TFYA30
Supramolecular Chemistry

Organization

Examiner and course responsible: Daniel Aili

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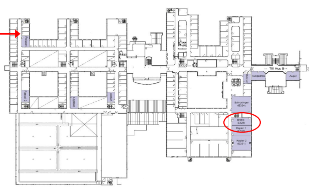


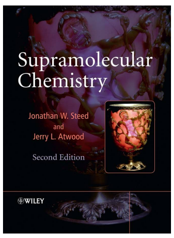
Organization

Teaching activities

- 10 Lectures x 2 h
- 3 Seminars x 2-4 h
- 2 Labs x 4 h
- 4 Classes

Literature

- Jonathan W. Steed, Jerry L. Atwood, "Supramolecular Chemistry" 2nd Ed., Wiley-Blackwell, 2009.
- Journal articles



Organization

Teaching activities

- 10 Lectures x 2 h
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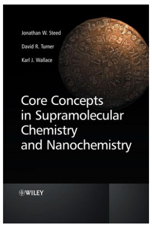
- 4 Classes

Alternative Literature

- Jonathan W. Steed, David R. Turner, Karl J. Wallace, "Core Concepts in Supramolecular Chemistry", Wiley, 2007.
  - Free E-book at the LiU Library
  - https://www.dawsonera.com/abstract/9780470858707



Aim

- Provide an introduction to the field of supramolecular chemistry with an emphasis on systems and applications for life sciences and life science technologies.
- Knowledge in state-of-the-art supramolecular systems for:
  - Biosensors
  - Drug delivery
  - Biomaterials
  - Bioorganic electronics

After the course you should

- be able to account for fundamental concepts, methods and theories of supramolecular chemistry.
- be able to understand and account for current problems and research in the field.
- have knowledge about the importance of supramolecular systems and their applications in life sciences and life science technologies.
- have practical experience from analytical methods for characterization of supramolecular systems.
- be able to interpret, analyze and evaluate experimental data of supramolecular interactions.

Organization – Seminars and classes

SE1: Lab seminar (mandatory)
SE2: Project seminar (mandatory)
SE3: Seminar on the origin of life

LE1 – LE4: Focused on the projects

Examination

1. Project work (in groups of 3 students): 2 ECT
   - Oral presentation + opposition (Fail/Pass)
   - Written report (Fail, 3, 4, 5)
2. Individual written assignment (Fail, 3, 4, 5): 2.5 ECT
3. Two lab exercises: 1.5 ECT
   - Active participation + individual written reports (Fail/Pass)

Final grade is calculated as the weighted average grade of (1) and (2) rounded up/down to the nearest integer.

Examination

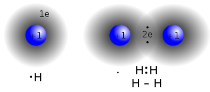
- **Project:** Groups of 2-3 students will work together to identify and describe in detail a novel supramolecular-based solution to a complex problem. Written report + oral presentation.
- **Written assignment:** Carried out individually. All students will receive a complex and extensive journal article to read and should write a detailed report describing, in your own words, the purpose, results, methods used and a comprehensive analysis of all supramolecular aspects of the work.

Supramolecular Chemistry!

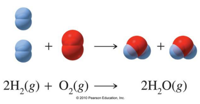
Supramolecular Chemistry?

The nature of the **covalent bond**:

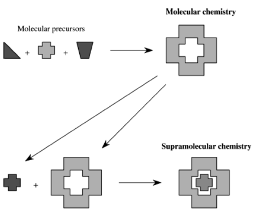
Chemical bond that involves sharing of electrons between atoms



Chemical reactions: Breaking and formation of covalent bonds



Supramolecular chemistry



The scope of covalent/molecular chemistry encompasses:

- Chemical nature of covalent molecules and their synthesis
- Redox properties
- HOMO-LUMO gap
- Polarity
- Vibration and rotation
- Magnetism
- Chirality

Supramolecular complexes are defined and characterized by:

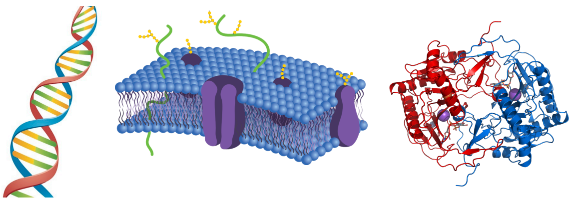
- Intermolecular interactions
- Degree of order
- Symmetry of packing
- Recognition

Supramolecular Chemistry!

Wikipedia:
" Supramolecular chemistry refers to the domain of chemistry beyond that of molecules and focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components. "

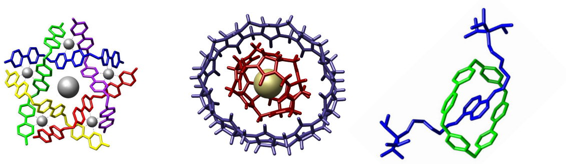
Jean-Marie Lehn (Nobel Laurate in Chemistry 1987):
- "Chemistry beyond the molecule"
- "The chemistry of molecular assemblies and of the intermolecular bond"

Supramolecular Chemistry!



In common: consist of a discrete number of molecules that are assembled as a result on non-covalent interactions

Supramolecular Chemistry!



In common: consist of a discrete number of molecules or components that are assembled as a result on non-covalent interactions

Organization - Lectures

1. Introduction, molecular recognition and host-guest chemistry
2. Self-assembly, self-organization, intermolecular forces
3. Thermodynamics of supramolecular interactions, analytical methods
4. Peptides and peptide-based structures & materials (Dr. Robert Selegård)
5. Carbohydrate chemistry (Prof. Peter Konradsson)
6. Protein & DNA/RNA-based supramolecular structures and materials
7. Natural and artificial lipid systems
8. Supramolecular systems for drug delivery and biosensing
9. Supramolecular catalysis and supramolecular polymers
10. Molecular motors (Prof. Bo Durbeej)

Covalent vs Supramolecular

Synthesis of (covalent) molecules:
- Robust molecules
- Well defined (atomistic) control over structure and composition in small molecules
- Difficult to synthesize large and complex molecules
- Often time consuming and resource intense

"Synthesis" of supramolecular complexes
- Dynamic structures that can form, dissociate, and change over time
- Stability and specificity of structures and components are defined by affinities
- Enables assembly of very complex and large structures

Whitesides, *Science* **1991**, 254, 1312.

Why interested in supramolecular chemistry

- Governs all aspects of life: DNA replication and transcription, protein synthesis, protein-protein interactions, cell-membrane assembly, cell-cell interactions etc.
  - Supramolecular chemistry give us insight into all those processes and also tools for "reverse engineering" – i.e. molecular biomimetic
- Supramolecular chemistry is a "technology" for making new synthetic structures, components, devices and materials!
  - Molecular "Lego"

Bridging sizes and materials

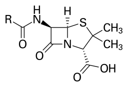
Size can span from nanometer scale structures to to macroscopic assemblies

Possible to combine with inorganic nanostructures, e.g. metal or semiconducting nanoparticles

Typically carbon-based but not always!

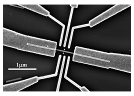
Supramolecular structures and materials

0.1 nm 1 nm 10 nm 100 nm 1 µm 10 µm 100 µm 1 mm



Organic synthesis ("Bottom up")

carbon-based



Lithographic ("top-down") fabrication

silicon-based

Efter Niemeyer, *Angew. Chem. Int. Ed.* **2001,** 40, 4128.

The origin of the field - milestones

1891 – Cyklodextrine was discovered (Villiersand Hebd)
1893 – Coordination chemistry was founded (Alfred Werner)
1894 – The "lock-and-key"-model for enzymes was published (Emil Fischer)
1906 – Introduction of the "receptor" concept (Paul Ehrlich)
1937 – The term "Übermoleküle" was coined to describe associated molecules (Wolf)
1948 – The term "clathrate" was introduced (Powell)
1958 – The "induced fit"-model for enzymes was published (Koschland)
1967 – The crown ethers were discovered (Pedersen)
1978 – The term "supramolecular chemistry" was introduced (Lehn)
1987 – The Nobel prize in chemistry to Cram, Lehn och Pedersen for groundbreaking work in supramolecular chemsitry
2016 – The Nobel prize in chemistry to Sauvage, Stoddart, och Feringa for their work on supramolecular molecular motors

Today

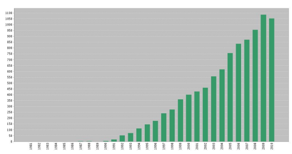
Wide and diverse research field

- Organic chemistry to material science

Concepts that are widely used in pharma-, medtech and biotech industry:

- Drug formulations
- Sensors and assays
- Materials

> 10 000 scientific papers published on the topic of supramolecular chemistry (ISI web of science)



1990 → 2011

Supramolecular structures/systems

Broadly divided in two categories depending on the properties of the components and the interactions involved

Host-Guest Chemistry

- Larger (often macrocyclic) molecule (i.e host) that bind at least one smaller (guest) compound
- Typically discrete complexes that can form larger structures through a self-organization process

Self-Assembly

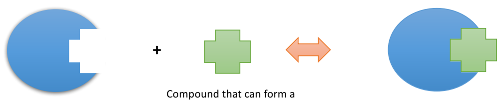
- Association of multiple components that are of the approximately same size
- Can result in formation of both discrete nanoscale structures as well as macroscopic complexes

Host-Guest Chemistry – the terminology

”Host”
(Receptor, Ligand)

”Guest”
(Substrate)

Supramolecule



Compound capable of recognizing and binding a guest in defined confinement by means of non-covalent interactions, e.g: crown ether or enzyme.

Compound that can form a complex with a host E.g. :

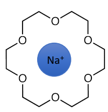
- Metal ion
- Co-factor
- Hormone

The complex formed can also be referred to as:

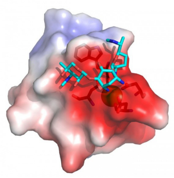
- ”Host-guest komplex”
- ”Inclusion komplex”
- ”Clathrate komplex”

… for example

Host: 18-crown-6
Guest: Na^+

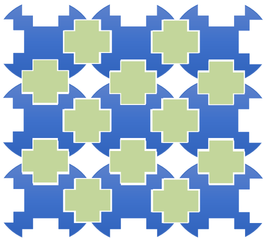


Host: Protein receptor
Guest: drug



(not drawn to scale)

Self-Assembly



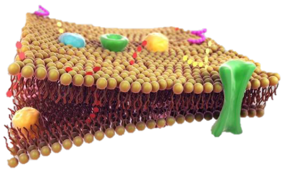
Defined as: *"The spontaneous and reversible association of molecules or ions to form larger, more complex supramolecular entities according to the information contained in the molecules themselves."* (Steed&Atwood, 2009)

Not necessarily an obvious host or guest!

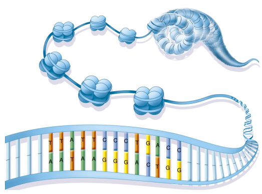
Self-Assembly

Most biomolecular complexes and many biological structures are formed as a result of self-assembly!

Cell membrane



Chromatin



Important parameters

The interactions are typically weak compared to covalent bonds and the formation of supramolecules depends on:

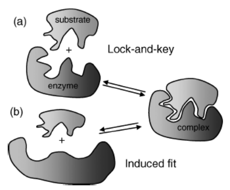
- Types of interactions (topic for next lecture)
- Solvent
- Size of the contact surface
- Number of interactions
- Cooperativity and additivity
- Preorganization effects
- Interactional complementarity
- Sterical and geometrical complementarity

Complementarity

- No steric clashes or constraints, i.e. good fit with respect to size and geometry of host and guest
- Interactions are available between host and guest and are well aligned in the complex
  - Hydrogen acceptor and donor pairs
  - Lewis acid and base pairs
  - Complementary charge distribution
  - ……

But, keep in mind that most molecules are not very rigid!

"Lock-and-Key" vs "Induced-fit"



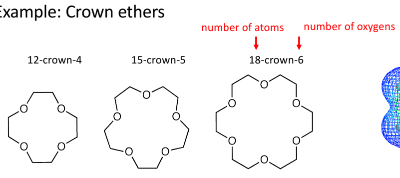
Lock-and-key: Rigid host/receptor! No binding unless excellent geometrical complementarity. (Proposed in 1894 by Emil Fischer)

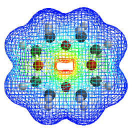
Induced-fit: Conformationally flexible host/receptor! Interactional complementarity drives geometric adaption to maximize interactions . (Proposed by Koschland in 1958.)

Affinity and Selectivity

High complementarity often result in high affinity!

Example: Crown ethers

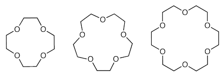




The lone electron pair of the oxygen atoms give the cavity a net negative charge

Charles Pedersen was awarded with the Noble prize in chemistry in 1987 for the discovery of the crown ethers

Crown ethers



	12-crown-4	15-crown-5	18-crown-6
Diameter (Å)	*1.2-1.5*	*1.5-2.2*	*2.6-3.2*
Li^+ (1.36 Å)	-0.57	1.21	-
Na^+ (1.94 Å)	1.67	3.32	4.28
K^+ (2.66 Å)	1.6	3.5	5.67
Cs^+ (3.34 Å)	1.63	2.74	4.5

Guest

(Log K_a in methanol)

Balance between steric complementarity and number of possible interactions!

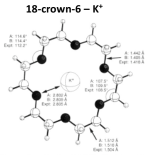
Note that solvatization energy increases as: $Cs^+ < K^+ < Na^+ < Li^+$

Crown ethers are not completely rigid

Crown ethers

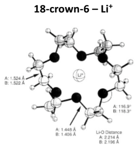
Structural flexibility enables the crown ethers to bind cat ions with different sizes but at cost of build up of strain.

18-crown-6 – K^+



Log K_a = 5.67

18-crown-6 – Li^+

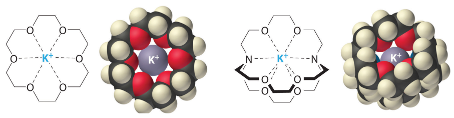


No association!

J. Am. Chem. Soc. **1994**, 116, 10657-10669.

Cryptands – the more rigid version

What happens when we make the host more rigid?

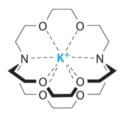


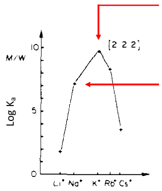
(a) Crown ether

(b) Cryptand

Cryptands

[2.2.2]cryptand





More than 10^5 times higher K_a than the corresponding crown ether (10^{10} vs $10^{1.6}$)!

Much more selective, i.e. large difference in affinity for different ions!

High complementarity result in high affinity!
Constrained flexibility results in high selectivity!

Selectivity is the basis for molecular recognition!

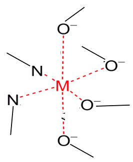
J.M. Lehn et al., *JACS*, **1975**, 97, 6700.

The chelate effect

Why do macrocyclic molecules (e.g. crown ethers) have such high affinities for cations?

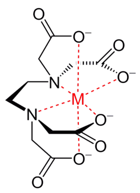
Single interaction pairs must be very strong to prevent rapid dissociation

In a chelator (or a macrocylic molecule) multiple interaction sites are provide by the the same molecules



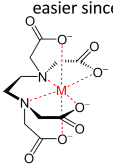
Connect the interacting moieties and the affinity increase by orders of magnitude

The chelate effect!



The chelate effect

- In order for a chelator to dissociate multiple interaction must be broken simultaneously
- When the first interaction has formed the next interactions form easier since the binding sites are already in close proximity



- The loss in entropy I smaller when only two species associate as compared to a multi-ligand complex
- Topological effects and preorganization can further improve the binding

Preorganization

A host is **preorganized** if no or very limited structural alterations is needed to effectively bind the guest. The host is optimally preorganized if:

- The geometry allows all interaction sites to be engaged without structural reorganization
- Binding do not result in a build up of strain in either host or guest, i.e. the free energy of the complex is the same as for the lowest energy conformation of the host and guest prior binding

Results in high selective since fewer guest can bind optimally to the host!

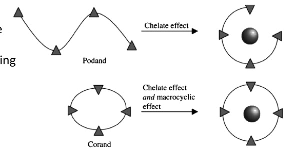


Fig 1. 11 Steed&Atwood

Preorganization & the macrocyclic effect

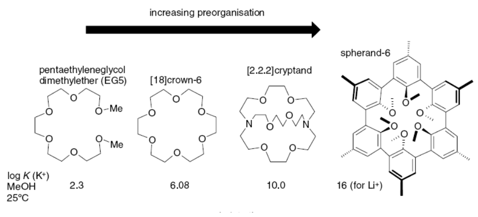


Fig 1. 12 Steed&Atwood

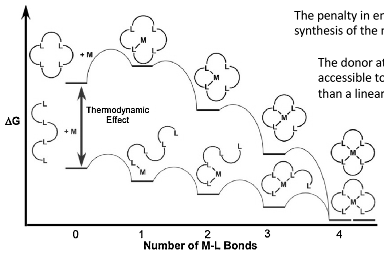
The macrocyclic effect

- A cylic host (e.g. a crown ether) is more preorganized than a linear host (e.g a normal linear ether) which result in both higher affinity and selectivity for binding of the guest:
  - More rigid (fewer degrees of freedom) leads to less conformational entropic loss upon binding of the guest
  - Can provide multiple optimally preorganized interaction sites without structural reorganization

Macrocyclic effect = $\Delta \log \beta = \log \beta_{macrocycle} - \log \beta_{linear}$

C. D. Swor, D. R. tyler, Coordination chem., 2011, 255, 2860.

The macrocyclic effect



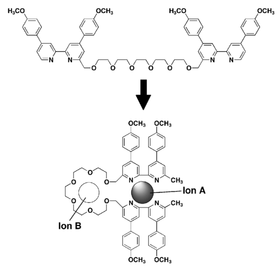
The penalty in entropy was "paid" during the synthesis of the molecule

The donor atoms in a macrocyclic host is less accessible to the solvent and thus less solvated than a linear host

C. D. Swor, D. R. tyler, Coordination chem., 2011, 255, 2860.

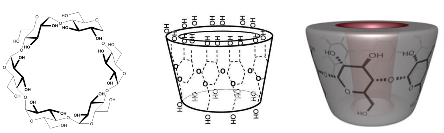
Cooperativity

- In many supramolecular complexes the total stabilizing energy is larger the sum of the interactions.
- Often a result of interlinked binding sites where one interaction result in structural alterations that make the next interactions more favorable.



Cyclodextrins – natural macrocycles

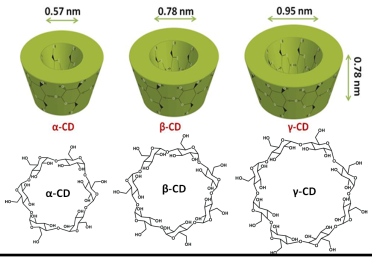
6-8 D-glucopyranosyl units linked through α-(1,4) glycosidic bonds



Hydrophilic outside (soluble in water), but hydrophobic inside.

Host for hydrophobic molecules

Cyclodextrin (CD)



Increasing the number of glucopyranosyl units result in larger cavity

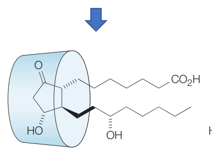
Affects the affinity and selectivity for the guest

Cyclodextrin (CD)

- CD s are often used as an additive in drug formulations:
  - Improve the solubility and biodistribution of hydrophobic drugs
  - Affects the pharmacokinetics of the drugs
  - Can protect the drug from oxidation
- CDs have been studied for more than 100 years but has not until recently been possible to produce with the purity required for drug formulations.

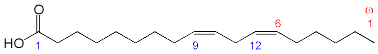
Cyclodextrins in drugs

- Nicorette (nikotin + β-CD)
- Voltaren (Diclofenac sodium + 2-Hydroxypropyl-γ-CD)
- Cetrizine (Cetrizine + β-CD
- Prostarmon E (Prostaglandin E_2 + β-CD)



Better solubility, stability and result in fewer side effects as compared to the non-complexed drug.

Cyclodextrins in drugs



Linoleic acid is used in many creams but oxidizes rapidly resulting in odor and poor performance.

Association with up to four a-CD prevents oxidation and make the complex water soluble.

C. W. Park, et al., J. Agric. Food Chem. **2002**, 50, 2977–2983.