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
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III. Conclusion & Outlook
Introduction

Photochromism is characterized by a light-induced reversible change in color, and was first described by Fritzche in 1867.
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\[
\text{O}_2, \text{hv} \quad \xrightarrow{\Delta} \quad \text{O}_2
\]
Introduction

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

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

- Naphthopyrans
- Spirooxazines
Introduction

While photoswitches are indeed photochromic, the reversible changes they go through extend beyond just a simple color change.

Photoswitches are small molecules that, upon exposure to light, undergo a reversible change in geometry, polarity, and/or charge distribution.
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**Photoswitches** are small molecules that, upon exposure to light, undergo a reversible change in geometry, polarity, and/or charge distribution.

![Diagram of photoswitch mechanism](image)

**T-type photoswitch**

back reaction occurs thermally
thermally labile
Introduction

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Photoswitches are small molecules that, upon exposure to light, undergo a reversible change in geometry, polarity, and/or charge distribution.

$\lambda_{\text{max(I)}} \xrightarrow{h_1} \lambda_{\text{max(II)}}$

$\Delta$

**T-type photoswitch**
back reaction occurs thermally labile

$\lambda_{\text{max(I)}} \xleftarrow{h_1} \lambda_{\text{max(II)}}$

$\lambda_{\text{max(I)}} \xrightarrow{h_2} \lambda_{\text{max(II)}}$

**P-type photoswitch**
back reaction occurs photochemically thermally bistable
Thermodynamic vs. Photodynamic Equilibria

Thermodynamic Equilibrium

Thermodynamic equilibrium

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

Principle of microscopic reversibility
Thermodynamic vs. Photodynamic Equilibria
Thermodynamic vs. Photodynamic Equilibria

Photodynamic Equilibrium

Excited state

P-type photoswitch

T-type photoswitch

Reaction coordinate

E
Thermodynamic vs. Photodynamic Equilibria

Photodynamic Equilibrium

![Diagram of thermodynamic vs. photodynamic equilibria](image)

Photostationary state

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

$\varepsilon = \text{extinction coefficient}$

$\Phi = \text{quantum yield}$

Principle of microscopic reversibility does not 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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**Photoisomerization**
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- acylhydrazones
- hemithioindigo

**Photocyclical ring-opening/closing**
- spiropyrans
- spirooxazines
- fulgides/fulgimides
- diarylethenes

* Other (less common) processes include photo-induced proton transfer and dimerization.
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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III. Conclusion & Outlook
Photopharmacology involves the introduction of a photoswitch into the molecular structure of a bioactive compound.

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

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![Diagram showing different types of drugs and their effects](image)

- Conventional drug
- Prodrug
- Reversibly photocontrolled drug

Problems caused by active drugs:
- Environmental toxicity and emergence of resistance

Toxicity:
- Adverse side effects
- Suboptimal dosage
- Drug resistance
Photopharmacology

Advantages of light as an external stimulus

- non-invasive
- can be regulated as desired (wavelength, intensity)
- can be delivered with high spatial and temporal precision

reversible control
Photopharmacology

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reversible control

Strategy 1 (Direct)

active isomer \[ \text{hv}_1 \text{hv}_2 \]

inactive isomer

Strategy 2 (Indirect)

high activity \[ \text{hv}_1 \text{hv}_2 \]

low activity
Popular Motifs

Azobenzenes (T-type)

\[
\begin{align*}
\text{photoisomerization} \\
\text{large changes in geometry and polarity} \\
\lambda_{\text{max}} (E) &= 320 \text{ nm (nππ*), 450 nm (nππ*)} \\
\lambda_{\text{max}} (Z) &= 270 \text{ nm (πππ*), 450 nm (nππ*)} \\
t_{1/2} (Z) &= 2 \text{ days} \\
\text{distance change} &= 3 \text{ Å} \\
\text{dipole moment change} &= 3 \text{ D}
\end{align*}
\]

Diarylethenes (P-type)

\[
\begin{align*}
\text{photoinduced cyclization/ring opening} \\
\text{large changes in flexibility and electronics} \\
\lambda_{\text{max}} \text{ (open)} &= 303 \text{ nm} \\
\lambda_{\text{max}} \text{ (closed)} &= 505 \text{ nm} \\
t_{1/2} \text{(closed)} &= \sim 4-5 \times 10^5 \text{ years} \\
\text{distance change} &= 1 \text{ Å} \\
\text{dipole moment change} &= \text{minimal}
\end{align*}
\]
Photostatins (PSTs)

Microtubule inhibitors are a class of chemotherapeutics known for antimitotic and pro-apoptotic effects.
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\[
\begin{align*}
\text{Combretastatin A-4 (CA4)} \\
\text{multiple analogues have progressed to clinical trials} \\
\text{trans isomer is much less potent}
\end{align*}
\]

\[
\begin{align*}
\text{trans-PST-1 (inactive)} \\
\text{cis-PST-1 (active)}
\end{align*}
\]
Photostatins (PSTs)

PST-1

PST-1P
Photostatins (PSTs)

- PSTs are more cytotoxic under 390 nm irradiation than in the dark
- PST-1P cytotoxicity can be modulated by applying light of different wavelengths

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

- 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
Photostatins (PSTs)

- 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
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
Photostatins (PSTs)

\[
\begin{align*}
\text{colchicine} & \quad \text{Combretastatin A-4} & \quad \text{Photostatin}
\end{align*}
\]

**In summary:**
- The *cis* isomer of PSTs are 250x more cytotoxic than the corresponding *trans* isomer.
- PSTs can modulate mitosis with spatial precision on the cellular level.
- PSTs can modulate microtubule activity on the time-scale of seconds.
- PSTs can switch microtubule activity on and off by simply using blue & green light.
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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"

(3R,3'R)-(P,P)-(E)-3
with two axial methyl groups
$C_2$-symmetry
$\Delta E = 0.0 \text{ kcal/mol}$

(3R,3'R)-(M,M)-(E)-3
with two equatorial methyl groups
$C_2$-symmetry
$\Delta E = +10.2 \text{ kcal/mol}$

(3R,3'R)-(P,P)-(Z)-4
with two axial methyl groups
$C_2$-symmetry
$\Delta E = 0.0 \text{ kcal/mol}$

(3R,3'R)-(M,M)-(Z)-4
$\Delta E = +11.1 \text{ kcal/mol}$
Biphenanthrylidene scaffold with axial chirality
"helicity"

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\begin{align*}
(3R,3'R)-(P,P)-(E)-3 & \quad \text{with two axial methyl groups} \\
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& \quad C_2\text{-symmetry} \\
& \quad \Delta E = +11.1 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
(P,P)-\text{trans-1} & \quad \text{at } 60^\circ \text{C} \\
(M,M)-\text{cis-2} & \quad \text{at } 20^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
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(M,M)-\text{trans-1} & \quad \text{at } 20^\circ \text{C}
\end{align*}
\]

Nature, 1999, 401, 152
First Generation Molecular Motor

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

Continuous, unidirectional, 360° rotation
Second Generation Molecular Motor

Continuous, unidirectional, 360° rotation

Asymmetric scaffold, more control elements

Nature, 1999, 401, 152
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
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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).
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Ideal systems should have:

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

\[ \lambda_{\text{max}}(\text{NBD}) = 213 \text{ nm} \]
\[ \lambda_{\text{max}}(\text{QC}) = 236 \text{ nm} \]
\[ \text{MW} = 92 \text{ g/mol} \]
\[ \Delta G_{\text{isom}}(\text{QC} \square \text{NBD}) = 89 \text{ kcal/mol} \]
\[ t_{1/2}(\text{QC}) = \sim 10^7 \text{ h} (1140 \text{ y}) @ RT \]
NBD Modifications: Red Shifting and QC Stabilization

Table 1. MOST Parameters of NBDs 1–8

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

NBD Dimer

NBD-NBD  \[ \xrightarrow{\Delta} \] QC-NBD \[ t_{1/2} = 2 \text{ days} \] \[ \xrightarrow{\Delta} \] QC-QC \[ t_{1/2} = 10 \text{ days} \]
NBD Dimer

\[
\text{NBD-NBD} \quad \xrightarrow{\Delta} \quad \text{QC-NBD} \quad t_{1/2} = 2 \text{ days}
\]

\[
\text{QC-NBD} \quad \xrightarrow{\Delta} \quad \text{QC-QC} \quad t_{1/2} = 10 \text{ days}
\]

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

ChemPhotoChem, 2019, 3, 268
**NBD Dimer**

![Chemical structures of NBD-NBD, QC-NBD, and QC-QC with reaction pathways and energy levels](image)

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

**UV-Vis of dimer isomers**

- Energy density > 0.3 MJ/kg
- Dimer & trimer systems showed energy densities up to 0.9 MJ/kg
NBD Dimer

NBD-NBD

QC-NBD
\[ t_{1/2} = 2 \text{ days} \]

QC-QC
\[ t_{1/2} = 10 \text{ days} \]

UV-Vis of dimer isomers

Energy density > 0.3 MJ/kg
dimer & trimer systems showed energy densities up to 0.9 MJ/kg
Designing Prototypical Storage Devices

(a) NBD 10 → QC 10

(b) Thermocouple 2

(c) Maximum temperature measured: 63.4 °C

(d) ΔT °C vs. Concentration (M)

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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!

- 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!