very little if any shift, whereas the signals for H_r and H_s are reversed in addition to being shifted. These observations indicate that the β-CD ring[23] encircles the bitolyl unit of **1**·2Cl. Although it is well-known[24] that β-CD usually avoids forming complexes with (di)cationic guests, isothermal titration calorimetry (ITC) reveals (Table 1) an association constant of $1.27\times10^3\,M^{-1}$ in water for the 1:1 complex, corresponding to a ΔG value[25] of −17.7 kJ mol^{-1}.

Table 1: Thermodynamic parameters[a] (ΔH, $T\Delta S$, K_a, and ΔG) for β-CD and γ-CD binding with **1**·2Cl, **5**·2Cl, $\mathbf{1}^{2+}\supset$CB[6], and $\mathbf{5}^{2+}\supset$CB[6].

Guest	Host	ΔH [kJ mol^{-1}]	$T\Delta S$ [kJ mol^{-1}]	K_a [M^{-1}]	ΔG [kJ mol^{-1}]
1·2Cl	β-CD	−11.6	6.1	1.27×10^3	−17.7
$\mathbf{1}^{2+}\supset$CB[6]	β-CD	−34.0	−8.9	2.56×10^4	−25.1
$\mathbf{1}^{2+}\supset$CB[6]	γ-CD	−24.5	−2.1	8.58×10^3	−22.4
5·2Cl	β-CD	−12.0	5.3	1.07×10^3	−17.3
$\mathbf{5}^{2+}\supset$CB[6]	β-CD	−30.6	−3.0	6.76×10^4	−27.6
$\mathbf{5}^{2+}\supset$CB[6]	γ-CD	−20.5	1.2	6.43×10^3	−21.7

[a] Data measured by ITC at 298 K in pure water.

The ^{1}H NMR spectrum (Figure 1d) of an equimolar mixture of **1**·2Cl, CB[6] and β-CD[26] in D_2O reveals that, while the signals for H_r and H_s become broad, those (Figure 1b) for H_o and H_q shift very little with respect to those for $\mathbf{1}^{2+}\supset$CB[6]. These observations imply that, not only are the propargyl groups of **1**·2Cl still included inside the CB[6] cavities, but the β-CD ring[23] is also still encircling the bitolyl unit. ITC performed on the complex formed between $\mathbf{1}^{2+}\supset$CB[6] and β-CD afforded a binding constant of $2.56\times10^4\,M^{-1}$, i. e., a 20-fold binding enhancement compared (Table 1) to $\mathbf{1}^{2+}\supset$β-CD. The large positive enthalpy change of −34.0 kJ mol^{-1} can be attributed to the positive coopera-

tivity between the β-CD and CB[6] rings arising from multiple hydrogen bonding between the CB[6] carbonyl groups and both the primary and secondary faces of the CD ring. The significant entropy loss is consistent with the co-conformational restrictions imposed upon the CB[6] and β-CD rings and can be associated with the large enthalpy change in the context of enthalpy-entropy compensation.

Having established the integrative self-sorting[27] of the hetero[3]pseudorotaxane $\mathbf{1}^{2+}\supset$[CB[6]·β-CD] from four components, we could address the syntheses of the hetero[4]-rotaxanes **3**·4Cl and **4**·4Cl, starting from β-CD and γ-CD, respectively, in the presence of **1**·2Cl and **2**·Cl in D_2O/H_2O. The stopper precursor **2**·Cl was obtained by reductive amination of 9-anthraldehyde with ethanolamine, followed by conversion of the alcohol to the chloride and treatment with NaN_3 to give a crude product, which was recrystallized from HCl (1M) in Me_2CO. Although well over a dozen compounds/complexes might be expected to be formed when **1**·2Cl, **2**·Cl, CB[6] and β-CD are reacted together, the outcome is very much more precise and discrete, thanks to self-sorting[27] and the "catalytic" 1,3-dipolar cycloadditions that occur between **1**·2Cl and **2**·Cl in the presence of CB[6] and β-CD in aqueous solution.

The presence of markedly positive cooperativity[9] in the formation of **3**·4Cl was established by the following sequence of experiments. The ^{1}H NMR spectrum (Figure 2a), recorded after heating **1**·2Cl and **2**·Cl in D_2O for 30 min, shows that **1**·2Cl and **2**·Cl do not react, i.e., we observe peaks that can be attributed to a simple mixture of these two compounds. When either β-CD or γ-CD were added to this mixture, the ^{1}H NMR spectrum (Figure 2b) revealed only the presence of $\mathbf{1}^{2+}\supset$CD and **2**·Cl when the mixture was treated in a similar manner. Slow rotaxane formation could be monitored by ^{1}H NMR spectroscopy after adding CB[6] to the D_2O solution containing **1**·2Cl and **2**·Cl. On heating this solution at 80 °C for 30 mins, a ^{1}H NMR spectrum (see Supporting Information) was recorded, showing less well-resolved resonances plus a new signal which emerged at $\delta \approx 6.4$ ppm for the triazole ring protons. Although slightly more of the [3]rotaxane was found to form on increasing the reaction time, the reaction was far from complete (Figure 2c), even after heating at 80 °C for 2.5 h and then allowing it to stand at room temperature for one week.

In sharp contrast, when **1**·2Cl, **2**·Cl, CB[6] and β-CD[28] were added to D_2O in the molar ratio 2:1:2:1 in a NMR tube, the ^{1}H NMR spectrum (Figure 2d), recorded a few minutes after mixing, showed that the reaction to form the hetero[4]-

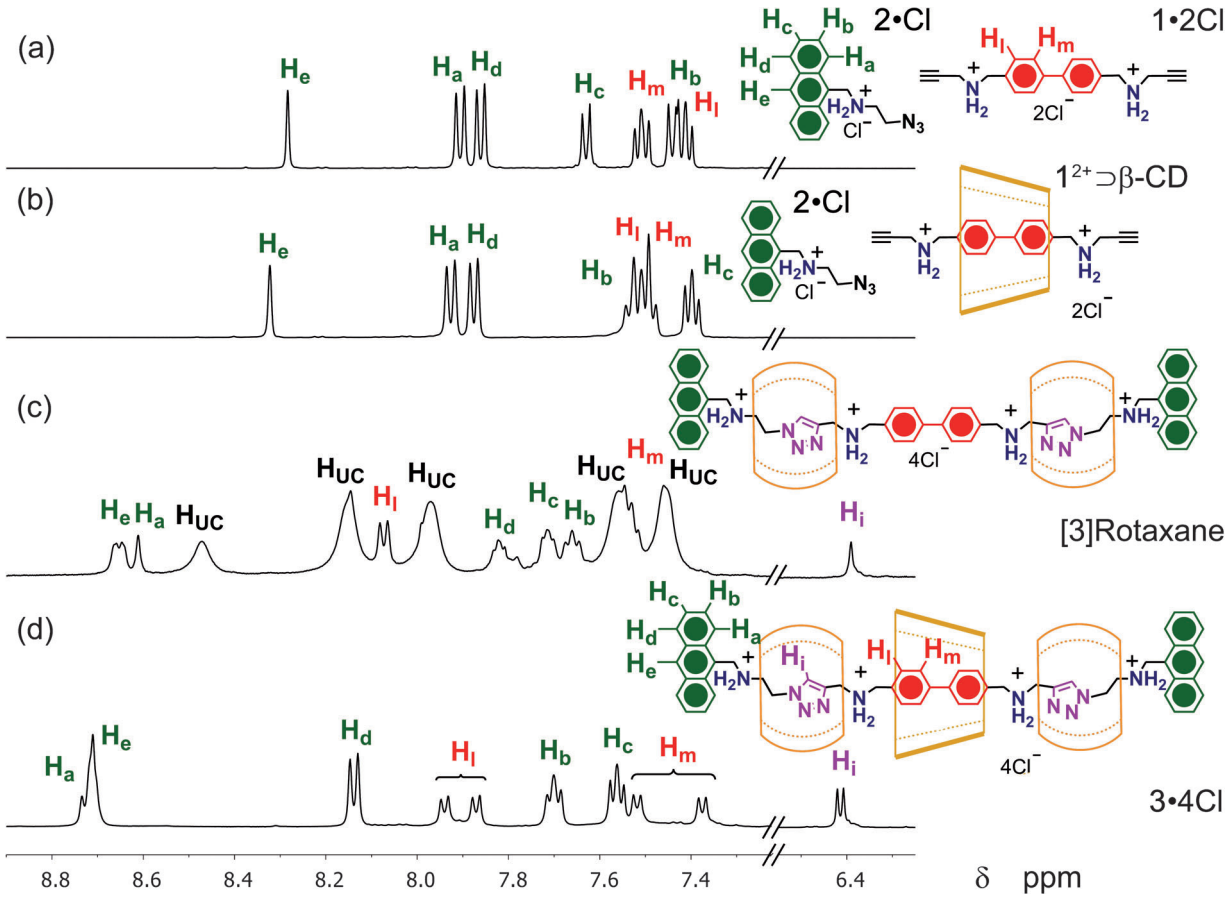

Figure 2. Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of a) a mixture of **1**·2Cl (5.5 mM) and **2**·Cl (12.7 mM) after heating at 80 °C for 2.5 h, b) a mixture of **1**·2Cl (5.5 mM), **2**·Cl (12.7 mM) and CB[6] (12.6 mM) after heating at 80 °C for 2.5 h and allowing to stand at room temperature for one week, c) a mixture of **1**·2Cl (5.5 mM), **2**·Cl (12.7 mM) and β-CD (6.1 mM) after heating at 80 °C for 2.5 h, and d) the hetero[4]rotaxane **3**·4Cl (2.5 mM) obtained from a mixture of **1**·2Cl, **2**·Cl, CB[6] and β-CD after heating at 80 °C for 1 min. Note that H_{uc} represents resonances for unreacted compounds.

rotaxane **3**·4Cl had gone to completion.[29] By the same token, the hetero[4]rotaxane **4**·4Cl was obtained all but quantitatively after adding γ-CD[28] (1 equiv) to **1**·2Cl (2 equiv), **2**·Cl (1 equiv) and CB[6] (2 equiv) dissolved in D_2O and heating at 80 °C for 5 min. When these reactions were repeated on a preparative scale, isolated yields of 95–97 % of **3**·4Cl and **4**·4Cl were obtained after heating at 60 °C for 30 min in water and purifying the crude product by gel permeation chromatography.

The incorporation of the CD tori—β-CD in **3**·4Cl and γ-CD in **4**·4Cl—with their primary and secondary faces introduces dissymmetry into both the CB[6] rings and the dumbbell components of the two hetero[4]rotaxanes. Not only are two resonances observed (Figure 2 d) for the triazole ring protons, H_i, but also for the H_m and H_l protons on the central bitolyl unit. Irrespective of this dissymmetry, it would appear that the CB[6]-"catalyzed" 1,3-cycloadditions to form both **3**·4Cl and **4**·4Cl are greatly accelerated (> 100-fold) on both the primary and secondary faces of the CD rings.[30]

Extending the highly efficient synthetic strategy of cooperative capture, it is possible to self-assemble and polymerize (Figure 3 a) the monomers **1**·2Cl and **5**·2Cl in the presence of CB[6] and the CDs—both β-CD and γ-CD—to obtain the polypseudorotaxanes **6**·(4*n*+5)Cl and **7**·(4*n*+5)Cl, respectively. After mixing all of the components together at 60 °C for 1 h, the ^{1}H NMR spectra (Figure 3 b and c) demonstrate that extensive polymerization had taken place, based on the fact that the peak integration ratio for the newly formed triazole rings protons H_i and the biphenyl protons of **1**·2Cl and **5**·2Cl ($H_{l1}+H_{m1}$ and $H_{l2}+H_{m2}$) is approximately 1:8.[31] The resonances for the alkyne protons H_n can be employed as internal references for the end group analysis of the polypseudorotaxanes **6**·(4*n*+5)Cl and **7**·(4*n*+5)Cl. The degrees of polymerization ($n+1$) were calculated to be 16.8 and 7.5 for the polypseudorotaxanes **6**·(4*n*+5)Cl and **7**·(4*n*+5)Cl, respectively, corresponding to the number-average molecular weights (M_n) of ca. 84 800 and 45 600, respectively. Capping the polypseudorotaxanes **6**·(4*n*+5)Cl and **7**·(4*n*+5)Cl with **2**·Cl, using the same synthetic methodology (Figure 4 a), gives the corresponding polyrotaxanes **8**·(4*n*+7)Cl and **9**·(4*n*+7)Cl, also in near quantitative yields. Following the capping reactions, the resonances H_a and H_e in the stoppers become well-resolved in the ^{1}H NMR spectra (Figure 4 b and the Supporting

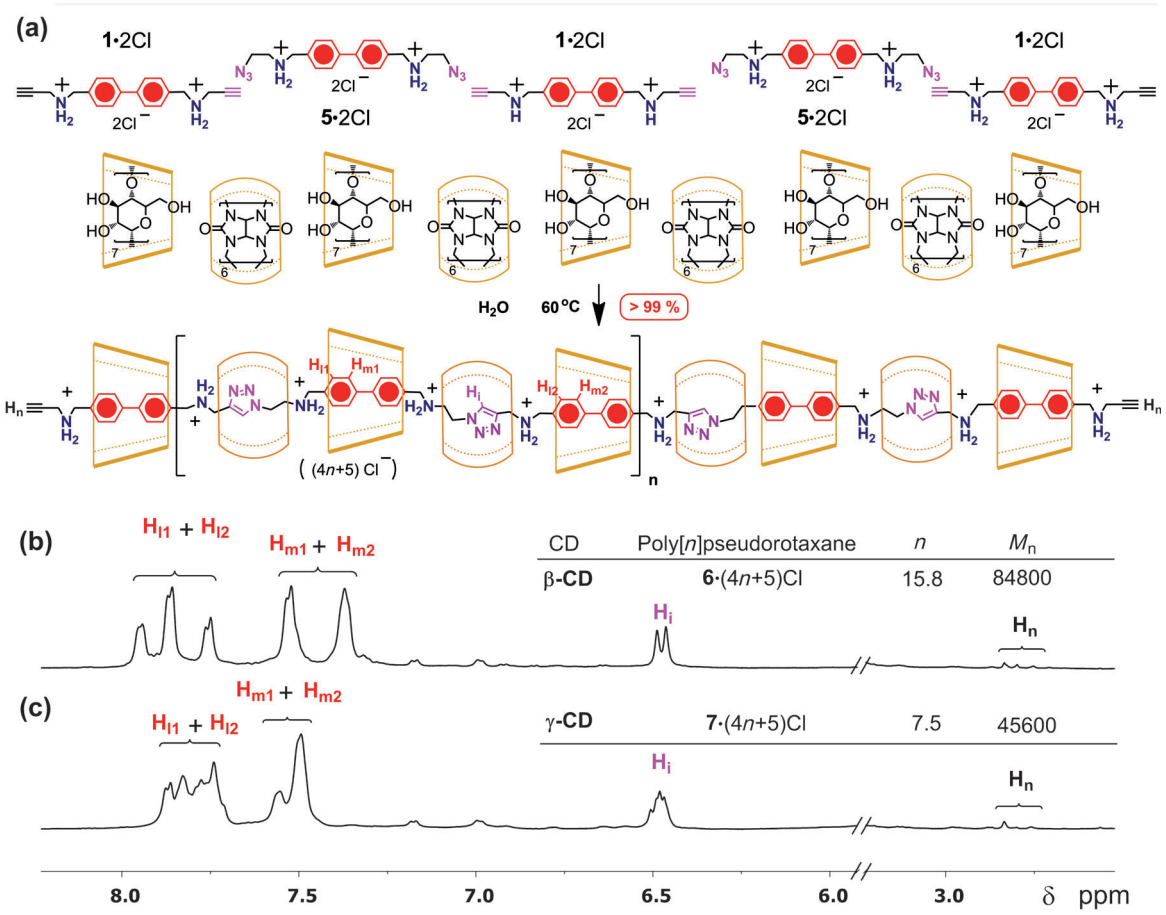

Figure 3. a) Syntheses of the polypseudorotaxanes **6**·(4*n*+5)Cl and **7**·(4*n*+5)Cl. b,c) Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of b) a mixture of **1**·2Cl (23.8 mM), **5**·2Cl (20.8 mM), CB[6] (58.0 mM) and β-CD (52.8 mM), and c) a mixture of **1**·2Cl (23.1 mM), **5**·2Cl (22.2 mM), CB[6] (60.0 mM) and γ-CD (46.2 mM), after heating at 80 °C for 30 min. The degrees of polymerization ($n+1$) and number-averaged molecular weights (M_n) were calculated by end-group analysis from the relative integrated intensities of the peaks for protons H_n with H_i. Although the CD rings are illustrated as being orientated relative to each other in a head-to-tail fashion, we have no reason to believe that their relative orientations are other than random.

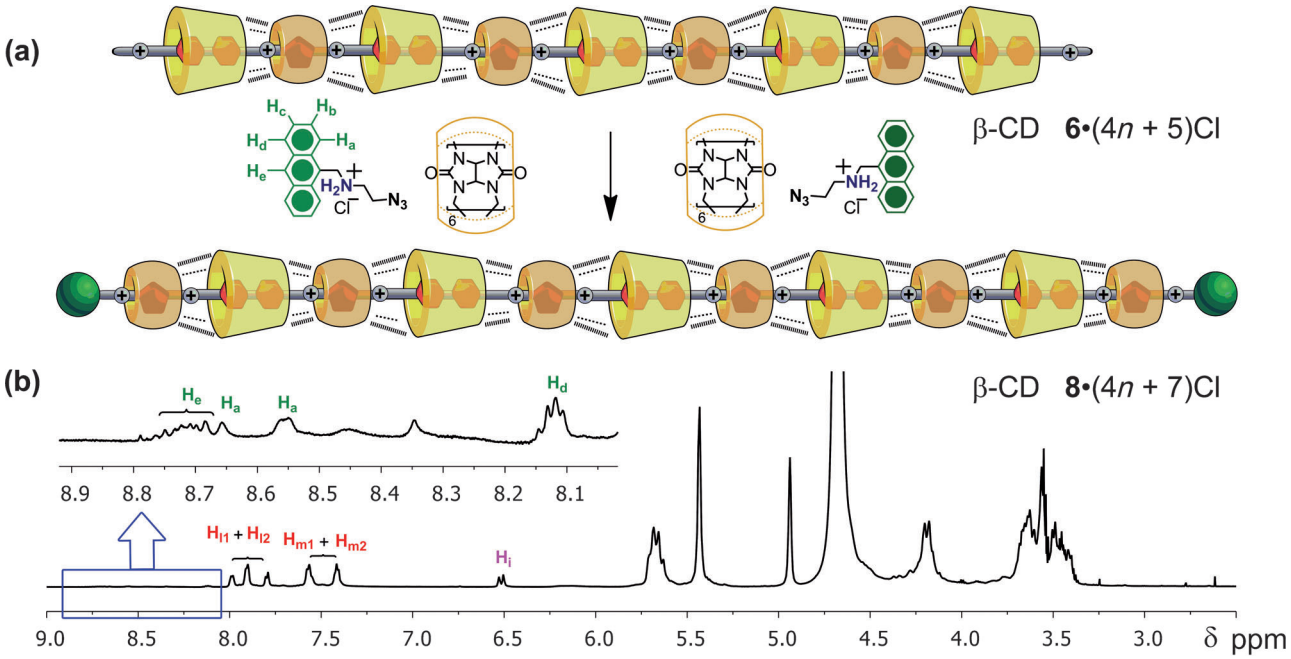

Figure 4. a) Graphical representation of the synthesis of the polyrotaxane **8**·(4*n*+7)Cl where the hatched lines represent the hydrogen-bonding interactions between the CB[6] and CD rings. b) Partial ^{1}H NMR spectrum (600 MHz, D_2O, 298 K) of **8**·(4*n*+7)Cl. Although the CD rings are illustrated as being orientated relative to each other in a head-to-tail fashion, we have no reason to believe that their relative orientations are other than random.

Information) and all of the alkyne resonances disappear, providing direct evidence for the formation of the polyrotaxanes **8**·(4*n*+7)Cl and **9**·(4*n*+7)Cl. End group analysis, probed using the resonances for H_a and H_e in the anthracenyl stoppers and for H_i in the triazole rings, reveals that these polyrotaxanes contain upwards of 64 rings on their dumbbells ($M_n \approx 86\,000$).

The potential for both faces of the CD tori in the two hetero[4]rotaxanes to enter into hydrogen bonding (Scheme 1) with the carbonyl groups on the rims of CB[6] is, we believe, the source of both the self-sorting[27] and the positive cooperativity[9] which is expressed in 1) the 1,3-dipolar cycloadditions[12–16] both being very fast and 2) the yields of the precisely ordered hetero[4]rotaxanes being really high. The CD-CB[6]-promoted azide–alkyne cycloadditions (C^2PAAC), not only aid and abet the syntheses of the rotaxanes, but they also self-regulate their constitutions and open up the real possibility of being able to synthesize high molecular weight polyrotaxanes.

Experimental Section

General procedure for NMR scale production of **3**·4Cl and **4**·4Cl: **1**·2Cl (1.0 equiv), **2**·Cl (2.1 equiv), CB[6] (2.1 equiv) and CD (1.1 equiv)—both β- and γ-CD—were added to an NMR tube, followed by D_2O (600 μL), and the ^{1}H NMR spectra were recorded immediately after mixing. Thereafter, the tube was placed in a water-bath at 80 °C for 1 min. The subsequent ^{1}H NMR spectra showed that the reactions to form **3**·4Cl and **4**·4Cl were complete inside 1 min.

Large scale preparation of **3**·4Cl and **4**·4Cl: **1**·2Cl (1.0 equiv), **2**·Cl (2.1 equiv), CB[6] (2.1 equiv) and CD (1.1 equiv)—both β- and γ-CD—were added to a 50 mL round-bottomed flask before H_2O (25 mL) was added. The reactions were stirred at 60 °C for 30 min and the insoluble residues were removed by centrifugation. The clear solutions were freeze-dried, yielding light yellow powders. These crude products were purified by size-exclusion chromatography (Sephadex G-75: H_2O) to afford the **3**·4Cl and **4**·4Cl in yields of 95–97 %.

3·4Cl (yield 97 %): **1**·2Cl (56.0 mg, 0.16 mmol), **2**·Cl (107.0 mg, 0.34 mmol), CB[6] (341.0 mg, 0.34 mmol) and β-CD (195.0 mg, 0.17 mmol). ^{1}H NMR (500 MHz, D_2O): $\delta = 8.72$ (d, $J = 11.9$ Hz, 6H), 8.14 (d, $J = 8.5$ Hz, 4H), 7.94 (d, $J = 7.9$ Hz, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.70 (t, $J = 7.5$ Hz, 4H), 7.61–7.54 (m, 4H), 7.52 (d, $J = 7.8$ Hz, 2H), 7.38 (d, $J = 7.9$ Hz, 2H), 6.41 (s, 1H), 6.40 (s, 1H), 5.56 (m, 24H), 5.35 (m, 24H), 4.91 (d, $J = 2.7$ Hz, 7H), 4.45 (m, 4H), 4.23 (m, 4H), 4.18–3.89 (m, 28H), 3.81–3.32 ppm (m, 50H). ^{13}C NMR (125 MHz, D_2O): $\delta = 156.2$, 156.0, 155.8, 138.6, 132.6, 131.7, 131.0, 129.4, 127.8, 125.9, 123.7, 122.0, 120.5, 102.5, 100.0, 81.2, 73.2, 71.9, 71.7, 69.9, 59.5, 51.2, 46.3, 45.4 ppm. HR-ESI-MS: calcd for $[M-4\,Cl]^{4+}$ m/z 992.8564, found m/z 992.8610.

4·4Cl (yield 95 %): **1**·2Cl (36.0 mg, 0.10 mmol), **2**·Cl (69.0 mg, 0.22 mmol), CB[6] (220.0 mg, 0.22 mmol) and γ-CD (143.0 mg, 0.11 mmol). ^{1}H NMR (500 MHz, D_2O): $\delta = 8.74$–8.63 (m, 6H), 8.13 (d, $J = 8.4$ Hz, 4H), 7.84–7.77 (m, 4H), 7.74–7.66 (m, 4H), 7.57 (dd, $J = 12.8$, 6.3 Hz, 4H), 7.44 (t, $J = 6.5$ Hz, 4H), 6.37 (s, 1H), 6.36 (s, 1H), 5.75–5.43 (m, 24H), 5.31 (m, 24H), 4.94 (s, 8H), 4.41 (s, 4H), 4.27–3.85 (m, 28H), 3.79–3.38 ppm (m, 56H). ^{13}C NMR (125 MHz, D_2O): $\delta = 156.3$, 156.2, 156.0, 155.9, 138.7, 138.2, 131.5, 131.1, 131.0, 130.9, 130.6, 130.4, 129.4, 127.7, 126.4, 125.8, 123.6, 120.2, 102.5, 101.7, 81.1, 80.5, 73.0, 72.2, 71.9, 70.0, 69.9, 60.0, 59.7, 51.2, 45.9, 45.7, 44.0, 43.8, 42.6 ppm. HR-ESI-MS: calcd for $[M-4\,Cl]^{4+}$ m/z 1033.3658, found m/z 1033.3664, $[M-3\,Cl]^{3+}$ m/z 1377.8221, found m/z 1377.8266.

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[29] The formations of the hetero[4]rotaxanes **3**·4Cl and **4**·4Cl were confirmed by 1) a correlation peak of a carbon signal (120 ppm) with H_i in the HSQC spectrum, 2) strong cross peaks between H_i and H_y of CB[6], accompanied by weak correlation peaks between H_i and H_x in the NOESY spectrum (see Supporting Information), and 3) a molecular ion peak at *m*/*z* 992.8610 ($[M-4\text{Cl}]^{4+}$) in HR-ESI mass spectrum.

[30] In the time-dependent ^{1}H NMR spectra for the formation of **3**·4Cl—immediately after mixing—the two peaks observed for the H_i protons peaks have slightly different intensities. This phenomenon is more significant (see Supporting Information) in the formation of **4**·4Cl. This observation indicates that the "catalysis" of the 1,3-cycloaddition proceeds at different rates, depending on whether it happens inside CB rings next to the primary or the secondary faces of the CD rings.

[31] It should also be noted that the molar ratio of CB[6] to CD rings is 1:1 in the polypseudorotaxanes, as indicated by their relative integrated intensities of their resonances in the relevant ^{1}H NMR spectra. This 1:1 molar ratio implies that, while each triazole ring is encircled by a CB[6] ring, each bitolyl unit is encircled by a CD ring.

