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Efficient syntheses of pillar[6]arene-based hetero[4]rotaxanes using a cooperative capture strategy

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While a single pillar[6]arene ring, nestling between two cucurbit[6]uril rings in a series of three hetero[4]rotaxanes, is conformationally mobile in solution, it adopts the energetically most favourable conformation with local C_{3v} symmetry in the solid state.

The development of mechanically interlocked molecules (MIMs) has attracted the attention of supramolecular chemists,[1] materials scientists[2] and nano-biotechnologists.[3] Rotaxanes, one of the most widely studied families of MIMs, are composed of one, or more, macrocyclic ring(s) encircling a rod which is substituted with stoppers at both ends, forming a dumbbell component. As a result of the mechanical bond formation, different properties are observed for rotaxanes when compared with their individual ring and dumbbell components.[4] Four strategies — namely, capping,[1] clipping,[5] slipping[6] and active templation[7] — have been developed and used widely in the preparation of rotaxanes. Recently, we have introduced another strategy — namely, cooperative capture[8] — to help obtain hetero[4]rotaxanes rapidly and efficiently, wherein a cyclodextrin[2a, 9] (CD) ring forms an H-bonding network with two neighbouring cucurbit[6]uril[10] (CB) rings, and, as a result, accelerates CB-templated 1,3-dipolar alkyne-azide cyclo-addition[11] (CB-AAC) reactions. Clearly, other macrocycles besides CD rings, that are able to form H bonds with CBs,

could also be good candidates for hetero[4]rotaxane formation using this cooperative capture strategy. For example, pillar[5]arene[12] (P5), a macrocycle containing five hydroquinone (HQ) units, bridged by CH_2 groups at their para positions, has also been shown[13] to be able to accelerate CB-AAC reactions. In addition, the reinforced H-bonding network,
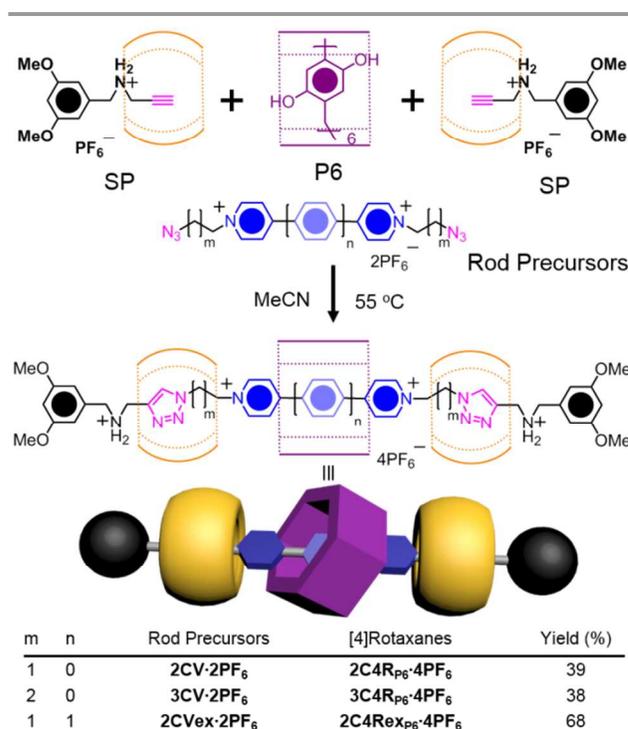
Scheme 1. Synthesis of hetero[4]rotaxanes **2C4R$_{P6}$·4PF$_6$**, **3C4R$_{P6}$·4PF$_6$** and **2C4Rex$_{P6}$·4PF$_6$** by combining the stopper precursor (SP), pillar[6]arene (P6) and the rod precursors **2CV·2PF$_6$**, **3CV·2PF$_6$** and **2CVex·2PF$_6$**, respectively.

m	n	Rod Precursors	[4]Rotaxanes	Yield (%)
1	0	2CV·2PF$_6$	2C4R$_{P6}$·4PF$_6$	39
2	0	3CV·2PF$_6$	3C4R$_{P6}$·4PF$_6$	38
1	1	2CVex·2PF$_6$	2C4Rex$_{P6}$·4PF$_6$	68

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formed between the CB and P5 rings expands the substrate selection of the CB-AAC reaction from involving 2-azidoethylpyridinium units up to having 5-azidopentylpyridinium units located at the termini of the rods. This observation has encouraged us to extend our investigations to pillar[6]arene[14] (P6), the next higher homologue of P5 containing six HQ units, in order to exploit the power of cooperative capture in the syntheses of hetero[4]rotaxanes.

In comparison with P5, P6 has a larger cavity and, as a result, binds guests in a different manner.[15] For example, the binding affinity of P5 for the methyl viologen dication is orders of magnitude higher than that[14b, 16] of P6 in Me$_2$CO. Ogoshi *et al.*[17] have observed that, on incorporation of a pyridinium dumbbell component, the yield (14%) of a dodeca-alkyl-P6-based rotaxane is significantly lower than that (60%) of a dodeca-alkyl-P5-based rotaxane. Herein, we describe (1) the syntheses of three hetero[4]rotaxanes, each containing one P6 ring, flanked by two CB rings in 38−68% yields and show that (2) while the P6 rings exhibit conformational flexibility in these MIMs in solution, there is (3) a preference, predicted by molecular mechanics calculations, for the P6 ring to adopt local C_{3V} symmetry in solution, and in one case, in the solid state.
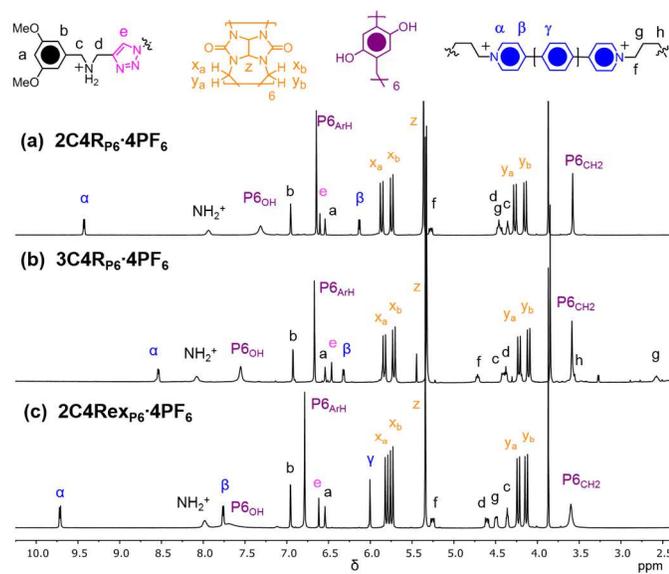

Fig. 1. ^{1}H NMR spectra (500 MHz, CD$_3$CN, 298 K) of the hetero[4]rotaxanes (a) **2C4R$_{P6}$**·4PF$_6$, (b) **3C4R$_{P6}$**·4PF$_6$ and (c) **2C4Rex$_{P6}$**·4PF$_6$. For the sake of clarity, only the structural formulae of each component are illustrated (top).

The P6-based hetero[4]rotaxanes — namely, **2C4R$_{P6}$**·4PF$_6$, **3C4R$_{P6}$**·4PF$_6$ and **2C4Rex$_{P6}$**·4PF$_6$ — were synthesised (Scheme 1) in a similar manner to that reported[13] previously. Typically, a mixture of the rod precursor (1 equiv), the P6 ring (1 equiv) and 2 equiv of the stopper precursor (SP) is stirred in MeCN at either 25 or 55 °C overnight. The hetero[4]rotaxane **2C4R$_{P6}$**·4PF$_6$ was isolated in 38% yield after stirring overnight at 25 °C. Raising the reaction temperature to 55 °C had little beneficial effect upon the yield. Although lengthening the linear spacers of the rod precursor **3CV**·2PF$_6$, resulted in a drop in yield of the **3C4R$_{P6}$**·4PF$_6$ to 8% after stirring overnight at

25 °C, we witnessed an increase in the yield of this hetero[4]rotaxane to 38% when the reaction temperature was raised to 55 °C.

In the ^{1}H NMR spectrum (Fig. 1a) of **2C4R$_{P6}$**·4PF$_6$, while H$_\beta$, which is shielded by the encircling P6 ring, resonates at δ = 6.1, signals for the protons corresponding to the P6 aromatic rings and OH groups in the hetero[4]rotaxane were observed as singlets at δ values at 6.9 and 7.3, respectively. This observation suggests that, in CD$_3$CN solution, the oxygen-through-the-annulus rotation of the HQ units in P6, while trapped on the dumbbell takes place rapidly on the ^{1}H NMR timescale. A similar phenomenon was observed in the ^{1}H NMR spectrum (Fig. 1b) of **3C4R$_{P6}$**·4PF$_6$, where the singlets for the P6 protons occur at 6.9 and 7.5 ppm.

Extending the spacer between the bipyridinium and azide groups to four CH$_2$ groups in the rod precursor **4CV**·2PF$_6$ led to a mixture of hetero[4]- and hetero[5]rotaxanes.[‡] In order to prevent the formation of multiple products, we employed **2CVex**·2PF$_6$ as the rod precursor, since the length of **4CV**·2PF$_6$ and **2CVex**·2PF$_6$ are almost identical, with the latter being more rigid in nature. Although molecular modelling (see ESI) shows that the length of the dumbbell is just long enough to accommodate two P6 rings to form a hetero[5]rotaxane, the hetero[4]rotaxane **2C4Rex$_{P6}$**·4PF$_6$ was isolated (68%) as a sole product from the reaction mixture at 55 °C. In the ^{1}H NMR spectrum (Fig. 1c) of **2C4Rex$_{P6}$**·4PF$_6$, H$_\gamma$, which is shielded by the P6 ring, appears as a singlet resonating at δ = 6.0, whereas H$_\beta$ and H$_\alpha$ resonate at 7.8 and 9.7 ppm, respectively. The resonances arising from the P6 aromatic rings and OH groups show two singlets, with those for the latter being much broader than the signals of the OH groups in the hetero[4]rotaxanes **2C4R$_{P6}$**·4PF$_6$ and **3C4R$_{P6}$**·4PF$_6$, suggesting that oxygen-through-the-annulus rotation of the HQ units in the P6 ring takes place more slowly on the ^{1}H NMR timescale compared with the analogous rotations in the other two hetero[4]rotaxanes **2C4R$_{P6}$**·4PF$_6$ and **3C4R$_{P6}$**·4PF$_6$.
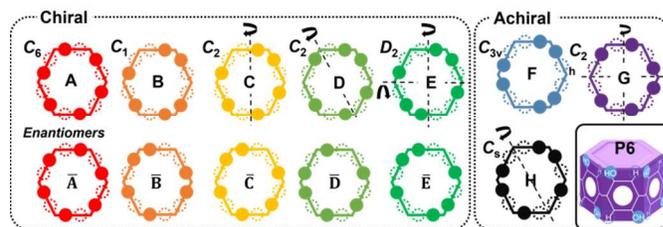

Fig. 2. Plan views of all the possible conformations P6 can adopt in solution. The solid and dashed circles represent P6 aromatic and OH protons, respectively. Flipping one or more HQ unit(s) of P6, starting from conformation **A**, generates conformations **B−H** in a stepwise manner.

The conformations of the P6 ring in the hetero[4]rotaxanes are interconverting rapidly at room temperature in CD$_3$CN solutions on account of the P6's large cavity (7.5 Å diam). In theory, P6 can adopt (Fig. 2) three (**F**, **G** and **H**) achiral conformations, as well as five (**A** − **E**) enantiomeric pairs of diastereoisomeric conformations,[18] in which **A**, **B**, **C**, **D** and **E** with their corresponding enantiomers **Ā**, **B̄**, **C̄**, **D̄** and **Ē**, possess

C_6, C_1, C_2, C_2 and D_2 symmetries, respectively, while conformations **F**, **G** and **H** have C_{3V}, C_{2h} and C_s symmetries, respectively. When we carried out the variable temperature (VT) ^{1}H NMR spectroscopic studies (see ESI) on all three hetero[4]rotaxanes, we were unable to identify any of the eight possible discrete diastereoisomeric conformations since, although the peaks associated with their CH$_2$, aromatic and OH protons broaden in the range +25 to −40 °C, they failed to re-emerge as well-resolved peaks at −40 °C. This observation indicates that the H-bonding interactions between the P6 and CB rings are not strong enough to slow down the oxygen-through-the-annulus rotation of the P6 ring on the ^{1}H NMR timescale at low temperatures in CD$_3$CN solution.

Slow vapour diffusion of iPr$_2$O into a MeNO$_2$ solution of **2C4Rex$_{P6}$**·4PF$_6$ afforded colourless plate-shaped single crystals. The solid-state structure of the hetero[4]rotaxane (Fig. 3) reveals that two CB rings encircle the two triazole functions on the dumbbell component, and are held in place by the strong H-bonding and cation-dipole interactions between the CO groups on the CB rims and the ammonium/pyridinium centres on the dumbbell. The P6 ring encircling the central **2CVex**$^{2+}$ unit is sandwiched between two CB rings such that they are located (centre to centre) 19.4 Å apart. The P6 ring, which is tilted at an angle of 112º with respect to the axle of the dumbbell, has C_{3V} symmetry, i.e., it adopts the **F** conformation in which six intra-ring H bonds are present, in addition to four inter-ring H bonds with [O···O] distances of 2.6 and 2.8 Å between the OH groups on the P6 ring and the CO groups of the CB rings.
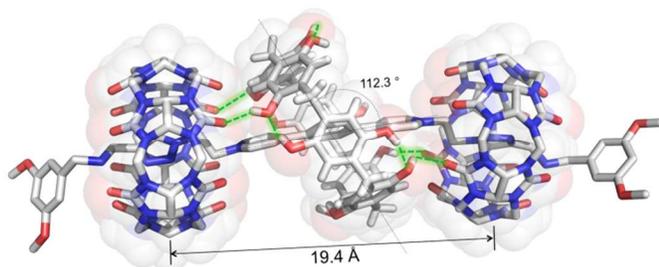

Fig. 3. Solid-state structure of the hetero[4]rotaxane **2C4Rex$_{P6}$** illustrated using capped sticks with the three rings highlighted by faint space-filling representations in the background. The principal inter-ring H-bonds are indicated by dashed green lines. H Atoms which do not participate in H-bonding interactions are omitted for the sake of clarity.

In order to gain a better understanding of (1) the intra- and inter-ring H bonds present between the P6 and two CB rings in the three hetero[4]rotaxanes and (2) the relative energies of the eight possible conformations adopted by their P6 rings, we carried out molecular mechanics calculations. All eight conformations (**A** – **H** in Fig. 2) were simulated by performing energy minimisations, followed by conformational searches (see Fig. 4 and ESI). In all three hetero[4]rotaxanes, the most stable conformation corresponds to that (**F**) in which the P6 ring adopts C_{3V} symmetry and allows the majority of the P6 ring phenolic OH groups to participate in (1) intra-ring H-bonding interactions with the neighbouring OH groups and (2)

inter-ring H-bonding interactions with the CO groups on the CB rings. In contrast, when the P6 ring adopts a C_6 symmetry (**A**) in the simulated structure (see ESI), although the inter-ring H-bonding interactions are maximised, the minimised energies for the hetero[4]rotaxanes are much higher than those where the P6 ring adopts the **F** conformation.[¶] These results suggest that the enthalpic contributions that stabilise the conformations of the P6 ring in the hetero[4]rotaxane by inter-ring H-bonding and intra-ring H-bonding are similar. The relative energies of the simulated conformations of the hetero[4]rotaxanes reveal that several conformations of the P6 ring could be major contributors to the rate accelerations of the CB-P-AAC reactions.[i]
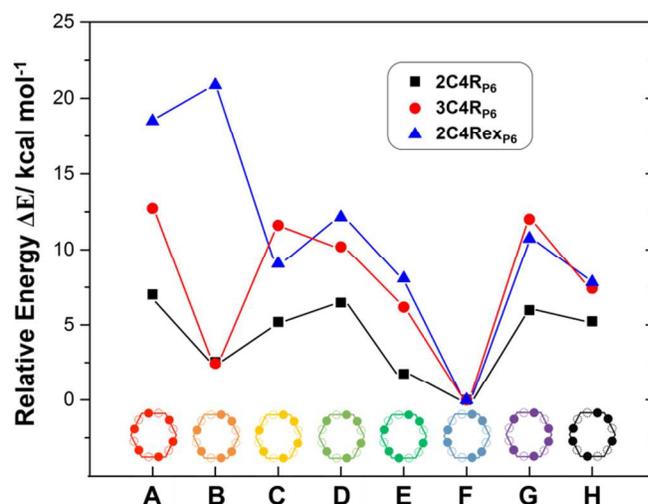

Fig. 4. Calculated relative energies employing Macromodel (OPLS-2005) of the hetero[4]rotaxanes **2C4R$_{P6}$**, **3C4R$_{P66}$** and **2C4Rex$_{P6}$** wherein the P6 ring adopts all its different conformations. The relative energies are normalised with respect to the most stable conformation, i.e., **F**.

In summary, we report an efficient synthesis of pillar[6]arene-based rotaxanes using the cooperative capture strategy. Although the binding affinity between the pillar[6]arene ring with the rod precursors are orders of magnitude lower than those[14b] involving pillar[5]arene, the three hetero[4]rotaxanes described in this communication incorporating pillar[6]arene, were obtained under mild reaction conditions in 38−68% yields, indicating the benefits of the formation of orthogonal hydrogen-bonding networks in facilitating the rotaxane formation. The oxygen-through-the-annulus rotations of pillar[6]arene rings in hetero[4]rotaxanes occur with ease. In the one hetero[4]rotaxane which crystallised, the pillar[6]arene ring adopts the achiral C_{3V} conformation, which was found to be the most energetically favourable one on the basis of molecular mechanics simulations. These results add yet another cooperative approach to the syntheses of mechanically interlocked molecules with high efficiencies and good constitutional integrities, as well as provide further insights into the importance of orthogonal hydrogen-bonding interactions in accelerating the cucurbit[6]uril templated alkyne-azide 1,3-dipolar cyclo-additions.

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Notes and references

‡ The products of this reaction are numerous because of the presence of P6.

§ Crystal data for hetero[4]rotaxane **2C4Rex$_{P6}$**·4PF$_6$: $2(C_{36}H_{36}N_{24}O_{12})$·$(C_{44}H_{52}N_{10}O_4)$·$(C_{42}H_{36}O_{12})$·$5(CH_3NO_2)$·$4(PF_6)$; colourless plates, $0.60 \times 0.18 \times 0.05$ mm^3, triclinic, space group $P\bar{1}$; $a = 16.0511(5)$, $b = 25.4637(9)$, $c = 30.2922(10)$ Å; $\alpha = 91.6273(18)$, $\beta = 94.4694(18)$, $\gamma = 90.902(2)°$; $V = 12336.4(7)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.184$ g cm^{-3}; $2\theta_{max} = 54.13°$; $T = 100(2)$ K; 41702 reflections collected, 29486 independent, 2765 parameters; $\mu = 1.804$ mm^{-1}; $R_1 = 0.1284$ [$I > 2.0\sigma(I)$], $wR_2 = 0.3725$ (all data); CCDC deposition number 983503.

¶ For example, **2C4R$_{P6}$**·4PF$_6$-**A** is about 18 kcal/mol higher than that of **2C4R$_{P6}$**·4PF$_6$-**F**. It also should be noted that both the intra-ring and inter-ring H-bonding distances between the phenolic OH groups and CO groups – [O···O] distances between 2.6 and 2.7 Å in the simulated structure – are close to those measured experimentally in the solid-state structure of the hetero[4]rotaxane **2C4Rex$_{P6}$**·4PF$_6$.

¦ These results are corroborated by the VT ^{1}H NMR experiments carried out, as it proved difficult to freeze out one conformation of the P6 ring on the hetero[4]rotaxanes even at low temperature.

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