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# Amide-based molecular shuttles (2001–2006)*

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*Abstract*: Stimuli-responsive molecular shuttles are rotaxanes in which the macrocycle can be translocated from one position on the thread to a second site in response to an external trigger. Here, we present a brief overview of the contributions of the Leigh group to the field from 2001 to 2006. In this short period of time, molecular shuttles have moved from little more than laboratory curiosities to truly functional molecular machines.

*Keywords*: molecular shuttles; hydrogen bonding; molecular machines; rotaxanes; submolecular motion.

## INTRODUCTION

Rotaxanes (from the Latin *rota* = wheel and *axis* = axle) are chemical species in which one or more macrocycles are threaded onto a linear component, de-threading from which is prevented by bulky "stoppers" [1]. Although macrocycle and thread are not covalently connected, rotaxanes are molecules, and not supramolecular complexes, since covalent bonds need to be broken to separate their components. Stimuli-responsive molecular shuttles are rotaxanes in which the movement of the macrocycle from one recognition site on the thread ("station") to another can be controlled by means of an external stimulus. In this review, we will describe the contributions of our group to the remarkable progress that the field of molecular shuttles has experienced in the last five years. But first, since the interest in molecular shuttles arises from the possibility of achieving controlled submolecular motion of their components with respect to one another, it is appropriate to briefly revise the physics that governs motion at the molecular level, which is fundamentally different from that that governs movement in the macroscopic world [2].

Molecules and their parts move incessantly and randomly at any temperature above 0 K. This chaotic movement is termed Brownian motion after Robert Brown who observed it in 1827 when looking at pollen particles suspended in water through a microscope. As a consequence of Brownian motion, any attempt to "push" or "pull" molecules in a particular direction by the one-off application of a force (as opposed to the continuous application of a force) is completely swamped by the random background motion of the environment. In many ways, trying to control motion at the molecular level is like trying to play pool on a table on which hundreds of balls are moving constantly and randomly. As soon as we strike the cue ball, it is immediately hit by others and proceeds on a random pathway irrespective of the direction that it was initially struck.

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In the macroscopic world, the equations of motion are governed by inertial terms (dependent on mass). This means objects do not move unless we give them specific energy to do so, but once we have given them that initial impetus they keep on moving in the same direction until all that energy is dissipated in the form of heat. Viscous forces (dependent on surface areas) dampen motion by converting kinetic energy into heat. As objects become smaller, inertial terms decrease in importance and viscous terms begin to dominate. At the molecular level, the effect of inertia is negligible so an object's behavior will be determined by the forces applied to it at that very moment, and by nothing in the past.

From a practical point of view, this change in the dominant physical terms has several implications. Firstly, when trying to produce controlled movement at the molecular level, we will need to "tame" Brownian motion rather than provoke movement by applying a force [3,4]. Generating controlled movement at the molecular scale, then, has more to do with *controlling* than with *generating*. Interlocked molecules seem to provide an ideal framework for this task, since the mechanical bond inflicts a restriction over the degrees of freedom with which their components can move with respect to one another, while still allowing motion along certain vectors.

## THE 1990S: FROM DEGENERATE TO STIMULI-RESPONSIVE MOLECULAR SHUTTLES

The ability of macrocycle and thread of a rotaxane to move with respect to one another is inherent to the mechanical bond. In particular, there are two main kinds of large-amplitude submolecular motion in rotaxanes: "pirouetting", which is the movement of a macrocycle *around* the thread of a rotaxane, and shuttling, which is the movement of a macrocycle *along* the thread.

Idealized free energy profiles for two-station degenerate and stimuli-responsive molecular shuttles are shown in Fig. 1 [4]. A rotaxane containing two chemically identical stations separated by an accessible activation energy barrier between them and located far enough apart, so that the shuttling movement can be distinguished from any other internal motion, can be considered the simplest example to study the shuttling phenomenon. In such a system, the macrocycle shuttles back and forth between the energetically degenerate stations, spending exactly half of its time over each of them (Fig. 1a).

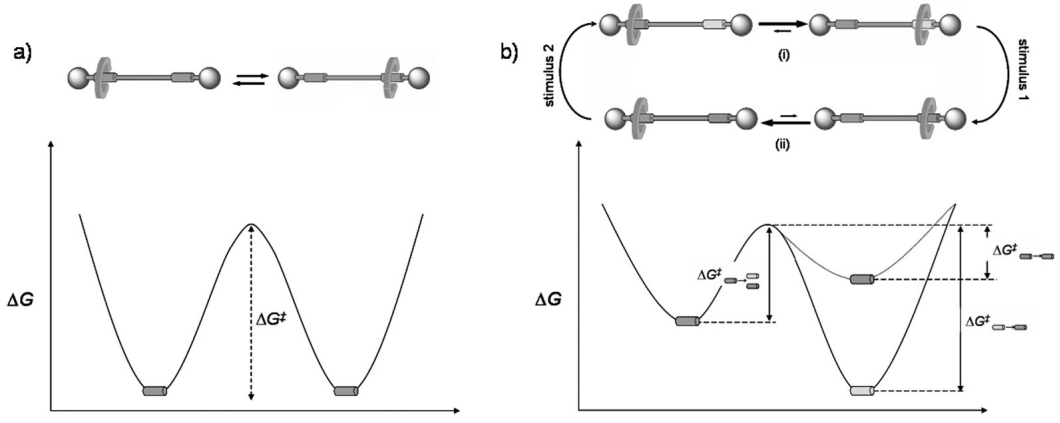


**Fig. 1** Ideal free energy profiles for two-station (a) degenerate and (b) stimuli-responsive molecular shuttles.

The first experimental observation of the shuttling motion in a [2]rotaxane of this type was reported by J. F. Stoddart's group in 1991 [5]. The thread in that molecular shuttle featured two hydroquinol recognition sites for the bisparaquat macrocycle. $^1$H NMR experiments showed that the macrocycle shuttles back and forth between the two stations in a temperature-dependent fashion. In that report, Stoddart noted that: "The opportunity now exists to desymmetrize the molecular shuttle by in-

serting nonidentical stations along the polyether thread in such a manner that these different stations can be addressed selectively by chemical, electrochemical, or photochemical means and so provide a mechanism to drive the bead to and fro between stations along the thread" [5]. Indeed, the first examples of stimuli-responsive molecular shuttles were described in the following years by the groups of Stoddart [6,7], Harriman [8], Nakashima [9], Leigh [10], Gibson [11], and Sauvage [12]. The minimum requirements for the design of stimuli-responsive molecular shuttles are summarized graphically in Fig. 1b. Firstly, we require one of the stations on the thread to be able to switch between two different states, one in which it shows "high" affinity for the macrocycle and one in which it is "low". Secondly, we require a nonswitchable station which exhibits a binding affinity somewhere in 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 macrocycle-to-station binding affinities. Therefore, when the switchable station is in its high-affinity state (Fig. 1b, i), the macrocycle spends most of its time over it, because its binding affinity is higher than that of the nonswitchable station. When the switchable station is addressed with stimulus 1, its affinity for the macrocycle is strongly diminished. In this new state (Fig. 1b, ii), the macrocycle will reside preferentially over the nonswitchable station, which is now the one with the highest affinity. The system can be restored to its original state by application of stimulus 2.

## AMIDE-BASED MOLECULAR SHUTTLES (2001–2006)

Unsurprisingly given their extraordinary dynamic properties, ever since the earliest reports the terms "molecular shuttle" and "molecular machine" have been closely associated [13,14]. In fact, it is sometimes assumed that a molecular shuttle *is* a molecular machine in its own right. But, can we consider all molecular shuttles as molecular machines? 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 popularizing the field, we are now in the position to give ourselves a more scientific and useful definition. Accordingly, we can describe molecular machines as *"a subset of molecular devices in which some stimulus triggers the controlled, large amplitude mechanical motion of one component relative to another which results in a net task being performed"* [4]. Controlled motion *and* performance of a useful task as a result of it are both *sine qua nons* for a chemical species to be called a molecular machine. While controlled submolecular motion is inherent to stimuli-responsive molecular shuttles, there are still relatively few examples in which it has been successfully exploited to *do something* potentially useful. We will first see how controlled submolecular motion has been achieved in our amide-based hydrogen-bonded molecular shuttles, to then revise the examples of real molecular machines based on rotaxanes of this type.

### Controlling motion in molecular shuttles

As we have seen previously (see Fig. 1b), the key to controlling the movement of the macrocycle of a rotaxane is to stabilize and/or destabilize the noncovalent interactions between it and the binding sites present on the thread by using an external stimulus. The nature of the macrocycle-station attractive forces directly determines the methods we can (or cannot) employ to influence them. Since we are going to limit this review to amide-based hydrogen-bonded molecular shuttles, the stimuli utilized will have to be able to influence hydrogen bond networks.

Molecular shuttle **1** features two potential hydrogen-bonding stations, a nonresponsive succinamide (succ), and a 3,6-di-*tert*-butyl-1,8-naphthalimide (ni) (Fig. 2) separated by a long $C_{12}$ alkyl spacer [15]. In its ground state, the naphthalimide is a very poor hydrogen bond acceptor, so the macrocycle prefers to bind the succinamide (see top equilibrium in Fig. 2; $K < 0.01$), as demonstrated by $^1$H NMR. Direct laser irradiation of **1** ($\lambda = 355$ nm) in the presence of a suitable electron donor (for ex-

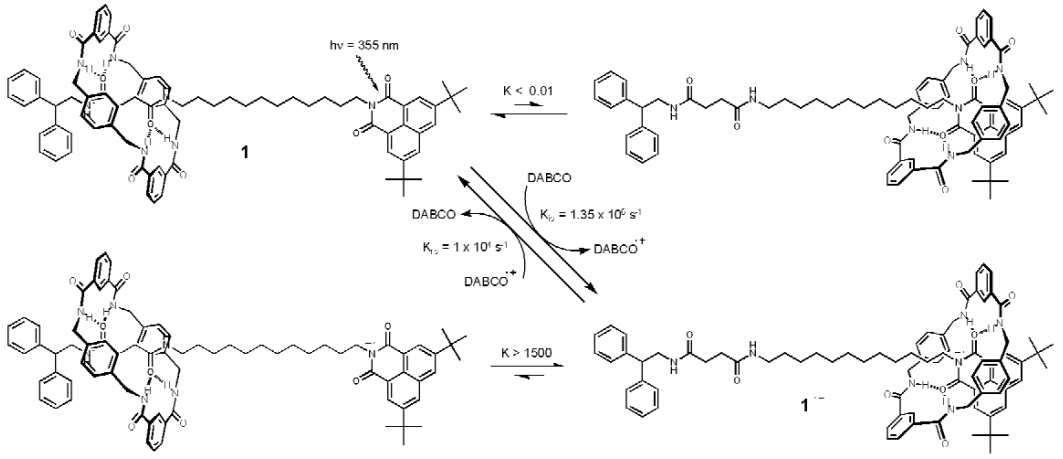


**Fig. 2** Photochemically induced shuttling in a hydrogen-bonded rotaxane. The structures labelled as **1** and **1**$^{\bullet-}$ show the preferred co-conformation for each state [15].

ample, 1,4-diazabicyclo[2.2.2]octane, DABCO) causes its photoreduction to the radical anion, **1**$^{\bullet-}$, in which ni$^{\bullet-}$ is now the best hydrogen-bonding site available (see bottom equilibrium in Fig. 2; $K > 1500$). Overall, the photoinduced shuttling of the macrocycle to the ni$^{\bullet-}$ station takes about 1 μs (induced shuttling, $k_{is} = 1.35 \times 10^6$ s$^{-1}$, MeCN) and, after charge recombination, the macrocycle shuttles back to its original position (recovery shuttling, $k_{rs} \sim 1 \times 10^4$ s$^{-1}$, MeCN). The same shuttling motion could also be achieved electrochemically, by direct reduction of **1** to **1**$^{\bullet-}$ [16]. A series of control experiments on structurally related analogs of **1** unambiguously demonstrated that the dynamic process observed is reversible shuttling of the macrocycle between the stations and is not due to any other conformational or co-conformational change (e.g., folding of the flexible alkyl chain).

In molecular shuttle **2**, photoinduced sub-nanosecond shuttling of the macrocycle was triggered solely by laser irradiation, without the need for an additive [17]. One of the stoppers of **2** is an anthracene-9-carboxamide chromophore, which is attached to a glycylglycine (glygly) hydrogen-bonding site which, in turn, is connected to a $C_{11}$ alkyl chain terminated by a second stopper. In nonpolar solvents (e.g., $CDCl_3$, 1,4-dioxane, etc.), **2** preferentially adopts a co-conformation in which the macrocycle binds the glygly station (see Fig. 3), leaving the carbonyl of the amide group close to the anthracene essentially free. Upon irradiation ($\lambda = 330$ nm), the anthracene-9-carboxamide adopts a nearly planar conformation, allowing for a considerable transfer of charge from the excited state of the anthracene to the carbonyl group of the amide to take place [18], thus making it a much better hydrogen-bonding acceptor and inducing shuttling of the macrocycle.

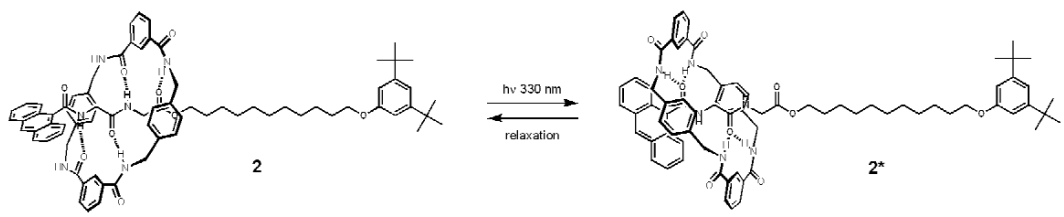


**Fig. 3** Photoinduced short-range shuttling in **2** [15]. The hydrogen-bonding network shown for the macrocycle for **2** is based on the crystal structure of a closely related analog.

In this case, the translational motion takes place over a somewhat short distance (~3 Å), which makes it more difficult to distinguish from other kinds of submolecular motion. In fact, as we will see later, molecular shuttle **2** was initially designed as a model compound for a family of solvent-switchable optically addressable shuttles, in which translation of the macrocycle occurs from the glygly station to the alkyl spacer in response to changes in polarity of the environment.

An example of these solvent-switchable shuttles is the fullerene-containing shuttle **3** [19]. The thread of shuttle **3** is stoppered by a fulleropyrrolidine on one end, close to which is a glygly hydrogen-bonding station. The long alkyl chain serves as a second, solvophobic station. In nonpolar solvents such as dichloromethane or chloroform, the macrocycle hydrogen bonds to the peptide residue; in highly polar solvents such as dimethyl sulfoxide (DMSO), the hydrogen bonding between the macrocycle and the peptide is disrupted by the competing solvent and polarophobic interactions locate the macrocycle preferentially over the alkyl chain (Fig. 4). This shuttling motion could be observed both by $^1$H NMR and time-resolved spectroscopy.

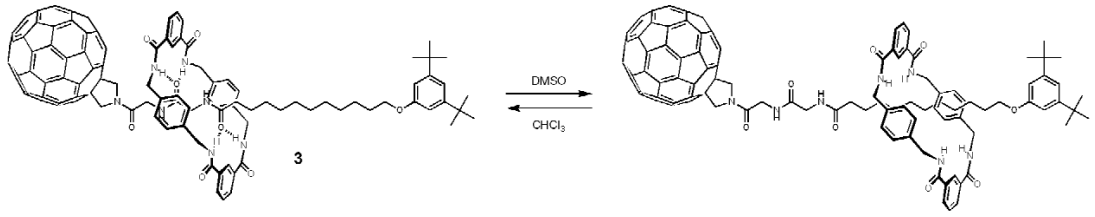


**Fig. 4** Fullerene-containing solvent-switchable shuttle **3** [19]. In nonpolar solvents ($CHCl_3$), the macrocycle hydrogen bonds to the glygly station, while in very polar solvents (DMSO), solvophobic interactions enforce encapsulation of the alkyl chain.

A molecular shuttle that responds to photo and thermal stimulation that shows exceptional positional integrity was later designed and synthesized [20]. Molecular shuttle *E/Z*-**4** operates through fumaramide-maleamide isomerizations (Fig. 5). While the fumaramide station is a close-to-perfect fit for the tetraamide macrocycle [21], its *cis*-isomer—maleamide—can only interact very weakly with it. The thread of rotaxane **4** includes, besides the fumaramide unit, a succinamide-ester station, which contains a poor hydrogen bond acceptor ester group and lacks the preorganization of the carbon–carbon double bond. Accordingly, the macrocycle in *E*-**4** is located primarily over the fumaramide station; in fact, this is the only co-confomer observable by $^1$H NMR. When *E*-**4** is irradiated with UV light ($\lambda$ = 254 nm), it is isomerized to the *cis*-isomer, *Z*-**4**. In *Z*-**4**, 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 has an enforced geometry of hydrogen-bonding groups which is not complementary to that of the macrocycle. To complete the shuttling cycle, *Z*-**4** can be converted to *E*-**4** by thermal isomerization of the double bond back to its more stable *trans*-isomer.

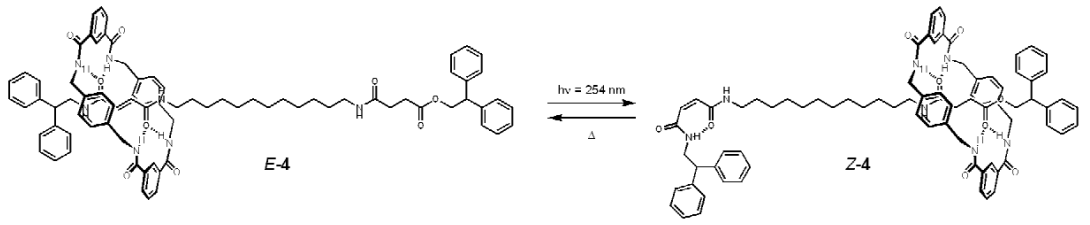


**Fig. 5** A light- and heat-switchable bistable molecular shuttle [20].

The first example of entropy-driven translational isomerism was serendipitously discovered when studying synthetic analogs of **4** [22]. The thread of molecular shuttle *E/Z*-**5** is identical to that in **4**, the only difference being the "endo" pyridyl macrocycle featured in *E/Z*-**5**. As expected, $^1$H NMR experiments (298 K, $CDCl_3$) show that in *E*-**5** the macrocycle resides over the fumaramide portion of the thread. Irradiation of a solution of *E*-**5** (254 nm) affords *Z*-**5**, in which shuttling of the macrocycle to the succinamide-ester station was confirmed by $^1$H NMR spectroscopy (308 K, $CDCl_3$). Unexpectedly, however, low-temperature $^1$H NMR experiments (258 K, $CDCl_3$) on *Z*-**5** show that the rotaxane adopts a co-conformation in which the macrocycle resides over the alkyl chain (Fig. 6).

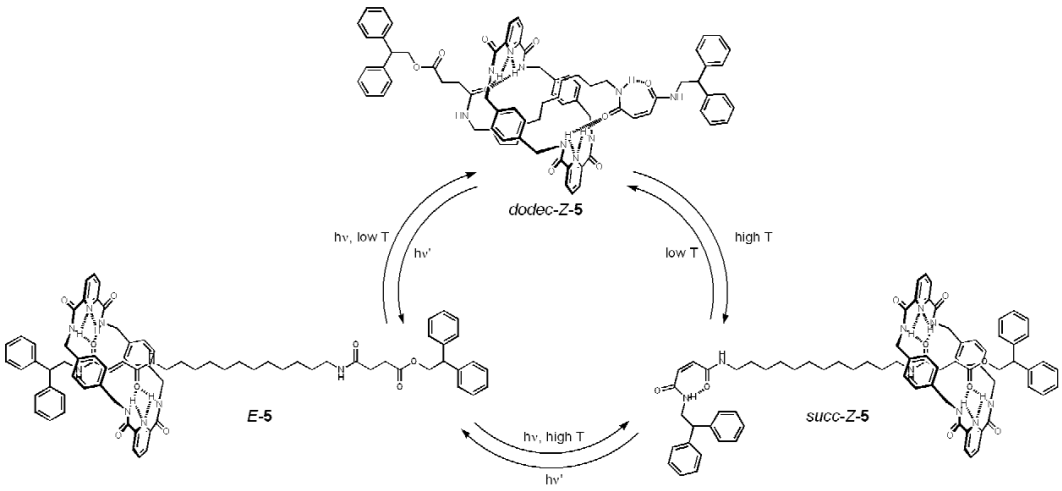


**Fig. 6** The first example of entropy-driven shuttling, a tristable molecular shuttle [22].

The temperature-driven co-conformational change can be explained by considering the different enthalpic and entropic contributions to the general stabilization of each of the two co-conformers observed for *Z*-**5**. In *succ-Z*-**5**, the poor enthalpic stabilization (there are two strong 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 organized. In *dodec-Z*-**5**, the high entropic cost paid by the system to organize the thread in an "S"-shape conformation is paid back by a better enthalpic stabilization (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 do not produce waste products, for instance—most biological machines work through chemical stimulation. In the search for an effective chemical means to provoke shuttling in hydrogen-bonded systems, we were able to exploit the reversibility of Diels–Alder chemistry to produce a chemically driven molecular shuttle, *E*-**6**/*Cp*-**6** (Fig. 7), the first molecular shuttle that works through the reversible formation of C–C bonds [23]. Addition of cyclopentadiene to shuttle *E*-**6** afforded *Cp*-**6** in good yield (90 %) as a 1:1 mixture of diastereomers. In *Cp*-**6**, 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 promotes its translocation to the succinamide-ester station. The shuttle works with outstanding positional integrity, and only the co-conformers depicted in Fig. 7 for each species are observed by $^1$H NMR. Because stereochemistry is conserved through a Diels–Alder–retro-Diels–Alder protocol (*E*-dienophile yields *trans*-adduct, which in

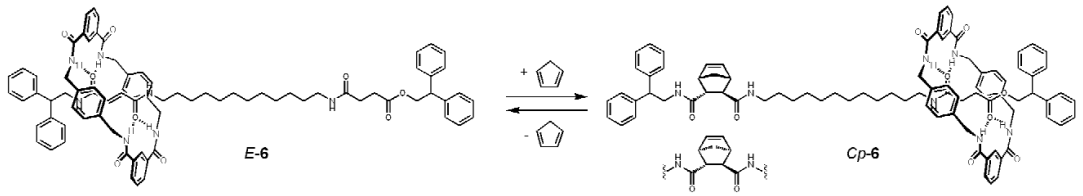


**Fig. 7** A molecular shuttle that works through the reversible formation of C–C bonds [23].

turn results in the *E*-educt upon retro-Diels–Alder), the shuttling could be reversed utilizing retro-Diels–Alder chemistry. Heating *Cp*-**6** to 250 °C under reduced pressure ($10^{-2}$ Torr) for 20 min afforded *E*-**6** in quantitative yield.

A molecular shuttle which functions through anion recognition via hydrogen-bonding interactions was reported in 2004 (Fig. 8) [24]. In rotaxane **7**·H, a succinamide station serves as the nonreactive station; as a second station, the thread 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 of the phenol to yield $\mathbf{7}^-$ was achieved with various bases (LiOH, NaOH, KOH, CsOH, $Bu_4NOH$, *t*-BuOK, DBU, and Schwesinger's phosphazine $P_1$ base), resulting in the macrocycle binding the phenolate anion with preference over the succinamide station in DMF-$d_7$. However, the shuttling was found to be extremely solvent-dependent.

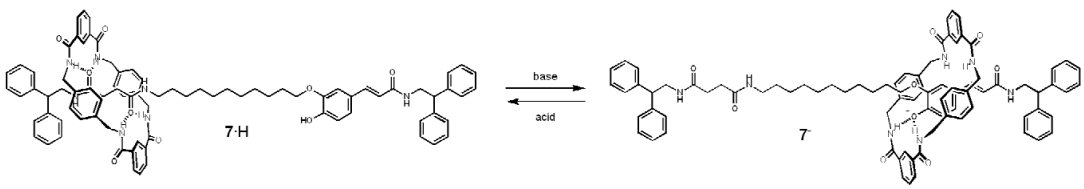


**Fig. 8** Shuttling through anion recognition in a hydrogen-bonded molecular shuttle [24].

Molecular systems based in hydrogen bond interactions usually perform best in "noncompeting" solvents—those with low hydrogen-bonding basicity and acidity [25]. However, if the deprotonation of **7**·H is carried out in $CDCl_3$ or $CD_2Cl_2$, the macrocycle does not shuttle to bind the phenolate. Instead, the thread folds over to allow the macrocycle to bind the phenolate and the succinamide station simultaneously (similarly to that observed in *dodec-Z*-**5**, see Fig. 6). In contrast, in DMF-$d_7$ shuttling does occur upon deprotonation of **7**·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 noncompeting solvents, like $CDCl_3$, 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 disfavored. In DMF-$d_7$, the hydrogen bond accepting solvent can compensate for this loss of stabilization. The shuttling process continues to take place even in $CD_3CN$, 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.

Competition between two or more different ligands for a single binding site is one of the most common means of chemical switching in biological molecular machines. However, the extension of this working mechanism to molecular shuttles is strongly disfavored, both enthalpically—the macrocycle-thread interactions in a rotaxane are normally chosen so as to maximize the efficiency of the template mechanism—and entropically, since the mechanical bond inherently preorganizes macrocycle and

thread for binding, making it difficult to find suitable competitive binders. Stepwise competitive binding of metal ions to molecular shuttle H**8** was successfully utilized to disrupt the initial hydrogen-bonding network and provoke shuttling (Fig. 9) [26]. The thread of rotaxane H**8** consists of a bis(2-picolyl)amino (BPA)-derivatized glygly station separated by a $C_{12}$ alkyl spacer from a succinamide-ester binding site. In H**8**, the macrocycle binds the glygly portion of the thread. Comparison of the $^1$H NMR spectra of the rotaxanes and threads confirmed that the occupancy of the macrocycle was approximately 90:10 in favor of the glylgly station in acetone-$d_6$ at 298 K. Addition of 1 equiv of $Cd(NO_3)_2{\cdot}4H_2O$ to H**8**, resulted in formation of H**8**·$Cd(NO_3)_2$ (Fig. 9) in which the little change (except for the BPA protons) in the $^1$H NMR spectrum indicated that the macrocycle remained preferentially over the glygly portion despite chelation of the terminal peptide carbonyl group to a metal. However, subsequent deprotonation of the internal glygly amide proton of H**8**·$Cd(NO_3)_2$ with 1 equiv of phosphazene base $P_1$-*t*Bu causes translocation of the macrocycle to the succinicamide ester station (**8**·$CdNO_3$, Fig. 9). Removal of the $Cd^{II}$ ion from **8**·$CdNO_3$ with excess $CN^-$ and reprotonation of the amide nitrogen atom with $NH_4Cl$ quantitatively regenerates H**8**.

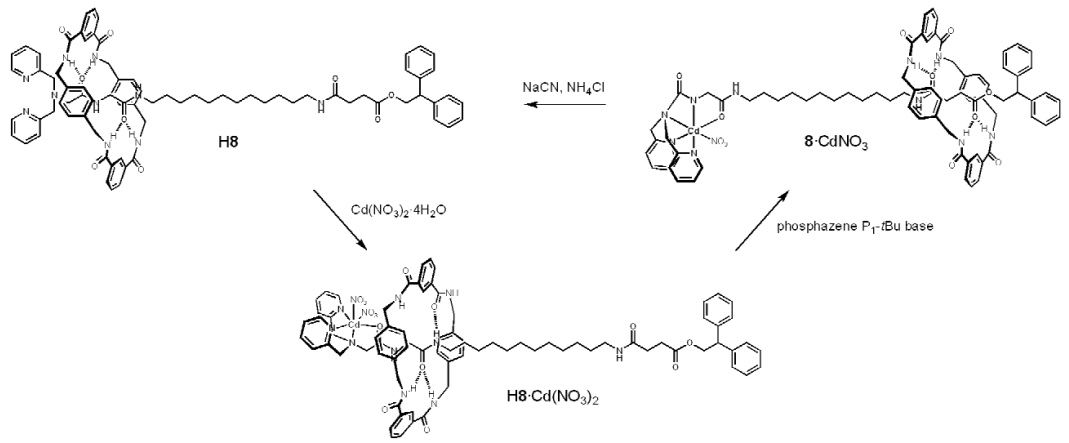


**Fig. 9** Stepwise competitive binding of $Cd^{II}$ to one of the stations provokes shuttling in **8** [26].

Another one of Nature's most widespread systems of regulating function—especially in proteins—is allosteric control. In allosteric systems, activity at a substrate-binding site is regulated by binding of an effector molecule to a second, different site. Molecular shuttle **9** features two possible binding sites for the tetraamide macrocycle, a succinamide, and a succinamide-ester, separated by an alkyl spacer. The succinamide is directly connected to the regulatory site, a BPA derivative, which can bind metal ions, while the succinamide-ester is terminated by a nonchelating stopper (Fig. 10) [27]. In **9**, the macrocycle spends over 95 % of its time over the succinamide station ($^1$H NMR, $CD_3CN$, 278 K). Upon addition of 1 equiv of $Cd(NO_3)_2$, however, the BPA site needs to change its configuration to be able to form the complex **9**·$Cd(NO_3)_2$, significantly increasing the steric demand around the succinamide station and reducing its affinity for the macrocycle, which consequently shuttles to bind the succinamide-ester via biased Brownian motion. The system could be reversed by removal of the $Cd^{II}$ with excess NaCN.

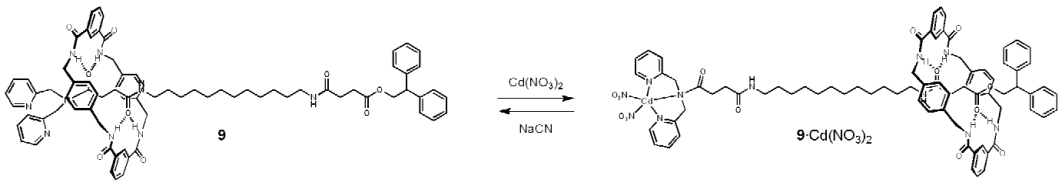


**Fig. 10** An allosterically regulated molecular shuttle, **9** [27].

## FROM MOLECULAR SHUTTLES TO MOLECULAR MACHINES

We have described how controlled submolecular motion in hydrogen-bonded molecular shuttles can be achieved in response to several kinds of stimuli. With a wealth of methods to provoke motion already in hand, the next step in the path toward molecular machines was the utilization of the shuttling motion to produce a useful response. In our group, submolecular translational motion was first utilized in synthetic chemistry. An otherwise "impossible molecule"—a rotaxane whose components bear no formal mutual recognition elements—was synthesized with the help of an interlocking auxiliary that works through a combination of fumaramide-maleamide isomerizations and solvophobic interactions [28]. In order to progress from laboratory to technological applications, it is clear that the machine and its components must be able to interact with the macroscopic world, either directly or through further interactions with other molecular-scale devices.

A simple design to construct molecular machines that mechanically switch "on" and "off" physical properties that depend upon distance is depicted in Fig. 11 [29].

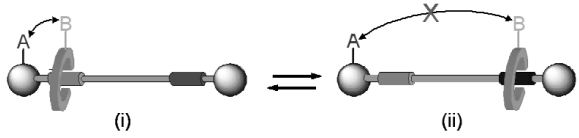


**Fig. 11** Exploiting a well-defined, large-amplitude positional change to trigger property changes. (i) A and B interact to produce a physical response (fluorescence quenching, specific dipole or magnetic moment, NLO properties, color, creation/concealment of a binding site, etc.); (ii) moving A and B far apart mechanically switches off the interaction [29].

To test this design, molecular shuttle *E/Z*-**10** was synthesized (Fig. 12) [30]. The thread of *E/Z*-**10** contains a chiral glycyl-L-leucine station and a photoactive fumaramide. In *E*-**10**, 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*-**10** to *Z*-**10**. In *Z*-**10**, 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*-**10** between 235 and 280 nm. The shuttling process was also confirmed by $^1$H NMR (298 K, $CDCl_3$).

Thanks to a small difference between the electronic absorption spectra of *E*-**10** and *Z*-**10**, 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*-**10** 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. Unlike most chiroptical switches, in which the presence or handedness of

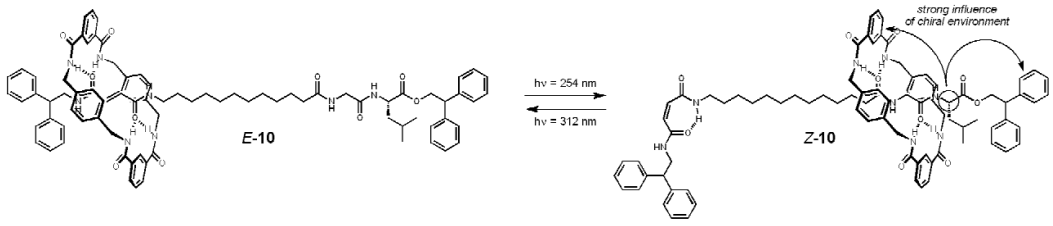


**Fig. 12** Chiroptical switching in a bistable molecular shuttle [30].

chirality is directly altered by irradiation [31], *E/Z*-**10** remains chiral and nonracemic with the same handedness throughout; it is the *expression* of chirality that is influenced by the shuttling process.

Based on the same basic design, shuttle *E/Z*-**11** features an anthracene derivative and a pyridinium-substituted macrocycle (Fig. 13) [29]. Pyridinium ions are known to quench anthracene's fluorescence via electron transfer. In *Z*-**11**, the macrocycle is located in close proximity to the anthracene, so quenching is expected to be very effective. *Z*-**11** can be converted to *E*-**11** 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 ($CH_2Cl_2$, $0.8 \times 10^{-5}$ M, $\lambda_{exc}$ = 365 nm) difference in luminescence, which was obvious even to the naked eye.

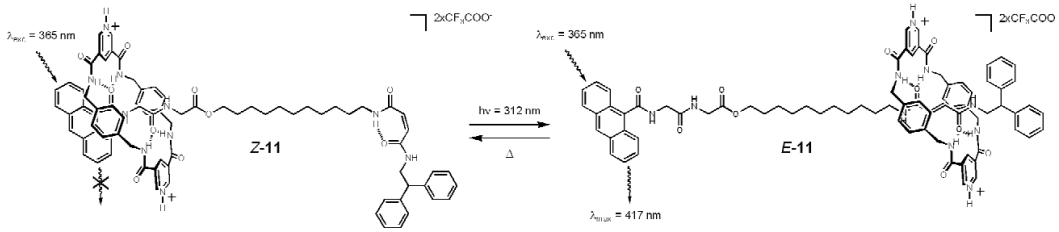


**Fig. 13** Fluorescence switching in a light-switchable molecular machine [29].

Molecular shuttles *E/Z*-**10** and *E/Z*-**11** 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!

Constructing molecular motors able to transport a cargo or "pump" a particle energetically uphill—in the way kinesins or $F_0$-$F_1$ ATPase do—is arguably the ultimate challenge in the field of molecular machinery. An example of a Browian flip-flop, a compartmentalized molecular shuttle capable of transporting its macrocycle energetically uphill, was recently achieved (Fig. 14) [32]. The thread of **12**, which includes a primary alcohol group, is used to attach a removable TBDMS group that acts as a "gate". Besides this, the functioning is analogous to that of molecular shuttle *E/Z*-**4** (Fig. 5). The removal and addition of the blocking group serves as a linking–unlinking stimulus between the two compartments on the thread. Making use of this and fumaramide-maleamide isomerizations as balance-breaking stimuli, the machine—the thread—is able to transport its macrocycle energetically uphill (for operation details, see Fig. 14). Note that in *fum-E*-**12** and *succ-E*-**12**, the chemical structure of the thread is identical (i.e., the machine has been reset), but in *succ-E*-**12**, the macrocycle resides over an energetically nonfavorable station: it has been transported energetically uphill. Resetting this compartmentalized molecular machine does not undo the work it has carried out or the task performed, a significant difference from a simple molecular switch and a characteristic one can recognize as "ratcheting" [33].

Although the shuttles presented above meet all the requirements to be accurately called molecular machines, they were designed and shown to work in solution only. Examples of molecular machines

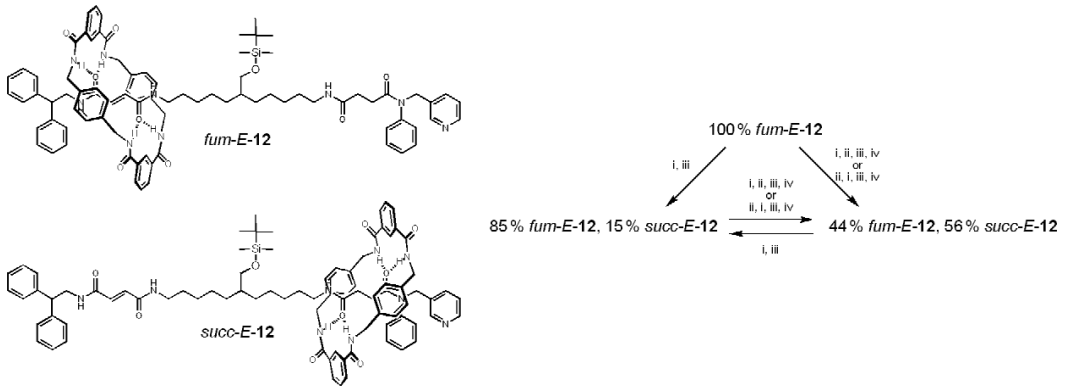


**Fig. 14** Chemical structures and operation of machine-substrate system **12**. Reaction conditions: (i) 80 % aqueous acetic acid, 60 °C, 1 h. (ii) hν at 312 nm (5 × 5 min irradiation), $CH_2Cl_2$, rt. (iii) TBDMSCl, imidazole, DMAP, $CH_2Cl_2$, rt, 1 h. (iv) Piperidine, $CH_2Cl_2$, rt, 12 h, quantitative [32].

that function in environments more amenable to current technologies (polymer films, solid state, etc.) are scarce indeed, and bridging the gap between solution phase (where molecular machines are unlikely to be more than test-tube curiosities in the short term) and the solid state (where they are more likely to find real applications) remains a formidable challenge. We will conclude this review with two of the first examples of rotaxane-based molecular machines that work in polymer films and on surfaces.

In solution, fluorescent molecular shuttle **13** responds to the polarity of the environment (Fig. 15) [34]. In nonpolar solvents, hydrogen-bonding interactions are favored and the macrocycle binds the peptide portion of the thread, whereas in polar, hydrogen bond-disrupting solvents, solvophobic interactions predominate and the macrocycle shuttles to the alkyl region (as in **3**, see Fig. 4). In analogy to *E/Z*-**11**, when the macrocycle is made to reside close to the anthracene *and* is protonated with $CF_3CO_2H$, quenching is very efficient.

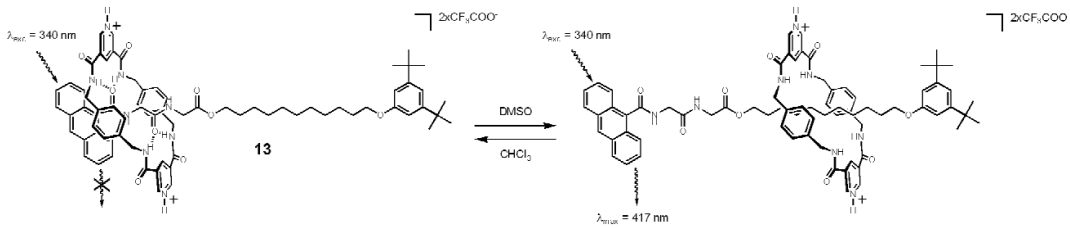


**Fig. 15** Solvent-switchable fluorescent shuttle **13** [34].

In order to see if the same principles that work in solution could be applied to environments more relevant to materials applications, a well-defined polymer analog of **13** was synthesized by transition metal-mediated living radical polymerization (ATRP) using ethyl methacrylate as a monomer and [2]rotaxane **14** as initiator. $^1$H NMR studies in $CDCl_3$ and DMSO-$d_6$ showed that the translational isomerism of P**14** in solution exactly mirrored that of the small molecule analog. Thin transparent films of P**14** on quartz slides were prepared through either conventional spin-coating techniques or by the evaporation of solutions of the polymer in dichloromethane. The quartz slides coated with P**14** films were fluorescent when illuminated with UV light, but fluorescence was no longer observed when they were exposed to $CF_3CO_2H$ vapors. Figure 16b shows a distinct pattern of dark bands resulting from thin films of P**14** being exposed to $CF_3CO_2H$ vapor through a striped aluminum mask and then illuminated with UV

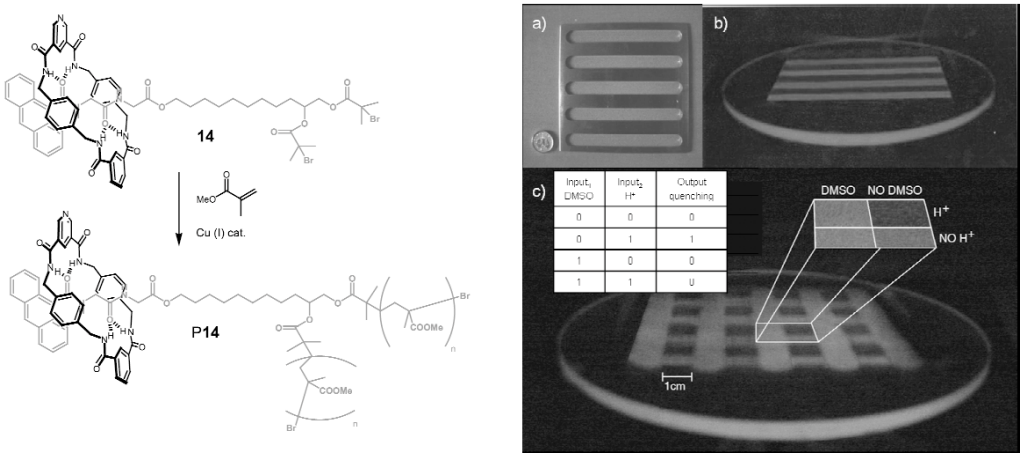


**Fig. 16** Left: chemical structures of **14** and P**14**. Right: (a) Aluminum grid used in the experiment. The coin shown for scale is a UK 5p piece. (b) Pattern generated when films of P**14** were exposed to trifluoroacetic acid vapor through the aluminum grid mask. (c) Criss-cross pattern obtained by rotating the aluminum grid 90° and exposing the film shown in (b) to DMSO vapor. 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.

light. When the resulting dark strips of P**14**·$(2H^+ 2CF_3CO_2^-)_n$ were exposed to DMSO vapor through the same mask rotated by 90º, a criss-cross pattern was produced (Fig. 16c) in which only segments that had been exposed to $CF_3CO_2H$ vapor but *not* to DMSO vapor were dark when illuminated with the UV source. The response of P**14** to the different combinations of two stimuli (DMSO and protons) corresponds to an INHIBIT Boolean logic gate.

In a further step toward real applications, a monolayer of light-driven molecular shuttle **15** (Fig. 17) was attached to a self-assembled monolayer (SAM) of 11-mercaptoundecanoic acid (11-MUA) on gold (Fig. 18) [35]. In this case, shuttling of the macrocycle in response to light stimulation is used to either conceal or reveal a fluoroalkane ("Teflon-like") residue and thereby modify the surface tension.

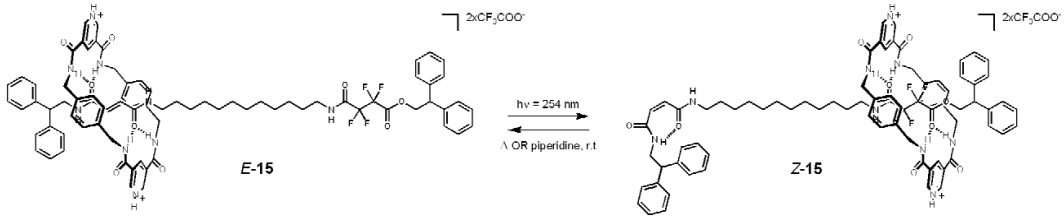


**Fig. 17** Translational isomerism in a fluorinated molecular shuttle [35].

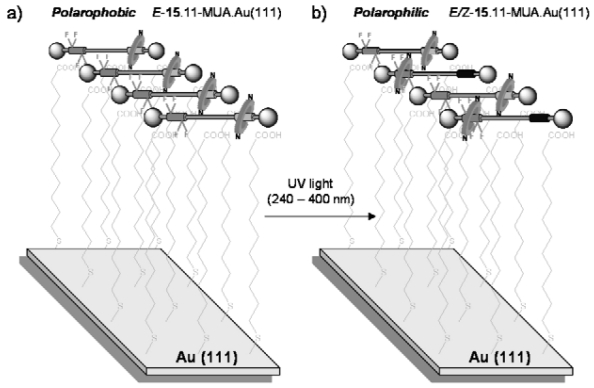


**Fig. 18** Schematic representation of the photo-responsive surface generated by physisorption of pure *E*-**15** onto a 11-MUA.Au (111) monolayer. Illumination with 240–400 nm light isomerizes some of the *E* olefins to *Z* causing a nanometer displacement of the rotaxane threads in the *Z*-shuttles which encapsulates the fluoroalkane units leaving a more polarophilic surface, *E/Z*-**15**·11-MUA·Au(111). The contact angles of droplets of a wide range of liquids change in response to the isomerization process [35].

The change in surface tension thus provoked was sufficient to transport μL droplets of diiodomethane along a flat surface, and, remarkably, even up a 12° incline. In this process, the molecular machines effectively employ the energy of the light source to collectively do work on the drop against gravity. In this experiment, approximately 50 % of the light energy absorbed by the rotaxanes was used to overcome the effect of gravity, with the work done stored as potential energy (Fig. 19).

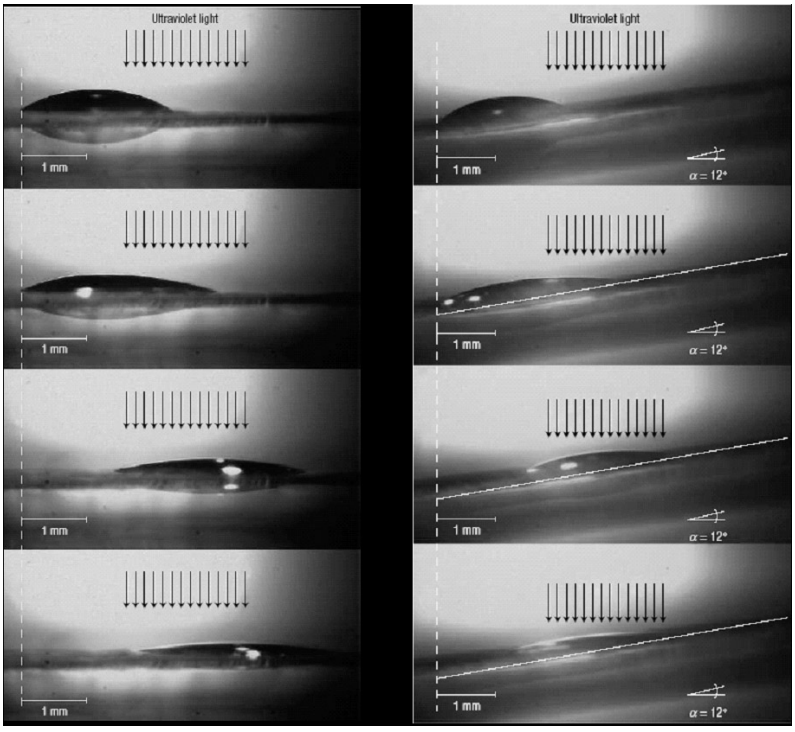


**Fig. 19** Lateral photographs of light-driven directional transport of a 1.25 μL diiodomethane drop across the surface of a E-7·11-MUA·Au(111) substrate on mica.

## CONCLUSIONS AND OUTLOOK

Molecular shuttles are currently seen as one of the most promising scaffolds for the construction of artificial molecular machines. Here, we have presented an overview of the contributions of the Leigh group to the field of molecular shuttles in the last five years. Through the text, we have seen how in that period of time the field has evolved from degenerate to stimuli-responsive molecular shuttles—capable of responding to a breadth of different chemical and physical stimuli—and from there to the synthesis and operation of real molecular machines capable of performing basic logic operations, or producing macroscopic transport. Recent advances in synthesis [36–41], the understanding of structure [42] and information transfer [43], and the development of motors [44,45]—a far more advanced and sophisticated form of controlled motion than simple shuttle systems—augur well for even more rapid advances in this field over the next few years.

However, despite these successes, the field of molecular machinery is still in its infancy. The valuable experience gathered so far, together with a better understanding of the physics underneath biological molecular machines will undoubtedly result in the widespread utilization of molecular machines for useful tasks. In the meantime, the effort of chemists, physicists, material scientists, biologists, engineers, and others might make some applications—such as changing surface properties or data storage—a reality even in the short term.

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