Photoactivated Directionally Controlled Transit of a Non-Symmetric Molecular Axle Through a Macrocycle**

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Dedicated to Professor Vincenzo Balzani on the occasion of his 75th birthday

The control of motion on the molecular scale is of fundamental importance for living organisms,^[1] and one of the most fascinating challenges in nanoscience.^[2,3] Artificial molecular machines have been realized on the laboratory scale,^[4] and utilization of such systems to construct responsive materials^[5] and surfaces,^[6] control catalytic processes,^[7] and develop test structures for information storage devices^[8] and drug deliverv^[9] has been investigated. Nevertheless, the construction of synthetic nanoscale motors capable of showing directionally controlled linear or rotary movements still poses a considerable challenge to chemists.^[10] Moreover, the use of such systems to perform the tasks that natural molecular motors do,[11] namely active transport of substrates over long distances or across membranes, remains a very difficult endeavor that is further complicated by the fact that most currently available synthetic molecular motors are based on sophisticated chemical structures and/or operation procedures.^[4,10] In this context, the development of (supra)molecular systems that exhibit directionally controlled relative motions of their components based on a minimalist design and activated by convenient inputs is of the highest importance.

Herein we describe the construction and operation of a simple supramolecular assembly in which a molecular axle passes unidirectionally through the cavity of a molecular ring in response to photochemical and chemical stimulation. A system of this kind constitutes a first step towards the construction of an artificial molecular pump; it can also lead to the realization of molecular linear motors based on rotaxanes and rotary motors based on catenanes.^[12]

The strategy that we have tackled is illustrated in Figure 1. The system is composed of a molecular ring and a nonsymmetric molecular axle that comprises 1) a passive pseudostopper (D) at one end; 2) a central recognition site (S) for the ring; and 3) a bistable photoswitchable unit (P) at the other end. Under the conditions employed, the axle pierces the ring exclusively with the photoactive gate in its initial

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Figure 1. a) Strategy for the photoinduced unidirectional transit of a non-symmetric axle through a molecular ring. b) Simplified potential energy curves (free energy versus ring-axle distance) for the states shown in (a) describing the operation of the system in terms of a flashing ratchet mechanism. Slower processes that do not take place under our conditions are represented by shaded cartoons and dashed lines.

form (α) for kinetic reasons,^[13] affording a pseudorotaxane in which the molecular ring encircles the recognition site S. Subsequently, light irradiation converts the α -P end group into the bulkier β form, a process which also causes a destabilization of the supramolecular complex. Therefore, a dethreading of the system is expected, which should occur by extrusion of the D moiety of the axle. Reset is obtained by photochemical or thermal conversion of the β -P gate back to the α state, thereby regenerating the starting form of the axle. Overall, the photoinduced directionally controlled transit of the axle through the ring would be obtained according to a flashing energy ratchet mechanism (Figure 1b).^[4b,14]

Clearly, the success of such a strategy relies on two basic requirements: 1) the kinetic barriers for the slippage of the axle end groups through the ring^[15] should follow the order: $E^{+}_{\alpha-P} < E^{+}_{\ D} < E^{+}_{\ \beta-P}$; and 2) the ring should form a more

stable pseudorotaxane with the axle bearing the α -P unit compared to that bearing the β -P unit. From a practical viewpoint, to enable a clean operation and characterization of the system, it is important that the differences in the energy barriers and stability constants are sufficiently large, and that the photochemical interconversion of the P gate between α and β forms is fast, efficient, and reversible.

In a previous investigation,^[16] we studied the threaded complex of axle EE-**1**H⁺, composed of a dialkylammonium hydrogen-bonding site equipped with two azobenzene end units, with the dibenzo[24]crown-8 ring **R** (Scheme 1).^[17] We



Scheme 1. Structure formulas and cartoon representation of the examined axle and ring components.

found that the threading–dethreading rate constants are slowed down by at least four orders of magnitude when the *E*-azobenzene end units are photoisomerized to the *Z* form, practically transforming the complex into a rotaxane; moreover, the stability constant drops by a factor of two (Table 1).^[18] The system exhibits excellent photoswitching and reversibility, and it is easy to synthesize. Encouraged by these results, we looked for a passive pseudo-stopper (D in Figure 1) with steric hindrance for slippage through **R** that is intermediate between that of the *E*- and *Z*-azobenzene end units of 1H^+ . It was shown earlier by Stoddart and co-workers^[19] that in chloroform/acetonitrile 3:1 the bis(cyclopentylmethyl)ammonium ion $2H^+$ (Scheme 1) is complexed by **R** in a pseudorotaxane fashion, with threading and dethreading rateconstant values that fall in between those observed for *EE*- $1H^+$ and *ZZ*- $1H^+$ with **R**.^[16] Therefore, we envisaged that the strategy shown in Figure 1 could be implemented with a nonsymmetric axle such as *E*- $3H^+$ (Scheme 1).

The synthesis of E-**3**H⁺ was performed by reductive amination of cyclopentanecarbaldehyde with (4-nitrophenyl)methanamine, reduction of the nitro group to amine through hydrogenation and subsequent Mill's coupling with *p*-methylnitrosobenzene in acetic acid followed by anion exchange with NH₄PF₆. The *E*-**3**H⁺·PF₆ salt was fully characterized by ¹H and ¹³C NMR, DQF-COSY, ESI-MS, and UV/ Vis absorption spectroscopy.

¹H NMR spectroscopic titration experiments in acetonitrile show that E-**3**H⁺ and **R** self-assemble to yield a pseudorotaxane (Supporting Information). The corresponding thermodynamic and kinetic data are reported in Table 1, together with those for the threading–dethreading of the symmetric axles EE-**1**H⁺, ZZ-**1**H⁺ and **2**H⁺ with **R**. It can be noted that the threading rate constant k_{in} for E-**3**H⁺ is nearly half that for EE-**1**H⁺, and two orders of magnitude larger than that for **2**H⁺. This observation clearly indicates that on the observed timescale, E-**3**H⁺ pierces the ring exclusively with its Eazobenzene terminus. The decrease of the threading constant by a factor of two compared with that for EE-**1**H⁺, which can thread the ring with both its extremities, is fully consistent with this picture.

Irradiation of E-**3**H⁺ at 365 nm affords Z-**3**H⁺ with a quantum efficiency of 0.17 and a yield of over 95% at the photostationary state. Also Z-**3**H⁺ forms a pseudorotaxane with **R**, and it has a threading rate constant that is nearly half that of **2**H⁺ and almost 20 times larger than that of ZZ-**1**H⁺ (Table 1). These results show that Z-**3**H⁺ threads **R** from its cyclopentyl terminus. It is noteworthy that the $E \rightarrow Z$ photoisomerization of the azobenzene end group of **3**H⁺ also takes place efficiently when this compound is surrounded by **R**. Therefore, we can kinetically control the threading–dethreading side of **3**H⁺ by photoadjusting the steric hindrance of its

Table 1: Kinetic and thermodynamic data for the self-assembly of the investigated complexes in CD₃CN at 298 K.^[a]

Complex	<i>К</i> ^[b] [Lmol ⁻¹]	$-\Delta G^{\circ^{[c]}}$ [kcal mol $^{-1}$]	$k_{in}^{[d]}$ [Lmol ⁻¹ s ⁻¹]	$-\Delta {G^{\#}}_{in}^{[e]}$ [kcal mol $^{-1}$]	$k_{out}^{[d]}$ [s ⁻¹]	$-\Delta {G^{\#}}_{out}{}^{[e]}$ [kcal mol $^{-1}$]	$t_{1/2}^{1}$
[<i>EE</i> -1H⊂ R]PF ₆	820	3.9	37 ^[g]	15	$4.5 \times 10^{-2[h]}$	19.3	15.4 s
[ZZ-1H⊂ R]PF ₆	400	3.5	2.9×10^{-3}	20.9	7.2×10 ⁻⁶	24.5	27 h
[2 H⊂ R]PF ₆	ca. 30	2	1.3×10^{-1}	18.6	4.4×10^{-3}	20.7	2.6 min
[<i>E</i> - 3 H⊂ R]PF ₆	225	3.2	22 ^[g]	15.6	0.1 ^[h]	18.8	6.3 s
[Z- 3 H⊂ R]PF ₆	230	3.2	5.1×10^{-2}	19.2	2.6×10^{-4}	22.3	46 min

[a] The reactions were followed with ¹H NMR spectroscopy by monitoring the changes in the relative intensities of the signals associated with the probe protons in the complexed and uncomplexed ammonium ions. [b] The *K* values were obtained from four single-point measurements of the concentrations of the complexed and uncomplexed cations, in the relevant ¹H NMR spectrum, by using the expression K = [complex]/[ring][axle]. [c] The free energies of association (ΔG°) were calculated from the *K* values by using the expression $\Delta G^{\circ} = -RT \ln K$. [d] The threading (k_{in}) and dethreading (k_{out}) rate constants were calculated by fitting the concentrations of complexed and uncomplexed ammonium ions, extracted from ¹H NMR kinetics experiments. [e] The free energies of activation for the threading ($-\Delta G^{+}_{in}$) and dethreading ($-\Delta G^{+}_{out}$) processes were calculated by using the relationships $-\Delta G^{+}_{in} = -RT \ln (k_{in}h/kT)$ and $-\Delta G^{+}_{out} = -RT \ln (k_{out}h/kT)$, respectively, where *R*, *h*, and *k* correspond to the gas, Planck, and Boltzmann constants, respectively. [f] The half-life of the complexes were calculated from the k_{in} and *K* values by using the expression $t_{i/2} = \ln 2/k_{out}$. [g] Determined by stopped flow UV/Vis absorption spectroscopy. [h] Calculated from the k_{in} and *K* values by using the expression $k_{out} = k_{in}/K$.

azobenzene end group below and above that of the photoinactive cyclopentyl pseudo-stopper located at the other end.

Unfortunately, in contrast with the results found for the $[EE-1H \subset \mathbf{R}]^+$ and $[ZZ-1H \subset \mathbf{R}]^+$ pseudorotaxanes, the stability constants of $[E-3H \subset \mathbf{R}]^+$ and $[Z-3H \subset \mathbf{R}]^+$ are identical within errors (Table 1). Therefore, the dethreading of $Z-3H^+$ from the ring cannot be caused by the same photochemical stimulus that triggers the azobenzene $E \rightarrow Z$ isomerization. To promote the disassembly of the complexes^[20] we used K⁺ ions, which act as competitive guests for $\mathbf{R}^{[21,22]}$ The addition of three equivalents of KPF6 causes the complete dethreading of both $[E-3H \subset \mathbf{R}]^+$ and $[Z-3H \subset \mathbf{R}]^+$; however, while the K⁺induced disassembly of the former complex is fast, the latter exhibits a dethreading half-life of 51 min (Figure 2a). This value is much shorter than the half-life of $[ZZ-1H \subset \mathbf{R}]^+$ in the presence of K^+ (ca. 25 h, Figure 2b)^[16] and is in excellent agreement with the half-life of $Z-3H^+$ determined from the self-assembly data (46 min, Table 1). These observations indicate that the chemically induced disassembly of Z-3H⁺ and **R** takes place by extrusion of the cyclopentyl unit of the former from the cavity of the latter.



Figure 2. Concentration–time profiles, obtained from ¹H NMR data in CD₃CN at 298 K, showing the K⁺-induced dethreading of a) [Z-3H \subset **R**]⁺ and b) [ZZ-1H \subset **R**]⁺. Conditions: a) 5.1 mM Z-3H⁺, 5.4 mM **R** (about 40% complexation of the axle molecules), 15.2 mM KPF₆; b) 4.8 mM ZZ-1H⁺, 7.6 mM **R** (about 65% complexation of the axle molecules), 16.7 mM KPF₆.

The results of a summarizing experiment that illustrates the directional transit of the axle through the ring are shown in Figure 3. E-3H⁺ pierces **R** with its E-azobenzene side to form the [E-3H \subset **R**]⁺ pseudorotaxane complex, which equilibrates rapidly with its separated components. Irradiation in the near UV converts quantitatively [E-3H \subset **R**]⁺ into [Z-3H \subset **R**]⁺, which has much slower assembly–disassembly kinetics. The successive addition of K⁺ ions promotes the dethreading of Z-3H⁺ from **R** by the passage of the cyclopentyl moiety through the cavity of the ring. It should be noted that equilibration of the [Z-3H \subset **R**]⁺ complex with its separated components, which would cause the loss of the information on the threading direction of E-3H⁺, is much slower than the time required for the activation of the dethreading stimulus (addition of K⁺). Therefore, after the



Figure 3. Representation of the photochemically and chemically controlled transit of **3**H⁺ through **R** and relevant ¹H NMR spectra (400 MHz, CD₃CN, 298 K). Conditions: i) 5.0 mm *E*-**3**H⁺ and 5.0 mm **R**; ii) 365 nm, 15 min; iii) 10 mm KPF₆; iv) 344 K, 2 h; v) 30 mm [18]crown-6. Marked signals are due to the [K⊂**R**]⁺ complex.

threading event the system is "locked" by photoisomerization, and the successive addition of potassium ions causes dethreading in the same direction along which threading of E-**3**H⁺ has initially occurred. The starting species E-**3**H⁺ can be fully regenerated by thermal $Z \rightarrow E$ isomerization (half-life of 8 days at room temperature; see the Supporting Information). Sequestration of K⁺ by an excess (3 equiv) of [18]crown-6 affords the re-assembly of [E-**3**H \subset **R**]⁺ and the full reset of the system.

This molecular device, however, if it would be incorporated in a compartmentalized structure (for example, embedded in the membrane of a vesicle), could not be used to pump the molecular axle and generate a transmembrane chemical potential^[12] because the ring component has two identical faces. However, we are ready to apply the strategy developed in this work to supramolecular assemblies based on threedimensional non-symmetric macrocycles with lengths that can approach the thickness of a bilayer membrane^[23] and in which face-selective threading can be realized.^[24] Indeed, the present system is characterized by a minimalist design, facile synthesis, convenient switching, and reversibility: all of these features can foster further research developments and constitute essential requirements for future real-world applications.

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