MOLECULAR MACHINES

Tiny steps

A molecular 'walker' can be made to move up and down a molecular 'track' by alternately locking and unlocking the two different types of covalent bonds that join the two components together. By changing the conditions under which one of the bond-forming/bond-breaking processes occurs, a directional bias for walking can be achieved.

Sijbren Otto

The molecules that nature has evolved to perform crucial biological tasks continue to inspire awe and admiration — especially in the synthetic chemists who strive to make molecules capable of mimicking these functions. Take, for example, the kinesin motor-protein that can be thought of as a railway engine inside the cell — it is able to transport cargo along extended tracks made from another protein, tubulin. Unlike a railway engine, however, kinesin does not have wheels, but two little 'feet' with which it 'walks' on the tubulin track. The 'engine' is fuelled[1] by the hydrolysis of adenosine triphosphate (ATP) and it travels in just one direction because of the unsymmetric architecture of the track. Moreover, the presence of either ATP or adenosine diphosphate (ADP) in the binding pocket of each of the kinesin molecule's feet determines which foot is released from the track during the walking process. A beautiful animation of a kinesin molecule walking down a tubulin track can be viewed online[2].

As reported in *Nature Chemistry*, a team of researchers led by David Leigh at the University of Edinburgh have now developed a small synthetic molecule–track system that mimics the action of kinesin[3]. In their design, Leigh and co-workers had to take a number of factors that affect movement at the molecular level into consideration. For example, whereas gravity will ensure that the feet of a walker remain firmly on the ground in the macroscopic world, in the molecular world gravity is of little importance and an alternative force has to be introduced to keep the walker on its track. In nature, non-covalent interactions are used to serve this purpose, but in a synthetic system it is difficult to achieve the necessary tight binding, while at the same time maintaining the ability to unbind the feet before taking another step.

Leigh's team has solved this problem by making clever use of reversible covalent bonds to achieve controlled binding and unbinding of the feet to the track (Fig. 1). The walker has one hydrazide foot and one thiol foot. The hydrazide can react with an aldehyde at either position 1 or 3 to form a hydrazone, and the thiol foot can form a disulfide linkage at either position 2 or 4. Depending on the acidity of the medium, either one or the other bond type becomes labile, but not both at the same time[4,5]. This orthogonality ensures that one foot is always bonded to the track and that the walker does not fall off. Under acidic conditions the hydrazone bonds readily fragment and re-form, allowing one foot to move, whereas under basic conditions the disulfide bonds break and form, allowing the other foot to move.

Starting from the compound in which the walker is bonded to positions 1 and 2 on the track (the 1,2-isomer), adding acid causes

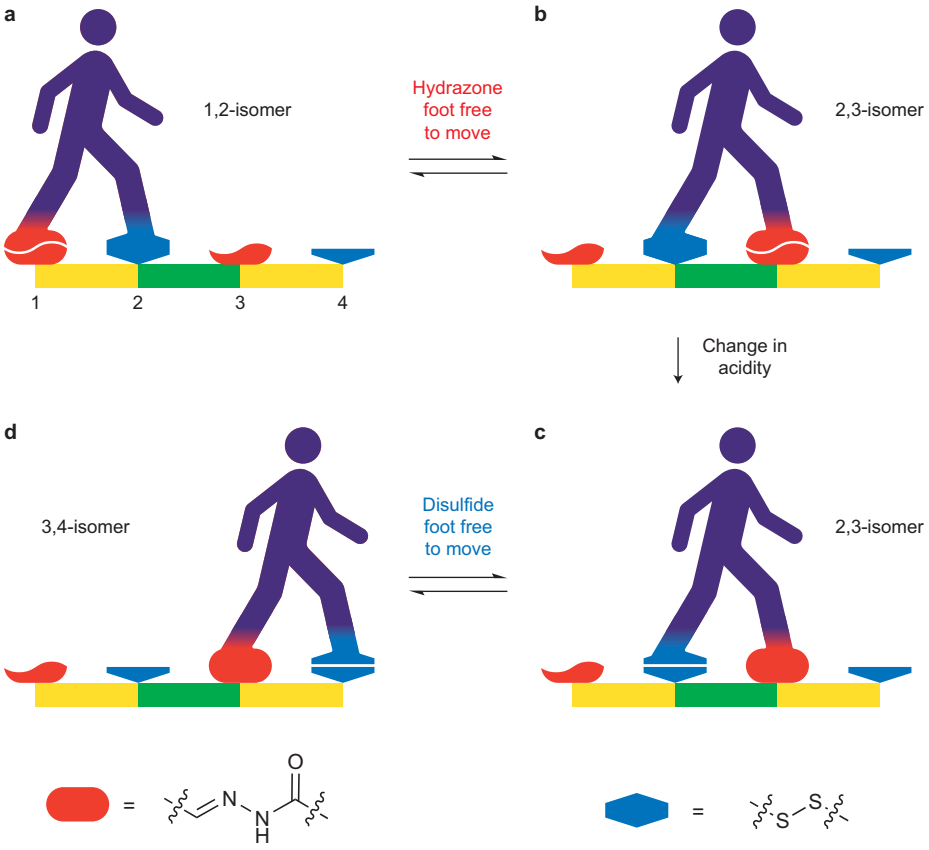

Figure 1 | Schematic representation of how a molecule featuring a thiol foot (blue) and a hydrazide foot (red) can walk along a short linear track with four stepping stones (numbered 1–4). **a**,**b**, Starting on the left of the track with the 1,2-isomer (**a**) switching on the reversible hydrazone chemistry under acidic conditions gives the walker the choice between stepping to position 3 (**b**), or remaining at position 1. **c**,**d**, Switching off the hydrazone chemistry and switching on disulfide exchange fixes the hydrazone foot in place (**c**), while allowing the disulfide foot to choose between two blue stepping stones, position 2 and position 4 (**d**). The unsymmetrical nature of the track is denoted by the coloured sections. For example, when the disulfide bond is cleaved in the 2,3-isomer, the thiol foot must either step across the yellow section to form the 3,4-isomer or back across the green section to reform the 2,3-isomer.

the hydrazone bond at position 1 to break. The newly freed hydrazide foot of the walker can then react at either position 1 to reform the 1,2-isomer, or at position 3 to form the 2,3-isomer, during which the walker has taken one step along the track. The process of hydrazone cleavage and formation occurs under thermodynamic control and the relative amounts of the 1,2- and 2,3-isomers (51:49) reflects the stability of these two different macrocyclic compounds. This mixture is then treated with base, which locks the hydrazone bonds in place, but enables the disulfide bond at position 2 to break and exchange with the disulfide at position 4 to form the 3,4-isomer (from the 2,3-isomer) — the walker has now taken two steps along the track from its original position. Cycling between acidic and basic conditions gives a mixture of the 1,2-, 2,3- and 3,4-isomers (and also a small amount of the 1,4-isomer) in a ratio of 39:36:19:6.

The bias for moving from left to right can be increased by replacing one of the reversible bond-breaking/bond-forming steps with a kinetically controlled sequence of reactions. Instead of performing the disulfide exchange reactions under reversible conditions, the disulfides are controllably cleaved to give free thiols, and then subsequently re-oxidized. This process gives a different product distribution of walker–track isomers than the reversible reaction, and further biases the direction of the walker. For example, after cycling the 1,2-isomer under the biasing conditions, 43% of the 3,4-isomer is formed, in contrast with only 19% being produced under the conditions where all of the bond-forming/bond-breaking steps are reversible.

In the present study the track is relatively short, allowing for just two steps. In principle, however, it should be possible to extend the approach to longer tracks and even cyclic tracks, although such systems may become increasingly difficult to analyse in as much detail as the present construct. Much of the beauty of the present system is in its (relative) simplicity. Unlike previously reported DNA-based walkers[6] it does not feature any components borrowed from nature. It also operates with a simple energy source — a change in acidity of the medium. One exciting possibility that is now almost within reach is to couple this type of walker to an oscillating reaction that rhythmically switches between two different pHs. Once such a system is set going, the walker should continue its journey without any human intervention.

On a more general note, the system is a clever new entry in the as yet limited number of man-made systems that operate out-of-equilibrium. All life forms as we know them are far from equilibrium and can only exist by coupling processes that are thermodynamically uphill to ones that go downhill. The design of new chemical systems that feature such coupling is a challenging endeavour. It pushes the boundaries of supramolecular chemistry and will be at the heart of the emerging fields of systems chemistry and synthetic biology. ❐

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References

1. Amos, L. A. *Cell Mol. Life Sci.* **65,** 509–515 (2008).
2. http://multimedia.mcb.harvard.edu/
3. von Delius, M., Geertsema, E. M. & Leigh, D. A. *Nature Chem.* **2,** 96–101 (2010).
4. Rodriguez Docampo, Z. & Otto, S. *Chem. Commun.* 5301–5303 (2008).
5. Orrillo, A. G., Escalante, A. M. & Furlan, R. L. E. *Chem. Commun.* 5298–5300 (2008).
6. Omabegho, T., Sha, R. & Seeman, N. C. *Science* **324,** 67–71 (2009).

QUANTUM COMPUTING

Chemistry from photons

The use of conventional computers to calculate molecular properties is hindered by the exponential increase in computational cost on increasing the size of the molecules studied. Using quantum computers could be the solution and the initial steps are now being taken.

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Calculating ground- and excited-state energies of molecules with high accuracy and precision remains a daunting task. Exact solutions for molecules consisting of more than about ten atoms remain beyond the scope of computational chemists even with the latest multicore-processing technology. The essence of the problem is the disparity between our classical description of molecules and the underlying quantum mechanics. A quantum computer — a quantum simulator that actually uses a quantum system to process data — offers the possibility of overcoming this mismatch[1] and nowhere is its potential application greater than for the calculation of molecular properties[2]. Writing in *Nature Chemistry*, Aspuru-Guzik, Lanyon and co-workers describe an initial experimental step down this path[3].

The challenge of quantum chemistry — applying quantum theory to the calculation of molecular properties — comes from the interactions and correlations of electrons. Simply placing electrons into the lowest available molecular orbitals and then calculating the energy can give a reasonable approximation, but because of the interactions between electrons, calculating exact energies requires including configurations where the electrons are in higher-energy orbitals. The number of possible electron configurations grows exponentially with the size of the molecule and so, therefore, do the resources required for an exact calculation. Despite the progress made in quantum chemistry — through the development of approximation methods that look at only a few-electron configurations[4] — an exponential increase in classical computational power leads to only a linear increase in the size of molecules considered. Conversely, an exponential improvement in quantum computer hardware would transform quantum chemistry.

A quantum computer is composed of two-level quantum systems, qubits, with variable interactions. Their theoretical power means that a quantum computer with 500 reliable qubits could perform an exact calculation on large and important molecules, such as caffeine[2], for example. Based on an extrapolation of Moore's law, this calculation would become possible on a classical computer in the next millennia, long after Moore's law is actually expected to end. Unfortunately, present quantum computers are composed of only a few qubits, but a linear improvement in their hardware would have the same effect on quantum chemistry as an exponential improvement in conventional computers.