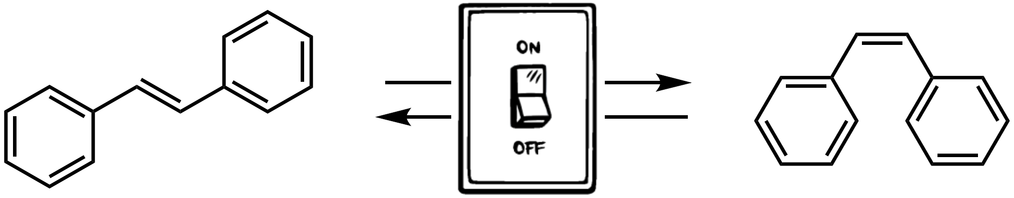
Molecular Photoswitches

Fundamentals and Applications



Angela Lin
Knowles Lab Group Meeting
Literature Talk
January 13, 2023

Outline

I. Introduction

II. Applications

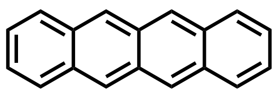
- Photopharmacology
- Molecular Motors
- Solar Energy Storage

III. Conclusion & Outlook

Outline

Introduction

Photochromism is characterized by a light-induced reversible change in color, and was first described by Fritzche in 1867.



Photochromic Materials: Preparation, Properties and Applications, First Edition, 2016
Pure Appl. Chem., 2001, 73, 639

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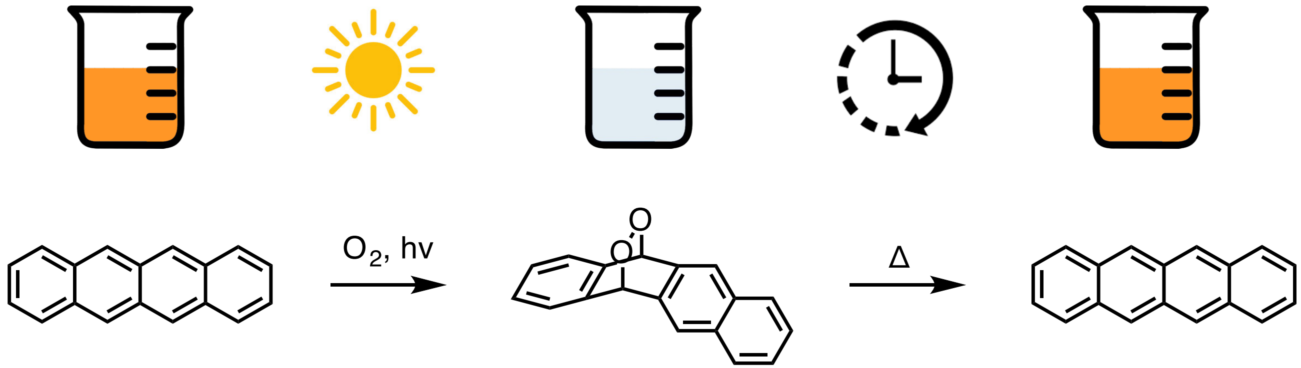

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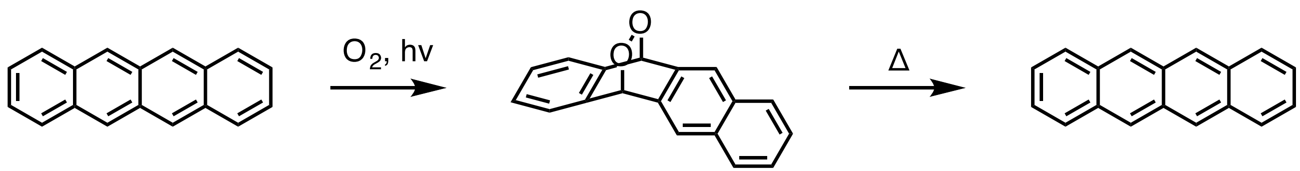
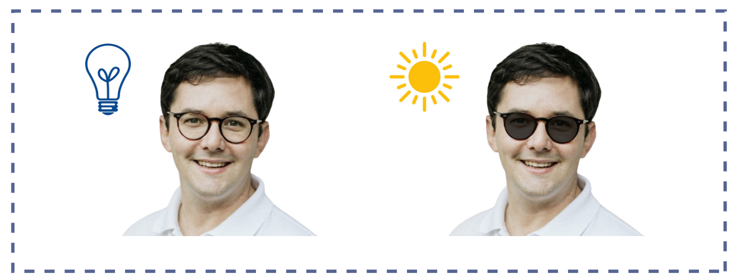
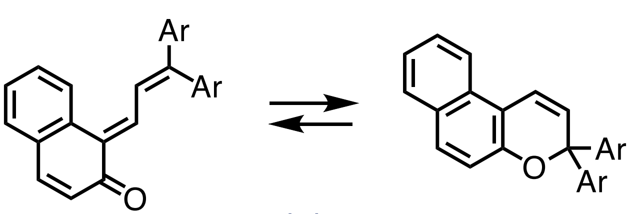
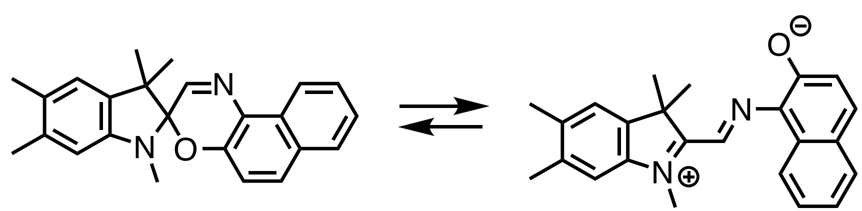


Since then, numerous photochromic compounds have been discovered and commercialized.





naphthopyrans



spirooxazines

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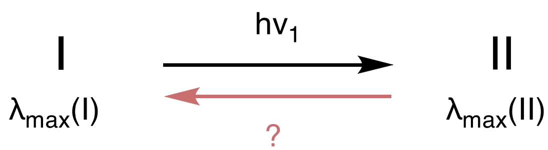

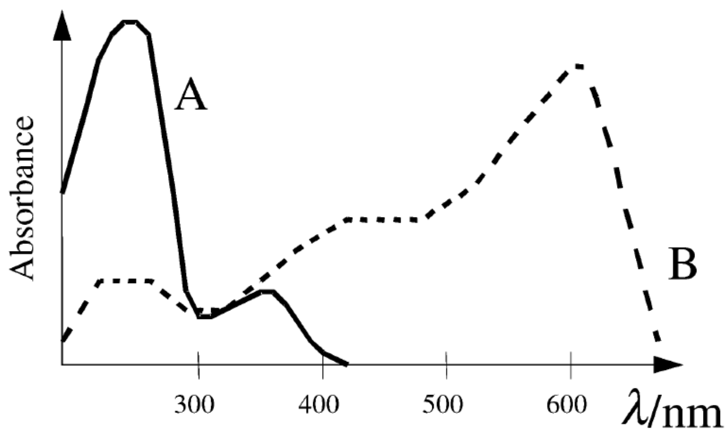

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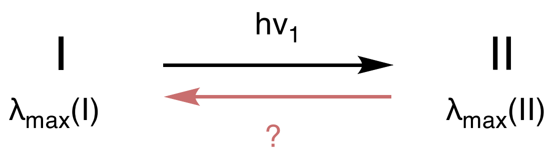

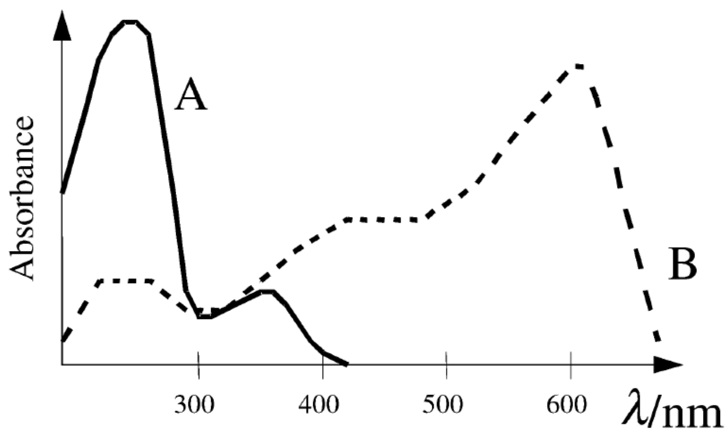

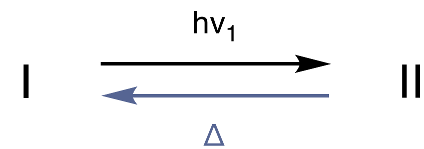

T-type photoswitch

back reaction occurs thermally

thermally labile

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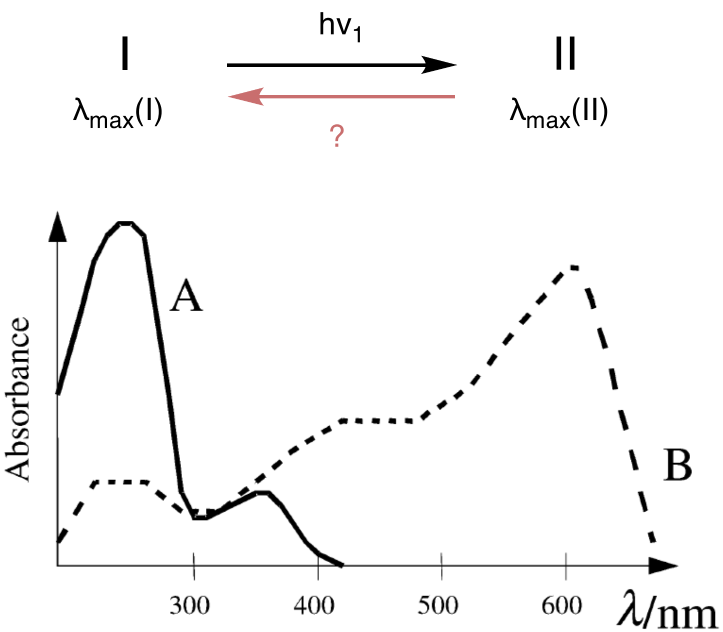

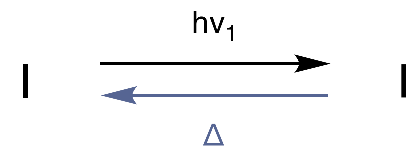

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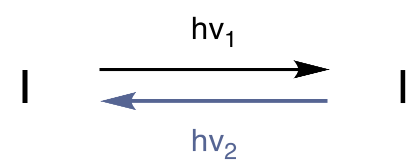


P-type photoswitch

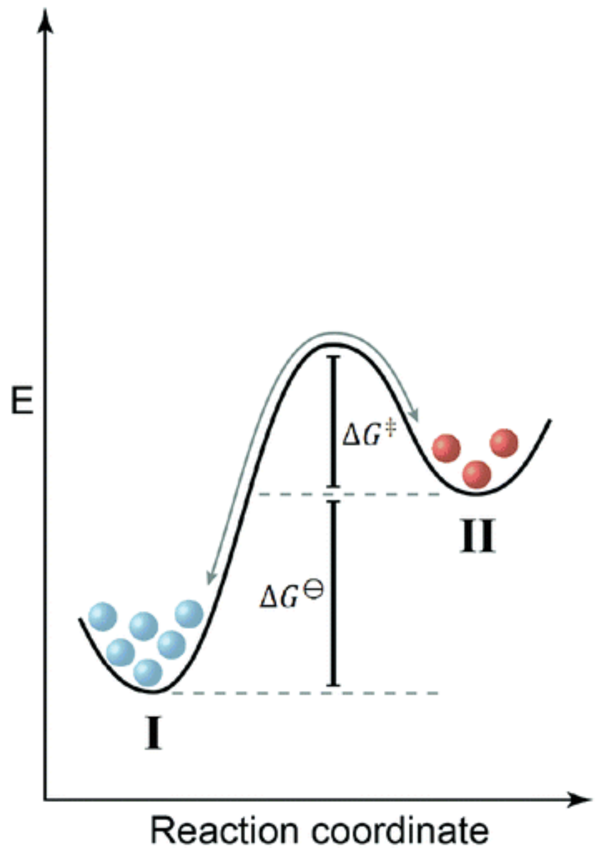
back reaction occurs photochemically

thermally bistable

Pure Appl. Chem., 2001, 73, 639

Thermodynamic *vs.* Photodynamic Equilibria

Thermodynamic Equilibrium



Thermodynamic equilibrium

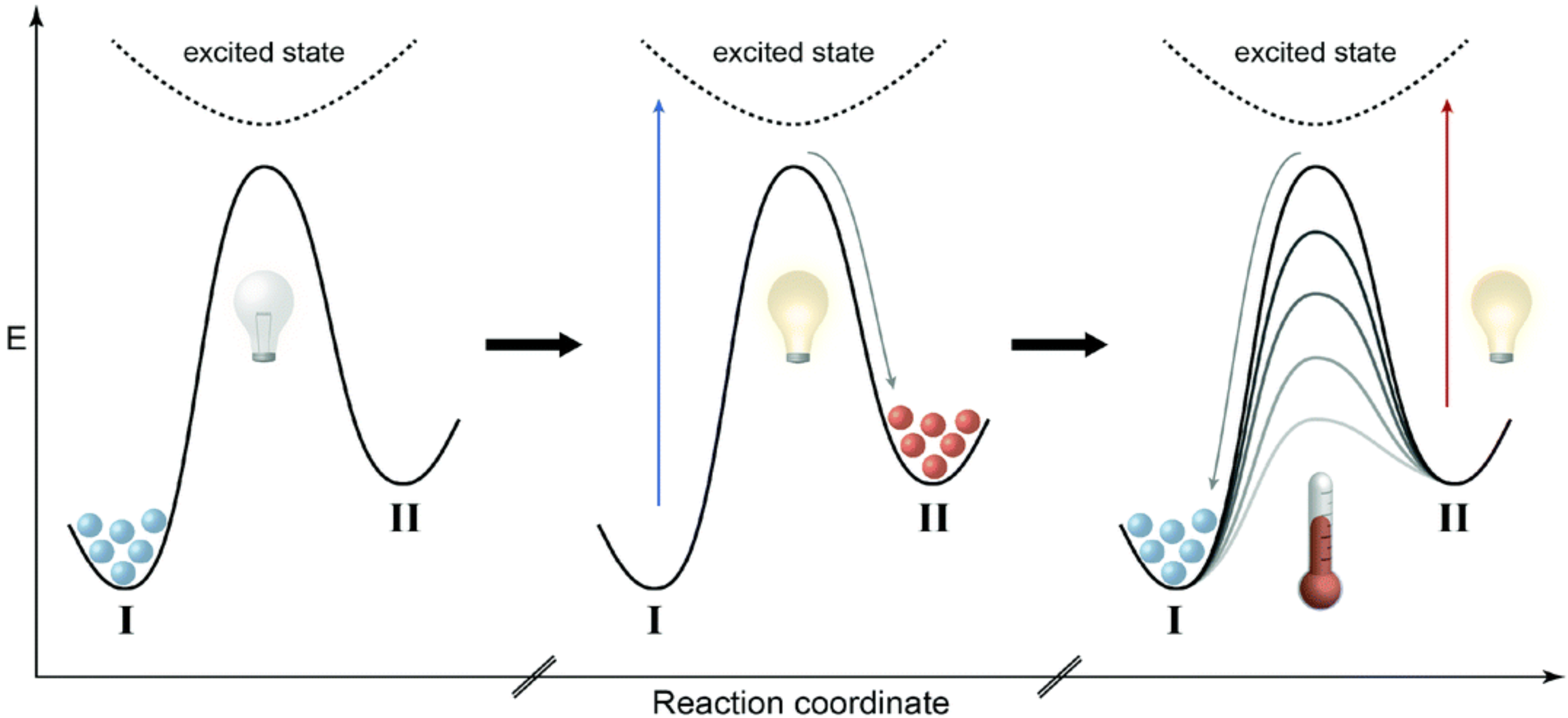
$$K_{eq}^{\Delta} = \frac{II}{I} = e^{\frac{\Delta G^{\theta}}{RT}}$$

Principle of microscopic reversibility

Chem. Soc. Rev. 2017, 46, 5536

Thermodynamic *vs.* Photodynamic Equilibria

Photodynamic Equilibrium



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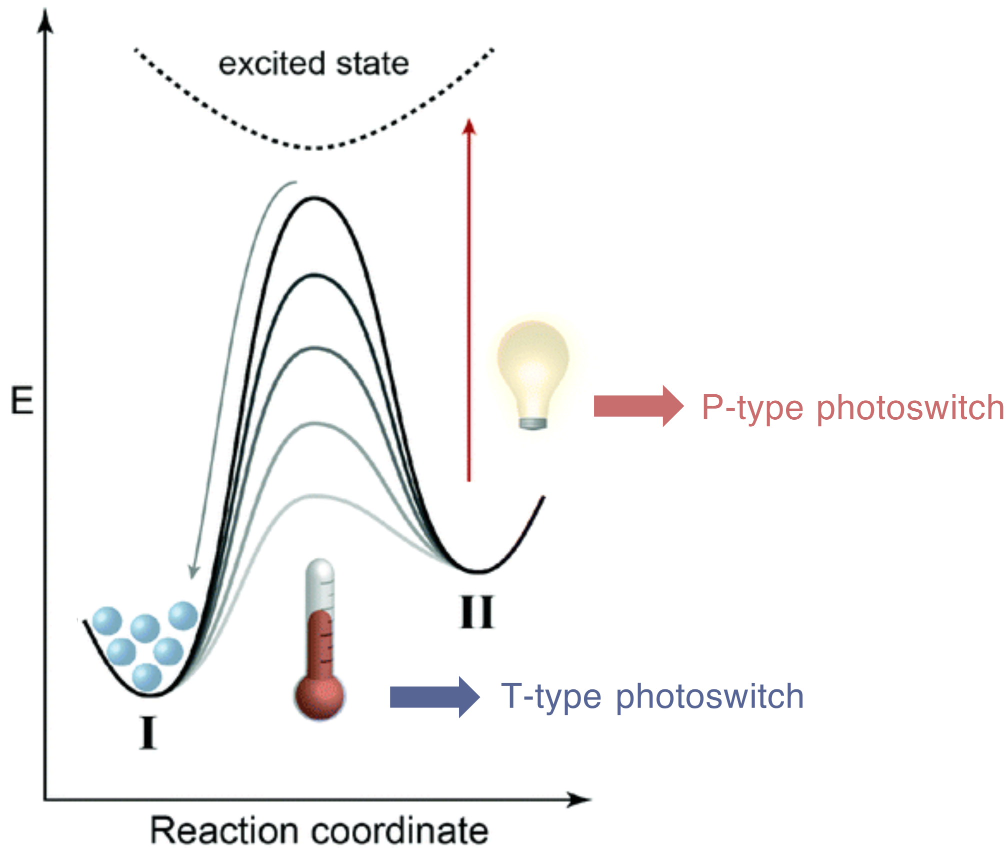

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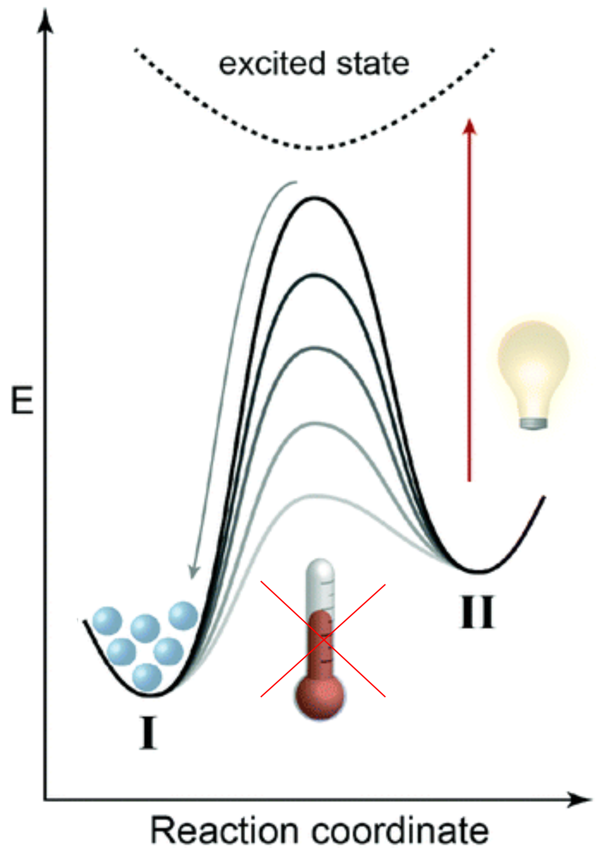


Photostationary state

$$K_{eq}^{\lambda} = \frac{II}{I} = \frac{\varepsilon_{I}^{\lambda}(\Phi_{I\rightarrow II}^{\lambda})}{\varepsilon_{II}^{\lambda}(\Phi_{II\rightarrow I}^{\lambda})}$$

ε = extinction coefficient
Φ = quantum yield

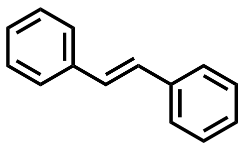
Principle of microscopic reversibility <u>does</u> <u>not</u> apply

Chem. Soc. Rev. 2017, 46, 5536

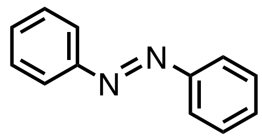
Types of Transformations

Common photoswitches generally operate through 2 types of transformations:

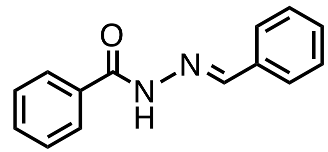
Photoisomerization



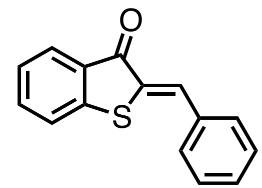
stilbenes



azobenzenes



acylhydrazones



hemithioindigo

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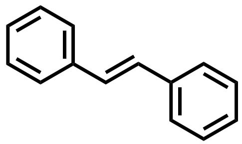

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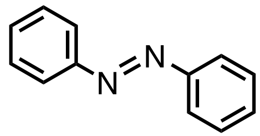

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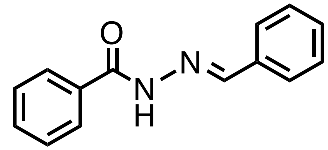

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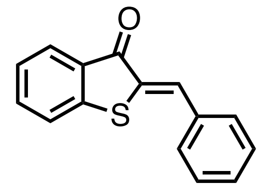
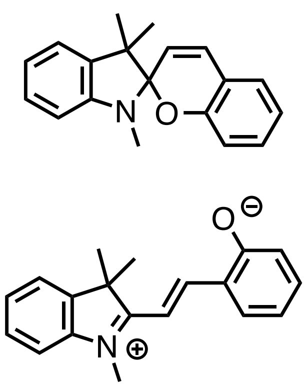
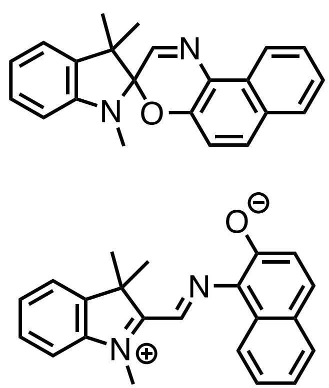


hemithioindigo

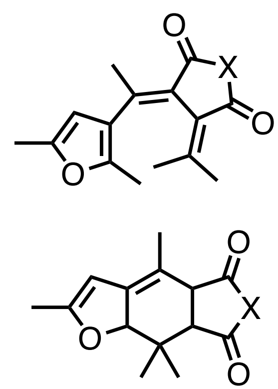
Photocyclic ring-opening/closing



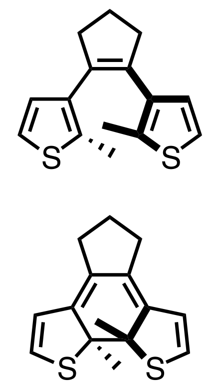
spiropyrans



spirooxazines



fulgides/fulgimides



diarylethenes

* Other (less common) processes include photo-induced proton transfer and dimerization.

Pure Appl. Chem., 2001, 73, 639

Design Considerations

- High quantum yields
- High extinction coefficients at the desired wavelength(s)
- High photostationary state
- Control over switching speed
- Tunable thermal stability of the isomers (half-life)
- Resistance against photodegradation (fatigue)

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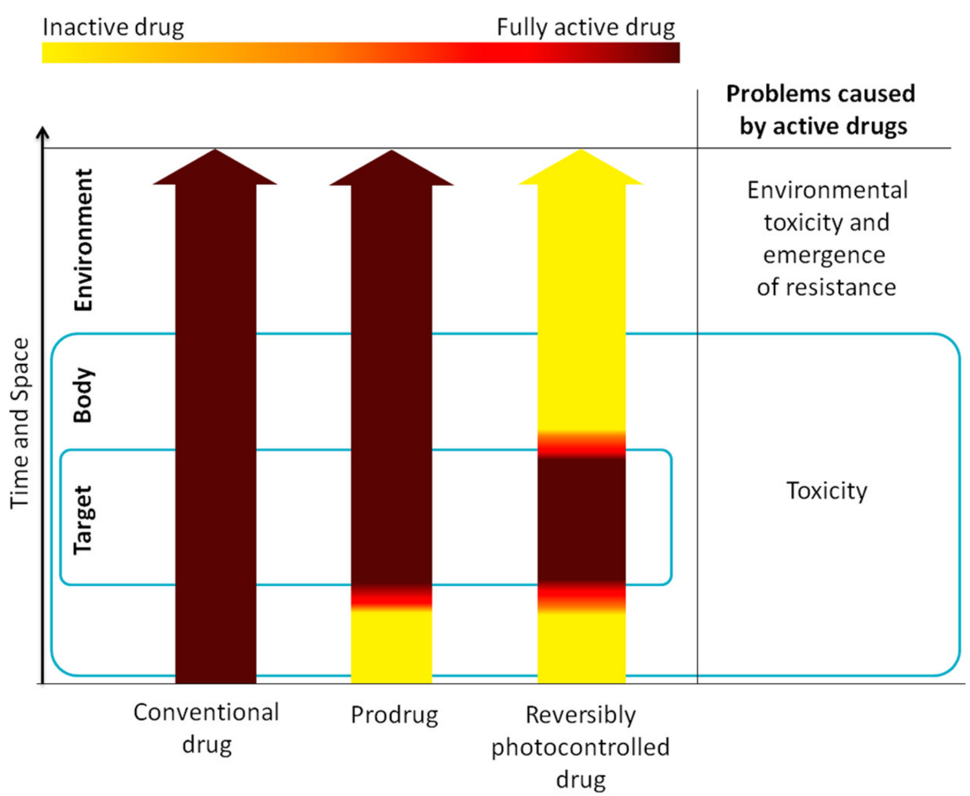
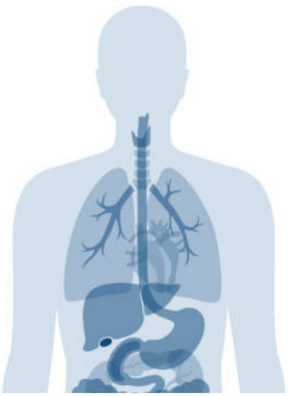
Photopharmacology

Photopharmacology involves the introduction of a photoswitch into the molecular structure of a bioactive compound.

Key issue in pharmacotherapy: lack of spatial and temporal control over drug activity





adverse side effects

suboptimal dosage

drug resistance

J. Am. Chem. Soc. 2014, 136, 2178

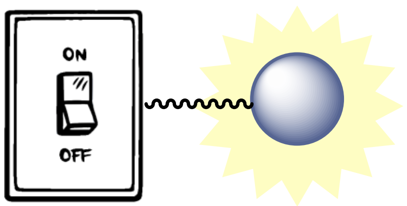
Photopharmacology

Advantages of light as an external stimulus

non-invasive

can be regulated as desired (wavelength, intensity)

can be delievered with high spatial and temporal precision



reversible control

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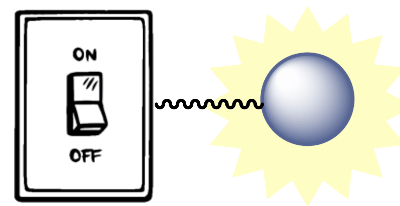
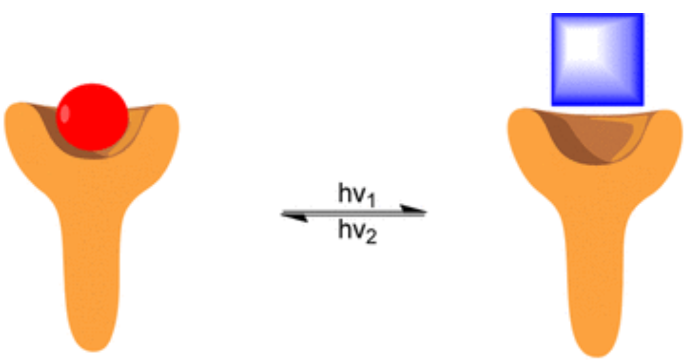


reversible control

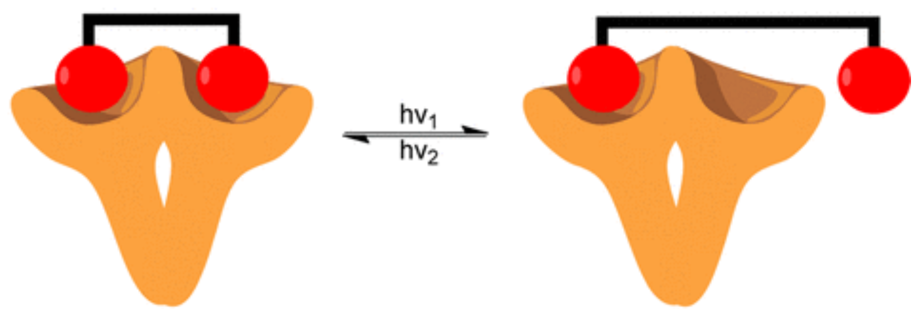
Strategy 1 (Direct)



active isomer

inactive isomer

Strategy 2 (Indirect)



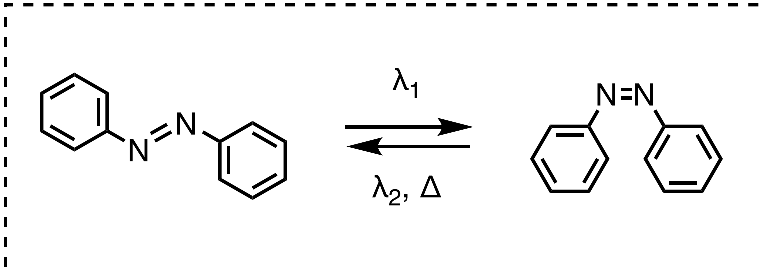
high activity

low activity

J. Am. Chem. Soc. 2014, 136, 2178

Popular Motifs

Azobenzenes (T-type)



photoisomerization

large changes in geometry and polarity

λ_{max} (E) = 320 nm (π□π*), 450 nm (n□π*)

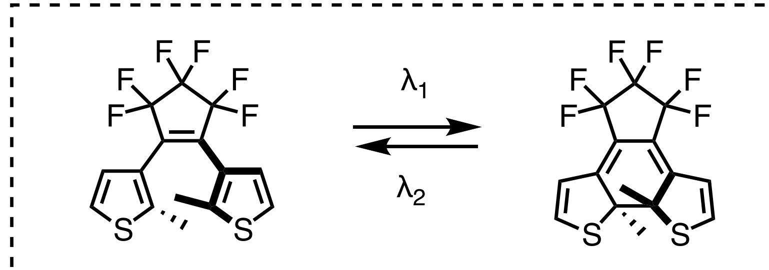
λ_{max} (Z) = 270 nm (π□π*), 450 nm (n□π*)

$t_{1/2}$(Z) = 2 days

distance change = 3 A

dipole moment change = 3 D

Diarylethenes (P-type)



photoinduced cyclization/ring opening

large changes in flexibility and electronics

λ_{max} (open) = 303 nm

λ_{max} (closed) = 505 nm

$t_{1/2}$(closed)= ~4-5 x 10^5 years

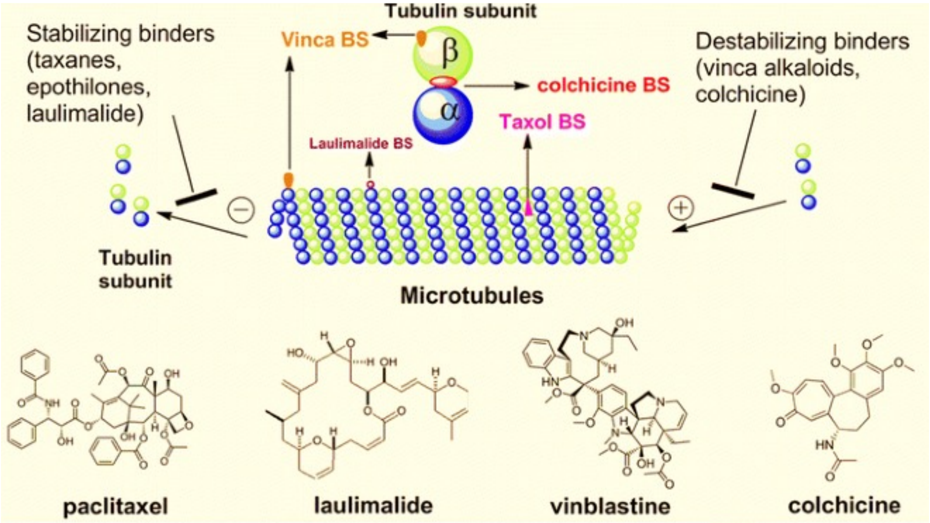
distance change = 1 A

dipole moment change = minimal

J. Am. Chem. Soc. 2014, 136, 2178
Chem. Rev. 2014, 114, 12174

Photostatins (PSTs)

Microtubule inhibitors are a class of chemotherapeutics known for antimitoic and pro-apoptotic effects.



Cell, 2015, 162, 403

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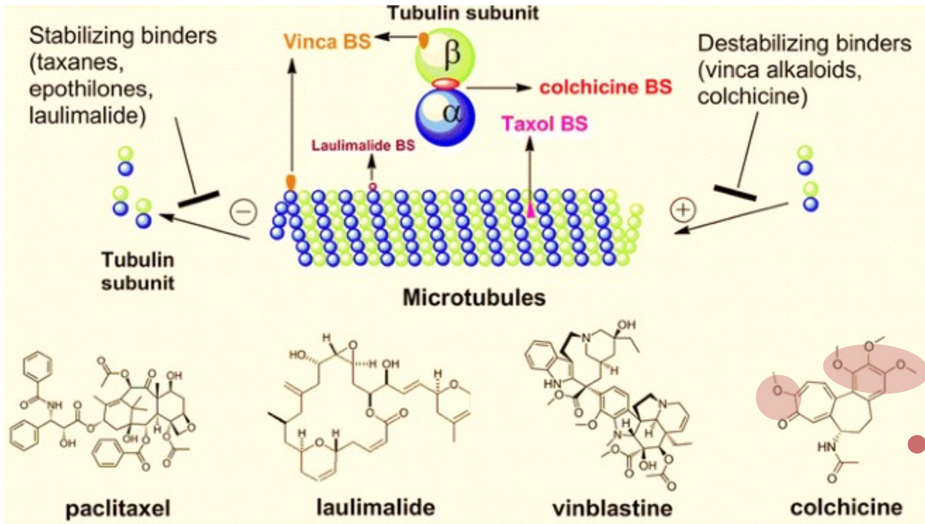

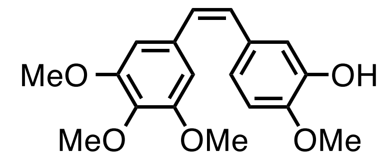

Combretastatin A-4 (CA4)

multiple analogues have progressed to clinical trials

trans isomer is much less potent

Cell, 2015, 162, 403

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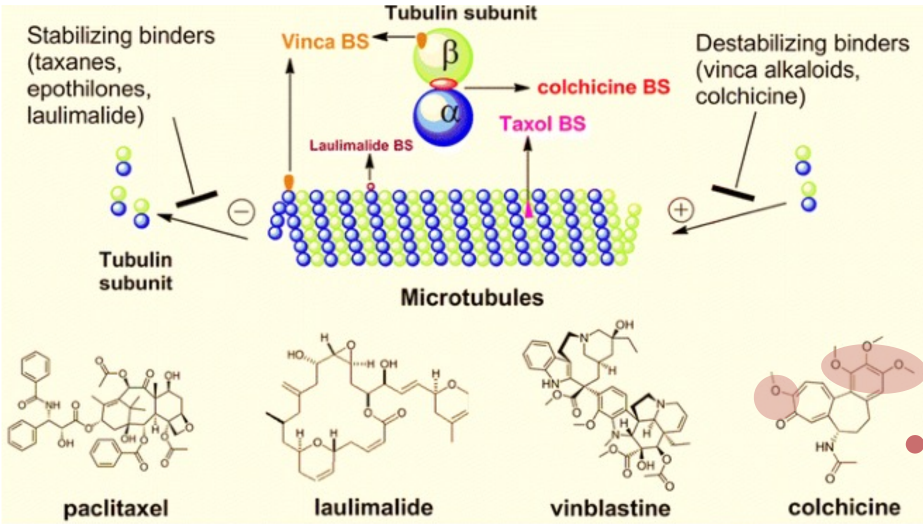

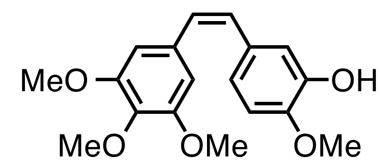

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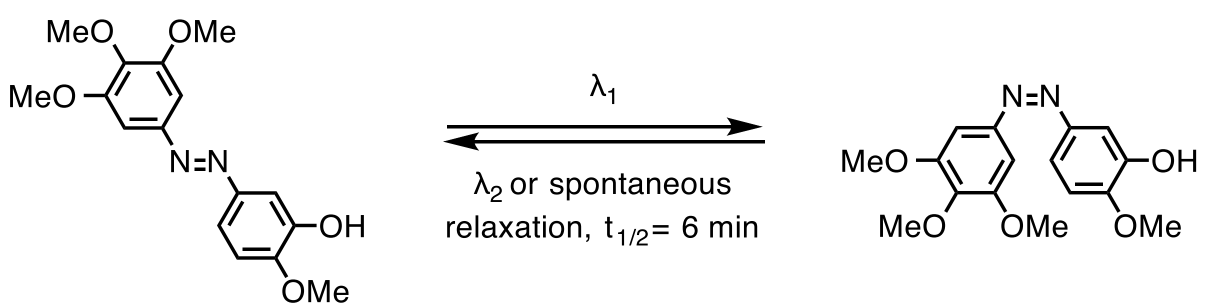
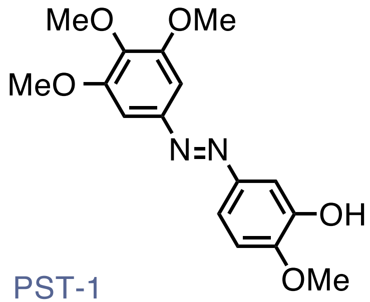


trans-PST-1 (inactive)

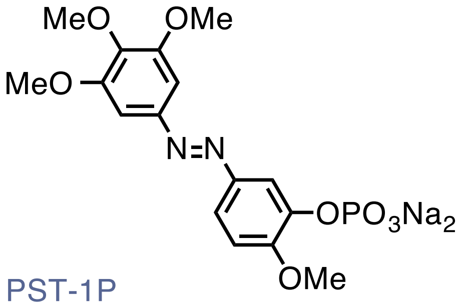
cis-PST-1 (active)

Cell, 2015, 162, 403

Photostatins (PSTs)



PST-1



PST-1P

Cell, 2015, 162, 403

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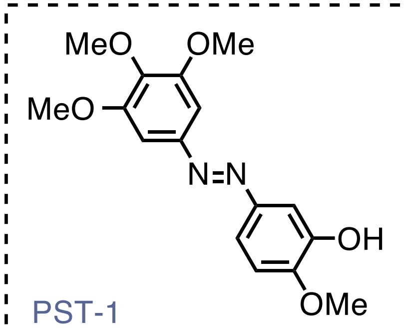

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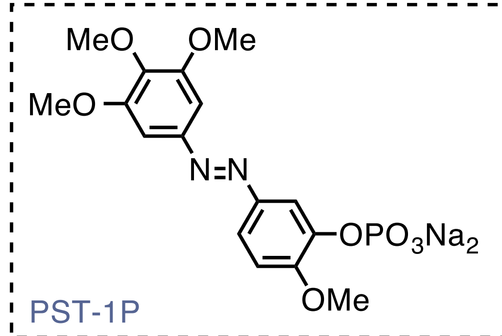

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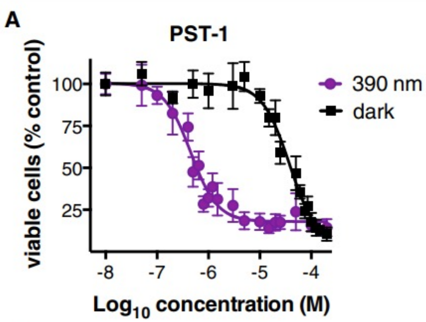
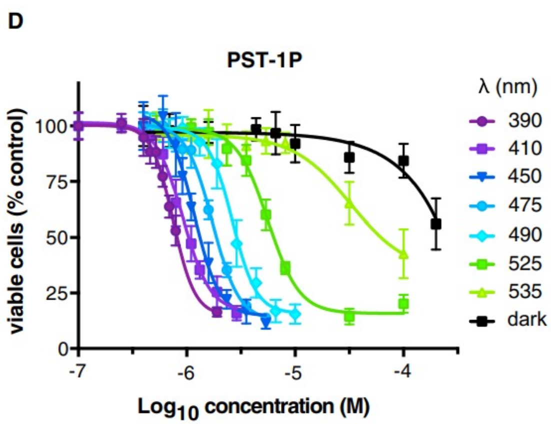


B

Compound	EC_{50} dark	EC_{50} 390 nm
PST-1	38 μM	0.5 μM
PST-2	25 μM	0.5 μM
PST-3	35 μM	2.1 μM
PST-4	43 μM	1.4 μM
PST-5	37 μM	1.0 μM
PST-1P	71 μM	0.7 μM
PST-2S	ND	5.4 μM
PST-1CL	ND	4.2 μM
CA4P	4 nM	-

C

λ (nm)	EC_{50} (μM)
370	0.97
380	0.70
390	0.75
400	0.91
410	0.93
435	0.98
450	1.2
465	1.5
475	1.7
490	2.6
505	2.6
515	3.0
525	5.6
535	32
dark	> 200



☐ *In cellulo studies with MDA-MB-231 human breast cancer cells and HeLa (cervical cancer) cells*

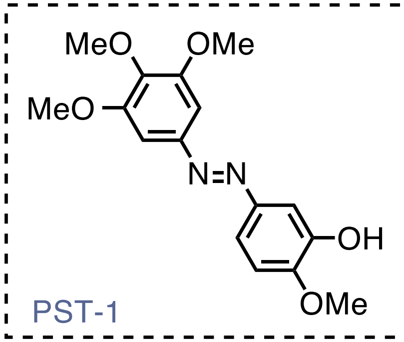
<u>Main takeaways:</u>

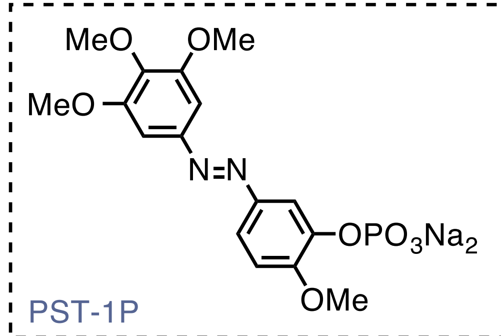
- PSTsare more cyctotoxic under 390 nm irradiation than in the dark

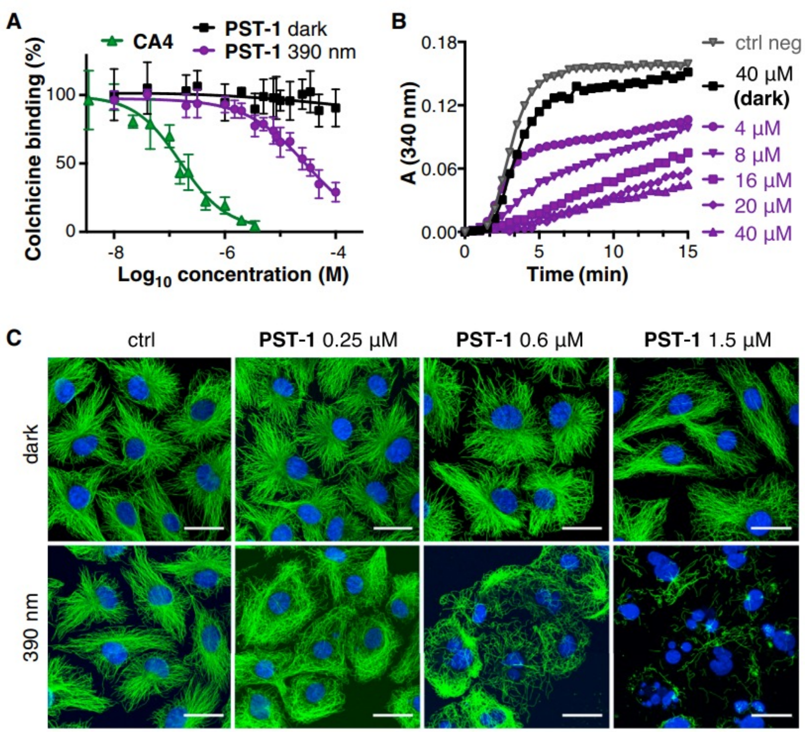
- PST-1Pcyctotoxicity can be modulated by applying light of different wavelengths

Cell, 2015, 162, 403

Photostatins (PSTs)







- *In vitro and in cellulo studies validating of tubulin as the molecular target of cis-PSTs*

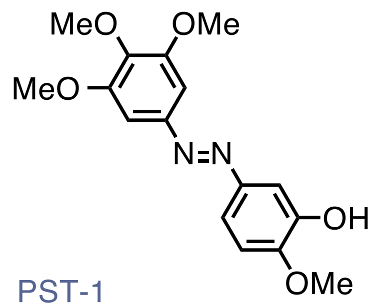
Main takeaways:

- PST-1 exposed to 390 nm light competes with colchicine for tubulin binding

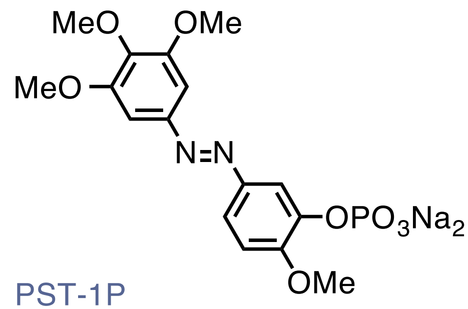
- PST-1 exposed to 390 nm light dose-dependently induces microtubule breakdown

Cell, 2015, 162, 403

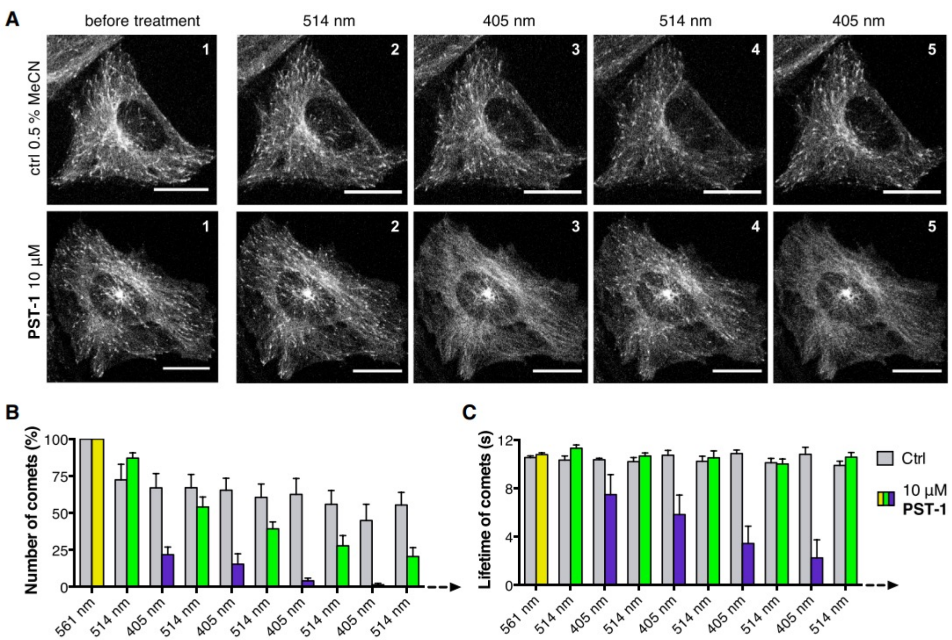
Photostatins (PSTs)



PST-1



PST-1P



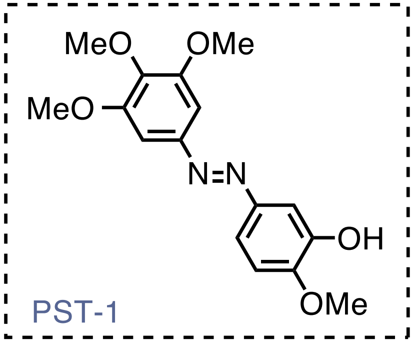
□ *In cellulo studies imaging end-binding protein EB3, which clusters at the plus tips of growing MTs and dissociates in phases of MT shrinkage*

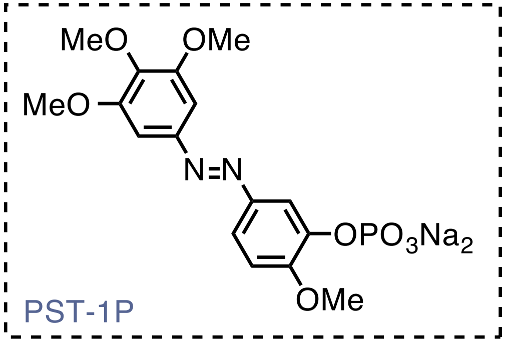
Main takeaways:

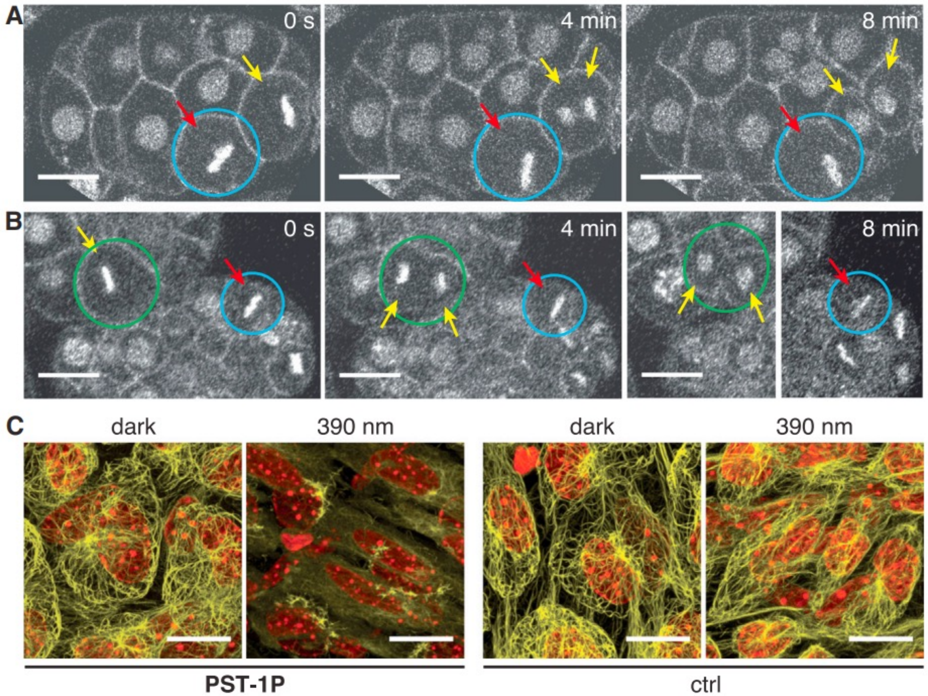
- *Cis-trans* photoisomerization of PST-1 by alternating blue and green light causes MT to stop and start again with <1s response time with full reversibility

Cell, 2015, 162, 403

Photostatins (PSTs)







- *In vivo studies with C. elegans embryo and live mouse muscle tissue*

405 nm light

405 nm + 514 nm light

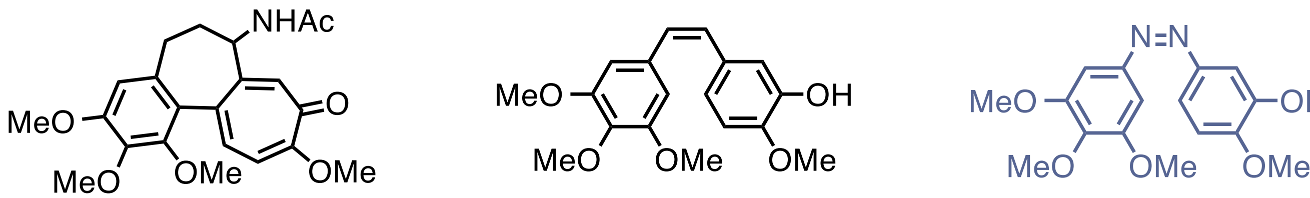
Main takeaways:

- PSTscan be operated with high spatial control on the single-cell level

- PSTsexhibit reversible *in vivo* control over MT dynamics

Cell, 2015, 162, 403

Photostatins (PSTs)



colchicine Combretastatin A-4 Photostatin

In summary:

- The *cis* isomer of PSTsare 250x more cyctotoxic than the corresponding *trans* isomer
- PSTscan modulate mitosis with spatial precision on the cellular level
- PSTscan modulate microtubule activity on the time-scale of seconds
- PSTscan switch microtubule activity on and off by simply using blue & green light

Cell, 2015, 162, 403

Outline

I. Introduction

II. Applications

- Photopharmacology
- Molecular Machines
- Solar Energy Storage

III. Conclusion & Outlook

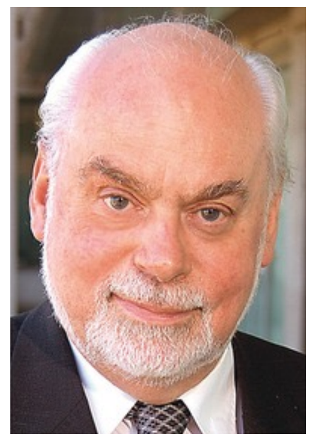
Molecular Machines

Molecular machines are molecules that convert chemical energy into mechanical forces and motion.

2016 Nobel Prize in Chemistry

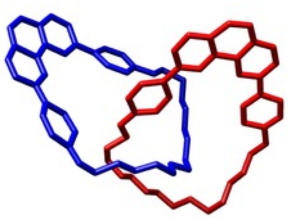
"for the synthesis and design of molecular machines"

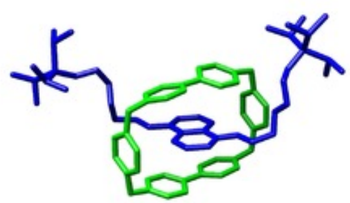
Jean-Pierre Sauvage

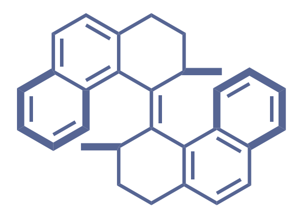


Sir. J. Fraser Stoddart

Bernard L. Fergina

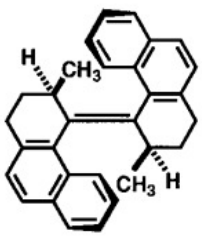




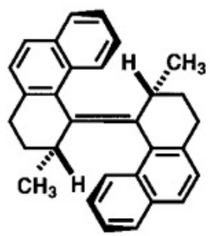


First Generation Molecular Motor

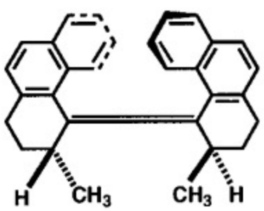
Biphenanthrylidene scaffold with axial chirality
"helicity"



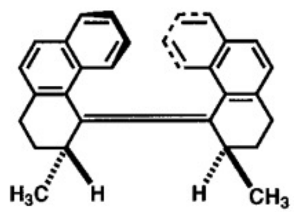
(3*R*,3'*R*)-(*P*,*P*)-(*E*)-3
with two axial methyl groups
C_2-symmetry
ΔE = 0.0 kcal/mol



(3*R*,3'*R*)-(*M*,*M*)-(*E*)-3
with two equatorial methyl groups
C_2-symmetry
ΔE = +10.2 kcal/mol

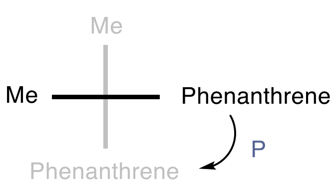


(3*R*,3'*R*)-(*P*,*P*)-(Z)-4
with two axial methyl groups
C_2-symmetry
ΔE = 0.0 kcal/mol

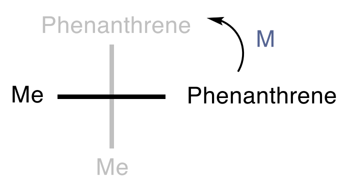


(3*R*,3'*R*)-(*M*,*M*)-(Z)-4

ΔE = +11.1 kcal/mol



P-(E)

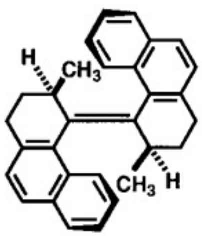


M-(E)

Nature, 1999, 401, 152

First Generation Molecular Motor

Biphenanthrylidene scaffold with axial chirality "helicity"



(3*R*,3'*R*)-(*P*,*P*)-(*E*)-3
with two axial methyl groups
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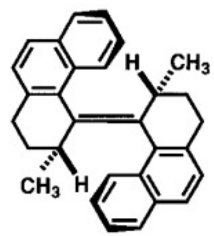
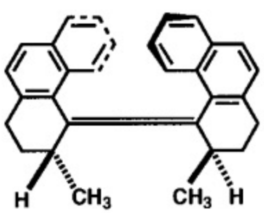


(3*R*,3'*R*)-(*M*,*M*)-(*E*)-3
with two equatorial methyl groups
C_2-symmetry
ΔE = +10.2 kcal/mol



(3*R*,3'*R*)-(*P*,*P*)-(*Z*)-4
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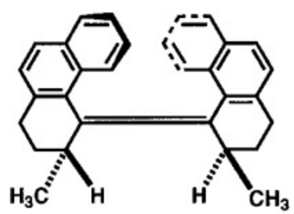

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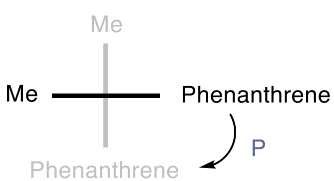
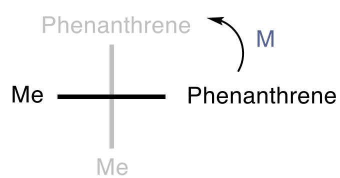
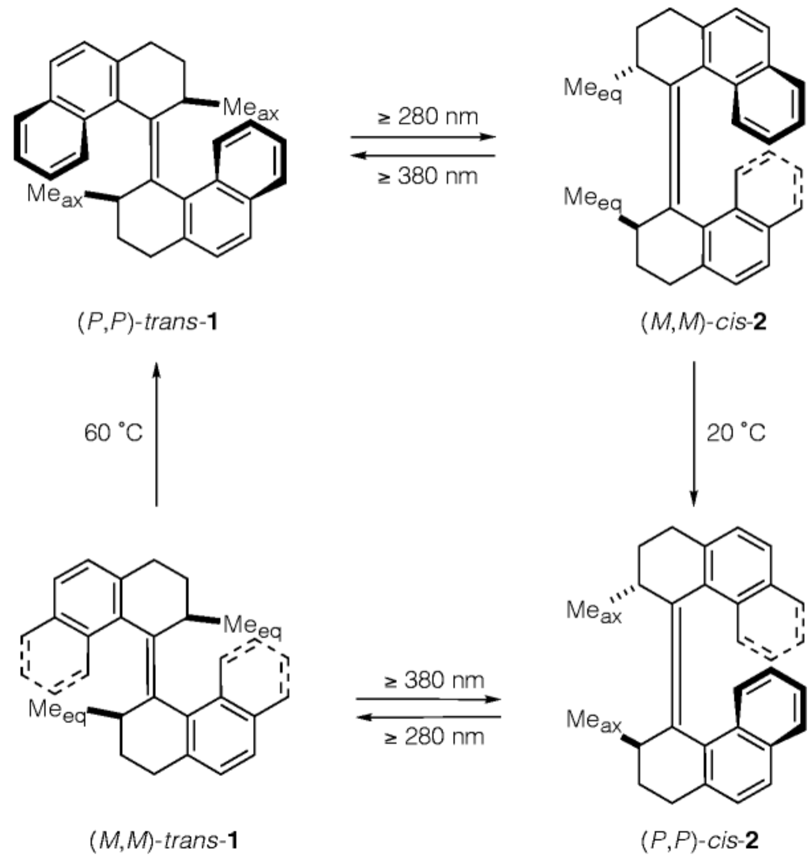
ΔE = +11.1 kcal/mol



P-(E)



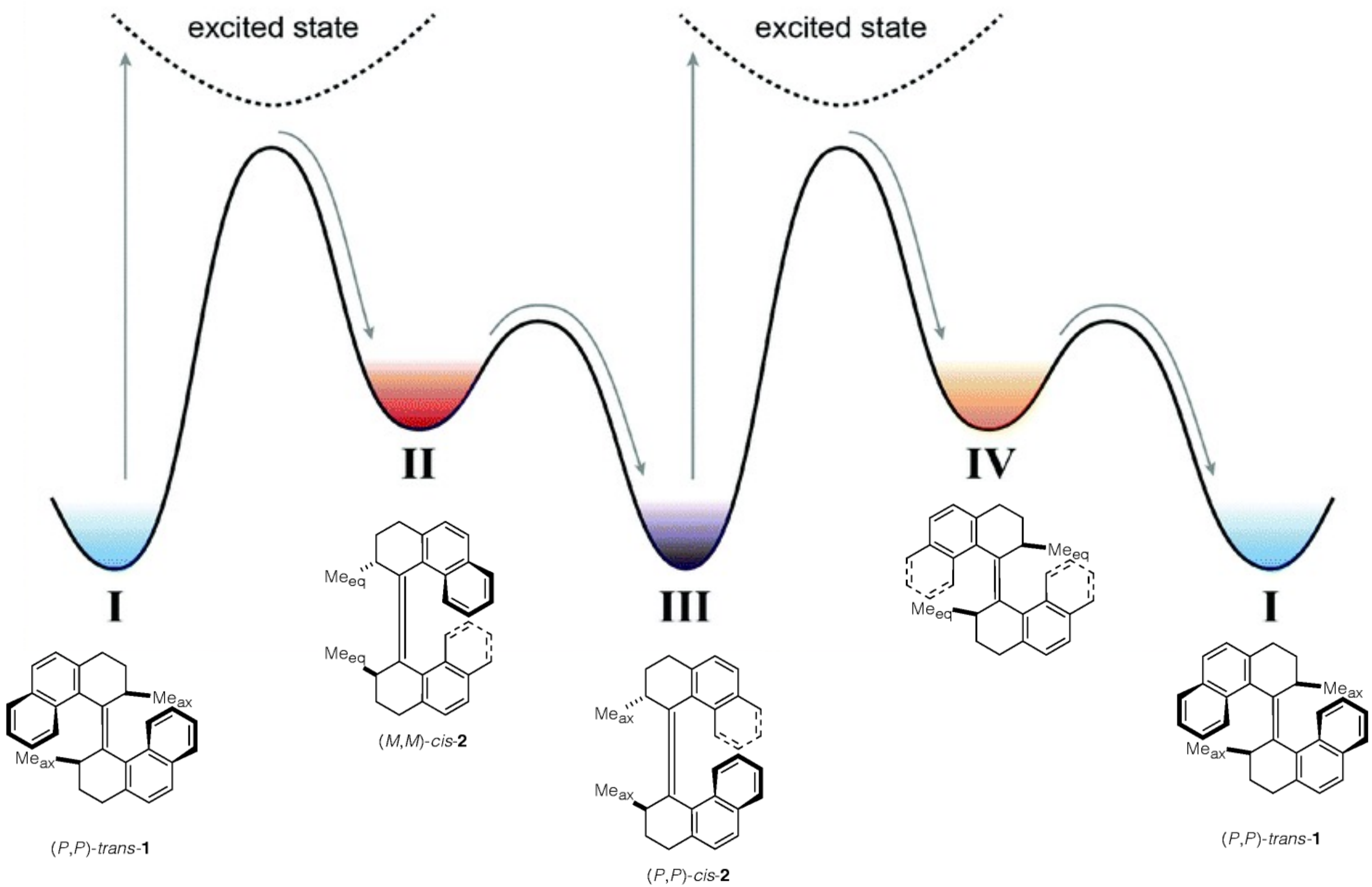
M-(E)



Nature, 1999, 401, 152

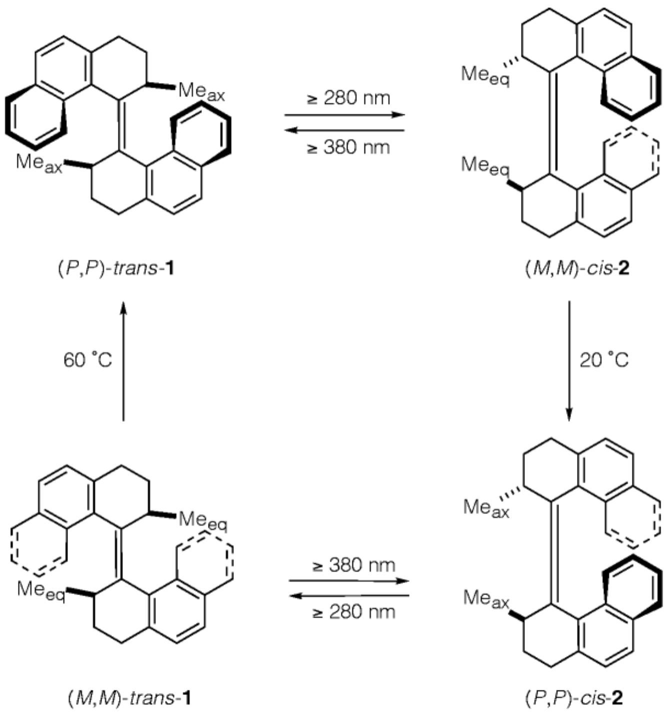
First Generation Molecular Motor

The first molecular motor was developed on the basis of coupling photo- and thermodynamic equilibria.



Nature, 1999, 401, 152
Chem. Soc. Rev. 2017, 46, 5536

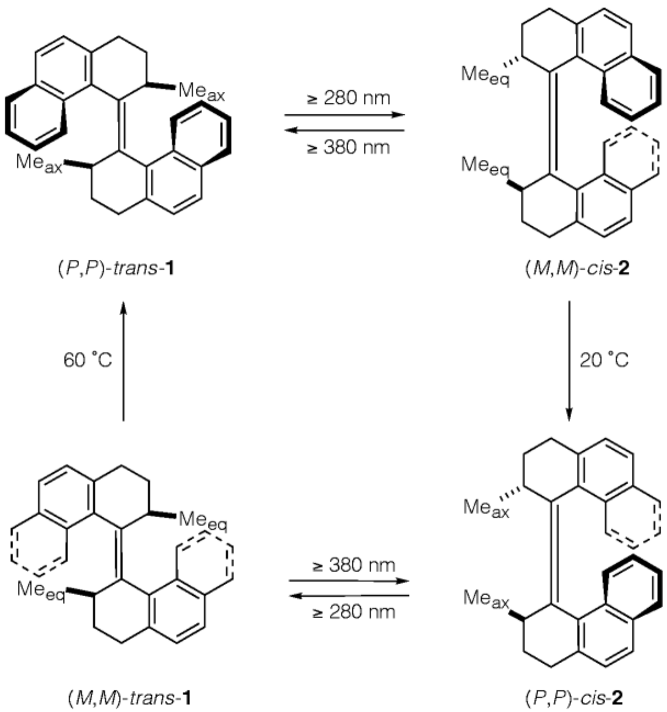
First Generation Molecular Motor

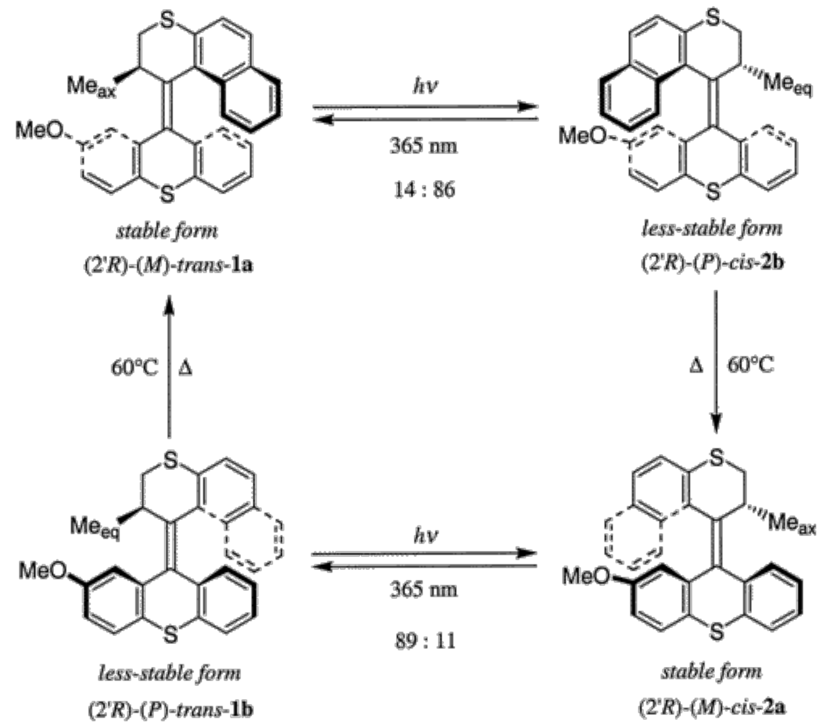


Continuous, unidirectional, 360^{o} rotation

Nature, 1999, 401, 152

Second Generation Molecular Motor



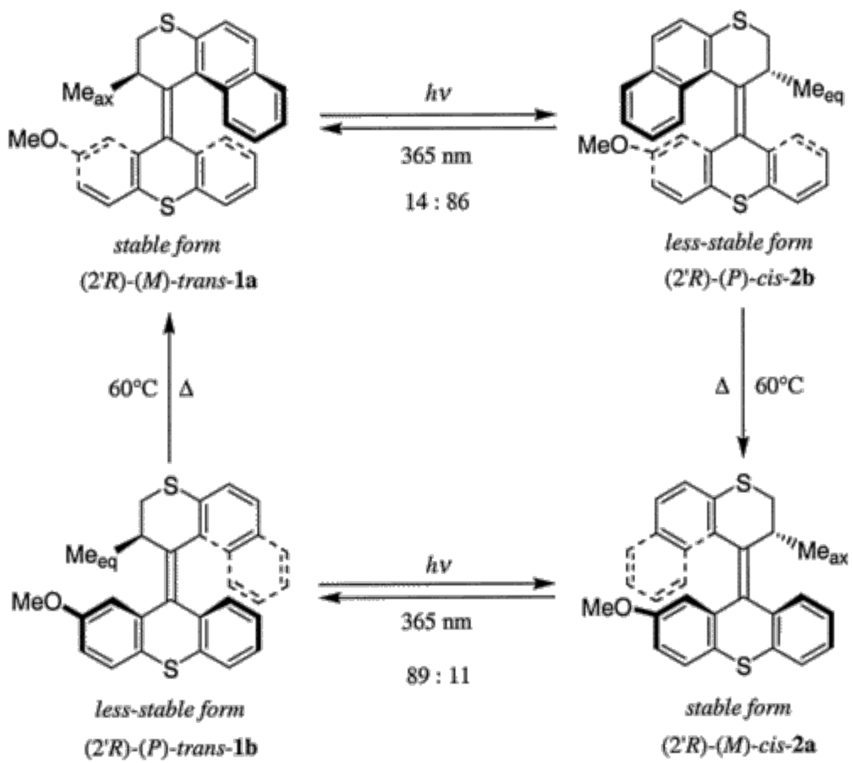


Continuous, unidirectional, 360^{o} rotation

Asymmetric scaffold, more control elements

Nature, 1999, 401, 152
J. Am. Chem. Soc. 2002, 124, 5037

Second Generation Molecular Motor



Design Principles

- Stilbene scaffold
- Distinct upper and lower parts
- Introduction of stereogenic center enables control over direction of rotary motion
- Introduction of bridging atoms enables control over speed of rotary motion

J. Am. Chem. Soc. 2002, 124, 5037

Outline

I. Introduction

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- Solar Energy Storage

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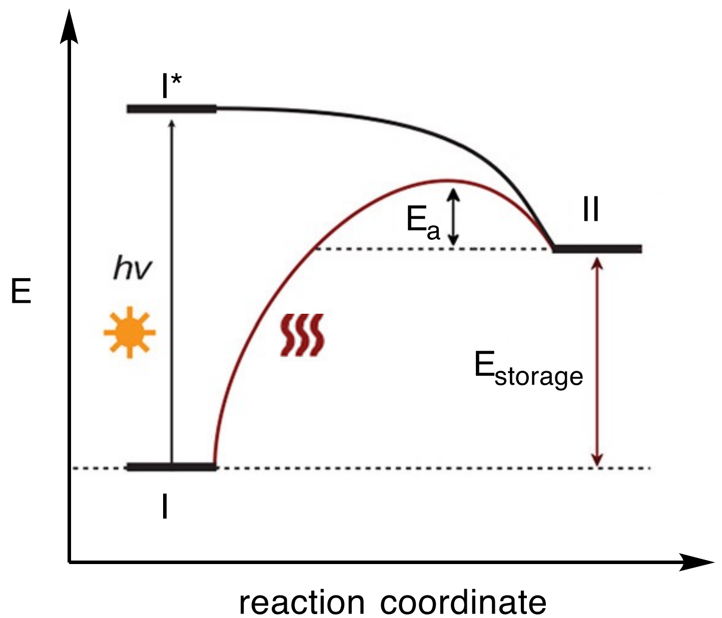
Solar Energy Storage

Molecular solar thermal (MOST) systems are based on use of photoswitches for energy storage.

Molecular photoswitches employed in this sense are also known as solar thermal fuels (STF).



ChemPhotoChem, 2019, 3, 268
Acc. Chem. Res. 2002, 53, 1478

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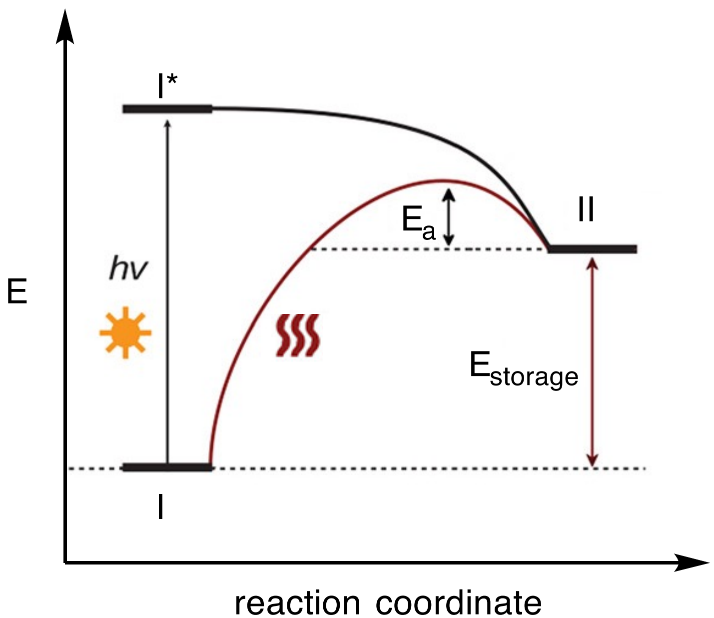

Ideal systems should have:

- an absorption onset of 300-600 nm
- high quantum yields of isomerization from I □ II
- low molecular weight (energy density >0.3 MJ/kg)
- a serviceable half life ($t_{1/2}$)

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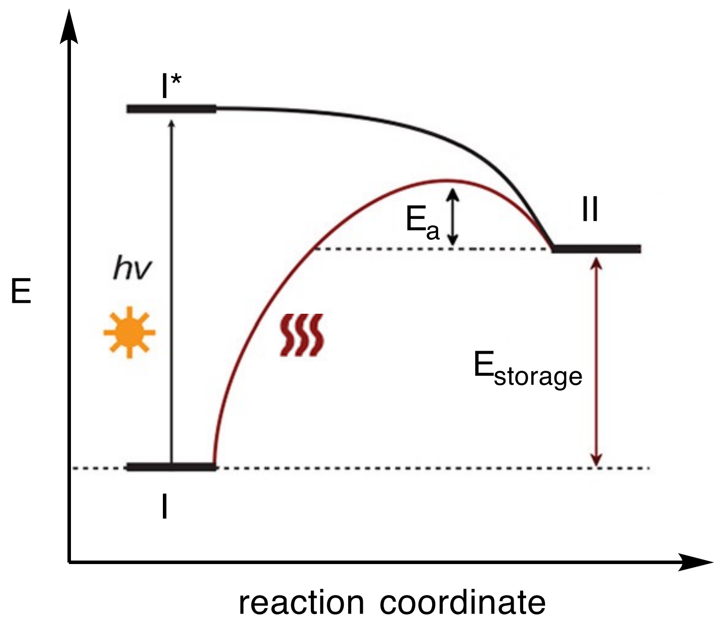

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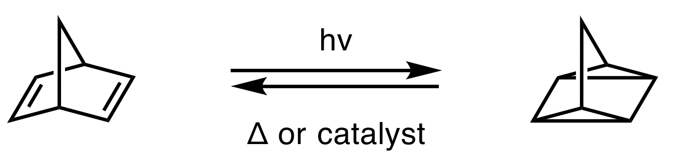


norbornadiene (NBD)

quadricyclane (QC)

λ_{max}(NBD) = 213 nm

λ_{max}(QC) = 236 nm

MW = 92 g/mol

ΔG_{isom}(QC□NBD) = 89 kcal/mol

$t_{1/2}$(QC) = ~10^7 h (1140 y) @ RT

ChemPhotoChem, 2019, 3, 268
Acc. Chem. Res. 2002, 53, 1478

NBD Modifications: Red Shifting and QC Stabilization

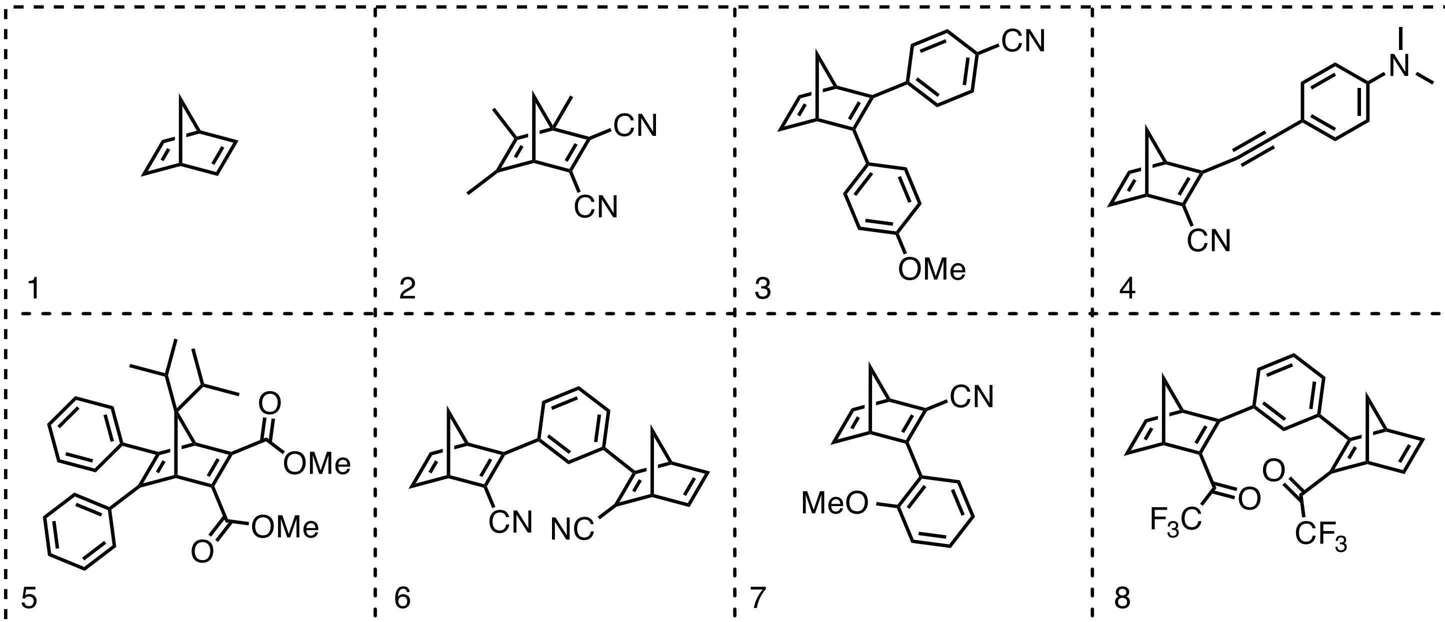
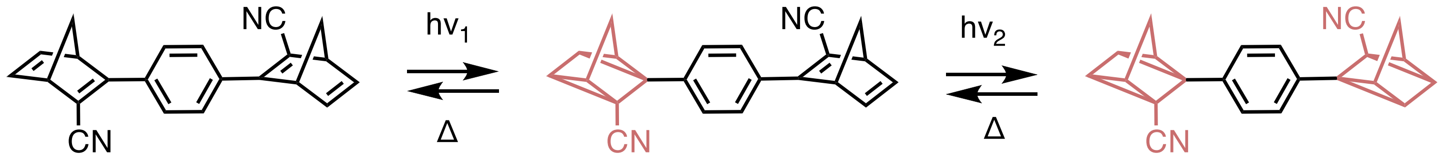


Table 1. MOST Parameters of NBDs 1−8

NBD	MW (g/mol)	λ_{onset}[a] (nm)	φ	$t_{1/2}$[b] (days)	$\Delta E_{storage}$ (kJ/mol)
1[23,37]	92	300	0.05		89
2[24]	184	360[c]	0.96	124[d]	88
3[13]	299	431	0.62	8.7	
4[14]	260	456	0.28	0.2	103
5[11]	445	414	0.88	2.3	46
6[38]	308	362	0.53	49	173
7[2]	223	368	0.70	2273	89
8[4]	450	466	0.77	0.7	216

Acc. Chem. Res. 2002, 53, 1478

NBD Dimer



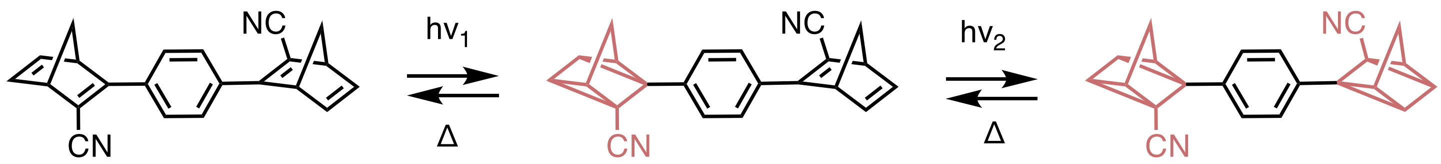
NBD-NBD

QC-NBD
$t_{1/2}$= 2 days

QC-QC
$t_{1/2}$= 10 days

ChemPhotoChem, 2019, 3, 268
Acc. Chem. Res. 2002, 53, 1478

NBD Dimer



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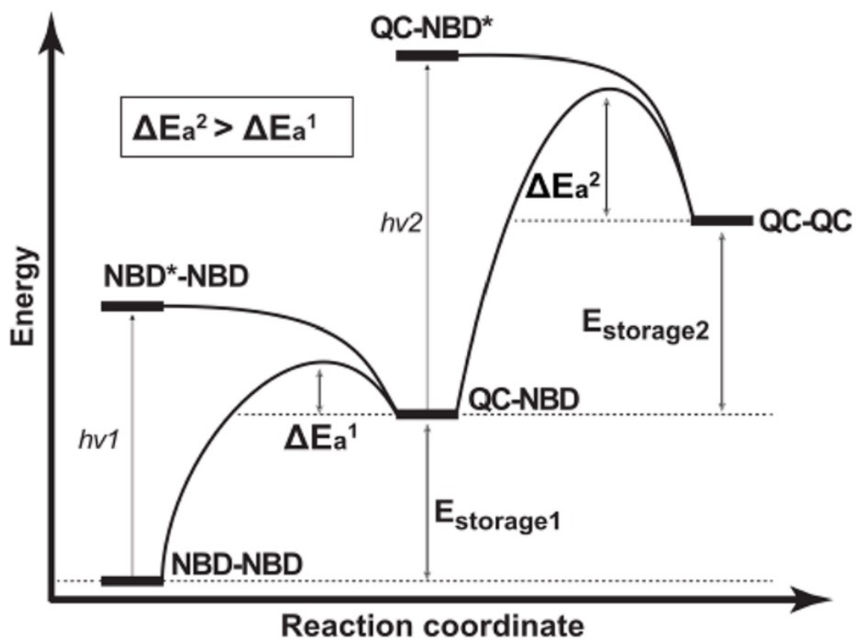

energy density > 0.3 MJ/kg
dimer & trimer systems showed energy densities up to 0.9 MJ/kg

ChemPhotoChem, 2019, 3, 268
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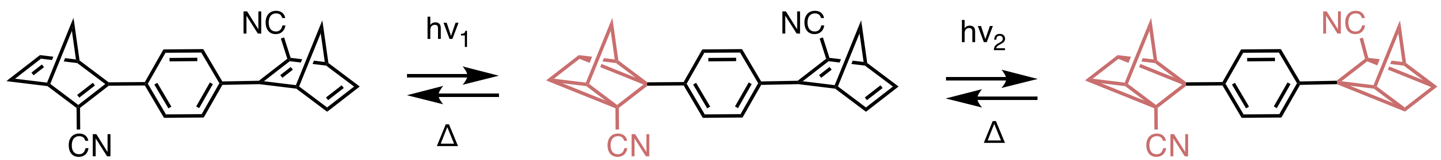
NBD Dimer



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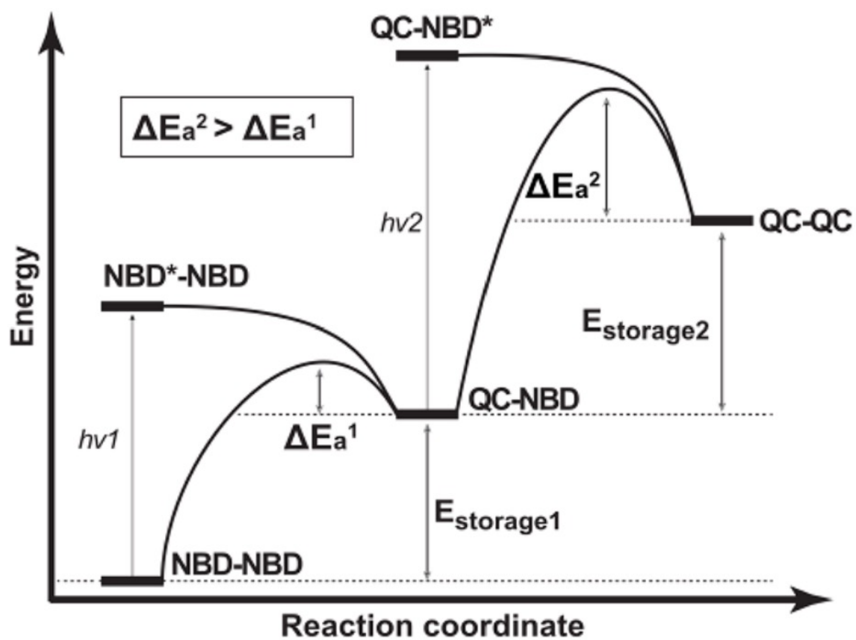
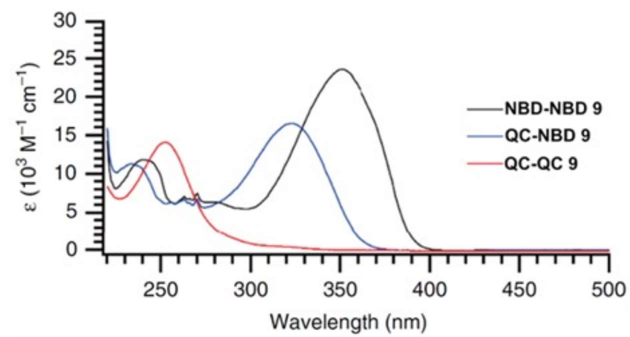


UV-Vis of dimer isomers



energy density > 0.3 MJ/kg
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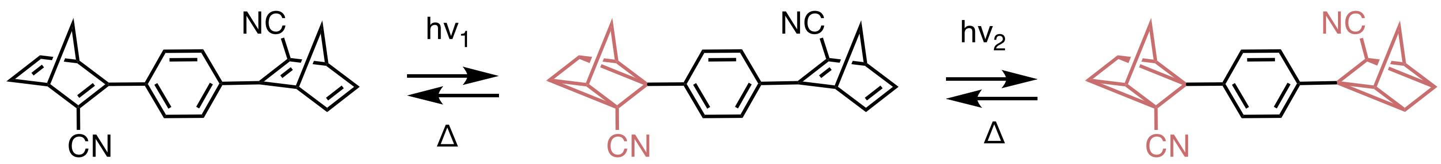
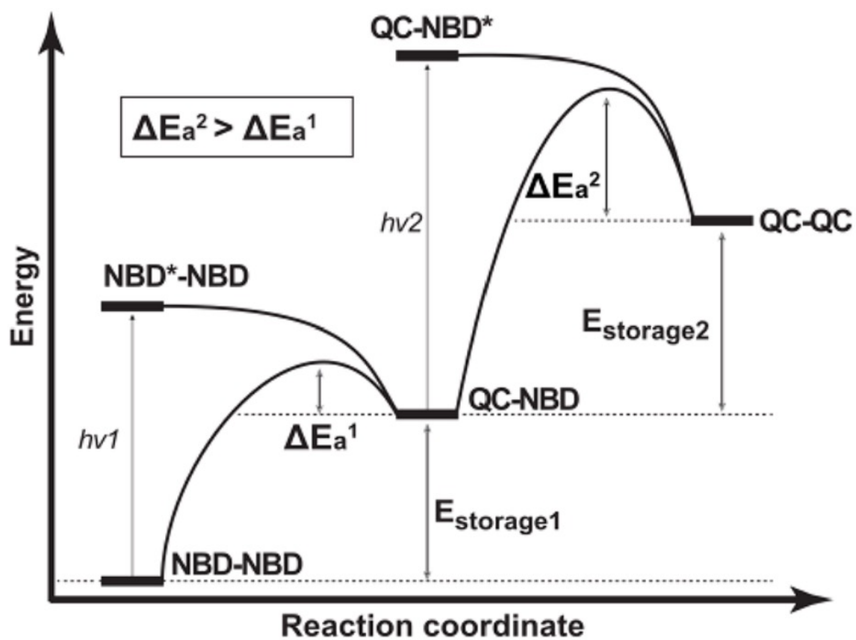
NBD Dimer



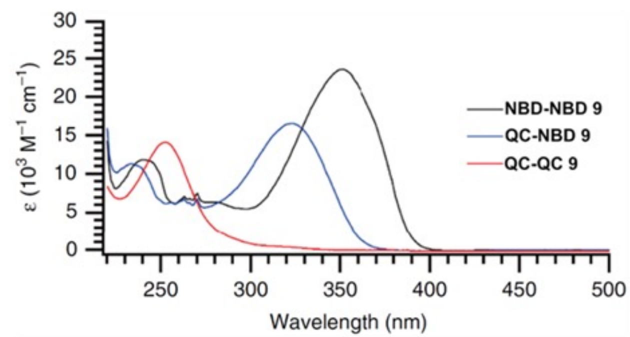
NBD-NBD

QC-NBD
$t_1/_2$= 2 days

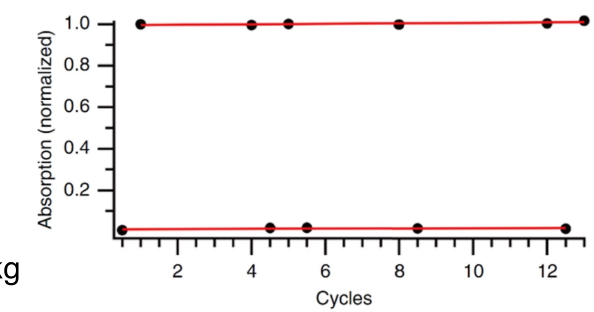
QC-QC
$t_1/_2$= 10 days



UV-Vis of dimer isomers



Degradation per cycle = 0.11%



energy density > 0.3 MJ/kg
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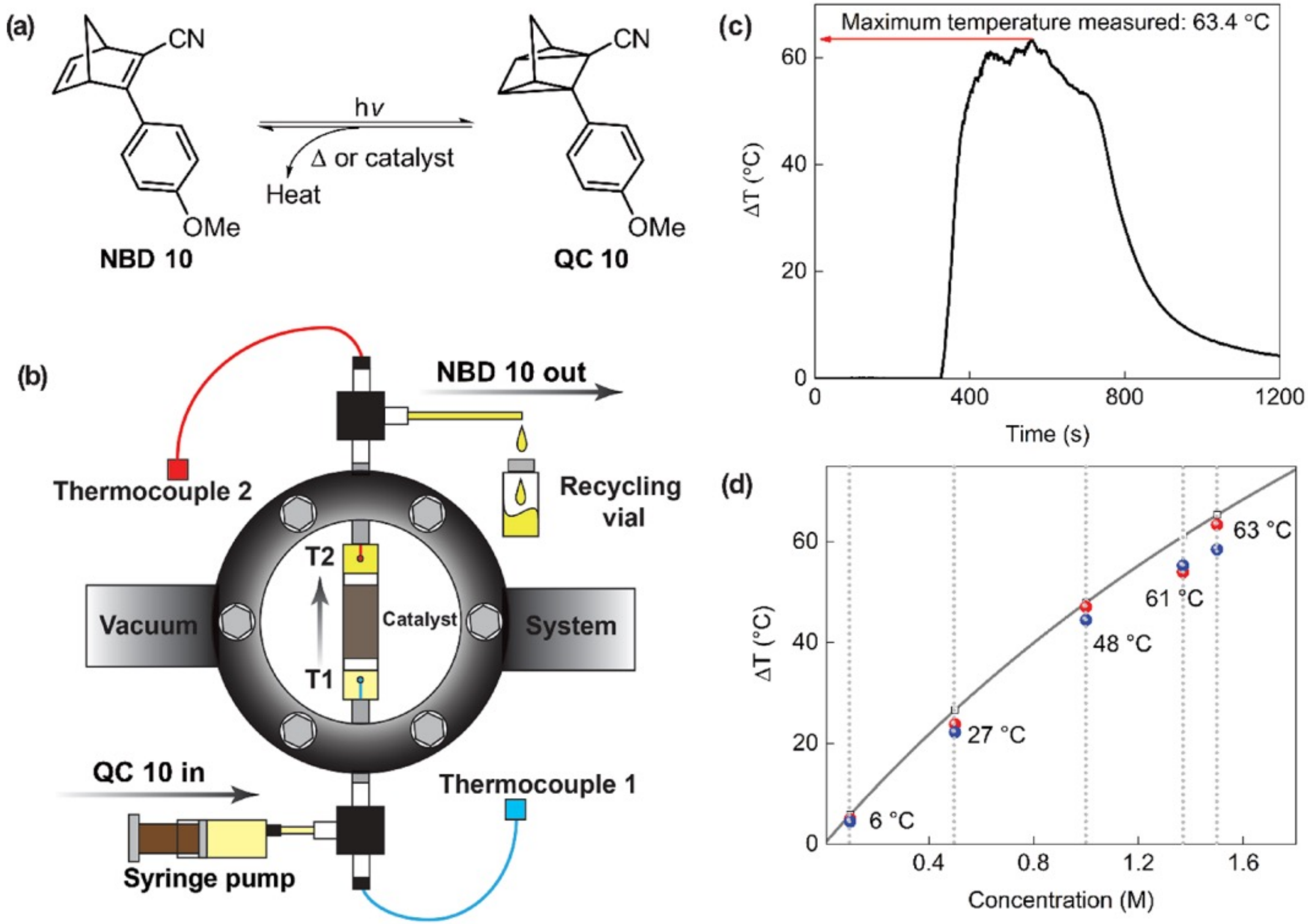
ChemPhotoChem, 2019, 3, 268
Acc. Chem. Res. 2002, 53, 1478

Designing Prototypical Storage Devices



Acc. Chem. Res. 2002, 53, 1478

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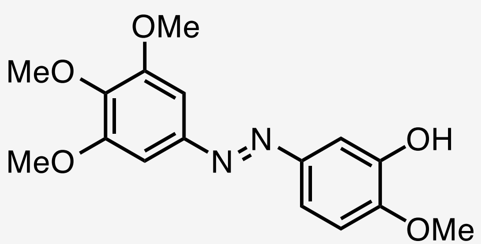
Conclusion & Outlook

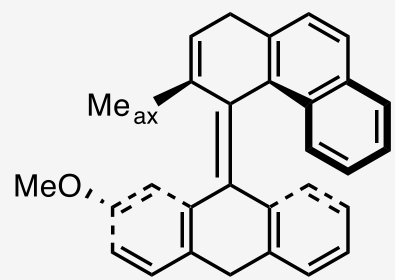
- Molecular photoswitches are a class of small molecules that can undergo a reversible change in their physical and chemical properties upon exposure to light.

- Photoswitches are highly versatile, as they can be triggered by different wavelengths of light, and can be designed to switch between various states, such as between an "on" and "off" state.

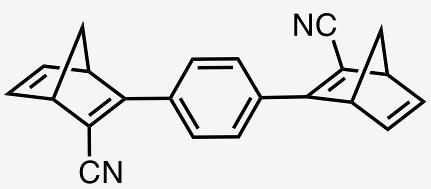
- They have a wide range of potential applications, including those in drug delivery, biomaterials, molecular machines, data and energy storage, sensing, and more !



Photopharmacology



Molecular motors



Solar energy storage

- The ideal photoswitch is the photoswitch that has been optimized for the task at hand.

- Future directions in this field looks towards visible light and NIR activation, improving photoefficiency, and systems including multiple photoswitches.

Thank you for your attention !