What is Supramolecular Chemistry?

- **J. M. Lehn:**
  „Supramolecular chemistry is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by the association of two or more chemical species“
- **F. Vögtle:**
  „In contrast to molecular chemistry, which is predominantly based upon the covalent bonding of atoms, supramolecular chemistry is based upon intermolecular interactions, i.e. on the association of two or more building blocks, which are held together by intermolecular bond"

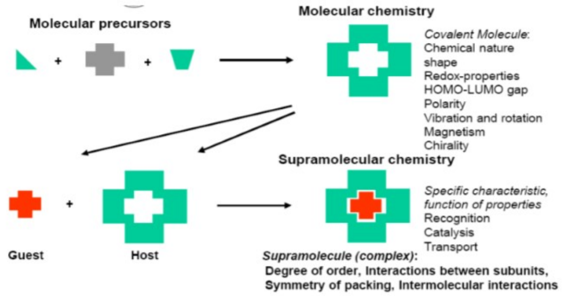


Fig. 1.1 Comparison between the scope of molecular and supramolecular chemistry according to Lehn.

Classification of Host-Guest Compounds

Table 1.1 Classification of common host-guest compounds of neutral hosts.

Host	Guest	Interaction	Class	Example
Crown ether	Metal cation	Ion - dipol	Complex (Cavitate)	$[K^+ \subset [18]$crown-6]
Spherand	Alkyl ammonium cation	Hydrogen bonding	Complex (Cavitate)	Spherand ($CH_3NH_3^+$)
Cyclodextrin	Organic molecule	Hydrophobic/van der Waals	Cavitate	(α-cyclodextrin) (*p*-hydroxy-benzoic acid)
Water	Organic molecule, halogen, etc.	Van der Waals/crystal packing	Clathrate	$(H_20)_6 \cdot (CH_4)$
Calixarene	Organic molecule	Van der Waals/crystal packing	Cavitate	(*p-t*-butylcalix[4]-arene)(toluene)
Cyclotrivera-trylene (CVT)	Organic molecule	Van der Waals/crystal packing	Clathrate	(CTV) · 0.5(acetone)

The Chelate and Macrocyclic Effects

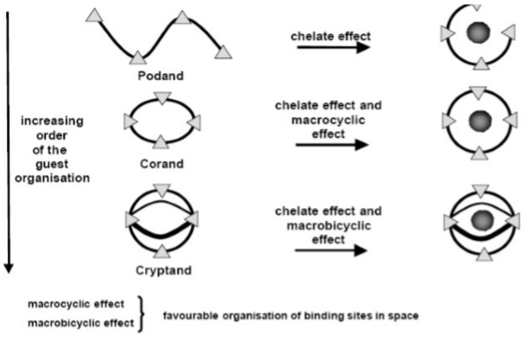


Fig. 1.7 The chelate, macrocyclic and macrobicyclic effect.

Classification of Host-Guest Compounds

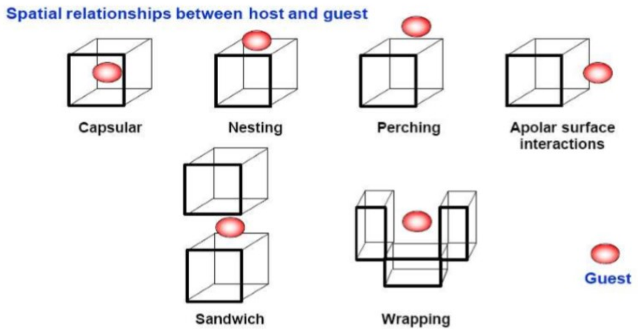
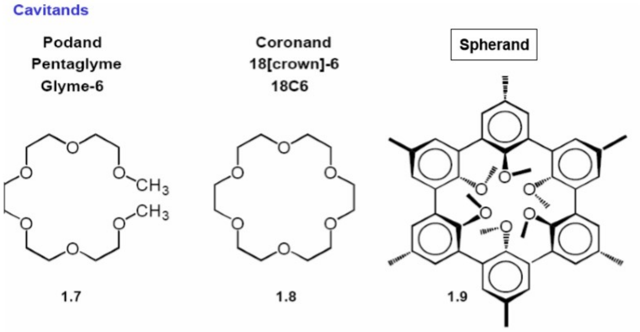


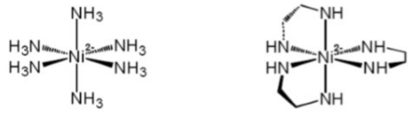
Fig. 1.5 Descriptive terms to illustrate spatial relationships between host and guest.

Classification of Host-Guest Compounds



The Chelate and Macrocyclic Effects

$$[Ni(NH_3)_6]^{2+} + 3\ NH_2CH_2CH_2NH_2 \xrightarrow{\log K\ =\ 8.76} [Ni(NH_2CH_2CH_2NH_2)_3]^{2+} + 6\ NH_3$$



1.10

1.11

$$\ln K = -\frac{\Delta G}{R\,.\,T} \qquad \Delta G = \Delta H - T\Delta S$$

$$\Rightarrow \quad \ln K = -\frac{\Delta H}{R\,.\,T} + \frac{\Delta S}{R}$$

K = complexation constant

The Chelate and Macrocyclic Effects

Strained ring

Optimum geometry for larger cations

Increasing flexibility

Less entropically favorable

Preorganization and Complementarity

- binding sites of host must complement to those of the guest
  (e.g. H-bond donor/acceptor abilities)
- spatial orientation of binding sites for efficient binding must be guaranteed

➡ **complementarity**

- low amount of conformational changes upon binding

➡ **host is preorganized**

Binding process: 1. conformational readjustment to maximize complementarity
(energetically unfavourable)
2. binding (energetically favourable)

Nature of Supramolecular Interactions

Driving Forces for the Formation of Supramolecular Structures

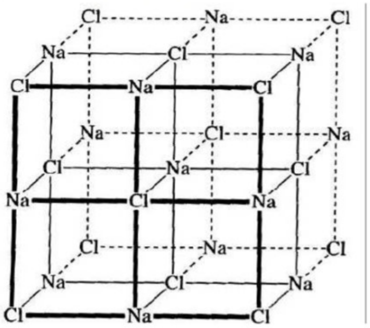
➢ hydrophobic interaction	<40 kJ/mol
➢ electrostatic interaction	~20 kJ/mol
➢ hydrogen bond interaction	12-30 kJ/mol
➢ van der Waals interaction	0.4-4 kJ/mol
➢ cation –π interaction	5-80 kJ/mol
➢ π–π stacking	0-50 kJ/mol

➢ The total inter-molecular force acting between two molecules is the **sum** of all the forces they exert on each other.

Nature of Supramolecular Interactions

Ion – Ion interactions (100 – 350 kJmol^{-1})

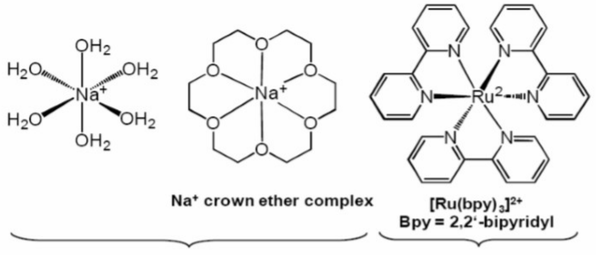
Strength comparable to covalent binding



NaCl ionic lattice

Nature of Supramolecular Interactions

1.6.2 Ion – dipol interactions (50 – 200 kJ mol^{-1})



Na$^+$ crown ether complex

[Ru(bpy)$_3$]$^{2+}$
Bpy = 2,2'-bipyridyl

mostly non-covalent

covalent contribution

Nature of Supramolecular Interactions

1.6.3 Dipol – dipol interactions (5 – 50 kJ mol^{-1})

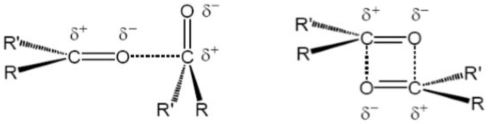


Fig. 1.12 Dipole – dipole interactions in carbonyl compounds

Nature of Supramolecular Interactions : Hydrogen Bonding

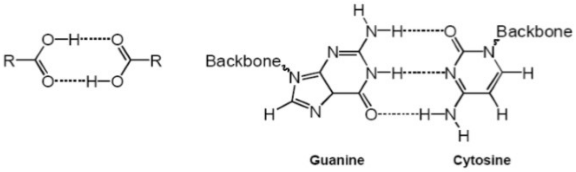
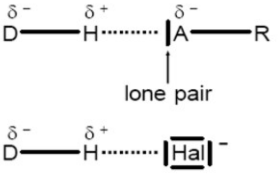


Fig. 1.15. Hydrogen bonded carboxylic acid dimers and base pairing in DNA by hydrogen bonding.

ideally linear arrangement

D—H······ A (angle 180°)

Nature of Supramolecular Interactions : Hydrogen Bonding

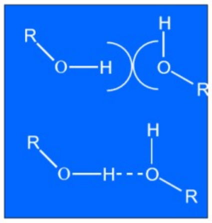


D ..... Donor
A ..... Acceptor

special case

- **special kind of dipole – dipole interaction**
- **strong H-bonds are 3-center-4-electron bonds**
- **highly directional in nature**

Nature of Supramolecular Interactions : Hydrogen Bonding

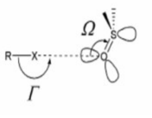


Van der Waals radius of H: 1.1Å, O 1.5Å. Therefore closest approach should be 2.6Å.

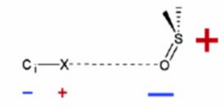
Actual separation is about 1Å less! Distance of 1.76Å.

Intermediate between vdw distance and typical O-H covalent bond of 0.96Å.

Nature of Supramolecular Interactions : Halogen Bonding



- **DMSO to haloarene halogen bonding geometry:**
  "head on" to C-X, Γ~ 158(13)°(Cl), 162(12)°(Br), and ~165(8)°(I);
  "side on" to S=O, Ω: 125-135°.



- **Increase of polarity of the both C-X and S=O bond increases the strength of interaction:**

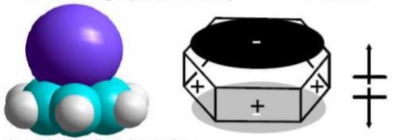
Nature of Supramolecular Interactions : The Cation – π Interaction

D. Dougerthy et al., „The Cation – π Interaction", Chem. Rev. 1997, 97, 1303-1324.

- **in transition metal complexes such as ferrocene $[Fe(C_5H_5)_2]$:**
  covalent bonds ➡ d - Orbitals
- **However: no covalent „weak" interaction of e.g. alkaline or alkaline earth metal cations with π-bonds (C=C double bonds)**

Gas phase interactions

K^+ ..... benzene 80 kJ/mol
K^+ ..... H_2O (one molecule) 75 kJ/mol



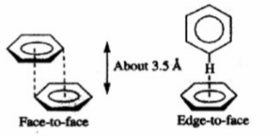
x) see also ion-dipole interactions

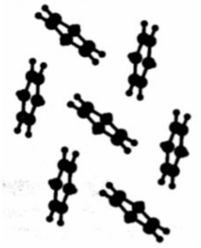
Fig. 1.18. Schematic drawing of the cation-π interaction showing the contact between the two. The quadrupole moment of benzene, along with its representation as two opposing dipoles is also shown.

Nature of Supramolecular Interactions : π – π Stacking

1.6.6 π–π Stacking (0 – 50 kJ/mol)

especially favorable: one electron rich and one electron poor aromatic





***face to face*: Graphite, DNA**
***edge to edge*: herring bone packing of benzene in the solid state**

Nature of Supramolecular Interactions : π – π Stacking

Sanders-Hunter - Model

C.A. Hunter, J.K.M. Sanders, „The Nature of π–π Interactions" J. Am. Chem. Soc. 1990, 112, 5525-5534.

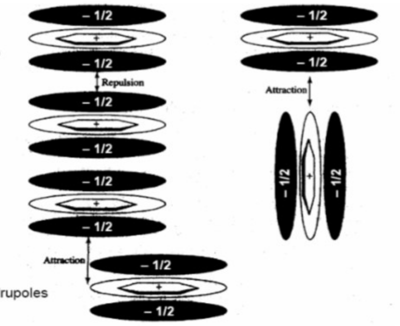


Fig. 1.21. Interacting π-quadrupoles

Nature of Supramolecular Interactions : π – π Interactions

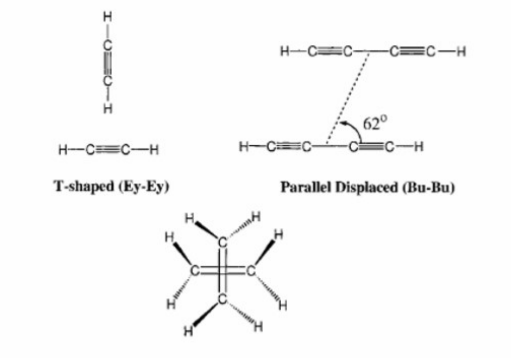


Figure 6. Minimum energy structures of the ethyne (Ey–Ey), 1,3-butadiyne (Bu–Bu), and ethene (Et–Et) dimers.

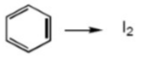
Nature of Supramolecular Interactions : Charge-Transfer Complex

Electron transfer from high energy occupied molecular orbitals of electron-rich compounds (donor D) into low-lying unoccupied orbitals of electron-poor systems (acceptor A)

➡ **charge transfer (CT) bands in the electronic absorption spectra**

➡ **plays a usually very small role in the energetics of host-guest equilibria**

examples:



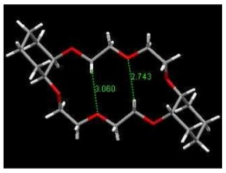
$R_3NI \longrightarrow I_2$

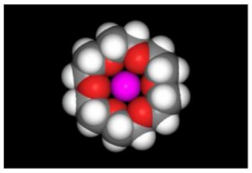
Nature of Supramolecular Interactions : Van der Waals Forces

- Strength of interaction is essentially a function of the surface area of contact. The larger the surface area the stronger the interaction will be.
- Regardless of other interactions found within a complex there will almost always be a contribution from vdw.
- This is what drives molecules to eliminate spaces or vacuums and makes it difficult to engineer porous or hollow structures and gives rise to the phrase "Nature abhors a vacuum".

Solubility Properties

X-ray crystal structure of :
dicyclohexyl[18]crown-6 and potassium complex of [18]crown-6.





Structures are different:
- In the solid state
- In polar and apolar solvent
- As a complex

Solubility Properties

- **Crown ethers such as [18]crown-6 are soluble in a wide range of solvents from water to alkanes**
- **log p [18]crown-6 = 0**

➡ **possibility of in-out movement of the O-atoms**

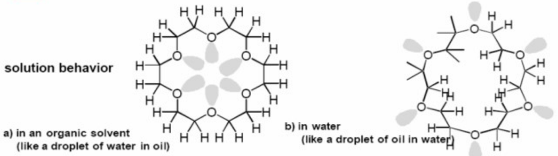


Fig. 2.6 Solution behavior of [18]crown-6 in **a)** an organic solvent, and in b) a hydrophilic medium

Structure a is unrealistic, why?

Solution Applications

- **phase transfer catalysis**
- **anion activation („naked anions“)**

➡ **lowering of E_A for reactions with the anion**

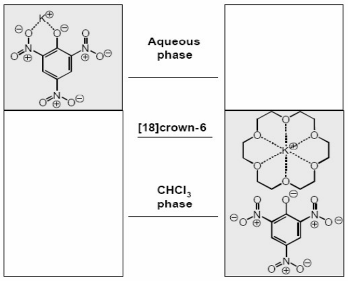
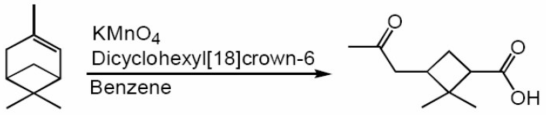
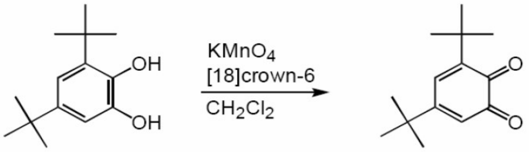


Fig. 2.7 Phase transfer catalysis by a crown ether

Solution Applications

Example: Oxidation of Organic Substrates with $KMnO_4$





Selectivity of Cation Complexation

Crown Ethers

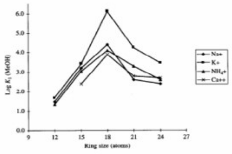


Fig. 2.8 Variation of binding constant as a function of crown ring size for various cations

- **All crown ethers are selective for K^+**

Table 2.1 Comparison of the diameters of different crown ethers with the ionic diameter of various metal cations.

Cation	Diameter (Å)	Crown ether	Cavity diameter (Å)
Li^+	1.36	[12]crown-4	1.20-1.50
Na^+	1.90	[15]crown-5	1.70-2.20
K^+	2.66	[18]crown-6	2.60-3.20
Cs^+	3.38	[21]crown-7	3.40-4.30
Cu^+	1.92		
Ag^+	2.52		
Mg^{2+}	1.44		
Ca^{2+}	2.20		
La^{3+}	2.34		
Lu^{3+}	2.00		
Zr^{4+}	1.72		

[1]Assuming most common coordination number.

Selectivity of Cation Complexation

Cryptands

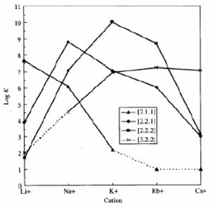


Fig. 2.11 Binding constants for various cryptands with alkali metal cations in methanol.

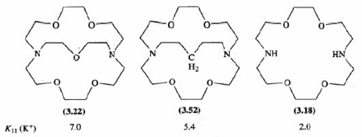


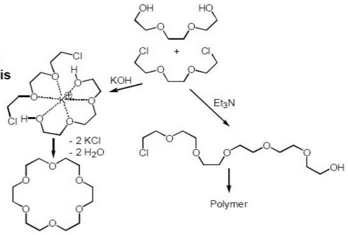
Fig. 2.12 Comparison of the K^+ binding constant (M^{-1}) for cryptand and corand hosts (MeOH, 25 °C).

- **Compared to crown ethers better preorganization**

The template Effect

2.1.8 The Template Effect

Possible pathways leading to cyclic and acyclic products in the synthesis of [18]crown-6

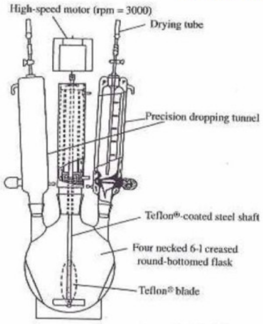


- **K^+ organizes the reactants about itself to give a reaction intermediate that is preorganized to form a cyclic product**

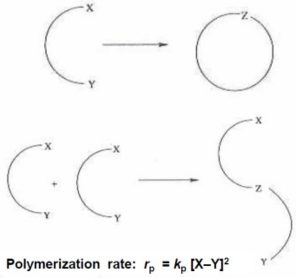
➡ **K^+ is a template for the formation of the macrocyclic crown ether**

➡ **Template effect is a kinetic effect and the crown ether is the kinetic product**

High-Dilution Synthesis



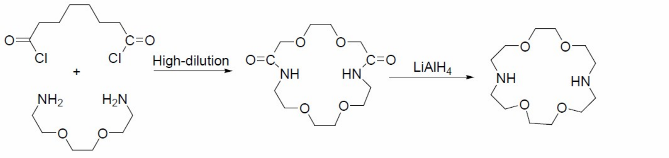
Cyclization rate: $r_c = k_c$ [X–Y]



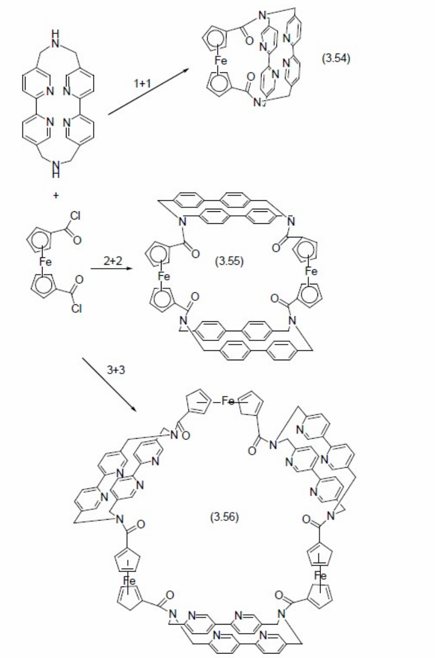
Polymerization rate: $r_p = k_p$ [X–Y]^2

$$\frac{r_c}{r_p} = \frac{k_c[X-Y]}{k_p[X-Y]^2} = \frac{k_c}{k_p[X-Y]}$$

High-Dilution Synthesis



High-dilution synthesis of diaza(18)crown-6.Note the use of acid chloride groups to enhance reaction rate.



Simultaneous(1+1),(2+2) and (3+3) cyclocondensation in bipyridyl-based cryptands

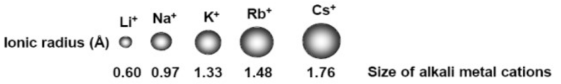
Soft Ligands for Soft Metal Ions

Selective binding of Alkali Metal Cations

Properties of alkali metal cations:

- Hard, nonpolarisable spheres.
- Little fixed preference for particular coordination geometries.
- Relatively high free energies of hydration.
- Affinity for highly charged, nonpolarisable bases.

These features make the design of suitable ligands that can displace water and bind both strongly and selectively to freely diffusing cations a difficult task.The only basis for selectivity between alkali metal cations is ionic size.



Size of alkali metal cations

The Hard and Soft Acids and Bases Theory

Metal ions must be divided into two classes:

1. Elements where the stability of the halogen complexes and the metal-halogen bond strength is in the order of F > Cl > Br > I with similar sequences for group 16 and 15 donor atoms. These are referred to as Class „a“ acceptors. Examples are Al^{3+}, Ti^{4+} and most *s*- and *p*-block ions, Mn^{3+}, Fe^{3+}, Co^{3+} and some other high oxidation state transition metal ions.

2. Elements where the stability is in the order F < Cl < Br < I, O < S ~ Se ~ Te, and N < P > As > Sb (complexes with P-donors are almost always more stable than As and Sb ligands). The majority of Class „b“ metal ions are derived from the transition metaly, e.g. Cu(I), Ag(I), Au(I), Pd(II) and Pt(II). Class „b“ elements tend to have a large number of *d*-electrons in their outer shell. The majority are also in the second and third transition series so size can be recognized as another factor that contributes to „b“ character. This is because metal ions become more polarisable as size increases, And valence electron penetration decreases.

Soft Ligands for Soft Metal Ions

Hard acids	***Hard Bases***
High positive charge	High electronegativify
Low polarisability	Difficult to oxidise
Small size (H^+, Al^{3+})	Low **po!arisability (F^-)**
Soft Acids	***Soft Bases***
Low positive charge	Low electronegativity
High polarisability	Easily oxidised
Larger size (Ag^+)	High polarisability
	High negative charge (H^-)

An interesting example of the HSAB principle is given by the reaction

$$LiI + CsF \rightleftharpoons LiF + CsI$$

This proceeds from left to right as predicted by HSAB but contrary to Pauling's electronegativity definition, which gives more bond energy for large electronegativity differences.

Soft Ligands for Soft Metal Ions

Low oxidation state complexes are usually stabilised by π-acid ligands such as CO, PR_3 (phosphines), olefins etc. The use of the word „acid“ here refers to Lewis acidity, i.e. electron acceptance. Binding to π-acid ligands occurs in a synergic fashion that comprises two components:

1. Donation of electron density from the ligand to an unoccupied metal *p*- or *s*-orbital in a σ-fashion (i.e. the electron density maximum lies along a line joining the two atomic centres – the inter-atomic vector) (Fig. 2.14).

2. Metal-to-ligand back-bonding (Fig. 2.15)., Donation of electron density from a filled metal *d*-orbital to an unoccupied, antibonding ligand orbital of either *p* or *d* character. Back bonding occurs in a π-fashion in which two maxima in metal-ligand bonding electron density occur on either side of the interatomic vactor. This has the effect of strengthening the M-L bond but weakening the bonds within the ligand itself (e.g. the C-O bond in CO) because the back donation Occurs into an antibonding ligand orbital, thus reducing the overall bond order.

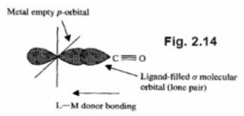


Fig. 2.14

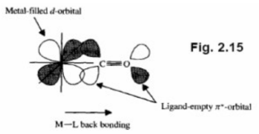


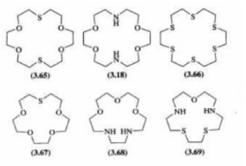
Fig. 2.15

Soft Ligands for Soft Metal Ions

2.1.10.1 Heterocrowns

Table 2.2 Comparative binding constants ($logK_{11}$) for hard and soft metal ions with various ligands.

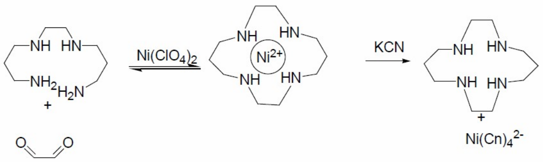
Cation	Ligand						
	[18]crown-6	(3.65)	(3.18)	[15]crown-5	(3.67)	(3.68)	(3.69)
K^+ (methanol)	6.10	1.15	2.04	-	-	-	-
K^+ (water)	2.10	-	<1	0.74	-	1.0	-
Ag^+ (methanol)	4.58	-	-	-	-	-	-
Ag^+ (water)	1.60	4.34	7.80	0.94	5.0	5.85	8.95
Tl^+ (water)	2.27	0.93	1.1	1.23	0.8	-	-
Ba^{2+} (water)	3.78	-	2.51	-	-	1.0	-
Pb^{2+} (water)	4.27	3.13	6.9	1.85	1.65	5.85	5.67



Soft Ligands for Soft Metal Ions

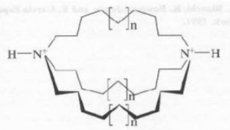
Macrocycle Synthesis through Schiff's Bases

- Thermodynamic equilibrium
- Template effect



Binding of Anions

1968 first anion binding of katapinands



(4.1) n = 0 : (4.1a)
n = 1 : (4.1b)
n = 2 : (4.1c)
4.1b = 1,11-diazabicyclo[9.9.9]nonacosane

- slow further development of anion coordination chemistry

Fig. 2.22:

Figure 4.1 Minimised structure of the chloride complex of katapinand (4.1a).

Binding of Anions

Reasons:

- Anions are relatively large and therefore require receptors of considerably greater size than cations. For example, one of the smallest anions, F$^-$, is comparable in ionic radius to K$^+$ (1.33 Å versus 1.38 Å). Other selected anion radii are shown in Table 4.1.
- Even simple inorganic anions occur in a range of shapes and geometries, e.g. spherical (halides), linear (SCN$^-$, N$_3^-$), planar (N0$_3^-$, PtCl$_4^{2-}$), tetrahedral (P0$_4^{3-}$, S0$_4^{2-}$), octahedral (PF$_6^-$, Fe(CN)$_6^{3-}$) as well as more complicated examples as in the case of biologically important oligophosphate anions.
- In comparison to cations of similar size, anions have high free energies of solvation and hence anion hosts must compete more effectively with the surrounding medium, e.g. $\Delta G_{hydration}(F^-) = -465 \text{ kJmol}^{-1}$, $\Delta G_{hydration}(K^+) = -295 \text{ kJmol}^{-1}$. Other solvation free energies are given in Table 4.1.
- Many anions exist only in a relatively narrow pH window, which can cause problems especially in the case of receptors based upon polyammonium salts where the host may not be fully protonated in the pH region in which the anion is present in the desired form.
- Anions are usually saturated coordinatively and therefore bind only via weak forces such as hydrogen bonding and van der Waals interactions.

Biological Anion Receptors

- between 70 and 75 % of enzyme substrates and cofactors are anions (e.g. ATP and ADP)
- also of biological importance: SO$_4^{2-}$, R-COO$^-$,

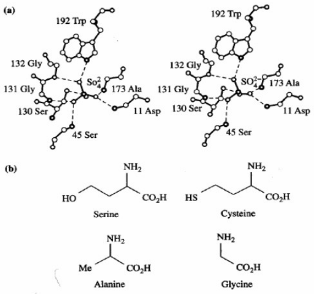


Fig. 2.23:

Concepts in Anion Host Design

FACTORS WITCH AFFECT ANION COMPLEXATION

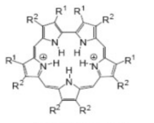
Prevailing interactions which take place in anion binding:

- hydrogen bonding
- ion-dipole and ion-ion interactions
- van der Waals interactions

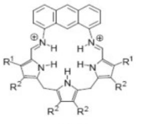
1. Size match between anion and host cavity
2. Complementarity (topological and shape selectivity)
3. Anion and host charge and anion polarisability
4. Solvent (polarity, hydrogen bonding and coordination ability), anion and host free energies of solvation
5. Anion basicity and host acidity
6. Other kinetic, enthalpic and entropic contributions to the anion-host interactions

Porphyrine Hosts

- expanded porphyrine macrocycles



4.14 sapphyrine



4.15

R^1 = Me, R^2 = Et

→ diprotonated sapphyrine forms a stable complex with fluoride (log *K* = 5.0) in methanol

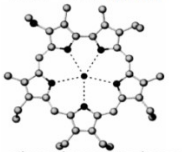
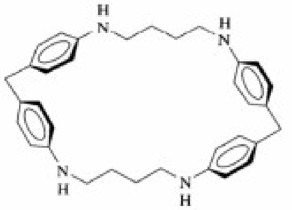


Fig. 2.29: X-ray crystal structure of the expanded porphyrine host **4.14** with encapsulated fluoride. The fluoride anion lies entirely within the plane of the macrycycle (after Shionoya *et al*., 1992)

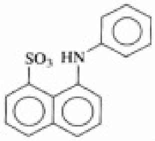
other anions are too large and cannot be encapsulated

→ binding of Cl$^-$ is possible with 4.15

Cyclophane Hosts



(4.16)



ANS
fluorescent

(4.17)

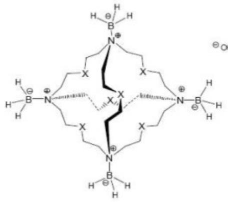
- binding of ANS relies on hydrophobic, π–π stacking interactions, hydrogen bonds and electrostatic interactions

Diphenylmethane used for:

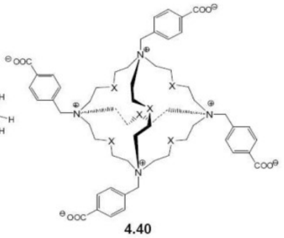
- Curvature
- Rigidity
- Binding ability

Neutral Hosts

- Zwitterions



4.39

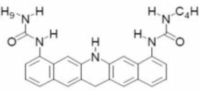


4.40

- 4.39 binds a wide variety of anions and is able to transport them into CHCl$_3$ solution
- 4.40 is very soluble in water. Binding of halides and CN$^-$ in water (log *K* ~ 5 – 6)

Neutral Hosts

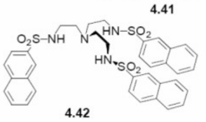
- Hydrogen Bonding Hosts



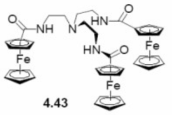
4.41

binding of carboxylate, phosphate and sulphonate

In aprotic solvents



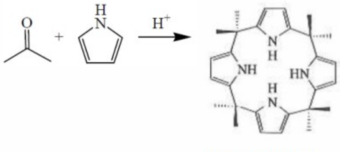
4.42



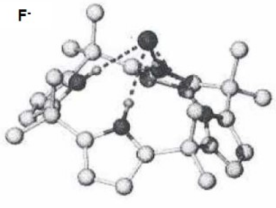
4.43

binding of HPO$_4^{2-}$ (log *K* ~ 4)

Neutral Hosts



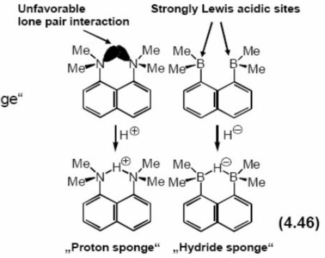
Calix[4]pyrrole



Perching mode
50-fold selectivity for F- over Cl-
K (F-) = 1.7 x 10^4 M^{-1} in DCM

Neutral Hosts

Hosts with Lewis acid atoms,
such as organo boron, silicon, mercury and tin compounds



(4.46)

Fig. 2.30: Comparison of „proton sponge“ and „hydride sponge“

cyclic analogs

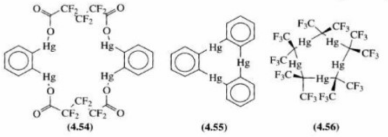
Binding of Neutral molecules

Significantly stronger binding is possible via:
- hydrogen bonding
- weak covalent interactions

Applications:
- separation of related compounds
- storage and slow release of compounds
- sensing of compounds
- catalysis

Anticrowns

Anticrowns:
oxygen atoms of crown ethers are replaced with Lewis acid atoms



(4.54) (4.55) (4.56)

4.54 binds THF which is coordinated at the Lewis acid sites of HG

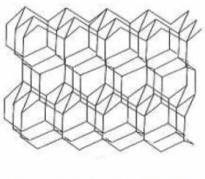
4.55 and 4.56 out of plane binding of halides

Clathrate Compounds

A. Inorganic solid-state clathrate compounds of:
- pores and channels forming inorganic solids (ice, zeolites)
- layered solids (clays, graphite, etc.)

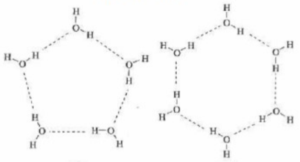
B. Organic solid-state clathrate compounds of:
- urea and other channel forming organic compounds
- cage forming organic compounds

Clathrate Hydrates



Pure ice forms regular lattice without any cavities capable to include guest molecules

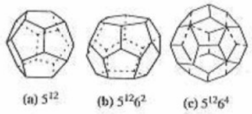
In the presence of hydrate-forming species, a template reaction occurs: polyhedral cavities are formed according to guest size



Clathrate Hydrates

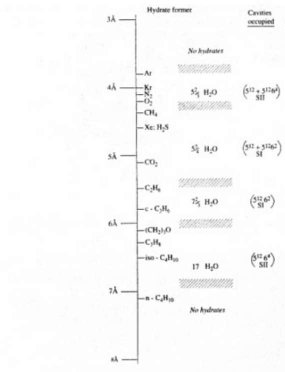
Cavity size (pm):

390 430 470



(a) 5^{12} (b) $5^{12}6^2$ (c) $5^{12}6^4$

Most common types of cavity found in clathrate hydrates I, II

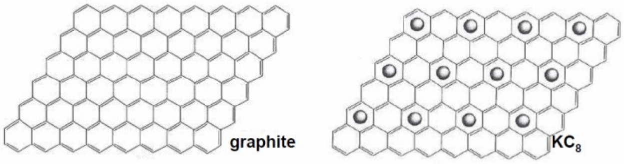


Comparison of guest sizes and cavities occupied as simple hydrates.

Layered Solids and Intercalates

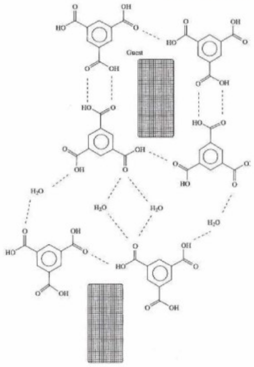
Layered material	Formula
(a) Uncharged layers	
(i) Insulators	
Clays	
Kaolinite, dickite	$Al_2Si_2O_5(OH)_4$
Serpentine	$Mg_3Si_2O_5(OH)_4$
Nickel cyanide	$Ni(CN)_2$
(ii) Electrically conducting layers	
Graphite	C
Transition metal dichalcogenides	MX_2 (M = Ti, Zr, Hf, V, Nb, Ta, Mo, W; X = S, Se, Te)
Metal(IV) oxyphosphates	$MOPO_4$ (M = V, Nb, Ta)
(b) Charged layers	
(i) anionic layers	
Clays	
Montmorillonite	$Na_x(Al_{2-x}Mg_x)(Si_4O_{10})(OH)_2$
Saponite	$Ca_{x/2}Mg_3(Al_xSi_{4-x}O_{10})(OH)_2$
Vermiculite	$(Na,Ca)_x(Mg_{3-x}Li_xSi_4O_{10})(OH_2)$
Muscovite	$KAl_2(AlSi_3O_{10})(OH)_2$
β-alumina	$NaAl_{11}O_{17}$
Alkali transition metal oxides	M^IXO_2 (M^I = alkali metal; X = Ti, V, Cr, Mn, Fe, Co, Ni)
(ii) Positively charged layers	
Hydrotalcite	$[Mg_6Al_2(OH)_6]CO_3 \cdot 4H_2O$

Layered Solids and Intercalates

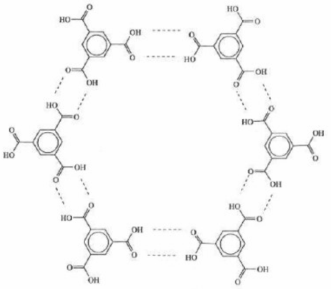


- Pure graphite: 3.35 Å spacing (optimal π–π stacking interactions) It readily forms intercalation compounds :
- MC_8 with metals (K, Rb, Cs, Ca, Sr, Ba, Sm, Eu, Yb) (LiC_6, none with Na) – metals provide electrons to the empty low-energy graphite π*-orbital – oxidizing graphite
- Reducible metal fluorides form fluoroanion complexes – reducing graphite
- Br_2, IBr, ICl (not with other halogens)

Trimesic Acid Clathrates



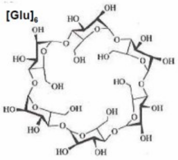
TMA.H_2O.[2/9 picric acid]



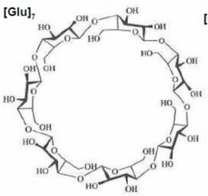
TMA.[0.5 n-tetradecane]

Intracavity Complexes - Cyclodextrins

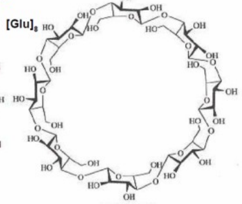
Glucopyranose units,
n = 5-10



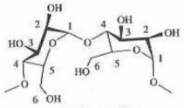
α-Cyclodextrin



β-Cyclodextrin
1500 tons per year, few €/kg



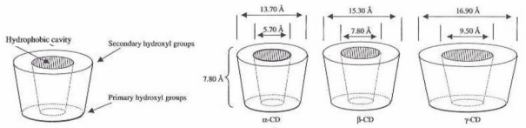
γ-Cyclodextrin



α-1,4-Glycosidic link

Known also those derived from mannose, galactose, …

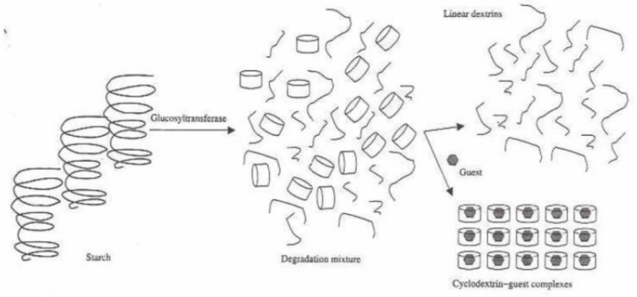
Intracavity Complexes - Cyclodextrins



	α-CD	β-CD	γ-CD
Number of Glu units	6	7	8
Cavity volume (Å^3)	174	262	427
Cavity volume (cm^3 g^{-1})	0.10	0.14	0.20
$[\alpha]_D$ (25 ℃)	150.5	162.0	177.4
Hydrolysis by α-amylase	Negligible	Slow	Rapid
Solubility in water	145 g dm^{-3}	18.5	232
Crystalline hydrate II	6 H_2O (2 in cavity)	11 H_2O (6.3 in cavity)	14.1 H_2O (7.1 in cavity)
Common guests	Benzene, phenol	Naphthalene	Anthracene, crown ethers, 2 glucose

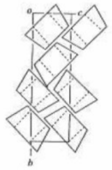
Intracavity Complexes - Cyclodextrins

Preparation

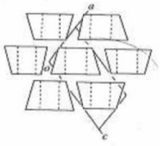


Intracavity Complexes - Cyclodextrins

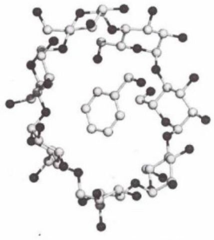
Packing of cyclodextrin units depends on guest size:
- cage and layer type – guest (small enough) can be enclosed fully within CD cavity



← Cage type
α-CD: benzene (height), methanol, propan-1-ol, I_2, krypton, etc.
β-CD: benzyl alcohol, benzene (width)
γ-CD: hydrate (only)



← Layer type



β-CD . benzyl alcohol

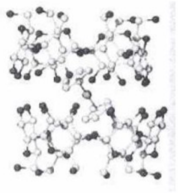
Intracavity Complexes - Cyclodextrins

Host-guest chemistry in solid state

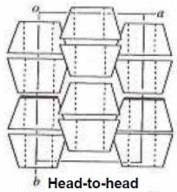
Packing of cyclodextrin units depends on guest size:
- channel type – guest (larger) requires extended
  - cavity of two CD units (head-to-head)
  - channel of more CD units (head-to-tail)

Head-to-tail

γ-CD . [Na([12]crown-4)$_2$]$^+$



2 α-CD . ferrocene



Head-to-head

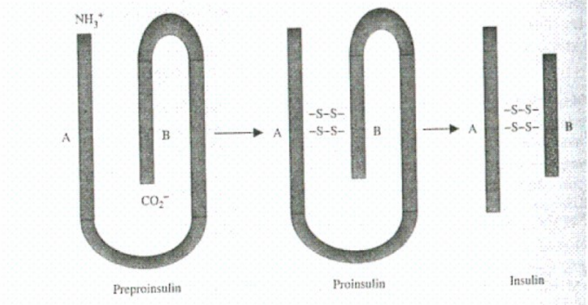
Intracavity Complexes - Cyclodextrins

Applications

Nontoxic, stable, relatively cheap

Slow-release and compound-delivery agents:
- Food: dramatically reduce the amounts of expensive flavour oils and spices, needed in order to achieve the required flavour strength (~ 60 times). Complexed flavourings are in addition much more resistant to oxidation, photochemical degradation, thermal decomposition. It is more easy to store, handle, weigh and traNsport them
- Cosmetics: slow-release fragrance, etc.
- Pharmaceutics: prevent premature drug metabolism (oral vs. Intravenous delivery), enhance solubility of poorly soluble drugs, relieve local irritation or drug-induced damage, mask unpleasant drug taste
- Analytical chemistry: separation methods – capillary electrophoresis, chromatography (LC, HPLC, GC), including separation of enantiomers (replace for expensive chiral stationary phases)

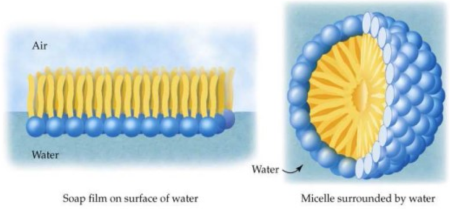
Self-Assembly with Covalent Modifications



Biosynthesis of insulin by self-assembly followed by covalent modification.

Self-Assembly

Self-organization – interactions between constituents parts of self-assembled entities and the integration of those interactions leading to collective behavior such as phase changes.

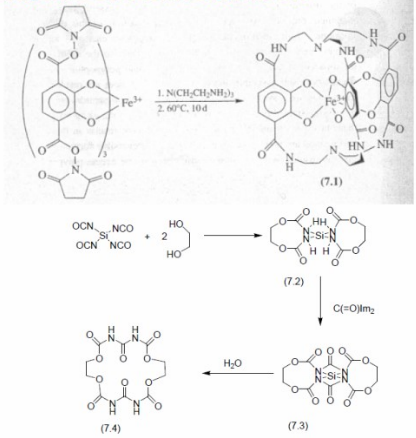


Soap film on surface of water

Micelle surrounded by water

Template effect in Synthesis

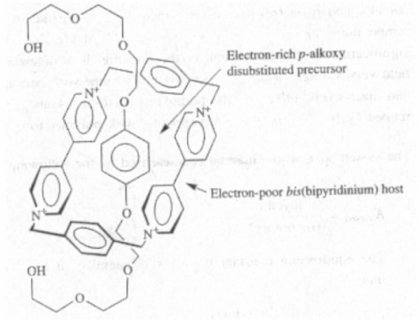
Metal ions as kinetic templates



Covalent template synthesis of an 18-membered macrocycle

Template Effect in Synthesis

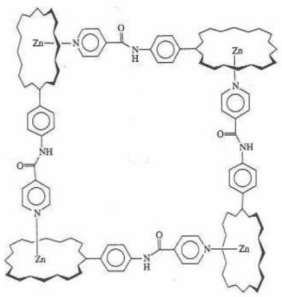
- A catenane or rotaxane precursor:

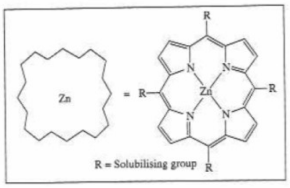


- Interpenetration of an electron-rich guest with an electron-poor macrocycle

A Thermodynamic Model of Self-Assembly

Zinc Porphyrine Complexes:
Zn-pyridyl bond is labile in organic solvents

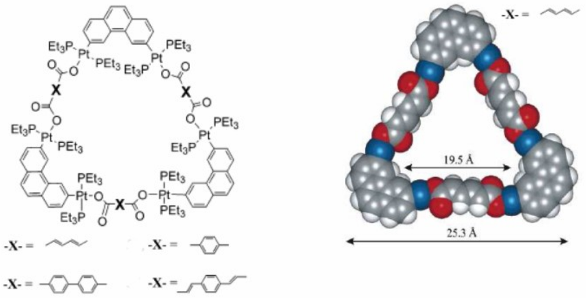




Also dimer and trimer due to the flexibility of the bridge

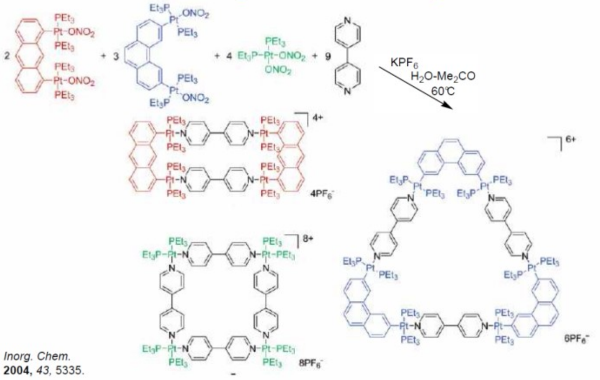
Self-Assembling Coordination Compounds

A. POLYGONS: Trinuclear Structures



One of the units with 60°

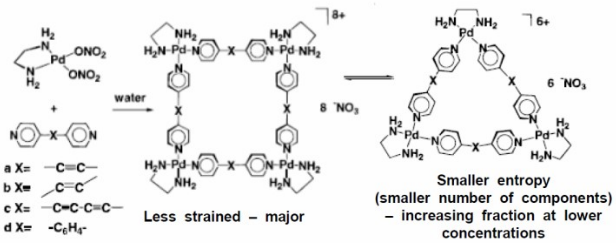
Self-Assembling Coordination Compounds



Inorg. Chem. **2004**, *43*, 5335.

Self-Assembling Coordination Compounds

A. POLYGONS: Tri- and Tetranuclear Structures



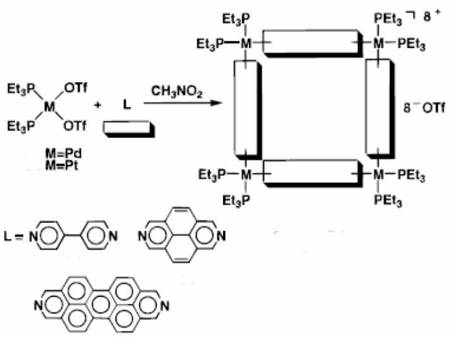
Less strained – major

Smaller entropy (smaller number of components) – increasing fraction at lower concentrations

Equilibrium monitored by ^{1}H NMR
Signals assigned in combination with Electron Spray MS
Molecular square (X=nothing) binds naphtalene

Self-Assembling Coordination Compounds

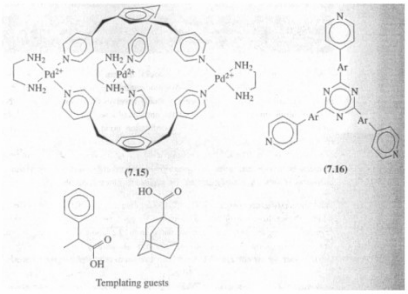
A. POLYGONS: Tri- and Tetranuclear Structures



With more sterically demanding ligands squares are exclusively formed

Self-Assembling Coordination Compounds

- Cryptand synthesizable only through induced fit of a guest because the linkers are flexible
- Templated with phenylpropionic acid or adamantanecarboxylic acid, not with cations or xylene
- Stable even after synthesis and removal of the guest, not necessarily a thermodynamic product



- (adamantanecarboxylic acid)$_4$@[Pd(en)]$_{12}$(**7.16**)$_8$]$^{12+}$, allosteric effect, 4.6 nm

Enzyme Mimics

Biochemical systems:

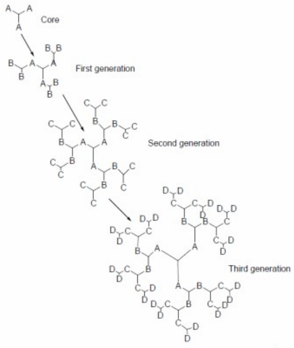
Binding is a trigger to events:

Binding induces a conformational change in the receptor that turns on a process

- **Hormones → chemical dephosphorylation reactions**
- **Neurotransmitters → nerve impulses (membrane depolarization)**

Dendrimers

- From the Greek "dendron" = tree
- Highly branched, monodisperse macromolecules
- Contains an highly porous core region and a densely packed outer layer (strongly depends on the length of the spacers, the branch ratio and the bulkiness of the end groups.
- Applications: hydrophobic pockets, light-harvesting ...



Schematic diagram showing the iterative preparation of dendrimers

Dendrimers

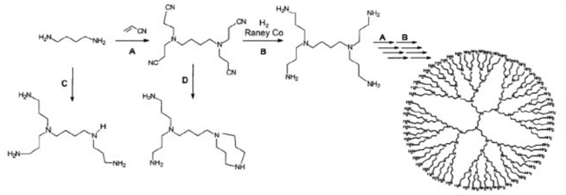
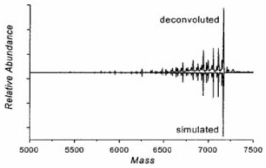


Figure 1. The synthesis of poly(propylene imine) dendrimers (reactions A and B) and alternative, unwanted reaction paths C and D. Path C illustrates "missed" Michael additions (either by an incomplete cyanoethylation or by a retro-Michael reaction). Path D illustrates unwanted cyclization reactions. Paths C and D describe defect reactions on going from one amine generation to the next.[27]

Nice NMR, CHN, HPLC, polydispersity etc.
but:
dendridic purity = 23% (ESI-MS)

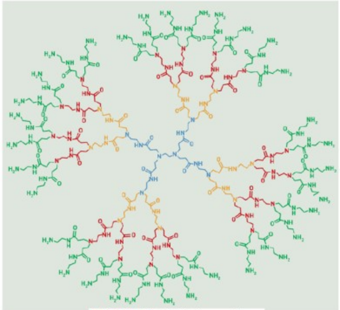
it corresponds roughly to 248 reactions performed with 99.5 % selectivity leading to 29 % purity



Dendrimers

- **Preparation of dendrimers**
- **The divergent synthesis (1978):**
  successive generations are added in an iterative manner from the core
  → many reactions per iteration leading to small defects
  → difficult to purify
  → can not be defect free, "macromolecular chemistry approach"
- **The convergent synthesis (1990):**
  construction from the outer surface inwards
  → less reactions per iteration leading to a massive defect in case of failure
  → relatively easy to clean after each stage
  → can be defect free, "organic chemistry approach"

Dendrimers

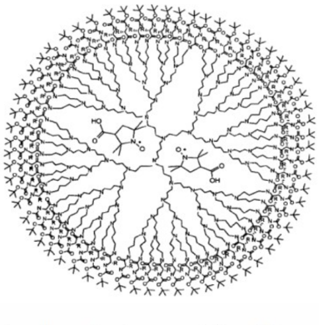


TENDRILS In this third-generation PAMAM dendrimer, the core is shown in blue and each successive generation is shown in a different color.

Figure 6. Structure of a Fréchet-type polyaryl ether dendritic wedge.

- **PAMAM family commercially available**

Dendrimers



A two-dimensional representation of the dendritic box (DAB-*dendr*-(NH*t*-BOC-L-Phe)$_{64}$ containing two 3-carboxy-PROXYL radicals

Dendritic box

- irreversible guest encapsulation by functionalization with bulky groups
- Release only by removal of the protecting groups
- Induced chirality in CD experiments with 4 rose Bengal molecules as guest → well-defined relative orientations

Dendrimers

Cytochrom c analogue

- **Protection from the aqueous solution**
- **Increase the redox potential by 0.4 V (more hydrophobic environment)**