A New Design Strategy for the Self-assembly of Molecular Shuttles

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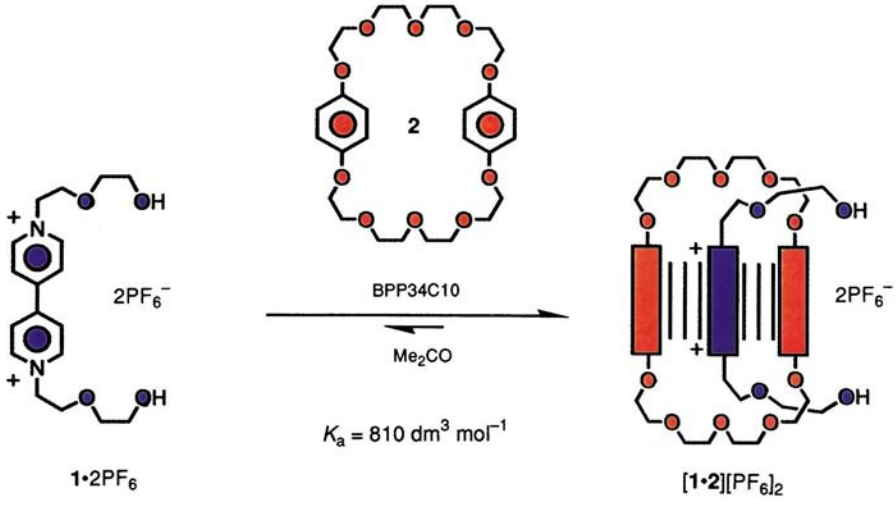
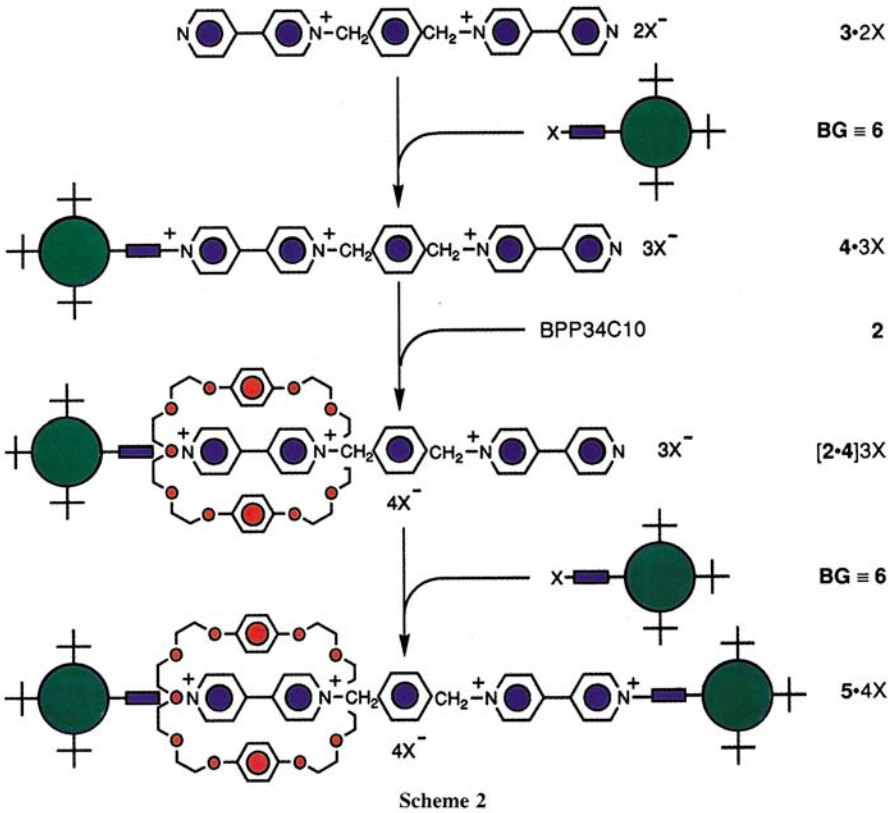
A strategy for the construction of a [2]rotaxane—comprised of a dumbbell-shaped component containing two π-electron-deficient 4,4′-bipyridinium units encircled by one π-electron-rich bisparaphenylene-34-crown-10 macrocycle—by a constitutionally determined self-assembly process is described.

The quest for nanometre-scale devices is one which has fascinated[1,2] the scientific community for many years. Natural systems display a diversity of functioning molecular and supramolecular structures within the size range 1 to 100 nm. They exhibit a common feature in that they are constructed from relatively simple building blocks by self-assembly.[3,4] This method for the construction of large, ordered and structured arrays has only recently come to the fore[5,6] in the realm of wholly synthetic chemical systems. Familiarity with host–guest[7] or supramolecular[8] chemistry has led us to design and



Scheme 1



Scheme 2

synthesise[9–13] so-called rotaxanes and pseudorotaxanes,† based on the interaction of a linear component containing π-electron-rich aromatic rings (*e.g.* hydroquinol) with the π-electron-deficient tetracationic macrocycle,[14] cyclobis(paraquat-*p*-phenylene). The success of this design logic in the construction of both molecular and supramolecular arrays has led us to speculate that a reversal of the roles of the molecular components should be feasible. This concept leads to structures in which the linear component contains the π-electron-deficient aromatic units and the encircling macrocyclic component contains the π-electron-rich aromatic rings.

One possible route to a new class of rotaxanes in which π-electron-deficient aromatic units are located in the linear component, is to take advantage of the pseudorotaxane geometry generated by complexation[15,16] of 4,4′-bipyridinium dications with bisparaphenylene-34-crown-10 (BPP34C10). The complex $[\mathbf{1}\cdot\mathbf{2}][PF_6]_2$ formed[16] (Scheme 1) between $\mathbf{1}\cdot 2PF_6$ and BPP34C10 **2** seemed particularly amenable to this approach, since the attachment of large blocking groups to the primary hydroxy functions of this complex might, in principle, produce a [2]rotaxane. However, this simple approach was found‡ to be flawed.

We decided that a fundamentally more appealing approach would be to design a [2]rotaxane in which the individual components are 'intelligent', in that they contain all of the information necessary to guide their assembly into a large molecular array without the need for any influence by reagents or catalysts. The strong and selective binding of 4,4′-bipyridinium dications by BPP34C10 offers the required directive influence. Moreover, it is known[11] that, although BPP34C10 binds 4,4′-bipyridinium dications strongly, the corresponding monoquaternary cations are not complexed. Thus, if we consider the reaction (Scheme 2) of the bismonoquaternary salt **3**·2X with a putative blocking group (**BG**) in the presence of **2**, then, although $\mathbf{3}^{2+}$ is not bound by BPP34C10, reaction of $\mathbf{3}^{2+}$ with one molar equivalent of **BG** will produce the trication $\mathbf{4}^{3+}$ which contains both a pyridylpyridinium monocation and a 4,4′-bipyridinium dication. The dicationic residue will then be complexed strongly by BPP34C10, giving the intermediate (1:1) complex $[\mathbf{2}\cdot\mathbf{4}]^{3+}$ which may then be captured by reaction with a further molar equivalent of **BG** producing the [2]rotaxane $\mathbf{5}^{4+}$. The selective complexation of *only* the dicationic residue within the trication $\mathbf{4}^{3+}$ by **2** ensures that *only one* molecule of BPP34C10 is incorporated. This constitutionally determined self-assembly of a [2]rotaxane requires that the blocking group **BG** must satisfy two criteria: (*i*) the blocking group must be sufficiently large to prevent the slippage of the BPP34C10 macrocycle over it and away from the linear tetracationic component of the [2]rotaxane $\mathbf{5}^{4+}$ and

† The name rotaxane is derived (G. Schill, *Catenanes, Rotaxanes and Knots*, Academic Press, New York, 1971) from the Latin words rota meaning 'wheel' and axis meaning 'axle'. In chemical terms, this type of molecule contains a linear component (the axle) encircled by a macrocyclic component (the wheel). In order to prevent the wheel from slipping off the axle, the linear component must be terminated at both ends by large blocking groups or stoppers. The addition of the prefix *pseudo* to the term rotaxane indicates that in a pseudorotaxane the wheels are free to dissociate from the axle as in a more conventional type of complex. In chemical terms, the molecular components of a pseudorotaxane are held together only by their mutual non-covalent bonding interactions.

‡ The first requirement for a successful blocking group is the ease of attachment to the primary hydroxy groups of the dication. Initially, the triphenylmethyl ether function was chosen, since it may be readily generated from the appropriate triphenylmethyl carbocation and an alcohol under mildly basic conditions. However, it was found that the blocking group of a size sufficient to prevent decomplexation of the BPP34C10 macrocycle—namely the tris(4-*tert*-butylphenyl) methyl group—was hydrolytically unstable (P. R. Ashton, D. Philp, N. Spencer and J. F. Stoddart, in *Molecular Recognition: Chemical and Biochemical Problems II*, ed. S. M. Roberts, RSC Special Publication, London, in the press). This approach to the construction of [2]rotaxanes had, therefore, to be abandoned.

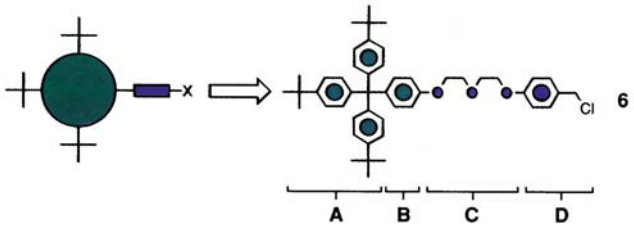
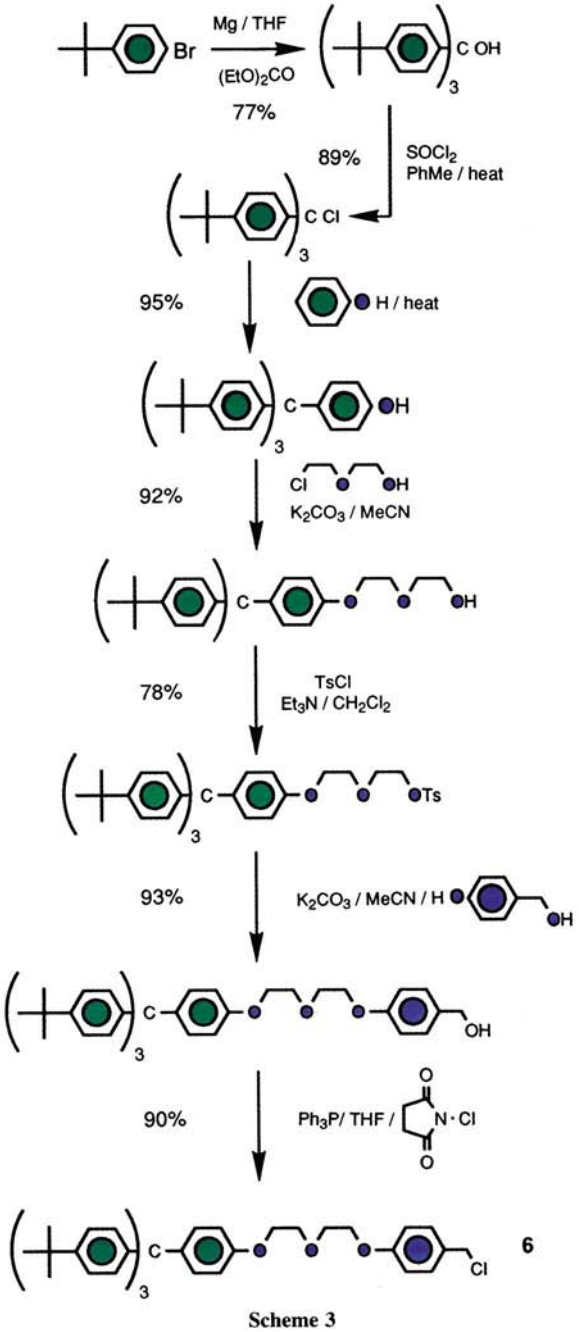


Fig. 1 The design of the blocking group **6** and its representation as a cartoon



Scheme 3

(*ii*) the blocking reagent must react rapidly with pyridylpyridinium cations. We identified the alkylating agent **6** (Fig. 1) as meeting these criteria: it contains the bulky tris(4-*tert*-butylphenyl)methyl group **A** to act as the stoppers in the [2]rotaxane. The aromatic spacer **B** removes the inherent instability associated with triarylmethyl ethers and also provides a convenient means of attaching the reactive alkylating group **D** *via* a second spacer **C**.

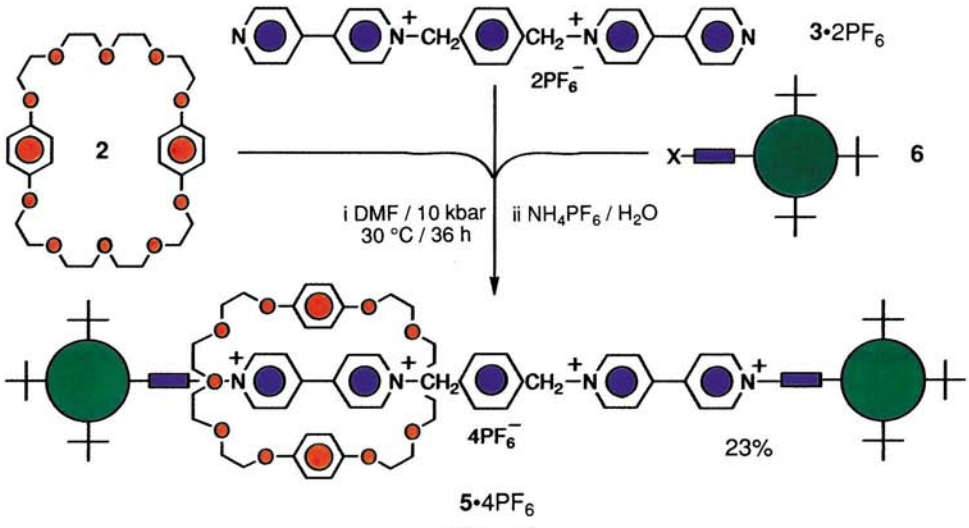
The synthesis§ of **6** has been accomplished (Scheme 3) in seven steps in 39% overall yield, starting from 4-*tert*-butylbromobenzene. The self-assembly (Scheme 4) of the [2]rotaxane **5**·4PF_6 was achieved simply by mixing **2**, **6** and **3**·2PF_6 in the molar ratios of 1.5 : 2 : 1 in dry dimethylformamide (DMF) and subjecting the reaction mixture to a pressure[17] of 10 kbar at 30 °C for 36 h (1 bar = 10^5 Pa). Isolation of the red precipitate, followed by counterion exchange (NH_4PF_6, H_2O, $MeNO_2$) and column chromatography [SiO_2 : CH_2Cl_2, MeOH, $MeNO_2$ (6 : 1 : 1)] afforded the [2]rotaxane¶ **5**·4PF_6 as a glassy orange solid in 23% yield.

The [2]rotaxane **5**·4PF_6 was initially characterised by FABMS‖ which revealed two peaks at *m/z* 2605 and 2460 corresponding to the loss of two and three counterions from the intact [2]rotaxane **5**·4PF_6. A smaller peak observed at *m/z* 2068 corresponds to the fragmentation and subsequent loss of the macrocycle **2** from the linear tetracationic component of $\mathbf{5}^{4+}$. Both ^1H and ^{13}C NMR spectroscopy indicated that, in CD_3COCD_3 solution at room temperature, the *one* BPP34C10 macrocycle is moving rapidly on the respective NMR timescales between the two equivalent 4,4′-bipyridinium dicationic sites within the tetracation $\mathbf{5}^{4+}$. The rapid

§ The alcohol obtained from the reaction of 4-*tert*-butylphenyl magnesium bromide with diethyl carbonate was chlorinated ($SOCl_2$, PhMe, heat) to yield tris(4-*tert*-butylphenyl)methyl chloride [69%; m.p. 211–213 °C; *m/z* (positive-ion FABMS) 446 for M^+; δ ($CDCl_3$, 220 MHz) 7.27.(6H, d, *J* 9 Hz), 7.10 (6H, d, *J* 9 Hz), 1.30 (27H, s)]. Reaction (150 °C, 2 h) of this chloride with molten phenol afforded 4-[tris(4-*tert*-butylphenyl)methyl]phenol [95%; m.p. 235–237 °C; *m/z* (positive-ion FABMS) 504 for M^+; δ ($CDCl_3$, 270 MHz) 7.27 (6H, d, *J* 9 Hz), 7.05–7.10 (8H, m), 6.69 (2H, d, *J* 8 Hz), 1.30 (27H, s)]. Alkylation (K_2CO_3, MeCN) of this phenol with 2-(chloroethoxy)-ethanol followed by tosylation (TsCl, Et_3N, CH_2Cl_2) gave 1-{2-[2-(toluene-*p*-sulfonyl)ethoxy]ethoxy}-4-[tris(4-*tert*-butylphenyl)methyl]benzene [73%; m.p. 197–199 °C; *m/z* (positive-ion FABMS) 746 for M^+; δ ($CDCl_3$, 300 MHz) 7.79 (2H, d, *J* 8 Hz), 7.20–7.30 (8H, m), 7.06–7.11 (8H, m), 6.74 (2H, d, *J* 8 Hz), 4.17–4.21 (2H, m), 3.99–4.03 (2H, m), 3.73–3.79 (4H, m), 2.38 (3H, s), 1.30 (27H, s)]. Selective *O*-alkylation (K_2CO_3/MeCN) of 4-hydroxybenzyl alcohol with this tosylate yielded 1-{2-[2-(4-hydroxymethylphenoxy)-ethoxy]ethoxy}-4-[tris(4-*tert*-butylphenyl)methyl]benzene [90%; m.p. 222–224 °C; *m/z* (positive-ion FABMS) 698 for M^+; δ ($CDCl_3$, 300 MHz) 7.28 (2H, d, *J* 8 Hz), 7.23 (6H, d, *J* 9 Hz), 7.06–7.11 (8H, m), 6.91 (2H, d, *J* 8 Hz), 6.79 (2H, d, *J* 8 Hz), 4.61 (2H, s), 4.11–4.18 (4H, m), 3.90–3.96 (4H, m), 1.30 (27H, s)]. The synthesis of **6** was completed by chlorination (*N*-chlorosuccinimide, Ph_3P, THF) of this benzylic alcohol, giving 1-{2-[2-(4-chloromethylphenoxy)ethoxy]-ethoxy}-4-[tris(4-*tert*-butylphenyl)methyl]benzene [90%; m.p. 180–183 °C; *m/z* (positive-ion FABMS) 716 for M^+; δ ($CDCl_3$, 300 MHz) 7.29 (2H, d, *J* 8 Hz), 7.23 (6H, d, *J* 9 Hz), 7.05–7.10 (8H, m), 6.89 (2H, d, *J* 8 Hz), 6.78 (2H, d, *J* 8 Hz), 4.54 (2H, s), 4.11–4.18 (4H, m), 3.89–3.95 (4H, m), 1.30 (27H, s)].

¶ **5**·4PF_6: m.p. >260 °C decomp. $C_{152}H_{178}N_4O_{16}P_4F_{24}$ requires M^+ 2894. Found (positive-ion FABMS) $[M\text{-}2PF_6]^+$ 2605. ^1H NMR: δ (CD_3COCD_3, 400 MHz, 298K): 9.31 (4H, d, *J* 6.5 Hz), 9.27 (4H, d, *J* 6.5 Hz), 8.46 (4H, d, *J* 6.5 Hz), 8.43 (4H, d, *J* 6.5 Hz), 7.89 (4H, s), 7.66 (4H, d, *J* 8.5 Hz), 7.23–7.29 (12H, m), 7.05–7.12 (20H, m), 6.82 (4H, d, *J* 9 Hz), 6.23 (4H, s), 6.04 (12H, s), 4.18–4.22 (4H, m), 4.10–4.14 (4H, m), 3.85–3.92 (8H, m), 3.76 (32H, bs), 1.29 (54H, s). ^{13}C NMR: δ (CD_3COCD_3, 75 MHz, 298K): 161.1, 157.7, 152.9, 149.4, 149.1, 148.0, 145.1, 140.3, 135.9, 132.7, 132.1, 131.4, 131.3, 127.3, 127.1, 125.9, 125.1, 124.9, 116.2, 115.6, 114.0, 71.3, 71.0, 70.7, 70.4, 70.2, 68.6, 68.3, 68.1, 65.1, 64.9, 63.8, 34.7, 31.5.

‖ FABMS was carried out on a Kratos MS80RF mass spectrometer (accelerating voltage, 3 kV; resolution 1000) coupled to a DS90 data system. The atom gun was an adapted saddle field source (Ion Tech Ltd.) operated at *ca.* 7 keV with a tube current of *ca.* 2 mA. Krypton was used to provide a primary beam of atoms. The sample was dissolved in a small volume of 3-nitrobenzylalcohol, which had previously been coated on to a stainless steel probe tip. Spectra were recorded in the positive-ion mode at a scan speed of 30 s per decade.



Scheme 4

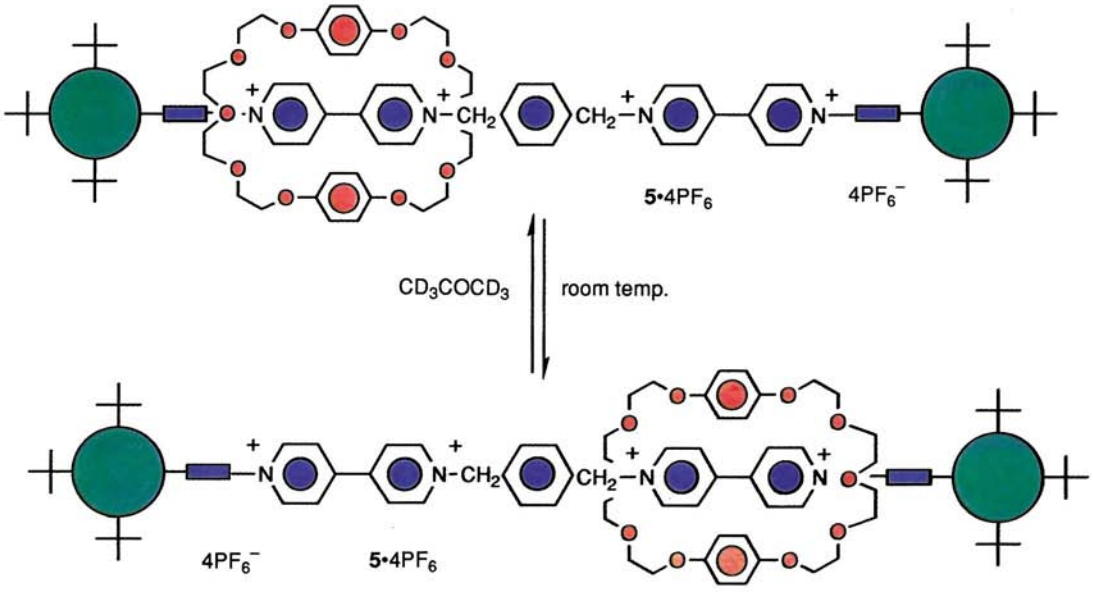
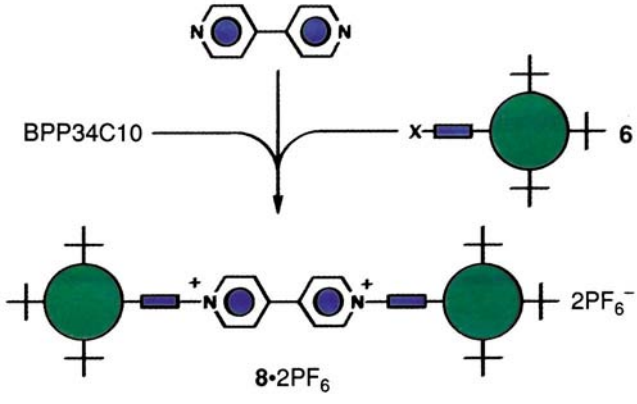


Fig. 2 The equilibration of the degenerate assemblies for the molecular shuttle **5**·4PF_6

equilibration (Fig. 2) between the two degenerate assemblies for the [2]rotaxane **5**·4PF_6 is indicated by the presence in the 400 MHz ^{1}H NMR spectrum of only two doublets at δ 9.31 and 9.27 for the protons α to nitrogen in the tetracationic component of $\mathbf{5}^{4+}$. Further evidence for this shuttling process came from the presence in the 75 MHz ^{13}C NMR spectrum of only two resonances, at δ 31.5 and 34.7, for the methyl and quaternary carbon atoms in the *tert*-butyl groups on the aromatic rings of the stoppers terminating the tetracationic component of $\mathbf{5}^{4+}$. This rapid equilibration between degenerate assemblies means that the system is behaving like a molecular shuttle.[12] On cooling the CD_3COCD_3 solution of the [2]rotaxane **5**·4PF_6 down to 198 K, the degenerate site-exchange process becomes slow on the ^{1}H NMR time-scale. This is demonstrated by the appearance of four signals for the protons α to nitrogen in the tetracationic component of $\mathbf{5}^{4+}$. An iterative computer lineshape analysis[18,19] of this signal at 198 K gave a free energy of activation of 9.9 kcal mol^{-1} (1 cal = 4.184 J) for the degenerate site-exchange process.



Scheme 5

This corresponds to the BPP34C10 ring moving from one dicationic binding site to the other within the tetracationic component of $\mathbf{5}^{4+}$ at the rate of 300 000 s^{-1} at 298 K.

In order to establish the exclusive nature of this self-assembly process, we performed a reaction between **6** and 4,4′-bipyridine **7** (Scheme 5) in the presence of BPP34C10 **2**. The only product detected was the 4,4′-bipyridinium salt $\mathbf{8}\cdot 2PF_6$: *no BPP34C10 was incorporated*. This result demonstrates the remarkable control operating during the self-assembly process.**

The self-assembly of the molecular shuttle $\mathbf{5}^{4+}$ demonstrates conclusively that it is possible to construct a wholly synthetic system with potential device-like properties on the nanometre-scale by relying upon the molecular recognition associated with weak noncovalent interactions between complementary components. The three immediate precursors of $\mathbf{5}^{4+}$ may be regarded as 'intelligent' insofar as they hold all of the information necessary to elaborate the molecular architecture of the [2]rotaxane $\mathbf{5}\cdot 4PF_6$ with complete control and precision, simply by reacting them together in DMF under ultra-high pressure conditions. No external reagent or template is required. We regard such highly programmed synthetic strategies[20] as crucial for the successful self-assembly of nanostructures capable of exhibiting device-like functions at the molecular level.

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** The synthesis of a [2]rotaxane starting from 4,4′-bipyridine, bisparaphenylene-34-crown-10 and 1,1-bis(4-*tert*-butylphenyl)-1-phenyl-4-iodobutane has been reported (Y. X. Shen, P. T. Engen, H. W. Gibson and J. S. Merola, *Abstr. 201 Am. Chem. Soc. National Meeting, Atlanta*, 14–19 April 1991, ORGN 325).

References

1 R. P. Feynman, *Sat. Rev.*, 1960, **432**, 45.
2 K. E. Drexler, *Engines of Creation*, Fourth Estate, London, 1990.
3 J. S. Lindsey, *New. J. Chem.*, 1991, **15**, 153.
4 J. F. Stoddart, In Ciba Foundation Symposium No. 158, *Host–Guest Molecular Interactions—From Chemistry to Biology*, Wiley, Chichester, 1991, 5.
5 G. M. Whitesides, J. P. Mathias and C. T. Seto, *Science*, 1991, **254**, 1312.
6 J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1304.
7 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.
8 J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89.
9 D. Philp and J. F. Stoddart, *Synlett*, 1991, 445.
10 P. R. Ashton, M. Grognuz, A. M. Z. Slawin, J. F. Stoddart and D. J. Williams, *Tetrahedron Lett.*, 1991, **32**, 6235.
11 P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vincent and D. J. Williams, *J. Am. Chem. Soc.*, 1992, **114**, 193.
12 P. L. Anelli, N. Spencer and J. F. Stoddart, *J. Am. Chem. Soc.*, 1991, **113**, 5131.
13 P. R. Ashton, D. Philp, N. Spencer and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1991, 1677.
14 B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1547.
15 B. L. Allwood, N. Spencer, H. Shahriari-Zavareh, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 1064.
16 P. R. Ashton, D. Philp, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 1680. See also, Y. X. Shen, P. T. Engen, M. A. G. Berg, J. S. Merola and H. W. Gibson, *Macromolecules*, 1992, **25**, 2786.
17 P. Ostazewski, M. Pietraszkiewicz and P. Salanski, *J. Incl. Phenom.*, 1987, **5**, 663.
18 W. B. Jennings, *J. Chem. Soc., Chem. Commun.*, 1971, 837.
19 J. Burdon, J. C. Hotchkiss and W. B. Jennings, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1052.
20 J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1992, in the press.