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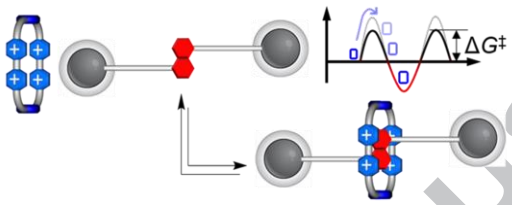

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Controlling association kinetics in the formation of donor–acceptor pseudorotaxanes

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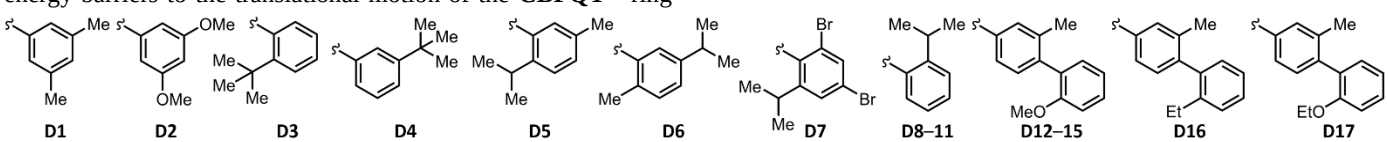
ABSTRACT

We report a systematic investigation of size-complementary stoppering groups used to determine the kinetics of threading a cyclophane, namely cyclobis(paraquat-*p*-phenylene), onto a series of molecular dumbbells. We have identified a set of simple functionalized phenyl and biaryl groups that present activation energy barriers between 16.7 and 26.6 kcal mol^{-1} to threading the dumbbells. These will be employed as 'steric speed bumps' to modulate kinetics in artificial molecular pumps that operate based upon a delicate balance of noncovalent bonding interactions.

Co-conformational switching in mechanically interlocked molecules[1] (MIMs), such as rotaxanes,[2] has traditionally been triggered by the application of external stimuli that alter the relative strengths of noncovalent bonding interactions between components, i.e., the energy minima.[3] Molecular switches, based on MIMs, are toggled between low energy states in a manner that is dependent on the equilibrium distributions of co-conformers. However, if control is also exercised over the transition state kinetics (the energy maxima) of such systems, in addition to altering the energy minima, populations of co-conformers can be driven to higher energy states that lie away from equilibrium.[4,5]

We have recently started to develop a series of artificial molecular pumps[5] based upon the rather unique molecular recognition properties of the cyclobis(paraquat-*p*-phenylene)[6] (**CBPQT**$^{4+}$) ring. In its tetracationic form, this redox-active cyclophane binds electron rich guests, such as 1,5-dialkoxynaphthalene derivatives, in its cavity by virtue of favorable donor–acceptor interactions. Upon reduction to its dicationic bisradical species, namely **CBPQT**$^{2(\bullet+)}$, the recognition properties of the ring change dramatically. Donor–acceptor interactions are diminished and radical–radical pairing interactions[7] predominate. Redox-stimulated switching between the two states of the ring, therefore, offers an effective means by which to control the energy minima in systems based upon **CBPQT**$^{4+}$ rings. In our research on artificial molecular pumps, we have sought to modulate the transition state energy barriers to the translational motion of the **CBPQT**$^{4+}$ ring by exploiting both electrostatic[8] and steric constraints.[5] Herein, we describe the systematic study of the size complementarity between bulky aromatic ring systems and the cavity of **CBPQT**$^{4+}$ in order to identify which groups impede the translation the ring by acting as 'steric speed bumps'.

We chose to investigate the rate of slippage[9] (Figure 1A) of the **CBPQT**$^{4+}$ ring onto a series of dumbbell-shaped molecules **D** in order to form donor–acceptor pseudorotaxanes. Despite the fact that **CBPQT**$^{4+}$ has been studied extensively for over 25 years,[6] there have been relatively few attempts made to identify steric barriers that control the kinetics of its association or dissociation with guest molecules.[5,10] Previous investigations in the contexts of cyclic polyethers,[11,12] cyclodextrins,[13] and amide macrocycles[14] have revealed the rigorous constraints of size complementarity[15] that govern the slippage of rings over bulky groups – rates of slippage or deslippage[16] vary dramatically with seemingly small changes in molecular structure and size. With this observation in mind, we set out to screen a family of dumbbells **D1**–**17** and to examine the change (Figure 1B) in the energy barrier to association ($\Delta G^{\ddagger}$) that occurs as small variations are made in the constitution of the stoppering groups. The symmetrical dumbbells **D1**–**17** contain (Figure 1C and Table 1) 1,5-dioxynaphthalene (DNP) recognition sites at their midriffs, flanked on either side by oligoethylene glycol chains that are terminated by aromatic ring systems of different sizes. The binding interaction (ΔG) between



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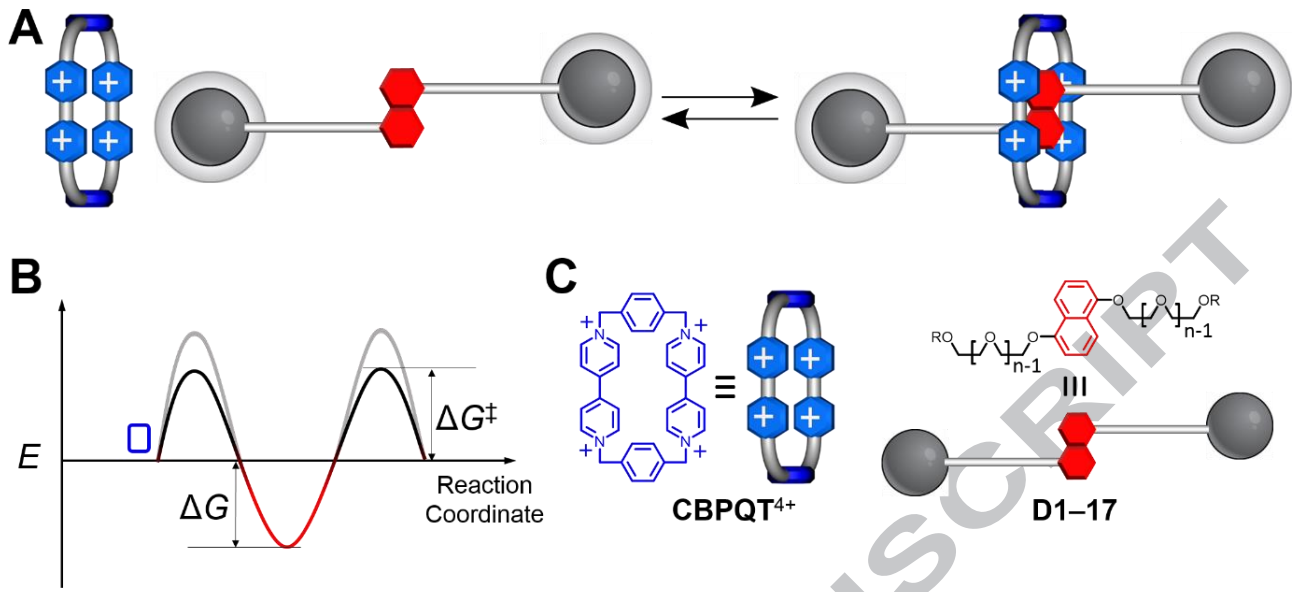

Figure 1. (A) Graphical representation of the formation of a pseudorotaxane from an electron deficient ring and a molecular dumbbell bearing an electron rich unit at its core. The steric hindrance experienced as the ring threads onto the end of the dumbbell dictates (B) the activation energy barrier ($\Delta G^{\ddagger}$) that must be overcome for the ring to access the electron rich site, where it experiences stabilizing (ΔG) noncovalent bonding interactions. (C) Structural formulas of the **CBPQT**$^{4+}$ ring and the series of dumbbells **D1**–**17**. The bulky end groups, R, and oligoethylene glycol chain length, n, are defined in Table 1.

Table 1
Experimentally determined free energies of activation, $\Delta G^{\ddagger}$, for the inclusion of dumbbell-shaped molecules **D1–17** within **CBPQT**$^{4+}$[a]

Entry	Dumbbell	n	Bulky End Group R	$\Delta G^{\ddagger}$ kcal mol^{-1}
1	**D1**	2	3,5-dimethylphenyl	<13[b]
2	**D2**	2	3,5-dimethoxyphenyl	**16.7**
3	**D3**	2	2-*tert*-butylphenyl	>28[c]
4	**D4**	2	3-*tert*-butylphenyl	>28[c]
5	**D5**	2	2-isopropyl-5-methylphenyl	>28[c]
6	**D6**	2	2-methyl-5-isopropylphenyl	<13[b]
7	**D7**	2	2,4-dibromo-6-isopropylphenyl	>28[c]
8	**D8**	2	2-isopropylphenyl	**16.9**
9	**D9**	3	2-isopropylphenyl	**15.7**
10	**D10**	4	2-isopropylphenyl	**15.4**
11	**D11**	6	2-isopropylphenyl	**15.8**
12	**D12**	2	3-methyl-4-(2′-methoxyphenyl)phenyl	**18.5**
13	**D13**	3	3-methyl-4-(2′-methoxyphenyl)phenyl	**18.5**
14	**D14**	4	3-methyl-4-(2′-methoxyphenyl)phenyl	**18.3**
15	**D15**	6	3-methyl-4-(2′-methoxyphenyl)phenyl	**18.3**
16	**D16**	3	3-methyl-4-(2′-ethylphenyl)phenyl	**26.6**
17	**D17**	3	3-methyl-4-(2′-ethoxyphenyl)phenyl	>28[c]

[a] Rates were measured[17] in MeCN at rt. [b] The immediate association observed with **CBPQT**$^{4+}$ prohibited exact determination of the activation energy barrier. [c] End group acts as a stopper that prevents association under the conditions of the experiments.

oligoethylene glycol-functionalized DNP derivatives and **CBPQT**•4PF_6 in MeCN solution is well established[3] and gives rise to an easily observable absorbance at approximately 550 nm resulting from charge transfer. Details of the synthesis and characterization of the dumbbells are given in the supplementary information. For each dumbbell, a series of experiments were performed in which an excess of **CBPQT**•4PF_6 was added to a solution of a dumbbell **D** in acetonitrile. A range of different concentrations of **CBPQT**•4PF_6 were employed and the pseudo-first-order rate constants, k_{obs}, were determined by monitoring the growth in the absorbance at 550 nm over time by UV-vis spectroscopy.[17] The rate constants for association, k_f, were deduced from plots (Figures S5 and S6) of k_{obs} against the concentrations of **CBPQT**$^{4+}$, allowing the activation energy barriers ($\Delta G^{\ddagger}$) to be calculated using the Eyring equation,

$$k_f = \frac{k_B T}{h} e^{\frac{\Delta G^{\ddagger}}{RT}}$$

where k_B is the Boltzmann constant, T is temperature, h is Planck's constant, and R is the ideal gas constant.

Dumbbells **D1**–**8** contain diethylene glycol chains terminated by phenyl groups bearing various substituents around their periphery. A 3,5-methylphenyl end group does not impede the formation of **D1**⊂**CBPQT**$^{4+}$ to an extent that is observable (Table 1, entry 1) under the experimental conditions, since complex formation occurs instantly in MeCN at temperatures between −40 °C and room temperature. The structurally similar 3,5-dimethoxyphenyl group of **D2**, on the other hand, causes the formation of **D2**⊂**CBPQT**$^{4+}$ to slow down to a timescale of several seconds at room temperature. Analysis of the threading process reveals (entry 2) an activation energy barrier of 16.7 kcal mol^{-1}. *tert*-Butylphenyl derivatives were observed to act as stoppers for **D4** and **D5** that prevent (entries 3 and 4) slippage altogether, whereas the behavior of the isomeric 2-isopropyl-5-methylphenyl and 2-methyl-5-isopropyl-phenyl end groups is dependent on their substitution pattern – acting as a stopper in the case of **D5** (entry 5) and allowing rapid association (entry 6) in the case involving **D6**. The 2,4-dibromo-6-isopropylphenyl group also serves (entry

7) as a stopper. The simple 2-isopropylphenyl of **D8**[5b] was found to have an influence similar to that of the 3,5-dimethoxyphenyl barrier of **D2** in slowing the rate of association to the second timescale, with an activation energy of 16.9 kcal mol^{-1}.

Hydrogen bonding interactions between the oligoethylene glycol chains of DNP derivatives and **CBPQT**$^{4+}$ are responsible for a large proportion of their positive binding interaction.[18] Isothermal titration calorimetry performed on of a series of 2-isopropyl-terminated dumbbells **D8**−**D11** confirmed (Table 2) that the association constant of DNP⊂**CBPQT**$^{4+}$ binding increases with the length of the oligoethylene glycol chain. We speculate that hydrogen bonding may also influence the transition state energy barriers in the formation of pseudorotaxanes. Indeed, comparison (Table 1, entries 8−11) of the measured $\Delta G^{\ddagger}$ values for **D8**−**D11** reveals a decrease in activation energy barrier of approximately 1 kcal mol^{-1} upon moving from a diethylene glycol chain to the extended analogs. This phenomenon is consistent with transition state stabilization by [C−H···O] contacts between the ether oxygen atoms of the chain with the pyridinium hydrogens.

Table 2
Thermodynamic data for the binding of **D8–11** with **CBPQT**$^{4+}$

Dumbbell	K_a M^{-1}	ΔH kcal mol^{-1}	ΔS cal mol^{-1} K^{-1}
D8	854 (60)	15.0 (4.7)	-36.8
D9	9150 (150)	17.8 (0.1)	-41.5
D10	17000 (900)	22.6 (0.3)	-41.9
D11	17600 (500)	17.6 (0.5)	-39.7

Large variations in activation energy barriers to association accompany the relatively small structural changes around the phenyl termini of dumbbells **D1**−**8**. As substituent size is not a continuous variable and there are finite options in choosing readily available substitution patterns, there is limited scope to 'fine-tune' the rate of passage of the **CBPQT**$^{4+}$ ring over simple phenyl derivatives in a rational manner. In order to avoid screening a vast number of compounds experimentally, we decided to assess a wide range of potential stoppering groups computationally. Relative energetic barriers for pulling a library of different end groups through **CBPQT**$^{4+}$ were screened using a simple molecular mechanics model.[17] As a model system for the dumbbells, constrained *n*-hexyl chains in their lowest-energy "zigzag" conformations were attached to the stoppers. After constraining the three spatial coordinates of the four methylene carbons present in the structurally minimized **CBPQT**$^{4+}$, the *n*-hexyl derivatives were pulled (Figure 2A) through the **CBPQT**$^{4+}$ rings along a minimized energy pathway with a stepsize of 0.4 Å. This process was achieved by running a series of sequential structural minimizations, with the distance between a faraway (>100 Å) dummy atom on the opposite side of the **CBPQT**$^{4+}$ ring and the oxygen directly attached to the *n*-hexyl-chains of the stoppers constrained. The calculated activation energy was taken (Figure 2B) as the maximum energy relative to that of the components at infinite separation. We found that the computationally predicted barriers presented by biaryl groups appear to have more potential for a continuous variation in the activation energy barrier to threading. 3,2′-Disubstituted derivatives, in particular, are appealing candidates on account of the out-of-plane twisting caused by steric congestion around the biaryl bond.

A series of homologous dumbbells **D12**−**17** containing three different biaryl end groups were selected, based upon the *in silico* screening and assessed (Table 1, entries 12−17) experimentally. Dumbbell **D12**, bearing 3-methyl-4-(2′-methoxyphenyl)phenyl stoppering groups, presents an energy barrier to association of 18.5 kcal mol^{-1}, corresponding to threading occurring over a period of several hours under the conditions of the experiments. In contrast to the 2-isopropylphenyl series, very little variation in $\Delta G^{\ddagger}$ was evident upon extending the oligoethylene glycol chain (**D12**−**15**), suggesting that the transition state conformation does not permit hydrogen bonding between the **CBPQT**$^{4+}$ ring and the dumbbell in this case. A slightly bulkier homologue of **D13** was also effective as a steric speed bump. Dumbbell **D16**, with 3-methyl-4-(2′-ethylphenyl)phenyl termini, exhibited an energy barrier of 26.6 kcal mol^{-1}. A further increase in size to 3-methyl-4-(2′-ethoxyphenyl)phenyl, as part of **D17**, took the biaryl end group into the realm of a stopper.

In conclusion, through a combination of *in silico* modeling and experimental measurements of the energy barriers to the formation of donor−acceptor pseudorotaxanes, we have identified a set of simple functionalized phenyl and biaryl groups that are complementary in size to the cavity of the cyclobis(paraquat-*p*-phenylene) ring. These steric speed bumps may be used to modulate kinetics in artificial molecular pumps or other types of molecular machines[19] that operate based upon a delicate balance of noncovalent bonding interactions.[5]

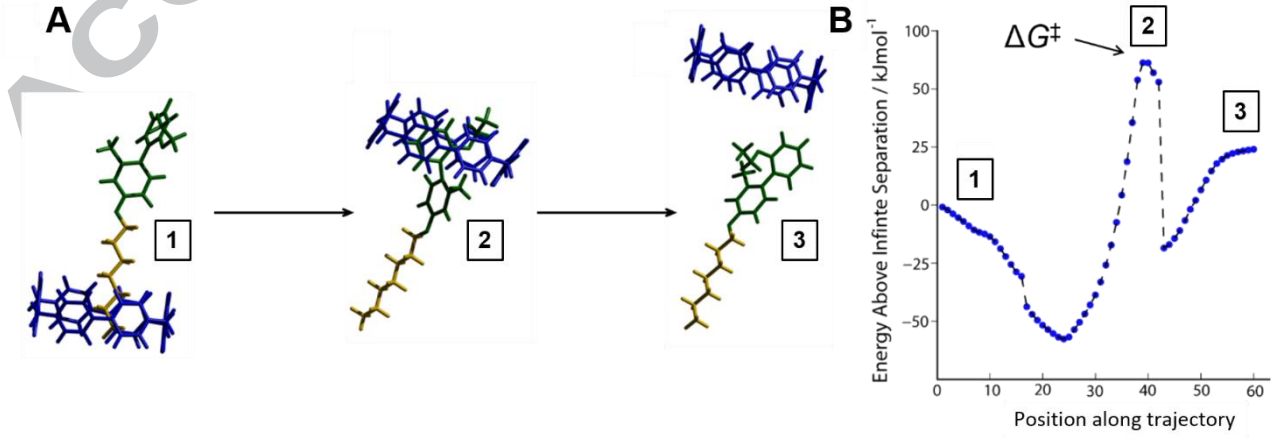

Figure 2. Screening of steric barriers *in silico*. (**A**) Illustration of the molecular mechanics modeling (OPLS-2005 force field) whereby the energy is calculated at regular 0.4 Å intervals as a steric barrier (green, end group of **D17** shown) is drawn through the aperture of a constrained **CBPQT**$^{4+}$ ring (blue). (**1**) **CBPQT**$^{4+}$ threads on from a constrained *n*-hexyl group (yellow), (**2**) reaches the highest energy point when the steric barrier is in the center of its cavity, and (**3**) finally passes over the barrier. (**B**) A typical potential energy curve as a steric barrier passes through **CBPQT**$^{4+}$, where the energy at point **2** is activation energy barrier $\Delta G^{\ddagger}$.

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Supplementary Material

Supplementary data (experimental procedures, spectroscopic characterization data, kinetics data, and details of computational simulations) associated with this article can be found, in the online version, at http://