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Self-Assembly of a Water-Soluble [2]Rotaxane with Carbohydrate Stoppers

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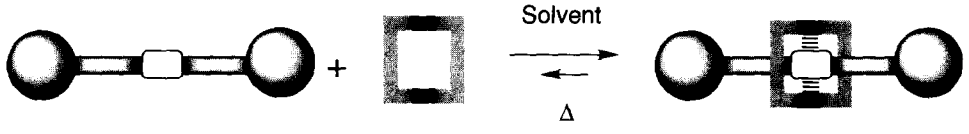
Abstract: A [2]rotaxane self-assembles spontaneously by 'slippage' in D_2O during one week at room temperature when a dumbbell-shaped compound, containing a hydroquinone ring recognition site and terminated by β-D-glucopyranose units, is mixed with cyclobis(paraquat-*p*-phenylene) tetrachloride. A [2]rotaxane with benzoylated D-glucopyranose residues is obtained when the dumbbell-shaped octabenzoate serves as a template for the formation of the cyclobis(paraquat-*p*-phenylene) tetracation in DMF. © 1997 Elsevier Science Ltd.

Perhaps the easiest way we know so far for self-assembling a rotaxane is to use an approach which involves the slipping[1] of the macrocyclic component(s) over the stoppers of the dumbbell-shaped component, as shown diagrammatically in **Scheme 1**. This approach — which we have referred to as slippage[2] — can be initiated by simply heating the components of the rotaxane in a solvent that does not diminish significantly the stabilising interactions between the recognition sites in the two components. To the present, the phenomenon of slippage has been exploited exclusively by us[3,4] to self-assemble a wide range of rotaxanes wherein the dumbbell-shaped components contain stoppers that are based on di- or trisubstituted tetraarylmethane moieties and have, as recognition sites, π-electron deficient units, such as the bipyridinium dication, whilst the complementary recognition sites of the macrocyclic component residues are in the form of two π-electron rich residues, such as hydroquinone or 1,5-dioxynaphthalene ring systems, in 34-crown-10 and 38-crown-10 macrocycles, respectively.

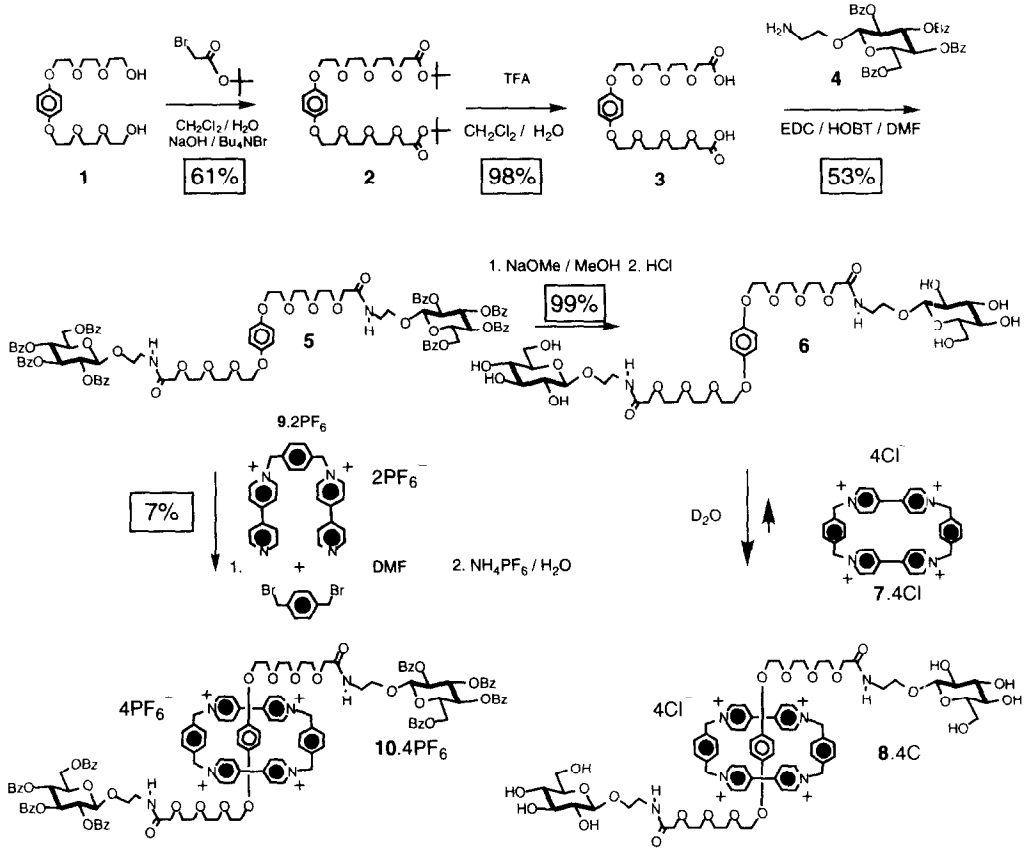


Scheme 1. Self-assembly by slippage — a thermodynamically-driven process.

Here, we describe how a [2]rotaxane, based on cyclobis(paraquat-*p*-phenylene) as a macrocycle containing two bipyridinium units, can be self-assembled as its tetrachloride in aqueous solution (D_2O) on to a dumbbell-shaped compound composed of a polyether chain intercepted by a hydroquinone ring and terminated by β-D-glucopyranose units linked to the polyether chains by spacers containing amide bonds. The corresponding benzoyl-protected [2]rotaxane can be self-assembled by templating the formation of the cyclobis(paraquat-*p*-phenylene) around the π-electron rich hydroquinone ring. It should be noted that a related carbohydrate-stoppered [2]rotaxane has been reported[5] in the literature recently.

The dumbbell-shaped compounds **5** and **6** were prepared according to the synthetic strategy outlined in **Scheme 2**. 1,4-Bis[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]benzene[6] (**1**) was reacted with *tert*-butyl 2-bromoacetate, using NaOH as a base and Bu_4NBr as a phase-transfer catalyst to yield the di-*tert*-butyl ester **2**, which was converted into the corresponding dicarboxylic acid **3** by hydrolysis under acidic (TFA) conditions. The dicarboxylic acid was then coupled with 2-aminoethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside[7] **4**,

using the standard conditions (EDC / HOBT / DMF) for amide bond formation to produce the dumbbell-shaped compound[8] **5**. Removal of the benzoyl protecting groups using NaOMe / MeOH afforded **6**, a dumbbell-shaped compound[9] which is now soluble in water and can therefore be mixed with cyclobis(paraquat-*p*-phenylene) tetrachloride[10] **7**.4Cl in equimolar proportions in D_2O. The equilibrium displayed in **Scheme 2** accounts for the development of an orange colour over a period of one week at room temperature as the [2]rotaxane **8**.4Cl is self-assembled. This orange colour arises as a result of charge transfer interactions [λ_{max} (ε) = 446 nm (375)] between the π-electron rich hydroquinone ring in the dumbbell-shaped component and the π-electron deficient bipyridinium units in the macrocyclic component of the [2]rotaxane. Further evidence for the structure of **8**.4Cl came from the LSIMS which reveals peaks at *m/z* = 1493, 1458, and 1421, corresponding to the molecular ion of the [2]rotaxane with loss of two, three and four Cl^- ions, respectively.



Scheme 2. The synthesis of the carbohydrate-containing dumbbell-shaped componds **5** and **6** and the self-assembly of the carbohydrate-containing [2]rotaxanes **8**.4Cl and **10**.4PF_6

Initially, the ^{1}H NMR (300 MHz, 304 K) spectrum of the equimolar mixture of **6** and **7**.4Cl recorded in D_2O showed two different sets of resonances for the protons of the tetracationic cyclophane. However, after one week at room temperature, only one set of resonances was observed. This fact is indicative of a slow-exchange process in which the cyclophane **7**.4Cl slips over the carbohydrate stoppers to form the thermodynamically-stable [2]rotaxane **8**.4Cl. The ^{1}H NMR spectrum of the [2]rotaxane **8**.4Cl reveals (**Table 1**) a downfield shift ($\Delta\delta$ = + 0.12) for the α-bipyridinium protons and an upfield shift ($\Delta\delta$ = – 0.12) for the β-

bipyridinium protons of the tetracationic cyclophane component. The observed chemical shifts are diagnostic of a situation[6] in which the dumbbell-shaped component is threaded through the cavity of the tetracationic cyclophane. It is important to note that this is the first time that the self-assembly of an interlocked molecular compound containing cyclobis(paraquat-*p*-phenylene) has been accomplished in aqueous solution. It is not improbable that hydrophobic forces[11] are contributing to the self-assembly process. Whatever the precise nature of the noncovalent bonding forces, they are clearly of sufficient magnitude to encourage the unprotected dumbbell-shaped compound **6** to slip through the cavity of cyclobis(paraquat-*p*-phenylene) as its tetrachloride salt **7**.4Cl and form the [2]rotaxane **8**.4Cl in D_2O solution.

Table 1. ^{1}H NMR Chemical Shift Data [δ Values (Δδ Values)] Recorded by a 300 MHz Spectrometer in D_2O at 304 K.

Compound	α-Bipyridinium-CH	β-Bipyridinium-CH	C_6H_4	CH_2N^+
7.4Cl	9.05	8.23	7.57	5.80
8.4Cl	9.17 (+ 0.12)	8.11 (– 0.12)	7.89 (+ 0.32)	5.85 (+ 0.05)

The self-assembly of the [2]rotaxane **10**.4PF_6 was achieved (**Scheme 2**) using a 'clipping' procedure. Reaction of the bispyridylpyridinium salt **9**.2PF_6 with *p*-xylylene dibromide in DMF using 1.5 molar equivalents of the dumbbell-shaped compound **5**, as a template for the macrocyclisation of the tetracationic cyclophane component, yielded the [2]rotaxane **10**.4PF_6 after counterion exchange (NH_4PF_6/H_2O). The LSIMS of this [2]rotaxane shows peaks at *m/z* = 2690, 2544, and 2400 which correspond to the molecular ion minus one, two and three PF_6^- counterions, respectively. The [2]rotaxane **10**.4PF_6, despite being a tetracationic salt, is soluble in common organic solvents. The presence of the highly lipophilic benzoyl groups clearly accounts for the solubility of [2]rotaxane **10**.4PF_6 in aprotic solvents.

In summary, two [2]rotaxanes with carbohydrate stoppers have been prepared using different self-assembly procedures. The solubilities of these compounds are influenced by the protection or otherwise of the terminal glucopyranose rings. When they are unprotected, the process known as 'slippage' can be effected in aqueous solution — which is Nature's solvent by and large. When the glucopyranose units are benzoylated, the [2]rotaxane **10**.4PF_6, formed by a 'clipping' process followed by counterion exchange, is rendered soluble in common organic solvents. Our next goal is to use self-assembly to carry out the novel preparation of a [2]rotaxane by 'slippage', followed by 'swelling' of the stoppers by protection of the hydroxyl groups in **8**.4Cl.

Large carbohydrate wedges, such as those generated during our recent work on carbohydrate-containing dendrimers,[12] could be used as stoppers in rotaxanes. In aqueous solution, it is the possible that these molecules will aggregate[13] and form novel architectures as a result of self-organisation,[14] which is controlled by noncovalent intermolecular interactions.[15]

Acknowledgments. This research was supported by the Engineering and Physical Sciences Research Council, and the Biotechnology and Biological Sciences Research Council in the United Kingdom. We thank them and Eusko Jaurlaritza, Unibersitate, Hizkuntza eta Ikerketa Saila in the Basque Country (Spain) for their support of a Postgraduate Fellowship (to M.G.-L.).

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7. Preparation of **4**: 2-(*N*-Benzyloxycarbonyl amino) ethanol was glucosylated with benzoylated bromoglucose in CH_2Cl_2 in the presence of $Hg(CN)_2$ and $HgBr_2$ for 24h. The reaction mixture was filtered, washed with 1M aqueous KI solution, saturated aqueous $NaHCO_3$ solution and finally with H_2O. The organic phase was dried ($MgSO_4$) and the solvents were removed *in vacuo* to obtain an amino-protected glucoside (93%), which, upon hydrogenolysis over 10% Pd/C in EtOAc/MeOH (2:1) for 30 h, afforded (71%) the desired free amino-glucoside **4** as a glassy solid which was fully characterised by LSIMS and ^1H and ^{13}C NMR spectroscopies.
8. Selected spectroscopic data for **5**: ^1H NMR (300 MHz, 304 K, $CDCl_3$): 3.40-3.55 (m, 12H), 3.59-3.71 (m, 4H), 3.72-3.81 (m, 14H), 3.89-3.97 (m, 2H), 4.00-4.03 (m, 4H), 4.12-4.18 (m, 2H), 4.44-4.50 (dd, J = 12, 5 Hz, 2H), 4.61-4.66 (dd, J = 12, 3 Hz, 2H), 4.86-4.88 (d, J = 8 Hz, 2H), 5.51 (app. t, J = 8 Hz, 2H), 5.66 (app. t, J = 10 Hz, 2H), 5.88 (app. t, J = 10 Hz, 2H), 6.78 (s, 4H), 7.19-7.56 (m, 26H), 7.78-8.03 (m, 16H); MS (LSIMS) *m/z*: 1756 $[M + Na]^+$.
9. Selected spectroscopic data for **6**: ^1H NMR (300 MHz, 304 K, D_2O): 3.14-3.20 (m, 2H), 3.24-3.42 (m, 12H), 3.52-3.73 (m, 18H, coincident with the water signal), 3.79-3.86 (m, 10H), 3.88-3.98 (bs, 4H), 4.08-4.10 (m, 4H), 4.20-4.35 (d, J = 8 Hz, 2H), 6.90 (s, 4H); MS (LSIMS) *m/z*: 901 $[M+H]^+$, 923 $[M + Na]^+$.
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