ADVANCED ORGANIC SYNTHESIS

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Carbon Species

stable (neutral)
carbanion radical carbene carbocation

unstable species

Acid-Base Chemistry

A - C - H → C : −
B - C - X → C +

Organometallic Chemistry

Y - C - H → Y - C - M
C : → C = M
C : → C - M

relatively stable complex
1. Stabilize unstable organic compounds

- strained, unstable
- does not exist at normal temperatures and pressures
- reacts with itself to form larger ring

**cyclobutadiene**

- stable
- well-behaved and easily-manipulated
- readily separated
- a convenient source of cyclobutadiene

**iron complex**
Cyclobutadiene iron tricarbonyl

Preparation:

Cyclooctatetraene
Cyclobutadiene iron tricarbonyl
Applications:

Synthesis of Cubane


Favorskii rearrangement

2. Change characters of organic compounds

- Benzene
  - surrounded by a cloud of negative electrons
  - prefer to interact with positively-charged molecules

- Chromium complex
  - Cr(CO)$_3$ sucks away electrons from benzene
  - prefer to interact with negatively-charged molecules
Benzene chromium tricarbonyl

Preparation:

\[ \text{Cr(CO)}_6 + \text{C}_6\text{H}_6 \rightarrow \text{Cr(C}_6\text{H}_6\text{)(CO)}_3 + 3 \text{CO} \]

Applications:

The aromatic ring of (benzene) tricarbonylchromium is substantially more electrophilic than benzene itself, allowing it to undergo nucleophilic addition reactions.

3. organometallic complexes: useful templates (as reagents)

Pauson-Khand Reaction: 1970s

The formal [2+2+1] cycloaddition of an alkene, alkyne, and carbon monoxide to form cyclopentenones:

Pauson-Khand Reaction

Proposed Mechanism

1. **Ligand substitution**
   - Reaction between a metal complex and a Michael acceptor.

2. **Cobaltacycle formation**
   - CO insertion into the metal center.

3. **Reductive elimination**
   - Removal of a metal atom to form a carbon-carbon bond.

4. **Reductive elimination**
   - Final step to produce the product.
Application to the synthesis of complex molecules

- **Formal total synthesis of** *dl*-Coriolin

Antibiotic and antitumor properties reported
taylorione: synthesis by Williams Kerr in 1990s

A total synthesis of the sesquiterpene, (+)-taylorione starting from (+)-2-carene
the key synthetic transformation is achieved in high yield by application of developed Pauson–Khand reaction techniques for gaseous olefins.
4. Catalyze Reactions: efficiency

in early 1990s, Robert H. (Bob) Grubbs at California Institute of Technology

Olefin metathesis تراساخت (جانشینی متقابل) الفين

- for some time had been used for synthesis of polymers but had been overlooked by organic chemists

\[
\begin{align*}
R\equiv\equiv & \xrightarrow{\text{olefin metathesis}} \qquad R\equiv

\begin{align*}
R\equiv\equiv & \xrightarrow{\text{catalyst}} \quad R\equiv + \quad \text{CH}_2\text{CH}_2
\end{align*}
\]

- alkenes are one of the most important building block
- abundant in nature's chemicals: vitamin A, quinine, chlorophyll
- manmade organic chemicals: pharmaceuticals, perfumes, flavoring
Olefin Metathesis

catalysts for olefin metathesis: many catalysts based on organometallic reagents "Ru", "Mo", "W"

Grubbs's catalyst
Olefin Metathesis

Carbon-carbon bond rearrangements in presence of metal carbene catalyst complexes especially those of molybdenum and ruthenium:


Ring-Closing Olefin Metathesis

simple starting material

50% + 35% (E-isomer)

cancer drug

Epothilone A
The Nobel Prize in Chemistry 2005

"for the development of the metathesis method in organic synthesis"

Yves Chauvin, born 1930 (74 years), French citizen. Directeur de Research Honoreur, Institut Français du Pétrole, Rueil-Malmaison, France.

Robert H. Grubbs, born 1942 (63 years) in Calvert City, KY, USA (US citizen). PhD in chemistry in 1968 from Columbia University, New York, NY, USA. Victor and Elisabeth Atkins Professor of Chemistry at California Institute of Technology (Caltech), Pasadena, CA, USA.

Richard R. Schrock, born 1945 (60 years) in Berne, IN, USA (US citizen). PhD in chemistry in 1971 from Harvard University, Cambridge, MA, USA. Frederick G. Keyes Professor of Chemistry at Massachusetts Institute of Technology (MIT), Cambridge, MA, USA.

Prize amount: SEK 10 million, will be shared equally among the Laureates.

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1. Combinatorial Chemistry

2. Supramolecular Chemistry

3. Molecular Machine

4. ......

5. ......
Combinatorial Chemistry

Combinatorial chemistry comprises chemical synthetic methods that make it possible to prepare a large number (tens to thousands or even millions) of compounds in a single process.

Combinatorial Library

These compound libraries can be made as mixtures, sets of individual compounds or chemical structures generated in silico. (An allusion to the Latin phrases in vivo, in vitro, and in situ)

In vitro (Latin for within the glass) refers to the technique of performing a given procedure in a controlled environment outside of a living organism.

In vivo (Latin for “within the living”) refers to experimentation using a whole, living organism as opposed to a partial or dead organism.

In silico is an expression used to mean “performed on computer or via computer simulation.”
Combinatorial chemistry can be used for the synthesis of small molecules and for peptides.
Applications of Combinatorial Chemistry

Chemical biology: **diversity-oriented synthesis** of small organic molecules

Material science: new approach for the discovery of new materials

Catalyst discovery: fast discovery of new catalysts

**Pharmaceutical industry:** rapid synthesis of a huge number of drug-like molecules
Solid Phase Synthesis (Basic principles)

- **solid-phase synthesis** is a method in which molecules are bound on a bead and synthesized step-by-step in a reactant solution; compared with normal synthesis in a liquid state, it is easier to remove excess reactant or byproduct from the product.

- The process was originally developed in the 1950s and 1960s by **Robert Bruce Merrifield** in order to synthesize peptide chains, and which was the basis for his 1984 **Nobel Prize in Chemistry**.
Merrifield Solid-Phase Peptide Synthesis (SPPS)

Synthesis of long peptides involving the following steps:
1. Attachment of the C-terminal amino acid to an insoluble polymeric support resin,
2. Elongation of the peptide chain,
3. Cleavage of the peptide from the resin:

Solid Phase Synthesis

1. resin + monomer
2. shake
3. wash
4. resin cleavage

Steps:
- Add resin and monomer
- Shake
- Wash
- Resin cleavage
- Wash
- Wash
## Solid Phase Library

<table>
<thead>
<tr>
<th>Solid Phase</th>
<th>Solution Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make a mixture of products</td>
<td>Makes only one product</td>
</tr>
<tr>
<td>Small amounts of products formed</td>
<td>Large amounts of products can be synthesized</td>
</tr>
<tr>
<td>Simple isolation of product by filtration</td>
<td>Work-up and purification more difficult</td>
</tr>
<tr>
<td>Require 2 extra reaction steps: linkage and cleavage</td>
<td>No extra steps needed</td>
</tr>
<tr>
<td>Limits to chemistry which can be performed</td>
<td>Wide range of reactions can be utilized</td>
</tr>
<tr>
<td>Automation available</td>
<td>Automation not as highly developed</td>
</tr>
<tr>
<td>Large excesses of reagent can be used to drive the reaction to completion</td>
<td>Cannot use large reagent excesses</td>
</tr>
</tbody>
</table>
Solid Phase Library

In 1991s, Houghten & Lam: synthesis of a huge peptide library

20 amino acids

\[20^2 = 400 \text{ dipeptides}\]

\[20^3 = 8000 \text{ tripeptides}\]

\[20^4 = 160,000 \text{ tetrapeptides}\]

Solid-phase synthesis

DNA: fully automatic (solution) peptide carbohydrate small molecule (drug-like)

In 1992, Jon Ellman: synthesis of non-peptide drug-like molecules by solid phase synthesis
Solid Phase Library Synthesis

- polymer supported synthesis: easy purification
- fast generation of diverse library of molecules in few steps
- limited reactions compared to solution reactions

- **Split-Mix** (split-pool) synthesis
- **Parallel synthesis**
Split-Mix Process

tag each bead!

3^3 = 27
Parallel synthesis

- no tagging beads!
- synthesis of small number of focused library
Supramolecular Chemistry

1. Molecular chemistry - Covalent bond

urea
150 years ago

Zoantharia

Palytoxin and Analogs
2. Supramolecular chemistry- Chemistry beyond molecules
Assembly of molecules – Molecular recognition

**Non-covalent bonds:**
- electrostatic forces
- hydrogen bonds
- van der Waals interactions
- dipole interactions
- hydrophobic interactions, etc

1987 Nobel Prize in Chemistry:
Supramolecular Chemistry

Donald J. Cram
Jean-Marie Lehn
Charles Pedersen
Target-Oriented Organic Synthesis

Known active sites of target proteins

Design and synthesis of target molecules

biological effects
The Binding between Drug and Biological Receptors through Non-Covalent Bonds

Figure 18. The binding between drug and biological receptors through hydrogen bonding, shown by $D =$ hydrogen donor sites and $A =$ hydrogen acceptor sites.
Preorganized Ionophores

**Preorganization**: both binding affinity and selectivity are considerably increased

W.C. Still

D.J. Cram
Crown ether
- 11 kcal/mol

Cryptand
- 18 kcal/mol

Crown ether

Cryptand
A carcerand is a **host** molecule that completely entraps its guest so that it will not escape even at high temperatures.

This type of molecule was first described by **Donald J. Cram** in 1985 and is derived from the Latin *carcer*, or prison. The complexes formed by a carcerand with permanently imprisoned guests are called **carceplexes**.
Carcerand
Chemosensors

organic molecules designed to bind and sense small molecules or metal ions and their applications

Signals:
- fluorescence
- color
- electric signal...
Chemosensors

\[
\begin{align*}
\text{Hg}^{2+} & \quad \text{Ag}^{+} \quad \text{Cu}^{2+} \quad \text{Cd}^{2+} \quad \text{Pb}^{2+} \quad \text{Zn}^{2+}
\end{align*}
\]
Figure 23. Recognition between barbiturates and a synthetic receptor—a prototype chemical sensor.
A **molecular machine**, or nanomachine is any discrete number of molecular components that produce quasi-mechanical movements (output) in response to specific stimuli (input).

The expression is often more generally applied to molecules that simply mimic functions that occur at the macroscopic level.

The term is also common in **nanotechnology** where a number of highly complex molecular machines have been proposed that are aimed at the goal of constructing a **molecular assembler**.

Molecular machines can be divided into two broad categories: **synthetic** and **biological**.
Biomolecular machines

Linear movement - muscle
(myosin moving along an actin filament)

ATP Synthase

Bacterial Flagellar Motor
Interlocked Molecules

Rotaxane
Rota (wheel) + axis (axle)

Catenane
Catena (chain)
Molecular shuttle moves
Artificial molecular machines

A catenane-based switching device for electric circuits.

Catenane: a molecule which consists of two or more connected rings like links in a chain. Catenane is derived from the Latin *catena* meaning "chain".
Catenane-based molecular rotor. A unidirectional rotation of the small rings along the large ring is achieved by their sequential complexation and decomplexation with four station parts A-D on exposure to light, heat, and chemical stimuli.
Molecular scissors

(a) [Chemical structure diagram]

(b) [Images depicting the molecular scissors in different states with a reaction arrow labeled $h\nu$ and $h\nu'$]
Artificial molecular machines

Chiral molecular motor composed of a tetrasubstituted alkene. Photoinduced and thermal-induced unidirectional rotation.