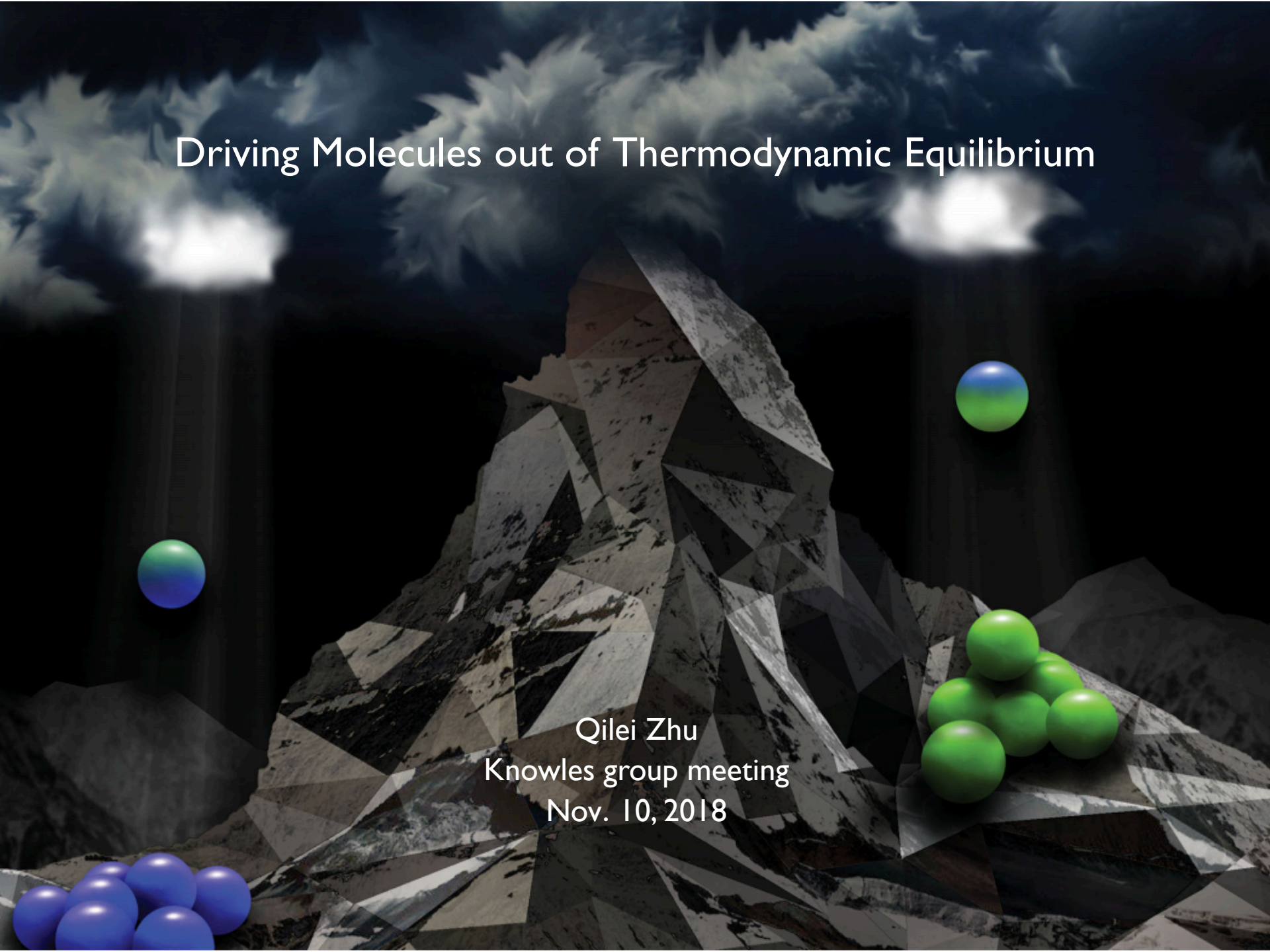
Driving Molecules out of Thermodynamic Equilibrium



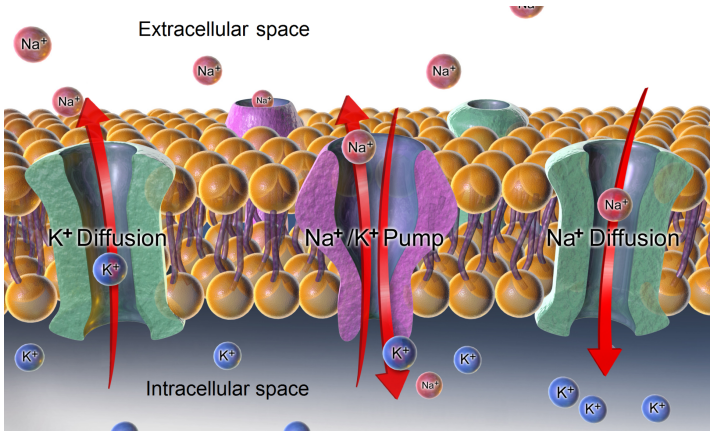
Qilei Zhu
Knowles group meeting
Nov. 10, 2018

Outline

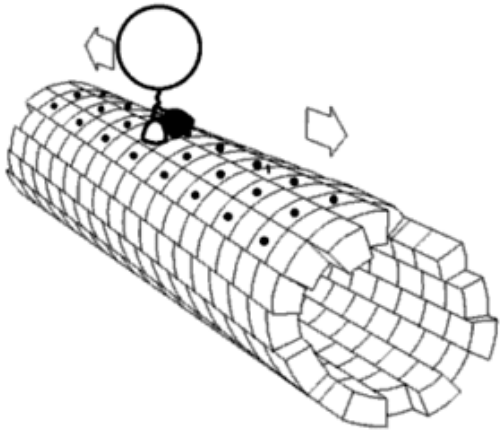
- Indroduction
- Molecular Motors and Pumps
- Dissipative Out-of Equilibrium Molecular Assembly
- Conclusion

God Loves Out-of-Equilibrium Systems

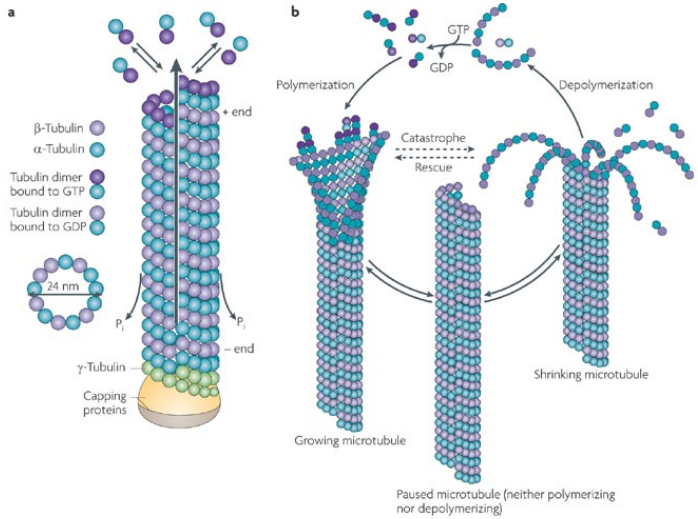
- Nature's Molecular Pumps, Motors and supramolecular assembly



Na^+/K^+-ATPase



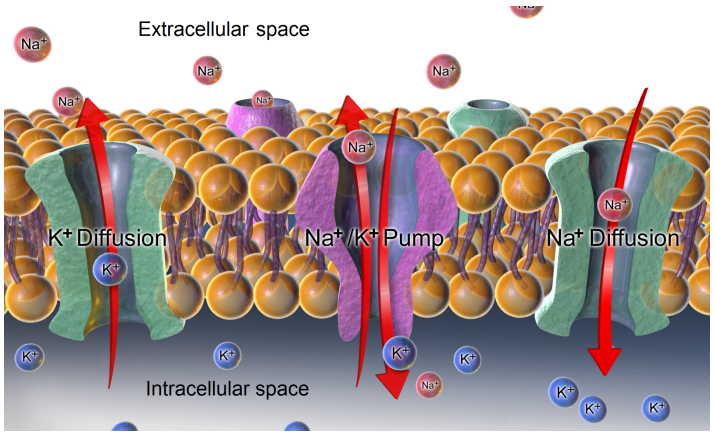
Kinesin



Microtubule

God Loves Out-of-Equilibrium Systems

- Nature's Molecular Pumps, Motors and supramolecular assembly



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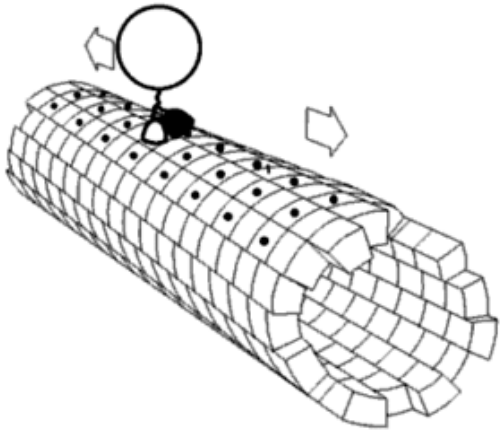
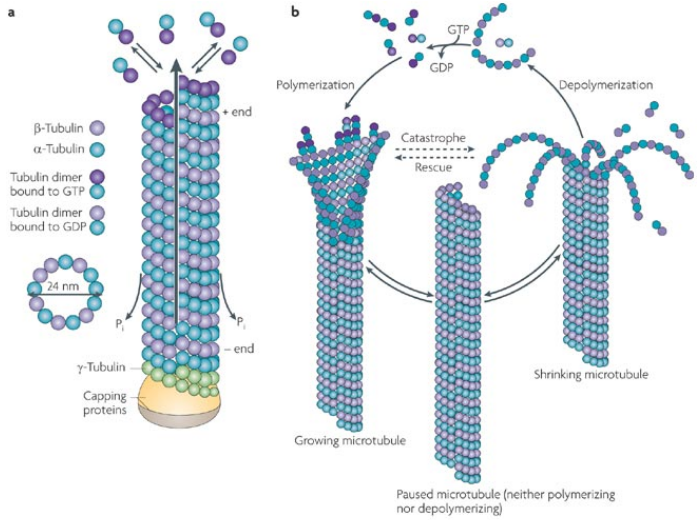


Kinesin



Microtubule

More about Kinesin:

Molecular weight: ~200kDa;

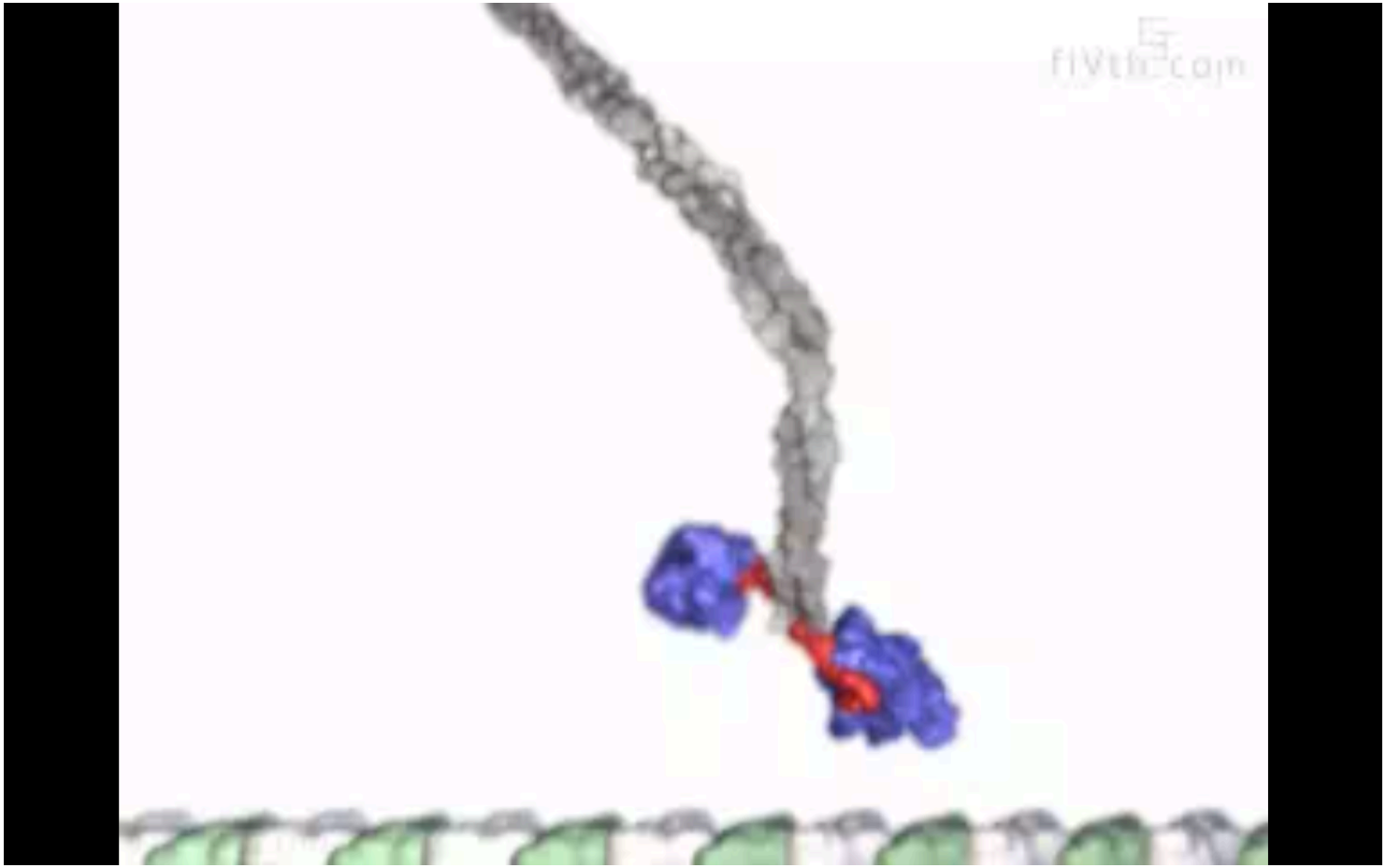
Stall force: 7.2 pN;

The force a kinesin can exert on its cargo is **2×10^6** times of its own gravitational weight, which means **45mg** of Kinesin can lift me.

Hulk can lift 100 tons when calm, which is **100** times of his body weight.

God Loves Out-of-Equilibrium Systems

- Mechanism of the Directional "Walk" of Kinesin



Outline

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Macroscopic vs. Molecular Machines

- World's smallest electric motor

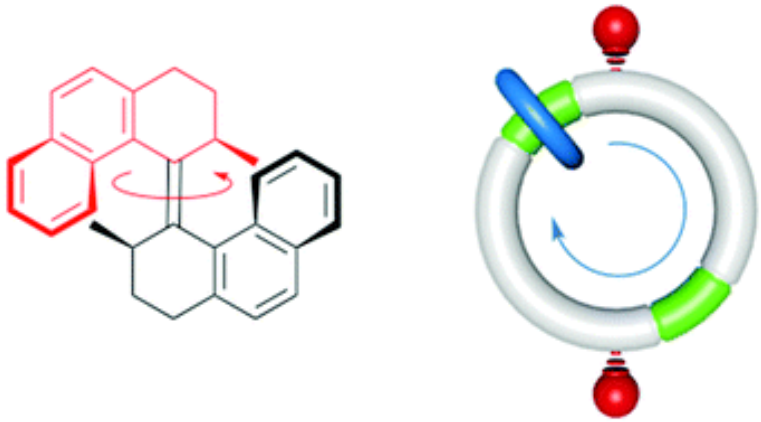
Macroscopic electric motor

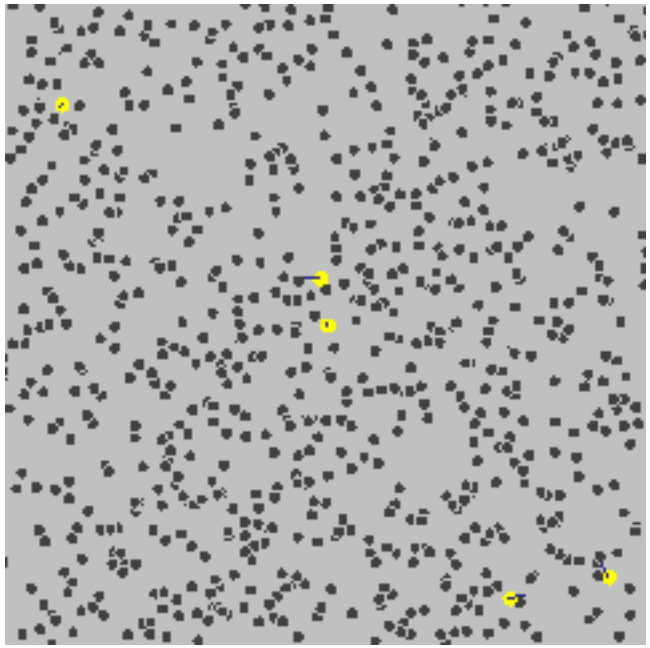
Richard Feymann's Chanllenge (1959): $1000 for building a functional motor with 1/64-inch cube, which was claimed within a year by William McLellan, a graduate student at Caltech.

Macroscopic vs. Molecular Machines

- Brownian Motion — Bless or Curse ?

Molecular motor





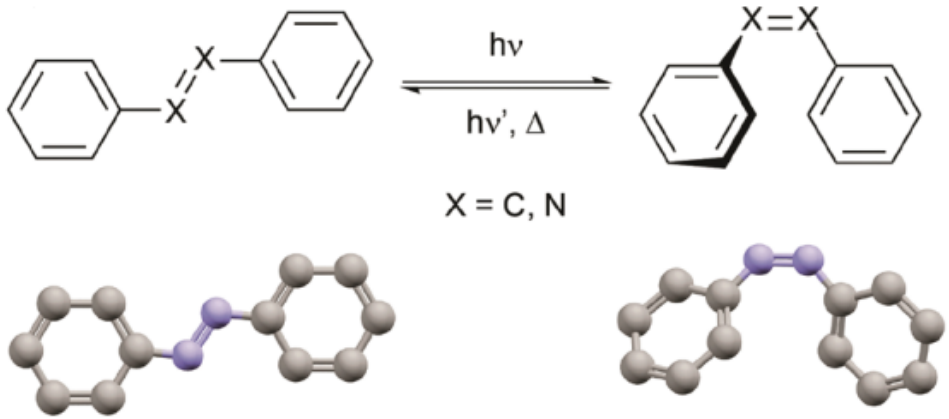
Mean velocity ar rt ~ 100 m/s (225 miles/h)

In an ordinary motor, energy is used to cause motion. In molecular motors, energy is used to cause a cessation of motion.

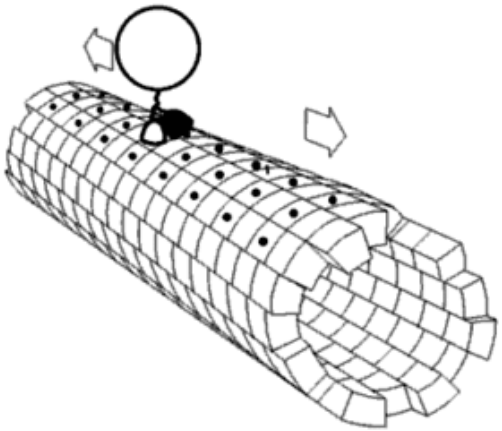
R. Dean Astumian, *Scientific American*, July, **2001**, 57.

Molecular Switch vs. Molecular Motors & Pumps

- **Molecular Switches:** switching between two (or more) different states responding to external environment change

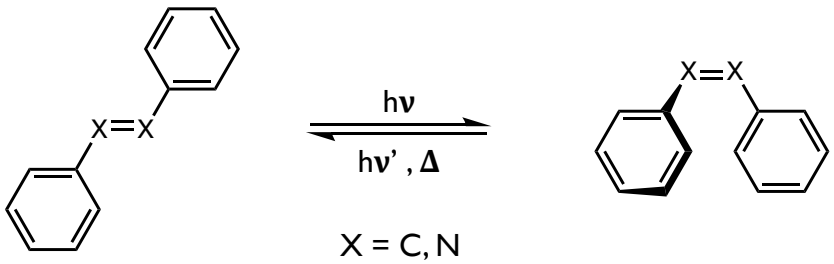


- **Molecular Motors & Pumps:** are able to drive chemical reactions uphill or chemical systems away from their "inherent" equilibria.



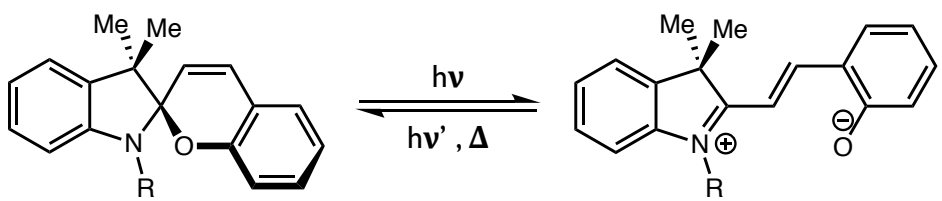
Frequently Used Photoswitches in Out-of-Equilibrium Systems

Azobenzene



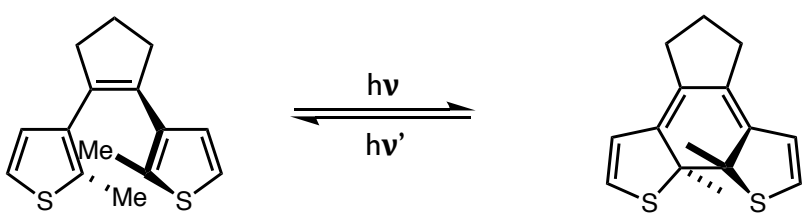
Associated with large structural change

Spiropyran



Dipole and acidity switch

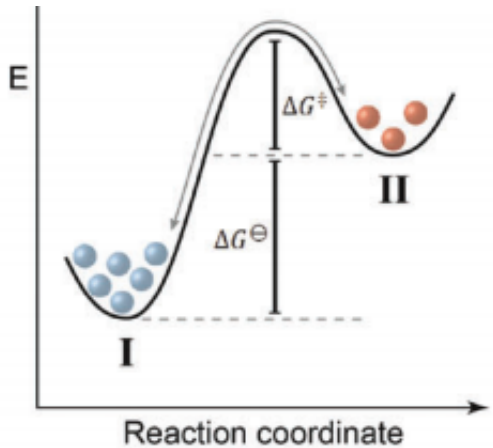
Diarylethene



Switching induces little geometry change, but a large electronic change.

J. H. van Esch, R. Eelkema, J. Boekhoven, *Chem. Soc. Rev.*, **2017**, *46*, 5519
M. Kathan, S. Hecht, *Chem. Soc. Rev.*, **2017**, *46*, 5536

Thermodynamic and Photodynamic Equilibrium



Thermodynamic equilibrated state

Principle of microscopic reversibility &
Principle of detailed balance

$$K_{eq}^{\Delta} = \frac{II}{I} = e^{-\frac{\Delta G^{\ominus}}{RT}}$$

J. H. van Esch, R. Eelkema, J. Boekhoven, *Chem. Soc. Rev.*, **2017**, *46*, 5519
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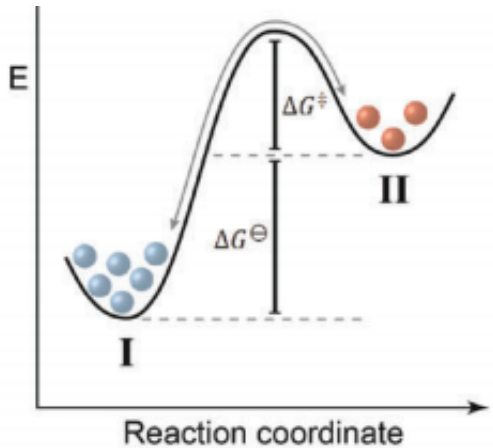
Thermodynamic and Photodynamic Equilibrium



Thermodynamic equilibrated state

Principle of microscopic reversibility &
Principle of detailed balance

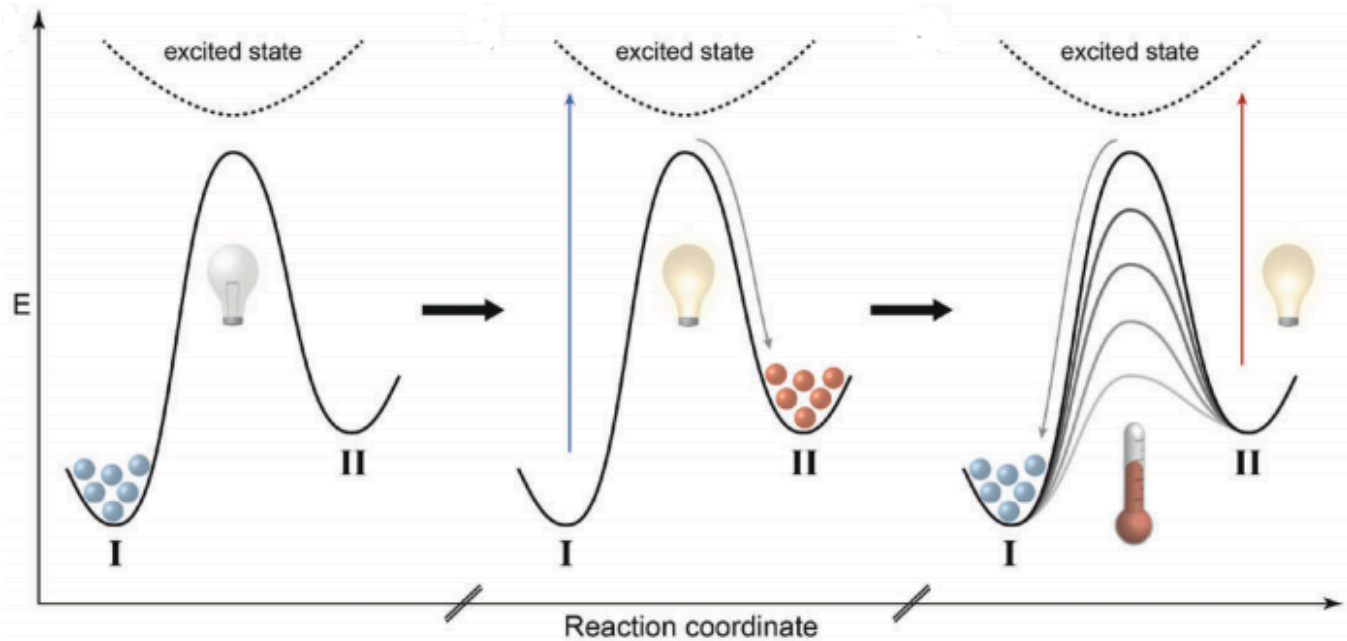
$$K_{eq}^{\Delta} = \frac{II}{I} = e^{-\frac{\Delta G^{\ominus}}{RT}}$$

Photostationary state

T-type: thermally bistable system
P-type: thermally labile system

In the absence of thermo back reactions:

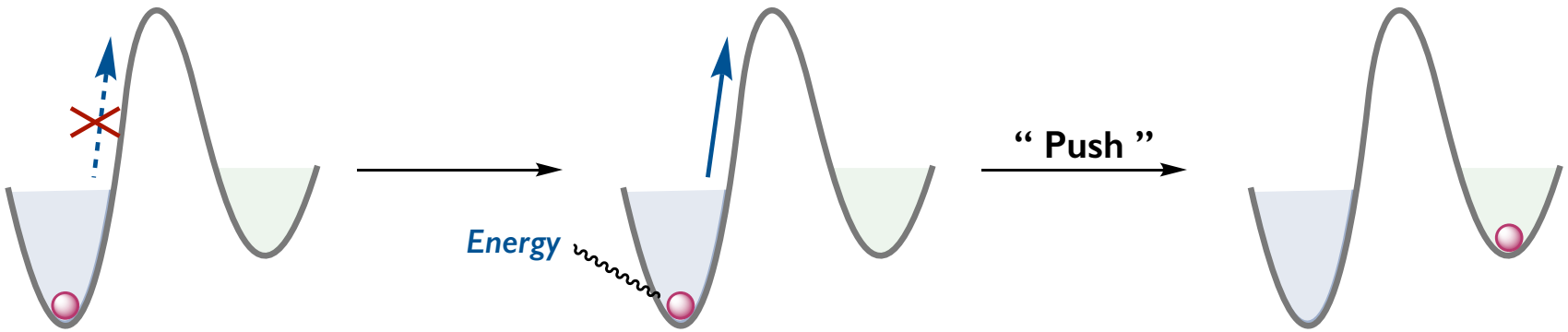
$$K_{eq}^{\lambda} = \frac{II}{I} = \frac{\varepsilon_{I}^{\lambda} \cdot \Phi_{I \to II}^{\lambda}}{\varepsilon_{II}^{\lambda} \cdot \Phi_{II \to I}^{\lambda}}$$



J. H. van Esch, R. Eelkema, J. Boekhoven, *Chem. Soc. Rev.*, **2017**, *46*, 5519
M. Kathan, S. Hecht, *Chem. Soc. Rev.*, **2017**, *46*, 5536

Mechanisms of Molecular Motors & Pumps

- Power Stroke vs. Brownian Ratchet



Selectivity or Accuracy ? Out-compete Brownian motion ?

R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.*, **2012**, *41*, 19
J. Howard, *Current Biology,* **2006**, *16*, 518.

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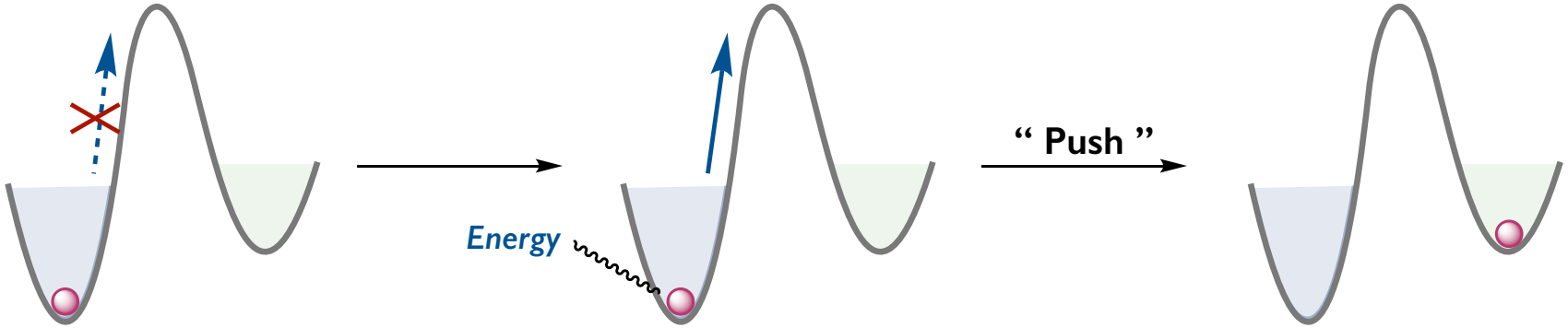

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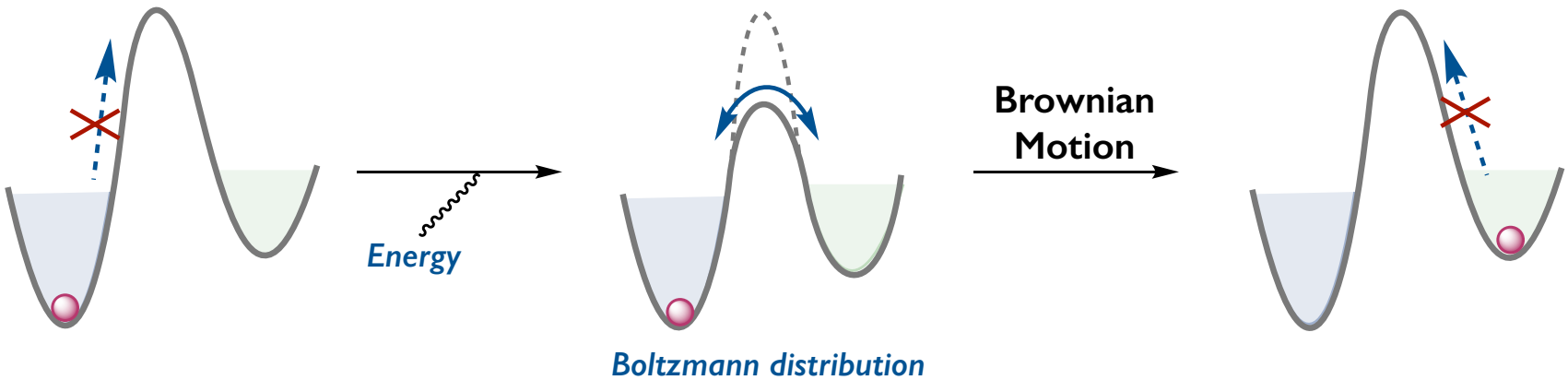


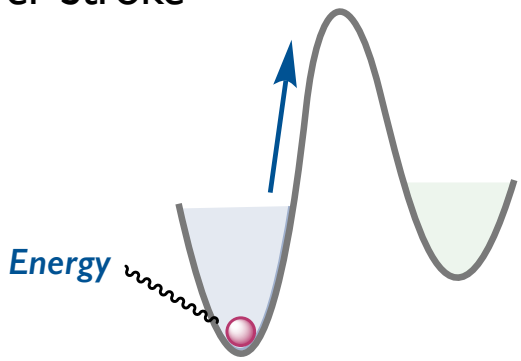
Dominant mechanism for biological molecular motors and pumps.
Spatial and temporal control of the potential surface.

R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.*, **2012**, *41*, 19
J. Howard, *Current Biology,* **2006**, *16*, 518.

Mechanisms of Molecular Motors & Pumps

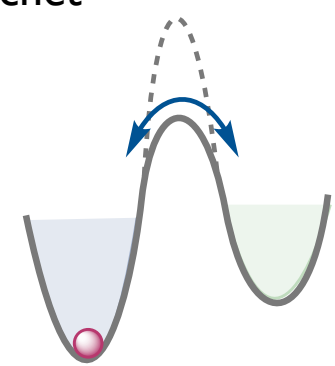
- How to tell ? — apply an external force (potential field) !

Power Stroke



Force has little effect on the forward rate constant.

Brownian Ratchet



A load force will have a big effect on the forward rate constant. (Change the Boltzmann distribution)

Example of Kinesin — Brownian Ratchet

J. Howard, *Current Biology,* **2006**, *16*, 518.
N. J. Carter, R. A. Cross, *Nature*, **2005**, *435*, 308

Mechanisms of Molecular Motors & Pumps

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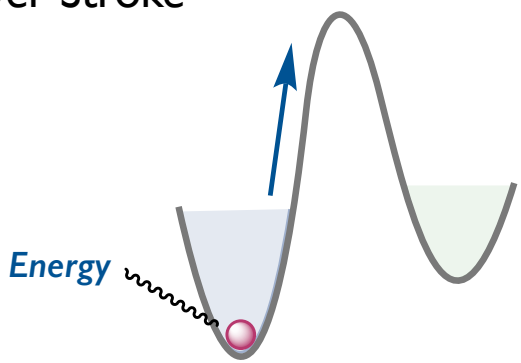

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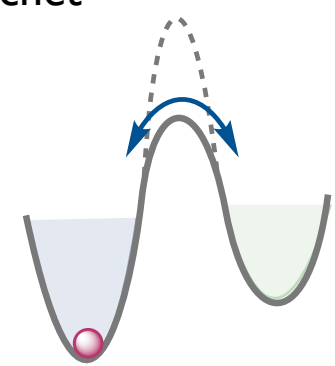

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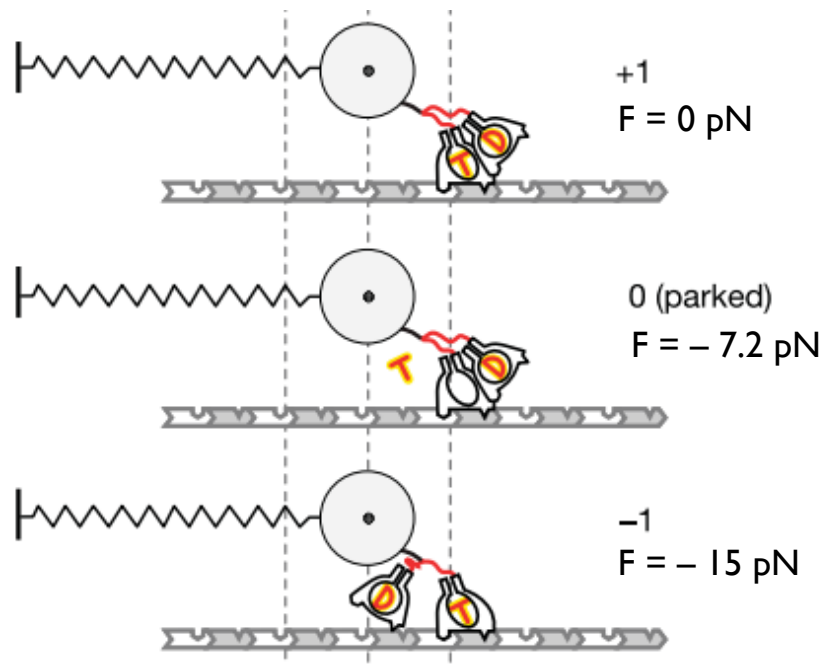
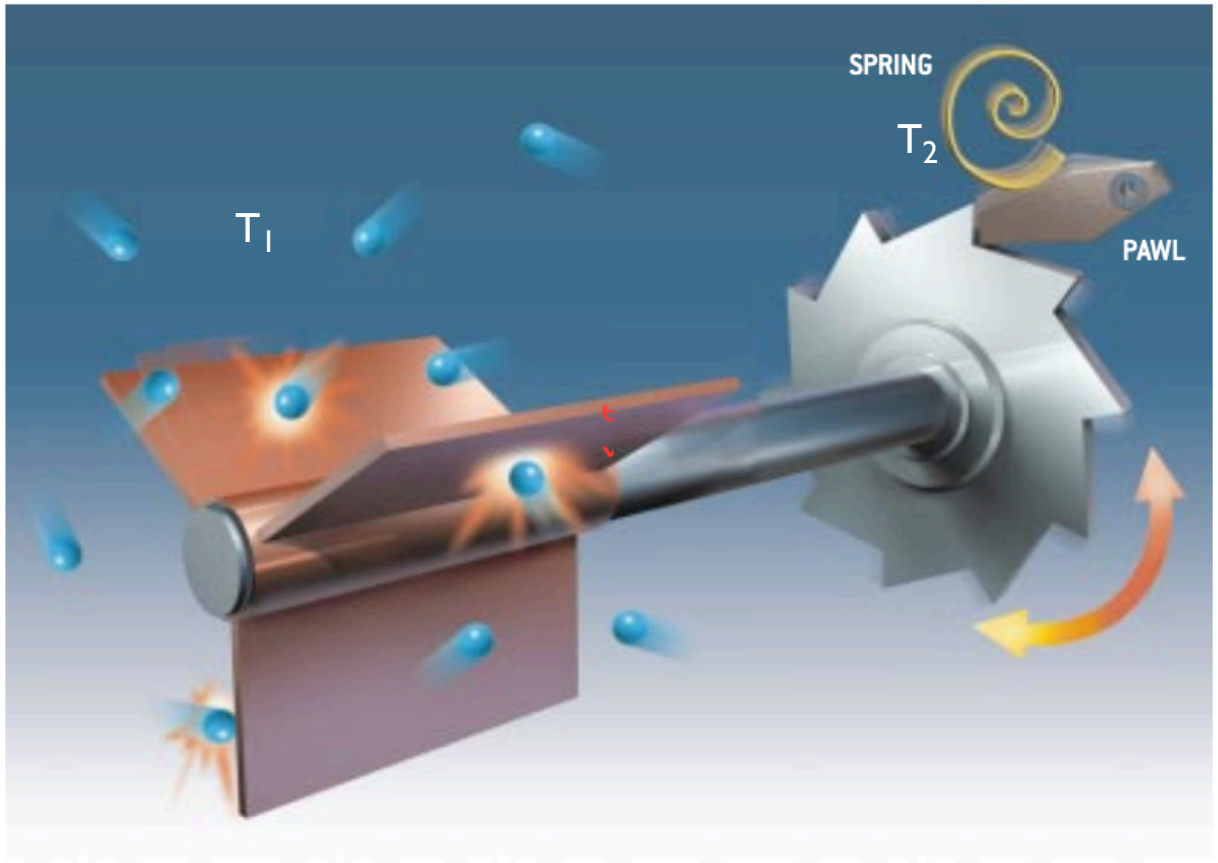


The directional bias can be reversed and the speed is force dependent suggest a diffusional search for its next step.

J. Howard, *Current Biology*, **2006**, *16*, 518.
N. J. Carter, R. A. Cross, *Nature*, **2005**, *435*, 308

Mechanisms of Molecular Motors & Pumps

- Feymann's Ratchet



$T_1 = T_2$,
no moving

$T_1 > T_2$,
counter-clockwise rotation

$T_1 < T_2$,
clockwise rotation

R. Dean Astumian, *Scientific American*, July, **2001**, 57.

Mechanisms of Molecular Motors & Pumps

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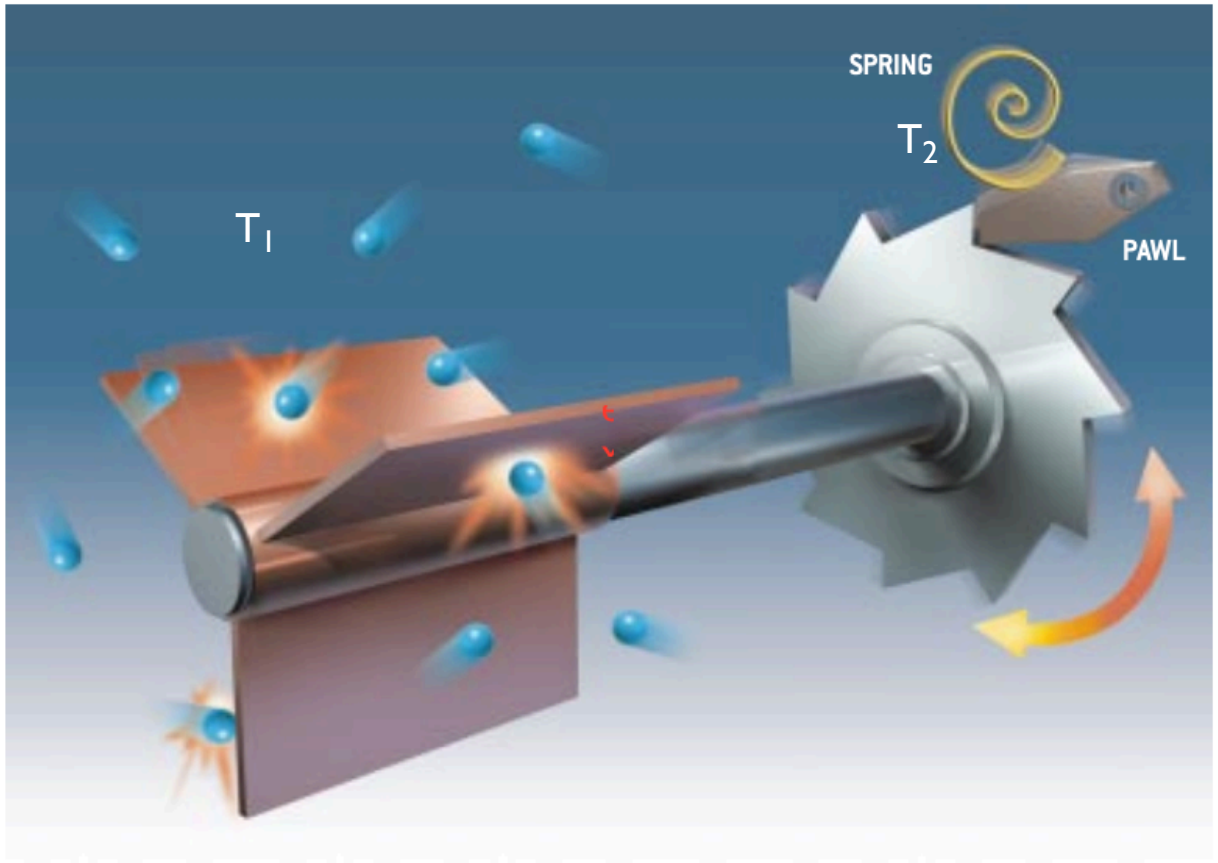


Three elements of ratcheting mechanism:

(1) Random motion (Brownian);

(2) Asymmetric gating;

(3) Non-equilibrium driving force;

$T_1 = T_2$, no moving

$T_1 > T_2$, counter-clockwise rotation

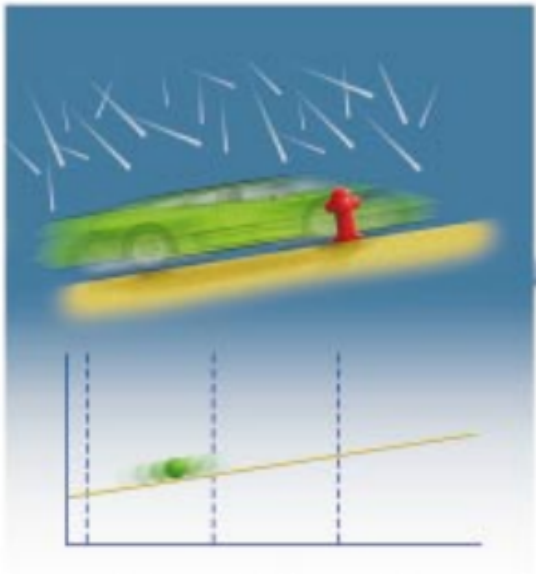
$T_1 < T_2$, clockwise rotation

R. Dean Astumian, *Scientific American*, July, **2001**, 57.

Mechanisms of Molecular Motors & Pumps

- Energy Ratchet — changing of potential surface is INDEPENDENT of position (configuration, status) of the particle
- Information Ratchet — changing of potential surface is DEPENDENT of position (configuration, status) of the particle

Example: driving uphill in a hailstorm with no gas!



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J. Howard, *Current Biology,* **2006**, *16*, 518.

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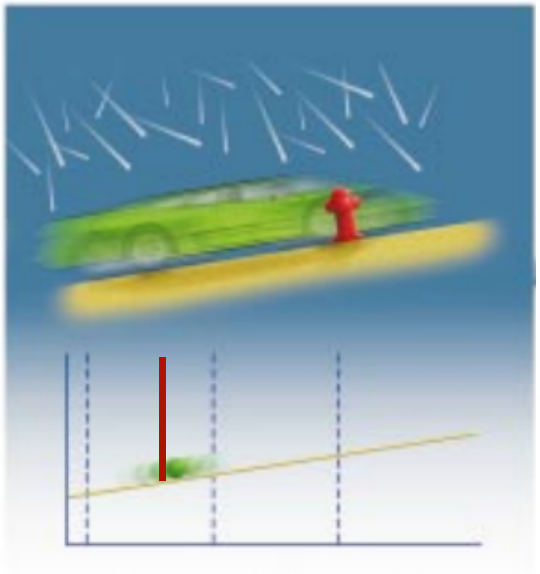

Move the brick as soon as your car going uphill!

R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.*, **2012**, *41*, 19
J. Howard, *Current Biology,* **2006**, *16*, 518.

Mechanisms of Molecular Motors & Pumps

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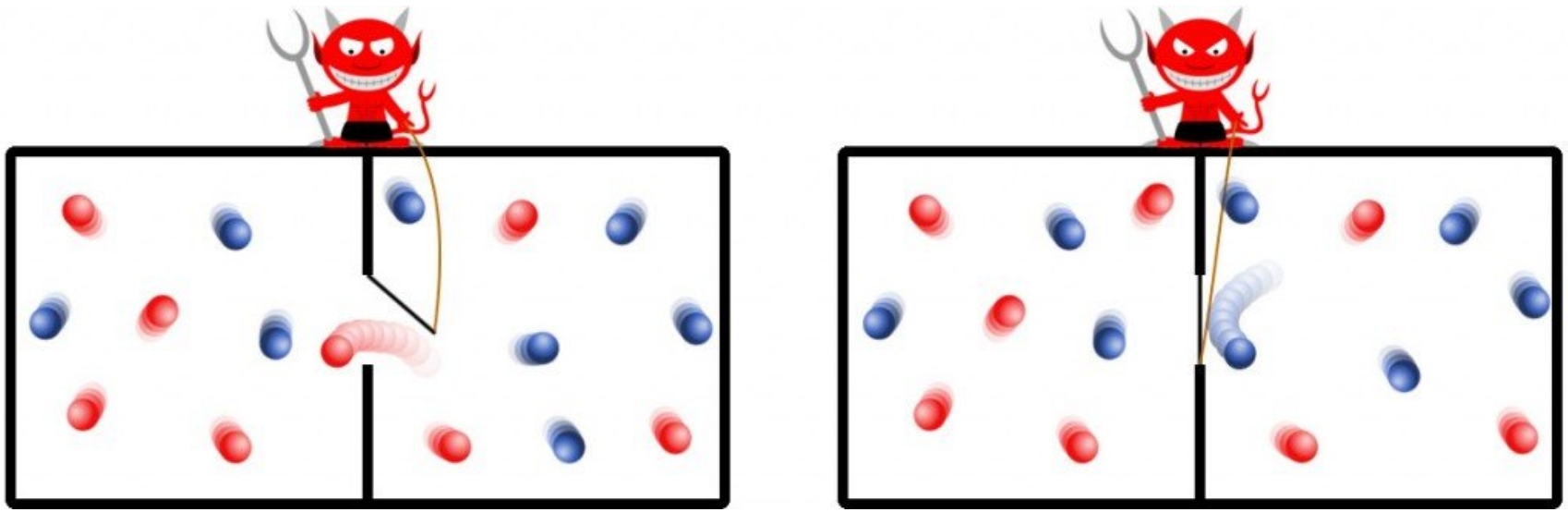
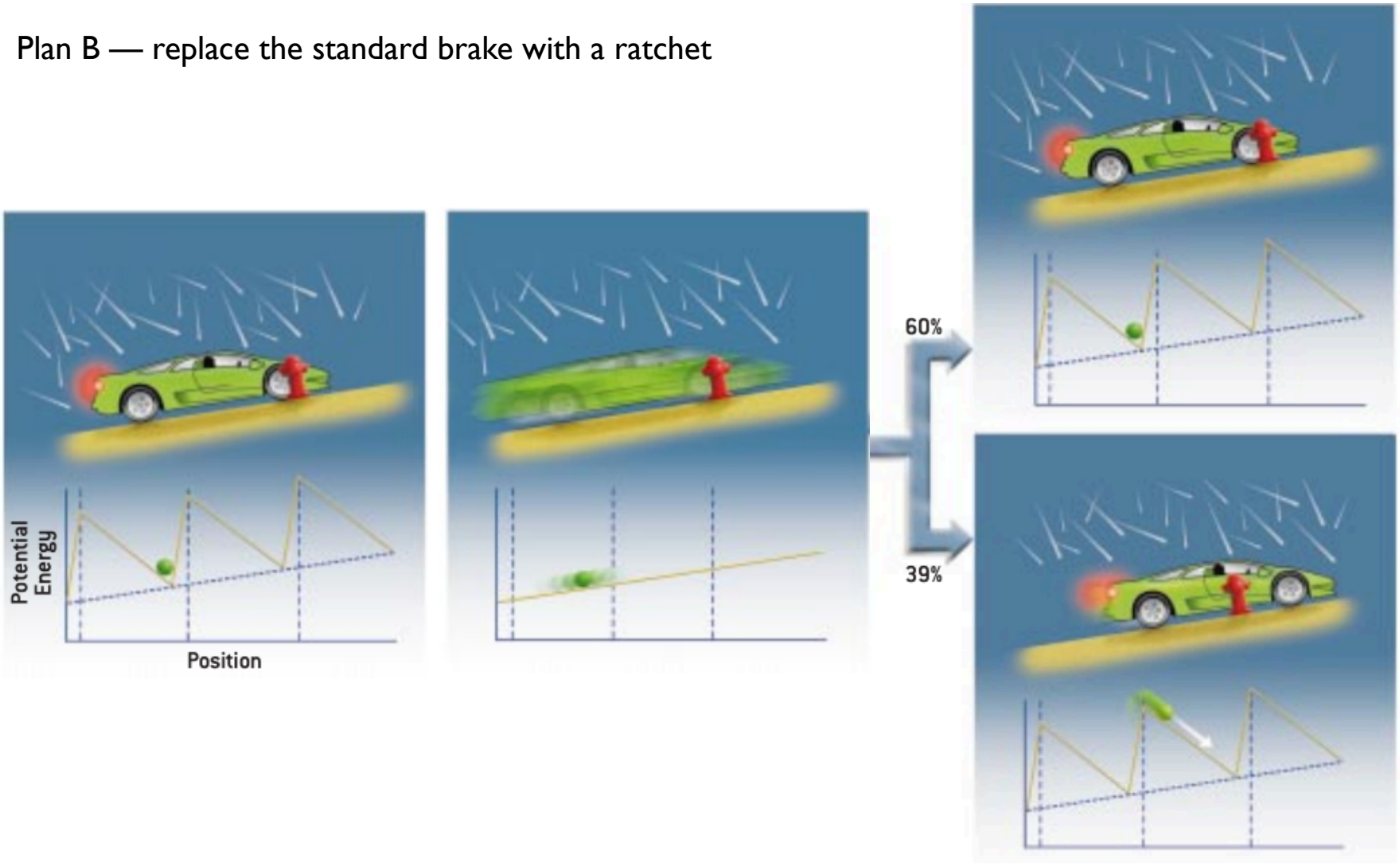


R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.*, **2012**, *41*, 19
J. Howard, *Current Biology,* **2006**, *16*, 518.

Mechanisms of Molecular Motors & Pumps

Example: driving uphill in a hailstorm with no gas!

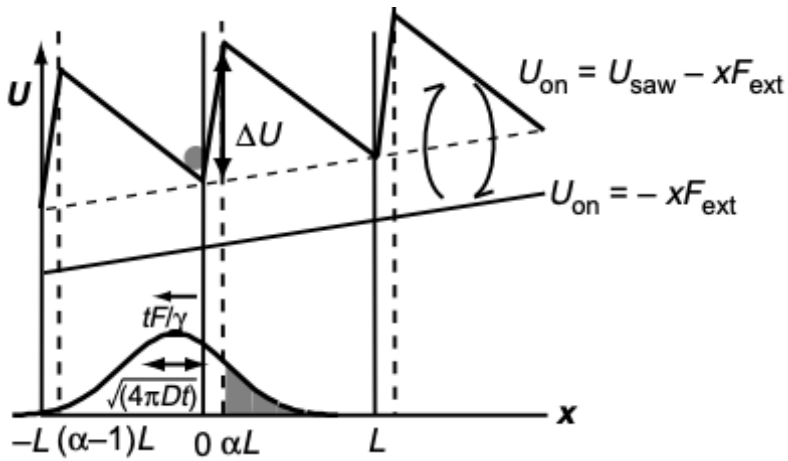
Plan B — replace the standard brake with a ratchet

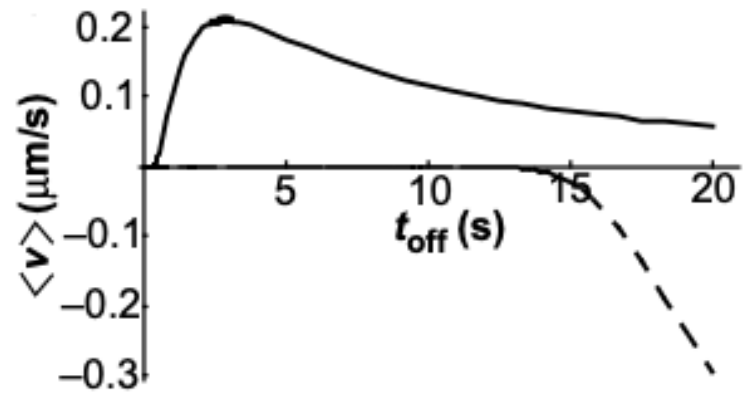


R. Dean Astumian, *Scientific American*, July, **2001**, 57.

Two Types of Energy Ratchet

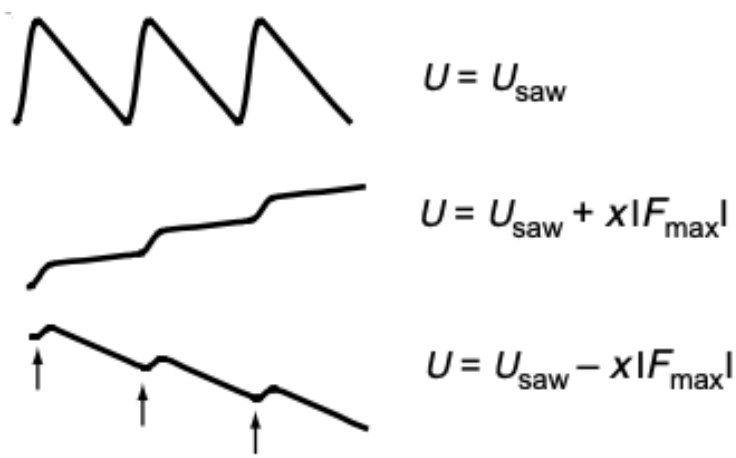
- "Flashing" Ratchet — A fluctuating potential





F_{ext} is too big !

- "Rocking" Ratchet — A fluctuating force



Particle drift to the left !

R. D. Astumian, *Science*, **1997**, *276*, 917

Summary of Key Concepts

Macroscopic motors

External force to drive

Molecular machines

External force to outcompete
or bias Brownian motion

Random motion;

Energy input;

Aymmetric bias;

Molecular switch

switch btw states

Molecular motors

able to do work

Power stroke

do work albeit Brownian motion

Brownian Ratchet

do work because of Brownian motion

"Flashing" ratchet

constant external force +
"on" and "off" ratcheting potential

Energy ratchet

potential surface independent
of the position of particle

Information ratchet

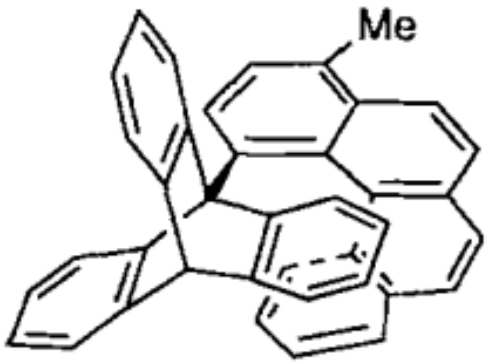
potential surface dependent
of the position of particle

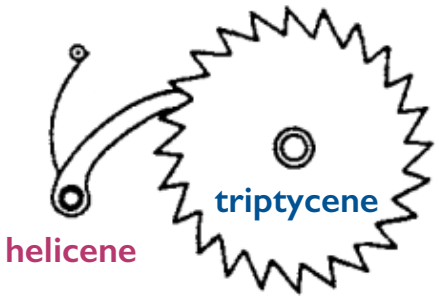
"Rocking" ratchet

fluctuating external force +
constant ratcheting potential

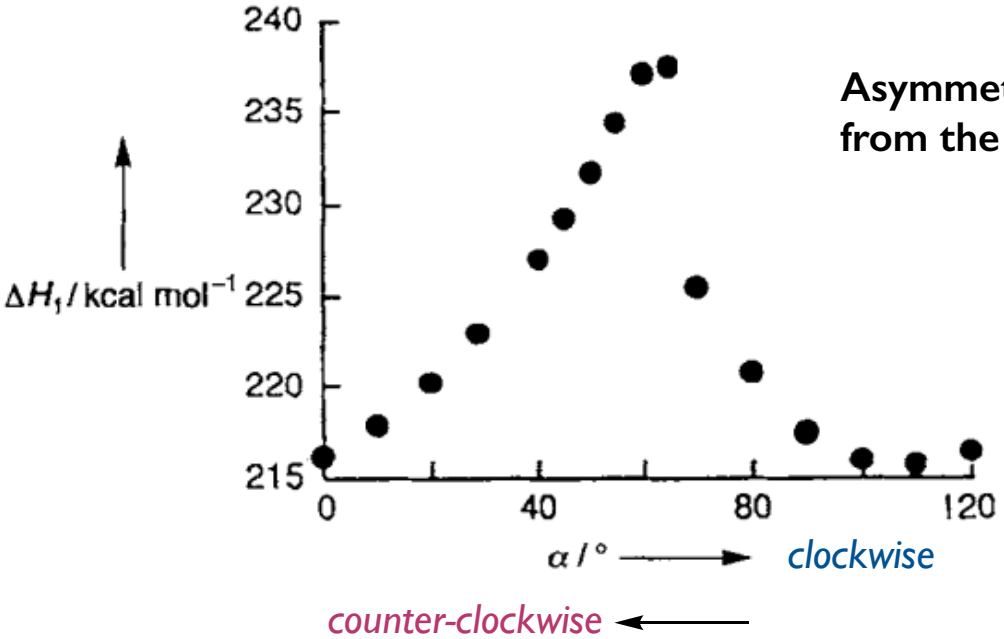
R. D. Astumian, *Science*, **1997**, *276*, 917

The First Molecular Ratchet





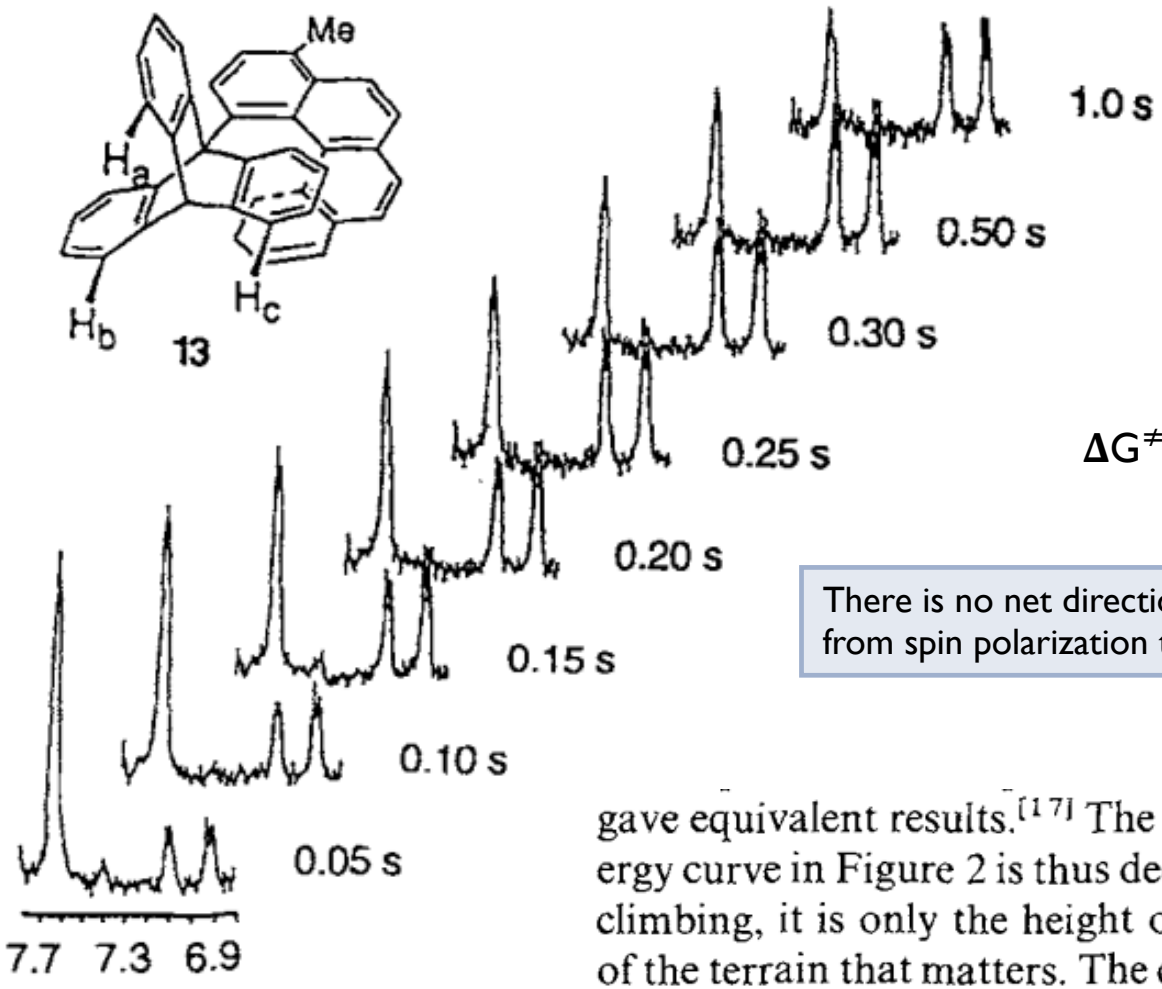
Calculated energy diagram for rotation



Asymmetric energy curve results from the helical chirality!

T. R. Kelly, *Angew. Chem. Int. Ed.*, **1997**, *36*, 1866

The First Molecular Ratchet



$\Delta G^{\neq}$ = 24.5 kcal/mol

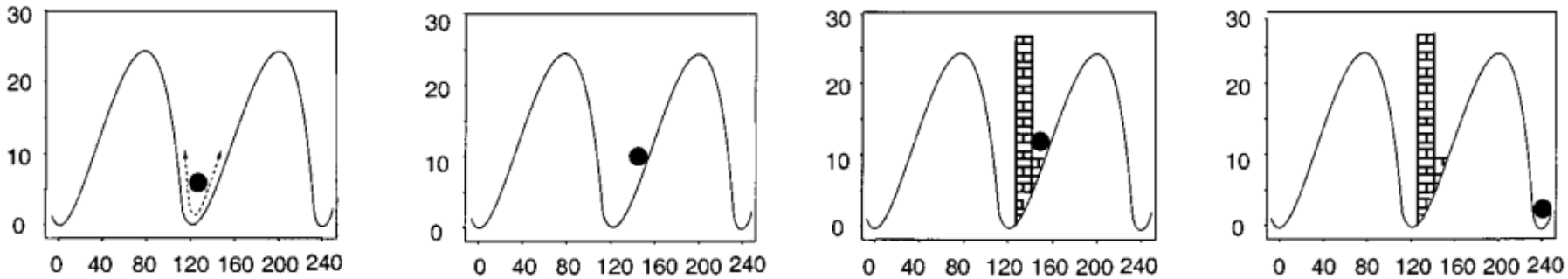
There is no net directional rotation of the molecular ratchet from spin polarization transfer NMR technique (at 160 °C).

gave equivalent results.[17] The asymmetry of the rotational energy curve in Figure 2 is thus deceptive: In contrast to mountain climbing, it is only the height of the summit, not the steepness of the terrain that matters. The chemical principle of microscopic reversibility prevails.

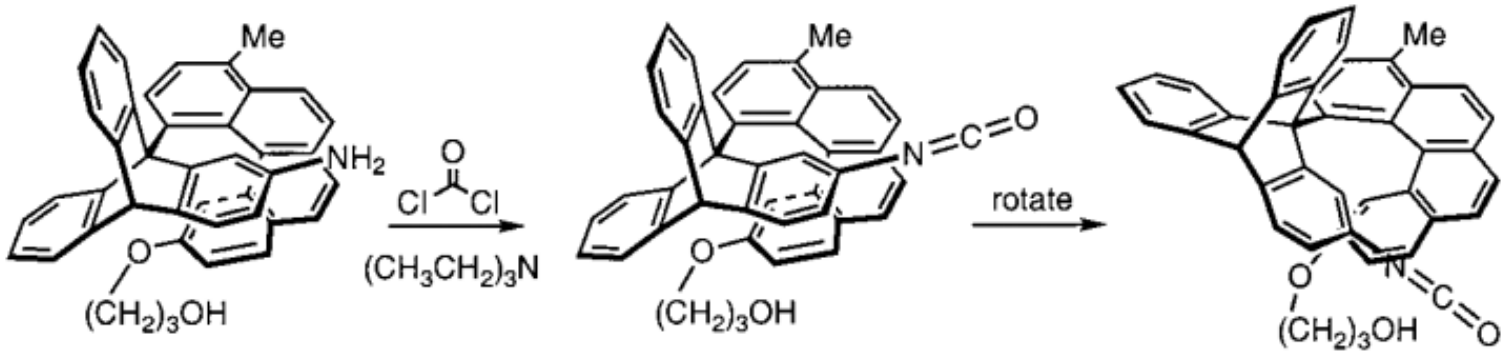
T. R. Kelly, *Angew. Chem. Int. Ed.*, **1997**, *36*, 1866

The First Molecular Ratchet

- Use chemical fuel to bias brownian motion



Clockwise Rotation



T. R. Kelly, *Nature*, **1999**, *401*, 150
T. R. Kelly, *J. Am. Chem. Soc.*, **2000**, *122*, 6935

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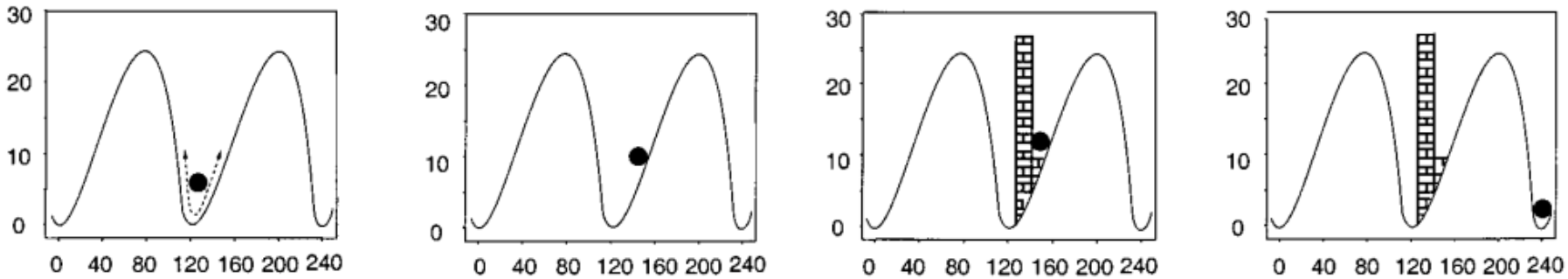
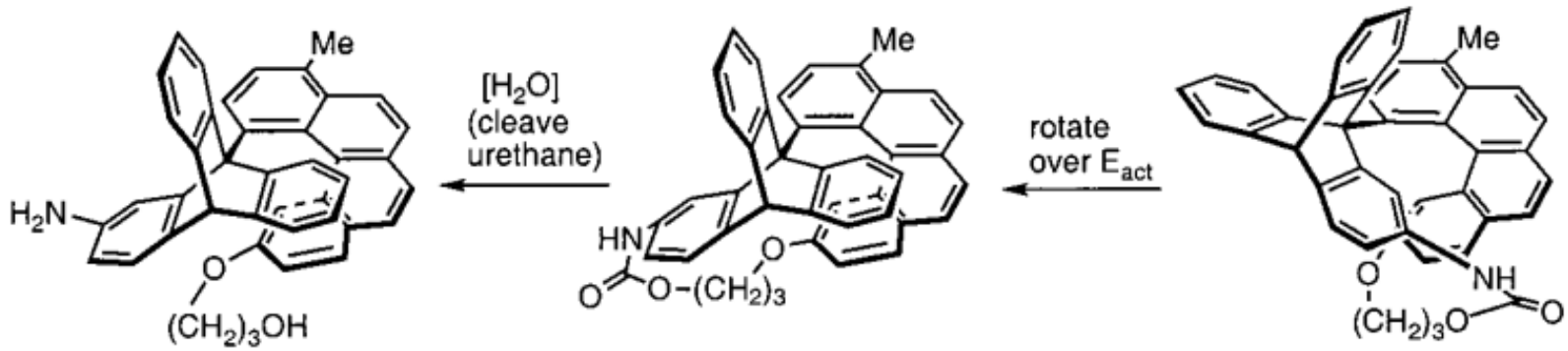


Clockwise Rotation

urethane formation

Rotation is significantly faster by shortening the chain!

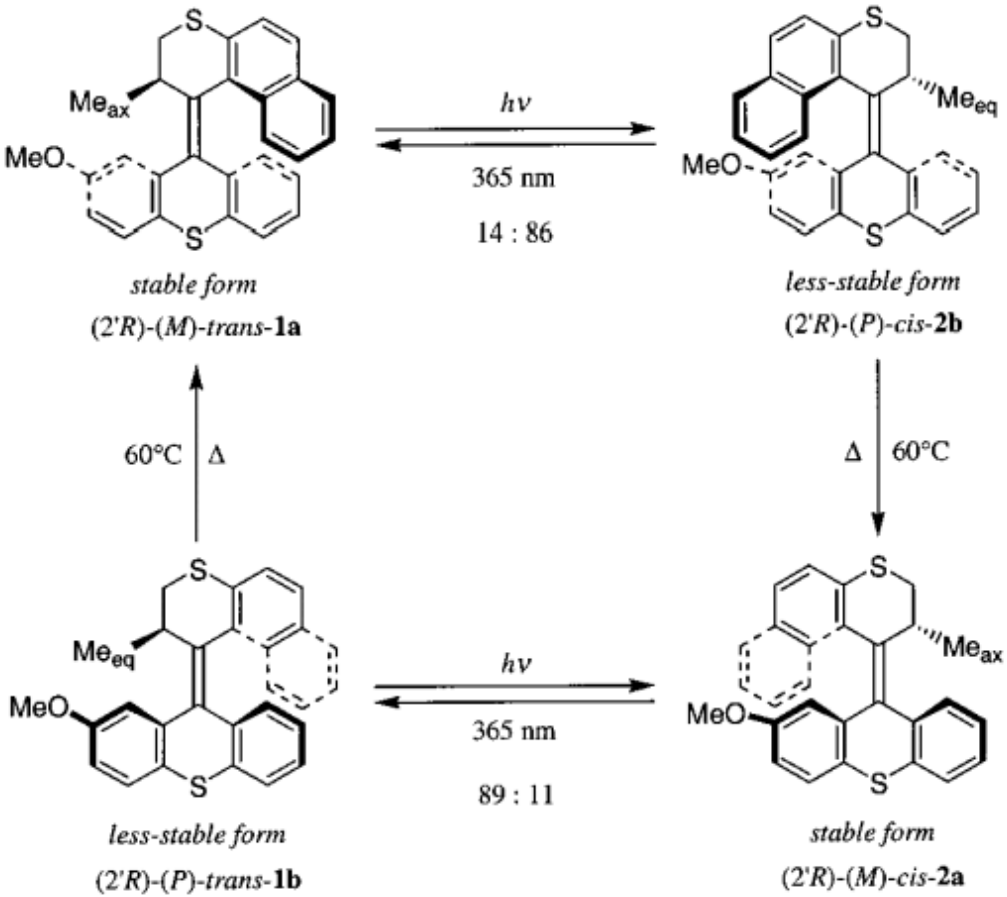


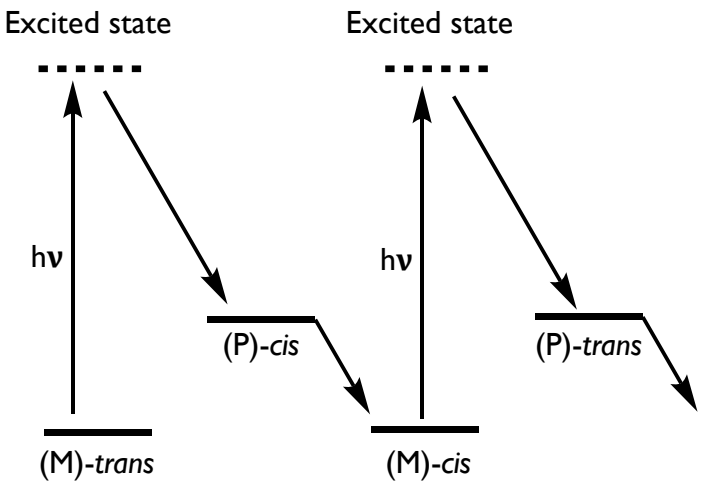
However, not a motor yet …

T. R. Kelly, *Nature*, **1999**, *401*, 150
T. R. Kelly, *J. Am. Chem. Soc.*, **2000**, *122*, 6935

First Molecular Motor

- Design principle





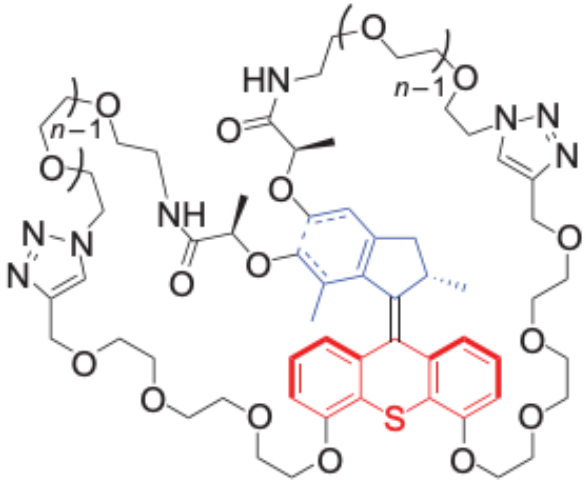
The diastereometric nature of two chiral elements determines the rotating direction.

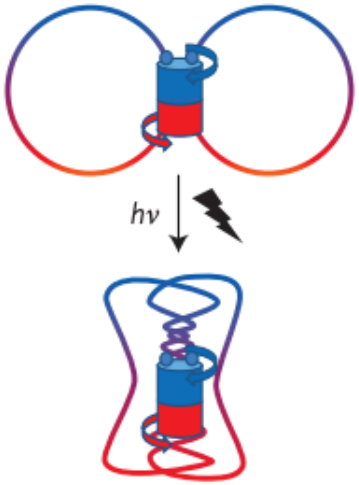
Light-driven motor that achieves uni-directional continuous 360° rotation, with controllable speed.

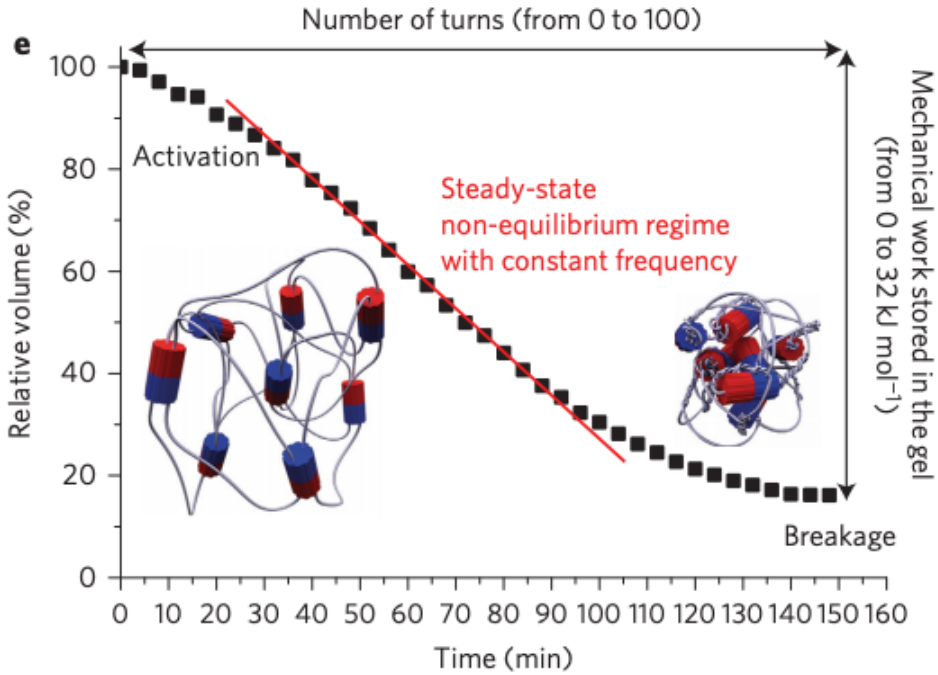
R. W. J. Zijlstra, R. A. van Delden, B. L. Feringa, *Nature*, **1999**, *401*, 152
B. L. Feringa, *J. Am. Chem. Soc.*, **2002**, *124*, 5037

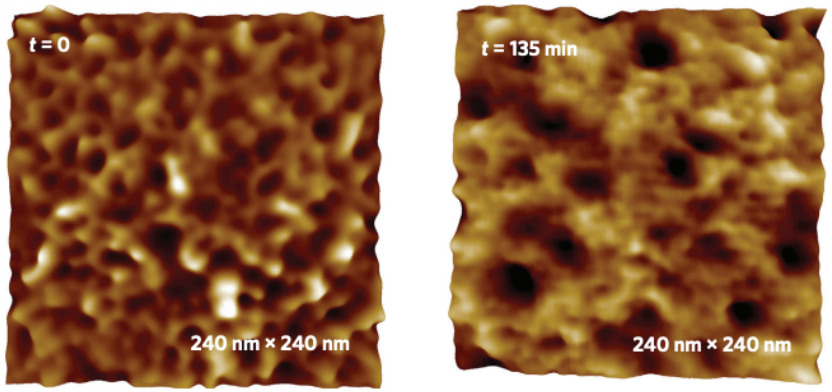
First Molecular Motor

- Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors — featuring continuous rotation





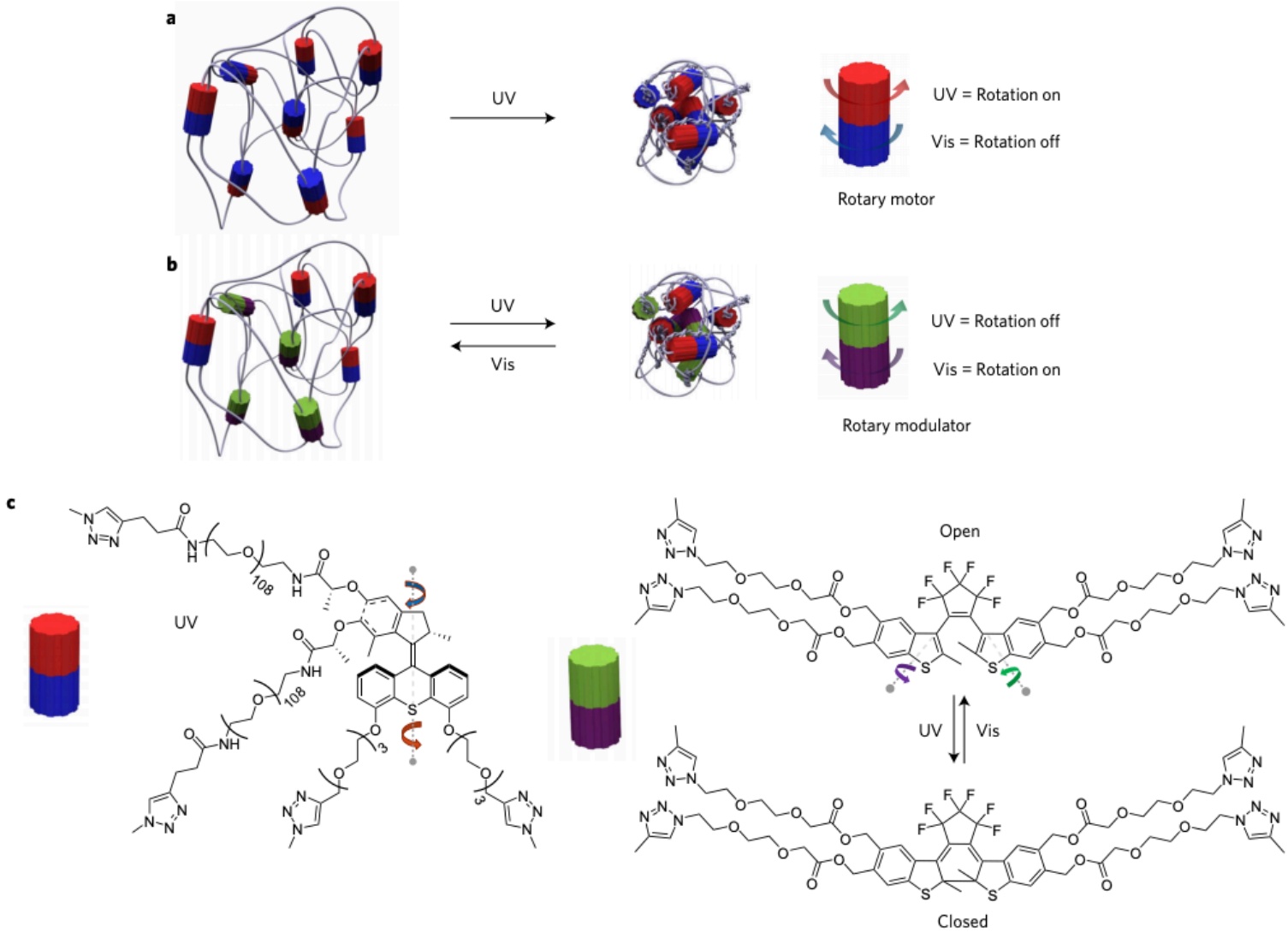




N. Giuseppone, *Nat. nanotech.*, **2015**, *10*, 161

First Molecular Motor

- Dual-light control of nanomachines that integrate motor and modulator subunits — featuring continuous rotation

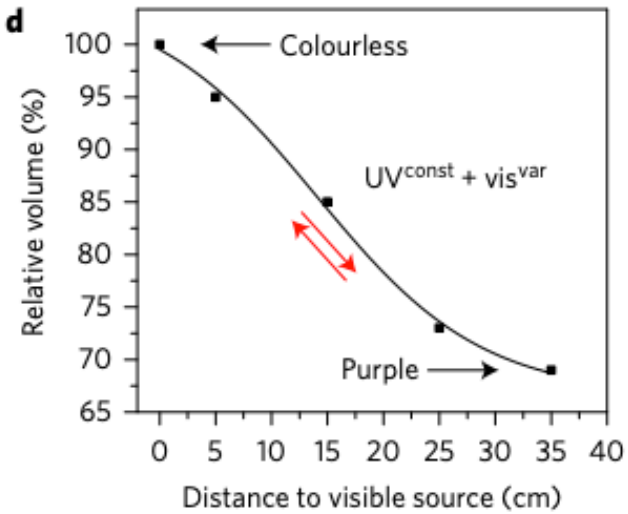


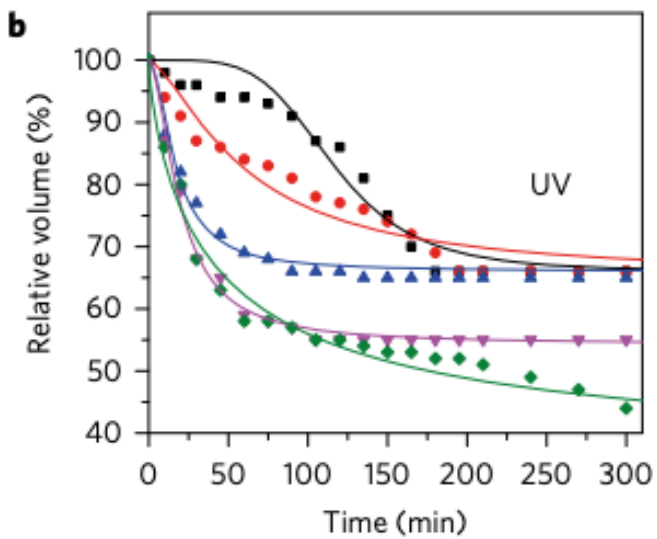
N. Giuseppone, *Nat. nanotech.*, **2017**, *12*, 540

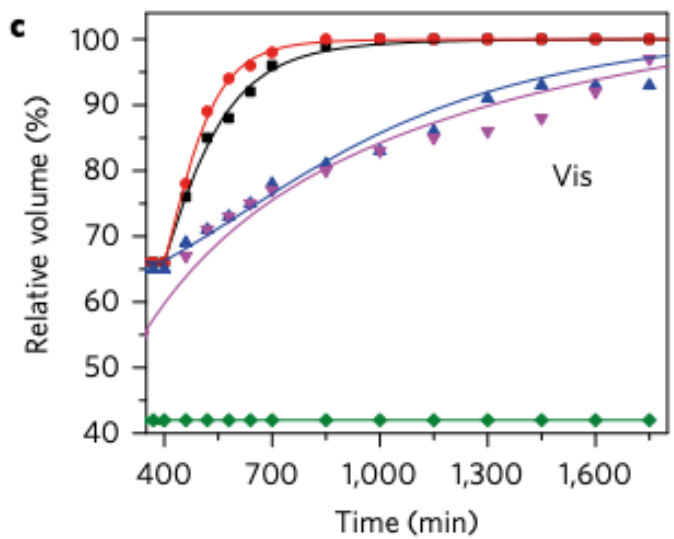
First Molecular Motor

- Dual-light control of nanomachines that integrate motor and modulator subunits — featuring continuous rotation

Compound	Modu-lator **2**	Motor **3** (equiv.)	Motor **4** (equiv.)
■ **Gel 50**	1.00	1	0.00
● **Gel 25**	0.50	1	0.50
▲ **Gel 12**	0.25	1	0.75
▼ **Gel 5**	0.10	1	0.90
◆ **Gel 0**	0.00	1	1.00

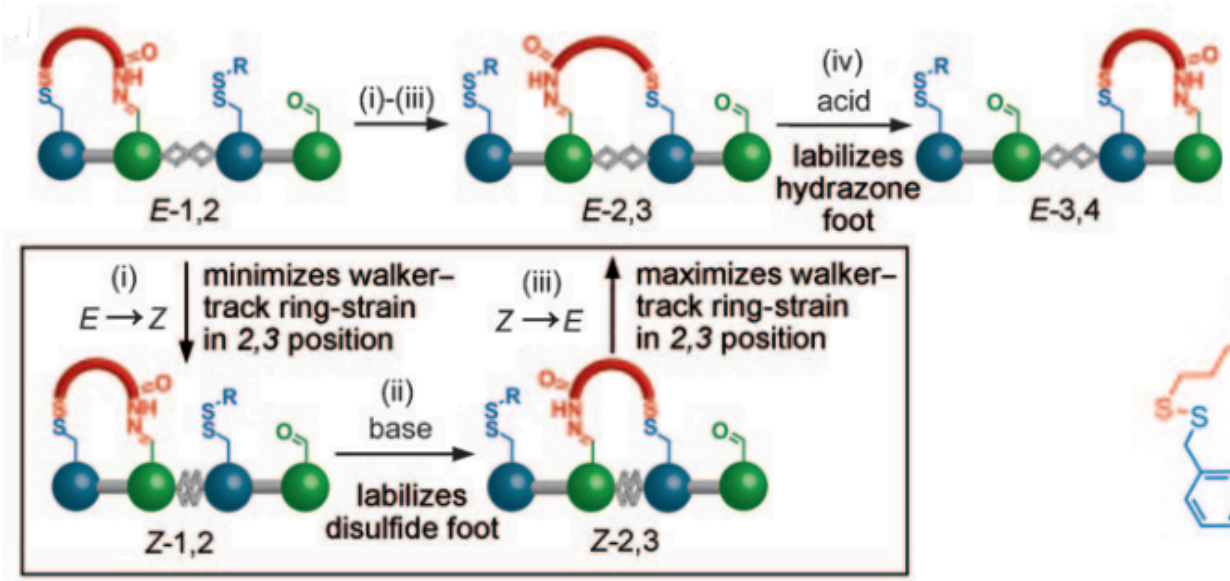


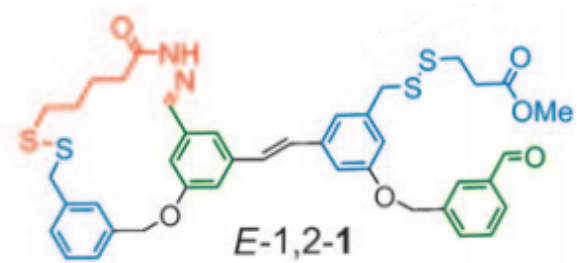


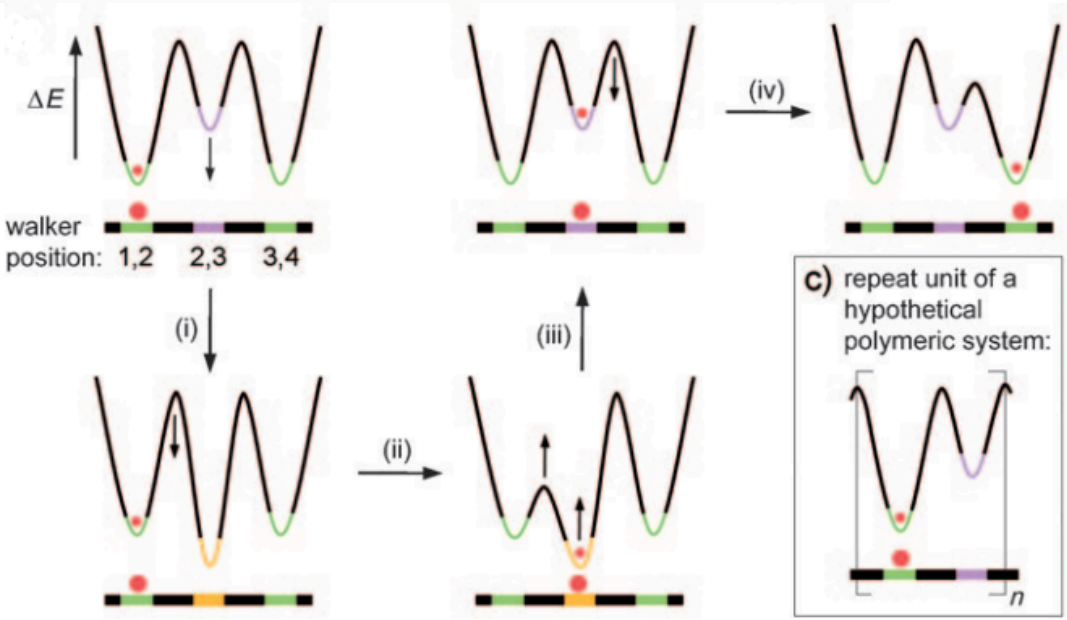


N. Giuseppone, *Nat. nanotech.*, **2017**, *12*, 540

Light-driven Transport of a Synthetic Molecular Walker in Either Direction along a Molecular Track



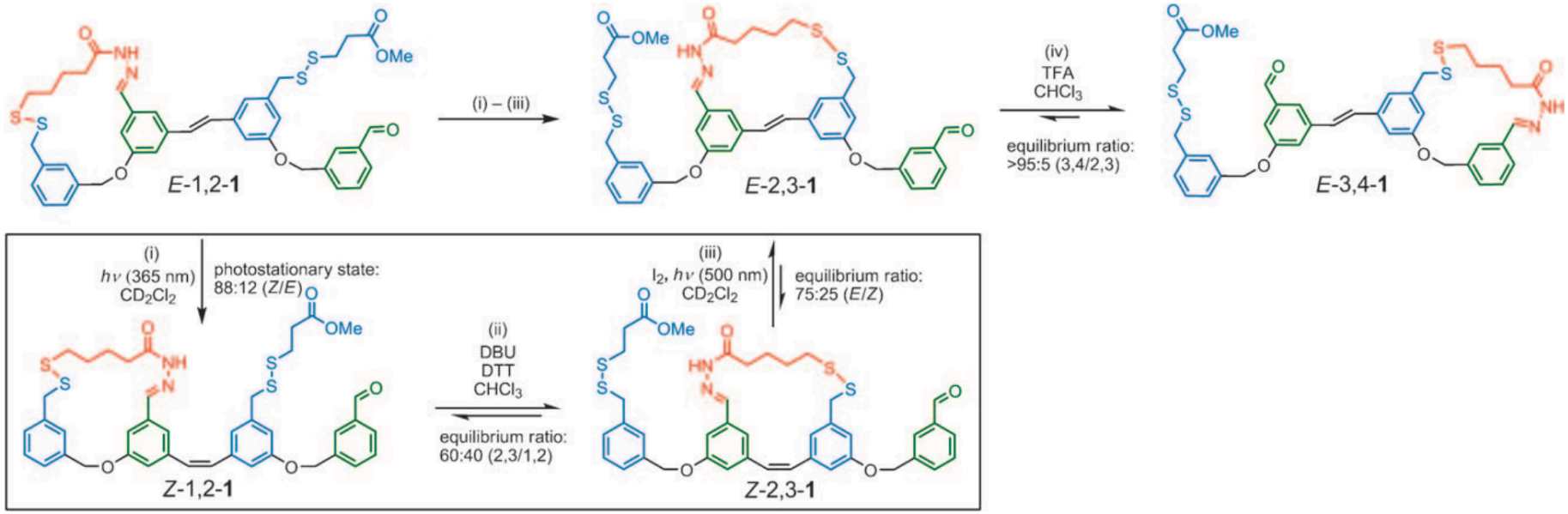


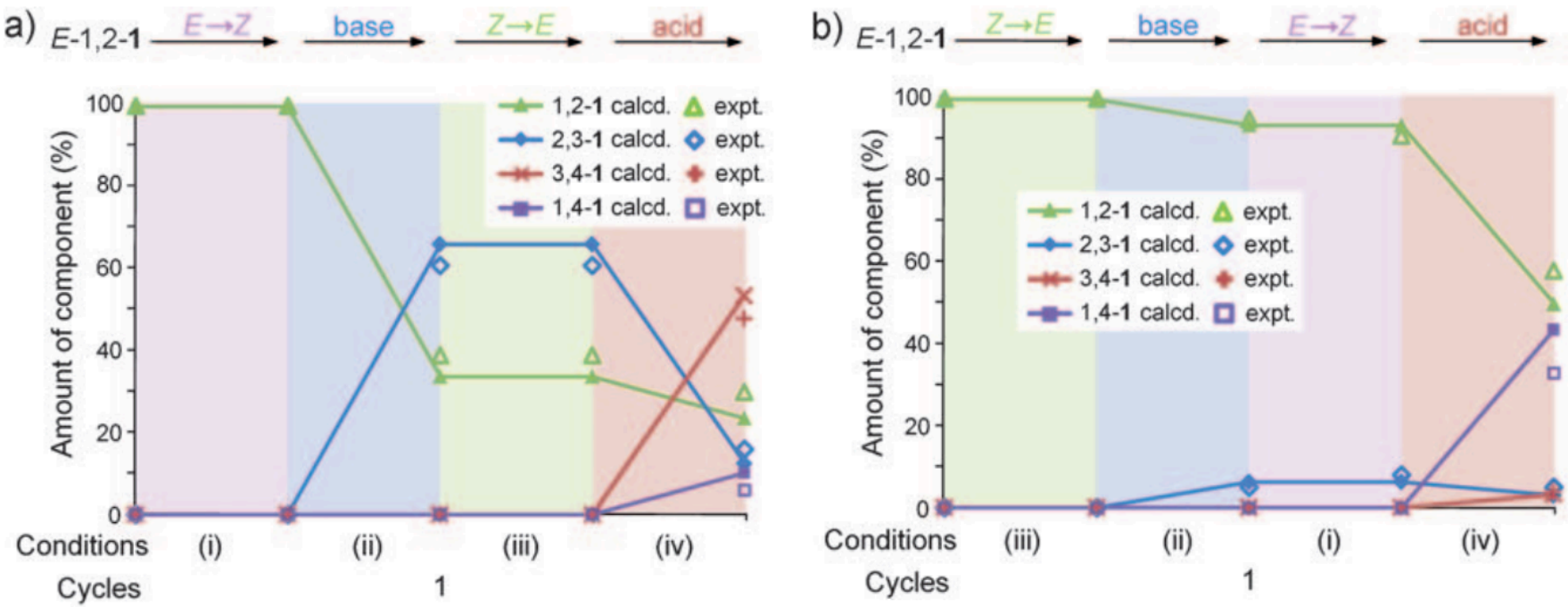


Acid: labilize hydrozone foot
Base: labilize disulfide foot

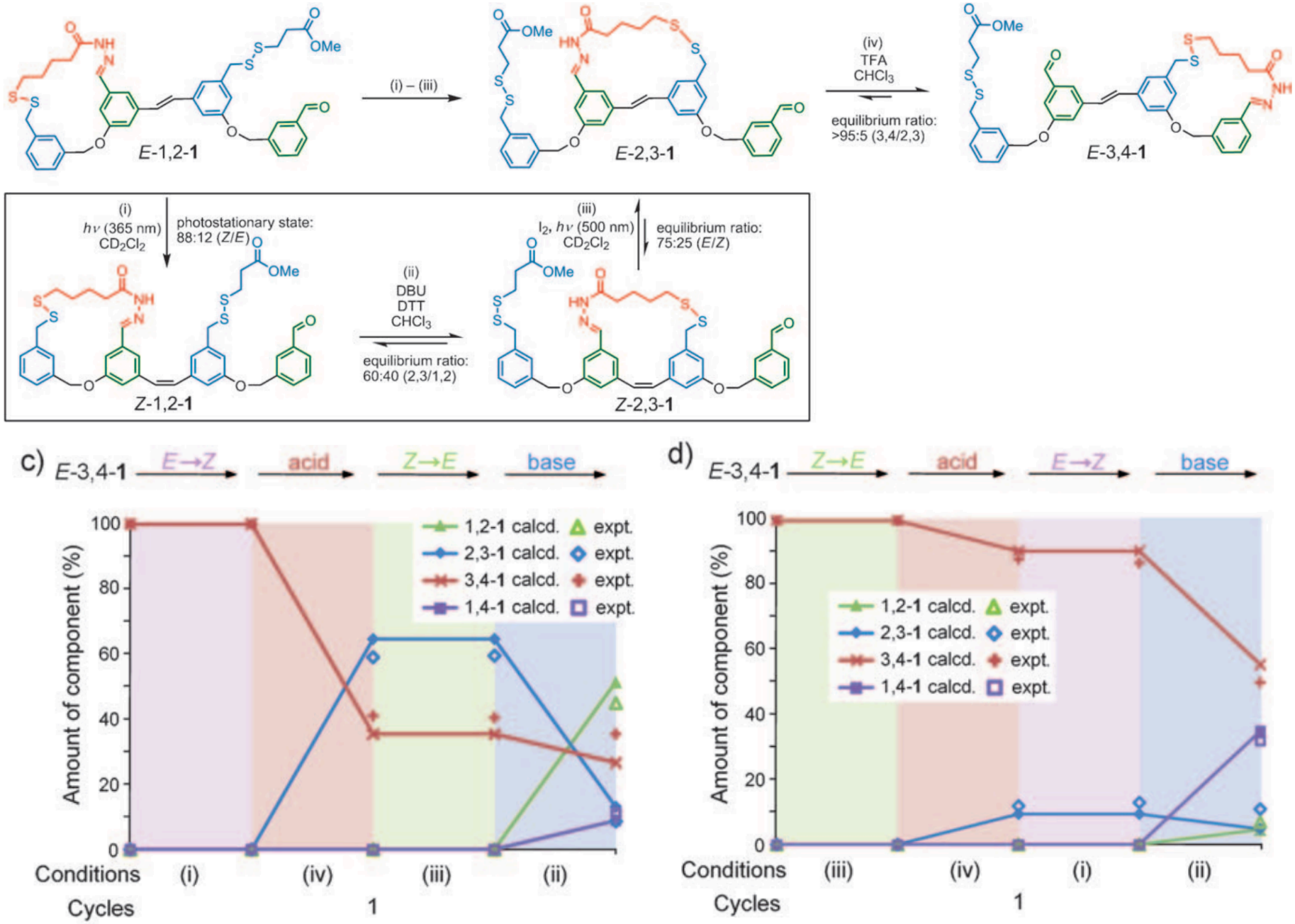
The key to achieve directionality lies in the isomerization of stilbene.

D.A. Leigh, Nat. Chem., **2010**, *2*, 96
D.A. Leigh, *Angew. Chem. Int. Ed.*, **2011**, *50*, 285

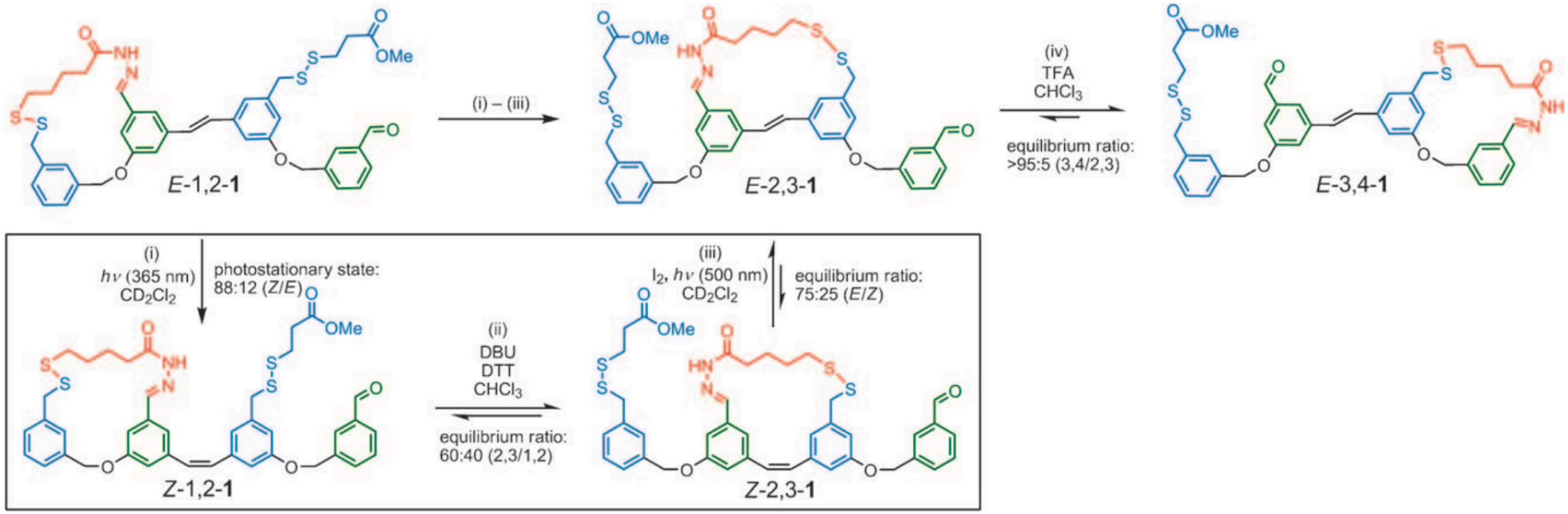


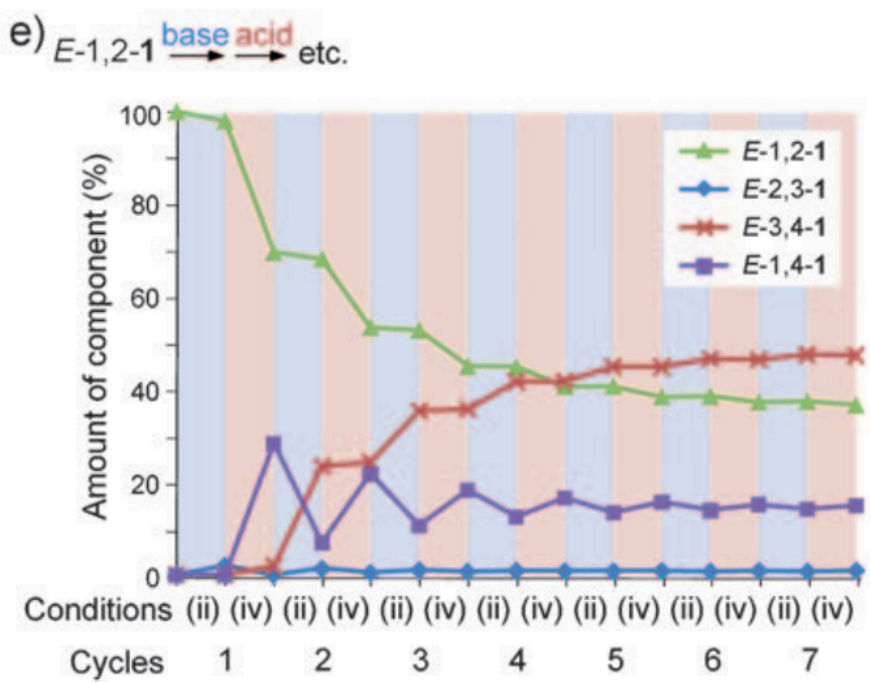


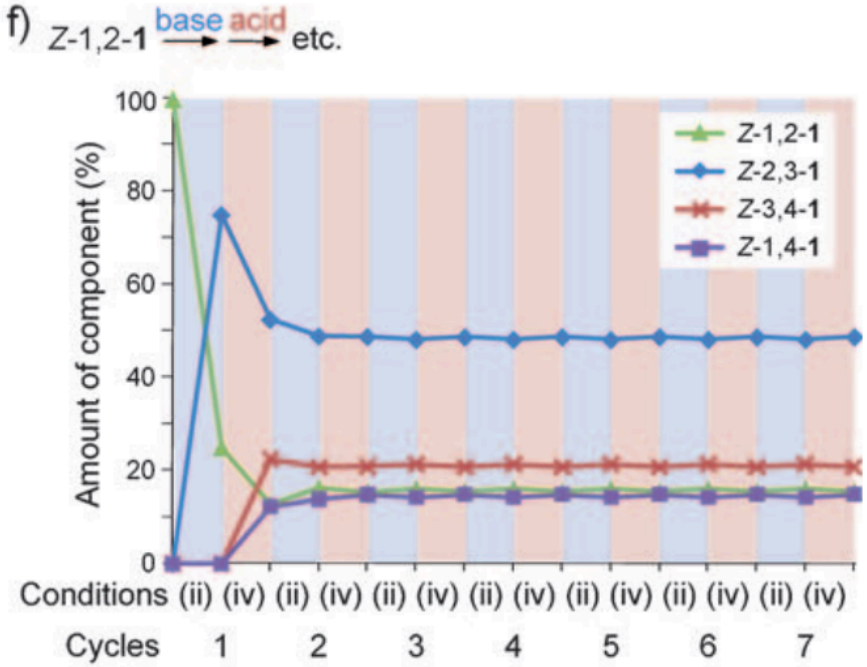
D.A. Leigh, Nat. Chem., **2010**, *2*, **96**
D.A. Leigh, *Angew. Chem. Int. Ed.*, **2011**, *50*, 285



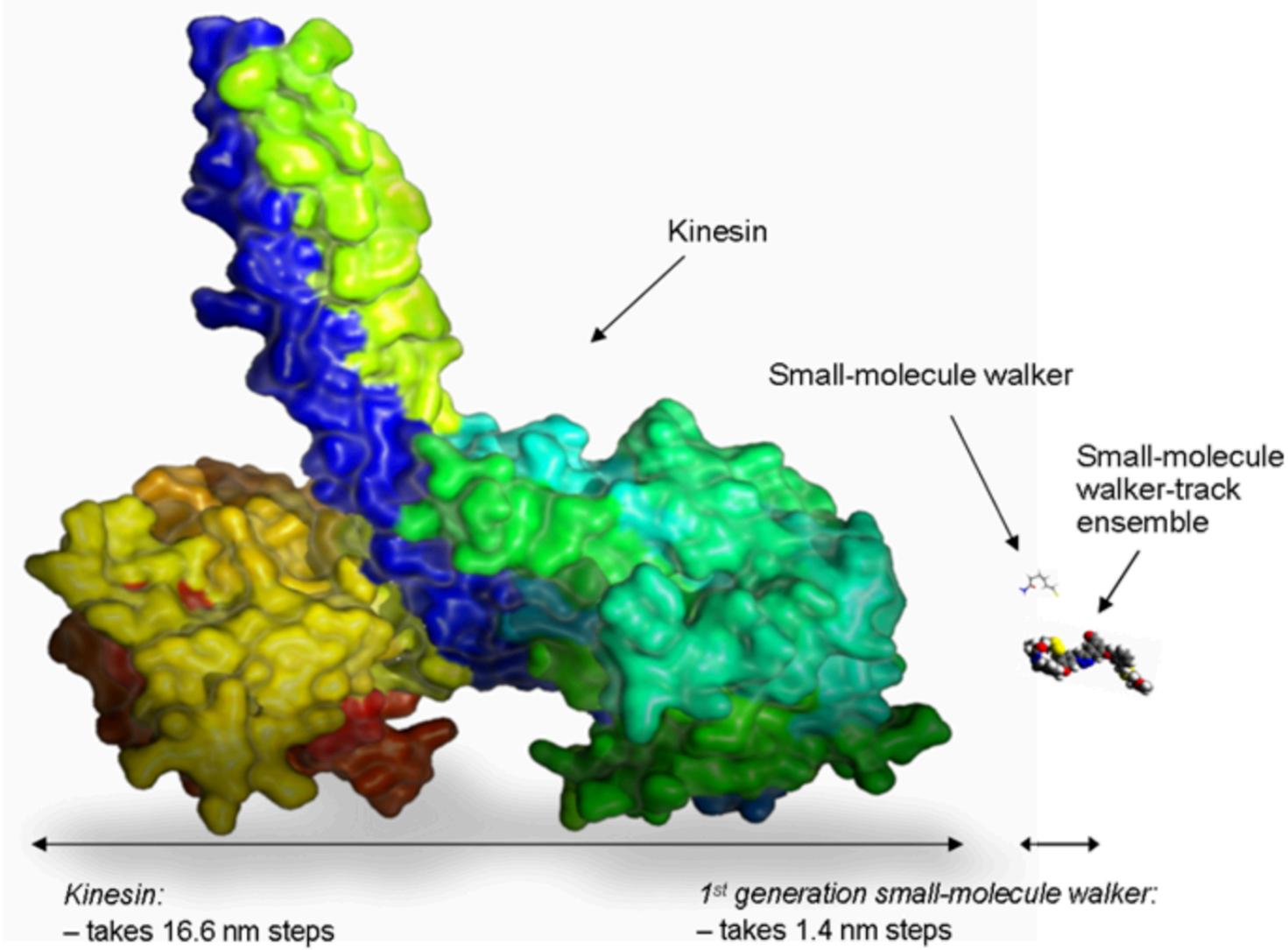
D.A. Leigh, Nat. Chem., **2010**, *2*, 96
D.A. Leigh, *Angew. Chem. Int. Ed.*, **2011**, *50*, 285







D.A. Leigh, Nat. Chem., **2010**, *2*, 96
D.A. Leigh, *Angew. Chem. Int. Ed.*, **2011**, *50*, 285

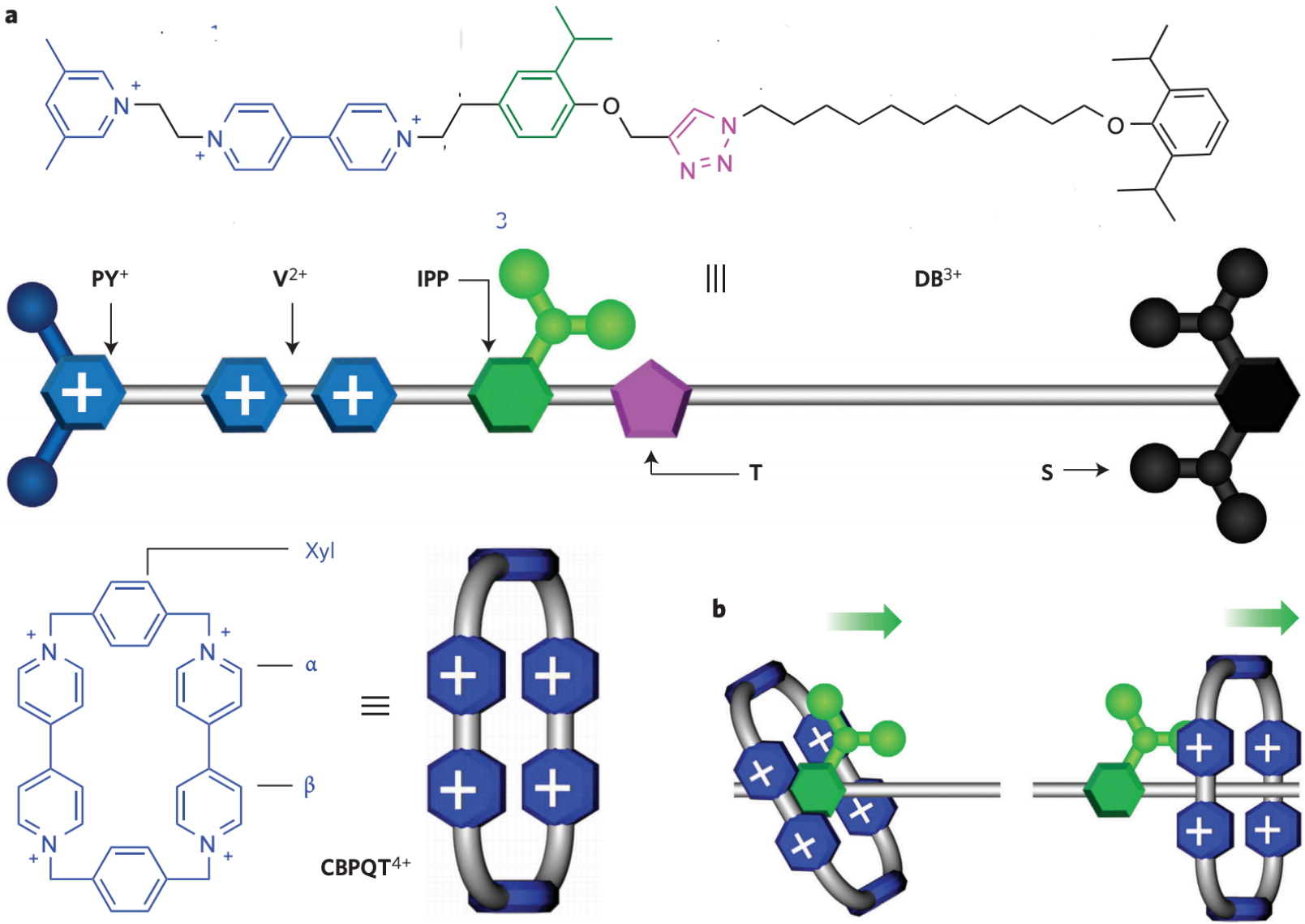


Kinesin:
- takes 16.6 nm steps
- takes one step per molecule ATP hydrolysed
- mean 75-150 steps before dissociating
- 250 kD walker
- carries cargo
- autonomous

- walks up to 1 micron along microtubule supramolecular polymers

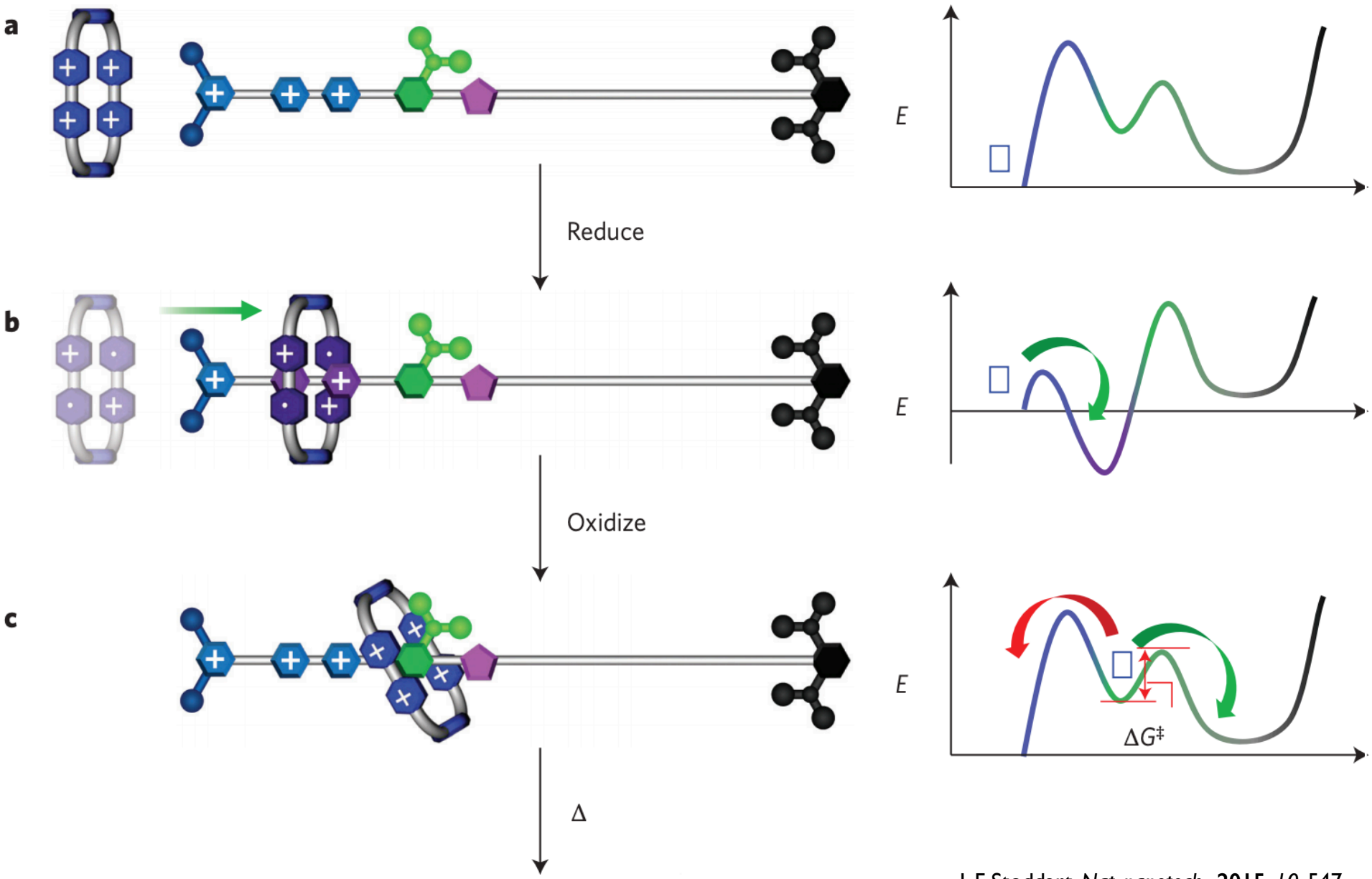
1st generation small-molecule walker:
- takes 1.4 nm steps
- takes one step per acid-base/redox oscillation
- mean 37 steps before dissociating
- 21 atom walker unit
- doesn't carry cargo (yet)
- requires sequential change of conditions (at present)
- walks along four-foothold track (so far)

An Artificial Molecular Pump



J. F. Stoddart, *Nat. nanotech.*, **2015**, *10*, 547

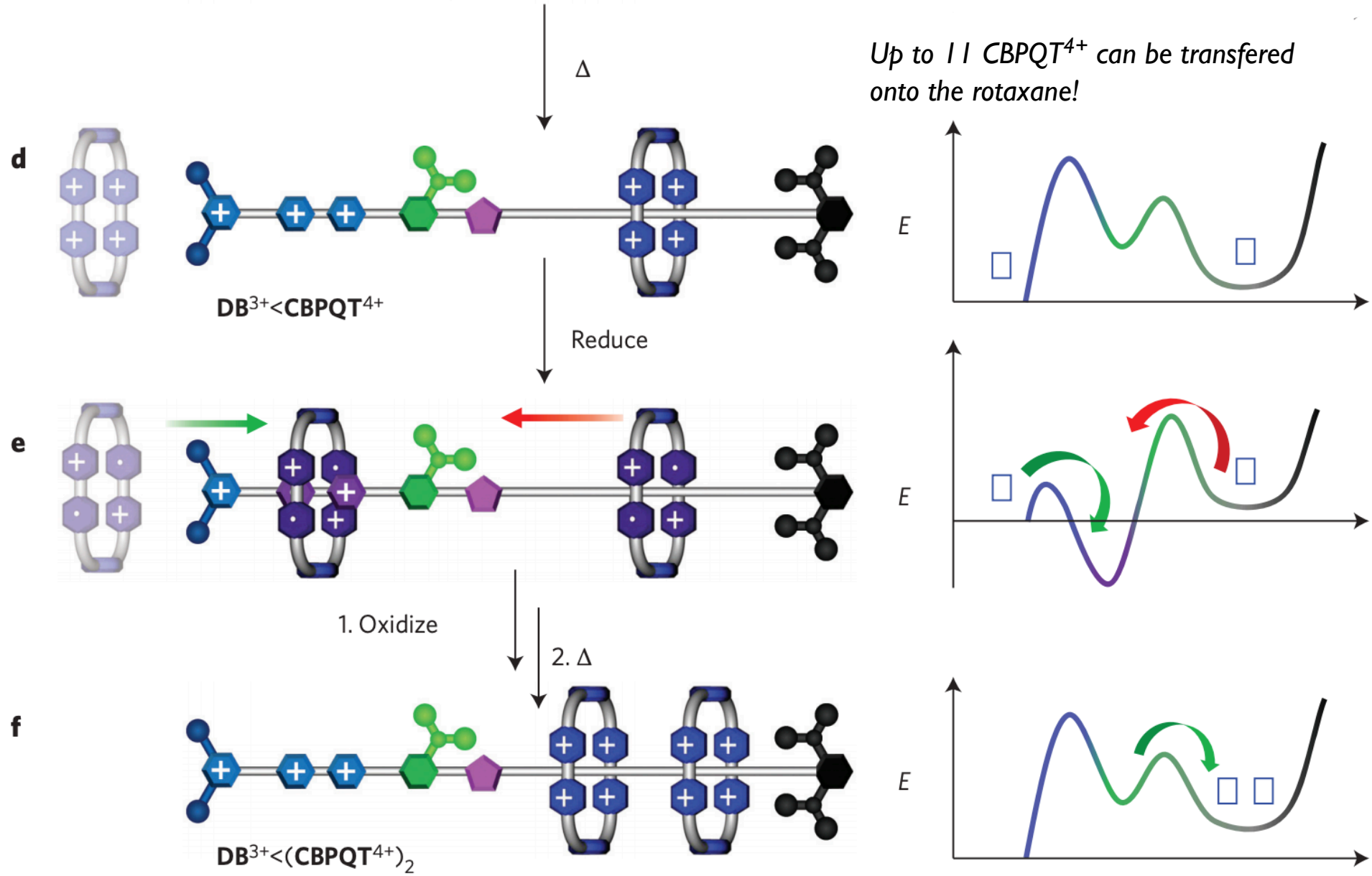
An Artificial Molecular Pump



J. F. Stoddart, *Nat. nanotech.*, **2015**, *10*, 547

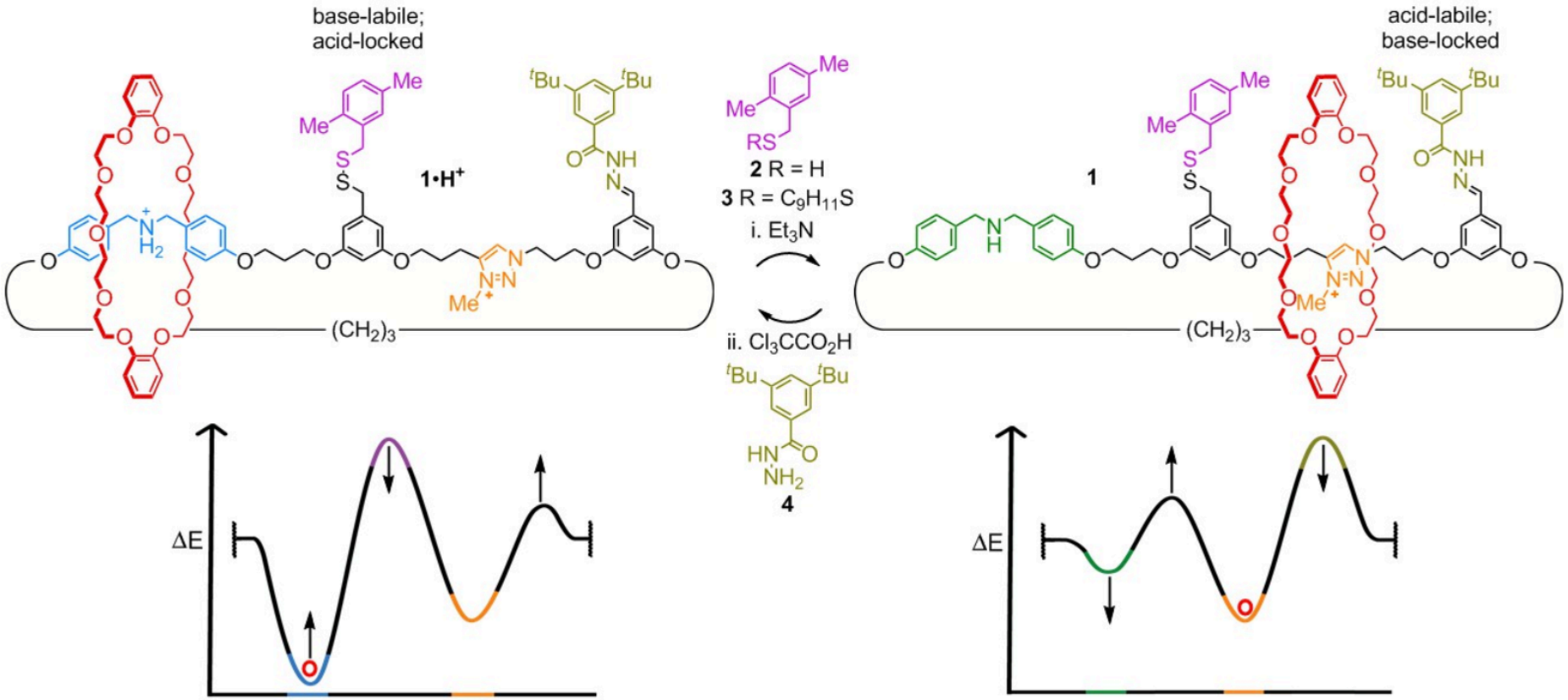
An Artificial Molecular Pump

Up to 11 CBPQT^{4+} can be transfered onto the rotaxane!

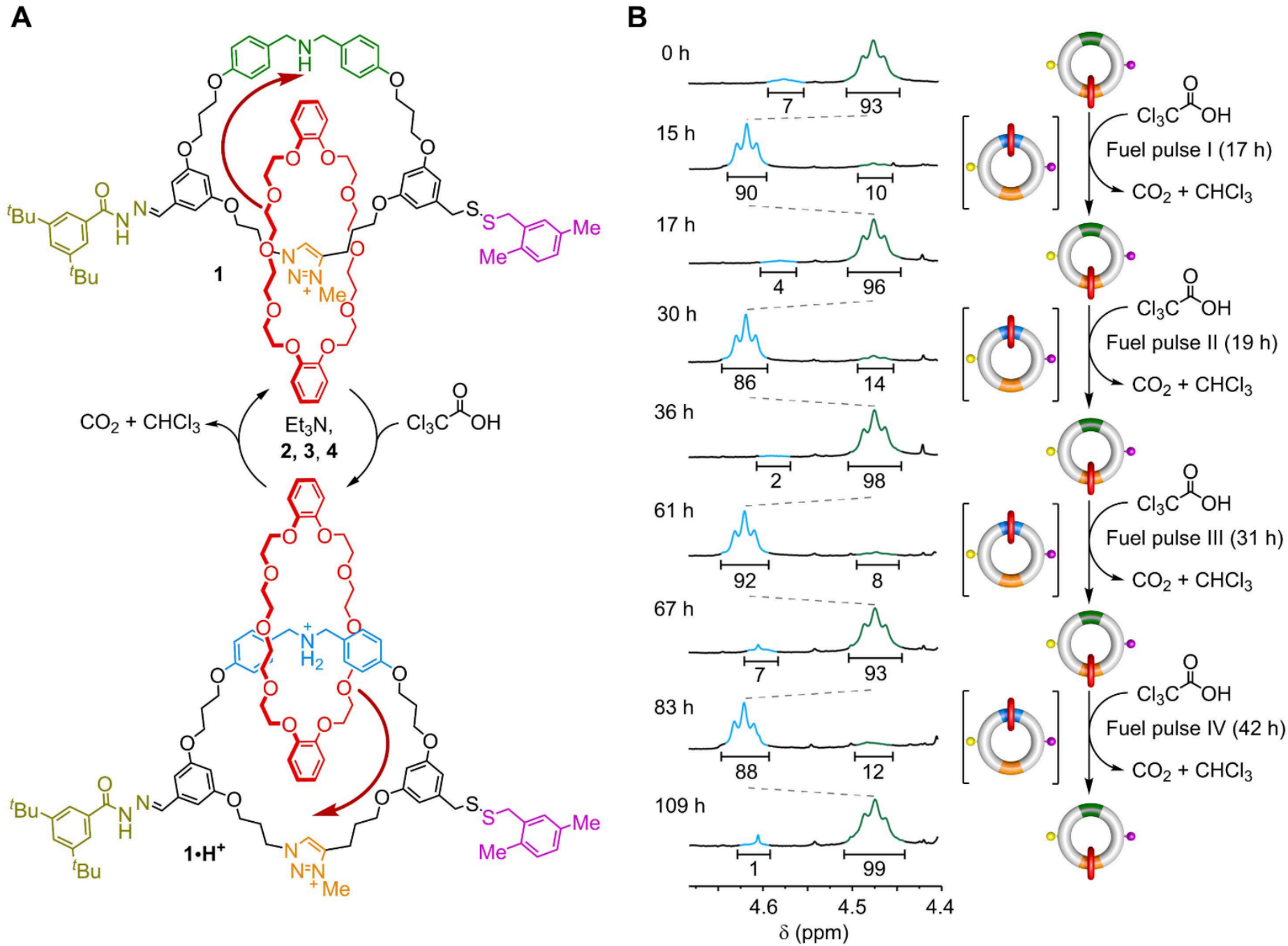


J. F. Stoddart, *Nat. nanotech.*, **2015**, *10*, 547

Rotary Molecular Motors Driven by Pulses of a Chemical Fuel

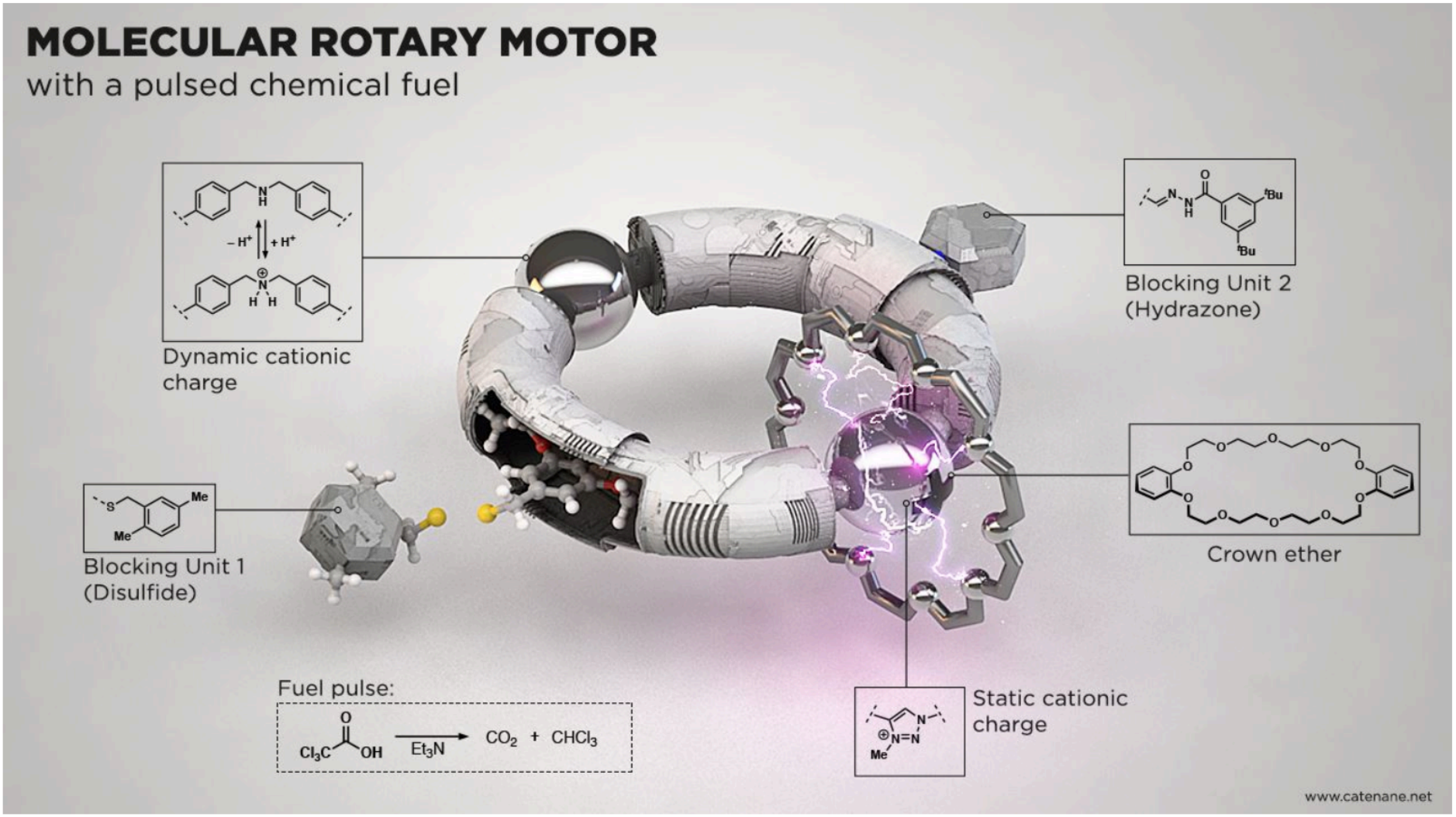


D.A. Leigh, Science, **2017**, *358*, 340



D.A. Leigh, Science, **2017**, *358*, 340

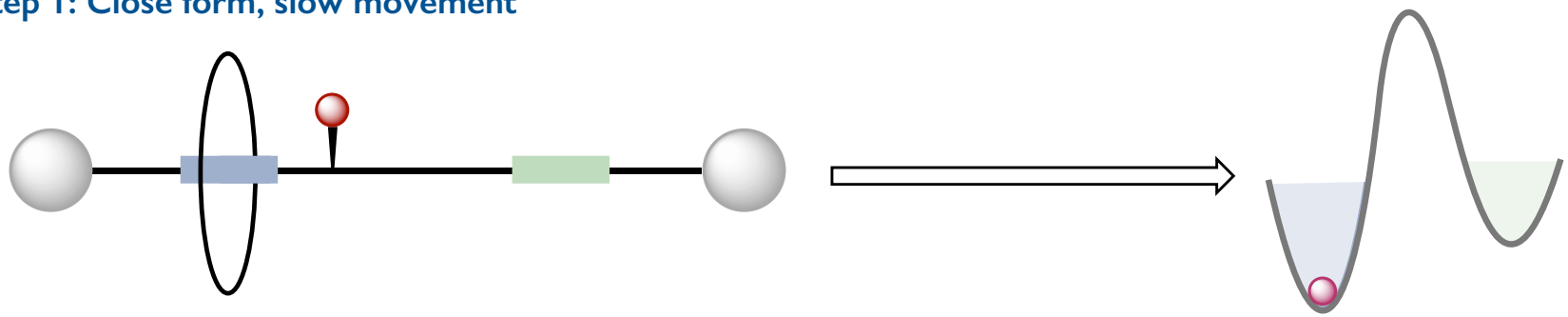
Rotary Molecular Motors Driven by Pulses of a Chemical Fuel



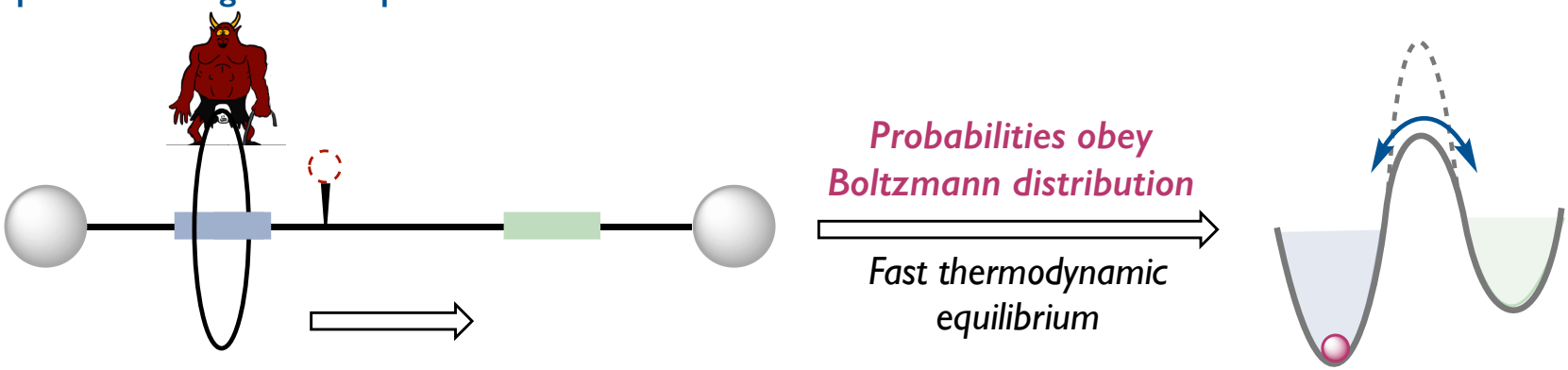
D.A. Leigh, Science, **2017**, *358*, 340

A Molecular Information Ratchet — No Change of the Relative Affinity

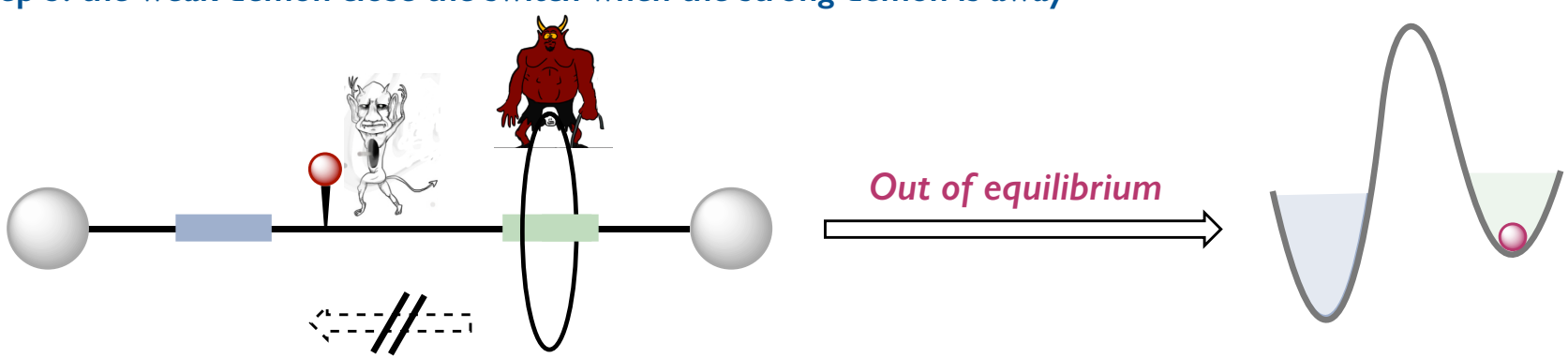
Step 1: Close form, slow movement



Step 2: the strong demon open the switch when close to it

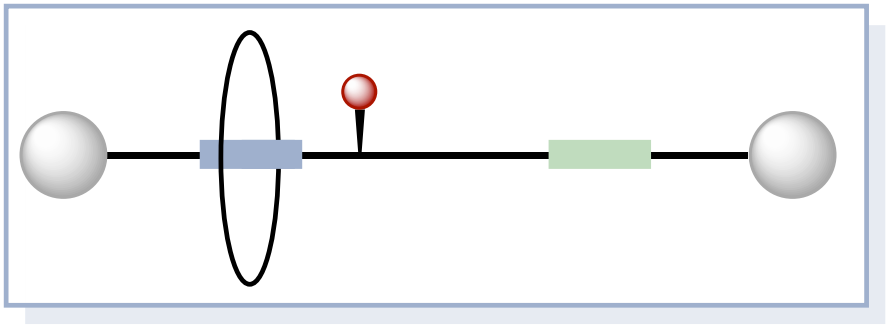


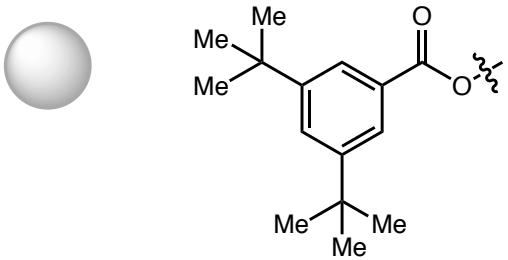
Step 3: the weak demon close the switch when the strong demon is away

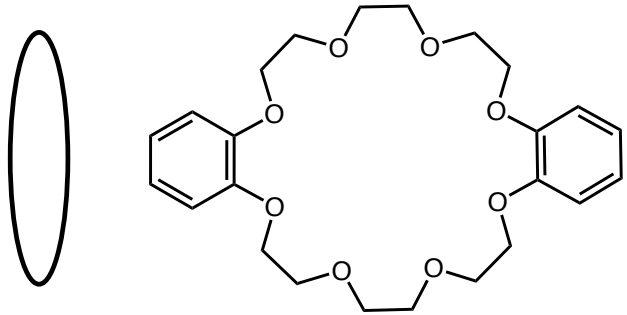


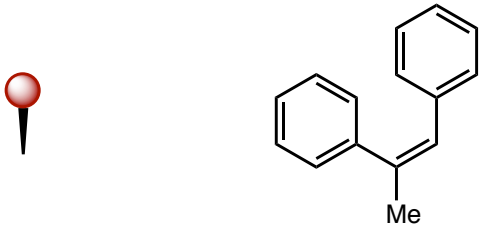
D. A. Leigh, *Nature*, **2007**, *445*, 523

A Molecular Information Ratchet — No Change of the Relative Affinity

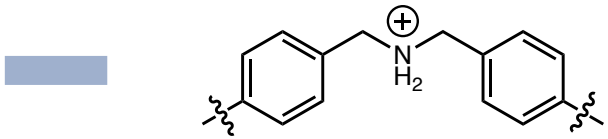


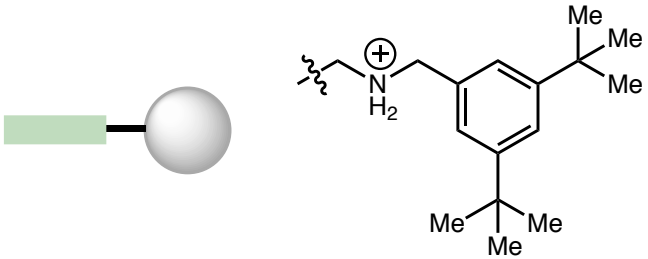


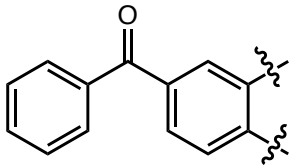




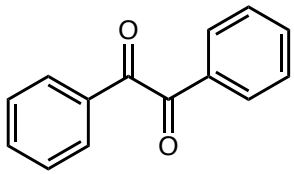
Z: "close" form
E: "open" form







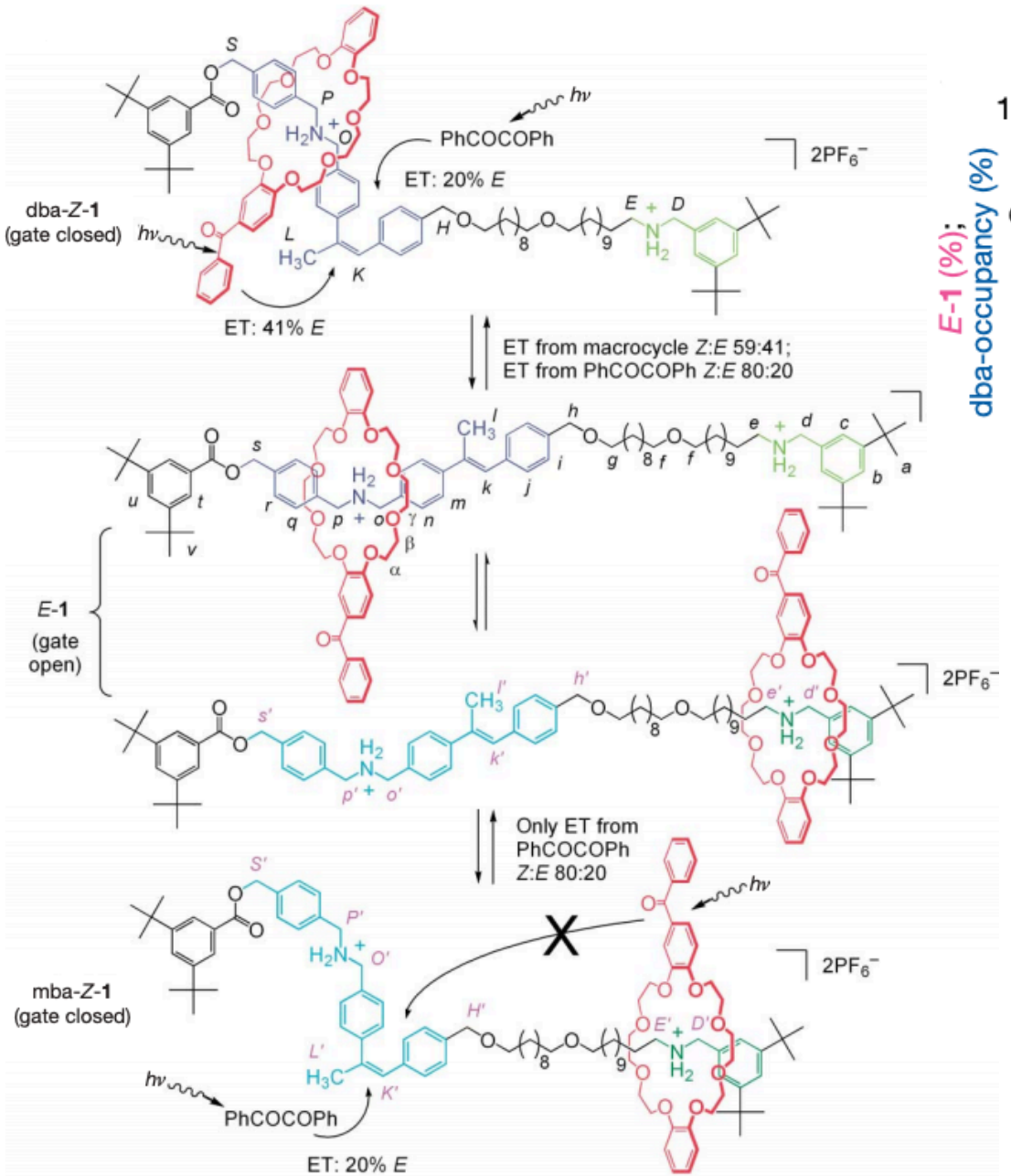
Photostationary state: 59% Z, 41% E

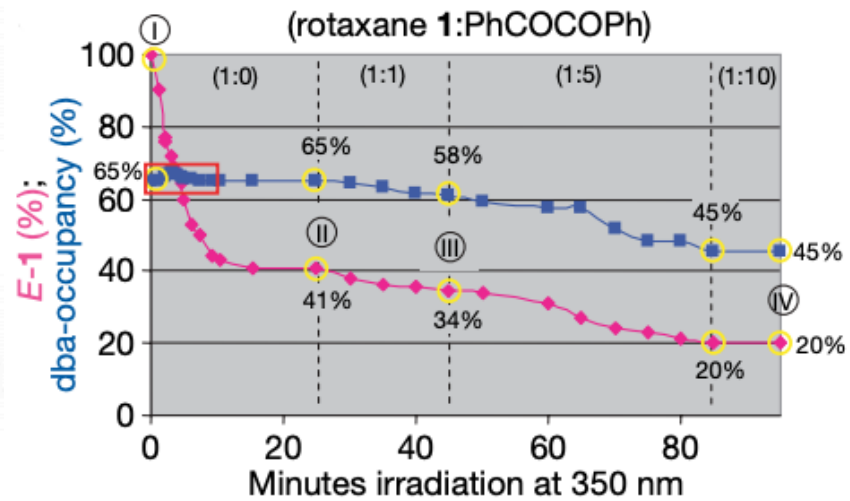


Photostationary state: 80% Z, 20% E

D. A. Leigh, *Nature*, **2007**, *445*, 523

A Molecular Information Ratchet — No Change of the Relative Affinity





$$\Delta G = Nk_B T\left[x_1 \ln\frac{x_1}{y_1} + (1-x_1)\ln\frac{(1-x_1)}{(1-y_1)}\right]$$

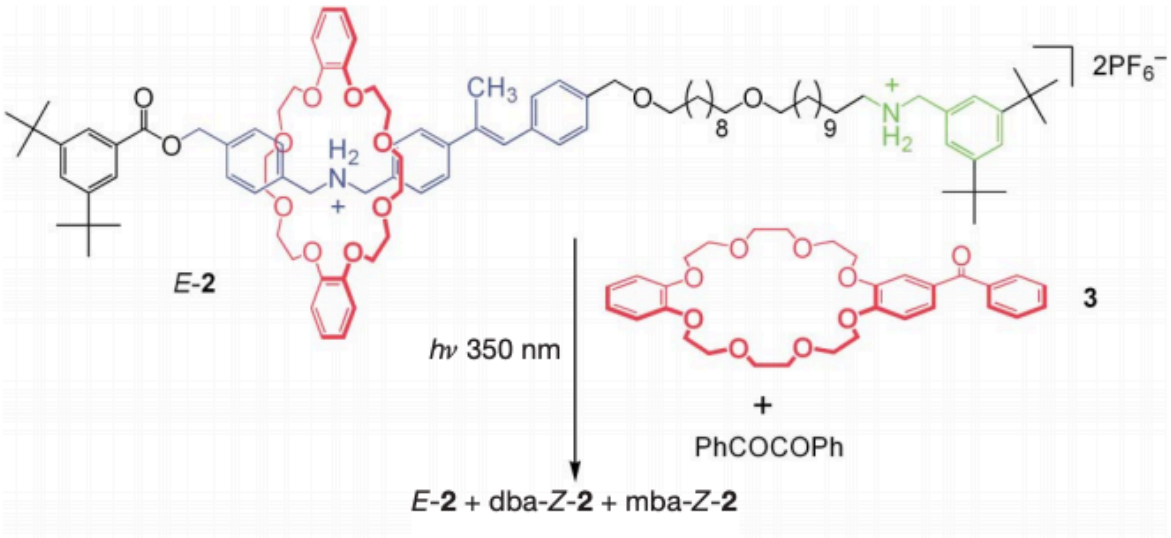
$x_1 = 0.45$; $y_1 = 0.65$

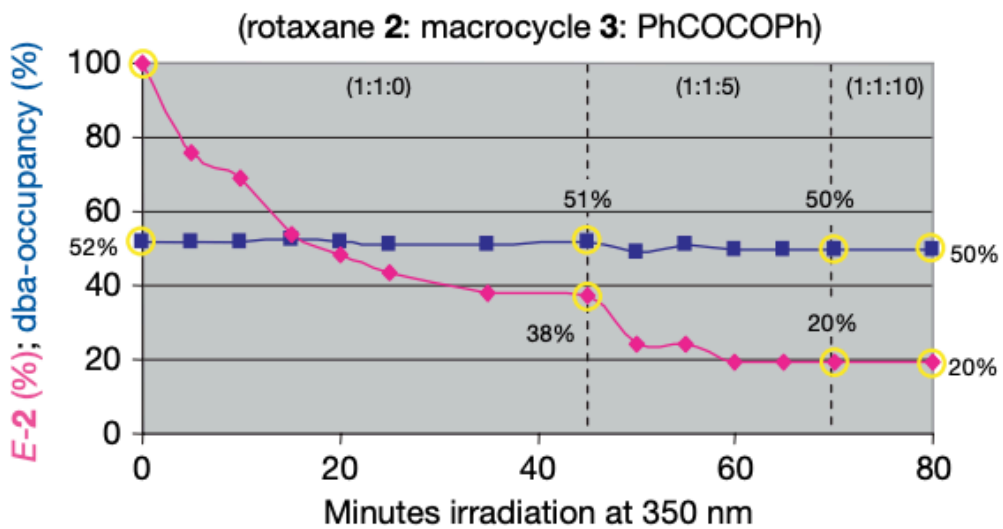
ΔG = 49 kcal/mol

Light-driven information ratchet.

D.A. Leigh, *Nature*, **2007**, *445*, 523

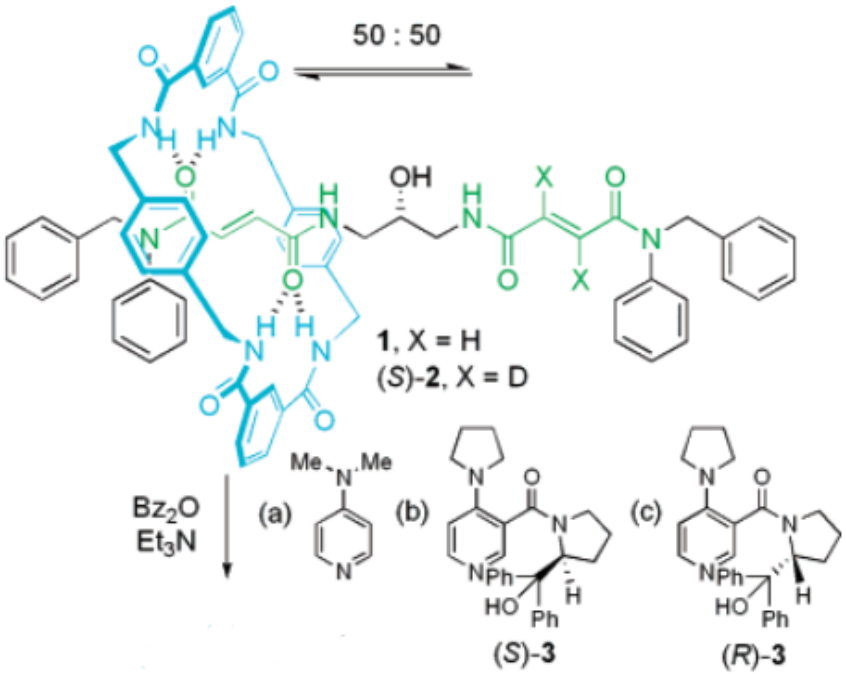
A Molecular Information Ratchet — No Change of the Relative Affinity



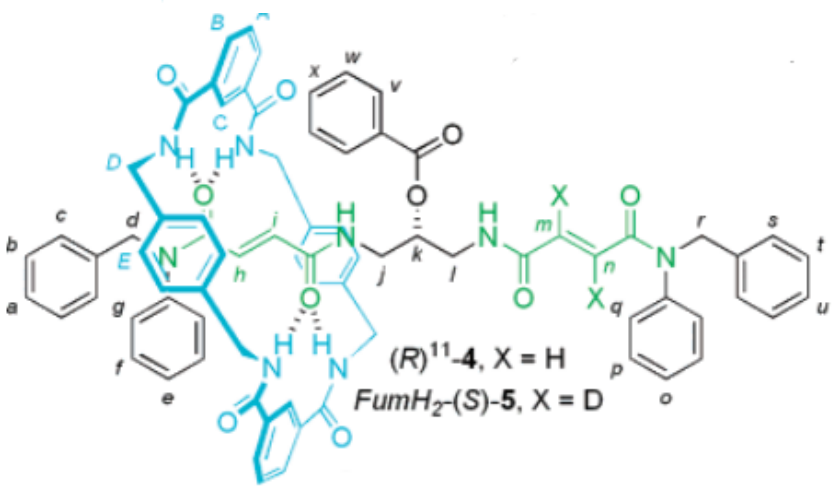


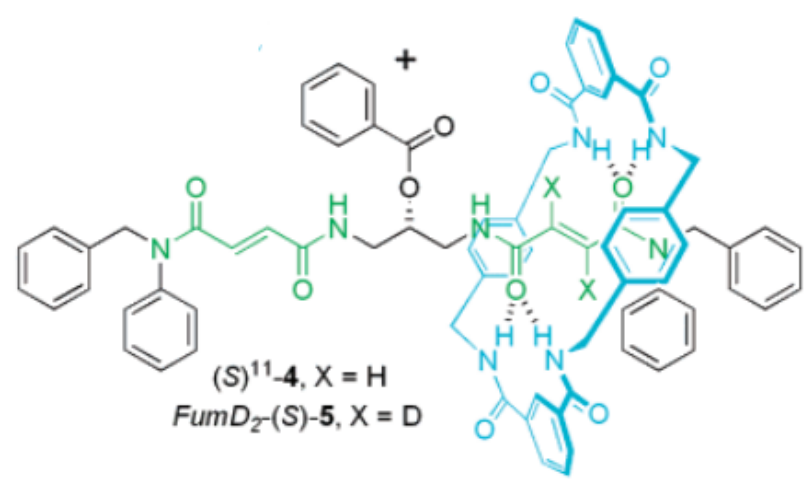
D.A. Leigh, *Nature*, **2007**, *445*, 523

A Chemically-Driven Molecular Information Ratchet



Substrate	Conditions	Product
1	(a)	(*R*)-**4**:(*S*)-**4** 50:50
1	(b)	(*R*)-**4**:(*S*)-**4** 33:67
(*S*)-**2**	(a)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 50:50
(*S*)-**2**	(b)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 33:67
(*S*)-**2**	(c)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 67:33

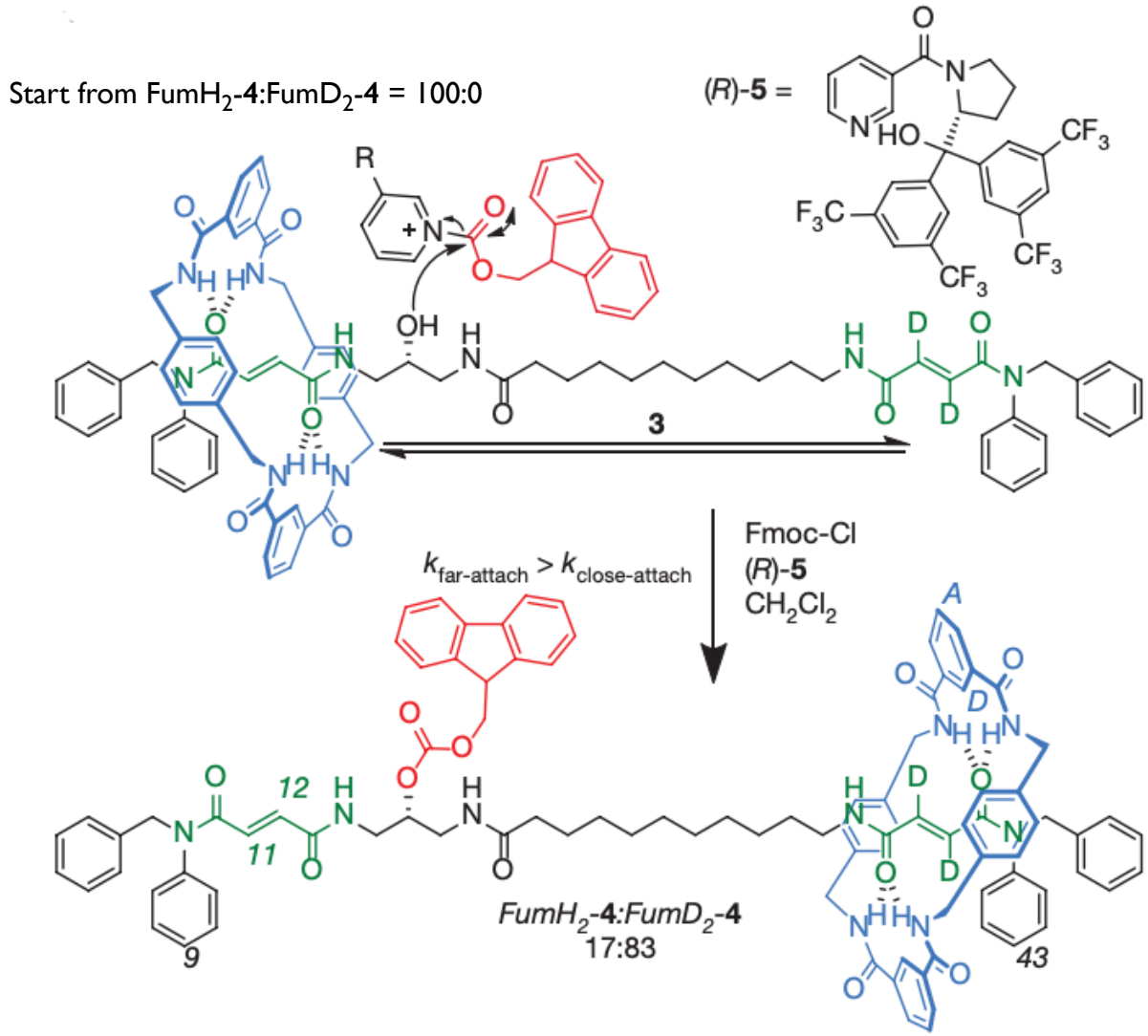




D. A. Leigh, A. M. Z. Slawin, *J. Am. Chem. Soc.*, **2008**, *130*, 1836

An Autonomous Chemically Fuelled Small Molecule Motor

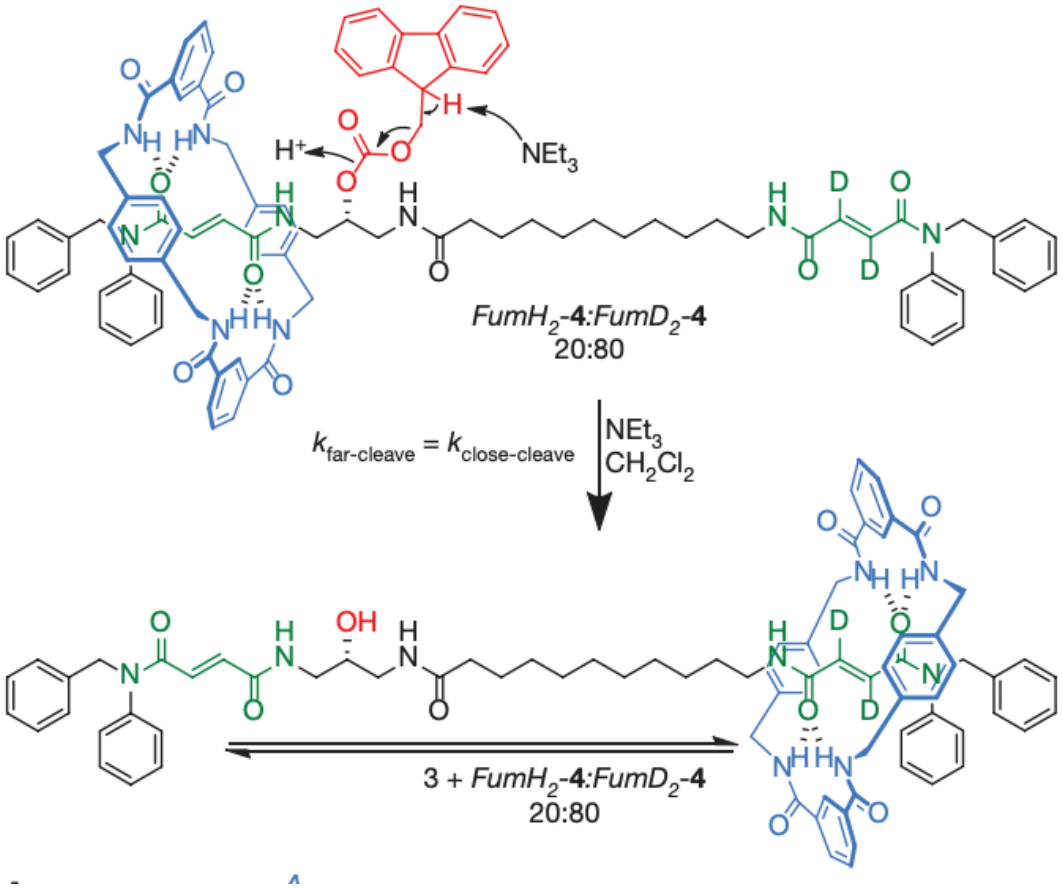
Component 1: biased Fmoc attachement



D.A. Leigh, *Nature*, **2016**, *534*, 235

An Autonomous Chemically Fuelled Small Molecule Motor

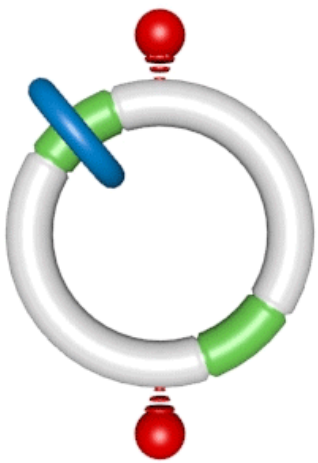
Step 11: unbiased Fmoc cleavage

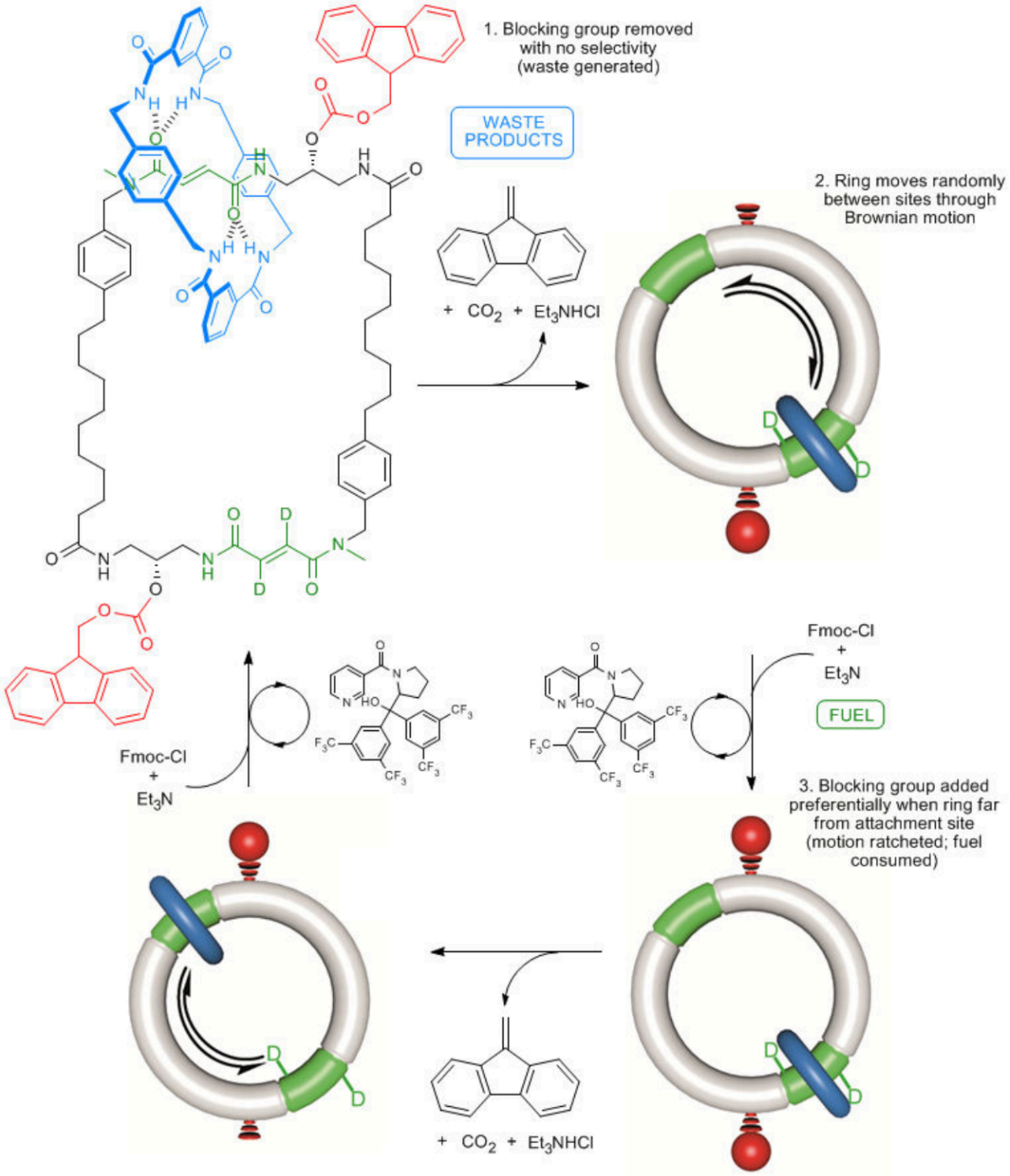


Recovered protected rotaxane has same $FumH_2$-**4**:$FumD_2$-**4** = 20:80

D.A. Leigh, *Nature*, **2016**, *534*, 235

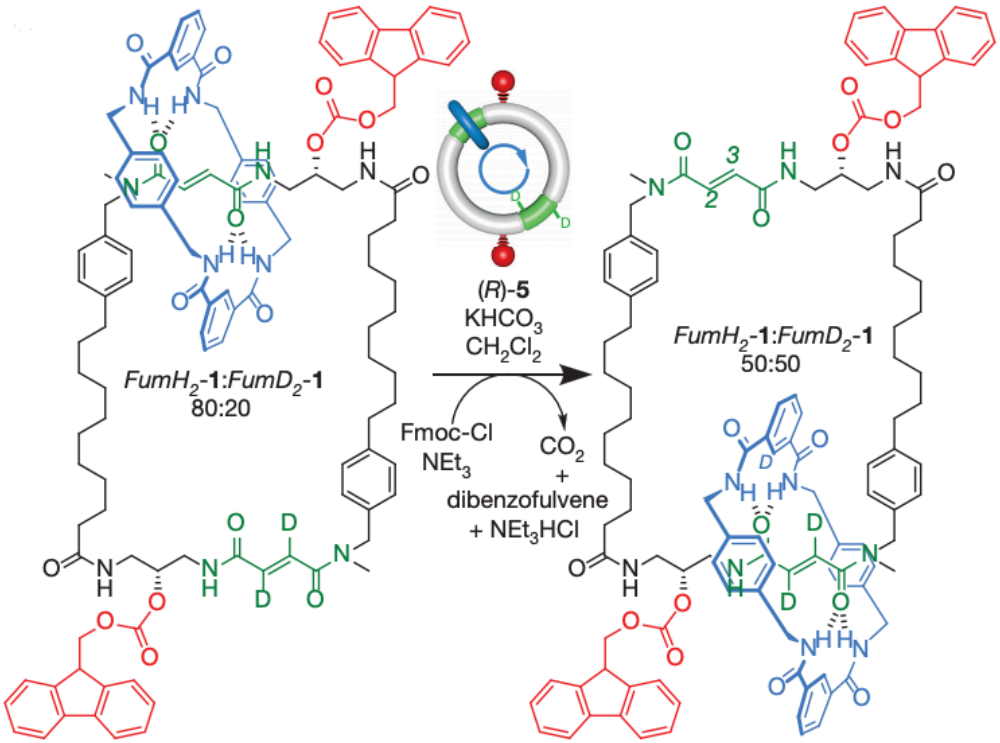
Step 11: Connect to form [2]catenane



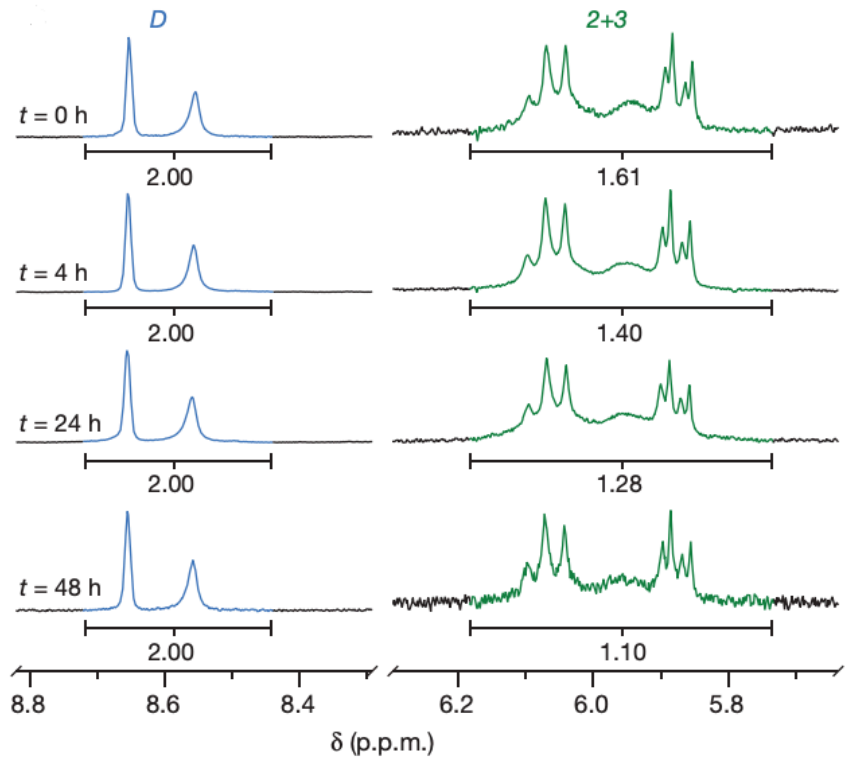


An Autonomous Chemically Fuelled Small Molecule Motor

Experimental observation

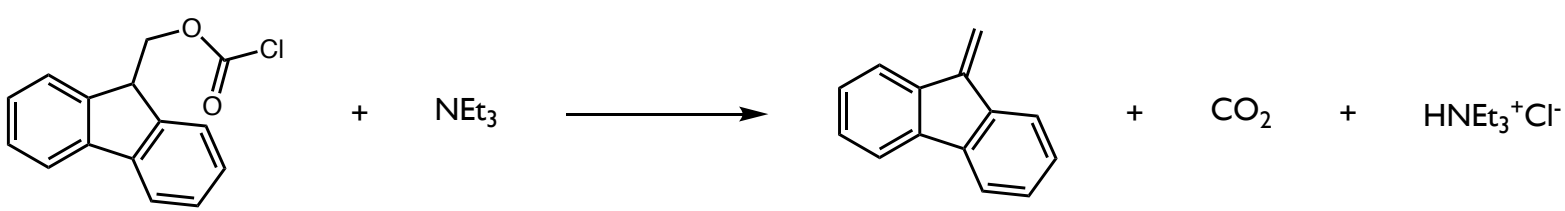


Hydrogen-bonded fumaramide H/D **2+3**



Estimated rotation time ~12h every 360°

Net reaction (energy source — 2 molecule of Fmoc-Cl per 360°)

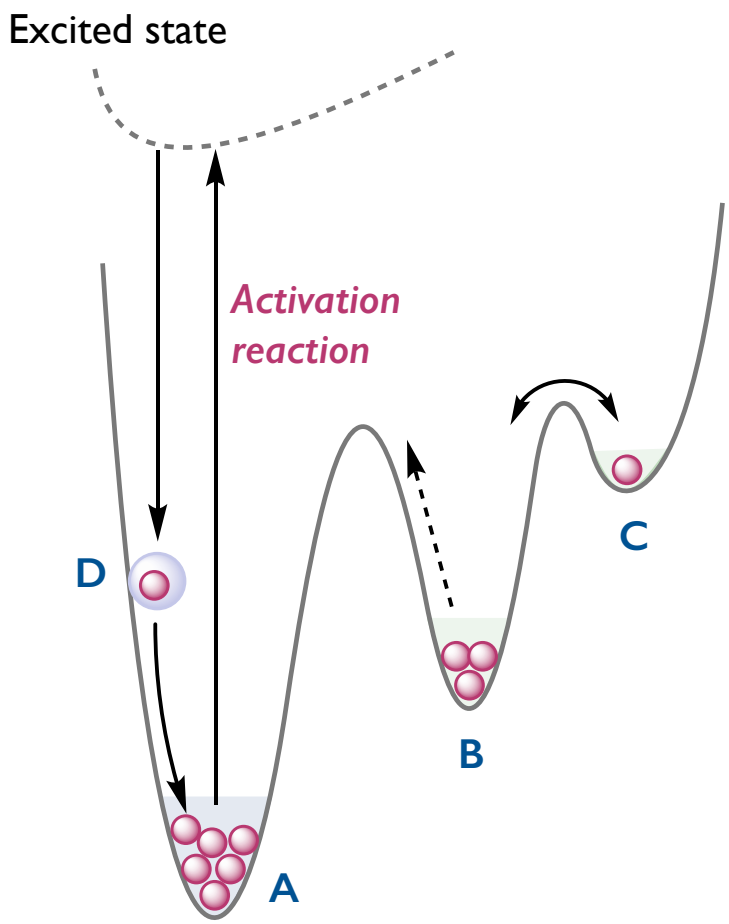


D.A. Leigh, *Nature*, **2016**, *534*, 235

Outline

- Indroduction
- Molecular Motors and Pumps
- Dissipative Out-of Equilibrium Molecular Assembly
- Conclusion

Equilibrium Assembly vs. Dissipative Assembly

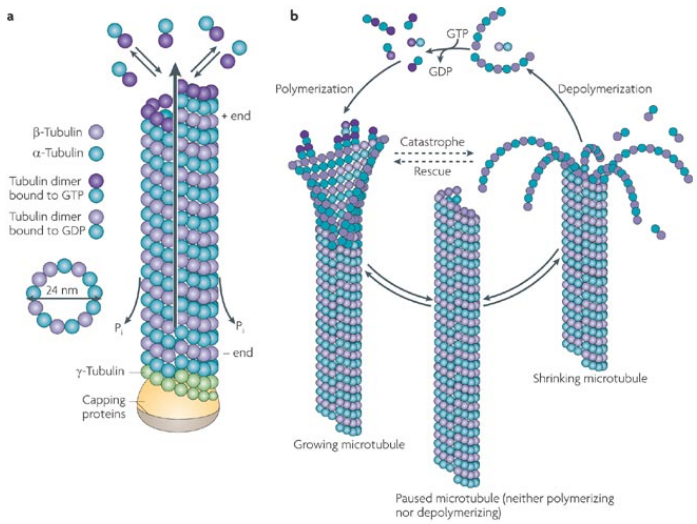


A: Equilibrium assembly. Global minimum. No net flow of energy or matter.

B: Kinetically trapped assembly. Local minimum. Infinite lifetime.

C: Metastable assembly. Finite lifetime.

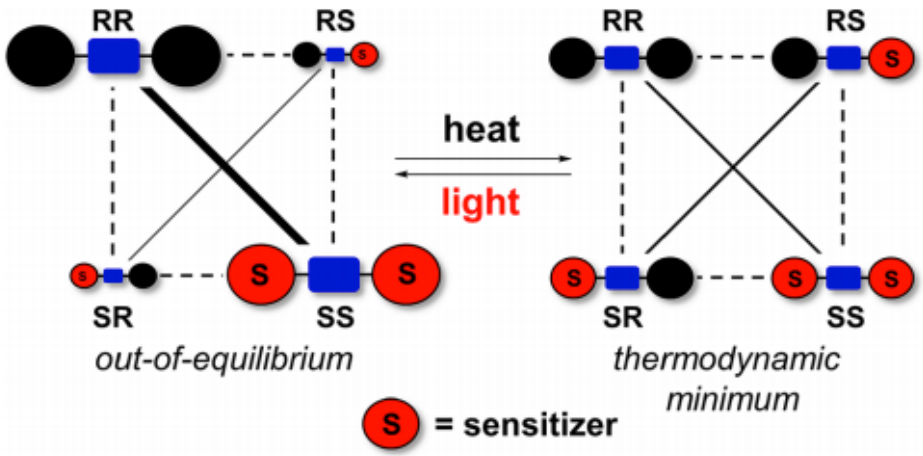
D: Dissipative assembly. Need to be coupled to a chemical reaction or other energy source

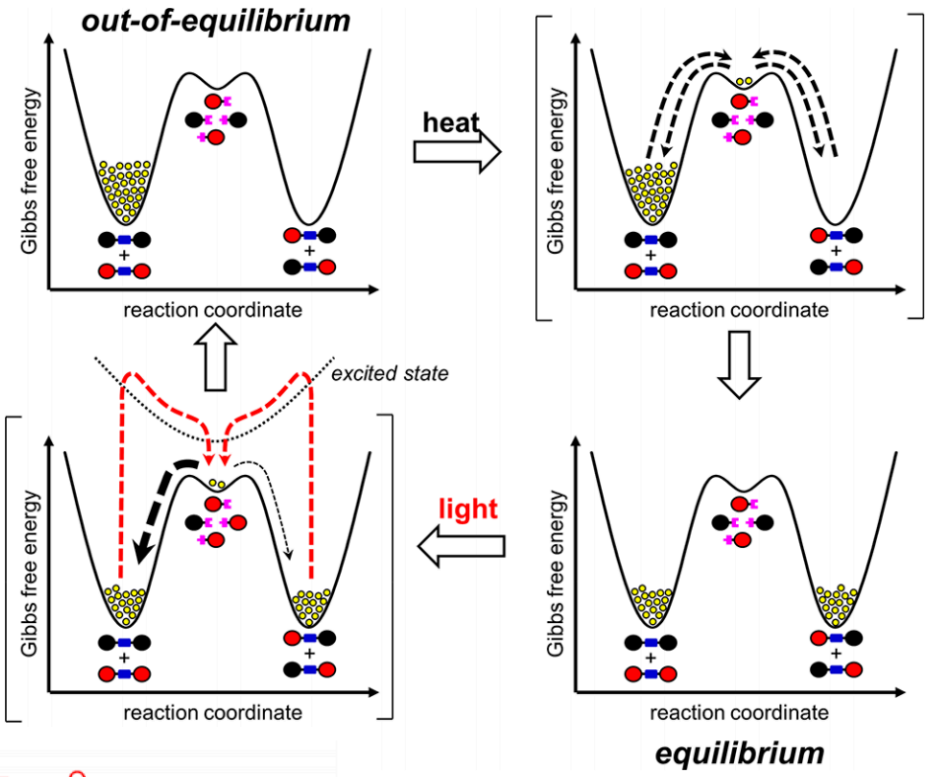


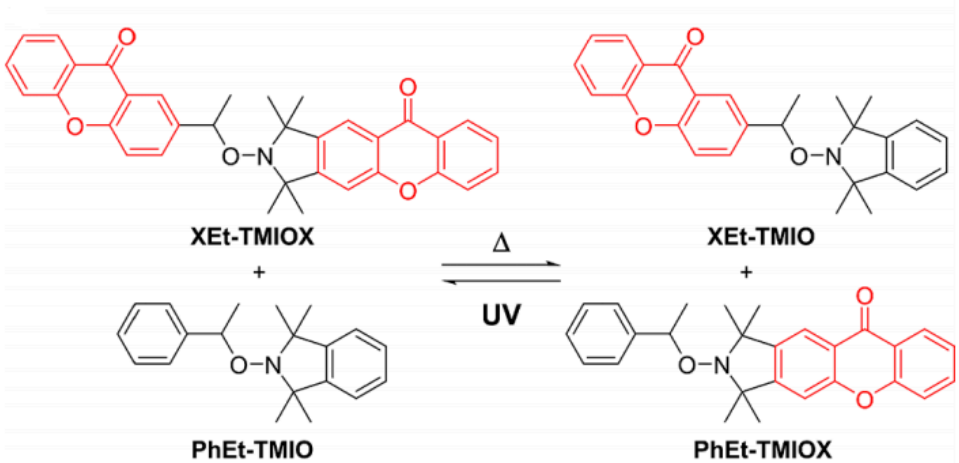
J. H. van Esch, R. Eelkema, J. Boekhoven, *Chem. Soc. Rev.*, **2017**, *46*, 5519
M. Kathan, S. Hecht, *Chem. Soc. Rev.*, **2017**, *46*, 5536

Out-of-Equilibrium Systems Chemistry

The photodynamic covalent bonds shift reaction networks using light energy

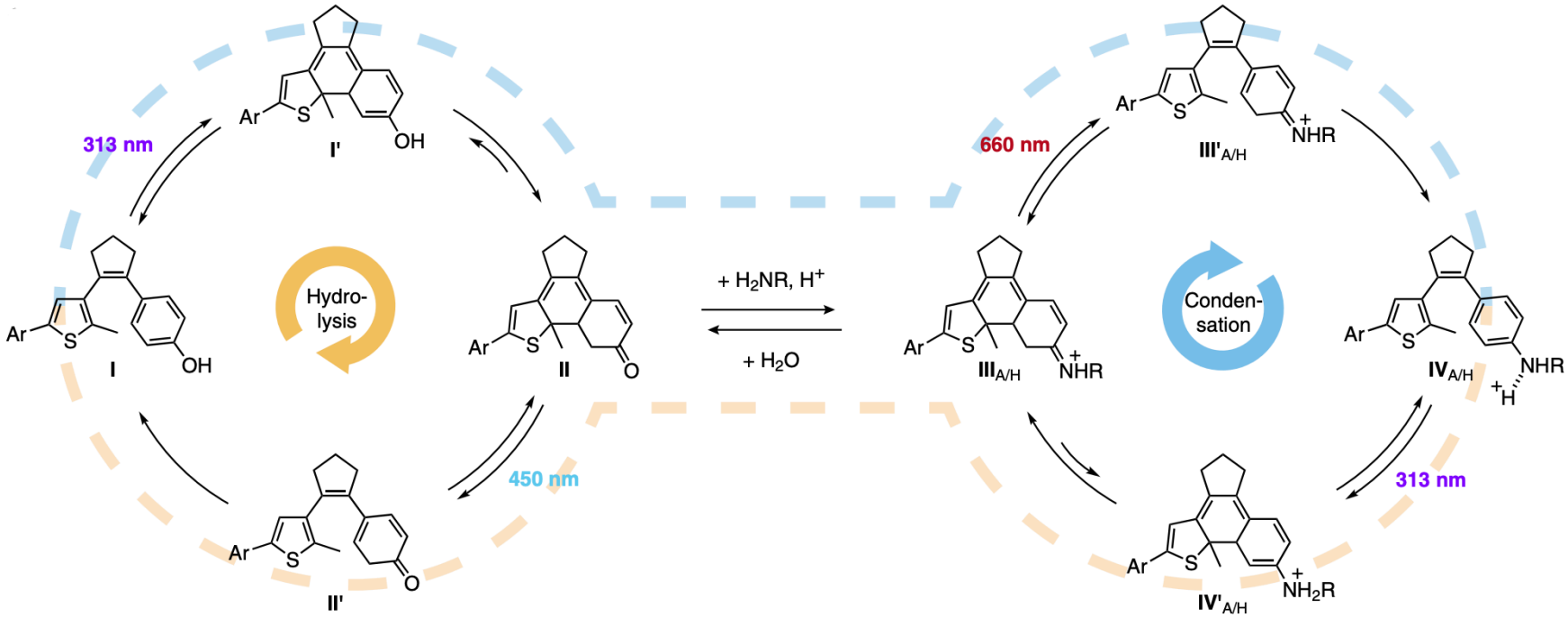


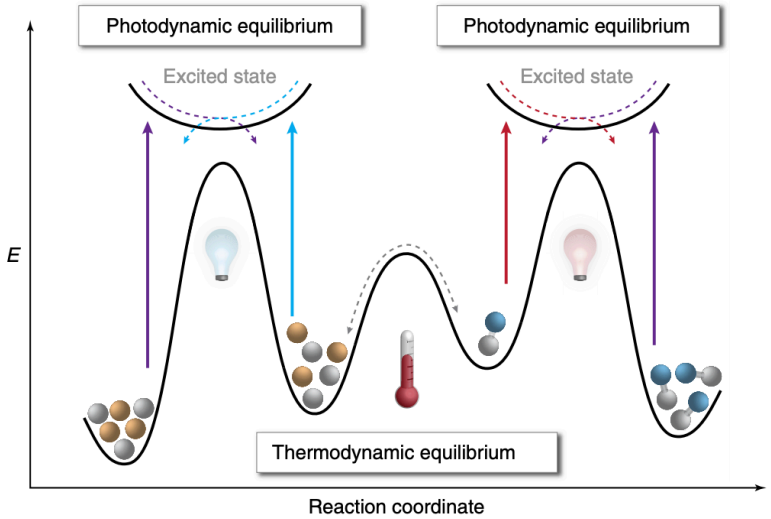




J.-M. Lehn, *J. Am. Chem. Soc*, **2018**, *140*, 7647

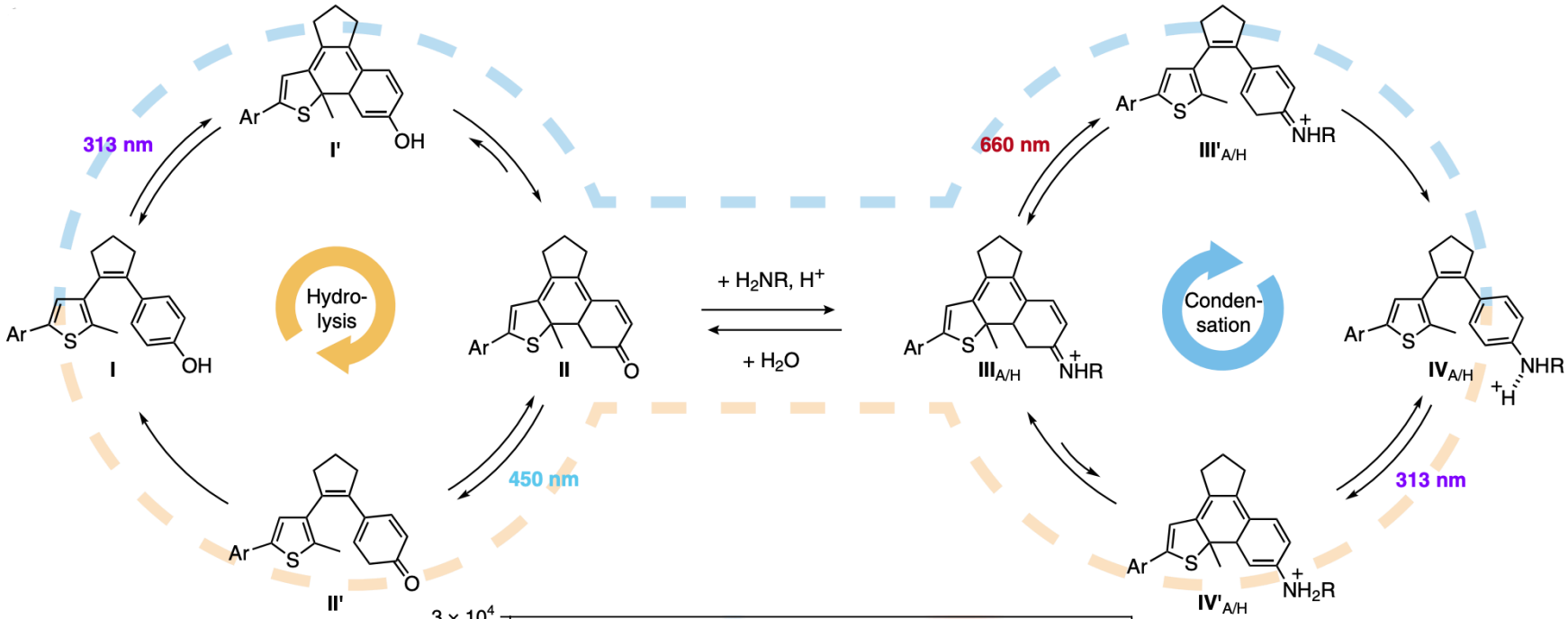
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems





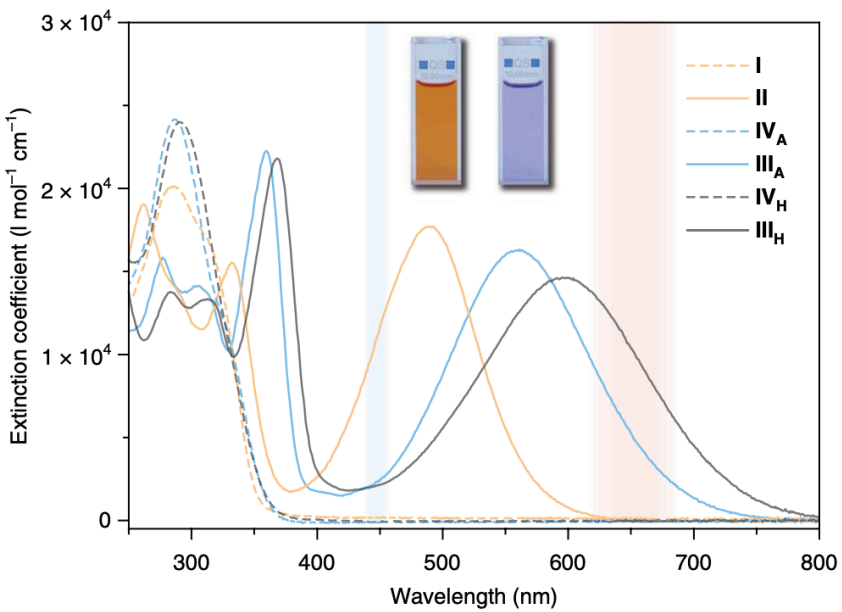
S. Hecht, *Nat. Chem.*, **2018**, *10*, 1031

Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems



Photostationary state distribution:

$$K_{eq}^{\lambda} = \frac{II}{I} = \frac{\varepsilon_{I}^{\lambda} \cdot \Phi_{I \to II}^{\lambda}}{\varepsilon_{II}^{\lambda} \cdot \Phi_{II \to I}^{\lambda}}$$

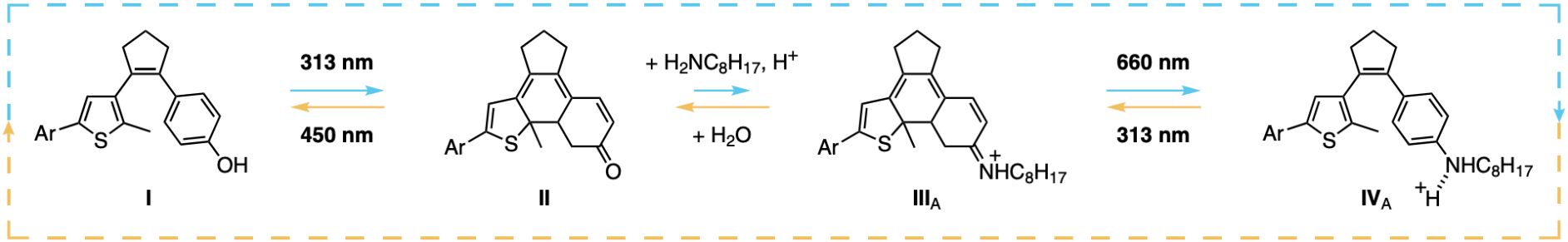


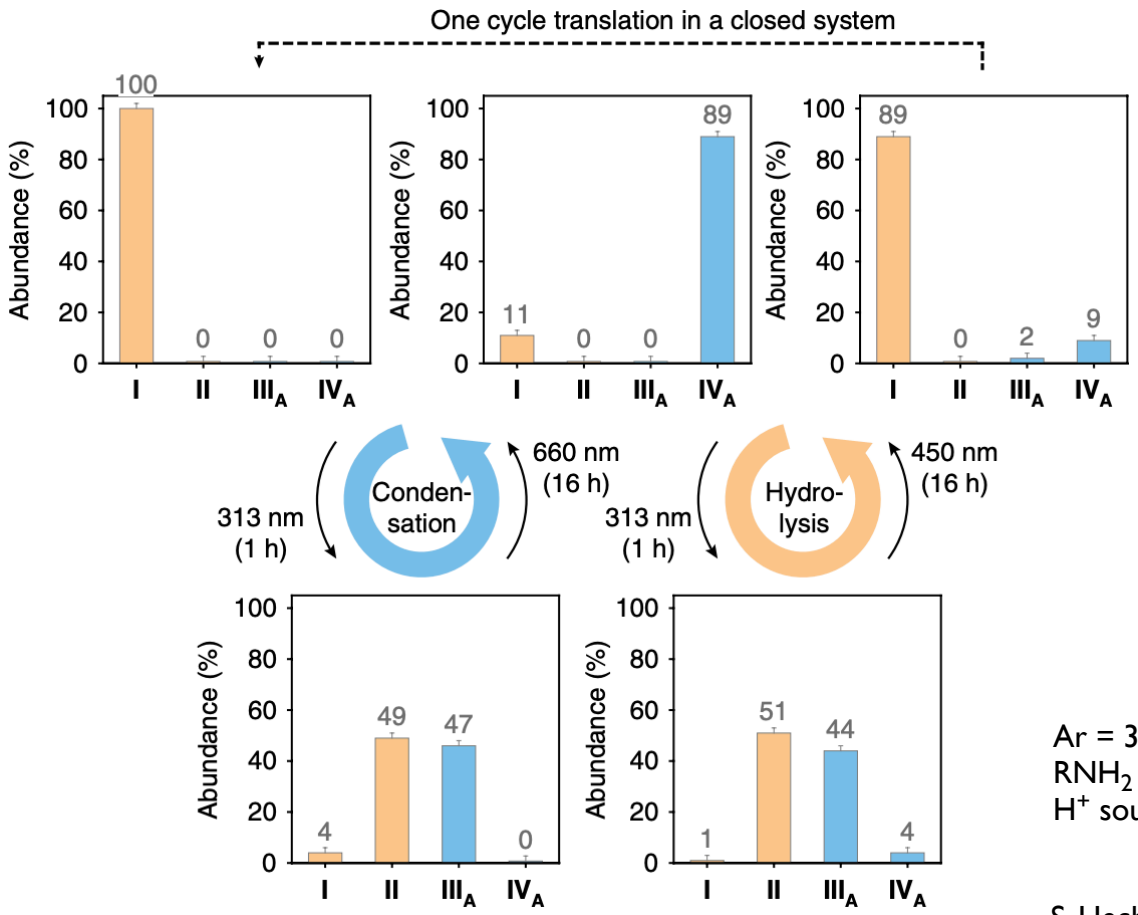
Crucial band separation of 70 nm of $\mathbf{III}_{A/H}$ vs. **II**

Quantum yield of ring opening of **II** is five times higher than $\mathbf{III}_{A/H}$

S. Hecht, *Nat. Chem.*, **2018**, *10*, 1031

Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

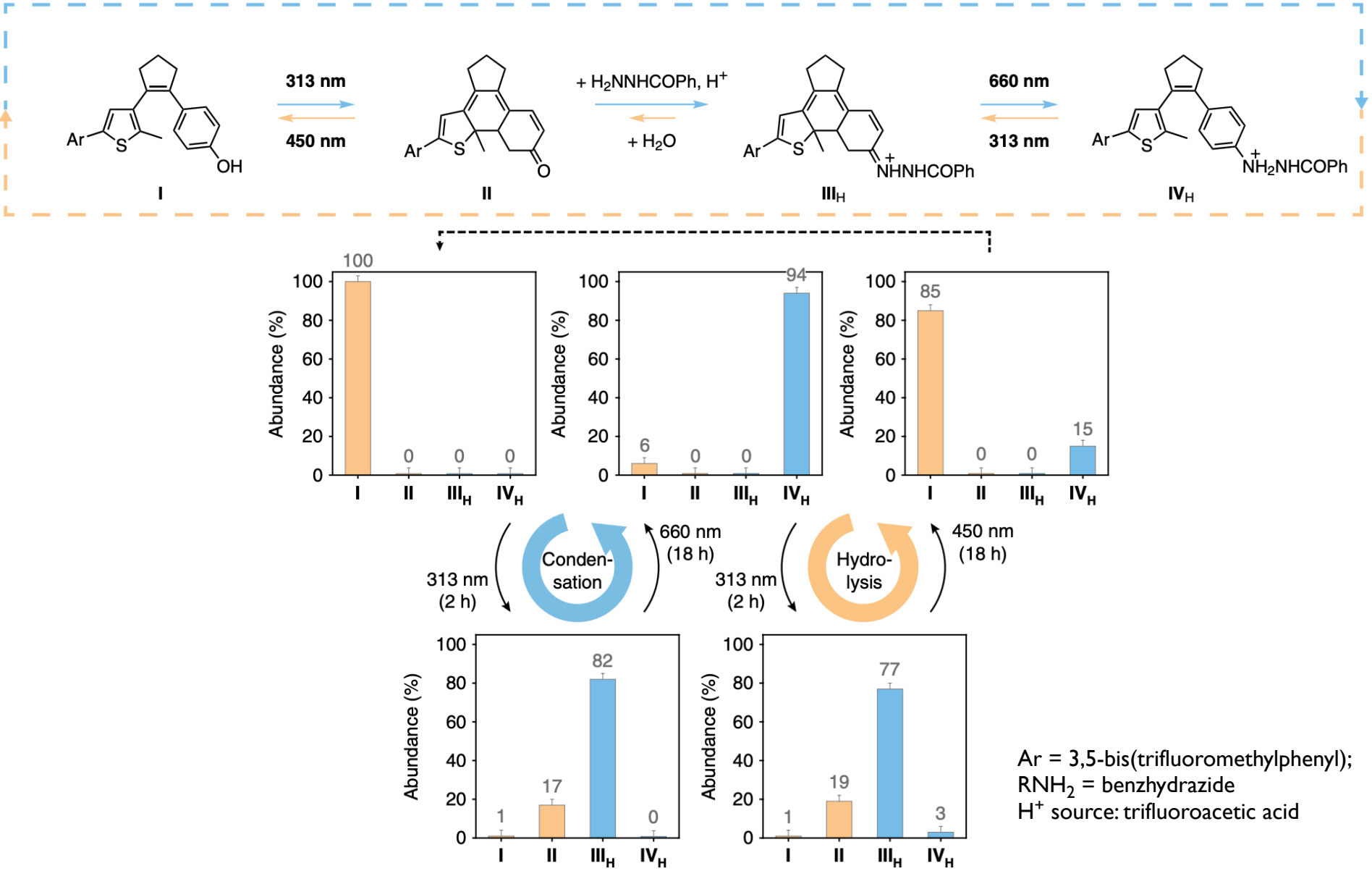




Ar = 3,5-bis(trifluoromethylphenyl);
RNH_2 = octylamine
H^+ source: benzoic acid

S. Hecht, *Nat. Chem.*, **2018**, *10*, 1031

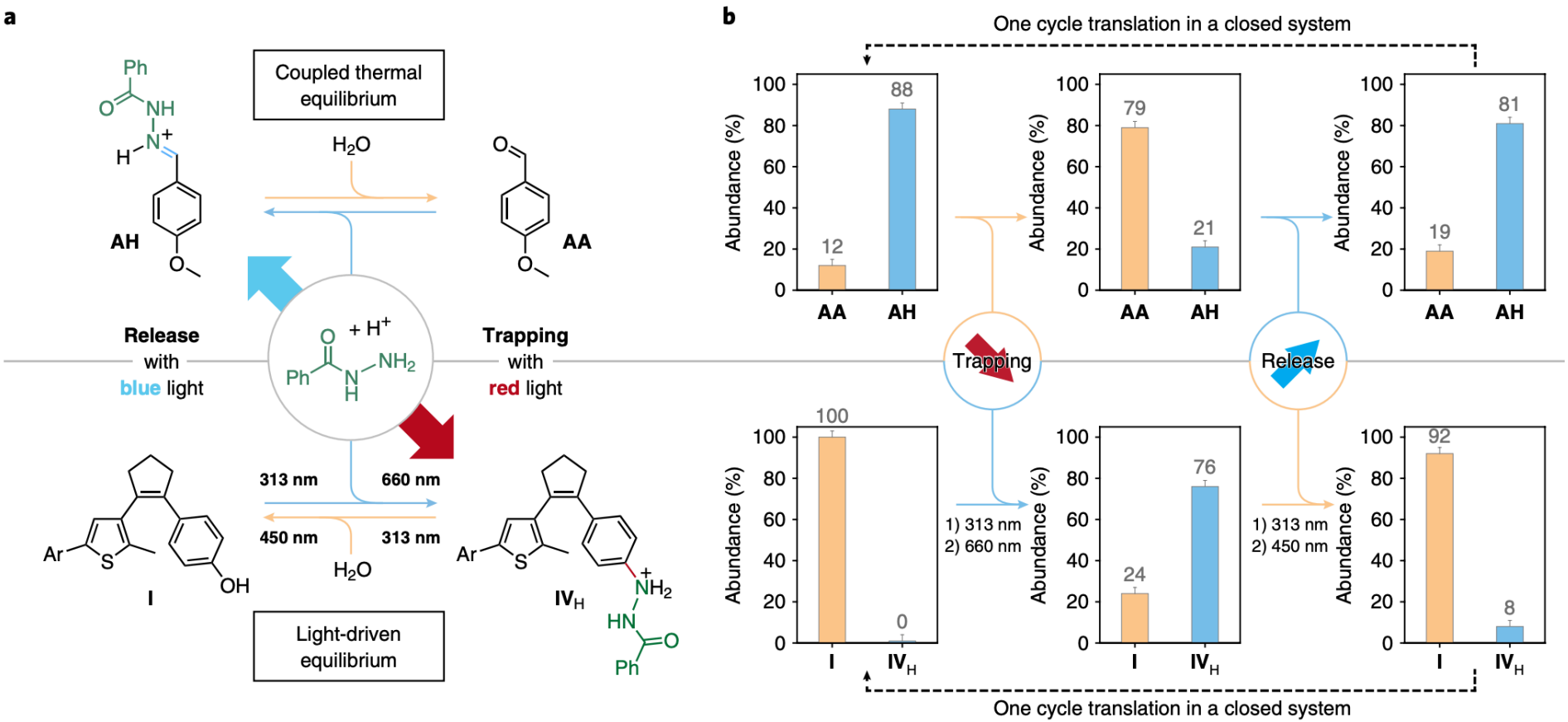
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems



Ar = 3,5-bis(trifluoromethylphenyl);
RNH_2 = benzhydrazide
H^+ source: trifluoroacetic acid

S. Hecht, *Nat. Chem.*, **2018**, *10*, 1031

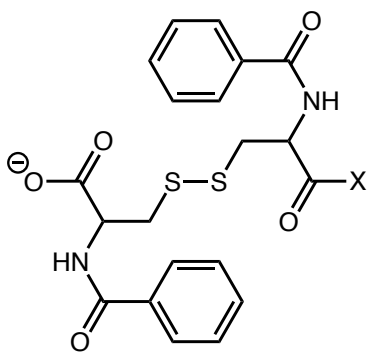
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems



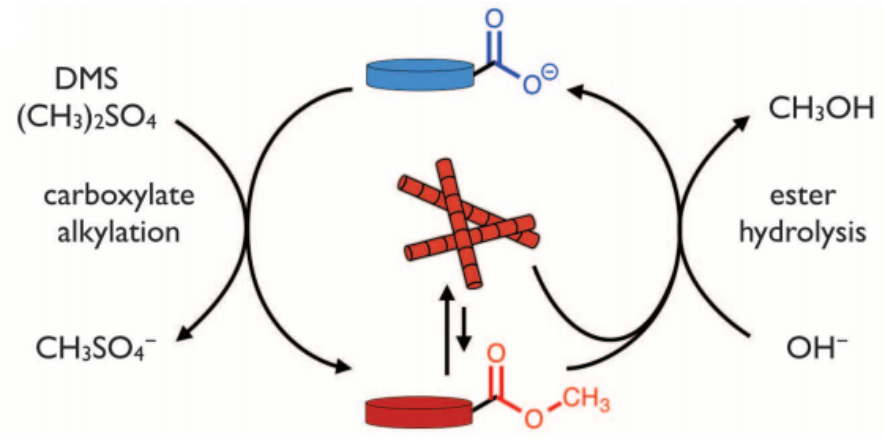
Ar = 3,5-bis(trifluoromethylphenyl);
RNH_2 = benzhydrazide
H^+ source: trifluoroacetic acid

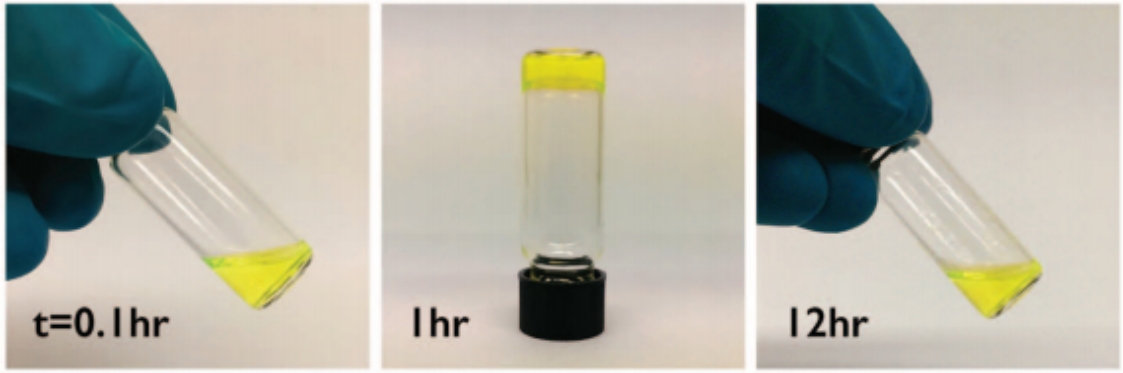
S. Hecht, *Nat. Chem.*, **2018**, *10*, 1031

Transient Assembly of Active Materials Fueled by a Chemical Reaction



1a: X = O^-
1b: X = OMe



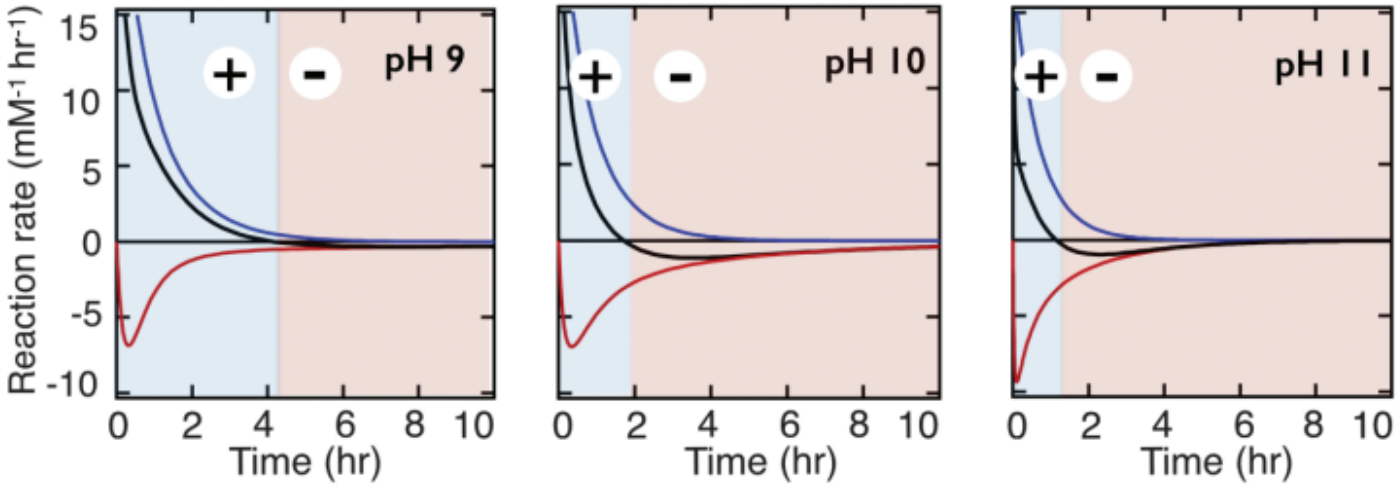


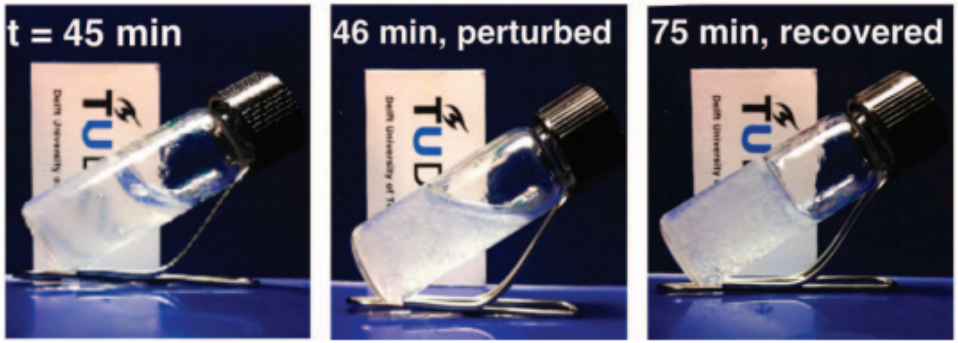
Conditions: pH = 11, $[\mathbf{1a}]_0$ = 50 mM, $[DMS]_0$ = 200 mM, with 1 μM fluorescein for coloring

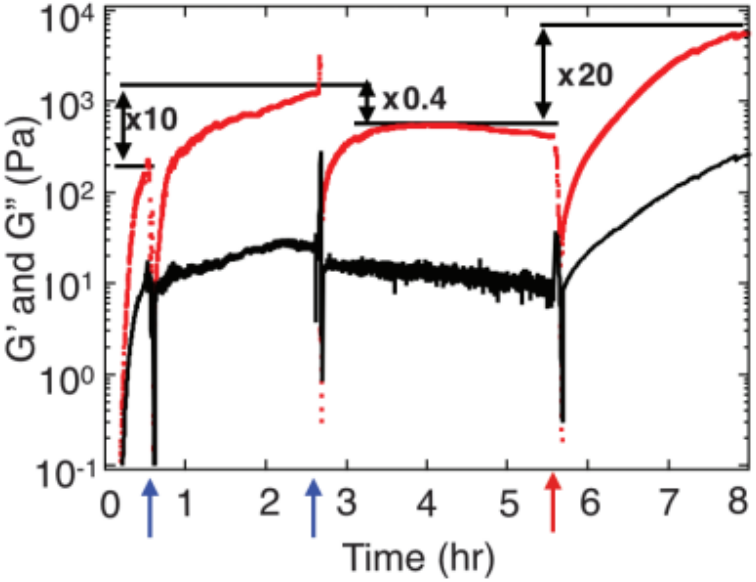
J. Boekhoven, J. H. van Esch, *Science*, **2015**, *349*, 1075

Transient Assembly of Active Materials Fueled by a Chemical Reaction

pH dependent kinetics and self-healing ability

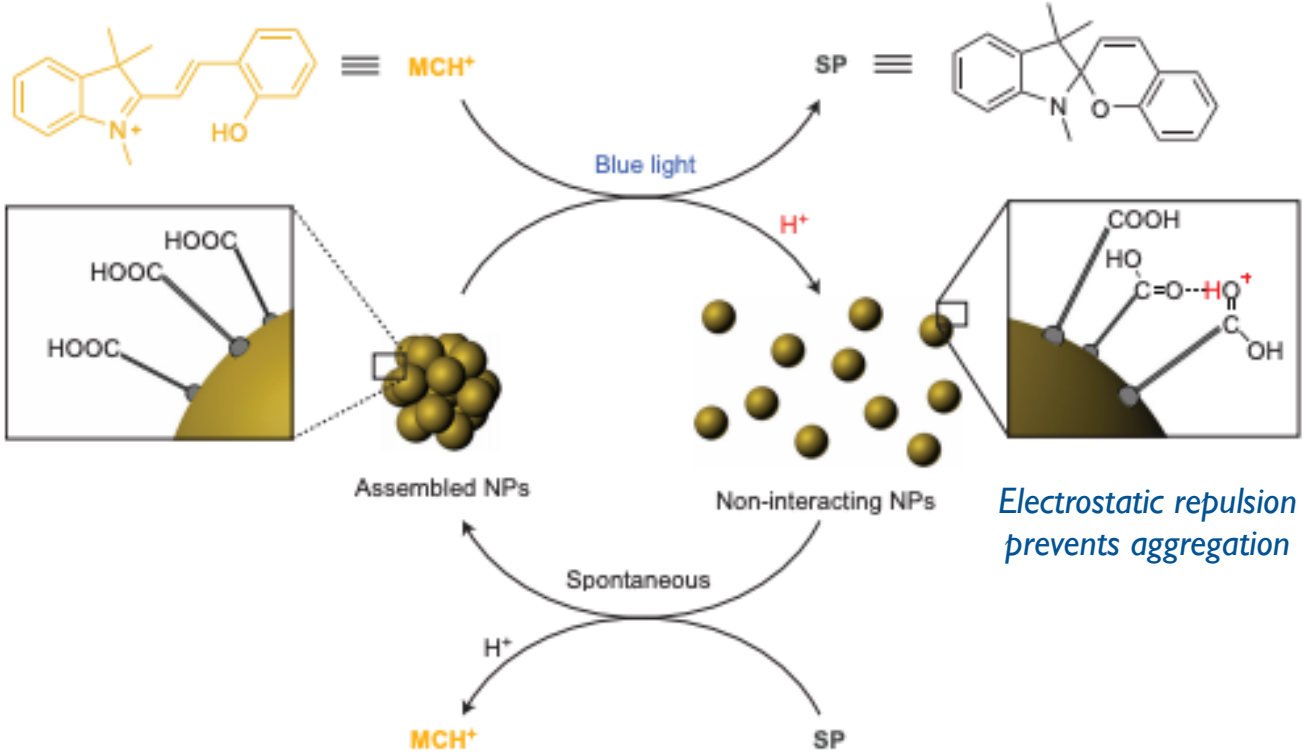


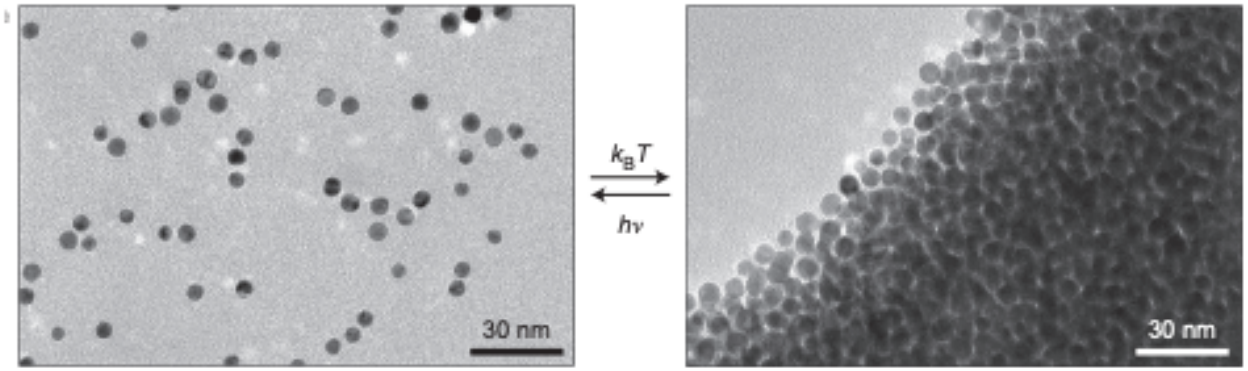




J. Boekhoven, J. H. van Esch, *Science*, **2015**, *349*, 1075

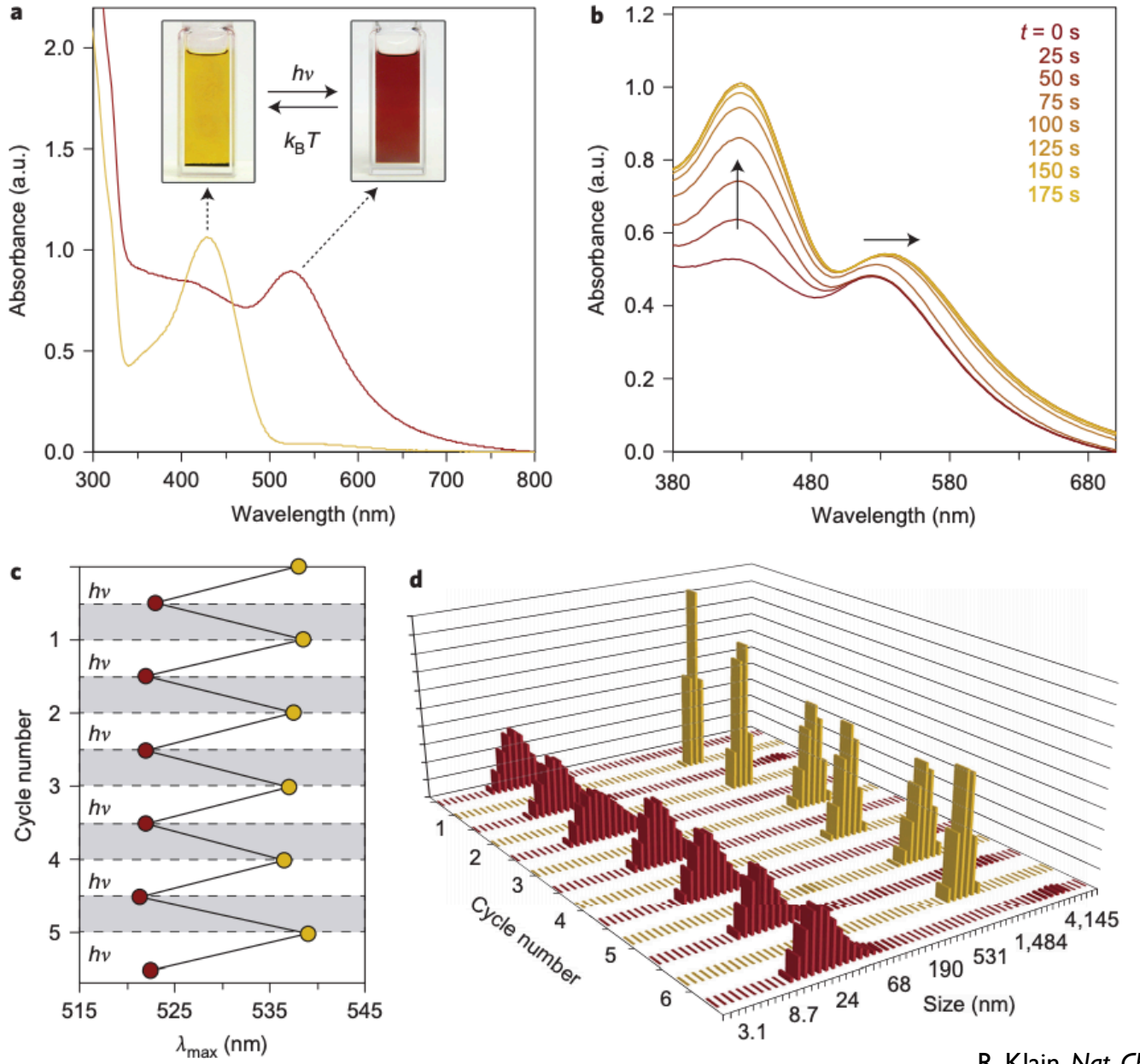
Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles





R. Klajn, *Nat. Chem.*, **2015**, *7*, 646

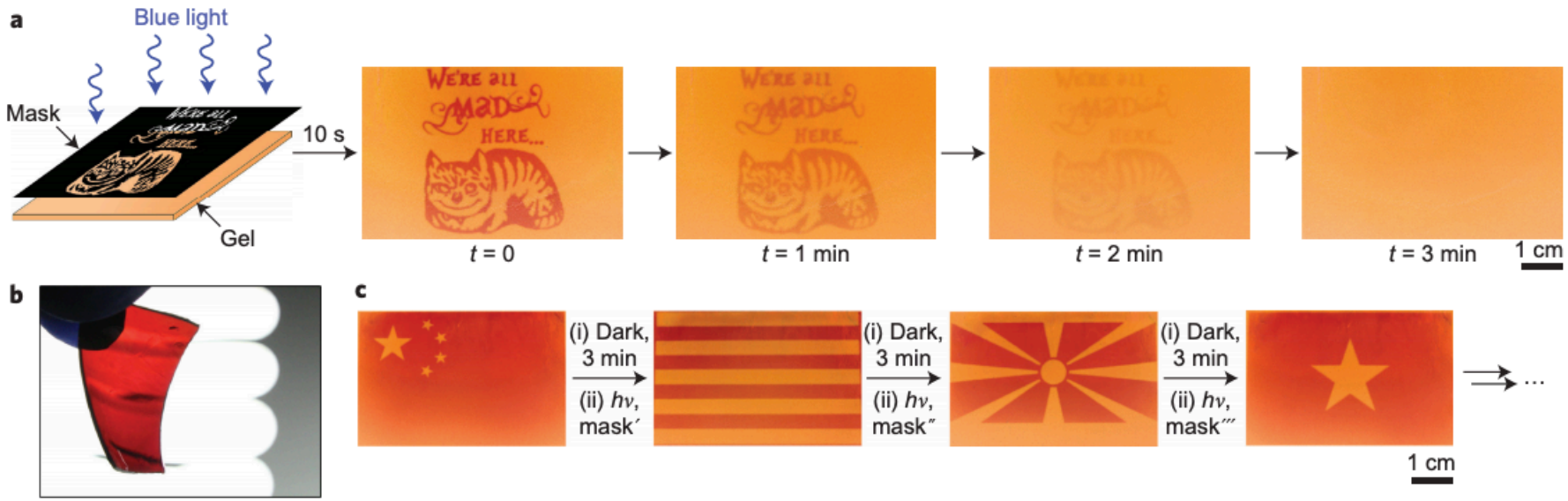
Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles

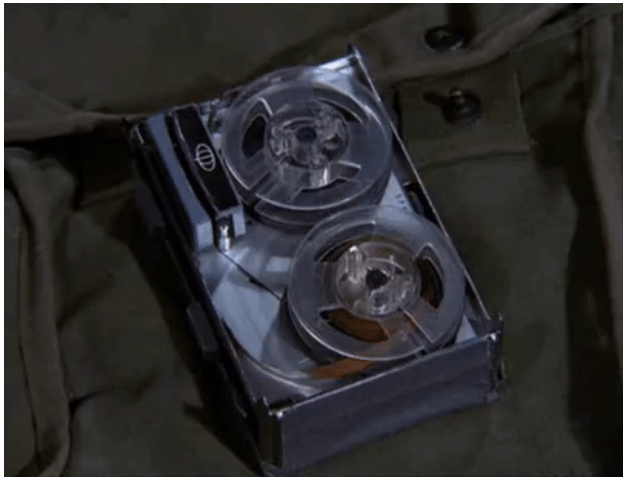


R. Klajn, *Nat. Chem.*, **2015**, *7*, 646

Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles

Writing self-erasing images with NPs in a photoresponsive gel





R. Klajn, *Nat. Chem.*, **2015**, *7*, 646

Outline

- Indroduction
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- Conclusion

Conclusion

- Design molecular motors and pumps featuring unidirectional movement and capabilities to do effective work, with high fatigue-resistence and simple structures.
- Drive chemical reactions and dynamic mixtures of molecules out-of-equilibrium. New strategies for spatial-temporal control and are needed.
- Potential application of out-of-equilibrium systems include solar-to-chemical energy conversion and storage, more efficient communication and information transfer.
- Maxwell's demon or angel ?