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Towards Controlling the Threading Direction of a Calix[6]arene Wheel by Using Nonsymmetric Axles

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Abstract: The possibility of obtaining full control on the direction of axle threading in calix[6]arene wheel **1** either from its upper or lower rim was evaluated in solution. To this aim, we prepared nonsymmetric axles characterised by a 4,4′-bipyridinium recognition unit with two alkyl side chains, one of which terminates with a stopper, and the other with either ammonium (**2**), hydroxy (**3**) or methyl (**4** and **5**) head groups. When the axles were mixed with **1** in apolar solvents at room temperature, the formation of oriented pseudorotaxanes derived from the threading of the axles from the upper rim was observed. The stability constants of such complexes are in the order of $10^7\,M^{-1}$ and are almost independent of the type of axle. A detailed thermodynamic and kinetic study revealed that stability constants and activation parameters for complex formation between **1** and axles **2** and **3** are of the same order of magnitude, suggesting a common threading process. However, upon heating a solution of **1** and **2** in benzene at 340 K, the formation of another supramolecular complex was observed, the structure of which is consistent with an oriented pseudorotaxane derived from the threading of axle **2** from the lower rim of the calixarene wheel. By carrying out the threading–stoppering reaction sequence between **1** and **2** in the presence of an excess of diphenylacetyl chloride, the orientational rotaxane isomers **R1** and **R2**, derived from lower- and upper-rim threading, respectively, were collected in about a ratio of 7:3 as the unique chromatographic fraction. Our results suggest that at room temperature the threading process is under kinetic control for all axles. On increasing the temperature only the threading behaviour of axle **2** is substantially modified, most likely because the process becomes thermodynamically controlled owing to the peculiar recognition properties of the ammonium head of this axle.

Keywords: calixarenes · molecular devices · rotaxanes · self-assembly · supramolecular chemistry

Introduction

The operation of molecular devices capable of performing programmed tasks is directly connected with the physicochemical properties and the spatial arrangement of the fragments or components that constitute their skeleton.[1–3] The design and synthesis of these systems can profit from the principles and methods of supramolecular chemistry,[4] although emergent properties are sometimes difficult to predict on the basis of the characteristics of the molecular components. Hence, the ability of a molecular device to perform a programmed task has to be experimentally examined through the acquisition of the thermodynamic and kinetic parameters associated with its functioning. This aspect is particularly important when these systems originate from self-assembly processes, respond to external stimuli and function as molecular machines.[1,2a,c–p,5] It thus appears that the development of devices with advanced functionalities, possibly suitable for practical applications, derives from an iterative process in which specific functions are conferred to the assembly through the fine-tuning of the properties stored on its components.[6]

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Pseudorotaxanes are supramolecular complexes minimally composed of a wheel-type host surrounding an axle-type guest.[7] The assembly/disassembly of the axle and wheel components of a pseudorotaxane, which resembles the threading/dethreading of a needle, can be controlled by external stimulation.[1,8] Studies on switchable pseudorotaxanes[9] are most important for the development of molecular machines based on rotaxanes, catenanes and related interlocked molecules. Specifically, the development of a pseudorotaxane motif capable of performing unidirectional threading and dethreading processes[10] under control of external stimuli (Figure 1a) would be important for the construction of rotary motors based on catenanes (Figure 1b) and processive linear motors based on rotaxanes (Figure 1c).[2h]

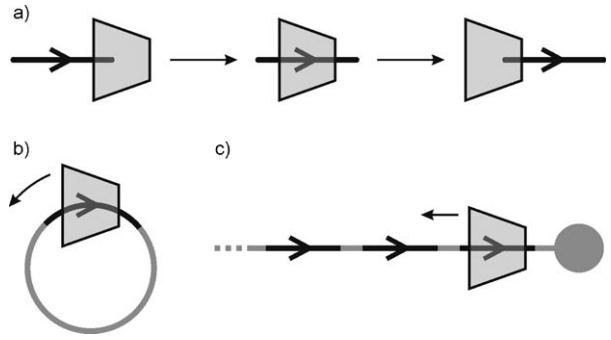
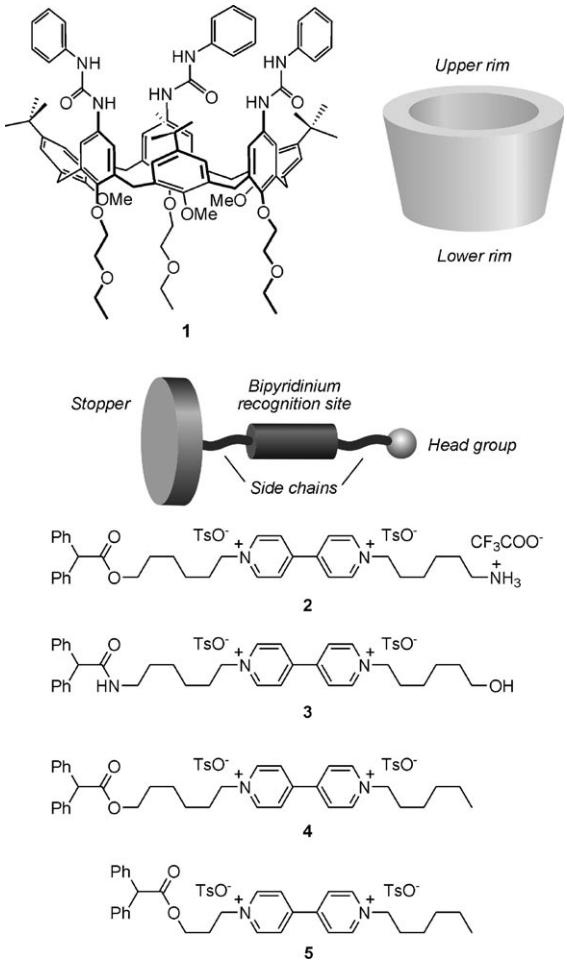


Figure 1. Representation of stimuli-controlled unidirectional threading/dethreading of a [2]pseudorotaxane (a), a rotary motor based on a [2]catenane (b) and a processive linear motor based on a [2]rotaxane (c).



Scheme 1. Structural formulae and schematic representation of wheel **1** and 4,4′-bipyridinium-based axles **2**–**5** used in this study. Ts = tosyl.

We recently demonstrated[6b,11–13] that the use of the heteroditopic nonsymmetric tris(phenylureido)calix[6]arene derivative **1** (Scheme 1) as a three-dimensional macrocyclic component for obtaining oriented pseudorotaxanes and rotaxanes brings about a significant increase in structural complexity because, in principle, it is possible to selectively address the threading of suitable axles from its upper or lower rim. In fact, we showed that in apolar media (e.g., benzene) **1** is able to act as a very efficient[11] wheel that can be threaded exclusively from the upper rim by axles derived from dialkyl-4,4′-bipyridinium salts to yield oriented pseudorotaxanes (Figure 2).[6b,12] This behaviour was explained by analysing the main chemical and structural features of **1** as a host, which are 1) a π-donor macrocyclic cavity that, because of its width, can include the positively charged bipyridinium unit of the axle, but not together with its counteranions; 2) three efficient hydrogen-bond donor ureidic groups at the upper rim that, by complexing the counteranions of the axle, can assist the insertion of the cationic portion of the axle into the cavity from this rim and 3) three methoxy groups at the lower rim that, in apolar media, are oriented towards the interior of the cavity in the NMR timescale, thereby hindering the access of the guest from this direction.

The use of a more polar solvent, for example, acetonitrile, has a profound effect on the threading outcome. In fact, sol-

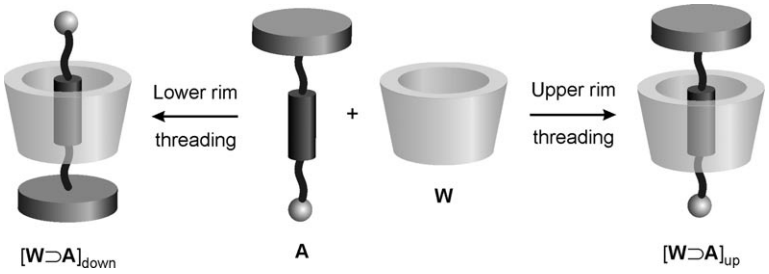


Figure 2. Representation of the two pseudorotaxane orientational isomers, "up" and "down", that can form upon threading a rivet-like nonsymmetric axle (A) through a nonsymmetric wheel (W).

vent polarity affects both the concentration of active guest available in solution and the binding ability of the wheel, by changing the extent of ion pairing of the axle and decreasing the pivoting role of the three ureidic groups of the host, respectively. Additionally, in acetonitrile the three methoxy groups of the calixarene reside outside the cavity in the NMR spectroscopy timescale, thus decreasing the steric crowding at the lower rim. As a result, bipyridinium-type axles can enter the wheel from both the upper and the lower rim, yielding a mixture of pseudorotaxane orientational isomers (Figure 2).[12] The stoppering reactions of such a mixture yielded a mixture of orientational rotaxane isomers, the proportion of which reflects the original ratio between the corresponding pseudorotaxane isomers.[12]

To obtain pseudorotaxanes and rotaxanes characterised by a univocal and programmable relative orientation of their components, it is important to gain a deep understanding of the structural, thermodynamic and kinetic factors that govern the threading processes.[10,11,14] Herein we report a study on the interplay between thermodynamic and kinetic control as key elements to determine the threading direction of different nonsymmetric axles in the nonsymmetric wheel **1**. We suggest that the nature of the head groups appended to the central 4,4′-bipyridinium recognition unit of the axle could play an active role during the processes that lead to the formation of oriented pseudorotaxanes.

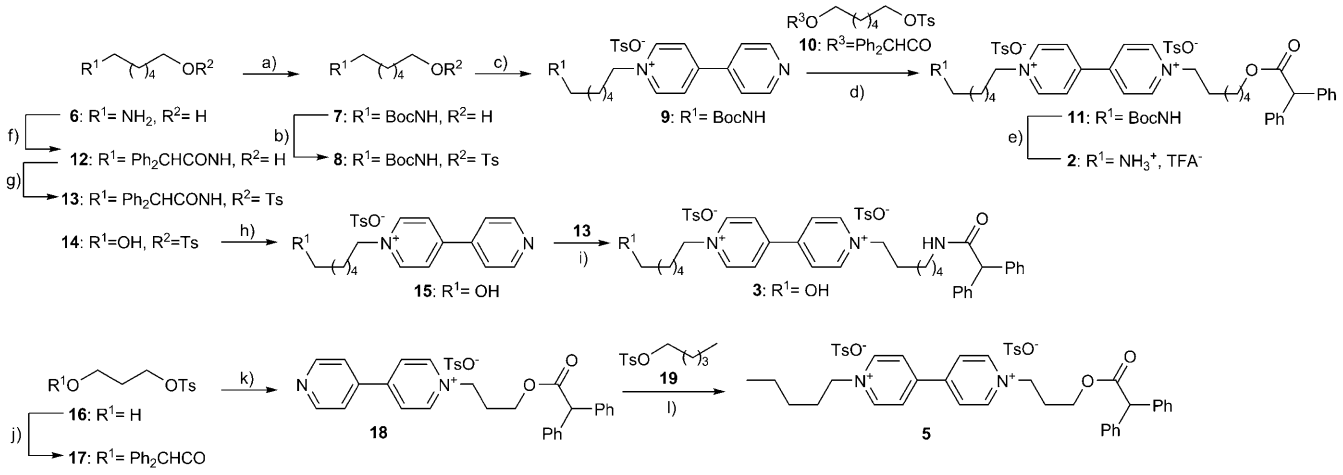
Results and Discussion

Design

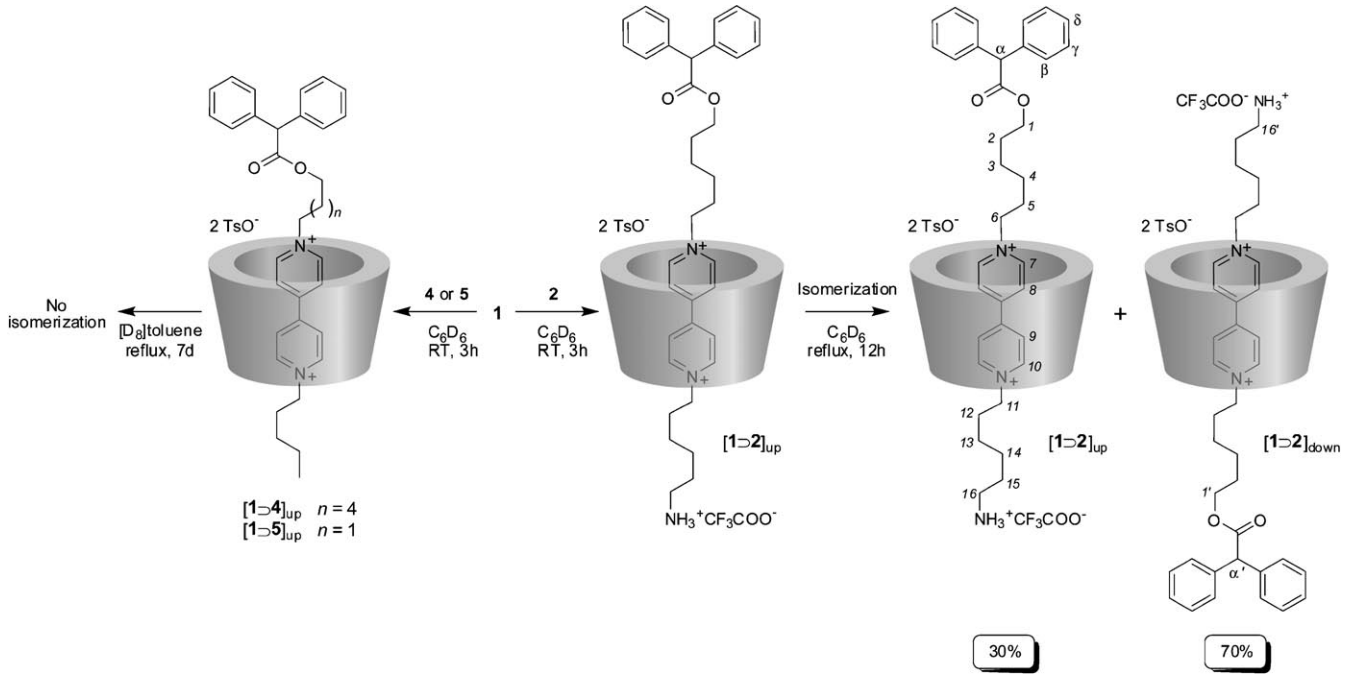
To evidence possible effects of the structural features of the axles on the threading direction into wheel **1**, we designed a family of nonsymmetric axles characterised by 1) a 4,4′-bipyridinium central unit which, by exhibiting an efficient recognition towards the cavity of **1**,[15] is able to drive the pseudorotaxane self-assembly; 2) two alkyl side chains, one of which has 3) a dumb stopper moiety, whereas the other one terminates with 4) a specific head group. The formulae of axles **2**–**5** investigated are shown in Scheme 1. The stoppers were either a diphenylacetic ester (**2**, **4** and **5**) or a diphenylacetic amide (**3**) groups, whereas we chose ammonium (**2**), hydroxy (**3**) and methyl (**4** and **5**) units as the head groups. Compounds **4** and **5** differ only in the length of the alkyl chain that connects the bipyridinium unit with the stopper. Axles **2**, **3** and **5** were synthesised in reasonable yield, as summarised in Scheme 2. Compound **4** was available from previous investigations.[6b,11]

NMR spectroscopic characterisation

Threading processes: In separate experiments, compounds **2**, **4** and **5** were equilibrated with **1** in C_6D_6 at room temperature for 3 h (Scheme 3). The purple solutions obtained after removal of the undissolved axle were then analysed at 298 K with ^{1}H NMR spectroscopy techniques. As expected, the structure of pseudorotaxanes [**1**⊃**4**] and [**1**⊃**5**] is in full agreement with a supramolecular complex derived from the insertion of the axle from the upper rim of the calixarene (Scheme 3 and Figures S2 and S12 in the Supporting Information).[6b] The same direction of threading into the wheel was also verified for [**1**⊃**2**] as evidenced, for example, by the resonances of the protons *1* and α (Figure 3a; see Scheme 3 for numbering). The fact that these protons resonate at $\delta =$ 4.16 and 5.25 ppm, respectively, is consistent with the orientation of the stopper at the upper rim of the calixarene. The presence of only one set of signals, in agreement with pseudorotaxanes with the stopper in proximity to the upper rim of the calixarene, suggests that under these experimental conditions neither the nature of the axle terminus nor unfavourable interactions between the different stoppers and the upper rim of the calixarene affect the direction of the threading process.



Scheme 2. Reagents and conditions: a) Boc_2O (Boc = *tert*-butyloxycarbonyl), MeOH, NEt_3, reflux, 1 h; b) TsCl, DMAP, NEt_3, CH_2Cl_2, 2 d; c) 4,4′-bipyridine, CH_3CN, reflux, 3d; d) CH_3CN, reflux, 15d; e) trifluoroacetic acid, 1 h; f) $Ph_2CHCOCl$, CH_3CN, 12 h; g) TsCl, NEt_3, CH_2Cl_2, 12 h; h) 4,4′-bipyridine, CH_3CN, reflux, 12 h; i) CH_3CN, reflux, 15 d; j) $Ph_2CHCOCl$, THF, 48 h; k) 4,4′-bipyridine, CH_3CN, reflux, 48 h; l) CH_3CN, reflux, 15 d.



Scheme 3.

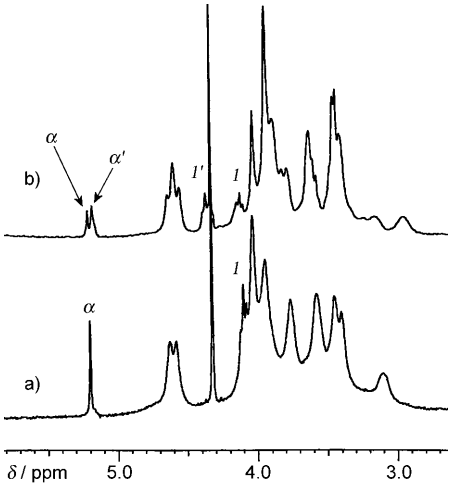


Figure 3. Expanded region of the ^{1}H NMR spectrum (C_6D_6, 300 MHz) of pseudorotaxane [**1**⊃**2**] at a) 298 K and b) after heating the reaction mixture at reflux for 12 h. α, *1*, and α′ and *1′* denote the resonances of axle **2** in $[\mathbf{1}\supset\mathbf{2}]_{up}$ and $[\mathbf{1}\supset\mathbf{2}]_{down}$, respectively. See Scheme 3 for numbering.

To verify whether the regiochemistry of these processes derives from kinetic control,[16] they were studied by ^{1}H NMR spectroscopy in [D_8]toluene at 370 K. The spectral region between $\delta = 4$ and 5 ppm where protons α and *1*, which are diagnostic for the orientation of the stopper with respect to the calixarene rims, resonate was studied. No isomerisation of the originally obtained pseudorotaxanes $[\mathbf{1}\supset\mathbf{4}]_{up}$ and $[\mathbf{1}\supset\mathbf{5}]_{up}$ was detected after 3 h (Scheme 3). The presence of only one orientational pseudorotaxane isomer was also observed by maintaining the same samples in toluene at reflux for 7 days; after that time, together with the original pseudorotaxane, decomposition byproducts of the axle were present in solution. On the contrary, in the case of pseudorotaxane $[\mathbf{1}\supset\mathbf{2}]_{up}$, a new set of signals that could be assigned to the other isomer with the stopper at the lower rim, $[\mathbf{1}\supset\mathbf{2}]_{down}$, started to appear upon heating (Figure S3 in the Supporting Information). Unfortunately, the extensive overlapping and broadening of the signals precluded the unambiguous assignment of all signals.

The experiment was then repeated in C_6D_6 by heating the sample containing **1** and **2** at 340 K for 12 h. Upon cooling to room temperature, two distinct signals for the methine proton of the diphenylacetyl stopper, consistent with the presence of two pseudorotaxane isomers, appeared at $\delta =$ 5.22 (α′) and 5.25 ppm (α) (Figure 3b, see Figure S4 in the Supporting Information for the full spectra). After peak deconvolution, the two signals were in a relative ratio of approximately 7:3. It seems, therefore, that at 340 K the dethreading of the original pseudorotaxane $[\mathbf{1}\supset\mathbf{2}]_{up}$ and subsequent rethreading to yield the more stable $[\mathbf{1}\supset\mathbf{2}]_{down}$ isomer takes place (Scheme 3). The fact that $[\mathbf{1}\supset\mathbf{2}]_{up}$ is not obtained as the exclusive product upon successive cooling to room temperature suggests that slipping of the ammonium head through the lower rim is prevented at this temperature, in keeping with the results of the threading experiment between **1** and **2**.

To gain more insight into these processes we added increasing aliquots of triethylamine to the above 7:3 pseudorotaxane mixture to deprotonate the ammonium head of **2**, and we analysed the resulting solutions by ^{1}H NMR spectroscopy. We found that the original relative ratio between

the two isomers remains constant even in the presence of a large (6 equiv) excess of base with respect to the ammonium group, and is unchanged also when this sample was heated at 340 K for 12 h.

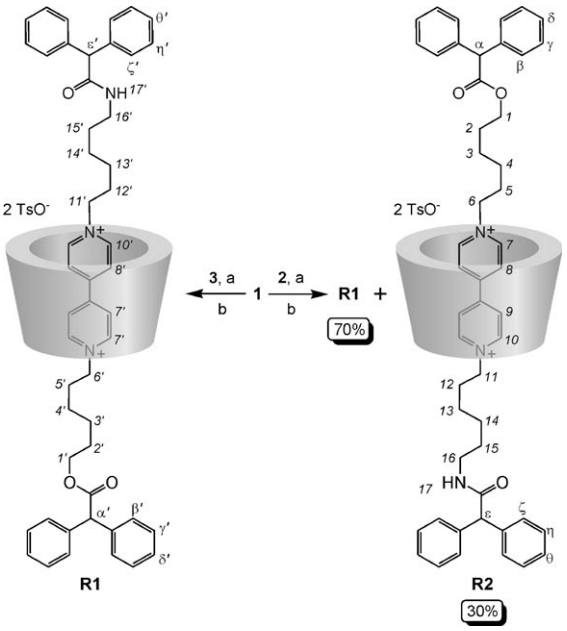
At this point, one can argue whether the lower-rim threading observed for **2** is possible, at least in principle, also for axles **4** and **5**. To investigate this issue, we carried out a new set of threading experiments using the more polar acetonitrile—a solvent in which the control elements that operate in benzene are no longer in action.[12] However, we decided to perform the ^{1}H NMR spectroscopic analysis of the reaction outcome in C_6D_6 because this solvent, owing to its large Aromatic Solvent Induced Shift (ASIS) effect, allows an unambiguous assignment of the resulting, rather complex, spectra without affecting the composition of the isomer mixture.[17] Therefore, acetonitrile was removed and the reaction products were redissolved in C_6D_6. Interestingly, an approximately 1:1 mixture of the two orientational pseudorotaxane isomers was observed for both **4** and **5**. Such a ratio did not change when the solution was heated at 343 K (see Figure S5 in the Supporting Information). It is worth emphasising that the composition of such a solution in benzene, prepared by dissolving the 1:1 isomer mixture, is different from that obtained by mixing the free axle and wheel components in benzene (see above). The above results also show that 1) the steric barrier associated with lower-rim threading of axles **4** and **5** can indeed be overcome in appropriate conditions, and 2) in acetonitrile the up and down orientational isomers are endowed with comparable stability. Point 2) is of particular importance because it shows that the relative stability of the pseudorotaxane isomers is unaffected by the distance of the stopper from the 4,4′-bipyridinium recognition site, thus excluding possible steric effects, in agreement with molecular models. The formation of a 1:1 mixture of up and down pseudorotaxanes at room temperature was also observed when these experiments were carried out using **2** as the guest. However, in this case, upon heating the solution at 340 K for 12 h the composition of the mixture changed from 1:1 to 7:3 in favor of the $[\mathbf{1}\supset\mathbf{2}]_{down}$ isomer, that is, to the same isomer ratio observed when **1** and **2** were mixed in C_6D_6 at 340 K (see above).

In summary, considering that the only remarkable difference between axle **2** and axles **4** and **5** is that **2** is equipped with a cationic ammonium head group, it is reasonable to think that the peculiar behaviour of axle **2** with respect to its threading into wheel **1** in apolar solvents is related to specific interactions between the ammonium unit of **2** and the various recognition sites incorporated in the structure of **1**.

Stoppering of the pseudorotaxanes

The successive step in our investigation was to exploit the results of the threading experiments described above for the synthesis of orientational rotaxane isomers[12] following a threading–stoppering strategy.[7]

Our findings indicate that, in apolar media, axles lacking the ammonium head enter into the wheel exclusively from the upper rim. Therefore, axle **3**, which terminates with an OH group, was employed for the synthesis of rotaxane **R1** (Scheme 4), which has a diphenylacetamido stopper at the upper rim and a diphenylacetyl stopper at the lower rim. According to a previously reported procedure,[12] a slight excess of axle **3** and wheel **1** were equilibrated at 340 K for 2 h in toluene. An excess of diphenylacetyl chloride was then added to stopper the pseudorotaxane that had formed, and the reaction mixture was stirred at 340 K for 7 days (Scheme 4). After purification by column chromatography, rotaxane **R1** was obtained in 63% yield.[18] The main features of the ^{1}H NMR spectrum of **R1**, recorded in C_6D_6, are the broad triplet at $\delta = 4.4$ ppm and the two singlets at $\delta =$ 5.19 and 5.22 ppm (Figure 4a; see Figure S6 in the Supporting Information for the full spectrum). On the basis of 2D NMR correlation experiments (Figures S7 and S8 in the Supporting Information), we assign these signals to the methylene OCH_2 *(1′)* and the methine protons ε' and α' of the axial component, respectively (see Figure 4a and Scheme 4 for numbering). The upfield shifts of the bipyridinium protons *7′*, *8′*, *9′* and *10′*, that resonate at $\delta = 7.02$, 6.60, 7.82 and 8.14 ppm, respectively, indicate that this soft cationic portion of the dumbbell is encircled by the soft aromatic π-donor domain of the wheel. ROESY experiments showed that the portion of the axle containing the ester moiety is positioned in proximity to the lower rim, whereas the amide stopper is at the upper rim of the calixarene. Indeed, in the expansion of the 2D ROESY spectrum reported in Figure 4b NOE correlations between the *tert*-butyl protons (*h*)



Scheme 4. Reagents and conditions: a) toluene, 340 K, 2 h; b) $Ph_2CHCOCl$, toluene, 340 K, 7 d.

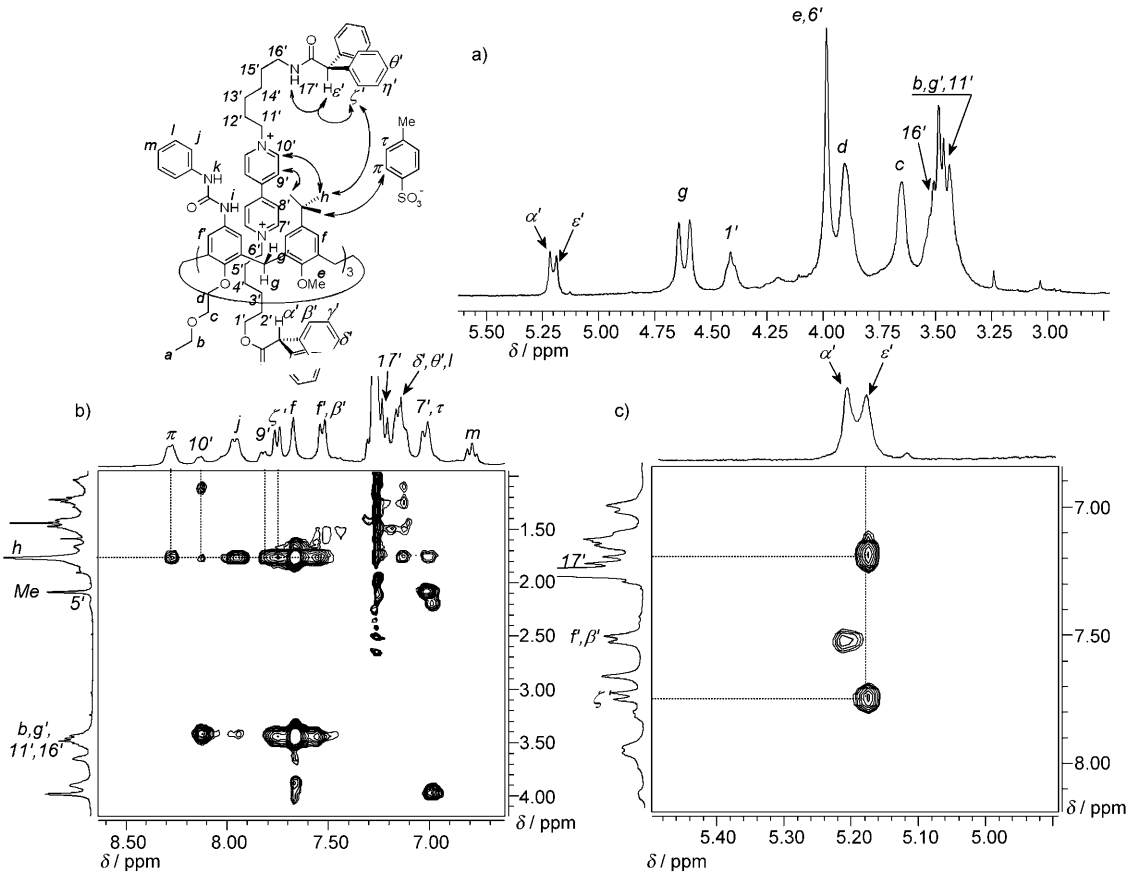


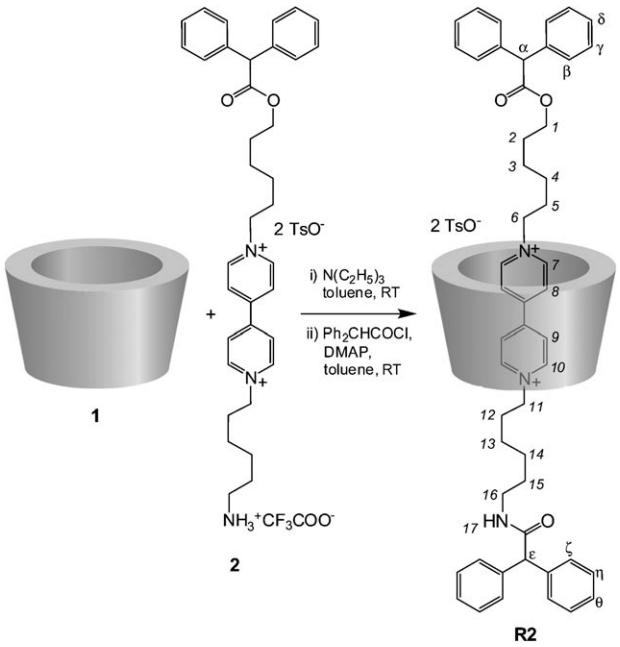
Figure 4. a) ^{1}H NMR spectrum (expanded region, 300 MHz, C_6D_6). b) and c) 2D ^{1}H–^{1}H ROESY spectrum (expanded regions, 300 MHz, C_6D_6, spin lock = 200 ms) of rotaxane **R1** showing the most representative correlations derived by the proximity of the axle–wheel protons (double arrows in the schematic representation and dotted lines in the expansions of the 2D spectrum).

of the wheel with the aromatic protons *9′* and *10′* of the bipyridinium unit are present. In addition, the NOE correlation between protons *h* of the wheel and protons *ζ′* belonging to the aromatic portion of the amide stopper, clearly confirms the orientation of the axle within the wheel.

The peculiar threading behaviour of axle **2** could open the way for the synthesis of the two orientational isomers **R1** and **R2** using only axle **2**, wheel **1** and diphenylacetyl chloride as components. It is worth noting that **R1** is obtained from upper-rim threading in the case of axle **3** and from lower-rim threading in the case of axle **2** (Scheme 4). By using the same reaction conditions adopted previously, axle **2** and wheel **1** were subjected to the threading–stoppering reaction sequence with diphenylacetyl chloride. After chromatographic purification of the resulting reaction mixture, the stoppered products were isolated in 35% yield. The ^{1}H NMR spectroscopic analysis showed that the reaction mixture contains rotaxanes **R1** and **R2** with a relative ratio of approximately 7:3, respectively (estimated from the integral of protons *1* and *1′*, see Scheme 4). Although attempts to separate these two isomers in a quantitative manner through chromatographic techniques gave unsatisfactory results, a fraction of almost pure **R1** could be isolated.

We also performed the threading–stoppering sequence described above in the presence of triethylamine, which is expected to deprotonate the ammonium head of **2**. We added diphenylacetyl chloride to the deep-red homogeneous solution obtained after mixing a slight excess of **2** to a solution of **1** in toluene at room temperature in the presence of triethylamine and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). At the end of the reaction rotaxane **R2**, obtained by upper-rim threading (Scheme 5), was isolated in 69% yield as the unique chromatographic fraction.

The signals relative to methine protons ε and α in the stopper are recognisable at $\delta = 5.08$ and 5.28 ppm, respectively, of the ^{1}H NMR spectrum of **R2** in C_6D_6 (Figure 5a; see Figure S9 in the Supporting Information for the full spectrum). As usual, the assignment of the resonances present in the spectrum of **R2** was carried out through a series of 2D NMR experiments. Several spatial correlations (ROESY, Figure S11 in the Supporting Information) were found between the protons of the phenylureido moieties of the wheel with protons *4–6* of the hexyl chain stoppered with the ester function. These data confirm that the axle chain with the ester moiety is positioned in proximity to the upper rim of the calix[6]arene wheel. The ROESY experiment also evidenced the presence of correlations between



Scheme 5.

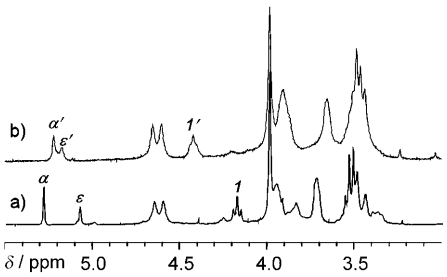


Figure 5. Portion of the ^{1}H NMR spectra (300 MHz, C_6D_6) showing the resonances of the methine proton of the two diphenylacetyl stoppers in rotaxanes a) **R2** and b) **R1**.

proton ε at $\delta = 5.08$ ppm with protons resonating at $\delta = 6.5$ and 7.7 ppm. The latter resonances were assigned, through COSY and TOCSY experiments (Figure S10 in the Supporting Information), to the protons *17* (NH) of the axle and ζ of the stopper, respectively. As a result, the signal at $\delta =$ 5.08 ppm was identified as that of the methine proton (ε) of the diphenylacetyl unit linked to the hexyl chain through the amide function.

UV/Vis spectroscopic investigations

Titration experiments: To determine the stability constants of the resulting pseudorotaxanes, we titrated compounds **2**–**5** with **1** in CH_2Cl_2 at 293 K.[19,20] In all cases, upon addition of the wheel to the axle solution we observed the appearance of absorption features in the spectral region comprised between 320 and 600 nm (Figure 6) which can be attributed to charge-transfer interactions between the π-electron-accepting 4,4′-bipyridinium unit of the axles and the π-electron-rich aromatic cavity of the wheel.[11,13,21] The titration

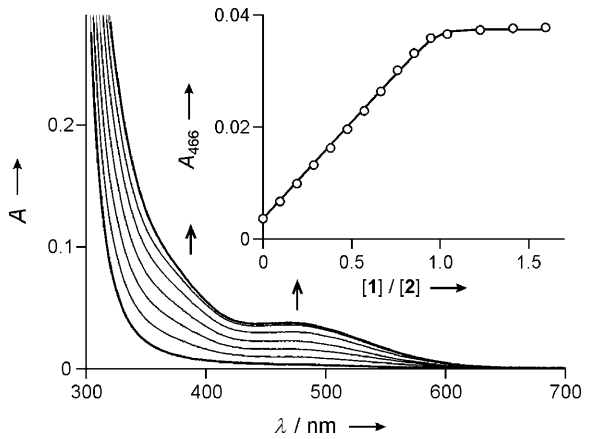


Figure 6. UV-visible absorption spectral changes observed upon titration of axle **2** (1.6×10^{-5} M) with increasing aliquots of a 1.15×10^{-3} M solution of wheel **1** in CH_2Cl_2 at 293 K. The inset shows the corresponding titration data obtained by monitoring the absorbance at 466 nm (○) and the fit according to a 1:1 association model (——). The optical path length was 5.00 cm.

curves (see, e.g., Figure 6, inset) were satisfactorily fitted with a 1:1 association model; the corresponding apparent stability constants are gathered in Table 1. On the basis of the results of the NMR spectroscopy characterisation, these values are obviously referred to the up orientational isomers.[20]

Table 1. Thermodynamic and kinetic parameters for the self-assembly of the examined pseudorotaxanes (CH_2Cl_2, 293 K).

Complex	Log K[a]	ΔG°_{293}[b] [kJ mol^{-1}]	$k_1\times10^{-7}$[c] [M^{-1}s^{-1}]	$\Delta H^{\neq}$[d] [kJ mol^{-1}]	$\Delta S^{\neq}$[d] [J K^{-1}mol^{-1}]
$[\mathbf{1}\supset\mathbf{2}]_{up}$	7.0 ± 0.6	-39 ± 3	2.9 ± 0.2	-8 ± 1	-126 ± 3
$[\mathbf{1}\supset\mathbf{3}]_{up}$	6.8 ± 0.2	-38 ± 1	9.6 ± 0.6	15 ± 2	-41 ± 5
$[\mathbf{1}\supset\mathbf{4}]_{up}$	6.7 ± 0.4	-38 ± 3			
$[\mathbf{1}\supset\mathbf{5}]_{up}$	7.2 ± 0.5	-40 ± 3			

[a] Apparent stability constant for the pseudorotaxanes. [b] Standard free-energy change at 293 K associated with the self-assembly process. [c] Threading rate constant. [d] Activation parameters obtained from Eyring plots.

All the values are quite large and identical within the experimental error, suggesting that the stability of the complexes derived from upper-rim threading is not affected by the nature of the head and/or the stopper unit of the axle component. In particular, the comparison between the stability constants of $[\mathbf{1}\supset\mathbf{4}]_{up}$ and $[\mathbf{1}\supset\mathbf{5}]_{up}$ (Table 1) shows that the stopper does not hamper the formation of the complex even if it is just three methylene units away from the bipyridinium unit.

To gather more information on the self-assembly processes, we performed temperature-dependent experiments for the two prototypical compounds **2** and **3**, which have a cationic (ammonium) and a neutral (hydroxy) head group, respectively. The range of temperatures that could be explored (from 277 K to 303 K) is limited by the low boiling point of CH_2Cl_2;[19] in this range, according to the NMR spectroscopy

data, we are most likely to be dealing with pseudorotaxanes obtained by upper-rim threading. The stability constants of the two complexes $[\mathbf{1}\supset\mathbf{2}]_{up}$ and $[\mathbf{1}\supset\mathbf{3}]_{up}$ are almost temperature independent (Table S1 in the Supporting Information), indicating that the association between the components is entropically driven. This finding could suggest that, as previously noticed,[11,13] solvophobic effects play a role in the self-assembly process.

Stopped-flow experiments: We studied the kinetics of association between wheel **1** and axles **2** and **3** in CH_2Cl_2 by means of stopped-flow spectrophotometry. The threading processes of both axles from the upper rim of the wheel are characterised by second-order rate constants higher than $10^7\,M^{-1}s^{-1}$ (Figure 7 and Table 1). Temperature-dependent

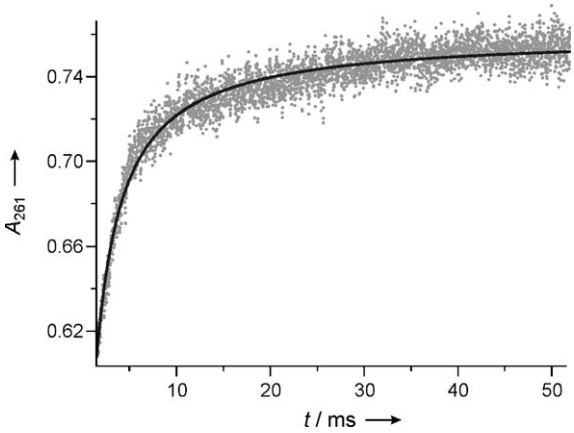


Figure 7. Stopped-flow kinetic trace recorded at 293 K for the absorbance change at 261 nm obtained upon mixing **1** and **2** in equimolar amounts in CH_2Cl_2. The solid line represents the data fitting according to a second-order rate equation. The concentration of the compounds after mixing was 1.0×10^{-5} M and the optical path length was 1.00 cm.

kinetic experiments were also performed in the range 277–303 K (Table S1 in the Supporting Information). Despite the limited temperature range, the Eyring plots (Figure 8) show a poor linearity, an observation which indicates that the self-assembly of these pseudorotaxanes are mechanistically complex phenomena.[22] Nevertheless, it is interesting to note that the temperature dependence of the threading rate constant is opposite for the two axles; in particular, negative and positive values for the activation enthalpy $\Delta H^{\neq}$ are found for the threading of axles **2** and **3**, respectively (Table 1). Dethreading rate constants, calculated as the ratio between the threading rate constants and the stability constants (Table S1 in the Supporting Information), are in the order of $10\,s^{-1}$.

Discussion

The axle and wheel components presented in this work are nonsymmetric; therefore, as depicted in Figure 2, two different orientational isomers can exist for the pseudorotaxanes corresponding to each axle–wheel combination.

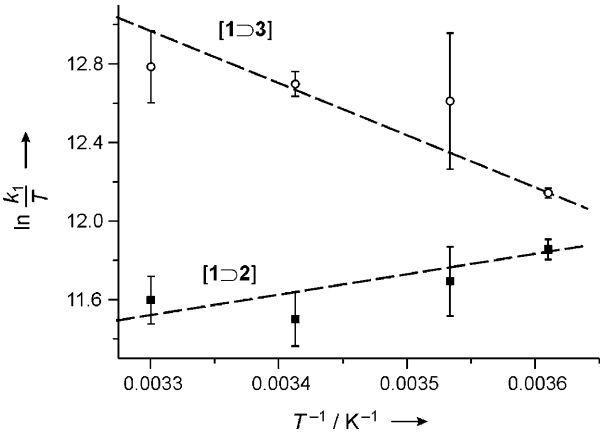


Figure 8. Temperature dependence (Eyring plot) of the threading rate constants of wheel **1** with axles **2** (■) and **3** (○) in the temperature range 277–303 K in CH_2Cl_2.

The central questions that arise in the interpretation of our results are as follows: 1) Is the different behaviour of the axles examined mainly related to thermodynamic or kinetic effects? 2) Which structural elements built in the molecular components are responsible for the control of the threading outcome? The answers to these questions are not easily found in the case of the present self-assembling systems. In this section we will try to address the above issues by combining all of the pieces of information that we have obtained from our multi-faceted experimental study.

Firstly, in apolar media at room temperature all of the axles enter the cavity exclusively from the upper rim. Such behaviour can have two different explanations: 1) the threading from the lower rim is kinetically disfavoured, or 2) the pseudorotaxane derived from lower-rim threading is thermodynamically unstable. Hypothesis 2, however, can be ruled out because, while the up isomer is the sole product obtained on mixing free wheel and axle, a previously prepared 1:1 mixture of the pseudorotaxane isomers does not equilibrate to yield the up species at the expense of the down isomer. Such behaviour clearly indicates that the threading process is kinetically controlled. Furthermore, it can be recalled that in CH_3CN both orientational isomers exhibit comparable stabilities, and the examined stoppers and head groups do not affect the stability of the corresponding up pseudorotaxanes in CH_2Cl_2. Indeed, molecular models show that the presence of the stopper on the lower rim does not cause an appreciable steric hindrance. Therefore, a difference in the relative stability of the two orientational isomers large enough that one of them would not be detected in NMR spectroscopy experiments[23] is not justified on the basis of these observations.

In this framework, the fact that lower-rim threading is kinetically blocked, whereas upper-rim threading is remarkably fast, can be accounted for by considering that 1) the methoxy groups at the lower rim, pointing towards the interior

of the cavity in apolar solvents (see Figure 9a), prevent the slipping of a molecular guest from this side, and 2) the ureidic anion receptors at the upper rim assist the rupture of the ion pair, which is a prerequisite for the insertion of the cationic axle into the wheel. These kinetic control elements are practically switched off in CH_3CN because in this solvent the methoxy groups at the lower rim point outward,[6b] and cation–anion interactions as well as anion coordination by hydrogen bonding are less important than in CH_2Cl_2.

Upon heating to 340 K, the up pseudorotaxanes obtained with axles **3**, **4** and **5** in benzene at room temperature did not isomerise. On the other hand, when a 1:1 mixture of orientational isomers (obtained in acetonitrile) was redissolved in benzene and heated, no change in the isomeric ratio was detected either. These observations clearly show that the threading process for axles **3**–**5** is under kinetic control, even at 340 K.

The behaviour of the ammonium-terminated axle **2** at 340 K in apolar solvents is the most interesting: it is the only guest that, at this temperature, is capable of threading the wheel from the lower rim. The fact that the same ratio of orientational isomers is obtained irrespective of the starting state (free components or 1:1 mixture of up and down pseudorotaxanes) suggests that, in this case, the self-assembly process is thermodynamically controlled, with the down isomer being slightly more favoured than the up one.

The peculiar behaviour of axle **2** must be related to the presence of the ammonium head group, which is a positively charged unit with hydrogen-bond donor capabilities. The fact that $[\mathbf{1}\supset\mathbf{2}]_{down}$ (Figure 9c) is more stable than the up isomer (Figure 9e) can be explained by considering that the ureidic units at the upper rim, which can act as both donors and acceptors of hydrogen bonds, are capable of binding the ammonium head group as well as coordinating its counteranion. The ability of **2** to slip through the lower rim at high temperature may be again related to the hydrogen-bonding properties of the ammonium unit. We hypothesise that the transition state corresponding to lower-rim threading/dethreading is stabilised by coordination of the ammonium group by the crown of oxygen atoms at the lower rim (Figure 9b), thereby forcing the methoxy units to point outward and rendering the cavity accessible from this side. We can also speculate that the negative value of the activation enthalpy corresponding to upper-rim threading/dethreading of **2** at around room temperature (Figure 8 and Table 1) may reflect the binding ability of the ammonium head group towards the ureidic units located at the upper rim (Figure 9d).

In summary, our results indicate that the ammonium head group of axle **2** represents, as a matter of fact, a second recognition site (besides the 4,4′-bipyridinium unit) affecting the pseudorotaxane self-assembly process from both kinetic and thermodynamic viewpoints. Such a construction is further supported by the fact that, on switching off the recognition properties of the ammonium head group by deprotonation, compound **2** seems to behave similarly to axles **3**–**5**, which have a dumb head group.

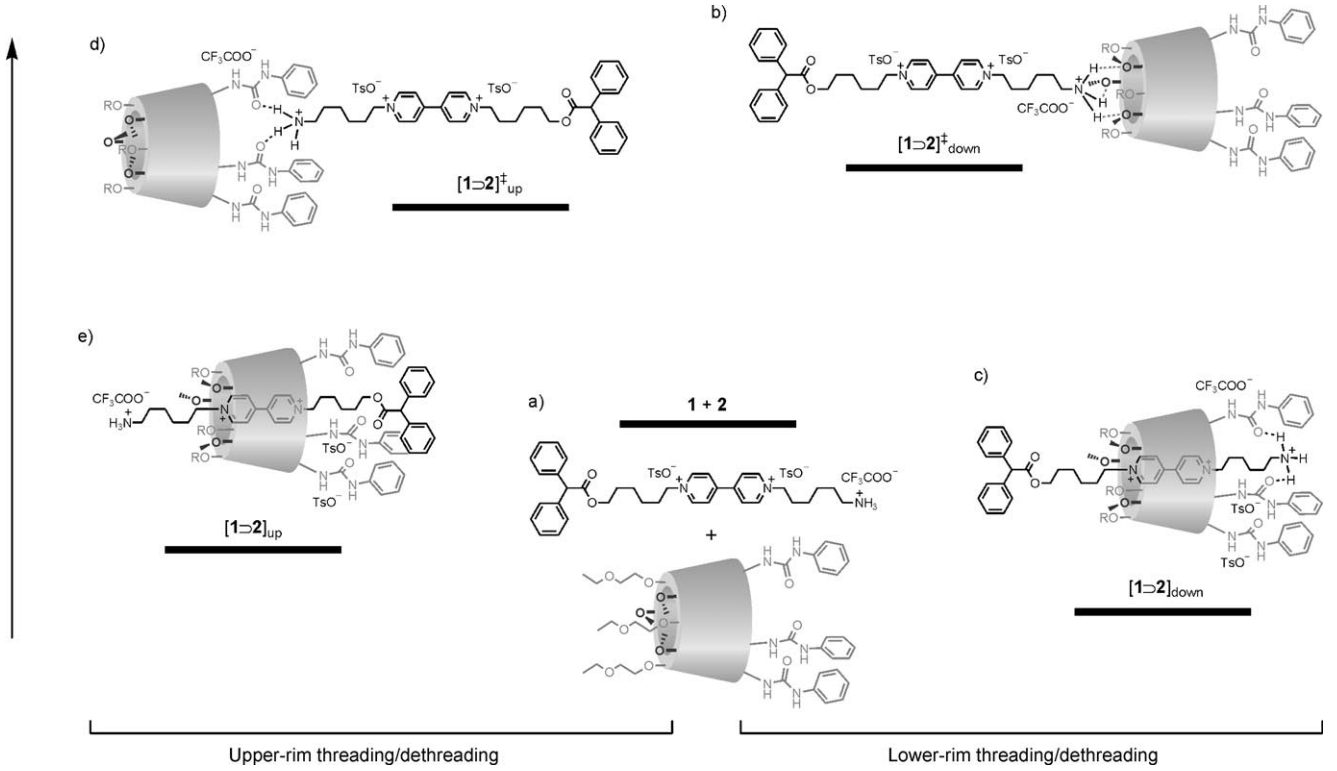


Figure 9. Simplified potential-energy diagram for the threading/dethreading processes of axle **2** into wheel **1**, and schematic representation of the possible structures of the species involved. See the text for more details.

Conclusion

We have designed, synthesised and investigated a family of pseudorotaxanes made of a tris(phenylureido)calix[6]arene wheel and rivet-like axles containing a 4,4′-bipyridinium unit. As the axle and wheel components are nonsymmetric, two different orientational isomers, up and down, can exist for each of the pseudorotaxanes examined (Figure 2).

At room temperature in apolar solvents we found that all axles thread the wheel from the upper rim for kinetic reasons. At higher temperature (340 K), the self-assembly processes of axles with uncharged head groups (**3**–**5**) are still kinetically controlled, and yield the up pseudorotaxane isomer as the sole threading product. Conversely, the axle with an ammonium head group (**2**) is capable of entering the cavity from the lower rim at 340 K; in this case the self-assembly is under thermodynamic control and the down isomer is the favoured threading product. We have exploited these features to implement the straightforward synthesis of orientational rotaxane isomers.

Our observations suggest that specific interactions between the ammonium head group of the axle and the two rims of the wheel can act as thermodynamic and kinetic control elements for the self-assembly process. These results represent a remarkable step forward for the construction of instructed chemical systems[2a,24] in which not only the equilibrium states but also the dynamic behaviour could be carefully controlled. Progress in such a direction will be significant for the development of advanced template-directed synthetic protocols.[25] Moreover, studies of this kind are an important premise for the design and construction of multicomponent molecular species in which ratcheting effects[2h,26] allow a full directional control of the intercomponent molecular motions.

Experimental Section

Synthesis of the compounds: Toluene and dichloromethane were dried using standard procedure, all other reagents were of reagent grade quality as obtained from commercial suppliers and were used without further purification. ^{1}H and ^{13}C spectra were recorded at 300 and 75 MHz respectively. Chemical shifts are expressed in ppm (δ) using the residual solvent signals as an internal reference. Mass spectra were determined in the ESI mode. Compounds **1**,[6b] **10**,[12] **14**,[27] **16**[27] and **19**[28] were synthesised according to literature procedures.

***N*-Boc-6-aminohexan-1-ol (7)**: Di-*tert*-butyl dicarbonate (11.5 g, 52.7 mmol) was added to a solution of **6** (3 g, 26 mmol) in a 9:1 (v/v) mixture of methanol/triethylamine (250 mL). After stirring under reflux for 1 h, the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (100 mL) and water (100 mL). The separated organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **7** as an oily compound (5.5 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0–1.5 (m, 17H), 2.9 (brs, 2H), 3.39 (t, ^3J(H,H) = 6.6 Hz, 2H), 3.50 (s, 1H), 5.0 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 26.3, 28.3, 29.9, 40.4, 62.3, 79.1, 156.1 ppm; ESI-MS(+): *m*/*z* (%): 240.1 (100); elemental analysis calcd (%) for $C_{11}H_{23}NO_3$: C 60.80, H 10.67, N 6.45; found: C 60.55, H 10.71, N 6.38.

6-(*tert*-Butoxycarbonylamino)hexyl tosylate (8): A solution of tosyl chloride (6.3 g, 33.3 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of **7** (5.6 g, 25.8 mmol), triethylamine (3.9 g, 38.4 mmol) and DMAP (0.12 g, 1 mmol) in CH_2Cl_2 (100 mL). After stirring for 48 h at room temperature, the reaction was quenched with water (100 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and filtered. The organic solvent was removed under reduced pressure and the oily residue was purified by column chromatography (*n*-hexane/ethyl acetate 9:1) to afford **8** as a white solid (7.7 g, 81%). M.p. 61.6–62.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2–1.3 (m, 4H), 1.3–1.4 (m, 11H), 1.5–1.4 (m, 2H), 2.32 (s, 3H), 2.9–3.0 (m, 2H); 3.95 (t, ^3J(H,H) = 6.6 Hz, 2H), 4.6 (brs, 1H), 7.31 (d, ^3J(H,H) = 8 Hz, 2H), 7.77 ppm (d, ^3J(H,H) = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 24.9, 26.0, 28.3, 28.6, 29.7, 40.3, 70.4, 127.7, 129.7, 133.0, 144.6, 155.9 ppm; ESI-MS(+): *m*/*z* (%): 394.0 (100); elemental analysis calcd (%) for $C_{18}H_{29}NO_5S$: C 58.20, H 7.87, N 3.77, S 8.63; found: C 58.53, H 7.61, N 3.45, S 8.24.

1-[6-(*tert*-Butoxycarbonylamino)hexyl]-4,4′-bipyridin-1-ium tosylate (9): Tosylate **8** (0.3 g, 0.8 mmol) was added to a solution of 4,4′-bipiridyne (0.2 g, 1.3 mmol) in acetonitrile (50 mL),. After stirring under reflux for 72 h, the solvent was removed under reduced pressure to afford a crude oily residue that was triturated twice with ethyl acetate (2×25 mL) to afford **9** as a white solid (0.37 g, 84%). M.p. 157–159 °C; ^{1}H NMR (300 MHz, CD_3CN): δ = 1.3–1.5 (m, 15H), 1.9–2.0 (m, 2H), 2.29 (s, 3H), 2.97 (q, ^3J(H,H) = 6.3 Hz, 2H), 4.56 (t, ^3J(H,H) = 7.5 Hz, 2H), 5.4 (brs, 1H), 7.12 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.59 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.78 (d, ^3J(H,H) = 7.2 Hz, 2H), 8.30 (d, ^3J(H,H) = 7.2 Hz, 2H), 8.81 (d, ^3J(H,H) = 7.2 Hz, 2H), 8.88 ppm (d, ^3J(H,H) = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 19.1, 24.6, 25.0, 26.6, 28.5, 30.2, 38.8, 60.5, 121.4, 121.9, 124.8, 125.0, 127.7, 133.7, 139.5, 141.5, 144.3, 149.6, 152.9 ppm; ESI-MS(+): *m*/*z* (%): 300 (100), 356 (70); elemental analysis calcd (%) for $C_{28}H_{37}N_3O_5S$: C 63.73, H 7.07, N 7.96, S 6.08; found: C 64.14, H 7.11, N 7.85, S 5.99.

1-[6-(*tert*-Butoxycarbonylamino)hexyl]-1′-[6-(2,2-diphenylacetoxy)hexyl]-4,4′-bipyridine-1,1′-diium ditosylate (11): A catalytic amount of KI was added to a solution of compounds **9** (0.38 g, 0.6 mmol) and **10** (0.75 g, 1.6 mmol) in acetonitrile (20 mL). The resulting mixture was heated at reflux for 15 days and then cooled to room temperature. Axle **7** was recovered from the mixture by suction filtration as a yellow solid that was triturated twice (2×20 mL) with ethyl acetate to afford **11** as a white solid (0.58 g, 90%). M.p. 116–118 °C; ^{1}H NMR (300 MHz, CD_3OD): δ = 1.3–1.5 (m, 19H), 1.5–1.7 (m, 2H), 1.9–2.0 (m, 4H), 2.34 (s, 6H), 3.01 (t, ^3J(H,H) = 6.3 Hz, 2H), 4.13 (t, ^3J(H,H) = 6.6 Hz, 2H), 4.6–4.7 (m, 4H), 5.06 (s, 1H), 7.2–7.4 (m, 14H), 7.69 (d, ^3J(H,H) = 8.1 Hz, 4H), 8.59 (d, ^3J(H,H) = 6.6 Hz, 4H), 9.16 (d, ^3J(H,H) = 6.6 Hz, 2H), 9.20 ppm (d, ^3J(H,H) = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 21.6, 26.5, 26.8, 27.0, 27.4, 29.1, 29.5, 30.9, 32.6, 32.7, 41.3, 58.5, 63.4, 63.5, 66.1, 127.2, 128.6, 129.9, 130.0, 130.1, 140.6, 142.0, 143.8, 147.3, 151.5 ppm; ESI-MS(+): *m*/*z* (%): 300 (80), 452 (100), 651 (25); elemental analysis calcd (%) for $C_{55}H_{67}N_3O_{10}S_2$: C 66.44, H 6.79, N 4.23, S 6.45; found: C 66.73, H 6.81, N 4.02, S 6.23.

Axle (2): A solution of **11** (0.3 g, 0.3 mmol) in trifluoroacetic acid (10 mL) was stirred at room temperature for 1 h. The solvent was completely removed under reduced pressure to give **2** as yellowish oil (0.25 g, 95%). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.4 (brs, 4H), 1.5 (brs, 4H), 1.6–1.7 (m, 4H), 1.9–2.2 (m, 4H), 2.30 (s, 6H), 2.92 (t, ^3J(H,H) = 6.5 Hz, 2H), 4.13 (t, ^3J(H,H) = 6.5 Hz, 2H), 4.65 (t, ^3J(H,H) = 7.5 Hz, 2H), 4.72 (t, ^3J(H,H) = 7.5 Hz, 2H), 5.06 (s, 1H), 7.1–7.3 (m, 14H), 7.68 (d, ^3J(H,H) = 8.1 Hz, 4H), 8.60 (d, ^3J(H,H) = 6.0 Hz, 4H), 9.17 (d, ^3J(H,H) = 6.0 Hz, 2H), 9.22 ppm (d, ^3J(H,H) = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 21.6, 26.5, 26.8, 27.0, 28.4, 29.5, 32.4, 32.6, 40.7, 58.5, 63.3, 63.4, 66.1, 127.2, 128.6, 129.9, 130.0, 130.1, 140.6, 142.1, 143.9, 147.4, 151.5, 151.6, 174.5 ppm; ESI-MS(+): *m*/*z* (%): 452 (95), 551 (100); elemental analysis calcd (%) for $C_{52}H_{60}F_3N_3O_{10}S_2$: C 61.95, H 6.00, N 4.17, S 6.36; found: C 62.07, H 6.13, N 4.12, S 6.29.

***N*-(6-Hydroxyhexyl)-2,2-diphenylacetamide (12)**: Diphenylacetyl chloride (0.39 g, 1.71 mmol) was added to a solution of 6-aminohexan-1-ol **6** (0.2 g, 1.71 mmol) and triethylamine (0.21 g, 2.0 mmol) in acetonitrile (20 mL). The resulting solution was stirred at room temperature for 12 h. The solvent was then removed under reduced pressure and the resulting solid residue taken up with ethyl acetate (20 mL) and with a 10% (w/v)

aqueous solution of HCl (20 mL). The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the solid residue was purified by column chromatography (hexane/ethyl acetate 3:7) to afford **12** as colourless oil (0.48 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2–1.4 (m, 4H), 1.4–1.6 (m, 4H), 2.4 (br s, 1H), 3.27 (q, ^3J(H,H) = 6.3 Hz, 2H), 3.58 (t, ^3J(H,H) = 6.3 Hz, 2H), 4.93 (s, 1H), 5.6 (br s, 1H), 7.2–7.4 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 29.3, 32.3, 39.6, 56.9, 59.1, 62.5, 127.2, 128.6, 128.8, 139.4, 171.8 ppm; ESI-MS(+): *m/z* (%): 335 (100); elemental analysis calcd (%) for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N 4.50; found: C 77.25, H 8.01, N 4.55.

6-(2,2-Diphenylacetamido)hexyl tosylate (13): Tosyl chloride (0.23 g, 1.22 mmol) and a catalytic amount of DMAP were added to a solution of compound **12** (0.25 g, 0.81 mmol) and triethylamine (0.17 g, 1.62 mmol) in CH_2Cl_2 (20 mL). After stirring for 12 h at room temperature, the reaction was quenched with water (20 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and filtered. The organic solvent was removed under reduced pressure and the oily residue was purified by column chromatography (hexane/ethyl acetate 7:3, then 6:4) to afford **13** as a colourless oil (0.17 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1–1.4 (m, 4H), 1.4–1.5 (m, 2H), 1.5–1.7 (m, 2H), 2.43 (s, 3H), 3.2 (br s, 2H), 3.98 (t, ^3J(H,H) = 6.3 Hz, 2H), 4.90 (s, 1H), 5.8 (br s, 1H), 7.2–7.4 (m, 12H), 7.76 ppm (d, ^3J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.0, 28.6, 29.2, 39.5, 59.0, 70.4, 127.1, 127.8, 128.6, 128.8, 129.8, 133.0, 139.5, 144.7, 171.8 ppm; ESI-MS(+): *m/z* (%): 316 (100), 489 (97); elemental analysis calcd (%) for $C_{27}H_{31}NO_4S$: C 69.65, H 6.71, N 3.01, S 6.89; found: C 69.82, H 6.75, N 2.99, S 6.75.

1-(6-Hydroxyhexyl)-4,4′-bipyridin-1-ium tosylate (15): 6-hydroxyhexyl tosylate (**14**) (1.29 g, 4.73 mmol) and 4,4′-bipiridyne (1.1 g, 7.1 mmol) were dissolved in acetonitrile (100 mL) and heated at reflux overnight. The solvent was then removed under reduced pressure to afford a crude solid residue that was triturated with ethyl acetate (2×25 mL) to give **15** as a white solid (0.60 g, 30%). M.p. 202–205 °C; ^{1}H NMR (300 Hz, CD_3CN): δ = 1.2–1.5 (m, 6H), 1.9–2.0 (m, 2H), 2.26 (s, 3H), 3.42 (t, ^3J(H,H) = 6.1 Hz, 2H), 4.57 (t, ^3J(H,H) = 7.6 Hz, 2H), 7.10 (d, ^3J(H,H) = 7.9 Hz, 2H), 7.59 (d, ^3J(H,H) = 7.9 Hz, 2H), 7.78 (d, ^3J(H,H) = 6.1 Hz, 2H), 8.29 (d, ^3J(H,H) = 6.1 Hz, 2H), 8.79 (d, ^3J(H,H) = 6 Hz, 2H), 8.93 ppm (d, ^3J(H,H) = 6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ = 20.9, 25.5, 25.9, 31.5, 32.7, 61.8, 122.6, 126.3, 126.5, 127.7, 129.1, 139.5, 141.8, 145.9, 151.5, 153.8 ppm; ESI-MS(+): *m/z* (%): 257 (100); elemental analysis calcd (%) for $C_{23}H_{28}N_2O_4S$: C 64.46, H 6.59, N 6.54, S 7.48; found: C 64.52, H 6.44, N 6.61, S 7.32.

Axle (3): A catalytic amount of KI was added to a solution of **13** (0.15 g, 0.32 mmol) and **15** (0.28 g, 0.64 mmol) in acetonitrile (20 mL). The reaction mixture was heated under reflux for 15 days. The resulting heterogeneous solution was cooled to room temperature to afford a yellow solid precipitate of **3** (0.12 g, 40%), which was collected by filtration. M.p. 133–135 °C; ^{1}H NMR (300 MHz, CD_3OD): δ = 1.2–1.6 (m, 12H), 1.9–2.1 (m, 4H), 2.34 (s, 6H), 3.2 (br s, 2H), 3.55 (t, ^3J(H,H) = 6.3 Hz, 2H), 4.6–4.7 (m, 4H), 4.94 (s, 1H), 7.2–7.3 (m, 14H), 7.66 (d, ^3J(H,H) = 8.1 Hz, 4H), 8.6 (br s, 4H), 9.17 (d, ^3J(H,H) = 6.6 Hz, 2H), 9.21 ppm (d, ^3J(H,H) = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 21.6, 26.7, 26.8, 27.3, 30.2, 30.7, 32.6, 32.8, 33.5, 40.3, 59.4, 62.9, 63.4, 63.5, 127.2, 128.3, 128.6, 129.3, 129.7, 130.2, 131.4, 141.6, 142.0, 144.0, 47.3, 151.5, 174.9 ppm; ESI-MS(+): *m/z* (%): 450 (35), 551 (100); elemental analysis calcd (%) for $C_{50}H_{59}N_3O_8S_2$: C 67.16, H 6.65, N 4.70, S 7.17; found: C 67.20, H 6.58, N 6.62, S 7.09.

3-(Tosyloxy)propyl 2,2-diphenylacetate (17): A solution of tosylate **16** (2.5 g, 10 mmol) and diphenylacetylchloride (2.3 g, 10 mmol) in THF (100 mL) was stirred at room temperature for 48 h. The reaction mixture was then diluted with water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the oily residue was purified by column chromatography (hexane/ethyl acetate 75:25) to afford **17** as a yellowish oil (2.67 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 2.45 (m, 2H), 3.66 (t, ^3J(H,H) = 6.1 Hz, 2H), 4.10 (t, ^3J(H,H) = 6.3 Hz, 2H), 5.05 (s, 1H), 7.3–7.4 (m, 12H), 7.81 ppm (d, ^3J(H,H) = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 28.4, 56.9, 60.8, 66.9, 127.4, 127.6, 128.2, 128.4, 132.8, 138.8, 143.6, 172.2 ppm; ESI-MS(+): *m/z* (%): 423 (100); elemental analysis calcd (%) for $C_{24}H_{24}O_5S$: C 67.90, H 5.70, S 7.55; found: C 67.92, H 5.80, S 7.48.

1-[3-(2,2-Diphenylacetoxy)propyl]-4,4′-bipyridin-1-ium tosylate (18): A solution of **16** (0.64 g 1.5 mmol) and 4,4′-bipiridyne (0.47 g, 3 mmol) in acetonitrile (50 mL) was heated at reflux for 48 h. After this period, the solvent was evaporated to dryness under reduced pressure. Purification of the crude solid residue by precipitation from a mixture hexane/CH_2Cl_2 afforded **18** as a yellow solid (0.5 g, 57%). M.p. 53–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.3–2.4 (m, 2H), 4.14 (t, ^3J(H,H) = 5.4 Hz, 2H), 4.79 (t, ^3J(H,H) = 6.6 Hz, 2H), 4.97 (s, 1H), 7.07 (d, ^3J(H,H) = 8.0 Hz, 2H), 7.2–7.3 (m, 10H), 7.53 (d, ^3J(H,H) = 6.5 Hz, 2H), 7.72 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.96 (d, ^3J(H,H) = 6.5 Hz, 2H), 8.76 (d, ^3J(H,H) = 6.5 Hz, 2H), 9.03 ppm (d, ^3J(H,H) = 6.6 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$): δ = 19.0, 27.9, 54.3, 56.5, 59.1, 119.2, 123.7, 123.6, 125.2, 126.4, 126.5, 136.1, 137.3, 138.8, 141.4, 143.7, 148.9, 151.1, 169.9 ppm; ESI-MS(+): *m/z* (%): 409 (100); elemental analysis calcd (%) for $C_{34}H_{32}N_2O_5S$: C 70.32, H 5.55, N, 4.82, S 5.52; found: C 70.14, H 5.50, N 4.77, S 5.61.

Axle 5: A solution of **18** (0.5 g, 0.9 mmol) and tosylate **19** (0.4 g, 2.3 mmol) in acetonitrile (50 mL) was poured in a sealed glass reactor where the reaction mixture was heated at 100 °C (**CAUTION!**) for 48 h. After cooling to room temperature, the reaction mixture was transferred from the reactor and the solvent was evaporated to dryness under reduced pressure. Purification of the crude solid residue by precipitation from a mixture CH_3CN/ethyl acetate afforded **5** as a white solid (0.45 g, 62%). M.p. 117–120 °C; ^{1}H NMR (300 MHz, CD_3CN): δ = 0.89 (t, ^3J(H,H) = 4.5 Hz, 3H), 1.3–1.4 (m, 4H), 1.9–2.0 (m, 2H), 2.24 (s, 6H), 2.3–2.4 (m, 2H), 4.24 (t, ^3J(H,H) = 5.9 Hz, 2H), 4.6–4.7 (m, 4H), 5.01 (s, 1H), 7.12 (d, ^3J(H,H) = 8.1 Hz, 4H), 7.2–7.3 (m, 10H), 7.58 (d, ^3J(H,H) = 6.9 Hz, 2H), 8.33 (d, ^3J(H,H) = 8.2 Hz, 4H), 8.46 (d, ^3J(H,H) = 6.9 Hz, 2H), 8.85 (d, ^3J(H,H) = 6.9 Hz, 2H), 8.97 ppm (d, ^3J(H,H) = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ = 16.2, 23.4, 24.9, 30.8, 32.7, 33.8, 59.1, 62.3, 64.8, 65.0, 120.5, 128.9, 130.0, 130.1, 130.3, 131.6, 133.1, 142.2, 147.6, 152.1, 175.1 ppm; ESI-MS(+): *m/z* (%): 651 (100); elemental analysis calcd (%) for $C_{46}H_{50}N_2O_8S_2$: C 67.13, H 6.12, N 3.40, S 7.79; found: C 67.24, H 6.00, N 3.33, S 7.82.

Rotaxane R1: Axle **3** (0.04 g, 0.04 mmol) was suspended in a solution of **1** (0.11 g, 0.08 mmol) in dry toluene (10 mL). The resulting heterogeneous mixture was stirred and heated at 70 °C until the solution turned to a deep-red colour (≈2 h). Diphenylacetyl chloride (0.01 g, 0.06 mmol) was then added and the reaction mixture was heated at 70 °C for a further 7 days. The solvent was completely removed under reduced pressure and the reddish solid residue containing a mixture of the two rotaxanes was purified by column chromatography (CH_2Cl_2/methanol 20:1; R_f = 0.3) to afford **R1** as a red solid (0.06 g, 63%). M.p. 301–303 °C; ^{1}H NMR (300 MHz, C_6D_6,): δ = 0.9 (br s, 2H), 1.0 (br s, 2H), 1.1–1.3 (m, 11H), 1.4–1.6 (m, 4H), 1.7 (br s, 2H), 1.77 (s, 27H), 1.8–2.0 (m, 4H), 2.09 (s, 6H), 2.2 (br s, 2H), 3.4–3.6 (m, 14H), 3.7 (br s, 6H), 3.9 (br s, 6H), 4.0 (br s, 11H), 4.4 (br s, 2H), 4.62 (d, ^2J(H,H) = 15 Hz, 2H), 5.19 (s, 1H), 5.22 (s, 1H), 6.6 (br d, 2H), 6.79 (t, ^3J(H,H) = 6.9 Hz, 3H), 6.9–7.1 (m, 8H), 7.1–7.2 (m, 15H), 7.2–7.4 (m, 7H), 7.53 (d, ^3J(H,H) = 7.6 Hz, 8H), 7.68 (s, 3H), 7.75 (d, ^3J(H,H) = 7.6 Hz, 8H), 7.8 (br d, 2H), 8.0 (br d, 6H), 8.1 (br s, 2Hs), 8.3 ppm (br d, 4H); ^{13}C NMR (75 MHz, C_6D_6): δ = 15.6, 21.2, 25.3, 25.9, 28.0, 28.7, 29.6, 30.1, 30.2, 30.8, 31.8, 31.9, 34.9, 39.4, 40.1, 57.7, 59.4, 60.7, 61.4, 65.1, 66.7, 70.3, 72.4, 117.1, 118.5, 121.6, 121.8, 125.0, 126.1, 126.9, 127.4, 132.5, 134.2, 137.9, 139.6, 139.9, 140.7, 171.3, 141.5, 143.3, 143.5, 144.7, 146.5, 148.5, 153.2, 153.9, 172.2 ppm; ESI-MS(+): *m/z* (%): 1105 (100) [**R1**–2Ts$^-$]$^{2+}$, 2210 [**R1**–H]$^+$; elemental analysis calcd (%) for $C_{154}H_{177}N_9O_{21}S_2$: C 72.42, H 6.98, N 4.94, S 2.51; found: C 72.85, H 6.77, N 4.72, S 2.39.

Rotaxane R2: Axle **2** (0.04 g, 0.04 mmol) was suspended in a solution of **1** (0.06 g, 0.04 mmol) in dry toluene (10 mL), and the resulting colorless solution was stirred at room temperature. After 2 h, when the solution was homogeneous, diphenylacetyl chloride (0.01 g, 0.05 mmol), triethylammine (0.01 g, 0.08 mmol) and a catalytic amount of DMAP were added. After 5 h the solvent was completely removed under reduced pressure and the reddish solid residue was purified by column chroma-

tography (CH_2Cl_2/methanol 20:1) to afford **R2** as a red solid (0.07 g, 69%). M.p. 251–253 °C; ^{1}H NMR (300 MHz, C_6D_6): δ = 0.5–0.7 (m, 4H), 0.8–1.0 (m, 2H), 1.18 (t, ^3J(H,H) = 6.9 Hz, 9H), 1.24 (brs 2H), 1.3–1.5 (m, 2H), 1.6 (brs, 6H), 1.78 (s, 27H), 2.1 (brs, 2H), 3.3–3.4 (m, 2H), 3.4–3.6 (m, 10H), 3.7 (brs, 6H), 3.8 (brs, 2H), 3.9 (brs, 6H), 3.93 (s, 9H), 4.11 (t, ^3J(H,H) = 6 Hz, 2H), 4.56 (d, ^2J(H,H) = 15 Hz, 6H), 5.02 (s, 1H), 5.22 (s, 1H), 6.5 (brt, 1H), 6.6–6.8 (m, 5H), 6.82 (d, ^3J(H,H) = 6.3 Hz, 2H), 7.0 (brt, 6H), 7.1–7.2 (m, 4H), 7.2 (brs, 8H), 7.5–7.6 (m, 14H), 7.67 (d, ^3J(H,H) = 6.3 Hz, 2H), 7.7–7.8 (m, 14H), 7.82 (d, ^3J(H,H) = 6.3 Hz, 2H), 9.42 (s, 3H), 9.62 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ = 15.2, 24.9, 25.4, 27.0, 27.1, 27.5, 28.4, 29.1, 29.5, 29.9, 30.3, 31.6, 34.6, 39.7, 57.4, 58.6, 60.3, 61.2, 64.6, 66.3, 69.9, 72.5, 116.4, 117.4, 121.1, 124.2, 124.9, 126.9, 128.5, 128.6, 128.7, 128.9, 129.2, 132.2, 134.0, 136.7, 139.2, 140.7, 143.0, 143.7, 145.3, 147.6, 148.1, 148.2, 152.8, 153.5, 171.0, 172.2 ppm; ESI-MS(+): *m/z* (%): 1105 (100) $[\mathbf{R2}-2Ts^-]^{2+}$, 2247 (5) $[\mathbf{R2}-2Ts^-+Cl^-]^+$; elemental analysis calcd (%) for $C_{154}H_{177}N_9O_{21}S_2$: C 72.42, H 6.98, N 4.94, S 2.51; found: C 72.75, H 6.88, N 4.98, S 2.45.

Absorption spectra and titration experiments: Measurements were carried out on air-equilibrated solutions in CH_2Cl_2 (Merck Uvasol) in the concentration range from 1.0×10^{-5} to 2.5×10^{-4} M. UV/Vis absorption spectra were recorded by using either 1 cm or 5 cm path length cells with a Perkin–Elmer Lambda 40 spectrophotometer for the spectra performed at ambient temperature, or a Varian Cary 50 Bio instrument for the experiments in which the temperature of the cell block was thermostated by using a circulating constant temperature bath maintained at the required temperature. Titrations were performed by adding, with a microsyringe, small aliquots (typically 20 μL) of a concentrated (2×10^{-4}–2×10^{-3} M) solution of wheel **1** to a solution (2.50 mL) of the axle species examined. The UV/Vis absorption changes were monitored throughout the titration. The apparent stability constants of the pseudorotaxanes were calculated by fitting the absorption titration spectra by means of the SPECFIT software[29] using a 1:1 association model. Because of the large values of the stability constants, titrations were performed in dilute conditions (the typical concentration of the titrated species was 1.0×10^{-5} M) to ensure that the curvature at the intersection of the two linear regions of the plot could be clearly seen. Moreover, the results of the fittings were tested by simulating the titration plots with stability constants higher and lower than those determined by the software.

Stopped-flow absorption experiments: Reaction kinetic profiles were collected on air-equilibrated solutions in CH_2Cl_2 (Merck Uvasol) at controlled temperatures (277, 283, 293 and 303 K) with an Applied Photophysics SX 18-MV equipment. The standard flow tube used had an observation path length of 1.0 cm, and the driving ram for the mixing system was operated at the recommended pressure of 8.5 bar. Under these conditions the time required to fill the cell was 1.35 ms (based on a test reaction). The concentration of the reactants after mixing was 1.0×10^{-5} M. To design the stopped-flow experiments, the absorption spectral variations obtained upon mixing equal volumes of equimolar solutions of **1** and either **2** or **3** in CH_2Cl_2 were measured by using a two-compartment spectrophotometric cell (path length: 2×0.44 cm). The absorption spectra recorded before mixing the solutions contained in the two compartments of the cell were compared to those obtained after mixing (see Figures S13 and S14 in the Supporting Information). The spectrum before mixing corresponds to the sum of the spectra of the separated components, whereas the spectrum after mixing corresponds to the spectrum of a solution containing the pseudorotaxane as well as some uncomplexed molecular components, depending on the self-assembly equilibrium. Such preliminary experiments revealed that the reactions could be monitored by the increase of the absorption in the 250–280 nm region (see Figures S15 and S16 in the Supporting Information). Regarding the stopped-flow traces, a baseline correction was applied to take into account the dependence of the instrument response on pressure. In all the experiments, the cell block and drive syringes were thermostated by using a circulating constant temperature bath maintained at the required temperature. The kinetic absorbance curves were analysed for $t \geq 2$ ms with a kinetic treatment for an equilibrium $A+B \rightleftharpoons C$ (second-order model) as implemented into the SPECFIT software.[29] In all cases, the data could be interpreted satisfactorily with a kinetic model for a 1:1 association equilibrium, giving second-order threading rate constants. The values are gathered in Table S1 in the Supporting Information together with those of the corresponding first-order dethreading rate constants.

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[18] During the stoppering procedure with diphenylacetyl chloride, axle **3** can partially exchange its tosylate anions with the chloride ions. In this particular case, a solution of rotaxane **R1** in CH_2Cl_2 can be washed twice with a 1 M aqueous solution of sodium tosylate and then with water to recover the original tosylate counteranions.

[19] The extremely low solubility of axles **2**–**5** in benzene or toluene did not allow the preparation of solutions of such components for titration and stopped-flow mixing experiments.

[20] Although benzene and dichloromethane might, in principle, exert different solvation effects on the components during the formation of the supramolecular complexes, ^{1}H NMR spectra of all pseudorotaxanes recorded in CD_2Cl_2 at 298 K confirm the presence of only one orientational isomer. This indicates that the nature of these two solvents does not affect the threading processes.

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