Slippage—an Alternative Method for assembling [2]Rotaxanes

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The exploitation of size-complementarity between the macrocyclic component and the stoppers of the dumbbell component of a [2]rotaxane, together with stabilising noncovalent bonding interactions that create a thermodynamic trap, have permitted the development of an alternative method, which can be termed *slippage*, for the syntheses of [2]rotaxanes in good yields.

The construction of molecules with novel architectures has fascinated[1] chemists since the very beginnings of synthetic chemistry. Recently, with the advent of host–guest,[2] or supramolecular,[3] chemistry, attention has focused increas-

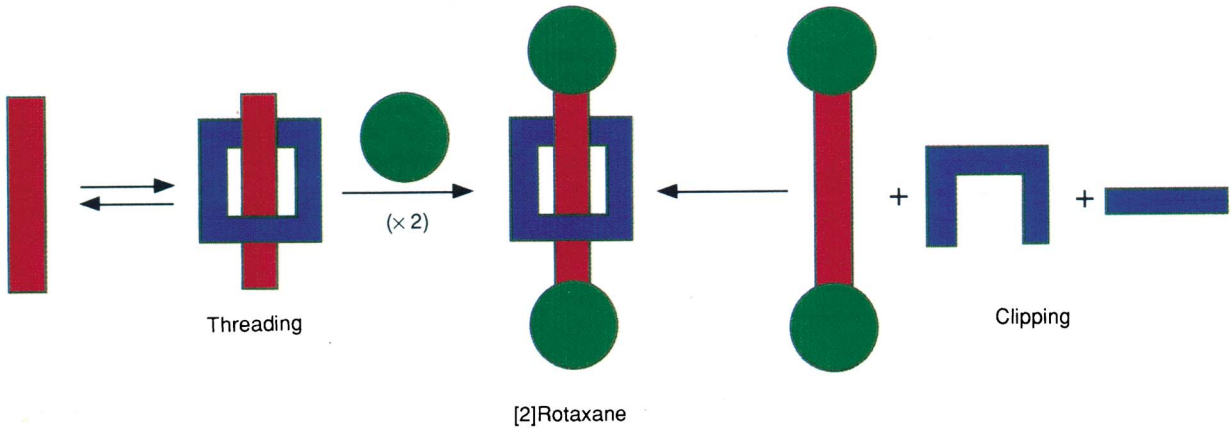


Fig. 1 The self-assembly of a [2]rotaxane by threading and clipping

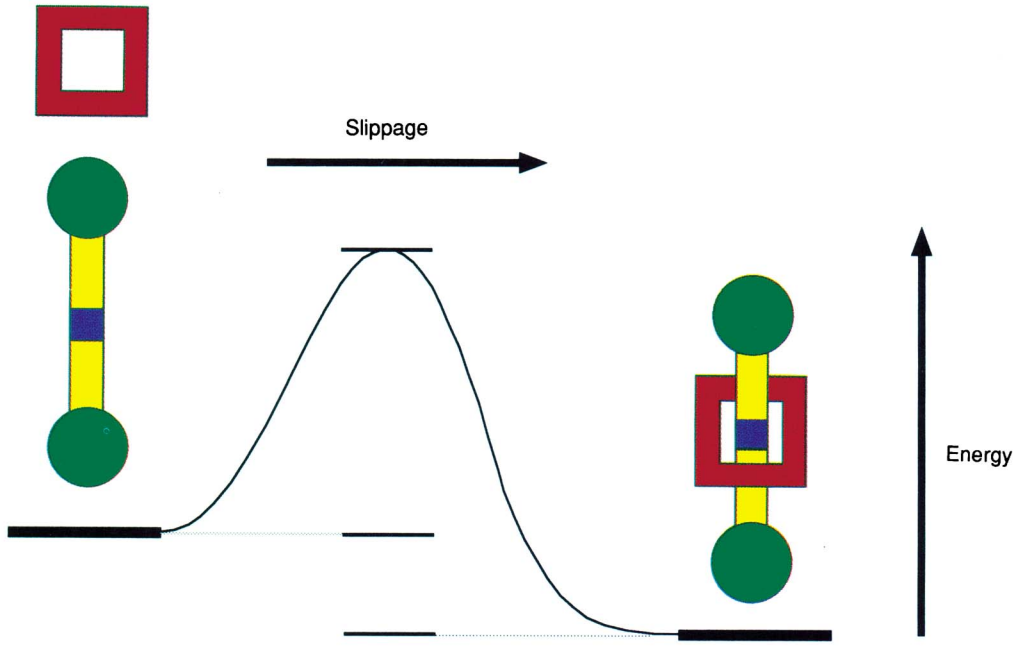


Fig. 2 The formation of a [2]rotaxane by slippage being driven thermodynamically

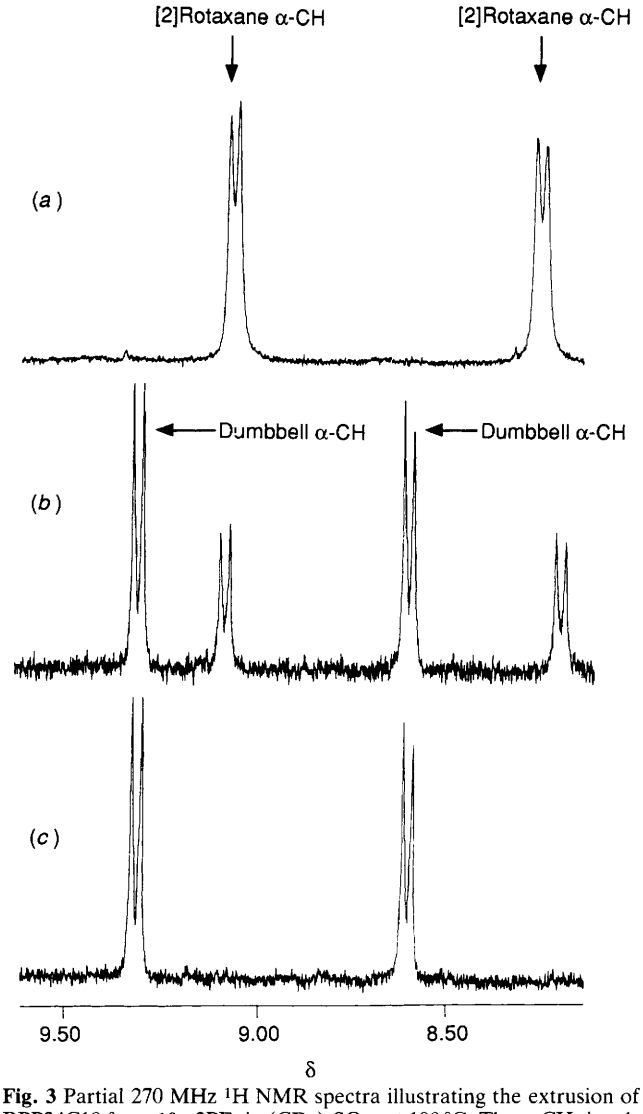


Fig. 3 Partial 270 MHz ^{1}H NMR spectra illustrating the extrusion of BPP34C10 from **10a**·2PF$_6$ in $(CD_3)_2SO$ at +100 °C. The α-CH signals of the 4,4′-bipyridinium dication present in **10a**.2PF$_6$ are illustrated (a) at the beginning of the reaction, (b) after 15 minutes, and (c) after 30 minutes at +100 °C

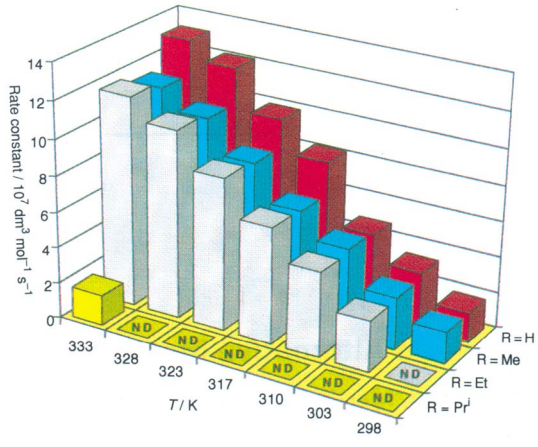
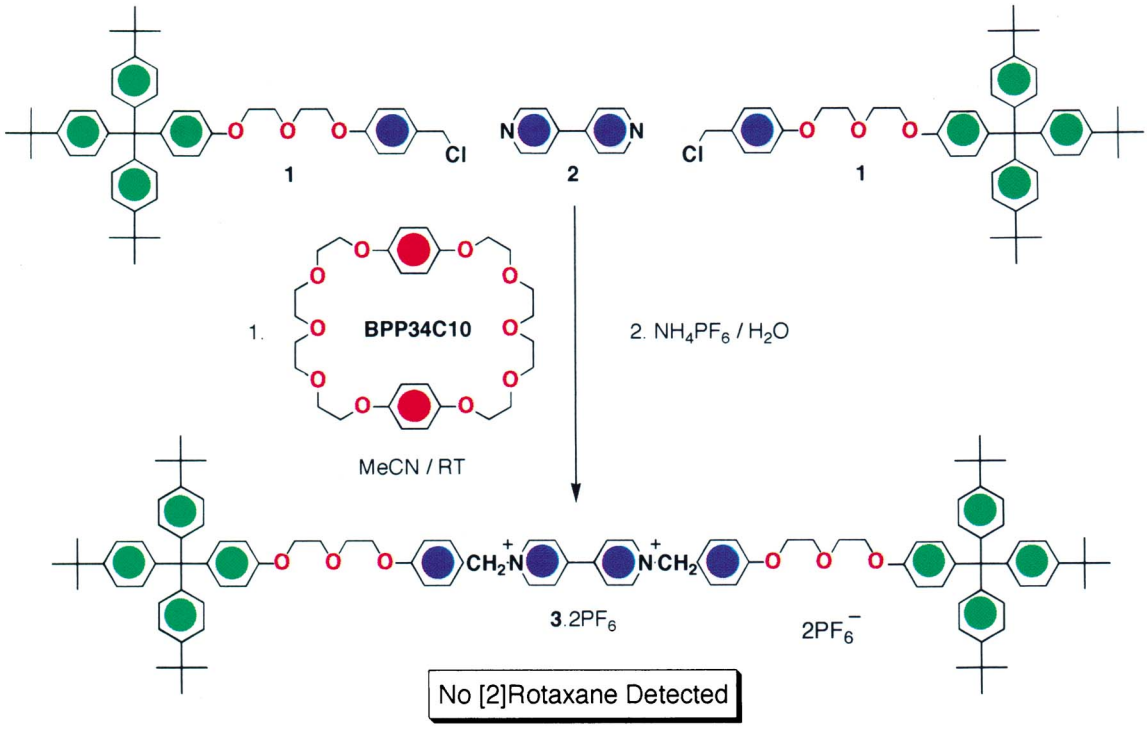


Fig. 4 Graphical representation of the observed second order rate constants for the formation of the [2]rotaxanes **10a–d**·2PF$_6$ from BPP34C10 and the dumbbells **9a–d**·2PF$_6$ in MeCN at various temperatures (ND = not determined)

ingly on the self-assembly of novel architectures, stabilised by noncovalent bond formation. Rotaxanes† provide an aesthetically appealing,[4–7] and potentially useful,[8–14] synthetic target (Fig. 1). The synthesis of rotaxanes has traditionally been approached in one of two different ways. The *threading* approach[4,5,7,10,11,14–18] (Fig. 1) relies on statistical or noncovalent bonding directed association of a thread-like molecule with a bead-like macrocyclic component of the forming rotaxane. This assembly is then trapped mechanically by covalent attachment of blocking groups (stoppers) which are of sufficient size to prevent the dissociation of the macrocycle from the dumbbell component. In the *clipping* approach[4–14] (Fig. 1), the bead-like macrocyclic component is assembled around the preformed dumbbell-shaped component to form the [2]rotaxane.

† 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 stoppers, *i.e.* blocking groups.



Scheme 1

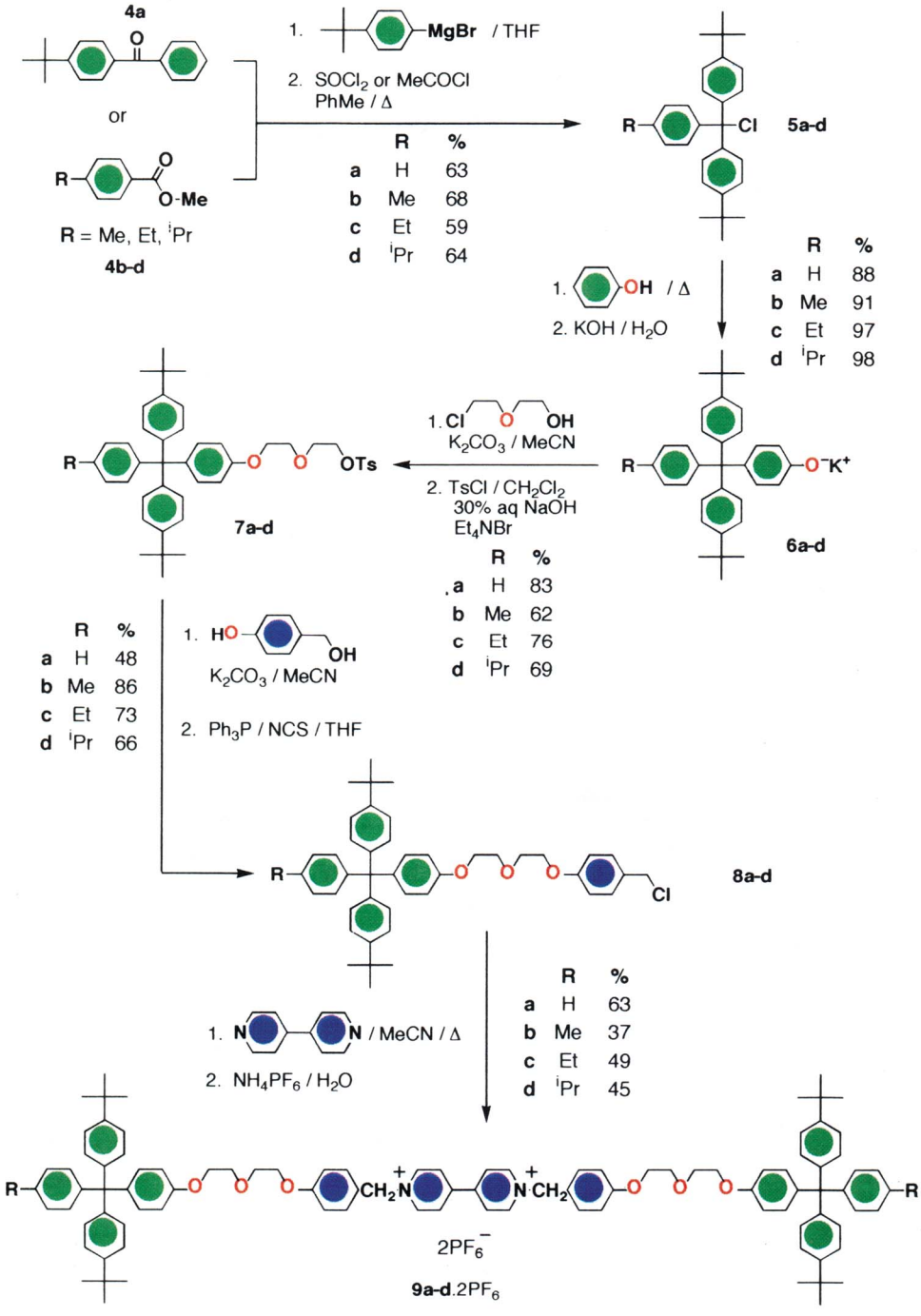
Recently, we devised[19] an 'intelligent' self-assembly[4–14,20,21] route to a [2]rotaxane with molecular shuttling properties, based on the mutual recognition between π-electron deficient 4,4′-bipyridinium dications and π-electron rich hydroquinol rings contained within a macrocyclic polyether. This self-assembly route proved to be highly selective in that it requires *two* 4,4′-bipyridinium dications to be present in the [2]rotaxane in order that *one* bisparaphenylene-34-crown-10 (BPP34C10) ring can be incorporated. Thus, when we reacted (Scheme 1) the benzylic chloride **1** with bipyridine **2**, in the presence of the crown ether BPP34C10, only dication $\mathbf{3}^{2+}$ was isolated from the reaction mixture—no [2]rotaxane could be detected. The stoppers incorporating tris(4-*tert*-butylphenyl)methyl groups in $\mathbf{3}^{2+}$ are too large to permit passage of BPP34C10 over them and allow interaction with the 4,4′-bipyridinium dication. We, therefore, reasoned that, by judicious adjustment of the size of the stoppers, we could arrive at a situation (Fig. 2) where the size complementarity between BPP34C10 and the stoppers was such that *slippage* of the macrocycle over them would be possible at elevated temperatures. The complexation of the 4,4′-bipyridinium dication within the dumbbell-shaped component by the macrocycle would then provide a *thermodynamic trap* for the crown ether, raising the activation energy (Fig. 2) for the extrusion process relative to that for slippage. Thus, the [2]rotaxanes formed by slippage should be stable at room temperature.

In order to investigate the slippage as a synthetic route to [2]rotaxanes, we synthesised‡ a range (Scheme 2) of 4,4′-bipyridinium dications **9a–d**, where the size of the stoppers was varied systematically. Heating **9a–c**·2PF_6 (R = H, Me, Et) with 4 equiv. of BPP34C10 in acetonitrile solution at 60 °C for 10 days permitted (Scheme 3) the isolation of the [2]rotaxanes **10a–c**·2PF_6 in 52, 45, and 47% yields, respectively. The yield of the [2]rotaxane **10a**·2PF_6 (R = H) could be increased to 87% when 8 equiv. of BPP34C10 were used under otherwise identical conditions. By contrast, no [2]rotaxane could be isolated when the dication **9d**·2PF_6 was heated with 4 equiv. of BPP34C10 in acetonitrile solution at 60 °C for 10 days, indicating that, when R = Pr^i, the stoppers are too large to permit slippage to occur at a preparatively useful rate. The [2]rotaxanes **10a–c**·2PF_6 exist as stable compounds, which can be chromatographed (SiO_2 : MeOH : $MeNO_2$: CH_2Cl_2 6 : 1 : 1) unchanged prior to being characterised§ by fast atom bombardment mass spectrometry (FABMS) and ^{1}H and ^{13}C NMR spectroscopies. However, extrusion of the BPP34C10 mac-

‡ The dumbbells **9a–d**·2PF_6 were synthesised (Scheme 2) in nine steps starting from either 4-*tert*-butylphenyl phenyl ketone (**4a**, R = H) or the appropriate methyl 4-alkylbenzoates (**4b–d**, R = Me, Et, Pr^i). Reaction of the ketone **4a** or the esters **4b–d** with 4-*tert*-butylphenylmagnesium bromide in tetrahydrofuran (THF), followed by chlorination ($SOCl_2$ or MeCOCl/PhMe/heat), afforded the corresponding tertiary chlorides **5a–d**. Friedel–Crafts arylation of **5a–d** (PhOH/heat) and treatment with 8 mol dm^{-3} aqueous KOH gave the potassium phenolate salts **6a–d**. Alkylation of **6a–d** with 2-(2-chloroethoxy) ethanol under mildly basic conditions, followed by tosylation using a phase-transfer procedure (TsCl/CH_2Cl_2/30% aq. NaOH/$PhCH_2Et_3NBr$), afforded the tosylates **7a–d**, which were then alkylated selectively using 4-hydroxybenzyl alcohol (K_2CO_3/MeCN). Chlorination of the resulting benzylic alcohols using *N*-chlorosuccinimide (Ph_3P/THF) gave the corresponding benzylic chlorides **8a–d**. Reaction of **8a–d** with 4,4′-bipyridine in refluxing MeCN, followed by chromatography (SiO_2 : MeOH : CH_2Cl_2 : $MeNO_2$: 2 mol dm^{-3} NH_4Cl 70 : 16 : 11 : 3) and counterion exchange (NH_4PF_6/H_2O) gave the dumbbells as their bis(hexafluorophosphate) salts **9a–d**·2PF_6.

§ **10a**.2PF_6: m.p. 146–149 °C decomp. $C_{126}H_{146}N_2O_{16}P_2F_{12}$ requires $[M]^+$ 2232. Found (positive-ion FABMS) $[M - 2PF_6]^+$ 1943. ^{1}H NMR: δ (300 MHz, CD_3CN): 9.04 (4H, d, *J* 7 Hz), 7.98 (4H, d, *J* 7 Hz), 7.69 (4H, d, *J* 9 Hz), 7.03–7.29 (34H, m), 6.74 (4H, d, *J* 9 Hz), 6.04 (8H, s), 5.85 (4H, s), 4.09–4.14 (4H, m), 4.00–4.06 (4H, m), 3.75–3.82 (8H, m), 3.69 (16H, bs), 3.60–3.65 (8H, m), 3.48–3.52 (8H, m), 1.26 (36H, s). ^{13}C NMR: δ (75 MHz, CD_3CN): 161.1, 157.7, 153.0, 149.6, 148.5, 147.2, 146.3, 145.3, 140.5, 132.8, 132.7, 131.6, 131.3, 128.5, 126.8, 126.4, 125.5, 116.3, 116.2, 115.7, 114.4, 71.4, 71.2, 70.7, 70.5, 70.3, 68.8, 68.5, 68.4, 64.9, 64.4, 34.9, 31.6.

10b·2PF_6: m.p. 137–140 °C decomp. $C_{128}H_{150}N_2O_{16}P_2F_{12}$ requires $[M]^+$ 2260. Found (positive-ion FABMS) $[M - 2PF_6]^+$ 1971. ^{1}H NMR: δ (300 MHz, CD_3CN): 8.86 (4H, d, *J* 7 Hz), 7.78 (4H, d, *J* 7 Hz), 7.62 (4H, d, *J* 9 Hz), 7.28 (8H, d, *J* 9 Hz), 7.04–7.14 (24H, m) 6.74 (4H, d, *J* 9 Hz), 6.00 (8H, s), 5.80 (4H, s), 4.12–4.19 (4H, m), 4.02–4.08 (4H, m), 3.78–3.86 (8H, m), 3.71 (16H, bs), 3.62–3.68 (8H,



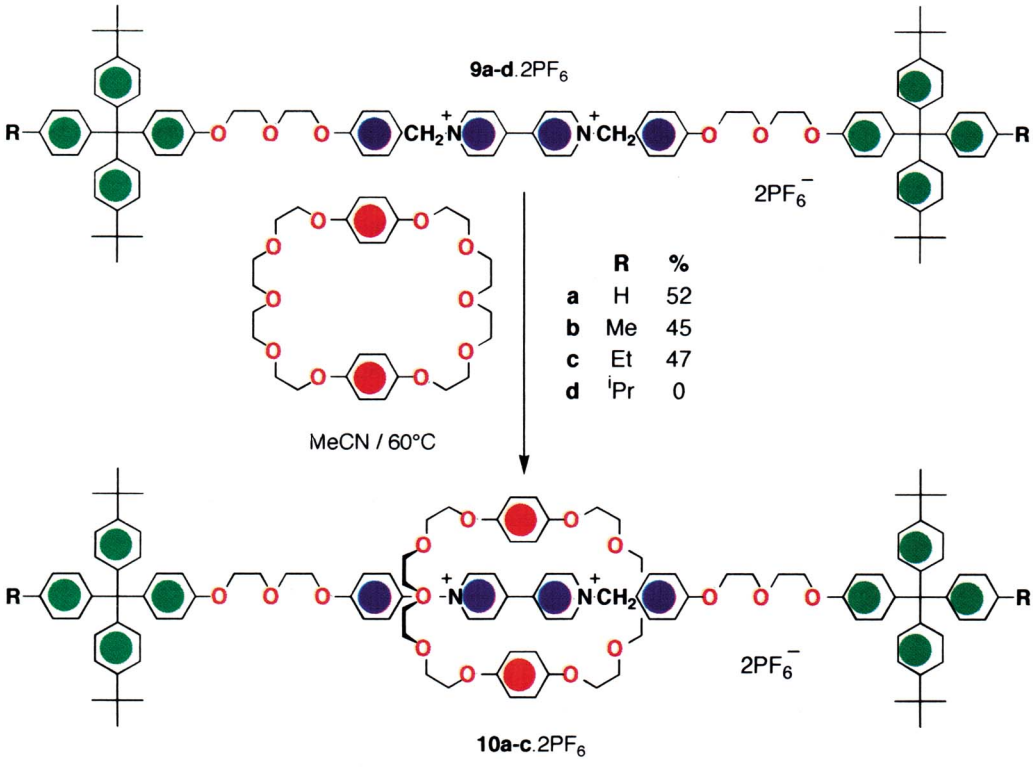
Scheme 2

m), 3.48–3.53 (8H, m), 2.27 (6H, s), 1.26 (36H, s). ^{13}C NMR: δ (75 MHz, CD_3CN): 161.3, 157.7, 153.1, 149.6, 148.5, 147.2, 146.3, 145.6, 140.8, 132.8, 132.6, 131.5, 131.3, 129.2, 126.8, 126.2, 125.5, 117.8, 116.5, 116.2, 115.7, 114.4, 71.5, 71.3, 70.7, 70.5, 70.3, 68.9, 68.6, 68.4, 65.1, 64.5, 35.0, 31.6, 20.9.

10c·$2PF_6$: m.p. 140–144 °C decomp. $C_{130}H_{154}N_2O_{16}P_2F_{12}$ requires $[M]^+$ 2288. Found (positive-ion FABMS) $[M - 2PF_6]^+$ 1999. ^{1}H NMR: δ (300 MHz, CD_3CN): 8.86 (4H, d, *J* 7 Hz), 7.78 (4H, d, *J* 7 Hz), 7.62 (4H, d, *J* 9 Hz), 7.28 (8H, d, *J* 9 Hz), 7.04–7.14 (24H, m), 6.74 (4H, d, *J* 9 Hz), 6.00 (8H, s), 5.80 (4H, s), 4.12–4.19 (4H, m), 4.02–4.08 (4H, m), 3.78–3.86 (8H, m), 3.71 (16H, bs), 3.62–3.68 (8H, m), 3.48–3.53 (8H, m), 2.54–2.62 (4H, q, *J* 7 Hz), 1.26 (36H, s), 1.14–1.20 (6H, t, *J* 7 Hz). ^{13}C NMR: δ (75 MHz, CD_3CN): 161.2, 157.7, 153.1, 149.5, 147.2, 146.2, 145.8, 145.5, 142.7, 140.7, 132.7, 132.6, 131.6, 131.3, 128.0, 126.2, 126.1, 125.4, 116.4, 115.7, 114.3, 71.4, 71.2, 70.7, 70.5, 70.3, 68.8, 68.5, 68.4, 65.1, 64.1, 35.0, 31.6, 28.8, 15.9.

rocycle from the [2]rotaxane **10a**·$2PF_6$ was observed¶ (Fig. 3) by ^{1}H NMR spectroscopy in $(CD_3)_2SO$ at +100 °C. While the signals for the α-CH and β-CH protons of the 4,4′-bipyridinium dication in **10a**·$2PF_6$—at δ 9.09 and 8.21, respectively—diminish in relative intensity, the signals for the α-CH and β-CH protons of the free dumbbell **9**·$2PF_6$—at δ 9.32 and 8.60, respectively—increase in relative intensity over a period of 30 min. When the same experiment was repeated at +60 °C in CD_3CN, extrusion was less than 25% complete after 6 h.

¶ An approximate first-order rate constant for the extrusion of the BPP34C10 macrocycle from the [2]rotaxane **10a**·$2PF_6$ in CD_3SOCD_3 at 100 °C of 1×10^{-3} s^{-1} was obtained from the ^{1}H NMR spectroscopic data.



Scheme 3

Second-order rate constants for the formation the [2]rotaxanes **10a–d**·2PF$_6$, derived‖ from UV–VIS spectrophotometry carried out over a range of temperatures, are illustrated graphically in Fig. 4. The data reveals that the rates of formation of the [2]rotaxanes **10a**·2PF$_6$, **10b**·2PF$_6$ and **10c**·2PF$_6$, where R is H, Me and Et, respectively, are almost identical. This result suggests that there is little difference in the steric barrier to slippage imposed by the stoppers when R = H, Me and Et. However, the rate of formation of the [2]rotaxane **10d**·2PF$_6$, where R = Pr^i, is some ten times less than the rates of formation of **10a–c**·2PF$_6$ at 60 °C. This observation is in agreement with the synthetic outcome, which suggests that slippage does not occur at a preparatively useful rate at 60 °C in MeCN when R = Pr^i. Arrhenius plots of the data for the formation of the [2]rotaxanes **10a–c**·2PF$_6$ reveal significant curvature at higher temperatures. This observation is indicative of the fact that the backward extrusion process, which dismembers the [2]rotaxanes at high temperatures, is becoming competitive with the forward slippage reaction.** Hence, the reaction no longer obeys a simple second-order rate law.

The successful syntheses in good yields of the [2]rotaxanes **10a–c**·2PF$_6$ demonstrate the preparative utility of the slippage method. Although size complementarity†† has been exploited previously[22] in the statistical synthesis‡‡ of [2]rotaxanes, the yields of the [2]rotaxanes obtained in these cases were very poor (<1.5%). The addition of a thermodynamic trap, in the form of noncovalent bonding interactions between the two components of a [2]rotaxane, not only enhances the overall yield obtained during the slippage process, but also increases the inherent stability and information content of the resulting structures. These features, together with the sheer synthetic simplicity of the experimental approach, recommend slippage as a viable and alternative synthetic procedure for the construction of larger [*n*]rotaxanes[23] and polyrotaxanes.[24]

We thank the SERC for financial support and Mr S. Greenland for his assistance in preparing some of the stoppers.

Received, 22nd April 1993; Com. 3/02321D

‖ The formation of the [2]rotaxanes **10a–d**·2PF$_6$ was followed using UV–VIS spectrophotometry. BPP34C10 and each of the dications **9a–d**·2PF$_6$ were mixed together in the relative molar proportions 4 : 1 in dry MeCN. The resulting solution was placed in a quartz cuvette and the evolution of the UV–VIS spectrum in the range 220 to 600 nm was followed over a period of 60 h by means of a computer-controlled Perkin-Elmer Lambda 2 Spectrophotometer fitted with a thermostatic temperature controller (control ± 0.2 °C). One spectrum was recorded every 10 min during the time course of the experiment. The data acquisition was performed on a fresh sample at seven different temperatures in the range 298 to 333 K for each of the dications **9a–d**·2PF$_6$. Second-order rate constants were extracted from the data by determining the concentrations of reactants and products from the spectroscopic data and applying the normal linearisation of the integrated second-order rate law for A + B going to products.

** Since the extrusion reaction is first order, running the synthetic reactions at higher concentrations should accelerate the forward slippage reaction and leave the rate of the reverse extrusion reaction unchanged.

†† For another recent example of the exploitation of size complementarity between host and guest in hemicarcerand chemistry, see D. J. Cram, M. T. Blanda, K. Park and C. B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7765. It should be mentioned that, in a study on the effect of $(CH_2)_n$ ring size on the threading reactions of macrocycles on and off 1,10-bis(triphenylmethoxy)decane, Harrison (*J. Chem. Soc., Chem. Commun.*, 1972, 231) has shown that, whereas $(CH_2)_{29}$ could be threaded and unthreaded over a triphenylmethyl group, $(CH_2)_{28}$ was too small and $(CH_2)_{30}$ and larger macrocyles formed only transient compounds, which separated into their components even at room temperature.

‡‡ The synthesis of a [2]rotaxane starting from 4,4′-bipyridine, bisparaphenylene-34-crown-10 and 1,1-bis(4-*tert*-butyl)-1-phenyl-4-iodobutane has been reported (Y. X. Shen, P. T. Engen, H. W. Gibson and J. S. Merola, *Abstr. 201, ACS National Meeting, Atlanta*, 14–19 April 1991, ORGN 325). However, no mechanistic rationalisation for the formation of the [2]rotaxane was offered.

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