Hydrogen-Bonded Synthetic Molecular Machines

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School of Chemistry
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A mi familia

To my family
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Abstract

Rotaxanes have unique properties that make them suitable for the construction of molecular machines. Especially remarkable is the ability of their intercomponents to move with respect to one another. This thesis reports on: 1) the development of two new methods to provoke the translation of the macrocycle along the thread ("shuttling") in hydrogen bonded, fumaramide-based [2]rotaxanes and 2) the utilization of that movement to provoke a potentially useful response.

The fumaramide template is perfectly preorganised to form four intercomponent hydrogen bonds with a benzylic amide macrocycle, affording [2]rotaxanes in "world record" yields. This preorganisation can be disrupted by photo-isomerisation (254 nm) of the E double bond to its Z counterpart. The newly formed maleamide template shows little affinity for the macrocycle. This has previously been exploited to synthesise light and heat switchable molecular shuttles.

A unique tristable molecular shuttle in which the macrocycle can be located in three different "stations" by means of thermal and photochemical stimuli is described in Chapter Two. In Chapter Three an alternative mechanism of shuttling for fumaramide-based molecular shuttles is reported. The reversibility of Diels-Alder chemistry is exploited to synthesise a chemically driven molecular shuttle. Addition of the diene to the fumaramide alkene results in both increase of the steric hindrance and disruption of the geometry of the template and therefore weakening of its binding ability towards the macrocycle.

A chiral two-station [2]rotaxane in which translational motion of the macrocycle along the thread results in a profound change in its optical properties (CD spectrum) is described in Chapter Four. Finally, a light-switchable optically-addressable molecular shuttle is discussed. A [2]rotaxane with a thread containing a fluorophore and a macrocycle functionalised to quench its fluorescence was synthesised. Shuttling of the macrocycle along the thread switched the fluorescence "on" and "off".
Declaration

The scientific work described in this Thesis was carried out in the School of Chemistry at the University of Edinburgh between September 2001 and September 2004. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification of this or any other University or institute of learning.
Attended Lectures and Meetings


2) The Role of Water in..., 5 March 2002, University of Tsukuba, Japan. 30 min presentation, “Hydrogen-bond Assembled Synthetic Molecular Shuttles”.


4) 225th ACS National Meeting, 23-27 March 2003, New Orleans, USA.


6) RSC-Organic Division, Scottish Regional Meeting, 17 December 2003, University of Edinburgh, UK. Poster presented: “Chiroptical Switching in a Bistable Molecular Shuttle”.

7) RSC-UK Macrocycles and Supramolecular Chemistry, 8-9 January 2004, University of Sheffield, UK. Poster presented: “Chiroptical Switching in a Bistable Molecular Shuttle”.


10) Exploiting Mechanical Motion In Molecular Architectures (EMMMA) network Meeting, June 2004, Leiden, Netherlands, Talk: “Optically Addressable Molecular Machines”.


12) ESF Euroconference. From Clever Molecules to Smart Materials. 11-16 September 2004. Poster presented: “Optically Addressable Molecular Machines”.

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Muchísimas gracias a mis padres por todo. Gracias a mis hermanas, Adela y Carmen, y a mi hermano, Juan, muchas gracias.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO:</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DMF (N,N'):</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>THF:</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TFA:</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>EDCI·HCl:</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>4-DMAP:</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>Et:</td>
<td>Ethyl</td>
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<tr>
<td>Me:</td>
<td>Methyl</td>
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<tr>
<td>NMR:</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>ppm:</td>
<td>part per million</td>
</tr>
<tr>
<td>mins:</td>
<td>minutes</td>
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<tr>
<td>δ:</td>
<td>chemical shift</td>
</tr>
<tr>
<td>(E):</td>
<td>\textit{trans} isomer</td>
</tr>
<tr>
<td>(Z):</td>
<td>\textit{cis} isomer</td>
</tr>
<tr>
<td>m.p.:</td>
<td>melting point</td>
</tr>
<tr>
<td>TLC:</td>
<td>Thin Layer Chromatography</td>
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<tr>
<td>FAB:</td>
<td>Fast Atom Bombardment</td>
</tr>
<tr>
<td>rt:</td>
<td>room temperature</td>
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<tr>
<td>CD:</td>
<td>Circular Dichroism</td>
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<td>mL:</td>
<td>millilitres</td>
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<tr>
<td>g:</td>
<td>grams</td>
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<tr>
<td>HRMS:</td>
<td>High Resolution Mass Spectrometry</td>
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<tr>
<td>Caled.:</td>
<td>calculated</td>
</tr>
<tr>
<td>VT:</td>
<td>Variable Temperature</td>
</tr>
</tbody>
</table>
Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. p-Xylylene diamine was distilled under reduced pressure and then recrystallised from ether. Column chromatography was performed using Kiesegel C60 (Merck, Germany) as the stationary phase. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 25 °C. Chemical shifts are reported in parts per million from low to high field and referenced to TMS. Coupling constants ($J$) are reported in hertz. Standard abbreviations indicating multiplicity are used as follows: br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. FAB mass spectrometry was carried out by the services at the University of Edinburgh. UV-vis spectra were recorded in a Perkin-Elmer Lambda 900 spectrometer. Fluorescence excitation and emission spectra were recorded using an Edinburgh Instruments FS-900 fluorimeter with L geometry at the magic angle of polarisation and at a constant temperature of 25 °C. Melting points (m.p.) were determined using a Electrothermal 9100 melting point apparatus and are uncorrected. CD measurements were recorded in the range 235-320 nm on a JASCO J-810 spectropolarimeter at 0.1 mM substrate concentration with a path length of 0.1 cm. Photo-isomerizations were carried out in quartz vessels using a multilamp photoreactor model MLU18 manufactured by Photochemical Reactors Ltd, Reading UK.
Ithaca

When setting out upon your way to Ithaca, wish always that your journey be long, full of adventure, full of lore. Of the Laestrygones and of the Cyclopes, of an irate Poseidon never be afraid; such things along your way you will not find, if lofty is your thinking, if fine sentiment in spirit and in body touches you. Neither Laestrygones nor Cyclopes, nor wild Poseidon will you ever meet, unless you bear them in your soul, unless your soul has raised them up in front of you.

Wish always that your journey be long; that many there be of summer morns when with such pleasure, such great joy, you enter ports now for the first time seen; that you may stop at some Phoenician marts, to purchase there the best of wares, mother-of-pearl and coral, amber, ebony, hedonic perfumes of all sorts-- as many such hedonic perfumes as you can; that you may go to various Egyptian towns to learn, and learn from those schooled there.

Your mind should ever be on Ithaca. Your reaching there is your prime goal. But do not rush your journey anywise. Better that it should last for many years, and that, now old, you moor at Ithaca at last, a man enriched by all you gained upon the way, and not expecting Ithaca to give you further wealth.

For Ithaca has given you the marvellous journey. Without her you would not have set your course. There is no more that she can give.

And if you find her poor, Ithaca will not have deceived you. Wise as you will have become, so full of experience, you will have understood by then what these Ithacas mean.

Constantine P. Cavafy
Synthetic Molecular Machines

"It is enough to create new names and estimations and probabilities in order to create in the long run new things."

F. Nietzsche.
Introduction

1.1 Making Artificial Molecular Machines

1.1.1 Why?

Little needs to be said to justify the interest in making artificial molecular-level machines. From myosin to F1-ATPase, Nature is full of examples of such devices\(^1\) and it is no exaggeration to say that life itself ultimately depends upon them. Constructing artificial molecular-level machines would help us understand their biological counterparts. Furthermore, molecular-size devices are the next logical step forward (or downwards) in the race for miniaturization.\(^2\) Because of this huge interest, although the field is still in its infancy, nanotechnology is in the news every other day. Just like football or any other trivial matter, everyone has an opinion on it and many views have been given on the possible outcome of such technology; from beneficial applications like molecular computing to self-replicating nanobots that will take over the world and give humankind a Stephen King-esque end. Nanoscience is even part of the political agenda. The following paragraph is extracted from the EU 2004 technical report on Nanotechnologies, and will serve to illustrate the broadness of the field (including physics, chemistry, genetics...) and the possible economical influence that nanotechnologies will have in the market in the next few years:

"Nanotechnologies refer to technologies of the very small, with dimensions in the range of nanometers. “Nannos” means “little old man” or “dwarf” in Greek. Nano (n) refers to the SI unit prefix for \(10^{-9} (= 0.000000001)\). [...] Nanotechnologies exploit specific properties that arise from structuring matter at a length scale characterized by the interplay of classical physics and quantum mechanics. Because nanotechnologies connect disciplines as diverse as physics, chemistry, genetics, information and
communication technologies (ICTs), and cognitive sciences, they offer the foundation of the so-called nano-bio-info-cogno (NBIC) “convergence”. Technology analysts expect nanotechnologies to benefit computing, medicine, materials, and the environment. The US National Science Foundation (NSF) estimates the nano market at $700 billion by 2008 and more than $1 trillion by 2015.”

In this introduction I will present a short review of the field of synthetic molecular machines to date, with the focus on rotaxane-based devices.

1.1.2 How? Taming Brownian Motion

Definitions for molecular devices and machines can be extrapolated from those of their macroscopic counterparts. Accordingly, if a device is “something invented and constructed for a special purpose” a molecular-level device can be defined as “an assembly of a discrete number of molecular components designed to perform a specific function”. And if a machine is “any combination of mechanisms for utilizing, modifying, applying or transmitting energy” a molecular-level machine is “an assembly of molecular components that can move relative to each other in response to an external stimulus, provided that movement can be used to modify, apply or transmit energy”.

Unfortunately, when it comes to designing and making molecular-level devices and machines, it is not viable to directly scale down macroscopic devices, since the physics that govern the nano-world are essentially different from those which rule the macroscopic world. Inertial forces predominate in the macroscopic world. This means objects do not move unless we give them specific energy to do so, and that once we have given them that initial impetus they will keep on moving until all that energy is dissipated - for example by friction in the form of heat. At the molecular level the effect of inertia is negligible. Atoms move constantly and randomly at any temperature above 0 K. This chaotic movement is termed Brownian motion, after botanist Robert Brown who observed it in 1827 when looking at pollen particles suspended in water through a
microscope. As a consequence of Brownian motion, at the molecular level objects (molecules) are always moving randomly and any attempt to make them move in a particular direction by applying a force on them will be outweighed by Brownian motion.  

From a practical point of view, this change in physics has several implications. Firstly, it is reasonable to say that the same techniques and tools that have proven useful to make macroscopic machines (even very small ones) are not a good choice when trying to make molecular-level machines. Working on the definition given above, if what we intend to do is to assemble molecular components, it seems sensible to opt for chemistry as the basic tool. Secondly, when trying to produce controlled movement we will need to “tame” Brownian motion, already present, rather than provoking the movement as we would need to do in the macroscopic world. This is in principle an intimidating task. In fact, even the motor proteins found in Nature do not seem to do very well at counterweighing Brownian motion. If we just consider the numbers, a typical motor protein consumes adenosine triphosphate (ATP) at a rate of 100-1000 molecules every second, which corresponds to a maximum possible power output in the region $10^{-16}$ to $10^{-17}$ W per molecule. When compared with the random environmental buffeting of $\sim 10^{-8}$ W experienced by molecules in solution at room temperature, it is surprising that they manage controlled motion at all. But Nature has found its way around this problem. To start with, all motor proteins known to date follow a “track”. Tracks reduce the degrees of freedom of the protein, so that motion does not need to be controlled in all three dimensions, only in one. To understand how motor proteins use Brownian motion to do work, we will consider kinesin as an example. Kinesin is a dimeric motor protein that transports membranous organelles, mRNA, and signalling molecules, amongst others. It consists of two identical catalytic “heads” that bind microtubules and ATP, connected to a “neck linker” which is in turn connected to a coiled spacer that leads to the cargo-binding domain. To carry out its function, kinesin takes 8.3 nm long steps along microtubules (polymers of tubulin, a dimer of $\alpha$-tubulin and $\beta$-tubulin) and, in doing so, hydrolyses ATP (Figure 1.1).
Kinesin has commonly been viewed by biologists as a motor that is fuelled by ATP, converting chemical into mechanical energy directly, just like a macroscopic motor would do. This led to a description of the movement of one head over the other as "akin to a judo expert throwing an opponent with a rearward-to-forward swing of the arm".\(^\text{10}\) However intuitive and aesthetic a metaphor, we now know that the inertial term is negligible in the nano world, so molecules cannot be "thrown forwards". Only recently it has been proposed that the motion of kinesins is fuelled by thermal energy, with ATP hydrolysis serving as a "switching mechanism" that makes one of the steps of the cycle virtually irreversible.\(^\text{11}\) According to this explanation, kinesins would use the following cycle to walk along the microtubules:

i. ATP binds to the leading head that is initially tightly bound to the microtubule and switches its conformation so that it is weakly bound to the microtubule. The kinesin's trailing head, to which adenosine diphosphate (ADP) is still bound after ATP hydrolysis and release of a phosphate, releases from the microtubule.

ii. ATP hydrolysis makes the switch mechanism irreversible by changing the protein conformation and its binding affinity.

iii. The unbound head is moved about randomly by Brownian motion in the cellular fluid until it encounters a new site where it can bind.

iv. Because of structural limits in the kinesin and spacing of binding sites on the microtubules, the moving head can reach only one possible binding site, 8 nanometres past the bound head, which temporarily remains attached to the microtubule.
v. The head binds to the new site, moving the kinesin and its cargo about 8 nanometres along the microtubule.

vi. The process starts again with the original two heads in interchanged positions.

Following this cycle, kinesin exerts work using the background thermal bath as energy source without contravening the Second Law of Thermodynamics, since an energy input — ATP hydrolysis — is necessary. Interestingly, this theory requires kinesin to walk with a “hand-over-hand” mechanism, rather than with an “inchworm” type movement, which has been proven true experimentally very recently.12

With regards to the design of artificial molecular machines, there are two main conclusions to extract from kinesin’s example. First, we need to incorporate a “track” (i.e. a fragment to which movement can be referred) as a restriction in the degrees of freedom of our molecular machine. Second, an “irreversible” step and an energy input are necessary if we want our molecular machine to do mechanical work. This condition is also necessary to achieve unidirectional motion in systems where directionality is an issue.

1.2 Synthetic molecular-level devices. The story so far.

Thus far, most examples of “molecular machines” in the literature are, in fact, molecular (or supramolecular) devices in which a certain degree of control over the movement of the components can be exerted. As discussed above, in order to achieve controlled motion at the molecular level, we need a molecular fragment to serve as reference point for the motion to be addressed and, if we want our molecular machine to do mechanical work, its working cycle must include an irreversible step and an energy input. In the next few pages, we will see some significant examples of molecular devices that show controlled motion, subdivided in different categories according to the kind of linkage between their components and whether or not they include an energy input in their working cycle.
1.2.1 Molecular devices linked through covalent bonds.

1.2.1.1 Inherent restrictions in motion by structure.

All of the examples in this section are molecules in which rotation around covalent bonds can be controlled (or, more precisely, restricted) by structural design only. Because they rely solely on Brownian motion and structural features, the devices mentioned here cannot do work against an opposing force.

The energy barriers to rotation around a C-C single bond are so low that this is generally regarded as a barrierless process at room temperature. To achieve some kind of control over it, it is necessary to raise those energy barriers; this has typically been achieved by increasing the steric demand around the bond around which we want to control rotation.

The restricted rotation of molecular components around a central carbon atom was first observed by Kwart and Alekman in 1968 when studying the $^1$H NMR of mesityl carbonium ions, 1, and their tetravalent precursors 2 (Figure 1.2).  

![Figure 1.2 Mesityl carbonium ion 1 and its tetravalent precursor 2 studied by Kwart and Alekman. The 3D models show how the methyl groups interdigitate like the cogs of a toothed wheel.](image)

In 1 and 2 the rotation of each mesityl ring about the bond linking it to the central carbon is relatively unrestricted. Calculations of internuclear distances between nonbonded atoms of a single pair of Me groups, one from each ring, showed no overlap of Van der Waals radii of the hydrogen atoms provided the rings could be assumed to rotate in
coordination and with the same angular velocity. In other words, although both aromatic rings can rotate independently, their concerted rotation is energetically favoured, so the rotation of one ring clockwise, say, leads to rotation of the other ring counter-clockwise and vice versa.

This first example inspired the design of many other similar systems, most celebratedly those investigated in the 1970s-1980s by Mislow and Iwamura. Later, the structurally complex but conceptually similar "molecular turnstiles" 3-5 (Figure 1.3) were introduced by Moore. Variable temperature $^1$H NMR studies on the methylene protons and $H_a$ and $H_b$ showed that the central aromatic ring of 4 spins rapidly on the NMR timescale at room temperature, while spindle rotation does not occur in turnstile 5 even at 85 °C due to steric constraints.

Figure 1.3 "Molecular turnstiles" reported by Bedard and Moore. The variable temperature $^1$H NMR of protons $H_a$ and $H_b$ provided evidence of spindle rotation in 4 and locked spindle in 5.
All of these devices show certain degree of restriction in the movement of their molecular components, but rotation occurs with no control over the directionality. In an attempt to achieve directional motion Kelly investigated the dynamic behaviour of a so-called “molecular ratchet”, 6.16,17

![Figure 1.4 Schematic representation of a macroscopic ratchet, structure of the “molecular ratchet” 6 and calculated enthalpy changes for rotation of the triptycene “wheel” around the helicene “pawl”.](image)

The structural features of 6 are identical to those of a macroscopic ratchet. The helical chirality of the helicene “pawl” generates an energy profile for rotation of the triptycen “wheel” that imitates the teeth on the macroscopic wheel (Figure 1.4), and might be expected to make rotation in one direction an energetically favoured process. However, 1H NMR experiments showed that rotation in 6 occurred at identical rates in both directions. This result serves as a reminder of the differences between the macroscopic and the molecular-level worlds. In the authors’ words: “In contrast to mountain climbing, [in the molecular-level world] it is only the height of the summit, not the steepness of the terrain that matters”.16 If we look at the problem from the point of view of thermodynamics, the number of molecules populating a certain energetic level depends on its state functions only, not on the pathway they followed to get there. Kelly’s molecular ratchet provides an illustration that the Second Law of Thermodynamics holds in the molecular world too: work cannot be exerted continuously
using the thermal bath as the only energy source, no matter how clever the structural design.\cite{7, 18}

### 1.2.1.2 Introducing an external “switching” mechanism.

This section includes some of the most fascinating examples of molecular machines reported to date. In contrast to the molecules discussed above, these include some sort of “switching” mechanism and can, in some cases, cause mechanical work to be done.

In 1994, Kelly and co-workers reported their studies on a “molecular brake”\cite{19}. The brake consists of a triptycene unit covalently connected to a 2,2'-bipyridine derivative (Scheme 1.1). The $^1$H NMR of 7 at 30 °C showed just one simple set of signals for the three aromatic rings in the triptycene “wheel”, providing evidence for its rapid rotation (“brake off”). Addition of Hg(O$_2$CCF$_3$)$_2$ resulted in profound changes in the $^1$H NMR spectrum; in 7-Hg all the signals corresponding to the triptycene unit appeared broad at 30°C. More importantly, at -30 °C, the three aromatic rings of the trypticene became inequivalent, consistent with the triptycene wheel’s spinning being stopped (“brake on”).

![Scheme 1.1 Chemically switchable molecular brake 7.\cite{19} Upon complexation, the bipyridine unit prevents rotation of the triptycene unit.](https://example.com/scheme1.png)

In 7-Hg, the 2,2'-bipyridine unit is forced into a conformation in which one of the pyridines is stuck between the triptycene aromatics – like a stick in the spokes of a
wheel – preventing its rotation. Additionally, Kelly’s molecular brake is a perfectly reversible system. Treatment of 7-Hg with EDTA removed the Hg$^{2+}$ ions, restoring 7. Based in the design of molecular ratchet 6, the first "chemically driven" unidirectional molecular rotor was reported by Kelly.$^{21,22}$ The partial unidirectional rotor, 8, consists of a [4]helicene “pawl” functionalised with a hydroxypropyl group and a triptycene “wheel” functionalised with an amine (Scheme 1.2)

For a better understanding of this system, the thermodynamics of molecular rotor 8 are shown schematically in Figure 1.5. Ignoring the amino group, all three possible positions for the helicene with respect to the triptycene “spokes” in 8 are energetically identical (Figure 1.5.a). Treatment of 8 with phosgene yielded isocyanate 9. Once the isocyanate has been formed, as the helicene oscillates randomly (Figure 1.5.b), sometimes the alcohol will come close enough to the isocyanate (9a) for a chemical reaction to occur to form 10 (Figure 1.5.c). Formation of the urethane is in this case the irreversible step
needed to achieve directionality mentioned above (Figure 1.5.d). Rotation in the same direction over the energy barrier to give \textbf{10a} is now an exothermic process (Figure 1.5.e and 1.5.f), while rotation in the opposite direction is virtually impossible without breaking the urethane.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.5.png}
\caption{Schematic representation of the thermodynamics of the unidirectional molecular rotor 8.}
\end{figure}

Hydrolysis of \textbf{10a} afforded \textbf{8a}, in which the chemical structure has been restored but a unidirectional 120° rotation has taken place. It is worth to note again that all the rotation steps are powered thermally, while the chemical reaction serves to bias Brownian motion in one direction. Although rotor \textbf{8} can only carry out one third of a full rotation, it demonstrates the principles required for a fully operating chemically driven rotary system and represents a noteworthy advance from the original restricted C-C bond rotation systems.

At the same time, Feringa and co-workers reported the first example of molecular motor displaying repetitive and controlled 360° unidirectional motion.\textsuperscript{23} Feringa’s rotor, \textbf{11}, is constituted by two tetrahydrophenanthrene units covalently connected by a C-C double bond. Each of the two helical groups can adopt a right-handed (\textit{P}) or a left-handed (\textit{M}) helical conformation and thermal interconversion of helicity is possible, while the
double bond shows cis-trans photo-isomerism. It is the controlled interconversion of all possible isomers of 11 that leads to a full 360° rotation.

![Diagram of Feringa's unidirectional rotor](image)

Scheme 1.3 Feringa's unidirectional rotor. The 360° unidirectional rotation is achieved in a four-step process involving alternative photo-isomerisation of the double bond and thermal interconversion of helicity.

Starting with \((P,P)\)-trans-11, UV irradiation at \(\lambda \geq 280\) nm at \(-55\) °C yielded the \((M,M)\)-cis isomer. Interconversion of helicity, while maintaining the cis configuration, is achieved by warming up the solution of \((M,M)\)-cis-11 to 20 °C to generate the more stable \((P,P)\)-cis-11, in which the two methylene groups occupy a less sterically demanding axial position. A further 180° rotation is obtained by \(Z \rightarrow E\) photo-isomerisation at \(\lambda \geq 280\) nm. This irradiation affords \((M,M)\)-trans-11 whose helicity can be inverted by heating the solution to 60 °C to obtain the original \((P,P)\)-trans-11 isomer, the most thermodynamically stable of the four isomers of the cycle. Because each step in
the cycle involves a change in helicity, the overall process could be monitored by following the changes in the CD spectrum. The correct functioning of the system depends crucially on the control of the temperature. Irradiation of \((P,P)\)-trans-11 at 60 °C results in continuous non-directional rotation.

This pioneering work was later followed by a complete investigation of structurally related compounds in the search for faster, more efficient rotors. The effect of structure on the rate-determining step of the rotation (the thermal isomerisations) was investigated in a series of second generation motors (Figure 1.6). For all examples in Figure 1.6, the slowest thermal isomerisation step has a lower kinetic barrier than that in 11. It was also observed that smaller bridging groups at Y and X reduced the activation barrier to this process.

![Figure 1.6 Second generation light-driven unidirectional rotors 12a-i and 13.](image)

A further increase in rate of rotation was achieved with the synthesis of 5-membered analogue 14. Despite the greater conformational flexibility of the cyclopentyl ring, a significant energy difference between pseudoequatorial and pseudoaxial positions of the appended methyl group still exists and unidirectional rotation occurs. Interestingly, one of the thermal isomerisations in this molecule is extremely fast, while the other is competitive with the previous systems.
In this section, we have discussed some examples of molecular machines with covalently linked components. Because this introduction focuses on molecular machines with moving components, many other molecular devices have been left out. It is still worth to mentioning them. Particularly well studied are the devices based on $E/Z$ isomerisation of stilbenes\textsuperscript{26-28} and azobenzenes\textsuperscript{29,30} or the interconversion of spiropyran with merocyanine\textsuperscript{31,32} or the ring opening and closing photo-reactions of fulgides.\textsuperscript{33,34}

All supramolecular devices,\textsuperscript{35,36} most of which are switchable host-guest systems and do not fall into the category of molecular machines have also been omitted.
1.2.2 Molecular devices linked through mechanical bonds.

Due to their extraordinary dynamic properties, interlocked architectures\textsuperscript{37-39} appear to be particularly well suited for the development of molecular machinery. Catenanes (from the Latin \textit{catena} = chain) are molecules\textsuperscript{40} in which two or more macrocycles are interlocked. Rotaxanes (from the Latin \textit{rota} = wheel and \textit{axis} = axle) are molecular species in which one or more macrocycles are threaded onto a linear component and de-threading is prevented by bulky “stoppers” (Figure 1.8).

\textbf{Figure 1.8} Cartoons representing a [2]catenane and a [2]rotaxane. The arrows show the main possible large-amplitude movements of one component with respect to the other: “pirouetting” (curved arrows) and “shuttling” (double-headed arrow).

Because the components of these species are not covalently but mechanically connected, they can move relative to each other in unique ways. One component can serve as a “track” that restricts the degrees of freedom along which the other component can move, carrying out the same function that microtubules do in the case of kinesin. There are two main kinds of large-amplitude motion in catenanes and rotaxanes: “pirouetting”, in which one ring rotates around the other – in the case of catenanes – or around the thread – in the case of rotaxanes; and “shuttling”, in which the macrocycle moves along the thread.\textsuperscript{41}
1.2.2.1 Synthesis of interlocked architectures.

It is claimed\(^4\) that in the early 1900s, Willstatter first discussed the possibility of synthesising linked macrocyclic rings. However, their actual synthesis was a formidable challenge. The first synthetic routes to this class of molecules were based on statistical approaches and were inherently extremely low yielding. In 1960, Wasserman reported the first “preparation of interlocking rings”, which was achieved in less than 1% yield.\(^4\) Seven years later, the first synthesis of a [2]rotaxane was described by Harrison and Harrison.\(^4\) This synthesis produced rotaxane in 6% yield, even after 70 reiterations using a solid-support protocol.

It was not until the early 1980s that Sauvage reported the first “templated” synthesis of a [2]catenane.\(^4\) In these landmark papers, Sauvage used Cu(I) to preorganise two phenanthroline ligands perpendicular to each other and then formed the macrocycles by alkylation of the terminal phenols with iodoethyleneglycol ethers of suitable length.
Following this strategy, Sauvage obtained catenane 15 in a synthetically viable 27% yield. More importantly, this templated synthesis was the first one to use non-covalent interactions – in this case metal-ligand bonding – to template the synthesis of an interlocked molecule. Later, similar metal-ligand interactions have been used to template the synthesis of rotaxanes and catenanes exploiting octahedral \(^{47,48}\) and square planar \(^{49}\) geometries.

The development of templated methods has continued to improve yields significantly and allowed the synthesis of sufficient amounts of rotaxanes and catenanes to study their dynamic properties. In 2001, Leigh and co-workers reported a world-record yield of 97% for the synthesis of \([2]\)rotaxane 18.\(^{50}\) In their synthesis, Leigh and co-workers utilised a fumaramide template, 16, in which the \(E\) double bond holds the two amide carbonyl groups in a close-to-ideal arrangement to form four strong hydrogen bonds with the tetraamide macrocycle. Remarkably, the effect of preorganisation is so dramatic that even the fumarate diester analogue 17 (ester carbonyls are very poor hydrogen bond acceptors)\(^{51}\) could be used to synthesise \([2]\)rotaxane 19 in 3% yield.
All of the syntheses mentioned above occur under kinetic control. As a result, if ring closure (assuming ring closure is the last step in the synthesis) does not proceed via a threaded precursor, non-interlocked macrocycles are formed. To compensate for this, most of these synthetic procedures involve using – or creating – a large excess of the macrocyclic precursor.

The synthesis of interlocked architectures under thermodynamic control allows for the system to self-correct such “mistakes”. Reversible covalent chemistry\(^{52}\) is used in this approach.\(^{53}\) This methodology is based on the fact that, typically, the non-interlocked precursors are less stable than the interlocked products because they lack the non-covalent interactions between the components present in the interlocked species. In 1994, Fujita reported the quantitative self-assembly of [2]catenane from preformed macrocyclic rings.\(^{54}\) This synthesis was based on the formation and breaking of Pd-N bonds and on hydrophobic interactions. Later, Sauvage identified the potential of applying ring closing metathesis\(^{55}\) (“RCM”) to the synthesis of interlocked architectures.\(^{56}\) Sauvage used the same phenanthroline ligands mentioned above (Scheme 1.5) but this time formed the macrocycles utilising olefin metathesis to form catenanes in high yield. In his systems, the metal template irreversibly binds the two ligands and preorganises them for interlocking. The application of metathesis ensured...
that the subsequent macrocyclisations occurred with the desired selectivity (i.e. to form the most stable species, the catenane).

Sanders attempted to use the RCM reaction to introduce true thermodynamic control into his systems, but suffered from poor yields as a result of the slow reaction kinetics.\textsuperscript{57}\textsuperscript{58} Leigh actually achieved this goal combining hydrogen bond-mediated assembly and a ring-opening-ring-closing metathesis ("RORCM") protocol to reversibly form catenanes in greater than 95% yield (Scheme 1.7).\textsuperscript{59}

![Image](image_url)

\textbf{Scheme 1.7} Leigh's 'Magic Rings': catenane synthesis under thermodynamic control.\textsuperscript{59}

When the macrocycle 20 is exposed to Grubbs' catalyst, it is reversibly ring-opened. The linear species is then able to thread through another macrocycle by hydrogen bonding to it, and subsequent ring-closure gives the [2]catenane 21. This RORCM process continues until equilibrium is established. Because the equilibrium mixture is governed by the recognition event between macrocycles and macrocycle's precursors, at high concentration (0.2M) 95% catenane 21 is formed, and at low concentration (0.0002M) catenane 21 can be converted to the macrocycle 20 in 95% yield. It is also possible to 'switch off' catenane formation by masking the recognition features of the molecules. Trifluoroacetylation of the amide groups within the catenane 21 followed by metathesis at high concentration and then deprotection results in just macrocycle formation.
To finish this section dedicated to the synthesis of interlocked architectures, we will briefly describe one of the most remarkable and recent examples. Stoddart's self-assembly of molecular Borromean rings is, arguably, the most marvellous example of synthesis of interlocked molecules. A Borromean ring is constituted by three macrocycles intertwined in such a way that each ring is "inside" one of the other two and "outside" the other (Figure 1.9). A unique feature of this structure is that cleavage of any of the three rings results in release of the other two free macrocycles.

![Figure 1.9 Two views of a Borromean ring.](image)

To achieve the synthesis of such a topologically intricate molecule, the UCLA group used a one-pot self-assembly method. This requires that each individual piece of the self-assembly process is carefully designed so that the multiple molecular recognition events between the pieces are maximized in the desired product. To this end, Stoddart's group chose to use a combination of metal-ligand and π-π stacking interactions to aid the construction of the Borromean rings. Their ligands include an "exo" bidentate ligand and a reversibly formed "endo" tridentate ligand (see Figure 1.10) that would fix the six crossover points in the right geometry when coordinated to Zn$^{2+}$. Additional π-π stacking interactions, evident in the X-ray crystal structure, also contribute to the stabilisation of the Borromean ring over other possible structures. Mixing equimolar amounts of ligands 22 and 23 and Zn(OAc)$_2$ in CD$_3$OD, Stoddart's group observed that, after 2 days under reflux, a highly symmetric compound was formed in ~90% yield. The Borromean ring system 24 was characterised by NMR, ESI mass spectroscopy and, significantly, X-ray diffraction.
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Figure 1.10 Stoddart's one-pot self-assembly of Borromean rings.\textsuperscript{60} From left to right: solid state structure of the Borromean rings 24; macrocycle reversibly formed from ligands 22 and 23 by imine bond-formation; starting materials, ligands 22 and 23.

The self-assembly of molecular Borromean rings exemplifies the state-of-the-art in the synthesis of topologically complex molecules. A challenging, structurally complex target made in a preparatively straightforward, extremely elegant way.

These examples illustrate the methods available for the synthesis of interlocked species. We will now focus on the study of the dynamic properties of rotaxanes, and how the large-amplitude motions inherent in their structure can be controlled.

1.2.3 Rotaxane-based molecular machines.

We have previously defined the two large-amplitude motions possible in a [2]rotaxane: pirouetting and shuttling (see Figure 1.8). By analogy to conformational changes in classical molecules, the relative movements between interlocked species are termed co-conformational changes.\textsuperscript{62}
While pirouetting is often observed to be occurring, its detailed experimental study by NMR can be difficult because most macrocycles are highly symmetric. Benzylic amide macrocycle-based rotaxanes possess a useful characteristic in this respect. The benzylic amide macrocycle typically adopts a chair-like conformation, which means that for each pair of benzylic protons (H_E, Figure 1.11), one is in an equatorial environment, while the other is in an axial. For a macrocycle on a symmetric thread, two ^1H NMR signals are therefore expected for the 8 benzylic protons in the molecule. In order to maintain the hydrogen bonds between the macrocyclic amide protons and the carbonyl oxygens on the thread, for a 180° rotation of the macrocycle around its thread to occur it has to result in a chair-chair flip. This co-conformational change therefore interconverts the axial and equatorial sets of protons twice during a full 360° revolution. It is possible to study chemical exchange processes such as this by variable temperature (VT) NMR techniques, including the coalescence method, or spin polarisation transfer by selective inversion recovery (SPT-SIR).

For example, the room temperature ^1H NMR spectrum in CDCl₃ of the glycylglycine-based [2]rotaxane 25 displays the fewest possible signals for the macrocycle protons, indicating rapid pirouetting of the ring at room temperature. In contrast, the pyridyl-2,6-dicarbonyl-based macrocycle in 26 displays a slightly stronger hydrogen bonding network between the components, which results in a reduction in pirouetting rate.

![Figure 1.11. Rotaxanes 25 and 26.](image_url) The arrow on 25 indicates the axis of rotation of the macrocycle.
Control over the rate of pirouetting of a benzylic amide macrocycle around the thread in fumaramide-based [2]rotaxanes has recently been achieved through $E/Z$ photo-isomerisation.$^{64}$ A series of fumaramide-based rotaxanes were synthesised and converted to their respective, $Z$ isomers (maleamide) by irradiation with UV light (Scheme 1.8).

Scheme 1.8 Fumaramide-based rotaxanes $E$-30-32 and their corresponding threads ($E$-27-28). Irradiation with UV light ($\lambda = 254$ nm) afforded their respective $Z$-isomers.$^{64}$

The change in geometry achieved by isomerisation diminishes the strength and number of hydrogen bonds between macrocycle and thread, and consequently the macrocycle spins significantly faster (up to six orders of magnitude). The $Z$ isomers can be
converted back into their $E$ analogues by simply heating them up in solution, since the fumaramide isomer is thermodynamically favoured.

Shuttling of the macrocycle along the thread can be observed if more than one binding site for the macrocyclic ring is present on the thread. The binding sites, sometimes referred to as stations, must present accessible free activation energy barriers between them and be located far enough apart so that the shuttling movement can be distinguished from any other internal motion. A [2]rotaxane containing two degenerate and well-separated stations (orange) on its thread can be considered the simplest example to study the shuttling phenomenon. In such system the macrocycle (light blue) shuttles back and forth between the two energetically identical stations, spending exactly half of its time over each of them (Figure 1.12).

\[ \Delta G \]

\[ \Delta G^\ddagger \]

**Figure 1.12** Idealised free energy profile in a degenerate two-station [2]rotaxane molecular shuttle.

The first two-station [2]rotaxane of this kind, 334$, was reported by Stoddart and co-workers in 1991 (Scheme 1.9)$^{65}$.
Molecular shuttle $33^{4+}$ consists of a tetracationic cyclophane macrocycle, a linear thread containing two hydroquinol stations (orange) and a polyether spacer. The macrocycle binds the stations via $\pi-\pi$ and charge-transfer interactions between the electron poor cyclophane and the electron rich hydroquinoles. As explained above, because both stations are energetically degenerate (they are chemically identical) the macrocyclic unit has no preference for either of them, so it shuttles between them continuously, in this case at a rate of $k = 2360 \text{ s}^{-1}$ in $(\text{CD}_{3})_{2}\text{CO}$ at 34 °C, measured by $^1\text{H}$ NMR spectroscopy. It was already noticed in Stoddart's 1991 paper that including two stations of different binding affinity in the thread could result in controlled shuttling. We will now see what the minimum requirements to achieve stimuli-responsive molecular shuttles of this kind are.

Firstly, we require one of the stations to be able to switch between a state in which it shows "high" affinity (green) and another one with "low" affinity (pink) for the macrocycle. Secondly, we require a non-switchable station (orange) which exhibits a binding affinity somewhere between the high and low affinity states of the switchable one. The macrocycle populates the stations following a Boltzmann distribution.
according to the difference in binding affinities. Therefore, when the switchable station is in its high affinity state (i), the macrocycle spends most of its time over the green station, because its binding affinity is higher than that of the intermediate, non-switchable station. When the switchable station is addressed with stimulus 1, it is transformed into its low affinity state. In this new state (ii), the macrocycle will reside preferentially over the non-reactive station which is now the one with the highest affinity. The system should ideally be reversible by application of another stimulus, 2 (Figure 1.13).

Figure 1.13 Idealised free energy profiles for a switchable molecular shuttle.

Figure 1.13 explains how the net flow of macrocycles from one station to the other is achieved. The external stimulus does not directly induce directional motion of the macrocycle, instead, by destabilizing the initially preferred binding site (stimulus 1) and/or increasing the binding strength of the less populated station (stimulus 2) the system is put out of co-conformational equilibrium. Relaxation towards the new global
energy minimum subsequently occurs via biased Brownian motion. In state (i), the activation energy for shuttling from the green to the orange station is greater than that for the reverse process. As a consequence, macrocycles shuttle “faster” from the orange to the green station than in the opposite direction. This ultimately results in a net flux of macrocycles to the green station. When stimulus 1 is applied, the difference in activation energies is reversed. It is now energetically easier to shuttle from the pink to the orange station than in the opposite way, so the system relaxes to an equilibrium in which the macrocycle spends most of its time over the orange station.

All stimuli-responsive molecular shuttles reported thus far work on these principles. We will now see several examples divided according to the kind of stimulus used.

### 1.2.3.1 pH-Switchable molecular shuttles.

Stoddart and Kaifer reported in 1994 the first example of a stimuli-responsive molecular shuttle. In rotaxane 34\textsuperscript{4+}, the biphenol and benzidine units present in the thread are both potential π-electron donor stations for the cyclophane macrocycle, and at room temperature rapid shuttling of the macrocycle occurs as in the related degenerate shuttle described above (Scheme 1.9). Cooling the sample to 229 K allows observation (by NMR and UV-visible absorption spectroscopy) of the two non-degenerate translational isomers in a ratio of 21:4 favouring encapsulation of the benzidine station. Protonation of the basic benzidine residue with CF\textsubscript{3}CO\textsubscript{2}D, affords 34\textsuperscript{2H\textsuperscript{6+}} in which electrostatic repulsion between the positively charged station and the cyclophane provokes the macrocycle to reside exclusively over the biphenol station. The system can be restored to its initial state on neutralisation with pyridine-d\textsubscript{5}. 
Interestingly, in 34\textsuperscript{4+} the shuttling can also achieved by electrochemically oxidizing the benzidine unit to its dication.

The main drawback of this pioneering work was the modest positional integrity that the shuttle exhibits when in its neutral state. Utilizing the well-known complexation of ammonium ions by crown ethers, Stoddart and co-workers went on to develop a new series of systems based on threads containing secondary alkylammonium species and crown ether macrocycles. Rotaxane 35H\textsuperscript{3+} (Scheme 1.11) was the first switchable molecular shuttle reported using these units.\textsuperscript{68,69} The crown ether macrocycle binds to the ammonium cation by means of [N\textsuperscript{+}-H\cdots O] hydrogen bonds as well as weaker [C-H\cdots O] bonds from methylene groups in the $\alpha$-position to the nitrogen. $^1$H NMR spectroscopy in CD\textsubscript{3}COCD\textsubscript{3} shows the crown ether sitting overwhelming over the cation at room temperature. Treatment of 35H\textsuperscript{3+} with diisopropylethylamine (i-Pr\textsubscript{2}NEt) resulted in deprotonation of the ammonium centre. The newly formed amine can only form very weak hydrogen bonds with the crown ether so the macrocycle now prefers to bind the alternative bipyridinium station (35\textsuperscript{2+}). The $^1$H NMR spectrum of the deprotonated rotaxane shows the system adopting the expected co-conformation with high positional integrity. The shuttling was further confirmed by UV-visible
spectroscopy, since when the macrocycle sits over the bipyridinium station it forms a yellow charge-transfer complex with it.

Scheme 1.11 A pH responsive molecular shuttle with excellent positional integrity in both chemical states.\textsuperscript{69}

Based on this system, the UCLA group went on to synthesise a “molecular elevator".\textsuperscript{70} The “elevator", 38\textbullet{}3H\textsuperscript{9+}, consists of a triple macrocyclic structure, 36, which acts as a platform, and a tripod of three thread-like components, 37\textbullet{}3H\textsuperscript{9+}. Although it is structurally much more complex, the elevator works based on exactly the same principles as molecular shuttle 35\textbullet{}H\textsuperscript{3+}, the only difference being an obvious one: over three equivalents of base or acid are required to provoke the shuttling.
A molecular shuttle which functions through anion recognition via hydrogen bonding interactions was reported in 2004 by Leigh and Keaveney. Rotaxane 39-H was synthesised exploiting the same five-component clipping strategy used in the high yielding fumaramide-based rotaxanes (see Scheme 1.6), but with a succinamide station serving as a template. As a reactive second station, the thread also includes a cinnamate derivative. In the neutral form the cinnamate phenol is a relatively poor hydrogen bond acceptor, so the macrocycle resides on the succinamide station >95% of the time (as evidenced by $^1$H NMR), where it can form four strong hydrogen bonds with the amide carbonyls. Deprotonation was achieved with several different bases (LiOH, NaOH, KOH, CsOH, Bu$_4$NOH, $t$-BuOK, DBU and Schwesinger's phosphazine P$_1$ base), yielding 39, and was expected to result in the macrocycle binding the phenolate anion with preference over the succinamide station. However, shuttling was found to be extremely solvent dependent.
Molecular systems based in hydrogen bond interactions usually perform best in 'non-competing' solvents – those with low hydrogen bonding basicity and acidity. However, if the deprotonation of 39-H is carried out in CDCl₃ or CD₂Cl₂, the macrocycle does not shuttle to bind the phenolate. Instead, the thread molecule folds over to allow the macrocycle to bind the phenolate and the succinamide station simultaneously. In contrast, in DMF-d₇ shuttling does occur upon deprotonation of 39-H, while the excellent positional integrity for the neutral form is maintained. This solvent dependence can be understood when we consider that the phenolate anion can only satisfy the hydrogen bonding requirements of two of the four NH groups in the macrocycle. In non-competing solvents, like CDCl₃, shuttling to bind the phenolate would mean to exchange four amide-to-amide with two amide-to-anion hydrogen bonds, and although the latter are significantly stronger, the loss of two interactions is
energetically disfavoured. In DMF-d₇, the hydrogen bond accepting solvent can compensate for this loss of stabilisation. The shuttling process continues to take place even in CD₃CN, only a moderate hydrogen bond acceptor, illustrating the strength of the amide-to-anion hydrogen bonds. Reprotonation of the phenol returns the system to its original state.

1.2.3.2 Redox-switchable molecular shuttles.

Apart from molecular shuttle 34⁺⁺ (see Scheme 1.10) which can also be switched electrochemically, the first redox-responsive [2]rotaxane was reported by Sauvage in 1999. Molecular shuttle 40⁺ exploits the different coordination numbers ("CN") preferred by copper(I) —CN ≤ 4- and copper(II) —CN = 5 or 6- to achieve controlled large-amplitude molecular motion. In rotaxane 40⁺ the macrocycle displays a bidentate phenanthroline ligand while the thread contains both a phenanthroline and a tridentate terpyridine units. Both of the phenanthroline ligands (thread precursor and macrocycle) are used to complex Cu(I) in a tetracoordinate fashion, templating the synthesis of the fully stoppered rotaxane (see Scheme 1.5). Upon electrochemical oxidation of Cu(I) to Cu(II) the tetrahedral geometry is destabilized and the new preferred co-conformer is that where the macrocycle resides over the terpyridine unite, allowing Cu(II) to form a five-coordinate species.
Perhaps the main downside of molecular shuttle $40^+$ is that the shuttling process occurs relatively slowly ($K = 1.5 \times 10^{-4} \text{ s}^{-1}$) because, although not stable, the Cu(II) tetracoordinate complex formed initially on oxidation is kinetically inert. A much faster redox-responsive molecular shuttle was reported by Leigh.\textsuperscript{73, 74}
The thread of [2]rotaxane 41 contains a succinamide and a naphthalamide station. In the neutral state, the tetraamide macrocycle prefers to reside over the succinamide station, as proven by $^1$H NMR, since the naphthalamide unit is only a poor hydrogen bond acceptor. However, the naphthalamide unit can be reduced both photochemically\textsuperscript{73} and electrochemically\textsuperscript{74} to form its radical anion. The naphthalamide radical anion is now the strongest hydrogen bond acceptor available, so the macrocycle binds to it preferentially. The movement of the macrocycle in 41 occurs extremely quickly ($\sim$1 $\mu$s) and could be studied by transient absorption spectroscopy (photochemically triggered shuttling) or cyclic voltammetry (electrochemically triggered shuttling). The shuttling process is reversed when the naphthalamide radical anion is oxidized back to its neutral form.
1.2.3.3 Solvent-switchable molecular shuttles.


\[ \text{Scheme 1.15 Solvent switchable molecular shuttles reported by Leigh.} \]

At room temperature in CDCl\textsubscript{3}, a non hydrogen-bonding disrupting solvent, the macrocycle shuttles rapidly between the two energetically degenerate stations and spends half of its time over each of them (see Figure 1.11). For the shuttling movement to occur, all four hydrogen bonds between the macrocycle and the peptide station must be broken. As the formation (and breaking) of hydrogen bonds depends greatly on the solvent nature, the shuttling process could be controlled by varying the solvent...
composition. Addition of as little as 0.1% CD$_3$OD to a CD$_2$Cl$_2$ solution of 44 doubles the shuttling rate (from 8 s$^{-1}$ to 16 s$^{-1}$ at 203 K). This increased shuttling rate with the addition of CD$_3$OD continues till up to 5%, when the shuttling rate is increased by more than two orders of magnitude (from 8s$^{-1}$ to 2300 s$^{-1}$ at 203 K). In response to a major change in the polarity of the environment of the rotaxane, from CDCl$_3$ to the polar, hydrogen bonding disrupting solvent DMSO-d$_6$, the macrocycle stops shuttling between the stations and resides exclusively over the lipophilic chain, as proven by $^1$H NMR spectroscopy.

1.2.3.4 Light-switchable molecular shuttles.

Together with electrochemistry, the use of light is arguably the most attractive means of switching molecular machines. It does not present one of the limiting factors to the long-term functioning of chemically-driven molecular machines, which is the build up of waste products as each cycle is repeated. Moreover, molecular-level machines that use light (or electrons) would be more amenable with the currently available technologies. The first example of a photoresponsive [2]rotaxane was published in 1997 by Nakashima and co-workers. Molecular shuttle $E/Z$-45 consists of an $\alpha$-cyclodextrin macrocycle, and a tetracationic thread containing an azobiphenoxy moiety, very closely related to azobenzene, and two bipyridinium stations. The well-known $E/Z$ isomerizations of azobenzenes and the ability of cyclodextrins to bind lipophylic compounds in water are exploited in this system to achieve shuttling. When the azobiphenoxy station is in its $trans$ form, $E$-45$^{4+}$, the cyclodextrin encapsulates it with preference over the more hydrophilic bipyridinium station.
Scheme 1.16 Photochemically-driven shuttling movement of an α-cyclodextrin in an azobenzene-containing thread through reversible E/Z photoisomerisation.\textsuperscript{76}

\textsuperscript{1}H NMR spectra of the non-interlocked thread in D\textsubscript{2}O at 30 °C shows two sets of resonances for the alkene protons of the azobenzene. In contrast, the \textsuperscript{1}H NMR of rotaxane \textit{E-45}\textsuperscript{4+} in DMSO-d\textsubscript{6} at the same temperature shows four separate signals for the same protons, due to the presence of the macrocycle over the azobiphenox station. Irradiation of \textit{E-45}\textsuperscript{4+} at 360 nm for 15 minutes causes \textit{E→Z} isomerisation of the azobenzene unit and affords \textit{Z-45}\textsuperscript{4+} in 67% yield. In \textit{Z-45}\textsuperscript{4+} the azobiphenox station does not fit into the cyclodextrin's cavity, so it shuttles to reside over the bipyridinium units. NOEs between the methylene spacer protons and the H-3 and H-5 protons of the α-cyclodextrin supported this co-conformation. The system can be reversed by irradiating \textit{Z-45}\textsuperscript{4+} at 430 nm.

More recently, a molecular shuttle that responds to photo and thermal stimulation was designed and synthesised by Leigh and co-workers.\textsuperscript{77} Molecular shuttle \textit{E/Z-46} operates through fumaramide-maleamide isomerizations. As mentioned above (see Scheme 1.8), \textsuperscript{64} while the fumaramide station is a close-to-perfect fit for the tetraamide macrocycle, its \textit{cis} isomer – maleamide – can only interact very weakly with it. The thread of rotaxane \textit{46} includes, besides the fumaramide unit, a succinamide-ester station, which contains a poor hydrogen bond acceptor ester group and lacks preorganisation. Accordingly, the
macrocycle in $E-46$ is located primarily over the fumaramide station; this is in fact the only co-conformer observable by $^1$H NMR. When $E-46$ is irradiated with UV light ($\lambda = 254$ nm), it is isomerised to its cis isomer, $Z-46$. In $Z-46$, the tetraamide macrocycle prefers to bind to the succinamide-ester with high positional integrity, since the newly formed maleamide is self-satisfied in terms of hydrogen bonding and presents the wrong geometry. To complete the shuttling cycle, $Z-46$ can be converted to $E-46$ by thermal isomerisation of the double bond back to its more stable trans isomer.

![Scheme 1.17 A light and heat-switchable molecular shuttle.77](image)

Although all of this introduction has thus far focused solely on [2]rotaxane-based molecular shuttles, the outstanding work of Leigh, Wong, Dehez and Zerbetto on
unidirectional rotation in catenane systems\textsuperscript{78} undoubtedly deserves to be an exception to that rule. A [2]catenane in which one of the macrocycles is larger and displays three binding stations of different affinity for the smaller one was designed. Two of those stations can be addressed by different stimuli in an orthogonal fashion, altering the order in relative binding affinities and provoking the smaller macrocycle to move sequentially from A to B to C to achieve net full rotation around the bigger one (Figure 1.15).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure115.png}
\caption{Stimuli-induced sequential movement of a macrocycle in a [2]catenane.\textsuperscript{78}}
\end{figure}

The chemical structures of [2]catenane \textit{47} and the related [3]catenane \textit{48} (Figure 1.16) were conceived as an extension of the work on molecular shuttle \textit{46} (Scheme 1.17). The big macrocycle in \textit{47} comprises two fumaramide stations with differing macrocycle binding affinities. In station B (red) the fumaramide the methyl groups on the fumaramide motif cause it to have lower affinity than the standard fumaramide station.\textsuperscript{79} The non-methylated fumaramide station (station A, green) is located next to a benzophenone unit. This allows selective, photosensitised isomerisation of station A by irradiation at 350 nm. Station B (red) can be photoisomerised by direct irradiation at
254 nm. The third station, a succinamide amide ester (station C, orange), is not photoactive and is intermediate in macrocycle binding affinity between the two fumaramide stations and their maleamide counterparts. A fourth station, an isolated amide group (shown as D in 48) which can make fewer intercomponent hydrogen bond contacts with the smaller macrocycle than A, B or C, is also present but only plays a significant role in the behaviour of the [3]catenane.

Let us first study the behaviour of [2]catenane 47. In the initial state (state I in Figure 1.15), the small macrocycle resides on the green, non-methylated fumaramide station. Isomerisation of this station by sensitised irradiation at 350 nm (green → blue) destabilises the system and the macrocycle finds its new energy minimum on the red station (state II). Subsequent photoisomerisation of this station by direct irradiation at 254 nm (red → pink) forces the macrocycle to move onto the succinic amide ester unit (orange, state III). Finally, heating the catenane (or treating it with photo-generated bromine radicals or piperidine) results in isomerisation of both the Z-olefins back to their E-forms (pink → red and blue → green) so that the original order of binding affinities is restored and the macrocycle returns to its original position on the green station (state I).
The $^1$H NMR spectra for each diastereomer show excellent positional integrity of the small macrocycle at all stages of the process. However, because the rotary movement is based on Brownian motion, rotation of the small macrocycle does not occur unidirectionally.

To bias the direction the macrocycle takes at each of the transformations, temporary barriers would be required in order to restrict Brownian motion in one particular direction. Such temporary barriers are intrinsically present in [3]catenane 48 (Figures 1.15 and 1.16). Irradiation at 350 nm of $E,E\text{-}48$ causes counter-clockwise rotation of the light-blue macrocycle to the succinic amide ester (orange) station to give $Z,E\text{-}48$. The light-blue macrocycle cannot rotate clockwise because the purple macrocycle effectively blocks that route. Photoisomerisation of the remaining fumaramide group is achieved by direct irradiation at 254 nm and causes the purple macrocycle to relocate to the single amide (dark green) station ($Z,Z\text{-}48$). Again, this occurs in a counter-clockwise fashion because the clockwise route is blocked by the light-blue macrocycle. This process, each macrocycle first moving and then blocking a direction of passage for the other macrocycle, is repeated throughout the sequence of transformations shown in Scheme 1.18. After three diastereomer interconversions, $E,E\text{-}48$ is again formed but 360° rotation of each of the small rings has not yet occurred, they have only swapped places. Complete unidirectional rotation of both small rings occurs only after the synthetic sequence (i)-(iii) has been completed twice.
1.2.3.5 Property changes in molecular shuttles.

In all of the systems mentioned above (and many others) controlled, large-amplitude motion of the molecular components can be achieved in response to external stimulation. The next step in the development of molecular machines is to utilize that controlled motion to produce a useful response. In this subsection, we will discuss some of these more advanced molecular machines.

The basic features of Sauvage’s metal-templated molecular shuttle 40⁺ (Scheme 1.13) were employed to synthesise a “molecular muscle” (49²⁺, Scheme 1.19) in which the shuttling motion results in extension and contraction of the molecular structure. To
achieve this, a dimeric rotaxane-like molecule was designed in which each monomer unit consists of a macrocyclic structure, displaying a bidentate phenanthroline ligand, connected to a thread-like portion which itself contains a phenanthroline ligand and a tridentate terpyridine site. Cu$I$ is used to template formation of the dimer in a tetrahedral geometry resulting in the threaded dimeric structure \(49^{2+}\). Unfortunately, in this case electrochemical oxidation to the Cu$^{III}$ species did not trigger motion, due to kinetic reasons. Instead, demetallation using KCN to give the free ligand system, followed by treatment with Zn(NO$_3$)$_2$ gives the contracted form, \(49^{4+}\), as evidenced by $^1$H NMR studies. During this process, the length of the molecule changes from approximately 85 Å to 65 Å, a reduction of 24%. The molecule can then be returned to its original length simply by treatment with excess [Cu(CH$_3$CN)$_4$]·PF$_6$. 
In molecular shuttle $E/Z\text{-}50$, a change in luminescence occurs upon shuttling. In $E\text{-}50\text{-}2H$, the $\alpha$-cyclodextrin ring resides preferentially over the trans-stilbene unit with this co-conformation being further stabilised by strong hydrogen bonds between hydroxyl groups of the cyclodextrin and the carboxylic acid groups of the isophthaloyl stopper – it is surprising that these hydrogen bond networks have not been found in the solid state structures of closely related rotaxanes reported by Anderson, and yet they are strong enough to “lock” the structure, even in a hydrogen-bonding solvent like water. Photoisomerisation of the trans-stilbene to its cis isomer was expected to cause shuttling of the $\alpha$-cyclodextrin macrocycle, because its cavity is too small for the cis-stilbene (see Scheme 1.16). However, the combined strength of the hydrophobic and hydrogen...
bonding interactions for $E$-$50$-$2H$ prevents isomerization by direct irradiation at 355 nm. Deprotonation of $E$-$50$-$2H$ using excess Na$_2$CO$_3$ effectively "unlocks" the co-conformation of $E$-$50$-$2H$ by weakening the hydrogen bonding network. When $E$-$50$-$2Na$ was irradiated at 355 nm isomerization of the stilbene unit was achieved to yield $Z$-$50$-$2Na$ (photostationary state 63:37 $Z:E$). Now, the cyclodextrin ring is forced to reside over the biphenyl group. The shuttling motion is accompanied by an increase of about 46% in the fluorescence intensity of the 4-aminonaphthalimide stopper ($\lambda_{\text{max}} = 530$ nm). This change is attributed to restriction of vibrational and rotational movement of the methylene and biaryl linkages thus disfavouring non-radiative relaxation processes. The shuttling and fluorescence changes are reversible on irradiation at 280 nm to regenerate $E$-$50$-$2Na$.

![Diagram](image_url)


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1.3 Summary and Outlook

In 1959, the Nobel Laureate Richard Feynman addressed these prophetic words to the American Physical Society as part of his lecture "There is Plenty of Room at the Bottom":

“What would be the utility of such machines? Who knows? I cannot see exactly what should happen, but I can hardly doubt that when we have some control of the arrangement of things on a molecular scale we will get an enormously greater range of possible properties that substances can have, and of the different things we can do.”

Since then, and as a result of a multidisciplinary scientific effort, the field of molecular machinery has progressed outstandingly. If we analyse Feynman’s words in detail, we can realise just how great this advancement has been. We have now made and studied systems in which the position of the molecular components can not only be controlled, but also altered at will. Even the first steps towards a greater range of substances with novel properties are now being taken.

There are, however, many issues still to address before molecular machines become truly useful tools. Amongst those, some appear particularly critical. Most of the molecular machines reported thus far work in solution, whereas applications are most likely to be found for them when those properties are somehow transferred to the solid state, surfaces or liquid-liquid interfaces. Another aspect to be considered is the necessity to look for inspiration from the molecular machines found in biology, rather than from macroscopic machines. This is necessary because the physics that govern the nano-world are different to those that rule the macroscopic world. It is now time to switch from molecular tweezers, wheel-barrows, etc, to molecular rotors, ion pumps, artificial photosynthetic systems, etc.

Despite the spectacular advances made in the last five decades, the field of molecular machinery is still in its early infancy. The valuable experience gathered so far, together with a better understanding of the physics underneath biological molecular machines
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will undoubtedly result in the widespread utilisation of molecular machines for useful tasks. In the meantime, the effort of chemists, physicists, material scientists, biologists, engineers and others might make some applications – like changing surface properties or data storage – a reality even in the short term.

1.4 Layout of this Thesis

This Thesis describes the synthesis of stimuli-responsive fumaramide-based molecular shuttles and the study of their properties. Chapter Two describes the first tristable molecular shuttle in which the macrocycle can be located in three different "stations" by means of thermal and photochemical stimuli. Chapter Three reports on the use of reversible C-C bond formation (and breaking) to induce shuttling for the first time. Chapters Four and Five represent two of the first examples of molecular shuttles in which submolecular motion can be exploited to produce a potentially useful response, namely an induced circular dichroism absorption (Chapter Four), and the quenching of fluorescence (Chapter Five).

Chapters Two to Five are presented in the form of articles that have already been published in peer-reviewed journals. No attempt has been made to rewrite the work out of context. Instead, a brief summary has been included at the start of each chapter to help put the research in perspective, and the contributions of others are gratefully acknowledged. Unfortunately, this layout – and the need to keep the Thesis to a reasonable length – leaves out most of the sad stories, both in synthesis and design. I do not repudiate the many failures, they have been very useful from a personal point of view, and have eventually led to several exciting results. However, a Thesis is meant to be the end of a PhD, and everybody likes happy endings.

I hope the reader will understand the benefits of this approach and forgive me for the little repetition (particularly in the introductions and references) that stems from it.
References and Notes

5) Except for molecules at low pressure in the gas phase.
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20) Often, this and other systems are referred to as a "chemically powered" or "chemically fuelled" in the literature. I prefer to use "chemically driven" as this rotor – and all the other examples of molecular machines in this introduction – are in fact powered by thermal noise (Brownian motion). The chemical reactions present provide the necessary energy consuming step to achieve directionality.


Rotaxanes and catenanes (and other interlocked architectures) are sometimes referred to as supramolecular complexes because their parts are not covalently connected. However, they are in fact molecules, since a covalent bond must be broken to separate the constituent parts.

In catenanes where the constituent rings are different (particularly if they are different size) the rotation of one ring (the smallest) around the other is also referred to as "shuttling".


"Slippage" is a synthetic strategy which relies on the macrocycle being able to squeeze over a judiciously chosen bulky stopper at elevated temperatures. An equilibrium is established between the threaded and free species in which the non-covalent interactions stabilise the complex. On lowering the temperature, the interlocked components no longer have sufficient energy to separate. Although slippage occurs under thermodynamic control, it is not mentioned in here because the products thus obtained are not rotaxanes, but rather "pseudorotaxanes" of considerable kinetic stability. Slippage could be used as a strategy to form rotaxanes if the stabilization gained from the ring binding on the thread was sufficient to mean that covalent bond breaking would be less energetically demanding than de-threading of the rings over the stoppers. To date no structures of this type have been reported.
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67) The effect that lowering the temperature has on this shuttle is easy to understand if one considers figure 1.13. If the difference between the activation energies for shuttling in one direction and the other is relatively small, at high temperatures (where there is plenty of energy available for the macrocycle to shuttle) the rates of shuttling become nearly identical. At low temperatures, the energy supply is effectively restricted, so the difference in shuttling rates is increased.


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79) This had already been observed as a significant decrease in yield when utilising methylated fumaramide as template for the synthesis of [2]rotaxanes when compared to non-methylated one (see ref. 48).


83) Isomerisation of the stilbene unit can only occur when thermal motion has moved the cyclodextrin away from it.
Chapter Two Synopsis

A light and heat-switchable bistable [2]rotaxane was reported by our group in 2003. The shuttle consisted of a thread containing both a fumaramide and a succinamide-ester station separated by a long spacer (a C\textsubscript{12} alkyl chain) and an isophtalamide macrocycle. Utilising a series of fumaramide-maleamide isomerisations, the macrocycle was shown to shuttle between the two possible stations with excellent positional integrity (see Scheme 1.17 in Chapter One).

With the idea of testing the structural requirements for this kind of molecular shuttle, we went on to synthesise a series of closely-related derivatives. In Chapter Two the unexpected behaviour of molecular shuttle E/Z-1, which features an “endo” pyridyl macrocycle, is reported. \(^{1}\)H NMR experiments (298K, CDCl\textsubscript{3}) prove that in E-1 the macrocycle spends most of its time (>95%) over the fumaramide unit, just like in its isophthaloyl analogue. The discrimination of the ring for the photoactive unit is maintained on lowering the temperature to 258K. Direct irradiation of a solution of E-1 at 254 nm affords the maleamide rotaxane, Z-1, in which shuttling of the macrocycle to the succinamide-ester station (co-conformer succ-Z-1) was confirmed by \(^{1}\)H NMR spectroscopy (308K, CDCl\textsubscript{3}). Unexpectedly, low temperature \(^{1}\)H NMR experiments (258K, CDCl\textsubscript{3}) on Z-1 suggest that the rotaxane adopts a co-conformation (dodec-Z-1) in which the macrocycle resides over the alkyl chain (Scheme 1).
Scheme 1 A tristable molecular shuttle.

The temperature-driven co-conformational change can be explained considering the different enthalpic and entropic contributions to the general stabilisation of each of the two co-conformers observed for Z-1. In succ-Z-1 the poor enthalpic stabilisation (there are two amide-to-amide and two weak amide-to-ester hydrogen bonds) is compensated by the lower entropic term associated with this co-conformation, in which the alkyl chain is not organised. In dodec-Z-1 the high entropic cost paid by the system to organise the thread in an “S” shape conformation is paid back by a better enthalpic stabilisation (formation of four strong amide-to-amide hydrogen bonds). Given that \( \Delta G_{\text{binding}} = \Delta H_{\text{binding}} - T \Delta S_{\text{binding}} \) if the \( \Delta S_{\text{binding}} \) terms of the two co-conformations are sufficiently different, the preference of the shuttle to adopt one co-conformation or the other can be controlled by varying the temperature. This constituted the first example of an entropy-driven molecular shuttle!

All three co-conformers (E-1, succ-Z-1 and dodec-Z-1) can be interconverted by means of several isomerization protocols. Studies of the VT-NMR of several model [2]rotaxanes as well as molecular dynamics calculations helped us to understand the
extraordinary behaviour of molecular shuttle E/Z-1 and shed light on the structural requirements for such an extraordinary tristable molecular shuttle.
Chapter Two

A tristable molecular shuttle

Published as: “Entropy-driven translational isomerism: A tristable molecular shuttle”.


Acknowledgments

The following people are gratefully acknowledged for their contributions to this chapter: Dr. G. Bottari synthesised molecular shuttle 1 for the first time and carried out most of the VT-NMR experiments; Dr. P. J. Nash synthesised rotaxane 4; Dr. J. K. Y. Wong synthesised rotaxane 6 and obtained its crystal structure; Dr. F. Dehez and Prof. F. Zerbetto carried out the computational simulations.
2.1. Introduction.

Stimuli-responsive molecular shuttles translocate a macrocycle between different sites ('stations') on a rotaxane thread under the influence of an external trigger.\(^1\) In bistable shuttles the relative macrocycle binding affinities of the stations are reversed by the stimulus, generally through it bringing about a chemical change in the molecule that targets the enthalpy of binding of the macrocycle to one or both stations.\(^2\) Immediately following the chemical transformation the molecule is no longer in the most energetically favoured co-conformation and the macrocycle moves along the thread to its newly preferred position through biased Brownian motion as the system relaxes to the global minimum.\(^3\) Although many external stimuli can be used to induce shuttling in this way (e.g. pH,\(^4\) light,\(^5\) electrochemistry\(^6\) etc.), a simple temperature change is not generally one of them.\(^7\) The Boltzmann distribution of the macrocycle between the different binding sites within a shuttle ensures that heating or cooling changes the degree of discrimination the macrocycle expresses for the various stations, but not the actual station preference of the macrocycle. However, in principle a change of relative station binding affinity with temperature is possible since \( \Delta G_{binding} = \Delta H_{binding} - T\Delta S_{binding} \). If the entropy terms are sufficiently different then the relative binding affinity of the macrocycle for the two stations can be reversed by increasing or lowering the temperature. Here we describe an example of this phenomenon.\(^8\) The [2]rotaxane where it occurs is, in fact, a tristable molecular shuttle, \(1\); the first rotaxane in which a ring can be switched between three different positions on a thread (Figure 2.1).\(^9\)
2.2. Results and discussion

Rotaxane E-1 was prepared in 32% yield from thread E-2 (Scheme 2.1). E-2 has previously been utilized as the thread for a light- and heat-switchable bistable molecular shuttle, 3, and contains two sites designed to hydrogen bond to a benzylic amide macrocycle, namely a fumaramide group (shown in green) and a succinic amide-ester (orange) unit, separated by a dodecane chain (purple). Shuttle 1 differs from 3 only in that the macrocycle contains endo-pyridine units instead of isophthalamide groups. Photoisomerisation of E-1 at 254 nm afforded the cis-rotaxane Z-1 in 54% yield. Since the xylylene units of the macrocycle shield the encapsulated regions of the thread, the position of the ring in E- and Z-1 could be determined by comparing the chemical shift of the protons in the [2]rotaxanes with those of the corresponding threads (Figure 2.2).
The \(^1\)H NMR spectra (400 MHz, 298K, Figure 2.2 a and b) confirm the position of the macrocycle over the fumaramide station of E-1 in CDCl\(_3\). The olefin protons \(H_i\) and \(H_j\) are shielded by more than 1.5 ppm in the rotaxane relative to the thread, while the chemical shifts of the succinic amide-ester protons \(H_c\) and \(H_d\) are unchanged. Lowering the temperature had no effect on the chemical shift values, the only significant change in the spectra being that the macrocycle \(H_E\) protons sharpen as the ring pirouetting about the thread becomes slow on the NMR timescale.
In Z-1, the strong binding fumaramide station is replaced with a group of much poorer macrocycle binding affinity (maleamide) and we expected the macrocycle to be displaced to the succinic amide ester site on the thread (i.e. co-conformer succ-Z-1), as occurs with Z-3.\(^5\) Whilst the chemical shifts differences (>1.2 ppm, COSY) of the H\(_e\) and H\(_d\) protons confirm that this is largely the case\(^10\) at room temperature and higher (e.g.
308 K, Figure 2.2d), to our surprise the $^1$H NMR spectrum of Z-1 proved highly temperature dependent. Indeed, at 258 K (Figure 2.2e) the major signals for $H_c$ and $H_d$ of Z-1 appear at the same chemical shifts as they do in the thread (Z-2). Not only that, but the olefin protons $H_i$ and $H_j$ are also unchanged indicating that the macrocycle is not primarily located over either of the designed stations! In fact, it is the alkyl protons of the C$_{12}$ chain that experience significant upfield shifts (up to 1 ppm at 258 K), showing that the pyridine macrocycle is actually positioned over the C$_{12}$ unit. In order to satisfy the macrocycles hydrogen bonding requirements, the amide groups of the thread must still act as hydrogen bond acceptors and so the alkyl chain presumably adopts some form of folded “S-shape” conformation so that the amides at both ends of the chain can reach the macrocycle binding sites, accounting for the shielding seen for the alkyl protons (Scheme 1, co-conformer dodec-Z-1). Interestingly, two sets of signals are observed for the macrocycle indicating that the two halves of the ring experience magnetically different environments (i.e. pirouetting of the macrocycle about the S-shaped thread is slow on the NMR timescale at 258 K).

What is the reason for Z-1’s unexpected behavior? The reversal of the binding affinity of the macrocycle for the succinic amide-ester and the alkyl chain stations at different temperatures suggests that the TAS term is reversing the relative $\Delta G_{\text{binding}}$ of the two stations (Figure 2.1). In co-conformer succ-Z-1 two hydrogen bonds from the macrocycle occur to an ester carbonyl group, a significantly weaker interaction than an amide-amide hydrogen bond, whereas in the dodec-Z-1 co-conformer four intercomponent amide-amide hydrogen bonds can be formed, providing ~2 kcal mol$^{-1}$ greater enthalpic stabilization. It seems that at low temperatures the energy gain from forming the two extra amide-amide hydrogen bonds overcomes the entropic cost required for the thread to bridge the macrocycle binding sites; a C$_{12}$ chain has >500,000 ($3^{12}$) possible C-C rotamers and a significant number of these degrees of freedom must be lost upon forming the dodec-Z-1 structure. Raising the temperature increases the contribution of the TAS term to the $\Delta G_{\text{binding}}$ of the dodec-Z-1 co-conformer much more than for succ-Z-1 until, at higher temperatures, the relative stabilities of the two positional isomers are actually
reversed and the Z-rotaxane predominantly adopts the enthalpically weaker but entropically more favorable succ-Z-1 co-conformation. Indeed, evidence that the stability of dodec-Z-1 is much more temperature-dependent than succ-Z-1 is provided by molecular dynamics simulations (see Experimental).

The structural requirements for temperature to markedly affect the position of the macrocycle on the thread are quite specific (Figure 2.3). Similar rotaxanes missing either station (4, Z,Z-5) or without the endo-pyridyl macrocycle (Z-3) do not show the same temperature-dependent \(^1\)H chemical shifts as Z-1. However, the “S” shape of the dodec-Z-1 co-conformer binding site is, remarkably, observed in the solid state structure of an isophthalamide macrocycle-containing [2]rotaxane of a thread consisting of two amide
groups separated by a C\textsubscript{12} chain (6, Figure 2.4). In fact, this type of structure may be a reasonably low energy co-conformation for many two amide-station [2]rotaxanes with flexible spacers, which with particular molecular components (poor alternative binding stations) and the right environmental conditions (low temperature), can sometimes become the global minimum arrangement seen for Z-1 at 258 K.

![Figure 2.4 X-Ray crystal structure of a benzylic isophthalamide macrocycle-based [2]rotaxane 6 where two amide groups are separated by a C\textsubscript{12} alkyl chain. The carbon atoms of the macrocycles are shown in blue, carbon atoms of the threads in yellow, oxygen atoms in red and nitrogen atoms in dark blue. The amide and C\textsubscript{12} methylene hydrogen atoms are shown in white while all others are removed for clarity. Intramolecular hydrogen bond distances and angles: O40-HN11/O40A-HN11A 1.92 Å, 156.4°.](image)

Changing the position of a macrocycle on a thread by varying the temperature is potentially a useful means of controlling translational isomerism in a rotaxane, not least because no chemical reaction is involved and no change to the covalent structure of the molecule occurs. The photostationary state of 1 at 312 nm consists of >95% of the trans-isomer (again, dissimilar behavior to shuttle 3 where the steady state at 312 nm is ~55:45 E:Z). This provides the tristable shuttle with the intriguing property that, starting with the ring on the central station (i.e. dodec-Z-1), the macrocycle can be moved selectively in one direction along the thread by irradiation with light at 312 nm, or selectively in the other direction by simply raising the temperature.
2.3. Experimental Section

The synthesis and the spectroscopic data of the precursors to rotaxanes E-1 and Z-1 have been previously reported \[ref 5g\].

\[2\]-(1,4,7,14,17,20-Hexaaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetra benzocyclohexacosane)-((E)-N-{12-[3-(2,2-diphenylethylcarbamoyl)-acryloylamino]-dodecyl}-succinamic acid 2,2-diphenylethyl ester)-rotaxane, E-1.

Rotaxane E-1 was prepared from the thread E-1 (0.19 g, 0.25 mmol) using a general procedure previously described\[5g\] for the synthesis of benzylic amide macrocycle-containing [2]rotaxanes. The crude product was subjected to column chromatography on silica gel using a gradient of CH$_2$Cl$_2$ to CH$_2$Cl$_2$/EtOAc (80/20) as eluent to obtain the desired compound as a colorless solid (E-1, 0.10 g, 32\%). $^1$H NMR (400 MHz, CDCl$_3$, 298K): $\delta$ = 9.47 (m, 4H, NH$_b$), 8.36 (d, $J$ = 7.6 Hz, 4H, CH$_b$), 8.04 (t, $J$ = 7.7 Hz, 2H, CH$_A$), 7.33-7.17 (m, 20H, ArCH), 6.82 (br s, 8H, ArCH$_2$), 6.12 (br s, 1H, NH$_b$), 6.05 (br s, 1H, NH$_h$), 5.73 (t, $J$ = 5.3 Hz, 1H, NH$_e$), 5.22 (d, $J$ = 14.5 Hz, 1H, CH$_{i,or}$), 5.16 (d, $J$ = 14.5 Hz, 1H, CH$_{i,or}$), 4.80-3.70 (br m, 8H, CH$_E$), 4.63 (d, $J$ = 7.6 Hz, 2H, CH$_b$), 4.34 (t, $J$ = 7.6 Hz, 2H, CH$_a$), 4.22 (t, $J$ = 8.0 Hz, 1H, CH$_m$), 3.97 (m, 2H, CH$_l$), 3.25 (dt, 2H, CH$_g$),
3.16 (dt, 2H, CH₂), 2.56 (t, J = 6.8 Hz, 2H, CH₂), 2.32 (t, J = 6.8 Hz, 2H, CH₂), 1.55 (m, 2H, -CH₂-CH₂), 1.44 (m, 2H, -CH₂-CH₂), 1.35-1.17 (m, 16H, -CH₂); ¹³C NMR (100 MHz, CDCl₃): δ = 172.8, 171.1, 165.2, 164.9, 163.6, 149.1, 141.4, 141.0, 138.7, 137.9, 129.0, 128.6, 128.2, 127.8, 127.3, 126.8, 124.9, 66.9, 50.3, 49.8, 44.7, 40.2, 39.6, 31.0, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 27.0, 26.8; HRMS (FAB) Calcd. for C₇₈H₈₆N₉O₉ [M+H]⁺ 1292.65485. Found 1292.65598.

[2]-(1,4,7,14,17,20-Hexaaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)−((Z)-N-{12-[3-(2,2-diphenylethylcarbamoyl)acryloylamino]-dodecyl}-succinamic acid 2,2-diphenylethyl ester)-rotaxane, Z-1.

Rotaxane Z-1 was obtained by photochemical isomerisation of E-1 (0.05 g, 0.04 mmol) at 254 nm in CH₂Cl₂ for 15 mins. The solution was concentrated under reduced pressure and subjected to chromatography on silica gel using a gradient of CHCl₃/EtOAc 3/1 as eluent to obtain the desired compound as a colorless solid (Z-1, 0.027 g, 54%). ¹H NMR (400 MHz, CDCl₃, 308K): δ = 9.21 (s, 4H, NH₂), 8.64 (br s, 1H, NH), 8.47 (d, J = 7.8 Hz, 4H, CH₂), 8.09 (br s, 1H, NH), 8.07 (t, J = 7.7 Hz, 2H, CH₂), 7.35-7.12 (m, 20H, ArCH), 6.94 (br s, 8H, ArCHF), 6.88 (br s, 1H, NH), 5.97 (d, J = 13.4 Hz, 1H, CH₁α,β), 5.83 (d, J = 13.4 Hz, 1H, CH₁α,β), 5.25-4.79 (br m, 4H, CH₂), 4.59 (d, J = 7.1 Hz, 2H, CH₂), 4.39-3.88 (br m, 4H, CH₂), 4.31 (t, J = 7.1 Hz, 1H, CH₂), 4.24 (t, J = 8.0 Hz, 1H,
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(CH₄), 4.01 (br dd, 2H, CH₂), 3.21 (br m, CH₆ + CH₇), 1.52-0.45 (br m, -CH₂- + CH₆ + CH₇); ¹³C NMR (100 MHz, CDCl₃): δ = 174.2, 171.9, 163.5, 158.1, 149.1, 141.0, 138.7, 129.0, 128.8, 128.6, 128.1, 127.7, 127.3, 126.9, 125.4, 60.4, 50.9, 49.7, 42.9, 39.7, 29.7, 29.5, 29.4, 29.2, 29.2, 26.8; HRMS (FAB) Calcd. for C₇₈H₈₆N₉O₉ [M+H]⁺ 1292.65485. Found 1292.65564.

Details of X-Ray Crystal Structure Determination

Crystallographic data for 6 (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-213301. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: teched@chemcrys.cam.ac.uk).

X-ray crystallographic data for compound 6 (CHCl₃/ether).

C₇₄H₈₀N₆O₆, M = 1149.44, crystal size 0.10 × 0.05 × 0.05 mm, monoclinic, P2₁/c, a = 11.4490(18), b = 8.8620(14), c = 31.166(5) Å, β = 94.141(4)°, V = 3153.9(9) Å³, Z = 2, ρcalcd = 1.210 Mg m⁻³; synchrotron radiation (CCLRC Daresbury Laboratory Station 9.8, silicon monochromator, λ = 0.68950 Å), μ = 0.077 mm⁻¹, T = 150(2) K. 10273 data (3210 unique, Rint = 0.0846, 2.07 < θ < 20.00°), were collected on a Siemens SMART CCD diffractometer using narrow frames (0.3° in ω), and were corrected semi-empirically for absorption and incident beam decay. The structure was solved by direct methods and refined by full-matrix least-squares on F² values of all data (G. M. Sheldrick, SHELXTL manual, Siemens Analytical X-ray Instruments, Madison WI, USA, 1994, version 5) to give wR = [Σ[w(Fo²-Fc²)²]/Σ[w(Fo²)²]]¹/² = 0.2654, conventional R = 0.1046 for F values of 3210 reflections with Fo² > 2σ(Fo²), S = 1.142 for 393 parameters. Residual electron density extremes were 0.563 and -0.765 Å⁻³. Amide hydrogen atoms were refined isotropically with the remainder constrained; anisotropic displacement parameters were used for all non-hydrogen atoms.
2.4 Computation Simulations

Simulations of Z-I were carried out at 258 and 298 K. Both the proposed dodec- and the succ- co-conformers were studied using molecular dynamics. While obtaining quantitative values of entropy from molecular modelling in solution is extremely difficult and requires very long computation times, the dynamics can still show the origin of the entropic effect. Figures 2.5a and 2.5b overlap six conformations, taken every 100 ps at 258 K, of the two main co-conformers. It appears that the alkane chain of the S-shaped system is nearly static. Some mobility is observed for the stoppers of the maleamide station (see also below).
Similarly, figures 2.5c and 2.5d overlap six conformations obtained at 298 K. Substantially larger movements of chain and stoppers are observed. For the dodec- co-conformer, however, the centre of the dodecanyl moiety is locked in place by the macrocycle and therefore the amplitude of its displacement is reduced. The pictures confirm that the alkane chain of the S-shaped system has a higher rigidity, i.e., lower entropy, than in the succinic bonded rotaxane.
A more quantitative approach considers the variation in time of the average interaction energy between macrocycle and thread. This is not an instantaneous value, rather it is the mean value obtained from the energies calculated up to a given moment in time. If the simulation is sufficiently long, the value eventually converges. Figure 2.6 (top) shows that in 200-300 ps, the interaction energy of the dodec-conformer readily converges. Satisfactorily, the interaction energy is larger at the lower temperature, where the system has a better chance to be static and little or no slippage occurs.
Figure 2.6 Variation along the dynamics of the average energy of interaction between the macrocycle and the thread. Top: dodec- co-conformer; bottom: succ- co-conformer.

Figure 2.6 (bottom) shows that in the succ- co-conformer, at 258 K, the average macrocycle-thread interaction still converges, although with some difficulty, in a similar time. At 298 K, instead, the energy is still varying after 500 ps of dynamics. From the comparison of figures 2.5b and 2.5d, the origin of the varying interaction can be assigned to the “banging” of the phenyl stoppers of the maleamide unit on the
macrocycle. At 258 K, the stopper and ring form a stable π-stack; at 298 K the π-stack is broken and formed periodically. The macrocycle-thread interaction is different when the π-complex is present. To reach a constant average value the process of breaking and forming the π-stack, which is still faster than the nmr timescale, must be sampled several times. This relatively slow motion becomes only activated with temperature and provides the crucial entropic contribution to the stability of the succ-co-conformer.

2.4.1. Computational details
Molecular dynamics calculations of Z-1 were performed in CHCl₃ with the TINKER program¹² using the MM3 model¹³ that has been successful in previous investigations on related systems.¹⁴ Initially, both conformers were optimized in the vacuum. Equilibration was then performed for 50 ps (the S-shaped system had the constraint of cross hydrogen bonding of the macrocycle with the two stations). Several cycles of simulated annealing with temperatures up to 1000 K selected the most stable geometries in the vacuum. The rotaxane was then inserted in a cubic box of 45 Å side with 669 solvent molecules. NVT simulations were performed with a time step of 1 fs and a cutoff radius of 15 Å. At either 258 or 298 K, the schedule consisted of (i) 50 ps with the geometry of the rotaxane frozen, (ii) 500 ps of equilibration, (iii) 500 ps of acquisition.
Chapter Two

References and Notes


2) Exceptions are environment-sensitive shuttles where the preferred position of the macrocycle is determined by the differing solvation of the binding sites in various solvent systems. a) A. S. Lane, D. A. Leigh, A. Murphy, J. Am. Chem. Soc. 1997, 119, 11092-11093. b) C. Gong, H. W. Gibson, Angew. Chem., Int. Ed. Engl. 1997, 36, 2331-2333. c) T. Da Ross, D. M. Guldi, A. Farran Morales, D. A. Leigh, M. Prato, R. Turco, Org. Lett. 2003, 5, 689-691. Indeed, as an alternative to cooling to 258 K in CDCl₃ the macrocycle in Z-1 (but not E-1) can be positioned over the dodecane chain at room temperature by dissolving it in d₆-DMSO.

3) The energy potentially available to do useful mechanical work through such a process corresponds to the ΔΔG(binding) of the macrocycle for the two stations in the chemically transformed shuttle.


7) A temperature change has been used to induce shuttling by bringing about a *cis-trans* isomerization reaction in one of the stations [ref 5g]. For a [2]rotaxane where a temperature increase is used to overcome a significant kinetic barrier to shuttling following a chemical change see ref 4c. A bistable [2]rotaxane that appears to undergo translational isomerism as a result of differences in the entropy of solvation of two stations has recently been reported [J. O. Jeppesen, K. A. Nielsen, J. Perkins, S. A. Vignon, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. Becher, J. F. Stoddart, *Chem. Eur. J.* **2003**, *9*, 2982-3007]
A series of interesting theoretical designs for entropy-driven mechanical motion in mechanically interlocked molecules have recently been suggested [A. Hanke, R. Metzler, Chem. Phys. Lett. 2002, 359, 22-26].


At 308 K the ratio of succ-Z-I:dodec-Z-1 is ~90:10; at 258 K it is ~15:85.


Chapter Three Synopsis

The light and heat-switchable molecular shuttles presented in Chapter Two and in the introduction, present the main advantage of showing exceptional positional integrity in all chemical states of the shuttle. Their main drawbacks are the relatively low yields of the photoisomerization reactions (typically ~50-60%) upon which they rely. Moreover, even though light is evidently one of the most attractive stimuli to use in this kind of molecular machines – since it produces no waste products – most biological molecular machines function through chemical stimulation.

With the twofold goal of improving the yields of the switching reactions and developing a chemically-driven molecular shuttle, we studied the possibility of using Diels-Alder chemistry on the fumaramide station to provoke the shuttling. Addition of cyclopentadiene to the fumaramide portion of shuttle E-1 afforded Cp-1 in good yield (90%) as a 1:1 mixture of diastereomers. In Cp-1, the two amide carbonyl groups of the newly formed station are in the wrong geometry to interact with the tetra amide macrocycle. This change in geometry, together with a significant increase in steric bulk, results in significantly decreased affinity of the macrocycle for the cycloadduct station. This was expected to incite shuttling of the macrocycle to bind to the succinamide-ester station. In fact, in Cp-1 the co-conformer in which the macrocycle binds the succinamide-ester is preferred (that is actually the only co-conformer observed) as proven by $^1$H NMR (CDCl$_3$, 298 K).

Because stereochemistry is conserved through a Diels-Alder-retro-Diels-Alder protocol (E dienophile yields trans-adduct, which in turn results in E-educt upon retro-Diels-Alder), the shuttling should be reversible utilizing retro-Diels-Alder chemistry. Heating Cp-1 to 250 °C under reduced pressure (10$^{-2}$ Torr) for 20 minutes afforded E-1 in quantitative yield. (Scheme 1).
Scheme 1 Shuttling through reversible covalent chemistry.

\[ \text{Scheme 1 Shuttling through reversible covalent chemistry.} \]

E/Cp-1 is the first molecular shuttle that functions through the reversible formation of C-C bonds. Both of the transformations E-1 → Cp-1 and Cp-1 → E-1 are preparatively simple and very high yielding, which makes the Diels-Alder-retro-Diels-Alder protocol a good candidate for switching more sophisticated molecular machines.

Remarkably -given the nature of the reactions employed and under suitable conditions- switching between E-1 and Cp-1 could be made to depend solely on the concentration of cyclopentadiene. This makes E/Cp-1 a close synthetic analogue of biological molecular motors, which typically depend on the concentration of ATP.
Chapter Three

Shuttling through reversible covalent chemistry


Acknowledgments

The following people are gratefully acknowledged for their contributions to this chapter: Dr. G. Priimov for preliminary studies on the Diels-Alder reaction; Dr. H. McNab and S. Wharton for the use of FVP equipment and advice on the retro-Diels-Alder reaction.
3.1. Introduction.

Biological machines utilize chemical reactions to control mechanical motion\(^1\) and establishing methods for generating large amplitude changes in the relative positions of the components of [2]rotaxanes (so-called 'stimuli-responsive molecular shuttles') is of interest for producing synthetic analogues of such systems.\(^2\) Molecular shuttles that undergo well-defined positional changes in response to redox processes,\(^3-10\) ion exchange,\(^11,12\) polarity changes,\(^13-16\) and photochemical\(^17-25\) and thermal\(^26\) stimuli have all been described but, somewhat surprisingly, the use of covalent bond-forming reactions in this regard has been limited to simple acid–base proton transfers.\(^27-31\) Here we describe the first example of shuttling through the formation (and breaking) of C–C bonds, using the well-established Diels–Alder\(^32,33\) ("DA") and retro-Diels–Alder\(^34\) ("r-DA") reactions.

3.2. Results and discussion.

Rotaxane \(E-1\) (Scheme 3.1) has previously been investigated as a photo-switchable molecular shuttle.\(^35\) The \textit{trans} double bond holds the two amide carbonyls of the fumaramide (green) station in a close-to-ideal arrangement for forming four strong H-bonds with the benzylic amide macrocycle.\(^36\) The succinic amide-ester station (orange) contains a poorly hydrogen bonding ester group and lacks preorganisation. Accordingly, the macrocycle in \(E-1\) is located primarily over the fumaramide unit (>95% of the time in CDCl\(_3\) at 298 K and >85% even in \(d_6\)-DMSO, a powerful hydrogen bond-disrupting solvent). Photo-isomerization of fumaramide to maleamide 'switches off' the binding affinity of the olefin station,\(^37\) resulting in the macrocycle translocating to the succinic amide-ester site.\(^35\) However, the double bond also opens up the possibility of utilising DA and r-DA chemistry to trigger the shuttling response. Addition of a diene to the fumaramide station would both change its H-bonding
geometry and increase the steric bulk between the amide groups. Indeed, CPK models suggest that a benzylic amide macrocycle would be unlikely to hydrogen bond simultaneously to both amide groups of a station derivatised as the cyclo-adduct with cyclopentadiene and the succinic amide-ester station should consequently become the positional energy minimum. Since stereochemistry is conserved through a DA-r-DA sequence (E dienophile results in trans adduct, which in turn yields E educt upon r-DA), the change in position of the macrocycle should be reversible through a r-DA reaction.

Scheme 3.1 Shuttling through reversible covalent bond formation. Absolute stereochemistry for \( Cp-2 \) and \( Cp-1 \) is depicted arbitrarily. Reaction conditions: i) isophthaloyl dichloride, \( p \)-xylylenediamine, \( \text{Et}_3\text{N}, \text{CHCl}_3 \), 57%; ii) cyclopentadiene, \( d_6\)-DMSO, 80 °C, 16 h, 90%; iii) 250 °C, \( 10^{-2} \) Torr, 20 min, \( \sim 100\% \); iv) cyclopentadiene, \( d_6\)-DMSO, 80 °C, 8 h, 93%; v) 250 °C, \( 10^{-2} \) Torr, 20 min, \( \sim 100\% \).
Accordingly, $E-1$ was treated with cyclopentadiene in $d_6$-DMSO at 80 °C for 16 h affording $Cp-1$ as a 1:1 mixture of diastereomers in 90% yield (Scheme 3.1). The $^1$H NMR spectra (CDCl$_3$, 400 MHz, 298 K) of rotaxanes $E-1$ and $Cp-1$ and the corresponding threads $E-2$ and $Cp-2$ are shown in Figure 3.1. In $Cp-1$ and $Cp-2$, the bicyclic adduct signals ($H_1$–$H_7$, dark blue, and $H_1'$–$H_7'$, red) appear at near-identical chemical shifts in both thread and rotaxane, while the succinic amide ester signals ($H_e$ and $H_d$, orange) are shifted $\sim$1.2 ppm upfield in $Cp-1$ with respect to $Cp-2$ due to the shielding effect of the xylylene rings of the macrocycle. Moreover, the NH fumaramide protons ($H_h$ and $H_k$, green) are deshielded by $\sim$1.5 ppm in $E-1$ with respect to $E-2$ through polarisation of the thread N–H bonds caused by the macrocycle H-bonding to the fumaramide carbonyl groups, but in $Cp-1$ it is the succinic amide-ester NH ($H_e$, orange) that is shifted 0.8 ppm downfield compared to its thread, with $H_h$ and $H_k$ not significantly affected. The spectroscopic data confirm that the translocation of the macrocycle from the fumaramide unit in $E-1$ to the succinic amide-ester station in $Cp-1$ proceeds with excellent positional integrity.
The covalent chemistry shuttling system proved perfectly reversible; the r-DA reaction could be accomplished by heating \( Cp-1 \) at 250 °C under reduced pressure (10⁻² Torr) for
20 minutes using the inlet oven of a flash vacuum pyrolysis (FVP) apparatus to quantitatively regenerate $E$-$1$.

An interesting consequence of the encapsulated architecture of the rotaxane is the effect the macrocycle has on the reactivity of the fumaramide station in the DA reaction.\textsuperscript{38-43} $E$-$2$ reacts with cyclopentadiene approximately twice as fast as $E$-$1$ in $d_6$-DMSO at 80 °C. If the macrocycle is acting as a non-covalently linked protecting group for the olefin during the DA reaction, the effect should be enhanced in $C_2D_2Cl_4$ since the macrocycle spends a greater amount of time over the fumaramide unit in non-polar solvents. Indeed, $E$-$2$ reacted to form $Cp$-$2$ at identical rates in $C_2D_2Cl_4$ and $d_6$-DMSO (ruling out an intrinsic solvent-effect on the DA reaction itself) but five times faster than $E$-$1$ in $C_2D_2Cl_4$ under otherwise identical conditions.

In conclusion, we have described the first example of a bistable stimuli-responsive molecular shuttle that functions through reversible C–C bond formation (DA and r-DA reactions). Both processes, $E$-$1$→$Cp$-$1$ and $Cp$-$1$→$E$-$1$, are high yielding, preparatively simple and generate large amplitude net positional changes, with excellent discrimination between the binding sites exhibited by the macrocycle in both chemical states of the shuttle. This increases both the number and breadth of methods available to switch the relative position of components in mechanically interlocked structures.
3.3. Experimental Section.

The synthesis and the spectroscopic data of rotaxane $E$-1 have been previously reported [ref 35].

$$[2](1,7,14,20\text{-Tetraaza-2,6,15,19\text{-tetraoxo-3,5,9,12,16,18,22,25\text{-tetrabenzocyclohexacosane)-2,2\text{-diphenylethyl 4-(12-(5\text{-carbamoyl)bicyclo[2.2.1]hept-2\text{-enecarboxamido)dodecylamino)-4-oxobutanoate. Rotaxane }C_p\text{-1}}$$

A solution of 0.025 g of $E$-1 (0.019 mmol) in 0.5 mL of $d_6$-DMSO in a NMR tube was treated with ~10 eq. of freshly cracked and distilled cyclopentadiene. The solution was degassed with N$_2$ and the NMR tube sealed. This solution was heated at 80 °C for 16 hrs and then allowed to cool to room temperature, extracted with CHCl$_3$ and washed with water. The organic phase was dried over MgSO$_4$, the solvent evaporated under reduced pressure and the residue purified by column chromatography (silica, CHCl$_3$/MeOH 98:2) to yield $C_p$-1 as a colourless solid (90%). Mp 180-182 °C; $^1$H NMR (CDCl$_3$, 400 MHz, 298 K) $\delta$ 8.30 (s, 2H, $H_C$ or $C'$), 8.27 (s, 2H, $H_C$ or $C'$), 8.19 (m, 8H, $H_B$ and $B$), 7.60 (t, $J =$
7.8Hz, 4H, \(H_A\) and \(A'\)), 7.46 (bt, 4H, \(H_D\) or \(D'\)), 7.39 (bt, 4H, \(H_D\) or \(D'\)), 7.35-7.10 (m, 40 H, \(H_{Ph}\)), 7.03 (s, 8H, \(H_F\) or \(F'\)), 7.01 (s, 8H, \(H_F\) or \(F'\)), 6.38 (bt, 1H, \(H_{k\alpha}\) or \(k'\)), 6.31 (m, 3H, \(H_{k\alpha}\) or \(k'\)), 6.15 (m, 2H, \(H_5\) and \(H_4\)), 6.05 (m, 2H, \(H_{h\beta}\) and \(H_5'\)), 5.85 (bt, 1H, \(H_{h\beta}\) or \(k'\)), 5.59 (m, 1H, \(H_4\)), 4.64-4.35 (m, 20H, \(H_{Ed}\) and \(H_{bd}\)), 4.19 (m, 4H, \(H_{e\alpha\epsilon}\) and \(H_{m}\)), 3.96-3.67 (m, 4H, \(H_{ld}\) and \(l'\)), 3.01-2.92 (m, 10H, \(H_{f\alpha\epsilon}\) and \(H_{g\alpha\epsilon}\) and \(g'\)), \(H_3\) and \(H_6\)), 2.81 (s, 1H, \(H_6\)), 2.76 (s, 1H, \(H_3\)), 2.63 (m, 1H, \(H_2\)), 2.56 (dd, \(J = 3.8\) Hz, \(J = 1.8\) Hz, 1H, \(H_2\)), 2.20 (d, \(J = 5.1\) Hz, 1H, \(H_1\)), 2.06 (d, \(J = 5.5\) Hz, 1H, \(H_1\)), 1.61-1.08 (m, 52H, \(H_{alkyl}\), \(H_e\) and \(c\)), \(H_d\) and \(d'\), \(H_7\) and \(H_7'\); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, 298 K) \(\delta\) 174.7, 174.6, 174.2, 174.0, 173.8, 173.3, 172.0, 171.9, 166.5, 166.4, 157.8, 141.8, 141.4, 140.7, 140.6, 138.1, 137.7, 137.6, 137.4, 134.7, 134.0, 133.9, 133.8, 133.1, 132.2, 131.4, 131.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.1, 127.0, 126.9, 126.7, 124.1, 124.0, 67.7, 67.6, 50.9, 50.7, 50.6, 50.4, 49.5, 48.8, 48.5, 48.3, 48.1, 45.1, 45.0, 44.3, 44.0, 43.9, 43.7, 39.9, 39.7, 39.6, 29.4, 29.3, 29.2, 29.1, 29.0, 28.7, 28.5, 26.8; HRMS calcd. for \(C_{85}H_{94}N_{70}O_9\) [M + H\(^+\)] 1356.71130 found (FAB, m-NBA matrix) 1356.71261.

2,2-diphenylethyl 4-(12-(5-(carbamoyl)bicyclo[2.2.1]hept-2-enecarboxamido)dodecylamino)-4-oxobutanoate. Thread \(C_p-2\)

The same procedure described above (8 h reaction time) was used to prepare \(C_p-2\) (93%) from \(E-2\). Mp 146-148 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz, 298 K) \(\delta\) 7.35-7.18 (m, 20H, \(H_{Ph}\)), 6.34 (m, 2H, \(H_3\) and \(Ph\)), 6.16 (m, 2H, \(H_3\) and \(Ph\)), 6.06 (dd, \(J = 5.7\) Hz, \(J = 2.7\) Hz, 1H, \(H_{Ph}\)).
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H₃), 5.82 (bt, 1H, H₅), 5.76 (bt, 1H, H₆), 5.66 (dd, J = 5.7 Hz, 2.7 Hz, H₄), 5.49 (bt, 2H, H₇ and H₈'), 4.63 (d, J = 7.6 Hz, 4H, H₉ and H₁₀), 4.35 (t, J = 7.6 Hz, 2H, H₁₁), 4.23 (t, J = 8.1 Hz, 1H, H₁₂ or H₁₃, 4.01-3.71 (m, 4H, H₁₄ and H₁₅), 3.17 (m, 8H, H₁₆ and H₁₇), 2.97 (s, 1H, H₁₈), 2.94 (s, 1H, H₁₉), 2.85 (m, 2H, H₂₀ and H₂₁), 2.80 (s, 1H, H₂₂), 2.58 (t, J = 6.9 Hz, 5H, H₂₃ and H₂₄), 2.33 (t, J = 6.9 Hz, 4H, H₂₅ and H₂₆), 2.24 (dd, J = 5.5 Hz, J = 1.8 Hz, 1H, H₂₇), 2.21 (dd, J = 5.5 Hz, J = 1.8 Hz, 1H, H₂₈), 1.51-1.14 (m, 44H, H₂₉ to H₄₃); ¹³C NMR (CDCl₃, 100 MHz, 298 K) δ 174.6, 174.3, 173.5, 173.2, 172.8, 157.8, 141.8, 141.0, 138.0, 137.7, 134.4, 134.0, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 126.9, 126.8, 126.7, 66.8, 50.9, 50.8, 50.7, 50.5, 49.8, 48.7, 48.6, 48.4, 48.3, 45.4, 45.1, 44.3, 43.8, 43.7, 39.6, 39.5, 31.0, 29.7, 29.6, 29.5, 29.4, 29.2, 26.8; HRMS calcd for C₃₃H₆₆N₃O₅ [M + H⁺] 824.50025 found (FAB, m-NBA matrix) 824.50116.
References and Notes


Chapter Four Synopsis

Chapters Two and Three describe two new methods to switch the position of a macrocycle in stimuli-responsive [2]rotaxanes. The next step in the path towards molecular machines would be the utilization of the shuttling motion to produce a potentially useful response. Chapter Four describes one of the first examples in which this is successfully achieved.

Molecular shuttle E/Z-1 contains a chiral glycyl-L-Leucine station and a photoactive fumaramide. In E-1, the macrocycle resides overwhelmingly over the fumaramide station -as in the shuttles described before- far away from the chiral center, and no circular dichroism ("CD") absorption is detected in the aromatic region (235-320 nm). The macrocycle is made to shuttle by photoisomerizing E-1 to obtain Z-1. In Z-1, the macrocycle is tightly bound around the chiral peptide, which results in the aromatic rings of both the macrocycle and the stoppers being held in a chiral environment. This could be observed as a strong and negative absorption in the CD spectrum of Z-1 between 235 and 280 nm.

Scheme 1 Chiroptical switching in a molecular shuttle.
The shuttling process was also confirmed by $^1$H NMR (298K, CDCl$_3$).

Thanks to a small difference between the electronic absorption spectra of E-1 and Z-1, two photostationary states of different composition could be obtained by irradiation at 254 and 312 nm. Thus we could obtain a large net change ($>1500$ deg cm$^2$ dmol$^{-1}$) in elliptical polarization by simply irradiating with light of different wavelengths. Shuttle E/Z-1 is satisfactorily fatigue-resistant, and five full switching cycles were completed by alternate irradiation at 254 and 312 nm without any observable decomposition.

This represents an innovative mode of switching to be explored for possible photonic and data storage applications. The hiding and revealing of chiral units could also find use in other areas where transmission of chirality results in a physical or chemical response, like asymmetric synthesis.
Chiroptical switching in a molecular shuttle


Acknowledgments
The following people are gratefully acknowledged for their contributions to this chapter:
Dr. G. Bottari synthesized shuttle $E/Z$-1 and obtained the circular dichroism spectra.
4.1. Introduction.

Although various methods for switching the positions of macrocycles in bistable rotaxane-based molecular shuttles have been developed,\textsuperscript{1,2} exploiting such movements to trigger property changes has thus far received little attention.\textsuperscript{3-5} Here we demonstrate one of the first examples of a property change achieved through a large amplitude translational motion in a rotaxane, a chiroptical switch in which light-induced shuttling of the macrocycle along the thread produces a strong induced circular dichroism (ICD) response when the macrocycle is hydrogen-bonded to a chiral peptide station.

4.2. Results and discussion.

Chiral dipeptides have previously been shown to induce an asymmetric response in the aromatic ring absorption bands of intrinsically achiral components of [2]rotaxanes through tight intercomponent binding in nonpolar solvents.\textsuperscript{6} The effect can be "switched off" by adding a polar solvent (e.g., MeOH) to break the hydrogen-bonding interactions between macrocycle and thread. Although triggered changes in optical properties are currently utilized in optical data storage and processing, waveguides, and other photonics applications,\textsuperscript{7,8} a solvent change is clearly unlikely to prove useful as a means of switching such real-world devices. However, the breaking (and making) of intercomponent interactions is also a feature of positionally bistable molecular shuttles. Accordingly, it seemed possible that optical properties could be influenced solely by switching the position of a macrocycle in a molecular shuttle that incorporates a chiral peptide "station".
Such a bistable shuttle, $E/Z$-1, is shown in Scheme 4.1. The idea is that in $E$-1 the macrocycle resides over the strongly macrocycle-binding fumaramide portion of the thread and the asymmetric centre is not close enough to any aromatic rings to influence
their absorption spectrum. Upon photoisomerization of the olefin station \((E-1\rightarrow Z-1)\), the ring moves to the glycyll-leucine (Gly-Leu) unit, locking the molecule in a co-conformation where aromatic rings (principally those of the C-terminal stopper\(^6\)) are held in a well-expressed chiral environment. The change in the position of the macrocycle should thus manifest itself in terms of a measurable change in the CD response.

Molecular shuttle \(E-1\) was synthesized from thread \(E-2\) in 58% yield (Scheme 4.1). Comparison of the \(^1\)H NMR spectra of the \(E\)-rotaxane and thread (Figure 4.1, a and b) shows the excellent discrimination of the macrocycle toward the different stations. While the Gly-Leu protons are only slightly affected by the aromatic shielding effect of the macrocycle, the \(E\)-olefin protons are significantly shifted upfield (~1.2 ppm), confirming that the co-conformer having the macrocycle over the olefin station is the major translational isomer in \(E-1\).
Figure 4.1 $^1$H NMR spectra (400 MHz, CDCl$_3$, 298 K) of (a) fumaramide thread E-2, (b) fumaramide rotaxane E-1, (c) maleamide thread Z-2, (d) maleamide rotaxane Z-1. The assignments correspond to the lettering shown in Scheme 4.1.

Light-induced $E \rightarrow Z$ isomerization$^9$ of the fumaramide unit reverses$^{10}$ the macrocycle-binding affinity of the two stations in the molecular shuttle because the cis-olefin (maleamide) is largely self-satisfying in terms of H-bonding and the amide carbonyl groups are no longer suitably orientated for binding to the macrocycle.$^9$ The $^1$H NMR spectra of Z-1 and Z-2 (Figure 4.1, c and d) reveal the concomitant change in the position of the macrocycle. The Z-olefin protons H$_d$ and H$_e$ occur at almost identical
chemical shifts in rotaxane and thread, whereas the Gly methylene protons are now shielded by 0.9 ppm.

![Figure 4.2](image)

**Figure 4.2** (a) CD spectra (0.1 mM in CHCl₃) at 298 K of Z-1 (blue), E-1 (purple), E-2 (green), and Z-2 (red). (b) UV-vis spectra of E-1 (purple) and Z-1 (blue) in CHCl₃ at 298 K, [ε] = mM⁻¹·cm⁻¹. Dotted line represents the Z-1/E-1 absorption ratio. (c) Percentage of E-1 in the photostationary state (from ¹H NMR data, 400 MHz, CD₃CN, 298 K) after alternating irradiation at 254 nm (half integers) and 312 nm (integers) for five complete cycles. The right-hand Y axis shows the CD absorption at 246 nm.

The shuttle design works remarkably well. When the macrocycle is tightly bound close to the Leu residue in Z-1, the aromatic rings of the rotaxane do, indeed, experience a well-expressed chiral environment as evidenced by CD spectroscopy. Of the two rotaxanes and two threads, only rotaxane Z-1 gives a CD response, which is both strong (-13k deg cm² dmol⁻¹) and, for the L-enantiomer, negative (Figure 4.2a). The absence of
any detectable signal for the \( E \)-rotaxane shows that the CD signal is genuinely only generated by controlling the position of the macrocycle in the shuttle. The most efficient ways of interconverting the rotaxane diastereomers are photochemical: 350 nm, catalytic benzophenone sensitizer, \( \text{CH}_2\text{Cl}_2 \), 70% for \( \text{E-1}\rightarrow \text{Z-1} \) and 400-670 nm, catalytic \( \text{Br}_2 \), \( \text{CH}_2\text{Cl}_2 \), >95% for \( \text{Z-1}\rightarrow \text{E-1} \) (Scheme 1). However, a modest difference in the electronic absorption spectra of \( \text{E-1} \) and \( \text{Z-1} \) (Figure 4.2b) results in different photostationary states for the isomers at 254 (56% \( \text{Z-1} \) in \( \text{CH}_2\text{Cl}_2 \); 49% \( \text{Z-1} \) in \( \text{CH}_3\text{CN} \)) and 312 nm (38% \( \text{Z-1} \) in either \( \text{CH}_2\text{Cl}_2 \) or \( \text{CH}_3\text{CN} \)), meaning that even for this first-generation system a large net change (>1500 deg cm\(^2\) dmol\(^{-1}\)) in elliptical polarization can be achieved solely through irradiation with light of different wavelengths. The photoisomerizations are highly reproducible with five complete switching cycles (\( \text{E-1}\rightarrow \text{Z-1}\rightarrow \text{E-1} \)) carried out with no decomposition detectable by NMR or CD spectroscopy (Figure 4.2c).

In conclusion, we have demonstrated a system where a large amplitude displacement of a macrocycle along a thread elicits a chiral optical response. In addition to this being a novel mode of switching to be explored for possible photonic and data storage applications, control of the expression of chirality in switchable interlocked systems through hiding or revealing chiral subunits could find important applications in areas where chiral transmission from one chemical entity to another underpins a physical or chemical response, such as the seeding of supertwisted nematic liquid crystalline phases or asymmetric synthesis.
4.3. Experimental Section.

**(2S)-**tert-Butoxycarbonylamino-4-methyl-pentanoic acid 2,2-diphenyl-ethyl ester

To a stirred solution of \( N-(\text{tert-butoxycarbonyl})-\text{L-leucine monohydrate} \) (3 g, 12 mmol) in anhydrous CHCl\(_3\) (150 mL) at 0 °C were simultaneously added under argon 4-DMAP (1.76 g, 14.4 mmol) and EDC·HCl (2.65 g, 13.8 mmol). After 5 min 2,2-diphenylethylamine (2.38 g, 12 mmol) was added and the reaction mixture allowed to stir for 16 h under inert atmosphere. The solution was then washed with 1N HCl (3 x 100 mL) and the organic layer dried over anhydrous MgSO\(_4\) and filtered. The filtrate was then evaporated under reduced pressure to obtain a colorless oil that was purified by column chromatography (petroleum ether:diethyl ether 12:1) to afford the desired compound as a colorless oil (4.65 g, 94.2%); \([\alpha]_D^5 = -28^\circ\) (c = 0.5, MeOH); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38-7.29 (m, 4H, ArCH (meta)), 7.28-7.20 (m, 6H, ArCH (ortho and para)), 4.82 (br m, 2H, CH\(H^b\) and NH\(H^a\)), 4.62 (br m, 1H, CH\(H^g\)), 4.42 (br dd, 1H, CH\(C^e\)), 4.23 (m, 1H, CH\(C^d\)), 1.48-1.40 (m, 10H, CH\(C^a\) and CH\(C^f\)), 0.82 (d, 3H, \(J=6.3\) Hz, CH\(F\)), 0.79 (d, \(J=6.5\) Hz, 3H, CH\(r\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.3, 155.3, 140.9, 140.7, 128.6, 128.2, 128.1, 126.9, 79.7, 67.2, 52.0, 49.8, 41.7, 28.3, 24.6, 22.5, 21.9; MS (FAB): \(m/z = 412\) \([M+H]^+\); Anal. Calcd for C\(_{25}\)H\(_{33}\)N\(_1\)O\(_4\): C 72.96, H 8.08, N 3.40. Found C 72.49, H 8.29, N 3.69.
(2S)-(2-tert-Butoxycarbonylamino-acetylamino)-4-methyl-pentanoic acid 2,2-
diphenyl-ethyl ester

To a stirred solution of (2S)-tert-Butoxycarbonylamino-4-methyl-pentanoic acid 2,2-
diphenyl-ethyl ester (2.30 g, 5.6 mmol) in anhydrous CHCl₃ (30 mL) was added TFA (7 mL). After 2 h the solution was reduced in volume and the remained TFA removed in vacuo. The resulting oil was taken up in anhydrous CHCl₃ (100 mL) and N-(tert-
butoxycarbonyl)-glycine (0.98 g, 5.6 mmol), 4-DMAP (0.82 g, 6.7 mmol) and EDCI-HCl (1.18 g, 6.2 mmol) added sequentially under argon at 0°C whilst stirring. After 16 h the solution was washed with 0.5N HCl (3 x 100 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the filtrate reduced in volume to obtain a yellow oil that was purified by column chromatography (CH₂Cl₂/EtOAc) (2.42 g, 91.2%); [α]°D = -23° (c = 0.5, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.29 (m, 4H, ArCH (meta)), 7.28-7.22 (m, 6H, ArCH (ortho and para)), 6.38 (d, J= 8.1 Hz, 1H, NH₆), 5.05 (br, 1H, NH), 4.80 (dd, J= 10.6 Hz, J= 8.3 Hz, 1H, CHH'₆), 4.59 (dd, J= 10.6 Hz, J= 7.3 Hz, 1H, CHH'₅), 4.53 (m, 1H, CH₇), 4.40 (br dd, 1H, CH₈), 3.73 (m, 2H, CH₉), 1.50-1.38 (m, 10H, CH₆ and CH₇), 1.34 (m, 2H, CH₈), 0.81 (d, J= 6.3 Hz, 3H, CH₉), 0.78 (d, J= 6.6 Hz, 3H, CH₁₀); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 169.1, 155.2, 140.7, 140.5, 128.6, 128.2, 128.1, 126.9, 79.7, 67.3, 50.7, 49.8, 44.2, 41.3, 28.2, 24.6, 22.6, 21.8; MS (FAB): m/z = 469 [(M+H)⁺]; Anal. Calcd for C₂₇H₃₆N₂O₅: C 69.21, H 7.74, N 5.98. Found C 69.84, H 7.52, N 6.42.
To a stirred solution of 11-aminoundecanoic acid (5 g, 24.8 mmol) in a mixture THF/H₂O (130 mL/130 mL) was added NaOH (2.18 g, 54.5 mmol). After 10 min di-tert-butyl dicarbonate was added and the reaction mixture let to stir for 20 h. The solution was reduced in volume, taken up with CHCl₃ (150 mL) and washed with 1N HCl (3 x 100 mL). The organic layer was then dried over MgSO₄, filtered and the filtrate reduced in volume to obtain a colorless powder that was recrystallized from hexane to obtain the title compound as a white solid (7.15 g, 95.8%); m.p.: 68 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.55 (br, 1H, NH), 3.12 (br, 1H, NH-CH₂), 2.37 (t, J= 7.5 Hz, 2H, CH₂-CO), 1.66 (m, 2H, CH₂-CH₂-CO), 1.54-1.41 (m, 11H, C(CH₃)₃ and CH₂), 1.40-1.24 (m, 12H, CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 179.1, 155.7, 79.1, 40.6, 34.0, 30.0, 29.4, 29.2, 29.1, 29.0, 28.9, 28.4, 26.7, 24.7; MS (FAB): m/z = 302 [(M+H)⁺]; Anal. Calcd for C₁₆H₃₁NO₄: C 63.75, H 10.37, N 4.65. Found C 63.28, H 10.08, N 4.62.
To a stirred solution of (2S)-(2-tert-Butoxycarbonylamino-acetylamino)-4-methylpentanoic acid 2,2-diphenyl-ethyl ester (2.62 g, 5.6 mmol) in anhydrous CHCl₃ (30 mL) was added TFA (6 mL). After 2 h the solution was reduced in volume and the remained TFA removed in vacuo. The resulting oil was taken up in anhydrous CHCl₃ (100 mL) and 11-tert-Butoxycarbonylamino-undecanoic acid (1.69 g, 5.6 mmol), 4-DMAP (0.82 g, 6.7 mmol) and EDCI·HCl (1.18 g, 6.2 mmol) added sequentially under argon at 0°C whilst stirring. After 16 h the solution was washed with 0.5N HCl (3 x 100 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the filtrate reduced in volume to obtain a colorless oil that was purified by column chromatography (CH₂Cl₂/EtOAc) to obtain the title product as a colorless oil (3 g, 82.1%); [α]D = -18° (c = 0.5, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.26 (m, 4H, ArCH (meta)), 7.25-7.20 (m, 6H, ArCH (ortho and para)), 6.62 (d, J= 7.8 Hz, 1H, NH₆), 6.34 (t, J= 5.0 Hz, 1H, NH₇), 4.78 (dd, J= 11.1 Hz, J= 8.6 Hz, 1H, CHH₆), 4.56 (dd, J= 11.1 Hz, J= 7.3 Hz, 2H, CHH₇ and NH₇), 4.45 (dd, J= 7.8 Hz, J= 7.0 Hz, 1H, CH₅), 4.38 (br dd, 1H, CH₅), 3.87 (d, J= 5.0 Hz, 2H, CH₅), 3.09 (m, 2H, CH₆), 2.20 (t, J= 7.7 Hz, 2H, CH₅), 1.62 (m, 2H, CH₂-CH₂), 1.50-1.39 (m, 10H, CH₂ and CH₃), 1.35-1.24 (m, 16H, CH₂ and CH₃), 0.78 (d, J= 6.6 Hz, 3H, CH₃), 0.76 (d, J= 6.6 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 172.3, 168.9, 157.9, 140.7, 140.5, 128.6, 128.2, 128.1, 126.9, 79.0, 67.3, 51.0, 49.8, 43.0, 41.0, 40.6, 36.3, 33.9, 30.0, 29.4, 29.3, 29.2, 29.1, 28.4, 26.8, 25.6, 24.6, 22.5, 21.8; MS (FAB): m/z = 652 [(M+H)+]; Anal. Calcd for C₃₈H₅₇N₃O₆: C 70.01, H 8.81, N 6.45. Found C 70.21, H 9.11, N 6.97.
To a stirred solution of 2,2-diphenylethylamine (0.50 g, 2.50 mmol), fumaric acid monoethyl ester (0.37 g, 2.50 mmol) and 4-DMAP (0.33 g, 2.70 mmol) in anhydrous CH$_2$Cl$_2$ (200 mL) at 0 °C was added EDCI·HCl (0.52 g, 2.7 mmol). After 24 h the solution was washed with a saturated solution of citric acid (3 x 50 mL) and H$_2$O (3 x 50 mL) and the organic layer dried over anhydrous MgSO$_4$, filtered and the filtrate reduced in volume to obtain a colorless solid. The title compound was purified by recrystallization from EtOAc (0.70 g, 85%). m.p. 112-113 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.34$-$7.27$ (m, 4H, ArCH (meta)), $7.26$-$7.19$ (m, 6H, ArCH (ortho and para)), $6.77$ (d, $J = 14.4$ Hz, 1H, CH$_{d\,\text{orme}}$), $6.72$ (d, $J = 14.4$ Hz, 1H, CH$_{d\,\text{orme}}$), $5.90$ (t, $J = 5.7$ Hz, 1H, NH$_t$), $4.25$-$4.15$ (m, 3H, CH$_a$ and CH$_f$), $3.98$ (dd, $J = 8.0$ Hz, $J = 5.7$ Hz, 2H, CH$_b$), $1.28$ (t, $J = 7.0$ Hz, 3H, CH$_g$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 165.6$, 163.6, 141.5, 136.0, 130.6, 128.9, 128.1, 127.0, 61.2, 50.3, 44.1, 14.1; MS (FAB): $m/z = 324 [(M+H)^+]$; Anal. Calcd. for C$_{20}$H$_{21}$NO$_3$: C 74.28, H 6.55, N 4.33. Found C 74.83, H 6.91, N 4.38.
To a stirred solution of \(N\)-(2,2-Diphenylethyl)-fumaramide acid ethyl ester (0.70 g, 2.20 mmol) in EtOH (50 mL) was added dropwise a solution of NaOH (0.10 g, 2.40 mmol) in H\(_2\)O (2.5 mL). After 16 h the solution was reduced in volume and washed several times with Et\(_2\)O to obtain a colorless powder which was recrystallized from CHCl\(_3\) (0.58 g, 91\%). m.p. >300 °C (decomp). \(^1\)H NMR (400 MHz, \(d_6\)-DMSO): \(\delta = 12.83\) (br s, 1H, OH), 8.57 (t, \(J = 5.7\) Hz, 1H, NH\(_2\)), 7.33-7.15 (m, 10H, ArCH), 6.87 (d, \(J = 15.4\) Hz, 1H, CH\(_{d\, or\, e}\)), 6.47 (d, \(J = 15.4\) Hz, 1H, CH\(_{d\, or\, e}\)), 4.22 (t, \(J = 8.0\) Hz, 1H, CH\(_{d\, or\, e}\)), (dd, \(J = 8.0\) Hz, \(J = 5.7\) Hz, 2H, CH\(_b\)); \(^{13}\)C NMR (100 MHz, \(d_6\)-DMSO) \(\delta = 168.0, 164.5, 143.1, 134.3, 134.0, 128.8, 128.2, 126.7, 50.3, 43.7\); MS (FAB): \(m/z = 296\) [(M+H)\(^+\)]; Anal. Calcd. for C\(_{18}\)H\(_{17}\)NO\(_3\): C 73.20, H 5.80, N 4.70. Found C 73.10, H 5.20, N 4.73.
(2S)-(2-[11-[(2,2-Diphenyl-ethylcarbamoyl)-(E)-acyroylaminio]-undecanoylaminio]-acetylamino)-4-methyl-pentanoic acid 2,2-diphenyl-ethyl ester

Thread E-2

To a stirred solution of (2S)-[2-[(11-tert-Butoxycarbonylamino-undecanoylaminio)-acetylamino]-4-methyl-pentanoic acid 2,2-diphenyl-ethyl ester (0.90 g, 1.38 mmol) in anhydrous CHCl₃ (20 mL) was added TFA (2 mL). After 2 h the solution was reduced in volume and the remained TFA removed in vacuo. The resulting oil was taken up in anhydrous DMF (80 mL) and N-(2,2-Diphenylethyl)-fumaramide acid (0.56 g, 1.88 mmol), 4-DMAP (0.31 g, 2.56 mmol) and EDCI-HCl (0.60 g, 3 mmol) added sequentially under argon at 0°C whilst stirring. After 16 h the solution was reduced in volume, taken up in CHCl₃ (150 mL) and washed with 0.5N HCl (3 x 100 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the filtrate reduced in volume to obtain a colorless compound that was purified by column chromatography (CHCl₃/MeOH) to yield E-2 (0.85 g, 74 %); m.p. 132°C; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.26 (m, 4H, ArCH (meta)), 7.26-7.19 (m, 6H, ArCH (ortho and para)), 7.04 (d, J= 14.9 Hz, 1H, CH₃), 7.00 (d, J= 7.4 Hz, 1H, NH), 6.87 (t, J= 5.9 Hz, 1H, NH), 6.75 (d, J= 14.9 Hz, 1H, CH₃), 6.54 (t, J= 5.2 Hz, 1H, NH), 6.18 (t, J= 5.4 Hz, 1H, NH), 4.74 (dd, J= 11.1 Hz, J= 8.6 Hz, 1H, CH₂), 4.55 (dd, J= 11.1 Hz, J= 7.3 Hz, 1H, CH₂), 4.55 (dd, J= 7.8 Hz, J= 7.4 Hz, 1H, CH₂), 4.37 (br dd, 1H, CH₂), 4.22 (t, J= 7.8 Hz, 1H, CH₂), 3.99 (d, J= 7.8 Hz, J= 5.4 Hz, 1H, CH₂), 3.91 (t, J= 5.2 Hz, 2H, CH₂), 3.32 (m, 2H, CH₂), 2.22 (t, J= 7.3 Hz, 2H, CH₂), 1.63 (m, 2H, CH₂), 1.55 (m, 2H, CH₂), 1.43 (m, 1H, CH₂), 1.36-1.26 (m, 14H, CH₃ and CH₄), 0.75 (d, J= 6.6 Hz, 3H, CH₃), 0.74 (d, J= 6.3 Hz, 3H, CH₄); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 172.4, 169.3, 165.0, 164.8, 142.0, 140.8, 140.6, 133.7, 132.5, 128.7), 128.6, 128.5, 128.2,
128.1, 128.0, 126.9, 126.8, 67.2, 51.0, 50.2, 49.8, 44.4, 43.2, 40.8, 39.9, 36.1, 29.3, 29.2, 29.1, 29.0, 28.9, 26.9, 25.6, 24.6, 22.6, 21.8; HRMS (FAB) Calcd. for C_{51}H_{65}N_{4}O_{6} [M+H]^+ 829.49041. Found 829.48997.

[2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzo[cyclohexacosane)-(2S)-(2-[11-3-(2,2-diphenyl-ethylcarbamoyl)-(E)-acryloylamino]-undecanoylamino]acetylamino)-4-methyl-pentanoic acid 2,2-diphenyl-ethyl ester)

Rotaxane, E-1

To a stirred solution of E-2 (0.40 g, 0.48 mmol) in anhydrous CHCl₃ (100 mL) was added simultaneously solutions of para-xylylenediamine (0.78 g, 5.76 mmol) and Et₃N (1.16 g, 11.5 mmol) in CHCl₃ (40 mL), and isophthaloyl dichloride (1.17 g, 5.76 mmol) in CHCl₃ (40 mL) over a period of 2 h using motor-driven syringe pumps. After a further 2 h the resulting suspension was filtered and the filtrate concentrated under reduced pressure to afford the crude product that was purified by column chromatography on silica gel using a gradient of CHCl₃ to CHCl₃/acetonitrile (1/1) as eluent to obtain the desired compound as a colorless powder (E-1, 0.38 g, 58%);
Rotaxane *E-1* can also be obtained by direct irradiation of a dilute solution of rotaxane *Z-1* in CH$_2$Cl$_2$ at 312nm for 20 min in a quartz vessel (*E-1*, 62%) using a multilamp photo-reactor, by irradiation of a solution of *Z-1* in CH$_2$Cl$_2$ at 350nm in the presence of catalytic bromine (*E-1*, >95%) or by thermal-isomerisation of its isomer *Z-1* at 130°C in C$_2$D$_2$Cl$_4$ for 6 days (*E-1*, 95%); m.p. 194 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.42 (s, 2H, ArCH$_C$), 8.15 (d, $J$= 7.3 Hz, 4H, ArCH$_B$), 7.67 (s br, 4H, NH$_D$), 7.60 (t, $J$= 7.3 Hz, 2H, ArCH$_A$), 7.34-7.25 (m, 8H, ArCH (meta)), 7.25-7.16 (m, 12H, ArCH (ortho and para)), 7.15 (br t, 1H, NH$_D$), 6.96 (s, 8H, ArCH$_E$), 6.90 (br t, 1H, NH$_C$), 6.79 (d, $J$= 7.6 Hz, 1H, NH$_B$), 6.32 (t, $J$= 4.9 Hz, 1H, NH$_I$), 5.81 (d, $J$= 15.2 Hz, 1H, CH$_{d, or e}$), 5.68 (d, $J$= 15.2 Hz, 1H, CH$_{d, or e}$), 4.78 (dd, $J$= 10.9 Hz, $J$= 8.3 Hz, 1H, CHH'$_p$), 4.54 (dd, $J$= 10.9 Hz, $J$= 7.3 Hz, 1H, CHH'$_p$), 4.48-4.41 (br d, 9H, CH$_E$ and CH$_I$), 4.38 (m, 1H, CH$_A$), 4.21 (t, $J$= 7.7 Hz, 1H, CH$_A$), 3.84 (br t, 2H, CH$_b$), 3.71 (d, $J$= 4.9 Hz, 2H, CH$_j$), 3.12 (m, 2H, CH$_g$), 2.12 (t, $J$= 7.5 Hz, 2H, CH$_h$), 1.54 (m, 2H, CH$_2$-CH$_h$), 1.46 (m, 3H, CH$_2$-CH$_g$ and CH$_j$), 1.29-1.17 (m, 14H, CH$_2$ and CH$_m$), 0.78 (d, $J$= 5.3 Hz, 3H, CH$_o$), 0.76 (d, $J$= 5.5 Hz, 3H, CH$_o$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.7, 172.3, 168.7, 166.7, 165.3, 165.0, 141.4, 140.7, 140.5, 137.1, 133.8, 131.3, 130.5, 129.8, 129.1, 129.0, 128.9, 128.6, 128.5, 128.1, 128.0, 127.8, 127.1, 127.0, 124.5, 67.4, 51.0, 50.3, 49.8, 44.7, 44.1, 42.9, 41.0, 40.1, 36.0, 29.1, 29.0, 28.7, 26.8, 25.5, 24.6, 22.5, 21.9; HRMS (FAB) Calcd. for C$_{83}$H$_{93}$N$_8$O$_{10}$ [M+H]$^+$ 1361.70147. Found 1361.70093.
A CH$_2$Cl$_2$ solution (20 mL) of E-2 (0.10 g, 0.12 mmol) in a quartz vessel was directly irradiated for 40 min at 254 nm using a multilamp photo-reactor. The reaction mixture was concentrated under reduced pressure to afford the crude product that was subjected to column chromatography on silica gel using a gradient of CHCl$_3$ to CHCl$_3$/EtOAc (1/3) as eluent to obtain the desired compound as a colorless powder (Z-2, 0.05 g, 54%); m.p. 121 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.49 (t, $J= 5.8$ Hz, 1H, NH$_t$), 7.97 (t, $J= 5.3$ Hz, 1H, NH$_t$), 7.35-7.18 (m, 20H, ArCH), 6.62 (d, $J= 7.8$ Hz, 1H, NH$_k$), 6.33 (t, $J= 5.2$ Hz, 1H, NH$_k$), 6.00 (d, $J= 13.1$ Hz, 1H, CH$_{d'ord'e}$), 5.92 (d, $J= 13.1$ Hz, 1H, CH$_{d'ord'e}$), 4.78 (dd, $J= 11.1$ Hz, $J= 8.3$ Hz, 1H, CH$_{H'p}$), 4.56 (dd, $J= 11.1$ Hz, $J= 7.3$ Hz, 1H, CH$_{H'p}$), 4.45 (m, 1H, CH$_i$), 4.38 (d, $J= 8.0$ Hz, 1H, CH$_q$), 4.26 (d, $J= 8.0$ Hz, 1H, CH$_q$), 3.95 (dd, $J= 8.0$ Hz, $J= 5.8$ Hz, 2H, CH$_h$), 3.83 (d, $J= 5.2$ Hz, 2H, CH$_h$), 3.24 (br dt, 2H, CH$_g$), 2.20 (t, $J= 7.6$ Hz, 2H, CH$_h$), 1.61 (m, 2H, CH$_2$-CH$_h$), 1.53 (m, 2H, CH$_2$-CH$_g$), 1.44 (m, 1H, CH$_o$), 1.36-1.27 (m, 14H, CH$_2$ and CH$_m$), 0.79 (d, $J= 6.6$ Hz, 3H, CH$_o$), 0.77 (d, $J= 6.6$ Hz, 3H, CH$_o$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.7, 172.3, 168.8, 165.1, 164.6, 141.8, 140.7, 140.6 7, 133.4, 131.3, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.0, 126.9, 126.8, 67.3, 51.0, 50.3, 49.8, 44.2, 43.0, 41.0, 39.8, 36.3, 29.3, 29.2, 29.1, 29.0, 28.9, 26.9, 25.5, 24.7, 22.5, 21.8; HRMS (FAB) Calcd. for C$_{51}$H$_{65}$N$_4$O$_6$ [M+H]$^+$ 829.49041. Found 829.49082.
[2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-
tetrabenzoazyclohexacosane)-(2S-(2-{11-[3-(2,2-diphenyl-ethylcarbamoyl)-(Z)-
adryloylamino]-undecanoylamino}--acytalamino)-4-methyl-pentanoic acid 2,2-
diphenyl-ethyl ester)

Rotaxane, Z-1

A CH$_2$Cl$_2$ (20 mL) solution of E-1 (0.26 g, 0.19 mmol) in a quartz vessel was directly
irradiated for 20 mins at 254 nm using a multilamp photo-reactor. The reaction mixture
was concentrated under reduced pressure to afford the crude product that was subjected
to column chromatography on silica gel using a gradient of CHCl$_3$ to CHCl$_3$/EtOAc
(1/1.5) as eluent to obtain the desired compound as a colorless powder (Z-1, 0.14 g, 56%
). Rotaxane Z-1 can also be obtained by irradiation of a solution of E-1 in CH$_2$Cl$_2$ at
350nm in the presence of benzophenone as a sensitiser (Z-1, 0.14 g, 56 %); m.p. 169 °C; $^1$H
NMR (400 MHz, CDCl$_3$) δ 8.60 (t, $J= 5.2$ Hz, 1H, NH$_A$), 8.48 (t, $J= 5.3$ Hz, 1H, NH$_C$),
8.34 (s, 2H, ArCH$_C$), 8.15 (d, $J= 7.8$ Hz, 4H, ArCH$_D$), 7.74 (d, $J= 7.3$ Hz, 1H, NH$_B$),
7.56 (t, $J= 7.8$ Hz, 2H, ArCH$_A$), 7.55 (br s, 4H, NH$_D$), 7.31-7.12 (m, 28H, ArCH$_B$ and
ArCH$_E$), 6.01 (d, $J= 13.4$ Hz, 1H, CH$_{d' or e'}$), 5.89 (d, $J= 13.4$ Hz, 1H, CH$_{d' or e'}$), 5.63 (d,
Chapter Four

\[ J = 3.8 \text{ Hz, } 1\text{H, } \text{NH} \], \( 4.76 \text{ (dd, } J = 11.1 \text{ Hz, } 1\text{H, } \text{CH}_2 \text{H}_p \), \( 4.58-4.43 \text{ (m, } 8\text{H, } \text{CH}_2 \text{)}, \( 4.40 \text{ (dd, } J = 11.1 \text{ Hz, } J = 7.3 \text{ Hz, } 1\text{H, } \text{CH}_2 \text{H}_p \), \( 4.28 \text{ (br dd, } 1\text{H, } \text{CH}_2 \text{)}, \( 4.25 \text{ (t, } J = 8.0 \text{ Hz, } 1\text{H, } \text{CH}_2 \text{)}, \( 4.19 \text{ (m, } 1\text{H, } \text{CH}_2 \text{)}, \( 3.92 \text{ (dd, } J = 8.0 \text{ Hz, } J = 5.8 \text{ Hz, } 2\text{H, } \text{CH}_2 \text{)}, \( 3.11 \text{ (m, } 2\text{H, } \text{CH}_2 \text{)}, \( 2.90 \text{ (d, } J = 3.8 \text{ Hz, } 2\text{H, } \text{CH}_2 \text{)}, \( 1.71 \text{ (t, } J = 8.0 \text{ Hz, } 2\text{H, } \text{CH}_2 \text{)}, \( 1.48-1.37 \text{ (m, } 3\text{H, } \text{CH}_2 \text{CH}_g \text{ and } \text{CH}_h \text{)}, \( 1.35-0.95 \text{ (m, } 16\text{H, } \text{CH}_2 \text{ and } \text{CH}_m \text{)}, \( 0.77 \text{ (d, } J = 6.8 \text{ Hz, } 3\text{H, } \text{CH}_2 \text{)}, \( 0.75 \text{ (d, } J = 6.8 \text{ Hz, } 3\text{H, } \text{CH}_o \text{); } ^{13}\text{C NMR (100 MHz, CDCl}_3 \text{) } \delta \text{ 173.7, 172.1, 169.6, 166.4, 166.3, 165.1, 164.7, 141.8, 140.5, 140.2, 137.5, 137.3, 133.7, 133.0, 131.7, 131.6, 131.5, 129.3, 129.2, 129.0, 128.7, 128.6, 128.1, 128.0, 127.9, 127.1, 127.0, 126.8, 123.8, 67.5, 51.4, 50.3, 49.8, 44.3, 44.1, 42.0, 40.5, 40.0, 36.0, 29.1, 29.0, 28.9, 28.8, 26.7, 24.9, 24.7, 22.5, 21.7; } \text{HRMS (FAB) Calcd. for } C_{83}H_{93}N_8O_{10} [M+H]^+ \text{ 1361.70147. Found 1361.69808.} \]
References and Notes


Chapter Five Synopsis

Encouraged by the results described in Chapter Four, we decided to test whether that basic design could be generalised to make molecular machines that mechanically switch "on" and "off" any physical property that can be made to depend upon distance. (Figure 1).

Figure 1 Exploiting a well-defined, large-amplitude positional change to trigger property changes. (i) A and B interact to produce a physical response (fluorescence quenching, specific dipole or magnetic moment, NLO properties, color, creation/concealment of a binding site or reactive/catalytic group, hydrophobic/hydrophilic region, etc.); (ii) moving A and B far apart mechanically switches off the interaction and the corresponding property effect.

Arguably, fluorescence quenching is the most suitable property to test this design, since it is known to depend heavily upon fluorophore-to-quencher distance. Incorporating a fluorophore and a quencher as groups A and B (Figure 1) should, in principle, produce an easily detectable difference in luminescence between states (i) and (ii).

Shuttle E/Z-1 works on the same principles as described in Chapter Four, but it features an anthracene derivative, which serves both as fluorophore and stopper, and a pyridinium-substituted macrocycle. Pyridinium ions are known to quench anthracene's fluorescence via electron transfer. In Z-1 the macrocycle is located in close proximity to the anthracene, as proven by $^1$H NMR (CDCl$_3$, 298K), so quenching is expected to be very effective. Z-1 can be converted to E-1 by irradiation at 312 nm ($\gamma = 40\%$ at the photostationary state). In the E isomer, the macrocycle resides preferentially over the fumaramide portion of the thread, far away from the anthracene group, thus preventing quenching. This translational isomerism, does, in fact, result in a dramatic 200:1
(CH₂Cl₂, 0.8μM, λ<sub>exc</sub>=365 nm) difference in fluorescence intensity, which is obvious even to the naked eye (Scheme I).

The bistability and integrity of the macrocycle positioning in CH₂Cl₂ means that starting with pure Z-1 (the 'off' state), the system can be written with light at 312 nm to give a photostationary E/Z-1 state which emits ~85 times more light than the starting material when addressed at a remote wavelength (λ<sub>exc</sub>=365nm). Once written it is essentially stable, unless treated with piperidine. All these features would make this system a good candidate for all-optical molecular-level data storage applications. More importantly, molecular shuttle E/Z-1 demonstrates the generality of the principle in which these molecular machines are based, suggesting that a similar strategy could indeed be used to mechanically switch "on" and "off" any distance-dependent property!
A light-switchable optically-addressable molecular shuttle


**Acknowledgments**

The following people are gratefully acknowledged for their contributions to this chapter: Dr. D. T. F. Dryden for the use of the fluorescence spectrometer; G. Teobaldi and Prof. F. Zerbetto for carrying out the molecular modelling calculations.
5.1. Introduction.

The widespread utilization of submolecular motion in key biological processes is inspiring scientists to try to bridge the gap between synthetic chemical systems, which, by and large, rely upon electronic and chemical effects and do not exploit molecular-level motion (a notable exception being liquid crystals), and the macroscopic world, where our everyday machines rely upon the controlled movement of multiple components to perform specific tasks. Most efforts toward this goal have focused on establishing methods (for example, the use of light) to control the positioning or movement of submolecular fragments, but relatively little attention has been given to what the effects of such motion might be. A bi-stable [2]rotaxane (a "molecular shuttle") was recently described in which a macrocycle could be moved with great positional integrity between two well-separated binding sites in response to a photostimulus. Here we show how this large positional change can be used to create a light-activated switch for fluorescence, exhibiting an exceptional 200:1 on-off intensity ratio between the translational states (between the photostationary state and the cis-isomer). We suggest that such "mechanical switching" could form the basis for many different types of synthetic property-changing devices and materials that, like biological systems, function through mechanical motion at the molecular level (Figure 5.1).
Figure 5.1 Exploiting a well-defined, large-amplitude positional change to trigger property changes. (i) A and B interact to produce a physical response (fluorescence quenching, specific dipole or magnetic moment, NLO properties, color, creation/concealment of a binding site or reactive/catalytic group, hydrophobic/hydrophilic region, etc.); (ii) moving A and B far apart mechanically switches off the interaction and the corresponding property effect.

5.2. Results and discussion.

Molecular shuttle $E/Z\text{-}1$ (Scheme 1) has several key features: A fumaramide-maleamide unit (dark blue-pink) provides a means of changing the position of the macrocycle on the thread by altering the binding affinity of one station for the macrocycle by several kilocalories per mole using various olefin isomerization reactions (photochemical, chemical, or thermal). A glycyglycine unit (orange) offers a nonreactive station of intermediate binding affinity between fumaramide and maleamide. The spacer between the stations, here a $C_{11}$ alkyl chain, can be chosen to suit the distance dependency of the property one wishes to influence. Here we illustrate the concept using fluorescence, introduced by attaching a 9-carboxyanthracene residue (which is sufficiently bulky to also act as a "stopper") to the peptide station. The macrocycle contains two pyridinium units, which are known to quench anthracene fluorescence through electron transfer. Since electron transfer can sometimes be remarkably efficient over long distances, we carried out INDO/S calculations (see Supporting Information) to confirm that the quenching should have the required high distance and orientation dependency in $E/Z\text{-}1$. Rotaxane $E\text{-}1$ was prepared in 48% yield from thread $E\text{-}2$ and converted into $Z\text{-}1$ by photoisomerization (Scheme 1).
Scheme 5.1 Synthesis of Bistable Molecular Shuttles E/Z-1. Reaction conditions: (i) potassium phthalimide, DMF, 80 °C, 16 h, 98%; (ii) NH₂NH₂·H₂O, EtOH, reflux, 1 h, then (Boc)₂O, KOH, MeOH, ~100%; (iii) 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDCI), 4-(dimethylamino)pyridine (DMAP), CH₂Cl₂, 60%; (iv) trifluoroacetic acid (TFA), CH₂Cl₂; (v) EDCI, DMAP, CH₂Cl₂/DMF, (E)-3-(2,2-diphenylethylcarbamoyl)acrylic acid 60%; (vi) 3,5-pyridinedicarbonyl dichloride, p-xylylenediamine, Et₃N, CHCl₃, 48%; (vii) TFA, CH₂Cl₂; (viii) 312 nm, CH₂Cl₂, 20 min, 60%; (ix) 312 nm, CH₂Cl₂, 20 min, 40%, or piperidine (3 equiv), CH₂O₂, rt, 16 h ~100% or C₂H₂O₄, 115 °C, 2 days, 90%. Z-2 is the cis-olefin isomer of E-2, its chemical structure is formally provided in the experimental section.

The ¹H NMR of Z-1 in CDCl₃¹⁰ (Figure 5.2) confirms the location of the macrocycle to be predominantly over the GlyGly residue. H₉ and H₁ are shielded by 0.6 and 0.8 ppm
with respect to their position in Z-2, and no significant shifts are observed for H₀ or Hₚ. In contrast, in E-1 the macrocycle resides overwhelmingly over the fumaramide station. H₀ and Hₚ are shifted 1.1 ppm upfield with respect to their positions in the thread, while Hₗ and Hₗ occur at identical chemical shifts in rotaxane and thread. The ¹H NMR signal for Hₙ and the significant shifts in the pyridine signals compared to the free base rotaxanes (see experimental section) confirm the protonation of the pyridine rings.

**Figure 5.2** Partial ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of (a) thread Z-2, (b) [2]rotaxane Z-1 (Hₙ δ = 13.36 ppm), (c) thread E-2, and (d) [2]rotaxane E-1 (Hₙ δ = 13.45 ppm). All samples contained 2 equiv of CF₃COOH. The assignments correspond to the lettering shown in Scheme 5.1.
The photostationary state (PSS) of $E$-1/$Z$-1 (or $E$-2/$Z$-2) at 312 nm in CH$_2$Cl$_2$ is 40:60 (electronic absorption spectra are provided in the experimental section) and, starting from either isomer, is reached within 20 min with no evidence of any decomposition. Fluorescence spectra ($\lambda_{\text{exc}} = 365$ nm) were obtained from 0.8 $\mu$M solutions of $E$-1 and $Z$-1 in CH$_2$Cl$_2$, CH$_3$CN, CH$_3$OH, and DMF (Figure 5.3). A remarkable 200:1 intensity ratio between the trans and cis shuttles (~85:1 between $Z$-1 and the PSS) is observed for the CH$_2$Cl$_2$ solutions at the maximum of $E$-1 emission ($\lambda_{\text{max}} = 417$ nm), $Z$-1's fluorescence being almost completely quenched by the pyridinium units and strongly red-shifted (experimental section) by intercomponent hydrogen bonding of the anthracene carboxyamide group to the macrocycle.$^{11,12}$ The emission spectra in the various solvents show an increase in $Z$-1 luminescence with increasing hydrogen bond basicity$^{10}$ (CH$_2$Cl$_2$ < CH$_3$CN < CH$_3$OH < DMF), consistent with a reduction in positional integrity of the macrocycle at the GlyGly station as the intercomponent hydrogen bonds are weakened. Conversely, the fluorescence intensity of $E$-1 generally decreases with this trend (opposite to the normally observed polarity effects on electron transfer and excited-state relaxation processes) as the macrocycle increasingly spends time away from the fumaramide station in positions within efficient quenching distance of the anthracene. The exception, the reduced fluorescence intensity of $E$-1 in CH$_2$Cl$_2$ compared to that in CH$_3$CN and CH$_3$OH, is presumably a result of some H-bond-induced intramolecular folding.
Figure 5.3 (a) Fluorescence emission spectra ($\lambda_{exc} = 365$ nm, 0.8 $\mu$M, 298 K) of E-1 (blue), Z-1 (pink), and the photostationary state (PSS, mauve). The difference in fluorescence intensity between Z-1 and E-1 or the PSS is clearly visible to the naked eye (inset: picture of the cuvettes under 365 nm UV light). (b) Fluorescence emission spectra ($\lambda_{exc} = 365$ nm, 0.8 $\mu$M, 298 K) of E-1 (blue) and Z-1 (pink) in each of CH$_2$Cl$_2$, CH$_3$CN, CH$_3$OH, and DMF. All the experiments were carried out after the addition of 2 equiv of CF$_3$COOH (TFA). Similar quenching and red-shifting was observed for the bis(methylpyridinium tetrafluoroborate) analogue of Z-1 ((i) Z-1, MeI, CH$_3$CN, (ii) AgBF$_4$). In the absence of TFA, E-1 and Z-1 exhibit fluorescence spectra similar to those of the corresponding isophthalamide macrocycle-based rotaxanes (i.e. nonquenched and, for Z-1, broadened and red-shifted). In contrast, both threads (E/Z-2) have fluorescence spectra indistinguishable from those of anthracene 9-carboxyamide and are unaffected by the addition of TFA.

The bi-stability and integrity of the macrocycle positioning in CH$_2$Cl$_2$ means that starting with pure Z-1 (the "off" state) the system can be written with light at 312 nm to give a photostationary E/Z-1 state which emits ~85 times more light than the starting material when addressed at a remote wavelength ($\lambda_{exc} = 365$ nm). Once written, it is essentially stable ($T_{1/2} \approx 24$ h at 115 °C) unless treated with piperidine. The most important feature of the system, however, is that it demonstrates a principle which could be used to make switches that can change any property that can be made to depend on the spatial separation of submolecular fragments (Figure 5.1). The use of stimuli-induced motion to bring individual components together to perform specific tasks (e.g.
electron transfer from one part to another) which produce an effect (e.g., fluorescence quenching), arguably makes such structures true mechanical molecular machines.
5.3 Experimental Section.

**General Procedure for the Photoisomerization of E/Z-1:**
Rotaxanes E or Z-1 (0.01-0.02 mmol) were dissolved in CH$_2$Cl$_2$ (20 mL) in a quartz vessel. To this solution 4-6 equivalents of trifluoroacetic acid were added, and the solution was degassed by bubbling N$_2$ for 10 minutes. The solution was directly irradiated at 312 nm using a multilamp photo-reactor (Model MLU18, Model 3022 lamps, Photochemical Reactors Ltd., Reading, UK.) for 20 minutes. The progress of the photoisomerization was monitored by TLC (CHCl$_3$/MeOH 98:2) or $^1$H NMR (CDCl$_3$). After the photostationary state was reached the reaction mixture was concentrated under reduced pressure to afford the crude product, then redissolved in CH$_2$Cl$_2$ and washed with sat. Na$_2$CO$_3$ prior to purification by column chromatography.

Rotaxanes E/Z-1 were characterized in their free-base form. For a $^1$H-NMR of the protonated rotaxanes see Figure 5.2 in the main text. The appearance of a broad signal with the correct integration for H$_A$ ($\delta = 13.36$ ppm for Z-1 and $\delta = 13.45$ ppm for E-1) together with the significant deshielding of H$_C$ (~0.4 ppm) upon treatment with CF$_3$COOH confirm the full protonation of the pyridine rings under our experimental conditions.
2-(11-Hydroxy-undecyl)-isoindole-1,3-dione

\[
\begin{align*}
\text{C}_{10}\text{H}_{27}\text{NO}_3 \\
\text{Mol. Wt.: 317.42}
\end{align*}
\]

To a solution of 10.1 g (40.2 mmol) of 11-bromo-1-undecanol in 100 mL of DMF, 8.2 g (44.2 mmol) of potassium phthalimide were added. The solution was then heated to 80°C and stirred for 2 h. After cooling to room temperature, the solution was filtrated, the solvent evaporated under vacuum and the residue redissolved in CH\(_2\)Cl\(_2\) and washed with water (3x100 mL) and brine (3x100 mL). The organic layer was dried over MgSO\(_4\) and concentrated under reduced pressure to give 12.5 g (98 %) of the title compound as a colorless solid. This compound showed identical spectroscopic data to that reported in H. Ihara, M. Takafuji, C. Hirayama, D. F. O’Brien, *Langmuir* 1992, 8, 1548.

(11-Hydroxy-undecyl)-carbamic acid tert-butyl ester

\[
\begin{align*}
\text{C}_{16}\text{H}_{33}\text{NO}_3 \\
\text{Mol. Wt.: 287.44}
\end{align*}
\]

2.0 g (6.3 mmol) of 2-(11-Hydroxy-undecyl)-isoindole-1,3-dione were dissolved in 20 mL of ethanol, then 1.5 mL (31.5 mmol) of hydrazine hydrate added and the solution refluxed until no more white precipitate was formed (~30 min). The solution was filtered and the solvent and the excess hydrazine removed under vacuum. The solid was redissolved in methanol and 1.4 g (6.3 mmol) of di-tert-butyl-dicarbonate and 0.256 g
(6.4 mmol) of NaOH were added. The solution was stirred until the reaction was completed. The solvent was evaporated under reduced pressure and the resulting oil dissolved in CHCl₃ and washed with water (3 x 50 mL). The organic phase was dried over MgSO₄ and the solvent removed under reduced pressure to yield 1.8 g (quant.) of the title compound as a colorless oil. \(^1\)H NMR (CDCl₃) \(\delta\) 4.55 (brs, 1H, NH), 3.63 (t, \(J = 6.6\) Hz, 2H, CH₂OH), 3.09 (q, \(J = 6.4\) Hz, 2H, BocNHCH₂), 1.55 (m, 2H, CH₂CH₂OH), 1.43 (s, 11H, t-Bu + BocNHCH₂CH₂), 1.27 (brs, 14H, alkyl). \(^1^3\)C NMR (CDCl₃) \(\delta\) 157.8, 62.6, 32.7, 29.9, 29.4, 29.3, 29.1, 28.3, 28.2, 28.0, 26.7, 25.7. FAB-MS (m-NBA matrix) m/z 288 [M + H⁺]

{2-[(Anthracene-9-carbonyl)-amino]-acetylamino]-acetic acid ethyl ester

\[
\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4
\]

Mol. Wt.: 364.39

This compound was prepared as described in G. W. H. Wurpel, A. M. Brouwer, I. H. M. van Stokkum, A. Farran and D. A. Leigh *J. Am. Chem. Soc.* **2001**, 123, 11327-11328 and showed identical spectroscopic data to those reported therein.
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(E) and (Z)-3-(2,2-Diphenyl-ethylcarbamoyl)-acrylic acids

These compounds were synthesized as described in A Altieri, G Bottari, F Dehez, D A Leigh, J K Y Wong and F Zerbetto, Angew. Chem. Int. Ed., 42, 2296-2300 (2003) and showed identical spectroscopic data to those reported therein.

{2-[(Anthracene-9-carbonyl)-amino]-acetylamino}-acetic acid 11-tert-butoxycarbonylamino-undecyl ester

1.4 g (4.8 mmol) of (11-hydroxy-undecyl)-carbamic acid tert-butyl ester, 1.0 g (2.9 mmol) of {2-[(anthracene-9-carbonyl)-amino]-acetylamino}-acetic acid and 0.585 g (4.8 mmol) of DMAP were suspended in 50 mL of CHCl₃ under nitrogen atmosphere, and the mixture cooled to 0 °C. Then 0.920 g (4.8 mmol) of EDCI were added in small portions and the mixture was warmed to room temperature and stirred for 6 h until it became a clear solution. The solution was washed with 2N HCl (2 x 100 mL), sat. NaHCO₃ (2 x 100 mL), and brine (2 x 100 mL). The organic phase was dried over
MgSO$_4$ and concentrated to give an oil which was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to give 0.950 g (60%) of the title compound as a pale yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 8.38 (s, 1H, $H_a$), 8.06 (d, $J$ = 8.8 Hz, 2H, $H_b$), 7.93 (d, $J$ = 8.8 Hz, 2H, $H_b$), 7.60 (brt, 1H, $H_d$), 7.46 (m, 5H, $H_c + H_d + H_b$), 4.85 (brt, 1H, $H_e$), 4.25 (d, $J$ = 5.6 Hz, 2H, $H_g$), 3.98 (t, $J$ = 6.7 Hz, 2H, $H_i$), 3.79 (d, $J$ = 5.6 Hz, 2H, $H_i$), 3.08 (brq, 2H, $H_m$), 1.58 (m, 2H, $H_m$), 1.46 (s, 11H, $H_1 + H_0$), 1.29 (brs, 14H, alkyl). $^{13}$C NMR (CDCl$_3$) $\delta$ 170.1, 169.7, 169.3, 157.9, 133.8, 131.2, 130.9, 128.3, 128.2, 127.9, 126.6, 125.7, 60.33, 43.1, 41.1, 40.5, 30.0, 29.4, 29.2, 28.4, 26.8, 25.7. FAB-MS (m-NBA matrix) 606 [M + H$^+$]

**Thread E-2**

A solution of 0.775 g (1.28 mmol) of {2-[(Anthracene-9-carbonyl)-amino]-acetylamino}-acetic acid 11-tert-butoxycarbonylamino-undecyl ester in 10 mL CH$_2$Cl$_2$ was treated with 0.5 mL (6.73 mmol) of trifluoroacetic acid (TFA). The solution was stirred until the deprotection was complete by TLC, and then the solvent and excess TFA were removed under vacuum. The residue was redissolved in 30 mL of CH$_2$Cl$_2$ and washed with 1M NaOH (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The resulting oil, 0.368 g (3.01 mmol) of DMAP and 0.756 g (2.56 mmol) of (E)-3-(2,2-Diphenyl-ethylcarbamoyl)-acrylic acid were suspended in 30 mL of CH$_2$Cl$_2$ and 10 mL of dry DMF and the mixture was cooled to 0°C under nitrogen atmosphere before adding 0.500 g (2.61 mmol) of EDCI in small portions. This mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was washed with 1M NaOH (2
x 25 mL), 2M HCl (2 x 25 mL) and brine (2 x 25 mL), the organic layer was dried over MgSO₄ and the liquid evaporated to dryness under reduced pressure. The residue was purified by flash chromatography (silica gel, 2% MeOH in CH₂Cl₂) to yield 0.601 g (60%) of the title compound as a pale yellow foam. Mp 220-222 °C dec. ¹H NMR (CDCl₃) δ 8.41 (s, 1H, Ha), 8.05 (d, J = 8.8 Hz, 2H, Ha), 7.93 (d, J = 8.8 Hz, 2H, Hb), 7.72 (brt, 1H, Hd), 7.67 (brt, 1H, Hb), 7.43 (m, 4H, Hc + Hd), 7.35 (brt, 1H, Hb), 7.15-6.98 (m, 12H, Ht + Hq + H0 or Hp), 6.77 (d, J = 14.9 Hz, 1H, Hp or Hq), 4.39 (d, J = 5.6 Hz, 2H, Hg), 4.10 (t, J = 6.7 Hz, Hj), 4.01 (d, J = 5.6 Hz, 2H, Hl), 3.96 (t, J = 7.9 Hz, 1H, Hk), 3.62 (m, 2H, Hj), 3.12 (brq, 2H, Hm), 1.60 (m, 2H, Hb), 1.38 (m, 2H, Hc), 1.16 (brs, 14H, alkyl). ¹³C NMR (CDCl₃) δ 170.4, 169.7, 169.4, 164.7, 164.5, 141.7, 133.5, 132.3, 130.0, 128.7, 128.6, 128.4, 128.1, 128.9, 127.8, 126.7, 125.5, 125.2, 62.3, 50.0, 44.1, 43.6, 41.4, 39.8, 29.4, 29.1, 29.0, 28.9, 28.7, 28.3, 26.7, 25.6. HRMS calcd. for C₄₈H₅₅N₄O₆ [M + H⁺] 783.41216. Found (FAB, m-NBA matrix) 783.41004

[2]Rotaxane E-1

To a solution of 0.94 g (1.2 mmol) of E-2 in 100 mL of CHCl₃ and Et₃N (exc.) were added simultaneously solutions of 2.9 g (14 mmol) of 3,5-pyridinedicarbonyl dichloride in 50 mL of CHCl₃ and 1.8 g (14 mmol) of p-xylylenediamine in 50 mL of CHCl₃ over a period of 3 hrs using motor-driven syringe pumps. The mixture was stirred overnight and then filtrated through a pad of celite. The filtrate was concentrated and purified by
flash chromatography (silica gel, 2%–5% MeOH in CHCl₃) to obtain 0.759 mg (48%) of the title compound as a pale yellow solid. Alternatively, Z-1 was irradiated at 312 nm for 20 min in CH₂Cl₂ solution using a Hg lamp and then washed with sat. Na₂CO₃ (aq.). The organic layer was dried over MgSO₄, concentrated and purified by column chromatography (silica gel, 2% MeOH in CHCl₃), to obtain the title compound in 40% yield. OR Z-1 was heated to 115 °C in C₂H₂O₄ (2 days) to obtain E-1 in 90% yield. Mp >300°C. ¹H NMR (CDCl₃) δ 9.21 (s, 4H, H₄), 8.85 (s, 2H, H₆), 8.47 (s, 2H, H₄ + H₆), 8.28 (brt, 1H, H₃m), 8.04 (d, J = 8.8 Hz, 2H, H₅), 7.98 (d, J = 8.8 Hz, 2H, H₆), 7.73 (brt, 4H, H₇), 7.64 (brt, 1H, H₅), 7.48 (m, 4H, H₆ + H₇), 7.32-7.08 (m, 10H, H₈), 6.98 (s, 8H, H₉), 6.78 (brt, 1H, H₆), 5.73 (d, J = 14.9 Hz, 1H, H₇ or H₈), 5.69 (d, J = 14.9 Hz, 1H, H₇ or H₈), 4.39 (s, 8H, H₁), 4.28 (d, J = 5.6 Hz, 2H, H₁), 4.13 (m, 3H, H₇ + H₈), 4.06 (d, J = 5.6 Hz, 2H, H₃), 3.76 (m, 2H, H₉), 3.02 (brq, 2H, H₄), 1.61 (m, 2H, H₅), 1.41 (m, 2H, H₆), 1.23 (brs, 14H, alkyl). ¹³C NMR (CDCl₃) δ 169.7, 169.0, 165.8, 165.3, 164.6, 151.6, 141.4, 136.7, 132.5, 130.9, 129.2, 128.8, 128.5, 128.2, 128.0, 127.7, 127.2, 127.1, 127.0, 125.6, 124.9, 65.7, 49.4, 44.1, 43.0, 41.3, 29.3, 29.1, 28.9, 28.4, 26.8, 25.7. HRMS calcd. for C₇₈H₇₈N₁₀O₁₀ [M + H⁺] 1317.61371 Found (FAB, m-NBA matrix) 1317.61527.
A solution of 0.775 g (1.28 mmol) of {2-[(anthracene-9-carbonyl)-amino]-acetylamino}acetic acid 11-tert-butoxycarbonylamino-undecyl ester in 10 mL CH₂Cl₂ was treated with 0.5 mL (6.73 mmol) of trifluoroacetic acid (TFA). The solution was stirred until the deprotection was complete by TLC, and then the solvent and excess TFA were removed under vacuum. The residue was redissolved in 30 mL of CH₂Cl₂ and washed with 1M NaOH (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over MgSO₄ and the solvent evaporated under reduced pressure. The resulting oil, 0.368 g (3.01 mmol) of DMAP and 0.756 g (2.56 mmol) of (Z)-3-(2,2-diphenylethylcarbamoyl)-acrylic acid were suspended in 30 mL of CH₂Cl₂ and 10 mL of dry DMF and the mixture was cooled to 0 °C under nitrogen atmosphere before adding 0.500 g (2.61 mmol) of EDCI in small portions. This mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was washed with 1M NaOH (2 x 25 mL), 2M HCl (2 x 25 mL) and brine (2 x 25 mL), the organic layer was dried over MgSO₄ and the liquid evaporated to dryness under reduced pressure. The residue was purified by flash chromatography (silica gel, 2% MeOH in CH₂Cl₂) to yield 0.551 g (55%) of the title compound as a pale yellow foam. Mp 218-220 °C dec. ¹H NMR (CDCl₃) δ 8.79 (brt, 1H, H_e), 8.43 (brt, 1H, H_q), 8.38 (s, 1H, H_a), 8.00 (d, J = 8.8 Hz, 2H, H_e), 7.91 (d, J = 8.8 Hz, 2H, H_b), 7.42 (m, 4H, H_c + H_d), 7.34 (brt, 1H, H_d), 7.24-7.14 (m, 11H, H_t + H_h), 5.80 (d, J = 13.2 Hz, 1H, H_o or H_p), 5.74 (d, J = 13.2 Hz, 1H, H_p or H_o), 4.22 (d, J = 5.6 Hz,
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2H, Hg), 4.15 (t, J = 7.9 Hz, 1H, H1), 4.00 (t, J = 6.7 Hz, 2H, H2), 3.85 (d, J = 5.6 Hz, 2H, H3), 3.80 (m, 2H, H4), 3.07 (brq, 2H, Hm), 1.56 (m, 2H, Hk), 1.41 (m, 2H, H1), 1.23 (brs, 14H, alkyl). 13C NMR (CDCl3) δ 170.3, 169.7, 169.0, 165.1, 164.6, 141.9, 133.2, 131.4, 130.9, 128.6, 128.5, 128.0, 126.9, 126.7, 125.6, 125.0, 62.8, 50.2, 44.1, 43.2, 41.3, 39.7, 29.4, 29.2, 29.1, 29.0, 28.4, 26.9, 25.7. HRMS calcd. for C48H55N4O6 [M + H]+ 783.41216. Found (FAB, m-NBA matrix) 783.41315.

[2]Rotaxane Z-1

To a solution of 0.94 g (1.2 mmol) of Z-2 in 100 mL of CHCl3 and Et3N (exc.) were added simultaneously solutions of 2.9 g (14 mmol) of 3,5-pyridinedicarbonyl dichloride in 50 mL of CHCl3 and 1.8 g (14 mmol) of p-xylylenediamine in 50 mL of CHCl3 over a period of 3 hrs using motor-driven syringe pumps. The mixture was stirred overnight and then filtrated through a pad of celite. The filtrate was concentrated and purified by flash chromatography (silica gel, 2%–5% MeOH in CH3Cl) to obtain 0.250 mg (y=17 %) of the title compound as a pale yellow solid. Alternatively, E-1 was irradiated at 312 nm for 20 min in CH2Cl2 solution using a Hg lamp and then washed with sat. Na2CO3 (aq.). The organic layer was dried over MgSO4, concentrated and purified by column chromatography (silica gel, 2% MeOH in CHCl3), to obtain the title compound in 60% yield. Mp >300°C 1H NMR (CDCl3) δ 9.15 (s, 4H, Ha), 8.75 (brt, 1H, He), 8.63 (s, 2H, Hc), 8.41 (s, 1H, Hg), 8.16 (brt, 5H, HD + Hf), 8.01 (brt, 1H, Hf), 7.91 (d, J = 8.8 Hz, 2H,
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H₆, 7.66 (d, J = 8.8 Hz, 2H, H₆), 7.38–7.18 (m, 14 H, Ht + Hc + Hd), 7.06 (s, 8H, Hf), 6.25 (brt, 1H, Hβ), 5.87 (d, J = 13.2 Hz, 1H, Hα or Hρ), 5.85 (d, J = 13.2 Hz, 1H, Hρ or Hα), 4.37 (m, 8H, Hε), 4.18 (t, J = 7.9 Hz, 1H, Hα), 3.96 (t, J = 6.7 Hz, 2H, Hβ), 3.85 (t, J = 6.5 Hz, 2H, Hγ), 3.71 (d, J = 5.6 Hz, 2H, Hδ), 3.06 (brq, 2H, Hm), 2.85 (brd, 2H, Hβ), 1.51 (m, 2H, Hν), 1.41 (m, 2H, Hμ), 1.20 (brs, 14H, alkyl). ¹³C NMR (CDCl₃) δ 169.8, 169.7, 169.4, 165.2, 164.9, 151.8, 141.6, 137.2, 133.2, 132.6, 131.1, 130.8, 129.7, 129.4, 129.1, 129.0, 128.7, 128.2, 127.9, 127.8, 127.0, 126.9, 125.7, 124.5, 65.7, 50.2, 44.3, 42.4, 41.2, 39.9, 29.3, 29.1, 29.0, 28.9, 28.9, 28.7, 28.3, 26.8, 25.7, 25.5. HRMS calcd. for C₇₉H₈₁N₁₀O₁₀ [M + H⁺] 1317.61371 Found (FAB, m-NBA matrix) 1317.61543.

[2]Rotaxane bis Me Z-1

C₇₉H₈₁B₂F₈N₁₀O₁₀
Mol. Wt.: 1800.2
Figure 5.4 Fluorescence emission spectra ($\lambda_{exc}=365$nm, 0.8 $\mu$M, 25°C, CH$_2$Cl$_2$) of E-1 (blue) and Z-1 (pink). The emission of Z-1 is nearly completely quenched and strongly red-shifted.

Figure 5.5 UV-vis spectra (CH$_2$Cl$_2$, 298 K) of E-1 (blue) and Z-1 (pink). The right hand Y axis shows their relative absorption ratio (black dotted line).
LUMO-LUMO electron transfer between anthracene and the pyridinium macrocycle

The anthracene fluorescence is quenched via electron transfer between the LUMO’s of the chromophore and that of the macrocycle. As in previous work,\textsuperscript{14,15} the relevant term was calculated with the INDO/S plus Configuration Interaction Singles model.\textsuperscript{16}

\begin{equation}
V = \left( \phi^{0}_{LUMO(anthracene)} \right)^{2} \langle F \phi^{0}_{LUMO(macrocycle)} \rangle \tag{1}
\end{equation}

where F is the Fock operator and the suffix zero indicates that the molecular orbitals are unperturbed and localized either on anthracene or on the macrocycle. Several approaches of the two moieties were explored. Only four of them are displayed in Figure 5.6. The most effective for the quenching are the rotaxane-like and the front-to-front approaches shown in figures 5.6a and 5.6b.

\textbf{Figure 5.6} Four possible approaches of the two moieties: a) rotaxane-like, b) front-to-front, c) side-to-side, d) edge-to-side
When the shortest CC distance was set to the typical C-C van der Waals distance, namely 3.2 Å, $V^2$ resulted in 1316.5, 5037.2, 3.1, 2.3 cm$^{-2}$. Various other side and edge approaches were tried and consistently gave small values. Figure 5.7 shows the distance dependence of $V^2$ for the first two cases, which are characterized by the larger values.

![Figure 5.7 Distance dependence of the orbital interactions that leads to quenching: empty squares are the rotaxane-like approach of figure 5.6a, the solid circles are the front-to-front approach of figure 5.6b.](image)

Even in these cases, the interaction is not particularly large, although it is sufficient to cause quenching. The value is similar to what found for the equatorial C$_{60}$/porphyrin dyad.\textsuperscript{14,15} Strong variations as a function of the approach between two moieties are of course well-known. For instance, in the same case mentioned above of a C$_{60}$/porphyrin dyad, the trans-2 isomer has $V^2$ nearly two orders of magnitude larger than its equatorial counterpart.\textsuperscript{14,15}
References and Notes


10) The shift differences in CD$_2$Cl$_2$ are similar to those in CDCl$_3$, but residual CHDCls obscures part of the olefin region.


12) Although Z-1 is shown in Scheme 1 with the macrocycle H-bonded to the anthracene-carboxyamide group, this is actually only significant in the excited
state of the fluorophore. In the ground-state minimum energy co-conformation it bridges the nonterminal amide group and the ester carbonyl (see $^1$H NMR shifts of $H_i$ and $H_j$ in Figure 5.3, a and b)].


Appendix
Stimuli-responsive molecular shuttles translocate a macrocycle between different sites ("stations") on a rotaxane thread under the influence of an external trigger.[1] In bistable shuttles the relative macrocycle binding affinities of the stations are reversed by the stimulus, generally through it bringing about a chemical change in the molecule that targets the enthalpy of binding of the macrocycle to one or both stations.[2] Immediately following the chemical transformation the molecule is no longer in the most energetically favored co-conformation and the macrocycle moves along the thread to its newly preferred position through biased Brownian motion as the system relaxes to the global minimum.[3] Although many external stimuli can be used to induce shuttling in this way, for example pH change,[4] light,[5] and electrochemistry,[6] a simple temperature change is not generally considered one of them.[7] The Boltzmann distribution of the macrocycle between the different binding sites within a shuttle ensures that heating or cooling changes the degree of discrimination the macrocycle expresses for the various stations, but not the actual station preference of the macrocycle. However, a change of relative-station binding affinity with temperature is possible in principle, since $\Delta G_{\text{binding}} = \Delta H_{\text{binding}} - T \Delta S_{\text{binding}}$. If the entropy terms are sufficiently different then the relative binding affinity of the macrocycle for the two stations can be reversed by increasing or lowering the temperature. Here we describe an example of this phenomenon.[8] The [2]rotaxane 1 is, in fact, a tristable molecular shuttle; the first rotaxane in which a ring can be switched between three different positions on a thread (Figure 1).[9]

Rotaxane $E$–1 was prepared in 32% yield from thread $E$–2 (Scheme 1). $E$–2 has previously[10] been utilized as the thread for a light- and heat-switchable bistable molecular shuttle 3, and contains two sites designed to hydrogen bond to a benzylic amide macrocycle, namely a fumaramide group and contains two sites designed to hydrogen bond to a succinic amide ester unit (orange), separated by a dodecane chain (purple). Shuttle 1 differs from 3 only in that the macrocycle contains endo-pyridine units instead of isophthalamide groups. Photoisomerization of $E$–1 at 254 nm afforded the cis-rotaxane $Z$–1 in 54% yield. Since the xylylene units of the macrocycle shield the encapsulated regions of the thread, the position of the ring in $E$– and $Z$–1 could be determined by comparing the chemical shift of the protons in the [2]rotaxanes with those of the corresponding threads (Figure 2).

The $^1$H NMR spectra (400 MHz, 298 K; Figure 2a and b, see page 5888) confirm the position of the macrocycle over the fumaramide station of $E$–1 in CDCl$_3$. The olefin protons $H_1$ and $H_2$ are shielded by more than 1.5 ppm in the rotaxane relative to the thread, while the chemical shifts of the succinic amide ester protons $H_3$ and $H_4$ are unchanged. Lowering the temperature had no effect on the chemical-shift values, the only significant change in the spectra being that the macrocycle $H_1$ protons sharpen as the ring pirouetting about the thread becomes slow on the NMR timescale.

In $Z$–1, the strong binding fumaramide station is replaced with a group of much poorer macrocycle-binding affinity (maleamid) and we expected the macrocycle to be displaced to the succinic amide ester site on the thread (that is, conformer succ–$Z$–1), as occurs with $Z$–3.[5] Whilst the chemical-shift differences (>1.2 ppm, COSY) of the $H_3$ and $H_4$ protons confirm this is largely the case[10] at room temperature and above (e.g., at 308 K; Figure 2d), to our surprise the $^1$H NMR spectrum of $Z$–1 proved highly temperature dependent. Indeed, at 258 K (Figure 2e) the major signals for $H_3$ and $H_4$ of $Z$–1 appear at the same chemical shifts as they do in the thread ($Z$–2). In addition the olefin protons $H_1$ and $H_2$ are also unchanged indicating that the macrocycle is not primarily located over either of the designed stations! In fact, it is the alkyl protons of the C$_2$ chain that experience significant upfield shifts (up to 1 ppm at 258 K), which indicates that the pyridine macrocycle is actually positioned...
over the C₁₂ unit. To satisfy the hydrogen-bonding requirements of the macrocycle, the amide groups of the thread must still act as hydrogen-bond acceptors and so the alkyl chain presumably adopts a folded “S-shape” conformation so that the amides at both ends of the chain can reach the macrocycle binding sites, thus accounting for the shielding seen for the alkyl protons (Scheme 1; co-conformer dodec-Z-1). Interestingly, two sets of signals are observed for the macrocycle indicating that the two halves of the ring experience magnetically different environments (pirotecting of the macrocycle about the S-shaped thread is slow on the NMR timescale at 258 K).

What is the reason for the unexpected behavior of Z-1? The reversal of the binding affinity of the macrocycle for the succinic amide ester and the alkyl-chain stations at different temperatures suggests that the TAS term is reversing the relative ΔG(binding) of the two stations (Figure 1). In co-conformer succ-Z-1 two hydrogen bonds from the macrocycle occur to an ester carbonyl group, a significantly weaker[11] interaction than an amide-amide hydrogen bond, whereas in the dodec-Z-1 co-conformer four intercomponent amide-amide hydrogen bonds can be formed, providing ~2 kcal/mol[11] greater enthalpic stabilization. It seems that at low temperatures the energy gain from forming the two extra amide-amide hydrogen bonds overcomes the entropic cost required for the thread to bridge the macrocycle binding sites; a C₁₂ chain has >500000 (3⁵⁵) possible C-C rotamers and a significant number of these degrees of freedom must be lost upon forming the dodec-Z-1 structure. Raising the temperature increases the contribution of the TAS term to the ΔG(binding) of the dodec-Z-1 co-conformer much more than for succ-Z-1 until, at higher temperatures, the relative stabilities of the two positional isomers are actually reversed and the Z-rotaxane predominantly adopts the enthalpically weaker but entropically more favorable succ-Z-1 co-conformation. Indeed, evidence that the stability of dodec-Z-1 is much more temperature dependent than succ-Z-1 is provided by molecular dynamics simulations (see Supporting Information).

The structural requirements for temperature to markedly affect the position of the macrocycle on the thread are quite specific (Figure 3). Similar rotaxanes missing either station (4 or Z,Z-5) or without the endo-pyridyl macrocycle (Z-3) do not show the same temperature-dependent ΔH chemical shifts as Z-1. However, the “S” shape of the dodec-Z-1 co-conformer binding site is, remarkably, observed in the solid-state structure of an isophthalamide macrocycle-containing [2]rotaxane of a thread consisting of two amide groups separated by a C₁₂ chain (6, Figure 4). In fact, this type of structure may be a reasonably low-energy co-conformation for many two-amide-station [2]rotaxanes with flexible spacers, which with particular molecular components (poor alternative binding stations) and the right environmental conditions (low temperature), can sometimes become the global minimum arrangement seen for Z-1 at 258 K.

Changing the position of a macrocycle on a thread by varying the temperature is potentially a useful means of controlling translational isomerism in a rotaxane, not least

Scheme 1. A tristable molecular shuttle 1. a) Pyridine 2,6-dicarbonyl chloride, p-xylylenediamine, Et₃N, CHCl₃, 32%; b) hv (254 nm), 20 min, CH₂Cl₂, 298 K, 54%; or hv (350 nm), catalytic benzophenone, 5 min, 65%; c) hv (312 nm), 35 min, CH₂Cl₂, 298 K, > 95%, or hv (400–670 nm), catalytic Br₂, 2 min, CH₂Cl₂, 298 K, > 100%; d) CDCl₃, 298 K, 54%; or hv (350 nm), catalytic benzophenone, 5 min, 65%; e) hv (312 nm), 35 min, CH₂Cl₂, 298 K, > 95%, or hv (400–670 nm), catalytic Br₂, 2 min, CH₂Cl₂, > 100%; g) hv (254 nm), 20 min, CDCl₃, 258 K, 54%.
because no chemical reaction is involved and no change to the covalent structure of the molecule occurs. The photostationary state of 1 at 312 nm consists of >95% of the trans-isomer (again, dissimilar behavior to shuttle 3 where the steady state at 312 nm is ~55:45 E:Z). This provides the bistable shuttle with the intriguing property that, starting with the ring on the central station (i.e., dodec-Z-1), the macrocycle can be moved selectively in one direction along the thread by irradiation with light at 312 nm, or selectively in the other direction by simply raising the temperature.

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[3] The energy potentially available to do useful mechanical work through such a process corresponds to the ΔAG_initial of the macrocycle for the two stations in the chemically transformed shuttle.


[7] A temperature change has been used to induce shuttling by bringing about a cis-trans isomerization reaction in one of the stations.(5) For a [2]rotaxane where a temperature increase is used to overcome a significant kinetic barrier to shuttling following a chemical change, see ref [4c]. A bistable [2]rotaxane that appears to undergo translational isomerism as a result of differences in the entropy of solvation of two stations has recently been reported (J. O. Jeppesen, K. A. Nielsen, J. Perkins, S. A. Vignon, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. Becher, J. F. Stoddart, Chem. Eur. J. 2003, 9, 2982–3007).


[10] At 308 K the ratio of succ-Z-1:dodec-Z-1 is ~90:10; at 258 K it is ~15:85.

Shuttling through reversible covalent chemistry†

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The first stimuli-responsive molecular shuttle that functions through reversible C–C bond formation is reported.

Biological machines utilize chemical reactions to control mechanical motion and establishing methods for generating large amplitude changes in the relative positions of the components of molecular shuttles (so-called 'stimuli-responsive molecular shuttles') is of interest for producing synthetic analogues of such systems. Molecular shuttles that undergo well-defined positional changes in response to redox processes, ion exchange, polarity changes, and photochemical and thermal stimuli have all been described but, somewhat surprisingly, the use of covalent bond-forming reactions in this regard has been limited to simple acid–base proton transfers. Here we describe the first example of shuttling through the formation (and breaking) of C–C bonds, using the well-established Diels–Alder ("DA") and retro-Diels–Alder ("r-DA") reactions.

Rotaxane E-1 (Scheme 1) has previously been investigated as a photo-switchable molecular shuttle. The trans double bond holds the two amide carbonyls of the fumaramide (green) station in a close-to-ideal arrangement for forming four strong H-bonds with the benzylic amide macrocycle (orange) containing a poorly hydrogen bonding ester group and lacks preorganisation. Accordingly, the macrocycle in E-1 is located primarily over the fumaramide unit (>95% of the time in CDCl₃ at 298 K and >85% even in d₆-DMSO, a powerful hydrogen bond-disrupting solvent). Photo-isomerisation of fumaramide to maleimide 'switches off' the binding affinity of the olefin station, resulting in the macrocycle translocating to the succinic amide-ester station. However, the double bond also opens up the possibility of utilising DA and r-DA chemistry to trigger the shuttling response. Addition of a diene to the fumaramide station would both change its H-bonding geometry and increase the steric bulk between the amide groups. Indeed, CPK models suggest that a benzylic amide macrocycle would be unlikely to hydrogen bond simultaneously to both amide groups of a station derivatised as the cyclo-adduct with cyclopentadiene and the succinic amide-ester station should consequently become the positional energy minimum. Since stereochecmistry is conserved through a DA–r-DA sequence (E dienophile results in trans adduct, which in turn yields E educt upon r-DA), the change in position of the macrocycle should be reversible through a r-DA reaction.

Accordingly, E-1 was treated with cyclopentadiene in d₆-DMSO at 80 °C for 16 h affording Cp-1 as a 1:1 mixture of diastereomers in 90% yield (Scheme 1). The 1H NMR spectra (CDCl₃, 400 MHz, 298 K) of rotaxanes E-1 and Cp-1 and the corresponding threads E-2 and Cp-2 are shown in Fig. 1. In Cp-1 and Cp-2, the bicyclic adduct signals (H5, H7, dark blue, and H3, H4, red) appear at near-identical chemical shifts in both thread and rotaxane, while the succinic amide ester signals (H8, orange) are shifted ~1.2 ppm upfield in Cp-1 with respect to Cp-2 due to the shielding effect of the xylene rings of the macrocycle. Moreover, the NH fumaramide protons (H9, green) are deshielded by ~1.5 ppm in E-1 with respect to E-2 through polarisation of the thread N–H bonds caused by the macrocycle H-bonding to the succinic amide-ester groups, but in Cp-1 it is the succinic amide-ester NH (H8, orange) that is shifted 0.8 ppm downfield compared to its thread, with H9 and H10 not significantly affected. The spectroscopic data confirm that the translocation of the macrocycle from the fumaramide unit in E-1 to the succinic amide-ester station in Cp-1 proceeds with excellent positional integrity.

The covalent chemistry shuttling system proved perfectly reversible: the r-DA reaction could be accomplished by heating Cp-1 at 250 °C under reduced pressure (10⁻² Torr) for 20 minutes using the inlet oven of a flash vacuum pyrolysis (FVP) apparatus to quantitatively regenerate E-1.

An interesting consequence of the encapsulated architecture of the rotaxane is the effect the macrocycle has on the reactivity of the fumaramide station in the DA reaction. E-2 reacts with cyclopentadiene approximately twice as fast as E-1 in d₆-DMSO...
Fig. 1 1H NMR (CDCl3, 400 MHz, 298 K) of a) thread E-2; b) rotaxane E-1; c) thread Cp-2 and d) rotaxane Cp-1. The assignments correspond to the lettering shown in Scheme I. For clarity only one of the diastereomers of Cp-1 is assigned in the figure; for more detail see the electronic supporting information.

at 80 °C. If the macrocycle is acting as a non-covalently linked protecting group for the olefin during the DA reaction, the effect should be enhanced in C2D2C4 since the macrocycle spends a greater amount of time over the fumaramide unit in non-polar solvents. Indeed, E-2 reacted to form Cp-2 at identical rates in C2D2C4 and d6-DMSO (ruling out an intrinsic solvent-effect on the DA reaction itself) but 5 x faster than E-1 in C2D2C4 under otherwise identical conditions.

In conclusion, we have described the first example of a bistable stimuliresponsive molecular shuttle that functions through reversible C-C bond formation (DA and r-DA reactions). Both processes, E-1 → Cp-1 and Cp-1 → E-1, are high yielding, preparatively simple and generate large amplitude net positional changes, with excellent discrimination between the binding sites exhibited by the macrocycle in both chemical states of the shuttle. This increases both the number and breadth of methods available to switch the relative position of components in mechanically interlocked structures.

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Notes and references
Chiroptical Switching in a Bistable Molecular Shuttle

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Although various methods for switching the positions of macrocycles in bistable rotaxane-based molecular shuttles have been developed,1 exploiting such movements to trigger property changes has thus far received little attention.2,3 Here we demonstrate one of the first examples of a property change achieved through a large amplitude translational motion in a rotaxane, a chiroptical switch in which light-induced shuttling of the macrocycle along the thread produces a strong induced circular dichroism (ICD) response when the macrocycle is hydrogen-bonded to a chiral peptide station.

Chiral dipeptides have previously been shown to induce an asymmetric response in the aromatic ring absorption bands of intrinsically achiral components of [2]rotaxanes through tight intercomponent binding in nonpolar solvents.4-5 The effect can be “switched off” by adding a polar solvent (e.g., MeOH) to break the hydrogen-bonding interactions between macrocycle and thread. Although triggered changes in optical properties are currently utilized in optical data storage and processing, waveguides, and other photonics applications,6 a solvent change is clearly unlikely to prove useful as a means of switching such real-world devices. However, the breaking (and making) of intercomponent interactions is also a feature of positionally bistable molecular shuttles. Accordingly, it seemed possible that optical properties could be influenced solely by switching the position of a macrocycle in a molecular shuttle that incorporates a chiral peptide “station”.

Such a bistable shuttle, E/Z-1, is shown in Scheme 1. The idea is that in E-1 the macrocycle resides over the strongly macrocycle-binding fumaramide portion of the thread and the asymmetric center is not close enough to any aromatic rings to influence their absorption spectrum. Upon photoisomerization of the olefin station (E-1→Z-1), the ring moves to the glycyl-L-leucine (Gly-Leu) unit, locking the molecule in a co-conformation where aromatic rings (principally those of the C-terminal stopper4) are held in a well-expressed chiral environment. The change in the position of the macrocycle should thus manifest itself in terms of a measurable change in the CD response.

Molecular shuttle E-1 was synthesized from thread E-2 in 58% yield (Scheme 1). Comparison of the 1H NMR spectra of the
E-rotaxane and thread (Figure 1, a and b) shows the excellent discrimination of the macrocycle toward the different stations. While the Gly-Leu protons are only slightly affected by the aromatic irradiation at the conformer having the macrocycle over the olefin station is the major significantly shifted upfield (−1.2 ppm), confirming that the co-translational isomer in E-1.

The shuttle design works remarkably well. When the macrocycle is tightly bound close to the Leu residue in Z-1, the aromatic rings of the rotaxane do, indeed, experience a well-expressed chiral environment as evidenced by CD spectroscopy. Of the two rotaxanes and two threads, only rotaxane Z-1 gives a CD response, which is both strong (−13k deg cm² dmol⁻¹) and, for the l-enantiomer, negative (Figure 2a). The absence of any detectable signal for the E-rotaxane shows that the CD signal is genuinely only generated by controlling the position of the macrocycle in the shuttle.

E-1 (purple) in CHCl₃ at 298 K. (c) Percentage of F in the photostationary state (F-1, NMR data, 400 MHz, CD2Cl2, 298 K) after alternating irradiation at 254 nm (half integers) and 312 nm (integers) for five complete cycles. The right-hand Y axis shows the CD absorption at 246 nm.

For a recent example of a light-driven mechanical mechanism which elicits a chiral response, see: Mutaoka, J.; Creidi, A.; Raymo, F. M.; Stoddart, J. F. Angew. Chem., Int. Ed. 2000, 39, 3348–3351.


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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References


6. For a recent example of a light-driven mechanical mechanism which elicits a chiral response, see: Mutaoka, J.; Creidi, A.; Raymo, F. M.; Stoddart, J. F. Angew. Chem., Int. Ed. 2000, 39, 3348–3351.


The widespread utilization of submolecular motion in key biological processes is inspiring scientists to try to bridge the gap between synthetic chemical systems, which, by and large, rely upon electronic and chemical effects and do not exploit molecular-level motion (a notable exception being liquid crystals), and the macroscopic world, where our everyday machines rely upon the controlled movement of multiple components to perform specific tasks. Most efforts toward this goal have focused on establishing methods (for movement of multiple components to perform specific tasks) that do not exploit molecular-level effects, and the macroscopic processes and materials that, like biological systems, function through logical processes is inspiring scientists to try to bridge the gap between synthetic chemical systems, which, by and large, rely upon electronic and chemical effects and do not exploit molecular-level motion (a notable exception being liquid crystals), and the macroscopic world, where our everyday machines rely upon the controlled movement of multiple components to perform specific tasks. Most efforts toward this goal have focused on establishing methods (for example, the use of light) to control the positioning or movement of submolecular fragments, but relatively little attention has been given to what the effects of such motion might be. A bi-stable [2]-rotaxane (a “molecular shuttle”) was recently described in which a macrocycle could be moved with great positional integrity between two well-separated binding sites in response to a photoswitch.\(^3\) Here we show how this large positional change can be used to create a light-activated switch for fluorescence, exhibiting an exceptional 200:1 on/off intensity ratio between the translational states (~~85:1 between the photostationary state and the cis-isomer).\(^3\) We suggest that such “mechanical switching” could form the basis for many different types of synthetic property-changing devices and materials that, like biological systems, function through mechanical motion at the molecular level (Figure 1).

Molecular shuttle E/Z-1 (Scheme 1) has several key features: A fumaramide—maleamide unit (dark blue—pink) provides a means of changing the position of the macrocycle on the thread by altering the binding affinity of one station for the macrocycle by several kilocalories per mole using various olefin isomerization reactions (photochemical, chemical, or thermal).\(^1\) A glycyglycine unit (orange) offers a nonreactive station of intermediate binding affinity between fumaramide and maleamide.\(^2\) The spacer between the stations, here a C\(_11\) alkyl chain, can be chosen to suit the distance dependency of the property one wishes to influence. Here we illustrate the concept using fluorescence, introduced by attaching a 9-carboxyanthracene residue (which is sufficiently bulky to also act as a “stopper”) to the peptide station. The macrocycle contains two pyridinium units, which are known to quench anthracene fluorescence through electron transfer.\(^8\) Since electron transfer can sometimes be remarkably efficient over long distances, we carried out INDO/S calculations (see Supporting Information) to confirm that the quenching should have the required high distance and orientation dependency in E/Z-1.

Rotaxane E-1 was prepared in 48% yield from thread E-2 and converted into Z-1 by photoisomerization (Scheme 1). The \(^1\)H NMR of Z-1 in CDCl\(_3\) (Figure 2) confirms the location of the macrocycle to be predominantly over the GlyGly residue. \(H_3\) and \(H_4\) are shielded by 0.6 and 0.8 ppm with respect to their position in Z-2, and no significant shifts are observed for \(H_5\) or \(H_6\). In contrast, in E-1 the macrocycle resides overwhelmingly over the fumaramide station.

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**Figure 1.** Exploiting a well-defined, large-amplitude positional change to trigger property changes. (i) A and B interact to produce a physical response (fluorescence quenching, specific dipole or magnetic moment, NLO properties, color, creation/concealment of a binding site or reactive/catalytic group, hydrophobic/hydrophilic region, etc.); (ii) moving A and B far apart mechanically switches off the interaction and the corresponding property effect.

**Scheme 1.** Synthesis of Molecular Shuttle E/Z-1

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\(^{a}\) Reaction conditions: (i) potassium phthalimide, DMF, 80 °C, 16 h, 98%; (ii) NH\(_2\)NH\(_2\)H\(_2\)O, EtOH, reflux, 1 h, then (Boc)\(_2\)O, KOH, MeOH, \(\sim100\%\); (iii) 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDCI), 4-(dimethylamino)pyridine (DMAP), CH\(_2\)Cl\(_2\), 60%; (iv) trifluoroacetic acid (TFA), CH\(_2\)Cl\(_2\); (v) EDCI, DMAP, CH\(_2\)Cl\(_2\)/DMF, (E)-3-(2,2-diphenylethyl)carbamoylacylic acid 60%; (vi) 3,5-pyridinedicarbonyl dichloride, p-xylendenediamine, Et\(_3\)N, CH\(_2\)Cl\(_2\), 48%; (vii) TFA, CH\(_2\)Cl\(_2\); (viii) 312 nm, CH\(_2\)Cl\(_2\), 20 min, 60%; (ix) 312 nm, CH\(_2\)Cl\(_2\), 20 min, 40%, or piperidine (3 equiv), CH\(_2\)Cl\(_2\), rt, 16 h \(\sim100\%\) or C\(_6\)H\(_5\)CN, 115 °C, 2 days, 90%. Z-2 is the cis-olefin isomer of E-2, its chemical structure is formally provided in the SI.

H\(_3\) and H\(_4\) are shifted 1.1 ppm upfield with respect to their positions in the thread, while H\(_3\) and H\(_4\) occur at identical chemical shifts in rotaxane and thread. The \(^1\)H NMR signal for H\(_3\) and the significant shifts in the pyridine signals compared to the free base rotaxanes (see SI) confirm the protonation of the pyridine rings.

The photostationary state (PSS) of E-1/Z-1 (or E-Z/Z-2) at 312 nm in CH\(_2\)Cl\(_2\) is 40:60 (electronic absorption spectra are provided...
Figure 2. Partial 1H NMR spectra (400 MHz, CDCl3, 298 K) of (a) thread Z-2, (b) [2]rotaxane Z-1 (H 4, δ = 13.36 ppm), (c) thread E-2, and (d) [2]-rotaxane E-1 (H 4, δ = 13.45 ppm). All samples contained 2 equiv of CF3COOH. The assignments correspond to the lettering shown in Scheme 1.

Figure 3. (a) Fluorescence emission spectra (λmax = 365 nm, 0.8 μM, 298 K) of E-1 (blue), Z-1 (pink), and the photostationary state (PSS, mauve). The difference in fluorescence intensity between Z-1 and E-1 or the PSS is clearly visible to the naked eye (inset: picture of the cuvettes under UV light). (b) Fluorescence emission spectra (λmax = 365 nm, 0.8 μM, 298 K) of E-1 (blue) and Z-1 (pink) in each of CH2Cl2, CH3CN, CH3OH, and DMF. All the experiments were carried out after the addition of 2 equiv of CF3COOH (TFA). Similar quenching and red-shifting was observed for the bis(methylpyridinium tetrafluoroborate) analogue of Z-1 ((i) Z-1, Mel, CH3CN, (ii) AgBF4). In the absence of TFA, E-1 and Z-1 exhibit fluorescence spectra similar to those of the corresponding isophthalamide macrocyclic-based rotaxanes (i.e. nonquenched and, for Z-1, broadened and red-shifted).

in the Supporting Information) and, starting from either isomer, is reached within 20 min with no evidence of any decomposition. Fluorescence spectra (λmax = 365 nm) were obtained from 0.8 μM solutions of E-1 and Z-1 in CH2Cl2, CH3CN, CH3OH, and DMF (Figure 3). A remarkable 200:1 intensity ratio between the trans and cis shuttles (~85:1 between Z-1 and the PSS) is observed for the CH2Cl2 solutions at the maximum of E-1 emission (λmax = 417 nm), Z-1's fluorescence being almost completely quenched by the pyridinium units and strongly red-shifted (Supporting Information) by intercomponent hydrogen bonding of the anthracene carboxamide group to the macrocycle.44 The emission spectra in the various solvents show an increase in Z-1 luminescence with increasing hydrogen bond basicity (CH2Cl2 < CH3CN < CH3OH < DMF), consistent with a reduction in positional integrity of the macrocycle at the GlyGly station as the intercomponent hydrogen bonds are weakened. Conversely, the fluorescence intensity of E-1 generally decreases with this trend (opposite to the normally observed polarity effects on electron transfer and excited-state relaxation processes) as the macrocycle increasingly spends time away from the furamidine station in positions within efficient quenching distance of the anthracene. The exception, the reduced fluorescence intensity of E-1 in CH2Cl2 compared to that in CH3CN and CH3OH, is presumably a result of some H-bond-induced intramolecular folding.

The bi-stability and integrity of the macrocycle positioning in CH2Cl2 means that starting with pure Z-1 (the "off" state) the system can be written with light at 312 nm to give a photostationary E/Z-1 state which emits ~85 times more light than the starting material when addressed at a remote wavelength (λmax = 365 nm). Once written, it is essentially stable (T1/2 ≈ 24 h at 115 °C) unless treated with piperidine. The most important feature of the system, however, is that it demonstrates a principle which could be used to make switches that can change any property that can be made to depend on the spatial separation of submolecular fragments (Figure 1). The use of stimuli-induced motion to bring individual components together to perform specific tasks (e.g. electron transfer from one part to another) which produce an effect (e.g., fluorescence quenching), arguably makes such structures true mechanical molecular machines.

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Supporting Information Available: Synthetic experimental procedures and INDO/S calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

References


(7) The shift differences in CDCl3 are similar to those in CD3CN, but residual CH2Cl2; obscures part of the olefin region.


(9) Although Z-1 is shown in Scheme 1 with the macrocycle H-bonded to the anthracencarboxamide group, this is actually only significant in the excited state of the fluorophore. In the ground-state minimum energy configuration it bridges the nonterminal amide group and the ester carbonyl (see ref 4d and 'H NMR shifts of H1 and H3 in Figure 3, a and b).


(11) After this manuscript was submitted, some fascinating light-switchable shuttles were reported in which a small change in the position of a cyclodextrin on a rotaxane thread changes the solvation sphere of a fluorophore stopper sufficiently to alter the fluorescence intensity by a ratio of ~1:5:1. [Wang, Q.-C.; Xu, D.-H.; Ren, J.; Chen, K.; Tian, H. Angew. Chem., Int. Ed. 2004, 43, 2661–2665].