Dynamic covalent chemistry:
Simple reactions for complex systems

Literture Presentation
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Dynamic covalent chemistry (DCvC):
The chemistry of reversible bond formation under equilibrium control
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The chemistry of reversible bond formation under equilibrium control

>17,000 papers in 2021 alone


Data from Google Scholar search for “dynamic covalent chemistry” in 2021.
The intersect of conventional synthesis and supramolecular chemistry

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

Static products
Small molecules
Covalent bonds
“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*

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

What criteria do we need to consider for dynamic reactions?

Dynamic covalent chemistry requires thermodynamic products under equilibrium.

- **“Covalent nature”**: Covalent bonds broken and formed.
- **Stable and detectable**: Lifetime: $1 \text{ ms} < t < 1 \text{ min}$, 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.

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.

Reaction criteria

- “Covalent nature”
- Stable and detectable
- Adaptable
- Mild
- Water and oxygen compatible
- “Freezeable”
Confirmation of reversibility and equilibrium

Dual entry-point analysis

Stationary state perturbation

What reactions fall under the desired criteria?

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

- Sulfur bonds
- Pericyclic reactions
- Radical reactions
- Carbon-carbon
- Other bond types
- Carbon-nitrogen
Carbon-nitrogen bond formations

Most common dynamic covalent bond

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

Most common dynamic covalent bond

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Carbon-nitrogen bond formations

**Carbon-nitrogen**

- Easily tunable
- Side reactivity can be problematic

**most common dynamic covalent bond**

- Dynamic Combinational Chemistry
- Reversible Covalent Binding
- Molecular Machines
- Covalent organic Frameworks

Carbon-carbon bond formations

Olefin metathesis leads the way

Carbon-carbon bond formations

Olefin metathesis leads the way

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

Covalent organic Frameworks

Adaptive Materials

Olefin metathesis leads the way

Carbon-sulfur bond formations

- 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

Carbon-sulfur bond formations

Olefin metathesis leads the way

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

Carbon-carbon

Versatile bond formation and breaking

- Reversible Covalent Binding
- Adaptive Materials
- Biocompatibility and reactivity modes
- Oxygen sensitive

Covalent organic Frameworks

Adaptive Materials

Other key bond formations

- Substrate limited (requires diols)
- Harsh equilibrium conditions

Useful but niche applications

Other bond types

Reversible Covalent Binding
Nanogels
Adaptive Materials
Pericyclic and radical bond formations

Pericyclic reactions

“Self-contained” reactivity

Radical reactions

Tailored substrates for desirable reactivity

“Self-contained” and orthogonal

Niche substrates and poor retro kinetics

Excellent self-healing properties

Limited largely to material applications
Pericyclic and radical bond formations

Pericyclic reactions

“Self-contained” reactivity

Radical reactions

Tailored substrates for desirable reactivity

Molecular Machines

Covalent organic Frameworks

Nanogels

Adaptive Materials

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”

Dynamic covalent chemistry: applications and examples

Dynamic covalent chemistry (DCvC):
The chemistry of reversible bond formation under equilibrium control
Dynamic covalent chemistry: applications and examples

Adaptive Materials

Reversible Covalent Binding

Covalent organic Frameworks

Photoswitchable Topology
Johnson: MIT

Onglyza: AstraZeneca
Saxagliptin

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
Topological interconvertible materials

Metallosupramolecular assembly combined with stimuli-induced chemistry

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Metallosupramolecular assembly combined with stimuli-induced chemistry

Topological interconvertible materials

UV light results in transformation of the ligand scaffold

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UV light results in transformation of the ligand scaffold

Topological interconvertible materials

UV light results in transformation of the ligand scaffold

\[ \text{Pd}_{24}\text{L}_{48} \quad \rightarrow \quad \text{Pd}_3\text{L}_6 \]

Topological interconvertible materials

Topological interconvertible materials

- **Healed** polymer
  - 40 °C
  - 4 h

- **Non-healable**
  - 40 °C
  - 4 h

- **Healed** polymer
  - 40 °C
  - 4 h
Topological interconvertible materials

Non-healable

40 °C
4 h

40 °C

“healed” polymer

Before UV

After UV

Swelling in CH₃CN

Day 0

Day 5

Day 20

4 h
Topological interconvertible materials


shear storage modulus “rigidity”

circular frequency
Reversible covalent binding in drugs

Adaptive Materials

Reversible Covalent Binding

Covalent organic Frameworks

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Reversible covalent binding in drugs

“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.”

Reversible covalent binding in drugs

Type 2 Diabetes treatment
Saxagliptin: $400M in 2021

Protein structure from Protein data bank: 10.2210/pdb2ONC/pdb
Reversible covalent binding in drugs

Sitagliptin
Non-covalent inhibitor
Arg358/Ser209

S-1 pocket

Tyr662/Glu205/Glu206

DPP-4
GLP-1 degrader

Reversible covalent binding in drugs

DPP-4
GLP-1 degrader

Saxagliptin
Reversible covalent inhibitor

Glu206

Covalent
Ser630

Tyr662/Glu205/Glu206

Nojima, H. et al. BC Structural Biology, 2016, 16, 11
Reversible covalent binding in drugs

Sitagliptin
Non-covalent inhibitor

S-1 pocket
Tyr662/Glu205/Glu206

Arg358 Ser209

Saxagliptin
Reversible covalent inhibitor

Glu206
Tyr662/Glu205/Glu206

Covalent Ser630

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

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

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

Saxagliptin
Reversible covalent inhibitor

Glu206

Tyr662/Glu205/Glu206

Covalent
Ser630

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

Wang, A. et al.. *BMC Pharmacology*, 2012, 2, 12
COFs for drug delivery

Adaptive Materials

Reversible Covalent Binding

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COFs for drug delivery

First successful report in 2005 from Yaghi:

Cote, A. et al. Science, 2005, 310, 1166
COFs for drug delivery

First successful report in 2005 from Yaghi:

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

$$\text{H}_2\text{N} - \begin{array}{c} 
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} - \begin{array}{c} 
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} \text{NH}_2$$

$$\begin{array}{c} 
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}$$

**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$_2$O$_3$ NPs target

Doxorubicin

COFs for drug delivery

Drug loading

Fe$_2$O$_3$ NPs
go through polyLysine

Doxorubicin (14.3 wt %)

Glioblastoma (brain tumor)
Magnetic hyperthermia therapy
Fe$_2$O$_3$ 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

Tumor conditions
lysosomes

Burst drug
release

pH 5.0
40 °C

Stable
pH 7.4 – 37 °C

Mild conditions:
- pH 6.0 at 37 °C: Slow drug release
- pH 7.4 – 37 °C: Stable

Tumor conditions:
- pH 5.0 at 40 °C: Burst drug release

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