Molecular Devices

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Light-Driven Transport of a Molecular Walker in Either Direction along a Molecular Track **

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Nature uses bipedal motor proteins that "walk" down intracellular tracks to perform essential tasks in a variety of key biological processes.[1] Although the molecular mechanisms through which these fascinating linear motors operate are beginning to be understood,[2] there are still few synthetic mimics that exhibit the most important characteristics of natural motors, namely repetitive, progressive, processive, and directional walker transport along a molecular track. Several walker–track systems based on DNA have been described,[3] and recently our research group reported a small-molecule system,[4] in which the migration of a walker unit along a four-foothold track could be biased in one direction through an information ratchet type of Brownian ratchet mechanism.[5,6]

Herein we report the design, synthesis, and operation of a small-molecule walker–track conjugate, in which the walker can be transported in either direction along a four-foothold molecular track (roughly 1.5 times more likely to take a step in one direction than the other), depending on the sequence of four applied stimuli: acid or base for mutually exclusive "foot" dissociation and UV light or visible light (plus iodine) to induce or release ring strain between the walker and the track.[7] The design (Figure 1) is closely related to the previously reported small-molecule walker–track system, which features a walker with one hydrazone foot (labile in acid; locked in base) and one disulfide foot (labile in base; locked in acid).[4] The crucial difference is that a stilbene unit has been added between the internal aldehyde and the disulfide footholds of the track (Scheme 1). The key to achieving directionality lies in the isomerization of the stilbene moiety, through which significant ring strain can be induced in the positional (constitutional) isomer in which the walker unit bridges the stilbene linkage (Figure 1 and Scheme 2b).[8] $E \rightarrow Z$ isomerization provides a driving force for the walker to "step" onto the central stilbene unit, while subsequent $Z \rightarrow E$ isomerization results in a majority of the walkers being transported away from the stilbene group in a direction determined by which foot–track interaction is labilized next. Such a manipulation of the thermodynamic minima (here by strain induction through stilbene isomerization) and kinetic barriers (here by addition of either base or acid) experienced by a substrate corresponds to an energy ratchet type of Brownian ratchet mechanism (Figure 1b).[6,9,10]

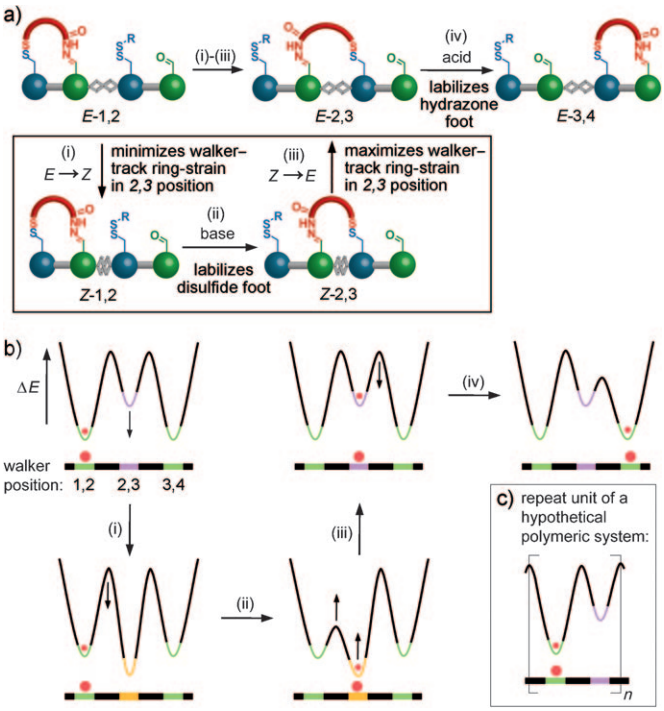

Figure 1. a) Operating mechanism of a light-driven walker–track system based on selectively labile "feet" and adjustable ring strain between the walker (red) and the track in one positional isomer. The reaction sequence shown results in transport of the walker from left to right; switching steps (ii) and (iv) would cause the walker to be transported from right to left. b) Potential energy profile experienced by the walker unit (an energy ratchet mechanism[6,10]). c) Repeat unit of a hypothetical polymeric system along which the walker could be transported in either direction depending on the order of the stimuli applied. Stimuli: (i) UV light, (ii) base, (iii) visible light and iodine, (iv) acid.[11]

Molecular walker–track conjugate *E*-1,2-**1**[12] was synthesized according to Scheme 1 (see the Supporting Information for experimental procedures and characterization data). The

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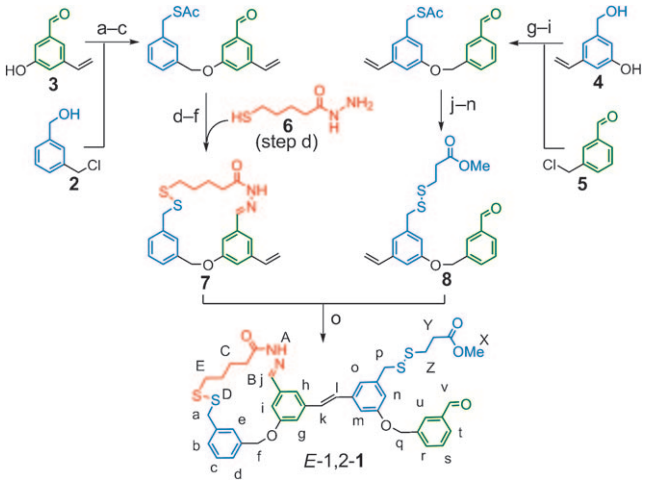
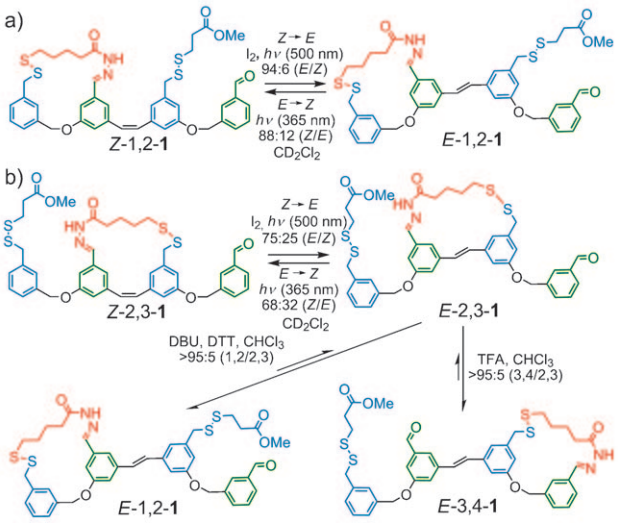


Scheme 1. Synthesis of molecular walker–track conjugate *E*-1,2-**1**. a) NaH, DMF, RT, 16 h; b) methanesulfonyl chloride (MsCl), NEt_3, CH_2Cl_2, 0 °C→RT, 1.5 h; c) potassium thioacetate (KSAc), DMF, RT, 3 h, 59% (three steps); d) AcOH (cat.), MeOH, RT, 2 h, 83%; e) NaOMe, MeOH, RT, 2 h; f) I_2, KI, CH_2Cl_2, RT, 5 min, 48% (two steps); g) NaH, DMF, RT, 16 h; h) MsCl, NEt_3, CH_2Cl_2, 0 °C→RT, 2 h; i) KSAc, DMF, RT, 3 h, 35% (three steps); j) $HC(OMe)_3$, *p*-toluenesulfonic acid (*p*-TsOH), MeOH, RT, 1 h; k) NaOMe, MeOH, RT, 3 h; l) 3-mercaptopropionic acid, I_2, KI, CH_2Cl_2, RT, 5 min; m) HCl (1 M), CH_2Cl_2, RT, 15 min, 69% (four steps); n) AcCl, MeOH, 0 °C→RT, 5 h, 76%; o) Ω_A-SIMes-CF_3 catalyst,[15] CH_2Cl_2, microwave (300 W), 100 °C, 3 h, 23%. See the Supporting Information for details.



Scheme 2. *Z*→*E* and *E*→*Z* stilbene isomerization of individual positional isomers of **1** and ring opening of *E*-2,3-**1** in either direction under dynamic covalent conditions (acid or base) to release ring strain between the walker and track. Conditions: *E*→*Z*: 0.1–10 mM, *hν* (365 nm; bandwidth: 10 nm), CD_2Cl_2, RT, 5 min; *Z*→*E*: 0.1 mM,[20] I_2 (ca. 10 equiv), *hν* (500 nm; bandwidth: 10 nm[20]), CD_2Cl_2, RT, 4–8 h. Dynamic disulfide exchange (basic conditions): 0.1 mM, D,L-dithiothreitol (DTT, 10 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 40 equiv), $(MeO_2CCH_2CH_2S)_2$ (20 equiv), $CHCl_3$, RT, 24 h. Dynamic hydrazone exchange (acidic conditions): 0.1 mM, excess CF_3CO_2H (TFA), $CHCl_3$, RT, 48 h.

initial position of the walker unit at footholds 1 and 2 of the track was established by the synthesis of macrocycle **7**, starting from the simple aromatic building blocks **2** and **3** and the bipedal walker unit **6**. Compound **8**, which contains thiol foothold 3 (masked as a disulfide with methyl 3-mercaptopropionate, a "placeholder" thiol[13]) and aldehyde foothold 4, was prepared from precursors **4** and **5**. The synthesis was completed by a ruthenium-catalyzed cross-metathesis reaction,[14] which afforded *E*-1,2-**1** in 23% yield.[15,16] The positional isomer where the walker unit is located on the other end of the molecular track, *E*-3,4-**1**, was prepared unambiguously through an analogous synthetic route (see the Supporting Information).

An investigation of the photochemistry of *E*-1,2-**1** and *E*-3,4-**1**, the positional isomers in which the walker unit is not located over the track stilbene unit, showed that it was possible to efficiently carry out direct (i.e., unsensitized) *E*→*Z* stilbene photoisomerization[17] at 365 nm in CD_2Cl_2 (Scheme 2a). The excellent diastereomeric ratios at the photostationary states (ca. 9:1 *Z*/*E*) are a result of the high molar absorptivities of the *E* isomers compared to the corresponding *Z* isomers.[18] The reverse process, that is, *Z*→*E* stilbene isomerization, also proceeded well in CD_2Cl_2 (>9:1 *E*/*Z*) by using iodine and narrow-bandwidth green light (500 nm; 10 nm bandwidth).[19,20]

We next confirmed that the strained[21] *E*-2,3-**1** isomer could be formed from *Z*-2,3-**1** and that, in a subsequent dynamic covalent[22] exchange reaction, the walker unit could be efficiently transported to either the 1,2 or the 3,4 position of the track, depending on the use of either base or acid (Scheme 2b). Irradiation of pristine *Z*-2,3-**1** (obtained from *Z*-1,2-**1** by base-induced disulfide exchange) at 365 nm generated a 75:25 (*E*/*Z*) photostationary state, which was subjected to conditions for disulfide (base) or hydrazone exchange (acid) in separate experiments. Under basic conditions, approximately 80% of the walker units from this *E*/*Z* mixture were transported to the 1,2-positional isomer (>95% of *E*-2,3-**1** converted into the 1,2 isomer; 25% of residual *Z*-2,3-**1**); under acidic conditions approximately 80% of the 3,4-positional isomer was formed (>95% of *E*-2,3-**1** converted into the 3,4 isomer; 30% of residual *Z*-2,3-**1**).

Having established that the key principles of the energy ratchet mechanism would operate by using individual positional isomers, we needed to establish a procedure for analyzing the mixture of isomers expected to be generated during the full sequence of operations of a statistical molecular-motor mechanism. Pleasingly, the composition of the walker–track system could be accurately determined after each step by 500 MHz ^{1}H NMR spectroscopy, even for complex mixtures that contain all eight isomers (*Z*/*E*-1,2-**1**, *Z*/*E*-2,3-**1**, *Z*/*E*-3,4-**1**, *Z*/*E*-1,4-**1**[11]). The partial ^{1}H NMR spectra of the six isomers involved in the major "passing-leg gait"[10a] mechanism (Figure 1a) are shown in Figure 2. Differences in chemical-shift values that are indicative of the position of the walker unit on the track arise for the protons of the four methylene groups in the walker unit (shown in red, H_B–H_E). Protons H_k and H_l serve as distinctive markers for the configuration of the stilbene olefinic bond

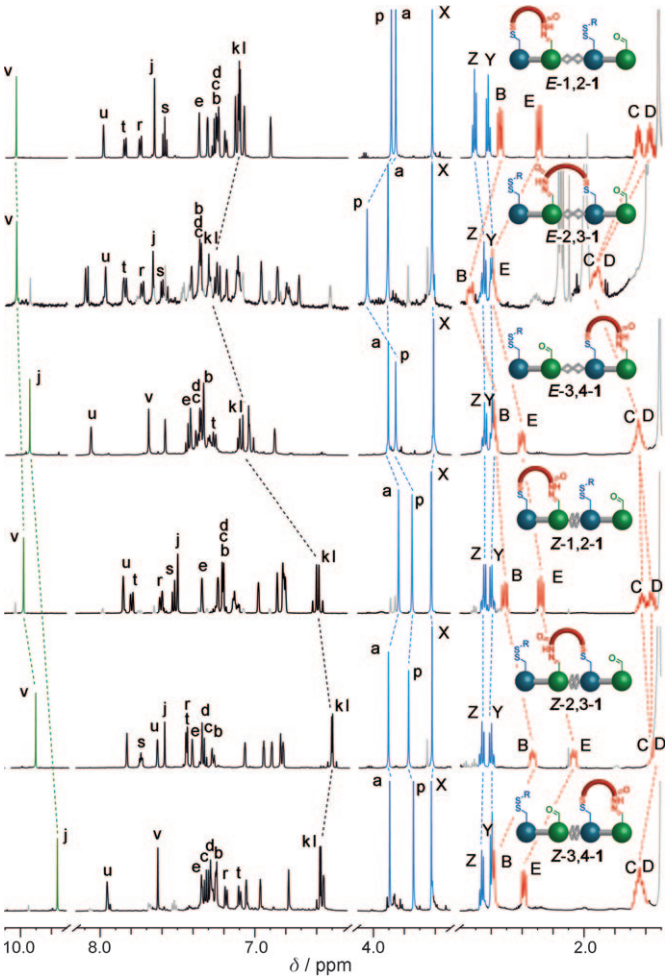


Figure 2. Partial ^{1}H NMR spectra (500 MHz, CD_2Cl_2, 298 K) of the six isomers of **1** involved in the passing-leg gait mechanism[10a] (Figure 1a and Scheme 3). The dashed lines connect some of the key signals that are indicative of the position of the walker unit or the configuration of the track olefin. The signals corresponding to minor isomers (e.g. the "*E*-2,3-**1**" spectrum contains 25% of *Z*-2,3-**1**), solvent, and other impurities are shown in gray. The lettering corresponds to the proton labeling shown in Scheme 1.

($\delta < 7$ ppm for *Z* and $\delta > 7$ ppm for *E* isomers). The signal at around $\delta = 10.0$ ppm (green, H_v or H_j), which corresponds to the free aldehyde group, and the signal at around $\delta = 3.8$ ppm (blue, H_a and H_p), which corresponds to the methylene disulfide protons, are also particularly useful probes because their chemical shifts vary with both the walker position and the stilbene configuration (see the Supporting Information for full ^{1}H NMR spectra of individual positional and configurational isomers).

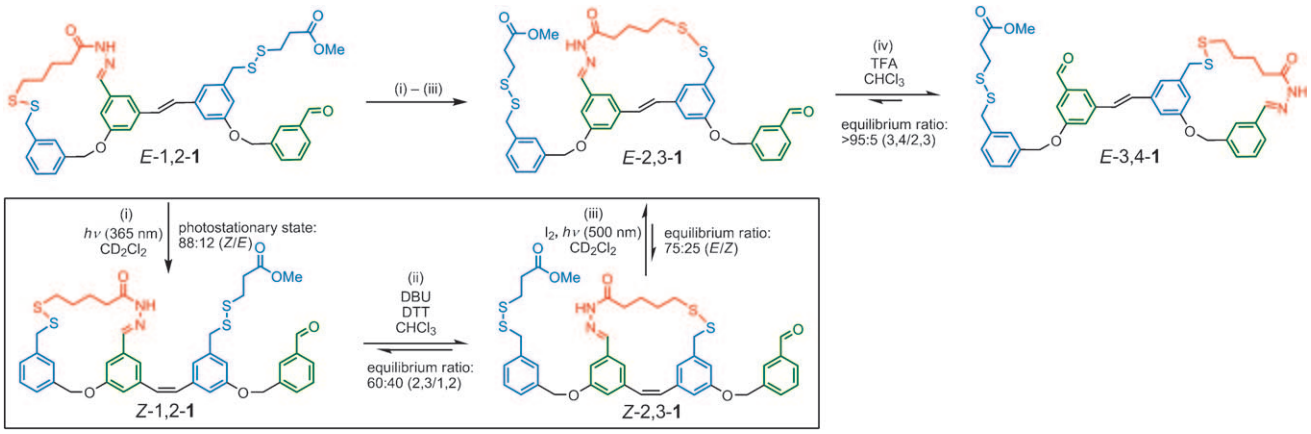
Directionally biased transport of the walker from left to right through the sequential application of the four external stimuli in the order i–ii–iii–iv is shown in Scheme 3. Starting from pristine *E*-1,2-**1**, photochemical $E \rightarrow Z$ isomerization (i) gives a photostationary state that consists of 88% of the *Z*-1,2-**1** isomer. Subjecting this mixture to the basic conditions (ii), in which the hydrazone linkage between the walker unit and the track is kinetically stable,[23] allows the disulfide foot to dissociate from the track and rebind at footholds 1 or 3. This process leads to an equilibrium in which the positional isomer *Z*-2,3-**1** is favored. Light-induced $Z \rightarrow E$ isomerization (iii) of the stilbene in this mixture results in 75% conversion of *Z*-2,3-**1** into the strained *E*-2,3-**1** isomer. In the following acid-catalyzed step (iv), the hydrazone foot is able to dissociate from the track and rebind at either foothold 2 or 4, while the disulfide foot acts as a fixed pivot.[23] This process results in a large majority (>95%) of walker units being transported away from the *E*-stilbene unit (2,3 position) towards the now energetically favorable 3,4 position (see Figure 1b for the schematic energy diagram that corresponds to these processes). Note that all the energy required to fuel directional transport in Scheme 3 is supplied through the $E \rightarrow Z$ photoisomerization reaction (i), which creates configurational strain in the track. The other three reactions (ii–iv), which are all under thermodynamic control, each dissipate some of that energy (even reaction (iii), which uses the energy to induce conformational strain between the walker and the track in the 2,3 position) in a way designed to achieve the desired directional migration of the walker.

The behavior of the walker–track system **1** under these operating conditions (Figure 3a), and when the stimuli are applied in a different order (iii–ii–i–iv; Figure 3b) or starting from a different positional isomer (*E*-3,4-**1**; Figure 3c,d), are shown in Figure 3. The amount of each *E*/*Z* isomer pair (1,2-**1**, 2,3-**1**, 3,4-**1**, and 1,4-**1**[11]) is shown after each step of the applied sequence of stimuli. The graphs show both the behavior of the system (solid symbols and lines) extrapolated from the experimentally determined equilibrium and steady-state ratios between each pair of exchanging isomers (Scheme 2a for example), and the experimentally determined composition during full-system operation (hollow symbols).[24]

Figure 3a shows the change in composition of the system during the reaction sequence intended to transport the walker from left to right, (i.e., that shown in Scheme 3), starting from *E*-1,2-**1**. After the full cycle of reactions, which corresponds to up to two steps being taken by the walker, 48% of the walker units are on the right-hand side of the track (3,4-**1**), 30% of the walker units are on the left-hand side (1,2-**1**), and the remainder are in the middle (16% 2,3-**1**) or have taken a "double step" from left to right (6% 1,4-**1**). In other words, 50% more walkers have taken two steps to the right under the operating sequence than have taken one step to the right and one step back (or remained on the left-hand side throughout).

Figure 3b shows the results of a change in the sequence of reactions; following the $E \rightarrow Z$ ring-strain-inducing reaction, the hydrazone foot–track interaction is labilized (under acidic conditions) rather than that of the disulfide. This reaction sequence (iii–ii–i–iv) should bias transport of the walker from right to left (see caption to Figure 1) and indeed, only 4% of 3,4-**1** is present in the mixture after these reactions are applied to 1,2-**1** (interestingly, a significant amount (33%) of the 1,4 "double step" isomer is formed through folding of the track[11]).

Figure 3c shows that the walker unit can be effectively transported from right to left by this sequence. Starting from *E*-3,4-**1**, 48% of the walkers are found on the left-hand side of



Scheme 3. Directionally biased (left to right) walker migration over one full cycle of operation starting from *E*-1,2-**1**, following the layout used in Figure 1. For clarity, only the major isomer is shown after each reaction (see Figure 3a for the composition of the entire system at each stage). Isomer ratios were obtained from the integration of the ^{1}H NMR spectra (see the Supporting Information). Conditions: (i) 0.1–10 mM, *hν* (365 nm; bandwidth: 10 nm), CD_2Cl_2, RT, 5 min (0.1 mM) to 1 h (10 mM); (ii) 0.1 mM, DTT (10 equiv), DBU (40 equiv), $(MeO_2CCH_2CH_2S)_2$ (20 equiv), $CHCl_3$, RT, 24 h; (iii) 0.1 mM,[20] I_2 (ca. 10 equiv), *hν* (500 nm; bandwidth: 10 nm[20]), CD_2Cl_2, RT, 6 h; (iv) 0.1 mM, TFA (excess), $CHCl_3$, RT, 48 h.

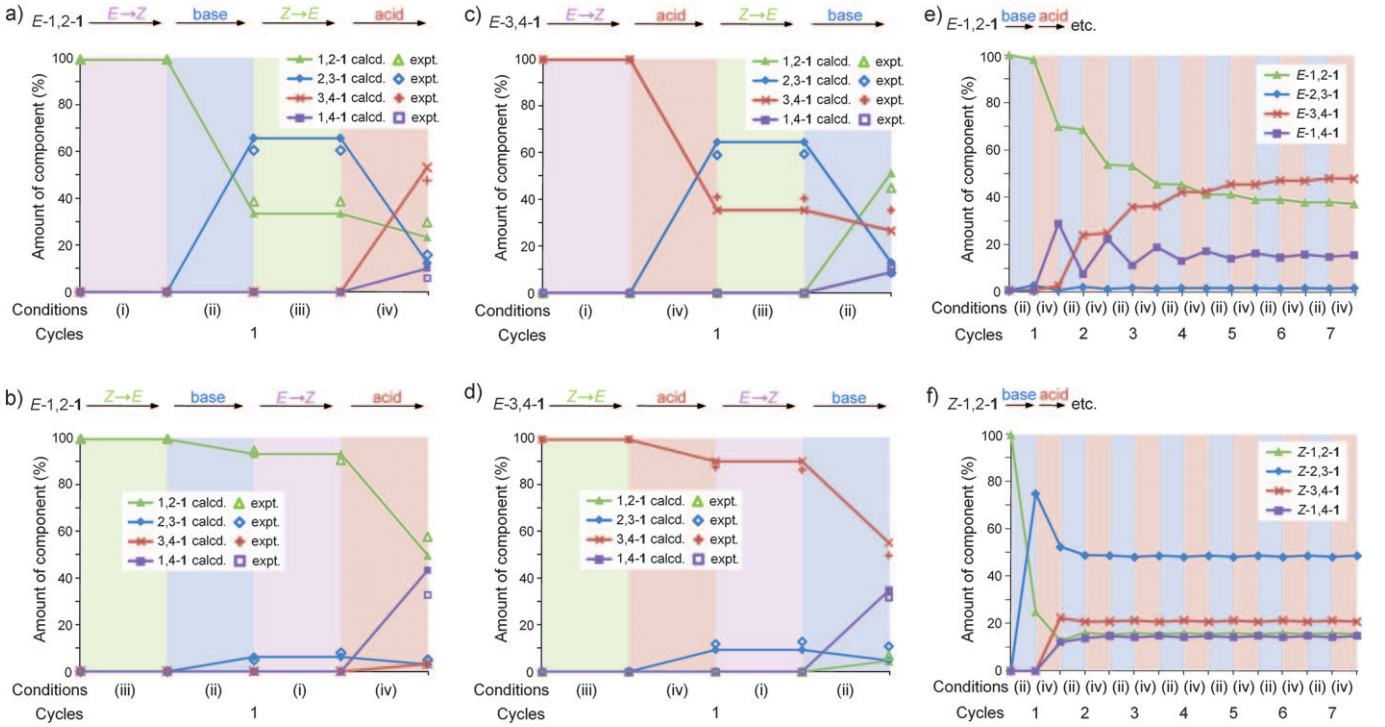


Figure 3. Dynamic behavior of walker–track system **1**, varying the starting position of the walker and the stimuli sequence (denoted through colored bands; purple: *E*→*Z* isomerization at 365 nm; blue: base-catalyzed disulfide exchange; green: *Z*→*E* isomerization at 500 nm (I_2 catalyst); red: acid-catalyzed hydrazone exchange). Experimental (expt.) and calculated (calcd.) product distribution[24] over one full cycle of operation: a) starting compound *E*-1,2-**1**, stimuli sequence i–ii–iii–iv; b) starting compound *E*-1,2-**1**, stimuli sequence iii–ii–i–iv (a mismatch as this sequence tends to transport the walker from right to left); c) starting compound *E*-3,4-**1**, stimuli sequence i–iv–iii–ii; d) starting compound *E*-3,4-**1**, stimuli sequence iii–iv–i–ii (a mismatch as this sequence tends to transport the walker from left to right). Calculated product distribution over seven base/acid cycles (no stilbene isomerization), starting from e) pristine *E*-1,2-**1** and f) pristine *Z*-1,2-**1**. The calculated data are based on simple mathematical extrapolation of the observed steady-state ratios between each *Z*/*E* isomer pair under conditions (i) and (iii) and the observed equilibrium ratios between individual positional isomers under conditions (ii) and (iv) (see Section 5 in the Supporting Information). Experimental data are based on the integrals of the ^{1}H NMR spectra of mixtures obtained after each step of the reaction sequence, margin of error ±3% (see Section 4 in the Supporting Information). A small amount of oligomers (ca. 5%) was also obtained during each experiment. Conditions: (i) 0.1–10 mM, *hν* (365 nm; bandwidth: 10 nm), CD_2Cl_2, RT, 5 min–1 h; (ii) 0.1 mM, DTT (10 equiv), DBU (40 equiv), $(MeO_2CCH_2CH_2S)_2$ (20 equiv), $CHCl_3$, RT, 12–48 h; (iii) 0.1 mM,[20] I_2 (ca. 10 equiv), *hν* (500 nm; bandwidth: 10 nm[20]), CD_2Cl_2, RT, 4–8 h; (iv) 0.1 mM, TFA (excess), $CHCl_3$, RT, 6–96 h.

the track after the full reaction sequence and only 36% remain on the right-hand side.

Figure 3d shows the effect of applying the right-to-left directionally biased reaction sequence starting with the isomer for which the walker is already on the left.

These results collectively illustrate the characteristics typical of energy ratchet mechanisms.[6,10a] Irrespective of the initial walker position on the track (e.g., starting from 1,2-**1** (Figure 3a), 3,4-**1** (Figure 3d), or any combination of walker positions) after the sequence i–ii–iii–iv (or iii–iv–i–ii) the majority of walkers are found on the right-hand side (3,4-**1**). Conversely, irrespective of the initial walker position on the track (Figure 3b and c), after the sequence iii–ii–i–iv (or i–iv–iii–ii) the majority of walkers are on the left-hand side (1,2-**1**). The position of the walker does not influence the sequence of reactions applied, nor their basic effect on the track,[25] and statistical "errors" (e.g., the walker does not take a step every time a foot–track interaction is labilized) are an intrinsic feature of the mechanism.

Figures 3e and 3f (*E*-stilbene track and *Z*-stilbene track, respectively) show the behavior of the system when no stilbene isomerization reactions are carried out. Repeatedly switching between treatment with acid and base (labilizing first one foot–track interaction and then the other) allows the distribution of the walkers on the track to approach the minimum-energy distribution.[4] In the case of the *E*-stilbene track (Figure 3e), the gap between footholds 2 and 3 is too wide for the walkers to bridge easily (note the very small amounts of the 2,3 isomer formed) and it would take seven full operational cycles to approach the steady state of the system, which features roughly equal amounts of walkers at each end of the track. With the *Z*-stilbene track (Figure 3f), the 2,3 position is, of course, very accessible to the walker units and so the steady-state is reached after only two cycles. However, the 2,3 position is actually energetically more favored than the ends of the tracks, so the majority of walkers remain in the center (49% *Z*-2,3-**1**). The differences in behavior and walker distribution produced by switching between acid and base alone (Figure 3e,f) and when additional stilbene isomerization is carried out (e.g., Figure 3a,c) show the dramatic effect that the energy ratchet mechanism has on walker transport.

The operations of walker–track conjugate **1** shown in Scheme 3 and Figure 3a,c correspond to a light-driven linear molecular motor system.[26] Significant directional bias, which stems from an energy ratchet mechanism, can transport the walker unit in either direction along the molecular track; the control over the sense of direction is a feature not found in biological linear motor proteins. While both the photochemical stilbene isomerization and the acid- and base-induced reversible foot-migration processes proceed with good efficiencies, a weakness of the present system lies in the flexibility of the track and the resulting folding products, which reduce the net directionality of transport and prevent improvement of the bias over multiple cycles. Furthermore, a hypothetical polymeric track based on the current design would utilize the light energy used to power directional transport very inefficiently by switching the configuration of many of the double bonds in the track each time, whereas only one double bond would actually "ratchet" the walker unit energetically uphill. Work aimed at overcoming these deficiencies is currently underway.

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[6] We use the term "ratcheting" in a manner that is consistent with its use in biology and nonequilibrium statistical physics: namely, it is the capturing of a positional displacement of a substrate through the imposition of a kinetic energy barrier that prevents the displacement being reversed when the thermodynamic driving force is removed; see M. N. Chatterjee, E. R. Kay, D. A. Leigh, *J. Am. Chem. Soc.* **2006**, *128*, 4058–4073. An information ratchet is a Brownian ratchet mechanism in which the position of the particle on a potential energy surface causes the potential energy surface to change (at an energetic cost), thus leading to directional transport of the particle. In an energy ratchet mechanism the potential energy surface is periodically or stochastically varied irrespective of the position of the particle in order to cause directional transport (for example, the relative depths of two pairs of minima and the relative heights of the maxima that connect them could be repeatedly switched, as in Figure 1b). See ref. [10a].

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[8] For elegant mechanistic studies based on ring strain in macrocycles that contain a "stiff stilbene" linkage, see: a) Q. Z. Yang, Z. Huang, T. J. Kucharski, D. Khvostichenko, J. Chen, R. Boulatov, *Nat. Nanotechnol.* **2009**, *4*, 302 – 306; b) T. J. Kucharski, Z. Huang, Q. Z. Yang, Y. C. Tian, N. C. Rubin, C. D. Concepcion, R. Boulatov, *Angew. Chem.* **2009**, *121*, 7174 – 7177; *Angew. Chem. Int. Ed.* **2009**, *48*, 7040 – 7043. For a dynamic covalent library that consists of macrocycles with internal acyl hydrazone and (photoswitchable) azobenzene linkages, see: c) L. A. Ingerman, M. L. Waters, *J. Org. Chem.* **2009**, *74*, 111 – 117.

[9] a) D. A. Leigh, J. K. Y. Wong, F. Dehez, F. Zerbetto, *Nature* **2003**, *424*, 174 – 179; b) J. V. Hernandez, E. R. Kay, D. A. Leigh, *Science* **2004**, *306*, 1532 – 1537; c) S. P. Fletcher, F. Dumur, M. M. Pollard, B. L. Feringa, *Science* **2005**, *310*, 80 – 82.

[10] a) E. R. Kay, F. Zerbetto, D. A. Leigh, *Angew. Chem.* **2007**, *119*, 72 – 196; *Angew. Chem. Int. Ed.* **2007**, *46*, 72 – 191; b) R. D. Astumian, *Phys. Chem. Chem. Phys.* **2007**, *9*, 5067 – 5083; c) R. D. Astumian, I. Derényi, *Eur. Biophys. J.* **1998**, *27*, 474 – 489; d) P. Hänggi, F. Marchesoni, *Rev. Mod. Phys.* **2009**, *81*, 387 – 442; e) R. D. Astumian, *Biophys. J.* **2010**, *98*, 2401 – 2409.

[11] The 1,4 isomers of **1**, which result from folding of the track (see the Supporting Information for structures), add an additional double-step mechanism to the major passing-leg gait mechanism (see ref. [4]). This pathway has the opposite bias to the main mechanism and so actually reduces the net directionality of the walker transport.

[12] *E* or *Z* denotes the configuration of the stilbene double bond in the track; the numerical prefixes (e.g., 1,2) specify the position of the walker unit on the four-foothold track.

[13] The sulfur foothold of the track was protected as a disulfide with a "placeholder" thiol in order to prevent oxidation of the free thiol to a dimeric disulfide by atmospheric oxygen.

[14] a) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370; b) S. P. Nolan, H. Clavier, *Chem. Soc. Rev.* **2010**, *39*, 3305 – 3316.

[15] Screening gave best results with the commercially available catalyst Ω_A-SIMes-CF_3, compound **2h** in: D. Rix, F. Caijo, I. Laurent, F. Boeda, H. Clavier, S. P. Nolan, M. Mauduit, *J. Org. Chem.* **2008**, *73*, 4225 – 4228.

[16] The styrene (Type II) olefins in **7** and **8** have similar reactivities and so the maximum yield of *E*-1,2-**1** expected from their statistical cross-metathesis is 50% (see ref. [14a]). This synthetic disconnection was chosen to prevent scrambling of the sensitive (different) disulfide and aldehyde/hydrazone functionalities in the final molecule.

[17] For an excellent review on the photochemistry of stilbene derivatives, see: H. Meier, *Angew. Chem.* **1992**, *104*, 1425 – 1446; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1399 – 1420.

[18] The photostationary equilibrium ratio for direct $Z \rightarrow E$ isomerization can be calculated as a function of the quantum yields (Φ) and molar absorptivities (ε) of the *E* and *Z* species (at a given wavelength): $[Z]/[E] = (\Phi_{E\rightarrow Z}\varepsilon_E)/(\Phi_{Z\rightarrow E}\varepsilon_Z)$, the quantum yield ratio is usually approximately 1 (see ref. [17]).

[19] The mechanism for iodine-mediated stilbene $Z \rightarrow E$ isomerization involves the reversible addition of I$^{\bullet}$ radicals (here photogenerated with green light) to the double bond. See, for example: S. Yamashita, *Bull. Chem. Soc. Jpn.* **1961**, *34*, 972 – 976.

[20] The iodine-mediated stilbene $Z \rightarrow E$ isomerization reactions were conducted at relatively low concentrations (0.1 mM) of the walker–track conjugate and with a narrow (10 nm) bandwidth of green light (500 nm) to avoid side-reactions of the disulfide groups.

[21] The length of the methylene spacer in the walker unit is crucial in order to generate ring strain in *E*-2,3-**1**, but not in *Z*-2,3-**1**. The choice of a four-carbon atom spacer was based on model studies and molecular modeling (semi-empirical, PM3).

[22] a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938 – 993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898 – 952; b) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652 – 3711; c) J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151 – 160.

[23] For studies on the dynamic chemistry of hydrazone–disulfide systems under mutually exclusive (acid–base) conditions, see: a) A. G. Orrillo, A. M. Escalante, R. L. E. Furlan, *Chem. Commun.* **2008**, 5298 – 5300; b) Z. Rodriguez-Docampo, S. Otto, *Chem. Commun.* **2008**, 5301 – 5303; c) M. von Delius, E. M. Geertsema, D. A. Leigh, A. M. Z. Slawin, *Org. Biomol. Chem.* **2010**, *8*, 4617 – 4624.

[24] Possible reasons for the minor differences between the data extrapolated from the individual isomer experiments and the experimental results from operation on the full system include insufficient equilibration time for dynamic covalent exchange processes, nonideal photochemical steady-state ratios in mixtures, and inaccuracies in ^{1}H NMR integration.

[25] The presence of the walker at the 2,3-position lowers the *E*/*Z* ratio at the photostationary state of the $Z \rightarrow E$ reaction (Scheme 2b), thus reducing the net directionality of the transport mechanism.

[26] In a double-labeling crossover experiment on the previously reported small-molecule walker–track system (see ref. [4]), an average step number (the number of steps after which 50% of the walkers are no longer attached to their original track) of 37 was obtained for the loss of processivity during disulfide and hydrazone exchange. The conditions for dynamic covalent bond exchange are the same in the present study, and walker dissociation is not observed during the photochemical experiments. Therefore, the average step number during the operation of **1** should be similar. The average step number for wild-type kinesin is approximately 100 (R. B. Case, D. W. Pierce, N. Hom-Booher, C. L. Hart, R. D. Vale, *Cell* **1997**, *90*, 959 – 966).

