Template Effects in the Self-Assembly of a [2]Rotaxane and a [2]Pseudorotaxane with the Same Binding Sites in the Linear Component

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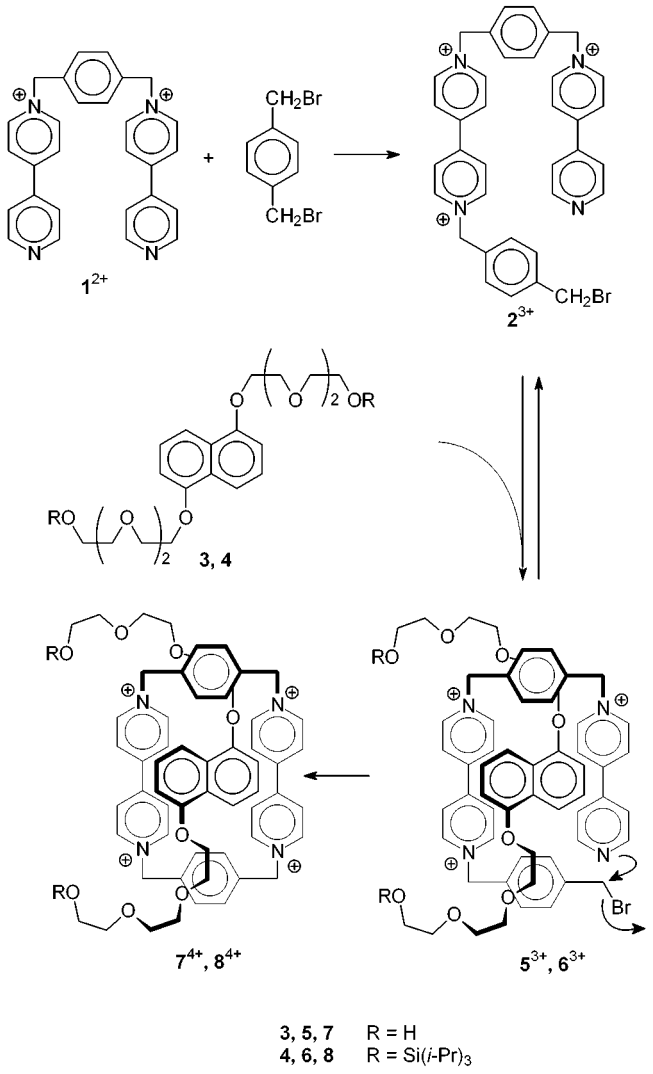
Introduction

In recent years self-assembly has become one of the preeminent themes of supramolecular chemistry, allowing the syntheses of a great variety of complex molecular systems.[1] The efficient preparation of rotaxanes, in particular, has enormously benefited from template-directed approaches.[2,3] Rotaxanes are molecules comprising one or more macrocycles threaded by a linear component bearing large stoppers at the ends to prevent the unthreading of the cyclic component. Three approaches can be employed for the self-assembly of a rotaxane:[3b,c] in the clipping approach, the cyclization of one component is carried out in the presence of a preformed dumbbell-shaped compound, which acts as the template for the ring closure; in the threading, the inclusion of an acyclic derivative inside the cavity of a macrocycle is followed by the covalent attachment of two stoppers to prevent the unthreading of the ring; in the last and less common one, the slipping approach, the two preformed components, the cyclic and the dumbbell-shaped compounds, are forced into associating one with the other by providing thermal energy.

Despite the numerous examples of template-directed syntheses of rotaxanes that can be found in the literature, no kinetic study of template effects in the formation of rotaxanes by the clipping approach has been reported to date, apart from a previous study dealing with the formation of a [2]pseudorotaxane constituted by cyclobis(paraquat-*p*-phenylene) and 1,4-bis[2-(2-hydroxyethoxy)ethoxy]benzene.[4]

Several examples of template-directed syntheses of rotaxanes are from the work of Stoddart and co-workers

Scheme 1



3, 5, 7 R = H
4, 6, 8 R = Si(*i*-Pr)$_3$

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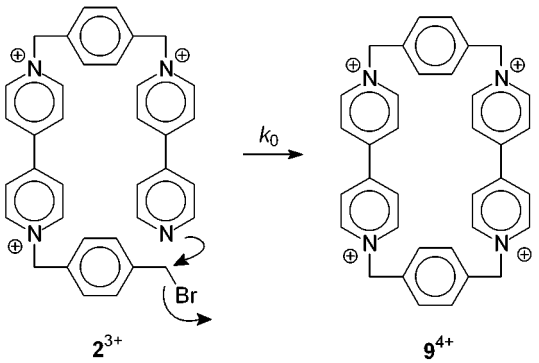
who, by using π-electron-rich and π-electron-deficient components, have prepared a variety of rotaxanes. Among them, the [2]rotaxane $\mathbf{8}^{4+}$ (Scheme 1) was obtained, with a 72% yield,[5] from *p*-bis(bromomethyl)benzene and the dication $\mathbf{1}^{2+}$. The remarkable yield is, to quote Stoddart, the highest ever obtained for the template-directed syntheses of [2]rotaxanes incorporating donor/acceptor interactions. According to the mechanism proposed by Stoddart for the formation of the tetracationic cyclophane,[6] one of the free nitrogen atoms of $\mathbf{1}^{2+}$ quaternizes upon treatment with the dihalide to afford the tricationic intermediate $\mathbf{2}^{3+}$, which can complex the polyethers **3** or **4**, containing the 1,5-dioxynaphthalene unit, to form $\mathbf{5}^{3+}$ or $\mathbf{6}^{3+}$, respectively. Complexes $\mathbf{5}^{3+}$ or $\mathbf{6}^{3+}$ are ideally predisposed to form the [2]pseudorotaxane $\mathbf{7}^{4+}$ or the [2]rotaxane $\mathbf{8}^{4+}$, respectively, via nucleophilic attack of the residual free nitrogen atom on the remaining benzylic halide site. Thus, the reaction occurs in two steps, and only the second one would benefit from the template effect.

Following our interest in the quantitative investigation of template effects,[4,7,8] the above-mentioned results prompted us to carry out a detailed kinetic study of the second step of the reaction shown in Scheme 1. The aim was to evaluate the template effects exerted by the polyethereal derivatives **3** and **4**, which have the same number and type of binding sites but differ in the terminal units, so as to clarify the role played by the two bulky triisopropylsilyl (TIPS) stoppers on the formation of [2]rotaxanes.

Results and Discussion

In a previous work, we obtained, by ^{1}H NMR in CD_3CN at 62 °C, the first-order rate constant ($k_0 = 8.3 \times 10^{-7}$ s^{-1}) for the cyclization of the trication $\mathbf{2}^{3+}$, in the absence of any added template, to yield cyclobis(paraquat-*p*-phenylene), $\mathbf{9}^{4+}$ (eq 1).[4]



(1)

In the present investigation, the kinetics of formation of $\mathbf{7}^{4+}$ and $\mathbf{8}^{4+}$ have been studied by UV−vis spectroscopy in acetonitrile at 62 °C, by following, at λ 520 nm,[9] the appearance of their charge-transfer band. To avoid polymerization reactions, the concentration of the substrate $\mathbf{2}^{3+}$ has been kept as low as possible (≈3−5 × 10^{-4} M). First-order rate constants (k_{obs}) have been obtained in the presence of variable excess amounts of the polyether template **3** or **4** (up to ≈0.07 M). The ratios k_{obs}/k_0, plotted in Figure 1 against the concentration of **3** and **4**, respectively, provide a measure of the rate enhancements produced by the presence of the templates.

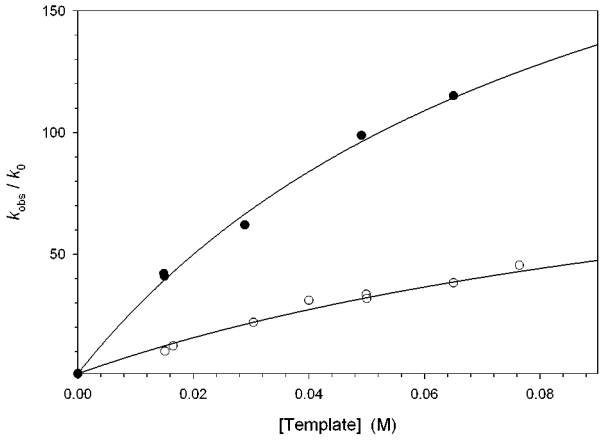
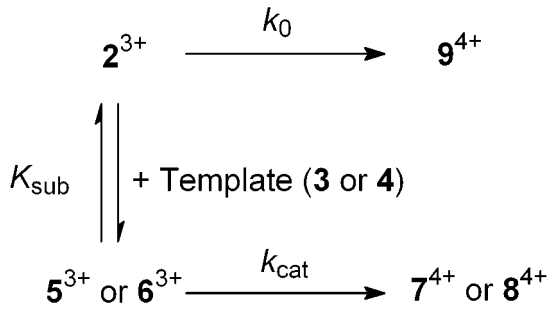


Figure 1. Rate enhancements produced by the templates **3** (●) and **4** (○) on the cyclization of the trication $\mathbf{2}^{3+}$. The points are experimental, and the curves are calculated (see text).

Scheme 2



The data in Figure 1 show that the ring closure of the trication $\mathbf{2}^{3+}$ is strongly accelerated by the presence of both templates **3** and **4**, up to approximately 120 and 45 times, respectively, at template concentrations of ≈0.07 M. The observed rate enhancements can be rationalized in light of the kinetic scheme shown in Scheme 2, which is in accordance with the mechanism suggested by Stoddart and co-workers.[6]

Assuming that the equilibrium of formation of complex $\mathbf{5}^{3+}$ or $\mathbf{6}^{3+}$ is fast with respect to the ring-closure reaction, the rate increase produced by the template, k_{obs}/k_0, is given by eq 2.[8]

$$\frac{k_{obs}}{k_0} = \frac{1 + K_{T\#}[\text{template}]}{1 + K_{sub}[\text{template}]} \qquad (2)$$

In eq 2, $K_{T\#}$ ($= k_{cat}K_{sub}/k_0$) and K_{sub} have the meaning of the association constant of the template with the cyclic transition state and with the open-chain precursor $\mathbf{2}^{3+}$, respectively. Catalysis will be observed when the template binds the transition state more strongly than the reactants.[10,11]

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Table 1. Association Constants in CH_3CN at 62 °C

template	K_{sub}, M^{-1}	$K_{T\#}$, M^{-1}	$K_{T\#}/K_{sub}$
3	11 ± 2	$(3.0 \pm 0.2) \times 10^3$	$(2.7 \pm 0.3) \times 10^2$
4	7 ± 2	$(8.5 \pm 0.8) \times 10^2$	$(1.2 \pm 0.2) \times 10^2$

If the concentration of the template is in large excess with respect to that of the substrate, as in our experiments, its actual concentration can be assumed to be constant during the reaction course and coincident with its analytical concentration; thus, nonlinear least-squares fit to eq 2 of k_{obs}/k_0 vs the analytical concentration of the template has provided the association constants reported in Table 1.

Both curves in Figure 1, calculated by inserting these values in eq 2, show a clear tendency to saturation. The saturation value, which is given by the ratio $K_{T\#}/K_{sub}$, is the maximum theoretical rate enhancement that would be attained when the substrate is completely bound to the template. The corresponding values, reported in Table 1, indicate that the complexed form of $\mathbf{2}^{3+}$ with template **3** is ca. 270 times more reactive than the free one, whereas that with template **4** is ca. 120 times more reactive. Such rate enhancements are due to the fact that the association of the acyclic trication $\mathbf{2}^{3+}$ with templates **3** and **4** is rather weak whereas the cyclic transition state shows a much greater ligand affinity toward them. This is mainly due to the preorganization of the cyclic transition state and, secondarily, to the development of a further positive charge on the initially neutral nitrogen atom. It is worth noting, however, that the cyclic transition state is not as good a ligand as cyclobis(paraquat-*p*-phenylene), $\mathbf{9}^{4+}$. In fact, it has been reported that $\mathbf{9}^{4+}$ binds 1,5-bis[2-(2-hydroxyethoxy)ethoxy]naphthalene (a molecule having one ethyleneoxy unit per side chain, less than **3**), in CH_3CN at 25 °C, with an association constant of 2.5×10^4 M^{-1},[12] which is about 1 order of magnitude greater than the constant $K_{T\#}$ obtained with the template **3**. An analogous observation was already made by us in a previous work dealing with the formation of a different [2]pseudorotaxane.[4]

Upon inspection of Table 1, it is apparent that, in going from guest **3** to guest **4**, both the association constants with the open-chain precursor $\mathbf{2}^{3+}$ (K_{sub}) and the cyclic transition state ($K_{T\#}$) are reduced. Whereas the effect is less important for the K_{sub} value, which is low for both guests, it is more pronounced for the $K_{T\#}$ value. As a consequence, the saturation value for guest **4**, given by the ratio $K_{T\#}/K_{sub}$, is more than halved by the substitution of the terminal hydrogens with the TIPS groups. Therefore, it appears that the two bulky TIPS groups, which are of course necessary to prevent the unthreading of the tetracationic ring, do reduce the template ability of the guest. The most obvious explanation for this behavior would be a destabilizing steric effect exerted by these groups. There is increasing evidence in the literature[8,13] that two structural features are required for optimum complexation of a guest molecule by cyclobis(paraquat-*p*-phenylene), namely an aromatic core, which is essential in placing the guest in the host cavity by the mechanism of apolar complexation, and two sidearms with suitably placed oxygen atoms that interact with the acidic α-hydrogens of the pyridinium rings of the host by [C—H···O] hydrogen bonding. The latter interactions should be the most affected by the steric hindrance of the two TIPS stoppers. To find support to this hypothesis, we have carried out a molecular modeling study of the [2]pseudorotaxane $\mathbf{7}^{4+}$ and the [2]rotaxane $\mathbf{8}^{4+}$. The calculations were carried out utilizing the MMFF force field,[14] as implemented in the MacroModel 6.0 molecular modeling system.[15] The X-ray structure of $\mathbf{8}^{4+}$ was used as a starting point for the energy minimization,[5] whereas for $\mathbf{7}^{4+}$ the initial structure was obtained by substituting the TIPS groups in the X-ray structure of $\mathbf{8}^{4+}$ with hydrogen atoms. Both structures were energy minimized, and the measured C—H···O distances are reported in Table 2 together with those obtained from the X-ray structure for $\mathbf{8}^{4+}$.

Table 2. Distances (Å) between the Oxygen Atoms and the Closest Pyridinium α-Proton[a]

	$\mathbf{7}^{4+}$ (calcd)	$\mathbf{8}^{4+}$ (calcd)	$\mathbf{8}^{4+}$ (exptl)
O1	3.24	3.34	3.24
O2	2.34	2.35	2.65
O3	2.41	2.44	2.65
O4	3.64	4.08	4.15

[a] Due to the C_i symmetry of the starting structures the corresponding oxygen atoms of the two chains share the same distances.

The calculated distances for $\mathbf{8}^{4+}$ agree quite satisfactorily with the experimental ones, thus indicating the reliability of our computational approach. By comparing the calculated distances found in $\mathbf{7}^{4+}$ and $\mathbf{8}^{4+}$, it is clearly evident that the presence of the TIPS groups mainly affects the C—H···O4 distance indicating that only the corresponding interaction is weakened by steric effects.

Besides steric effects, one should also take into account entropic effects. There is little doubt that the interaction between the oxygen atoms of the sidearms and the pyridinium α-protons restricts the conformational motion of the polyethereal chains with a consequent entropy loss. The entropy associated with internal rotations depends not only on potential energy barriers but also on the reduced moments of inertia of the rotating groups.[16] An increase of the reduced moments of inertia has the effect of decreasing the spacing between the energy levels of internal rotations, and thus of increasing the conformational entropy at temperatures above absolute zero. The two heavy TIPS groups placed at the end of the sidearms in the template **4** make the conformational entropy of **4** significantly greater than that of the template **3**. It follows that restriction of conformational motion of the sidearms upon binding occurs with a greater entropy loss in the case of **4** with respect to **3**, and this would reflect in lower binding constants. Some data in the literature seem to support the importance of entropy loss due to conformational restriction upon binding. For example, the binding constants of $\mathbf{9}^{4+}$ with compounds **10**, **11**, and **12** in CH_3CN at 25 °C are 180, 320, and 54 M^{-1}, respectively (Chart 1).[12]

Compounds **10** and **11** differ by the nature of the terminal groups, SH and CH_3, respectively. The methyl

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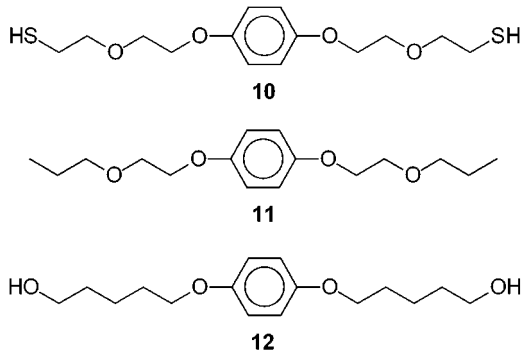
Chart 1



group has a greater steric hindrance than the sulfhydryl group but is lighter; thus, the order of the binding constants cannot be explained by a steric effect but rather by a mass effect. Also interesting is the comparison of the binding constants with compounds **11** and **12**. It has been noted that the positioning of the oxygen at the terminal end of compound **12** would actually allow it to better wrap around and interact with the bipyridinium rings than when the oxygen is positioned closer in on the chain as in compound **11**.[12] However, binding of the terminal oxygen in **12** would involve a greater loss of conformational freedom of the sidearm than binding of the second oxygen in **11** because in the latter case the terminal propyl group remains free to move.

In conclusion, the results presented here indicate that, in the self-assembly of a rotaxane by the clipping approach, the kinetic advantage brought out by the guest is lowered by the presence of two bulky and heavy groups at the end of the linear component. This effect is probably the result of a combination of steric effects and of the greater loss of conformational entropy upon binding with the cyclic transition state.

Experimental Section

Materials and Methods. 1,1″-[1,4-Phenylenebis(methylene)]-1′-(4-(bromomethyl)benzyl)bis(4,4′-bipyridinium) tris(hexafluorophosphate) ($\mathbf{2}^{3+}\cdot 3PF_6$) was from our previous work.[4] 1,5-Bis[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]naphthalene (**3**) and 1,5-Bis[2-[2-(2-triisopropylsilyloxy)ethoxy]ethoxy]-ethoxy]naphthalene (**4**) were prepared according to literature procedures.[5] HPLC-grade acetonitrile (Carlo Erba) was used in the kinetic experiments without further purification.

Molecular Modeling. Molecular mechanics calculations were carried out with the MacroModel 6.0 molecular modeling system[15] running on a Silicon Graphics O2 R10000 workstation. The structures were energy minimized to a gradient lower than 0.0001 kJ mol^{-1} $Å^{-1}$, in the MMFF force field,[14] employing the Polak−Ribiere conjugate gradient (PRCG) method.[17] The electrostatic interactions were calculated in vacuo ($\epsilon_r = 1$) by using the partial atomic charges of the MMFF force field.

Kinetic Measurements. Kinetic measurements were carried out, at 62 °C, in acetonitrile, in a 3 mL cuvette (optical path 1 cm) kept in the thermostated cell compartment of the spectrophotometer. In a typical run, 100 μL of a 0.010 M solution of $\mathbf{2}^{3+}\cdot 3PF_6$ was added to a 2.5 mL solution of either the template **3** or **4** at the appropriate concentration. The appearance of the charge-transfer band of $\mathbf{7}^{4+}$ or $\mathbf{8}^{4+}$ was followed at λ 520 nm. In all of the cases, a clean first-order behavior was observed.

Relative kinetic constants (k_{obs}/k_0, where $k_0 = 8.3 \times 10^{-7}$ s^{-1}) at the various template concentrations (corrected for the volume increase at 62 °C and given in parentheses in L^{-1} mol) were as follows:

Template **3**: 1 (0), 41.0 (1.50×10^{-2}), 42.2 (1.49×10^{-2}), 62.1 (2.89×10^{-2}), 98.8 (4.91×10^{-2}), 115.1 (6.50×10^{-2}). Template **4**: 1 (0), 10.2 (1.51×10^{-2}), 12.41 (1.65×10^{-2}), 22.1 (3.04×10^{-2}), 31.1 (4.00×10^{-2}), 33.6 (4.99×10^{-2}), 31.9 (5.00×10^{-2}), 38.3 (6.50×10^{-2}), 45.5 (7.64×10^{-2}). All data are plotted in Figure 1.

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