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Shuttling through reversible covalent chemistry†

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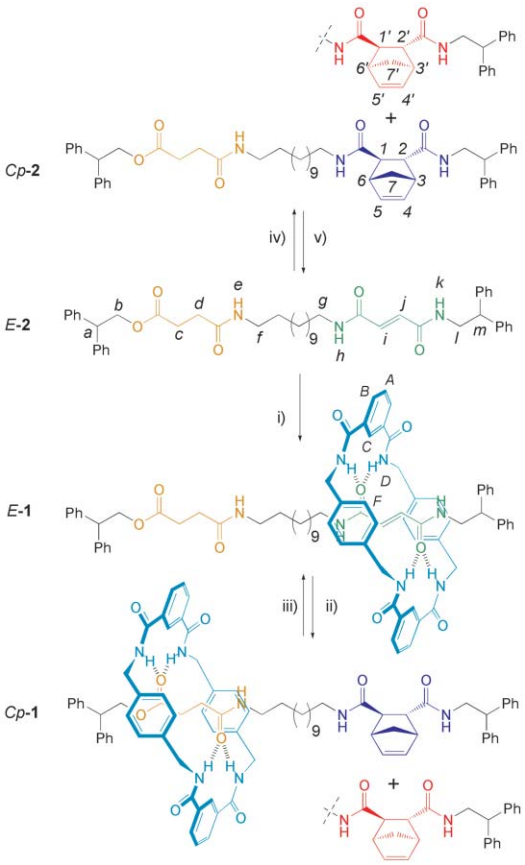
The first stimuli-responsive molecular shuttle that functions through reversible C–C bond formation is reported.

Biological machines utilize chemical reactions to control mechanical motion[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] ion exchange,[4] polarity changes,[5] and photochemical[6] and thermal[7] 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.[8] Here we describe the first example of shuttling through the formation (and breaking) of C–C bonds, using the well-established Diels–Alder[9] ("DA") and retro-Diels–Alder[9,10] ("r-DA") reactions.

Rotaxane *E*-**1** (Scheme 1) has previously been investigated as a photo-switchable molecular shuttle.[11] 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.[12] 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,[13] resulting in the macrocycle translocating to the succinic amide-ester site.[11] 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.

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 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 Fig. 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_c and H_d, orange) are shifted ~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



Scheme 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, Et_3N, $CHCl_3$, 57%; ii) cyclopentadiene, d_6-DMSO, 80 °C, 16 h, 90%; iii) 250 °C, 10^{-2} Torr, 20 min, ~100%; iv) cyclopentadiene, d_6-DMSO, 80 °C, 8 h, 93%; v) 250 °C, 10^{-2} Torr, 20 min, ~100%.

~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.[14] *E*-**2** reacts with cyclopentadiene approximately twice as fast as *E*-**1** in d_6-DMSO

† Electronic supplementary information (ESI) available: experimental procedures and physical data for *Cp*-**1** and *Cp*-**2**. See http://www.rsc.org/suppdata/cc/b4/b412570c/

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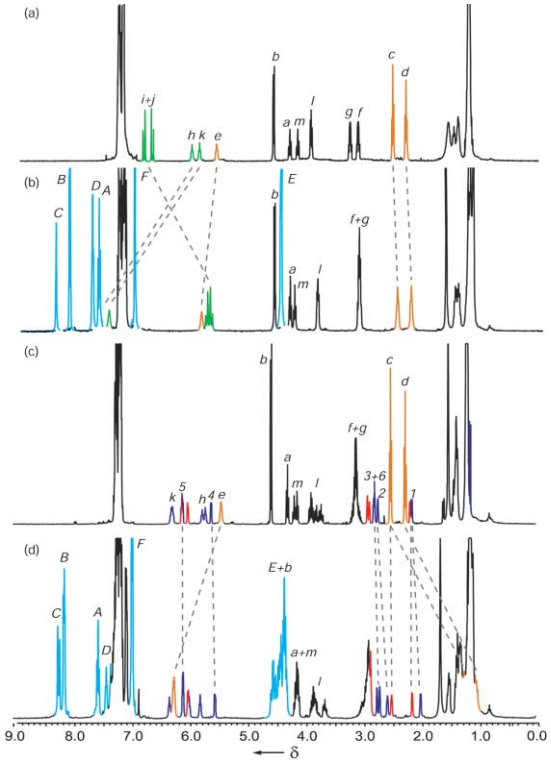

Fig. 1 ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) of a) thread *E*-**2**; b) rotaxane *E*-**1**; c) thread *Cp*-**2** and d) rotaxane *Cp*-**1**. The assignments correspond to the lettering shown in Scheme 1. For clarity only one of the diastereomers of *Cp*-**1** is assigned in the figure; for more detail 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 $C_2D_2Cl_4$ 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 5× 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.

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