

Supramolecular Interactions

Ion-Ion Interactions

Ion-Dipole Interactions

Dipole-Dipole Interactions

Hydrogen Bonding

Halogen Bond

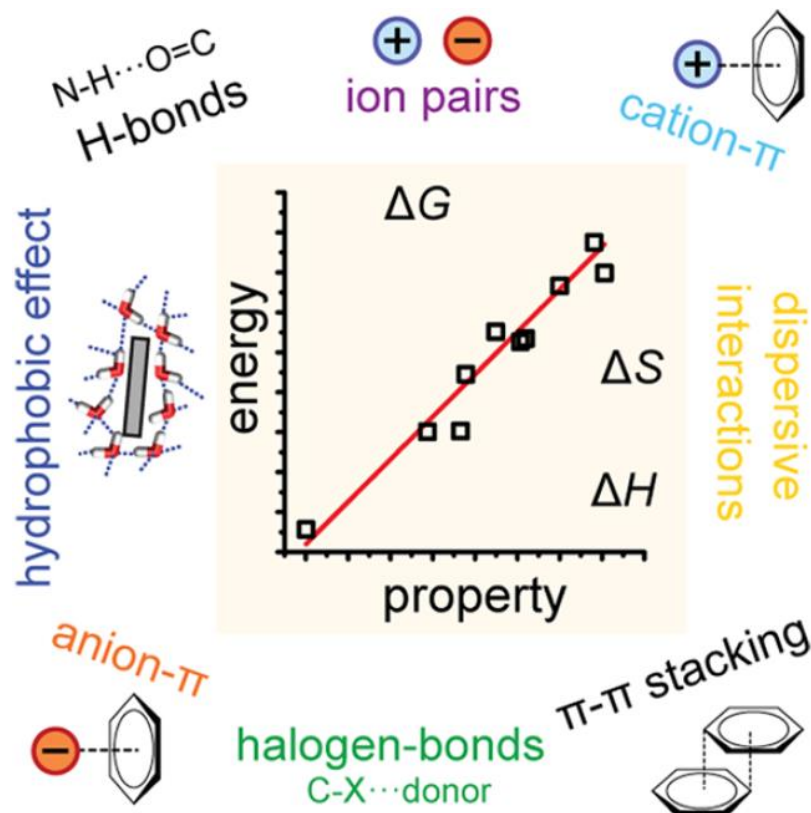
Cation- π Interactions

π - π Interactions

Anion- π Interactions

Van der Waals

Hydrophobic



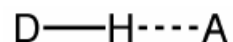
'Experimental Binding Energies in Supramolecular Complexes'

[F. Biedermann, H.-J. Schneider Chem. Rev. 2016, 116, 5216.](#)

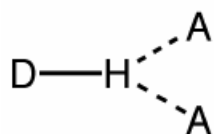
The Hydrogen Bond

- Hydrogen bonding is the **most directional** of all the intermolecular interactions and is a widely used interaction in forming supramolecular structures.
- H-bonds connect atoms X and Y that have electronegativities larger than that of hydrogen, namely, C, N, O, F, P, S, Cl, Se, Br, and I. The XH group is generally referred to as the proton donor (D) and the Y atom is called the proton acceptor (A) group.
- The strength of a H-bond increases with an increase in the dipole moment of the X-H bond and the electron lone pair on atom Y. Hence, the **strongest H-bonds are formed between atoms N, O, and F** acting as X and Y, although C-H can also act as a donor.
- **π H-bonds** involve an interaction between a partially positive hydrogen atom and the electrons of unsaturated double and/or triple bonds
- The strength of such bonds can range from very weak to substantial, typically falling in the approximate range of **4 - 120 kJ mol⁻¹**. The thermodynamic stabilities of H-bonded complexes in solution are very dependent on the solvent. The stabilities are usually **highest in apolar solvents** without H-bonding properties, such as alkanes.

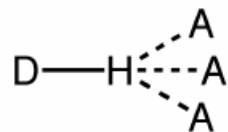
Examples of Hydrogen Bonds



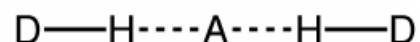
Simple



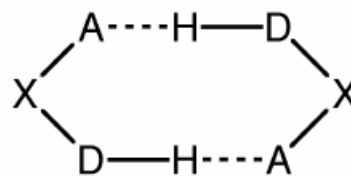
Bifurcated



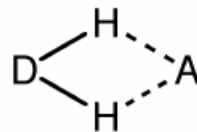
Trifurcated



Bridging



Cyclic dimer



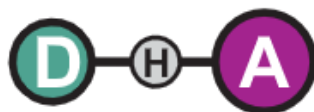
Cyclic

Hydrogen bond formation covers a wide variety of interaction types.

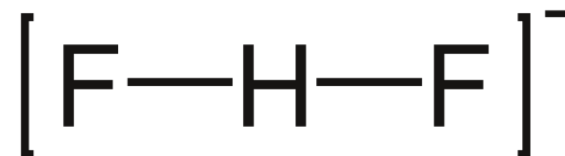
Very Strong Hydrogen Bonds



conventional H-bond



short strong H-bond
(SHB)



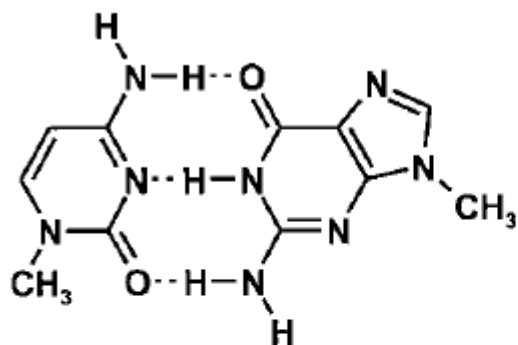
“These results suggest that the SHB lies at the tipping point where hydrogen bonding ends and chemical bonding begins.”

[Dereka et al., *Science* **2021**, 371, 160.](#)

Experimental Detection of Hydrogen Bonds

- **NMR-Spectroscopy:** The electron densities at the protons involved in H-bonds are decreased, and consequently their NMR signals are shifted to lower magnetic fields. The magnitude of the chemical shift is indicative of the strength of the H-bond.
- **IR-Spectroscopy:** The formation of H-bonds causes a large red-shift (up to 100 cm^{-1}) of the fundamental X-H stretching vibration, and occurs as a consequence of a lengthening of the X-H bond. In addition, the intensity of the new band is significantly increased, sometimes by more than an order of magnitude, and broadened.
- **X-Ray and Neutron Diffraction:** X-ray and neutron diffraction see hydrogen atoms in a different way and with different accuracy (± 0.02 and $0.001\text{ \AA}$, respectively), because X-ray scattering occurs by the electronic cloud of the H atom, whereas neutron scattering occurs mainly by the H nucleus.
- **Mass Spectrometry:** The detection of H-bonded structures by mass spectrometry is severely hampered by the difficulty of ionizing these structures in a nondestructive way. Several ion-labeling techniques in combination with soft ionization methods, such as electrospray ionization (ESI) and matrix-assisted laser-desorption/ionization (MALDI), have significantly improved this.

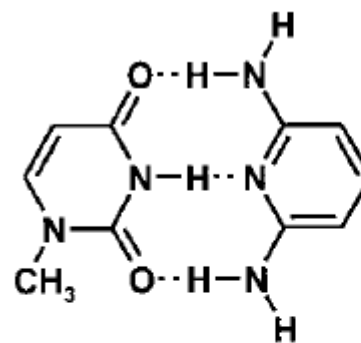
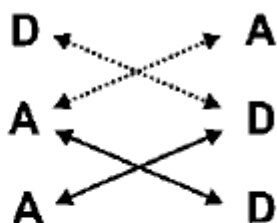
Self-Assembly by Hydrogen Bond



C·G

AAD·DDA

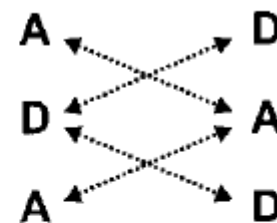
$K_{\text{ass}} \approx 10^4 \text{ M}^{-1}$



U·DAP

ADA·DAD

$K_{\text{ass}} \approx 10^2 \text{ M}^{-1}$

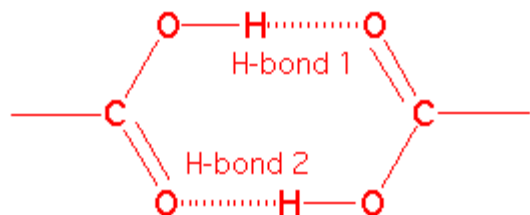


 **attractive secondary interaction**
 **repulsive secondary interaction**

‘Noncovalent Synthesis Using Hydrogen Bonds’

[P. Timmerman et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2382.](#)

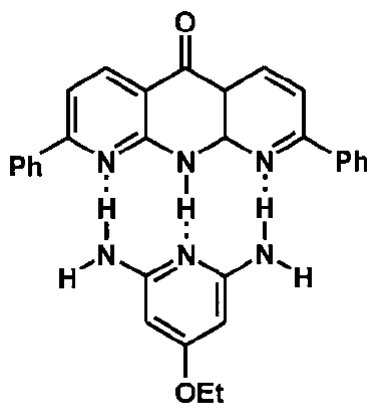
Stability of H-Bonded Dimers in CDCl_3



Carboxylic Acids
Amides
Urea

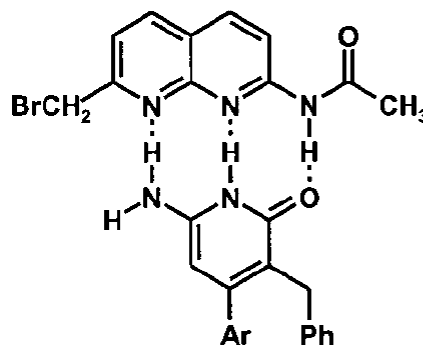
$$\text{AD} \times \text{DA}$$

$$K_a = \sim 60 \text{ M}^{-1}$$



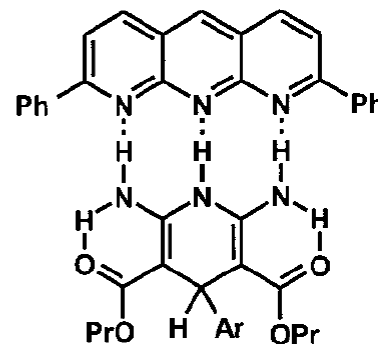
$$\text{ADA} \times \text{DAD}$$

$$K_a = 78 \text{ M}^{-1}$$



$$\text{AAD} \times \text{DDA}$$

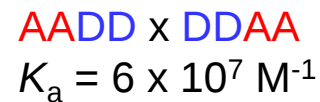
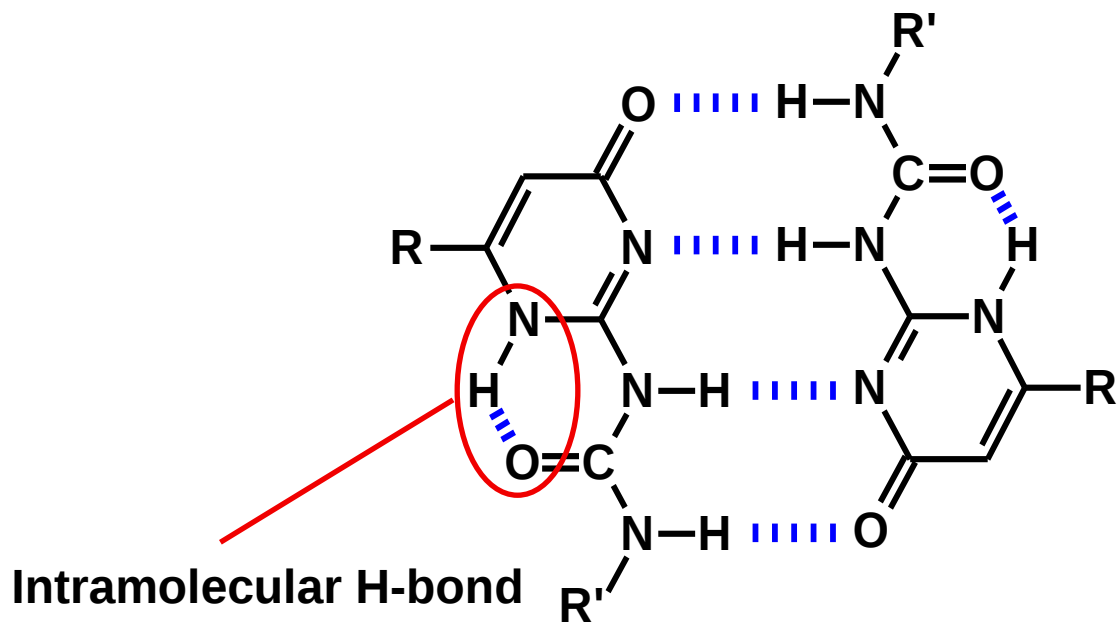
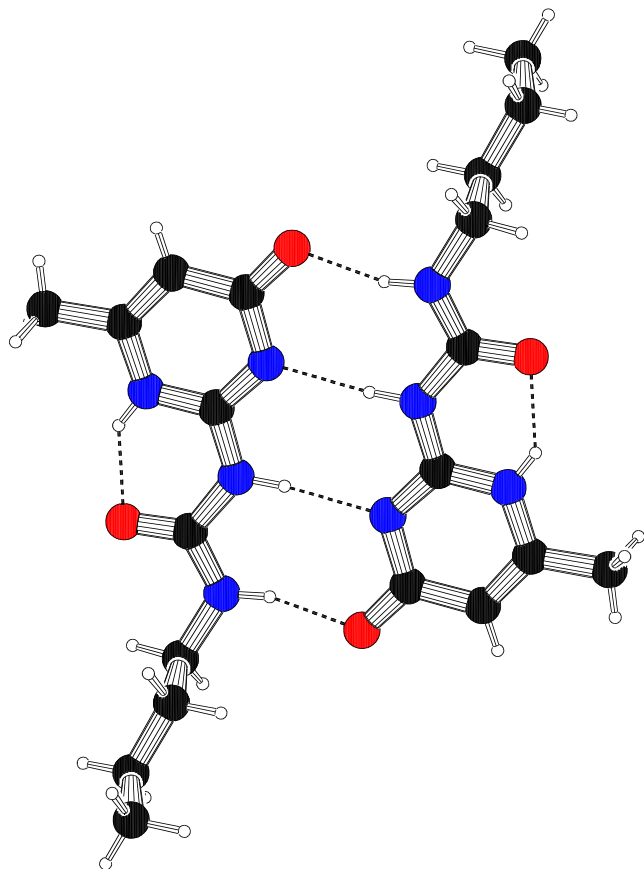
$$K_a = 1700 \text{ M}^{-1}$$



$$\text{AAA} \times \text{DDD}$$

$$K_a > 10^5 \text{ M}^{-1}$$

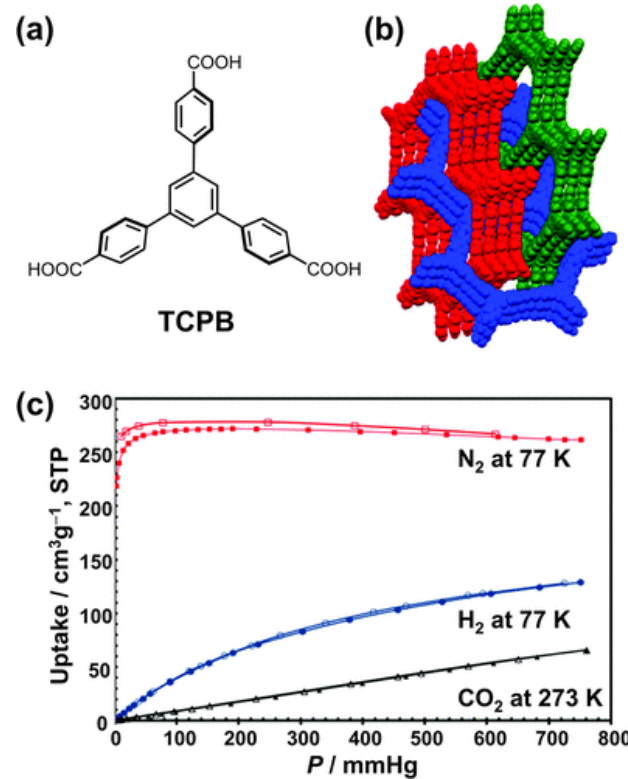
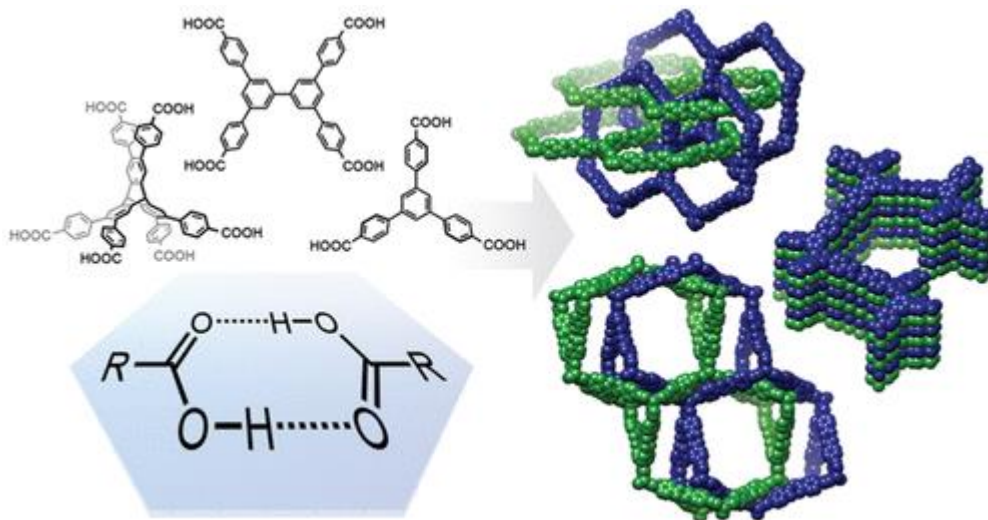
A Dimer with 4 H-Bonds



‘Self-Complementarity Achieved through Quadruple Hydrogen Bonding’

E. W. Meijer et al. *Angew. Chem. Int. Ed.* **1998**, 37, 75.

Hydrogen-Bonded Frameworks

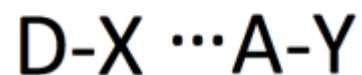


‘Hydrogen-Bonded Organic Frameworks: A Rising Class of Porous Molecular Materials’

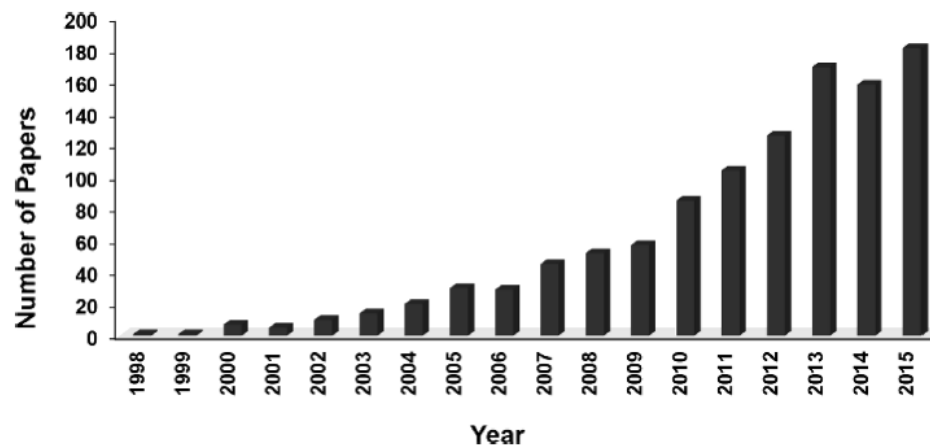
[J. Fraser Stoddart et al. *Acc. Mater. Res.* 2020, 1, 77.](#)

Halogen Bonding

Hydrogen Bond



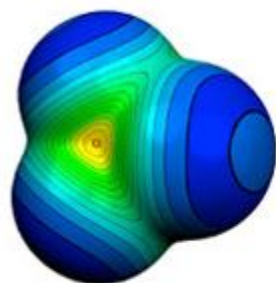
Halogen Bond



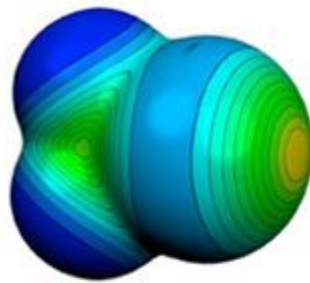
‘The Halogen Bond’

[P. Metrangolo et al. *Chem Rev.* 2016, 116, 2478.](#)

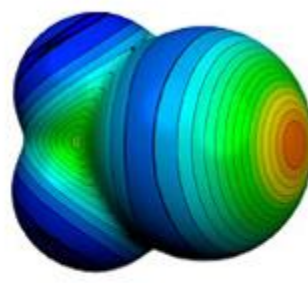
The σ -Hole Model



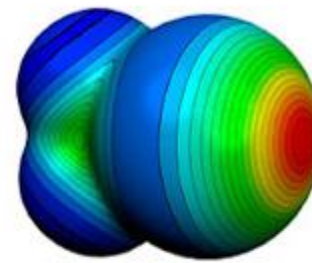
CF_4



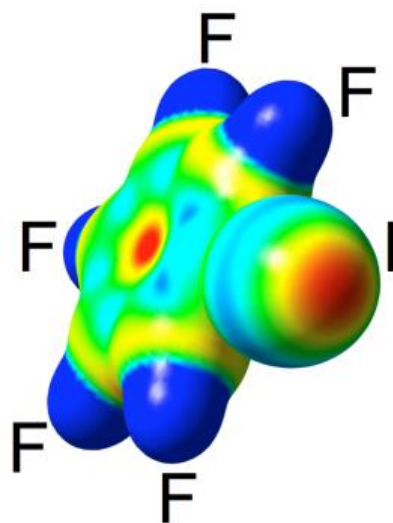
CF_3Cl



CF_3Br



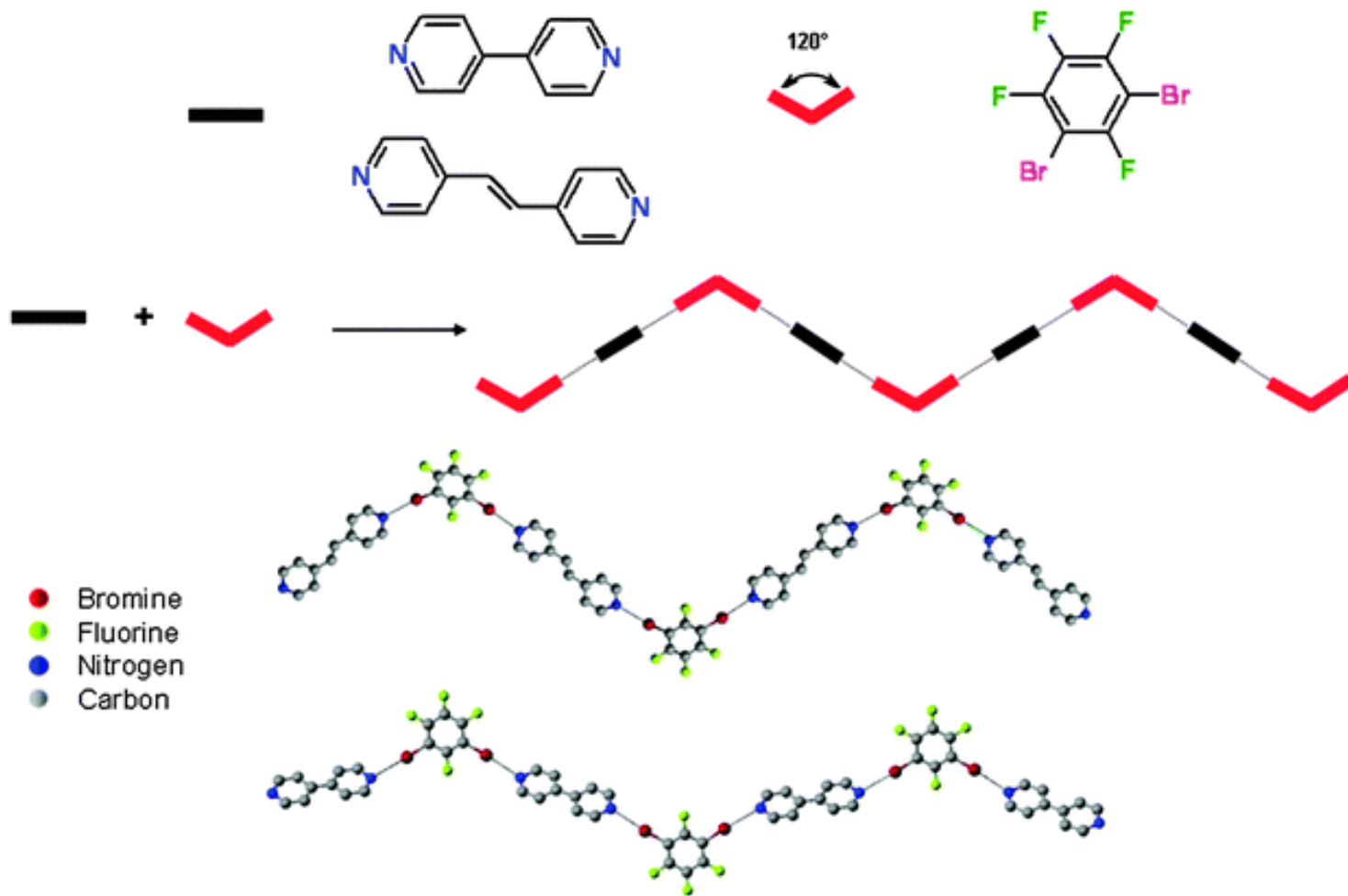
CF_3I



Blue: Negative

Red: Positive

Example

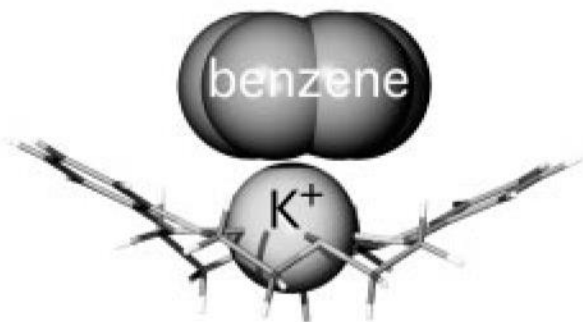


‘Halogen Bonding in Supramolecular Chemistry’

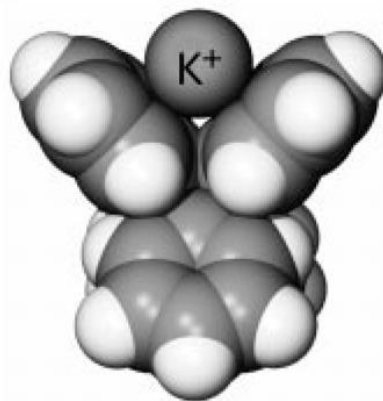
[P. D. Beer et al. *Chem Rev.* 2015, 115, 7118.](#)

Cation- π Interactions

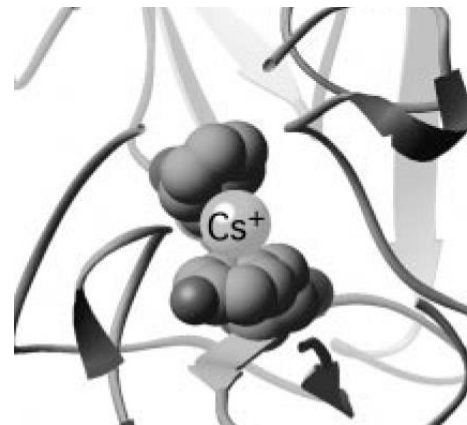
- Transition metal cations form very stable complexes with π -donor ligands. For alkali and earth alkaline metal cations, the interaction is weaker but still significant (**5 – 80 kJ mol⁻¹**)
- Cation- π interactions are important within proteins since Phe, Tyr and Trp comprise 8.4% of all known protein sequences.
- Cation- π interactions between alkali metals and olefins seem to be less important.



Dibenzo-18-crown-6 K⁺ complex



K(BPh₄)



Methylamine Dehydrogenase

‘The Cation- π Interaction’

[D. A. Dougherty et al. *Chem. Rev.* **1997**, *97*, 1303.](#)

Energetics of Cation- π Interactions

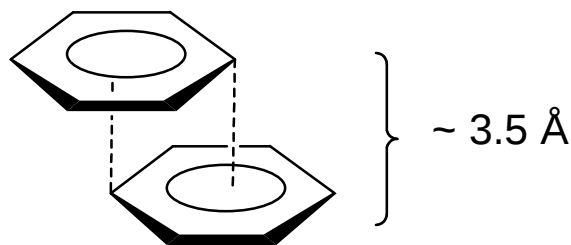
Interaction	$-\Delta H$ (kcal/mol)
$\text{Na}^+ + \text{C}_6\text{H}_6$	28.0 ± 0.1
$\text{Na}^+ + \text{H}_2\text{O}$	24.0
$\text{Na}^+ + \text{HOCH}_3$	26.6
$\text{K}^+ + \text{C}_6\text{H}_6$	18.3
$\text{K}^+ + \text{H}_2\text{O}$	17.9

Na^+ and K^+ are soluble in water and not in benzene because several water molecules fit around one M^+ cation whereas only a few bulky benzene molecules can coordinate to M^+ .

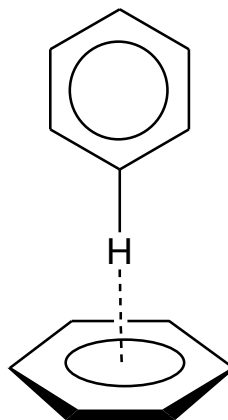
‘Experimental Evidence for Alkali Metal Cation- π Interactions’

[*Gokel et al. Eur. J. Org. Chem. 2000, 2967.*](#)

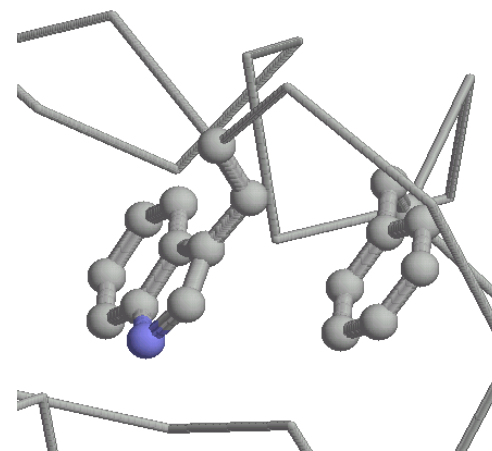
π - π Interactions



Face-to-face



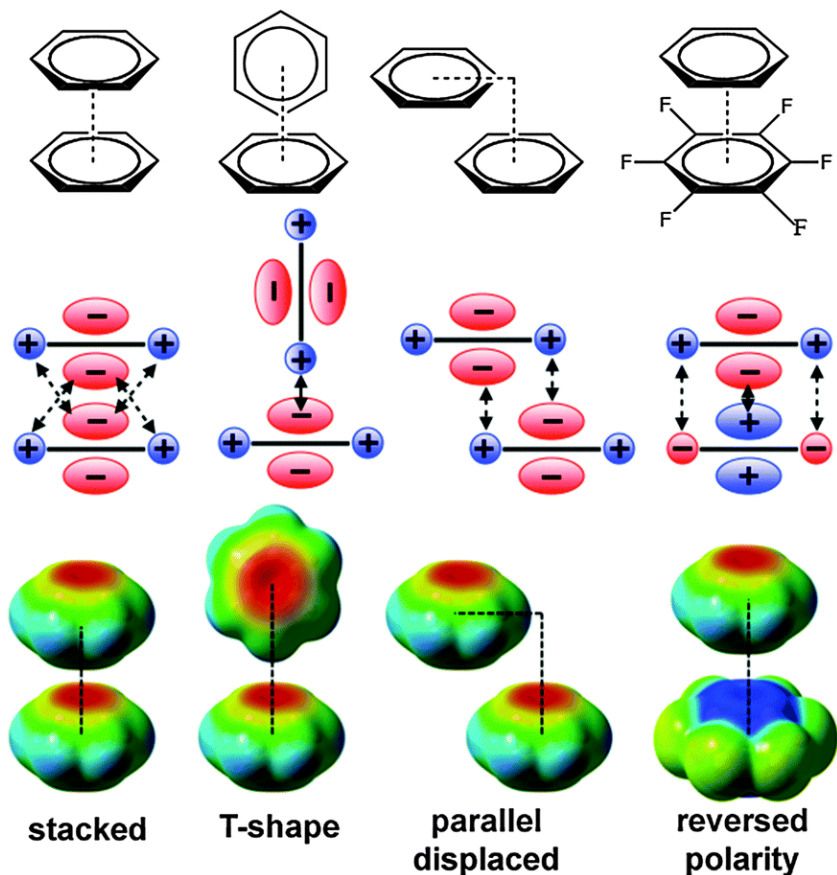
Edge-to-face



Tryptophane stacking against phenylalanine.

Weak electrostatic interactions between aromatic rings, often in situations where one is electron rich and the other electron poor (**0 – 50 kJ mol⁻¹**). There are two types: face-to-face and edge-to-face (can be regarded as a hydrogen bond of CH to π -electrons)

A Model for π - π Interactions



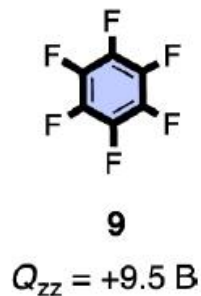
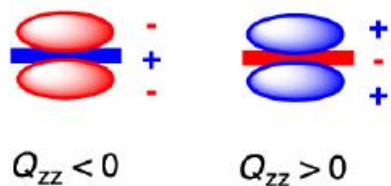
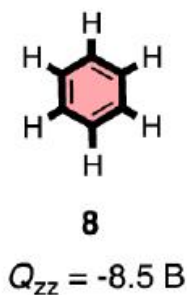
The stability of these structures can be rationalized by the attractive/stabilizing arrangements of the quadrupole moments associated with the aromatic ring.

In these arrangements there is a partial negative π electron density above and below the plane of the ring and a partial positive charge on the periphery of the rings. This charge distribution leads to favorable electrostatic interactions in the T-shape and parallel displaced conformers, with the stacked or traditional π - π structure the least favored. However, if the ring polarity of one of the rings is reversed, e.g. by fluorinating the benzene ring, the stacked π - π structure is favored

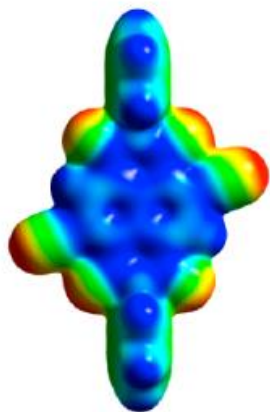
'The Nature of π - π Interactions'

[C. Hunter, J. K. M. Sanders *J. Am. Chem. Soc.* **1990**, *112*, 5525.](#)

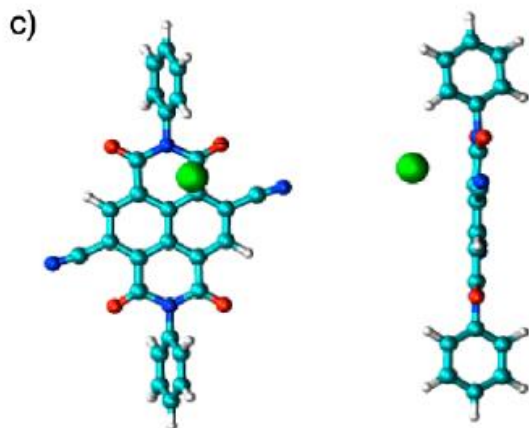
Anion- π Interactions



Most aromatic systems are π -basic, have a negative quadrupole moment $Q_{zz} < 0$, and can therefore attract cations.



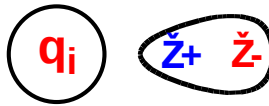
$Q_{zz} = +39 \text{ B}$



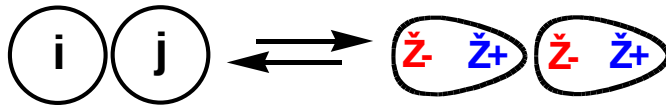
$E_{\text{int}} = -135 \text{ kJ mol}^{-1}$

To attract anions rather than cations, the quadrupole moment perpendicular to the aromatic plane has to be inverted. This can be done; the most popular example for π -acids is hexafluorobenzene **9** with $Q_{zz} = +9.5 \text{ B}$.

Induction and Dispersion Interactions



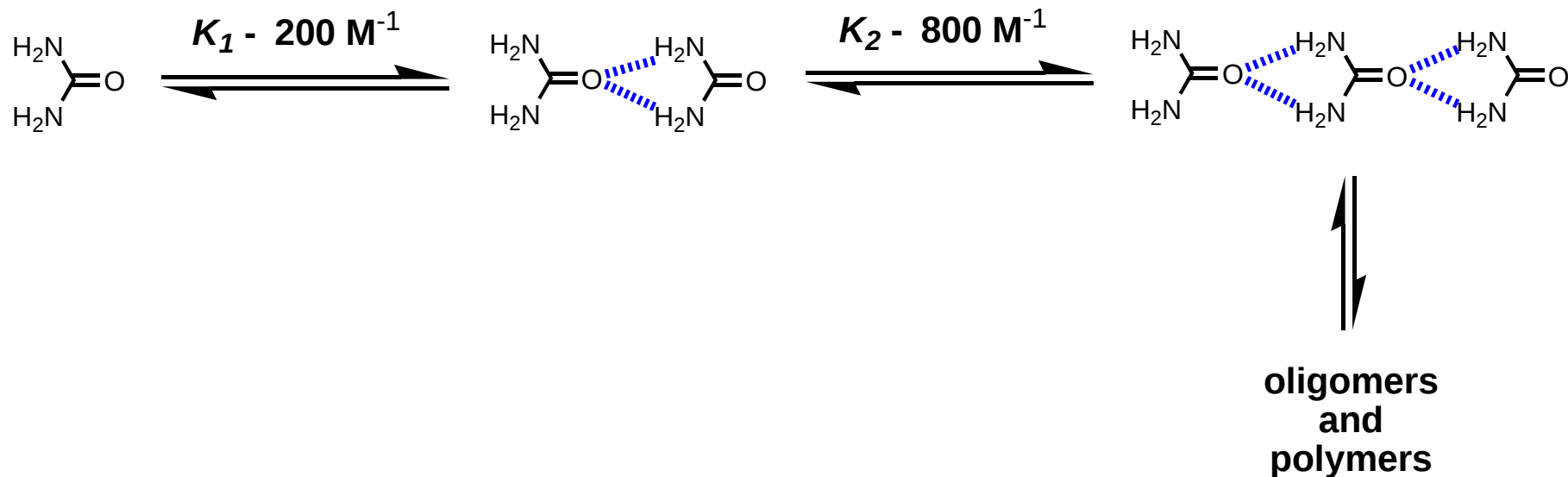
$$\text{Induction} = c \frac{q_i^2 \alpha_j}{r_{ij}^4}$$



$$\text{Dispersion} = \frac{B_{ij}}{r_{ij}^6}$$

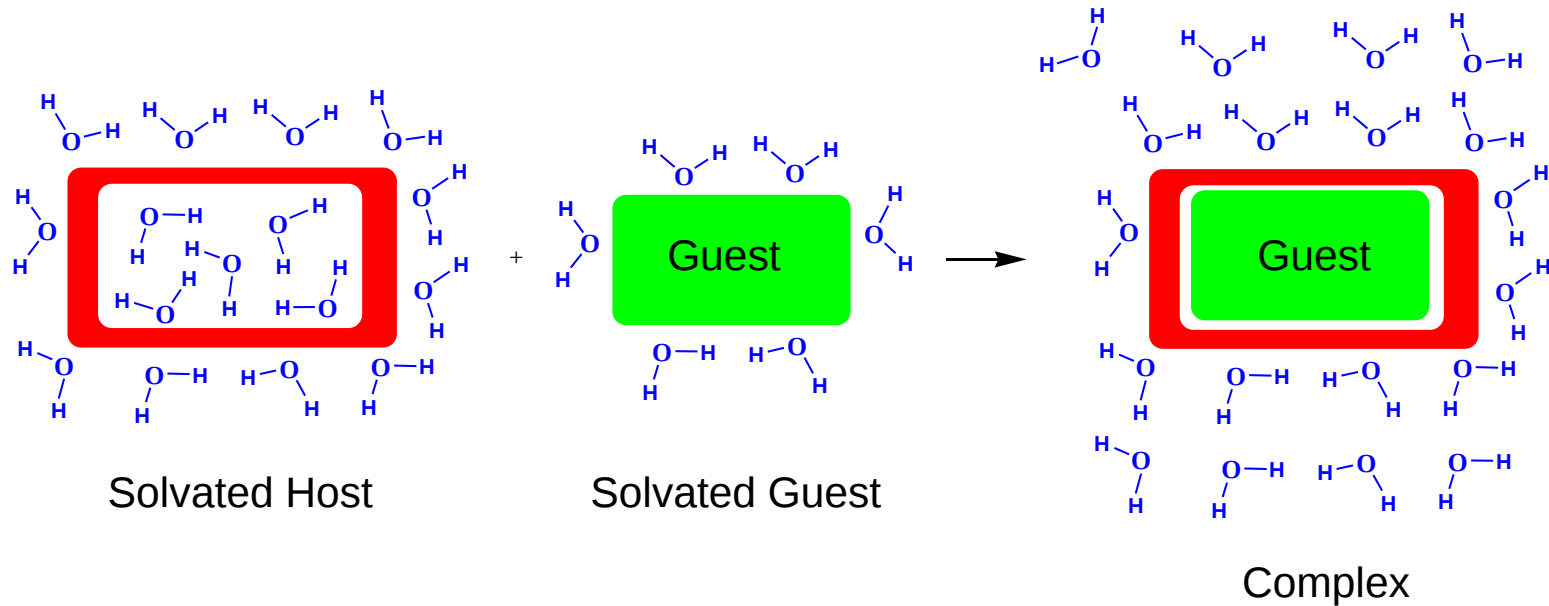
- Dispersion (Van der Waals) interactions are attractive electrostatic forces which arise from the mutual polarization of electron clouds.
- They are non-directional and very weak (< 5 kJ mol⁻¹).

Induction Interactions in Organic Molecules



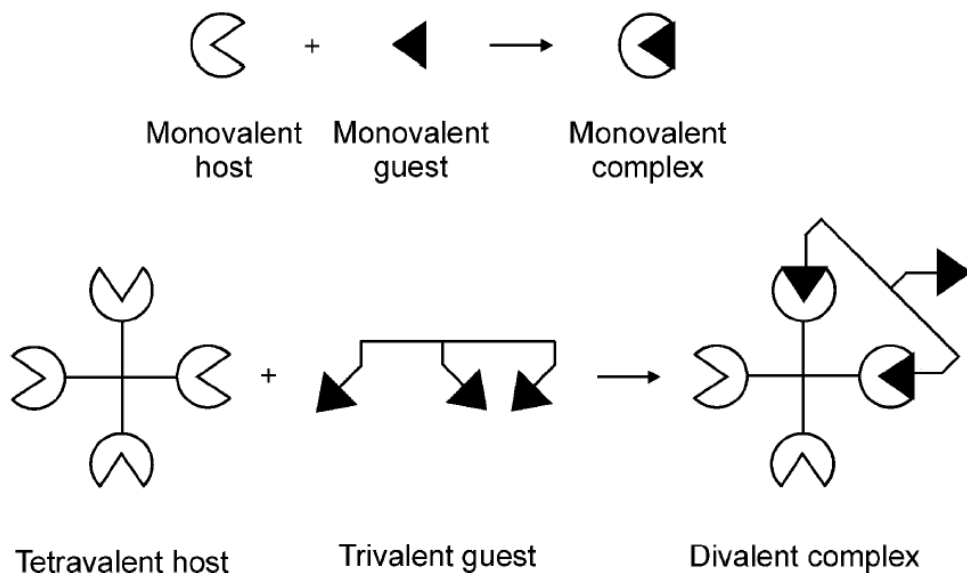
Urea forms a linear hydrogen-bonded polymer in benzene. The value of K_1 is 400 M^{-1} , and the value of K_2 is 800 M^{-1} . The difference is attributed to polarization of the molecules by the hydrogen bonds in the dimer that make the second set of hydrogen bonds in the trimer stronger.

Hydrophobic Effects



- The Hydrophobic effect is the driving force for the association of apolar molecules in aqueous solution.
- The hydrophobic effect is considered to be the major driving force for the folding of globular proteins. It results in the burial of the hydrophobic residues in the core of the protein.

Multivalency

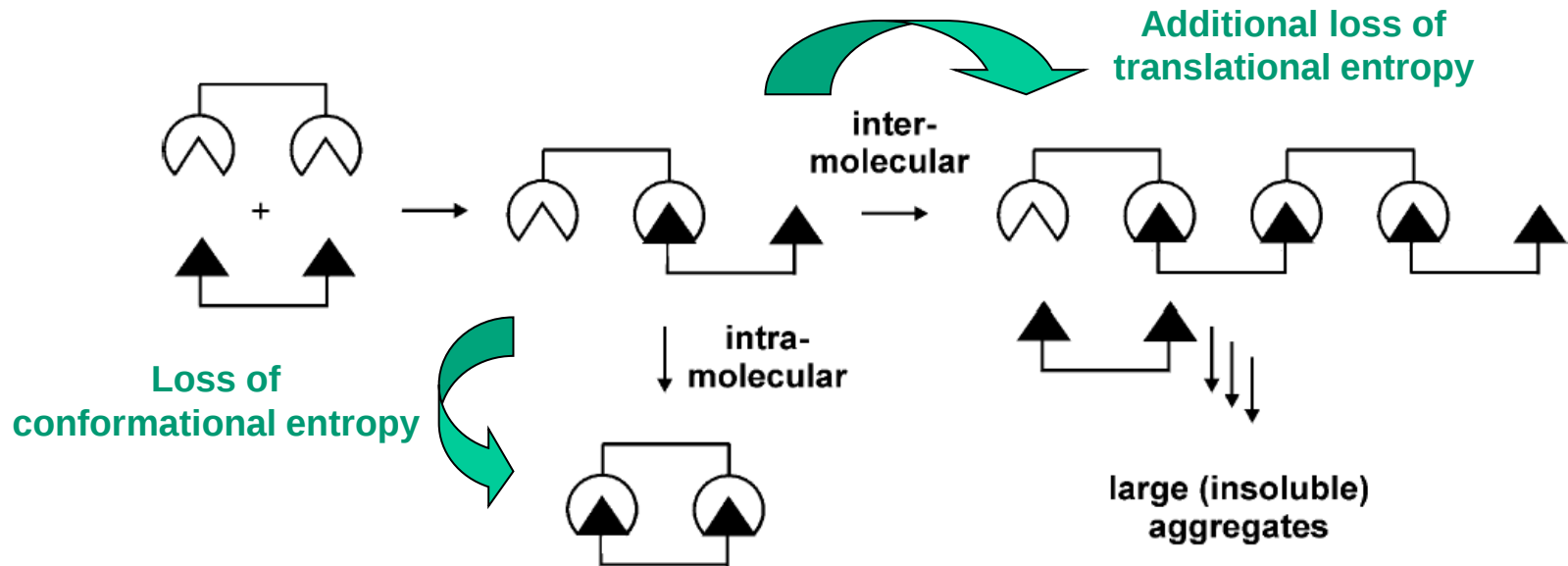


Multivalency describes the binding of two (or more) entities that involves the simultaneous interaction between multiple, complementary functionalities on these entities. The valency of the complex is defined by the number of shared interactions between the two interacting entities. All interactions involving more than one host–guest interaction are considered multivalent.

‘Multivalency in Supramolecular Chemistry and Nanofabrication’

[J. Huskens et al. *Org. Biomol. Chem.* **2004**, *2*, 3409.](#)

Multivalent vs. Intermolecular Binding



The traditional idea is that multivalency is mainly governed by entropy. Intramolecular multivalent binding would be entropically favorable as the multivalent complex is assumed to involve the same rotational and translational entropy loss as its corresponding monovalent interaction. The loss of conformational entropy upon intramolecular binding has to be taken into account.

Binding Constants of Multivalent Assemblies

$$\Delta G_{\text{avg}}^{\text{poly}} = \Delta G_N^{\text{poly}} / N$$

$$\Delta G = -RT \ln(K)$$

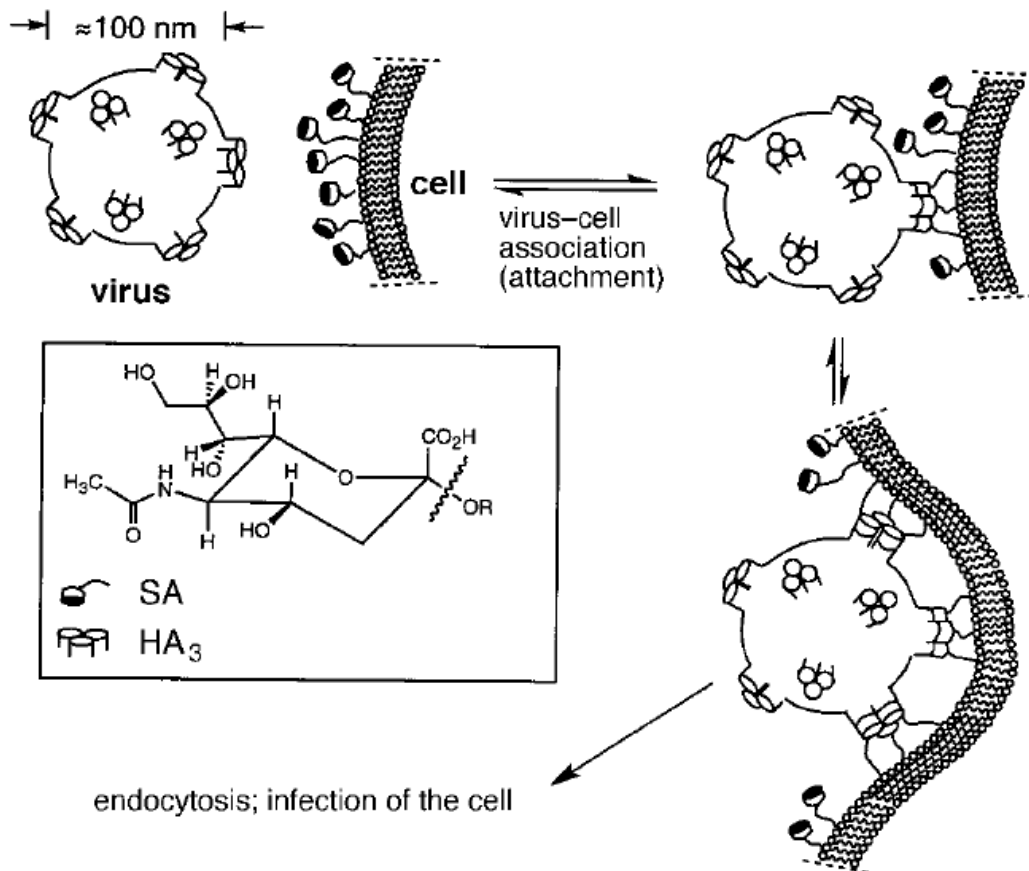
$$K_N^{\text{poly}} = (K_{\text{avg}}^{\text{poly}})^N$$

The binding energies add – the binding constants multiply! For a divalent system based on two interactions with $K_1 = K_2 = 10^3$, the total binding constant is $K = 10^6$.

→ **VERY GOOD WAY TO ACHIEVE HIGH BINDING CONSTANTS**



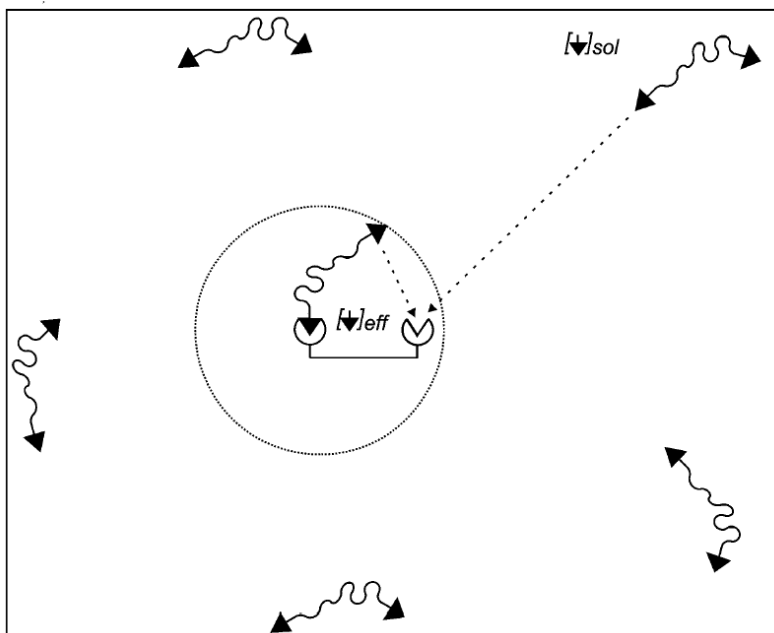
Multivalency in Biology



The attachment of an influenza virus to a target cell occurs through multiple simultaneous interactions between hemagglutinin (HA) and sialic acid (SA).

Multivalency is ubiquitous in biology !!

Effective Concentration



Schematic representation of the concept of effective concentration, demonstrating the increased probability of interaction for intramolecular binding events. A free host site experiences an effective guest site concentration $[B]_{eff}$ in a solution with guest site concentration $[B]_{sol}$. The dotted circle represents the probing volume that the pendent host site can probe to find available guest sites.

The concept of effective concentration gives rise to a concentration-dependent binding mode for multivalent interactions, favoring intramolecular binding at low concentrations and intermolecular binding at high concentrations.

Cooperativity

$$\Delta G_{\text{avg}}^{\text{poly}} = \alpha \Delta G^{\text{mono}}$$

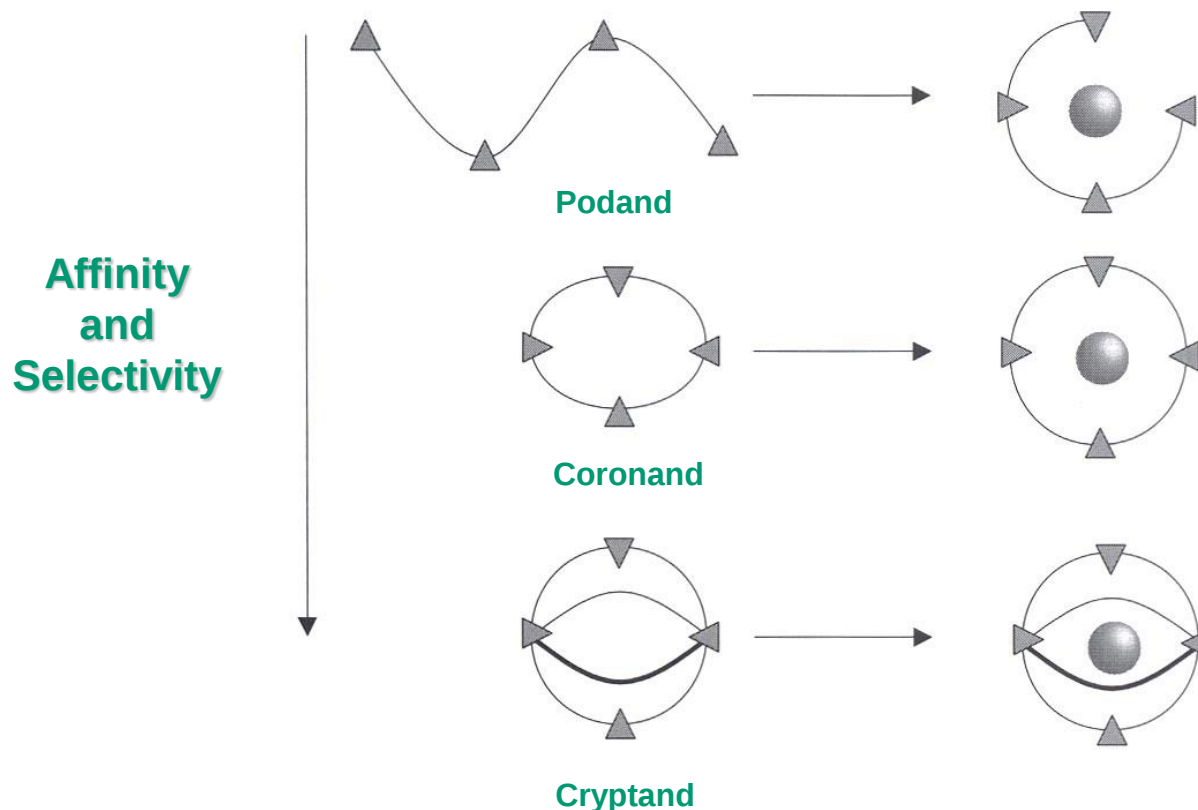
$\alpha > 1$: positively cooperative (synergistic)

$\alpha = 1$: noncooperative (additive)

$\alpha < 1$: negatively cooperative (inhibiting)

For example, the binding of four O₂ molecules to tetrameric hemoglobin occurs with cooperativity; that is, the free energy of binding of the second oxygen molecule to hemoglobin is more favorable than the binding of the first. The degree of cooperativity, α , in such nonpolyvalent systems is greater than one and unitless.

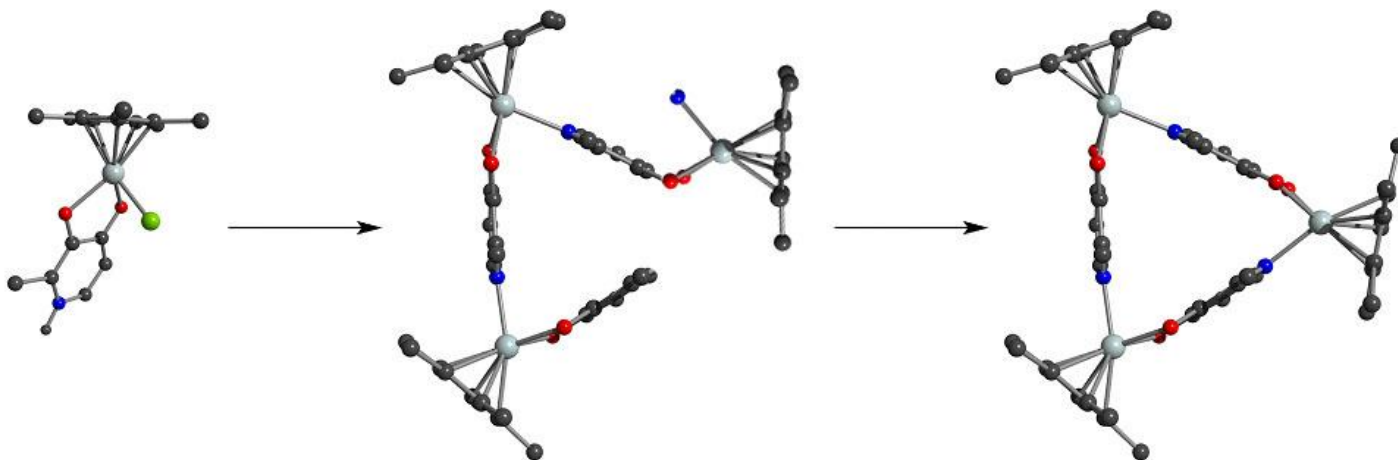
Preorganization



This concept, first proposed by Donald Cram, can help rationalize the strength of binding between the components in particular supramolecular systems. In essence, Cram proposed that the more closely the binding sites of a host molecule are structurally preorganized for binding to a guest, the greater will be the binding strength between host and guest in the resulting assembled species.

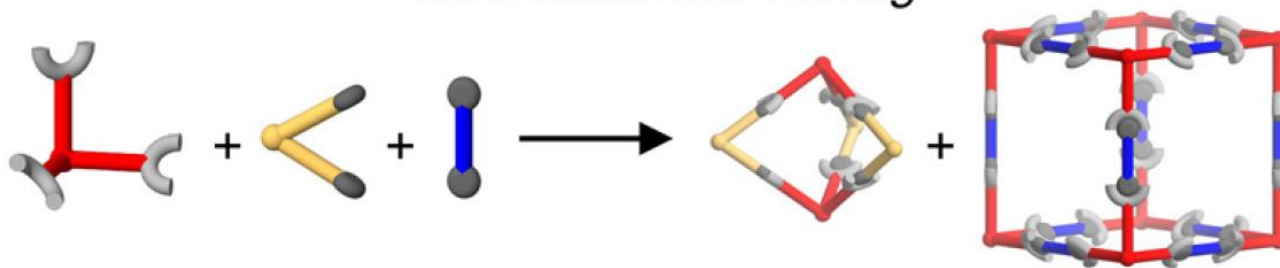
Error Correction

- An important outcome of employing relatively weak noncovalent interactions for the construction of supramolecular assemblies is that their formation is reversible.
- As a consequence, supramolecular systems have an inherent capacity for error correction that is not normally available to systems, which were built by covalently bonds.

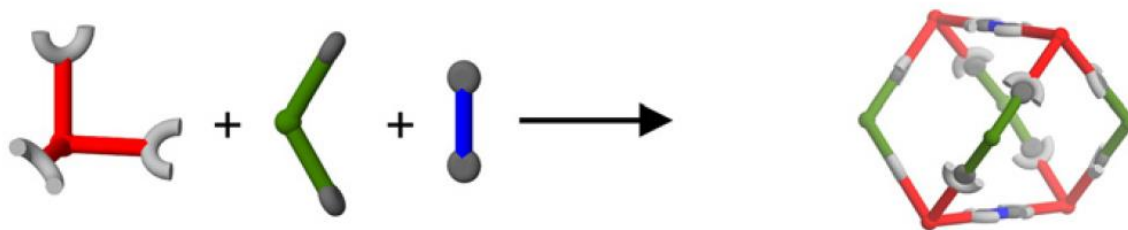


Self Sorting

narcissistic self-sorting



social self-sorting



Dynamic Covalent Chemistry

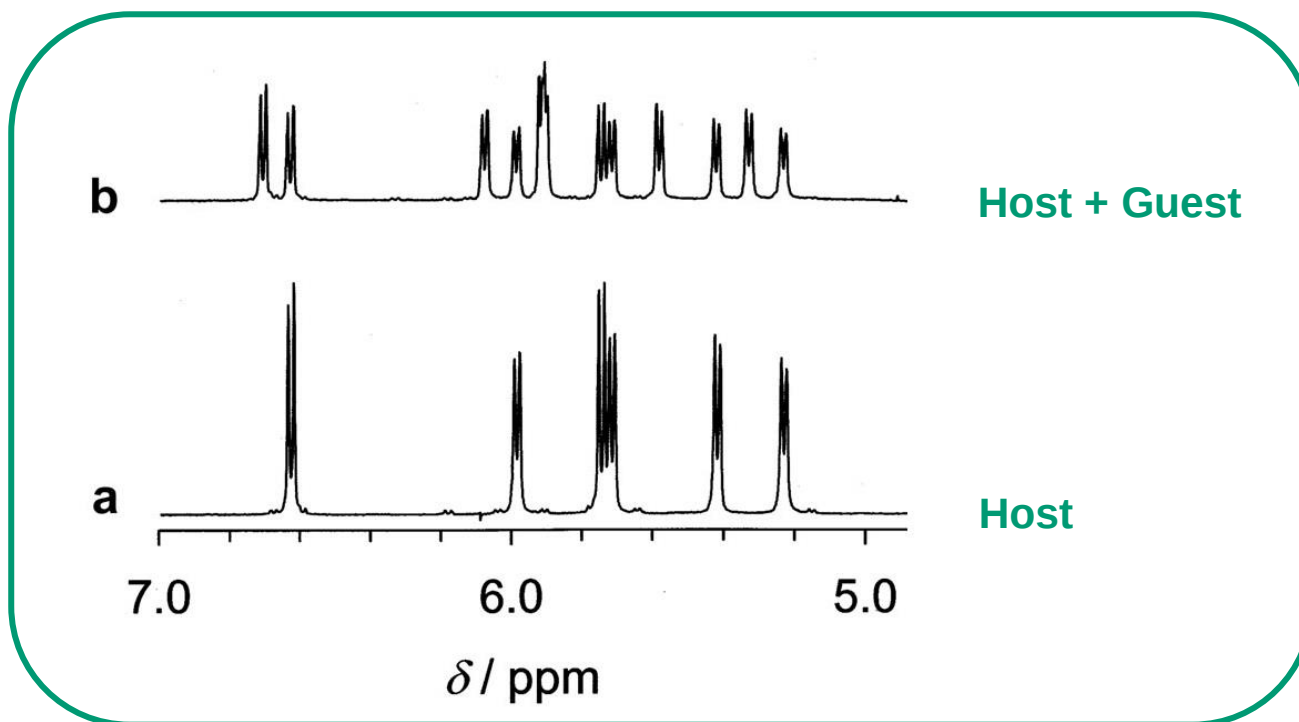


Some covalent bonds are labile, i.e. they undergo fast exchange reactions (selected examples are shown above). These dynamic covalent bonds can be used for the construction of covalent 'assemblies' under thermodynamic control.

'Recent Advances in Dynamic Covalent Chemistry'

[W. Zhang et al. Chem. Soc. Rev. 2013, 42, 6634.](#)

Determination of Binding Constants by NMR Spectroscopy – Slow Exchange



Die amount of free host and of the host-guest-complex can be determined by integration of the respective signals. → Direct calculation of the binding constant is possible.

Determination of Binding Constants by NMR Spectroscopy – Slow Exchange

Example 1:

$$K = [\text{Host-Guest}] / [\text{Host}][\text{Guest}] = 10^4 \text{ M}^{-1}$$

$$[\text{Host-Guest}] = 0.1 \text{ mM}$$

$$[\text{Guest}] = 0.1 \text{ mM}$$

$$[\text{Host}] = 0.1 \text{ mM}$$

Example 2:

$$K = [\text{Host-Guest}] / [\text{Host}][\text{Guest}] = 1 \text{ M}^{-1}$$

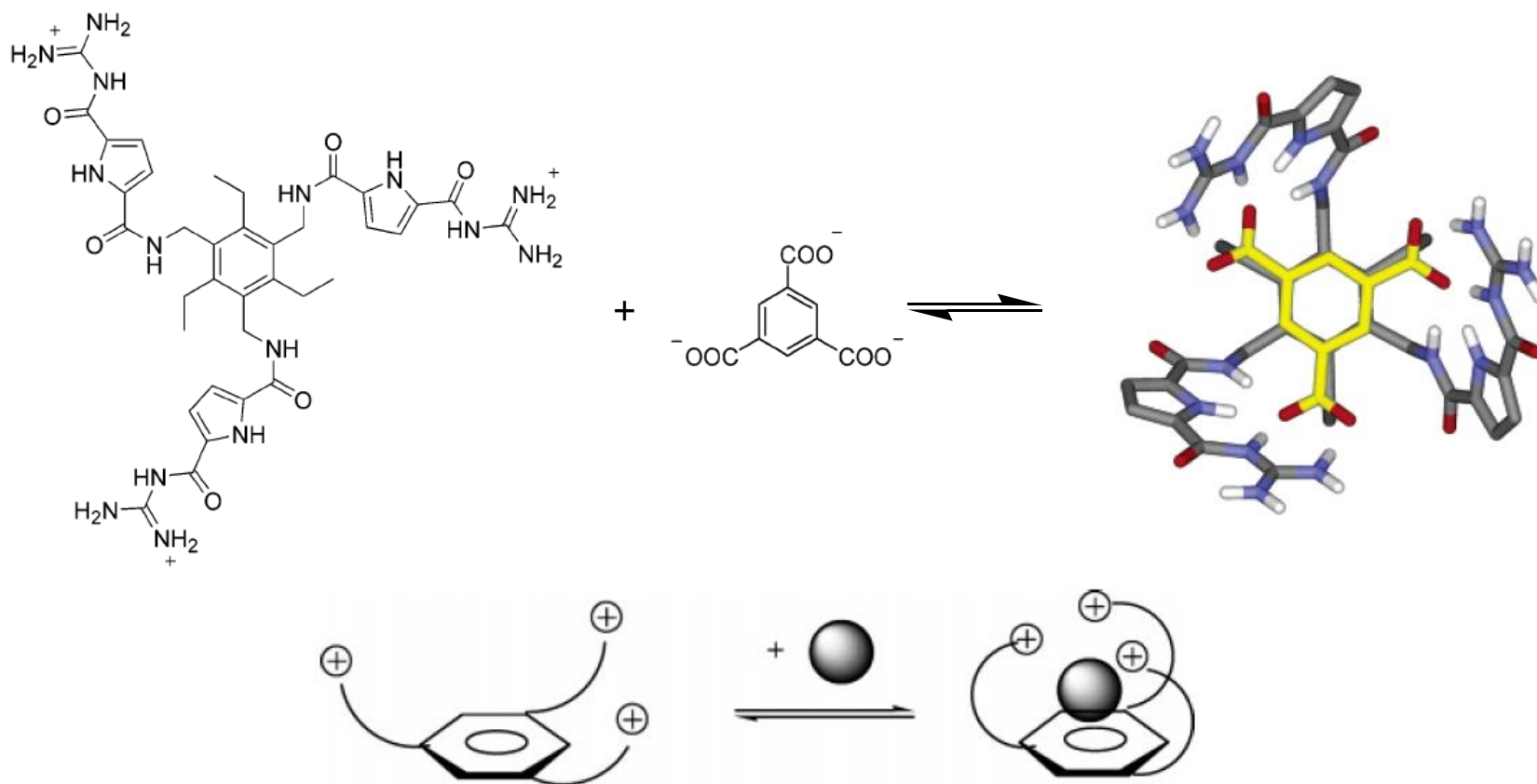
$$[\text{Host-Guest}] = 0.1 \text{ mM}$$

$$[\text{Guest}] = 10 \text{ mM}$$

$$[\text{Host}] = 10 \text{ mM}$$

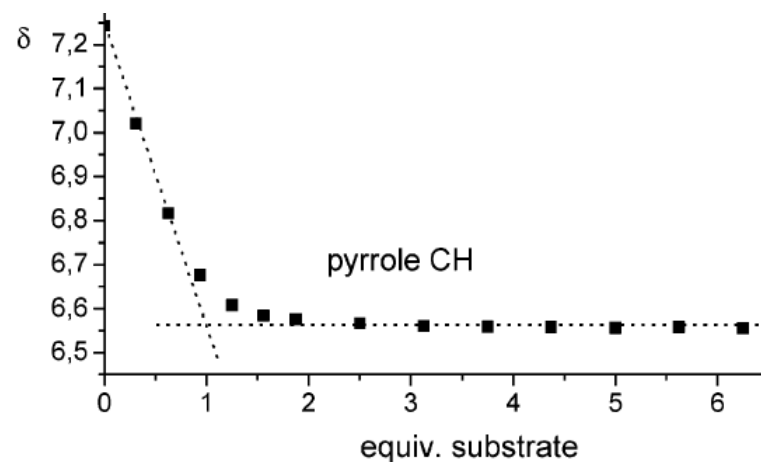
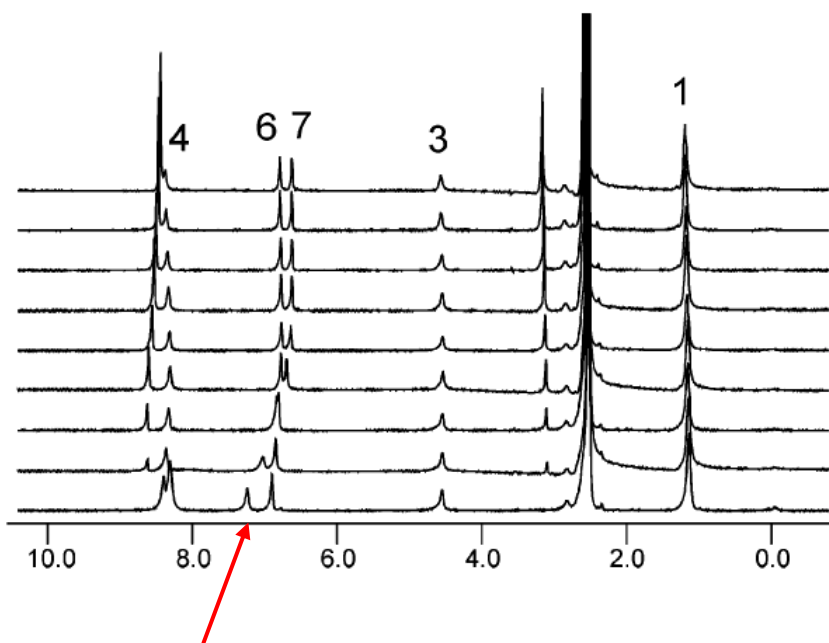
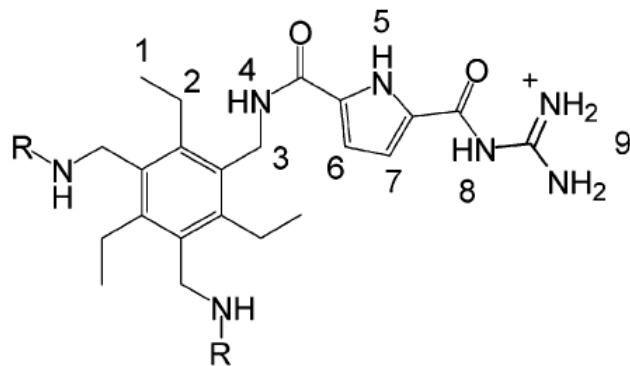
Binding constants should be between 1 M^{-1} and 10^4 M^{-1} .

Determination of Binding Constants by NMR Spectroscopy – Fast Exchange

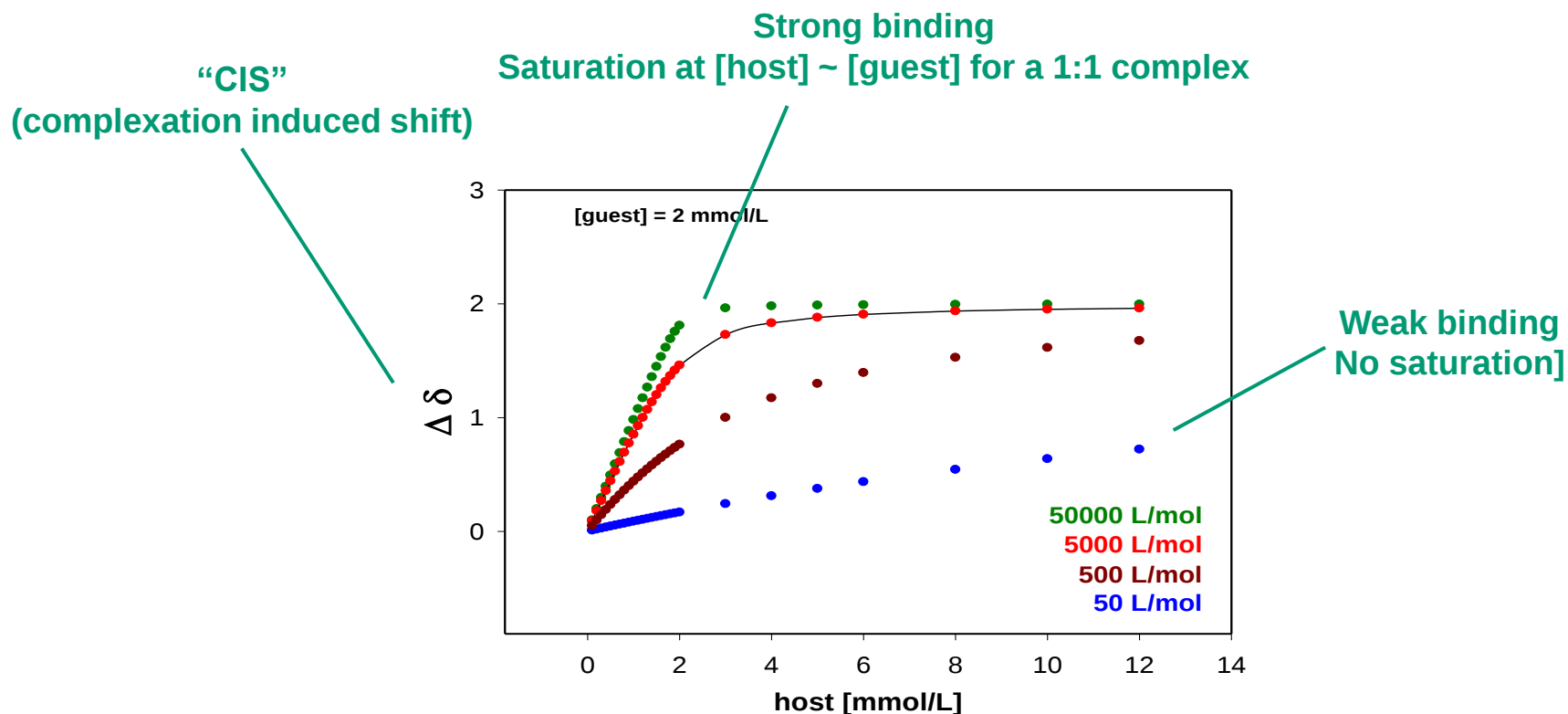


[C. Schmuck et al. *J. Am. Chem. Soc.* **2005**, *127*, 3373.](#)

Determination of Binding Constants by NMR Spectroscopy – Fast Exchange



Binding Constants by NMR Titrations

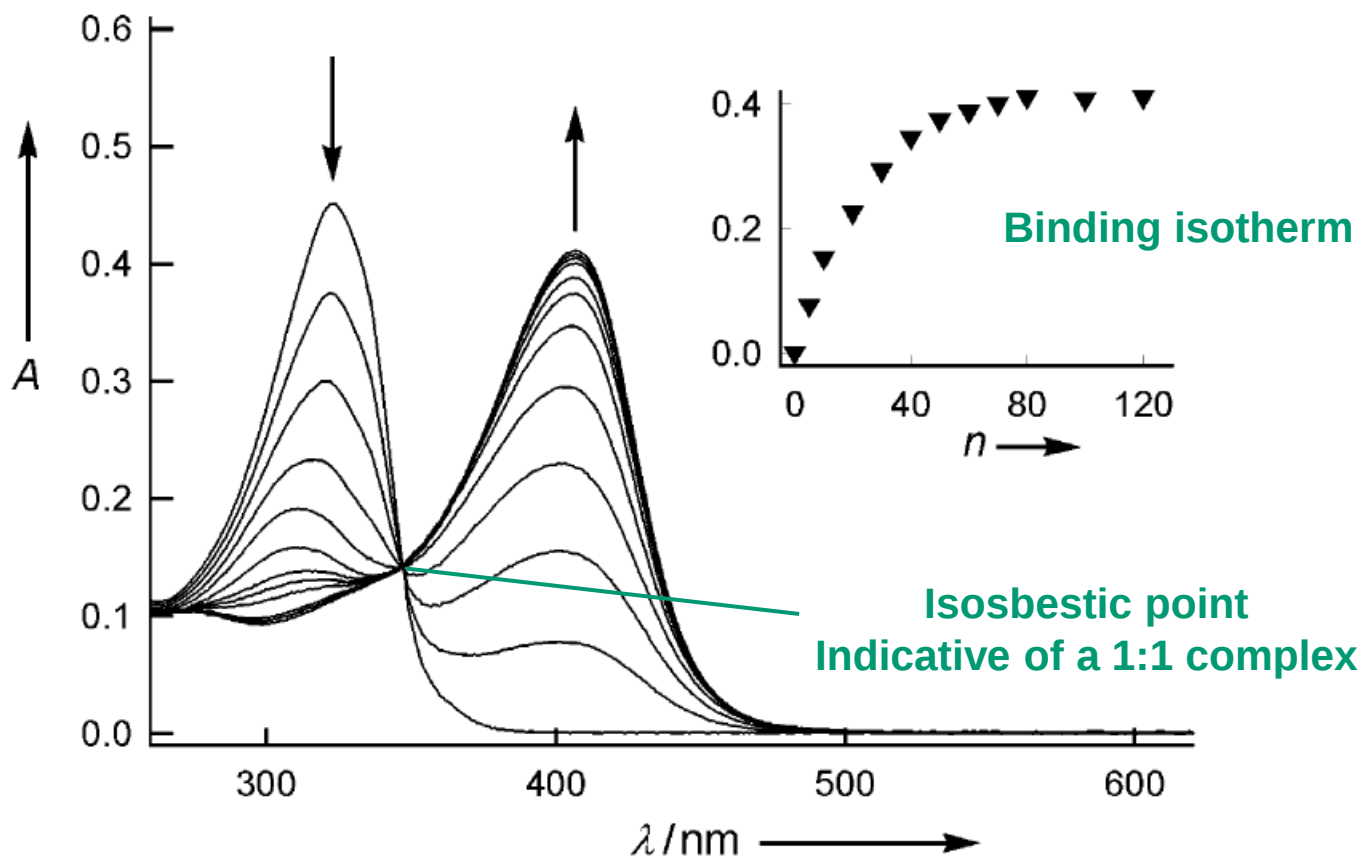


The binding constant can be obtained by nonlinear fitting of the binding isotherm. The equation depends on the stoichiometry of the host-guest complex.

‘Determining association constants from titration experiments in supramolecular chemistry’

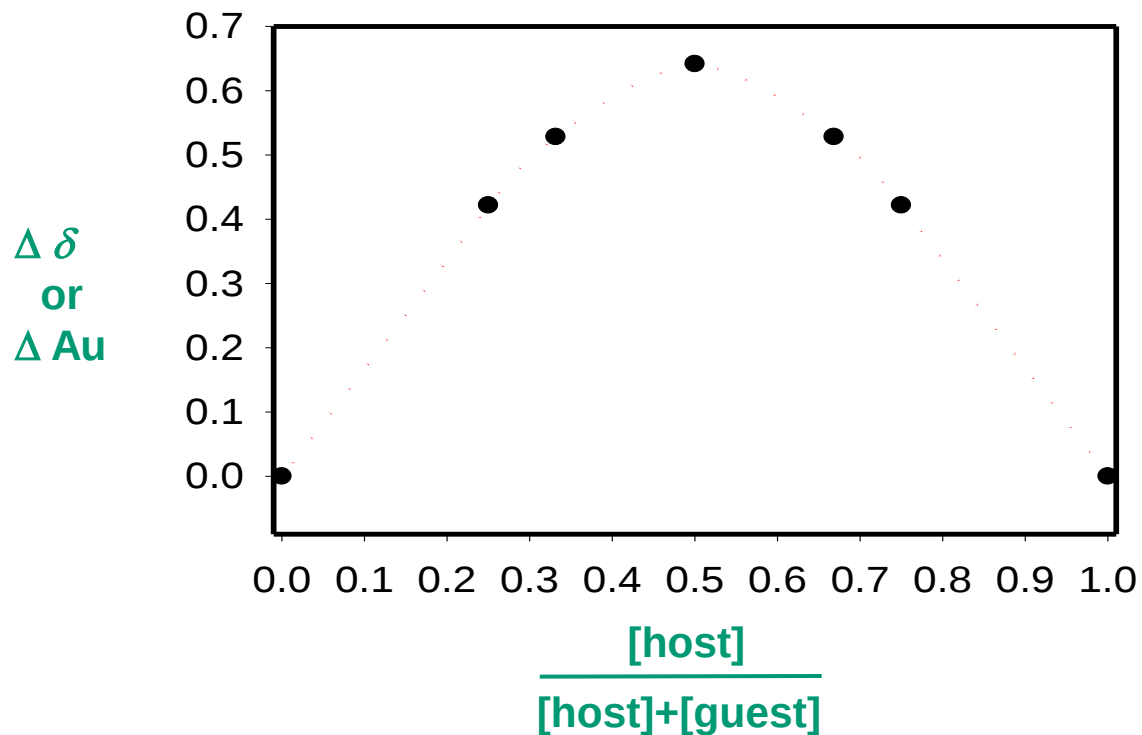
[P. Thordarson *Chem. Soc. Rev.* **2011**, *40*, 1305.](#)

Binding Constants by UV-Vis Titrations



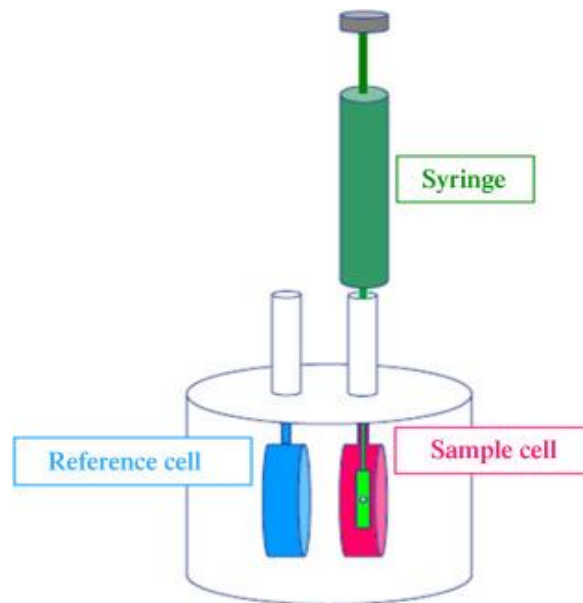
The binding constant can be obtained by nonlinear fitting of the binding isotherm. The equation depends on the stoichiometry of the host-guest complex. More sensitive than NMR $\rightarrow$ binding constants $> 10^4 \text{ M}^{-1}$ can be measured (limit $\sim 10^7 \text{ M}^{-1}$).

Job plot



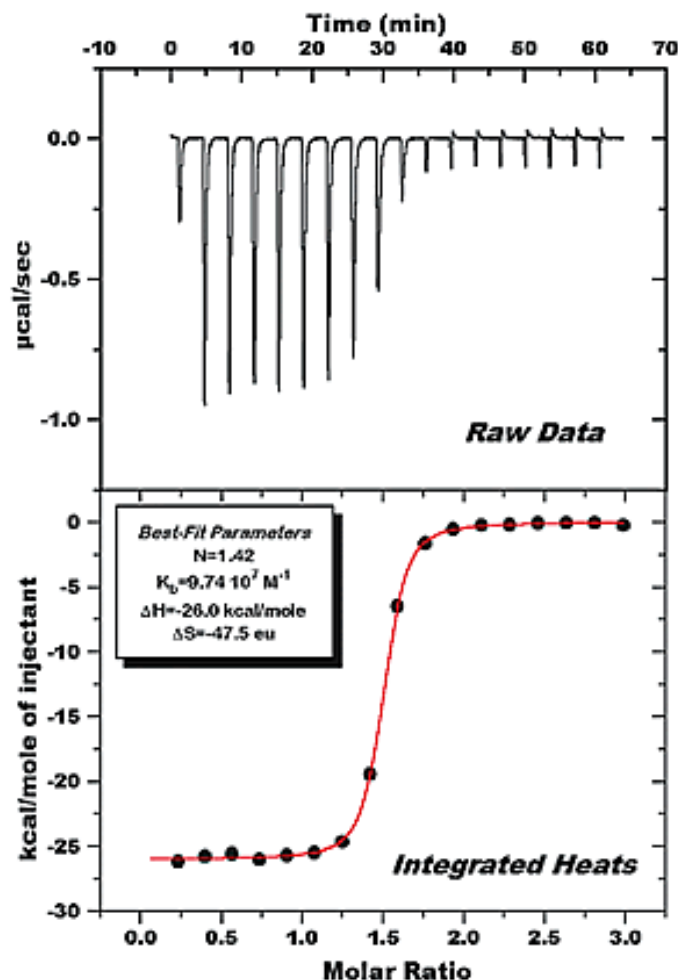
Binding stoichiometry can be determined by making up a series of solutions with varying host-guest ratios such that the total concentration of host and guest is constant. For a 1:1 complex, such a Job plot should give a maximum at 0.5.

Isothermal Titration Calorimetry (ITC)



‘Isothermal Titration Calorimetry in Supramolecular Chemistry’
[F. P. Schmidtchen *Analytical Methods in Supramolecular Chemistry*.](#)

Binding Constants by Isothermal Titration Calorimetry (ITC)



ITC measures the heat change associated with the binding event. This allows accurate determination of binding constants (K_D), reaction stoichiometry (n), enthalpy (ΔH) and entropy (ΔS), thereby providing a complete thermodynamic profile of the molecular interaction in a single experiment. The range of binding constants which can be directly measured with ITC is between 10^2 to $\sim 10^9 \text{ M}^{-1}$.

Determination of Binding Constants

Other Methods

- **Fluorescence-Titrations:** Analogous to UV-Vis or NMR titrations ($10^2 \text{ M}^{-1} < K < 10^7 \text{ M}^{-1}$).
- **Electrochemical Methods:** Can be used when either the host or the guest is electroactive (has a charge or forms a redox couple). Most commonly used: potentiometry, which allows to determine the concentration of an ion using the concentration dependence of the cell potential.
- **Mass Spectrometry:** Modern, soft ionization techniques are required. Quantitative data can be obtained with the help of calibration curves.
- **Kinetic methods:** The binding constant is calculated from the on- and off-rates of complexation. Can be useful for very slow complexation processes or for unstable compounds which decompose before reaching the equilibrium.

$$K_a = \frac{k_{\text{forward}}}{k_{\text{back}}} = \frac{\text{on-rate}}{\text{off-rate}}$$