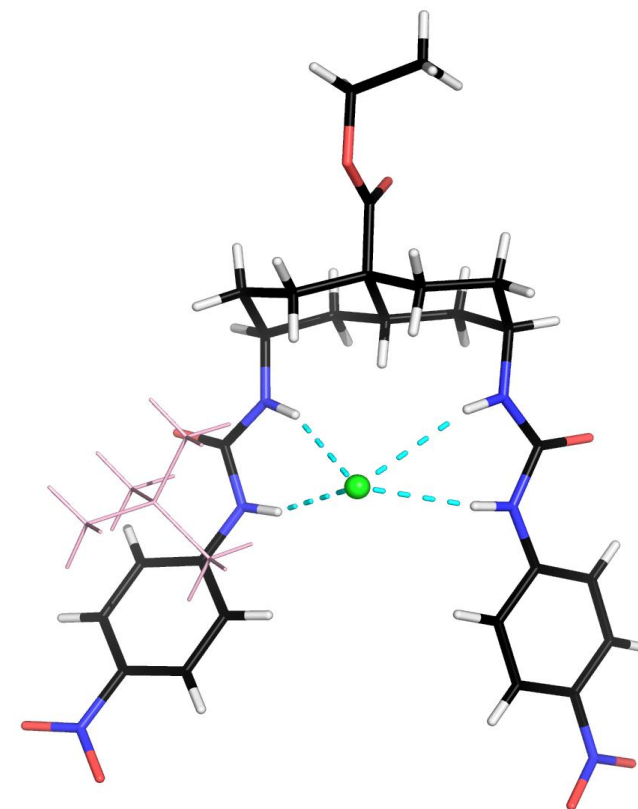


## Supramolecular Pharmacy

### 1. Introduction to supramolecular chemistry (non-covalent interactions)

**Ing. Ondřej Jurček, Ph.D. et Ph.D.**  
Assistant Professor  
Department of Natural Drugs



# Course Information

- 2 h/week on Tuesdays, 8:00-9:40 Učebna botaniky, 221
- 3 credits
- Attendance (- 2 classes), completion by a written exam complemented by a discussion
- In case of missing more than 2 classes there will also be a mid-term test on lecture week 6 (29.10., 8:00-8:30)

Literature: Selected chapters of Supramolecular Chemistry, Jonathan W. Steed, Jerry L. Atwood, ISBN: 978-1-119-58251-9, complemented by selected research articles with suprapharmaceutical relevance to selected topics.

# Syllabus

1. **Introduction** to supramolecular, material chemistry, and nanoscience. Drug delivery strategies. Natural products and renewable raw materials
2. **Macrocyclic compounds** in drug delivery
3. **Metallo-supramolecular cages**: ligand design, preparation, characterization, and application
4. Artificial **anion transporters and covalent cages** for pharmaceutical applications
5. Polymers and their applications

# Syllabus

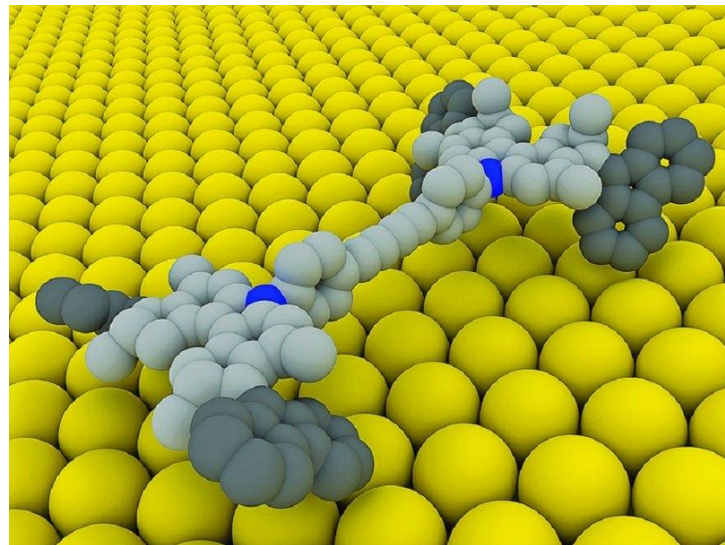
6. **Mid-term test (8:00-8:30)**, followed by **Gels and metallogels**: components, preparation, characterization, and applications
7. **Co-crystallization and polymorphism**, their description, synthesis, characterization, and applications
8. **Porous solid materials**, silicates, Metal-Organic Frameworks (MOFs), preparation, characterization, and applications
9. **MOFs in medicinal applications**: drug loading and delivery strategies
10. **Nanoparticles** in drug delivery (nanocrystals, micelles, liposomes, and other)

# Syllabus

11. Photomedicine

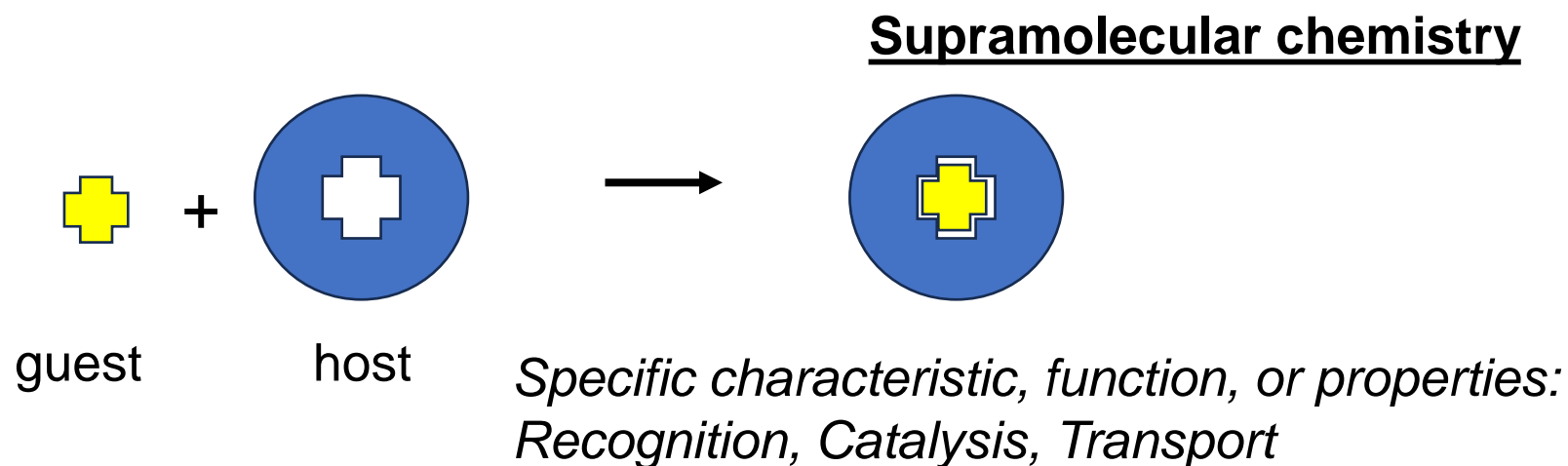
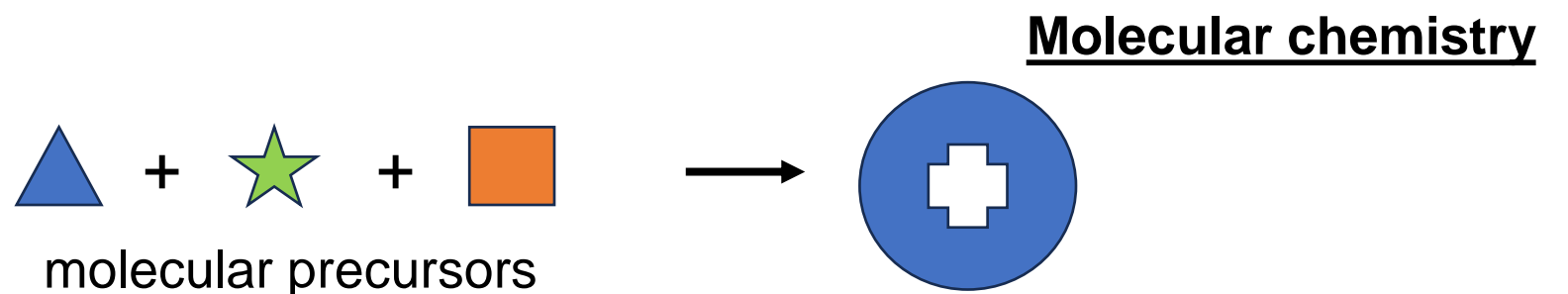
12. Molecular machines

Would you be interested in any other field of supramolecular chemistry?



# What is the Supramolecular Chemistry?

- it is chemistry beyond molecule, chemistry of molecular assemblies and the intermolecular bond (J.-M. Lehn – Nobel Prize winner in 1987)
- some also say that it is chemistry of non-covalent bond



## **Covalent molecule:**

Chemical nature, shape, redox properties, HOMO-LUMO gap, polarity, vibration and rotation, magnetism, chirality

## **Supramolecule (complex):**

Degree of order, interactions between subunits, symmetry of packing, intermolecular interactions

# Importance of Supramolecular Chemistry

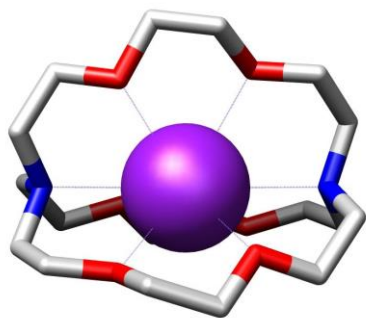
- supramolecular chemistry is everywhere among us, *e.g.*, ranging from human body (DNA double helix, various cellular transports, ion channels) to toilet fresheners...

The field of Supramolecular Chemistry has been twice recognized by the **Nobel Prize in Chemistry**:

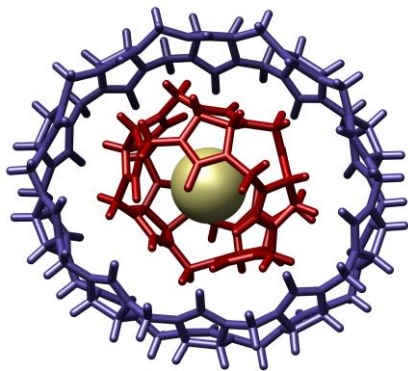
**1987**: Jean-Marie Lehn, Donald J. Cram, Charles J. Pedersen "for their development and use of molecules with structure-specific interactions of high selectivity,,

**2016**: Jean-Pierre Sauvage, Sir J. Fraser Stoddart, Bernard L. Feringa "for the design and synthesis of molecular machines"

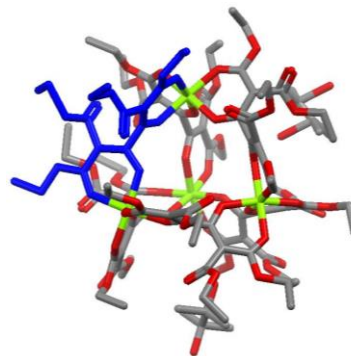
# 30 years of Supramolecular Chemistry



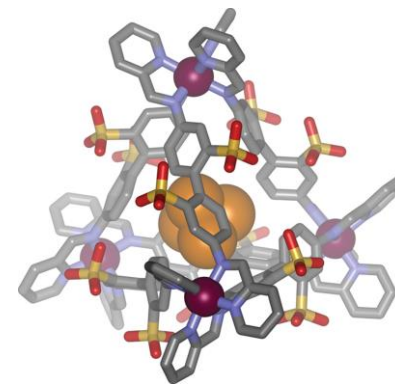
cryptands



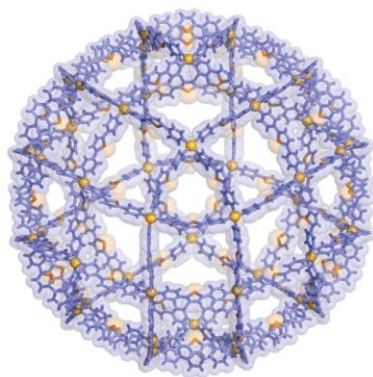
host-guest



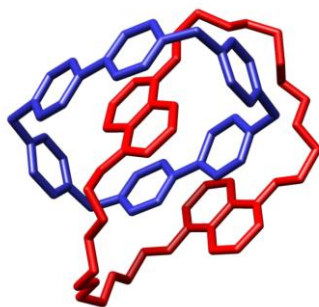
Mg<sub>4</sub>L<sub>6</sub>



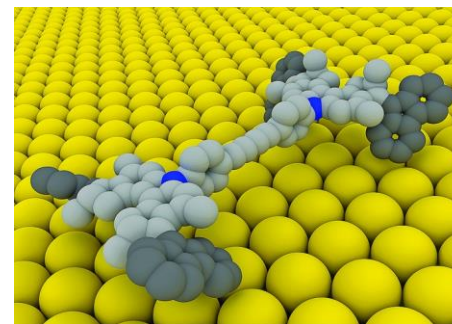
air-stable P<sub>4</sub>



sphere Pd<sub>48</sub>L<sub>96</sub>



blue box



molecular machines



# History

- 1891 – Villiers and Hebd: cyclodextrin inclusion compounds
- 1893 – Alfred Werner: coordination chemistry
- 1894 – Emil Fischer: lock and key concept
- 1939 – Linus Pauling: hydrogen bonds are included in the groundbreaking book *The Nature of the Chemical Bond*
- 1953 – Watson and Crick: structure of DNA
- 1967 – Charles Pedersen: crown ethers
- 1969 – Jean-Marie Lehn: synthesis of the first cryptands
- 1973 – Donald Cram: spherand hosts produced to test the importance of preorganisation
- 1978 – Jean-Marie Lehn: introduction of the term 'supramolecular chemistry', defined as the 'chemistry of molecular assemblies and of the intermolecular bond'
- 1983 – Jean-Pierre Sauvage introduces catenanes (mechanical bond)

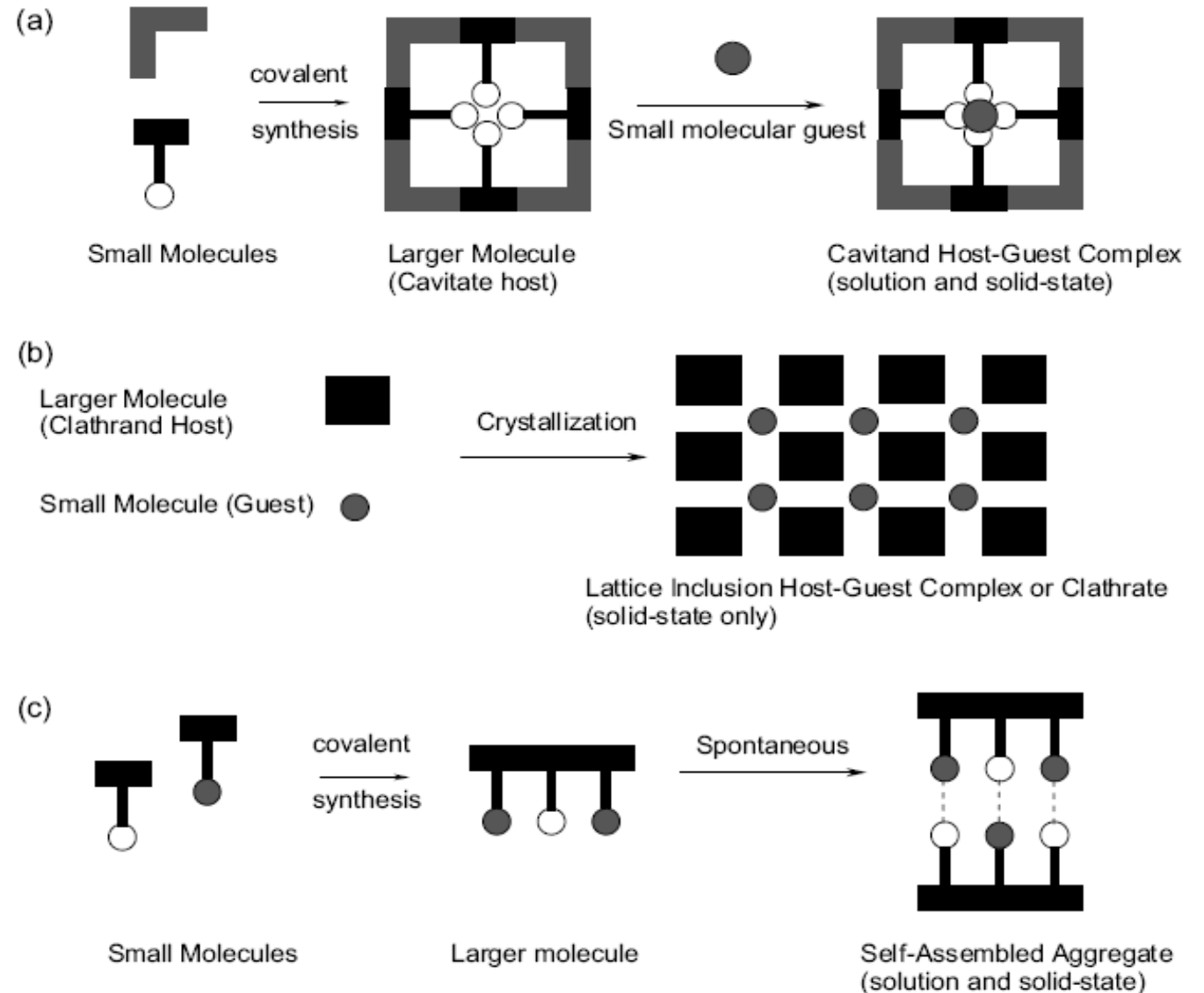
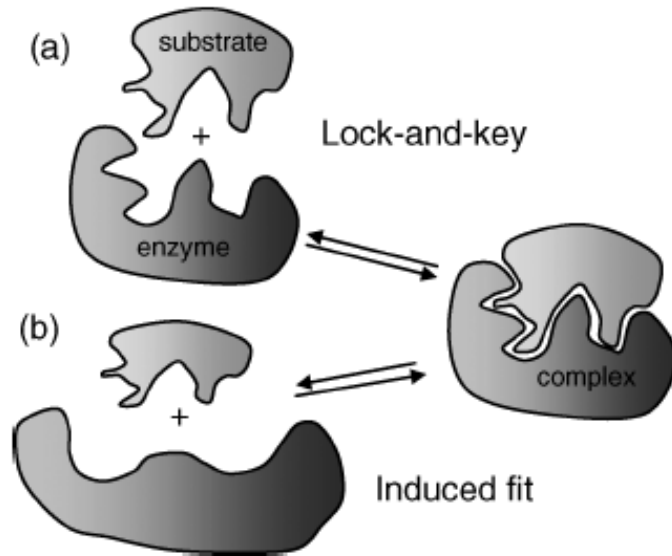
# History

- 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
- 2004 – J. Fraser Stoddart: the first discrete Borromean-linked molecule, a landmark in topological synthesis
- 2016 – Jean-Pierre Sauvage, Sir J. Fraser Stoddart, Bernard L. Feringa "for the design and synthesis of molecular machines"



# What do we study?

- Molecular recognition, attraction, activity
- Lock and key concept
- Binding constant

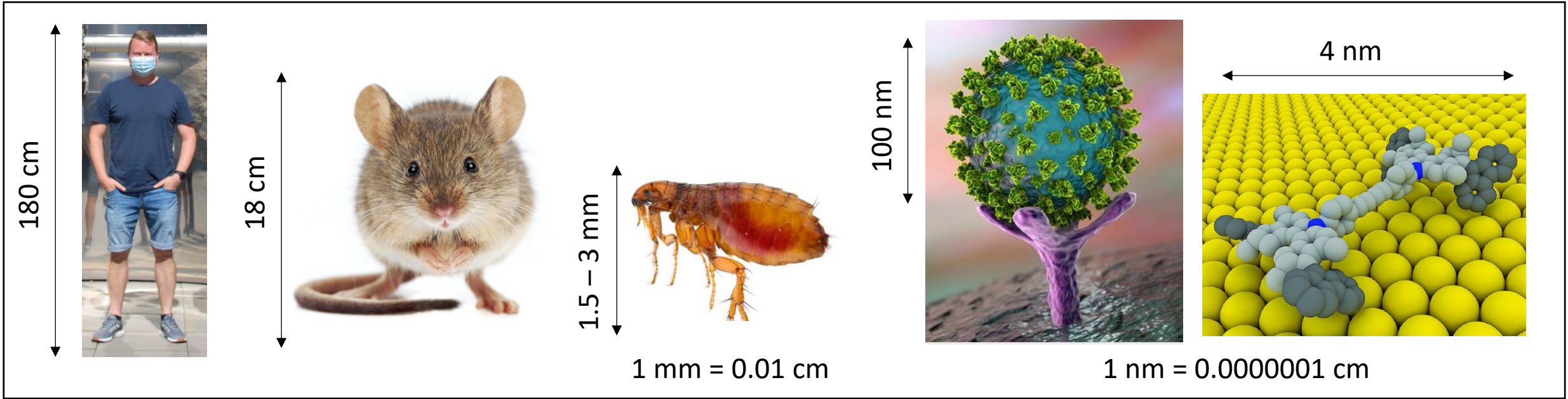


# Paul Ehrlich, father of chemotherapy

- The recognition by Paul Ehrlich in 1906 that molecules do not act if they do not bind, 'Corpora non agunt nisi fixata'; in this way Ehrlich introduced the concept of a biological receptor.
- Ehrlich, for example, was working on the treatment of a range of infectious diseases. As part of his work he noticed that the dye methylene blue has a surprising affinity for some living cells, staining them an intense blue. 'If only certain cells are coloured,' reasoned Ehrlich, 'then may there not be dyestuffs which colour only the carriers of illnesses and at the same time destroy them without attacking the body's own cells?' Ehrlich eventually went on to develop the arsenic-based anti-syphilis drug Salvarsan in 1910, one of the most effective drugs known for that disease (replaced in 1940s by penicillin). In the process he became the founder of modern chemotherapy.



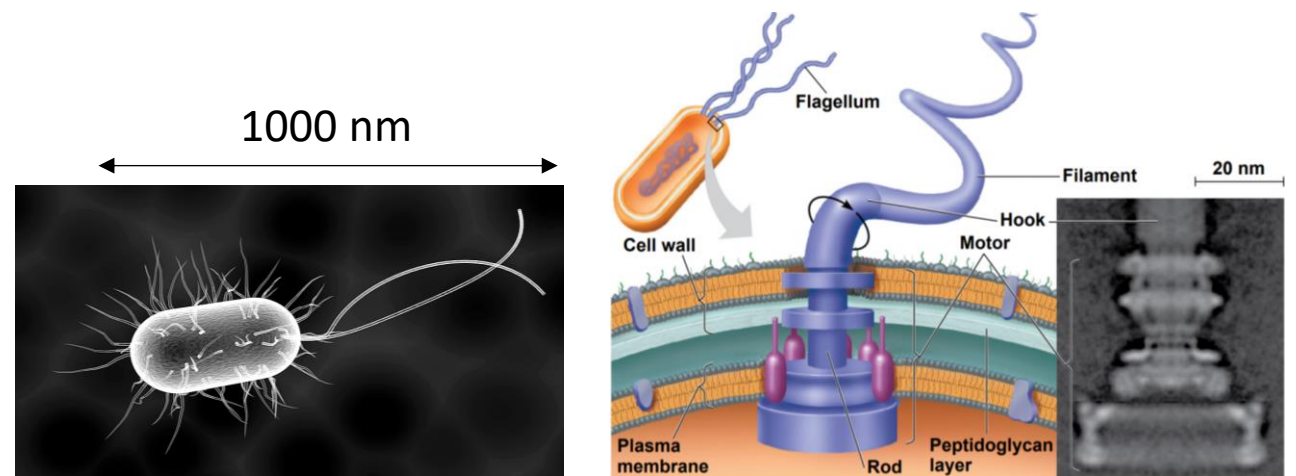
# What is the size here?



Nanomachines are 1000 x thinner than hair

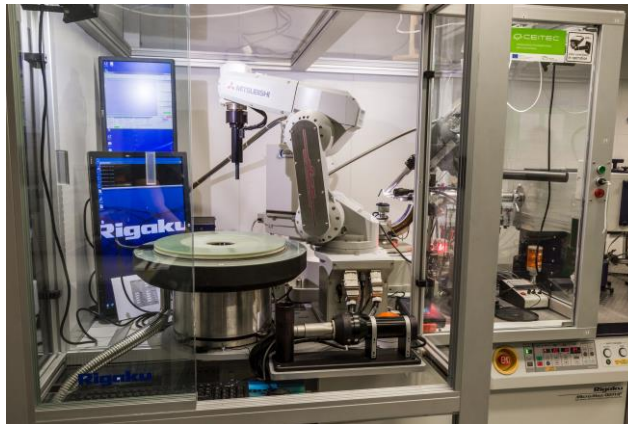
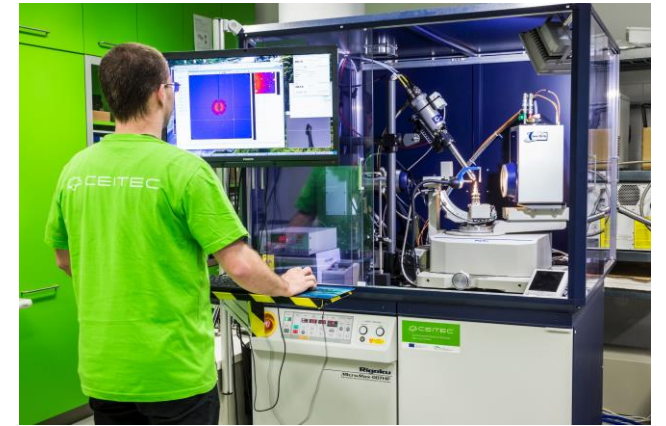
Inspiration in nature from bacteria

Richard Feynman – nanotechnology



# How do we study these?

- nuclear magnetic resonance (NMR) spectroscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction, mass spectrometry (MS), etc., will be introduced in each chapter



# What non-covalent forces are studied in supramolecular chemistry?

1. Ion-ion interactions = ionic bond,  $100\text{-}350\text{ kJ mol}^{-1}$  (close in strength to covalent)
2. Ion-dipole interactions,  $50\text{-}200\text{ kJ mol}^{-1}$
3. Dipole-dipole interactions,  $5\text{-}50\text{ kJ mol}^{-1}$
4. Hydrogen bonding,  $4\text{-}60\text{ kJ mol}^{-1}$
5. Halogen bonding
6. Interactions of  $\pi$ -systems (cation- $\pi$ , anion- $\pi$ ,  $\pi$ - $\pi$ )
7. Van der Waals forces and close packing

Hydrophobic effects

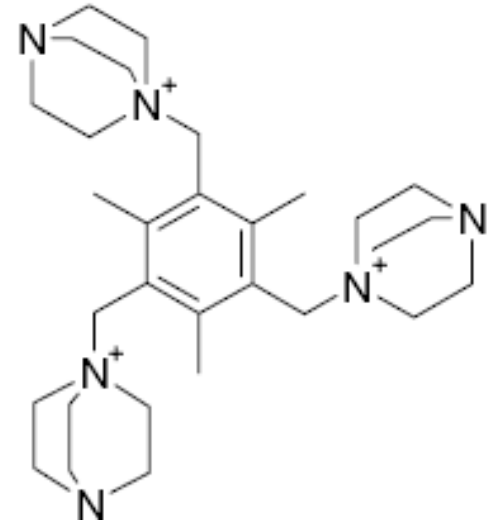
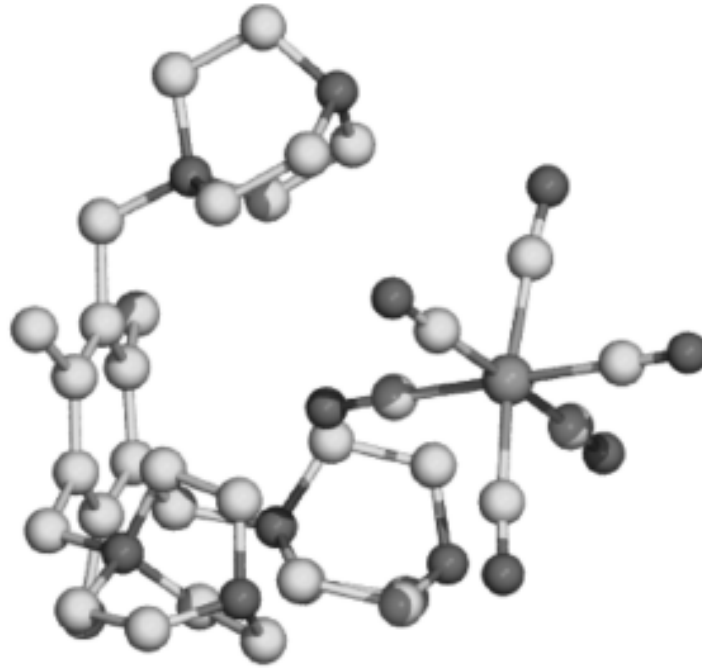
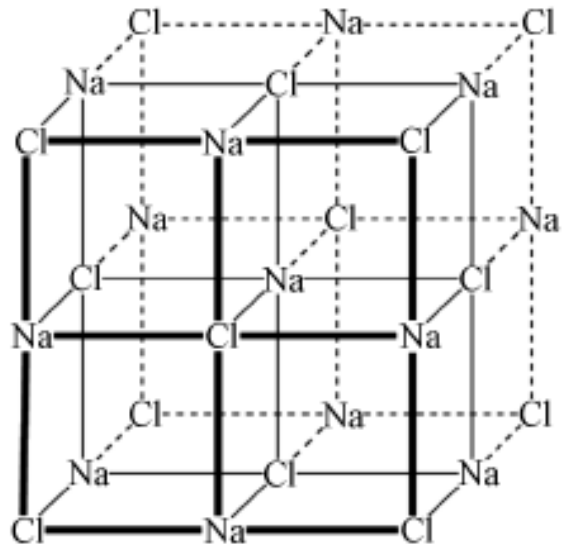
Solvation

Cooperativity (chelating effect)



# Ion-ion interactions

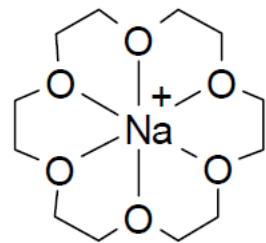
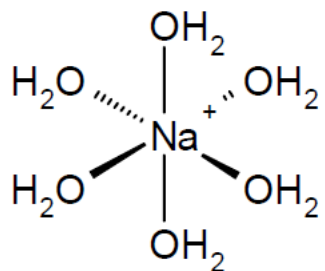
- 100-350 kJ mol<sup>-1</sup>



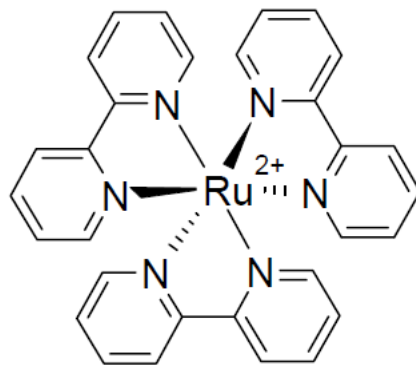


# Ion-dipole interactions

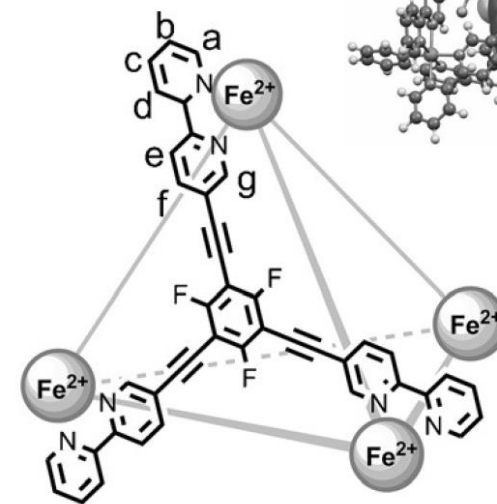
- 50-200 kJ mol<sup>-1</sup>, observable in liquid and solid state
- Na<sup>+</sup> has similar environment + chelate effect + preorganization



Na<sup>+</sup> crown ether complex



bpy = 2,2'-bipyridyl

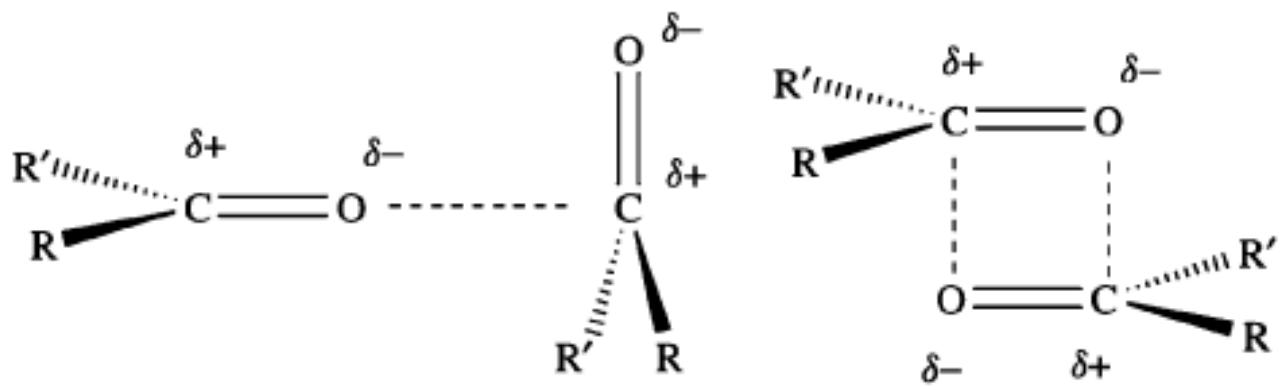


Angew. Chem. Int. Ed. 2015, 54, 14890–14893

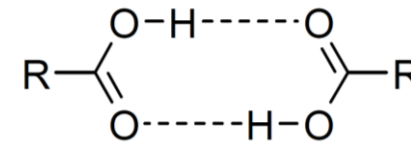
- Ion-dipole also includes coordinative bonds, electrostatic, some have covalent component = strong. They have also well-defined geometries which is very useful in design and crystal engineering of supramolecular complexes. They are also kinetically labile allowing reorganization.

# Dipole-dipole interactions

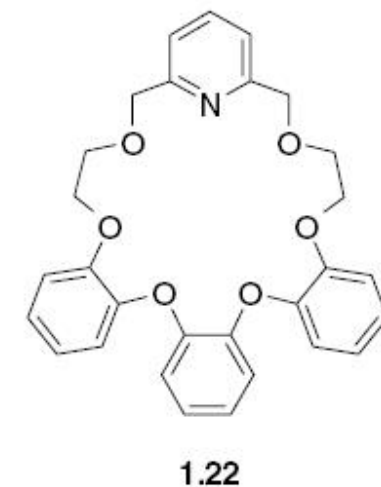
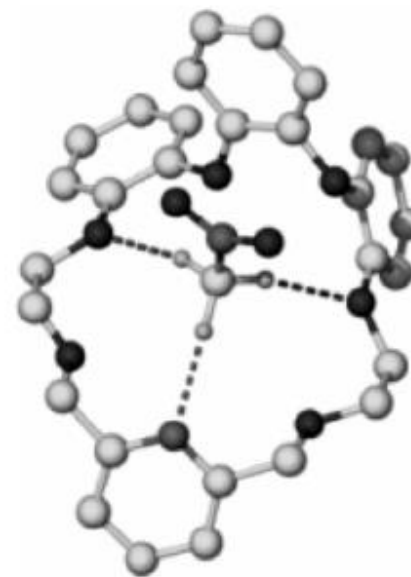
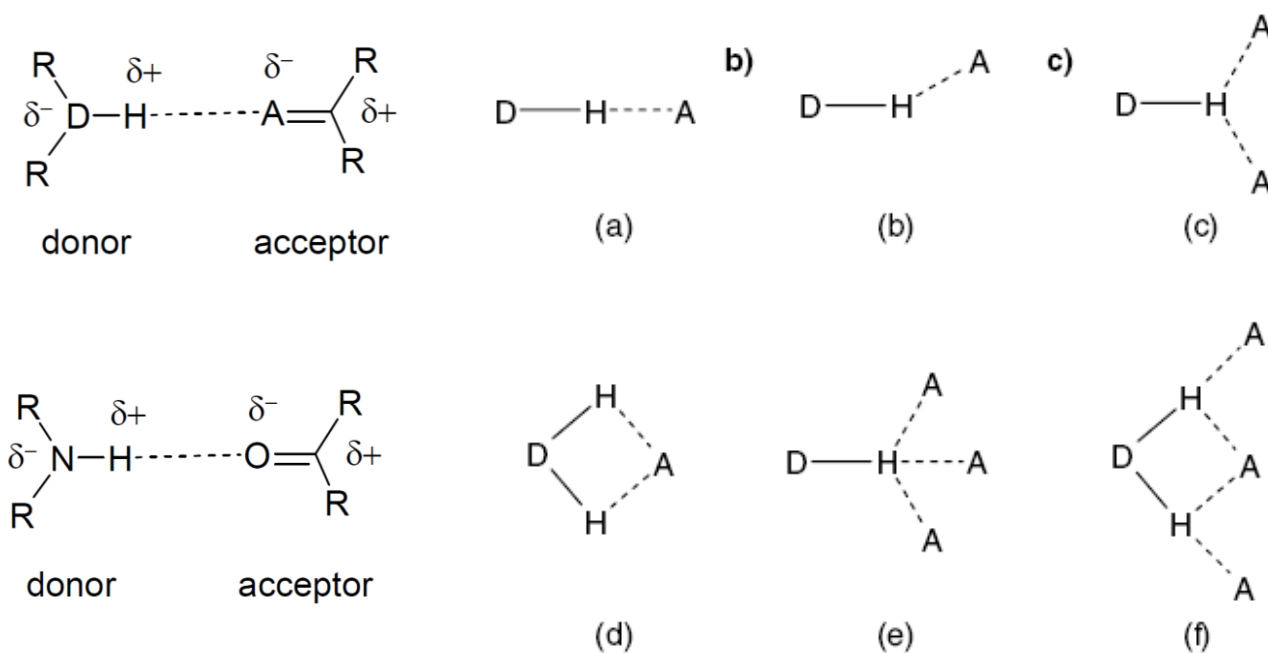
- 5-50 kJ mol<sup>-1</sup>, relatively strong in solid state, weak in liquid state (acetone b.p.)
- Often observed for organic compounds with carbonyls



# Hydrogen bonding



- 4-60 kJ mol<sup>-1</sup>, very important in solid and liquid state
- D-H---A (donor-H---acceptor) „masterkey interaction in supramolecular chemistry“
- Hydrogen atom is attached to electronegative atom (N, O, S, even C) and attracted to a neighbouring dipole of adjacent molecule or functional group
- Responsible for shape of proteins, enzyme recognition, DNA
- Strength is relative to distance between atoms measured in X-ray

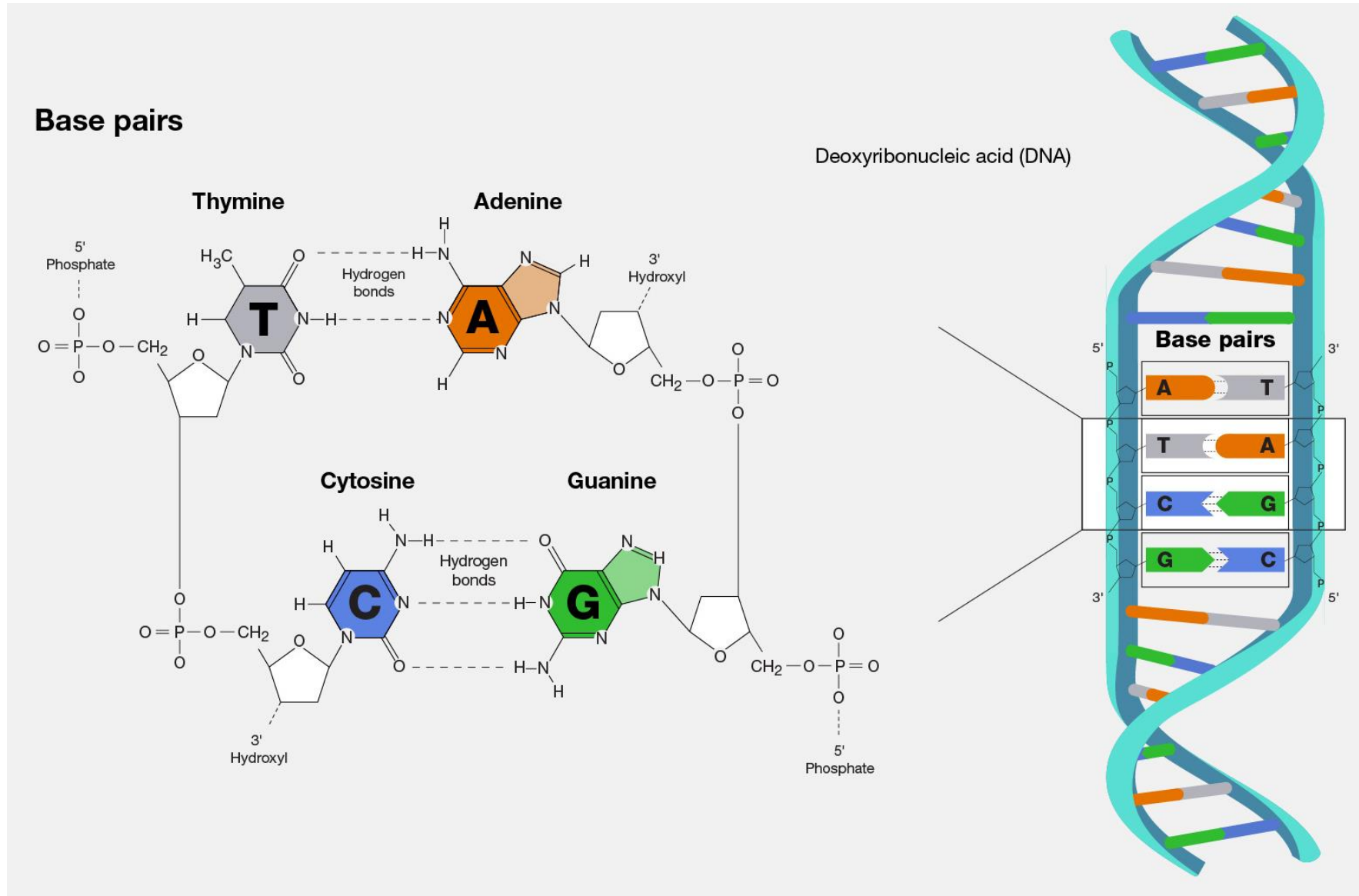


X-ray crystal structure showing C—H...N (2.21Å) and C—H...O (2.41Å, average)

# Hydrogen bond categories

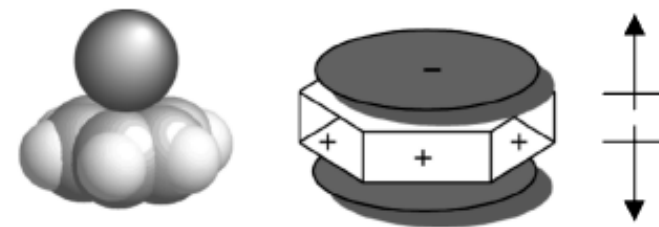
	Strong	Moderate	Weak
A—H $\cdots$ B interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol <sup>-1</sup> )	60–120	16–60	<12
Bond lengths (Å)			
H $\cdots$ B	1.2–1.5	1.5–2.2	2.2–3.2
A $\cdots$ B	2.2–2.5	2.5–3.2	3.2–4.0
Bond angles (°)	175–180	130–180	90–150
Relative IR vibration shift (stretching symmetrical mode, cm <sup>-1</sup> )	25%	10–25%	<10%
<sup>1</sup> H NMR chemical shift downfield (ppm)	14–22	<14	?
Examples	Gas phase dimers with strong acids/bases	Acids	Minor components of bifurcated bonds
	Proton sponge	Alcohols	C—H hydrogen bonds
	HF complexes	Biological molecules	O—H $\cdots$ $\pi$ hydrogen bonds

# Hydrogen bonding in DNA



# Interactions of $\pi$ -systems

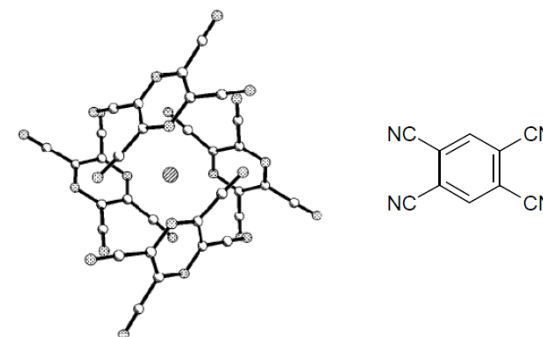
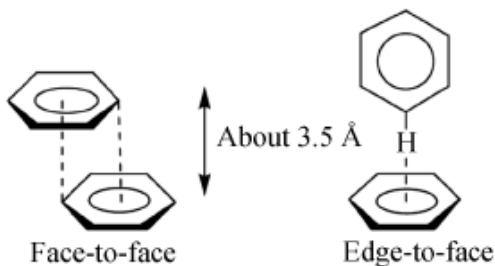
- Interactions of double, triple bonds, and aromatic rings: cation- $\pi$ , anion- $\pi$ ,  $\pi$ - $\pi$ 
  - **cation- $\pi$**  – usually with alkaline/alkaline earth metals



- **anion- $\pi$**  – rare, the interaction between anion and  $\pi$ -electron system seems repulsive, but there is a charge difference between an overall neutral aromatic ring and anion gives possibility for a weak electrostatic attraction

- **$\pi$ - $\pi$**  – direct overlap is repulsive, face-to-face or edge-to face mode

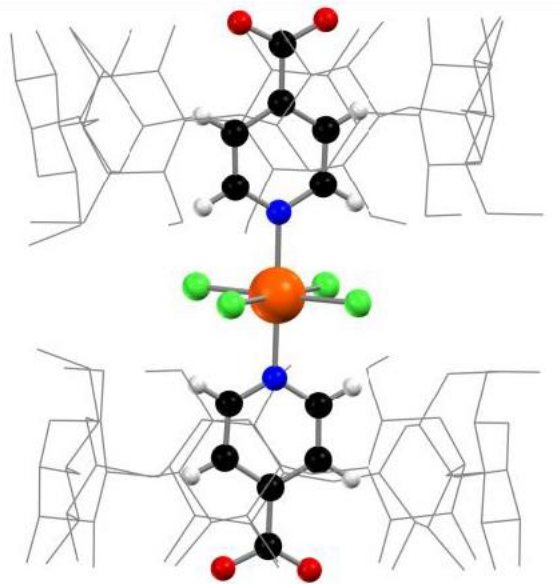
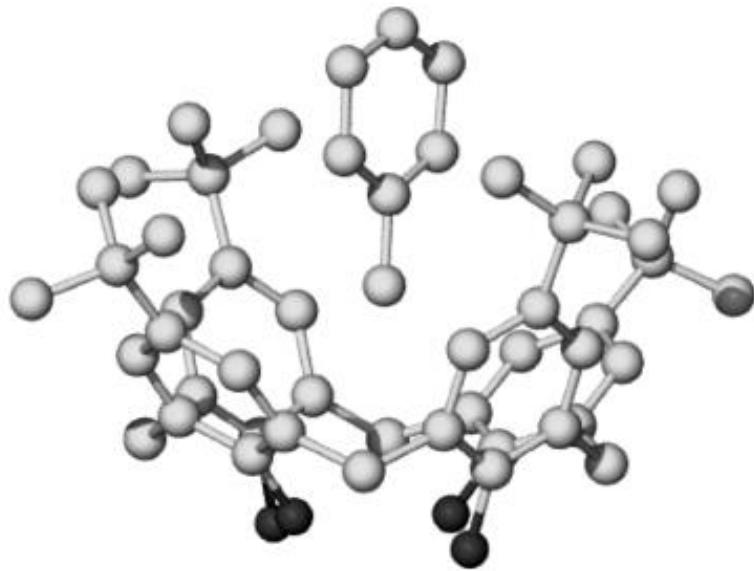
stabilizes the double  
helix of DNA



J.K. Kochi et al. *Angew. Chem. Int. Ed.* 2004  
(43) 4650.

# Van der Waals forces

- Polarization of an electron cloud by the proximity of and adjacent nucleus resulting in weak nondirectional electrostatic attraction
- Typically inclusion complexes
- Interaction energy is proportional to the surface area of contact
- Usually refers to C $\cdots$ C, C $\cdots$ H, or H $\cdots$ H interactions

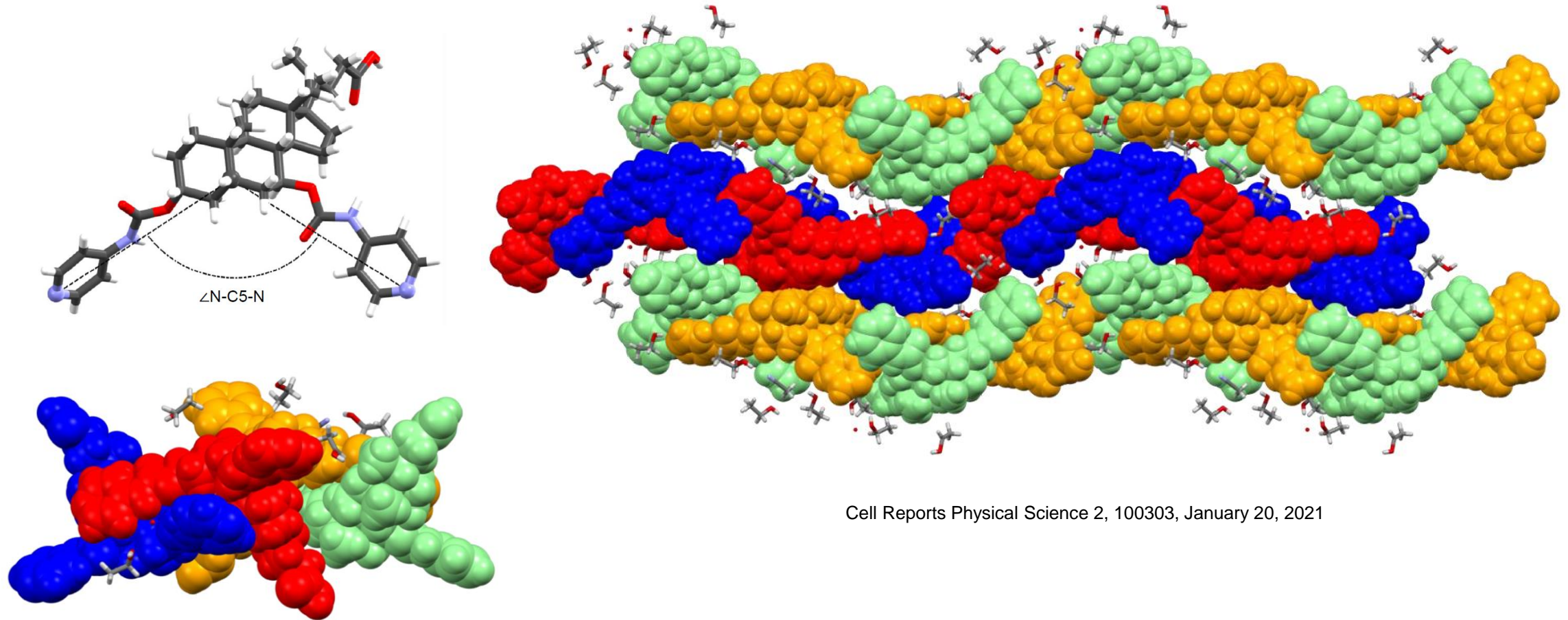


Cell Reports Physical Science 4, 101461, July 19, 2023



# Close packing

- Nature abhors a vacuum.
- Close packing in crystal structure caused by maximizing the favorable van der Waals interactions

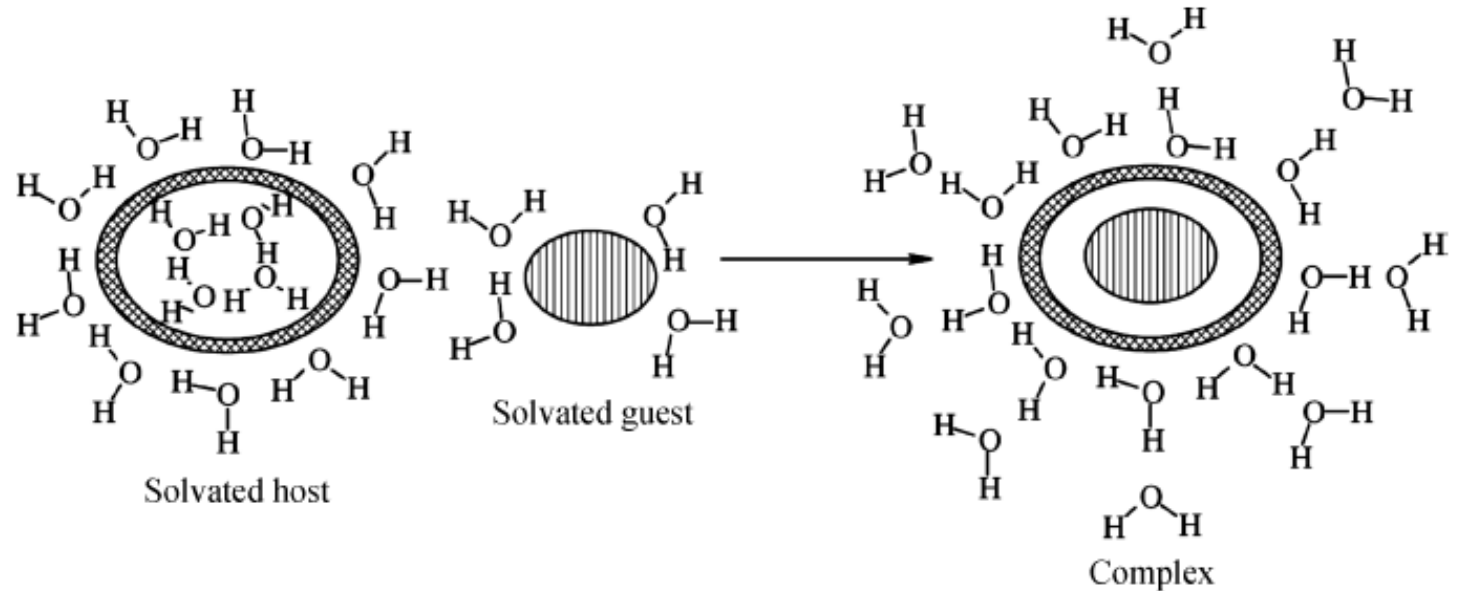
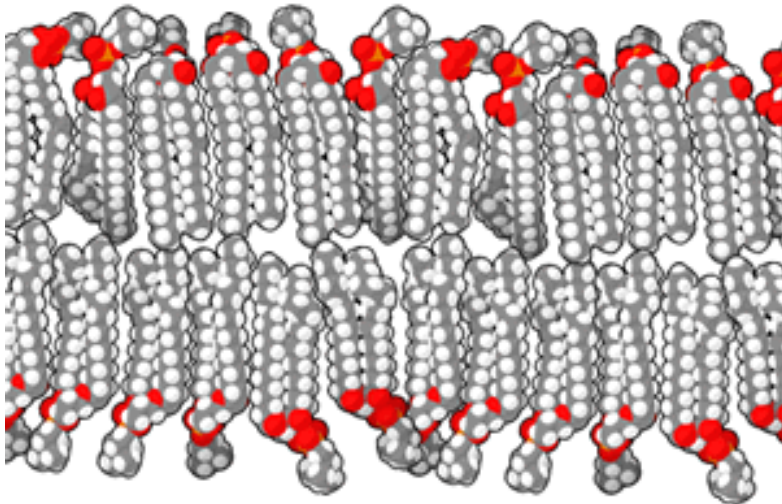


Cell Reports Physical Science 2, 100303, January 20, 2021



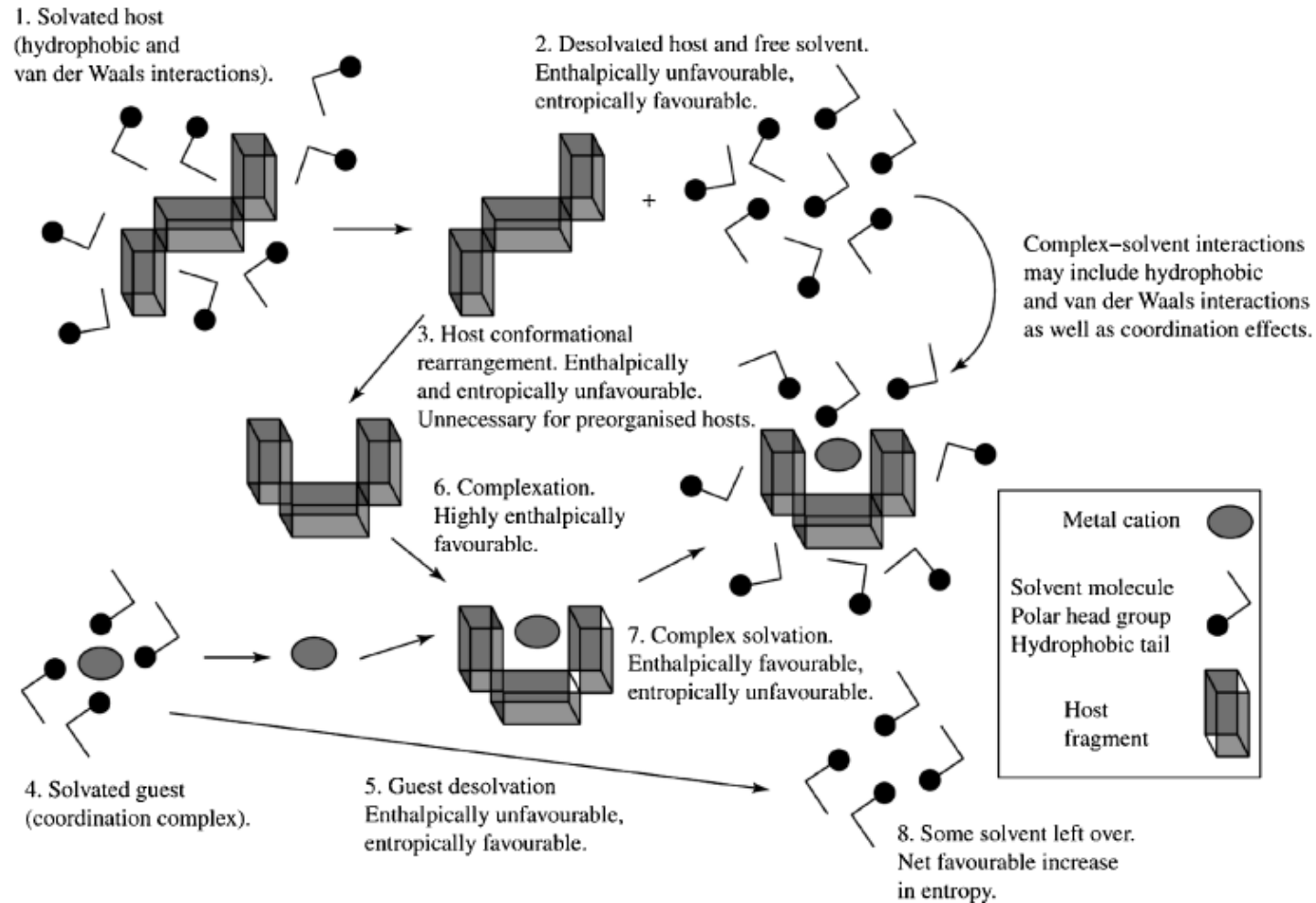
# Hydrophobic effects

- Exclusion from polar solvents, especially water (water has strong intermolecular attraction via hydrogen bonding so it is difficult for nonpolar compounds to stay in)
- Important for protein and polynucleotide structures, phospholipid bilayer (cell wall), organic inclusion complexes in water (cyclodextrin)
- Energy gain: high energy water inside cavity released (enthalpy), two organic molecules in solution creates two „holes“ in the continuous structure of water (entropy)



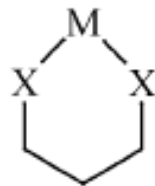
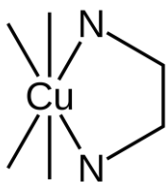
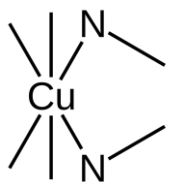
# Solvation

- Very important in liquid but also in solid state
- Solvent competes for noncovalent interactions and is in large excess
- Polar versus nonpolar solvents and binding constants of host-guest complexes



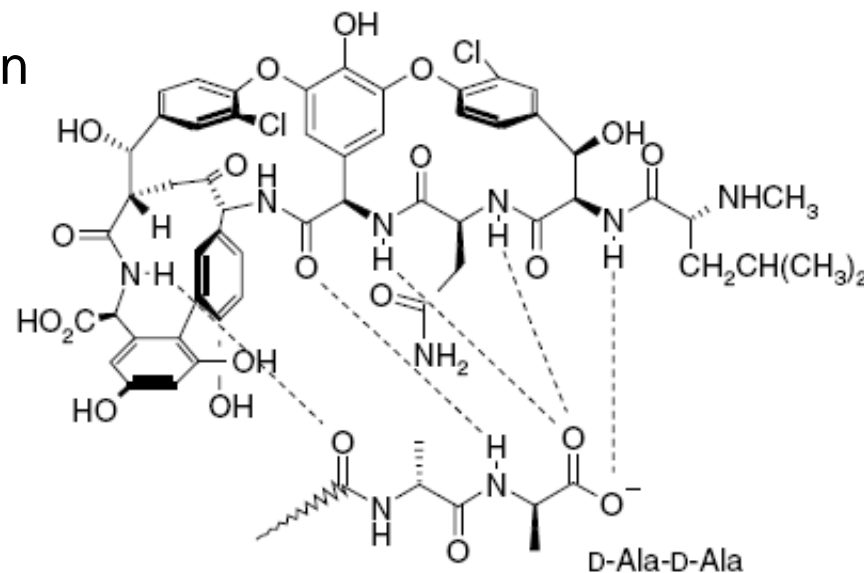
# Cooperativity, chelating effect

- **Cooperativity** is when two or more binding sites of host cooperate on guest binding; positive and negative cooperativity
- **Chelate effect**: metal complexes of multidentate ligands are significantly more stable than closely related complexes with monodentate ligands
- The stabilization depends on size of chelate ring and the size of metal cation



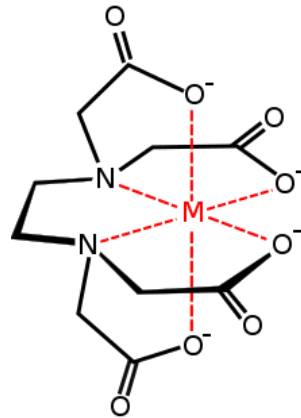
Strained ring    Optimum geometry    Increasing flexibility—less entropically favourable  
for larger cations

vancomycin

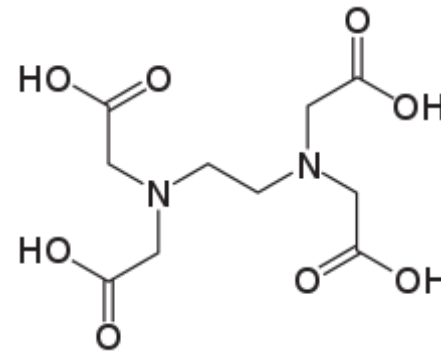


# Cooperativity, chelating effect

- Polydentate ligands: proteins, polysaccharides, polynucleic acids, metalloenzyme
- In 1960s developed method of enhancing mineral absorption by chelating with amino acids
- EDTA was developed, but this is too stable, coordinating also other metals
- Antidote for poisoning by mercury, arsenic, (iron) and lead (approved by FDA)
- Calcium edetate against disodium edetate (treatment of hypercalcemia – cornea)

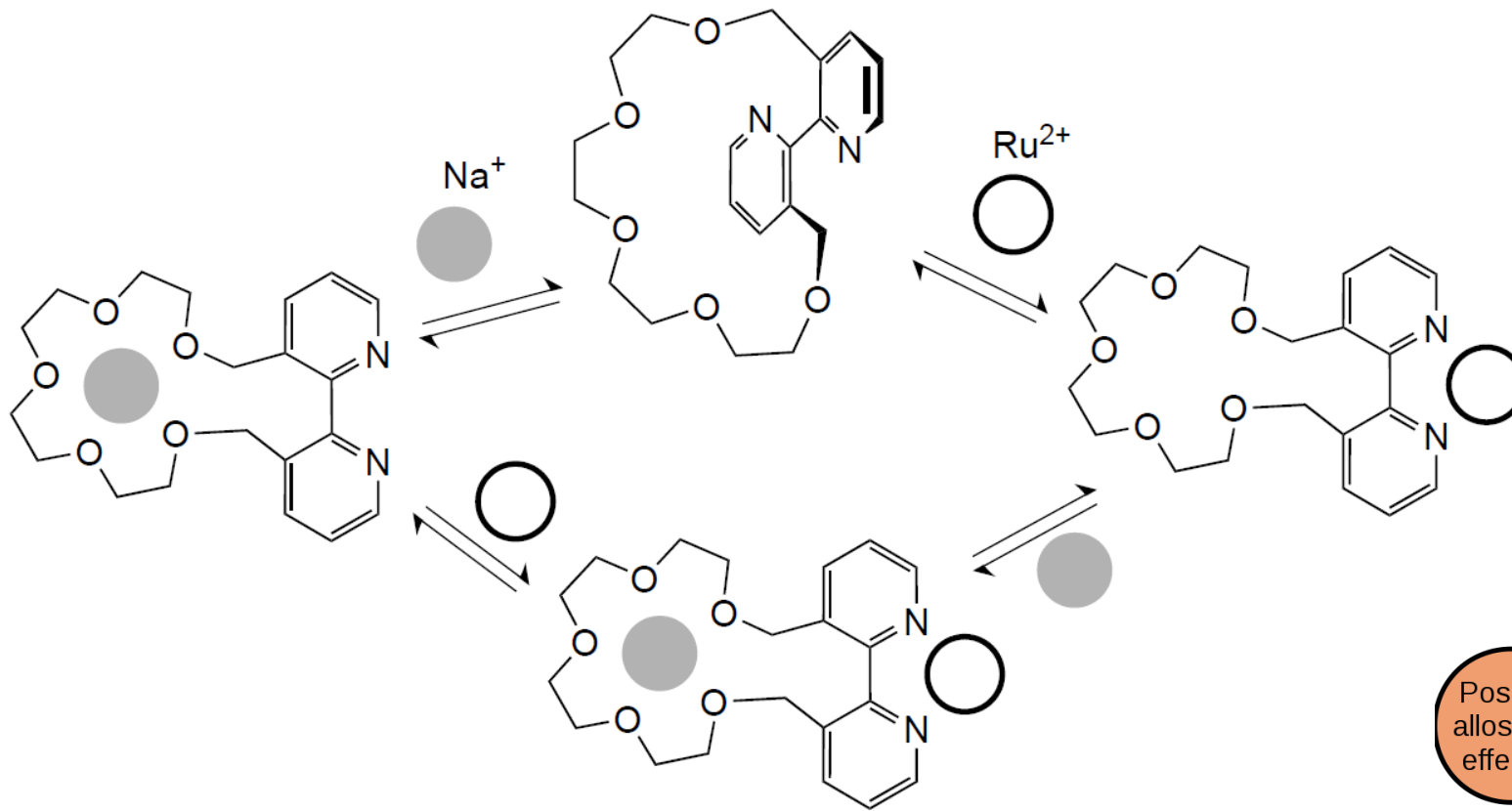


EDTA

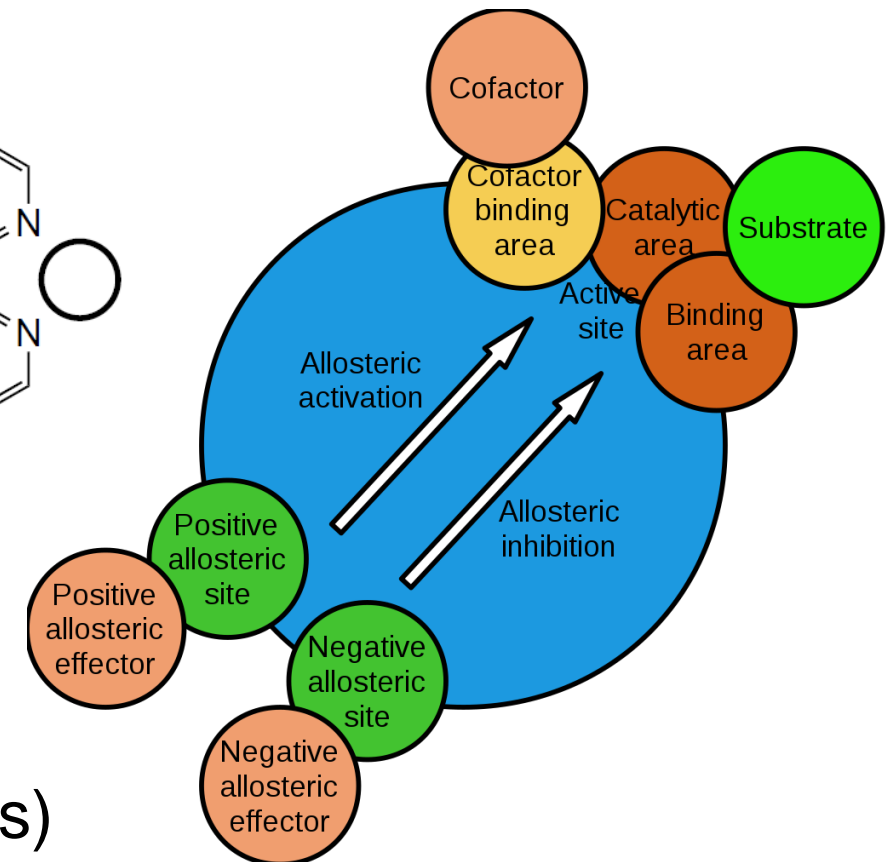


# Allosteric effect in supramolecular chemistry

- **Allosteric effect:** Cooperativity in cases where the binding of a first guest influences (particularly enhances) the affinity of a host for a second guest at a remote site

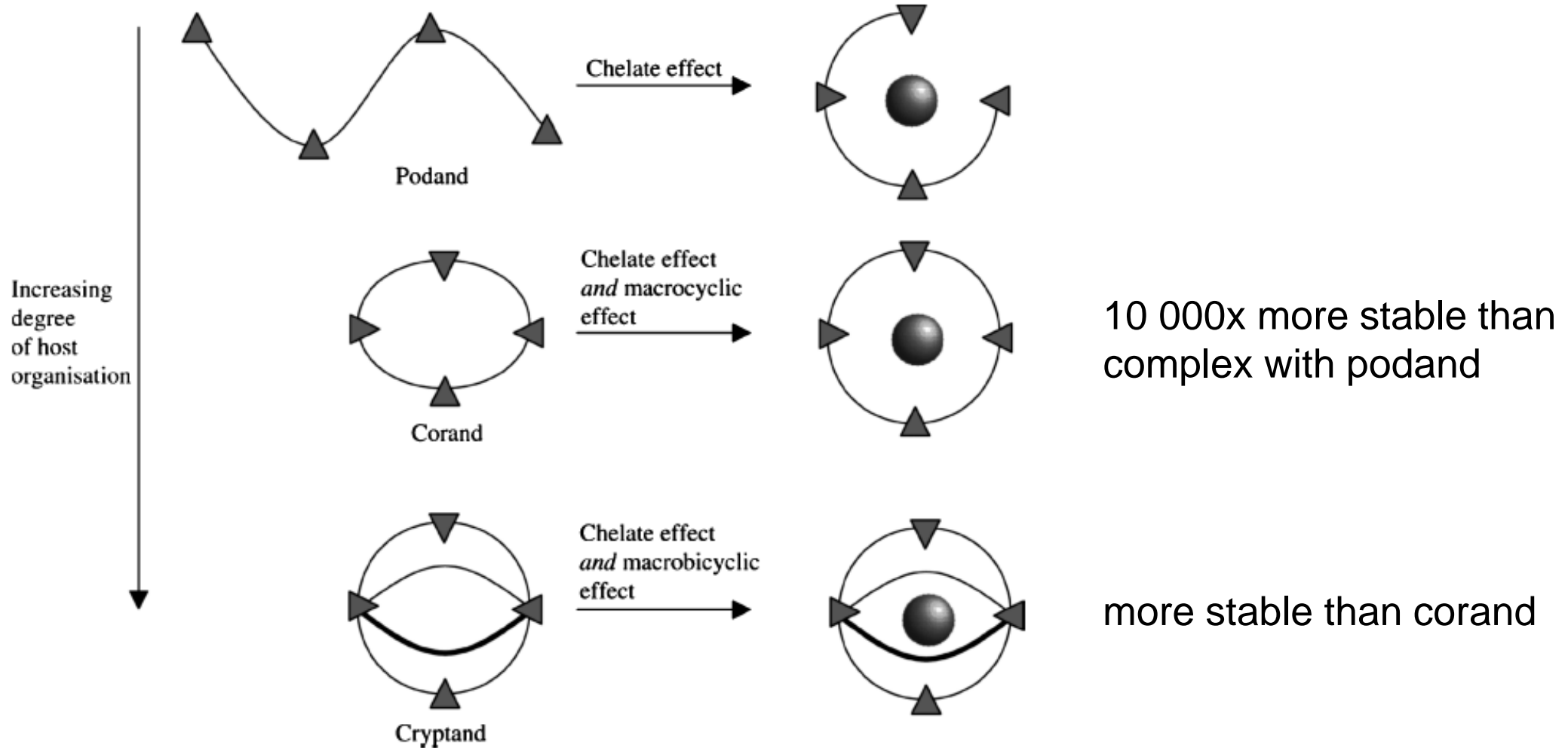


Allosteric regulation (enzymes)



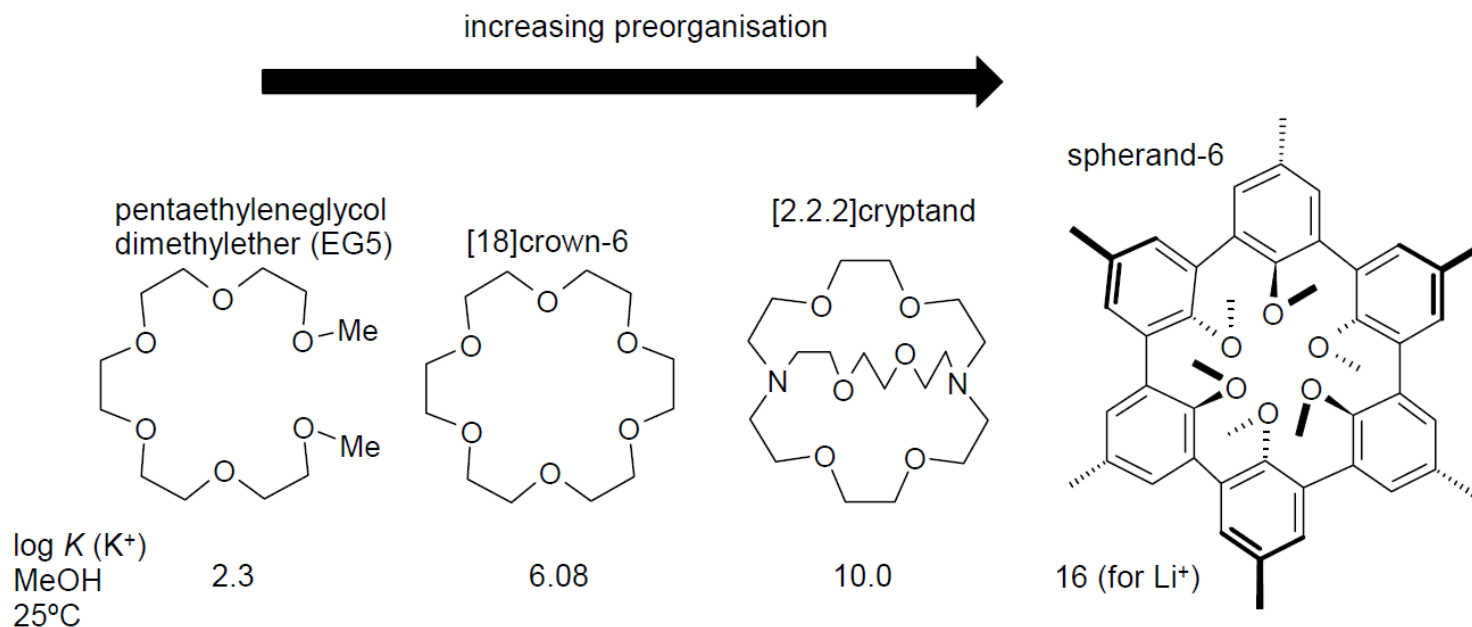
# Preorganization

- Binding sites are organized in space prior to guest binding



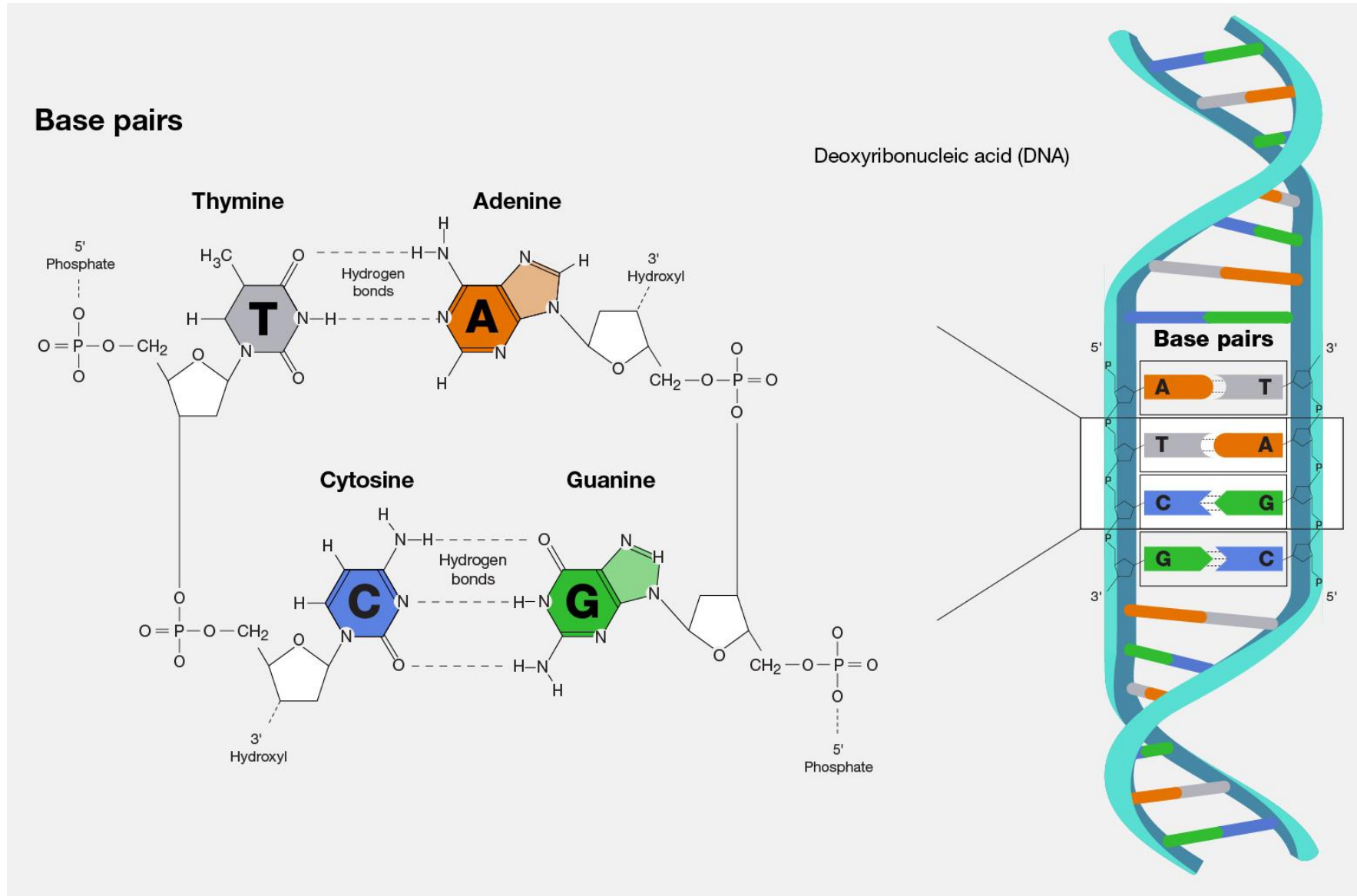
# Complementarity

- A host must have binding sites that are of the correct electronic character to complement those of the guest (hydrogen bond donors must match acceptors, Lewis acids must match Lewis bases, etc.) and they must be in correct conformation (spatial organization)
- Donald Cram said: To complex, host must have binding sites which cooperatively contact and attract binding sites of guests without generating strong nonbonded repulsions





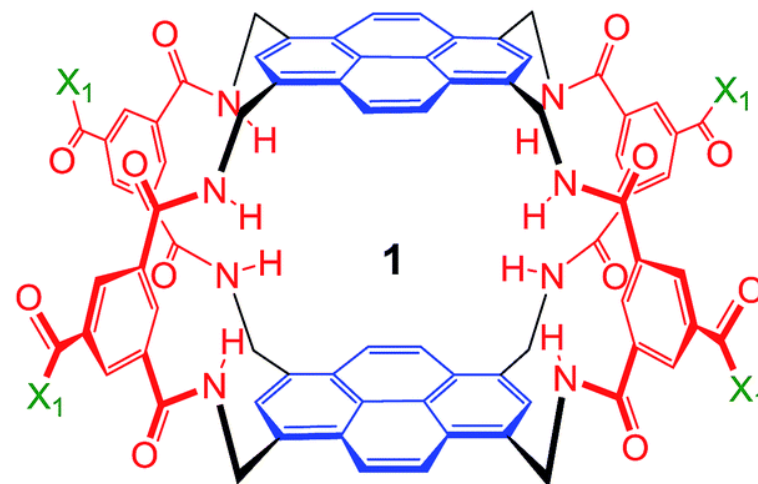
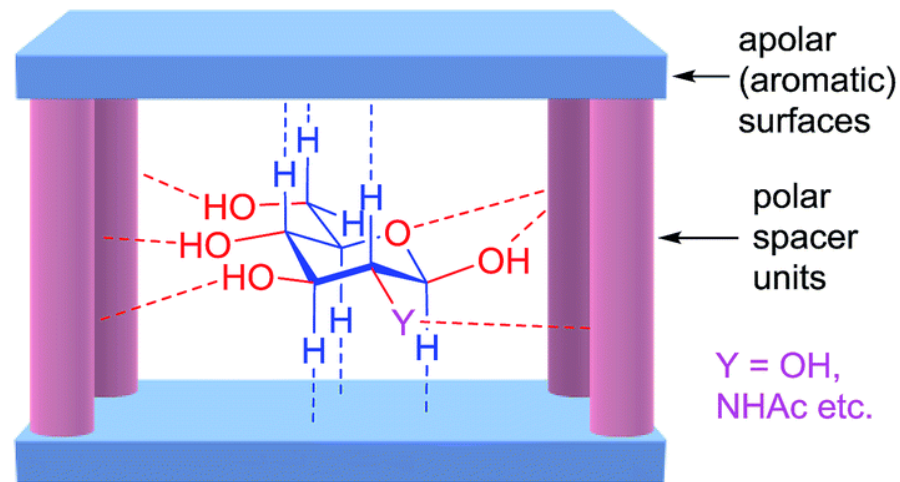
# Complementarity





# Host design

- Considering the chelate, macrocyclic effect, complementarity, and preorganization
- Considering the target, e.g., metal cation – size, charge density, hardness
- Spacing the binding side, the more interactions the better, complementarity
- Character of the host - solubility



X<sub>1</sub> = water-solubilising group, Chem. Sci., 2017, 8, 4056-4061

# Summary

- What does supramolecular chemistry study?
- What forces are important in supramolecular chemistry?
- What are the basic principles of design in supramolecular chemistry?

**In the next class...**

**Host-guest chemistry (cyclodextrins)**

**Thank you for your attention!**