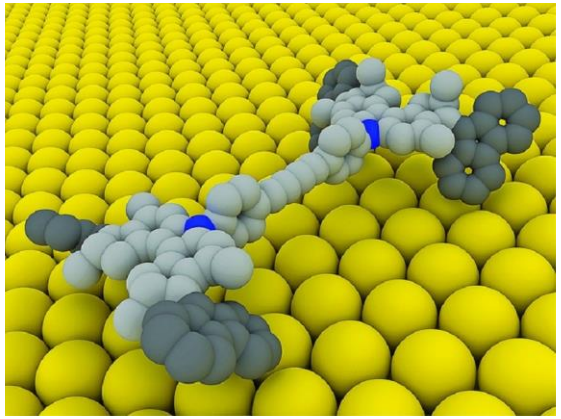
MUNI PHARM
Department of Natural Drugs

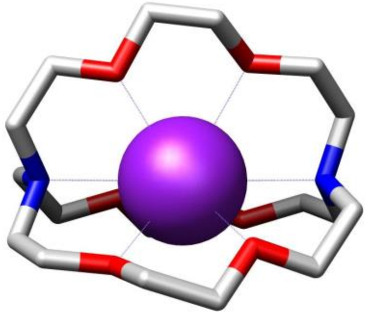


Supramolecular Pharmacy

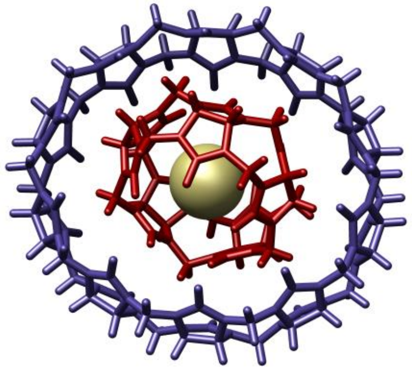
13. Molecular machines and nano/microrobots

Ondřej Jurček

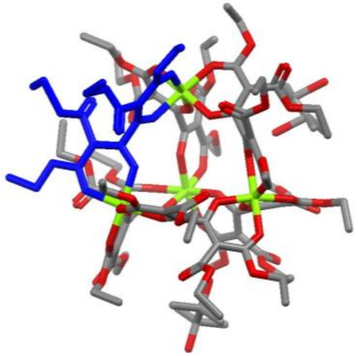
30 years of Supramolecular Chemistry



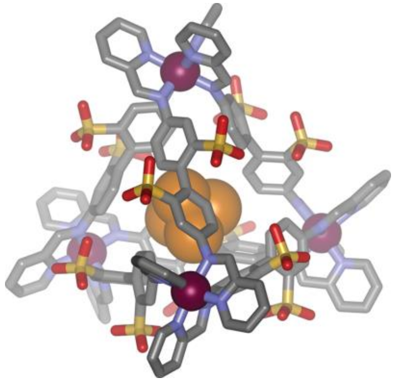
cryptands



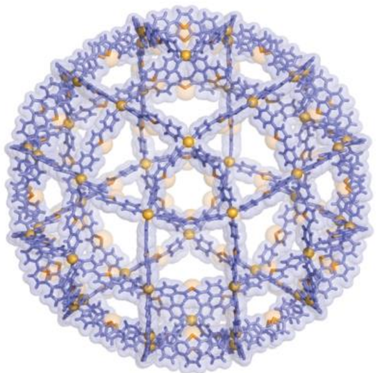
host-guest chemistry



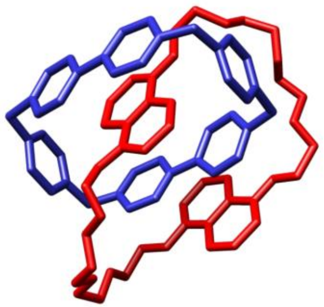
Mg_4L_6 cage



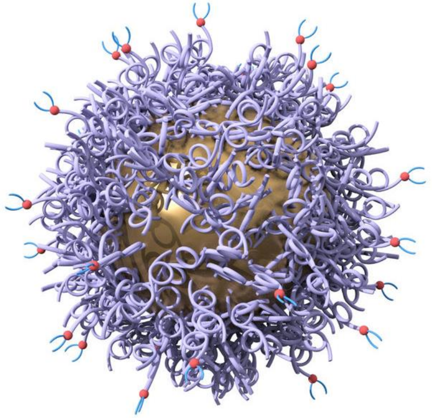
air-stable P_4 inside a cage



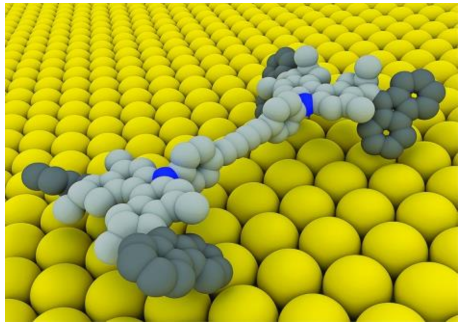
sphere $Pd_{48}L_{96}$



blue box catenane



nanoparticles



molecular machines nanocar

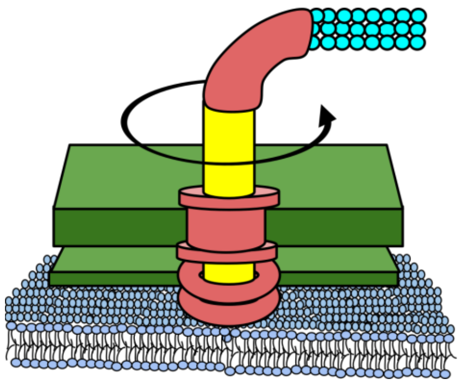
History

- 1987 – Award of the Nobel prize for Chemistry to Donald J. Cram, Jean-Marie Lehn and Charles J. Pedersen "for their development and use of molecules with structure-specific interactions of high selectivity„
- 1991 – J. Fraser Stoddart introduces rotaxanes
- 1999 – Bernard L. Feringa developed molecular motor
- 2016 – Award of the Nobel prize for Chemistry to Jean-Pierre Sauvage, Sir J. Fraser Stoddart, Bernard L. Feringa "for the design and synthesis of molecular machines"

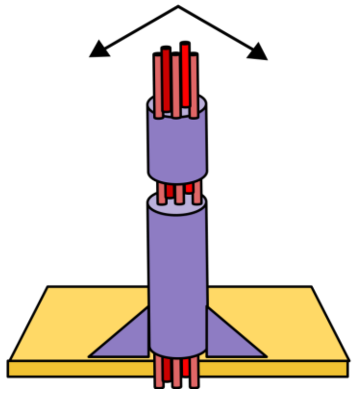
Biological molecular machines

- Motor proteins such as myosin (muscle contraction); kinesin (moves cargo inside cells away from the nucleus along microtubules); and dynein (moves cargo inside cells towards the nucleus and produces the beating of flagella)
- ATP synthase which harnesses energy from proton gradients across membranes to drive a turbine-like motion used to synthesize ATP
- DNA polymerases for replicating DNA, RNA polymerases for producing mRNA, or the ribosome for synthesizing proteins

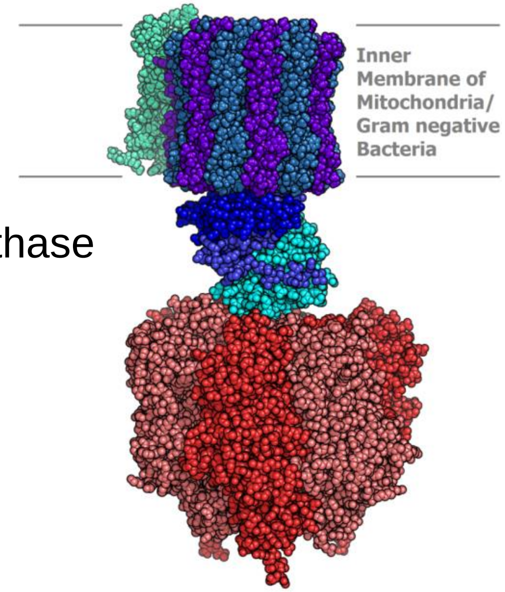
Prokaryotic flagellum



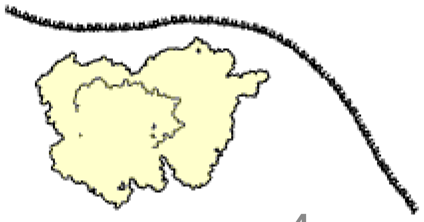
Eukaryotic flagellum



ATP synthase



Ribosome synthesis of protein



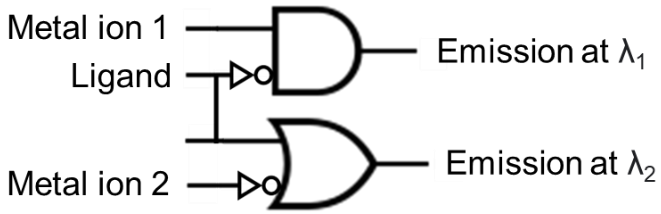
Wikipedia

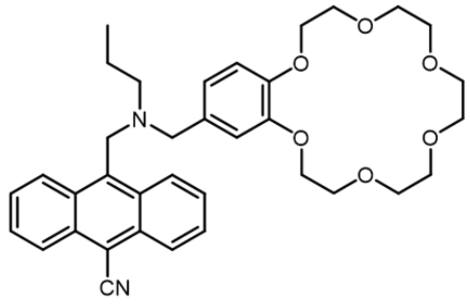
Artificial Molecular Machines

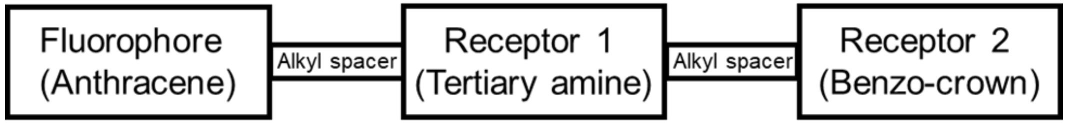
- Machine is a piece of equipment with several moving parts that uses power to do a particular type of work
- **Artificial molecular machine (AMMs)** = class of molecules typically described as an assembly of a discrete number of molecular components intended to produce mechanical movements in response to specific stimuli
- AMMs require presence of moving parts, the ability to consume energy, and the ability to perform a task
- AMMs exploit the existing modes of motion in molecules, such as rotation about single bonds or *cis*-*trans* isomerization
- Well-orchestrated symphony of molecular interactions is required to translate molecular-level motion, which is usually induced on the sub-nanometer level, into effects that can be measured and used on the micro and macro levels
- A broad range of AMMs has been designed, featuring different properties and applications; some of these include **molecular motors, switches,** and **logic gates**.

Logic gates

- Molecular logic gates work with one or more input signals based on physical or/and chemical processes and with output signals based on spectroscopic phenomena





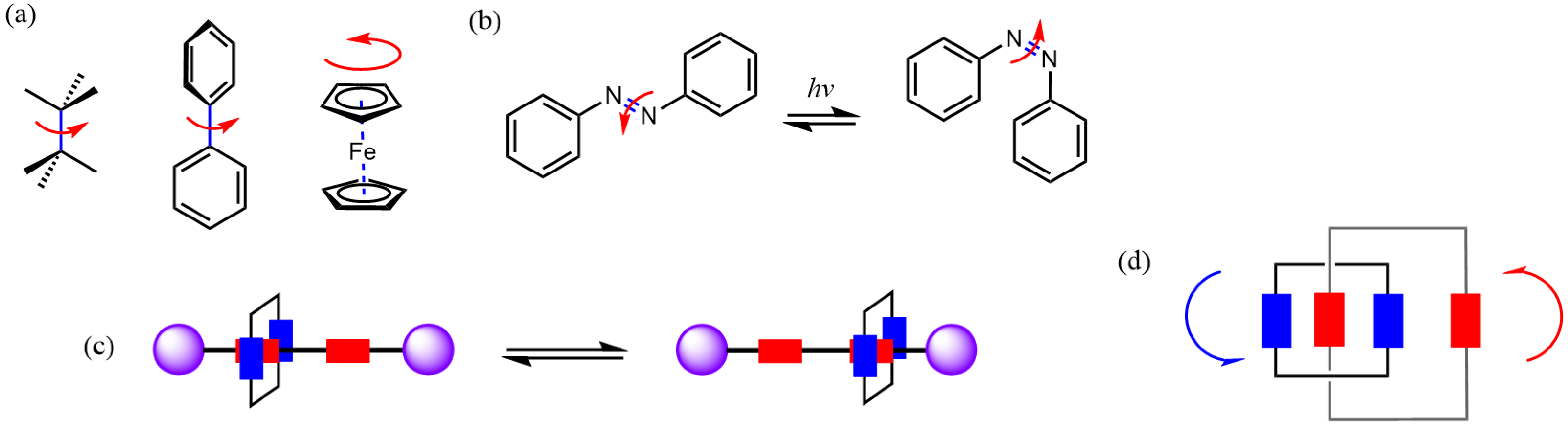


Input		Output (Q)						
								
A	B	AND	OR	INH	XOR	NAND	NOR	XNOR
0	0	0	0	0	0	1	1	1
0	1	0	1	0	1	1	0	0
1	0	0	1	1	1	1	0	0
1	1	1	1	0	0	0	0	1

Wikipedia: Molecular logic gate

Artificial Molecular Machines

- A major starting point for the design of AMMs is to exploit the existing modes of motion in molecules (light or chemically driven systems)

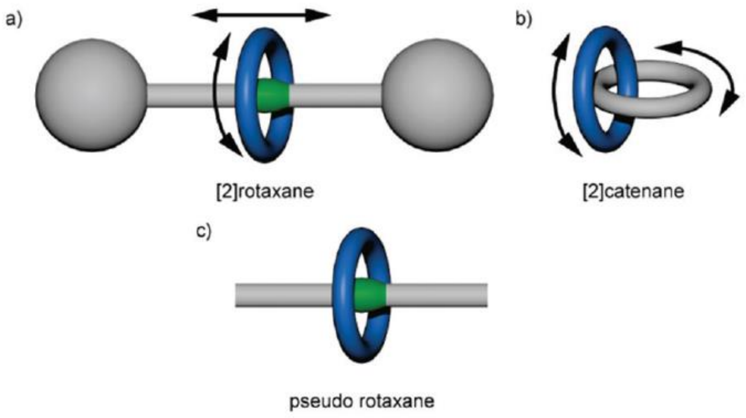


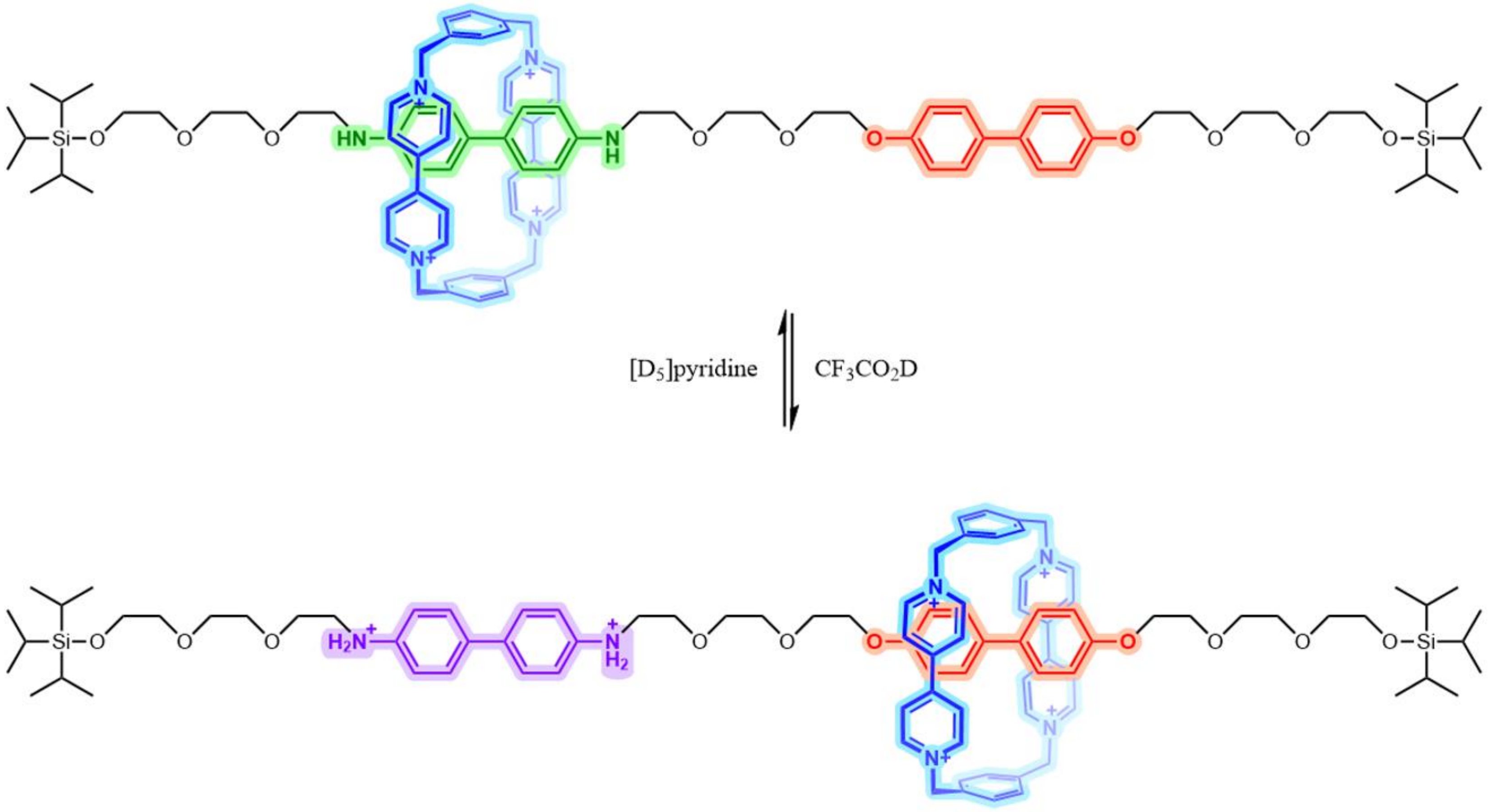
- Alignment, order, directionality, tracks, signaling, communication, compartmentalization, amplification, fuel, regeneration, replication, waste management, temporal and spatial control, and feedback loops are just a few things to consider in design

a) I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358. b) Wikipedia: Molecular machines

Invention of molecular shuttle by Sir F. Stoddart (1991)

Building upon the assembly of mechanically linked molecules such as catenanes and rotaxanes as developed by Jean-Pierre Sauvage in the early 1980s

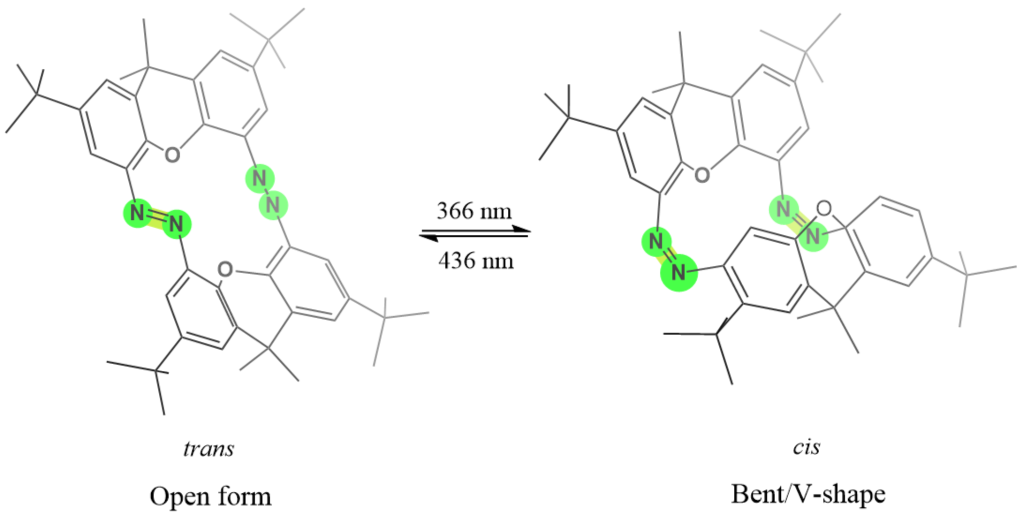


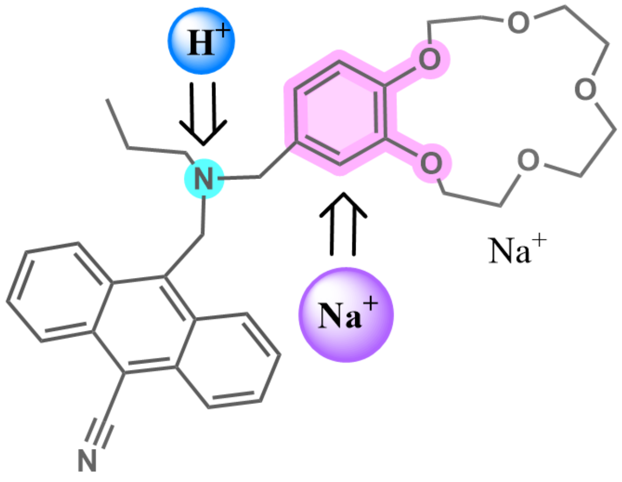


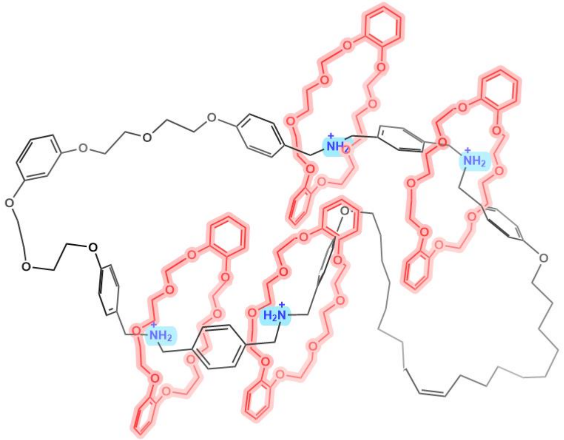
Stoddart et al. *J. Am. Chem. Soc.* 1991, 113, 13, 5131–5133

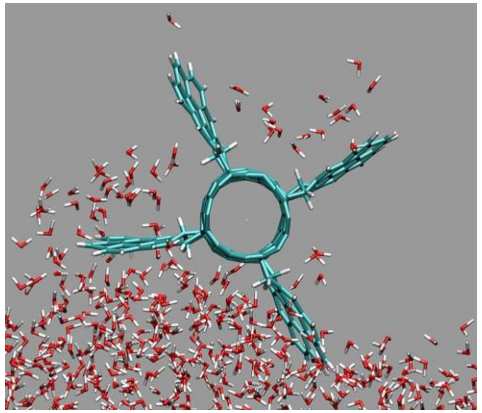
Types of artificial molecular machines

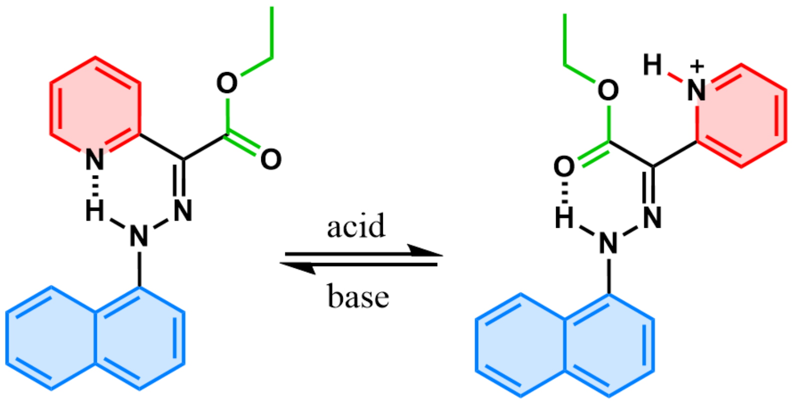
- Molecular hinge
- Molecular logic gate
- Molecular necklace
- Molecular propeller
- Molecular shuttle
- Molecular switch
- Molecular tweezers
- Molecular motor
- Nanocar







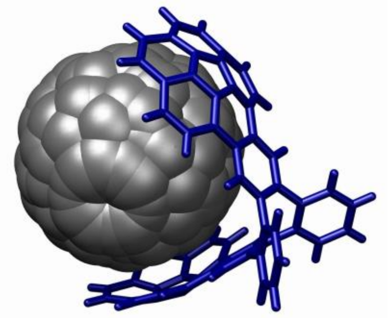


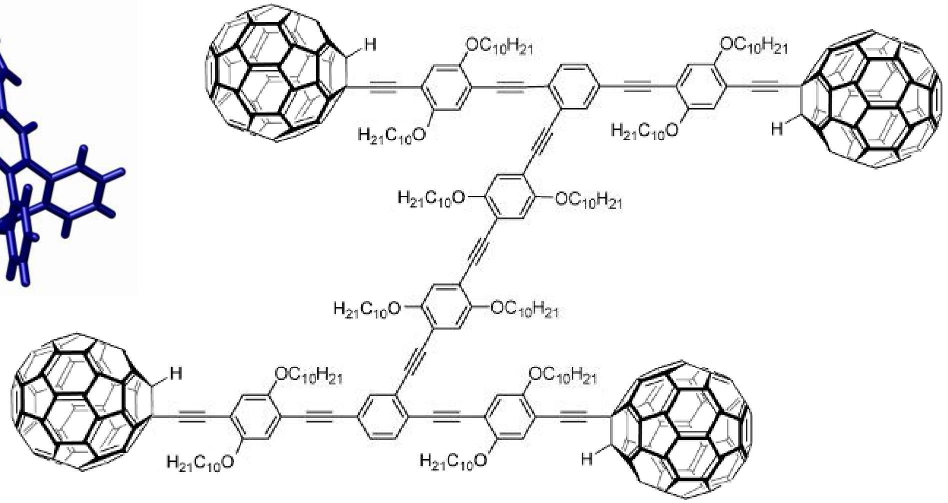


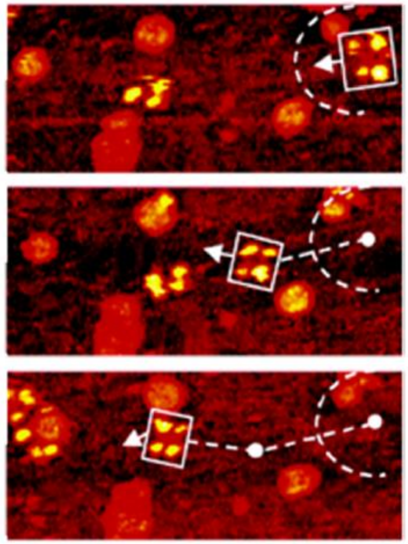
a) Feringa, Leigh et al. *Chem. Soc. Rev.* 2017, 46, 2592. b) Wikipedia: Molecular machines.

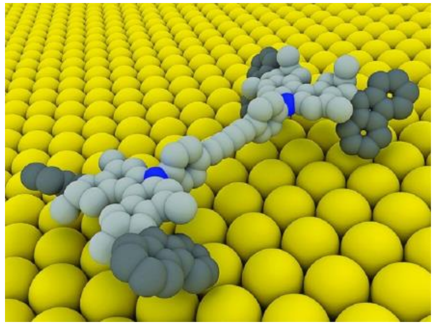
Types of artificial molecular machines

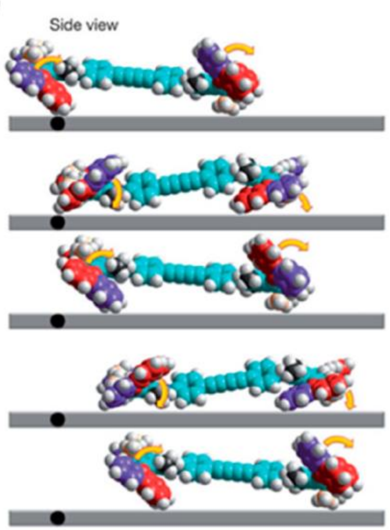
- Molecular hinge
- Molecular logic gate
- Molecular necklace
- Molecular propeller
- Molecular shuttle
- Molecular switch
- Molecular tweezers
- Molecular motor
- Nanocar

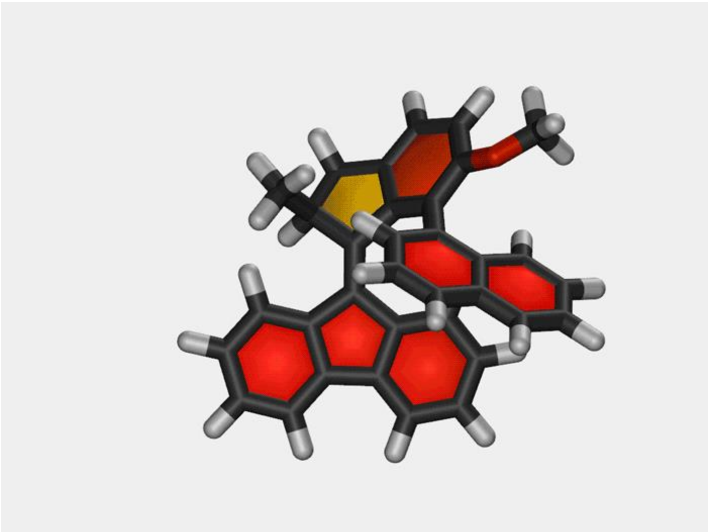


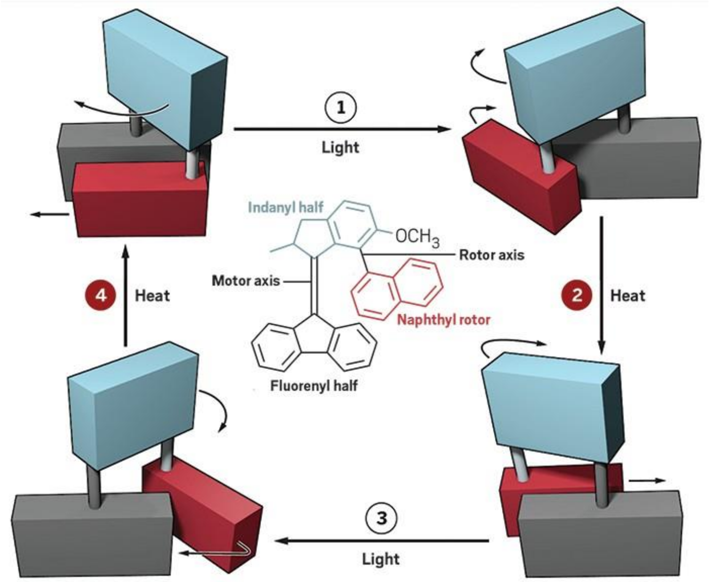








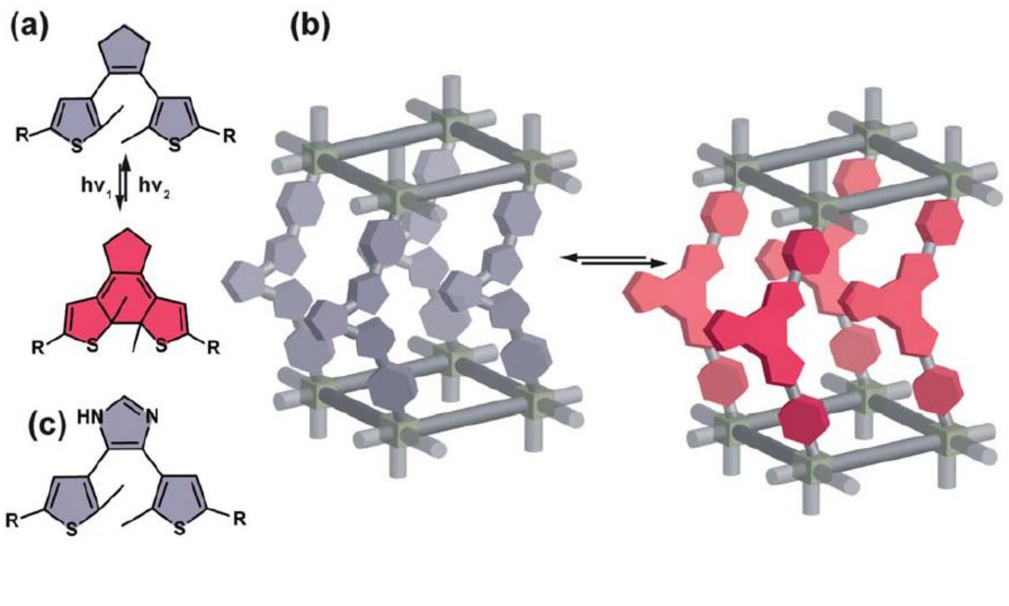


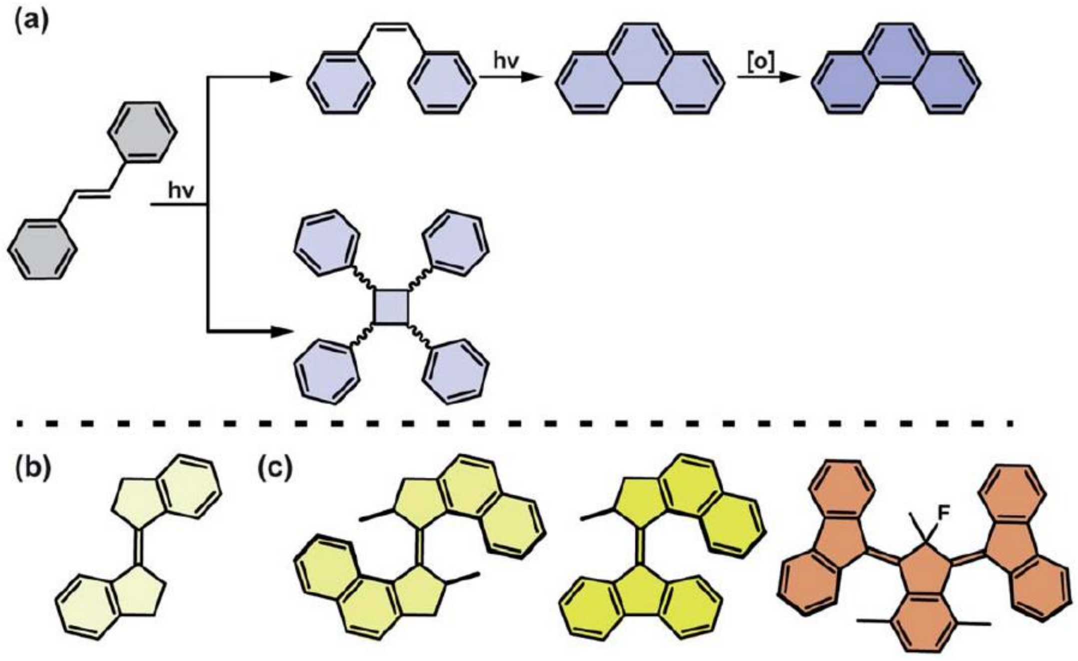


https://cen.acs.org/articles/95/i23/Molecular-motor-turns-rotor.html

Molecular machines in contact with environment

- Manner of providing the interface with environment is by integrating them into bulk materials (crystals, polymers, or liquid crystals) or by attaching molecular machines to surfaces
- ***Crystalline***: good to transfer machine‘s work in length (well-defined, ordered, periodic structure), *e.g.,* incorporating switches such as diarylethenes
    - crystal bending

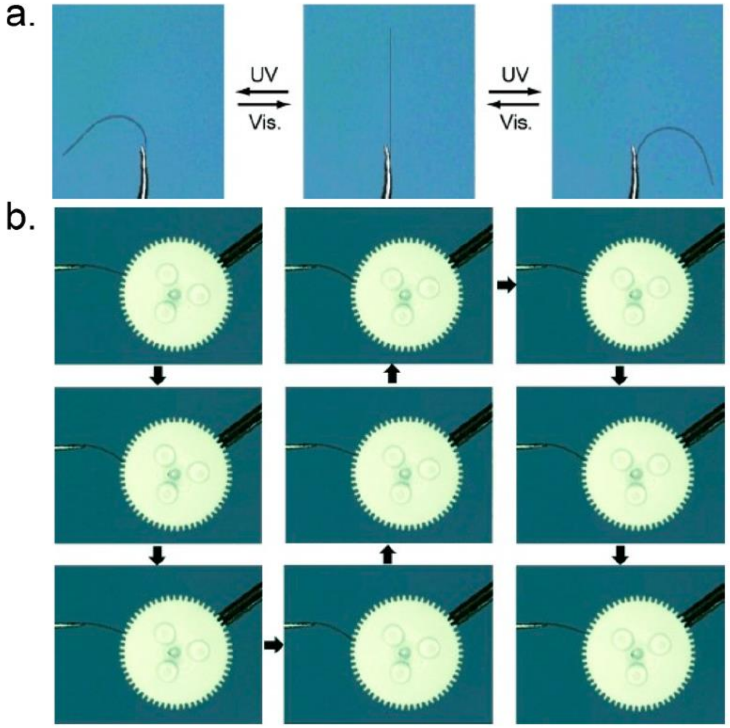


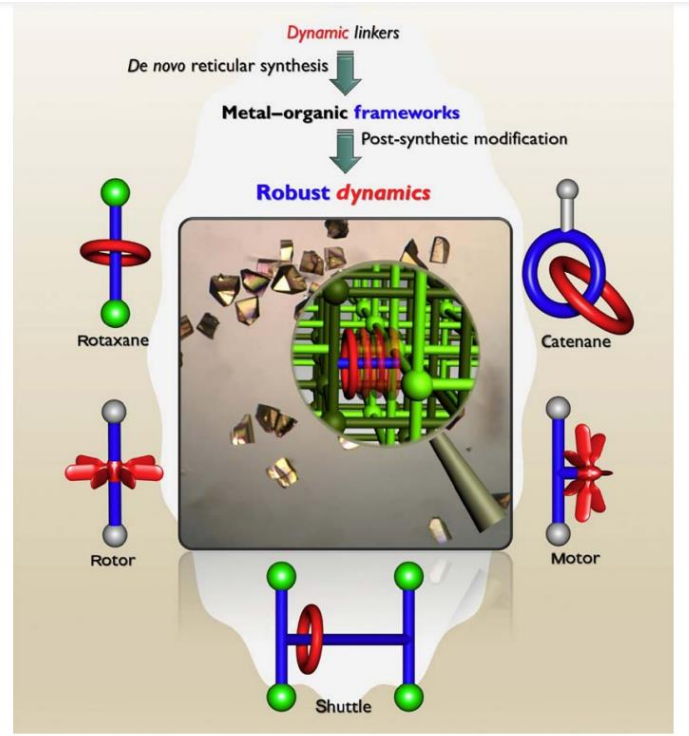


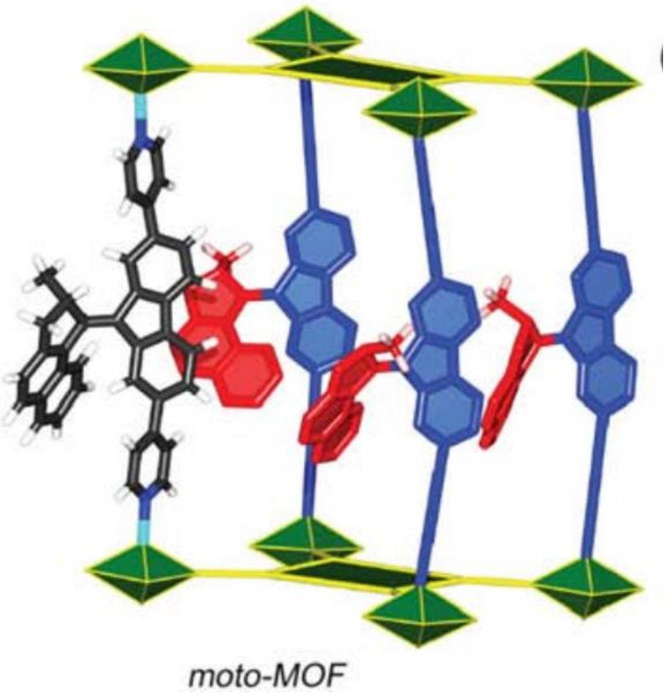
Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

Crystalline molecular machines

- Drawbacks: crystals are brittle, limited in size and possess narrow structural space
- Using light as trigger – limited penetration depth, which limits the thickness of crystals to be used (limiting the amount of work)
- Latest development is to incorporate molecular switches, rotors, and motors into MOFs





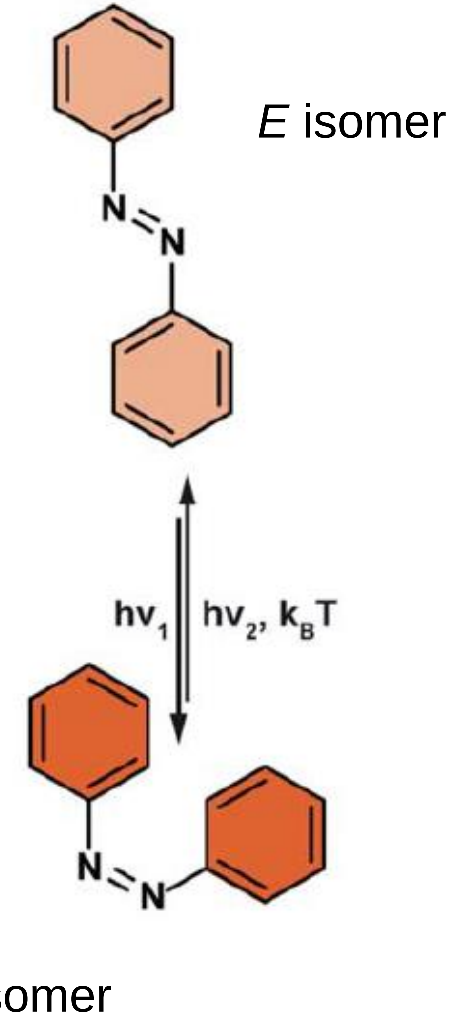


a) I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358. b) Terao et al. *Angew. Chem., Int. Ed.* 2012, 51, 901−904.
c) Martinez-Bulit et al. *Trends Chem.* 2019, vol. 1 (6), 588.

Molecular photoswitches

- ***Azobenzene photoswitches***

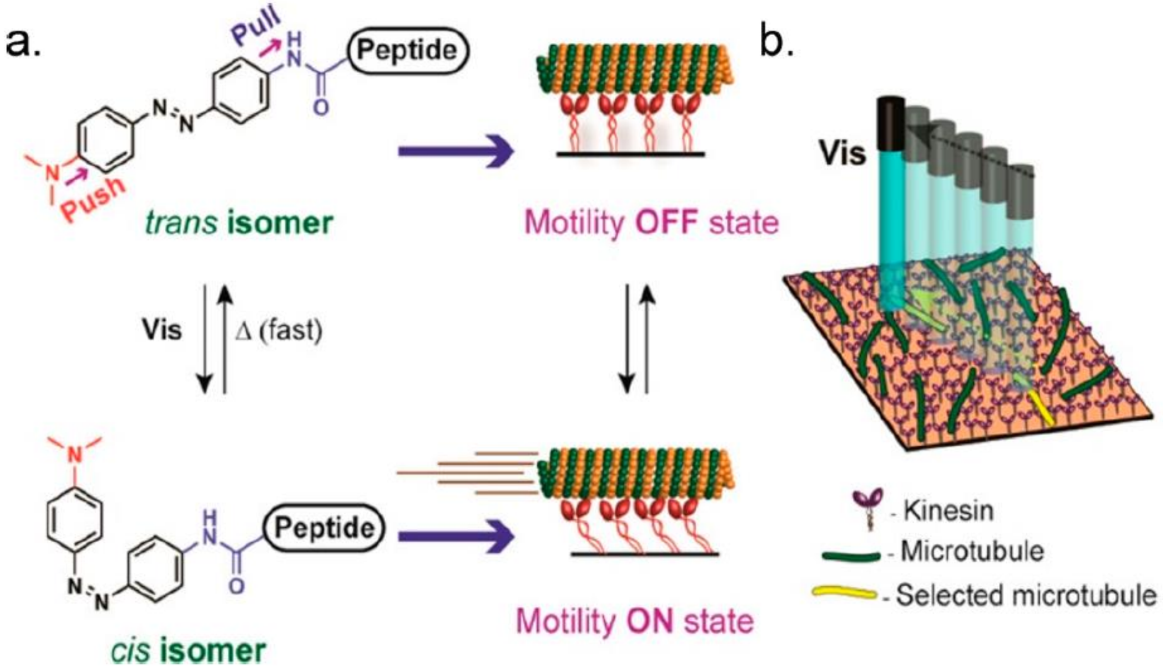
    - the most common used photoswitches (simple synthesis, photostability, reliability)
    - the planar *E* isomer goes into bulkier *Z* isomer
    - azobenzenes show high quantum yields for both *Z/E* and *E/Z* photoisomerizations, and high photostationary state ratios
    - nearly all the photophysical and photochemical properties of azobenzenes, in particular quantum yield, thermal stability of *Z*-isomer, photostationary state ratios, excitation wavelengths, can be tuned easily by introducing appropriate substituents at the azobenzene core
    - well-described in literature

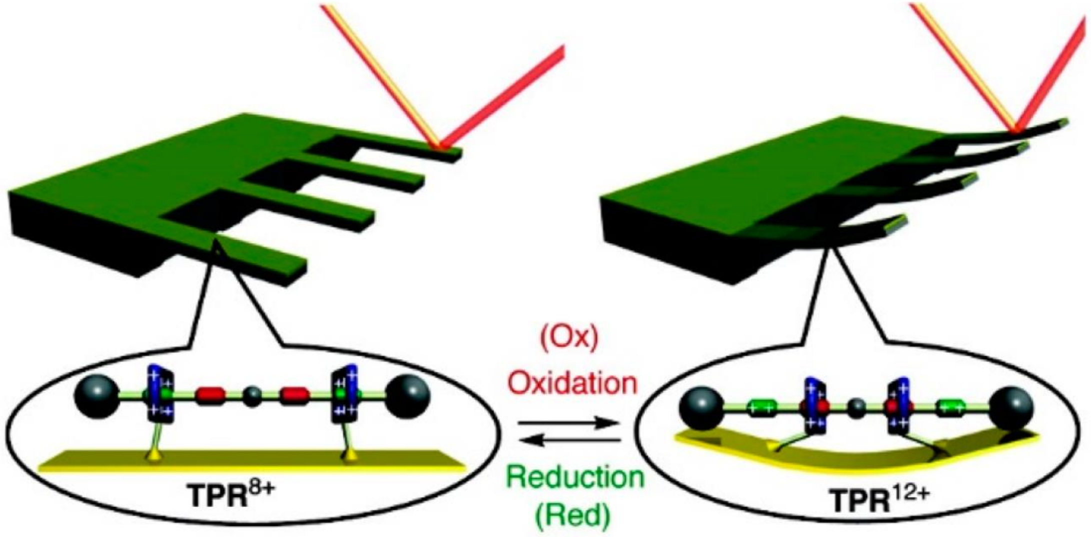


Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Surface mounted molecular machines

- The surface limits the degrees of freedom available to the molecules, imparts a certain amount of order on them, and is a convenient way for interfacing and scaling molecular events with/to the macroscopic world
- Performing work is by using their motion in producing stress on the surface – making them bend

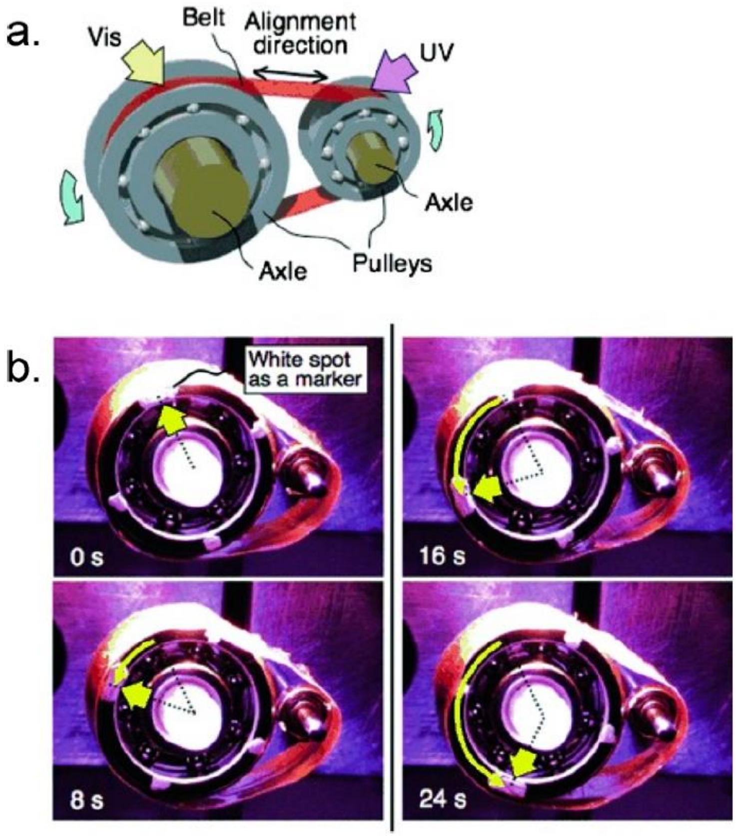


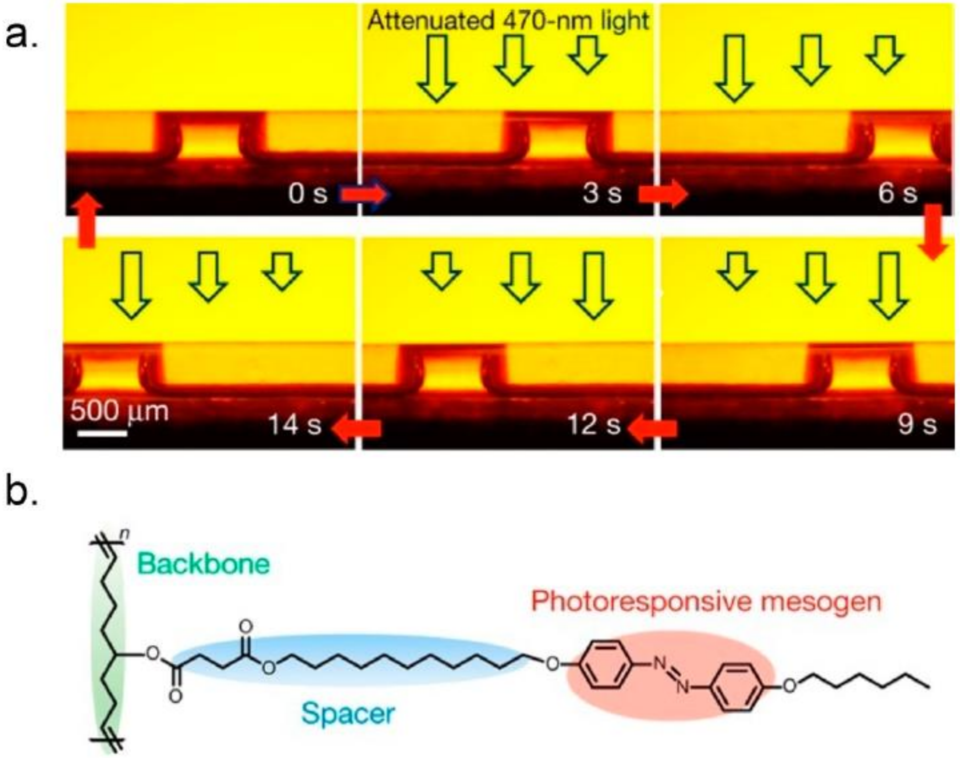


I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358.

Liquid crystal-polymer molecular machines

- Azobenzenes are the most used
- Light-penetration depth issue needs to be addressed as well, but it might be easier to tackle in polymers using negative photochromic compounds

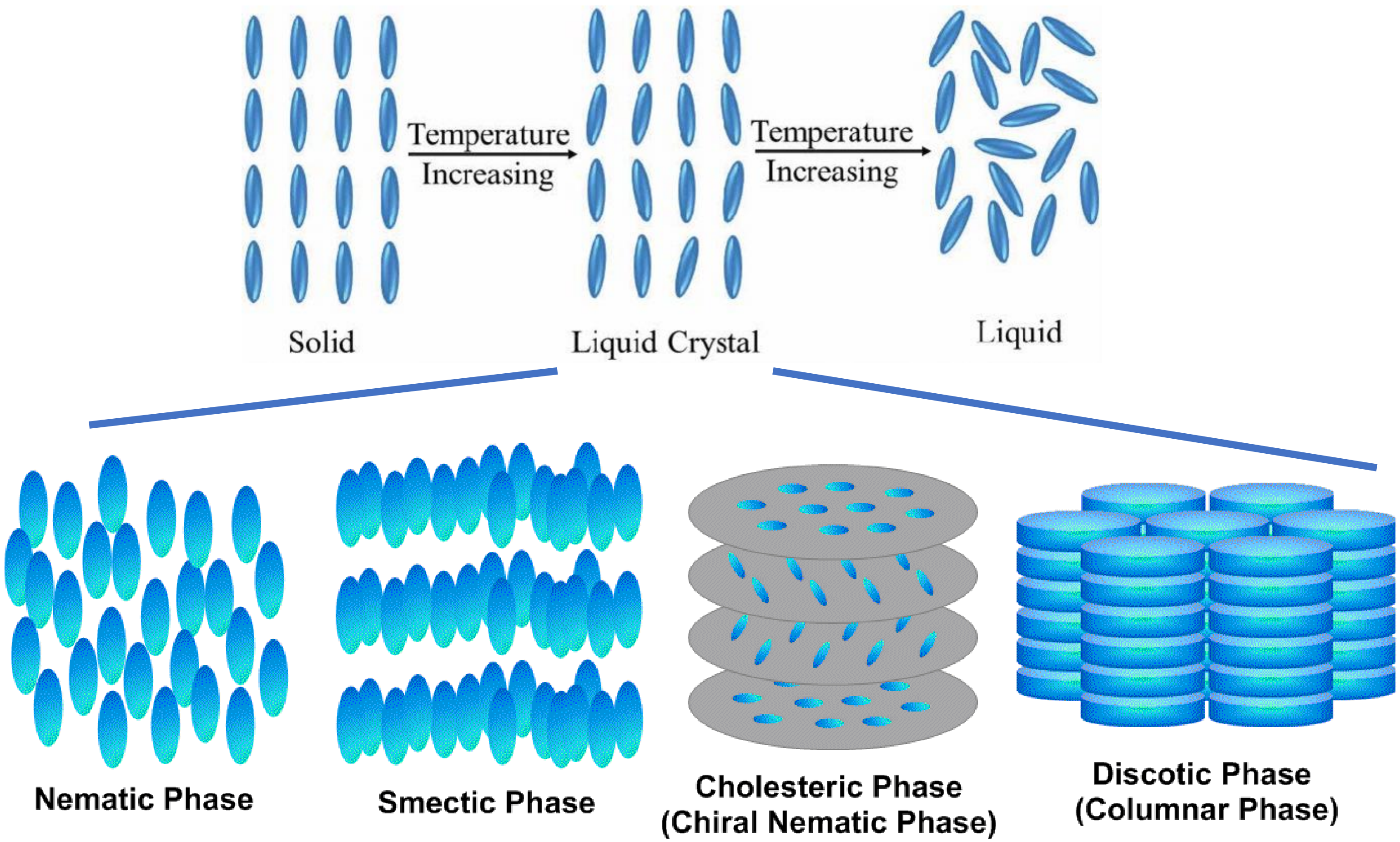


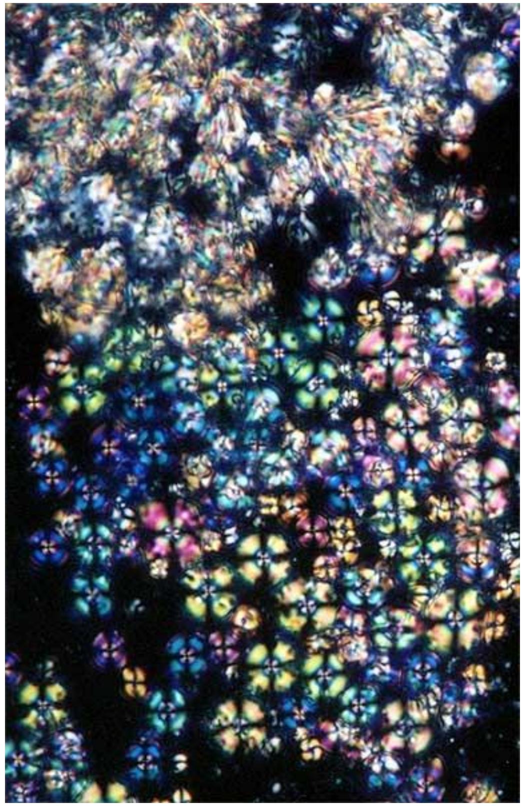


I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358.

Liquid crystals (LCs)

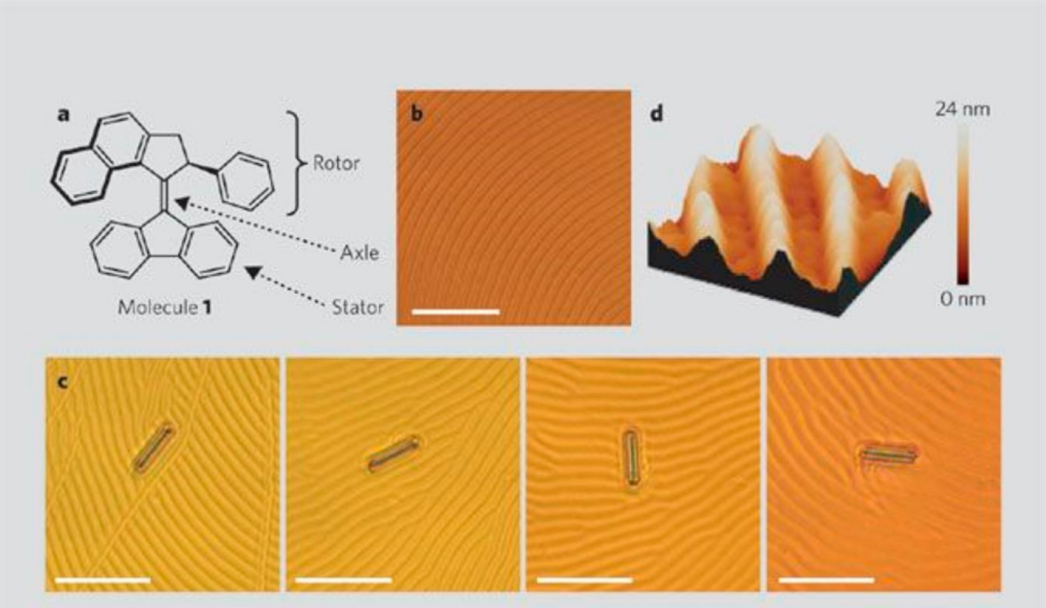
- Properties are between those of conventional liquids and those of solid crystals. For example, a liquid crystal can flow like a liquid, but its molecules may be oriented in a common direction as in solid.

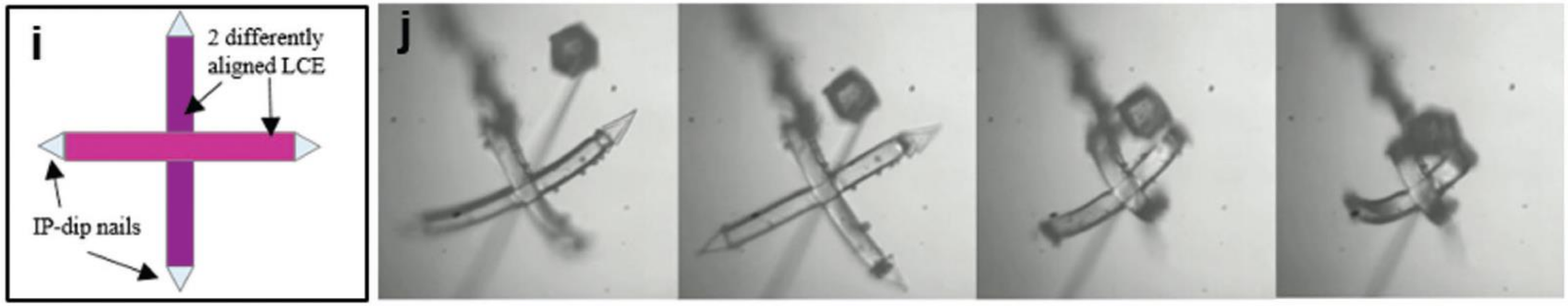




Liquid crystal (LC) molecular machines

- Ordered soft materials that can amplify, through their long-range self-assemby the tiniest of molecular motion; *i.e.*, they can be considered as molecular amplifiers
- LC can also translate chiral information
- Challenge is that they are liquid

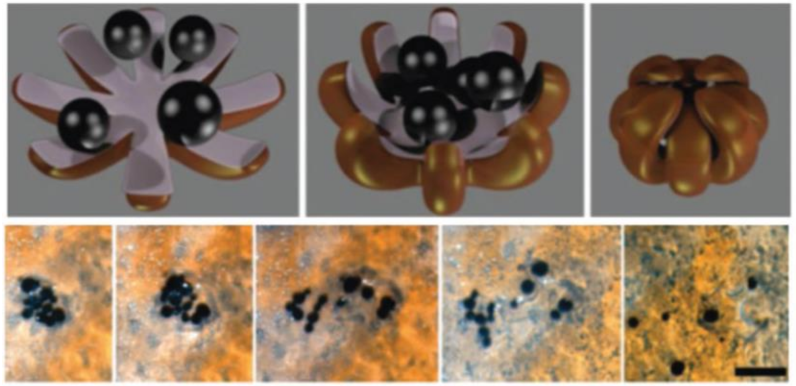


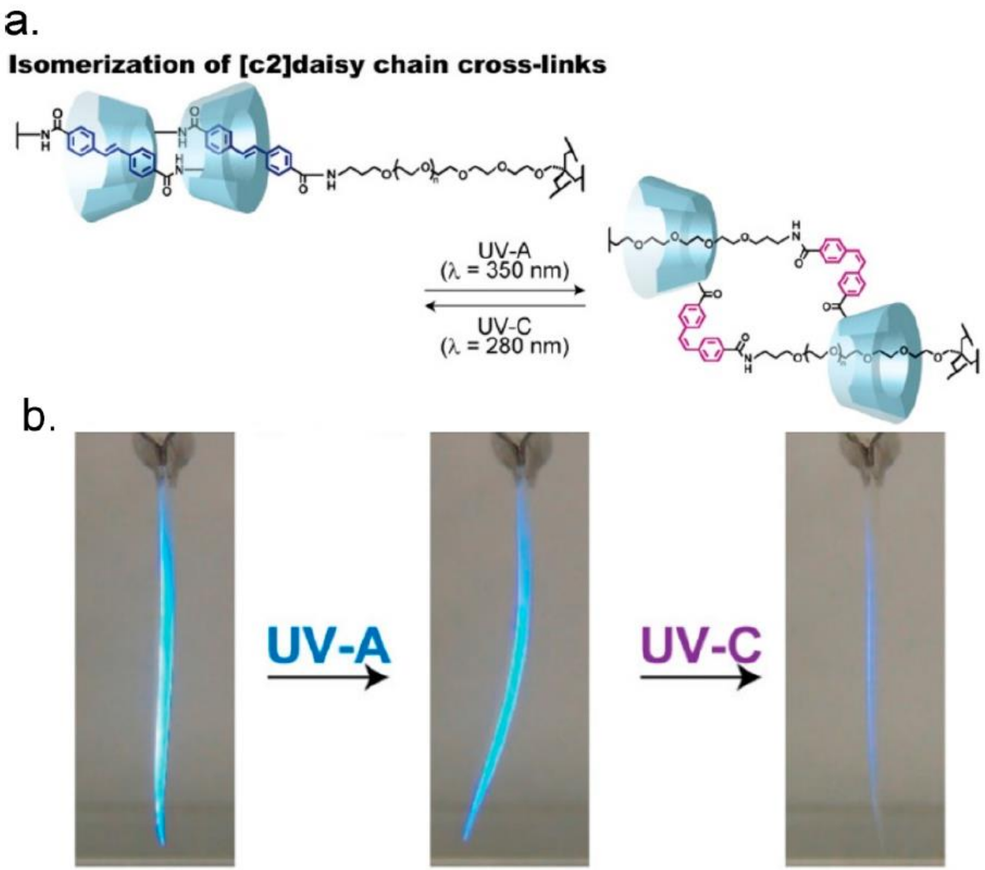


a) I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358. b) Nocentini et al. *Adv. Optical Mater.* 2018, 6, 1800207.

Molecular machines in polymers

- Irregular amorphous polymers possess difficulty in imparting synchronized and ordered motion
- Artificial muscles = α-cyclodextrin (α-CD) binds stronger with *trans*-stilbene than with *cis*-stilbene, allowing for the light-induced sliding of the α-CD ring from the stilbene station to a poly(ethyleneglycol) collection area upon *trans* → *cis* isomerization

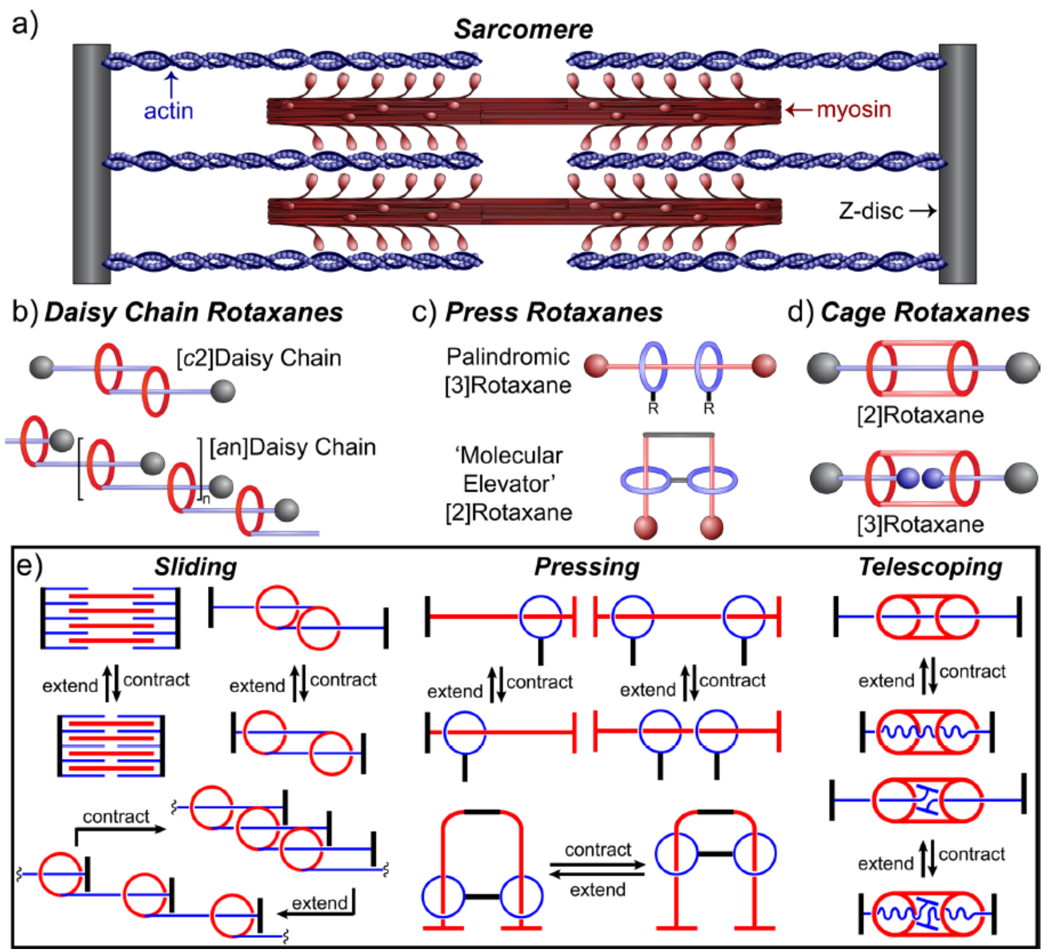


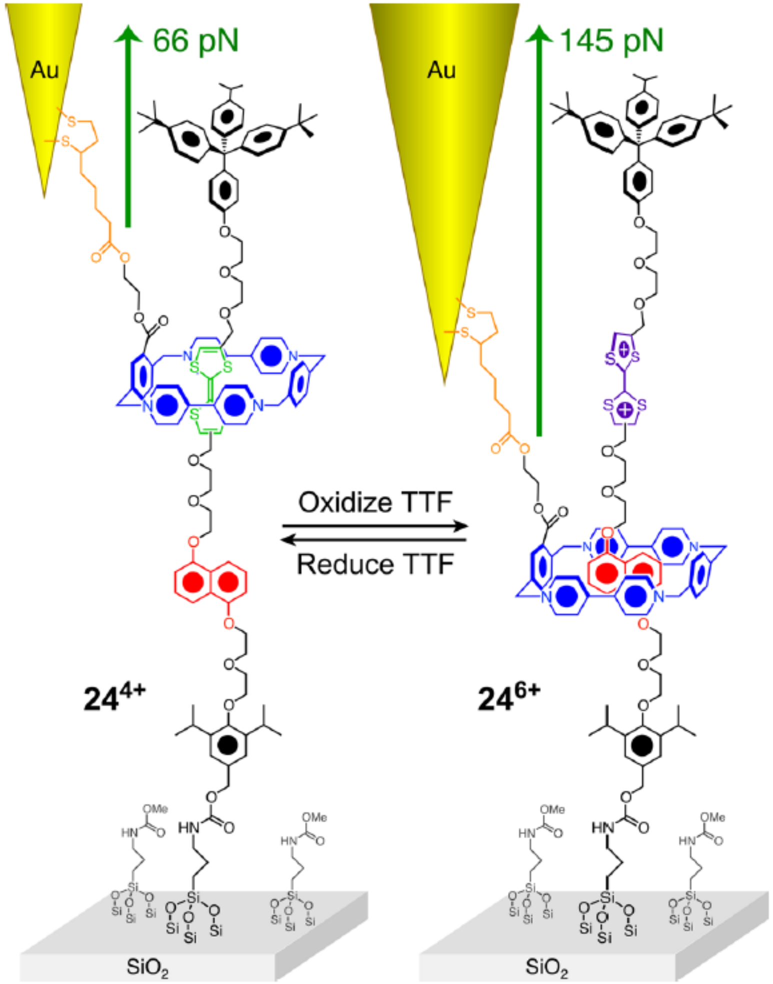


a) Stoddart et al. *Acc. Chem. Res.* 2014, 47, 2186−2199. b) I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358.
c) Nocentini et al. *Adv. Optical Mater.* 2018, 6, 1800207.

Rotaxane-based molecular muscles

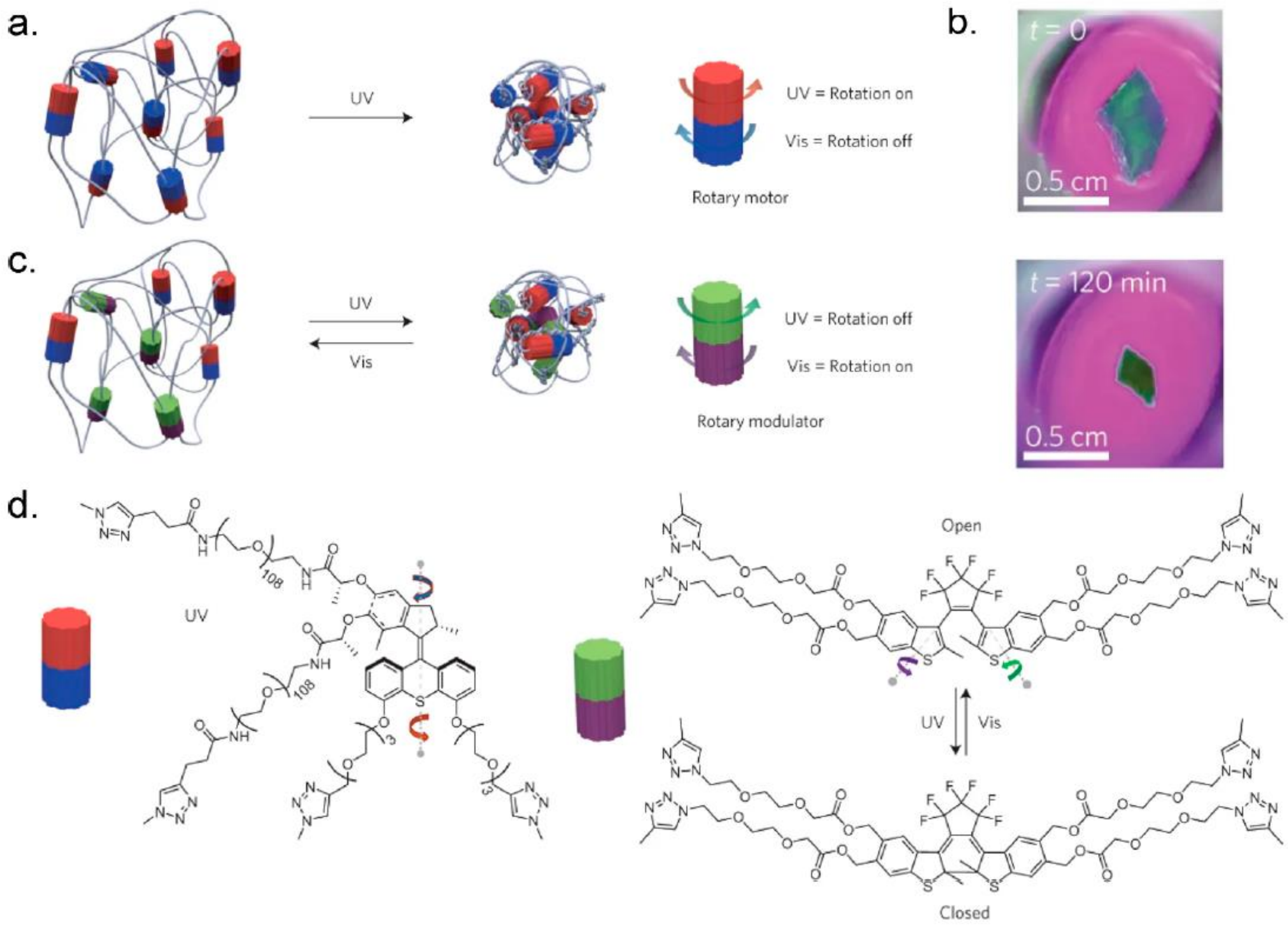
- “daisy chain”, “press”, and “cage” rotaxanes driven by ions, pH, light, solvents, and redox stimuli





Stoddart et al. *Acc. Chem. Res.* 2014, 47, 2186−2199.

Molecular machines in polymers



Drawbacks

- the switching process in such materials is slow, resulting in long irradiation times that lead to photodegradation, which restricts the number of switching cycles that can be obtained
- polymers only work in solution, *i.e.*, not as free-standing dry polymers, which further encumbers their practical use

a) Li et al. *Nat. Nanotechnol.* 2015, 10, 161−165. b) Foy et al. *Nat. Nanotechnol.* 2017, 12, 540−545.

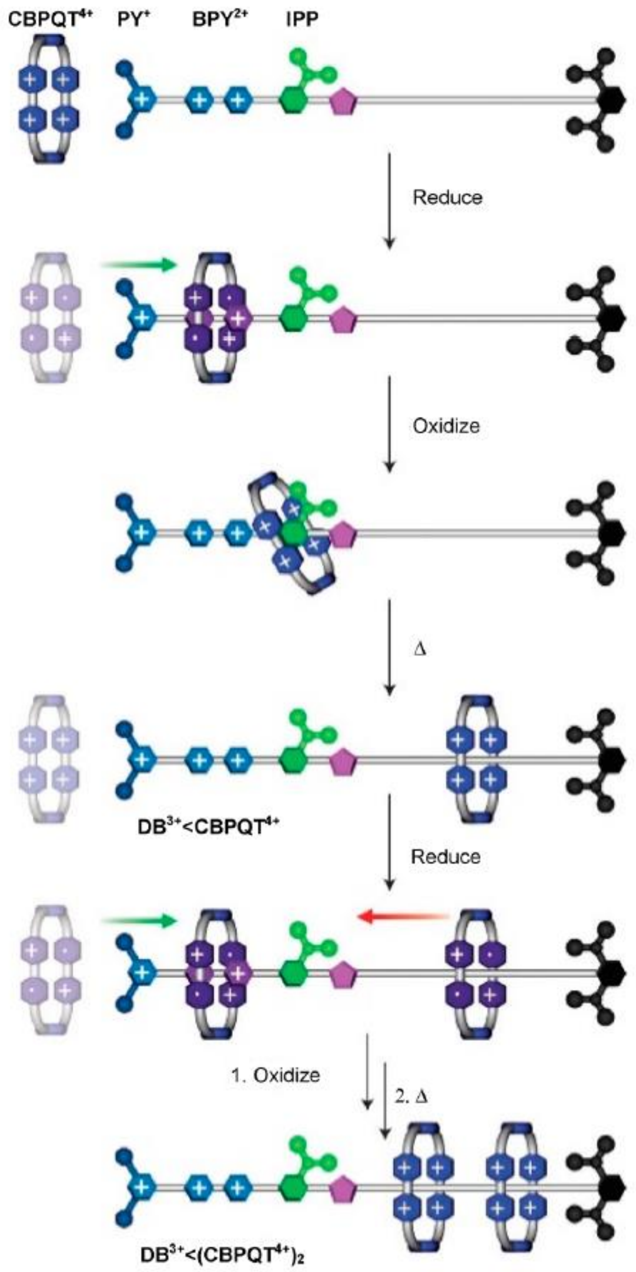
Machines in solution

- Disorder in solution makes it very challenging to extract useful work from artificial molecular machines (back-and-forth pending according to Brownian motion)

- Artificial cell needs to be designed for artificial molecular machines to function in solution

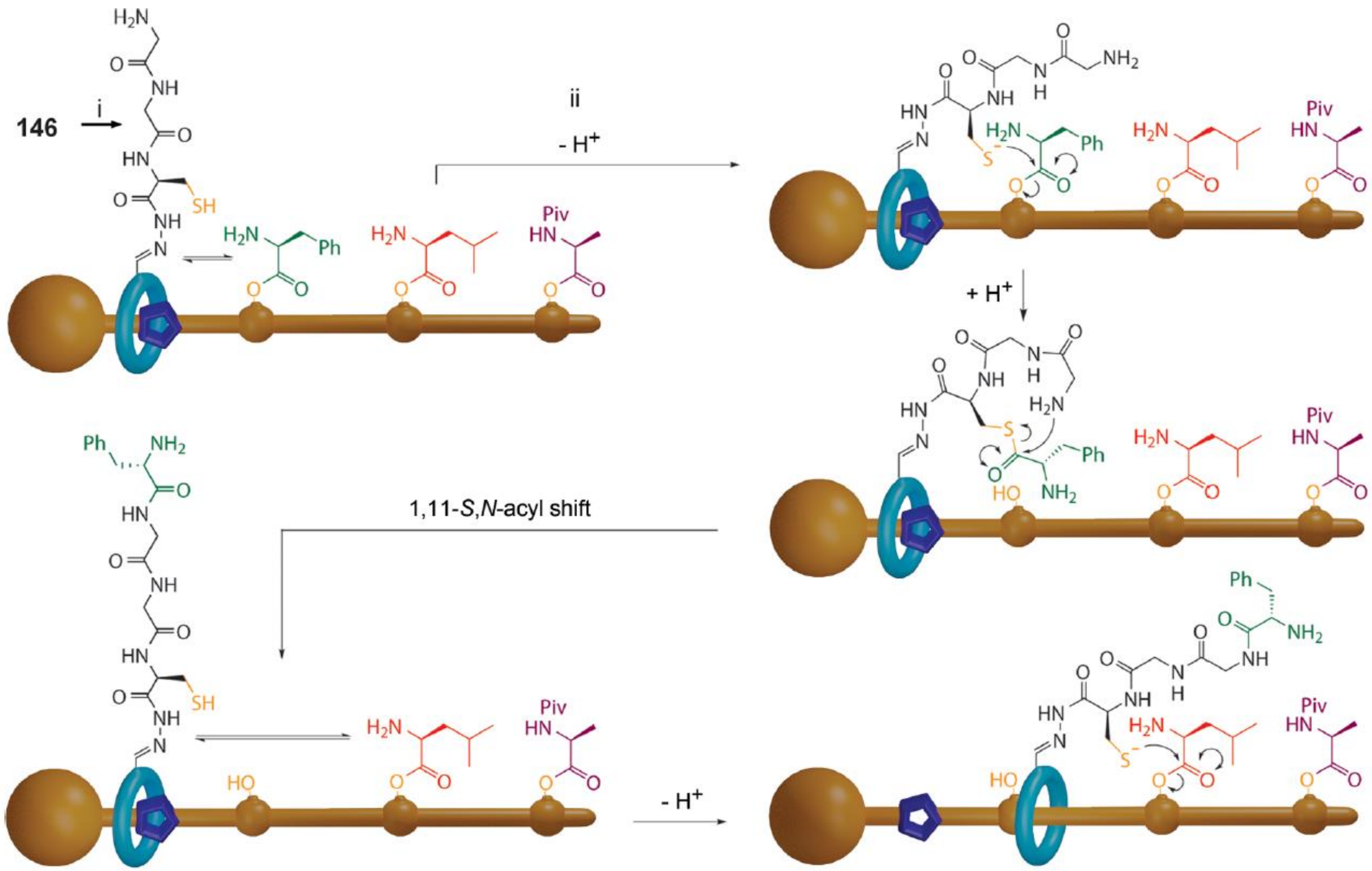
- Pump is driving the system out-of-equilibrium by virtue of kinetically trapping the rings on the collection area, but still there is no work being produced as there is no way yet to take advantage of the stored energy

- Possible work, incorporate them into membranes so that the pump will move the macrocycles from one side of the membrane to another, thus creating a chemical gradient



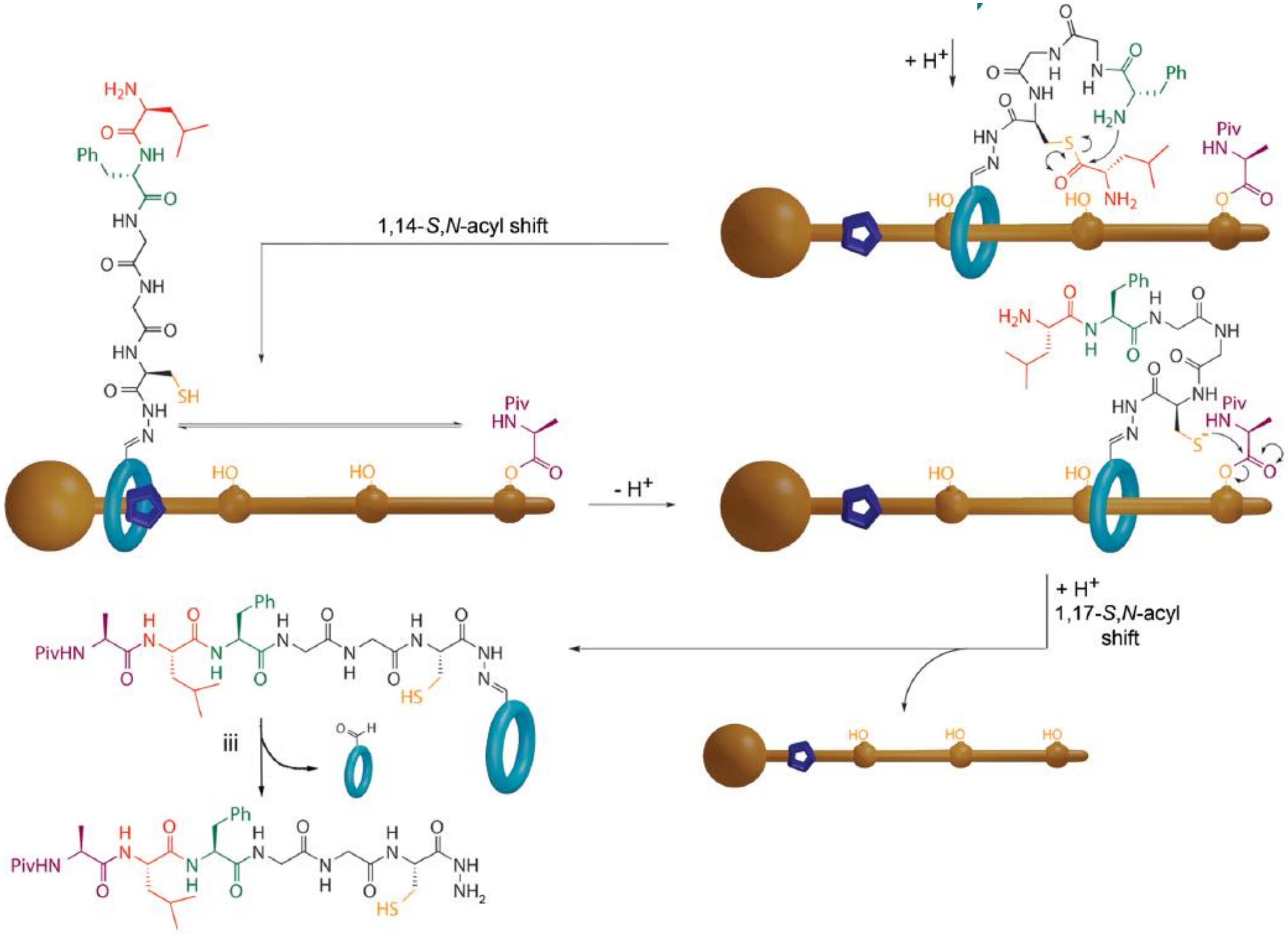
I. Aprahamian *ACS Cent. Sci.* 2020, 6, 347−358.

Leigh‘s peptide synthesizer



a) Leigh et al. *Chem. Rev.* 2015, 115, 10081−10206. b) Leigh et al. *Science* 2013, 339, 189−193.

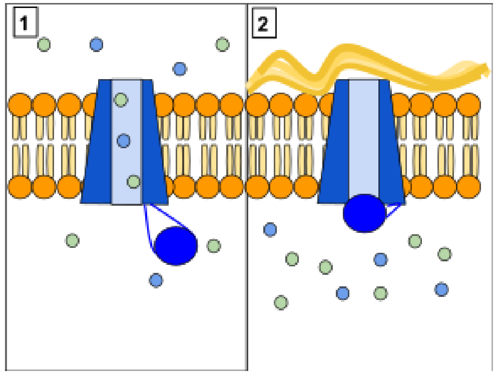
Leigh‘s peptide synthesizer

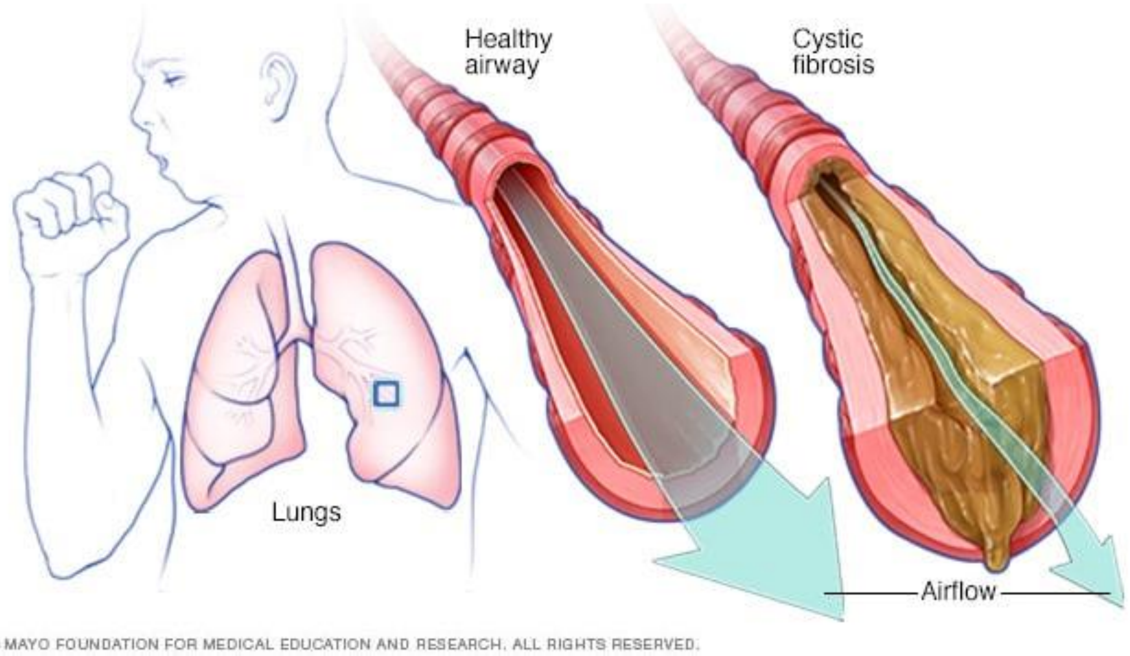


a) Leigh et al. *Chem. Rev.* 2015, 115, 10081−10206. b) Leigh et al. *Science* 2013, 339, 189−193.

Cystic fibrosis

- Inherited disorder that causes severe damage to the lungs, digestive system and other organs in the body
- No functional copies (alleles) of the gene cystic fibrosis transmembrane conductance regulator (CFTR)
- Product of this gene (the CFTR protein) is a chloride ion channel important in creating sweat, digestive juices, and mucus
- It regulates flow of Cl^- and H_2O
- Developing supramolecular chloride transporters could treat this disease

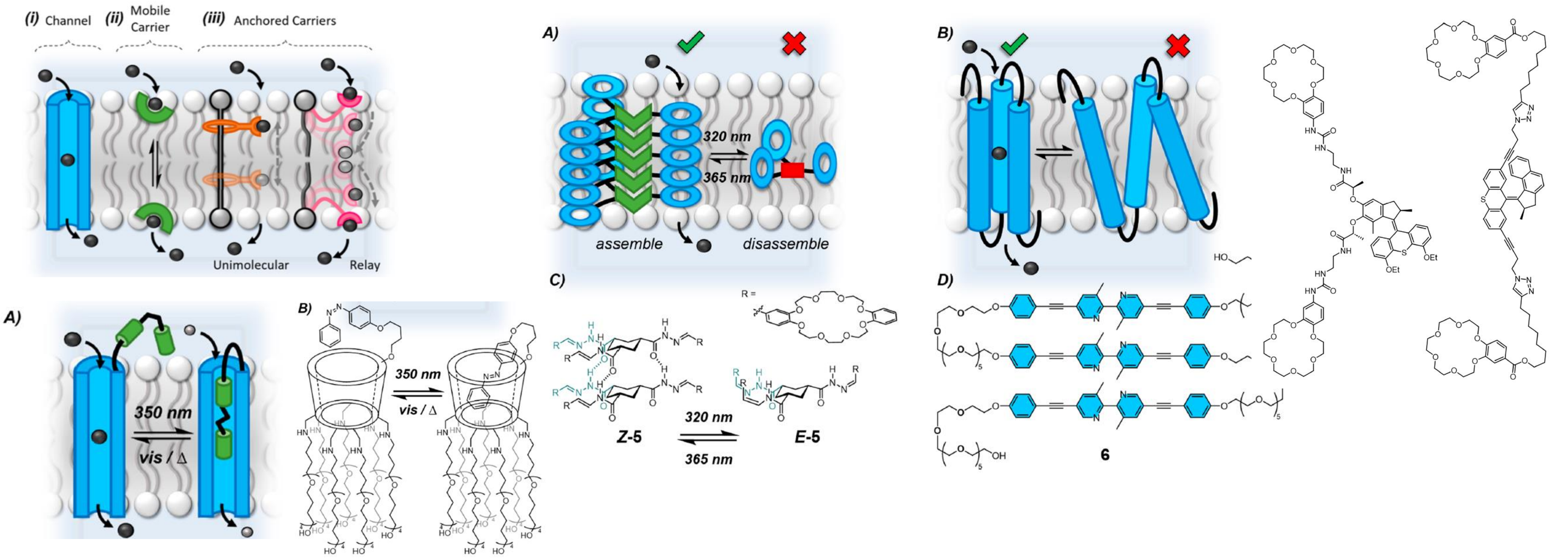




https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

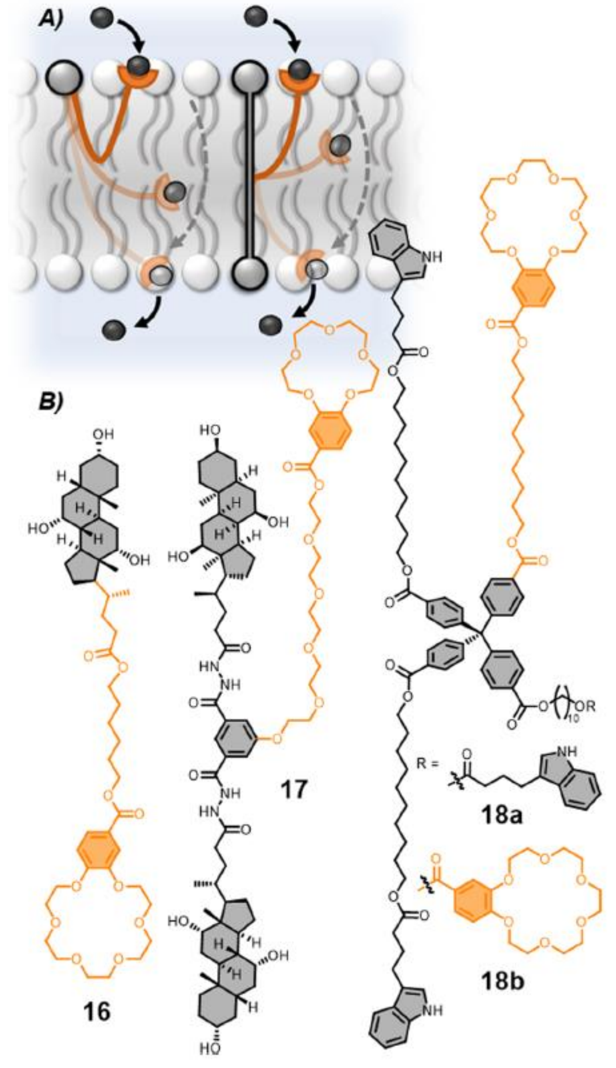
Molecular machines in transmembrane transport

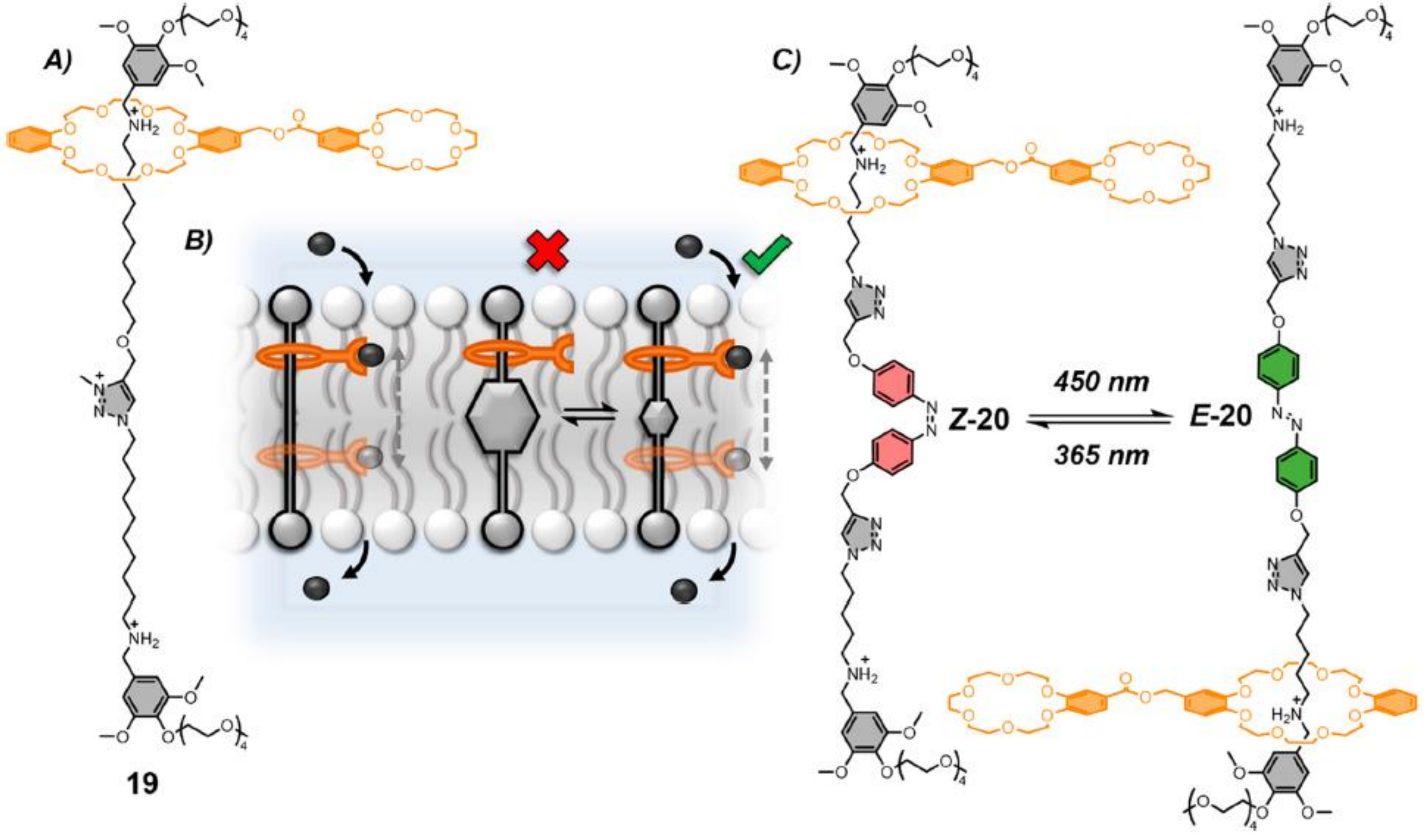
- In nature, ion transport is mediated primarily by transmembrane protein channels or sophisticated biomolecular machine ion pumps and, to a lesser extent, by mobile carrier (also referred to as ionophores)



Langton et al. *J. Am. Chem. Soc.* 2023, https://doi.org/10.1021/jacs.3c08877

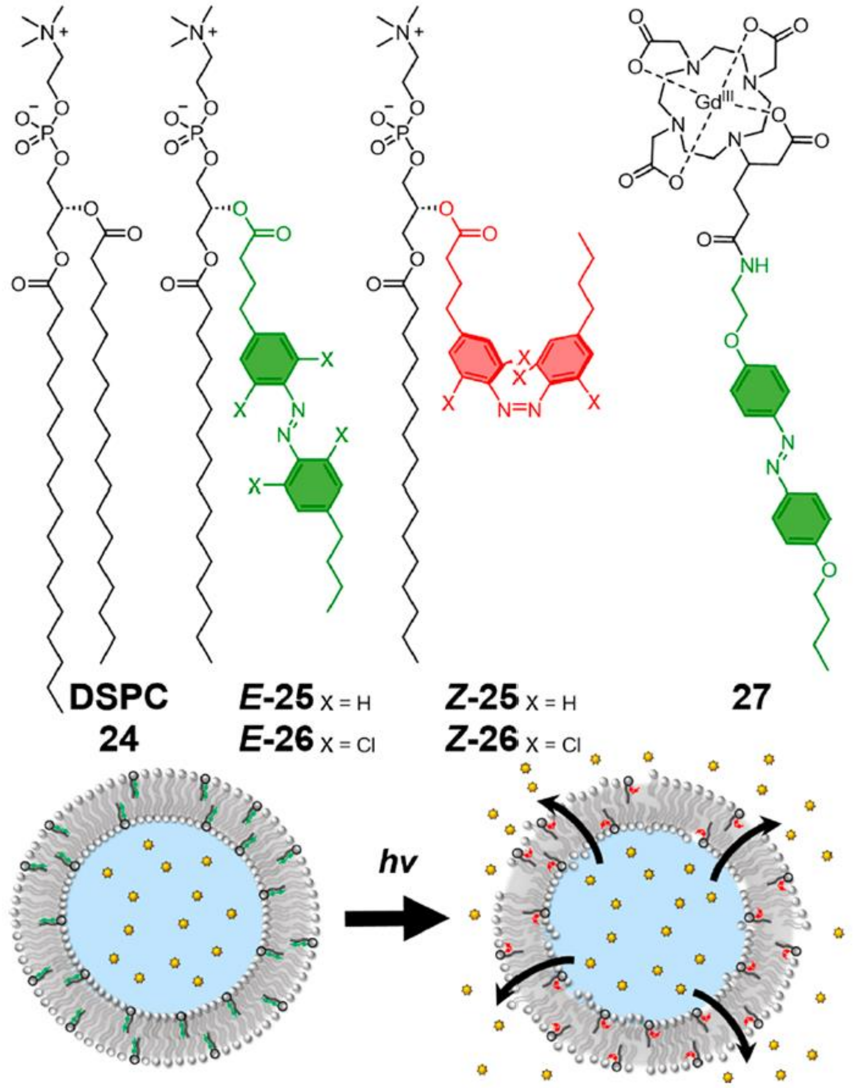
Molecular machines in transmembrane transport

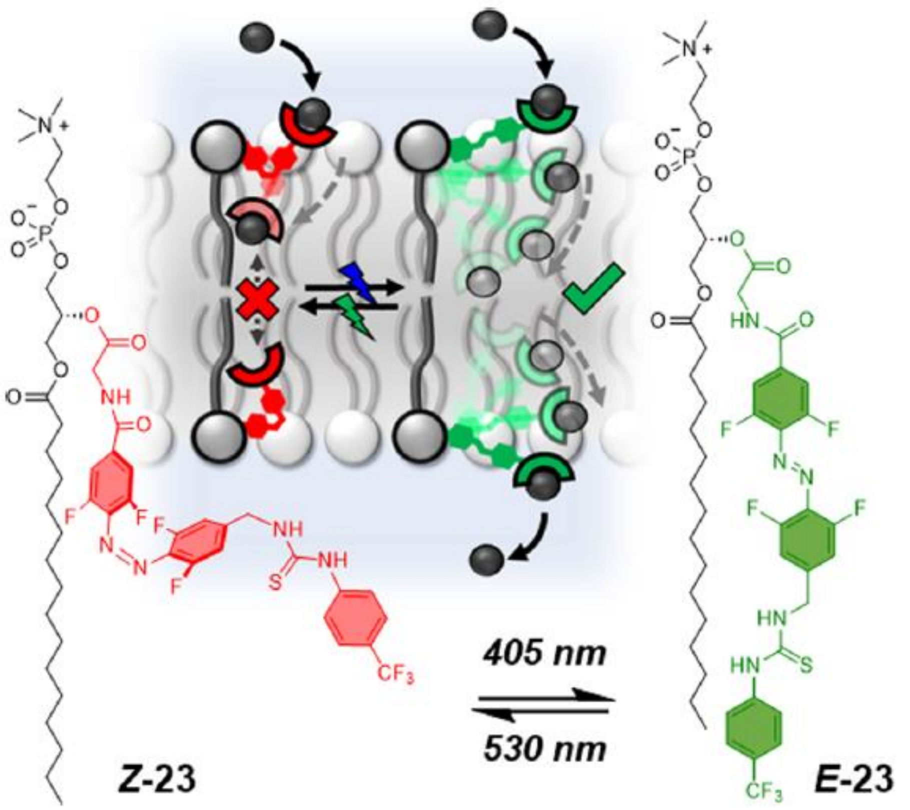


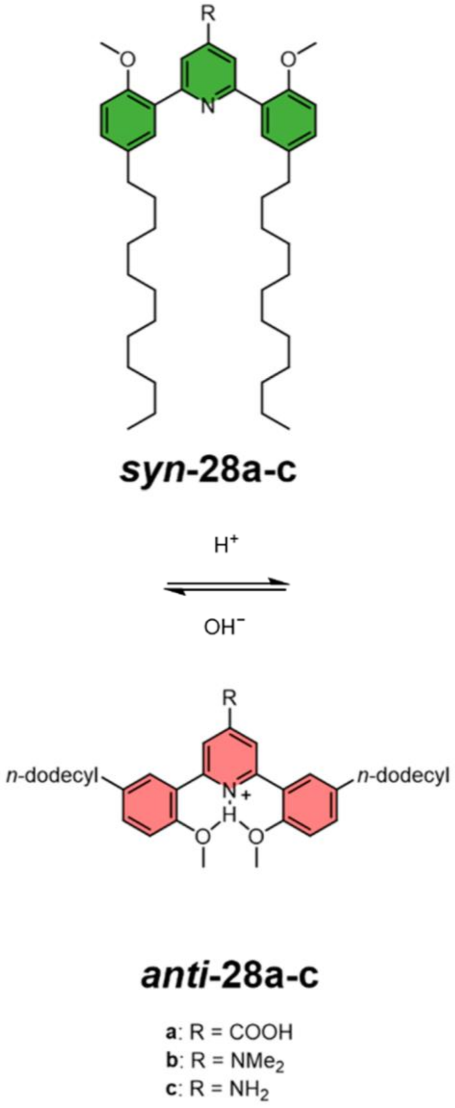


Langton et al. *J. Am. Chem. Soc.* 2023, https://doi.org/10.1021/jacs.3c08877

Molecular machines in transmembrane transport







Langton et al. *J. Am. Chem. Soc.* 2023, https://doi.org/10.1021/jacs.3c08877

Nanorobots

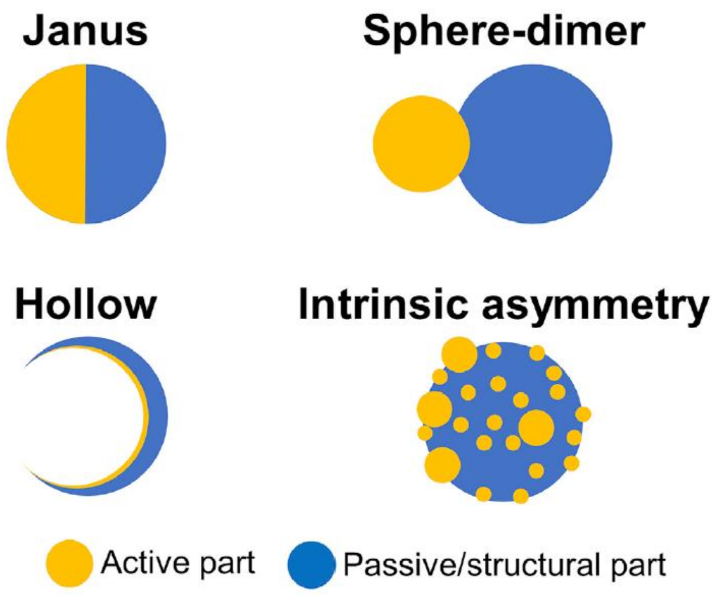
- Nanotechnology engineering discipline of designing and building nanorobots with devices ranging in size from 0.1 to 10 micrometres and constructed of nanoscale or molecular components

  - DNA machines (nubots) - smart biomaterial drug delivery system
  - Biohybrids combine biological and synthetic structural elements for biomedical or robotic applications
    - Bacteria-based - use of biological microorganisms, like *Escherichia coli* or *Salmonella typhimurium* (uses a flagellum for propulsion purposes)
    - Virus-based - retroviruses can be retrained to attach to cells and replace DNA (retroviral gene therapy)
    - Human cell-based
  - Inorganic nanoparticles

a) Pumera et al. *Chem* 2020, 6, 867–884. b) Nocentini et al. *Adv. Optical Mater.* 2018, 6, 1800207.

Types of nanorobots

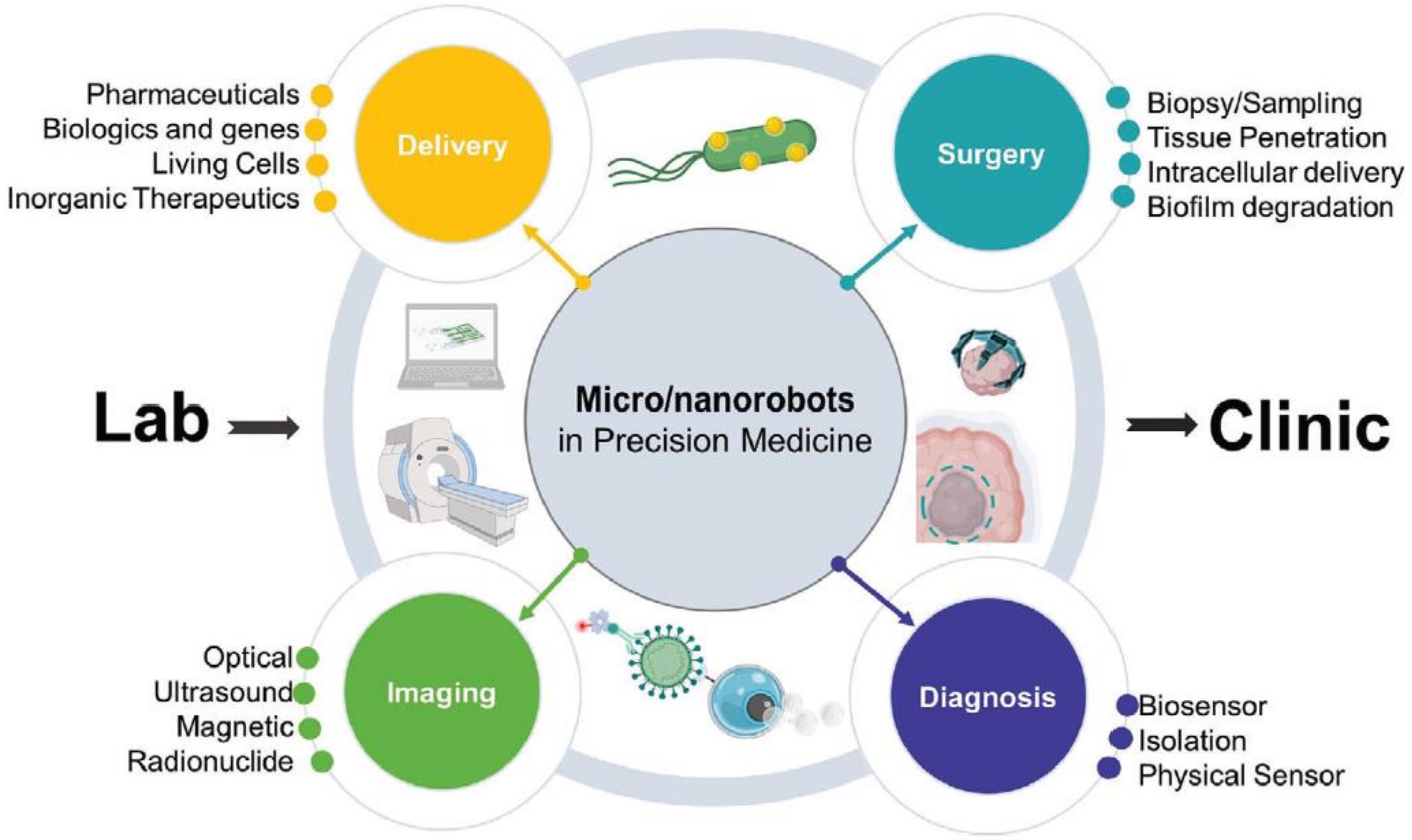
- Janus particles, sphere-dimers, hollow geometries, and nanomotors with intrinsic asymmetry



Nanorobot	Preparation Method	Size [nm]	Fuel or Energy Source	Application
Sphere	liposome carrier, magnetic nanoparticles	50	magnetic field	magnetotaxis, NIR drug release
Dimers	silica-sphere templates, metal sputtering	1,000	H_2O_2	–
	TiO_2/MnO_2 UV photoreduction	320	H_2O_2	–
	voluminous wet-chemistry SiO_2-AuNPs	70–120	–	environment-triggered drug release enzyme-controlled intra-cellular cargo delivery
	voluminous, seeded growth	250	NIR	photo-thermal therapy
Janus	2D amphipathic cross-linked network	100	–	–
	2D dendritic porous silica, PMMA embedding	250	H_2O_2	cargo delivery
	2D mesoporous silica carriers, Au|Pd|Pt|SiO_2, half cap, Mg	50–120	H_2O_2, NIR, H_2O	active|on-chip|*in vivo*|intra-cellular drug delivery, cell membrane cloaking
	MOF + metal sputtering 2D	200	H_2O_2	–
Hollow	2D, PS sphere template, e-beam evaporation	1,000	acoustic field	–
	polymerosomes, PtNP loading	150–400	H_2O_2 NIR	drug delivery,photo-thermal therapy, H_2O_2 chemotaxis
Asymmetry	thermally induced solid-state reduction	100	bubble propulsion	environmental remediation
	voluminous, mesoporous silica, urease	481	urea	cancer therapy, antibody targeting

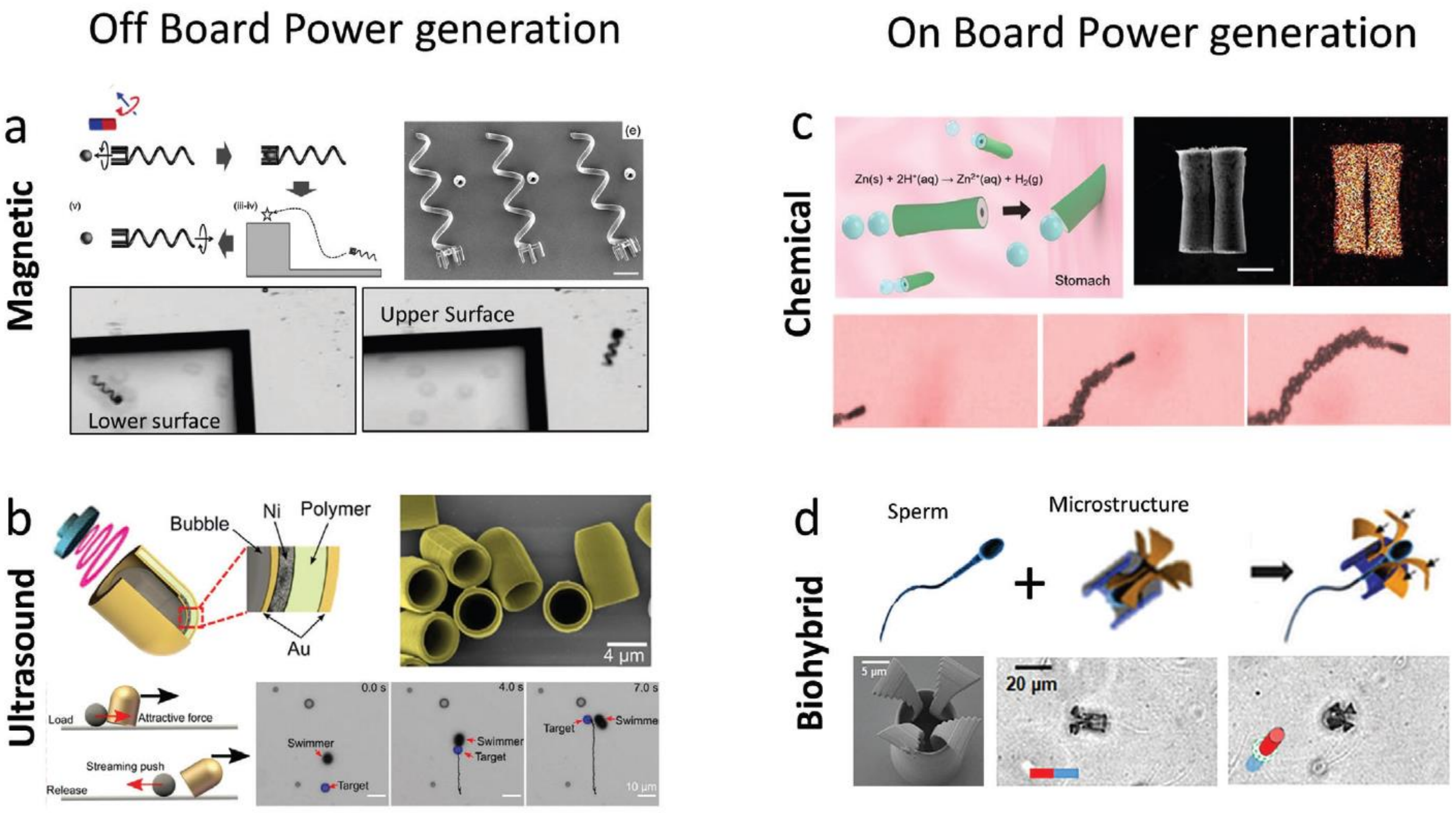
a) Pumera et al. *Chem* 2020, 6, 867–884. b) Nocentini et al. *Adv. Optical Mater.* 2018, 6, 1800207.

Micro- and nanorobots in precision medicine



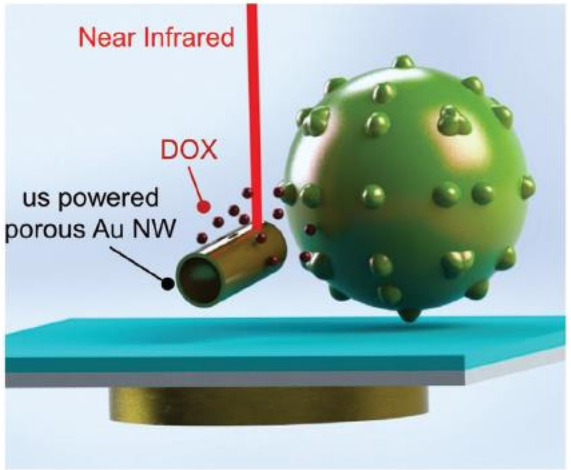
Soto et al. *Adv. Sci.* 2020, 7, 2002203.

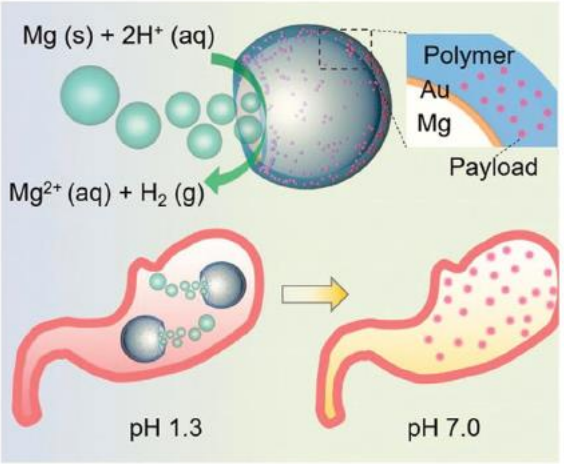
Powering nano-, microrobots

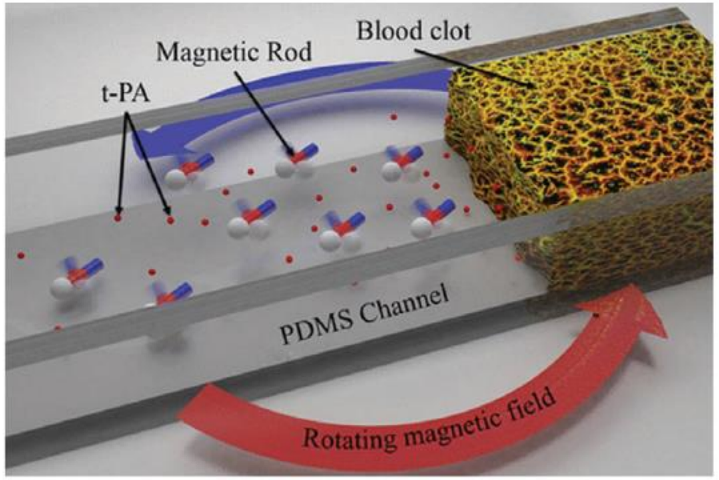


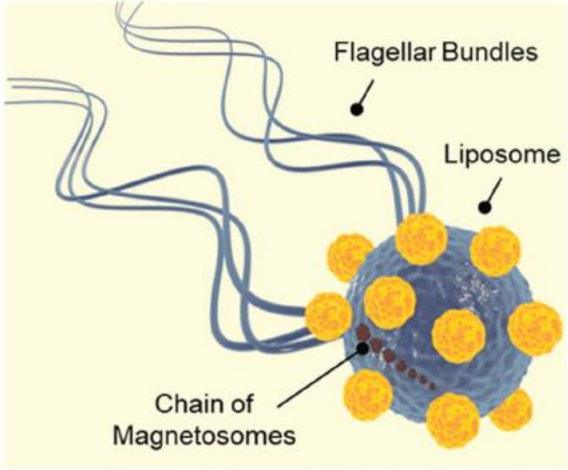
Soto et al. *Adv. Sci.* 2020, 7, 2002203.

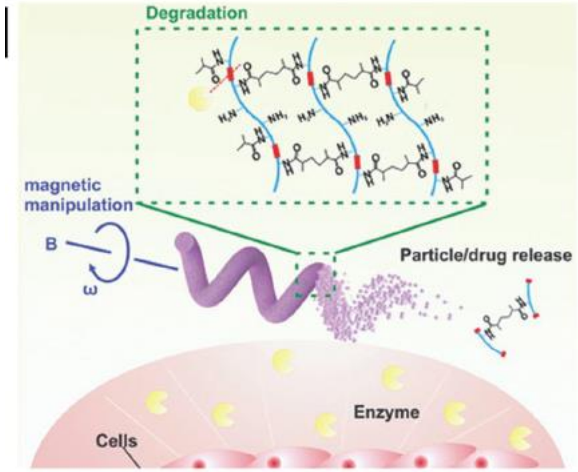
Drug delivery using micro/nanorobots

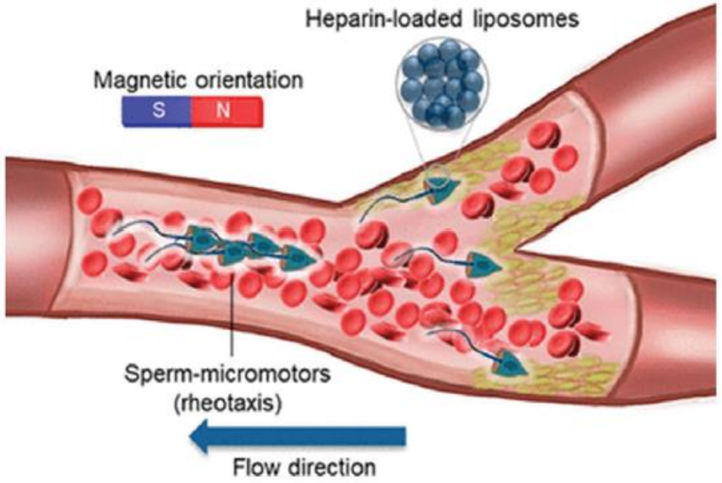






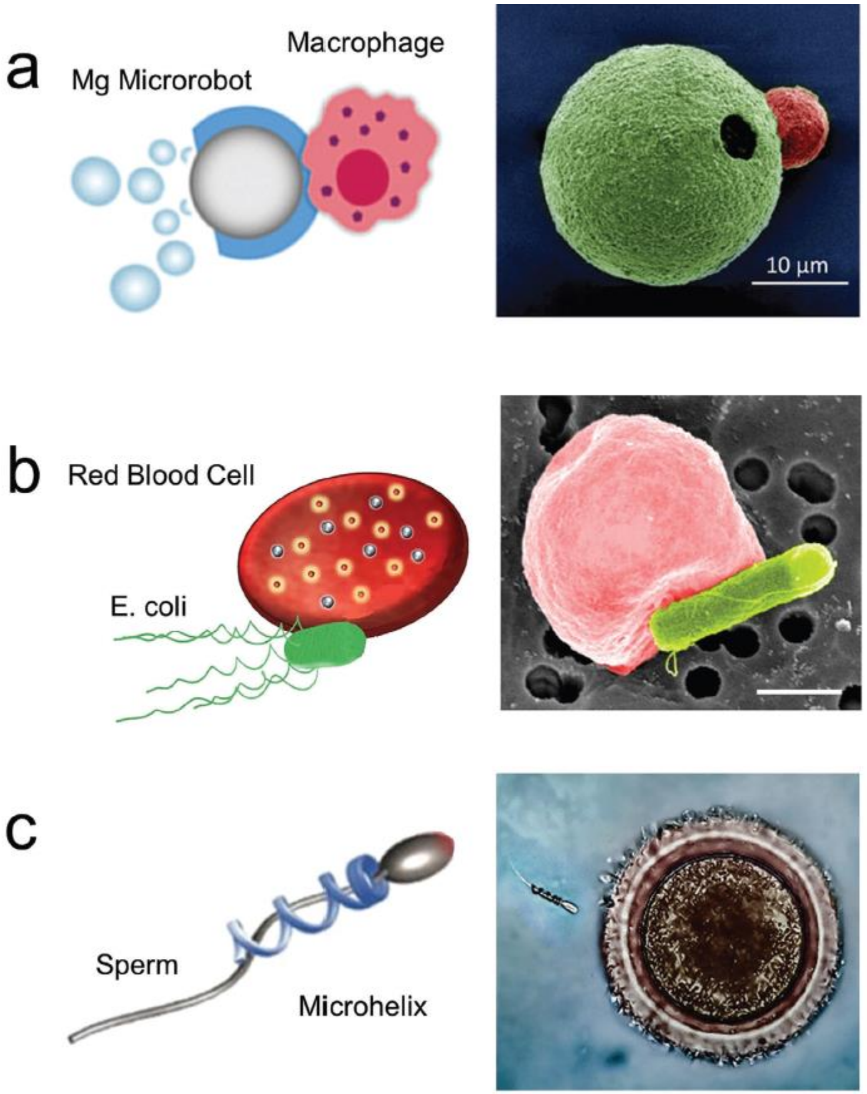


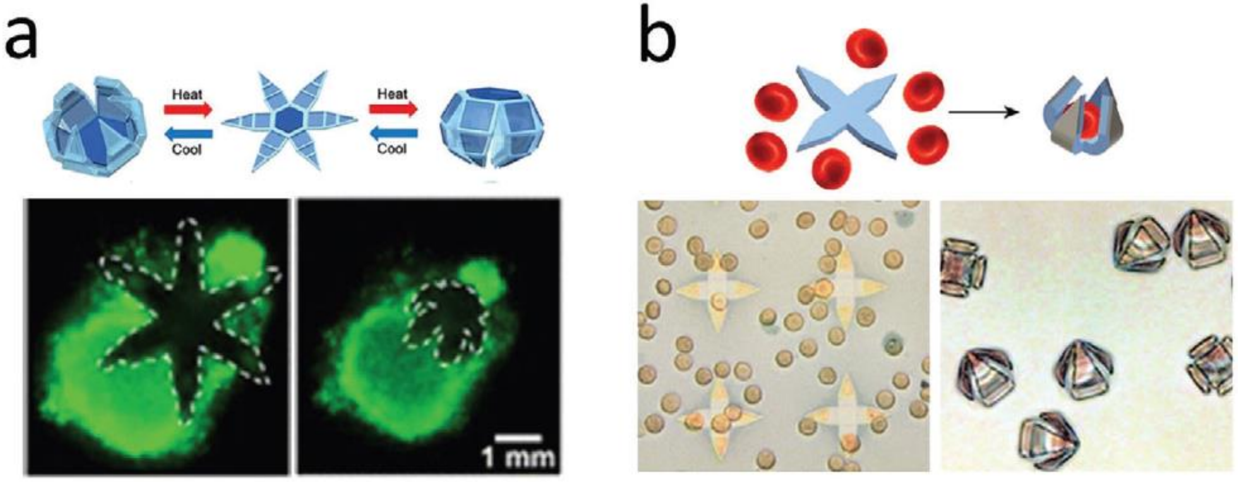


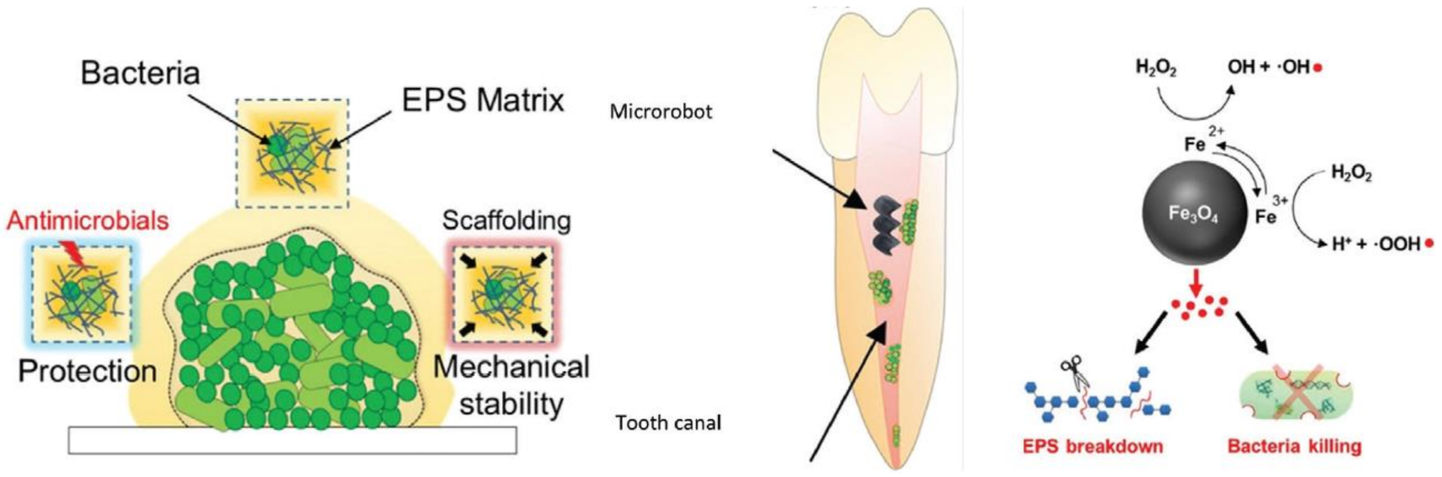


Soto et al. *Adv. Sci.* 2020, 7, 2002203.

Cell delivery, biopsy, sampling using micro/nanorobots







Soto et al. *Adv. Sci.* 2020, 7, 2002203.

Potential Nanorobot Hazards

- Important prerequisite for successful use is that the nanorobots can evade the immune systems of the organisms (DNA nanorobots can be immunogenic)
- Control of nanorobot propulsion and navigation – whether by chemical propulsion, magnetic fields, sound waves, bioreceptor binding and/or light – potentially making the nanorobots travel to places in the human body and elsewhere where they are not supposed to

- Discussions about nanomaterial and nanoparticle definitions shall be led

1. What is the toxicity of nanorobots and their constituents to humans and other organisms?
2. Are nanorobots more hazardous than previous generations of passive nanomaterials?
3. How many nanorobots are expected to be produced and used in the future?
4. What is the likely future exposure of nanorobots to humans and organisms in the environment?
5. In which ways can the propulsion and navigation of different nanorobots be obscured?
6. How can existing regulations be adapted to cover potential risks of active nanomaterials such as nanorobots?
7. How can nanorobots be designed to be safe?
8. How can the benefits of nanorobots be quantified and compared to the potential risks?
9. What is peoples' risk perception of nanorobots?
10. What are the main societal concerns related to nanorobots?

Arvidsson et al. *Environ. Sci.: Nano* 2020, 7, 2875.

Sadly, this is the end…

And now the final test!

Thank you for your attention and attendance during the course!