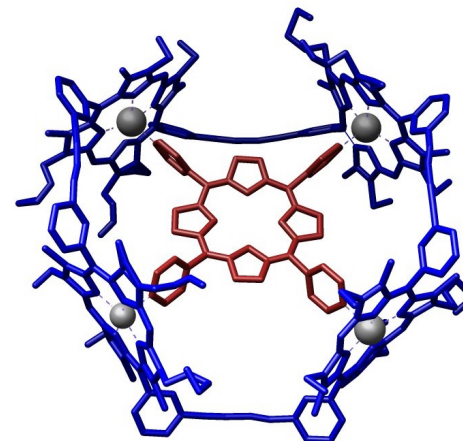
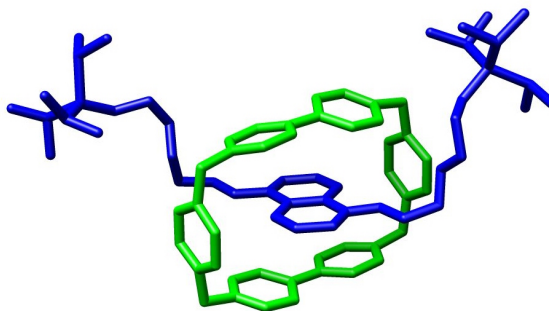
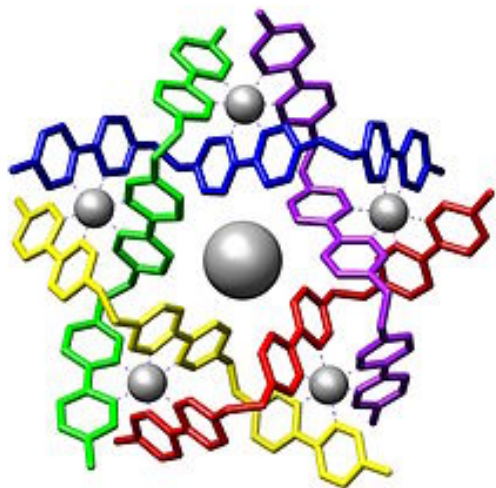




Supramolecular Chemistry and Molecular Self-Assembly

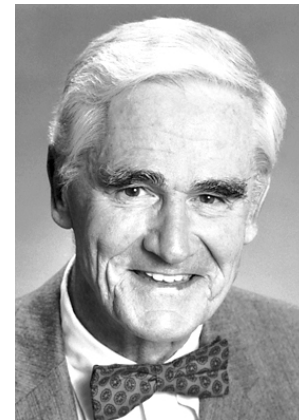
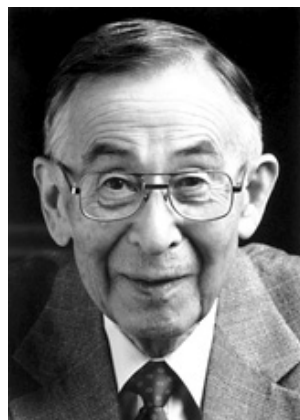
M2 – Ecole polytechnique - Université Paris-Saclay
France



Dr. Grégory Nocton, CNRS researcher
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Laboratoire de Chimie Moléculaire
Ecole polytechnique, CNRS
[greg.nocton@polytechnique .edu](mailto:greg.nocton@polytechnique.edu)

What is supramolecular chemistry?

Nobel prize in 1987: Lehn (Strasbourg), Pedersen (DuPont), Cram (UCLA)

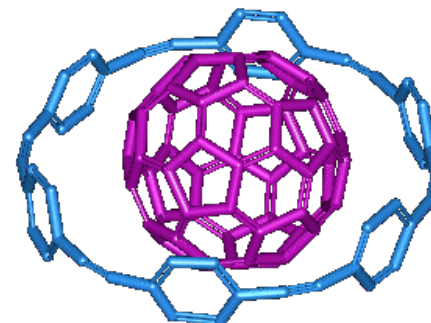
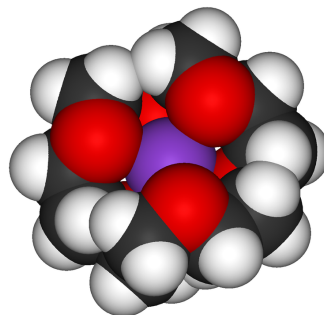
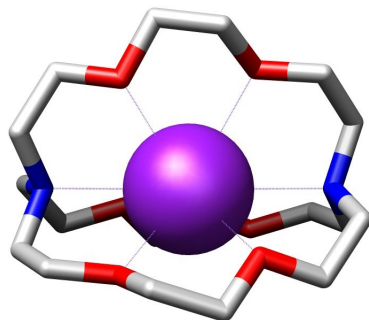


“Chemistry of molecular assemblies and of the intermolecular bond”

“The chemistry beyond the molecule”

Originally “Host-guest” chemistry

Now it contains a lot of different self assemblies (self organization)

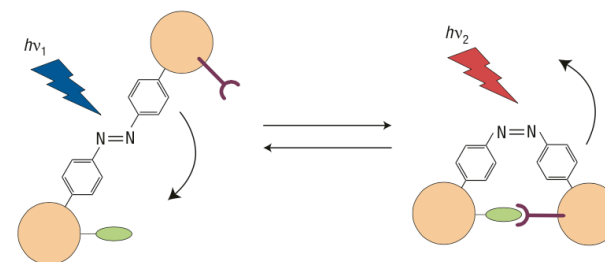
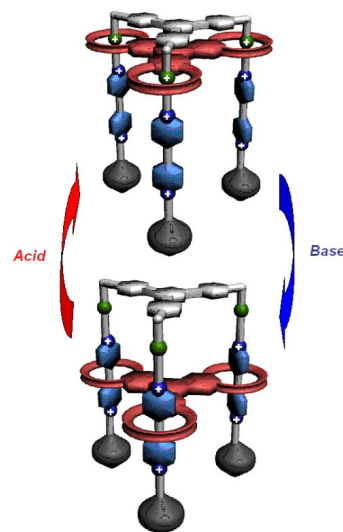
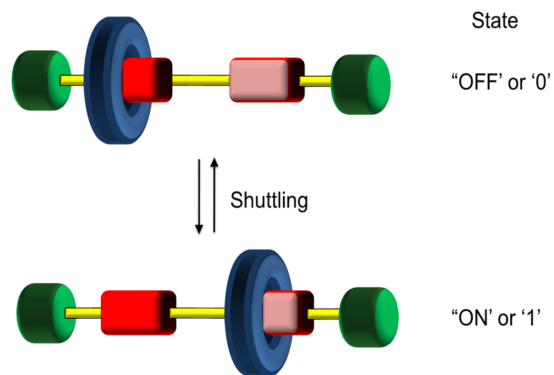


What is supramolecular chemistry?

Nobel prize in 2016: Sauvage (Strasbourg), Stoddart (Northwestern), Feringa (Croningen)



“Molecular Machines”



Outline

1. Thermodynamic and kinetic aspects
2. Calyxarenes, dendrimers and other examples
3. Supramolecular chemistry in diagnosis and therapeutic chemistry
4. Supramolecular chemistry in the environment
5. Discussion

What is Supramolecular Chemistry: Host-Guest Chemistry, Lehn's definition

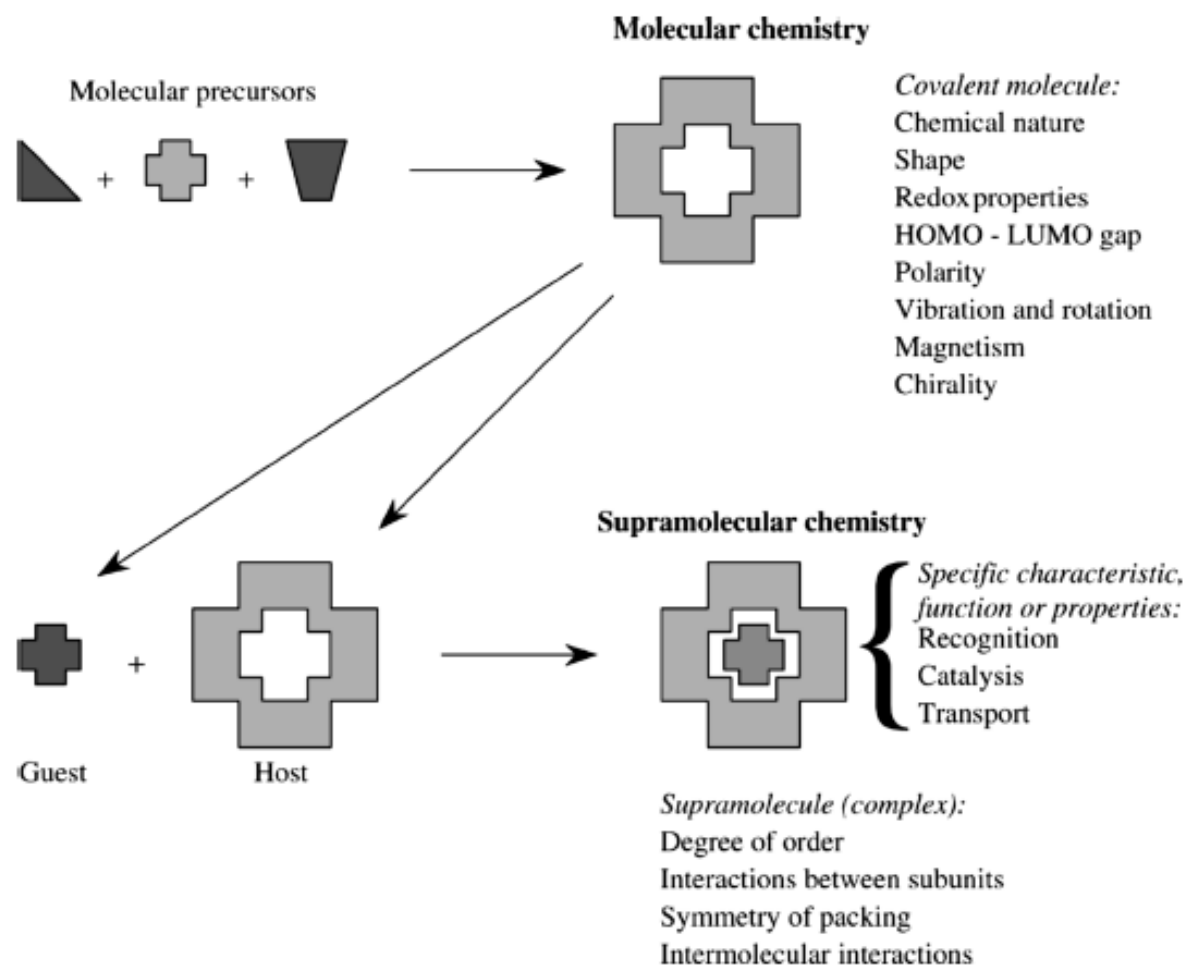
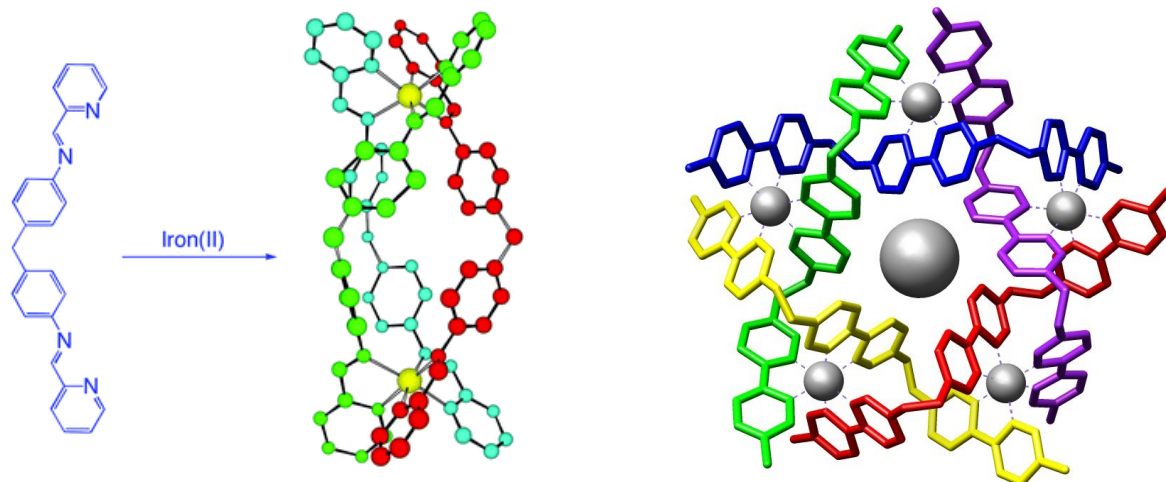
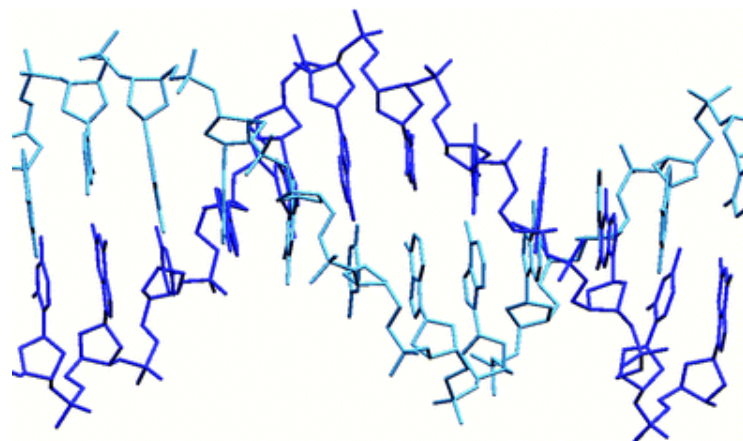


Figure 1.1 Comparison between the scope of molecular and supramolecular chemistry according to Lehn.¹

Thermodynamic and Kinetic Aspects in Supramolecular Chemistry



Supramolecular assembly...
Coordination complex?



Hydrogen bonding
Other forces? Which ones?
Can we quantify them?

Hannon, M. J. *Chem. Soc. Rev.*, **2007**, 36, 280

The historical context

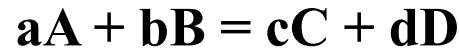
(See DC lecture)

The fun part

The thermodynamics
(the numbers, equations...)

The sad part?

Some Basics: Remember Solution Chemistry?



$$K_{eq} = \frac{(a_C)^c \cdot (a_D)^d}{(a_A)^a \cdot (a_B)^b} \quad \text{and} \quad a_i = \gamma_i [i]$$

$$K'_{eq} = \frac{(\gamma_C)^c \cdot (\gamma_D)^d}{(\gamma_A)^a \cdot (\gamma_B)^b} \times \frac{[C]^c \cdot [D]^d}{[A]^a \cdot [B]^b}$$

γ_i is the deviation to the ideality

$$\log \gamma_{\pm} = -|z^+ z^-| A \sqrt{I}$$

$$\gamma_{\pm} = (\gamma_+^p - \gamma_-^q)^{\frac{1}{p+q}}$$

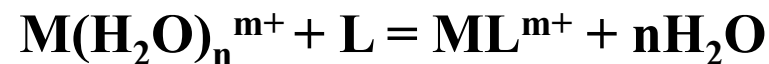
$$I = \frac{1}{2} \sum_i z_i^2 [i]$$

Experimentally, the ionic force and the temperature are fixed

The value of K_{eq} is given within this framework

The Binding Constant of a Ligand

This is defined by the equilibrium constant for the reaction shown below:

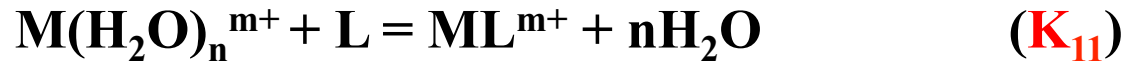


$$K = \frac{[ML^{m+}]}{[M(H_2O)_n^{m+}] \cdot [L]}$$

Guest	Host	Solvent	K_{11}/M^{-1}	$\Delta G^\circ/kJ\ mol^{-1}$
Na ⁺	ClO ₄ ⁻	H ₂ O	3.2	-3
Iodine	Hexamethylbenzene	CCl ₄	1.35	-0.8
Tetracyanoethylene	Hexamethylbenzene	CH ₂ Cl ₂	17	-7.1
7,7,8,8-Tetracyanoquinodimethane	Pyrene	CH ₂ Cl ₂	0.94	~0.0
Salicylic acid	Caffeine	H ₂ O	44	-9.7
Hydrocortisone	Benzoate ion	H ₂ O	2.9	-2.5
Methyl <i>trans</i> -cinnamate	Imidazole	H ₂ O	1.0	0.0
<i>p</i> -Hydroxybenzoic acid	α -Cyclodextrin	H ₂ O	1130	-17.6
Caffeine	Caffeine	H ₂ O	19	-7.1
Phenol	Dimethylformamide	C ₆ H ₆	442	-15.0
K ⁺	[18]crown-6	H ₂ O	100	-11.4
K ⁺	[18]crown-6	Methanol	10 ⁶	-34.2
K ⁺	[2.2.2]cryptand	Methanol	10 ¹⁰	-57.0
Fe ³⁺	enterobactin	H ₂ O	10 ⁵²	-296

The Binding Constant

If a sequential process involving the binding of more than one metal ion is involved, then two K can be measured for the complexes **1:1** and **2:1** complexes : **K₁₁** and **K₂₁**



$$K_{21} = \frac{[M_2L^{(2m)+}]}{[M(H_2O)_n^{m+}] \cdot [ML^{m+}]}$$

At this stage, we define an overall binding constant **β₂₁**

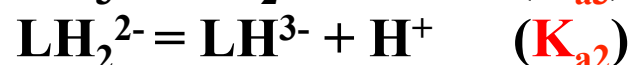
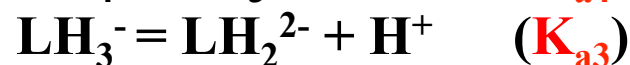
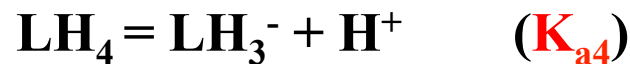
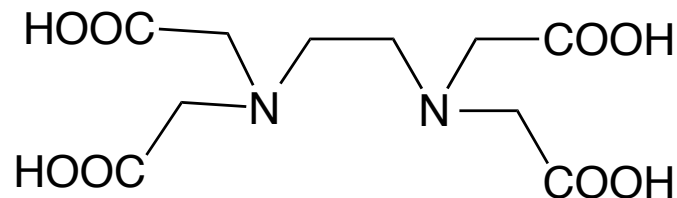
$$\beta_{12} = K_{11} \times K_{21}$$

$$\beta_{xn} = \frac{[M_xL_n]}{[M]^x [L]^n}$$

The Global Constant

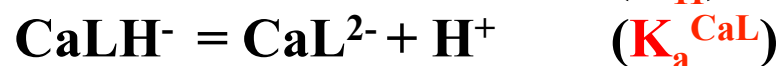
If we now consider the protonation constants...

Example, the EDTA ligand, LH_4



$$\text{pK}_a = -\log K_a: 2.0, 2.7, 6.1 \text{ and } 10.2$$

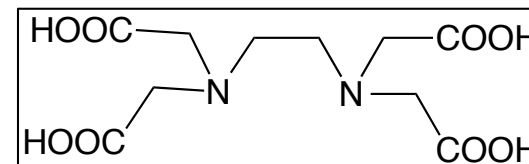
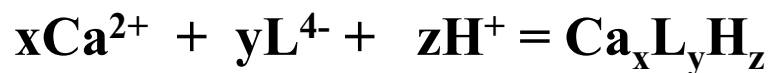
And its complex of Ca^{2+}



$$\text{pK}_a^{\text{CaL}} = 3.2$$

We need to define the global constant taking all these single reactions in consideration

The Global Constant

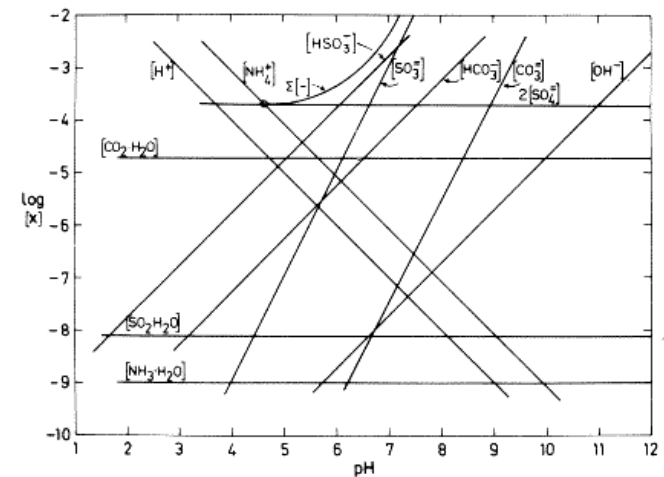
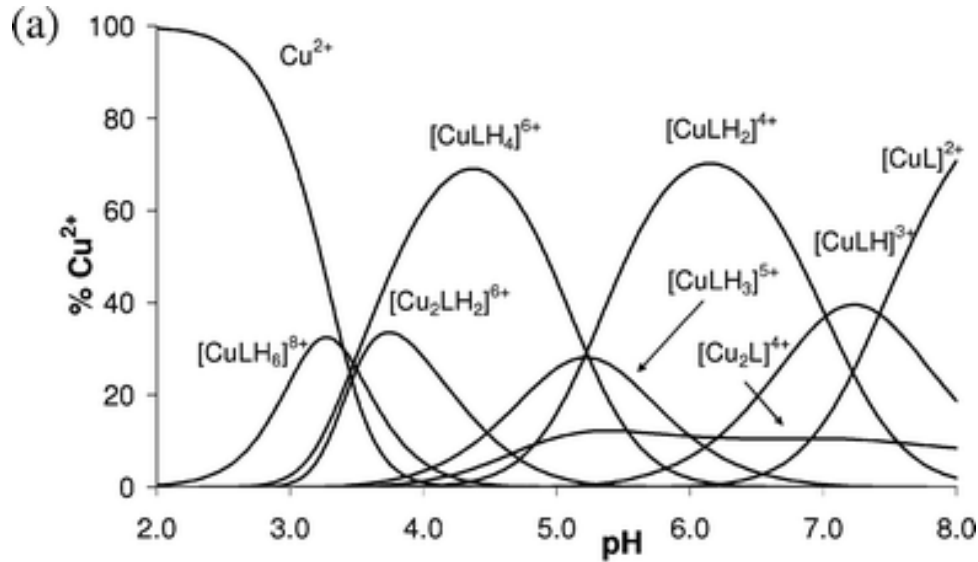
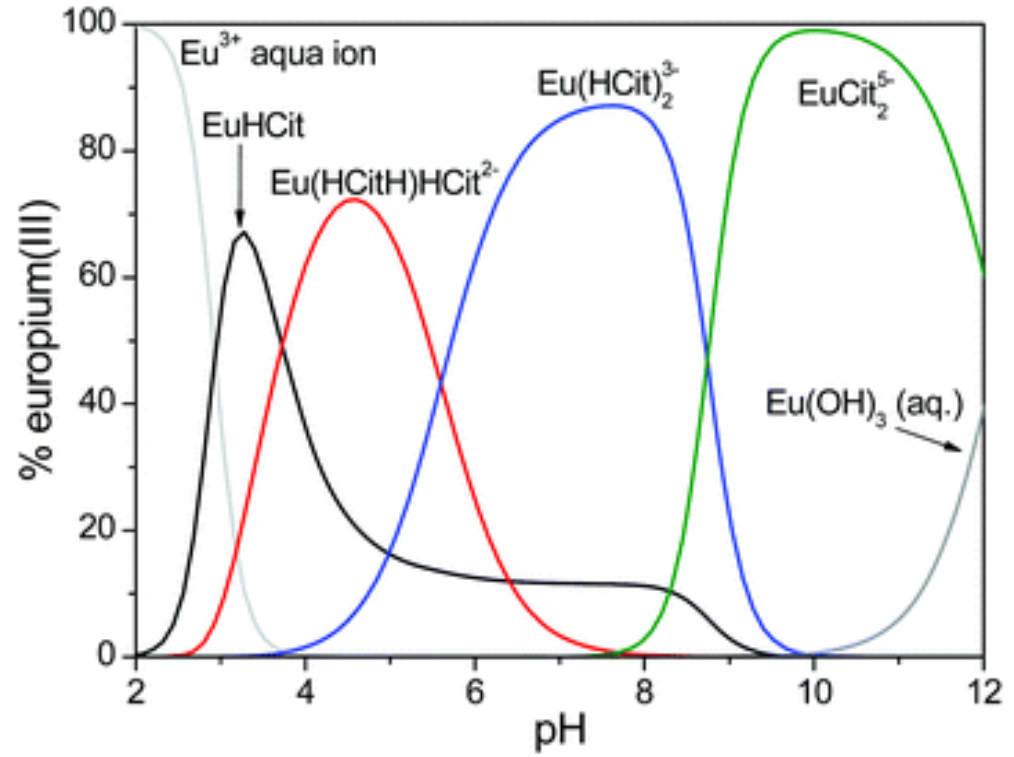
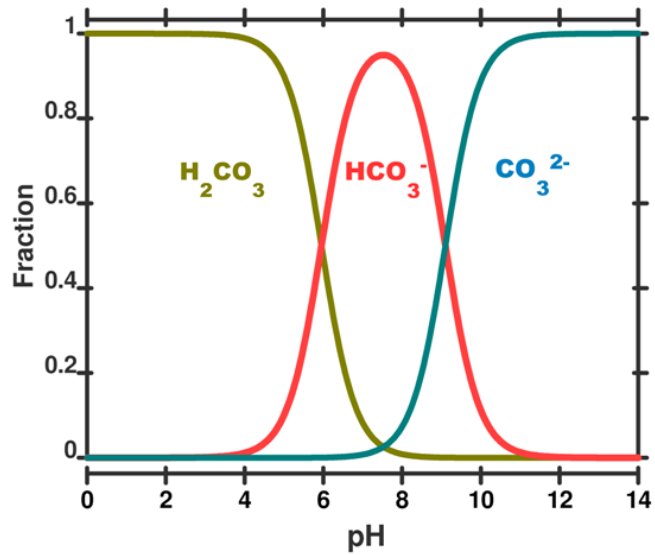


β_{011}	0	1	1	LH	$\log\beta_{011} = \text{pk}_{a1}$
β_{012}	0	1	2	LH ₂	$\log\beta_{110} = K$
β_{013}	0	1	3	LH ₃	$\log\beta_{111} = \text{pk}_a^{\text{CaL}}$
β_{014}	0	1	4	LH ₄	$\beta_{111} = \beta_{110} \cdot \frac{1}{K_a^{\text{CaL}}}$
β_{110}	1	1	0	CaL	$\text{pk}_a^{\text{CaL}} = \log\beta_{111} - \log\beta_{110}$
β_{111}	1	1	1	CaLH	
β_{00-1}	0	0	-1	OH ⁻	$\text{H}_2\text{O} = \text{OH}^- + \text{H}^+ \quad \text{pk}_e = 13.78$
β_{10-1}	1	0	-1	Ca(OH)	} Hydroxos formation
β_{11-1}	1	1	-1	CaL(OH)	

β_{10-1} is the deprotonation of one water molecule attached to the metal center:
acidity of the cation

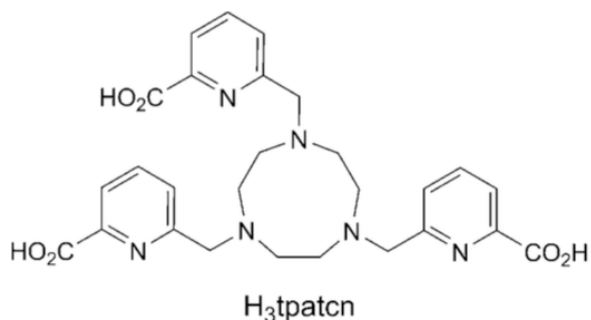
β_{11-1} is the hydrolysis of the complex

Speciation Diagrams



Measurements of Binding Constants

- Potentiometric titration



- Determining all the successive pK_a of the ligand: Use of a software (*HYPERQUAD*)

- Determining the pM of the metal adding the pK_a value in the fit.

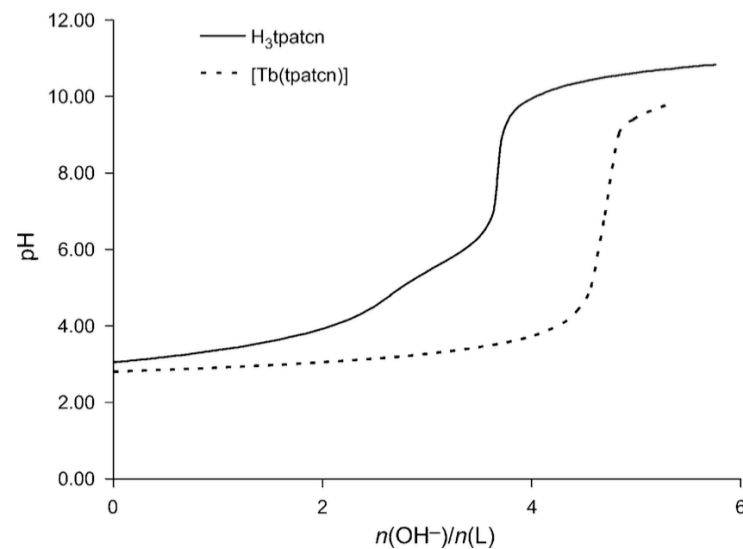
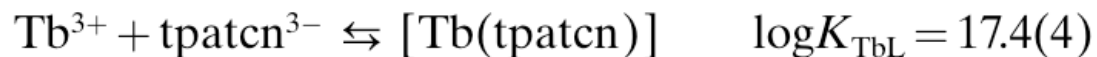


Fig. 3. Normalized titration curves (pH vs. $n(OH^-)/n(tpatcn^{3-})$) for $H_3tpatcn$ (0.75 mM) and $[Tb(tpatcn)]$ solns. ($H_3tpatcn = 0.38$ mM, $Tb = 0.38$ mM)



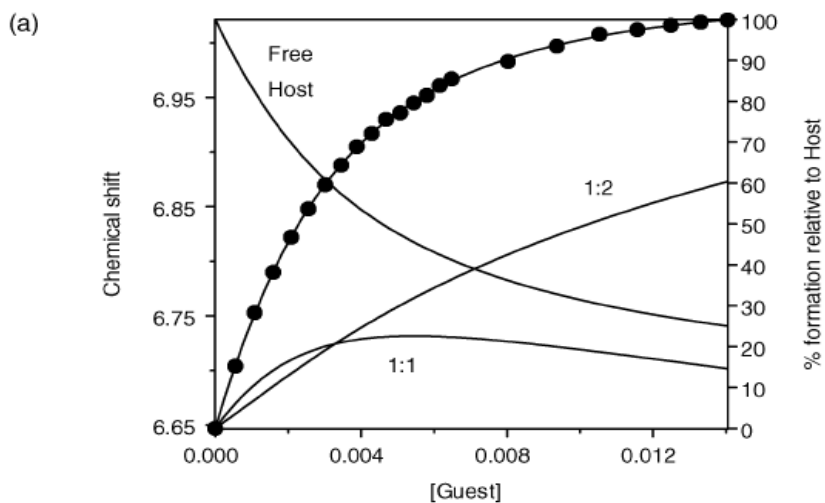
Nocton et al. *Helvetica Chem. Acta*, 2009, 92, 2257

Precise measurements but very long ... one needs a couple of weeks to get the data

With very high β value, one need to perform competitive titrations

Measurements of Binding Constants

- NMR titration



$$\delta_{calc} = \sum_{m=1}^{m=i} \sum_{n=0}^{n=j} \frac{\delta_{mn} \beta_{mn} m [G]^m [H]^n}{[G]_{total}}$$

Again a computer program helps fitting the data to give

β_{11} and β_{12} .

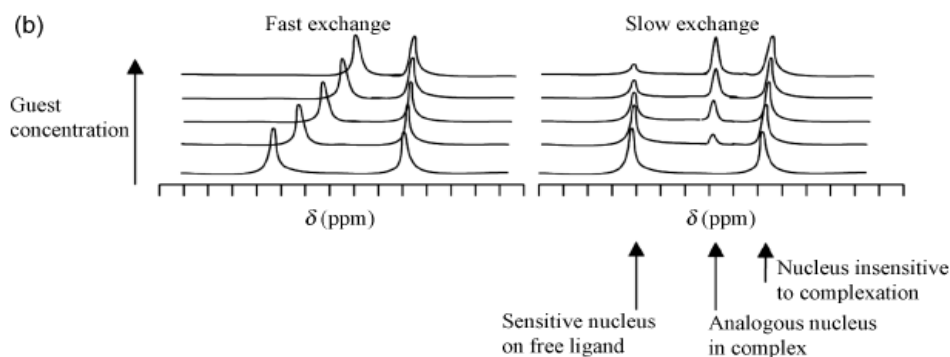


Figure 1.4 (a) NMR titration plot (isotherm) and corresponding speciation plots for a system undergoing fast equilibration on the NMR time scale, with $\log \beta_{11} = 2.3$ and $\log \beta_{12} = 4.5$. (b) Schematic NMR spectra of slowly equilibrating mixtures of free host, guest and host-guest complex.

Measurements of Binding Constants

- Method of continuous variation (Job plots)

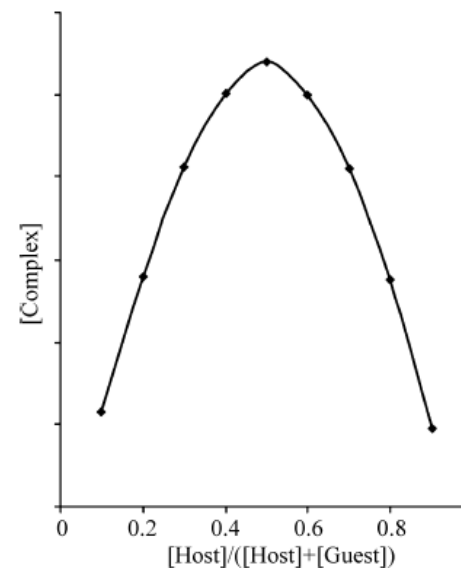
Monitoring the variation of concentration of the host-guest complex in these samples allows a plot of [Complex] vs. [Host]/([Host] + [Guest]) to be constructed

[Complex] \propto $\Delta\delta$ X mole fraction of host

- Fluorescence titration

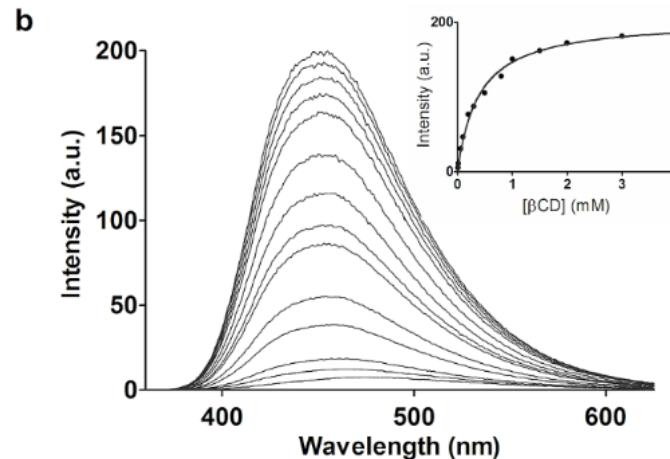
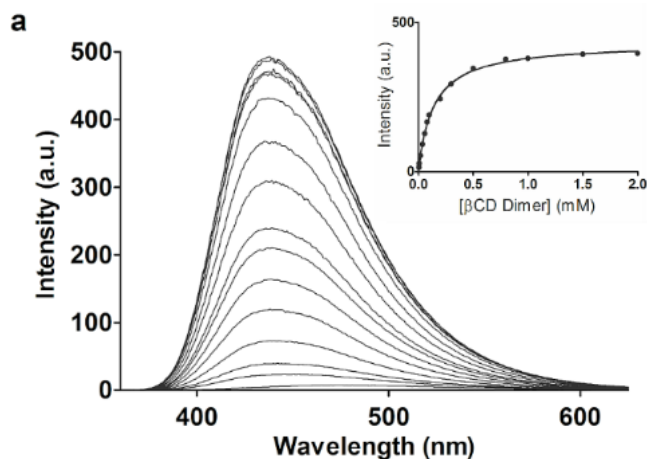
$$F = k_G [G] + k_{11} [HG] \quad F_0 = k_G^0 [G]_{total}$$

$$\frac{F}{F_0} = \frac{k_G / k_G^0 + (k_{11} / k_G^0) K_{11} [H]}{1 + K_{11} [H]}$$



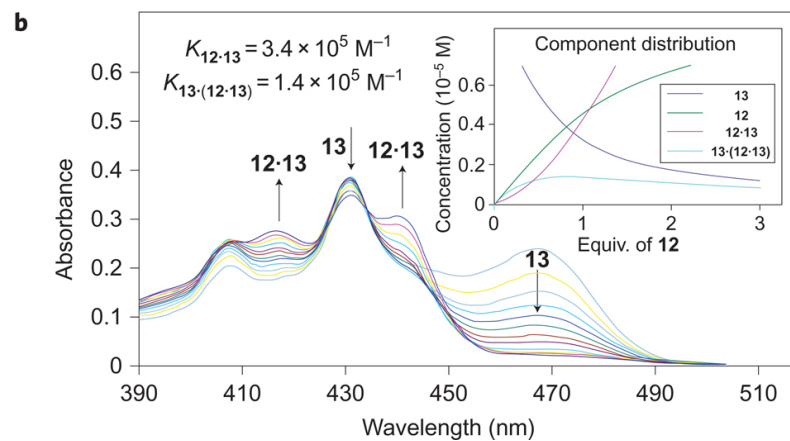
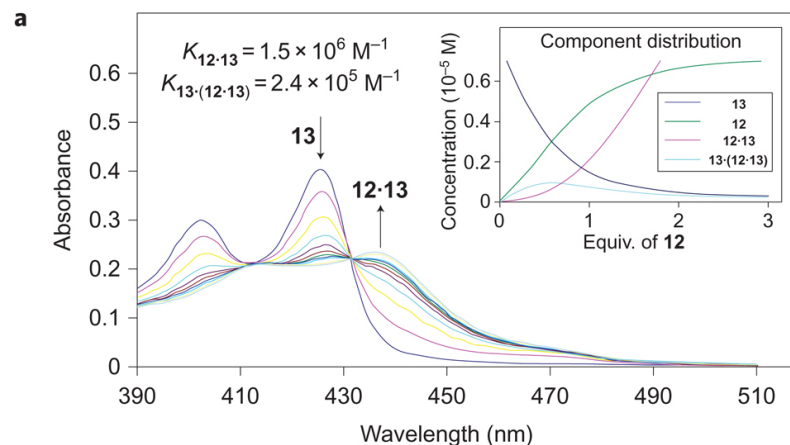
Job plot of a 1:1 complex

Städe, L. W. *et al. Beilstein J. Org. Chem.* **2015**, *11*, 514



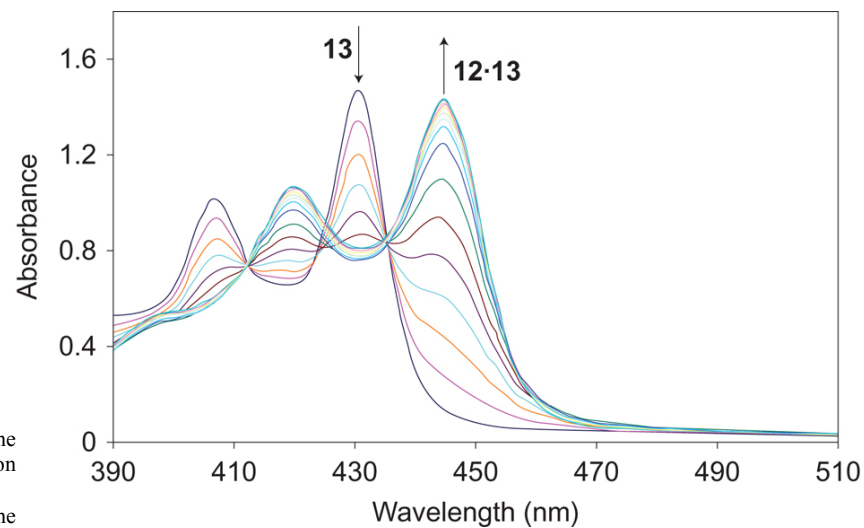
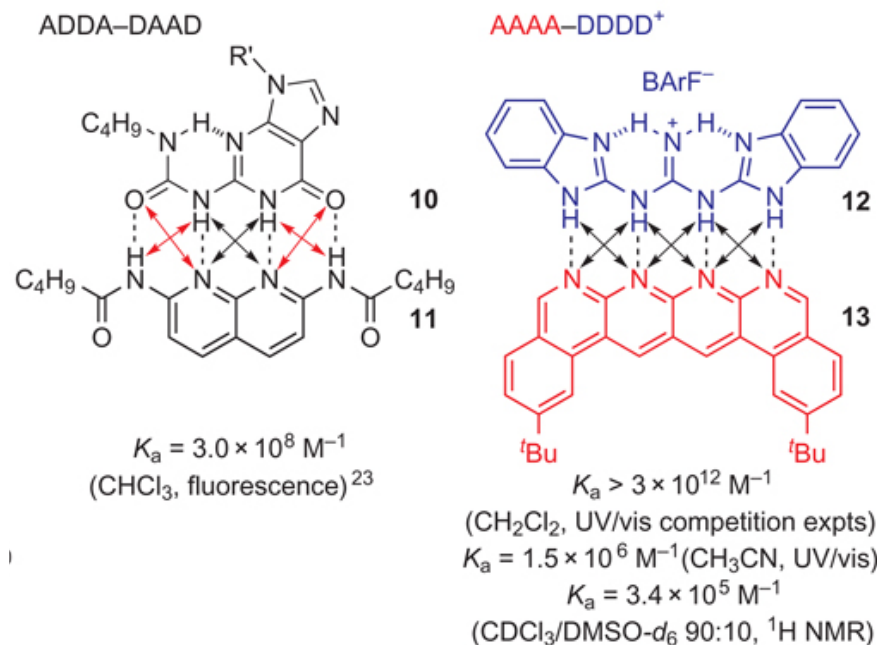
Measurements of Binding Constants

- UV-Vis Spectrophotometric titration



a, UV/vis spectra of 13 ($8 \times 10^{-6} \text{ M}$) following addition of 12 (0 to 5 equiv.), while maintaining the concentration of 13 constant, in CH_3CN at 298 K. Component distribution over the course of the titration experiment is also illustrated (inset).

b, UV/vis spectra of 13 ($1 \times 10^{-5} \text{ M}$) following addition of 12 (0 to 4.5 equiv.), while maintaining the concentration of 13 constant, in a solution of 10% DMSO in CHCl_3 at 298 K.



Measurements of Binding Constants

- Calorimetric titration (Isothermal titration calorimetry ITC)

Evaluation of the heat (enthalpy) evolved from a carefully insulated sample as a function of added guest or host concentration

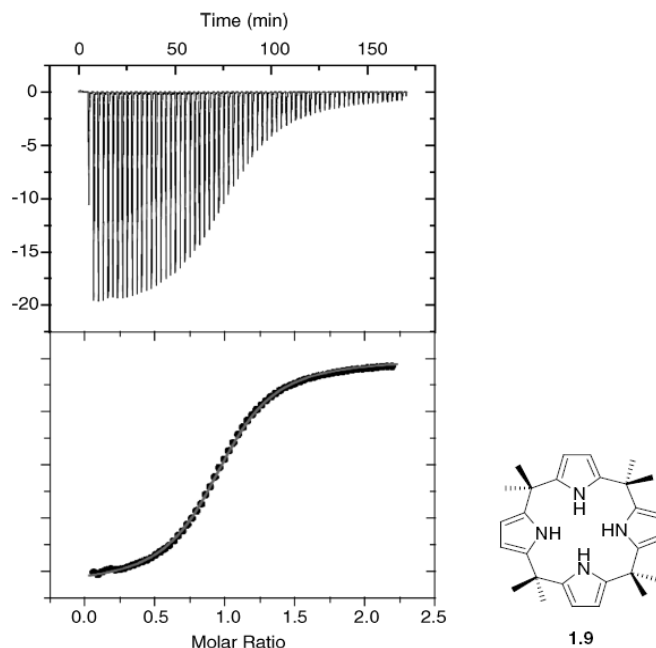


Figure 1.7 ITC data at 25 °C for the binding of $\text{NBu}_4^+\text{Cl}^-$ by **1.9** in nitromethane – the top plot represents the raw data with the calorimetric response in $\mu\text{cal s}^{-1}$ for each addition of $\text{NBu}_4^+\text{Cl}^-$ while the lower plot is the titration isotherm fitted to a 1:1 model with kcal per mol $\text{NBu}_4^+\text{Cl}^-$ added vs. mole ratio of $\text{NBu}_4^+\text{Cl}^-$ to **1.9**. (Reproduced with permission from [8] © 2006, American Chemical Society).

- Extraction experiments

The distribution (or partition) coefficient, K_d , of a metal cation between an aqueous (aq.) and organic phase (org.) may also allow determination of constants.

On need to measure the extraction coefficient and the distribution coefficient.

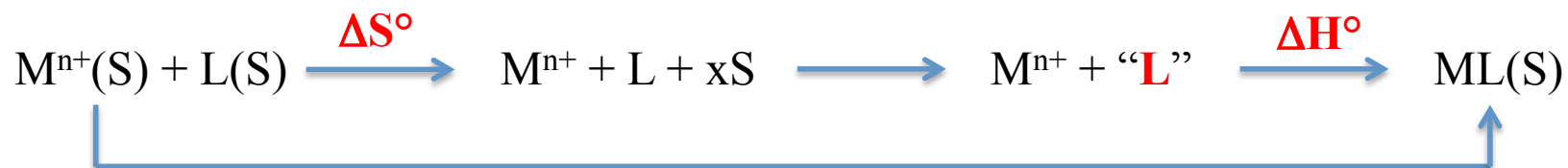
Enthalpy and Entropy Contributions

- **Solvent effect:** removing a solvent molecule
 - $\Delta H^\circ > 0$ **not favorable**
 - $\Delta S^\circ > 0$ **favorable**

Note that $\Delta H^\circ_{\text{water}} \gg 0$ because water is highly ordered
It is less in other solvents (pyridine, dmsO, CH_3CN)

The ligand plays a role in its ability to give electron (donating ability)
If the donating ability is large, **the enthalpy is larger**

- **Ligand rearrangement (see macrocyclic effect)**
 - $\Delta H^\circ > 0$ **not favorable**
 - $\Delta S^\circ < 0$ **not favorable**
- **Association**
 - $\Delta H^\circ < 0$ **favorable**
 - $\Delta S^\circ < 0$ **not favorable**



Cooperativity and the Chelate Effect

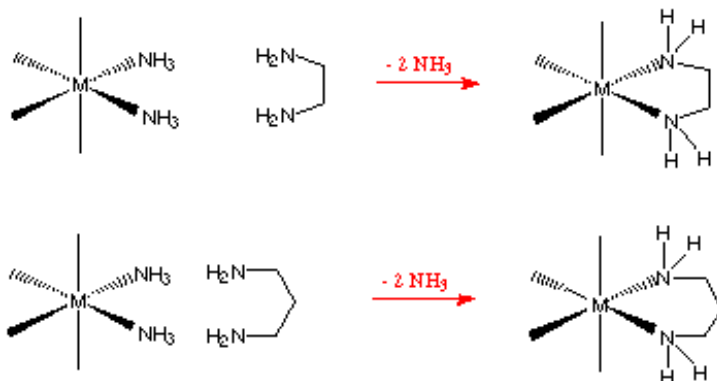
When two or more binding sites (A and B) on a host cooperate so that the interaction of a whole system is synergetically greater than the sum of the parts, we talk about cooperativity. We should consider **positive** but also **negative** effects.

$$\Delta G_{AB}^0 = \Delta G_A^i + \Delta G_B^i + \Delta G^S$$

$$\Delta G_A^i = \Delta G_{AB}^0 - \Delta G_B^0$$

$$\Delta G^S = \Delta G_A^0 + \Delta G_B^0 - \Delta G_{AB}^0$$

Chelate effect



$$K_{eq} = \frac{[L_nM(en)] \cdot [NH_3]^2}{[L_nM(NH_3)_2] [en]} \quad \text{Chelate effect: } K \gg 1$$

Entropic effect

Statistical effect and kinetic effect (the binding of the second D is accelerated and a higher local concentration favor the binding because of local concentration)

Cooperativity and the Chelate Effect

Chelate effect and flexibility

Chelate effect is highly dependent of the size of chelate ring

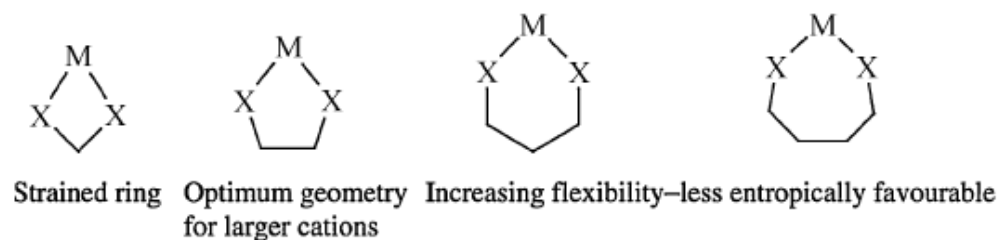
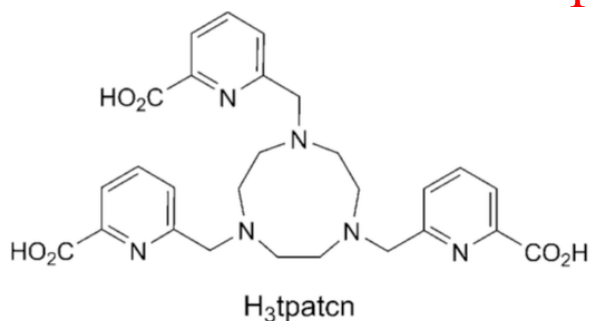


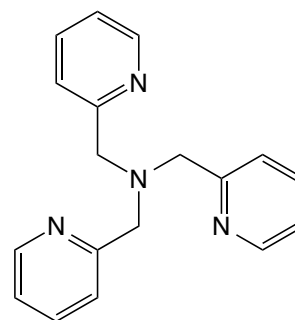
Figure 1.8 Ring size dependence of the stabilisation offered by the chelate effect.

It is related to the statistical likelihood to have donor pointing at the metal

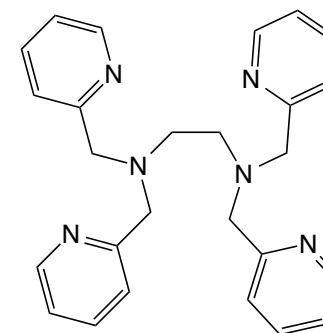
Podant ligands: examples of positive cooperativity



Nocton et al. *Helvetica Chem. Acta*, **2009**, 92, 2257



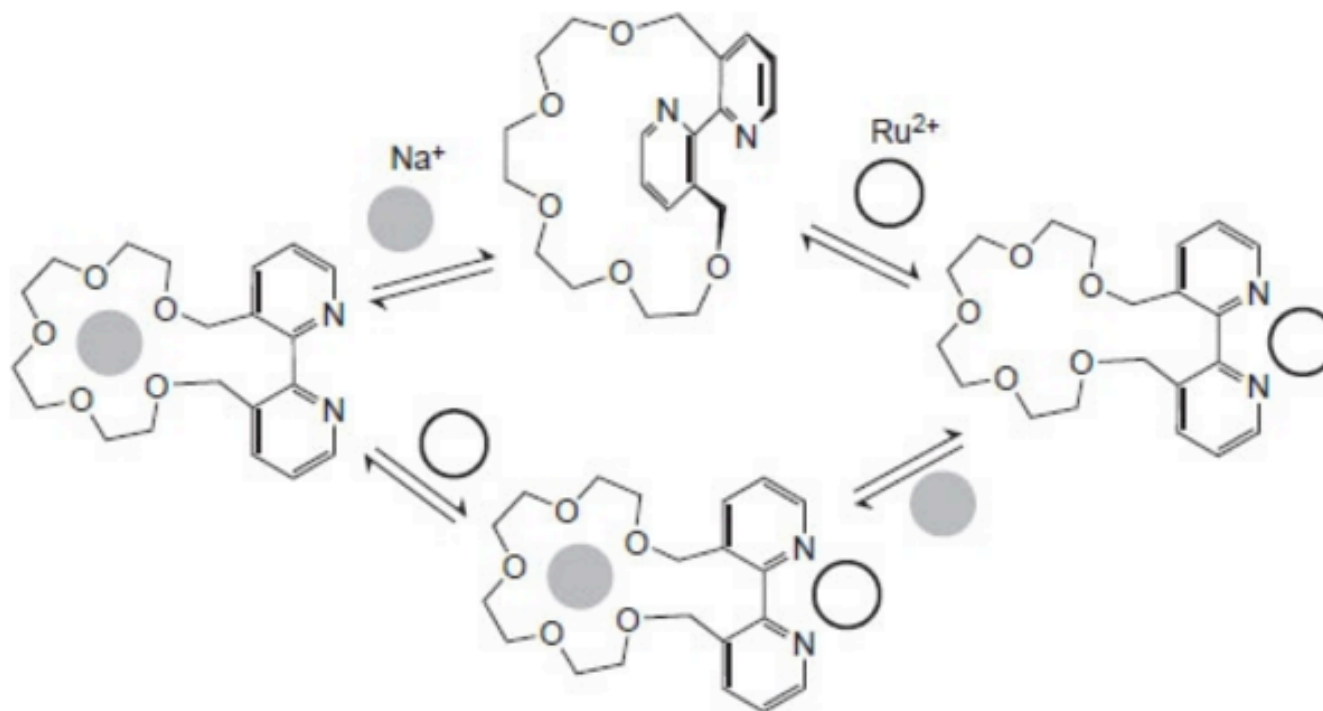
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Cooperativity and the Chelate Effect

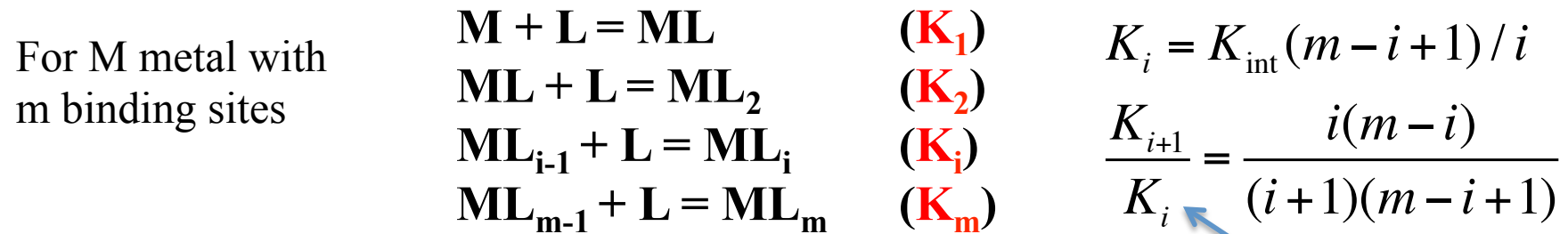
Cooperativity in cases where the binding of a first guest influences the affinity of a host for a second guest at a remote site is termed *allosteric effect*



Allosteric enhancement of Na⁺ binding by preorganization of the polyether binding site by Ru(II) and *vice versa*.

Cooperativity and the Chelate Effect

Cooperativity may be recognized by the deviation from well-defined statistical relationship



r is the **occupancy**: average number of occupied binding site on M (bond site / total sites)

Measure of cooperativity

$$r = \frac{mK_{\text{int}} [L]}{1 + K_{\text{int}} [L]} \quad \text{If non-cooperative system}$$

Scatchard and Hill equations

$$\frac{r}{[L]} = -K_{\text{int}} r + mK_{\text{int}}$$

$$\log \left(\frac{r}{m-r} \right) = \log [L] + \log K_{\text{int}}$$

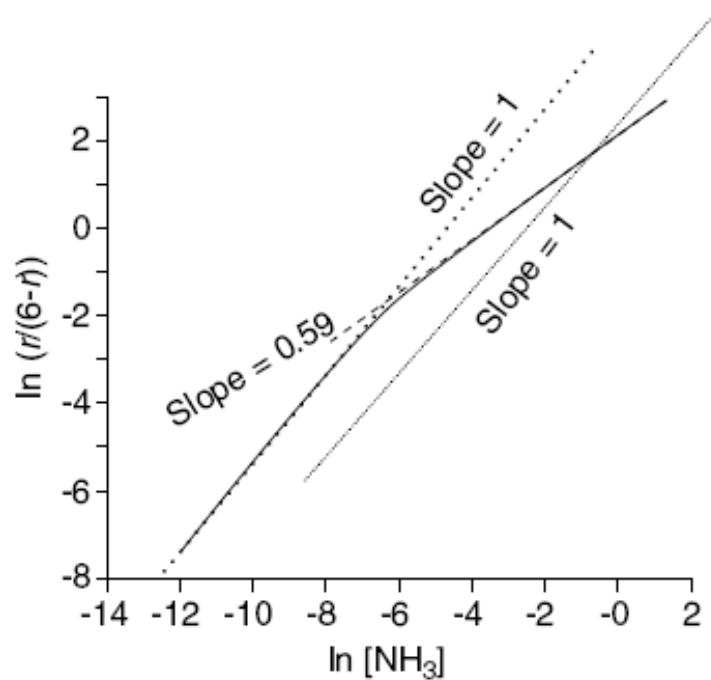
Cooperativity and the Chelate Effect

Scatchard and Hill equations

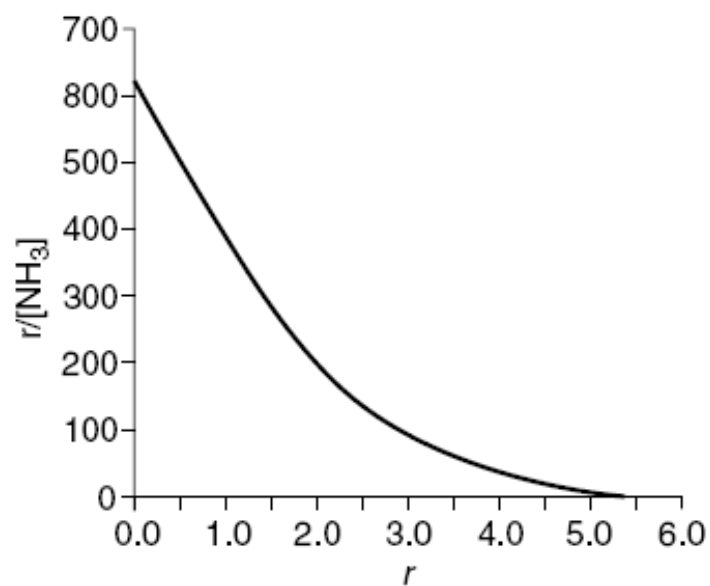
Only valid for intramolecular processes

$$\frac{r}{[L]} = -K_{\text{int}}r + mK_{\text{int}}$$

$$\log\left(\frac{r}{m-r}\right) = \log[L] + \log K_{\text{int}}$$



(a)



(b)

Figure 1.10 (a) Hill plot and (b) Scatchard plot for the successive intermolecular connections of ammonia to bivalent nickel to give $[\text{Ni}(\text{NH}_3)_i]^{2+}$, the concentration of the free ligand $[L]$ is computed by using the known stability constants. $[\text{Ni}]_{\text{total}} = 1 \times 10^{-3} \text{ M}$; $[\text{NH}_3]_{\text{total}}$ varies between 10^{-5} and 1 M. (Reproduced from [12] by permission of the Royal Society of Chemistry).

Preorganization and Complementarity

Cram, D. *Angew. Chem. Int. Ed.*, 1986, 25, 1039

Macrocyclic effect

Organization of the binding sites prior to guest binding: *preorganization*

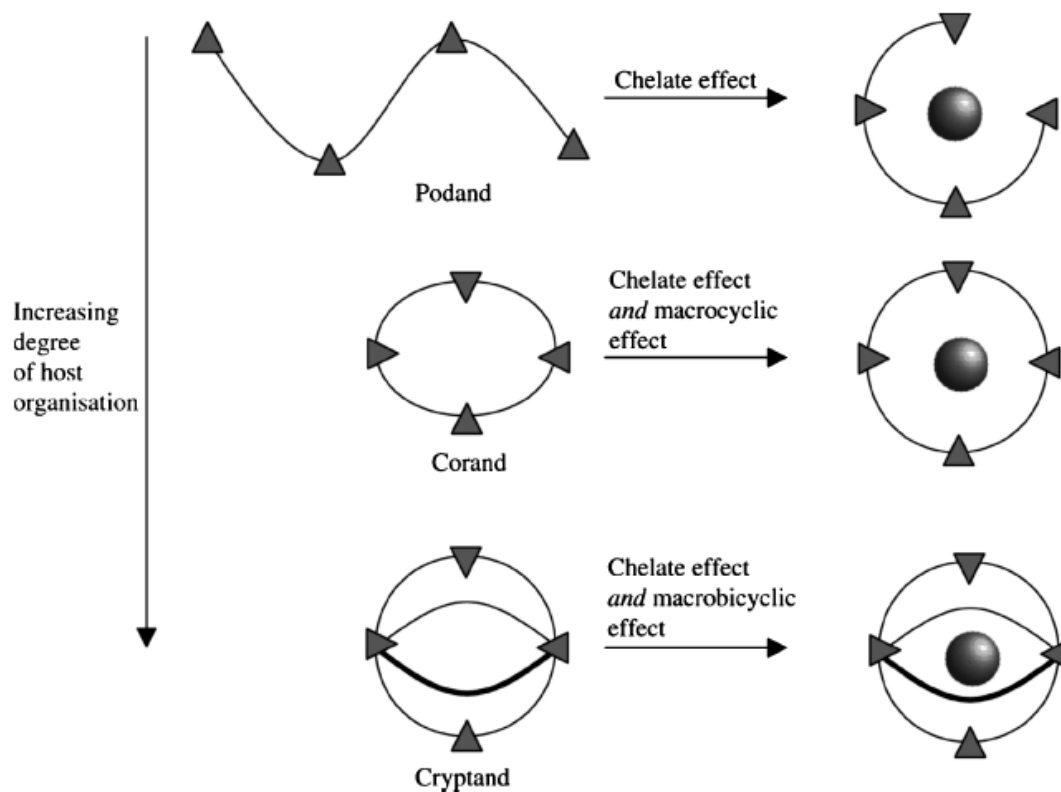


Figure 1.11 The chelate, macrocyclic and macrobicyclic effects.

The corollary of preorganization **is in the guest binding kinetics**. Rigidly preorganized host may have significant difficulties in passing through a complexation transition state.

Preorganization and Complementarity

Macrocyclic effect: *complementarity*

In order to bind, a host must have binding sites that are of the correct electronic character (polarity, hydrogen bond/donor acceptor ability, hardness or softness)

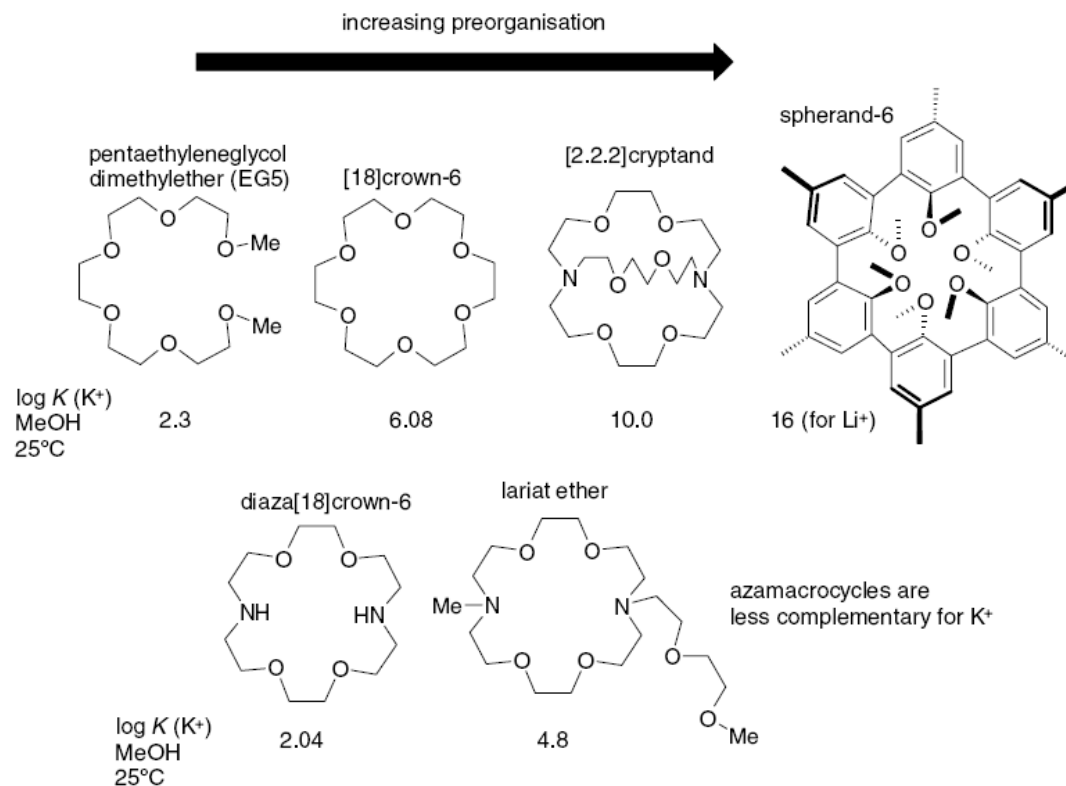
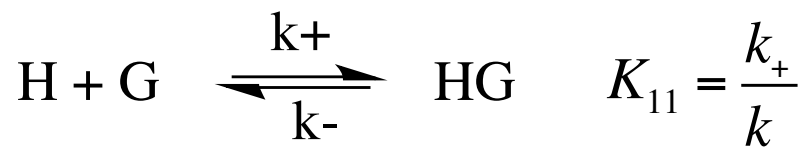


Figure 1.12 Comparison of the effects of preorganisation and complementarity on the magnitudes of the binding constant of polyether hosts for alkali metal cations. The figure for Li⁺ is given for the highly preorganised spherand-6 since it is too small to accommodate K⁺.

“To complex, host must have binding sites which cooperatively contact and attract binding sites of guest without generating strong nonbonded repulsion”

Thermodynamic and Kinetic Selectivity and Discrimination



$$\textit{selectivity} = \frac{K_{\text{guest}1}}{K_{\text{guest}2}}$$

$$\frac{d[\text{HG}]}{dt} = k_+ [\text{H}][\text{G}] - k_- [\text{HG}]$$

If concentration of host is in excess over the concentration of guest

$$k_{\text{obs}} = k_+ [\text{H}] + k_-$$

For a 1:1 complex

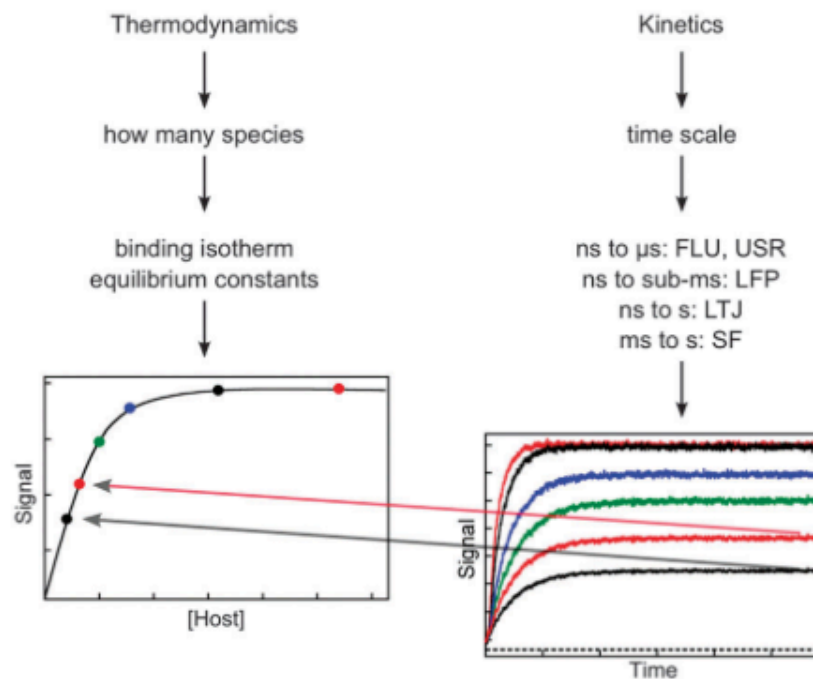


Fig. 3 Considerations for the experimental design based on thermodynamic and kinetic studies. The amplitude of the kinetic studies at increasing concentrations of host (from the bottom to top in the right hand graph) has to fall onto the binding isotherm determined in thermodynamic studies (dots in left hand graph). The techniques for kinetic studies are:^{7,8} time-resolved fluorescence (FLU), ultrasonic relaxation (USR), laser flash photolysis (LFP), laser temperature jump (LTJ) and stopped-flow (SF).

Thermodynamic and Kinetic Selectivity and Discrimination

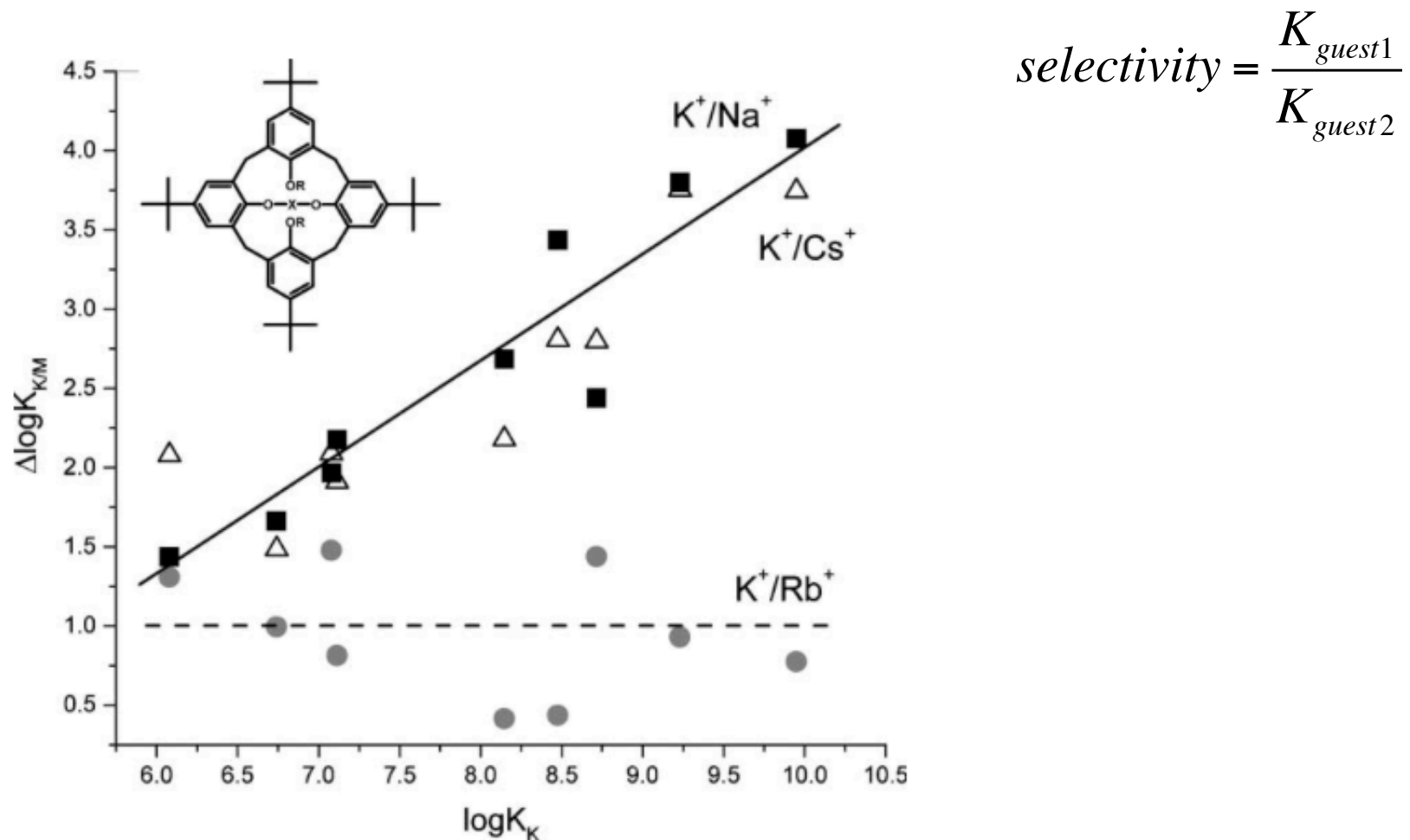
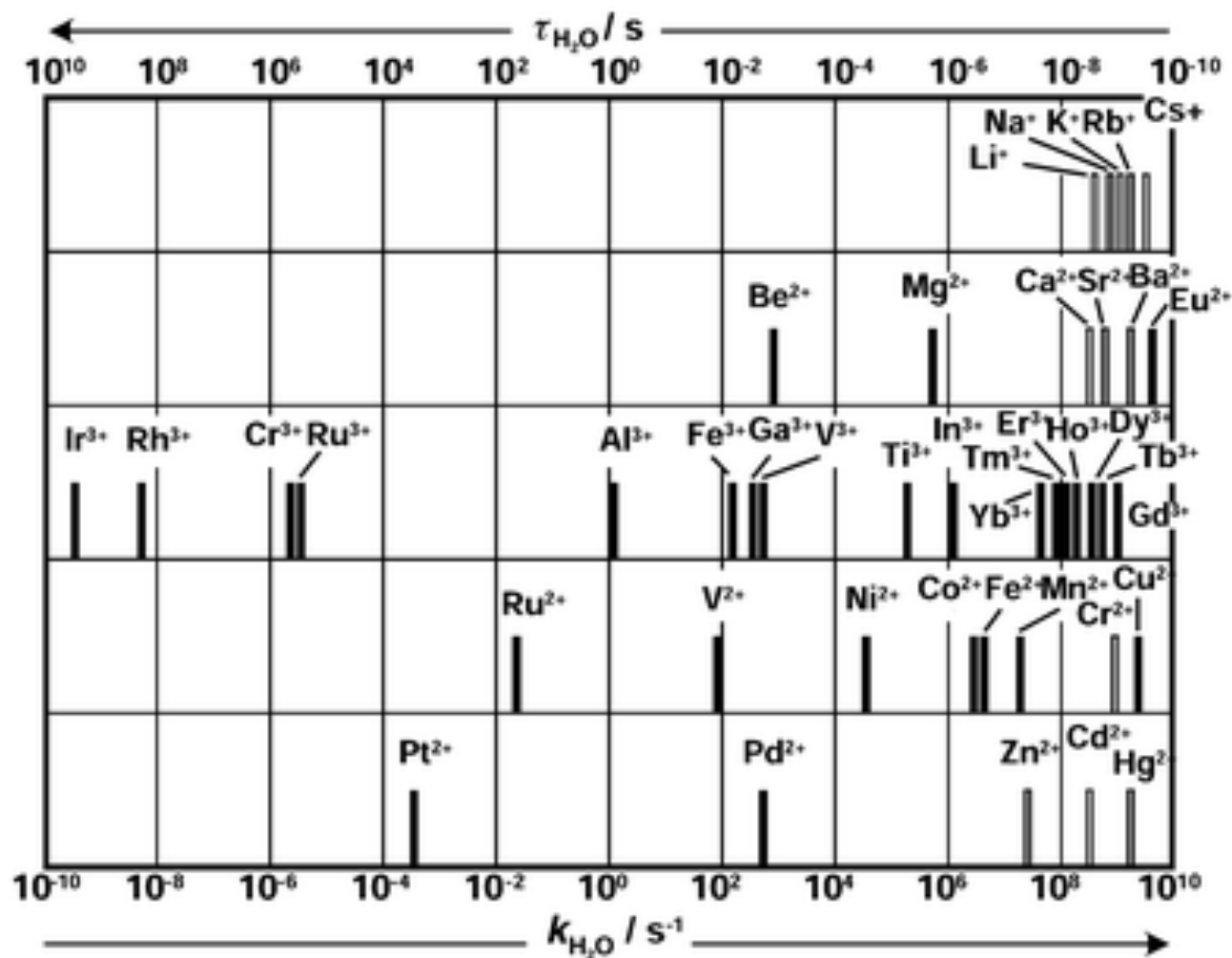


Fig. 3 Selectivity $\Delta \log K$ with calixarene-crown ether complexes ($X = \text{CH}_2\text{CH}_2(\text{OCH}_2\text{CH}_2)_n$, $n = 3$ or 4 , $R = \text{Me}$, Et , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$ or $\text{CH}_2\text{C}_6\text{H}_5$), for K^+ vs. Na^+ (squares), for K^+ vs. Cs^+ (triangles), and for K^+ vs. Rb^+ (circles); experimental data from ref. 12.

Thermodynamic and Kinetic Selectivity and Discrimination



Mean lifetimes of a single water molecule in the first coordination sphere of a given metal ion, τ_{H_2O} , and the corresponding water exchange rate constant k_{H_2O} .

Thermodynamic and Kinetic Selectivity and Discrimination

Crystal field activation energies

Dissociative, associative and interchange mechanism

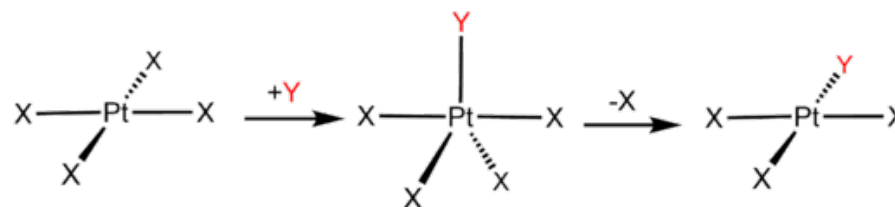
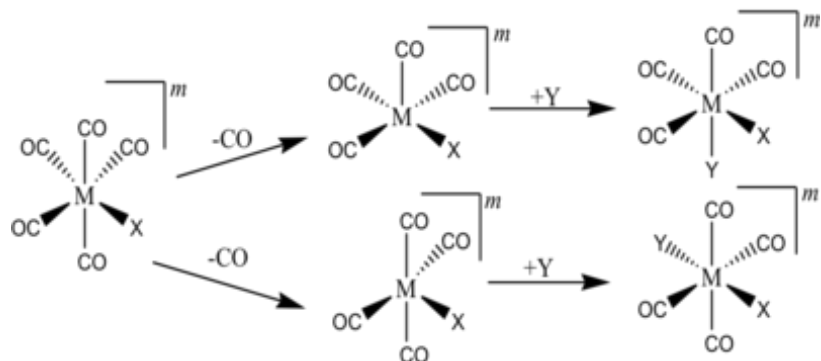


Table 3.7 Crystal field activation energies (in Dq) for dissociation mechanism
Octahedral \rightarrow square pyramid

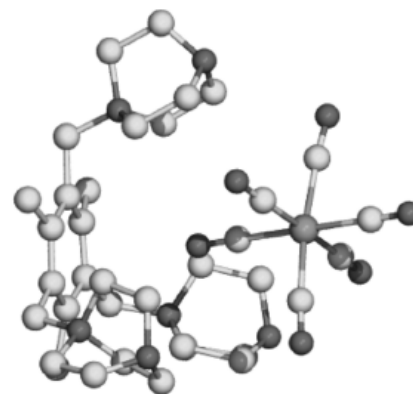
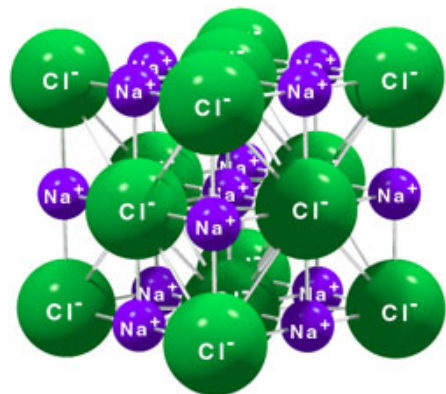
System	Strong Fields		C.F.A.E.	Weak Fields		C.F.A.E.
	Octa- hedral	Square Pyramid		Octa- hedral	Square Pyramid	
d^0	0	0	0	0	0	0
d^1	4	4.57	-0.57	4	4.57	-0.57
d^2	8	9.14	-1.14	8	9.14	-1.14
d^3	12	10.00	2.00	12	10.00	2.00
d^4	16	14.57	1.43	6	9.14	-3.14
d^5	20	19.14	0.86	0	0	0
d^6	24	20.00	4.00	4	4.57	-0.57
d^7	18	19.14	-1.14	8	9.14	-1.14
d^8	12	10.00	2.00	12	10.00	2.00
d^9	6	9.14	-3.14	6	9.14	-3.14
d^{10}	0	0	0	0	0	0

Table 3.8 Crystal field activation energies (in Dq) for displacement mechanism
Octahedral \rightarrow pentagonal bipyramid

System	Strong Fields		C.F.A.E.	Weak Fields		C.F.A.E.
	Octa- hedral	Pentagonal Bipyramid		Octa- hedral	Pentagonal Bipyramid	
d^0	0	0	0	0	0	0
d^1	4	5.28	-1.28	4	5.28	-1.28
d^2	8	10.56	-2.56	8	10.56	-2.56
d^3	12	7.74	4.26	12	7.74	4.26
d^4	16	13.02	2.98	6	4.93	1.07
d^5	20	18.30	1.70	0	0	0
d^6	24	15.48	8.52	4	5.28	-1.28
d^7	18	12.66	5.34	8	10.56	-2.56
d^8	12	7.74	4.26	12	7.74	4.26
d^9	6	4.93	1.07	6	4.93	1.07
d^{10}	0	0	0	0	0	0

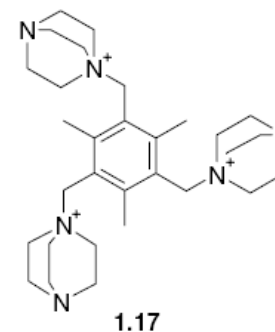
Nature of Supramolecular Interactions

- Ion – Ion interactions, bond energy 20-75 kcal.mol⁻¹



(b) Fe(CN)₆³⁺

$$E = \frac{q^+ q^-}{\epsilon r}$$

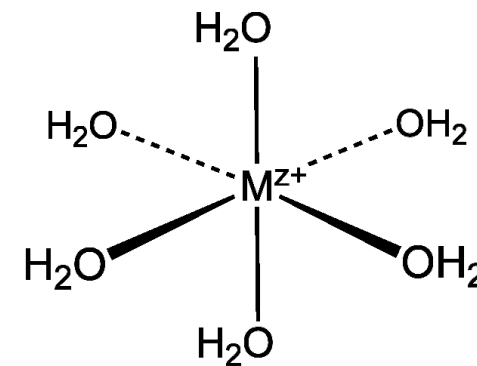
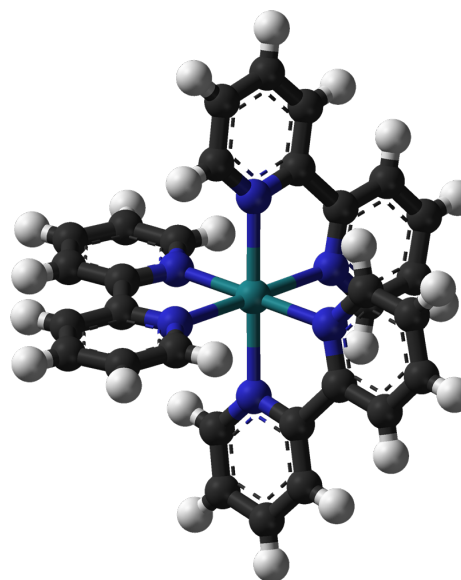
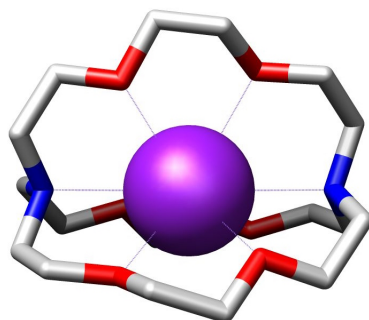


- Ion – Dipole interactions

Bond energy 12-50 kcal.mol⁻¹

Interaction with a polar molecule

$$E = \frac{q^+ \mu}{\epsilon r^2}$$



Garratt, P. J. *Tetrahedron*, 1998, 54, 949

Nature of Supramolecular Interactions

- **Dipole – Dipole interactions,**
Bond energy: 5 kcal.mol⁻¹

$$E = \frac{2\mu_1\mu_2}{\epsilon r^3}$$

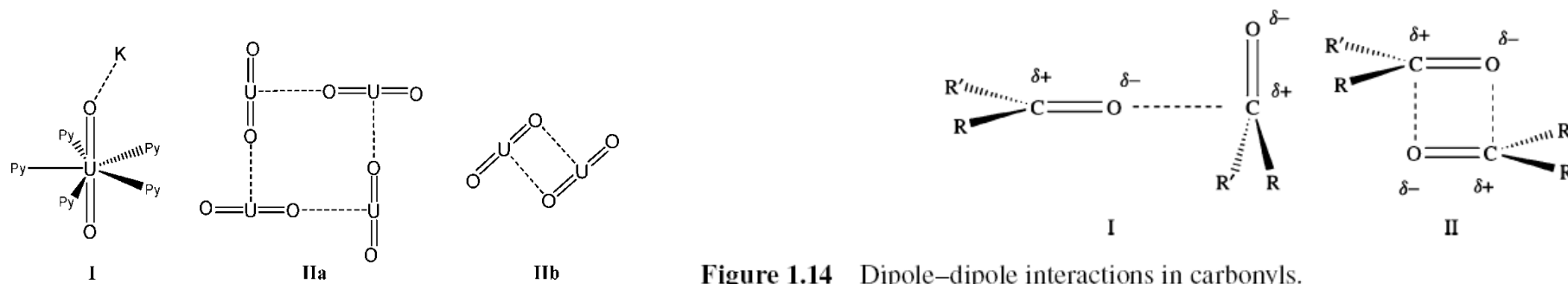
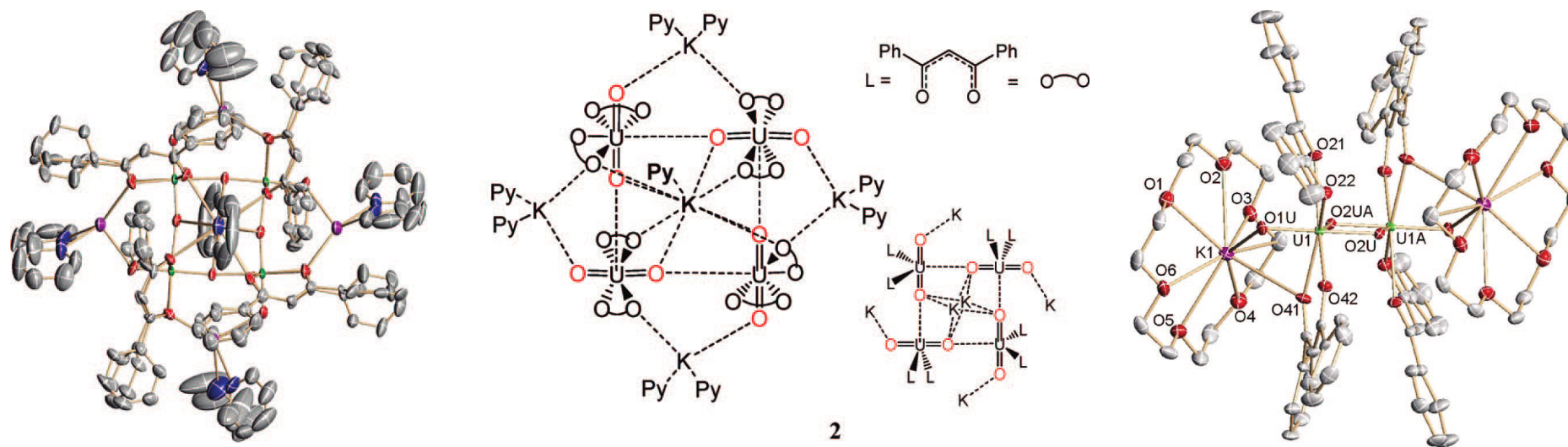


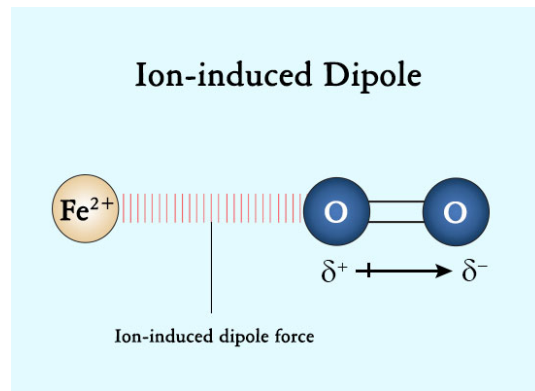
Figure 1.14 Dipole–dipole interactions in carbonyls.



Nature of Supramolecular Interactions

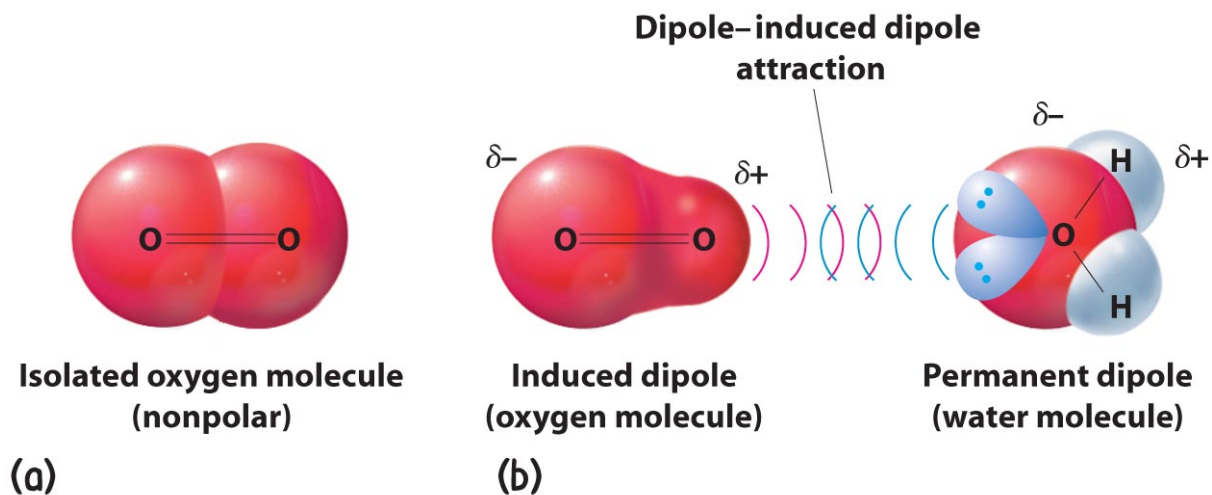
- Ion - Induced dipole

$$E = -\frac{1}{2} \frac{Q^2 \alpha}{r^4}$$



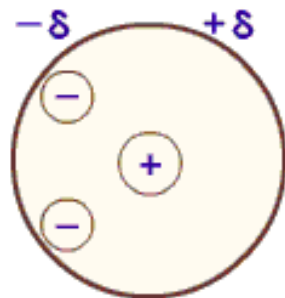
- Dipole – induced dipole interaction

$$E = -\frac{\mu^2 \alpha}{r^6}$$

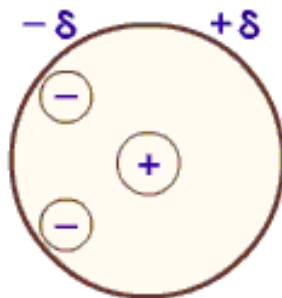


Nature of Supramolecular Interactions

- London forces



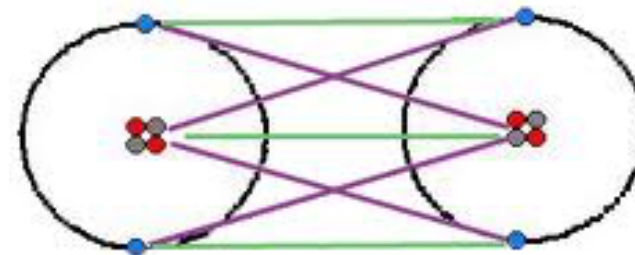
Instantaneous dipole in an atom



A dipole induced by an instantaneous dipole of the neighbouring atom

$$E = f\left(\frac{1}{r^6}\right)$$

London forces between two Helium atoms



— Repulsive forces
— Attractive forces

- Clockmann Equation

Interaction between A and D

$$\Delta E = \frac{-q_D q_A}{\epsilon r} + 2 \frac{(C_D C_A \beta)^2}{E_D - E_A} + \Delta E_{sol}$$

C_A and C_D is orbital overlap

E_A and E_D in energy of frontiers orbitals

β is the how much overlap at transition state

If $E_D - E_A$ is big:
hard – hard interactions

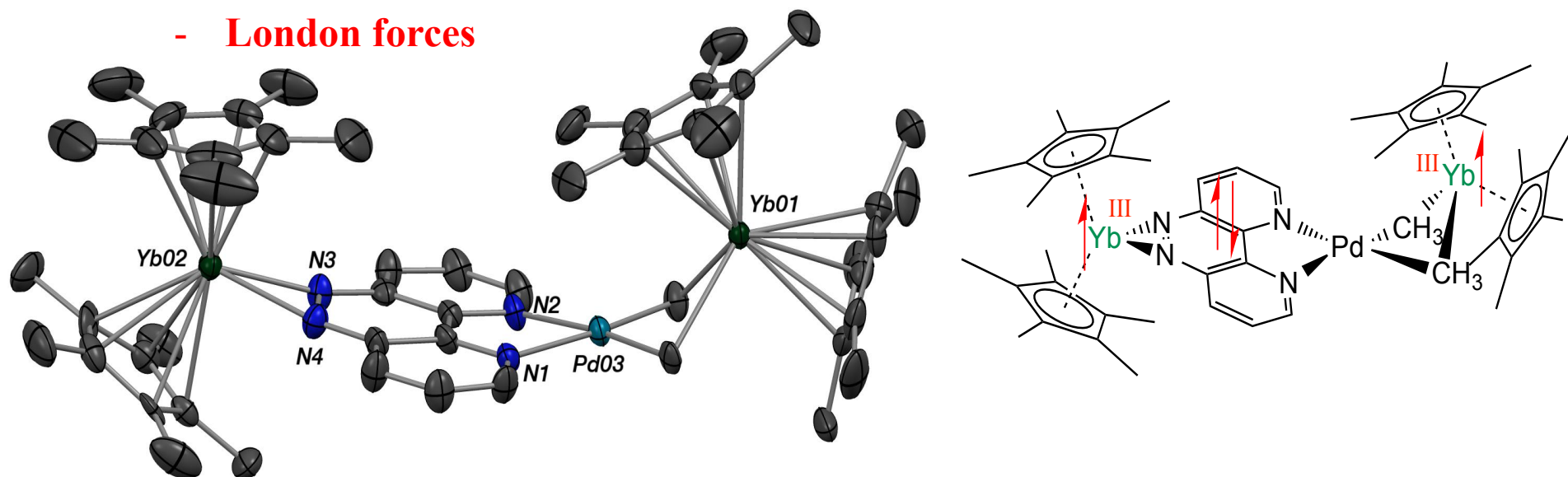
$$\Delta E \approx \frac{-q_D q_A}{\epsilon r}$$

If $E_D - E_A$ is small:
soft – soft interactions

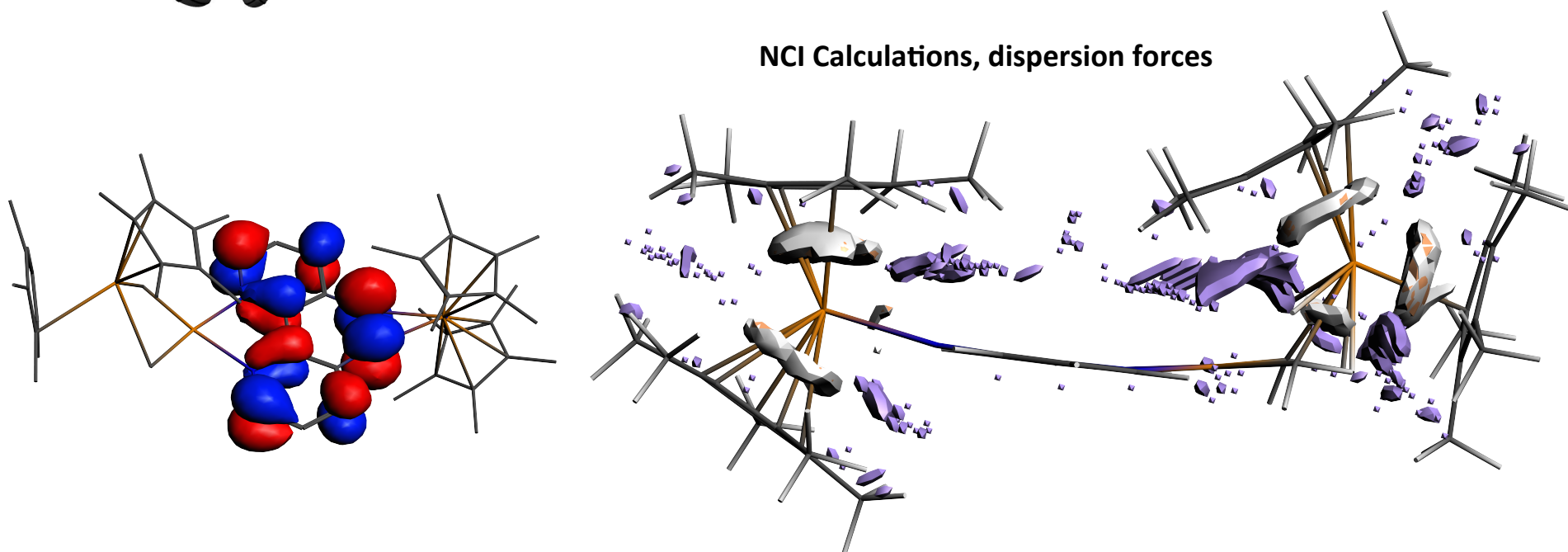
$$\Delta E \approx 2 \frac{(C_D C_A \beta)^2}{E_D - E_A}$$

Nature of Supramolecular Interactions

- London forces



NCI Calculations, dispersion forces

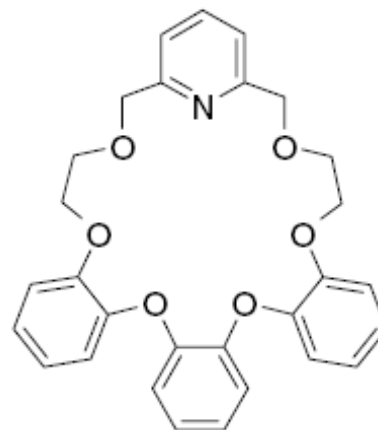
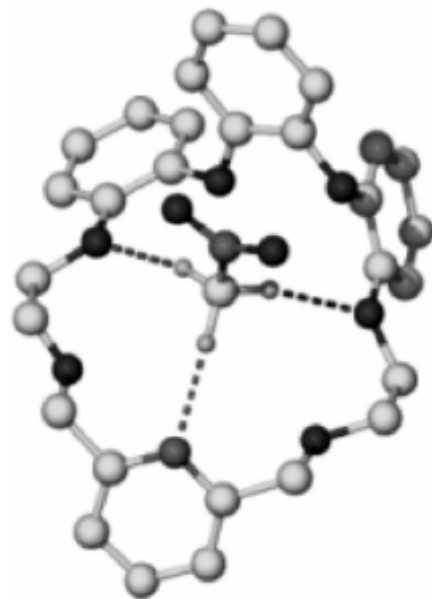
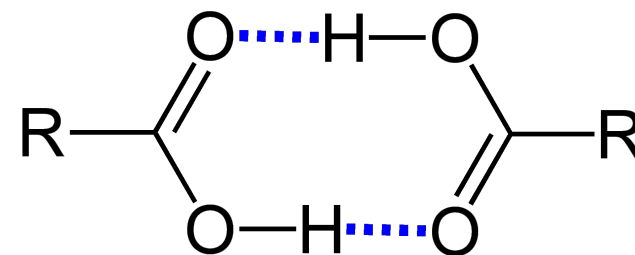
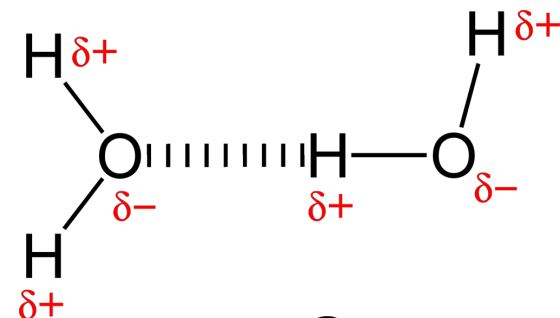


Nature of Supramolecular Interactions

- **Hydrogen bonding:** D-H ... A

Bond energy: 1-15 kcal.mol⁻¹

$$E = \frac{q_1 \mu_2 \cos \theta}{4\pi \epsilon_0 r^2}$$



1.22

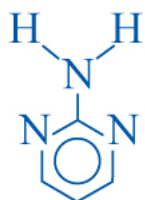
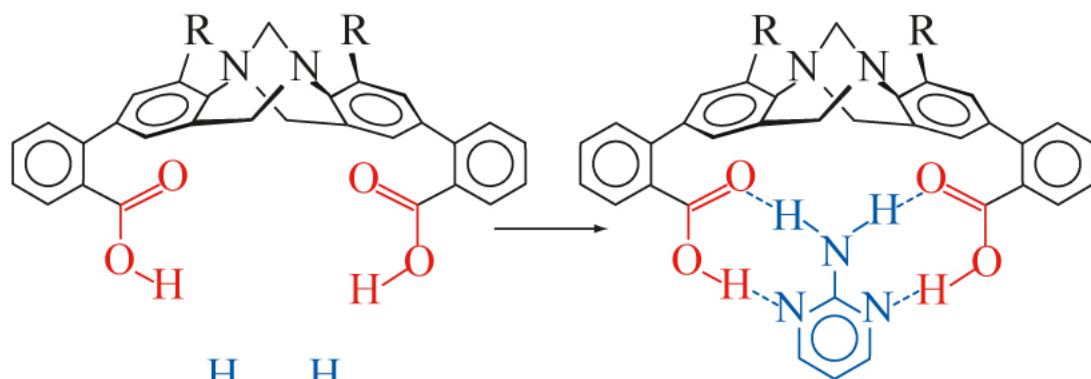
Figure 1.15 X-ray crystal structure showing C—H...N (2.21Å) and C—H...O (2.41Å, average) hydrogen bonding in a complex of crown ether **1.22** with nitromethane.¹⁷

Nature of Supramolecular Interactions

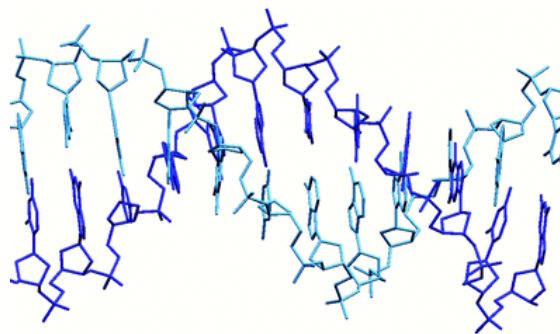
- **Hydrogen bonding:**

D-H ... A

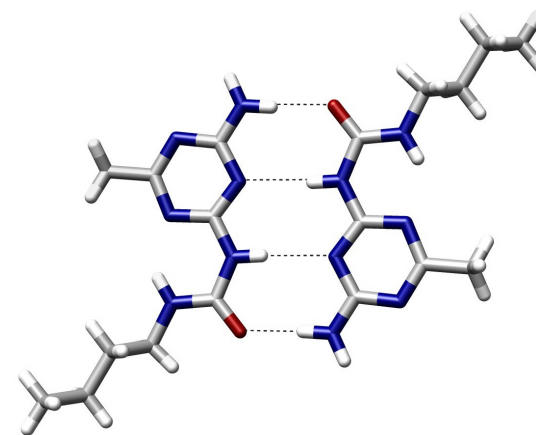
Bond energy: 1-15 kcal.mol⁻¹



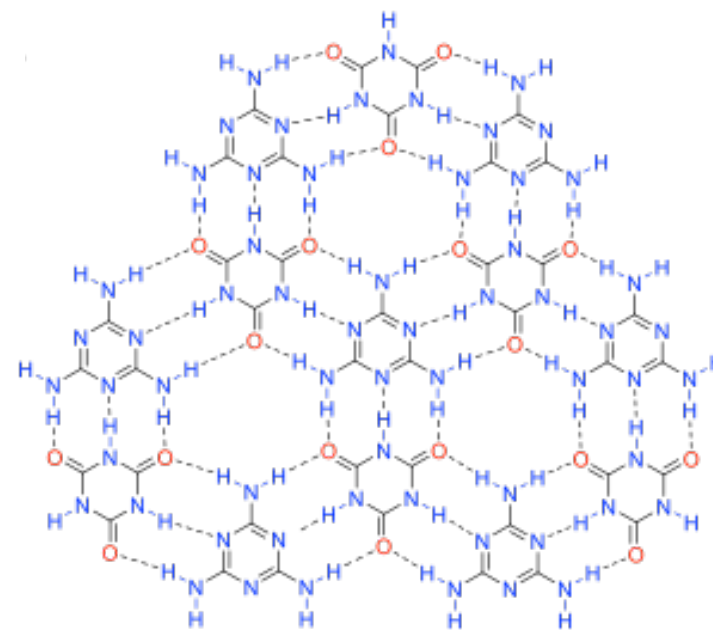
2-aminopyrimidine



Hannon, M. J. *Chem. Soc. Rev.*, **2007**, 36, 280



Meijer, *Angew. Chem. Int. Ed.* **1998**, 37, 75



Hydrogen bond network in cyanuric acid-maleimide crystal

Nature of Supramolecular Interactions

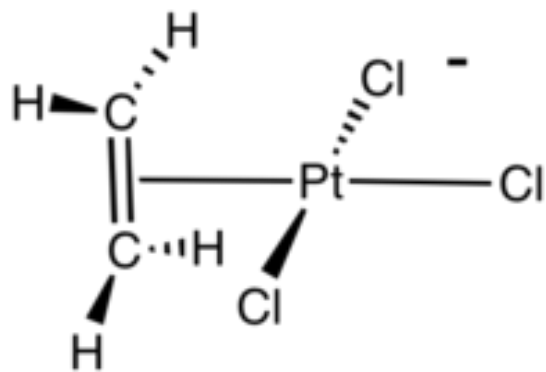
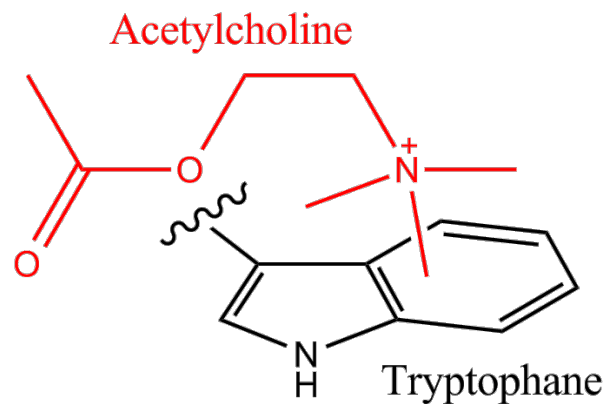
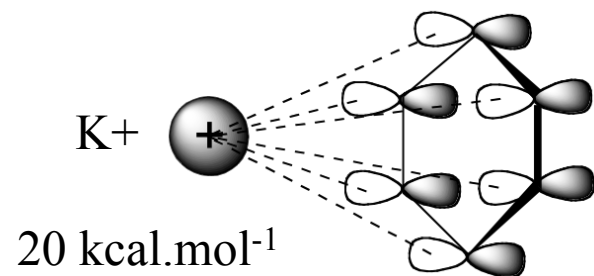
- Hydrogen bonding:

	Strong	Moderate	Weak
A—H...B interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol ⁻¹)	60–120	16–60	<12
Bond lengths (Å)			
H...B	1.2–1.5	1.5–2.2	2.2–3.2
A...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 ⁻¹)	25%	10–25%	<10%
¹ 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...π hydrogen bonds

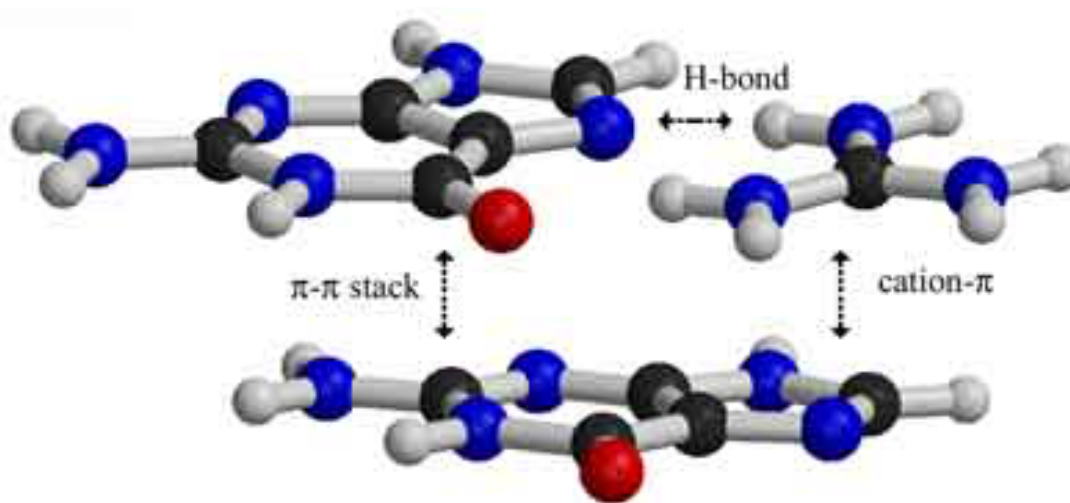
Nature of Supramolecular Interactions

Dougherty, D. *Chem. Rev.*, 1997, 97, 1303

- Cation - π interactions

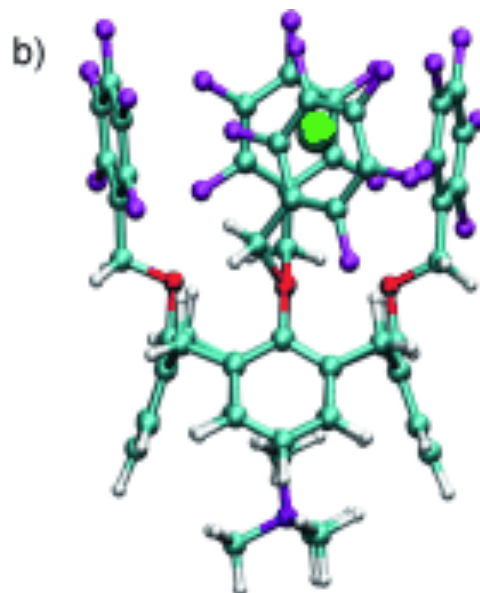
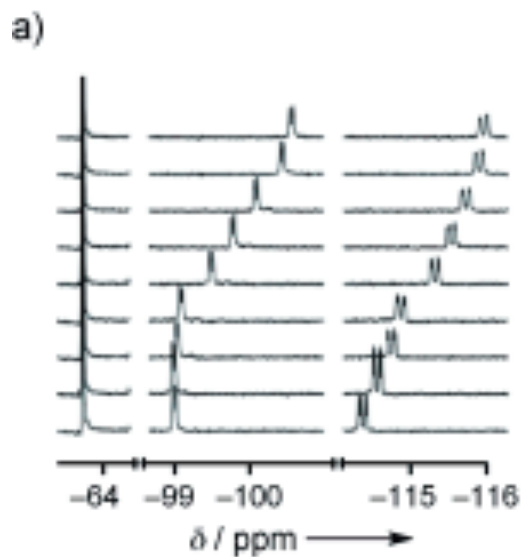
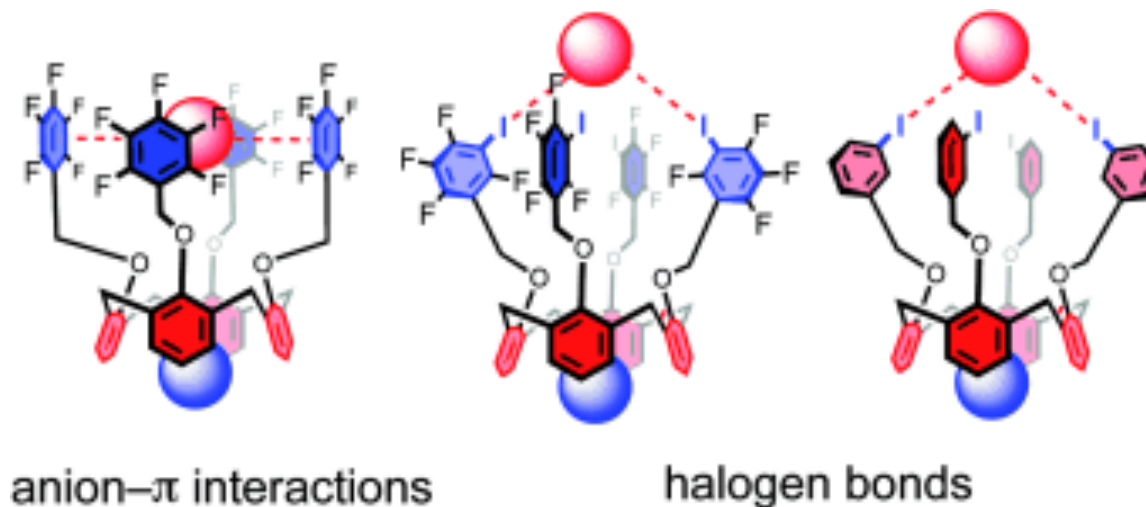
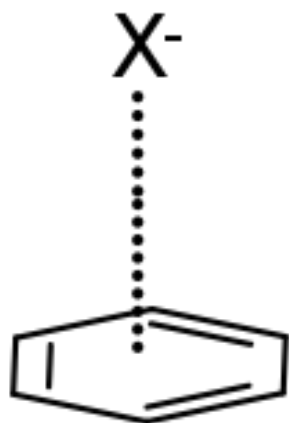


Zeise's Salt



Nature of Supramolecular Interactions

- Anion- π interactions

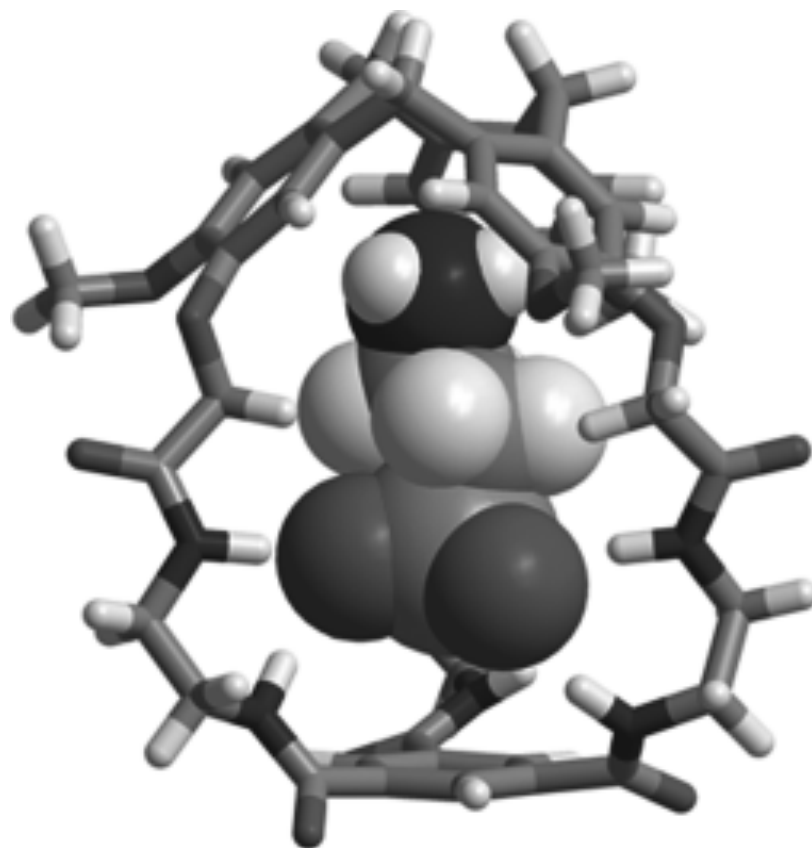
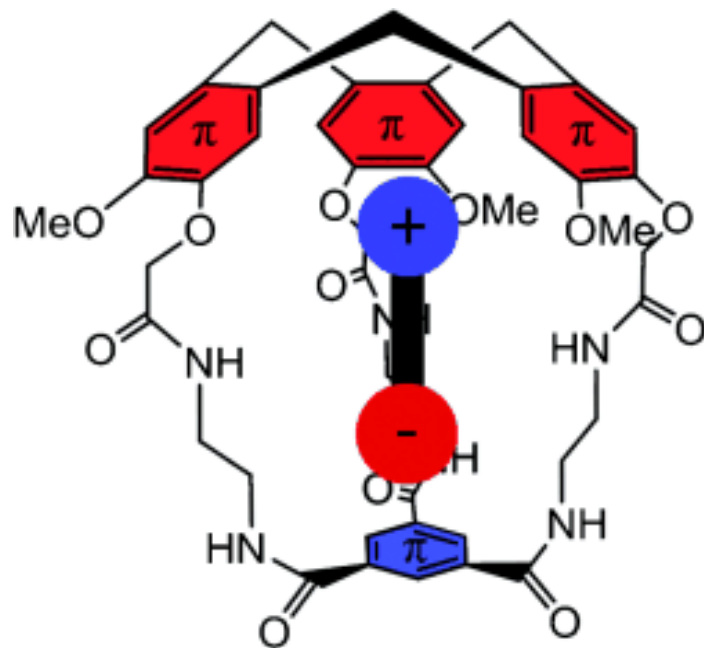


Jentzsch, A. V. *Angew. Chem. Int. Ed.*,
2011, 50, 11675

Nature of Supramolecular Interactions

Combined Cation- π and Anion- π Interactions for Zwitterion Recognition

Perraud, O. *Angew. Chem. Int. Ed.*, 2011, 51, 504



Nature of Supramolecular Interactions

- π - π interactions

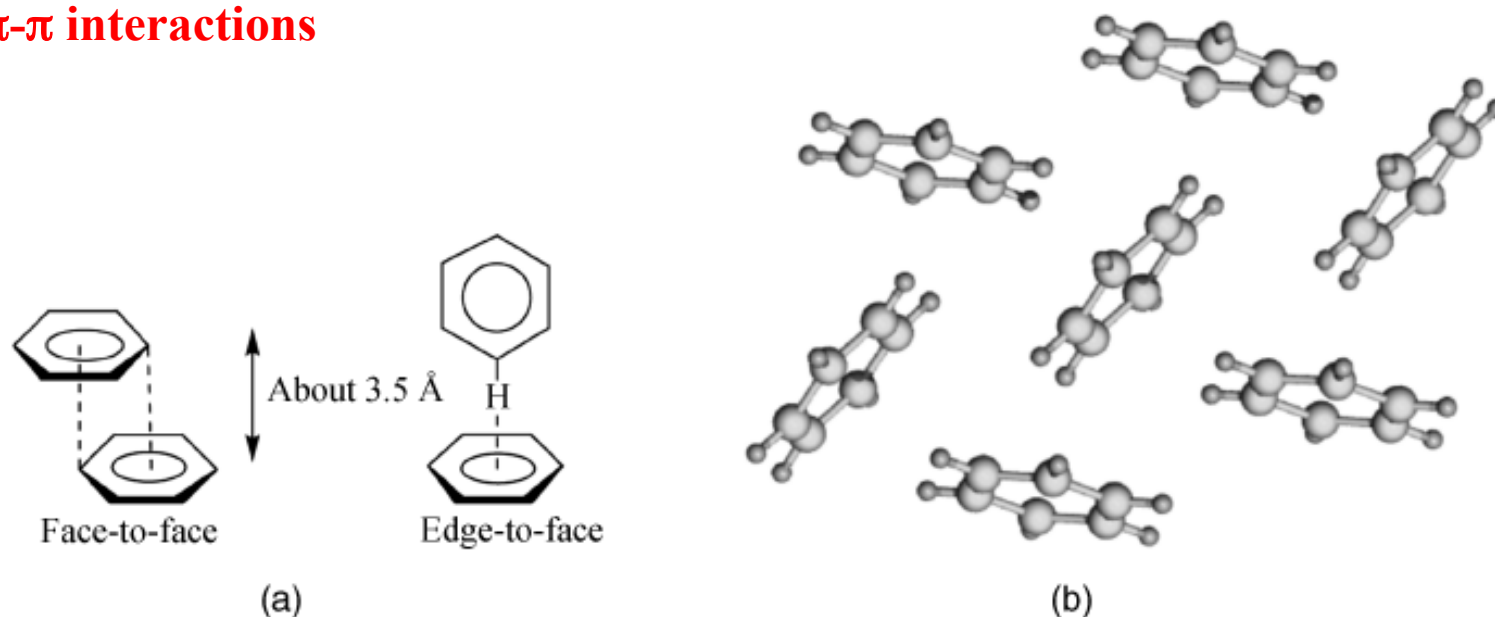


Figure 1.20 (a) Limiting types of π - π interaction. Note the offset to the face-to-face mode (direct overlap is repulsive). (b) X-ray crystal structure of benzene showing herringbone motif arising from edge-to-face interactions.

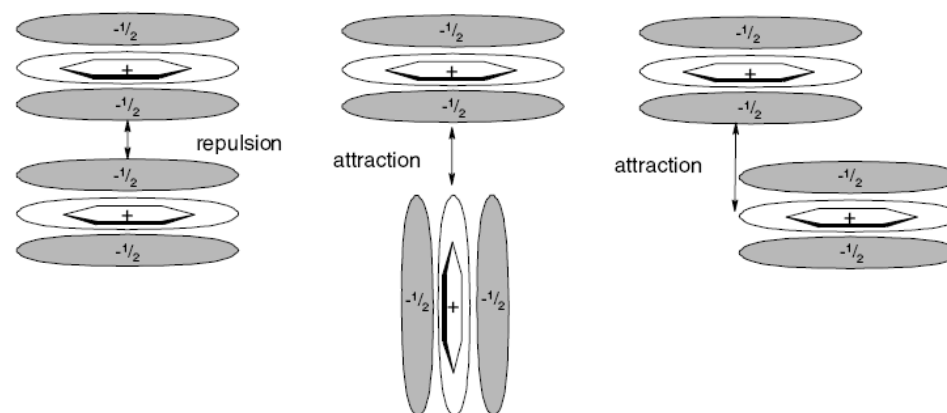
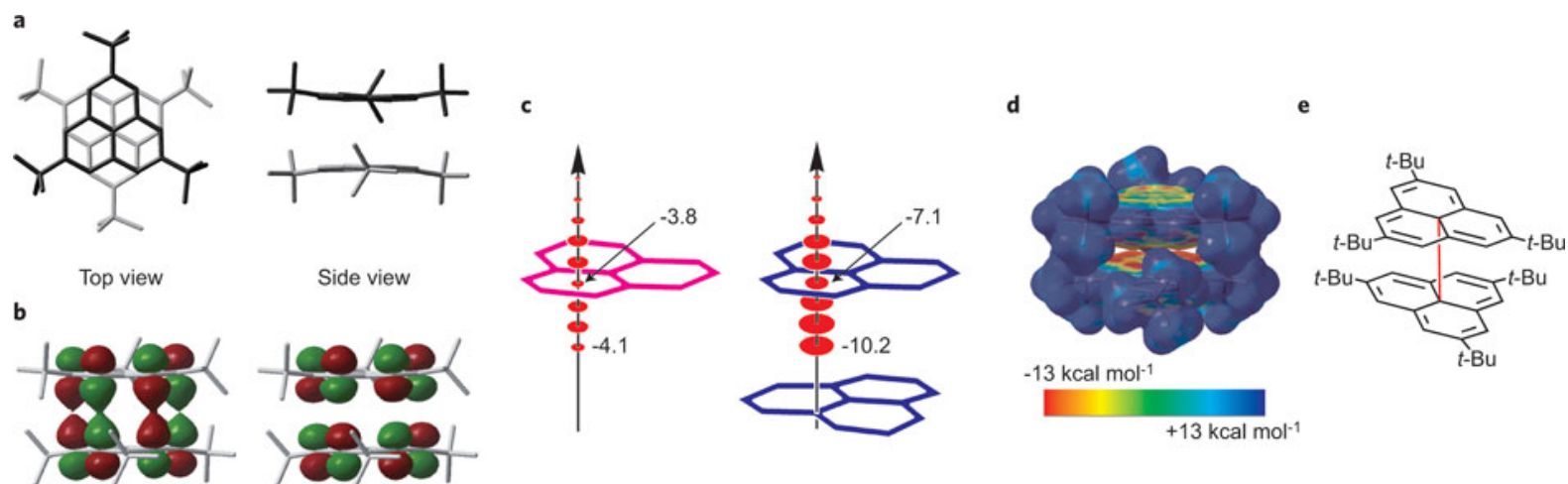
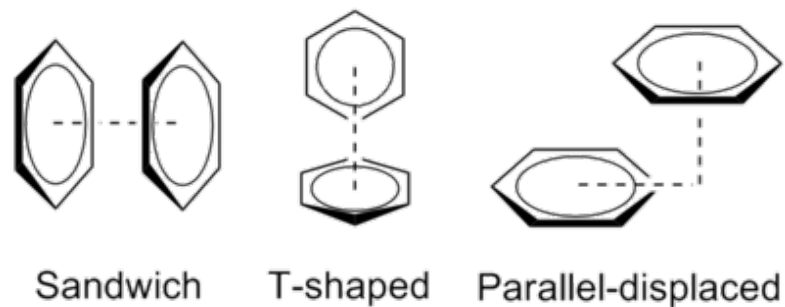
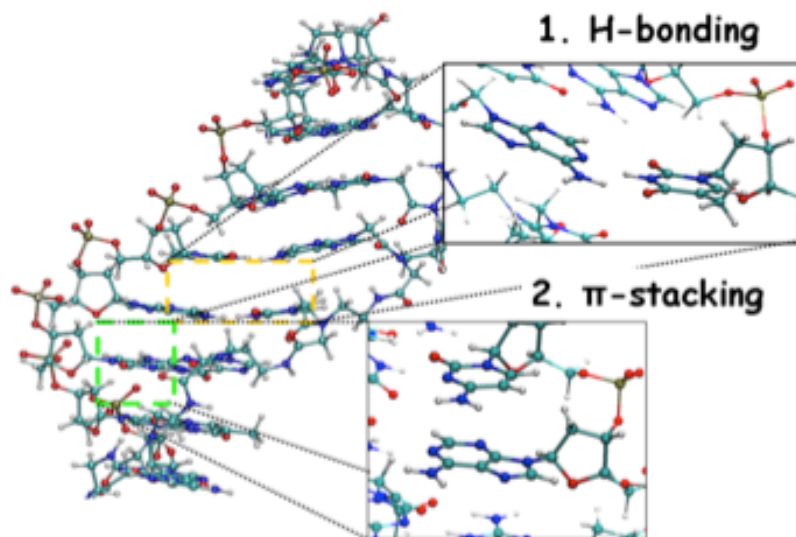


Figure 1.21 Interacting π -quadrupoles.

Nature of Supramolecular Interactions

- π - π interactions



Nature of Supramolecular Interactions

- Van der Waals Forces and Crystal Close Packing

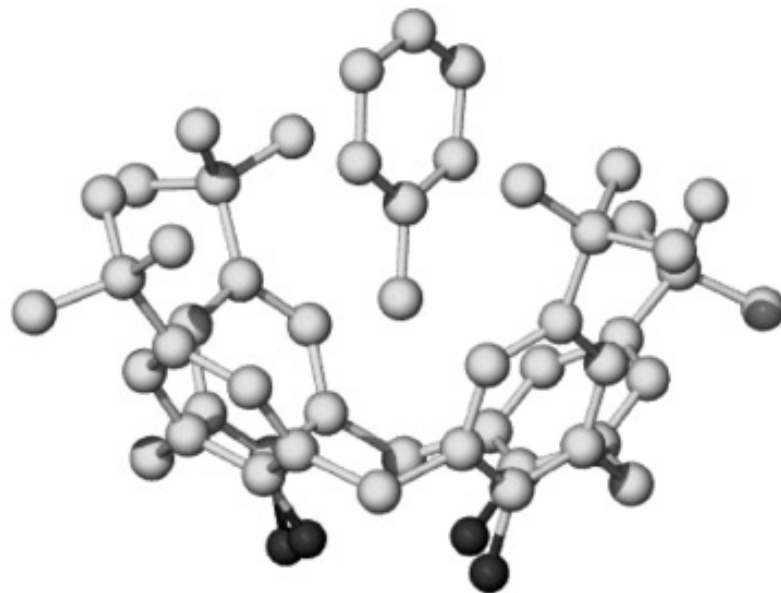
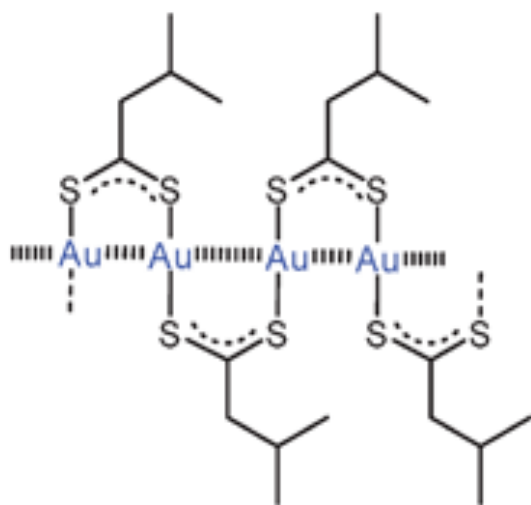


Figure 1.23 X-ray crystal structure of a typical van der Waals inclusion complex *p-tert-butylcalix[4]arene*·toluene.²⁴

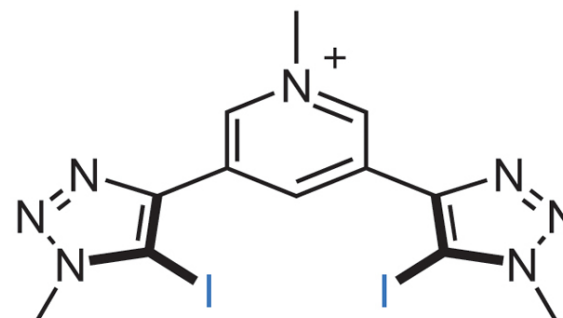
Nature of Supramolecular Interactions

- Close Shell Interactions, comparable in strength that moderate hydrogen bond

Pyykkö, P. *Chem. Rev.*, **1997**, 97, 597

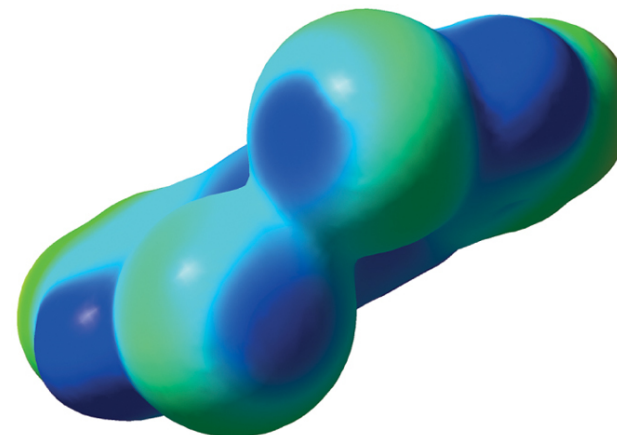
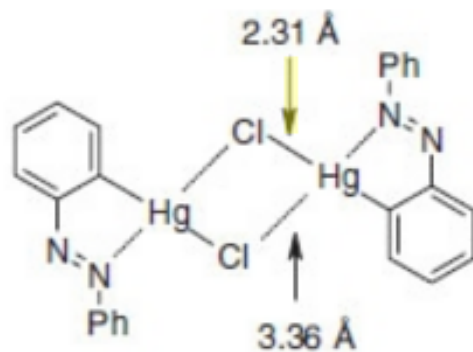


Halogen bonding



Taylor, M. S. *Nature Chem.*, **2014**, 6, 1029

Secondary bonding (Alcock 1972)



General depiction of a halogen bonding interaction (top), the structure of a bis(iodotriazole) halogen-bond donor (middle), and an electrostatic potential map (bottom) showing the 'σ-hole' (blue region of partial positive potential) on each iodine atom.

Solvation and Hydrophobic Effects

- Hydrophobic effects

Hydrophobic effects arise from the exclusion of non-polar groups or molecules from aqueous solution. This situation is more energetically favorable because water molecules interact with themselves or with other polar groups or molecules preferentially

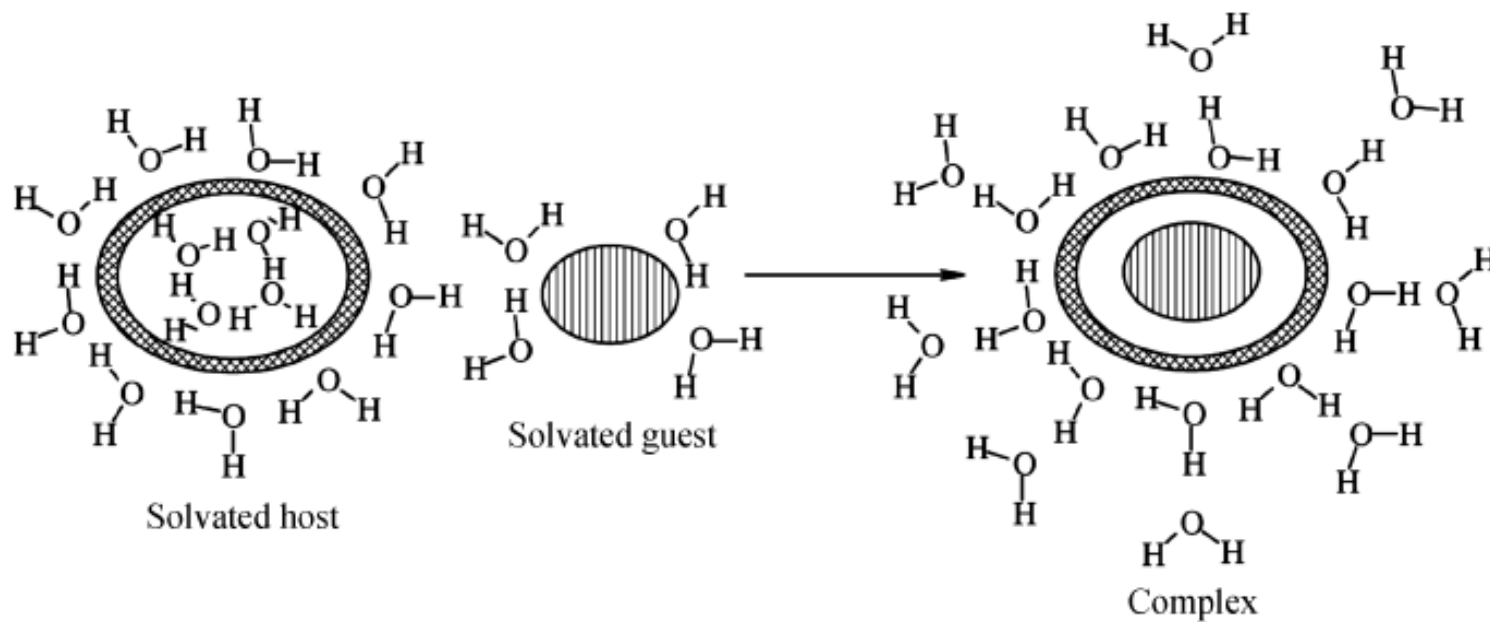


Figure 1.26 Hydrophobic binding of organic guests in aqueous solution.

Solvation and Hydrophobic Effects

- Solvation effects

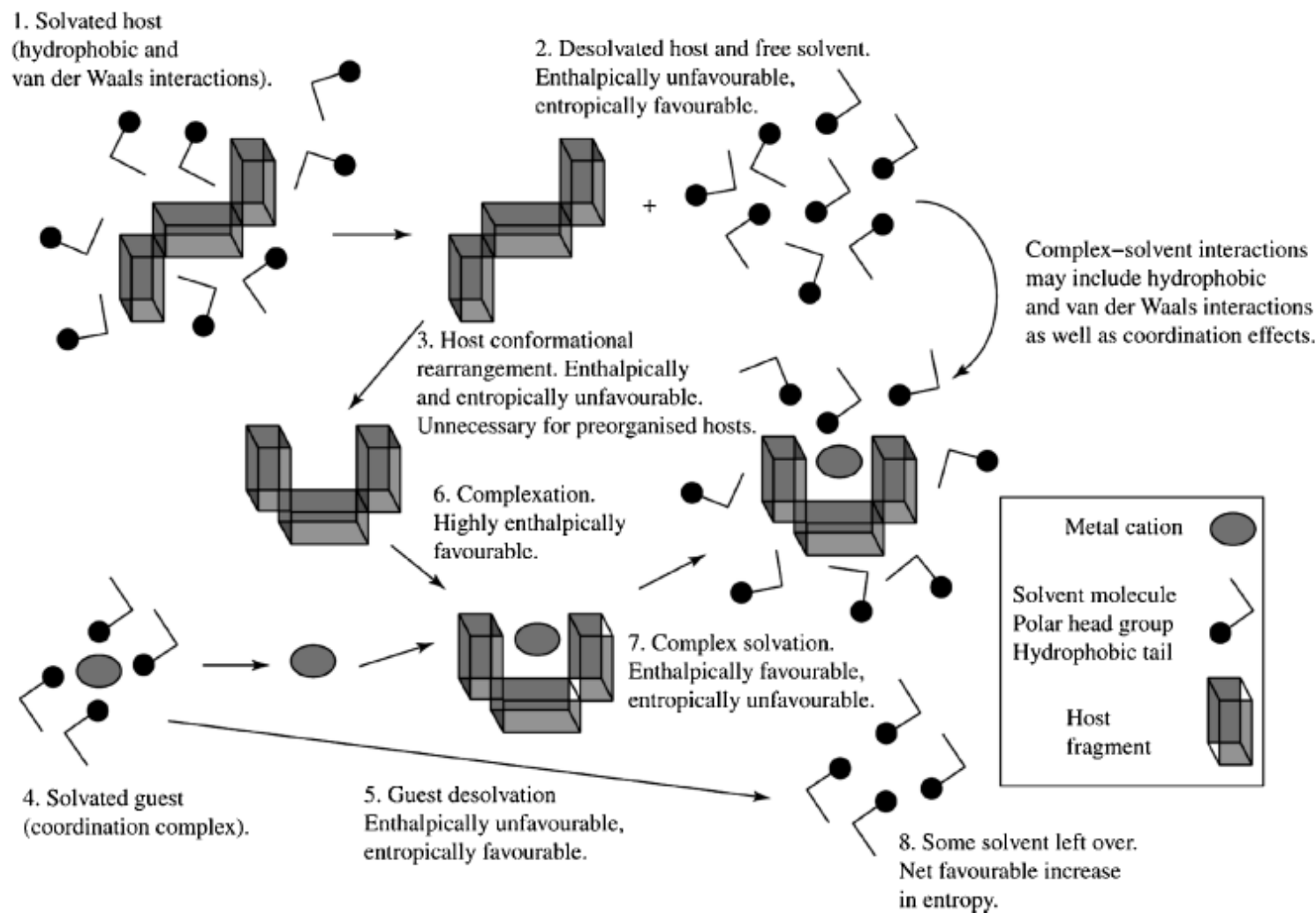
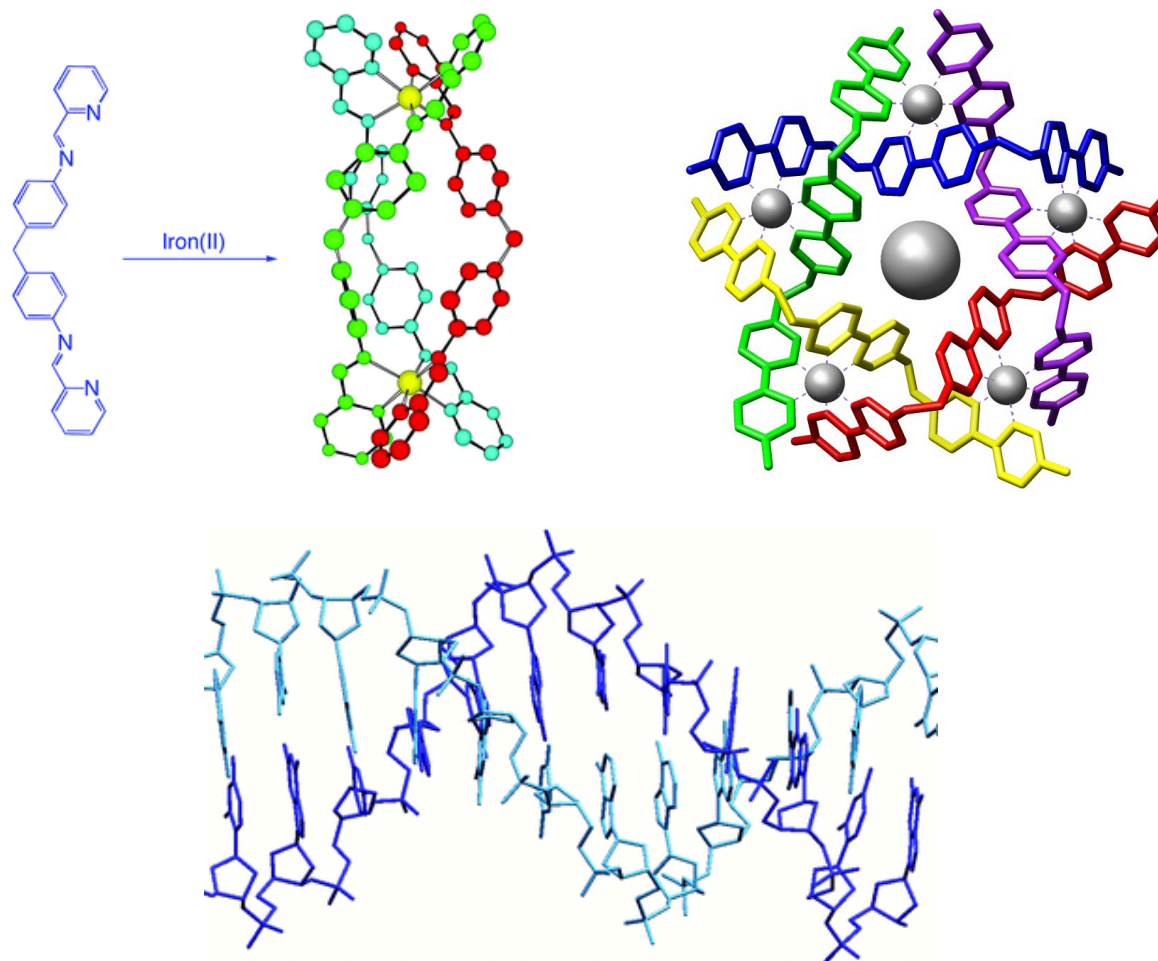


Figure 1.27 Solvation considerations during the host-guest complexation of a metal cation.

Conclusion: add all these effects.... and you have a nice supramolecular system



Hannon, M. J. *Chem. Soc. Rev.*, **2007**, 36, 280