Hydrogen-bonded synthetic molecular machines

From myosin to F_1-ATPase, Nature is full of examples of molecular 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.

Initially, the term "molecular machine" was (and sometimes still is) used in a purely iconic manner: the structures *looked* like pieces of machinery – or they carried out a function that in the macroscopic world would require a machine to perform it. Whilst these early reports were unquestionably the key to popularising the field, we are now in the position to give ourselves a more ambitious definition. Accordingly, we can describe molecular machines as *"a subset of molecular devices (functional molecular systems) in which some stimulus triggers the controlled, large amplitude mechanical motion of one component relative to another (or of a substrate relative to the machine) which results in a net task being performed."*[2]

With the objectives outlined in that definition in mind, my thesis addressed: the search for new methods to achieve controlled submolecular motion in stimuli-responsive molecular shuttles; the development of a general design to exploit this controlled motion to produce a potentially useful response; and, remarkably, the extension of the work in solution to polymer films and surfaces.

Controlling sub-molecular motion in molecular shuttles

The first example of entropy-driven translational isomerism was serendipitously discovered in our group.[3] ^{1}H NMR experiments (298K, CDCl$_3$) prove that in *E*-**1** the macrocycle resides over the fumaramide portion of the thread. Irradiation of a solution of *E*-**1** (254 nm) affords *Z*-**1**, in which shuttling of the macrocycle to the succinamide-ester station was confirmed by ^{1}H NMR spectroscopy (308K, CDCl$_3$). Unexpectedly, low temperature ^{1}H NMR experiments (258K, CDCl$_3$) on *Z*-**1** suggested that the rotaxane adopts a co-conformation in which the macrocycle resides over the alkyl chain (Scheme 1).
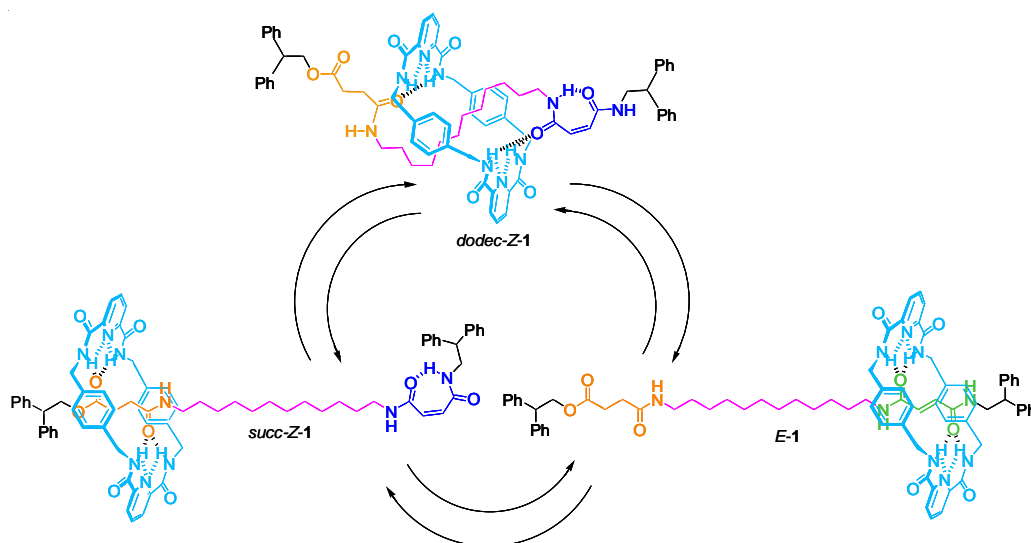
Scheme 1 A tristable molecular shuttle.

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. In *dodec*-*Z*-**1** the high entropic cost required to organise the thread in an "S" shape is paid back by a better enthalpic stabilisation (formation of four strong amide-to-amide hydrogen bonds). Given that $\Delta G_{binding}=\Delta H_{binding}-T\Delta S_{binding}$ if the $\Delta S_{binding}$ 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.

Whilst light and heat have obvious advantages as means of switching molecular shuttles – they don't produce waste products, for instance – most biological machines work through chemical stimulation. In the search for an effective chemical means to provoke shuttling in our hydrogen bonded systems, we were able to exploit the reversibility of Diels-Alder chemistry to produce a chemically-driven molecular shuttle, *E/Cp*-**2**, the first molecular shuttle that works through the reversible formation of C-C bonds.[4]

Addition of cyclopentadiene to shuttle *E*-**2** afforded *Cp*-**2** in good yield (90%). In *Cp*-**2**, the two amide carbonyl groups are in the wrong geometry to interact with the macrocycle. This, together with a significant increase in steric bulk, results in decreased affinity of the macrocycle for the cycloadduct station, which incites its shuttling to bind the succinamide-ester station.

The shuttling process is perfectly reversible. Heating *Cp*-**2** to 250 $^{\circ}$C under reduced pressure for 20 minutes afforded *E*-**2** in quantitative yield.

E-**2**   *Cp*-**2**
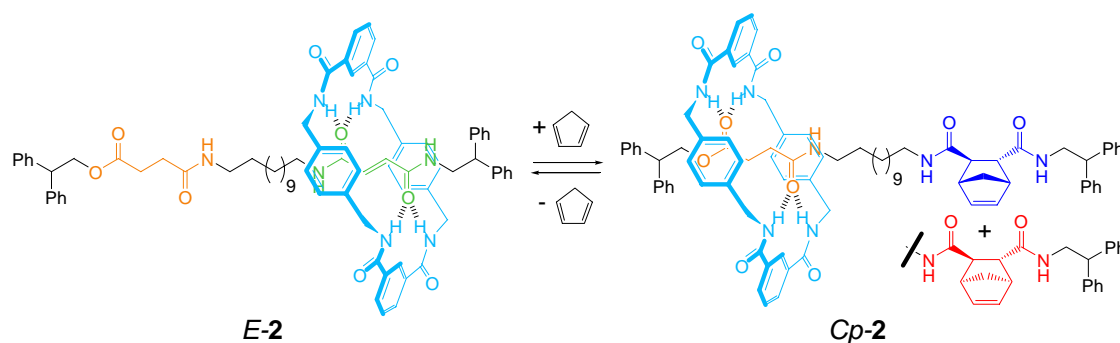
Scheme 2 Shuttling through reversible covalent chemistry.

## From molecular shuttles to molecular machines

With a wealth of methods to provoke controlled submolecular motion already in hand, the next step in the path towards molecular machines was the utilization of the shuttling motion to produce a useful response. A simple design to construct molecular machines that mechanically switch "on" and "off" physical properties that depend upon distance is depicted in Figure 1.[5]
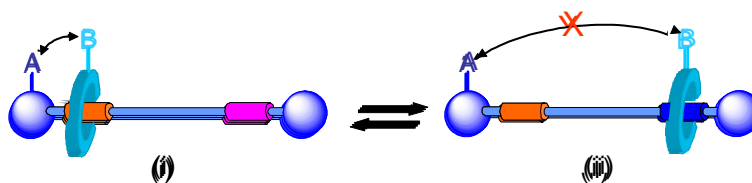
Figure 1 Exploiting a well-defined, large-amplitude positional change to trigger property changes. (i) A and B interact to produce a physical response (fluorescence quenching, specific dipole or magnetic moment, NLO properties, color, creation/concealment of a binding site, etc.); (ii) moving A and B far apart mechanically switches off the interaction.

Based on this design, shuttle *E/Z*-**3** features an anthracene derivative and a pyridinium-substituted macrocycle. Pyridinium ions are known to quench

anthracene's fluorescence via electron transfer. In Z-**3** the macrocycle is located in close proximity to the anthracene, so quenching is expected to be very effective. Z-**3** can be converted to E-**3** by irradiation at 312 nm. In the E isomer, the macrocycle resides far away from the anthracene, thus preventing quenching. This results in a dramatic 200:1 (CH$_2$Cl$_2$, 0.8 x 10^{-5} M, λ_{exc}=365 nm) difference in lumninescence, which is obvious even to the naked eye.[5]
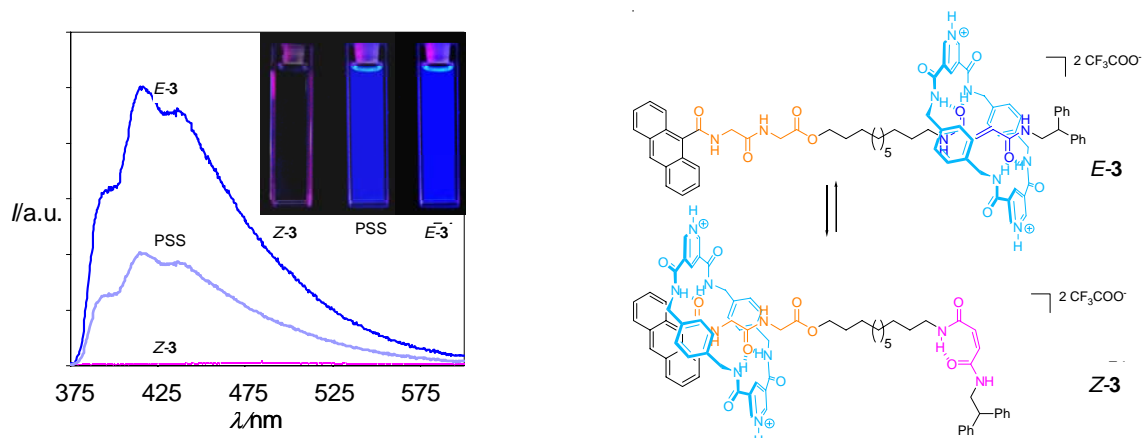
Scheme 3 A light-switchable optically-addressable molecular shuttle.

To further test this design, molecular shuttle E/Z-**4** was synthesized.[6] In this case, shuttling of the macrocycle from the fumaramide (E-**4**) to the glycine-leucine portion (Z-**4**) makes it wrap the chiral center of the leucine residue, which results in a large induced circular dichroism response.
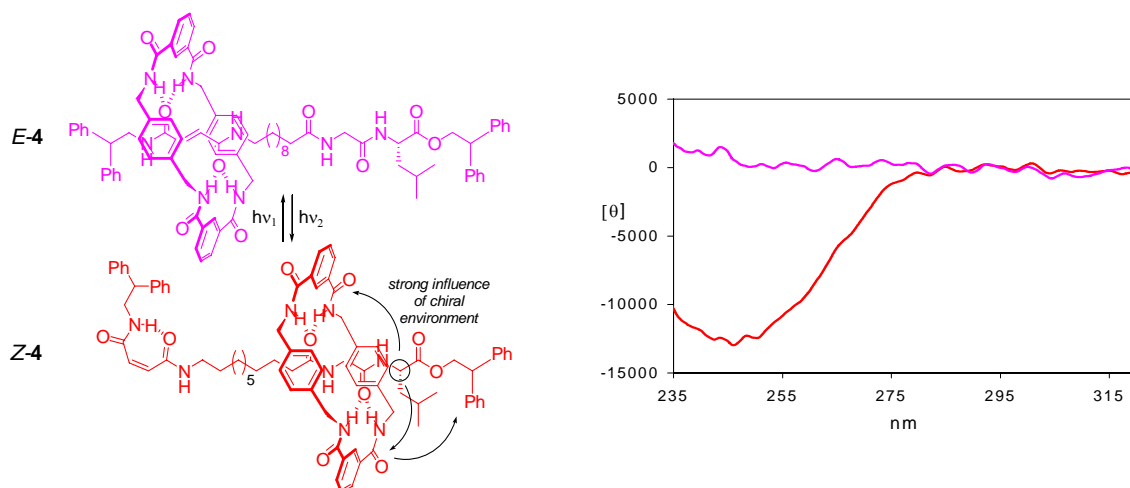
**Scheme 4** Chiroptical switching in a molecular shuttle.

Thanks to a small difference between the electronic absorption spectra of *E*-**4** and *Z*-**4** photostationary states of different composition were 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 irradiating with light of different wavelengths. Shuttle *E/Z*-**4** is satisfactorily fatigue-resistant, and five switching cycles were completed without decomposition.

Molecular shuttles **3** and **4** demonstrate the validity of the design on which they are based, suggesting that a similar strategy could be used to mechanically switch "on" and "off" any distance-dependent property!

Molecular machines get to work

Although the shuttles presented above meet all the requirements to be truthfully called "molecular machines", they were designed and proven to work in solution only. Prior to this work, examples of molecular machines that functioned in environments more amenable to current technologies (polymer films, solid state, etc.) were scarce indeed, and bridging the gap between solution phase – where molecular machines were doomed to be little more than test-tube curiosities – and the solid state – where they are more likely to find real applications – remained a formidable challenge.

In solution, fluorescent molecular shuttle **5** responds to the polarity of the environment.[7] In non-polar solvents, hydrogen bonding interactions are favored and the macrocycle binds the peptide portion of the thread, whereas in polar, H-bond disrupting solvents, solvophobic interactions predominate and the macrocycle shuttles to the alkyl region (Figure 2b). In analogy to *E/Z*-**3** when the macrocycle is made to reside close to the anthracene *and* is protonated with CF_3CO_2H, quenching is very efficient (Figure 2c).
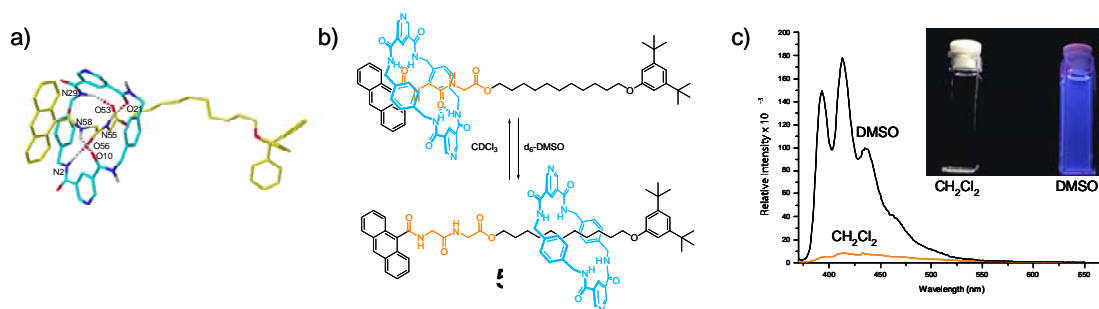
Figure 2 a) X-ray crystal structure of a close synthetic analogue of **5**, showing the H-bond network between the peptide portion of the thread and the macrocycle. b) Translational isomerism in **5**. c) Fluorescence spectra (λ_{exc}= 340 nm, 1 x 10^{-5} M, 298 K) of rotaxane **5** (2H$^+$ 2CF$_3$CO$_2^-$) in CH$_2$Cl$_2$ and DMSO. Inset: picture of the cuvettes illuminated at 254-350 nm.

In order to see if the same principles that work in solution could be applied to environments more relevant to materials applications, we synthesised a well-defined polymer analogue of **5** by transition metal mediated living radical polymerization (ATRP) using ethyl methacrylate as a monomer and [2]rotaxane **6** as initiator. ^{1}H NMR studies in CDCl$_3$ and [D$_6$]DMSO showed that the translational isomerism of **P6** in solution exactly mirrored that of the small molecule analogue. Thin transparent films of **P6** on quartz slides were prepared through either conventional spin-coating techniques or by the evaporation of solutions of the polymers in dichloromethane. The quartz slides coated with **P6** films were fluorescent when illuminated with UV light, but when they were exposed to CF$_3$CO$_2$H vapours fluorescence was no longer observed. Figure 5b shows a distinct pattern of dark bands resulting from thin films of **P6** being exposed to CF$_3$CO$_2$H vapour through a striped aluminium mask (Figure 5) and then illuminated with UV light. When the resulting dark strips of **P6.**(2H$^+$ 2CF$_3$CO$_2^-$)$_n$ were exposed to DMSO vapour through the same mask rotated by 90º, a criss-cross pattern was produced (Figure 5) in which only segments that had been exposed to CF$_3$CO$_2$H vapour but *not* to DMSO vapour were dark when illuminated with the UV source. The response of **P6** to the different combinations of two stimuli (DMSO and protons) corresponds to an INHIBIT Boolean logic gate.
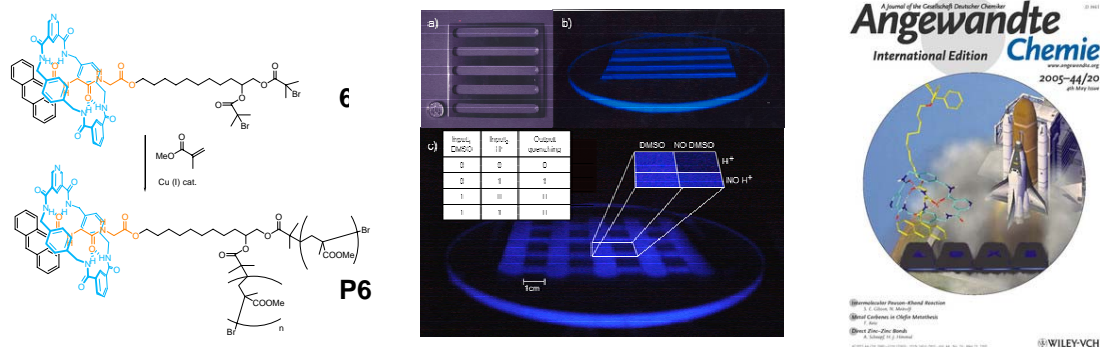
Figure 3 Left: chemical structures of **6** and **P6**. Middle: a) Aluminium grid used in the experiment. The coin shown for scale is a UK 5p piece. b) Pattern generated when films of **P6** were exposed to trifluoroacetic acid vapour through the aluminium grid mask. c) Criss-cross pattern obtained by rotating the aluminium grid 90° and exposing the film shown in (b) to DMSO vapour. Only regions exposed to trifluoroacetic acid but not to DMSO are quenched. The truth table for an INHIBIT logic gate is shown in the inset. Right: "Molecular shuttles take off", front cover of *Angew. Chem., Int. Ed.*, Issue 20, *44*, (2005).

In a further step towards real applications, a monolayer of light-driven molecular shuttle **7** was attached to a SAM of thiols on gold (Figure 4). In this case, shuttling of the macrocycle in response to light stimulation is used to either conceal or reveal a fluoroalkane ('Teflon-like') residue, which dramatically alters the wettability properties of the surface.
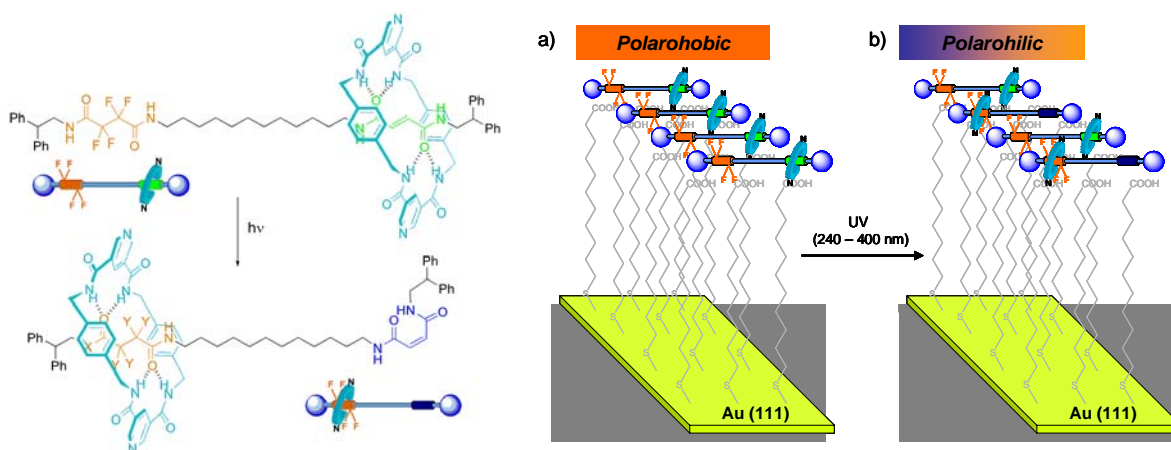
Figure 4 Left: chemical structures of *E*-**7** and *Z*-**7**. Right: schematic representation of a photo-responsive surface based on switchable fluorinated molecular shuttles.

The change in surface tension thus provoked was sufficient to transport microlitre droplets of diiodomethane along a flat surface, and, remarkably, even up a 12° incline, working against gravity.
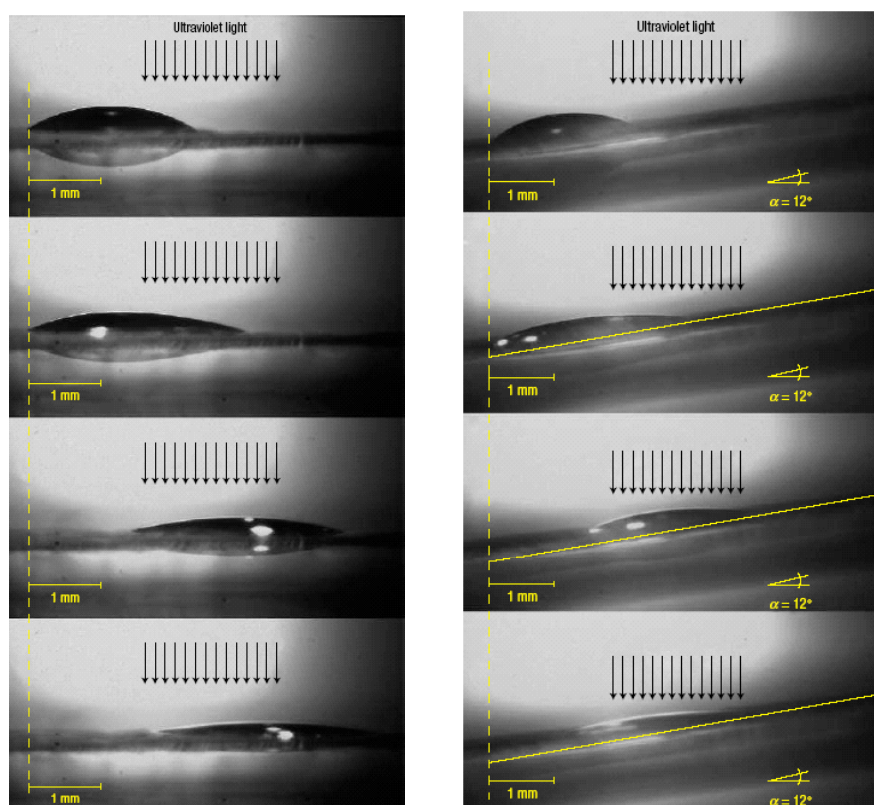
Figure 5 Lateral photographs of light-driven directional transport of a 1.25 μl diiodomethane drop across the surface of a *E*-**7**.11-MUA.Au(111) substrate on mica.

This was the first demonstration controlled motion in synthetic molecular machines being used to transport an object and do macroscopic work, using the same mechanism that biology does, namely biasing Brownian motion.

As a whole, the work presented here represents a significant advance in the field of molecular machinery. Two new methods to control motion in interlocked architectures have been developed. A simple yet solid design to mechanically switch

"on" and "off" *any* physical property that depends (or can be made to depend) upon distance has been successfully tested. And, perhaps more importantly, two of the first examples of molecular machines that work in polymer films and on surfaces have been synthesized and studied, suggesting that some possible applications of artificial molecular machinery – like changing surface properties or data storage – might become a reality even in the short term.

References

[1] M. Schliwa, *Molecular Motors*, Wiley-VCH, Weinheim, **2003**.

[2] E. R. Kay, A. Leigh David, in *Functional Artificial Receptors* (Eds.: A. D. Schrader, A. D. Hamilton), Wiley-VCH, Weinheim, **2005**.

[3] G. Bottari, F. Dehez, D. A. Leigh, P. J. Nash, E. M. Perez, J. K. Y. Wong, F. Zerbetto, *Angew. Chem., Int. Ed.* **2003**, *42*, 5886-5889.

[4] D. A. Leigh, E. M. Perez, *Chem. Commun.* **2004**, *20*, 2262-2263.

One of the top ten most requested *Chem. Commun.* articles in October 2004.

[5] E. M. Perez, D. T. F. Dryden, D. A. Leigh, G. Teobaldi, F. Zerbetto, *J. Am. Chem. Soc.* **2004**, *126*, 12210-12211.

[6] G. Bottari, D. A. Leigh, E. M. Perez, *J. Am. Chem. Soc.* **2003**, *125*, 13360-13361.

[7] D A Leigh, M A F Morales, E M Pérez, J K Y Wong, C G Saiz, A M Z Slawin, A J Carmichael, D M Haddleton, A M Brouwer, W J Buma, G W H Wurpel, S León and F Zerbetto, *Angew. Chem. Int. Ed.,* **2005,** *44*, 3063-3067.

For highlights of this paper see **'Molecular Memories Start to Gel'**, *Materials Update*, 26 May 2005; **'Switches Based on Submolecular Movement'**, *Materials Today*, July/August 2005, page 21.

[8] J Berná, D A Leigh, M Lubomska, S M Mendoza, E M Pérez, P Rudolf G Teobaldi and F Zerbetto, *Nature Materials*, **2005,** *4*, 704-710.

For highlights of this paper see: **'Drop in attendance at motor show'**, D Fitzmaurice *Nature Mater*, **4**, 657 (2005); **'Drop by drop'**, *Nature*, **437**, 4-5 (2005); **'Liquid drop takes big nano step'**, *BBC news*, 7th September 2005; **'Scientists develop molecule machine'** *The Guardian*, 8th September 2005; **'Nanomachines' represent huge stride in technology'** *Financial Times*, 8th September 2005; **'Small motor, huge power'** *The Times*, 8th September 2005; **'Nanotech team move water droplets'** *BBC news*, 29 August 2005; **'Good Morning Scotland'**, *BBC Radio Scotland*, 29 August 2005; **'Molecular motors push liquid uphill'**, *New Scientist*, 29 August 2005; **'Scientists take the effort out of moving objects'**, *The Herald*, 29 August 2005; **'Lasers used to move water'**, *Metro,* 30 August 2005; **'Forscher lassen Flüssigkeit**

bergauf fließen' (in German), *Netzeitung Wissenschaft*, 29 August 2005; **'La nanotecnología da un "enorme" paso de un milímetro'** (in Spanish), *El Pais*, 08 September 2005; **'Las 'nanomáquinas' terapéuticas'** (in Spanish), *El mundo*, 08 September 2005; **'Petit et Costaud!'** (in French), *Le Point*, 08 September 2005; **'Druppel tart zwaartekracht dankzij moleculaire motoren'** (in Dutch), *Kennislink*, 2005; **'분자 모터로 액체를 밀어 올린다'** (in Korean), *Science Donga*, October issue 2005; **'Máquinas moleculares sintéticas capaces de transportar objetos macroscópicos'** (in Spanish), *Anales de Química*, **101(3)**, 80 2005.