Molecular Motors

DOI: 10.1002/anie.201006946

Synthetic Molecular Bipeds**

*Emilio M. Pérez**

dynamic covalent chemistry · macrocycles · molecular devices · molecular motors · photochemistry

There are relatively few species of animals that are habitual bipeds. Evolution seems to have favored other types of terrestrial locomotion, so that only birds and a few mammals—including humans, kangaroos, and wallabies—utilize their two rear limbs to move from one place to another. This fact, together with an understandable unawareness of Australian fauna, led Plato to famously define humans as "featherless bipeds".[1]

Among motor proteins, however, bipedalism is the preferred mode of locomotion. Kinesins (Figure 1)[2] and dyneins utilize two "feet" to move along microtubules, as so do myosins to move along actin filaments.[3] Some key common features of these motor proteins are: 1) processivity: when one foot is detached from the track to allow for movement, the other foot remains bound to the track, so that the protein remains attached over many steps (ca. 100 in the case of most kinesins); 2) directionality: for instance, kinesins typically move towards the plus end of microtubules, while dyneins move towards the minus end; 3) repetitive and progressive operation: they can repeatedly perform similar mechanical cycles without undoing the physical task performed at each step; 4) functionality: the motion of the proteins is exploited to carry out biologically relevant tasks. Motor proteins transport cargoes—in the case of dyneins and kinesins—or exert a force that results in muscle contraction—in the case of myosins.

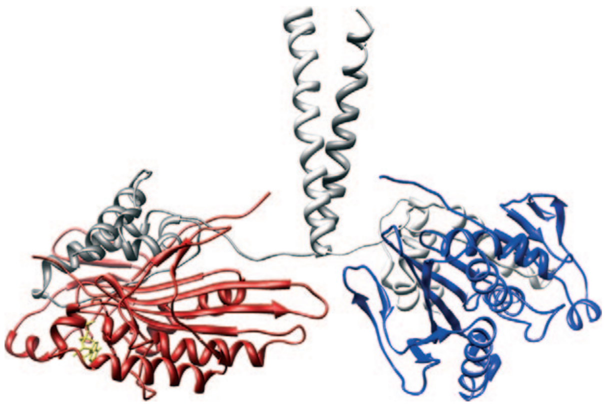
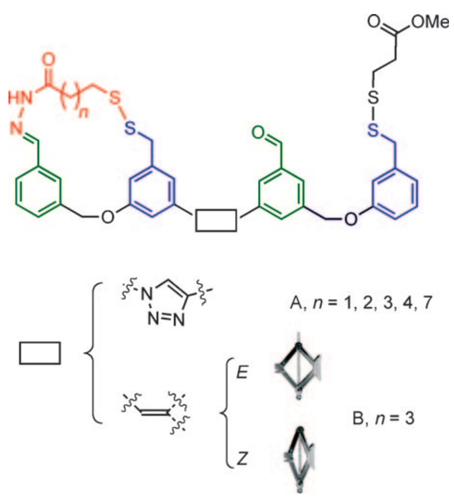


Figure 1. Solid-state structure of kinesin binding adenosine diphosphate (ADP).[2] The feet are shown in different colors (blue and red) for clarity. The red foot is bound to ADP (shown in yellow). The neck linker to the cargo-binding domain is shown in gray.

It is no wonder that scientists have been fascinated by such machines, and have tried to produce artificial systems that show similar features.[4] Until very recently, the only successful artificial systems were built with building blocks directly borrowed from nature, and several astonishing examples of DNA-based walkers have already been reported.[5]

Leigh and co-workers have succeeded in designing and synthesizing small-molecule track–walker systems.[6] In order to attain the processivity displayed by naturally occurring motor proteins while achieving a degree of control over the attachment and detachment of the feet, the research team used the toolbox of reactions of dynamic covalent chemistry,[7] in a compromise between the lability and tunability of weak noncovalent interactions and the stability of covalent bonds. In particular, they used disulfide (sensitive to base and/or redox chemistry) and hydrazone (sensitive to acid) exchange to achieve the walking motion. The structures of the track–walker systems are shown in Scheme 1. The walker unit (red)



Scheme 1. Chemical structure of the track–walker systems.

[*] Dr. E. M. Pérez
IMDEA Nanociencia, Facultad de Ciencias, Módulo C-IX, 3ªplanta
Avda. Fco. Tomás y Valiente, 7
Ciudad Universitaria de Cantoblanco, 28049, Madrid (Spain)
E-mail: emilio.perez@imdea.org
Homepage: http://www.nanociencia.imdea.org

[**] The MICINN of Spain is acknowledged for a Ramón y Cajal Fellowship, cofinanced by the European Social Fund.

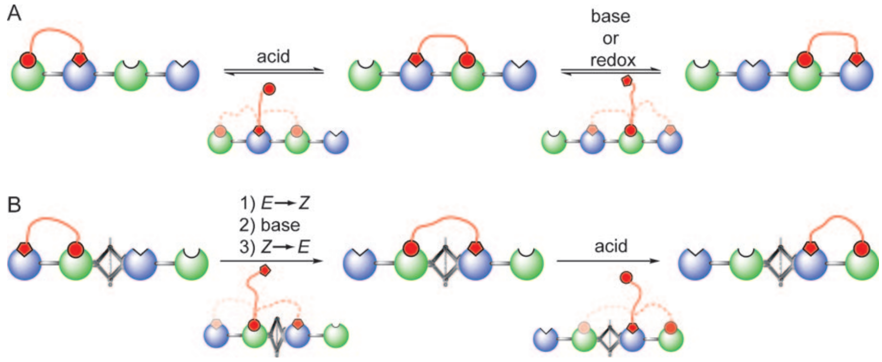


Figure 2. Operation of track–walker systems A and B. Color codes as in Scheme 1; pentagons represent disulfide–thiol foot and footholds and circles represent hydrazide–hydrazone foot and footholds. The placeholder is not represented for clarity. Below the arrows the intermediates are shown.

comprises thiol and hydrazide units, which are separated by alkyl spacers. The track unit, in turn, features four footholds: two thiols (blue) for the formation of disulfide linkages, and two aldehydes (green) for the formation of hydrazone bonds. In the case of system A, the two halves of the track are connected through a rigid triazole unit.[6a,b] On the other hand, the track in system B features a stilbene-type olefin, which, through *E*/*Z* photoisomerizations, allows for the control of the distance between the two central footholds of the track, as represented by the car jack in Scheme 1 and Figure 2.[6c] Finally, methyl 3-mercaptopropanoate (black) is utilized as a reference to track the movement of the walker unit.

The track–walker system A can be operated through changes in the pH value, by addition of trifluoroacetic acid (TFA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Under acidic conditions, hydrazone exchange takes place (circles in Figure 2), and the hydrazide foot of the walker explores both aldehyde footholds, until reaching thermodynamic equilibrium. Very importantly, under these conditions, the disulfide linkage (pentagons in Figure 2) is stable, in order to prevent dissociation of the walker from the track. On addition of DBU, the hydrazone foot is locked and the disulfide bond becomes labile. Alternating the acid and base results in a net displacement of the walker unit to the right (Figure 2), since the walker was initially synthesized occupying the two left external footholds.[6a]

By varying the length of the spacer in system A, it was found that for $n=1$ and 2 the walker unit cannot actually walk, since its strides are too short to bridge the two internal footholds. For $n=3$, 4, and 7, the acid–base switch allows the system to walk until reaching the minimum energy distribution. Notably, in the cases of $n=3$ and 4, carrying out the disulfide exchange under kinetically controlled redox stimulation provides a means to bias the direction of motion sufficiently to transport the walker directionally. Interestingly, the motion of the system switches to the opposite direction when changing from $n=3$ to $n=4$. On the other hand, no directionality was observed when operating the system where $n=7$.[6b]

System B includes a stilbene unit in the track, which provides a means to increase or decrease ring strain when the walker unit bridges the two internal footholds. Prior to the first disulfide exchange reaction, an $E\rightarrow Z$ photoisomerization brings the two central footholds closer, thus inducing the walker unit to preferentially occupy the central position to form a less strained macrocycle (see Figure 2B).[8] With the walker unit in place, the double bond is restored to its *E* configuration, thus increasing the ring strain and favoring displacement of the walker unit to the right when the hydrazone links are labilized. The net result is that the walker is approximately 1.5 times more likely to take steps to the right than to the left.[6c]

The molecular devices reported by Leigh and co-workers represent the first examples of small-molecule synthetic bipeds.[9] So far, the research team has produced systems which show three out of four of the main characteristics of naturally occurring walking motor proteins. The most advanced walker system (B in Figure 2) utilizes four different stimuli in order to repeatedly take directionally biased steps along its track without detaching from it (i.e., it shows processivity, directionality, and repetitive operation). In principle, such systems should also be capable of walking along polymeric tracks. Surely, synthesizing such tracks and devising systems that can exploit their motion to transport cargoes—to achieve functionality—are two of the major challenges that lie ahead.

Received: November 5, 2010
Published online: ■■ ■■, ■■■■

[1] In fact, Plato did so only indirectly, at least in writing: "I say that we should have begun at first by dividing land animals into biped and quadruped; and since the winged herd, and that alone, comes out in the same class with man, should divide bipeds into those which have feathers and those which have not." Platon, *Statesman (a Dialogue)*, (translated by B. Jowett), Polit Press, **2010**, pp. 63–64.

[2] F. Kozielski, S. Sack, A. Marx, M. Thormahlen, E. Schonbrunn, V. Biou, A. Thompson, E. M. Mandelkow, E. Mandelkow, *Cell* **1997**, *91*, 985.
[3] M. Schliwa, *Molecular Motors*, Wiley-VCH, Weinheim, **2003**.
[4] For a comprehensive review on synthetic molecular machines, see: E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem.* **2007**, *119*, 72; *Angew. Chem. Int. Ed.* **2007**, *46*, 72.

[5] a) T. Omabegho, R. Sha, N. C. Seeman, *Science* **2009**, *324*, 67; b) H. Gu, J. Chao, S.-J. Xiao, N. C. Seeman, *Nature* **2010**, *465*, 202; c) K. Lund, A. J. Manzo, N. Dabby, N. Michelotti, A. Johnson-Buck, J. Nangreave, S. Taylor, R. Pei, M. N. Stojanovic, N. G. Walter, E. Winfree, H. Yan, *Nature* **2010**, *465*, 206.

[6] a) M. von Delius, E. M. Geertsema, D. A. Leigh, *Nat. Chem.* **2010**, *2*, 96; b) M. von Delius, E. M. Geertsema, D. A. Leigh, D.-T. D. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 16134; c) M. J. Barrell, A. G. Campaña, M. von Delius, E. M. Geertsema, D. A. Leigh, *Angew. Chem.* **2011**, *123*, 299; *Angew. Chem. Int. Ed.* **2011**, *50*, 285.

[7] P. T. Corbett, J. Leclaire, L. Vial, J.-L. Wietor, K. R. West, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652.

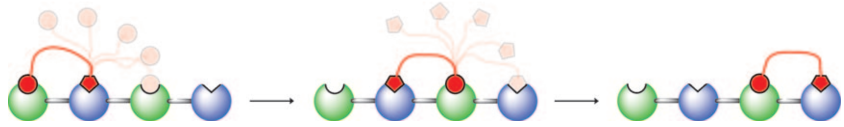
[8] For a detailed study on the opening and closing of these macrocycles, see: M. von Delius, E. M. Geertsema, D. A. Leigh, A. M. Z. Slawin, *Org. Biomol. Chem.* **2010**, *8*, 4617.

[9] For selected examples of nonlinear synthetic molecular motors, see: a) R. Eelkema, M. M. Pollard, J. Vicario, N. Katsonis, B. S. Ramon, C. W. M. Bastiaansen, D. J. Broer, B. L. Feringa, *Nature* **2006**, *440*, 163; b) S. P. Fletcher, F. Dumur, M. M. Pollard, B. L. Feringa, *Science* **2005**, *310*, 80; c) V. Balzani, M. Clemente-Leon, A. Credi, B. Ferrer, M. Venturi, A. H. Flood, J. F. Stoddart, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1178.

Molecular Motors

E. M. Pérez* ■■■■–■■■■

Synthetic Molecular Bipeds



Standing on their own two feet! Inspired by naturally occurring molecular motors such as kinesins, dyneins, and myosins, a series of small-molecule walker systems have been synthesized (see picture). These artificial molecular motors are capable of moving directionally along their associated tracks, and show most of the features of their natural counterparts.

