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Slippage—a simple and efficient way to self-assemble [*n*]rotaxanes

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Abstract - Slippage is a relatively simple phenomenon that provides an efficient way to self-assemble [*n*]rotaxanes. The procedure is based on the size complementarity between the dumbbell-shaped and macrocyclic components of the rotaxane. The macrocycle has to possess a cavity that is just large enough to slip over the bulky stoppers attached to both ends of the dumbbell-shaped component under the influence of an appropriate amount of thermal energy. A series of cooperative noncovalent bonding interactions between complementary recognition sites incorporated within the macrocyclic and dumbbell-shaped components are then responsible for stabilising the resulting assembly — namely a rotaxane. The kinetics of the so-called slippage approach to rotaxanes have been investigated by varying systematically the sizes of the macrocycles as well as the sizes of the stoppers attached to the ends of the dumbbell-shaped components. The potential of this approach to self-assemble kinetically- and thermodynamically-stable molecular compounds has been demonstrated with the production of numerous linear and branched [2]-, [3]-, and [4]-rotaxanes, as well as with the stepwise construction of a linear [3]rotaxane incorporating a dumbbell-shaped component encircled by two constitutionally different macrocyclic components.

INTRODUCTION

A rotaxane (1-12) is a molecular assembly composed of a dumbbell-shaped component encircled by one or more macrocycles. In order to prevent dismembering of the rotaxane, bulky groups termed stoppers have to be attached covalently to both ends of the dumbbell-shaped component. As a result, a mechanical bond is responsible for holding together the macrocyclic and dumbbell-shaped components and, despite the fact that these components are not covalently linked to each other, a rotaxane is by most definitions a *molecular* compound. The total number of constituent components of a rotaxane is indicated in square brackets: thus, an [*n*]rotaxane incorporates one dumbbell and n - 1 macrocycles. Recently, we have developed (13-16) (Fig. 1) supramolecular approaches to self-assemble (17-22) [n]rotaxanes incorporating complementary π-electron deficient bipyridinium-based and π-electron rich dioxybenzene- or dioxynaphthalene-based polyether components. Cooperative noncovalent bonding interactions, such as π-π stacking (23-29) between the complementary aromatic units and hydrogen bonding (30-39) between the polyether oxygen atoms and the acidic hydrogen atoms on the bipyridinium units, are mainly responsible for these self-assembly processes. The threading methodology involves the complexation of a linear guest by a preformed macrocycle to afford a *supramolecular* complex — namely, a [2]pseudorotaxane. Subsequent covalent attachment of two stoppers at the ends of the guest yields a *molecular* assembly — namely, a [2]rotaxane. In the case of clipping, a dumbbell-shaped compound is preformed and subsequently employed to template (40-42) the macrocyclisation of the macrocyclic component.

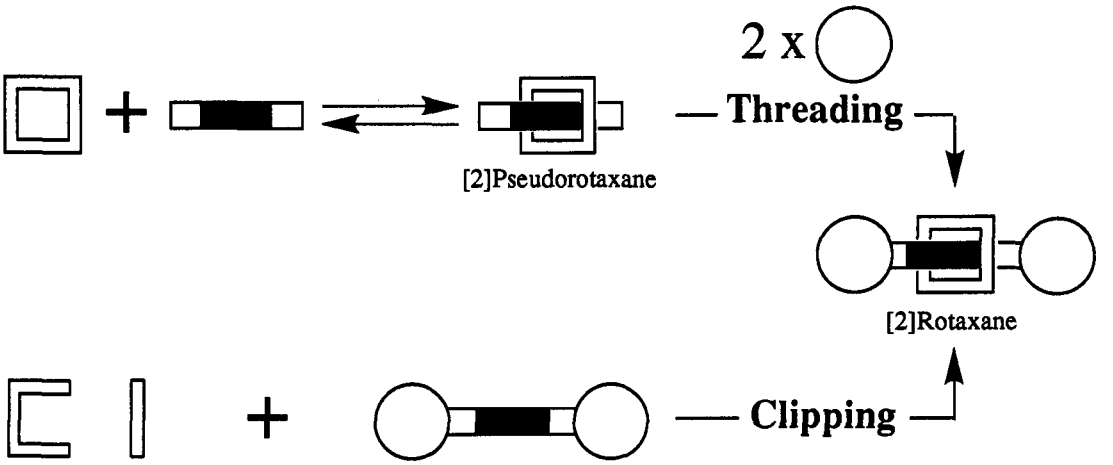


Fig. 1 Schematic representation of the threading and clipping approaches to self-assembling a [2]rotaxane.

THE SLIPPAGE APPROACH TO [*n*]ROTAXANES

The self-assembly of a [2]rotaxane (**R**) as a result of a slipping procedure is illustrated schematically in Fig. 2. A solution of a preformed dumbbell-shaped compound (**D**) and a preformed macrocycle (**M**) of appropriate size is heated at a temperature T in order to overcome the energy barrier $\Delta G^{\ddagger}_{on}$ associated with the slipping-on of **M** over the stoppers of **D**. The opposite process, involving the slipping-off of the macrocycle over the stoppers of **R**, can also occur if the system possesses enough energy to surpass the energy barrier $\Delta G^{\ddagger}_{off}$. Thus, after a certain interval of time at the temperature T, an equilibrium between the newly-formed [2]rotaxane **R** and the starting compounds **D** and **M** is established. Nonetheless, as a result of cooperative noncovalent bonding interactions between complementary recognition sites incorporated by

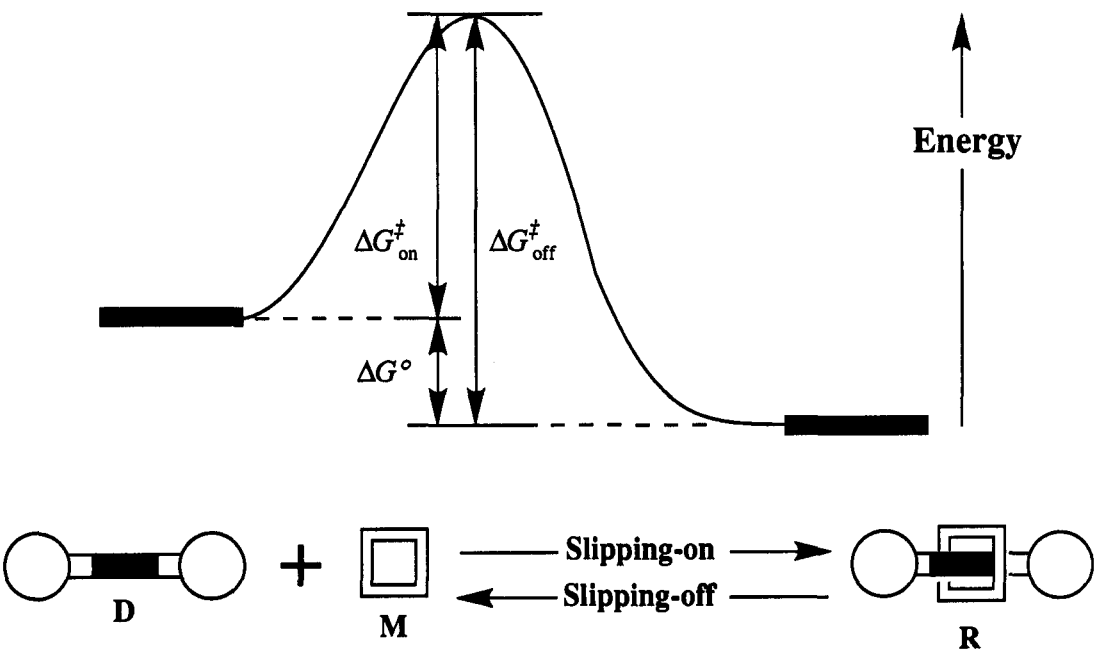


Fig. 2 Schematic representation of the slippage approach to self-assembling a [2]rotaxane.

R corresponds to *i*-Pr, the dumbbell-shaped compound **4** and the macrocycle **7** are recovered unaltered — *i.e.*, the energy of activation $\Delta G^{\ddagger}_{on}$ is too high and no rotaxane formation occurs.

KINETIC STUDIES

The preliminary experiments summarised in Scheme 1 demonstrated that the key factor in the slippage approach to self-assembling rotaxanes is the size complementarity between the macrocyclic component and the stoppers attached to both ends of the dumbbell-shaped component. The hydroquinone-based macrocyclic polyether **7** can slip-on over the tetraarylmethane-based stoppers of the dumbbell-shaped compound when *R* is H, Me, and Et. On the contrary, when *i*-Pr groups are employed instead for *R*, then no slippage occurs, suggesting that the cavity of the macrocycle **7** is not large enough to pass over the bulky '*i*-Pr-stoppers' under the experimental conditions employed. In order to gain further insight into the size complementarity requirements of slippage, the possibility of investigating the kinetics of the process by varying systematically the size of the cavity of the macrocyclic component and the size of the stoppers of the dumbbell-shaped components was envisaged. Acetonitrile solutions containing equimolar amounts of one of the macrocyclic polyethers **7-12** (Fig. 3), incorporating dioxybenzene- (hydroquinone-) and/or dioxynaphthalene-based ring systems and one of the dumbbell-shaped compounds **3-6**, incorporating tetraarylmethane-based stoppers in which the *R* groups are Et, *i*-Pr, Cyclohexyl, and *t*-Bu, respectively, were prepared and heated at a temperature *T* for a certain period of time (48). The developing charge transfer band associated with the newly-formed [2]rotaxane was monitored by UV-visible absorption spectroscopy until no change in the absorbance *A* was observed — *i.e.*, until equilibrium was reached.

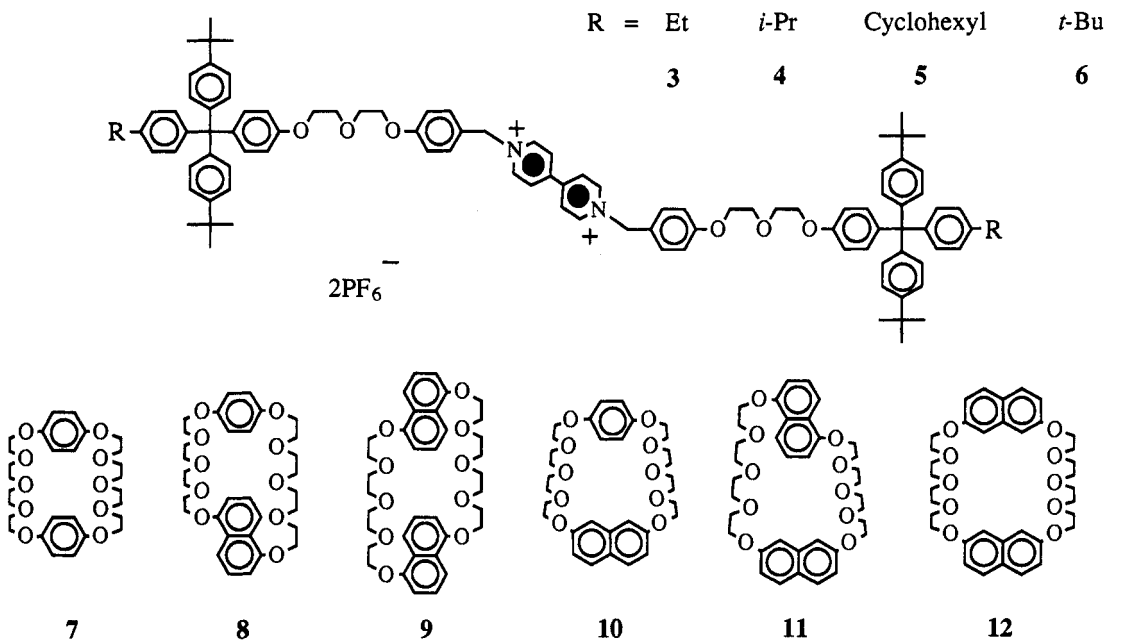


Fig. 3 Macrocyclic polyethers and dumbbell-shaped compounds employed to investigate the kinetics associated with the slippage processes.

Fig. 4a shows the plot of the absorbance *A* measured at 506 nm against time *t* in the case of the slippage of the macrocycle **9** over the stoppers of the dumbbell-shaped compound **3**. After approximately 20000 s, the equilibrium between the rotaxane and the *free* components was reached and a value of *A*, which remained constant with time, was measured. The partial UV-visible absorption spectrum (Fig. 4b) of the reaction

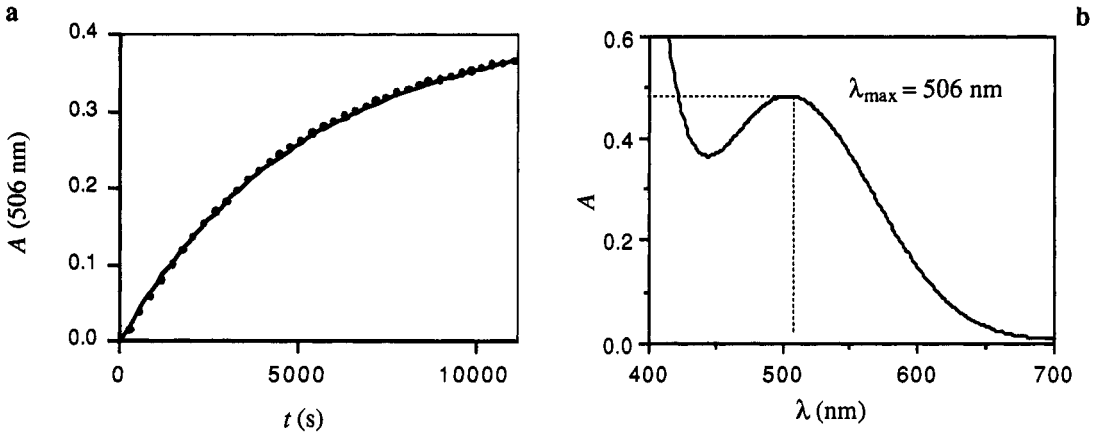


Fig. 4 (a) Plot of the absorbance A measured at 506 nm against time t in the case of the slippage of the macrocycle **13** over the stoppers of the dumbbell-shaped compound **3** where R = Et. (b) Partial UV-visible absorption spectrum of the reaction mixture measured after 20000 s showing the charge trasnfer band of the [2]rotaxane .

mixture recorded at equilibrium shows the charge transfer band associated with the [2]rotaxane centred on 506 nm. Nonlinear curve-fitting of the data plotted in Fig. 4a using equation (1) afforded a value for the rate constant k_{on} associated with the slipping-on process (49). The same procedure was employed for all the other solutions and the free energies of activation — both $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ — and of association ΔG° (Fig. 2) listed in Table 1 were derived from the values of the rate constants k_{on}.

$$A = \frac{\varepsilon [C_0^2 C_e (1 - e^{k_{on} t \frac{(C_0^2 - C_e^2)}{C_e}})]}{C_e^2 - C_0^2 e^{k_{on} t \frac{(C_0^2 - C_e^2)}{C_e}}} \qquad (1)$$

As expected, the free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ decrease as the size of the macrocyclic component decreases (50) (from left to right in Table 1) and increase as the size of the stoppers of the dumbbell-shaped component increases (from top to bottom in Table 1). The macrocycles **7** and **8** are able to slip-on over the 'Et-stoppers' of the dumbbell-shaped compound **3** only. On the contrary, the macrocycles **9** and **10** slip-on over both 'Et-stoppers' and '*i*-Pr-stoppers' of the dumbbell-shaped compounds **3** and **4**, respectively, but not over the 'Cyclohexyl-stoppers' of **5**. The macrocycle **11** is able to slip-on over both the '*i*-Pr-stoppers' and 'Cyclohexyl-stoppers' of **4** and **5**, respectively, but not over the '*t*-Bu-stoppers' of **6**. However, when **11** and the dumbbell-shaped compound **3** bearing 'Et-stoppers' are mixed in solution, the equilibrium is reached immediately — *i.e.*, the 'Et-stoppers' are too small for the macrocycle **11**. Similarly, on mixing the macrocycle **12** with equimolar amounts of any of the dumbbell-shaped compounds **3-6**, equilibrium is reached immediately. In all the macrocycles **7-12**, the two aromatic units are separated by the same length of polyether chain. Thus, the differences in the size of their cavities are mainly a result of the nature of the aromatic units and of their substitution patterns. The C-C distances between the carbon atoms bearing the methoxy substituents as well as the O-O distances between the oxygen atoms of 1,4-dimethoxybenzene, 1,5-dimethoxynaphthalene, and 2,7-dimethoxynaphthalene are listed in Fig. 5. Since these values can be considered virtually unchanged in the hydroquinone and dioxynaphthalene units incorporated within the macrocycles **7-12**, the parameters $X_{C\text{-}C}$ and $X_{O\text{-}O}$ can be defined for each macrocycle as the sum of the C-C and O-O distances, respectively, of its two aromatic

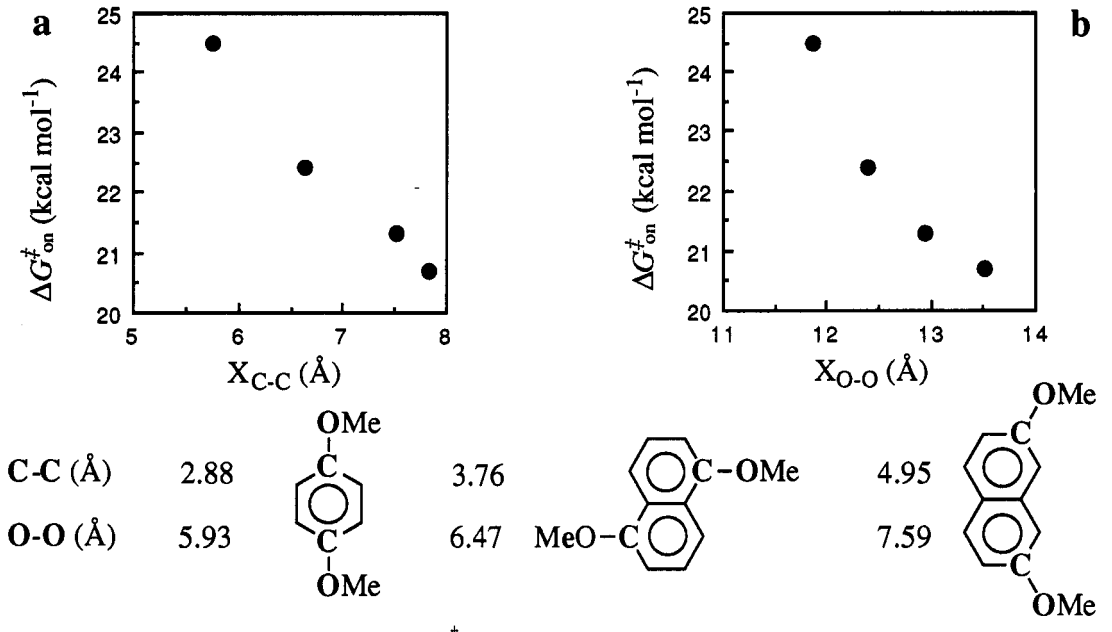


Fig. 5 Plots of the free energy of activation $\Delta G^{\ddagger}_{on}$ for the slipping-on of the macrocycles **7-10** over the stoppers of the dumbbell-shaped compound **3** and (a) $X_{C\text{-}C}$ and (b) $X_{O\text{-}O}$.

Table 1. Free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ and of association ΔG° for the slipping of the π-electron rich macrocyclic polyethers **7-12** over the stoppers of the π-electron deficient dumbbell-shaped compounds **3-6** in CD_3CN at 50°C.

Dumbbells	Parameters	Macrocycles					
		7	**8**	**9**	**10**	**11**	**12**
3	$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	24.5	22.4	21.3	20.7	—[e]	—[e]
	$\Delta G^{\ddagger}_{off}$ [b] (kcal mol^{-1})	26.1	25.5	24.9	22.9	—[e]	—[e]
	$-\Delta G^{\circ}$ [c] (kcal mol^{-1})	1.6	3.1	3.6	2.2	—[e]	—[e]
4	$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	—[d]	—[d]	23.9	24.5	21.8	—[e]
	$\Delta G^{\ddagger}_{off}$ [b] (kcal mol^{-1})	—[d]	—[d]	28.6	26.6	24.4	—[e]
	$-\Delta G^{\circ}$ [c] (kcal mol^{-1})	—[d]	—[d]	4.7	2.1	2.6	—[e]
5	$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	24.2	—[e]
	$\Delta G^{\ddagger}_{off}$ [b] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	26.3	—[e]
	$-\Delta G^{\circ}$ [c] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	2.1	—[e]
6	$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	—[d]	—[e]
	$\Delta G^{\ddagger}_{off}$ [b] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	—[d]	—[e]
	$-\Delta G^{\circ}$ [c] (kcal mol^{-1})	—[d]	—[d]	—[d]	—[d]	—[d]	—[e]

[a] Free energy of activation for the slipping-on process. [b] Free energy of activation for the slipping-off process. [c] Free energy of association. [d] No rotaxane formation occurs. [e] Saturation was reached immediately.

Table 2. Enthalpic and entropic contributions to the free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ and of association ΔG° for the slipping of the π-electron rich macrocyclic polyether **9** over the stoppers of the π-electron deficient dumbbell-shaped compound **3** in CD_3CN at various temperatures.

Parameters	Temperatures			
	30°C	40°C	50°C	60°C
$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	20.7	21.1	21.3	21.8
$\Delta H^{\ddagger}_{on}$ [b,j] (kcal mol^{-1})	10.1	10.1	10.1	10.1
$-T\,\Delta S^{\ddagger}_{on}$ [c,j] (kcal mol^{-1})	10.6	11.0	11.3	11.7
$\Delta G^{\ddagger}_{off}$ [d] (kcal mol^{-1})	24.6	24.8	24.9	25.0
$\Delta H^{\ddagger}_{off}$ [e,j] (kcal mol^{-1})	20.7	20.7	20.7	20.7
$-T\,\Delta S^{\ddagger}_{off}$ [f,j] (kcal mol^{-1})	3.9	4.1	4.2	4.3
$-\Delta G^{\circ}$ [g] (kcal mol^{-1})	3.9	3.7	3.6	3.2
$-\Delta H^{\circ}$ [h,j] (kcal mol^{-1})	10.0	10.0	10.0	10.0
$-T\,\Delta S^{\circ}$ [i,j] (kcal mol^{-1})	6.1	6.3	6.5	6.7

[a] Free energy of activation for the slipping-on process. [b] Enthalpic contribution to the free energy of activation $\Delta G^{\ddagger}_{on}$. [c] Entropic contribution to the free energy of activation $\Delta G^{\ddagger}_{on}$. [d] Free energy of activation for the slipping-off process. [e] Enthalpic contribution to the free energy of activation $\Delta G^{\ddagger}_{off}$. [f] Entropic contribution to the free energy of activation $\Delta G^{\ddagger}_{off}$. [g] Free energy of association. [h] Enthalpic contribution to the free energy of equilibrium ΔG°. [i] Entropic contribution to the free energy of association ΔG°. [j] The enthalpic and entropic terms were evaluated from the straight plots of the free energy values against temperature.

units. As expected, monotonic correlations between the free energy of activation $\Delta G^{\ddagger}_{on}$ for the slipping-on of the macrocycles **7-10** over the stoppers of the dumbbell-shaped compound **3** and $X_{C\text{-}C}$ (Fig. 5a) and $X_{O\text{-}O}$ (Fig. 5b) are observed. The enthalpic and entropic contributions (Table 2) to the free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ and of association ΔG° were derived from the straight plots of the free energies against temperature. In the case of the free energies of activation $\Delta G^{\ddagger}_{on}$ associated with the slipping-on process, small differences are observed between the enthalpic and entropic terms. On the contrary, in the case of the free energies of activation $\Delta G^{\ddagger}_{off}$ associated with the slipping-off process, the enthalpic term is significantly larger than the entropic one — *i.e.*, the noncovalent bonding interactions between macrocyclic and dumbbell-shaped components have to be destroyed in order to achieve the slipping-off of the macrocyclic component over the stoppers of the rotaxane. Consistently, the enthalpic term associated with the free energy of association ΔG° is predominant confirming that the cooperative noncovalent bonding interactions between the recognition sites incorporated between macrocyclic and dumbbell-shaped components are the main driving forces for the overall process. The slippage of the macrocycle **9** over the stoppers of the dumbbell-shaped compound **3** was followed in a range of different solvents at 30°C. Differences were observed (Table 3) in the values of the free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ which range in intervals of *ca.* 1.0 and *ca.* 3.5 kcal mol^{-1}, respectively. The highest values for the free energies of association ΔG° were determined in $(CD_3)_2CO$ and THF-d_8, suggesting that the slippage processes are more efficient — leading to high yields of the resulting rotaxanes — in these two solvents. Interestingly, when $CDCl_3$ or CD_2Cl_2 are employed as the solvent, the equilibrium between macrocycle **9**, dumbbell-shaped compound **3**, and the resulting [2]rotaxane is reached immediately, as demonstrated by the sudden

appearence of a red colour. These results suggest that desolvation of the polyether linkages of the macrocyclic component and of the bipyridinium recognition site incorporated within the dumbbell-shaped component has to precede the actual slipping-on process. A low degree of solvation is achieved in low polar solvents, such as $CDCl_3$ or CD_2Cl_2, and, as a result, much lower free energies of activation are associated with the slippage processes in these solvents.

Table 3. Free energies of activation $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ and of association ΔG° for the slipping of the π-electron rich macrocyclic polyether **9** over the stoppers of the π-electron deficient dumbbell-shaped compound **3** in various solvents at 30°C.

Parameters	Solvents					
	$(CD_3)_2CO$	CD_3CN	CD_3NO_2	$(CD_3)_2SO$	THF-d_8	DMF-d_7
$\Delta G^{\ddagger}_{on}$ [a] (kcal mol^{-1})	20.4	20.7	21.0	21.1	21.3	21.4
$\Delta G^{\ddagger}_{off}$ [b] (kcal mol^{-1})	25.2	24.6	24.4	22.6	26.1	23.6
$-\Delta G^{\circ}$ [c] (kcal mol^{-1})	4.8	3.9	3.4	1.5	4.8	2.2

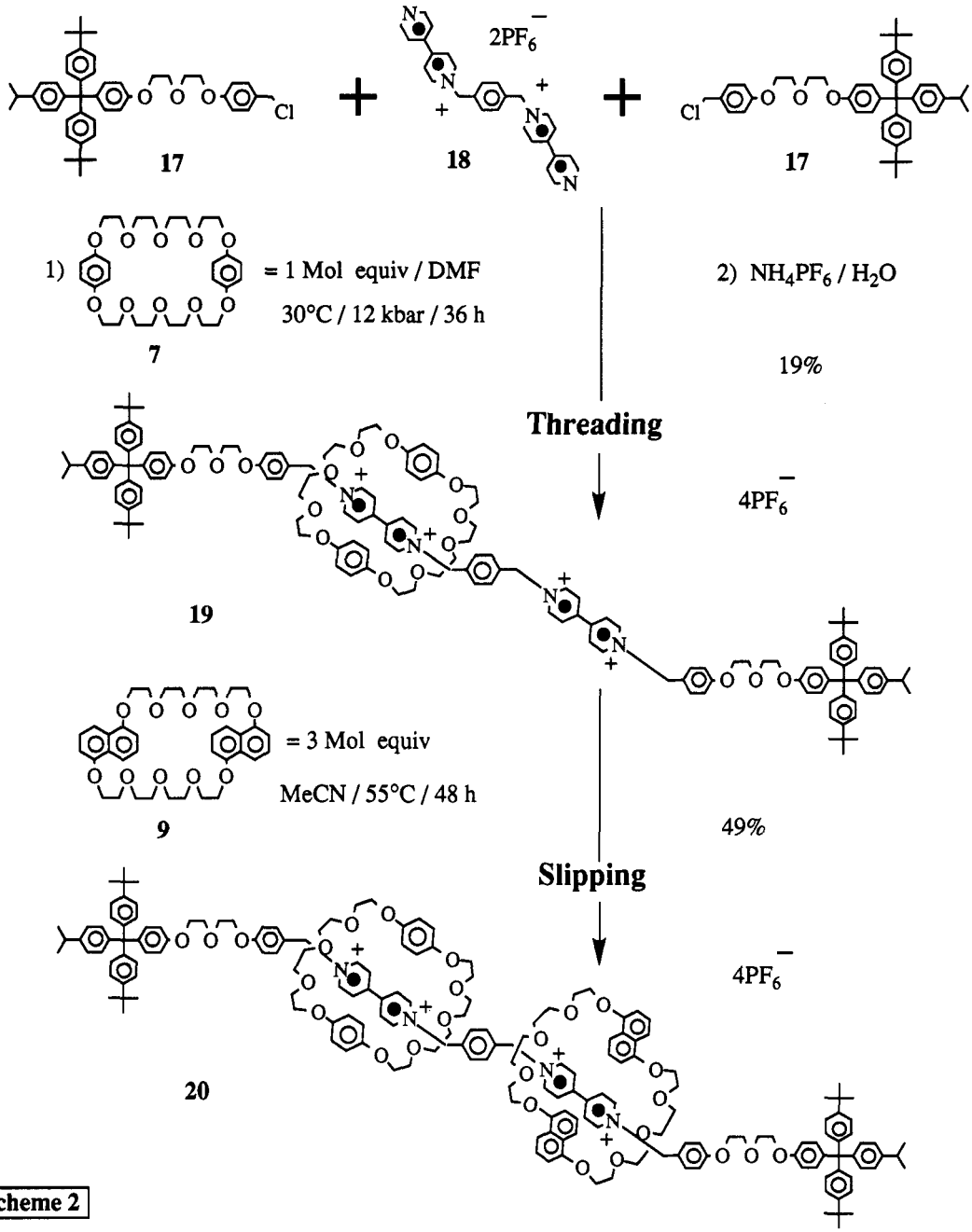
[a] Free energy of activation for the slipping-on process. [b] Free energy of activation for the slipping-off process. [c] Free energy of association.

THE SELF-ASSEMBLY OF A [3]ROTAXANE INCORPORATING TWO CONSTITUTIONALLY-DIFFERENT MACROCYCLIC COMPONENTS

Slippage provides a simple and efficient way to self-assemble [*n*]rotaxanes. This procedure has allowed us to prepare successfully a number of linear and branched [2]-, [3]-, and [4]-rotaxanes in good yields (46, 47, 51, 52). However, the most striking example of the potential of the slipping methodology to construct precisely and efficiently complex molecular assemblies is illustrated in Scheme 2. The [3]rotaxane **20** incorporates a dumbbell-shaped component comprising two bipyridinium-recognition sites encircled by two constitutionally-different macrocyclic polyethers. The self-assembly of **20** which was achieved (53) in two steps — *i.e.*, by threading-followed-by-slipping — relies mainly on the careful matching of the size complementarity between the macrocyclic components and the stoppers and on the particular order in which they are self-assembled. Reaction of the bis(hexafluorophosphate) salt **18** with the chloride **17** in the presence of one molar equivalent of the hydroquinone-based macrocycle **7** afforded the [2]rotaxane **19** in a yield of 19 %, after column chromatography and counterion exchange. The [2]rotaxane **19** incorporates '*i*-Pr-stoppers' over which the hydroquinone-based macrocycle **7** cannot slip-off (*vide-supra*) under the ordinary experimental conditions employed during slippage. On the contrary, as a result of the presence of one *free* bipyridinium recognition site within the dumbbell-shaped component of **19**, the larger 1,5-dioxynaphthalene-based macrocyclic polyether **9** can be induced to slip-on over the '*i*-Pr-stoppers' of the [2]rotaxane **19**. Thus, heating an equimolar acetonitrile solution of **19** and **9** at 55°C over 48 h afforded the [3]rotaxane **20**, which was isolated in a yield of 49 % after column chromatography.

CONCLUSIONS AND REFLECTIONS

The slippage approach to self-assembling [*n*]rotaxanes relies upon the stereoelectronic complementarity between macrocyclic and dumbbell-shaped components which self-assemble into kinetically- and thermodynamically-stable molecular compounds — namely rotaxanes — under the influence of appropriate amounts of thermal energy. The size complementarity between the macrocyclic polyether and the stoppers



Scheme 2

attached to both ends of the dumbbell-shaped component is crucial for the successful outcome of the overall process. Subtle changes in the size of either the macrocyclic polyether or of the stoppers result in significant changes of the rate associated with the process and, in some instances, in even preventing the self-assembly of the rotaxanes. Indeed, monotonic correlations between the free energy of activation associated with the slipping-on process and the size of the macrocyclic component are observed. The main driving forces for the slippage processes (54) are the cooperative noncovalent bonding interactions existing within the rotaxane assembly between the complementary recognition sites incorporated by design within macrocyclic and dumbbell-shaped components. These noncovalent bonding interactions are (i) π-π stacking between the π-electron deficient bipyridinium units present within the dumbbell-shaped

components and the π-electron rich aromatic units incorporated within the macrocyclic polyethers and (ii) hydrogen bonding between the polyether oxygen atoms and the acidic hydrogen atoms on the bipyridinium units. By employing the slippage methodology, a number of linear as well as branched [2]-, [3]-, and [4]-rotaxanes have been self-assembled in good yields. In particular, the potential of the slipping methodology to self-assemble efficiently and precisely complex molecular structures has been demonstrated with the synthesis of a [3]rotaxane incorporating two constitutionally-different macrocyclic components. The self-assembly of such a [3]rotaxane was realised by careful matching of the size complementarity of the components and by combining, in the appropriate consecutive order, the acts of threading and slippage. The efficiency and relative simplicity of slippage suggest the possibility of employing this attractive method of self-assembly to construct complex molecular assemblies, such as oligo- and poly-rotaxanes possessing device-like characteristics (55-72).

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