Dynamic covalent chemistry:
Simple reactions for complex systems

Literature Presentation

29 March 2022

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MacMillan Group

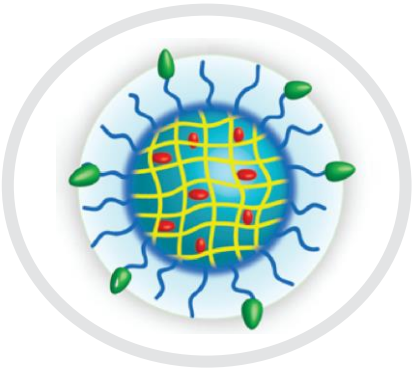
Princeton University

Dynamic covalent chemistry

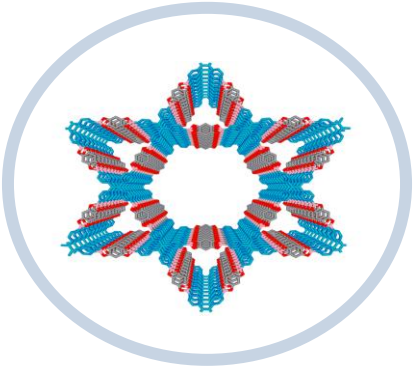
Dynamic
Combinational Chemistry

Reversible Covalent
Binding

Molecular
Machines



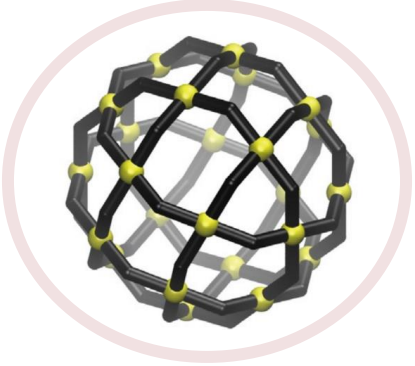
Nanogels



Covalent organic
Frameworks

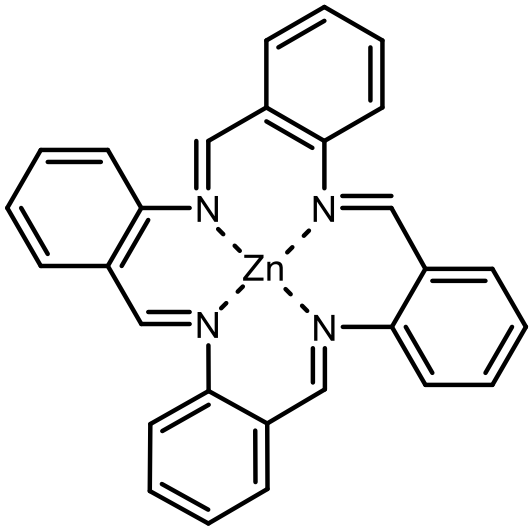
Dynamic covalent chemistry (DCvC):

The chemistry of reversible bond formation under equilibrium control



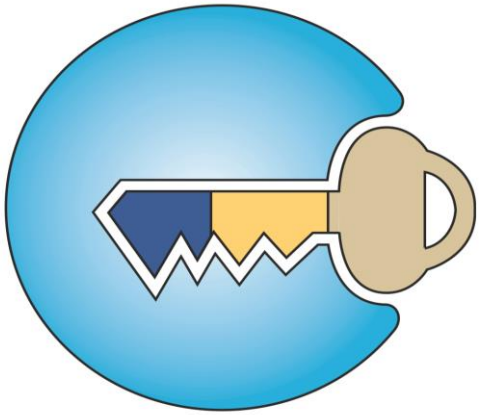
Adaptive
Materials

DCvC has seen a rapid expansion in the past two decades



Aminobenzaldehyde Macrocyclization
Prof. Seidel: 1920

>17,000 papers in 2021 alone



Dynamic combinatorial libraries
Prof. Lehn: 1999

Dynamic covalent chemistry (DCvC):

The chemistry of reversible bond formation under equilibrium control

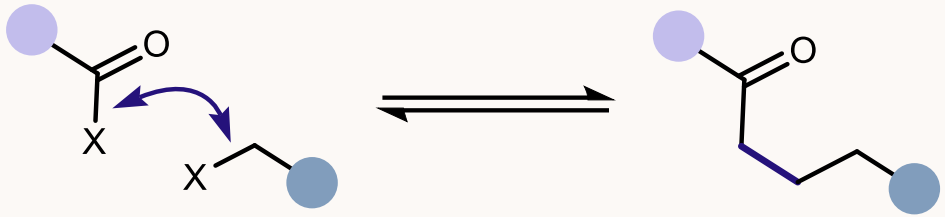
F. Seidel. Chem. Ber. **1926**, 59, 1894.

Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455.

Data from Google Scholar search for “dynamic covalent chemistry” in 2021.

The intersect of conventional synthesis and supramolecular chemistry

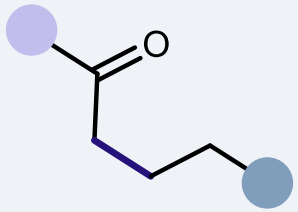
Dynamic covalent chemistry



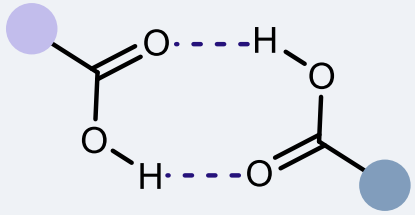
Combine the strength of covalent bonds with the adaptability of supramolecular chemistry

- **Static products**
- **Small molecules**
- **Covalent bonds**

Conventional synthesis



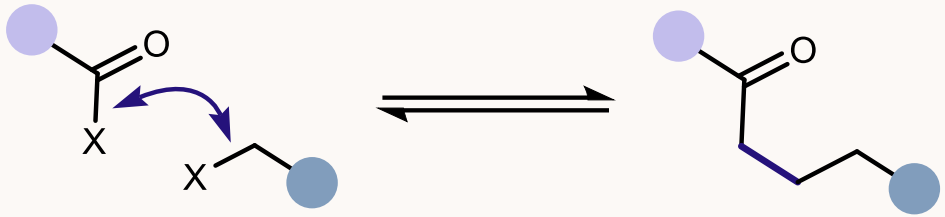
Supramolecular chemistry



- **“Adaptive” products**
- **Complex systems**
- **Weak intermolecular interactions**

The intersect of conventional synthesis and supramolecular chemistry

Dynamic covalent chemistry



Combine the strength of covalent bonds with the adaptability of supramolecular chemistry

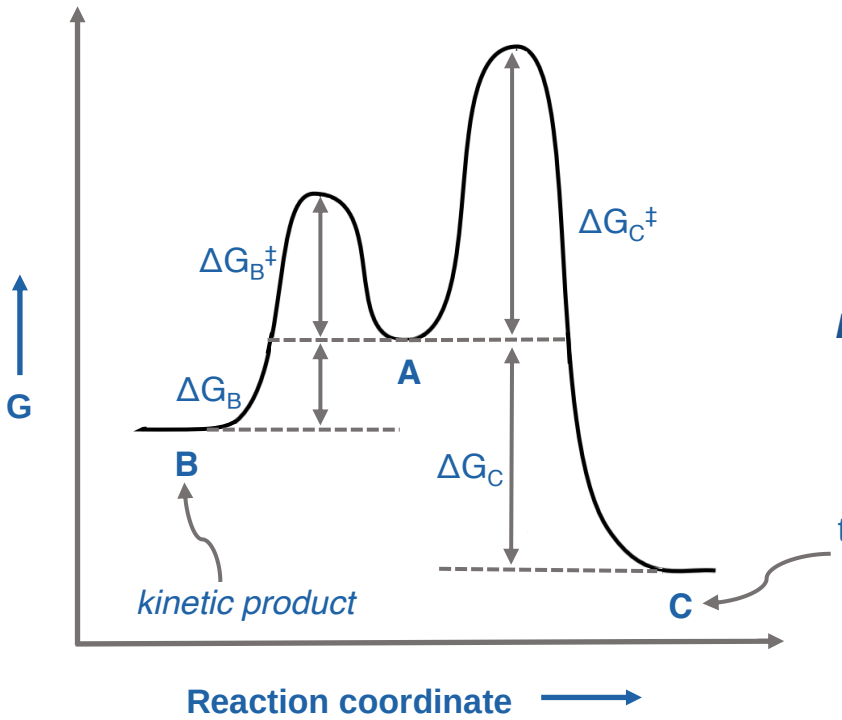
Error correction

Complex self assembly

Molecular architectures

Material recycling

Thermodynamic equilibrium and dynamic chemistry



Kinetically controlled reactions dominate molecular synthesis

Supramolecular chemistry uses thermodynamic equilibrium

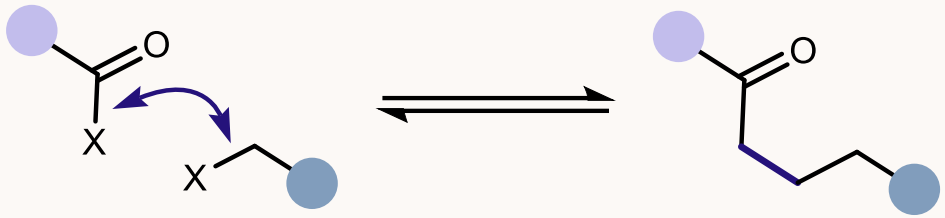
***Dynamic** covalent chemistry requires thermodynamic products under equilibrium*

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT\ln K_{eq}$$

Rowan, S.J. et. al. *Angew. Chem, Int. Ed.* **2002**, *41*, 898.

What criteria do we need to consider for dynamic reactions?

Dynamic covalent chemistry



***Dynamic** covalent chemistry requires thermodynamic products under equilibrium*

"Covalent nature"

Covalent bonds broken and formed

Stable and detectable

*Lifetime: 1 ms < **t** < 1 min*
Stability and rate tradeoff

Adaptable

Influenced by stimuli

Mild

System tolerance

Water and oxygen compatible

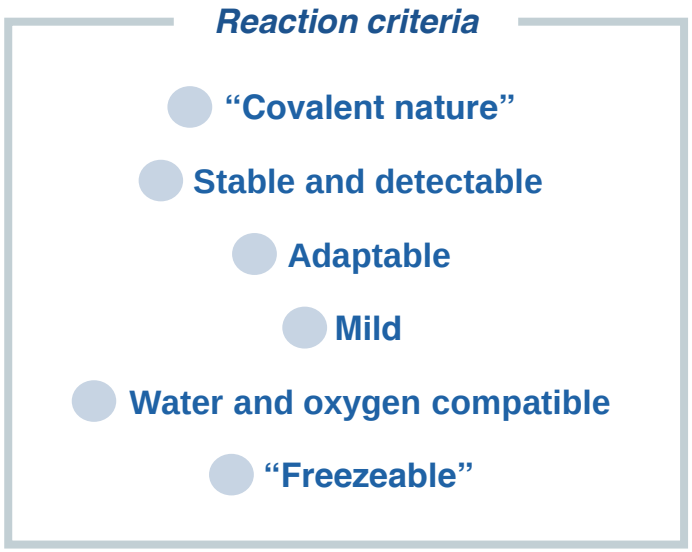
Robust chemistry without
Irreversible "dead ends"

"Freezeable"

Equilibrium halting
for analysis

Zhang, W. Jin, Y. Eds; *Dynamic Covalent Chemistry: Principles, Reactions, and Applications,* Wiley, **2017**

What criteria do we need to consider for dynamic reactions?

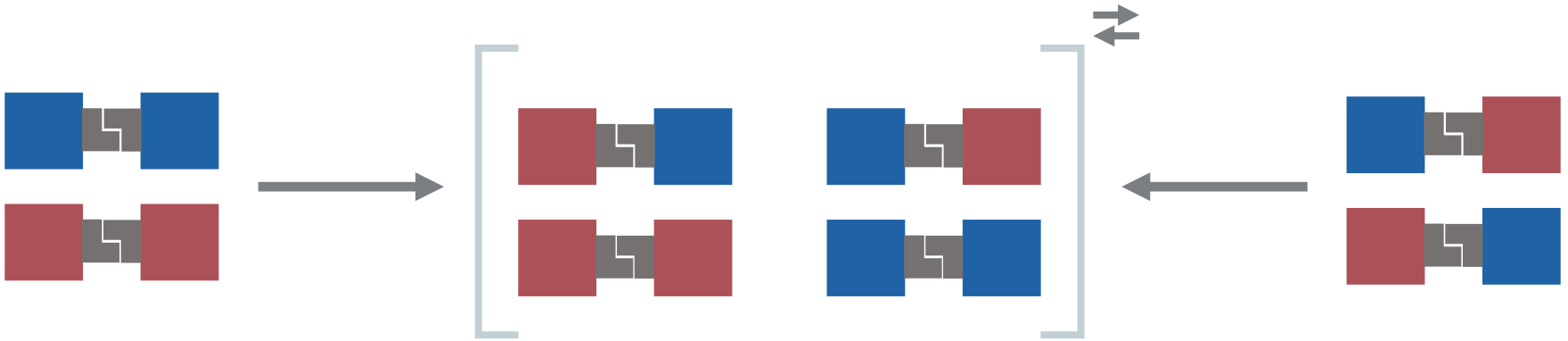


Once a reaction and system meets the criteria, one needs to establish equilibrium has been reached

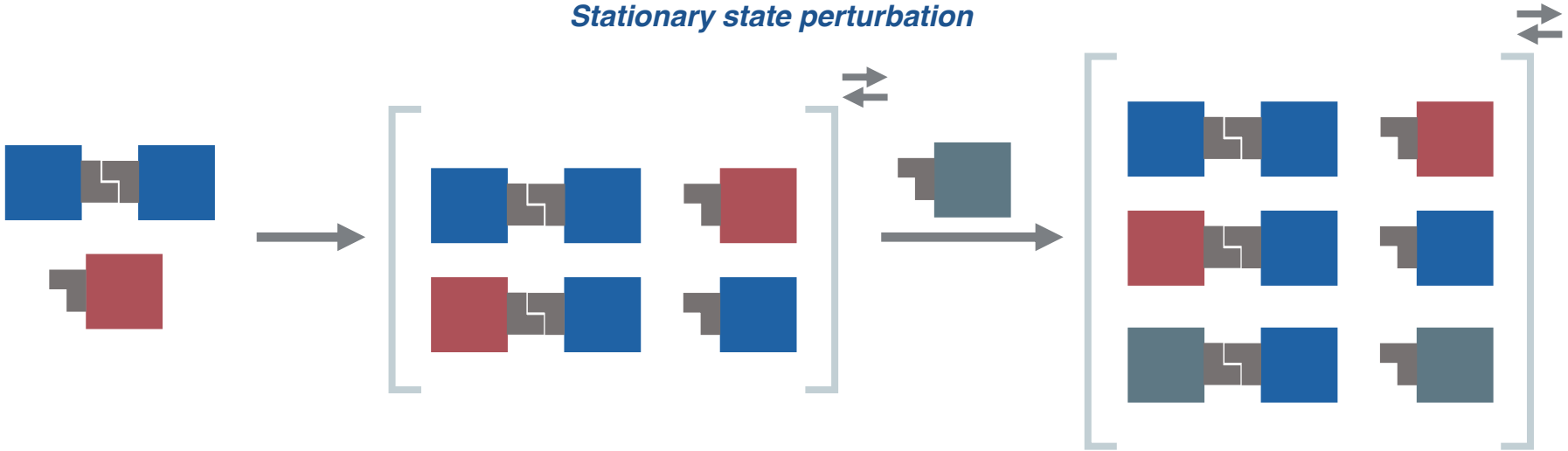
Zhang, W. Jin, Y. Eds; *Dynamic Covalent Chemistry: Principles, Reactions, and Applications,* Wiley, **2017**

Confirmation of reversibility and equilibrium

Dual entry-point analysis



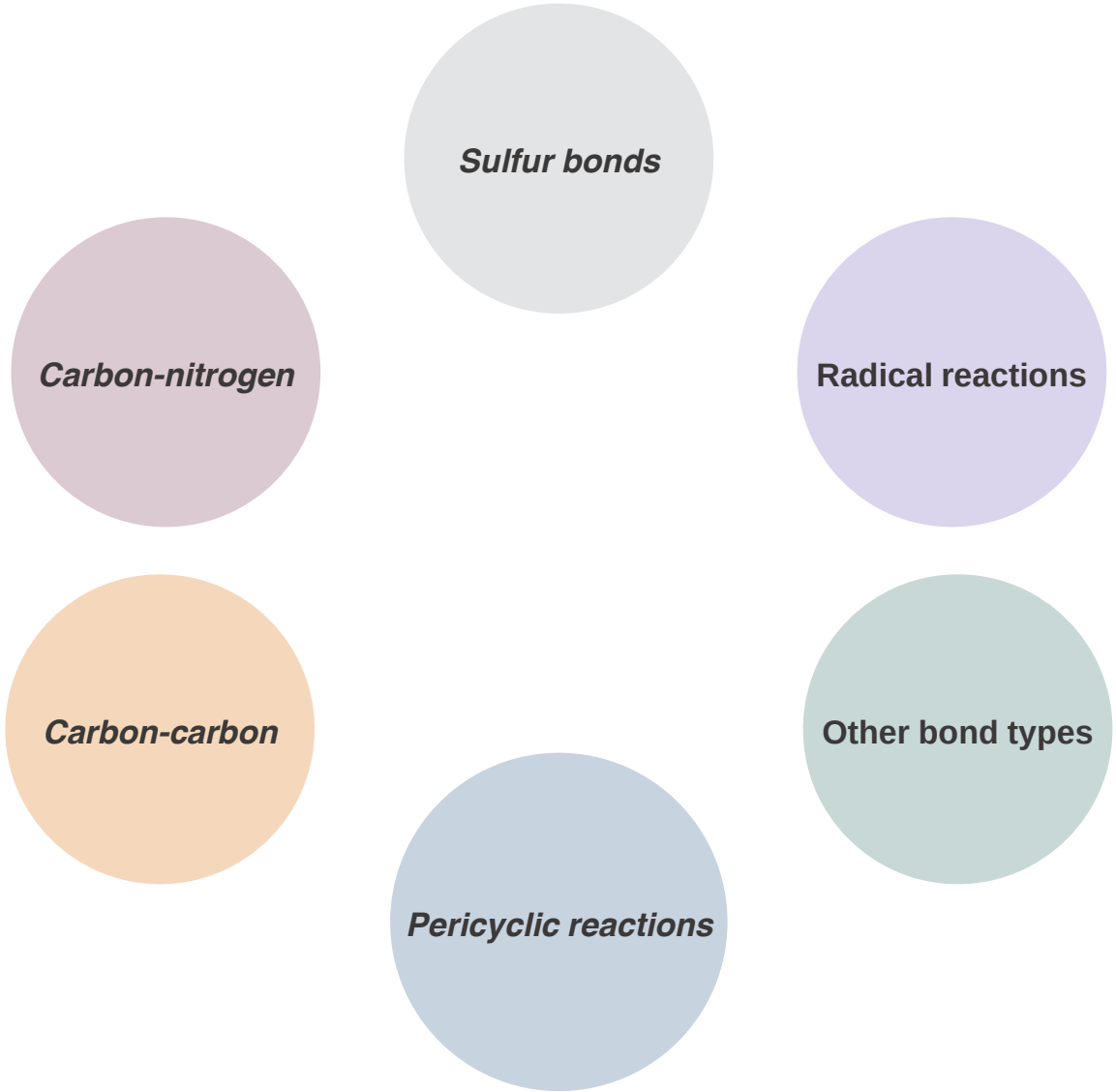
Stationary state perturbation



Zhang, W. Jin, Y. Eds; Dynamic Covalent Chemistry: Principles, Reactions, and Applications, Wiley, **2017**

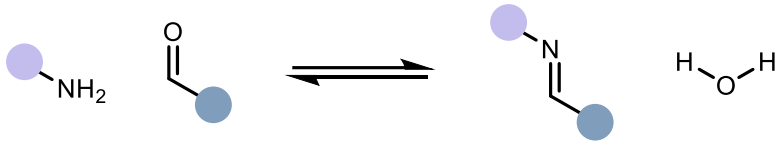
What reactions fall under the desired criteria?

A variety of reactions achieve the desired reaction criteria… however each has its own set of challenges



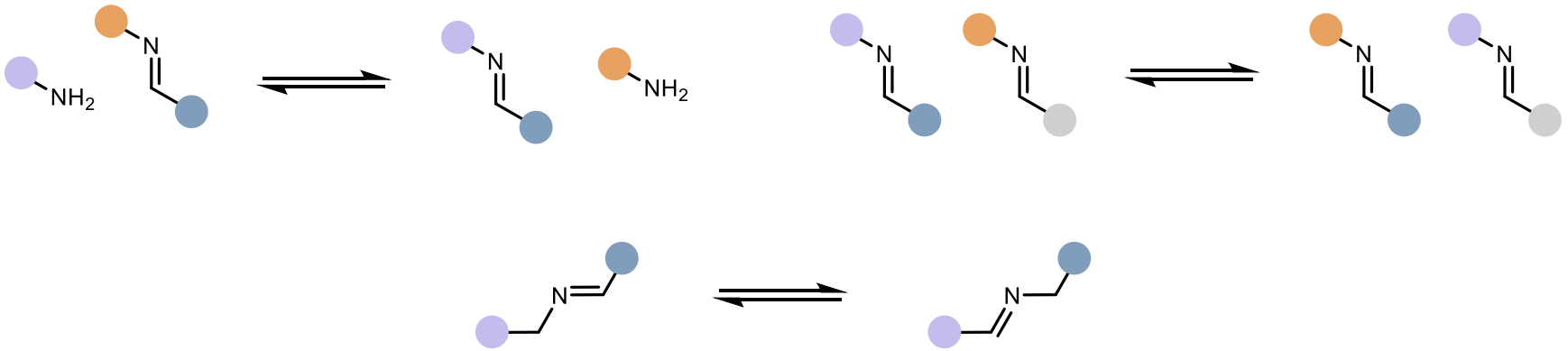
Carbon-nitrogen bond formations

Carbon-nitrogen



most common dynamic covalent bond

Majority of strategies exploit imine bond formations in one form or another



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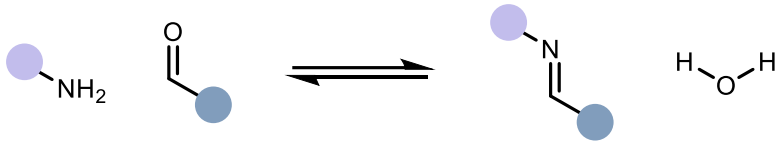

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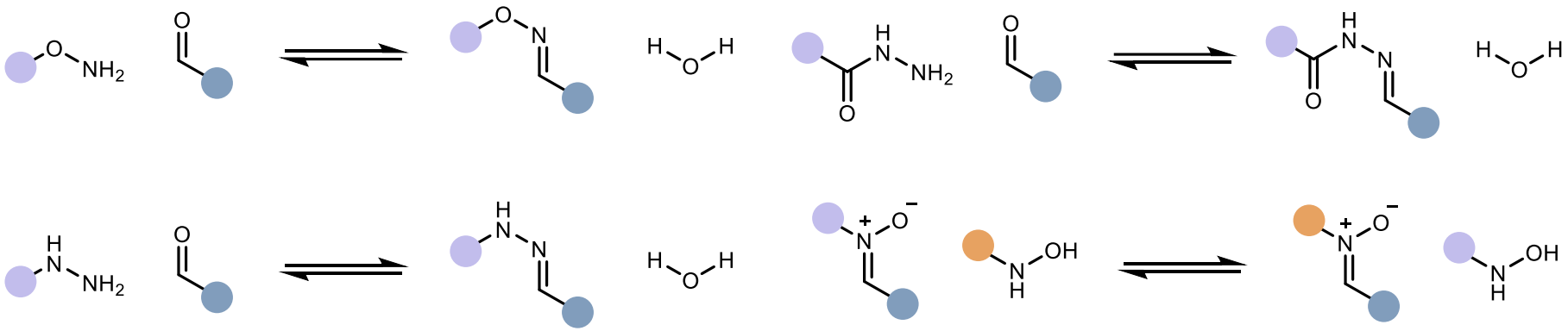

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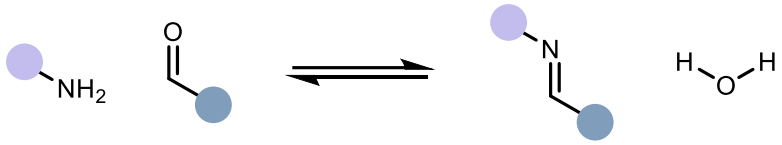

most common dynamic covalent bond

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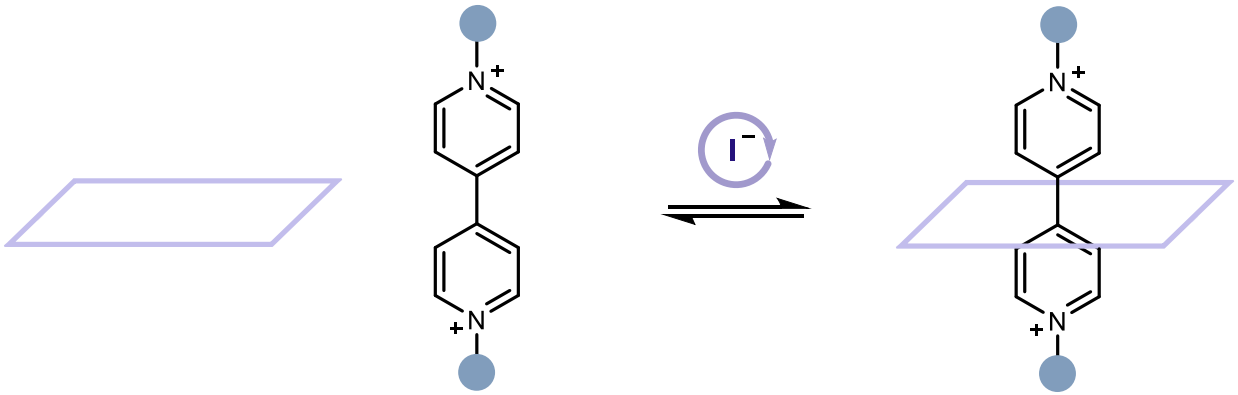

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Carbon-nitrogen bond formations

Carbon-nitrogen

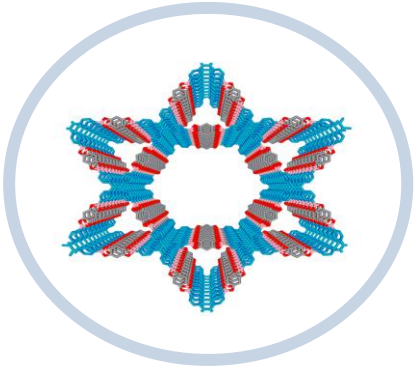
most common dynamic covalent bond

- **Easily tunable**
- **Side reactivity can be problematic**

Dynamic Combinational Chemistry

Reversible Covalent Binding

Molecular Machines



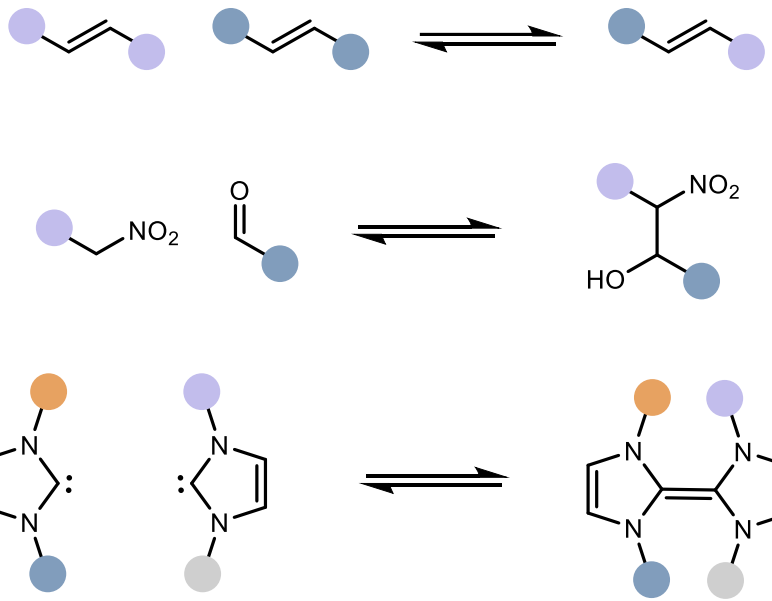
Covalent organic Frameworks

Zhang, W. Jin, Y. Eds; *Dynamic Covalent Chemistry: Principles, Reactions, and Applications,* Wiley, **2017**

Carbon-carbon bond formations

Carbon-carbon

Olefin metathesis leads the way



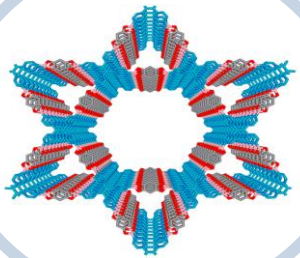
Zhang, W. Jin, Y. Eds; *Dynamic Covalent Chemistry: Principles, Reactions, and Applications,* Wiley, **2017**

Carbon-carbon bond formations

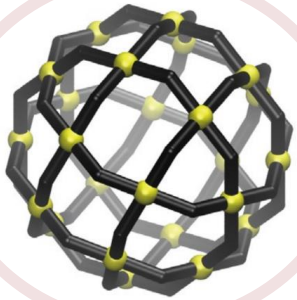
Carbon-carbon

Olefin metathesis leads the way

- **Mild conditions and functional group tolerance**
- **Difficult to freeze and catalyst inhibition**



Covalent organic Frameworks



Adaptive Materials

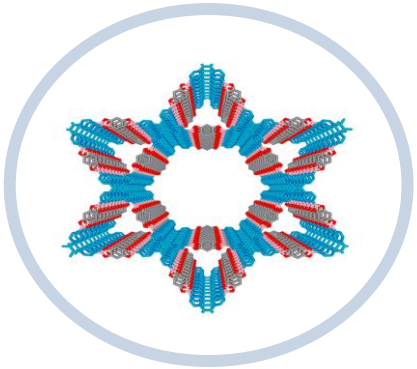
Zhang, W. Jin, Y. Eds; Dynamic Covalent Chemistry: Principles, Reactions, and Applications, Wiley, **2017**

Carbon-sulfur bond formations

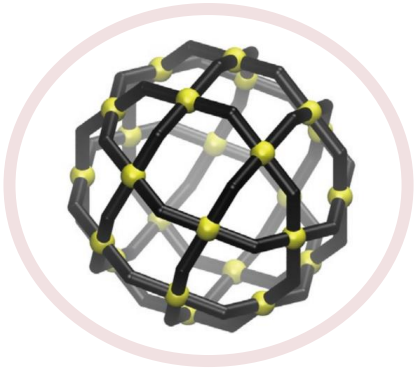
Carbon-carbon

Olefin metathesis leads the way

- **Mild conditions and functional group tolerance**
- **Difficult to freeze and catalyst inhibition**



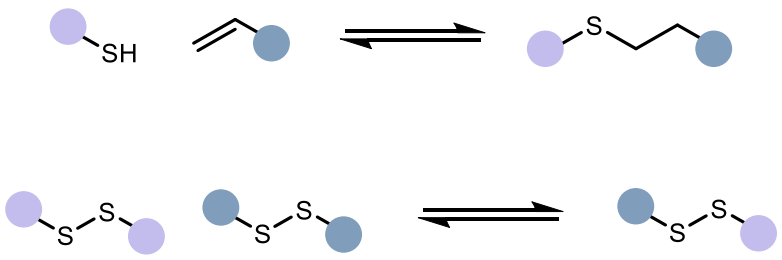
Covalent organic Frameworks



Adaptive Materials

Sulfur bonds

Versatile bond formation and breaking



- **Biocompatibility and reactivity modes**
- **Oxygen sensitive**

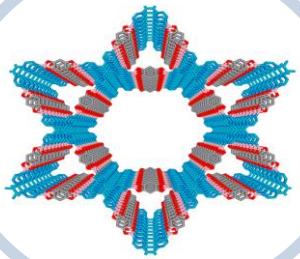
Zhang, W. Jin, Y. Eds; Dynamic Covalent Chemistry: Principles, Reactions, and Applications, Wiley, **2017**

Carbon-sulfur bond formations

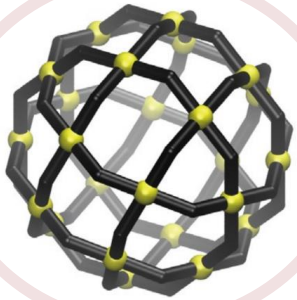
Carbon-carbon

Olefin metathesis leads the way

- **Mild conditions and functional group tolerance**
- **Difficult to freeze and catalyst inhibition**



Covalent organic Frameworks

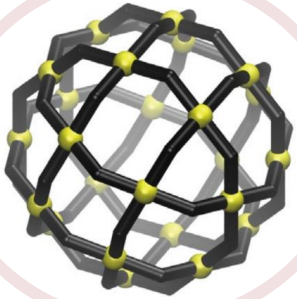


Adaptive Materials

Sulfur bonds

Versatile bond formation and breaking

Reversible Covalent Binding



Adaptive Materials

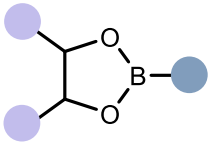
- **Biocompatibility and reactivity modes**
- **Oxygen sensitive**

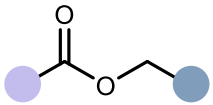
Zhang, W. Jin, Y. Eds; *Dynamic Covalent Chemistry: Principles, Reactions, and Applications,* Wiley, **2017**

Other key bond formations

- **Substrate limited (requires diols)**
- **Harsh equilibrium conditions**

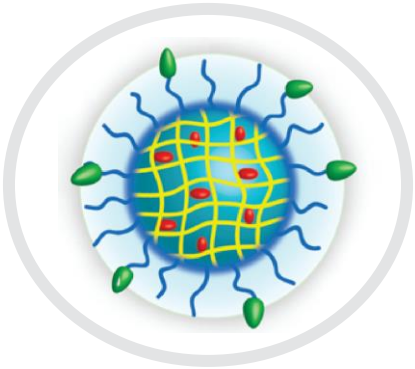
Useful but niche applications





Other bond types

Reversible Covalent Binding



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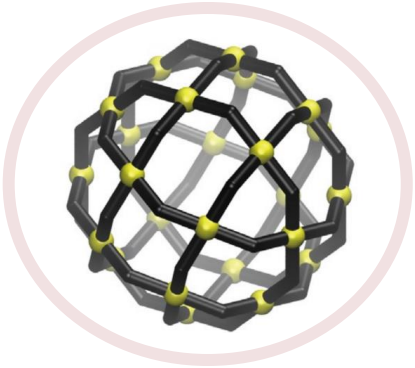

Adaptive Materials

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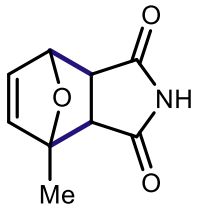
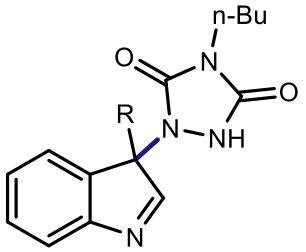
Pericyclic and radical bond formations

Pericyclic reactions



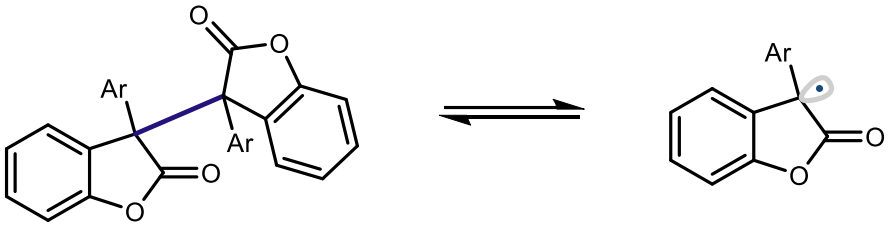


"Self-contained" reactivity

"Self-contained" and orthogonal

Niche substrates and poor retro kinetics

Radical reactions



Excellent self-healing properties

Limited largely to material applications

Tailored substrates for desirable reactivity

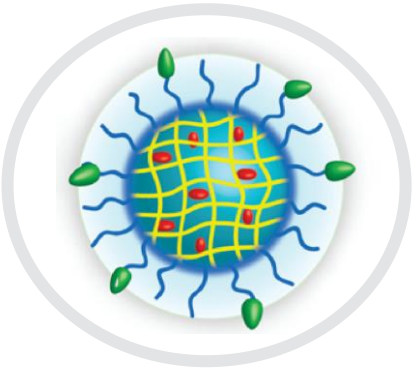
Zhang, W. Jin, Y. Eds; Dynamic Covalent Chemistry: Principles, Reactions, and Applications, Wiley, **2017**

Pericyclic and radical bond formations

Pericyclic reactions

"Self-contained" reactivity

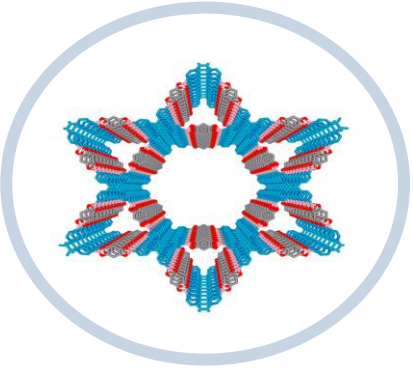
Molecular Machines



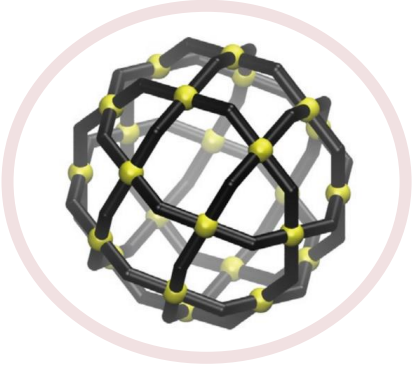
Nanogels

Radical reactions

Tailored substrates for desirable reactivity



Covalent organic Frameworks



Adaptive Materials

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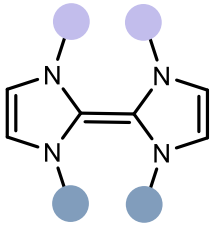
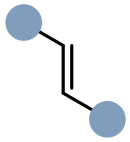
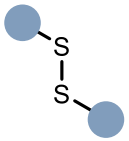
Specific terminology: exchange symmetry

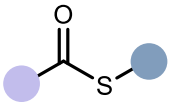
Symmetric bonds

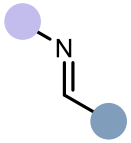


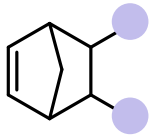




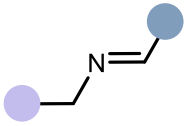
Unsymmetric bonds

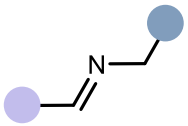






Trans-symmetric bonds





Reaction criteria

- "Covalent nature"
- Stable and detectable
- Adaptable
- Mild
- Water and oxygen compatible
- "Freezeable"

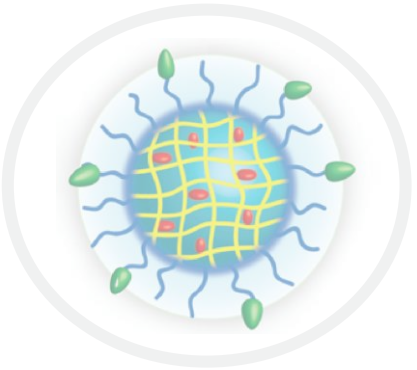
Zhang, W. Jin, Y. Eds; Dynamic Covalent Chemistry: Principles, Reactions, and Applications, Wiley, **2017**

Dynamic covalent chemistry: applications and examples

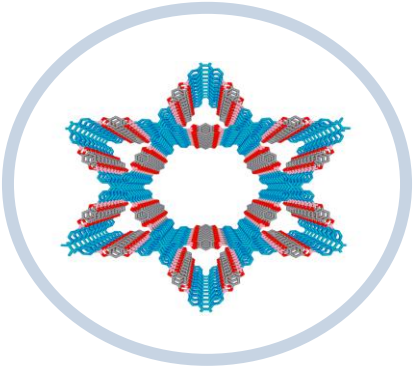
Dynamic
Combinational Chemistry

Reversible Covalent
Binding

Molecular
Machines



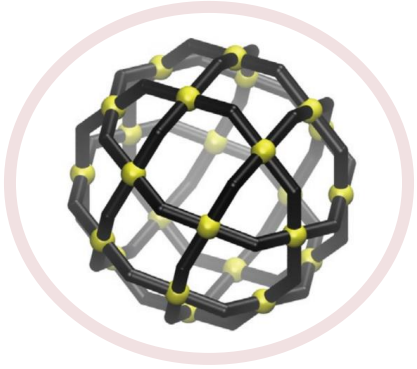
Nanogels



Covalent organic
Frameworks

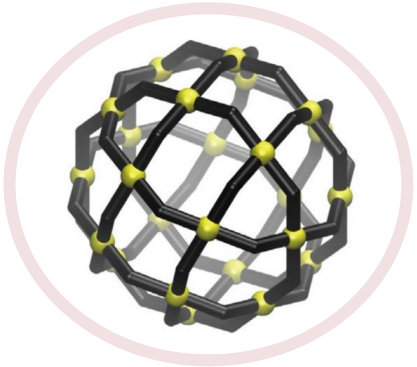
Dynamic covalent chemistry (DCvC):

The chemistry of reversible bond formation under equilibrium control

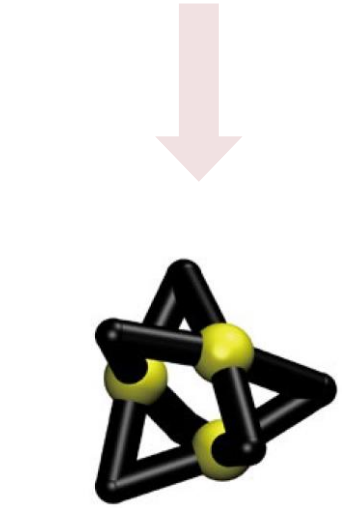


Adaptive
Materials

Dynamic covalent chemistry: applications and examples

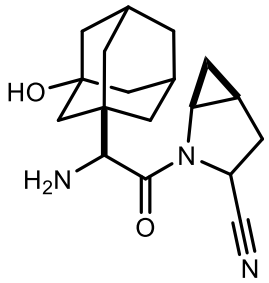


Adaptive Materials

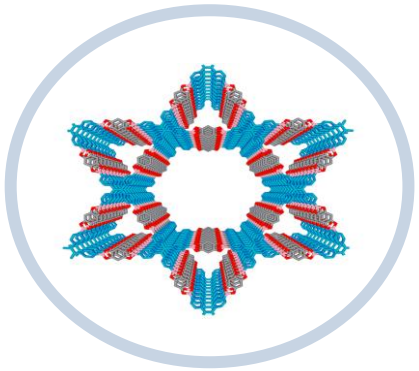


Photoswitchable Topology
Johnson: MIT

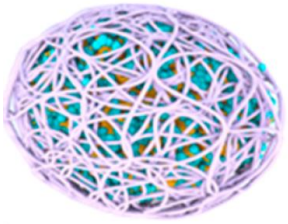
Reversible Covalent Binding



Onglyza: AstraZeneca
Saxagliptin



Covalent organic Frameworks



Drug/MRI delivery
Trabolsi: NYU Abu Dhabi

Topological interconvertible materials

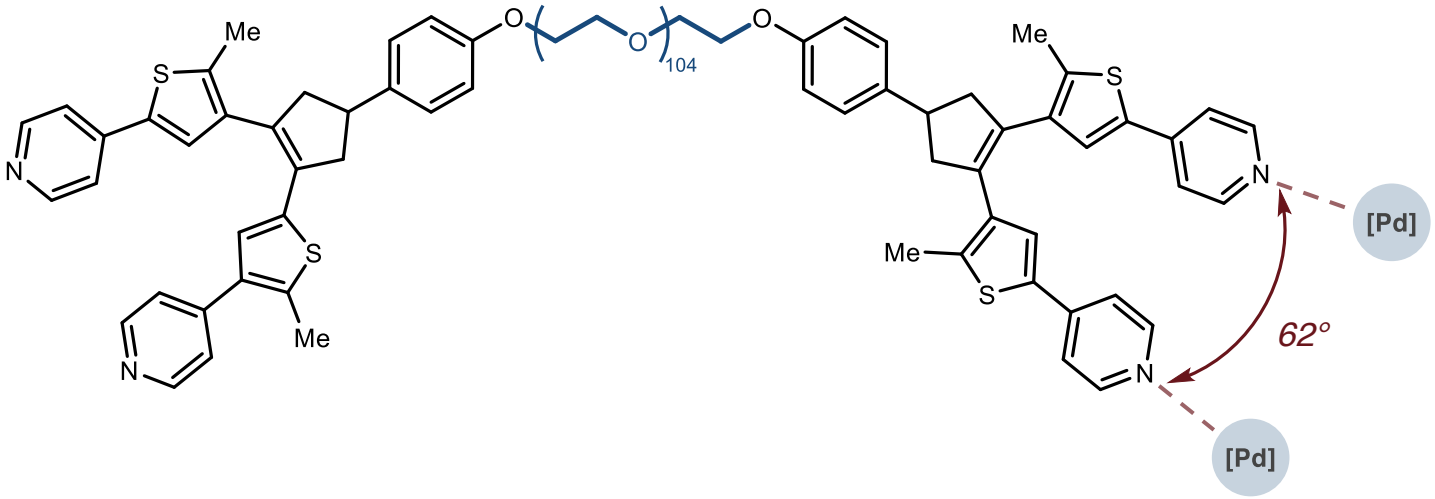
*"**Organic chemists are masterful at exercising control in zero dimension**.*
One subculture of organic chemists has learned to exercise control in one dimension.
*These are polymer chemists… **but in two or three dimensions, it's a synthetic wasteland."***

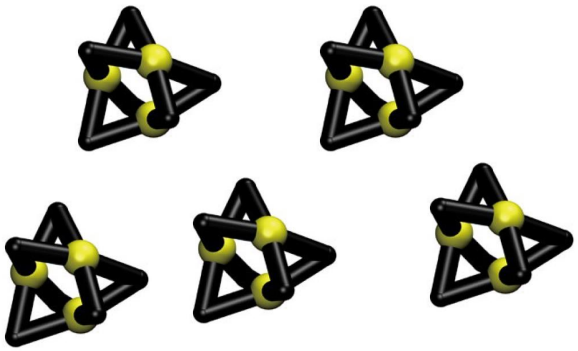
-Roald Hoffmann,
"How should chemists think" 1993

Hoffmann, R. *Scientific American*, **1993**, 268, 66

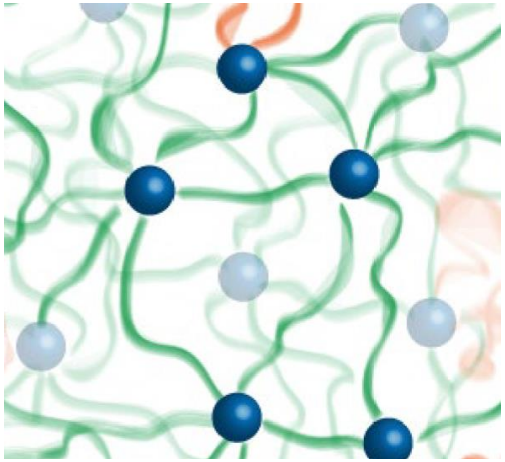
Topological interconvertible materials

Metallosupramolecular assembly combined with stimuli-induced chemistry





Pd_3L_6



Gu, Y., Alt. E., Wang, H., Li, X., Willard, A., Johnson, J. Nature, **2018**, 560, 65

Topological interconvertible materials

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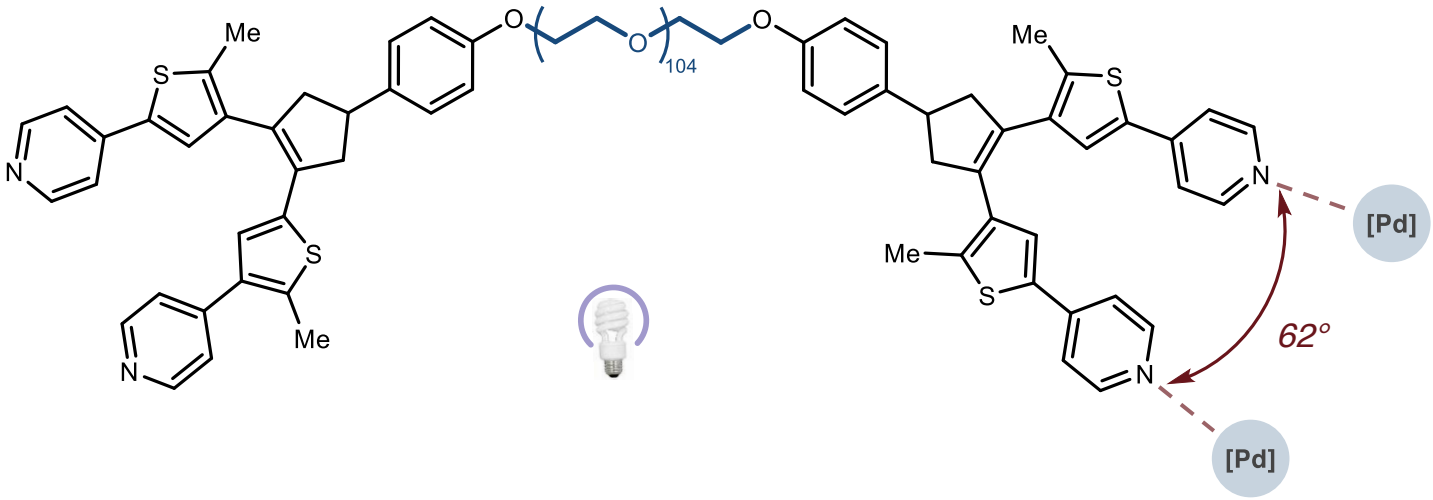
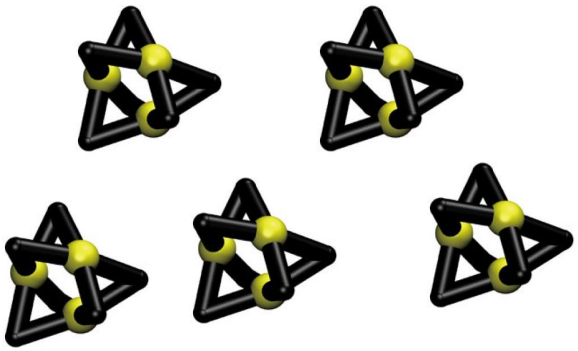
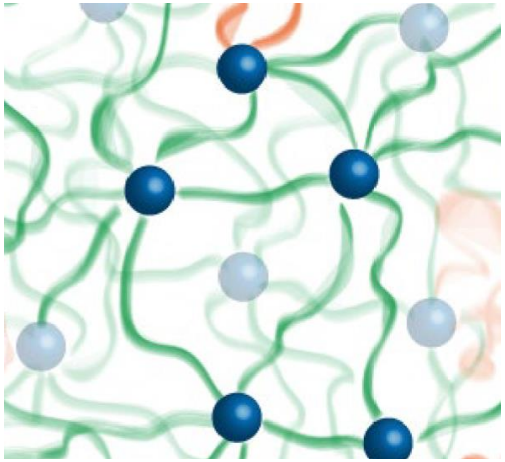




Pd_3L_6



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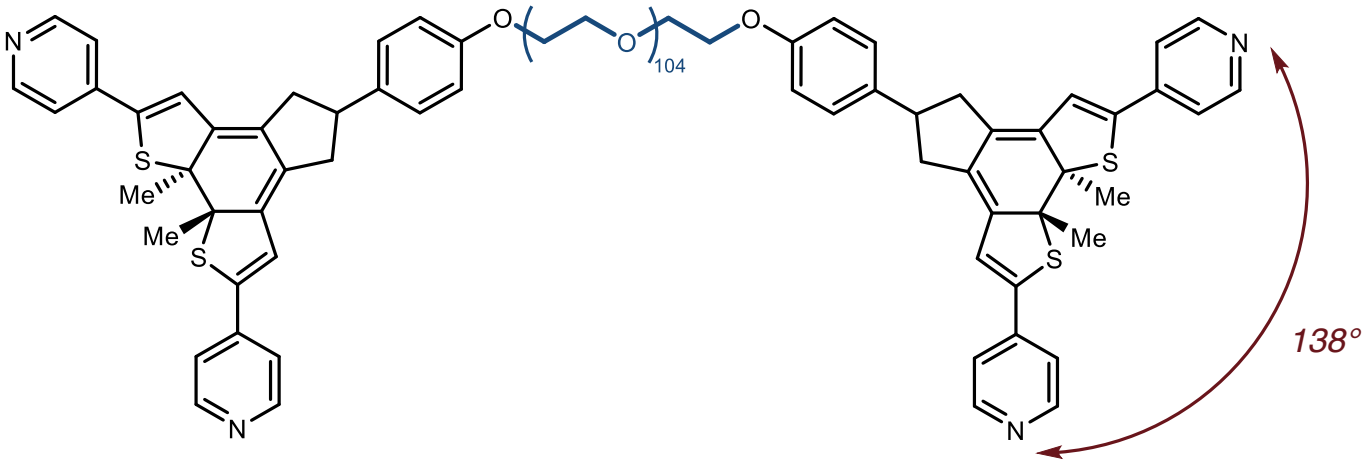
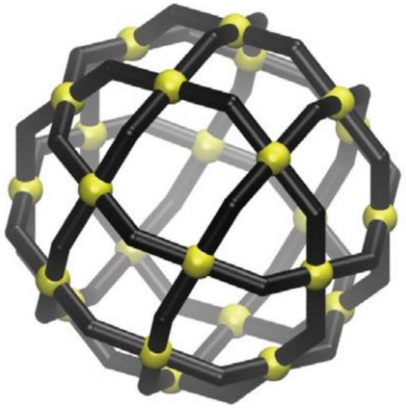
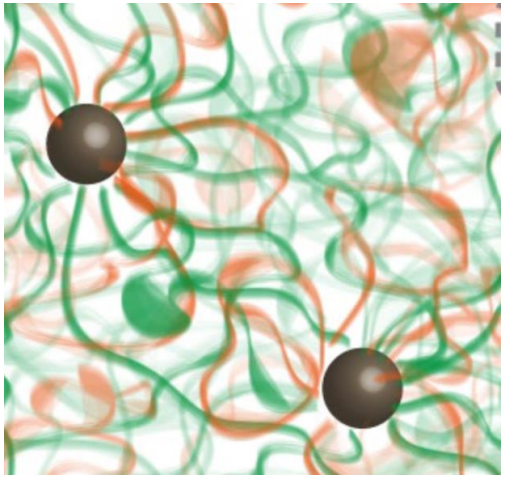
Topological interconvertible materials

UV light results in transformation of the ligand scaffold





$Pd_{24}L_{48}$



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Topological interconvertible materials

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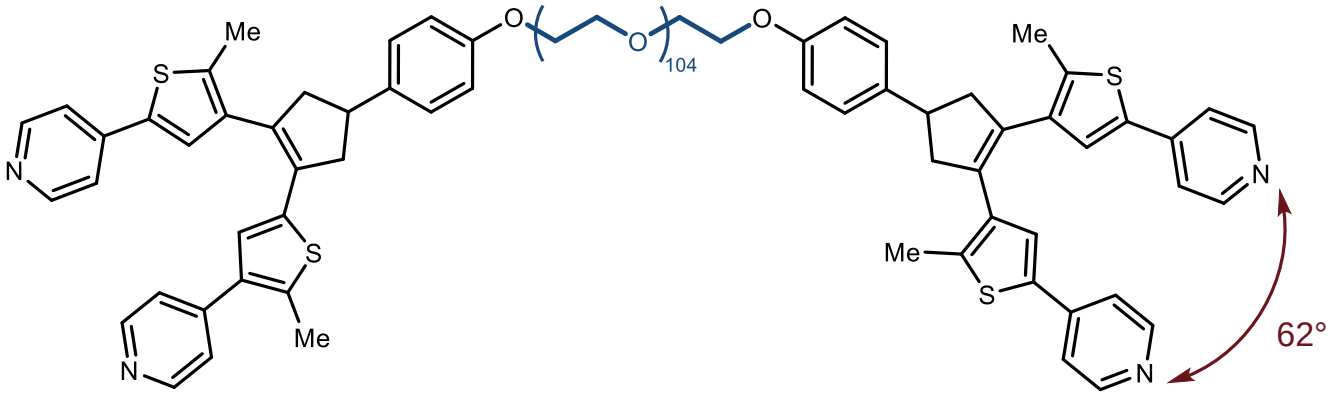

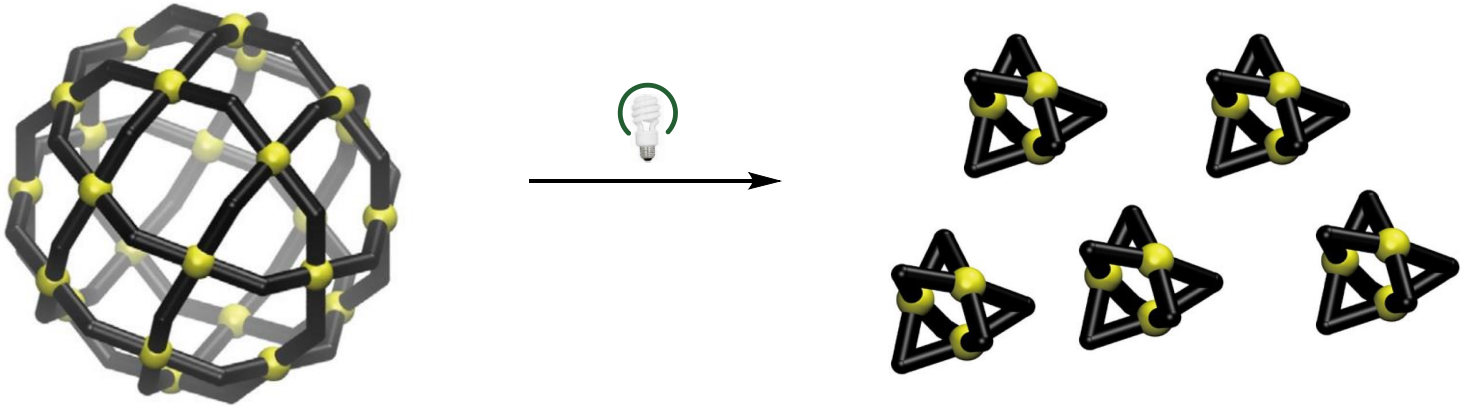

$Pd_{24}L_{48}$ Pd_3L_6

Gu, Y., Alt. E., Wang, H., Li, X., Willard, A., Johnson, J. *Nature*, **2018**, 560, 65

Topological interconvertible materials

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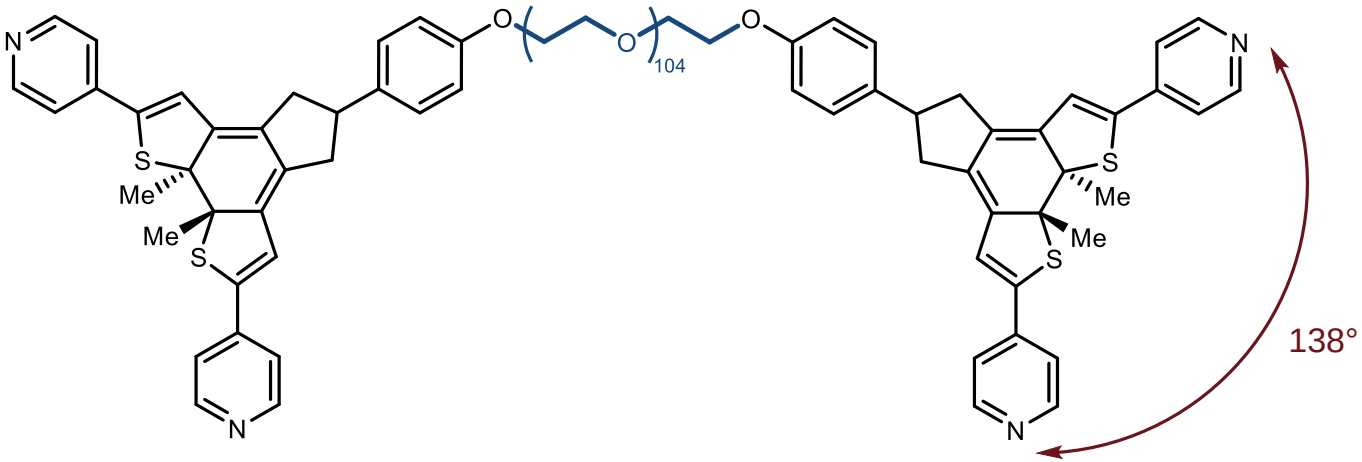

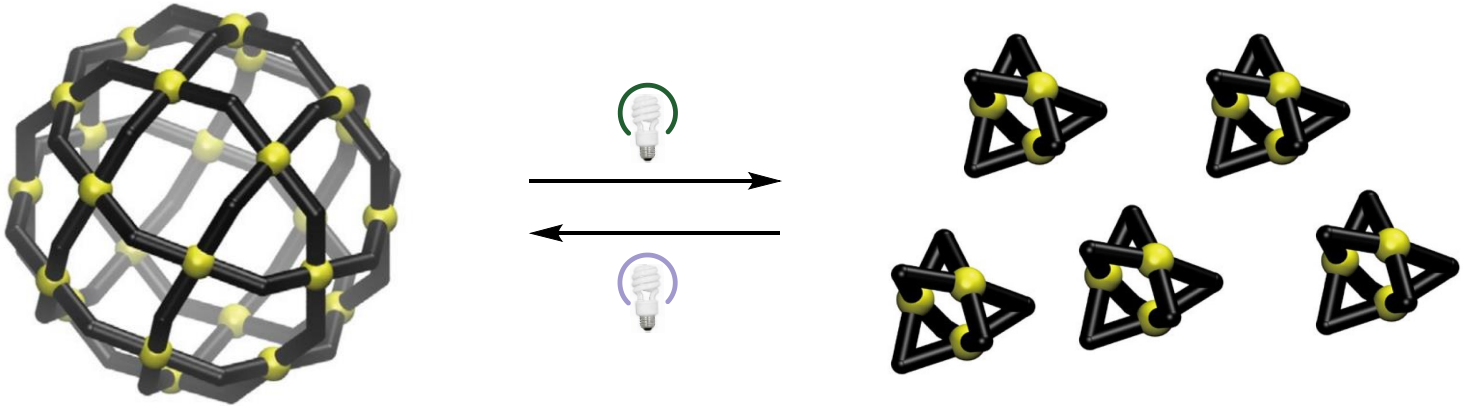

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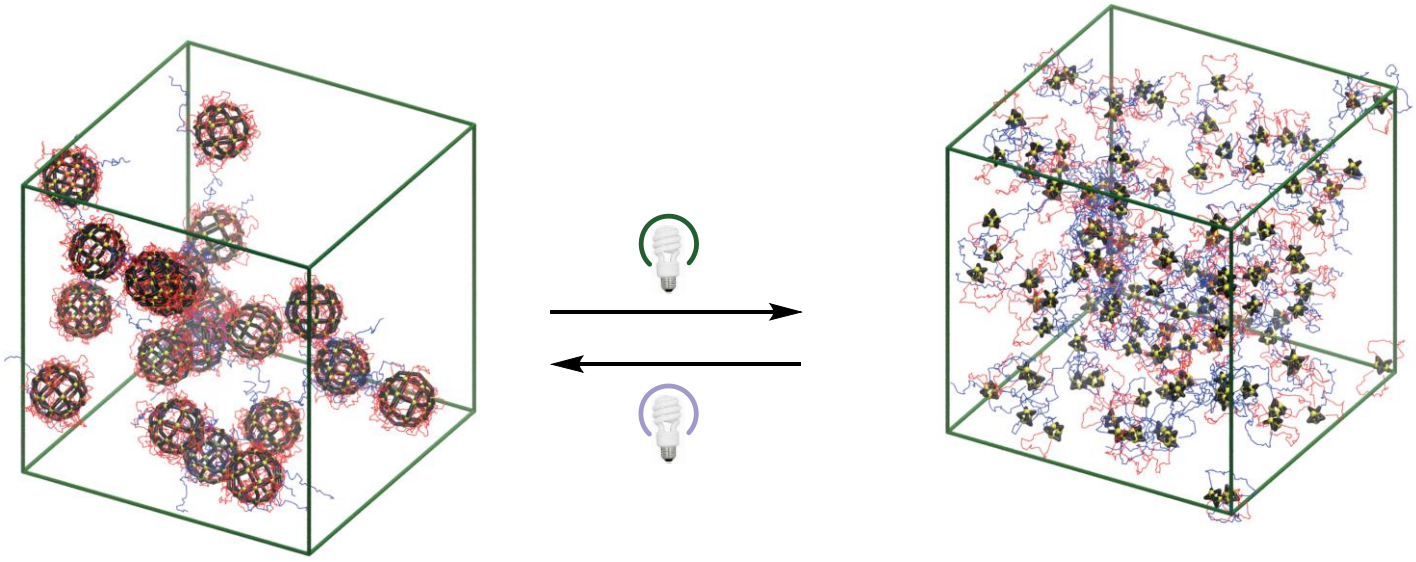
Topological interconvertible materials



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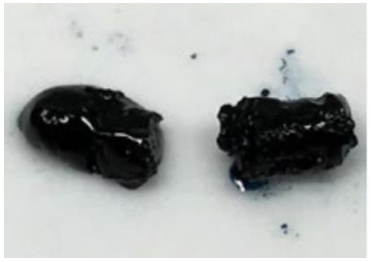
Topological interconvertible materials

40 °C

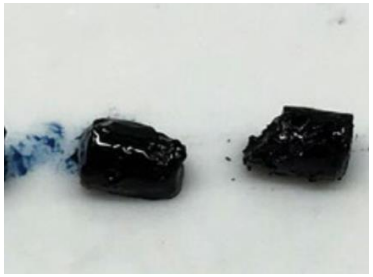
4 h

"healed" polymer



40 °C

4 h



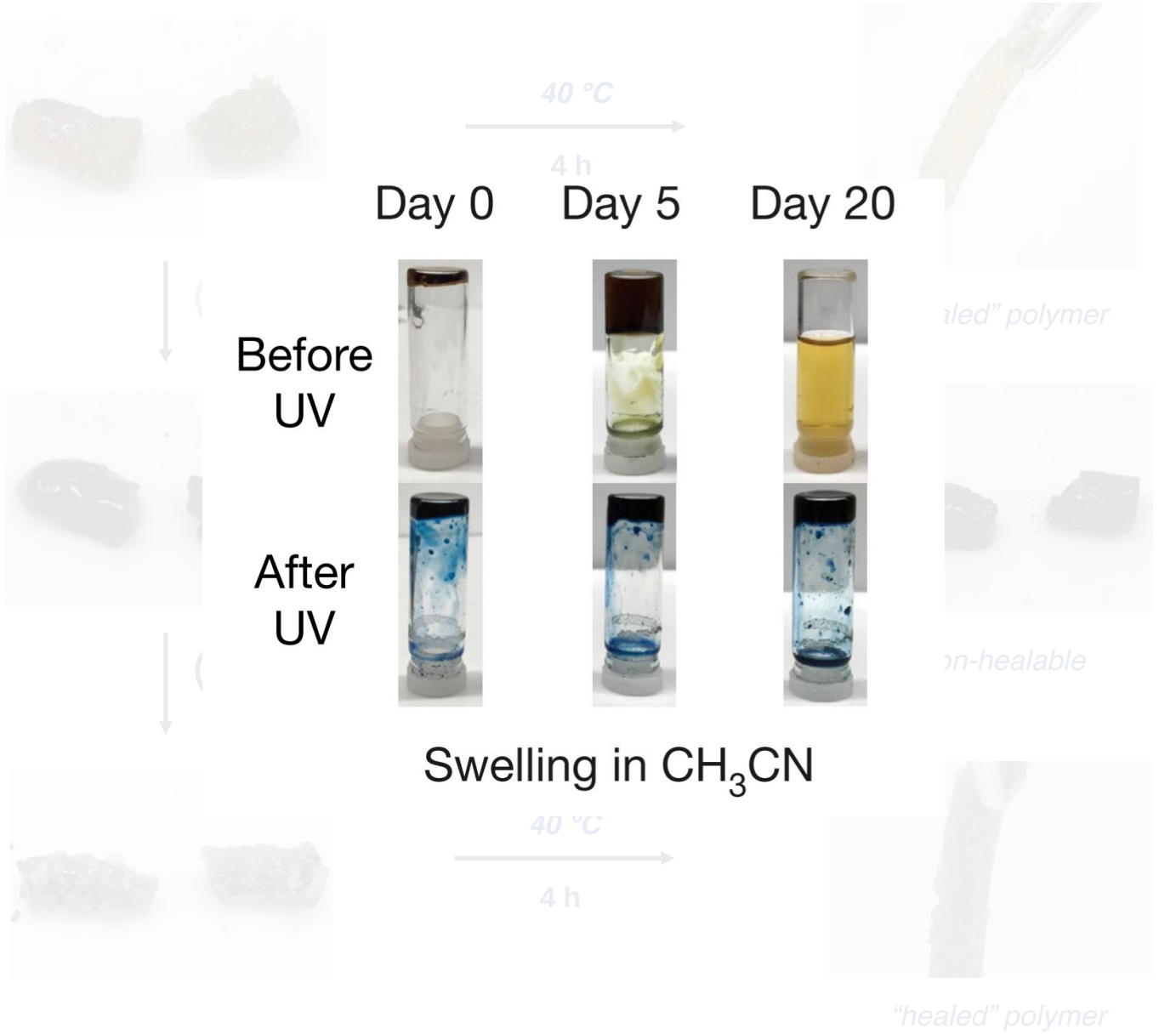
Non-healable

40 °C

4 h

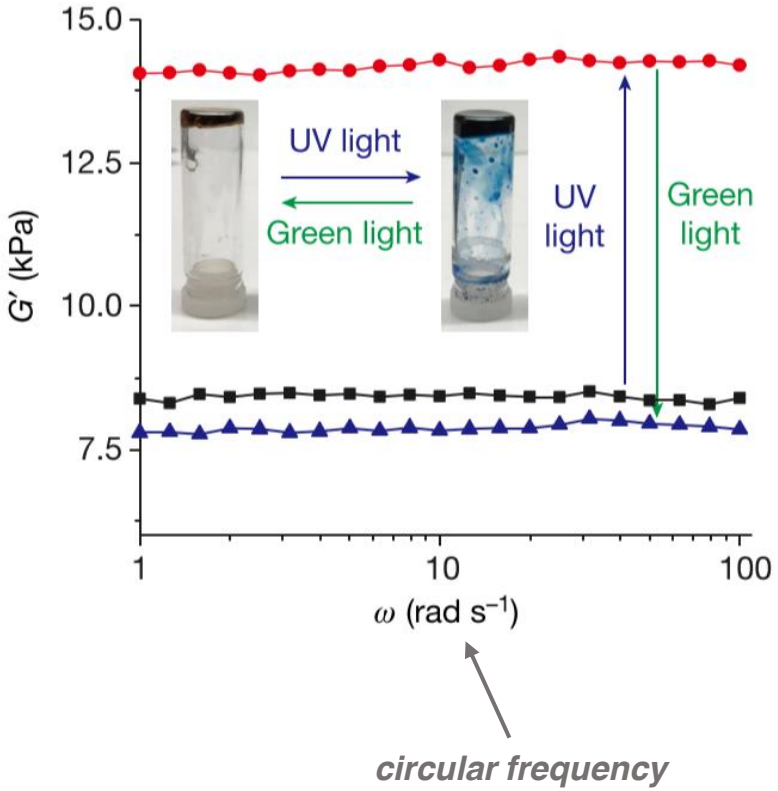
"healed" polymer

Topological interconvertible materials



Topological interconvertible materials

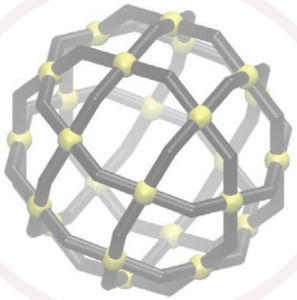
shear storage modulus "rigidity"



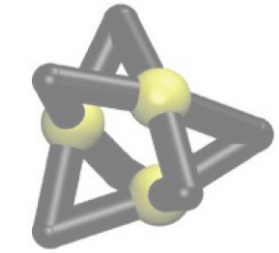
circular frequency

Gu, Y., Alt. E., Wang, H., Li, X., Willard, A., Johnson, J. Nature, **2018**, 560, 65

Reversible covalent binding in drugs

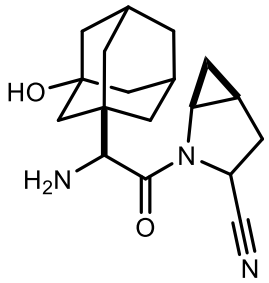


Adaptive Materials

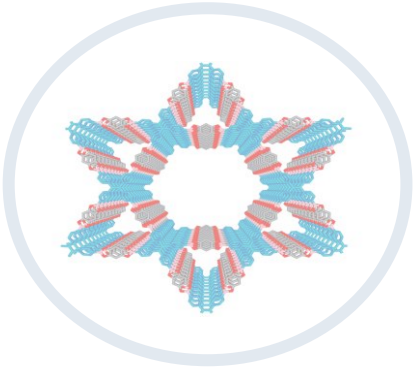


Photoswitchable Topology
Johnson: MIT

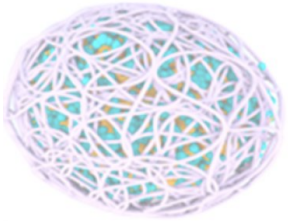
Reversible Covalent Binding



Onglyza: AstraZeneca
Saxagliptin



Covalent organic Frameworks



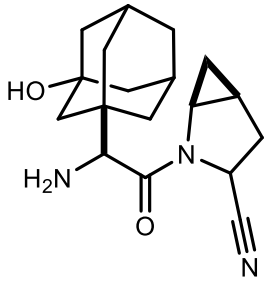
Drug/MRI delivery
Trabolsi: NYU Abu Dhabi

Reversible covalent binding in drugs

Reversible Covalent Binding

"In the field of drug design, reversible covalent drugs have drawn
Increasing attention as they provide longer residence time,
higher potency, and less drug resistance."

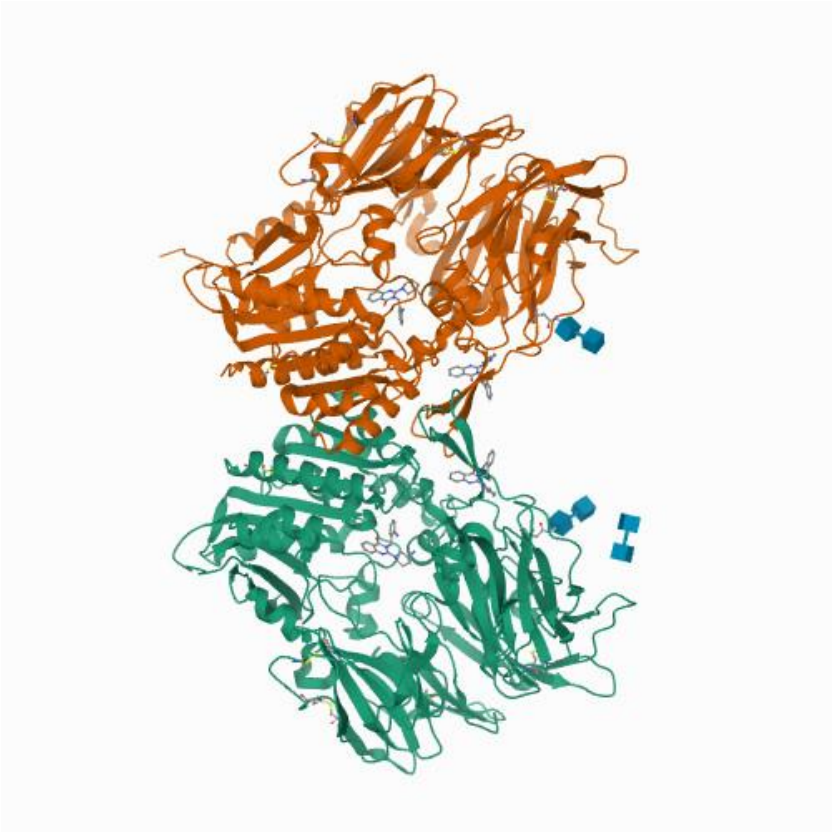
Combination of traditional non-covalent approach to medicines and covalent inhibitors



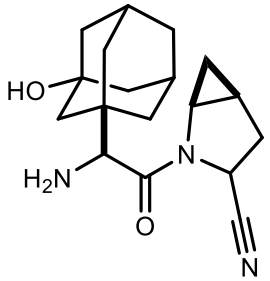
Type 2 Diabetes treatment
Saxagliptin: $400M in 2021

Baillie, T. *Angew. Chem. Int. Ed.*, **2016**, 55, 13408

Reversible covalent binding in drugs



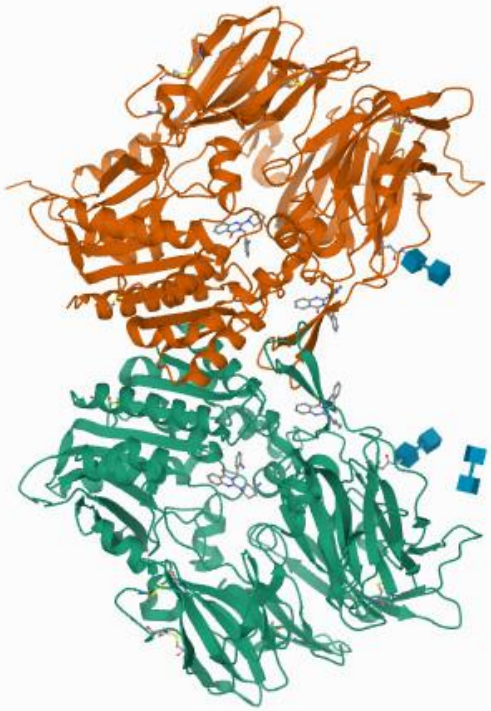
DPP-4
GLP-1 degrader



Type 2 Diabetes treatment
Saxagliptin: $400M in 2021

Protein structure from Protein data bank: 10.2210/pdb2ONC/pdb

Reversible covalent binding in drugs

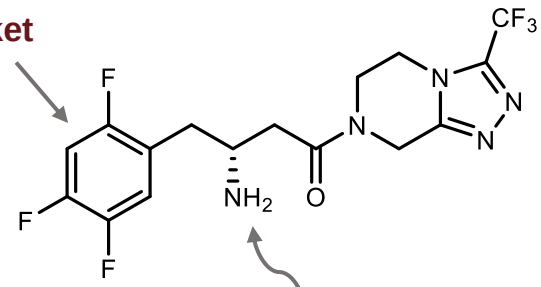


DPP-4
GLP-1 degrader

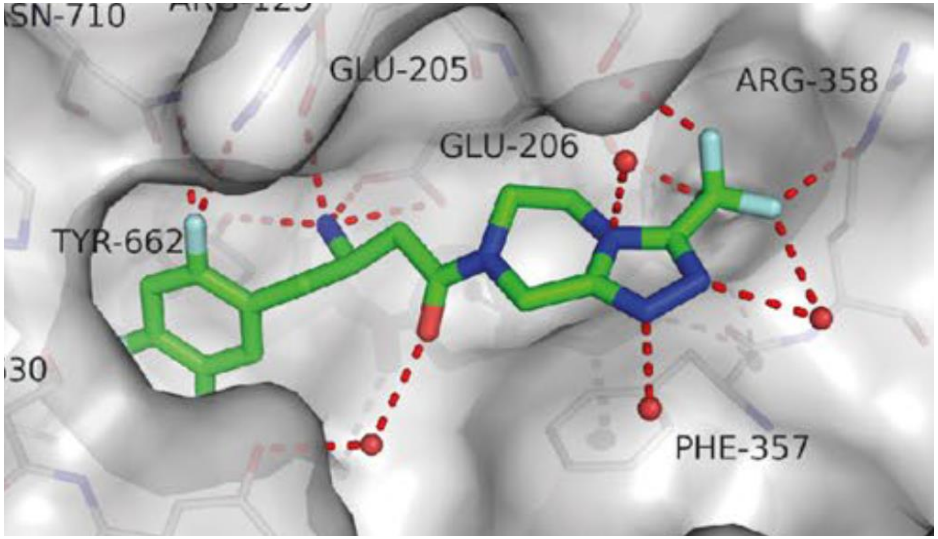
Sitagliptin
Non-covalent inhibitor

Arg358/Ser209

S-1 pocket

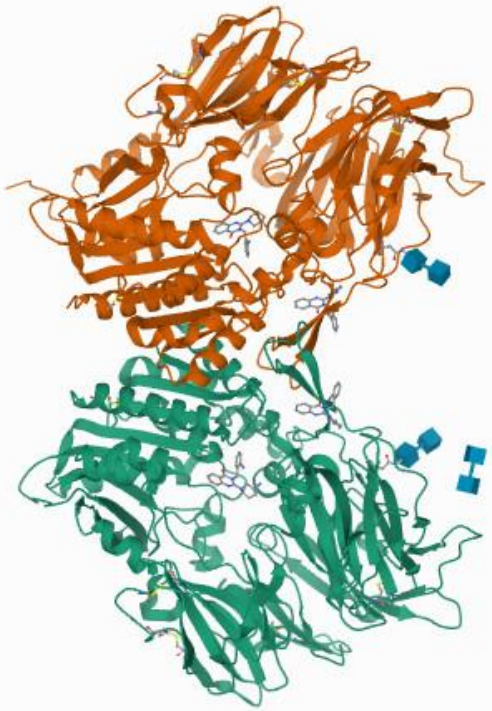


Tyr662/Glu205/Glu206



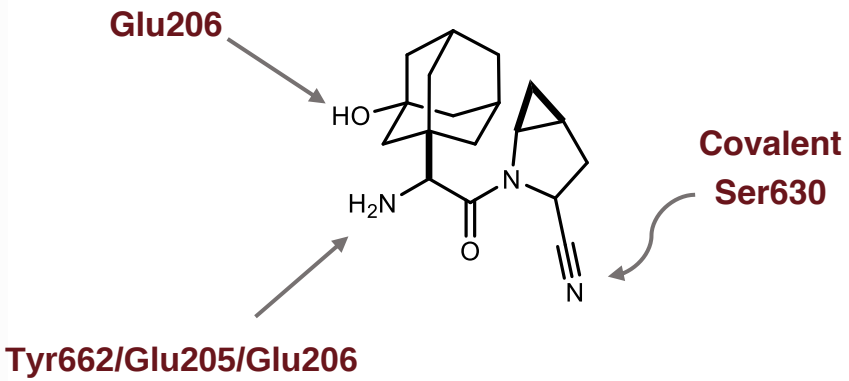
Nojima, H. et al. *BC Structural Biology*, **2016**, 16, 11

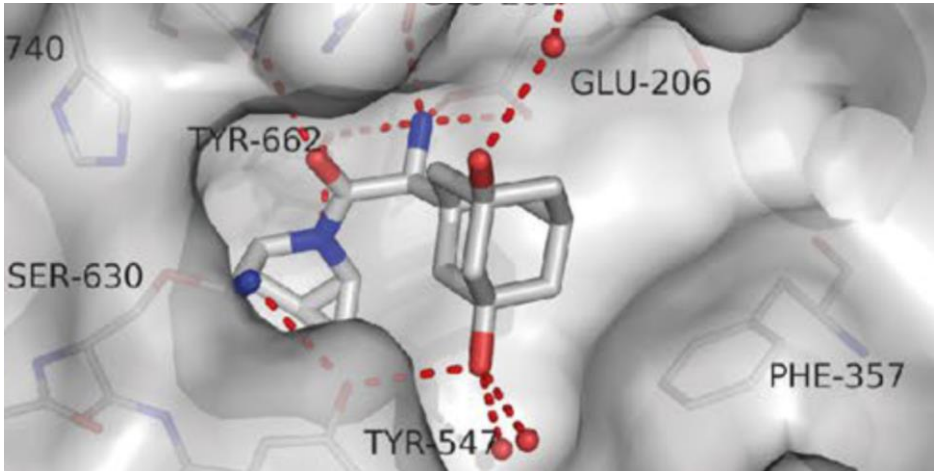
Reversible covalent binding in drugs



DPP-4
GLP-1 degrader

Saxagliptin
Reversible covalent inhibitor





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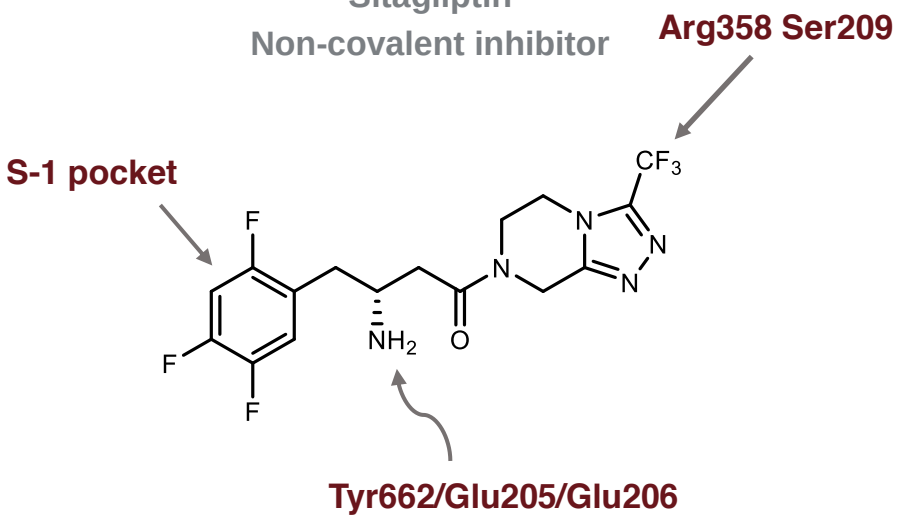
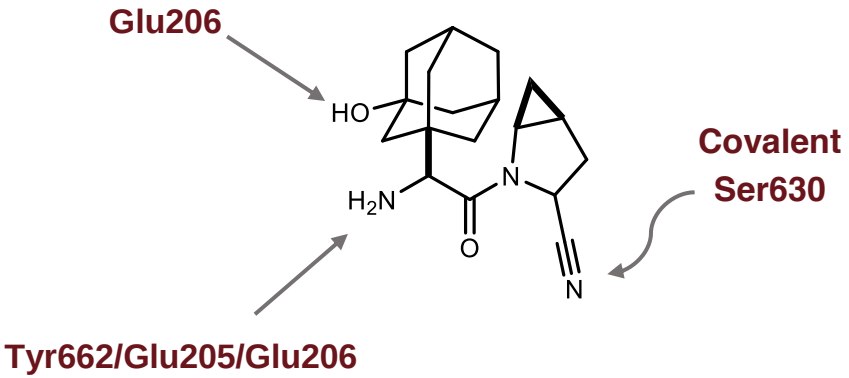
Reversible covalent binding in drugs

Sitagliptin
Non-covalent inhibitor



DPP4 K_i: 18 (nM)
On/off: > 100 / > 580 10^5 $M^{-1}s^{-1}$
$t_{1/2}$ (min.): < 2

Saxagliptin
Reversible covalent inhibitor



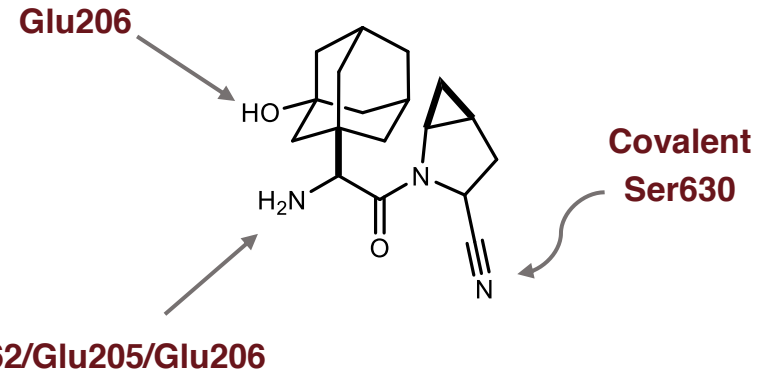
DPP4 K_i: 1.3 (nM)
On/off: 4.6 / 23 10^5 $M^{-1}s^{-1}$
$t_{1/2}$ (min.): 50

Wang, A. et al.. *BMC Pharmacology,* ***2012***, 2, 12

Reversible covalent binding in drugs

Reversible Covalent Binding

Saxagliptin
Reversible covalent inhibitor

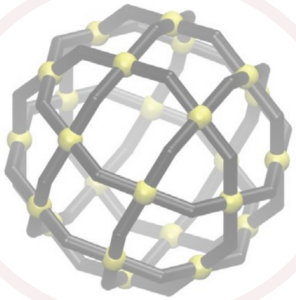


Reversible covalent binding is a rapidly growing area in drug discovery.

DPP4 K_i: 1.3 (nM)
On/off: 4.6 / 23 10^5 $M^{-1}s^{-1}$
$t_{1/2}$ (min.): 50

Wang, A. et al.. *BMC Pharmacology,* ***2012***, 2, 12

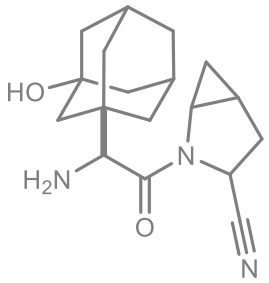
COFs for drug delivery



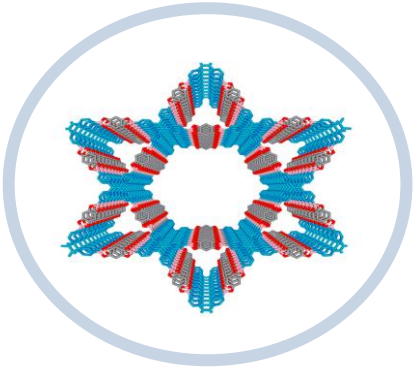
Adaptive Materials

Photoswitchable Topology
Johnson: MIT

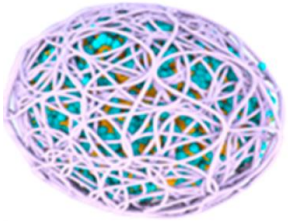
Reversible Covalent Binding



Onglyza: AstraZeneca
Saxagliptin



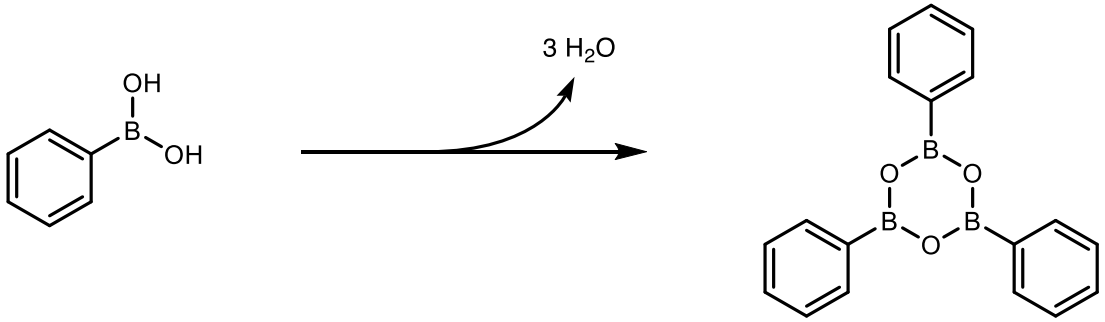
Covalent organic Frameworks

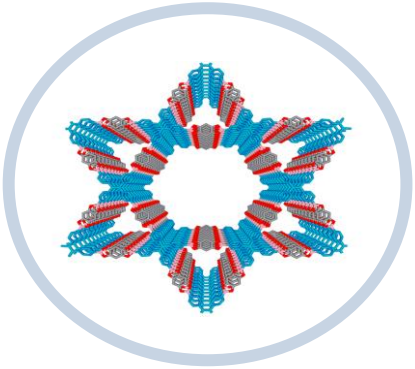


Drug/MRI delivery
Trabolsi: NYU Abu Dhabi

COFs for drug delivery

First successful report in 2005 from Yaghi:



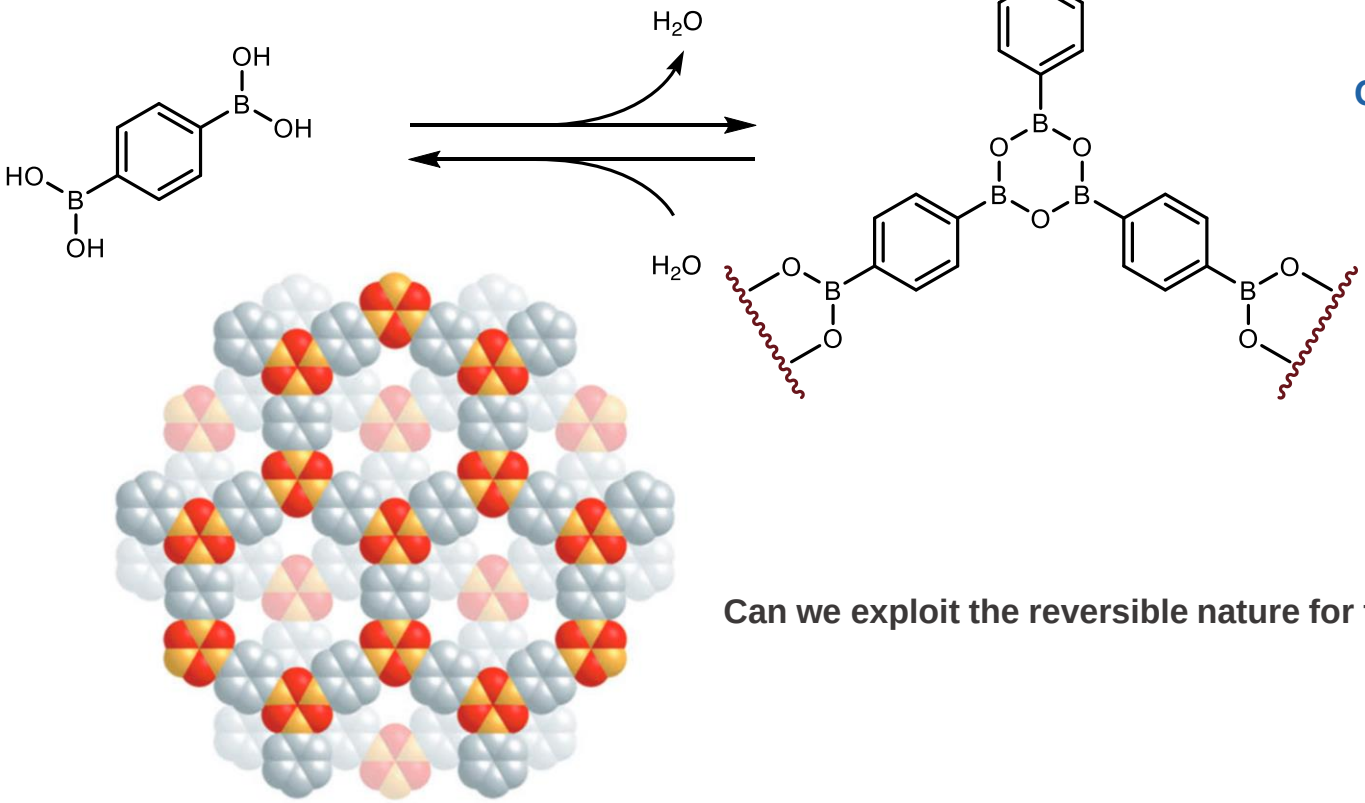


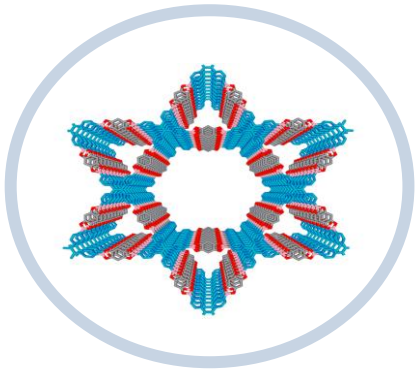
Covalent organic Frameworks

Cote, A. et al.. *Science, **2005***, 310, 1166

COFs for drug delivery

First successful report in 2005 from Yaghi:





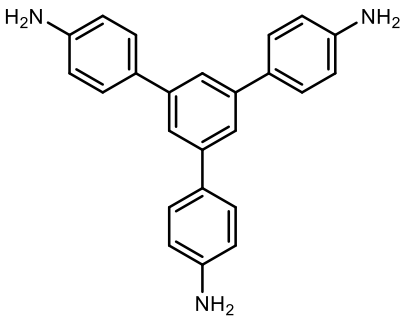
Covalent organic Frameworks

Can we exploit the reversible nature for targeted drug delivery?

Cote, A. et al.. Science, **2005**, 310, 1166

COFs for drug delivery

Trabolsi group: JACS 2020



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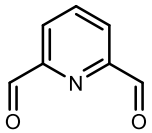
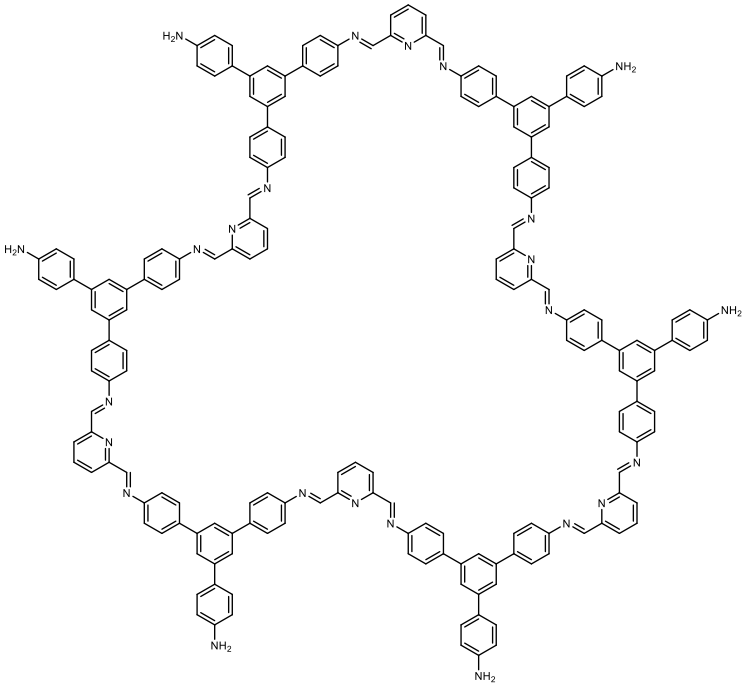


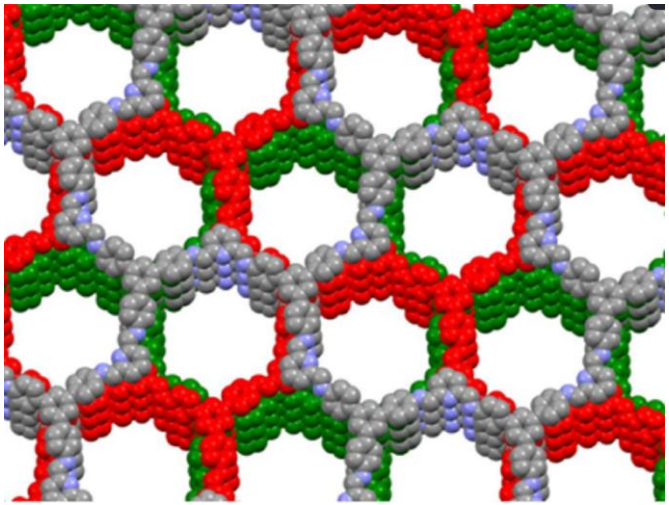
DFP

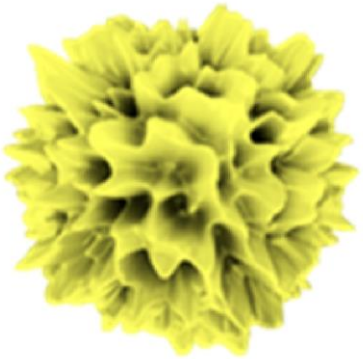
Imine formation

pH 5, 40 °C



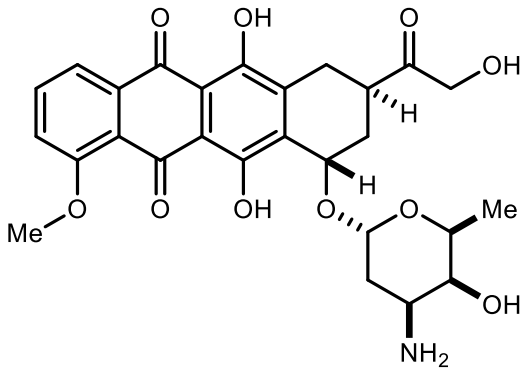
TAB-DFP-nCOF





Benyettou F., et al.. JACS, **2020**, 142, 18782

COFs for drug delivery

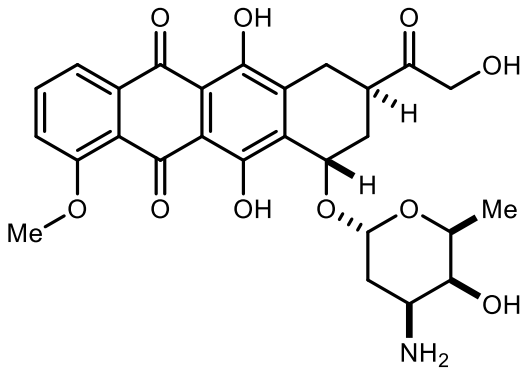


Doxorubicin (14.3 wt %)

Glioblastoma (brain tumor)
Magnetic hyperthermia therapy
Fe_2O_3 NPs target

Benyettou F., et al.. *JACS,* ***2020***, 142, 18782

COFs for drug delivery



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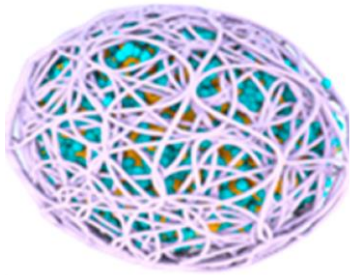
Fe_2O_3 NPs target

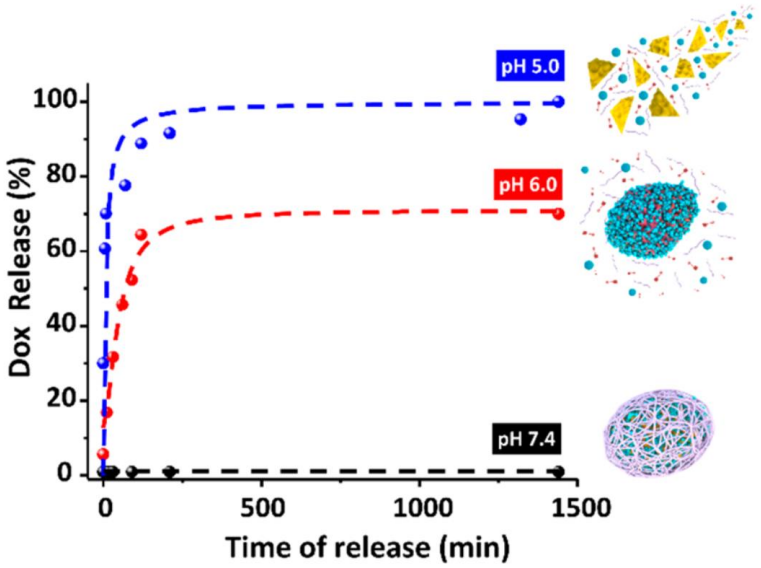
PolyLysine provides additional physiological protection

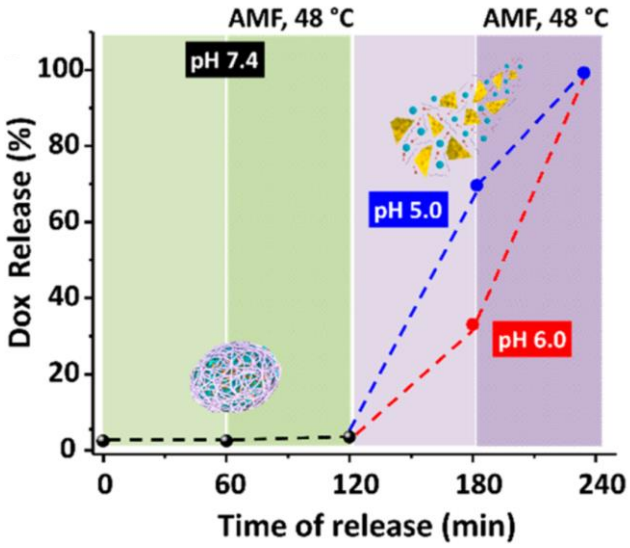
Benyettou F., et al.. *JACS, **2020***, 142, 18782

COFs for drug delivery



Stable
pH 7.4 – 37 °C





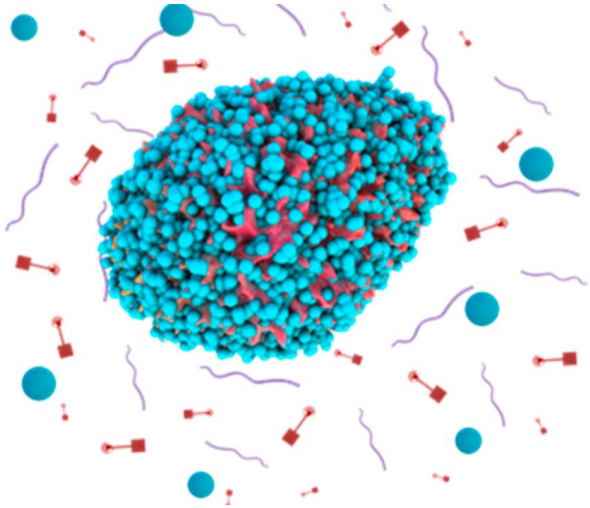
Benyettou F., et al.. JACS, **2020**, 142, 18782

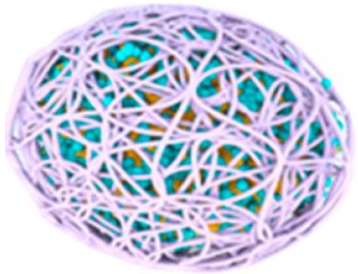
COFs for drug delivery

Mild conditions
endosomes

Slow drug release

pH 6.0 **37 °C**



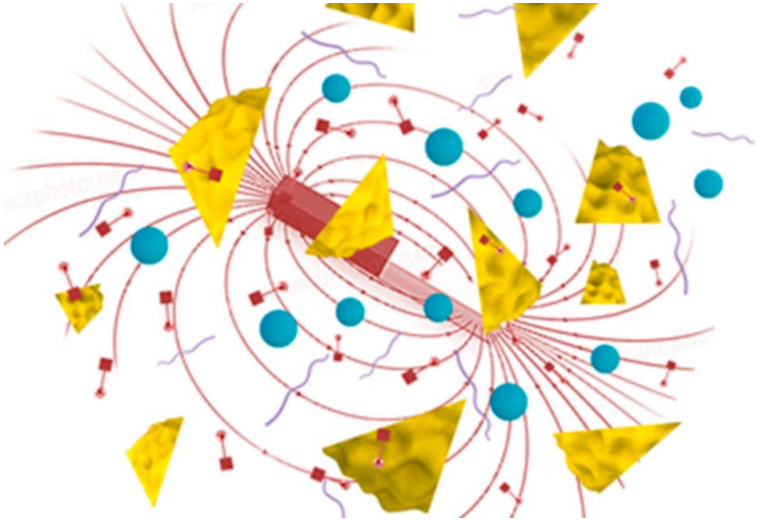


Stable
pH 7.4 – 37 °C

Tumor conditions
lysosomes

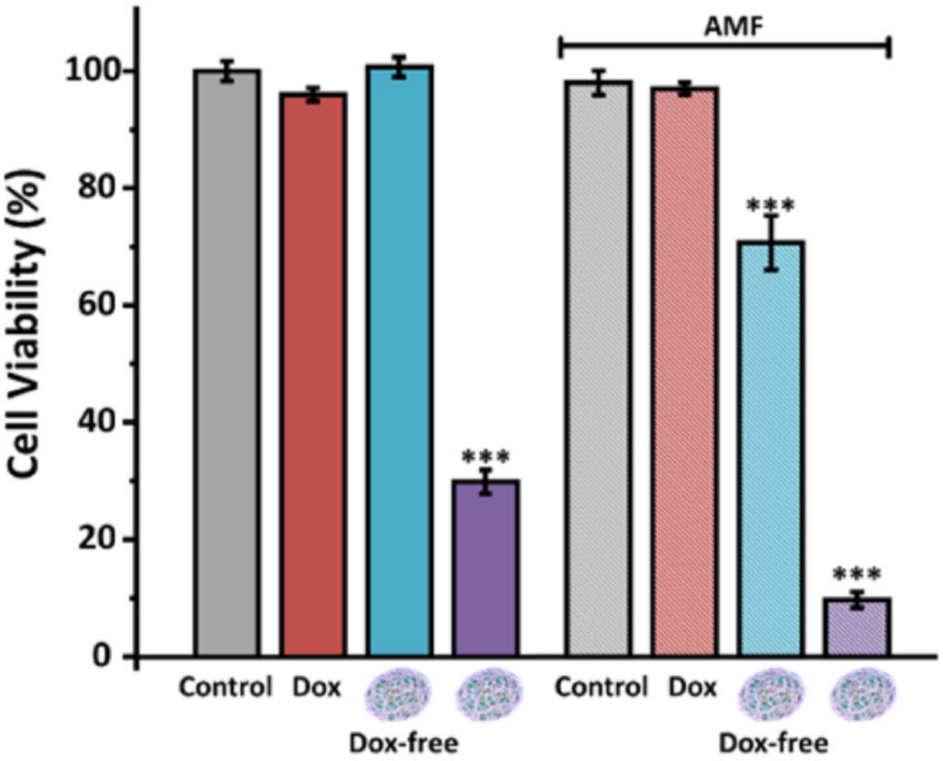
Burst drug release

pH 5.0 **40 °C**



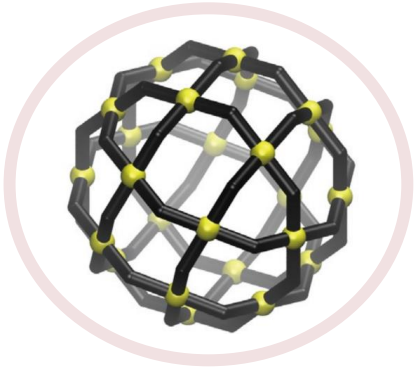
Benyettou F., et al.. *JACS*, ***2020***, 142, 18782

COFs for drug delivery

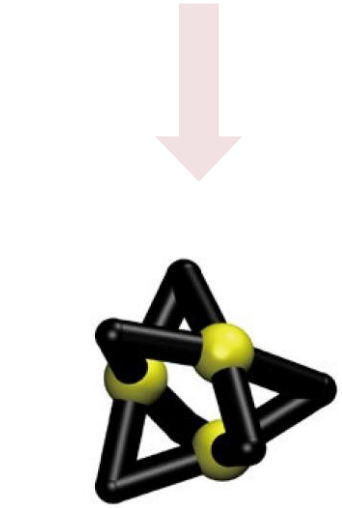


Benyettou F., et al.. JACS, **2020**, 142, 18782

Dynamic covalent chemistry: applications and examples

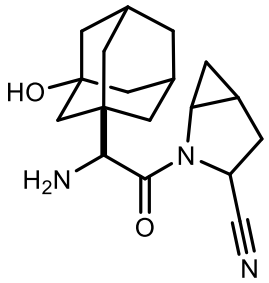


Adaptive Materials

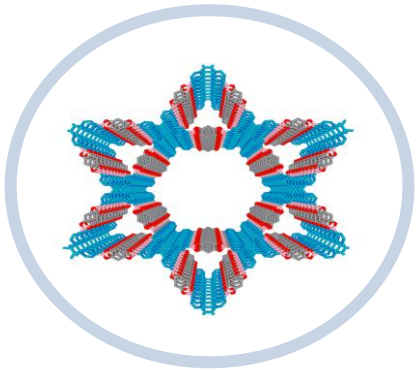


Photoswitchable Topology
Johnson: MIT

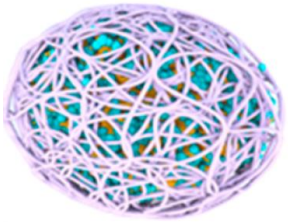
Reversible Covalent Binding



Onglyza: AstraZeneca
Saxagliptin



Covalent organic Frameworks



Drug/MRI delivery
Trabolsi: NYU Abu Dhabi