Molecular Shuttles

Entropy-Driven Translational Isomerism: A Tristable Molecular Shuttle**

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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[4a,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 $\Delta G_{binding} = \Delta H_{binding} - T\Delta S_{binding}$. 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 **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[5g] 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 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).

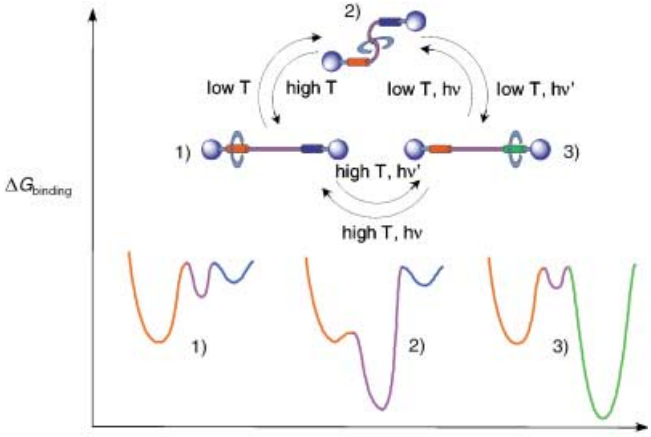

Figure 1. Macrocycle translation in a tristable molecular shuttle. Macrocycle movement between 1) and 2) is an entropy-driven process involving no change to the covalent structure of the molecule.

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_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 (that is, co-conformer succ-*Z*-**1**), as occurs with *Z*-**3**.[5g] Whilst the chemical-shift differences (> 1.2 ppm, COSY) of the H_c and H_d protons confirm that 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_c and H_d of *Z*-**1** appear at the same chemical shifts as they do in the thread (*Z*-**2**). In addition 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), which indicates that the pyridine macrocycle is actually positioned

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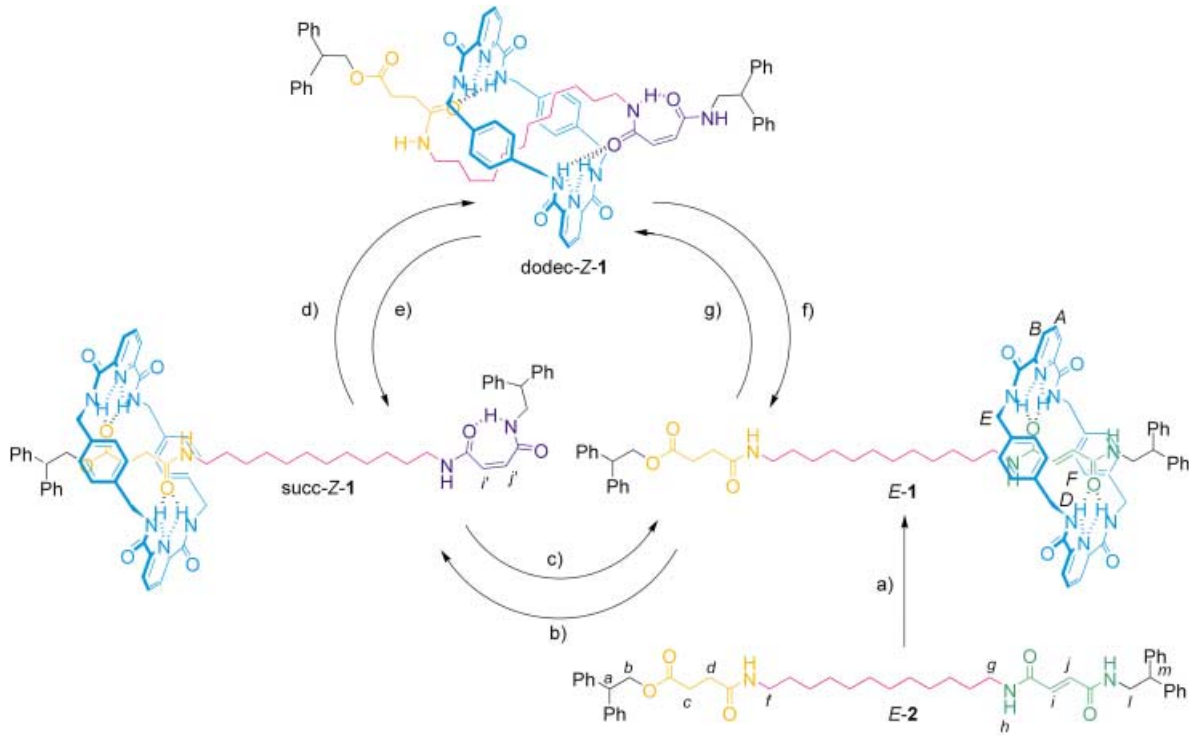

Scheme 1. A tristable molecular shuttle **1**. a) Pyridine 2,6-dicarbonyl chloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, 32%; b) *hν* (254 nm), 20 min, CH_2Cl_2, 298 K, 54%, or *hν* (350 nm), catalytic benzophenone, 5 min, 65%; c) *hν* (312 nm), 35 min, CH_2Cl_2, 298 K, >95%, or *hν* (400–670 nm), catalytic Br_2, 2 min, CH_2Cl_2, 298 K, ~100%; d) $CDCl_3$, 258 K, 85%; e) $CDCl_3$, 308 K, 90%; f) *hν* (312 nm), 35 min, CH_2Cl_2, >95%, or *hν* (400–670 nm), catalytic Br_2, 2 min, CH_2Cl_2, ~100%; g) *hν* (254 nm), 20 min, $CDCl_3$, 258 K, 54%.

over the C_{12} 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 (pirouetting 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 $T\Delta S$ term is reversing the relative $\Delta G_{binding}$ 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^{-1} [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 C_{12} chain has >500000 (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 $T\Delta S$ term to the $\Delta G_{binding}$ 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 ^1H 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_{12} 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

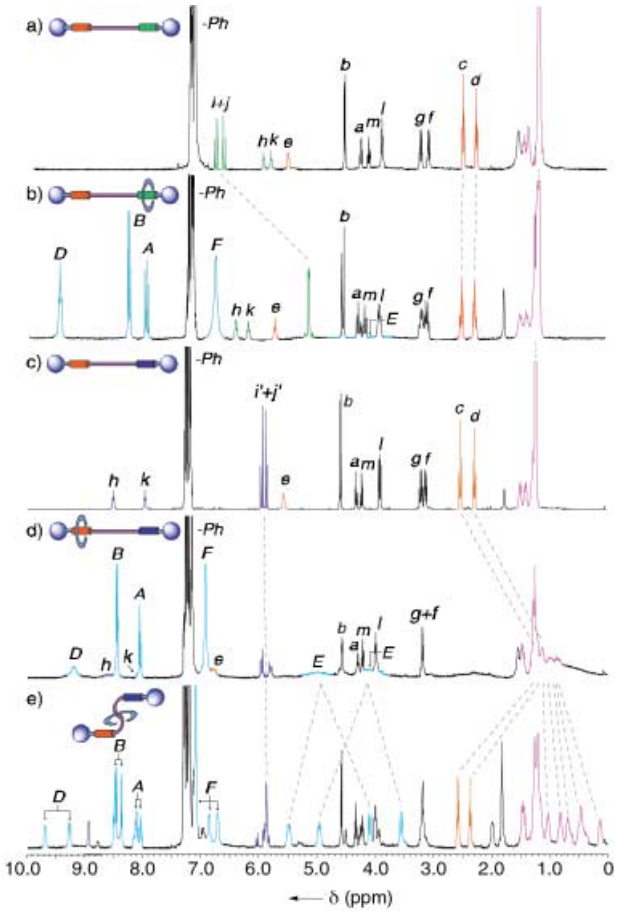

Figure 2. 400 MHz ^{1}H NMR spectra ($CDCl_3$) of a) thread *E*-**2** at 298 K, b) rotaxane *E*-**1** at 298 K, c) thread *Z*-**2** at 308 K, d) rotaxane *Z*-**1** at 308 K, and e) rotaxane *Z*-**1** at 258 K. The assignments correspond to the lettering shown in Scheme 1.

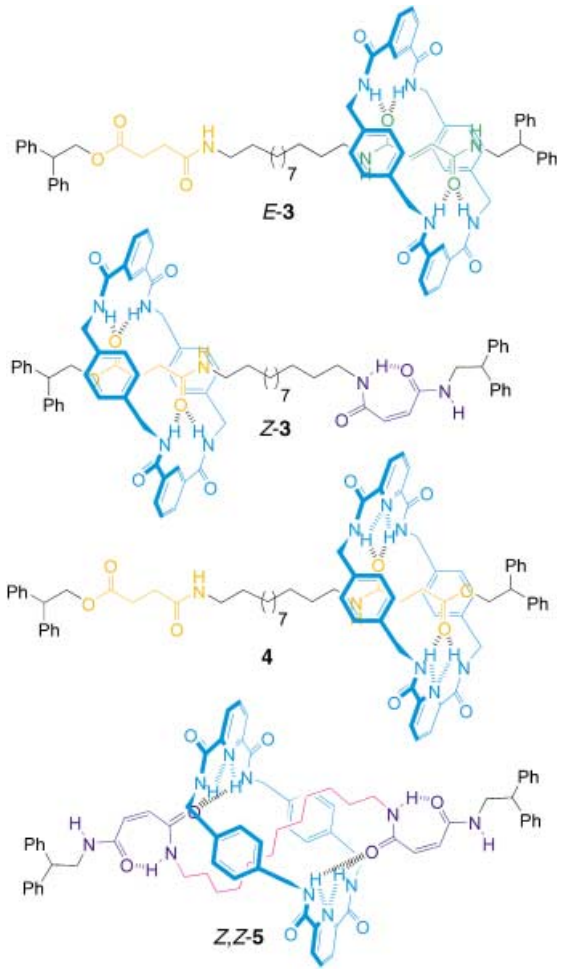

Figure 3. Rotaxane structures related to *Z*-**1**, which do not show temperature-dependent translational isomerism.

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.

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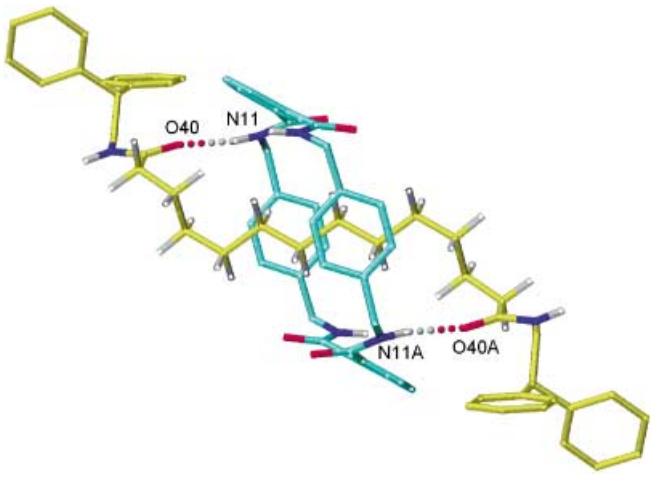

Figure 4. X-ray crystal structure of a benzylic isophthalamide macrocycle-based [2]rotaxane **6** where two amide groups are separated by a C_{12} alkyl chain. Atoms: C (macrocycle) blue, C (thread) yellow, O red, N dark blue. The amide and C_{12} methylene hydrogen atoms are shown in white while all others are removed for clarity. Intramolecular hydrogen-bond distances and angles: O40-HN11/O40A-HN11A 1.92 Å, 156.4°.

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

[11] F. G. Gatti, D. A. Leigh, S. A. Nepogodiev, A. M. Z. Slawin, S. J. Teat, J. K. Y. Wong, *J. Am. Chem. Soc.* **2001**, *123*, 5983 – 5989.

