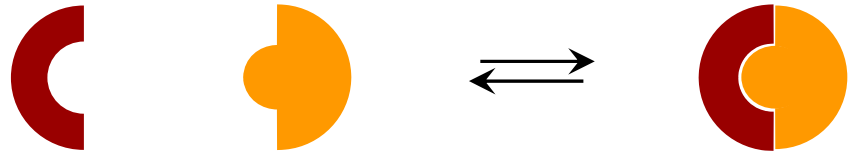
Complementarity and preorganization



Host *Guest* *Supramolecule (host-guest complex)*

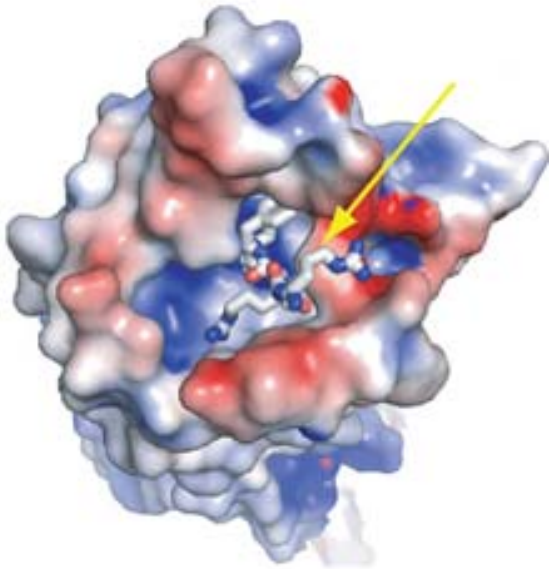
A **supramolecular receptor** (*host*) is a **synthetic** (*abiotic*) molecules that **selectively** (and **reversibly**) **binds** (*recognizes*) a selected **substrate** (*guest*).

$$K = \frac{[Supramolecule]}{[Host][Guest]}$$

Molecular recognition occurs through weak (non covalent, reversible…) interactions

HOW ?

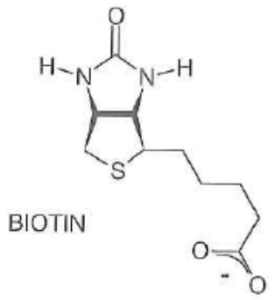
Nature's receptors

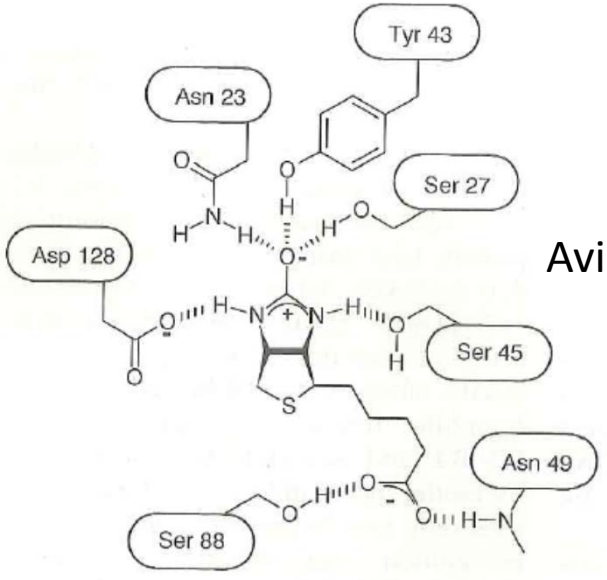


Neurotensin (see arrow) in the binding pocket of Neurotensin Receptor 1 (NTSR1)

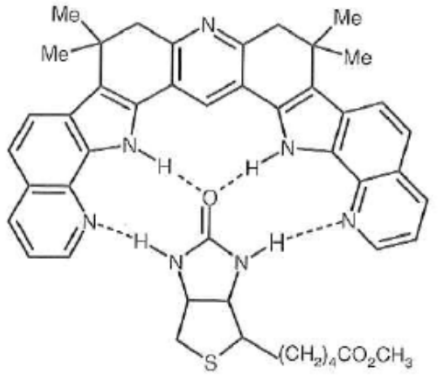
Which is the difference between the binding pocket and the remaining protein surface?

Nature's vs manmade receptors





Avidin



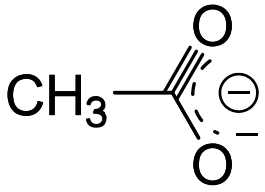
$K = 10^{13}\ M^{-1}\ (H_2O)$

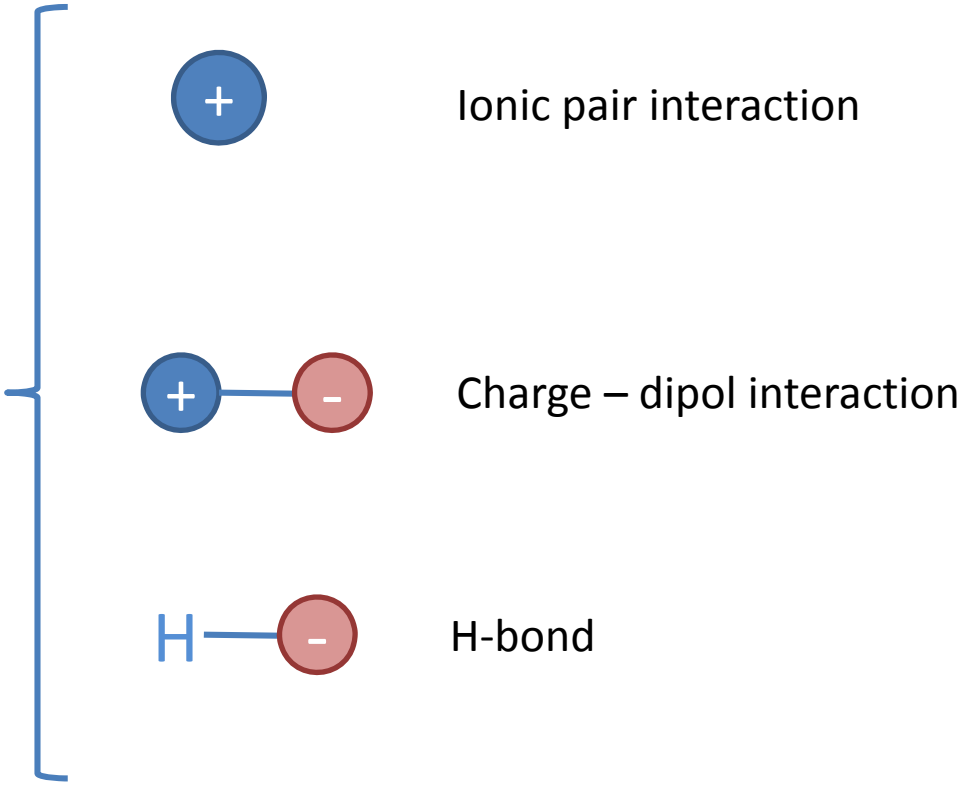
$K = 10^{4}\ M^{-1}\ (CDCl_3)$

- Many interactions
- Tridimensional structure

Designing a receptor: the interactions

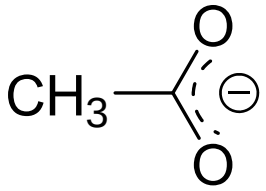
Guest:

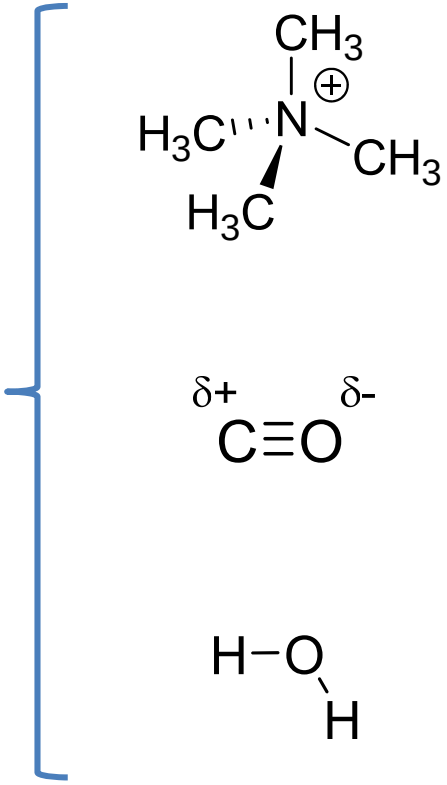




K_a = 1.000.000 M^{-1} ⟹ ΔG = 34 KJ/mol

Interacting molecules are not receptors

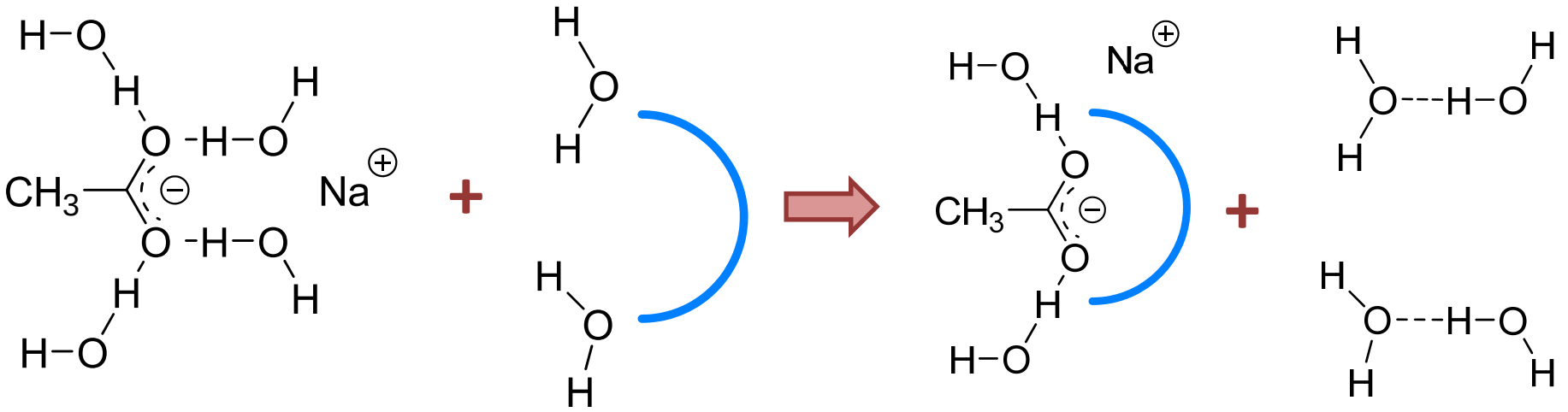
Guest: 



Receptors ?

- Weak binding
- No selectivity

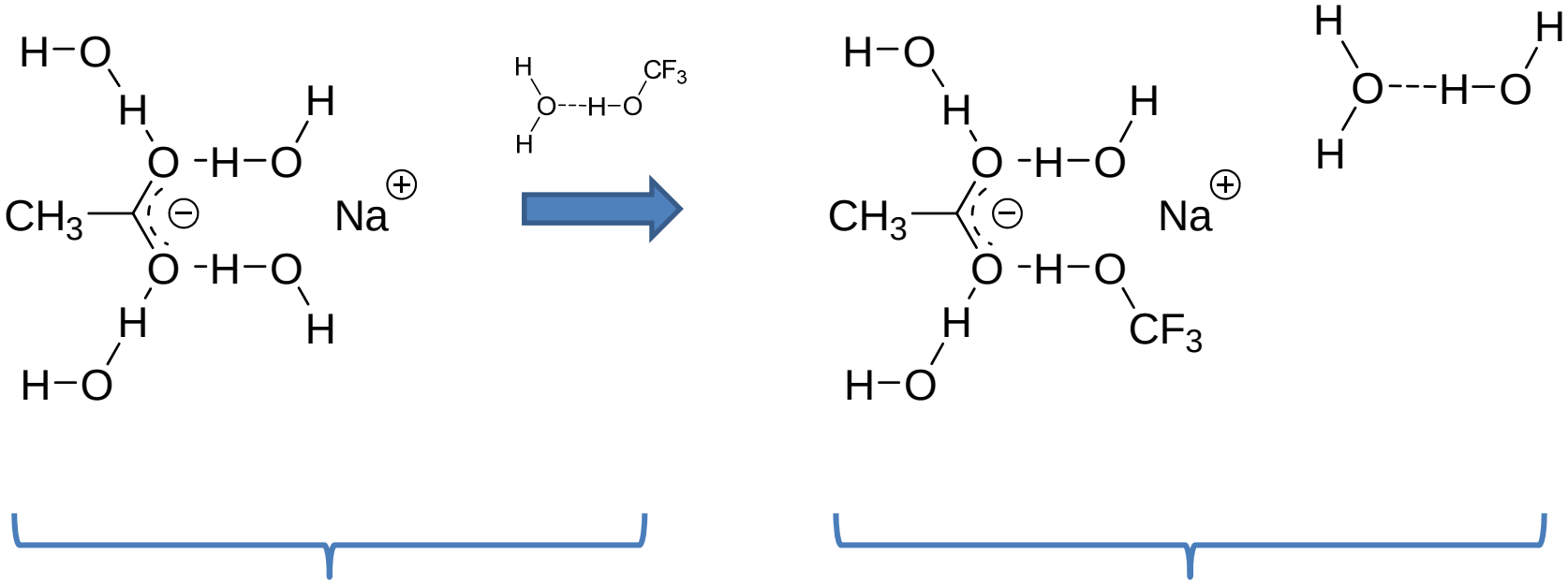
Recognition at play



- Multiple interactions lead to selectivity
- Recognition involves desolvation, H-G intraction are not the only one to consider
- Water is 55 M !!
- Entropy must be taken into account

From binding to recognition

Using a good interaction

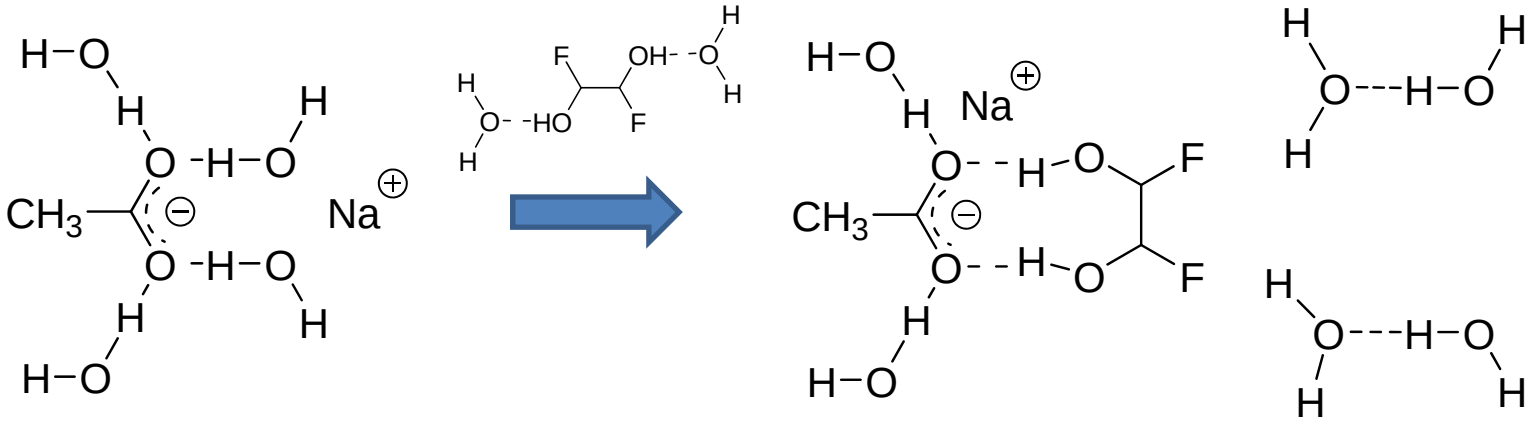


2 “medium strenght” H-bonds

1 weaker H-bond, 1 stronger H-bond

From binding to recognition

If a single interaction is too weak, what about many?



$$\Delta G = \alpha\Delta G_1 + \beta\Delta G_2 + \ldots.$$

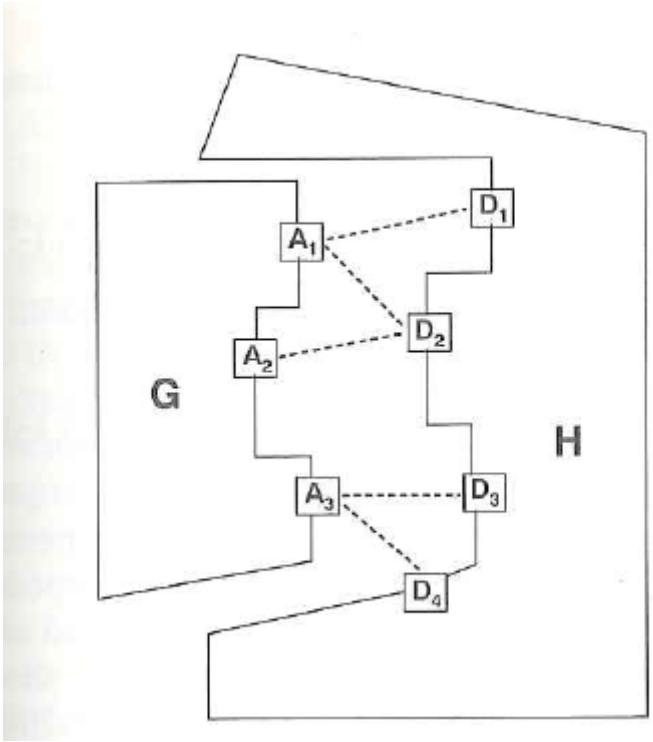
$\Delta H = \Delta H_1 + \Delta H_2 + \ldots.$ Adding up interaction increases (in most cases) binding strength

ΔS

From two species to three species ($\Delta S < 0$)

Difluoroethanol looses conformational entropy ($\Delta S > 0$)

Summing up-contributions



$$K = \frac{[HG]}{[H][G]} = e^{-\frac{\Delta G_0}{RT}}$$

$$\Delta G_0 = \Delta G_{A1D1} + \Delta G_{A1D2} + \Delta G_{A2D2} + \Delta G_{A3D3} + \Delta G_{A3D4}$$

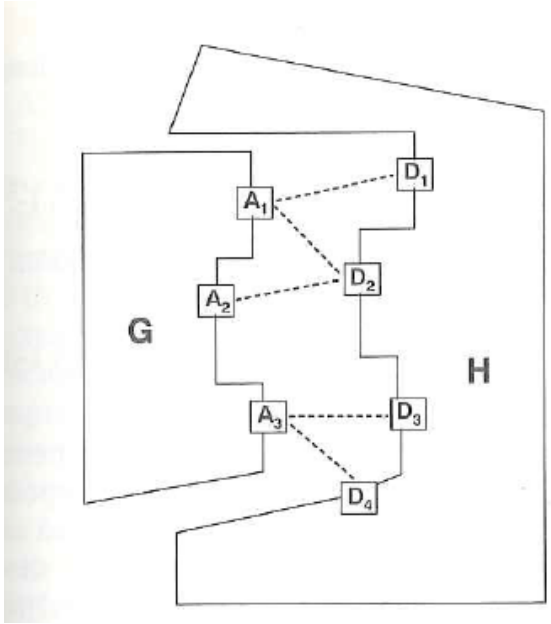
Summing up-contributions

$$\Delta G_0 = \Delta G_{A1D1} + \Delta G_{A1D2} + \Delta G_{A2D2} + \Delta G_{A3D3} + \Delta G_{A3D4}$$

$$\Delta G_0 = \sum \Delta G_{ij}$$

$$K = \prod K_{ij}$$

M^{-1} $(M^{-1})^n$



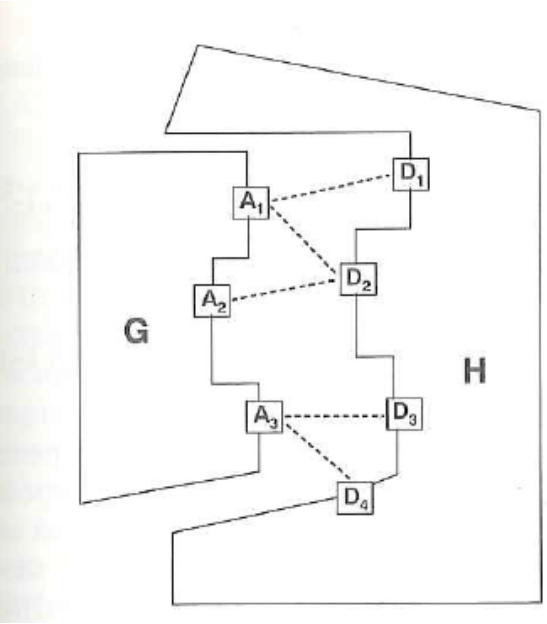
$$\chi_i = \frac{[H,G]_i}{[S]}$$

$$K_{ij}(\chi) = \frac{\chi_{A_i - D_j}}{\chi_{A_i}\chi_{D_j}} = \frac{[A_i - D_j]/[S]}{[A_i]/[S]\,[D_j]/[S]} = [S]K_{ij}(\chi)$$

$$K_{ij}(\chi) = [S]K_{ij}(M)$$

Generic association entropy

$$K = \prod K_{ij}$$

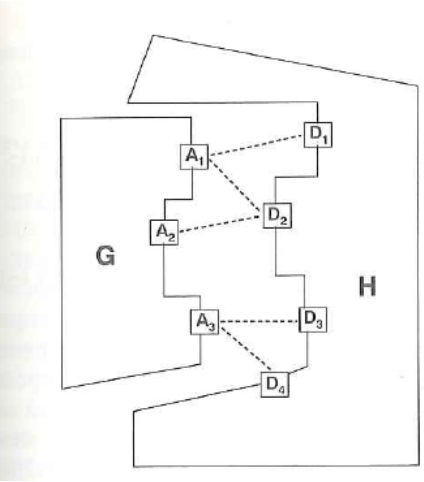


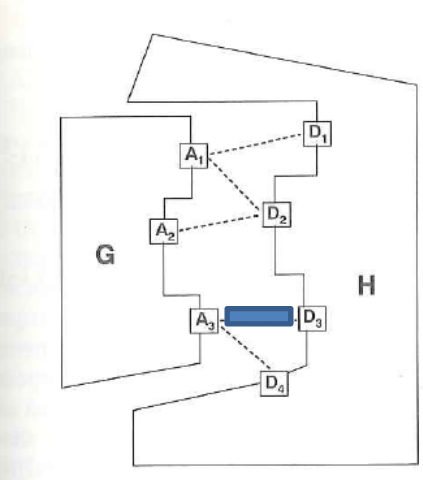
$$K(M) = \frac{K(\chi)}{[S]} = \frac{\prod K_{ij}(\chi)}{[S]} = \frac{[S]^n \prod Kij(M)}{[S]} = [S]^{n-1} \prod Kij(M)$$

-RT*ln*[S] entropic correction applied to all the interactions but one
(non specific dilution entropy contribution, 10 KJ mol^{-1} at 25 °C)

3 interactions, K_{ij} = 1 M^{-1} $\Rightarrow$ K = 3 × 10^3 M^{-1} (water, 55.6 M)

Individual free energy contributions





One interaction removed

$$K = \frac{[HG]}{[H][G]}$$

$$K_{i-1j-1} = \frac{[H_{i-1}G_{j-1}]}{[H_{i-1}][G_{j-1}]}$$

$$\frac{K}{K_{i-1j-1}} = K_{ij}$$

$$-RTlnK_{ij} = \Delta\Delta G_{ij}$$

Intramolecular free energy contribution of each single interaction to the formation of the supramolecule. It can be positive!

$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

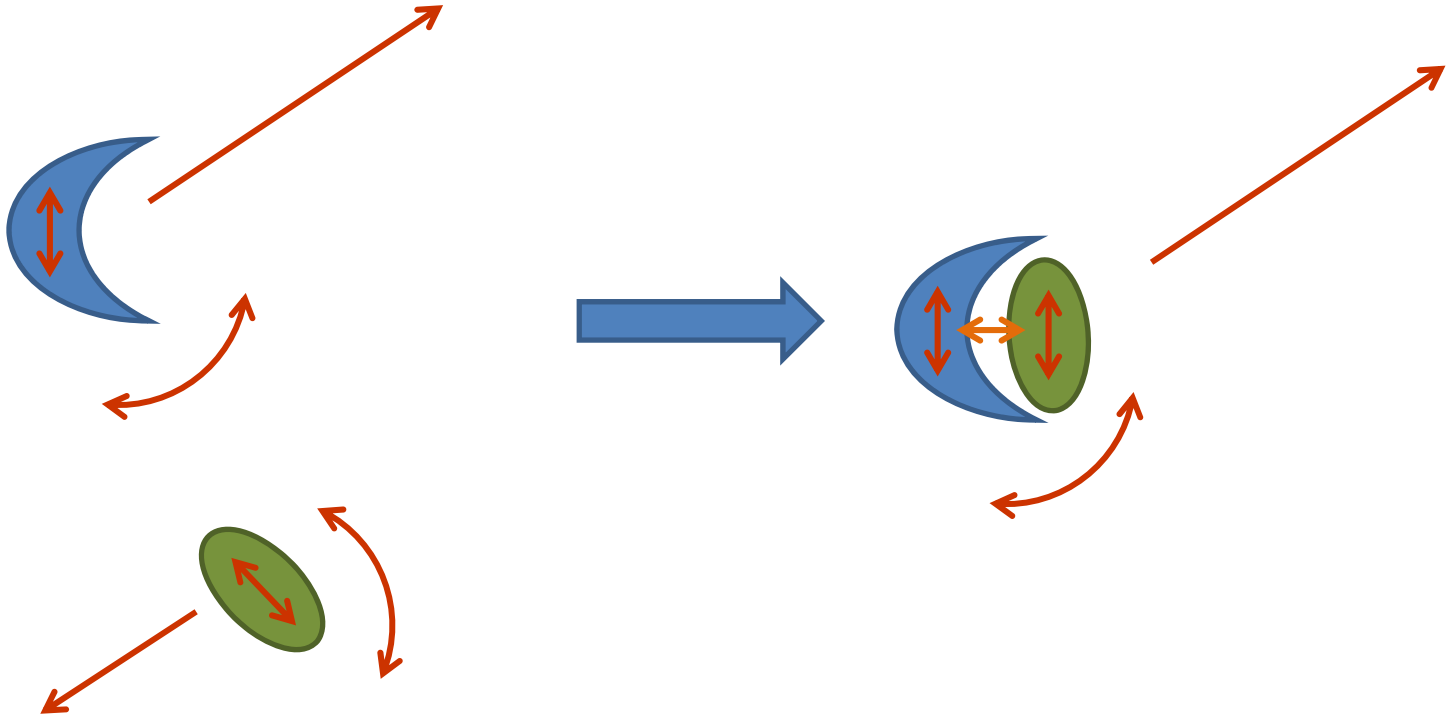
Intermolecular free energy contribution for the association of the host and guest. It is mainly an entropic contribution but it may contain solvatation contributions.

$$K = K_{ass} \prod K_{ij}$$

Gas phase entropy of association

Entropic contributions to association:

- Translational entropy
- Rotational entropy
- Internal rotation entropy
- Vibrational entropy



Gas phase entropy of association

Translational entropy

$S_{transl} \propto \ln MW$

140 J mol^{-1} K^{-1} (MW 100 Da)

Host (large) + Guest (small)

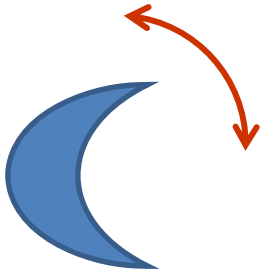
$\Delta S_{transl} \approx S_{transl}(host)$

$\Delta S_{transl} \approx -135\ Jmol^{-1}K^{-1}$

$T\Delta S_{tranl} \approx 40\ KJmol^{-1}$

Gas phase entropy of association

Rotational entropy



$$\Delta S_{rot} \approx -100\, Jmol^{-1}K^{-1}$$

$$T\Delta S_{tranl} \approx 30\, KJmol^{-1}$$

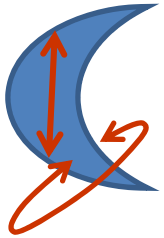
$$S_{transl} \propto \ln(MW, Shape)$$

100 J mol^{-1} K^{-1} (MW 100 Da)

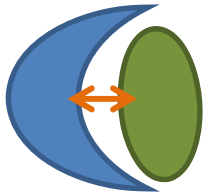
Gas phase entropy of association

Internal rotational and vibrational entropy

$$S_{vibr} \approx 0 - 1\ Jmol^{-1}K^{-1}$$



$$S_{intern.rot.} \approx 10 - 20\ Jmol^{-1}K^{-1}$$ x bond



Low frequency (ν < 200 cm^{-1}) vibration give a substantial contribution to entropy

Gas phase/solution entropy of association

Table A 1. Selected association entropies ($J\,mol^{-1}K^{-1}$) for different types of interactions compiled from published data.[16, 19–21]

Reaction	*Interaction*	*Phase*	ΔS_{ass}	*Ref.*
Dimerization of cyclopentadiene	covalent	gas	− 167	16
		liquid	− 154	16
Complexation of MeOH with Et_3N	H-bond	gas	− 81	19
		CCl_4 solution	− 39	20
Complexation of *p*-xylene with tetracyanoethylene	charge transfer	gas	− 65	21
		CH_2Cl_2 solution	− 31	21

$$\Delta S_{ass} = \Delta S_{trasl} + \Delta S_{rot} + \Delta S_{intern.rot.} + \Delta S_{vibr}$$

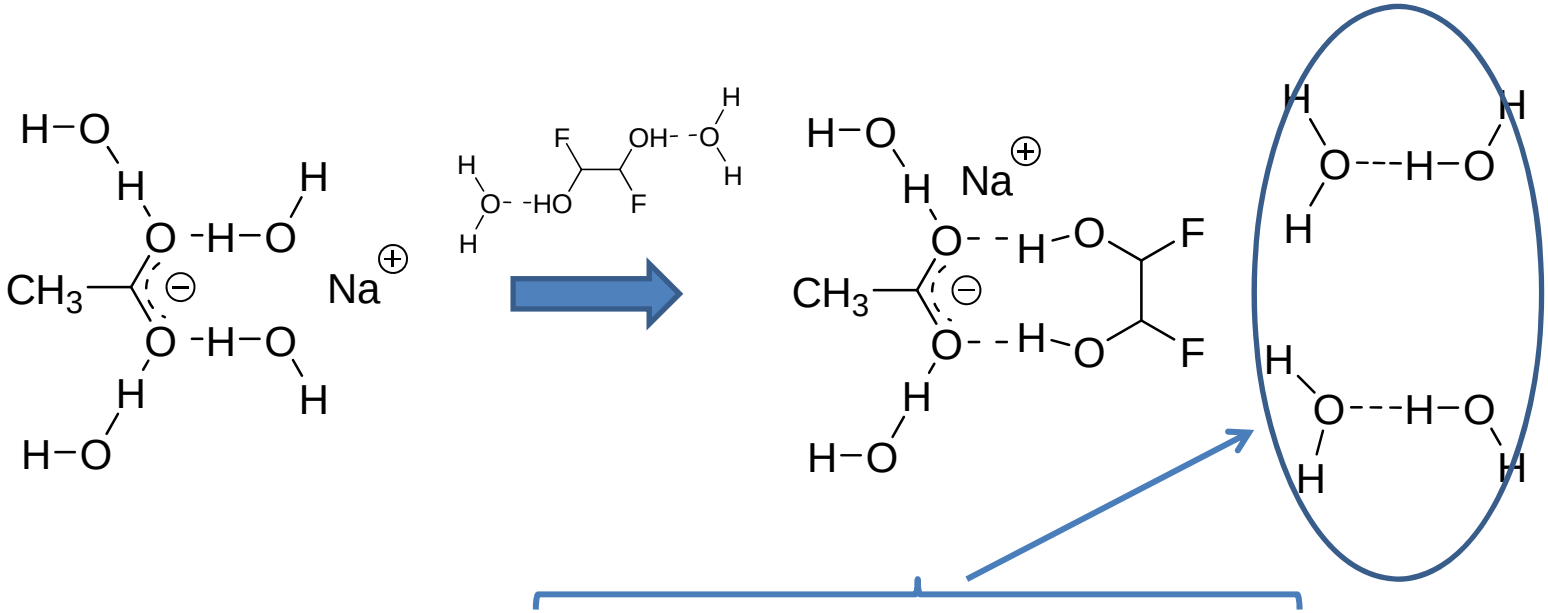
Solvation Entropy

$$\Delta S_{ass} = -135 - 140 + 0 - 5 = -240 \text{ J mol}^{-1} \text{ K}^{-1}$$

$$\Delta S_{ass} = -135 - 140 + 15 + x = -220 + x \text{ J mol}^{-1} \text{ K}^{-1}$$

$$X = 140 \text{ J mol}^{-1} \text{ K}^{-1}$$

Association and solvation



$$\Delta G = \Delta G_{HG}(gas) + \Delta G_{H}(desolv) + \Delta G_{g}(desolv) + \Delta G_{HG}\ (solv)$$

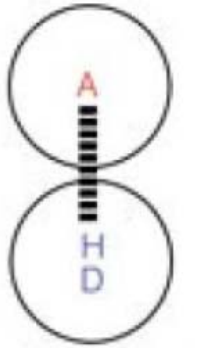
The solvation contribution reduces the entropic cost of association

The solvent-solvent interaction may reduce the enthalpic cost of desolvation

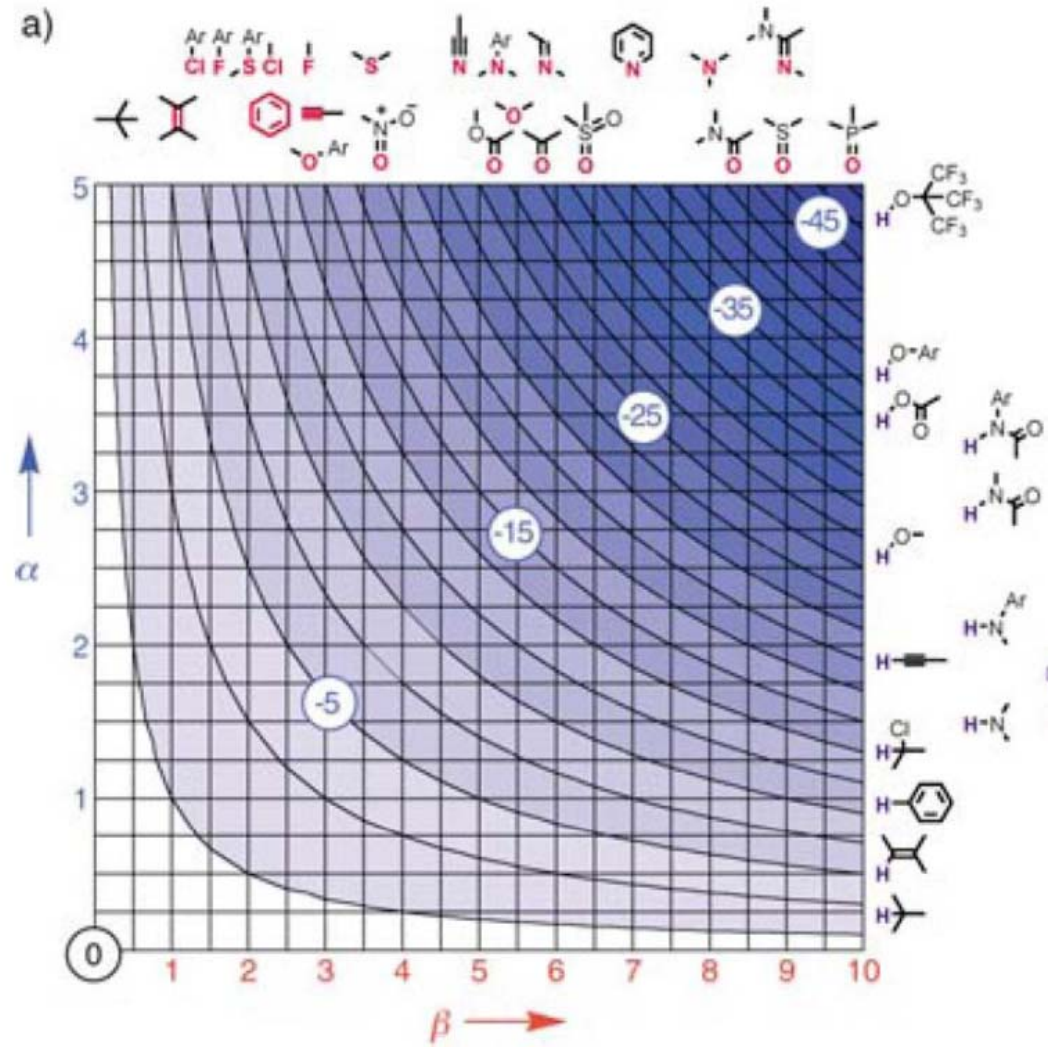
Association and solvation

Hunter $\alpha\,\beta$

vacuum



b

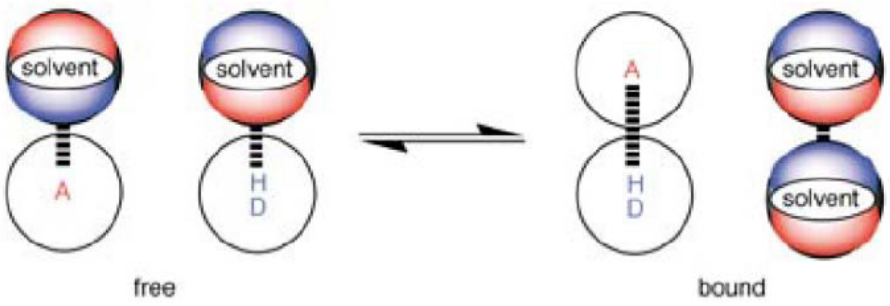


$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

C.A. Hunter, ANIE 2004, 43, 5310

Association and solvation

Hunter $(\alpha - \alpha_s)(\beta - \beta_s)$



$\alpha\,\beta_S \quad \alpha_S\,\beta \qquad\qquad \alpha\,\beta \quad \alpha_S\,\beta_S$

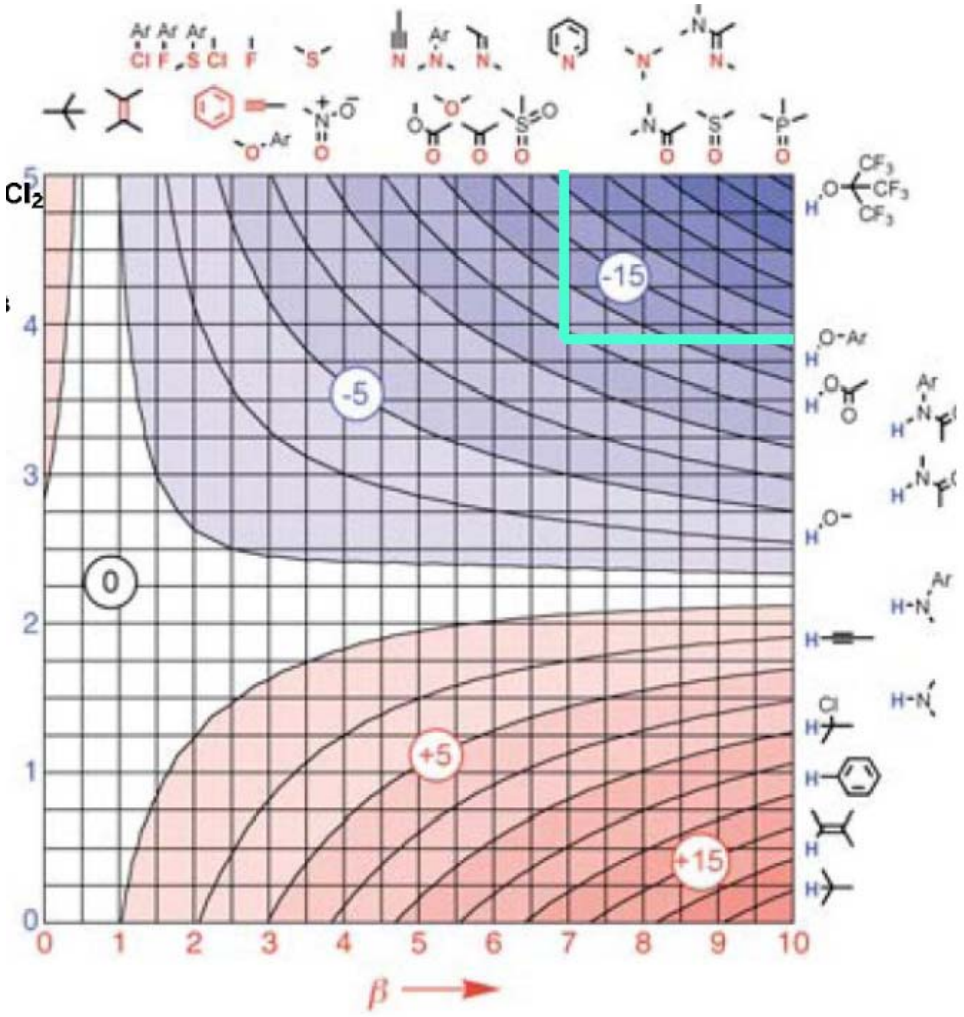
$$\Delta G = (\alpha\,\beta_S + \alpha_S\,\beta) - (\alpha\,\beta + \alpha_S\,\beta_S) \quad +c$$
$$= \quad (\alpha - \alpha_S)(\beta - \beta_S) \quad +c$$

$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

C.A. Hunter, ANIE 2004, 43, 5310

Association and solvation

$CHCl_3$

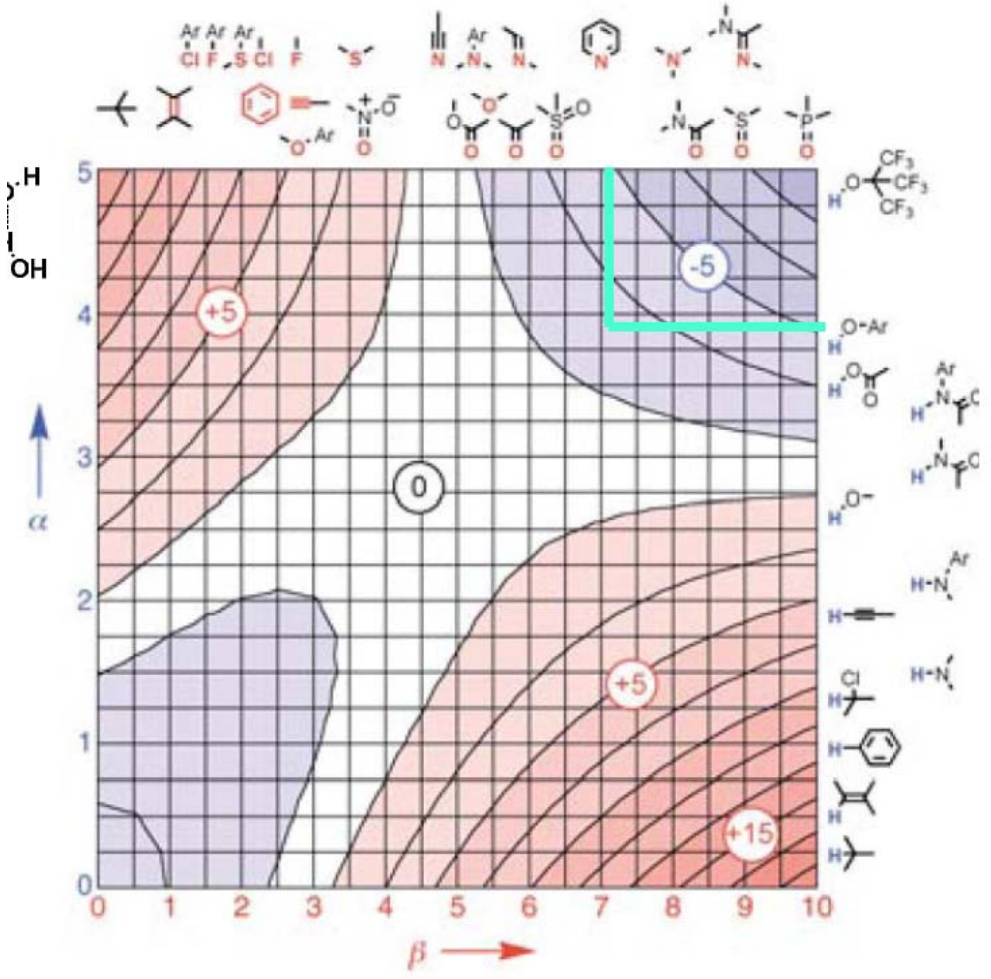


$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

C.A. Hunter, ANIE 2004, 43, 5310

Association and solvation

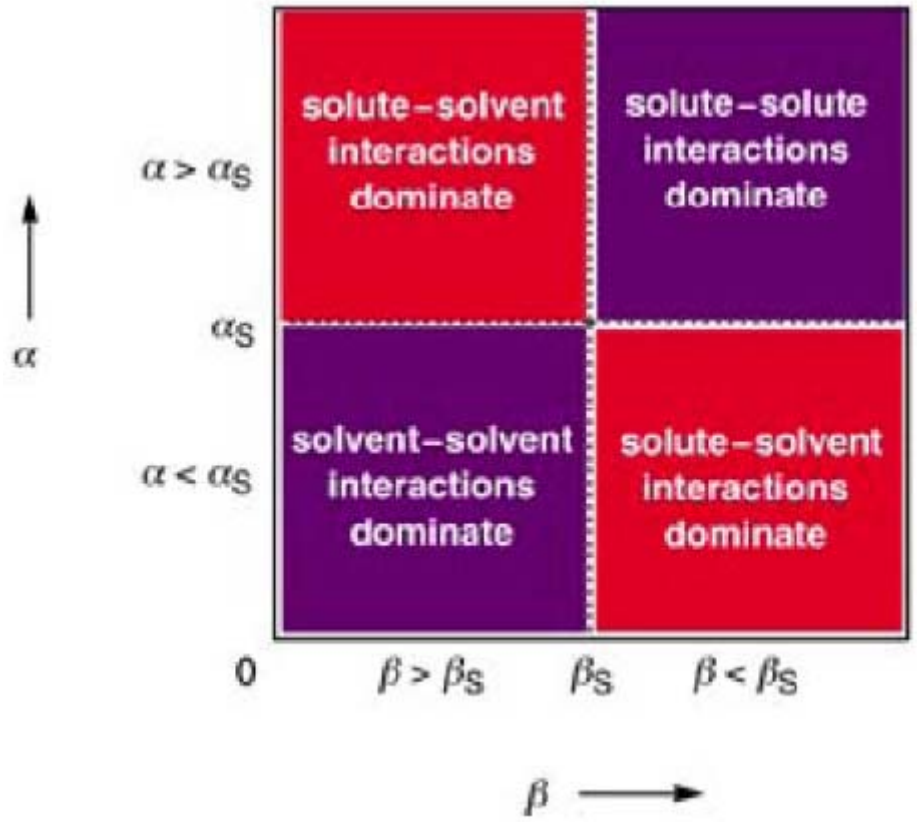
H_2O



$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

C.A. Hunter, ANIE 2004, 43, 5310

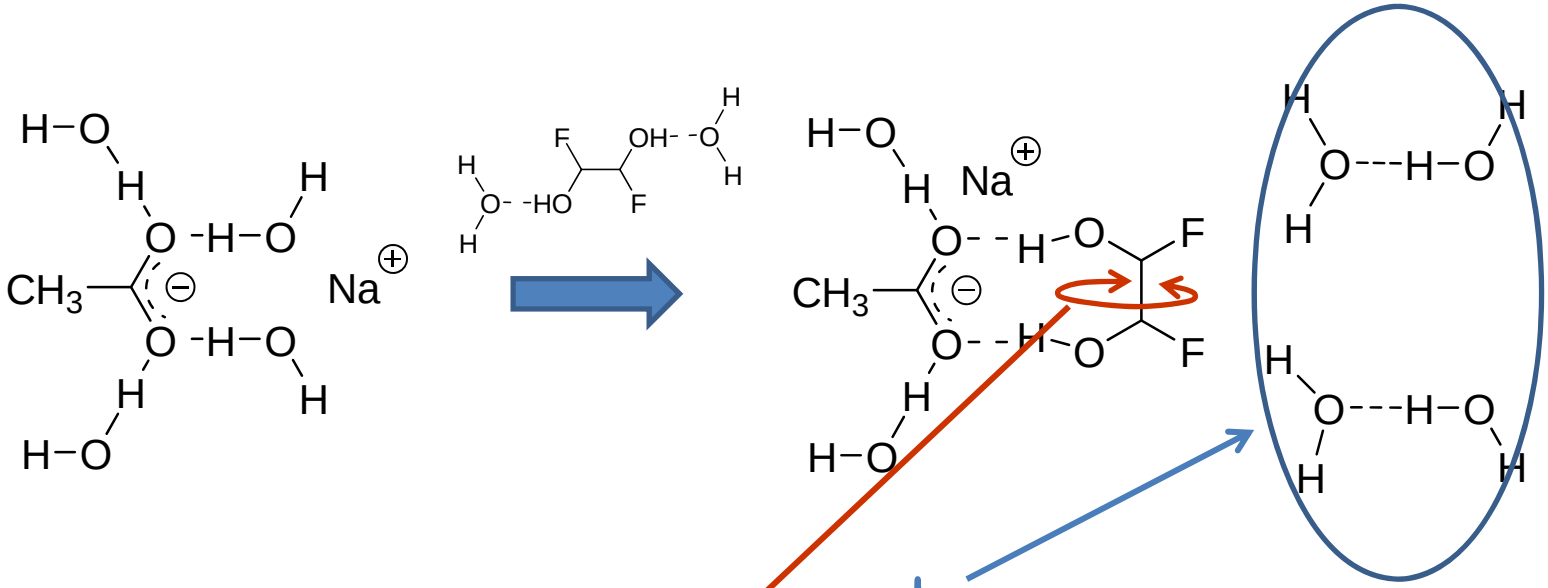
Association and solvation



$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

C.A. Hunter, ANIE 2004, 43, 5310

Internal association entropy: preorganization



$$\Delta G = \Delta G_{HG}(gas) + \Delta G_{H}(desolv) + \Delta G_{g}(desolv) + \Delta G_{HG}\ (solv)$$

The solvation contribution reduces the entropic cost of association
The solvent-solvent interaction may reduce the enthalpic cost of desolvation

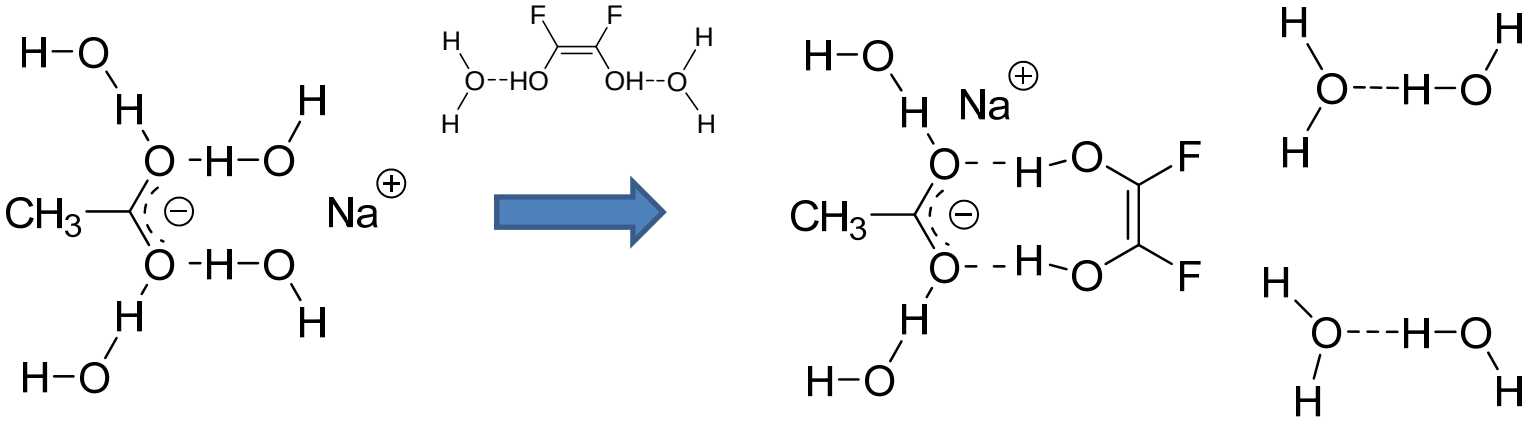
Freezing of internal rotation may imply significant additional entropic costs:

$3 \times 15\ J\ mol^{-1}\ K^{-1} = 45\ J\ mol^{-1}\ K^{-1} \Rightarrow 13\ KJ\ mol^{-1}$ (25°C)

1000-fold reduction of K

Preorganization

Making the host more rigid is an advantage?



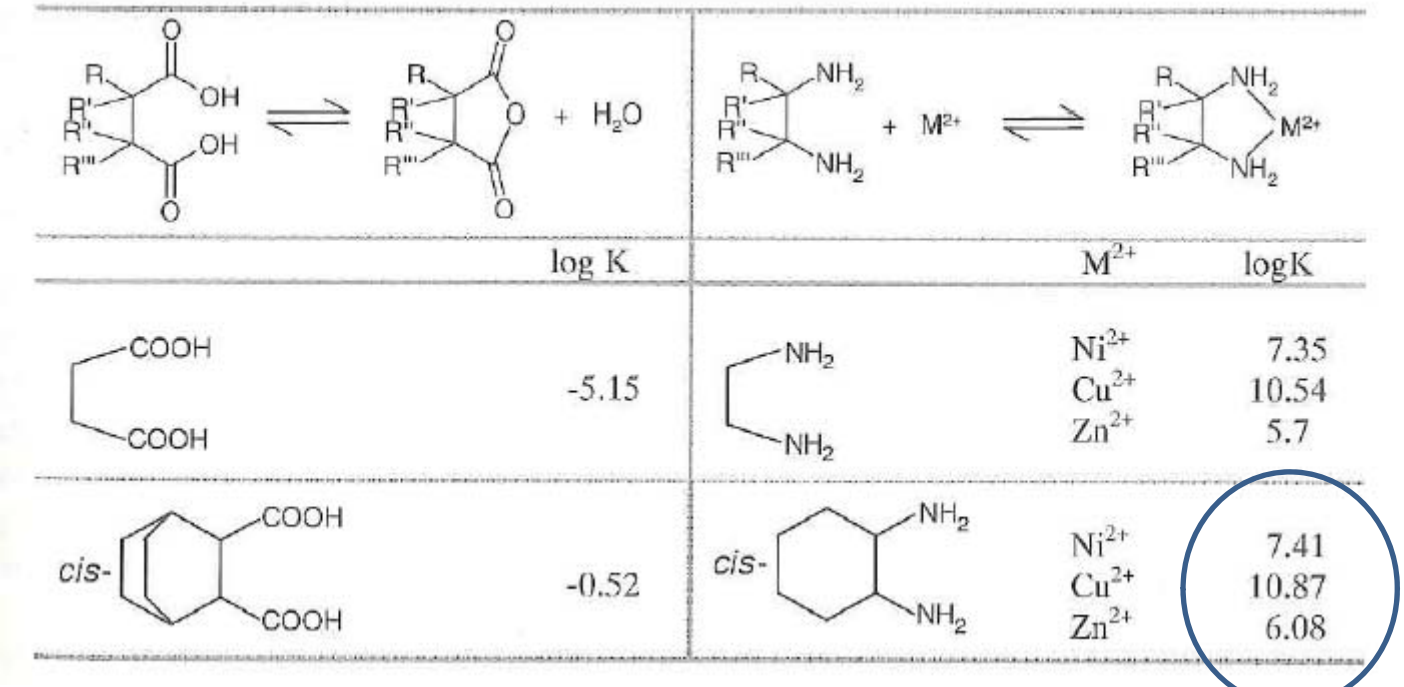
No entropy loss by the host in binding the guest.

Preorganization “the more highly hosts and guests are organized for binding and low solvation prior to their complexation, the more stable will be their complexes” (Cram)

What about the supramolecule?

Preorganization

Making the host more rigid is an advantage?



	log K		M^{2+}	logK
flexible	-5.15		Ni^{2+}	7.35
			Cu^{2+}	10.54
			Zn^{2+}	5.7
rigid	-0.52		Ni^{2+}	7.41
			Cu^{2+}	10.87
			Zn^{2+}	6.08

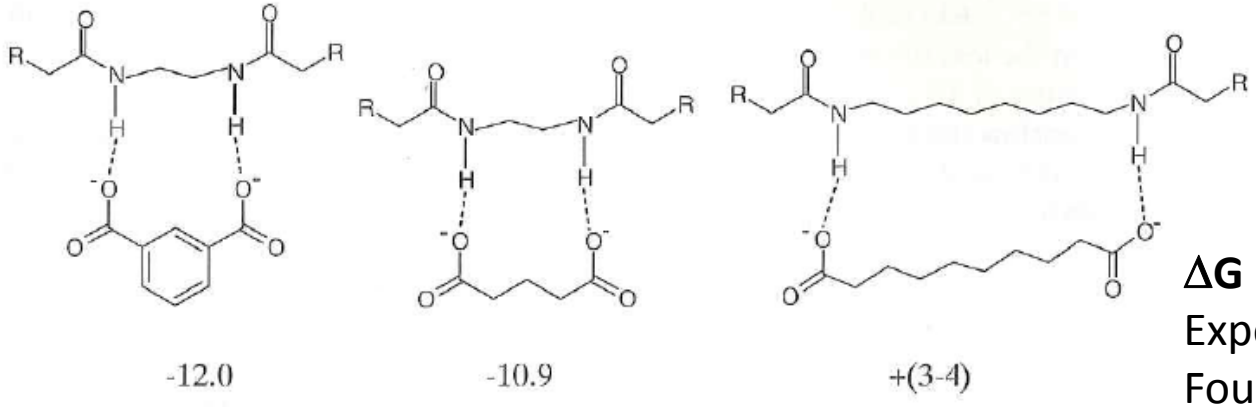
Expected reduction (3 rotors) = 1000-fold

Low frequency vibrations compensate
the entropy loss arising from rigidification

Preorganization

Making the host more rigid is an advantage?

H-Bonded complexes (in $CDCl_3$)[27a]

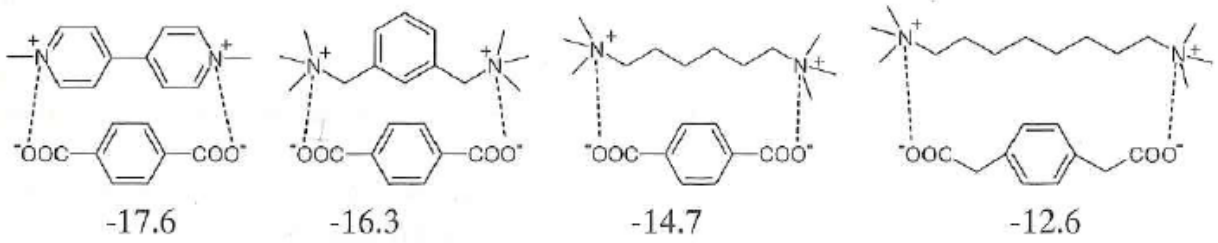


ΔG increase

Expected = 3-5 KJ mol^{-1} per rotor

Found = ~ 1.3 KJ mol^{-1} per rotor

Ion pairs (in water at zero ionic strength) [27b]



Scheme A 2. Association free energies ΔG (kJ mol^{-1}) of selected host–guest complexes with a varying number of single bonds between binding sites, from published data.[27a,b]

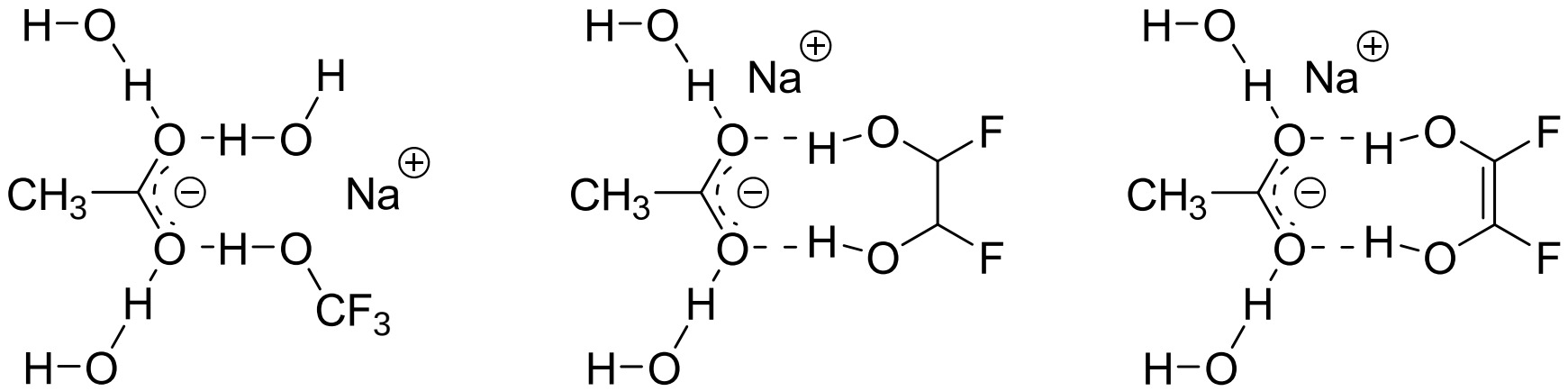
ΔG increase

Expected = 3-5 KJ mol^{-1} per rotor

Found = ~ 0.4 KJ mol^{-1} per rotor

Entropy-enthalpy compensation

Increasing the interaction and host more rigidity is always an advantage?



Increase in binding sites makes the supramolecule more rigid.

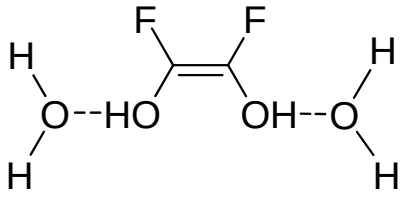
Entropic contribution by low frequency vibration may compensate the entropic loss for reduced internal rotations

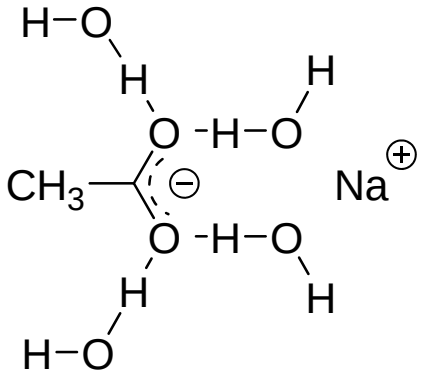
In some cases when binding becomes more enthalpically favorable, it becomes more entropically unfavorable. The net effect is that ΔG remains fairly constant.

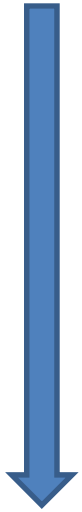
Complementarity

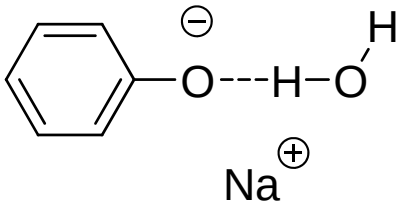
Why preorganization?

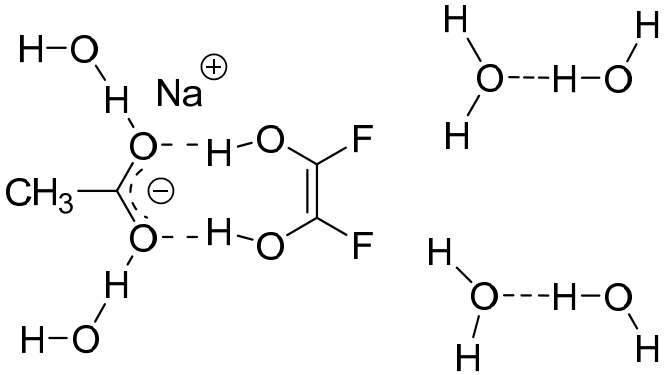
1) Selectivity







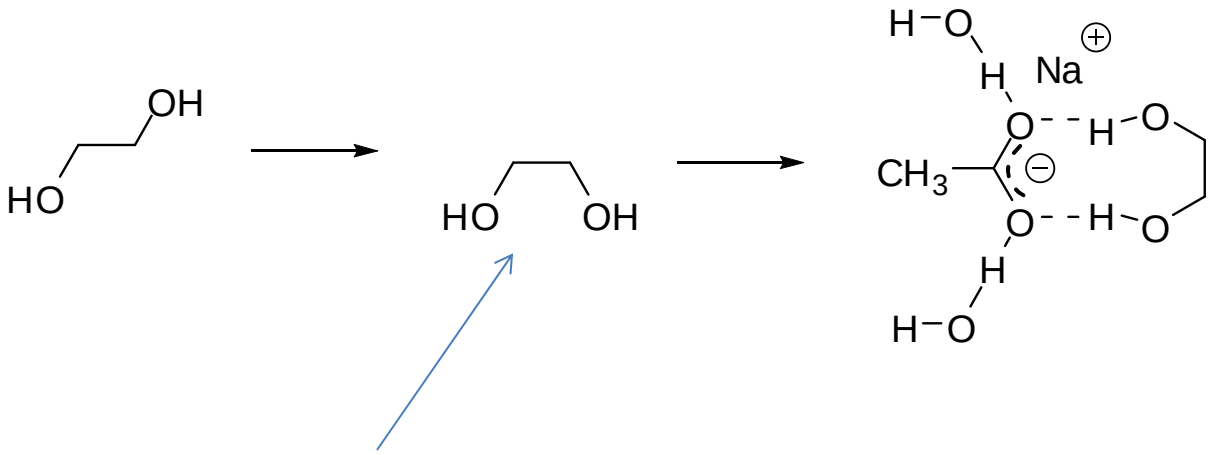




Complementarity

Why preorganization?

2) Cost for higher energy conformation



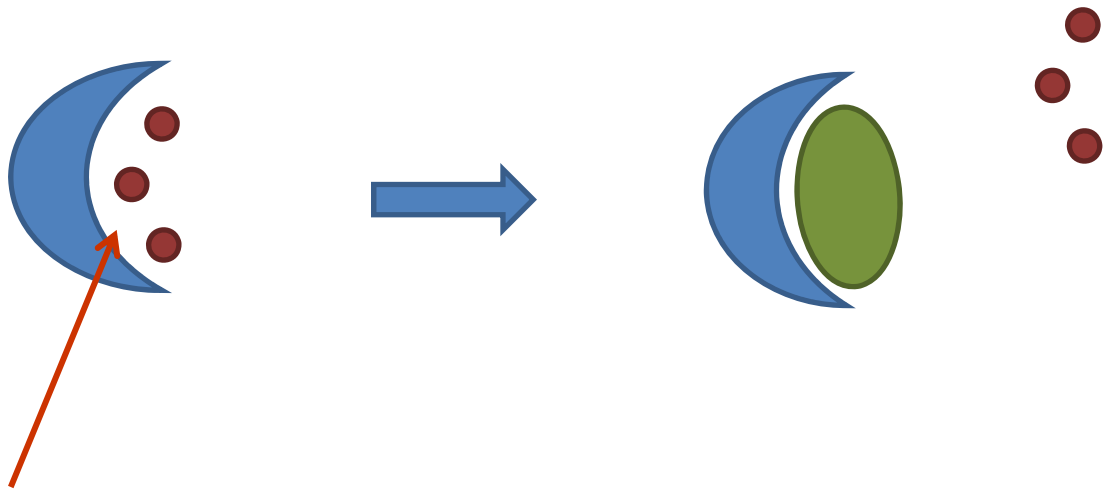
gauche-like conformation

2.5 KJ mol^{-1} for each

Complementarity

Why preorganization?

3) Desolvatation



Few solvent molecules can accommodate a cavity

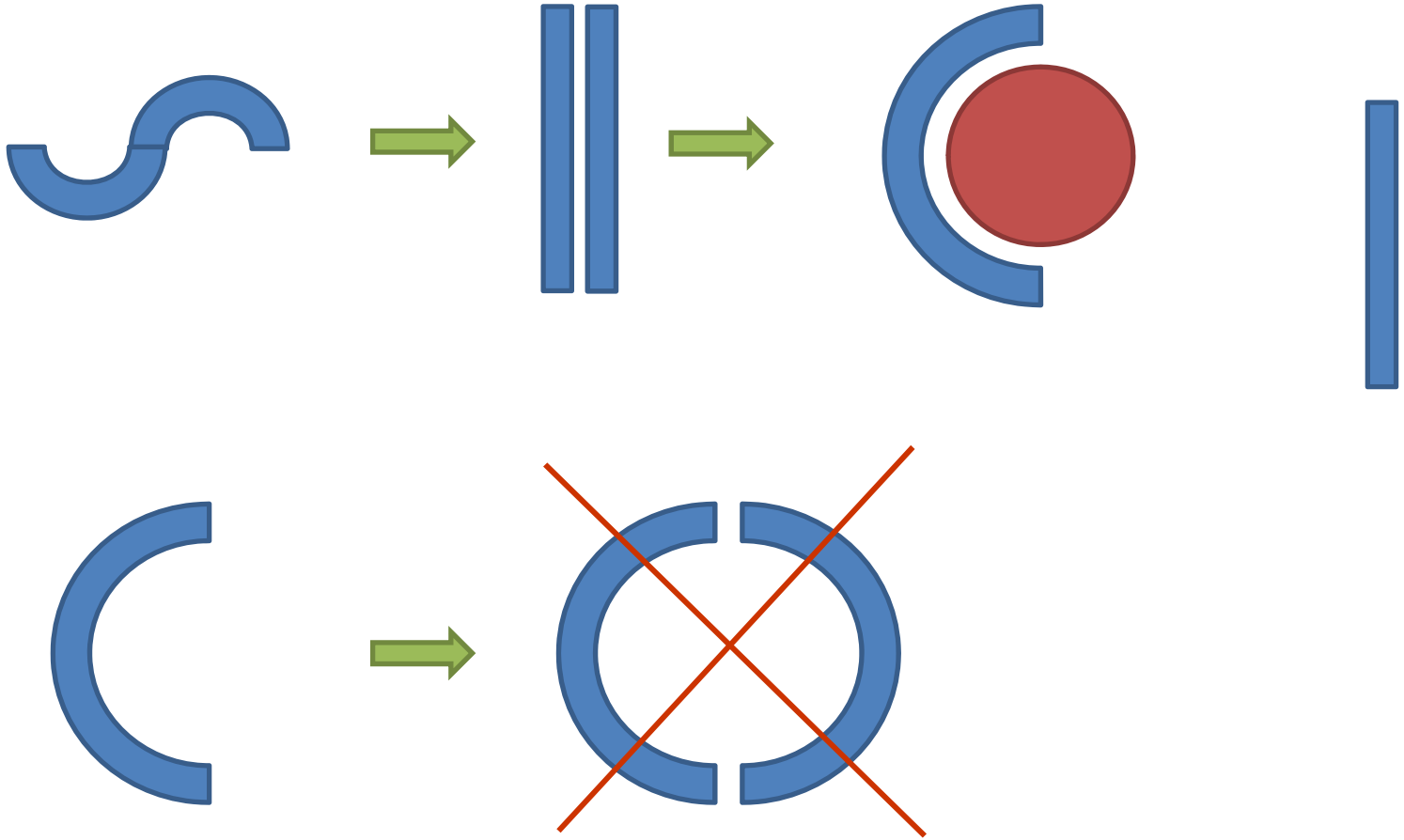
Less interacting solvent $\Rightarrow$ high enthalpy

$$\Delta G = \Delta G_{HG}(gas) + \Delta G_{H}(desolv) + \Delta G_{g}(desolv) + \Delta G_{HG}\ (solv)$$

Complementarity

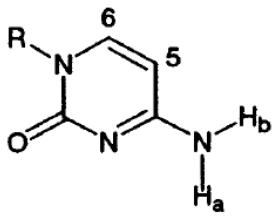
Why preorganization?

4) Host self-aggregation

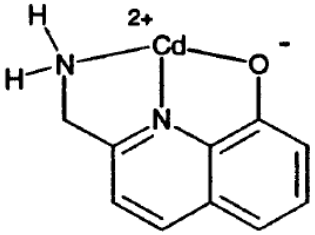


Complementarity

"to complex, hosts must have binding sites which can simultaneously contact and attract the binding sites of the guests without generating internal strains or strong nonbonded repulsions." (Cram)



Cytidine



LCd

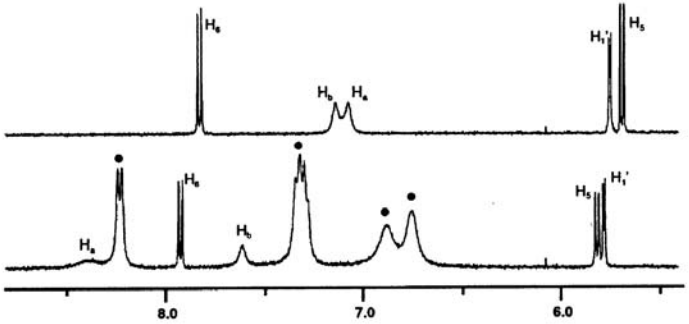
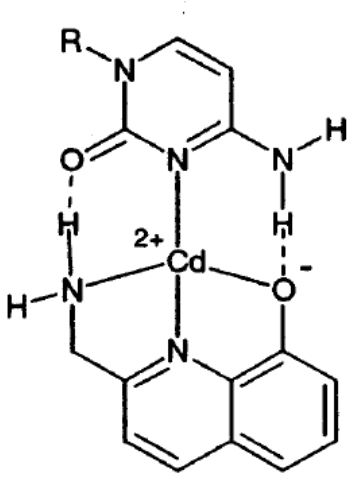
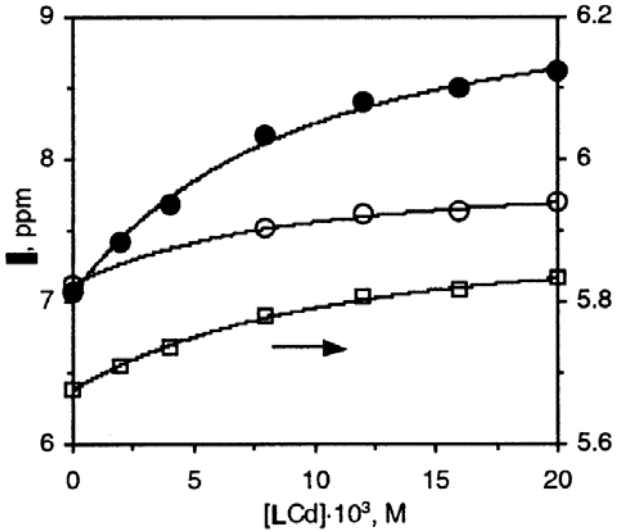


Figure 1. ^{1}H NMR spectra of (a) cytidine (3.0 mM), (b) cytidine (3.0 mM) and **L**Cd (15 mM, 60% of the ternary complex formed). The symbol (●) indicates the signals relative to **L**Cd.

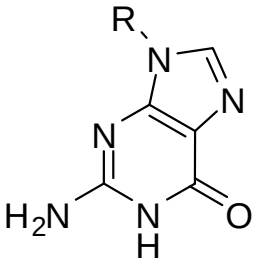


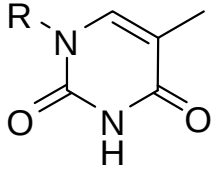
LCdC

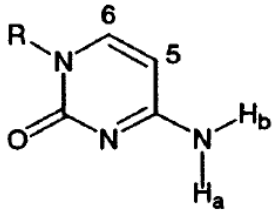


Complementarity

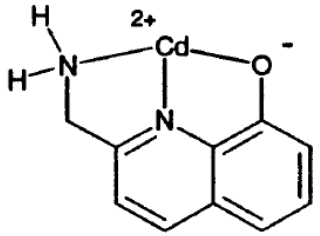
"to complex, hosts must have binding sites which can simultaneously contact and attract the binding sites of the guests without generating internal strains or strong nonbonded repulsions." (Cram)







Cytidine



LCd

Table 1. Association Constants for the Complexes between the Nucleosides and Receptors at 25 °C

receptor	nucleoside	K, M^{-1}
LZn	**C**	<5
LCd	**C**	117
LCd	**A**	<2
LCd	**G**	<2
LCd	**T**	<2

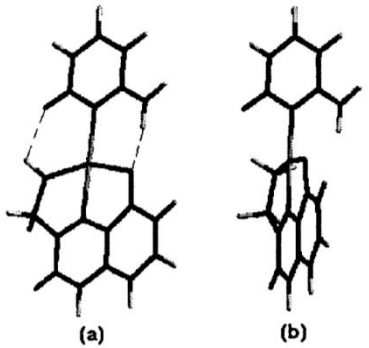


Figure 3. Computed structures of (a) **L**Cd**C** (hydrogen bond indicated with dashed lines) and (b) **L**Zn**C**.

Complementarity

Table 1. Association Constants for the Complexes between the Nucleosides and Receptors at 25 °C

receptor	nucleoside	K, M^{-1}
LZn	**C**	<5
LCd	**C**	117
LCd	**A**	<2
LCd	**G**	<2
LCd	**T**	<2

$\Delta G = 11.8$ KJ/mol

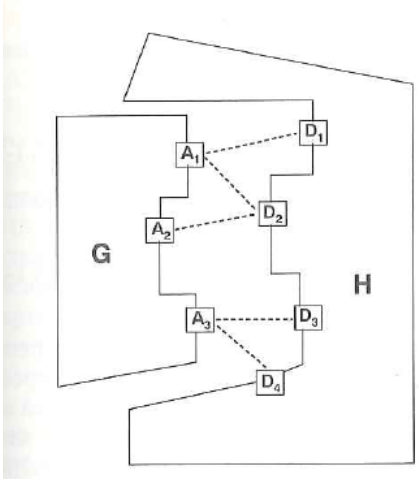
$\Delta G < 5$ KJ/mol

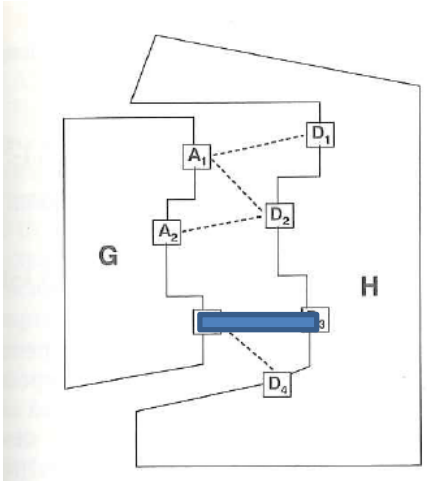
$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

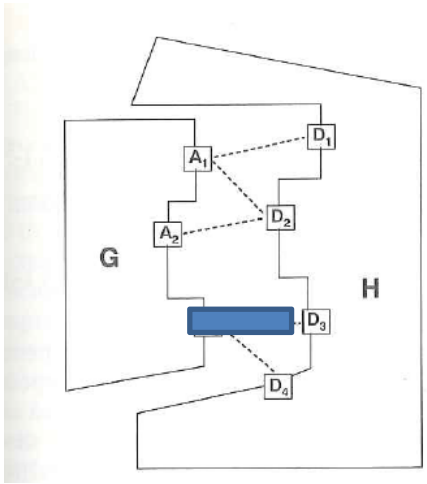
- $\Delta G_{ass} \sim 0$ KJ/mol
- $\Delta G_{HB} \sim 3$ KJ/mol
- $\Delta G_{MC} \sim 6$ KJ/mol

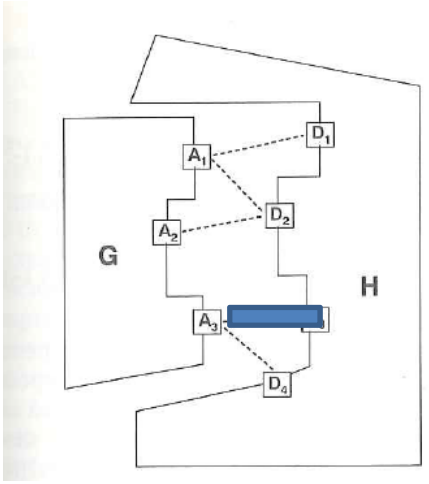
Negative contribution of the missing interactions!!

The double mutant cycle



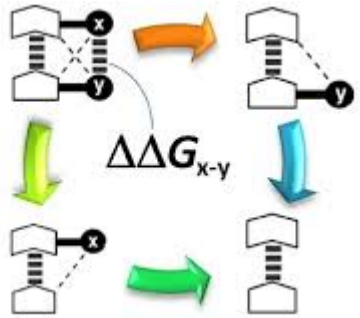






$$K = \frac{[HG]}{[H][G]} \qquad K_{i-1,j-1} = \frac{[H_{i-1}G_{j-1}]}{[H_{i-1}][G_{j-1}]} \qquad K_{i,j-1} = \frac{[H_iG_{j-1}]}{[H_i][G_{j-1}]} \qquad K_{i-1,j} = \frac{[H_{i-1}G_j]}{[H_{i-1}][G_j]}$$

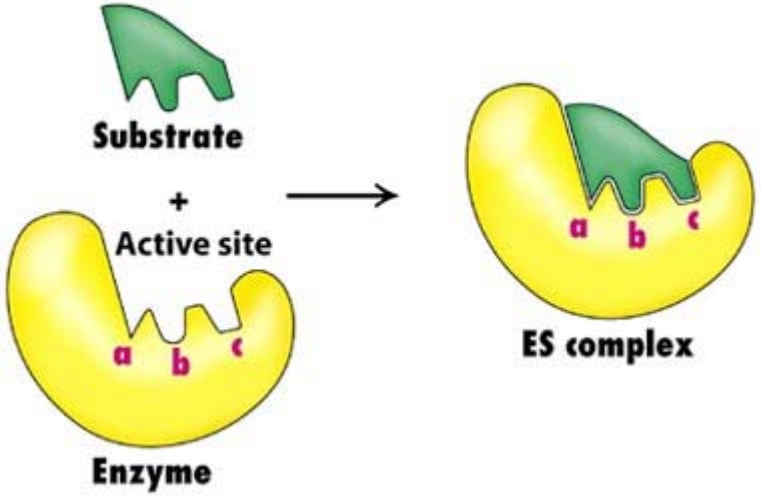
$$\Delta\Delta G_{ij} = \Delta G_{ij} - \Delta G_{i-1,j} - \Delta G_{i,j-1} + \Delta G_{i-1,j-1}$$

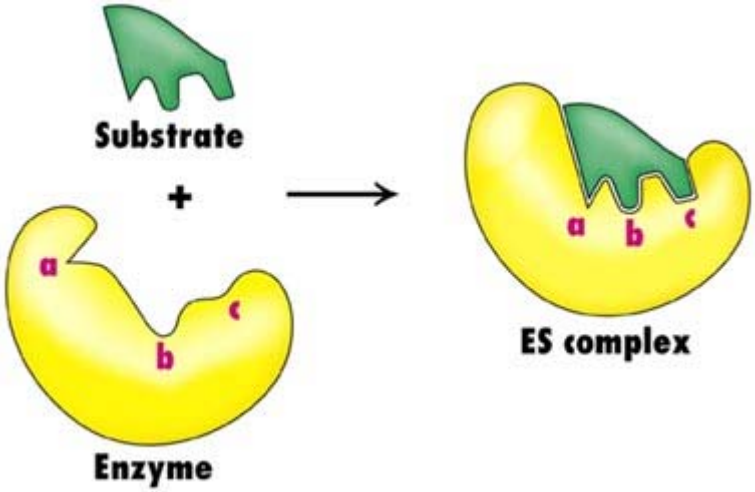


Lock and key

"Lock and key": at the beginnning of XX century Emil Fischer proposed this concept to explain the extremely high selectivity of the interactions between proteins and their substrates.

The idea was that the protein (**receptor**) contain a poket with a shape complementary to that of the substrate

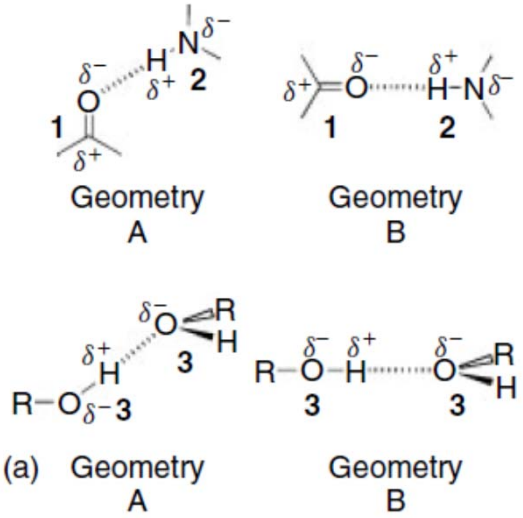


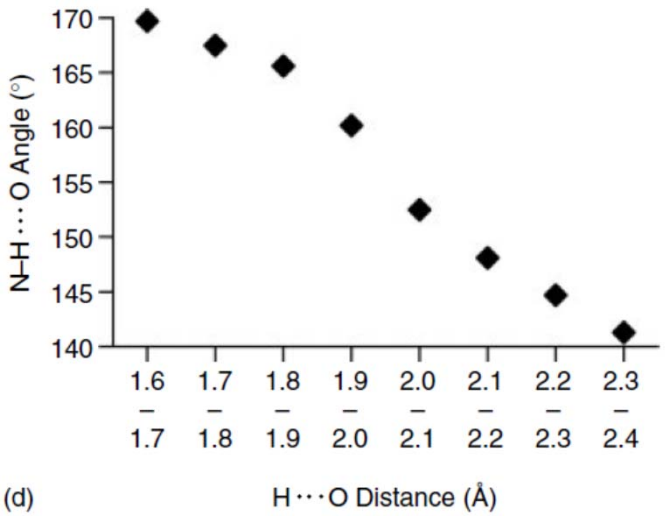


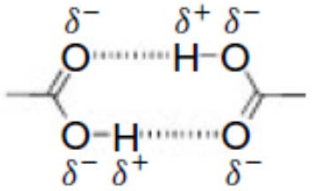
The idea was brilliant but not completely correct: the proteing changes its shape upon binding assuming the one complementary to the substrate. (**induced fit**)

Preorganization, complementarity, multiple interaction, shape fit $\Rightarrow$ **Selectivity**

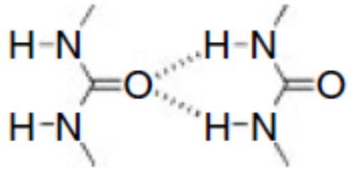
Hydrogen bonds in receptors







(b) **4·4** Strong

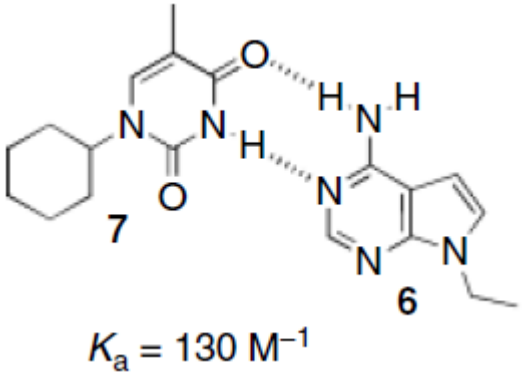


(c) **5·5** Weak

Hydrogen bonds in receptors

$$\Delta G = \sum \Delta\Delta G_{ij} + \Delta G_{ass}$$

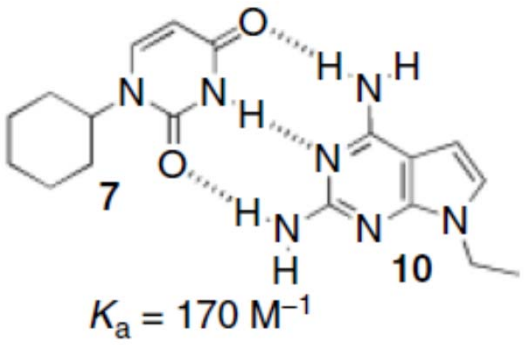
$$\Delta G_{ass} = -RTln\Delta S_{ass} \sim -RTln[S]$$



2 HB

K_a = 130 M^{-1}

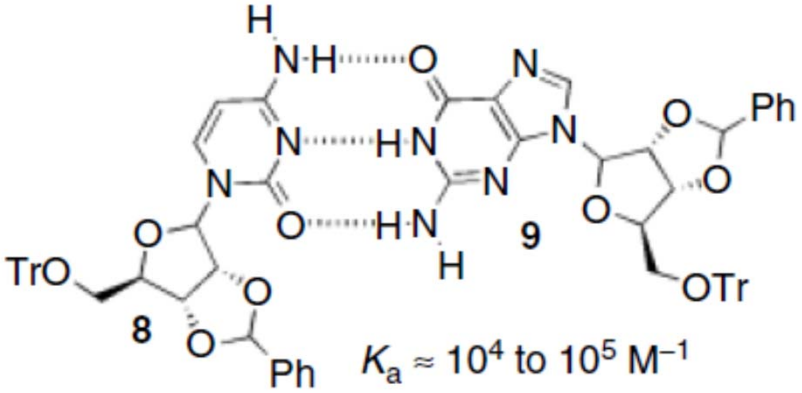
ΔG = -12.1 kJ mol^{-1}



3 HB

K_a = 170 M^{-1}

ΔG = -12.5 kJ mol^{-1}



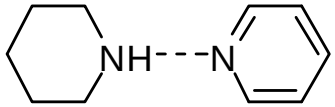
3 HB

$K_a \approx 10^4$ to 10^5 M^{-1}

ΔG = -25 to -30 kJ mol^{-1}

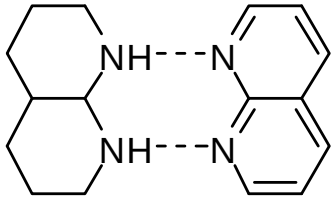
$CHCl_3$

Hydrogen bonds in receptors

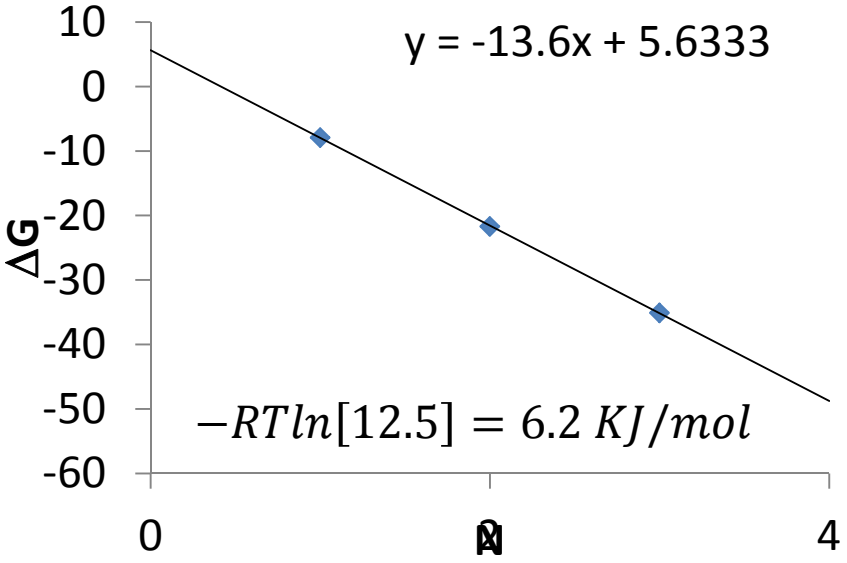


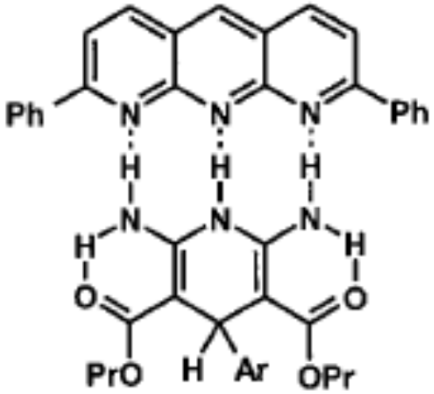
K_{ass} = 25 M^{-1}

ΔG = -7.9 kJ mol^{-1}



K_{ass} = 6.4×

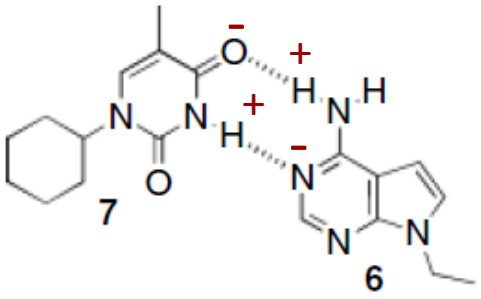




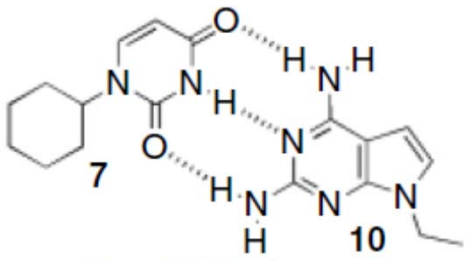
$K_{ass} = 1.5 \times 10^{6}\ M^{-1}$

ΔG = -35.1 kCal mol^{-1}

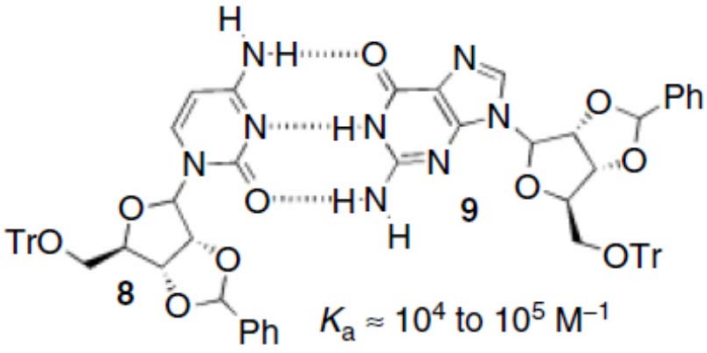
Hydrogen bonds in receptors



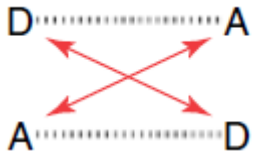
K_a = 130 M^{-1}



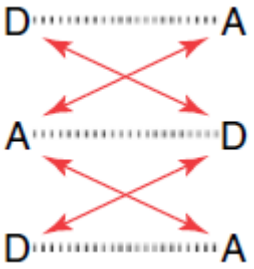
K_a = 170 M^{-1}



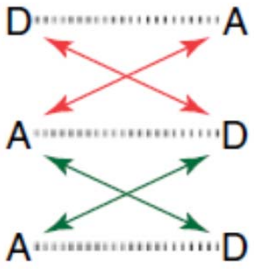
$K_a \approx 10^4$ to 10^5 M^{-1}



DA

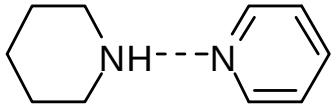


DAD

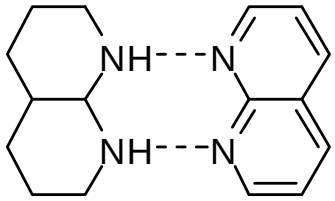


DAA

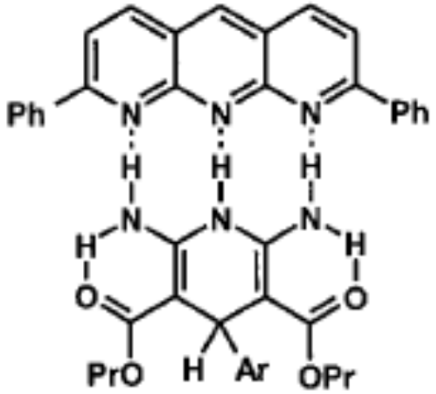
Hydrogen bonds in receptors



K_{ass} = 25 M^{-1}

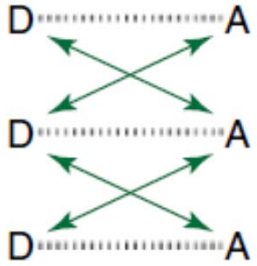


K_{ass} = 6.4×10^3 M^{-1}



K_{ass} = 1.5×10^6 M^{-1}

AA

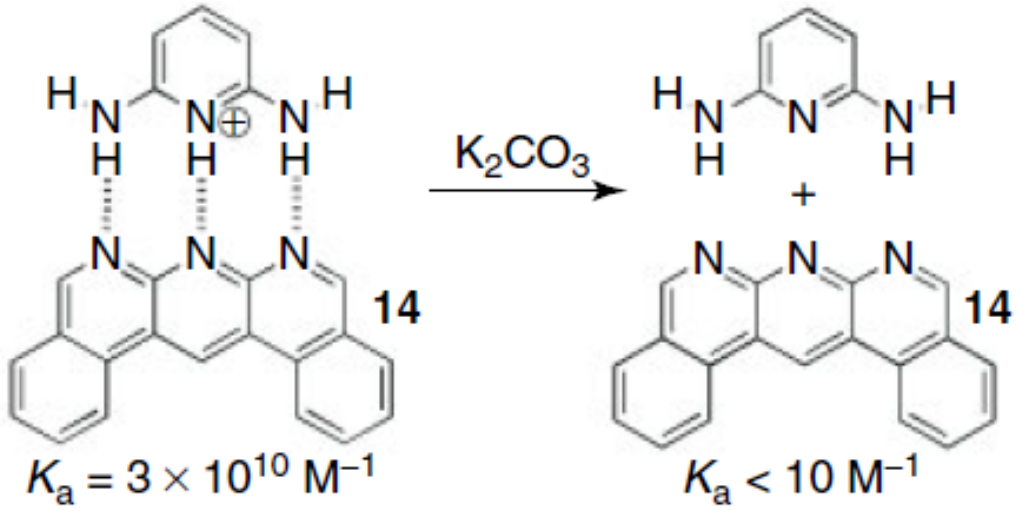


AAA

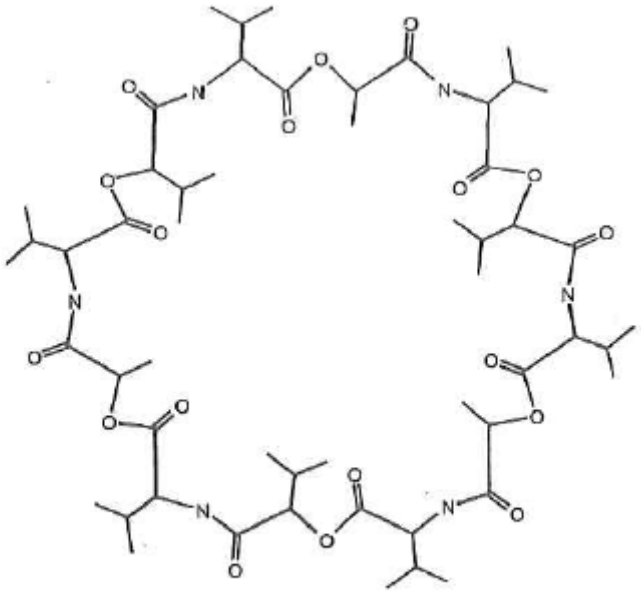
Each H-bond contributes with 7.8 kJ mol^{-1}
Each secondary interaction contributes with ± 2.9 kJ mol^{-1}

7.8+2.9+2.9=13.6 kJ mol^{-1}

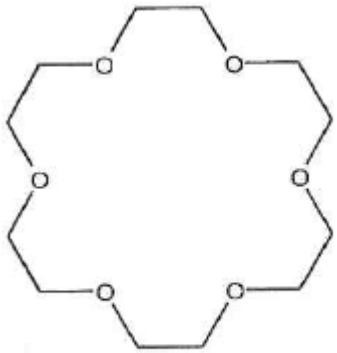
Hydrogen bonds in receptors



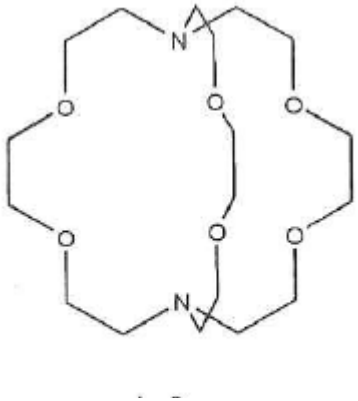
Dipole-ion interactions in receptors



Valinomycin



Crown ethers



Criptands

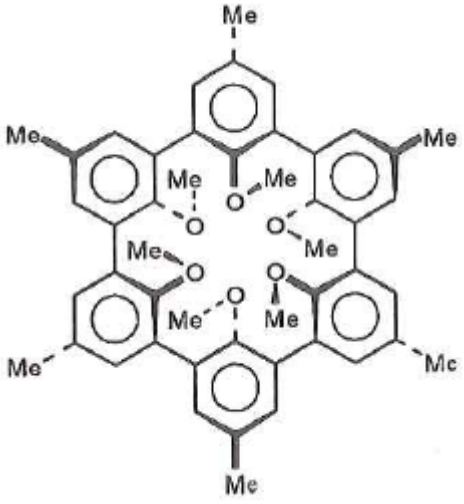
Podands

Chelate effect

Macrocyclic effect

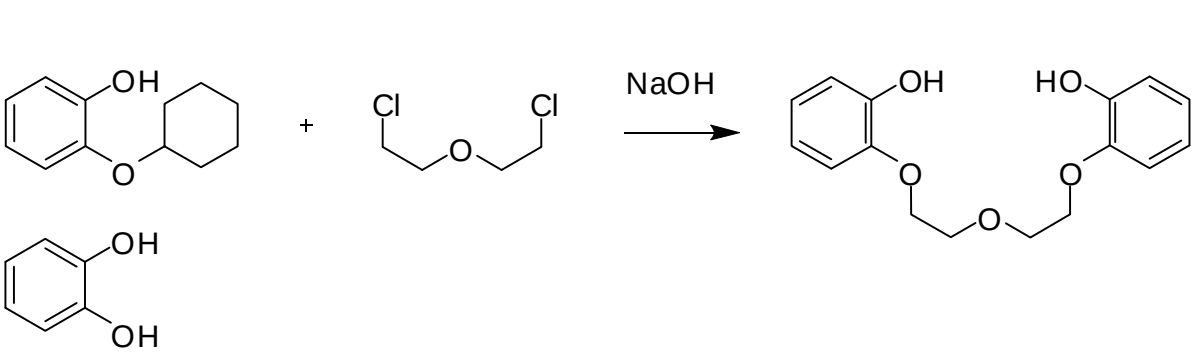
Criptate effects

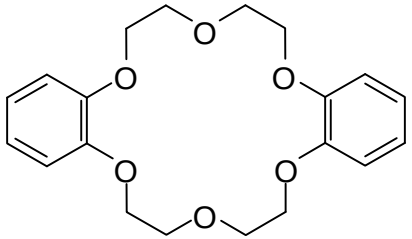
Preorganization



Carcerands

Dipole-ion interactions in receptors





Crown eters (Pedersen)

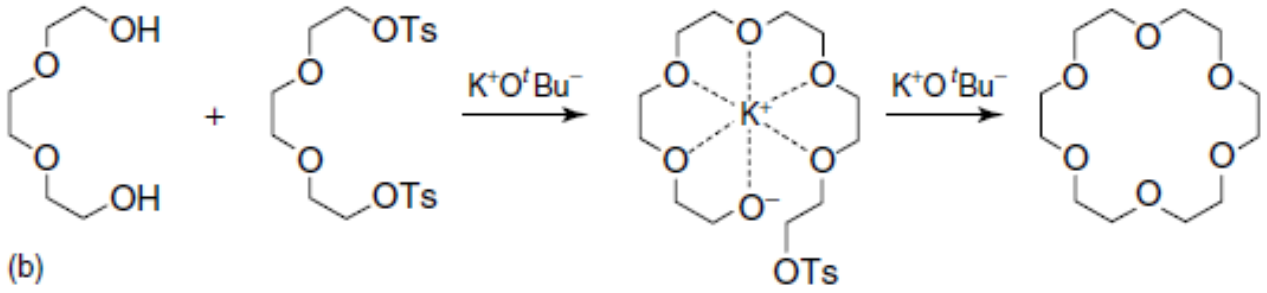
July 5th, 1962
JACS 1967

Capable to solubilize alkali ions salts in organic solvents

Accelerate the reactions of anionic nucleophiles

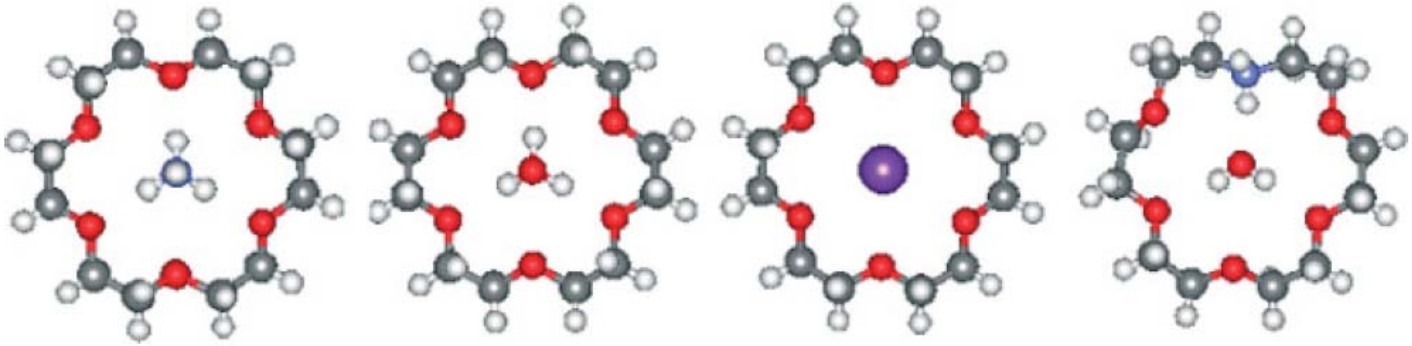
Template synthesis

The problem encountered by Pedersen in his 1967 paper was that while crowns containing aromatic groups could be formed in yields of 20–80%, simple crowns such as 18-crown-6 were only isolated in less than a 2% yield.

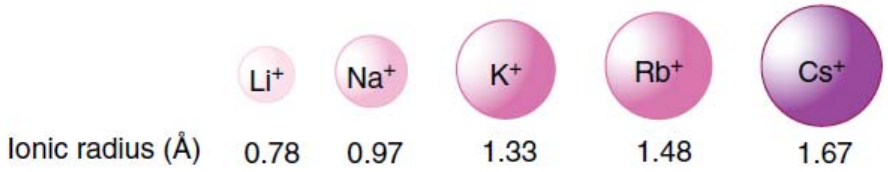


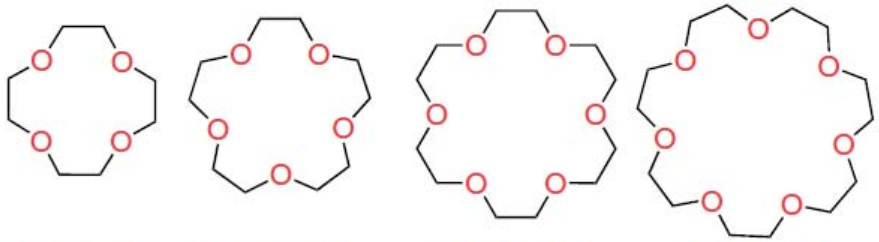
The problem was solved by Greene (1972) who used the appropriate metal cation to **template** the formation of the crown in much the same way as transition metals had been used as templates for other, nitrogen containing, ligands.

Crown eters



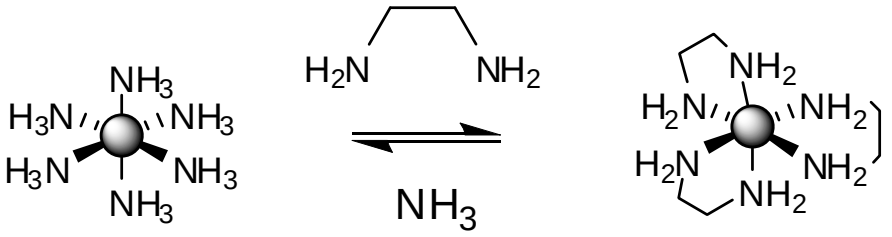
NH_4^+ H_3O^+ K^+ H_2O





Chelate effect: cooperativity?

A chelator is a ligand that has more than one donor atom that is capable of binding to a metal ion simultaneously (coordination chemistry).



M = Ni^{2+}

log K = 8.76

$$K_m = [S]^{n-1} \prod Kij$$

mED + Ni^{2+} = $(Ni^{2+})ED_m$

NH_3 + Ni^{2+} = $Ni(NH_3)^{2+}$

$$\log K_m = \alpha log\beta_n + (n-1)\log[solvent]$$

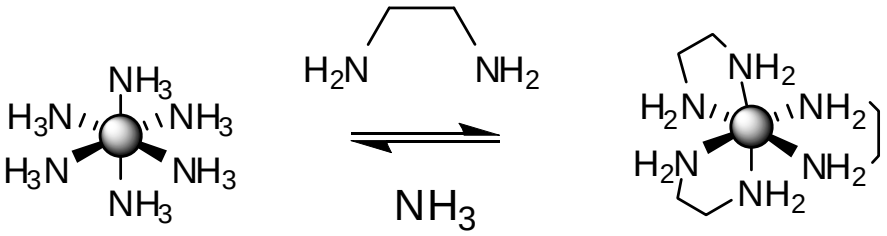
$$\log K_m = 1.152 log\beta_n + (n-1)\log[55.5]$$

nNH_3 + Ni^{2+} = $Ni(NH_3)_n^{2+}$

Amine basicity

Chelate effect: cooperativity?

A chelator is a ligand that has more than one donor atom that is capable of binding to a metal ion simultaneously (coordination chemistry).



$$\log K_m = 1.152 log\beta_n + (n-1)\log[55.5]$$

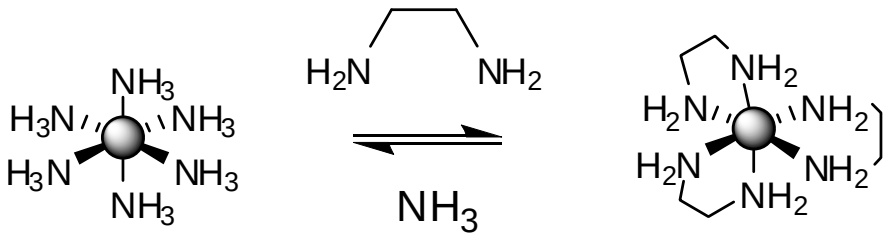
Table A3. Thermodynamics of complexation of Ni^{2+} with ammonia and polyamines in aqueous solution (all equilibrium constants in M^{-1} and thermodynamic parameters in kJ mol^{-1}).[37d]

	Ligand	*log* β_n[a]	*log* K_1[a]	*log* $K_{1,calc}$[b]	ΔG	ΔH	$T\Delta S$
1	$(NH_3)_2$	5.06			−28.8	−32.6	−3.77
2	$H_2NCH_2CH_2NH_2$		7.35	7.59	−41.9	−37.7	4.18
3	$(NH_3)_4$	8.09			−46.5	−65.3	−18.8
4	$CH_2NH(CH_2)_2NH_2$ | $CH_2NH(CH_2)_2NH_2$		14.4	14.6			
5	$(H_2NCH_2CH_2NH_2)_2$	13.48			−77.4	−76.6	0.84
6	$(NH_3)_6$	9.05			−51.7	−100	−48.3
7	$CH_2N(CH_2CH_2NH_2)_2$ | $CH_2N(CH_2CH_2NH_2)_2$		19.1	19.2			
8	$(H_2NCH_2CH_2NH_2)_3$	17.64			−101.1	−117	−15.9

[a] experimental values; [b] calculated with equation (A2-2); Reprinted with permission from the *Journal of Chemical Education*, 69, 1992, pp. 615–621; Copyright 1992, Division of Chemical Education, Inc.

Chelate effect: cooperativity?

A chelator is a ligand that has more than one donor atom that is capable of binding to a metal ion simultaneously (coordination chemistry).



M = Ni^{2+}

log K = 8.76

$\Delta H° = -29$ kJ mol^{-1}

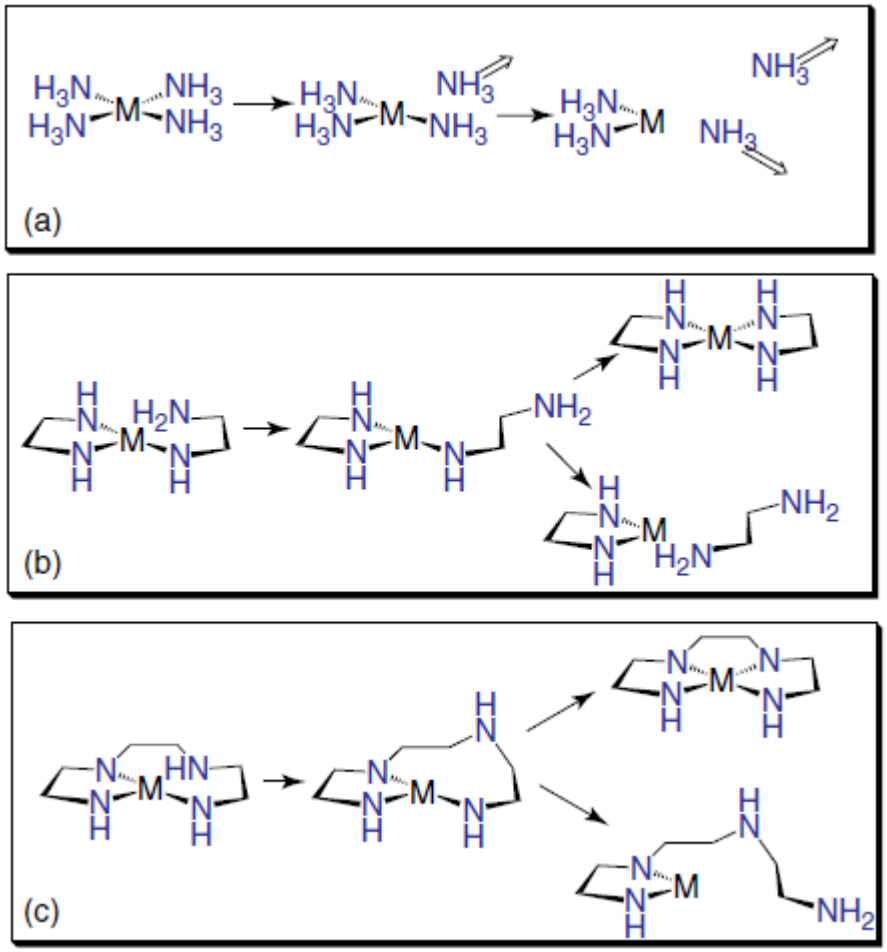
$-T\Delta S° = -25$ kJ mol^{-1}

1. Greater basicity of primary amines
2. Weaker solvatation of primary amines
3. Decresed repulsive interaction between binding sites
4. Steric interactions and strain in the complex

1. Conformational changes
2. Greater number of free species

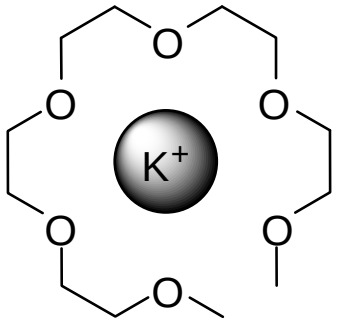
Chelate effect

"**Multiple juxtapositional fixedness**" (MJF): dissociation of a multidentate ligand is hampered by the need of having multiple dissociation events simoultaneusly.



MJF is a kinetic effect which is operative also on binding: once the first donor has bound the metal, binding of the others is made easier by local proximity.

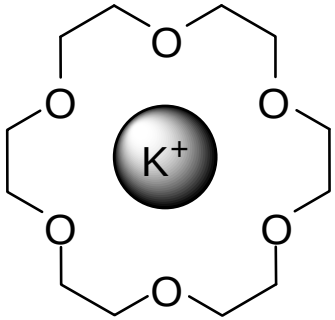
Macrocyclic effect



Log K (MeOH, 25 °C) = 2.0

ΔH = -36.4 KJ/mol

ΔS = -25 KJ/mol

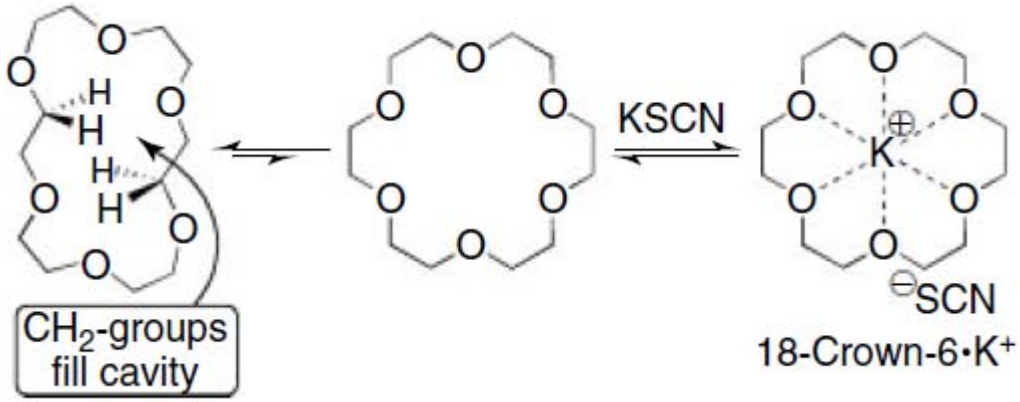


Log K (MeOH, 25 °C) = 6.1

ΔH = -56.0 KJ/mol

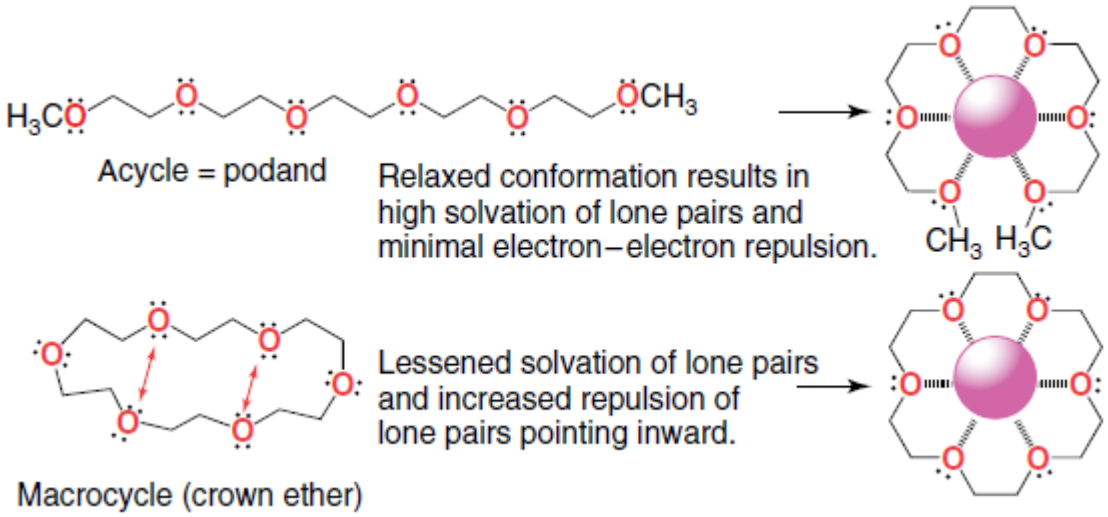
ΔS = -21 KJ/mol

Its is much more an enthalpic than entropic effect!



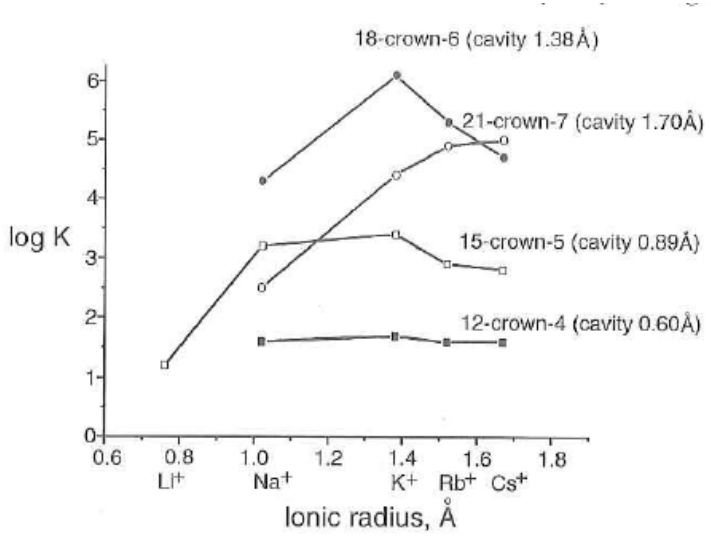
Preorganization?

Macrocyclic effect

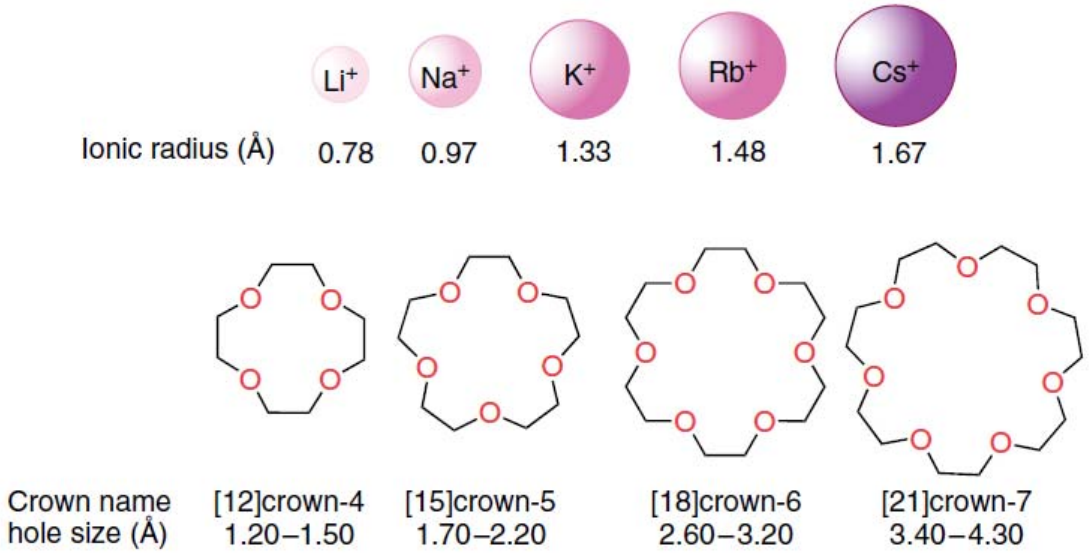


- Incresed basicity due to the bridges
- smaller number to gauche conformation to build up
- Repulsion between the binding sites (relaxed by complexation)
- Desolvatation made less «expensive» by steric crowding
- Absence of strain

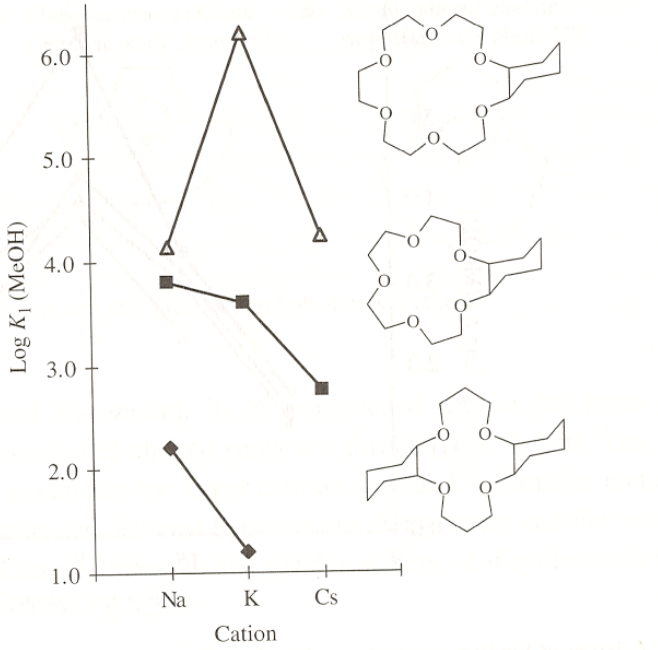
Crown ethers: shape selectivity



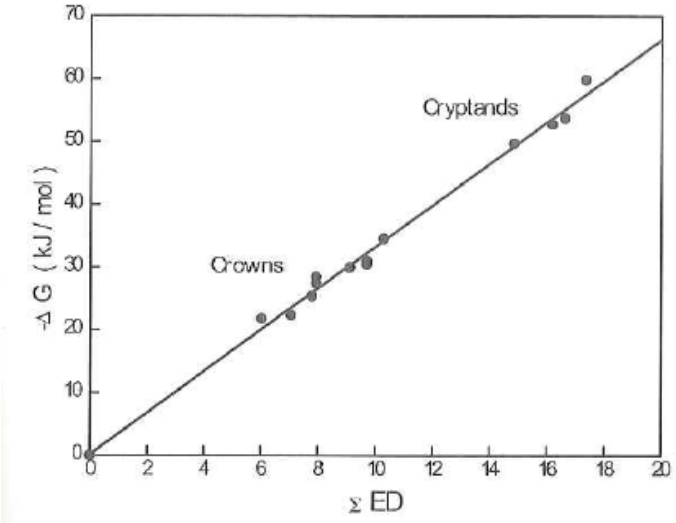
- Many crown ethers are selective for K^+
- 18-crown-6 binds everything better



Crown eters: shape selectivity

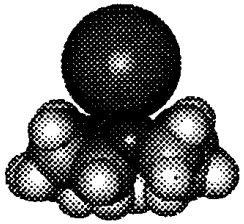


- Size selectivity
- 18-crown-6 binds everything better

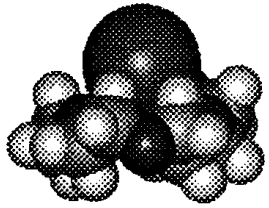


- Affinity mainly depends on the number of donors

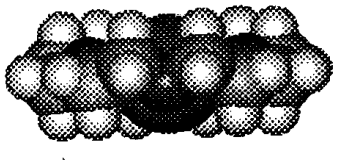
Crown eters: shape selectivity



K^+12C4



K^+15C5

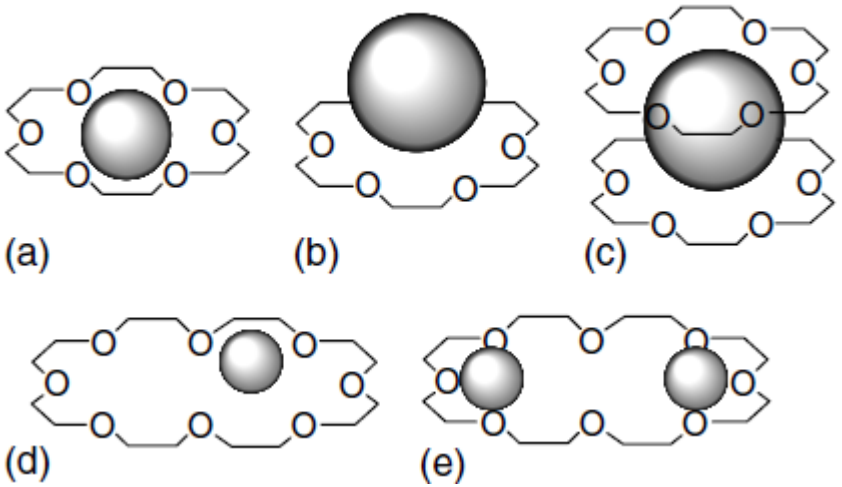


K^+18C6

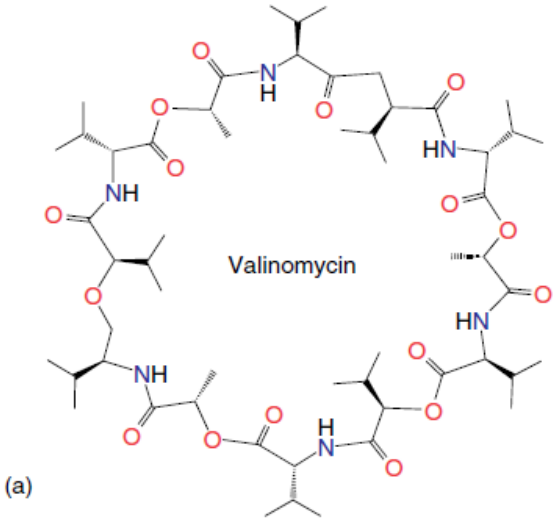
Flexibiliy!

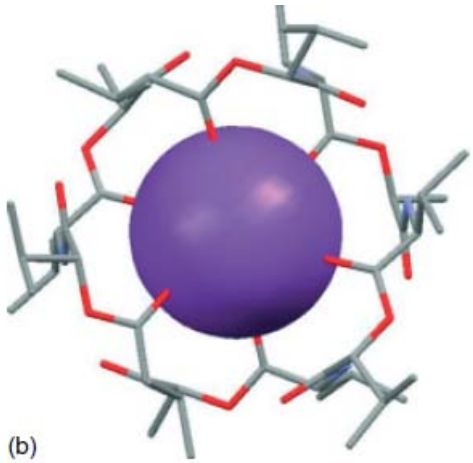
But also:

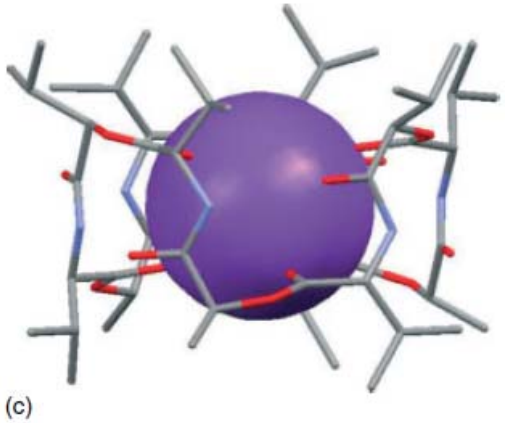
- Number of donors
- Solvatation of the cation
- Chelate ring size
- Cation charge

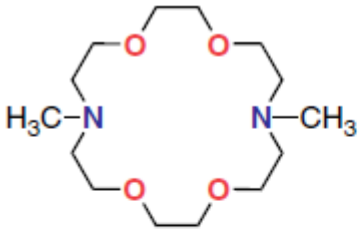


Lariat eters: increased affinity

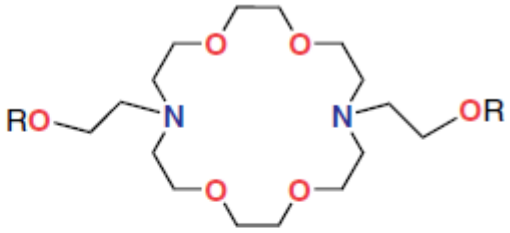




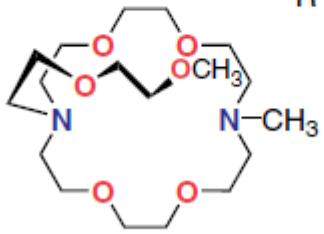




[2.2]NCH_3



R = H [2.2]BHE
R = CH_3 [2.2]BME

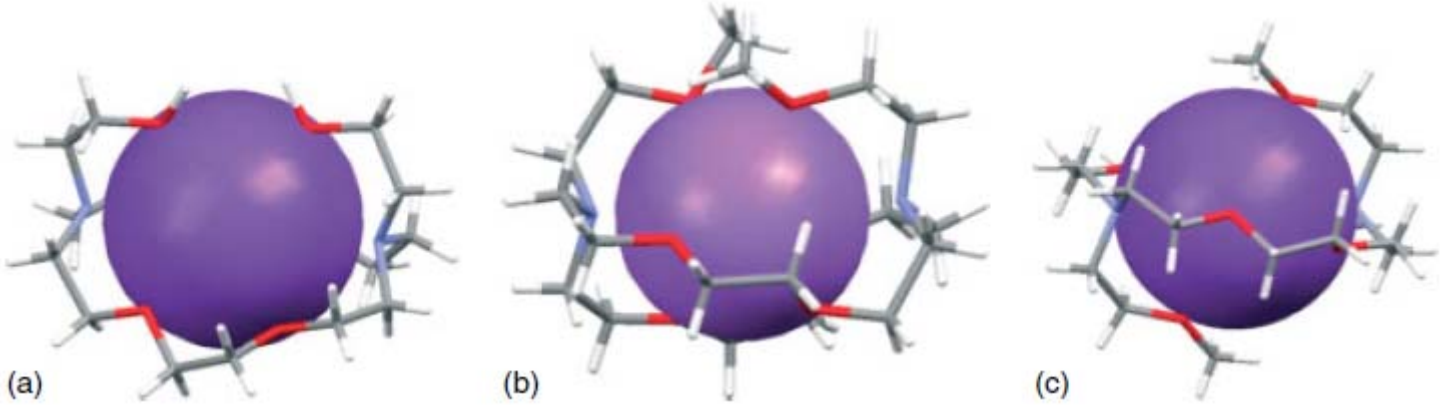


[2.2.2]open

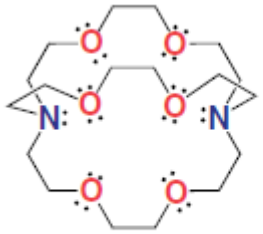
Lariat eters

Table 4 Binding constants (log K) in methanol at 25 °C for selected cations with crown and lariat ethers.

Crown	Na^+	K^+	Ca^{2+}	NH_4^+
[12]crown-4[43]	1.7	1.74	nd	1.3
[15]crown-5[43]	3.24	3.43	2.36	3.03
[18]crown-6[43]	4.35	6.08	3.90	4.14
[21]crown-7[43]	2.54	4.35	2.80	3.27
[2.2]$N(CH_3)_2$[45]	3.62	5.0	4.20	—
[2.2]BME[47]	4.57	5.30	4.48	—
[2.2]BHE[48]	4.87	5.08	—	—

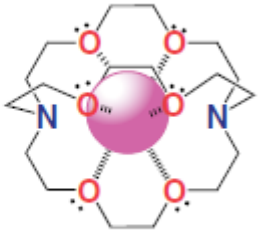


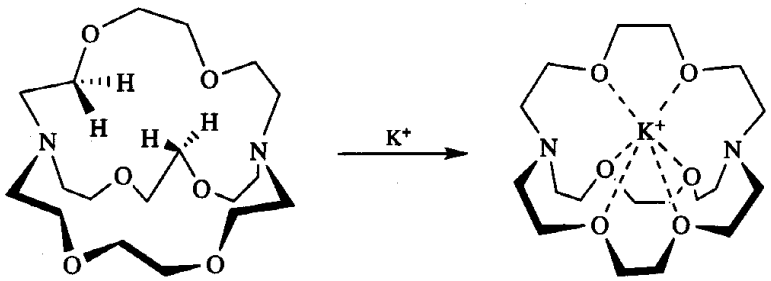
Criptands: criptate effect



Macrobicycle (cryptand)

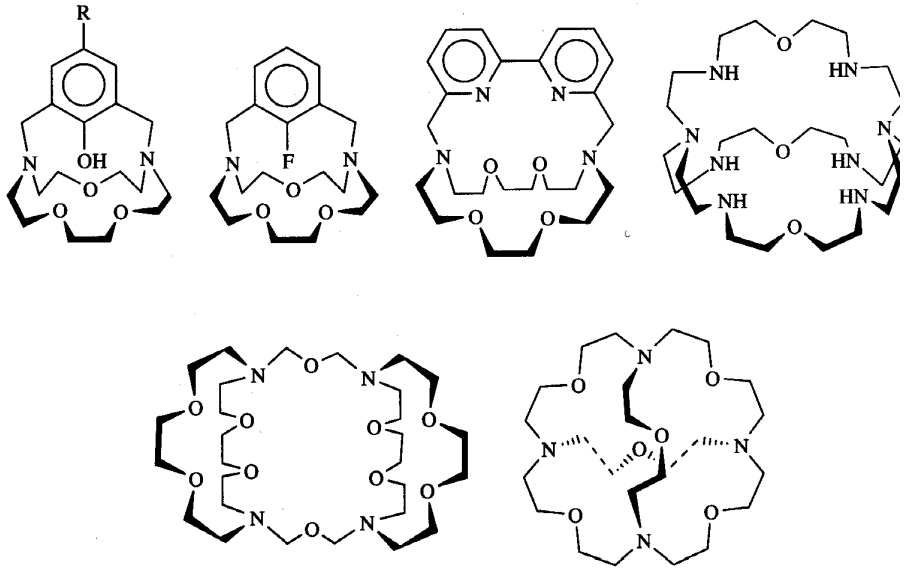
Limited solvation of lone pairs in cavity but lone pair repulsion in the cavity is retained.



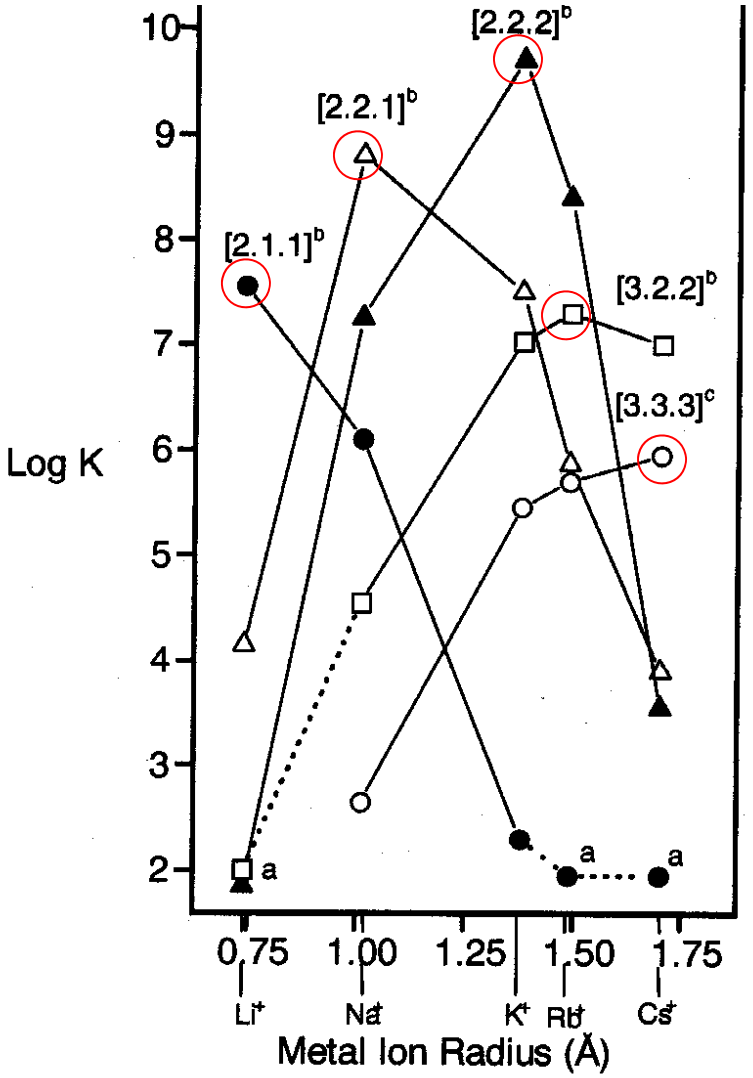


2.2.2

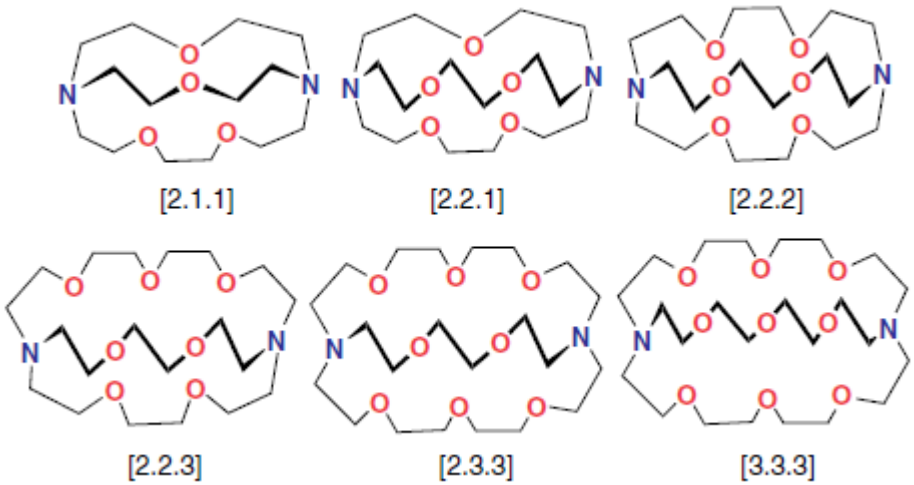
Other examples



Criptands: shape selectivity



- Incresed preorganization and complemetarity lead to higher affinity and selectivity
- Kinetics of binding and dissociation become slower



Sperands: preorganization

Spherands are a category of macrocyclic receptors with rigid cavities whose donor sites (normally oxygen) are fixed in space in relation to each other and directed inward for complexation with a range of complementary guests, which often have a spherical shape

As a consequence of the rigidity, conformational changes on complex formation are minimal and the rigid electron-pair-lined cavities in uncomplexed spherands have been postulated to be effectively nonsolvated.

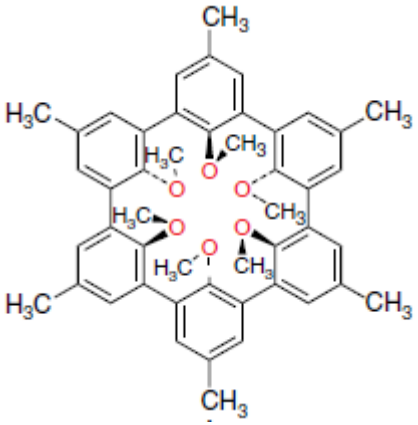
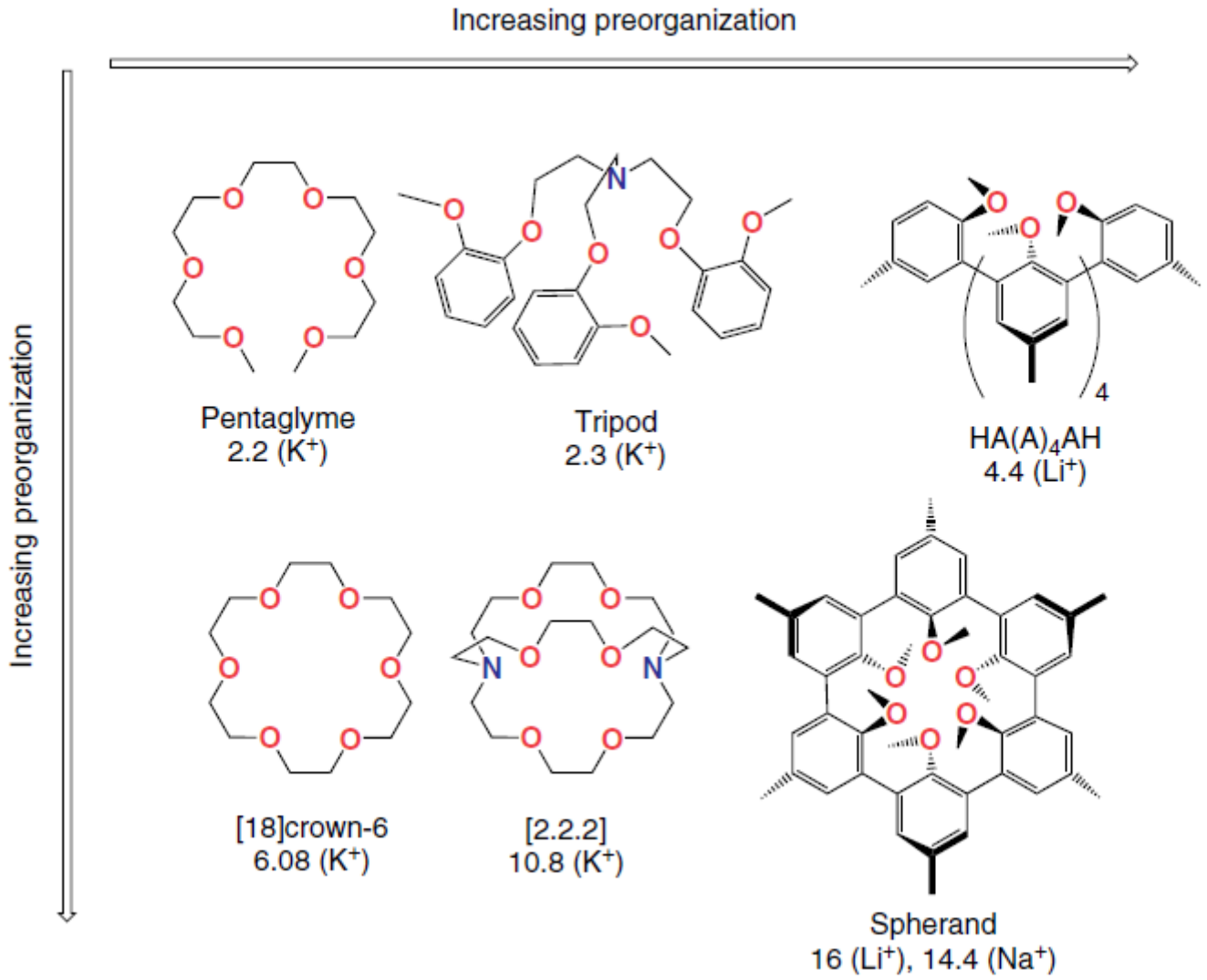


Table 3 Stability constants (log K) in methanol at 25 °C for the binding of alkali metal ions with ionophores that have increasingly complex design and dimension.[33]

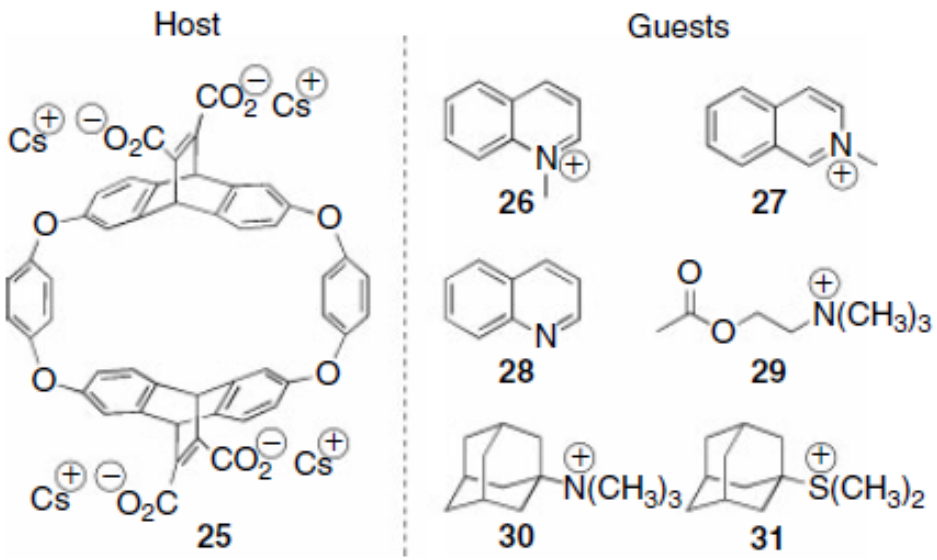
Ionophore	Li^+	Na^+	K^+	Rb^+	Cs^+
Pentaglyme	—	1.5	2.2	—	—
Tripod	<2	2.2	2.3	<2	—
Valinomycin	<0.7	0.9	4.7	5.2	4.4
[18]Crown-6	~0	4.4	6.1	5.4	4.7
[2.2.2]Cryptand	2.6	8.0	10.8	9.0	4.4
Spherand[a]	>16.8	14.1	—	—	—

[a] In $CDCl_3$ saturated with H_2O.[35]

Preorganization and affinity



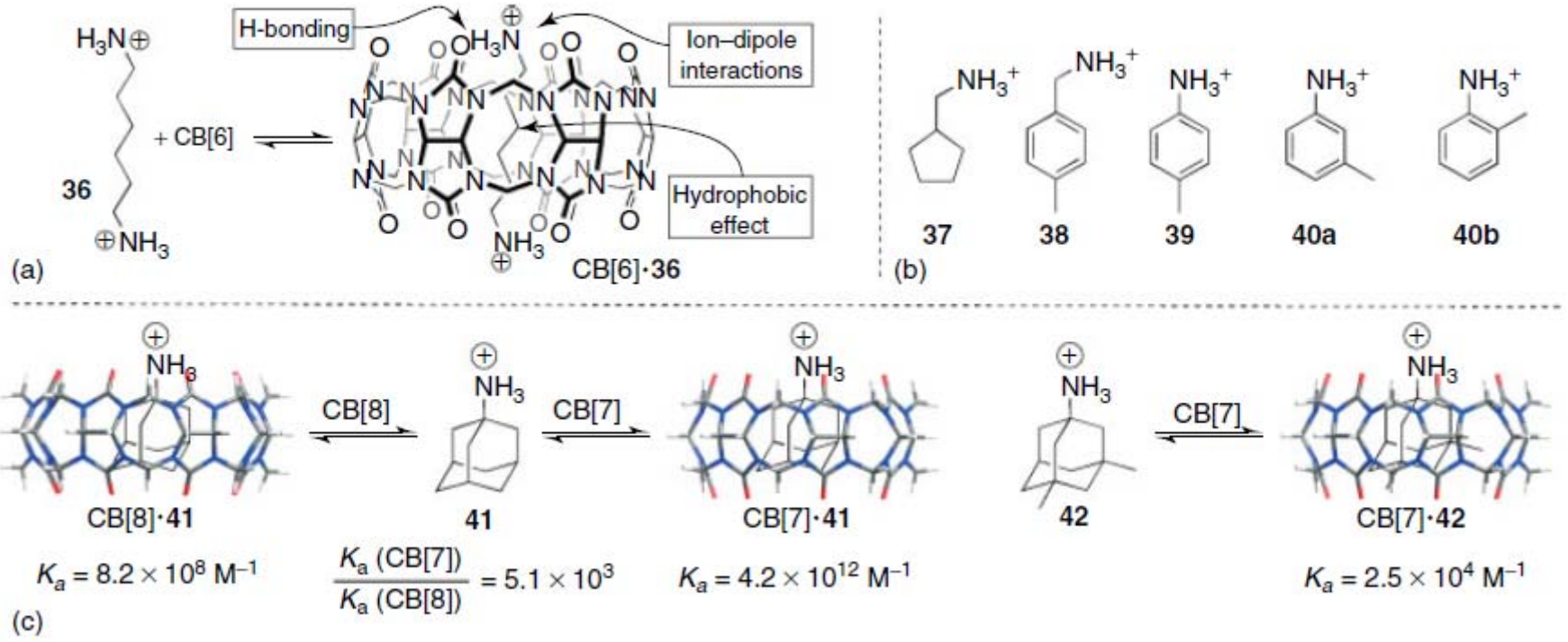
Other receptors: cyclophanes



Host	ΔG (Kcal/mol)
26	-8.4
27	-7.3
28	-5.3
29	-6.2
30	-6.7

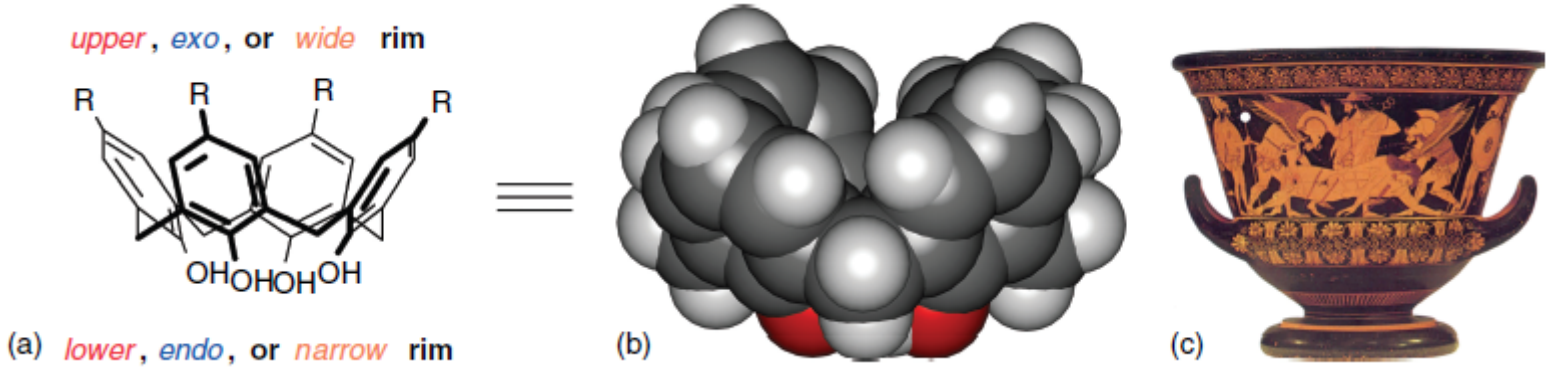
Water, borate buffer pH 10.0

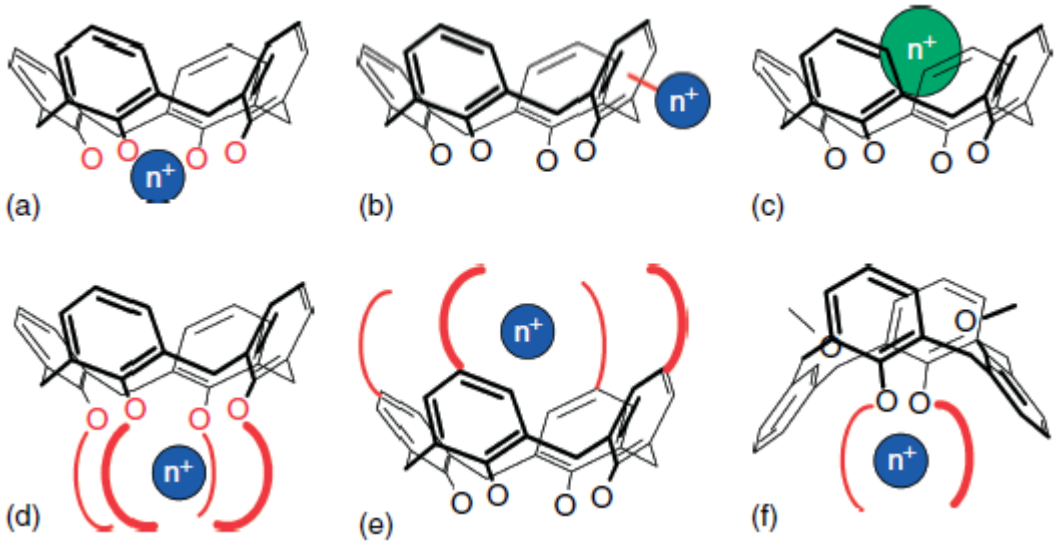
Other receptors: cucurbit[n]urils



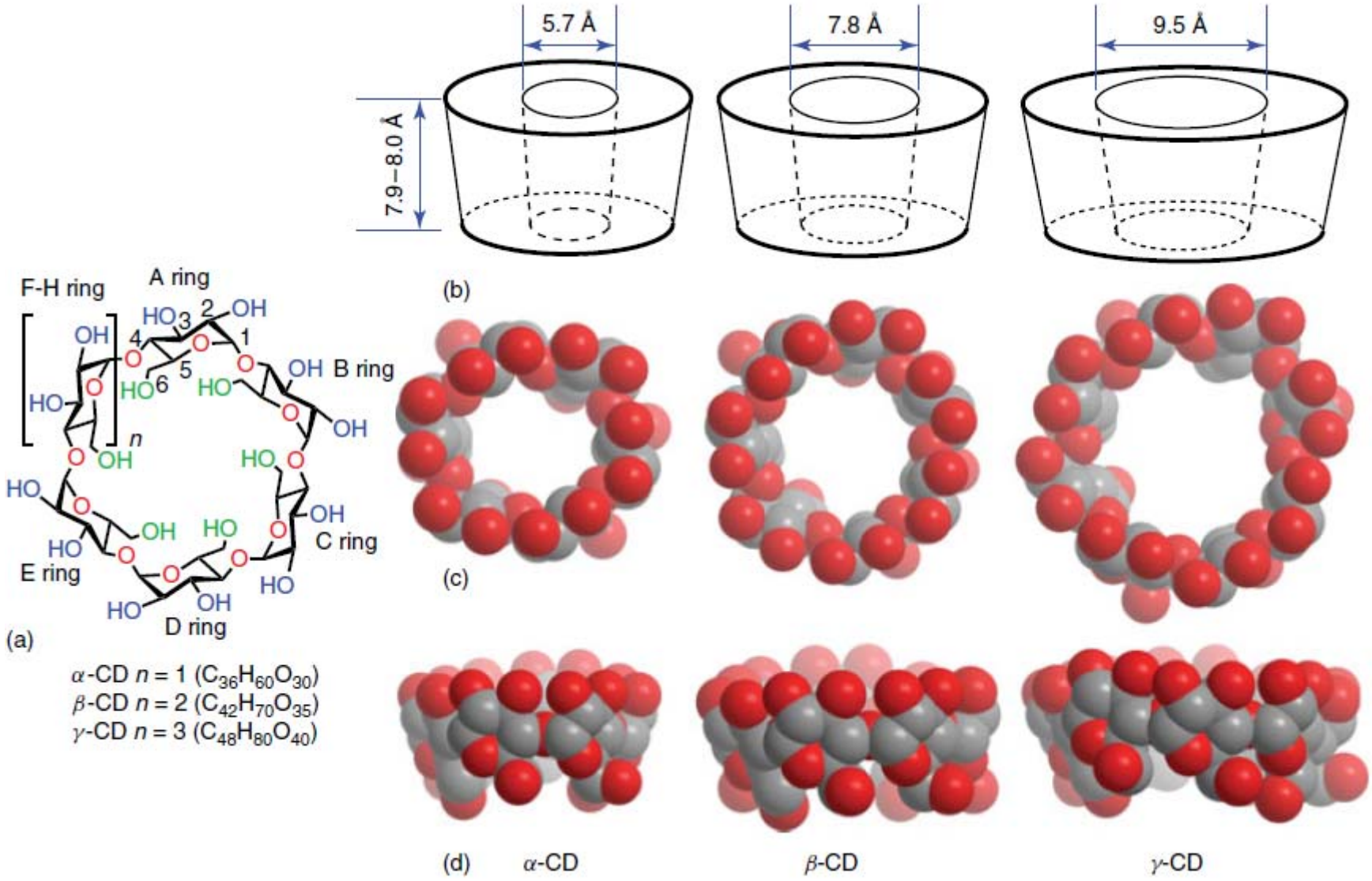
Host	K_{ass} (1/M)
36	4.5 x 10^8
37	3.3 x 10^5
38	3.2 x 10^2
39	1.3x 10^3
0a	-
40b	-

Other receptors: calix[n]arenes



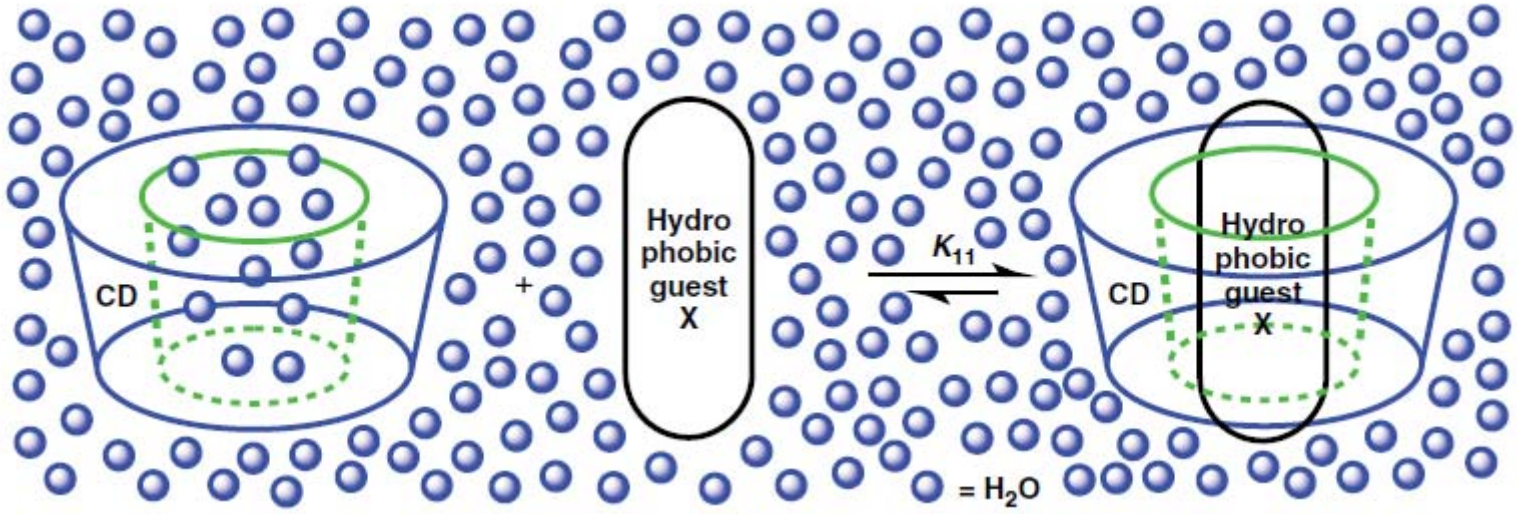


Other receptors: cyclodextrins

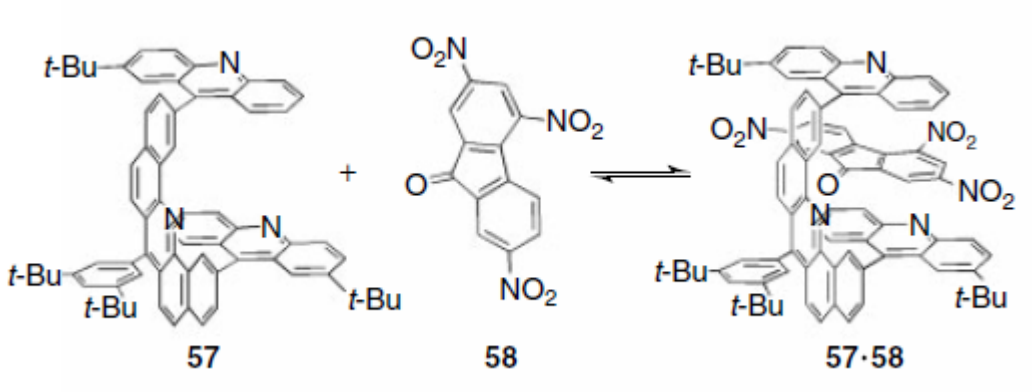


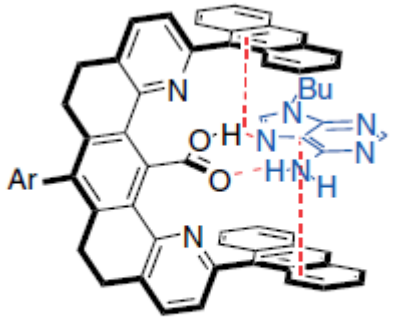
α-CD $n = 1$ ($C_{36}H_{60}O_{30}$)
β-CD $n = 2$ ($C_{42}H_{70}O_{35}$)
γ-CD $n = 3$ ($C_{48}H_{80}O_{40}$)

Other receptors: cyclodextrins



Other receptors: tweezers and clefts





$K_a = 2.5 \times 10^4\ M^{-1}$ ($CDCl_3$)