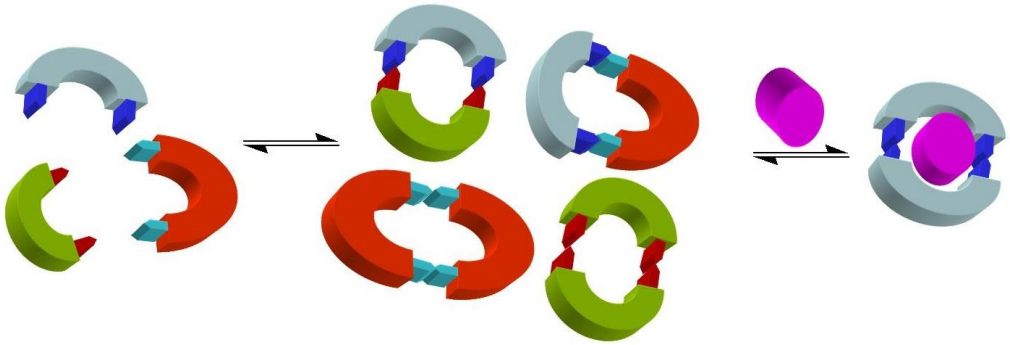
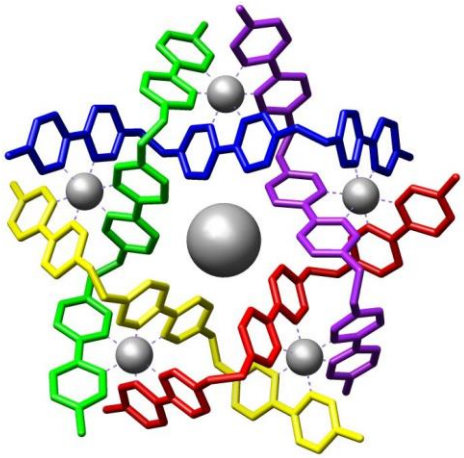




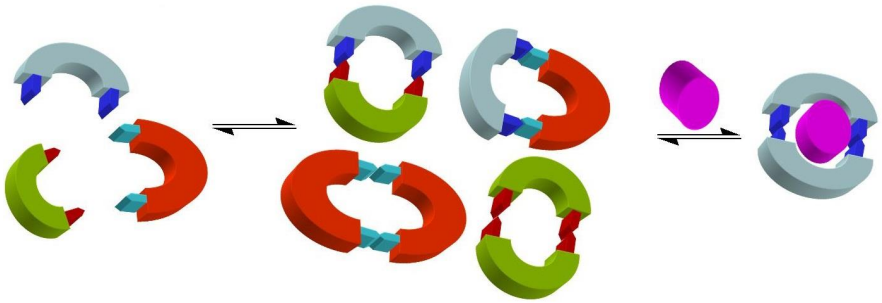
A quick survey through non-covalent interactions

Dr. Frank Biedermann, Institut for Nanotechnologie (INT)

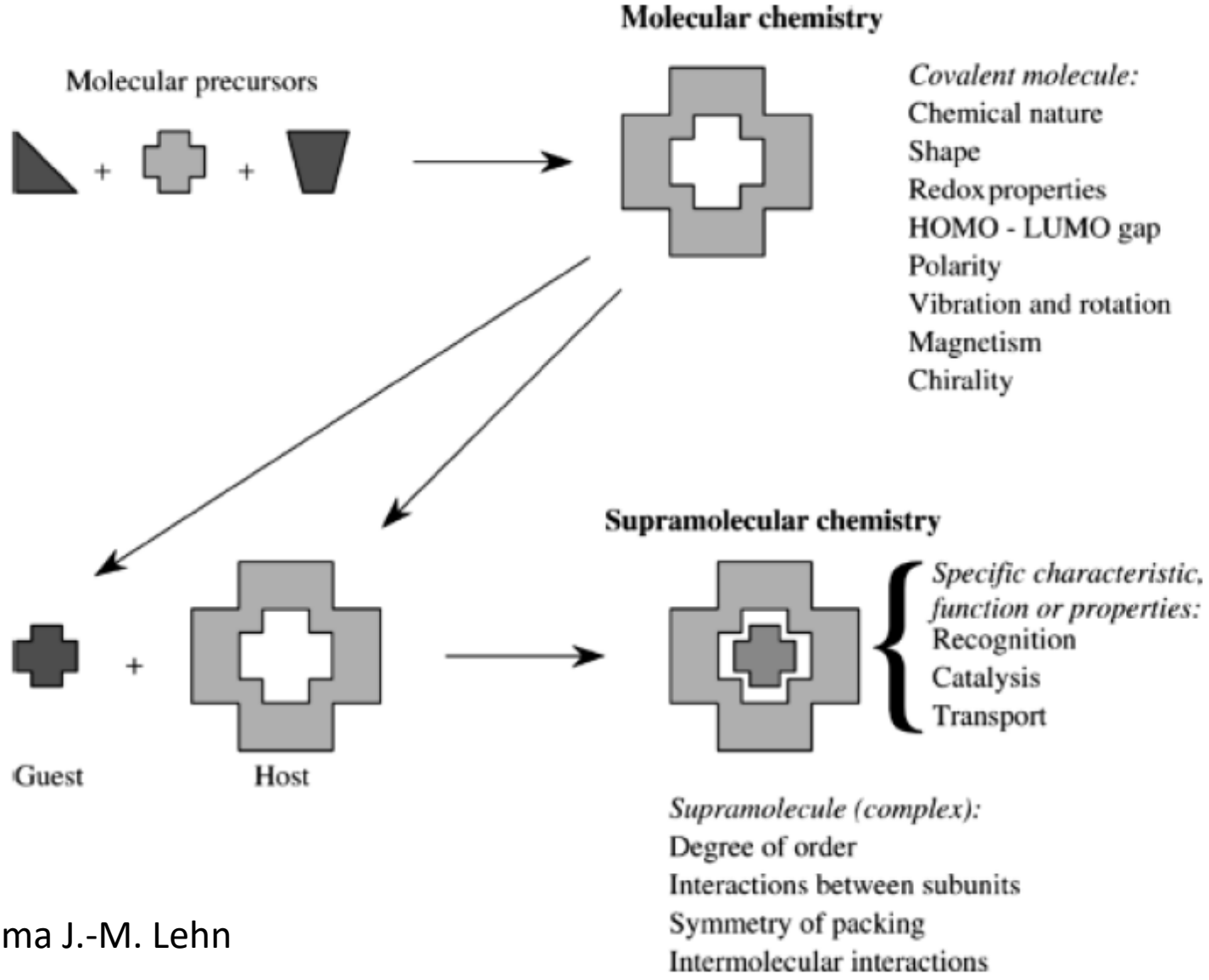
E-Mail: frank.biedermann@kit.edu

Definition

- 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”
- 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“
- J.M.L.: “Supermolecules” are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond”



moleculare vs. Supramoleculare Chemie

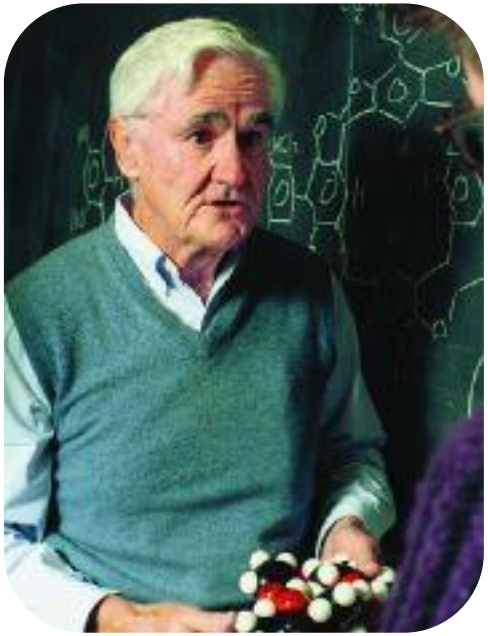


Schema J.-M. Lehn

History

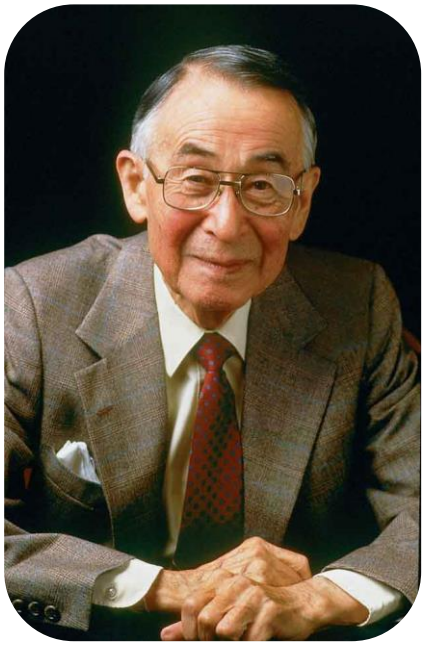
- 1873: **Intermolecular Interactions**, Johannes D. van the Waals
- 1891: **Cyclodextrin-Complexes**, A. Villiers
- 1893: **Koordination Chemistry**, Alfred Werner
- 1894: **Lock-and-Key-Prinzip**, Emil Fischer
- 1906: **Receptor Concept**, Paul Ehrlich
- 1937: „**Übermolekül“ through Self-Assembly**, K. L. Wolf
- 1953: **DNA Structure**, James Watson & Francis Crick (& Rosalind Franklin)
- 1967: **Crown ether**, Charles Pederson
- 1969: **Cryptands**, Jean-Marie Lehn
- 1973: **Pre-organisation**, Donald Cram
- 1978: **Phrase „Supramolecular Chemistry“**, Jean-Marie Lehn
- ……..

History: **Nobel Prize in Chemistry 1987**



Donald J. Cram
Los Angeles

Jean-Marie Lehn
Strasbourg



Charles J. Pedersen
Dupont, Wilmington

„for their development and use of molecules with structure-specific interactions of high selectivity “

History: **Nobel Prize in Chemistry 2016**

Jean-Pierre Sauvage
Strasbourg

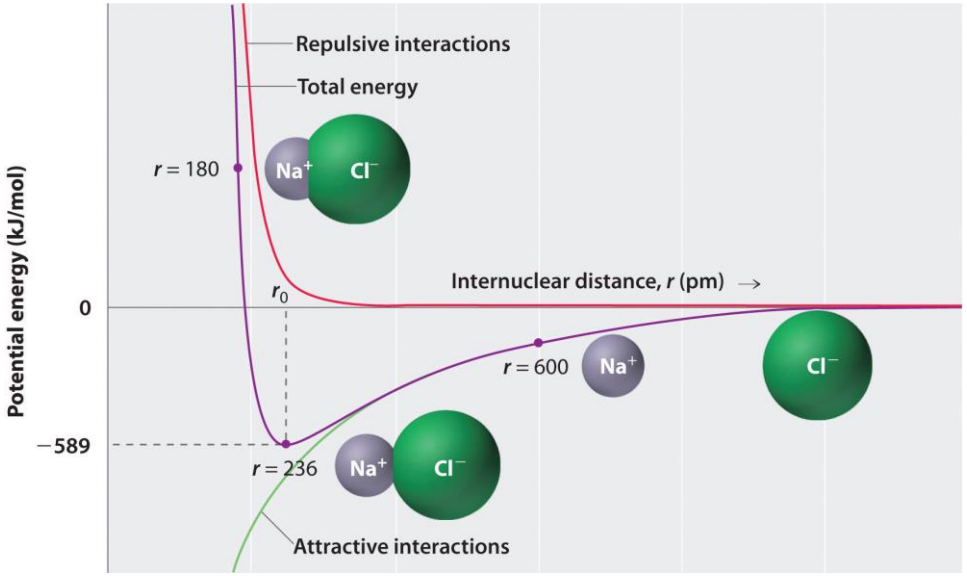
Ben L. Feringa
Groningen

Fraser Stoddart
Northwestern University

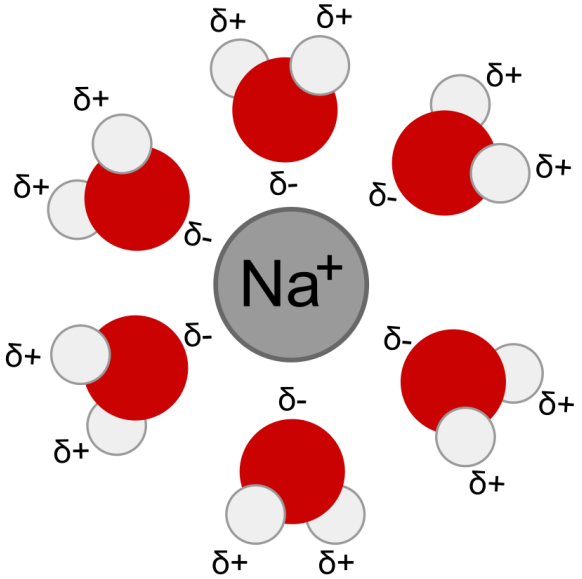
„for the design and synthesis of molecular machines“

Types of Non-Covalent Interactions

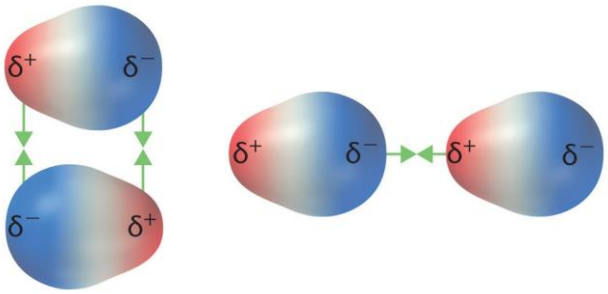
Ion-Ion Int.



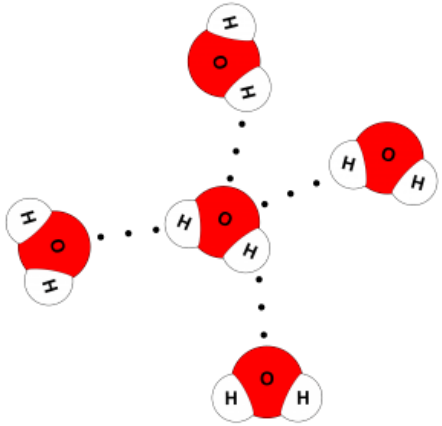
Ion-Dipol Int.



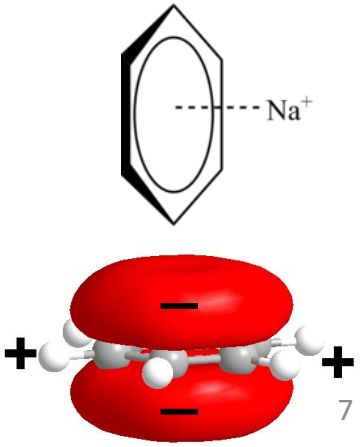
Dipol-Dipol Int.



H-Bonds

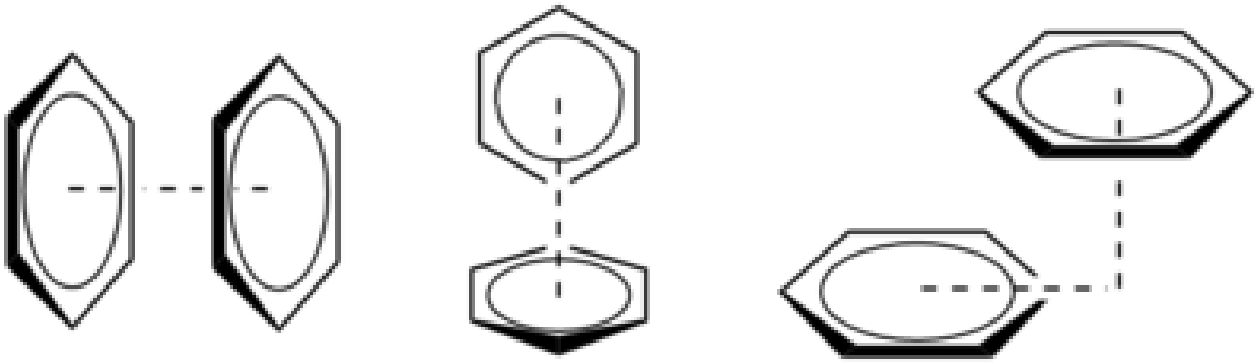


cation-π Int.



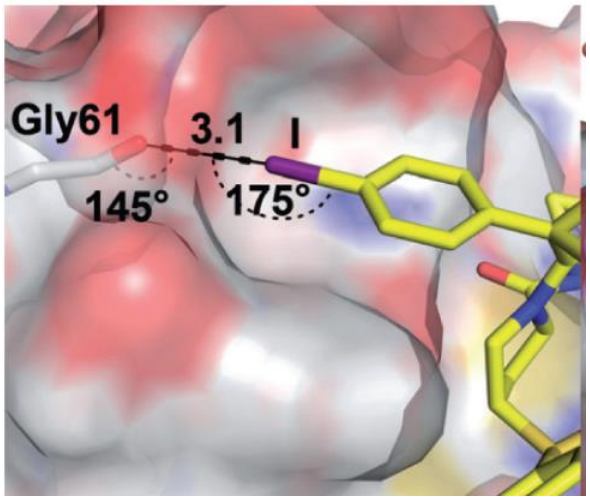
Types of Non-covalent Interactions

π-π-Interaction

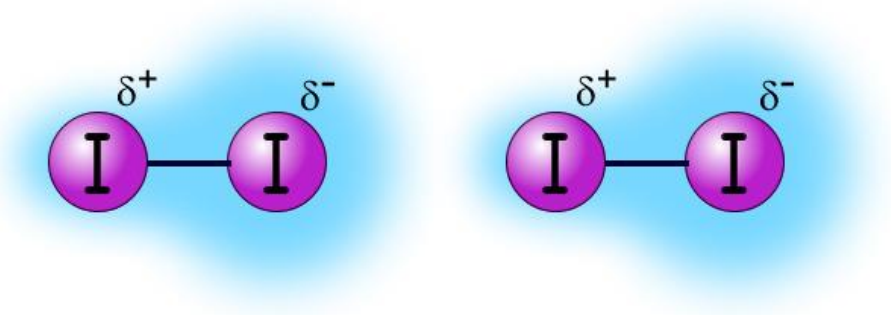


Sandwich T-Form Slipped arrangement

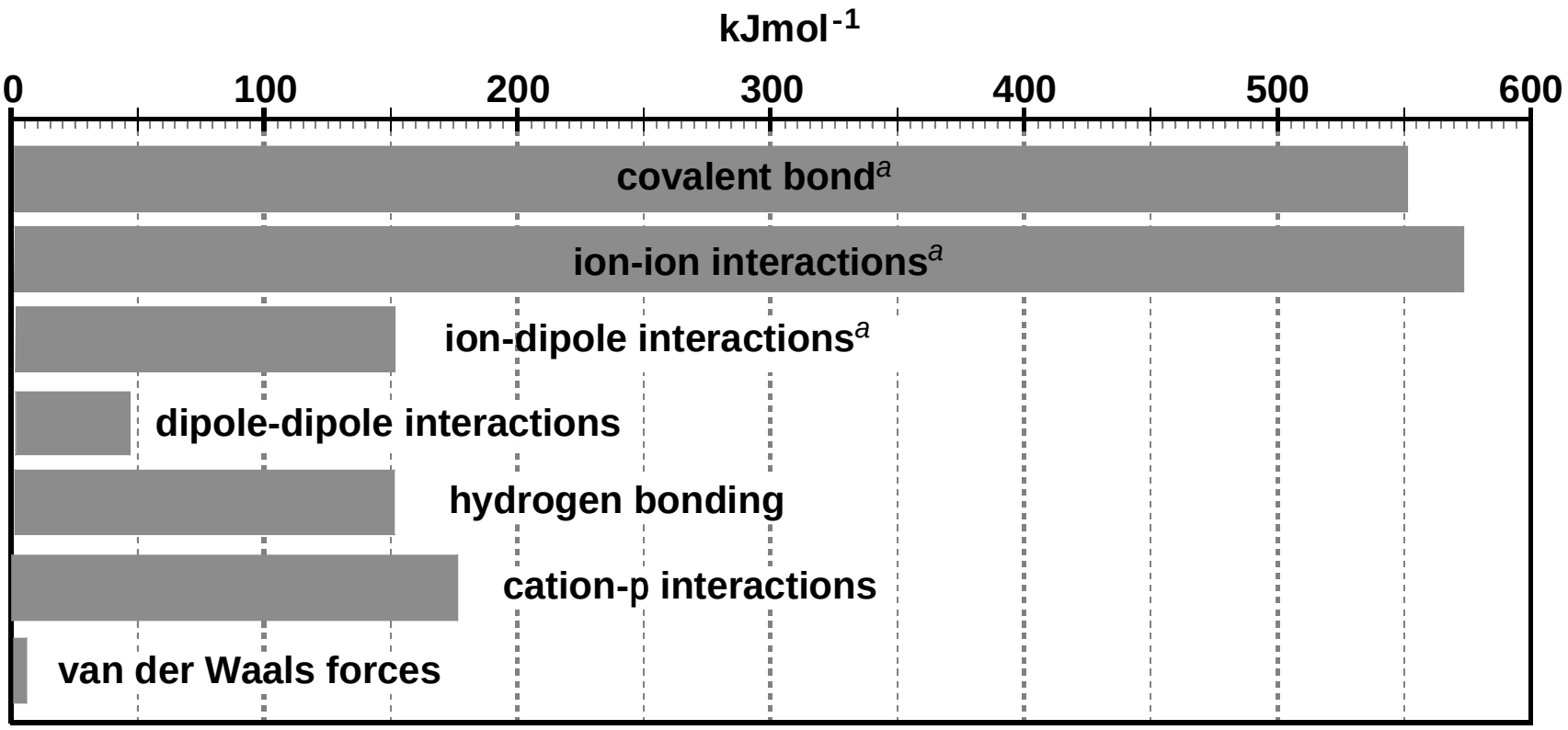
Halogen-Bond



Dispersions Int. (van the Waals Bond)



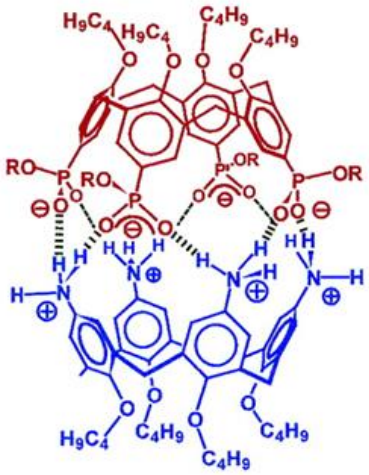
Types of Non-covalent Interactions

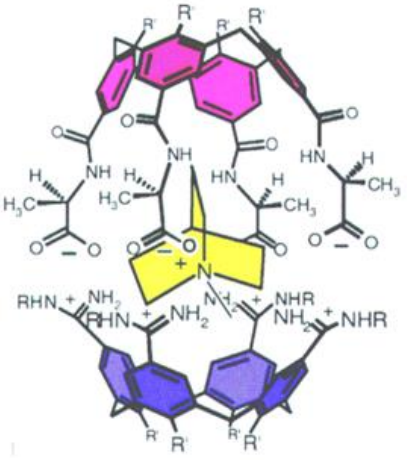


Supplementary information for *Synthetic Receptors for Biomolecules: Design Principles and Applications*

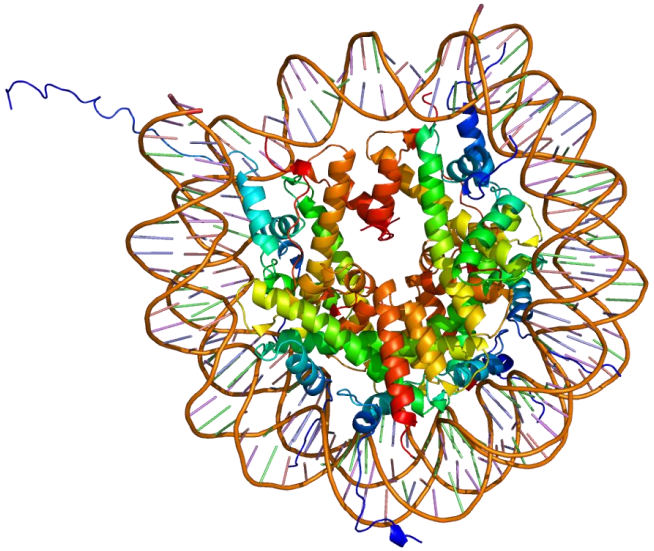
Ion-Ion Interactions

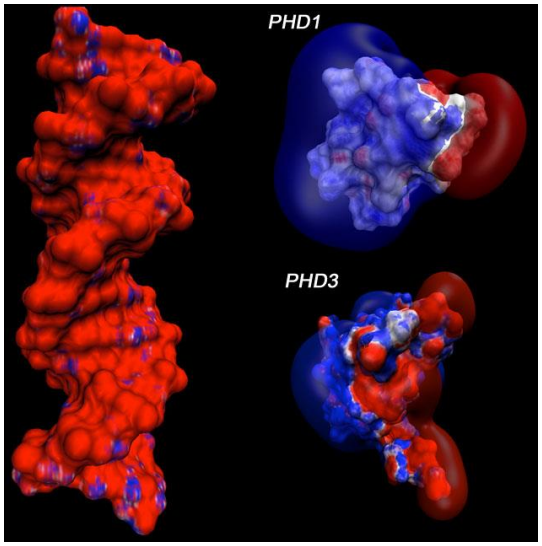
Molecular capsules



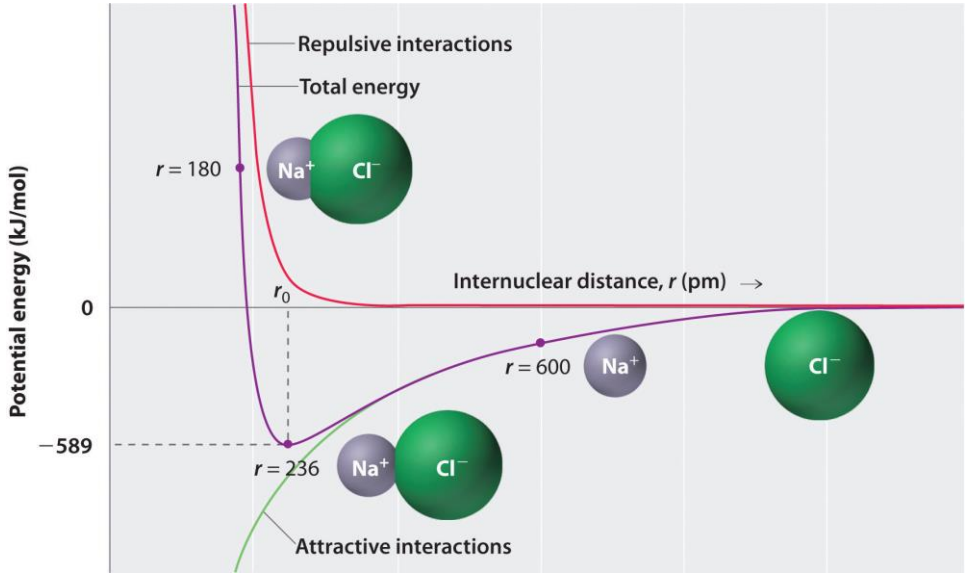


DNA-wrapping and Gen-Regulation through Histones





Ionic Interactions



Elektrostatic Potential

$$E = \frac{Q_1 Q_2}{4\pi\varepsilon r}$$

Repulsive Int.

$$E = \frac{B}{r^n}$$

Born–Landé equation

$$E(r_0) = -\frac{Mz^2e^2}{4\pi\epsilon_0 r_0}\left(1 - \frac{1}{n}\right)$$

For NaCl lattice:
Madelung const. = 1,748

Salt lattice	calculated lattice energy (kJ/mol)	experiment. lattice energy (kJ/mol)
NaCl	756	787
LiF	1007	1046
$CaCl_2$	2170	2255

Fuoss Equation for Ion Pairs in Solution

$$K = (4\pi N a^3/3000)\exp(z_A z_B e^2/\varepsilon k T a)$$

bei 298 K

$$K = 0.00252\, a^3 \exp(560 z_A z_B/\varepsilon a)$$

$$\mathrm{d}\ln K/\mathrm{d}T = \Delta H/\mathrm{R}T^2$$

$$\Delta H = -(z_A z_B e^2/\varepsilon k T a)\mathrm{R}T^2\left(\frac{\mathrm{d}\ln\varepsilon}{\mathrm{d}T} + 1/T\right)$$

$$\Delta S = \mathrm{R}\ln(4\pi N a^3/3000) - (z_A z_B e^2/\varepsilon k T a)\mathrm{R}T\left(\frac{\mathrm{d}\ln\varepsilon}{\mathrm{d}T}\right)$$

für Wasser

$$\mathrm{d}\ln\varepsilon/\mathrm{d}T = -0.00455$$

Für Wasser bei 298 K

$$\Delta H = 6.3(z_A z_B/a)\ \mathrm{kJ\ mol^{-1}}$$

Test for $CaSO_4$

radius(Ca^{2+}) = 1.14 Å
radius(SO_4^{2-}) = 1.49 Å
a ≈ 2.63 Å

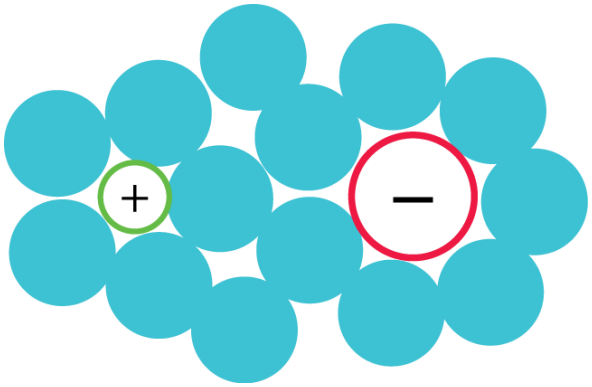
with $z_A = z_B = 2$
and ε = 80.4 for water

K = 1690 M^{-1}
with $\Delta G = -RT\cdot\ln K$
ΔG = −18.4 kJ/mol

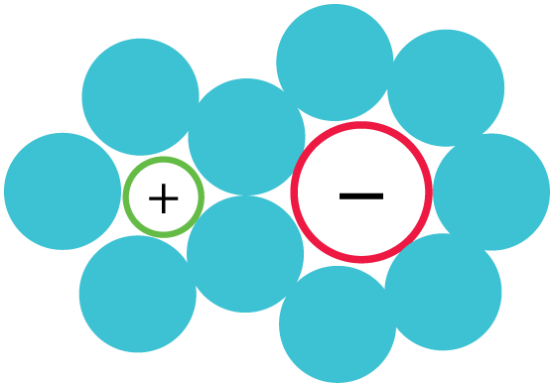
and
ΔH = 9.6 kJ/mol (endotherm)
$T\Delta S$ = −28.0 kJ/mol

Comparison to experiments?

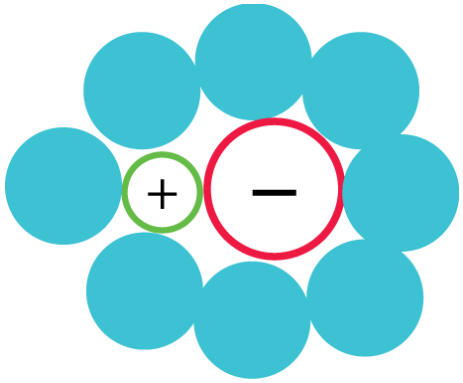
Ionic Interaction in Solution



solvent-separated ion pair



solvent-bridged ion pair



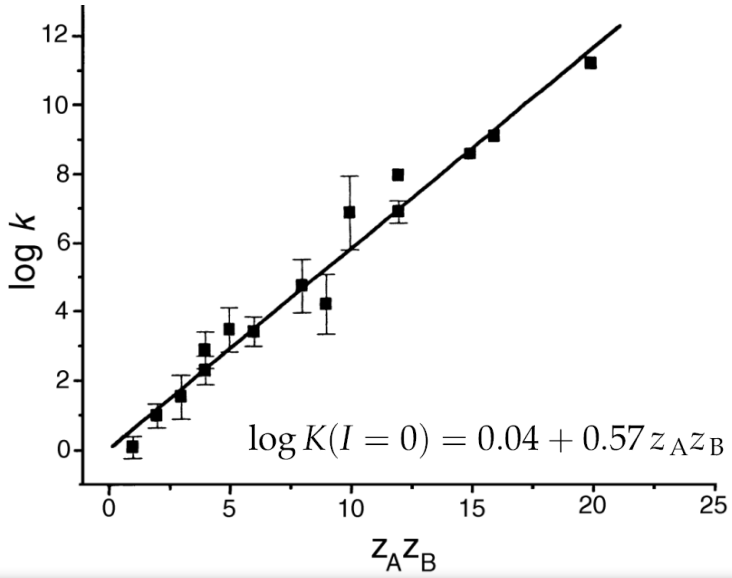
contact ion pair

Table B1. Selected thermodynamic ion-pairing parameters (kJ mol^{-1}) at 25°C in water.[9,12]

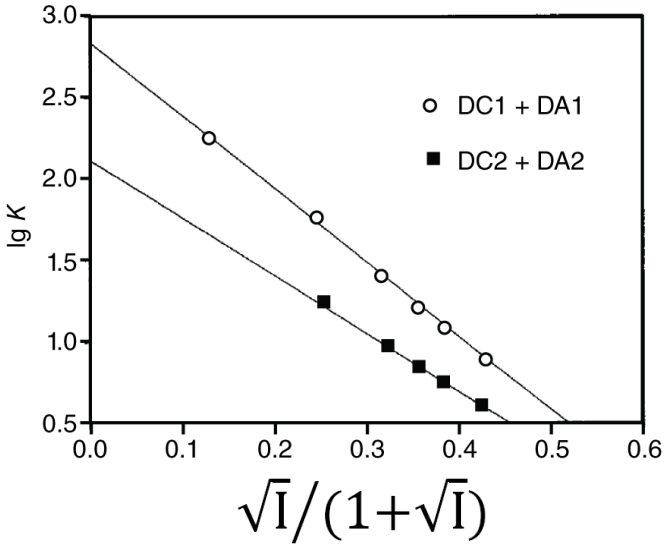
Ion pair	ΔG	ΔH	$T\Delta S$	Ref.
$Ca^{2+}SO_4^{2-}$	−13.2	6.9	20.1	9
$Zn^{2+}SO_4^{2-}$	−13.6	16.8	30.4	9
$Ca^{2+}(EDTA)^{4-}$	−59.9	−27.0	32.9	9
$La^{3+}Fe(CN)_6^{3-}$	−21.3	8.4	29.7	9
$Co(NH_3)_6^{3+}Cl^-$	−9.7	2.7	12.4	12
$Co(NH_3)_6^{3+}ClO_4^-$	−9.1	−3.6	5.5	12
$Li^+Co(C_2O_4)_3^{3-}$	−5.2	6.4	11.6	12
$Cs^+Co(C_2O_4)_3^{3-}$	−9.3	−1.5	7.8	12

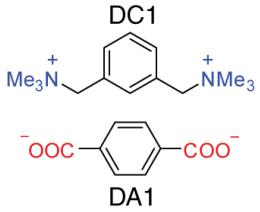
ion pair	$\Delta_{IP}G°$	$\Delta_{IP}H°$	$\Delta_{IP}S°$
$MgSO_4$	−12.6	5.8	61.7
$CaSO_4$	−13.0	6.7	66.1
$MnSO_4$	−13.0	7.8	69.8
$CoSO_4$	−13.2	5.7	63.4
$NiSO_4$	−13.3	5.4	62.7
$ZnSO_4$	−13.2	6.2	65.1
$CdSO_4$	−13.6	8.4	73.8

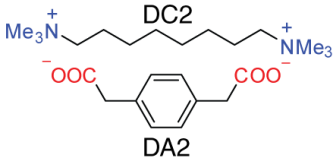
Experimental Results for Ionic-Interactions



- Good correlation between ΔG and · z_A · z_B, for 200 ion pairs in water
- Agreement with Fuoss Equation







- Lowering of the ionic bond strength upon salt addition
- Agreement with Debye-Hückel Theory

$$\lg K = \lg K_0 + m\sqrt{I}/(1+\sqrt{I})$$

Problems with Theoretical Models for Ion Pairing

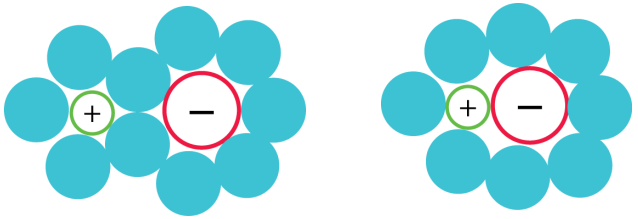
Cation	*Anion*	*log K*
Li^+	$Cr(C_2O_4)_3^{3-}$	0.843
Na^+		1.513
K^+		1.570
Rb^+		1.586
Cs^+		1.617
trans-Co	Cl^-	0.20
$(En)(NO_2)_2^+$	Br^-	0.30
	I^-	0.41
	ClO_4^-	0.43

$$K = \exp\left(z_A z_B e^2 / \varepsilon k T a\right)$$

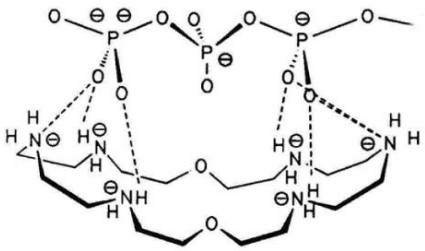
Theory predicts a smaller K with a larger distance.
Experimentally, the opposite was found!

Fuoss theory (full equation) predicts K-Minimum at $a = 2.4 \cdot z_A \cdot z_B$. This was never experimentally found.

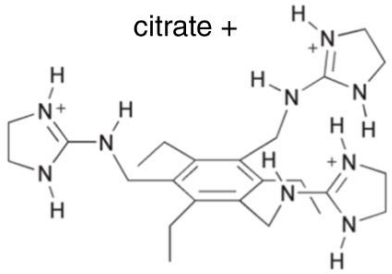
Models do not consider specific solvation structures of the ions, particularly small and highly charged ones.



Experimental Findings for Ionic Interactions: Organic Ions



lg K = 11.0 n_H = ca. 12



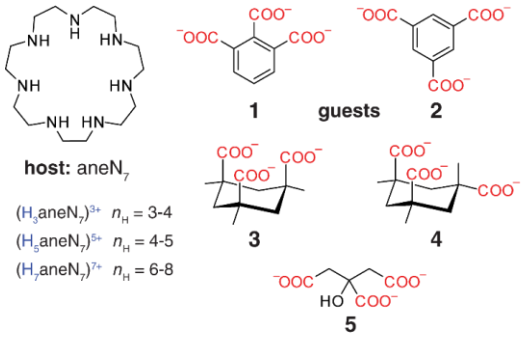
lg K = 3.5 n_H = ca. 3

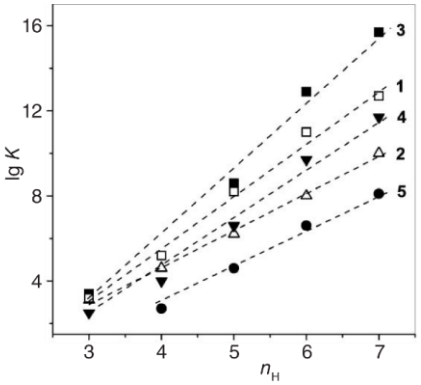
often additivity observed

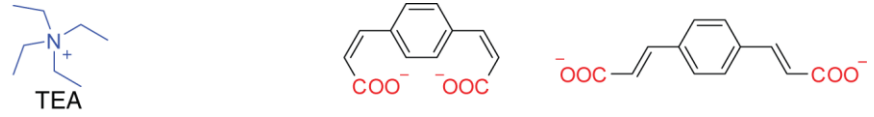
$$\Delta G_{total} = N \cdot \Delta G_{Inkrement}$$

Experimental Trends:

- Per ion pair, that forms, ca. **2-8** kJ/mol (often ~5 kJ/mol) gain in ΔG in water.
- Distance dependency
- Ion pair-formation in water mostly entropically driven, enthalpy ~ 0.







d	=	6.0	11.6	Å
$-\Delta G$(TEA)	=	11.0	5.5	kJ/mol
$-\Delta G$(MGU)	=	17.0	<3	kJ/mol

Hydrogen Bonds

Pauling's Definition (1939)

Under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms instead of only one, so that it may be considered to be acting as a bond between them.

Steiner–Saenger Defintion

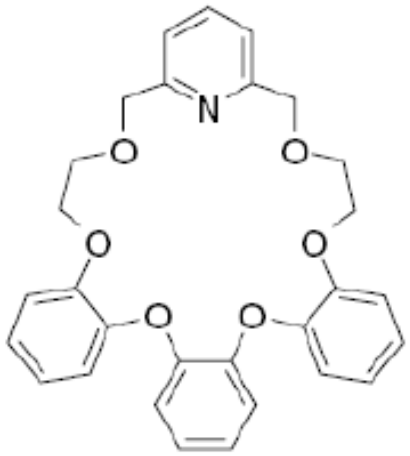
Any cohesive interaction X–H•••A where H carries a positive and A a negative (partial or full) charge and the charge on X is more negative than on H.

O–H···O^-	O–H···O	N–H···O
O–H···π	N–H···π	C–H···O
Os–H···O	C–H···Ni	C–H···π

Weak Hydrogen Bonds

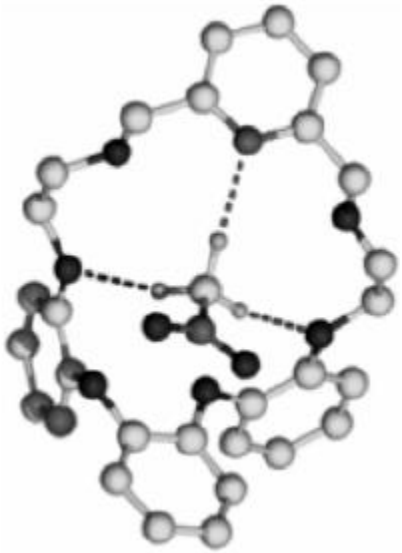
Desiraju–Steiner definition (1999)

The weak hydrogen bond is an interaction X–H···A wherein a hydrogen atom forms a bond between two structural moieties X and A, of which one or even both are of moderate to low electronegativity



C-H als H-bond-Donor

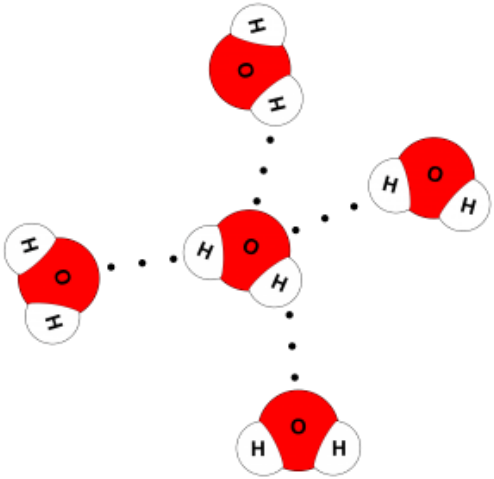
+ $H_3C\text{-}NO_2$



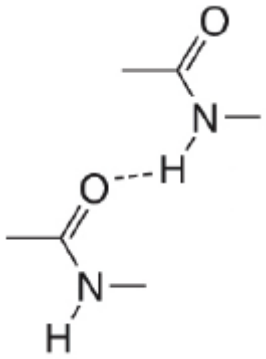
Hydrogen Bonds

New IUPAC Definition:

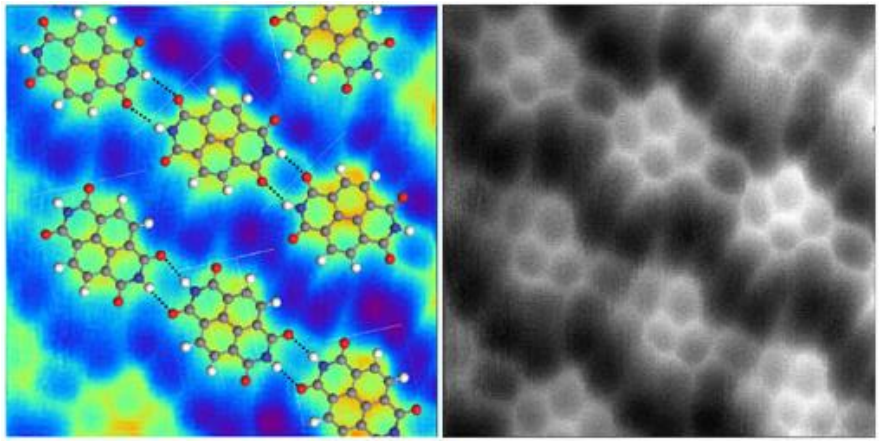
"The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation."



H-bond-network of water

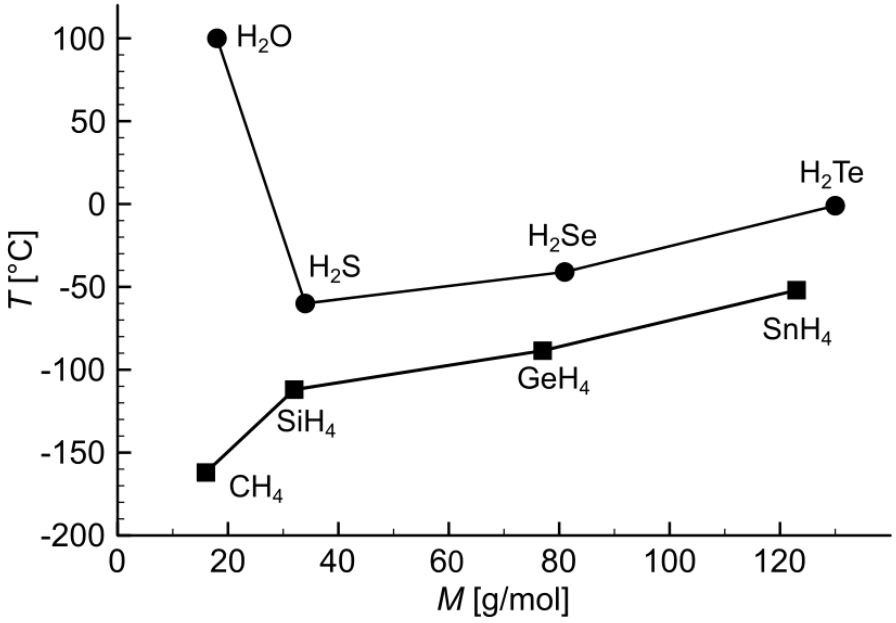


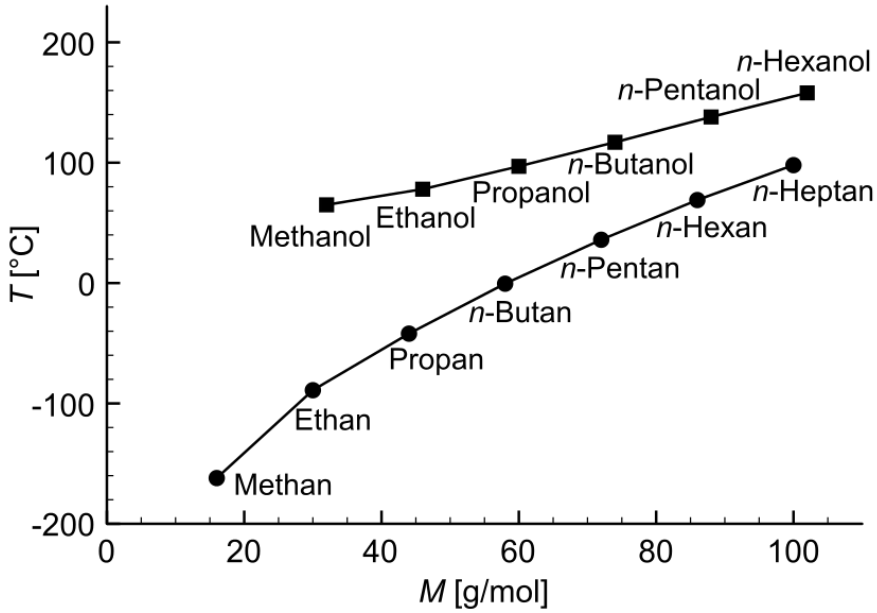
Amid-Dimer in CCl_4

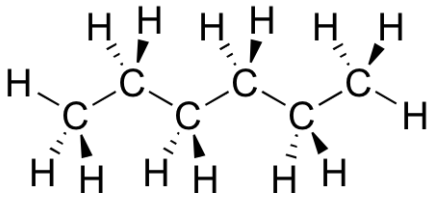


„Visualization" of H-bonds by Dynamic Force Microscopy
Nat. Commun. **2014**, Article # 3931

Influence of Hydrogen Bonds on the Boiling Point

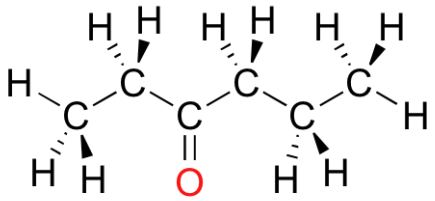






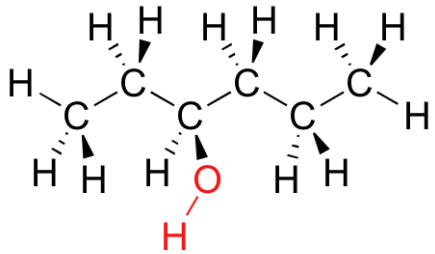
hexane

bp = 69°C



3-hexanone

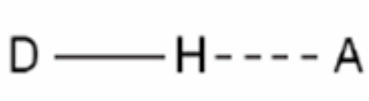
bp = 123 °C



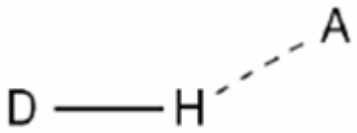
3-hexanol

bp =135°C

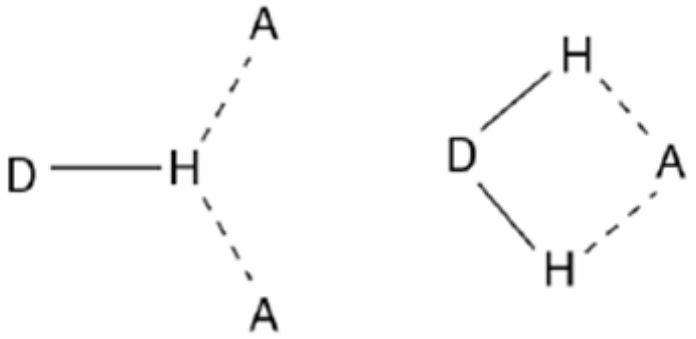
Classification of Hydrogen Bonds



linear



bent

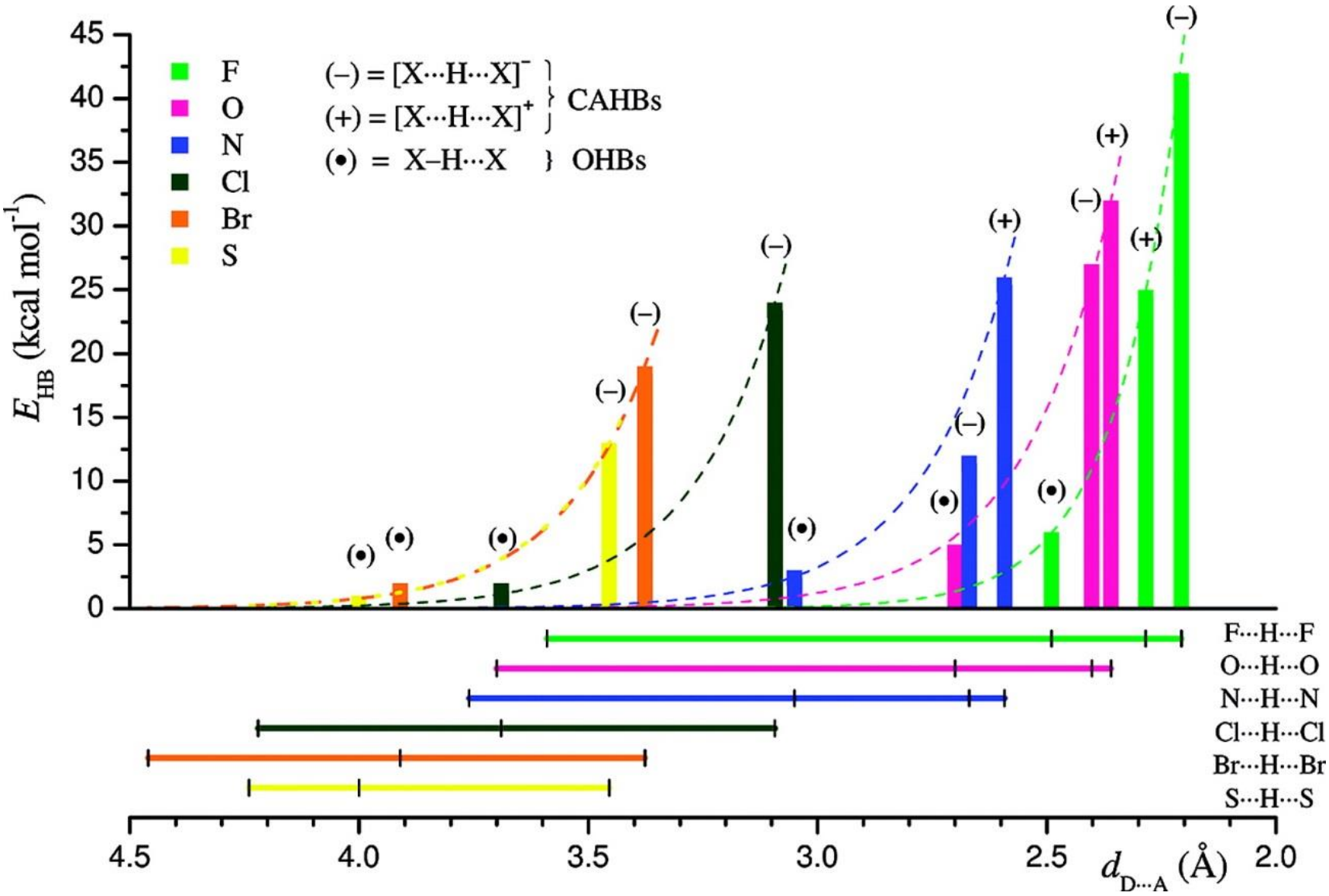


bifurcated

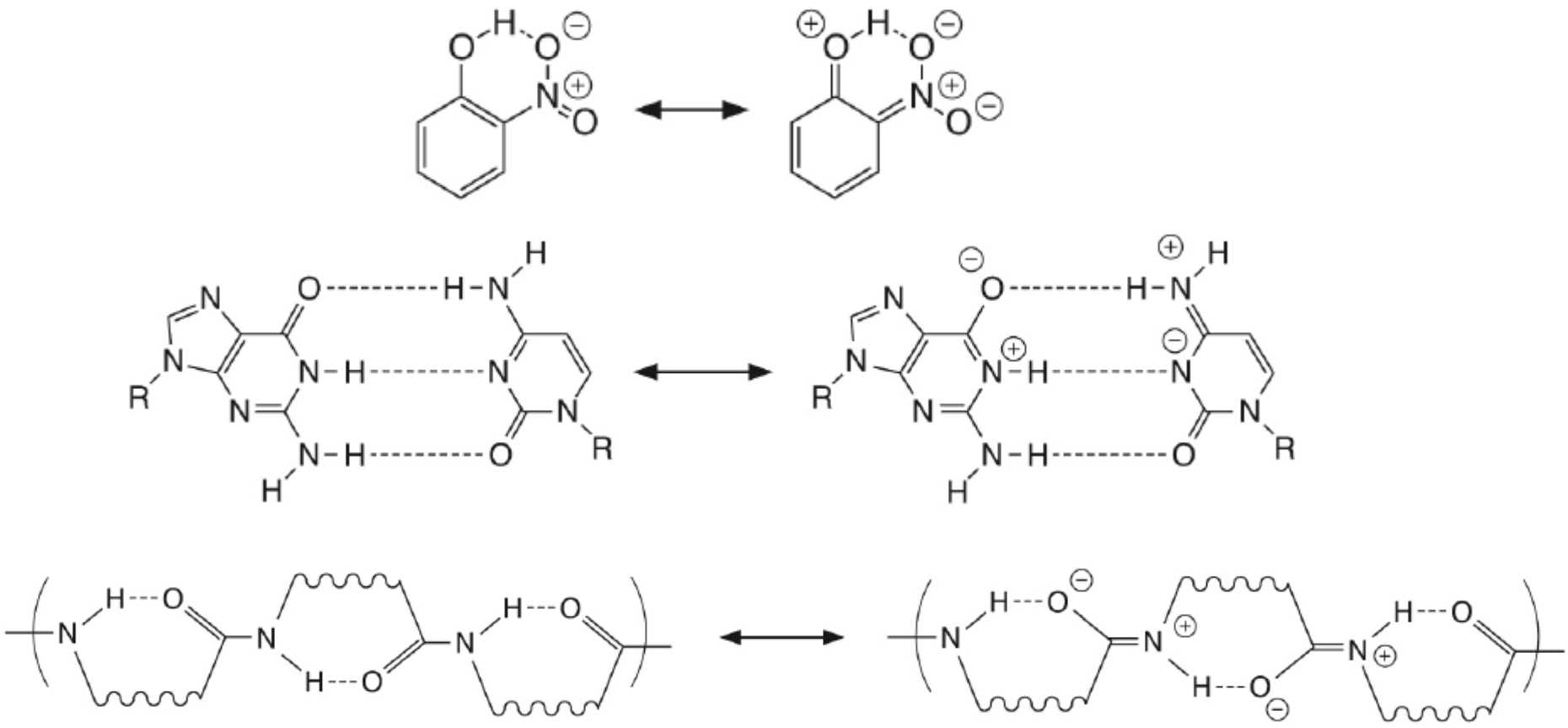
Interaction/property	Strong	Moderate	Weak
D–H···A	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol^{-1})	60–120	16–60	< 12
Bond length (Å)			
H···A	1.2–1.5	1.5–2.2	2.2–3.2
D···A	2.2–2.5	2.5–3.2	3.2–4.0
Bond angle (degrees)	175–180	130–180	90–150
Example	HF complexes	Acids	C–H···A
	$H_5O_2^+$	Alcohols	D–H···π
	—	DNA/RNA	—

From Book: Supramolecular Chemistry, Wiley

Distance-Energy Relation of Hydrogen Bonds

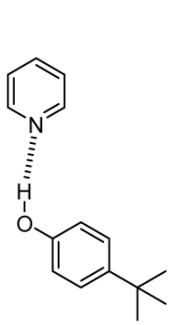


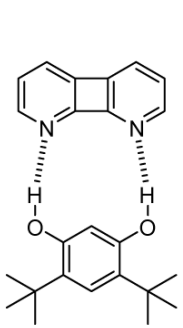
Mesomerie-stabilisierte Hydrogen Bonds

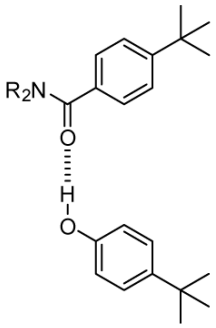


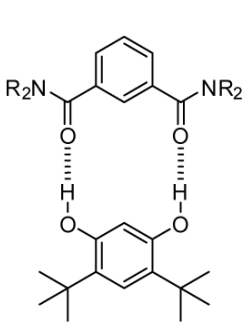
Mesomeric structures with charges
=> Stronger H-bonds

Correlation of the Bond Energies









ε_{rel} ↓ solvent	$-\Delta G$ (kJ/mol) one H-bond	$-\Delta G$ (kJ/mol) two H-bonds	$-\Delta G$ (kJ/mol one H-bond	$-\Delta G$ (kJ/mol two H-bonds
C_6H_{12}	12	22	-	-
CCl_4	9	19	11	19
$CHCl_3$	8	15	-	-
$(CHCl_2)_2$	8	13.5	-	-

Empirical equation for 1:1 associations complexes with H-bonds in CCl_4

Abraham $\lg K = 7.354\ \alpha_2^H\beta_2^H - 1.094$

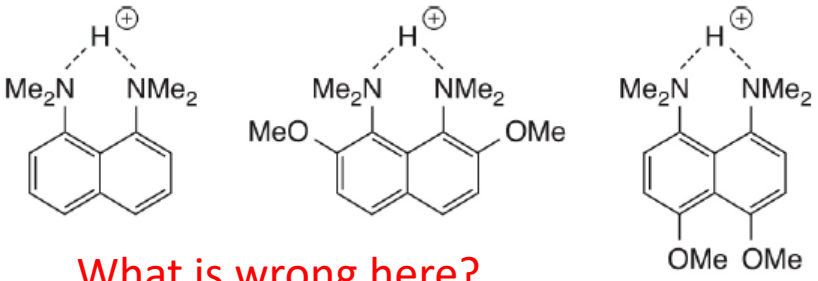
measured for >1000 pairs, $R^2 = 0.9912$

e.g. with $\alpha_2^H = 0.57$ for 4-CH3-Ph-OH and $\beta_2^H = 0.69$ for Ph-CO-NR'R''
$\Delta G_{calc} = 10$ kJ/mol in CCl_4 (Experiment: 11 kJ/mol)

e.g. with $\alpha_2^H = 0.57$ for 4-CH3-Ph-OH and $\beta_2^H = 0.52$ for Pyridin
$\Delta G_{calc} = 6$ kJ/mol in CCl_4 (Experiment: 9 kJ/mol)

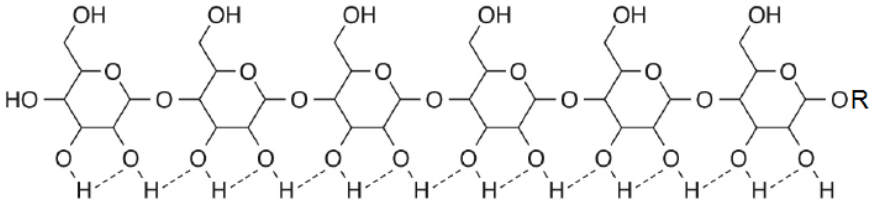
Intramolecular Hydrogen Bonds

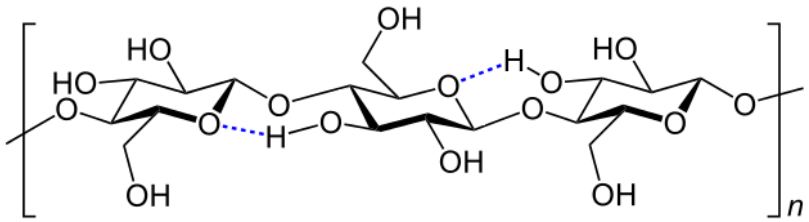
„Proton sponges“

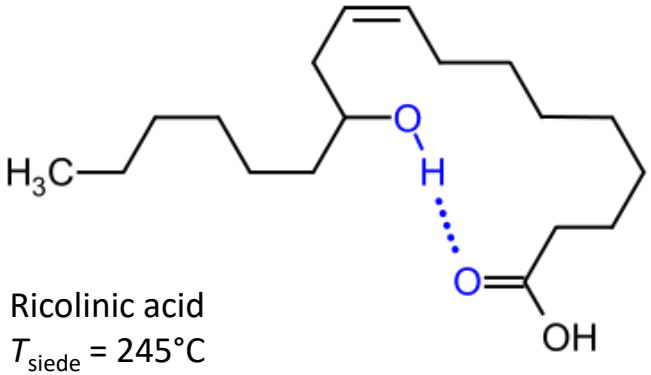


What is wrong here?

Graphical depiction with errors. These are linear bonds!





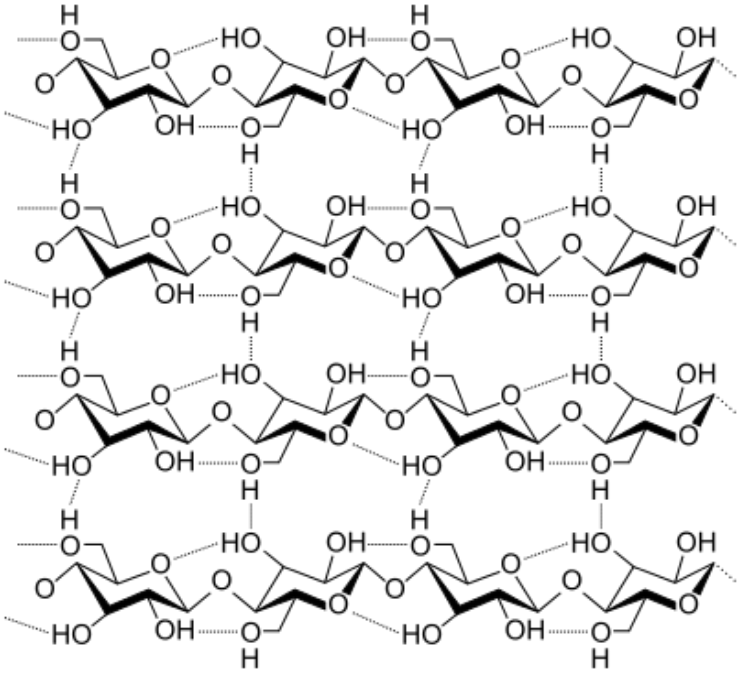


Ricolinic acid
T_{siede} = 245°C

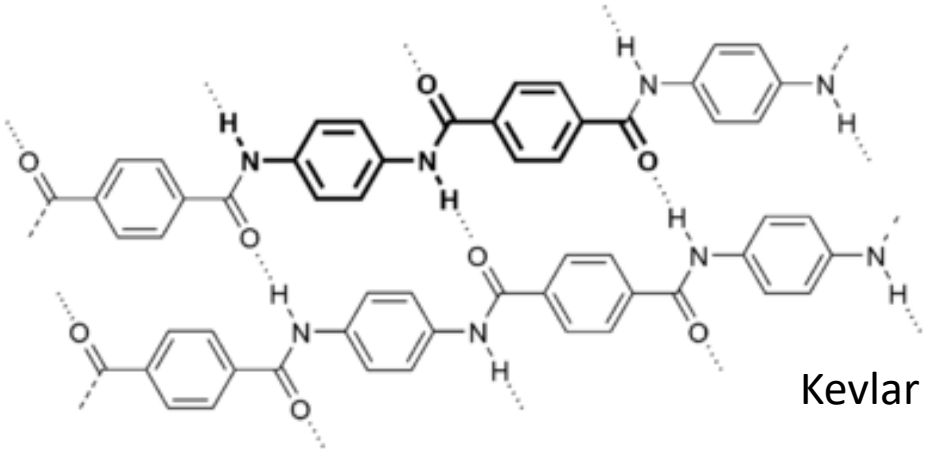
Comparison: Oelic acid T_{siede} = 360°C

Intramolecular H-bonds increase the rigidity of molecule

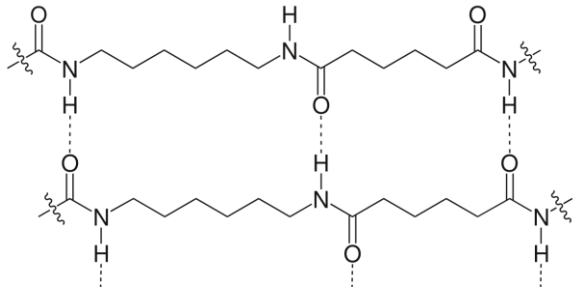
Self-assembly through Hydrogen Bonds



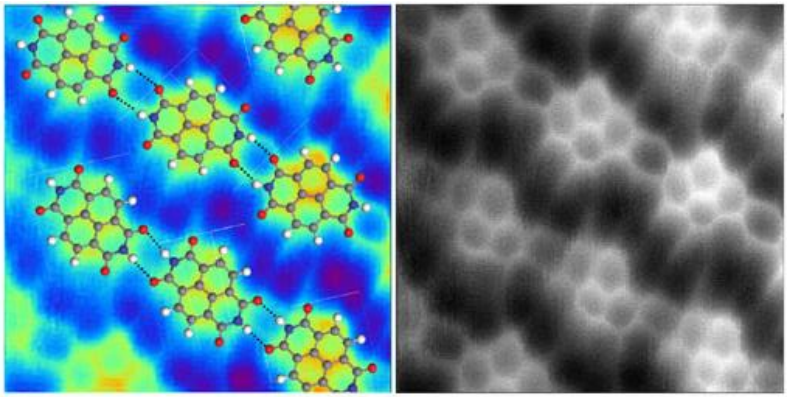
Cellulose

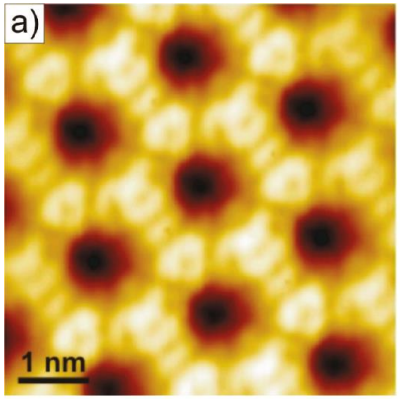


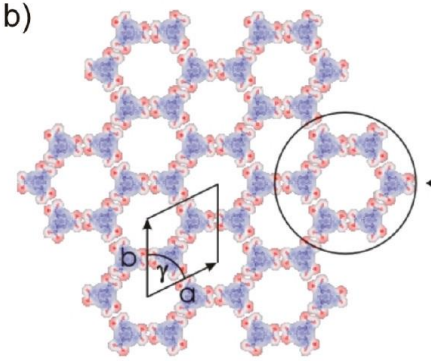
Kevlar



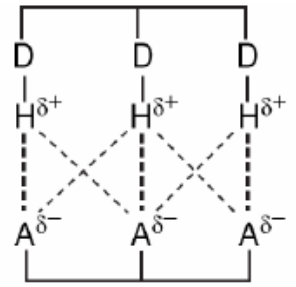
Nylon6,6



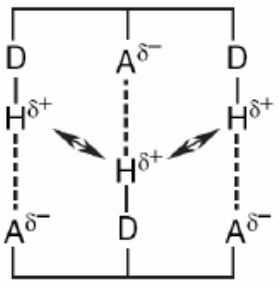




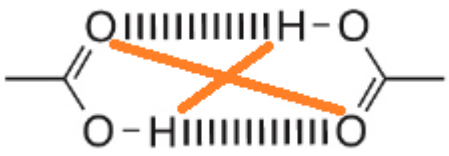
Secondary Interactions for Hydrogen Bonds

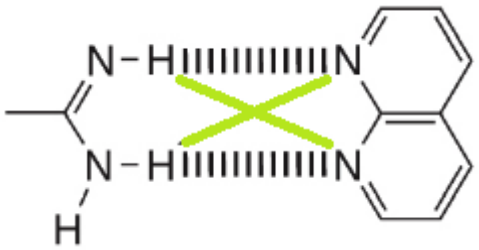


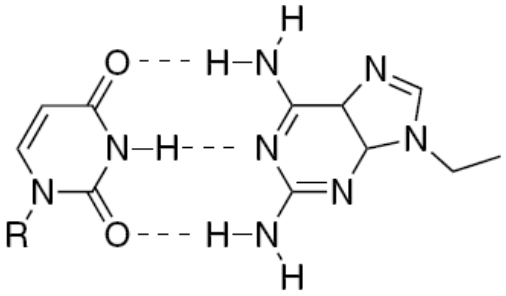
attractive

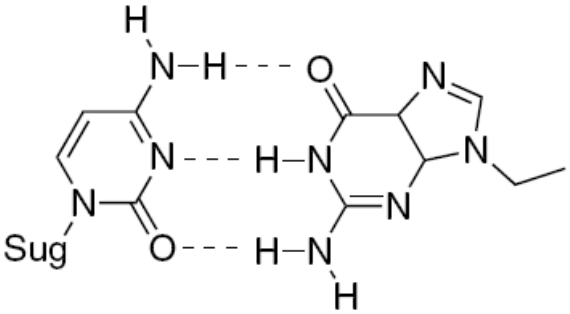


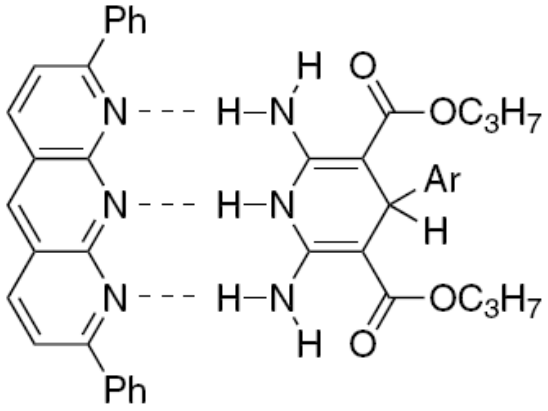
repulsive



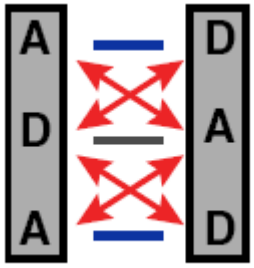




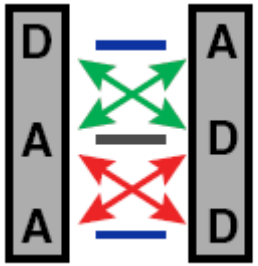




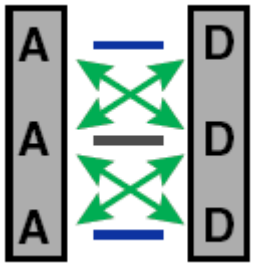
$K = 10^2\ M^{-1}$ in $CDCl_3$



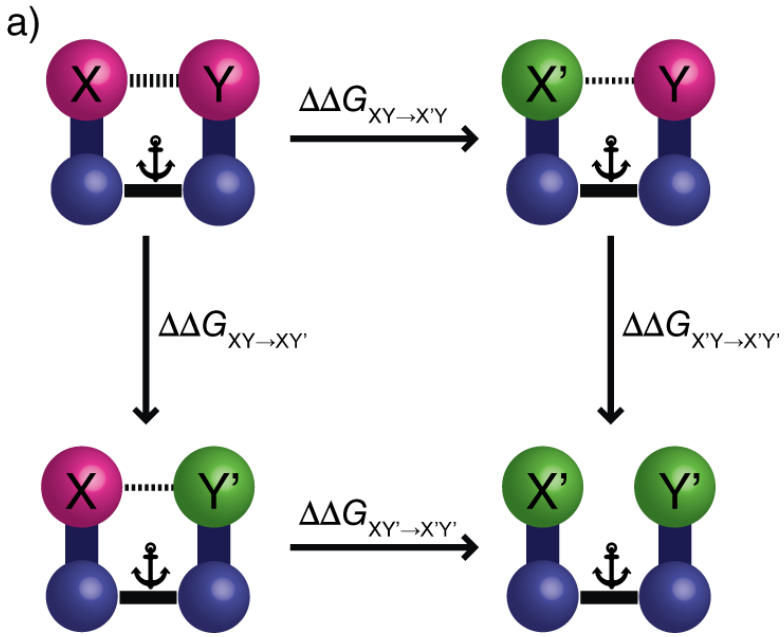
$K = 10^4\ M^{-1}$

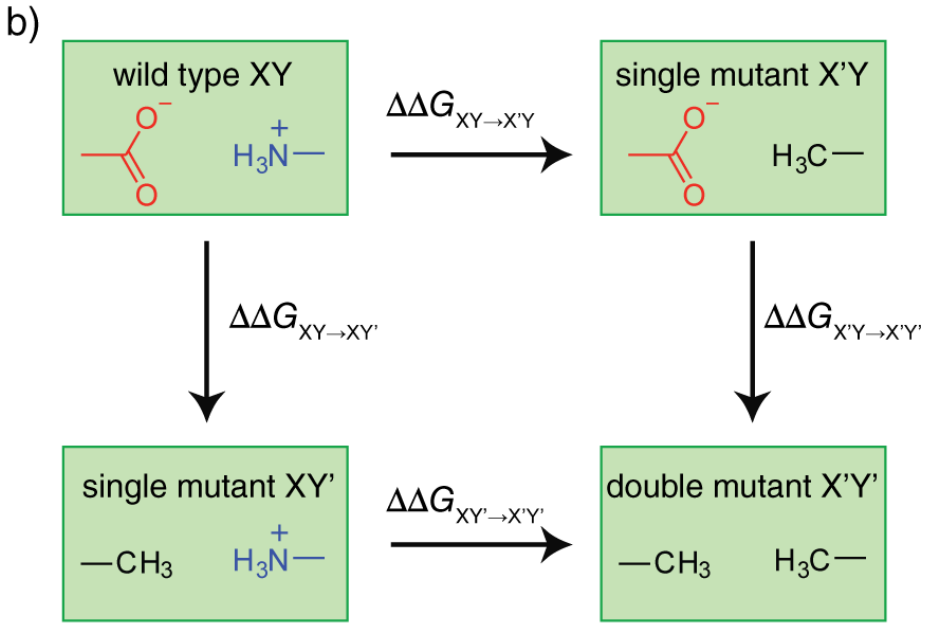


$K > 10^5\ M^{-1}$

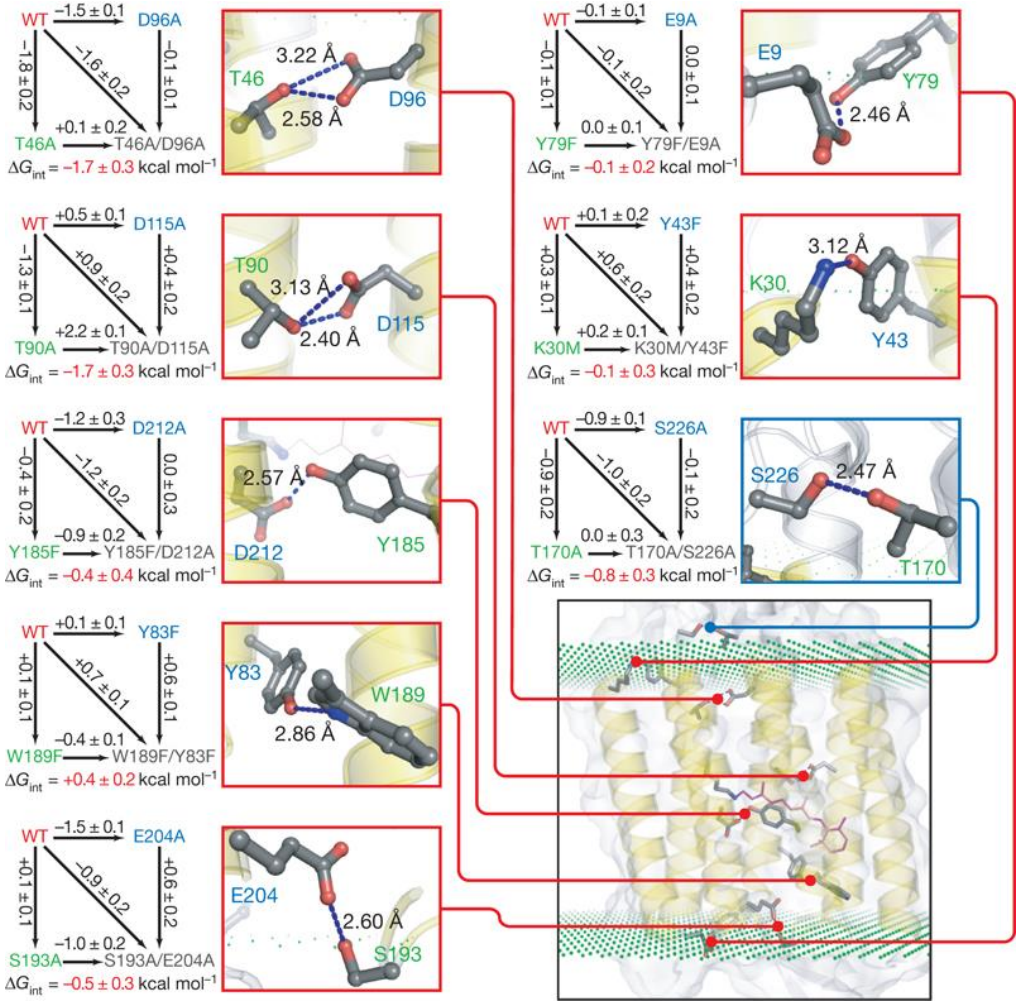


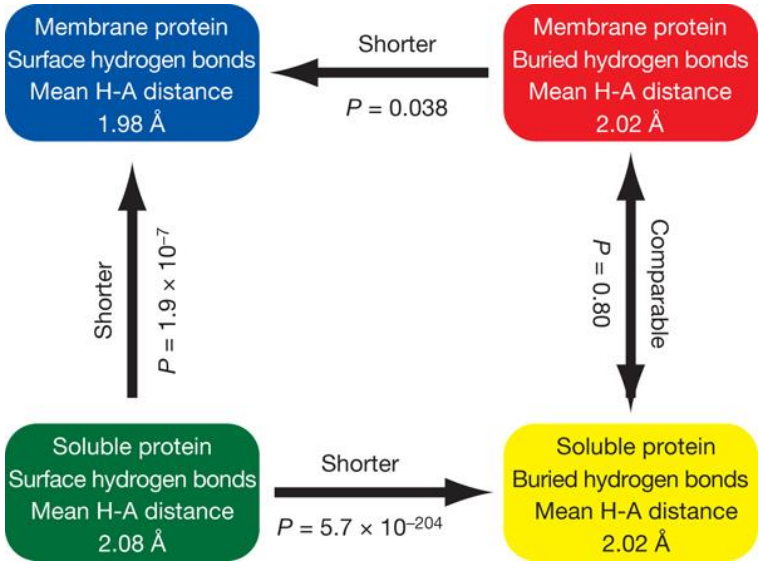
Double Mutant Analysis





Hydrogen Bonds in Membrane Proteins

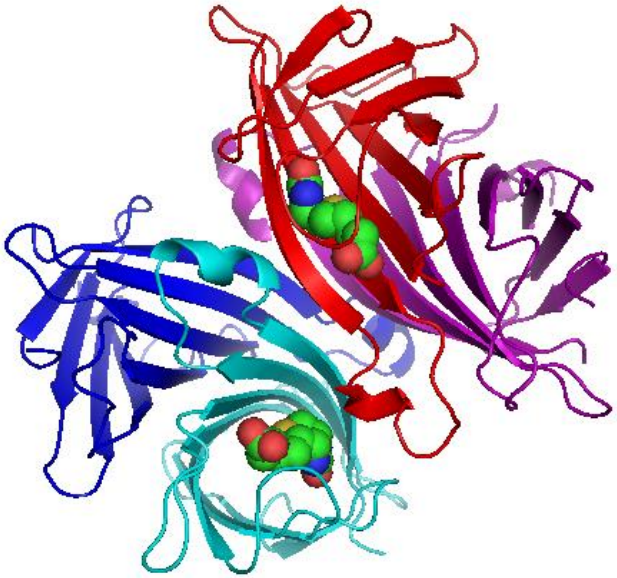


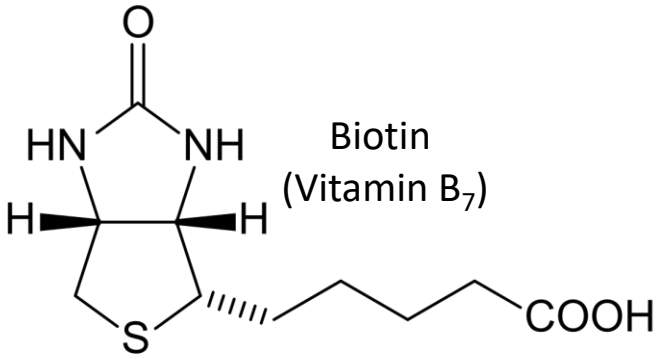


Nature **2008**, *453*, 1266.

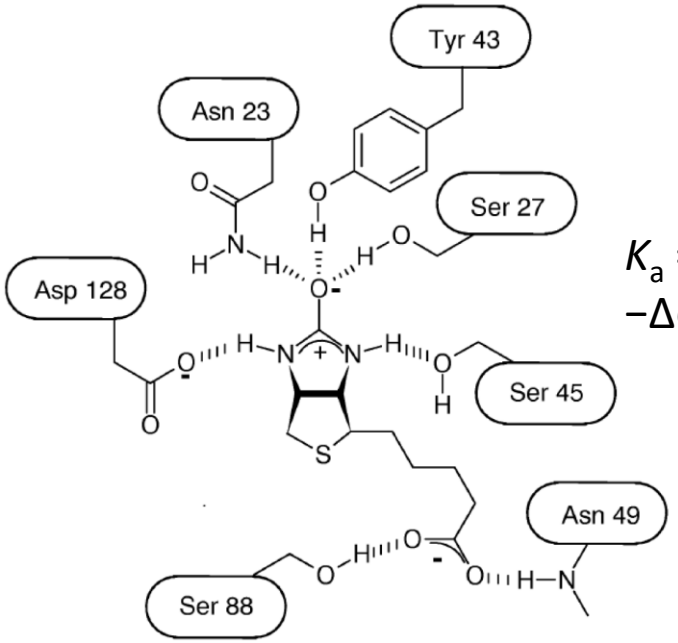
Sometimes hydrogen bonds stabilize, and sometimes destabilize protein folding!
(On average only 3 kJ/mol stabilisation per H-bond pair)

Streptavidin-Biotin: Biological Record-affinity



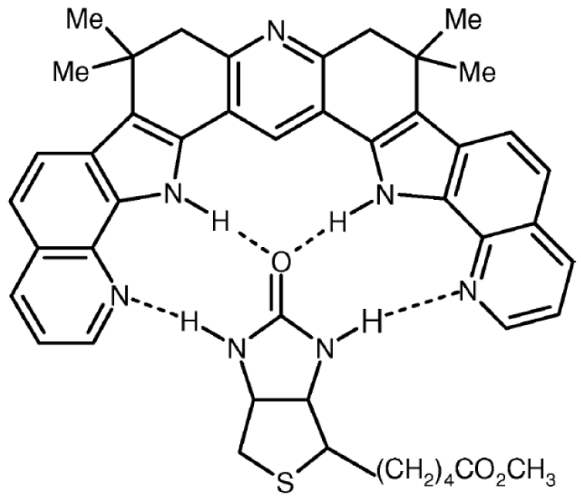


Biotin
(Vitamin B_7)



$K_a = 3 \cdot 10^{13}\ M^{-1}$ in H_2O
$-\Delta G = 76.4$ kJ/mol

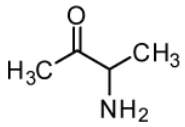
Synthetisches Analoga

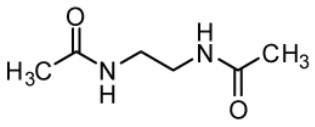


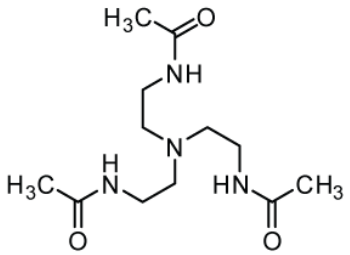
$K_a = 9 \cdot 10^{3}\ M^{-1}$ in $CHCl_3$
$-\Delta G = 22.6$ kJ/mol

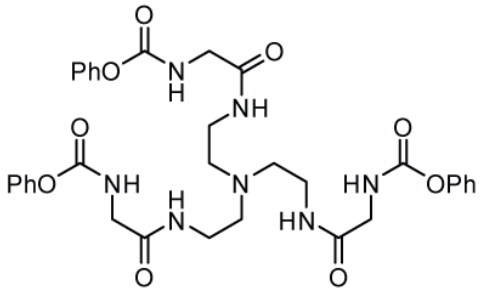
Anion-Binding through Hydrogen Bonds

in $CHCl_3$



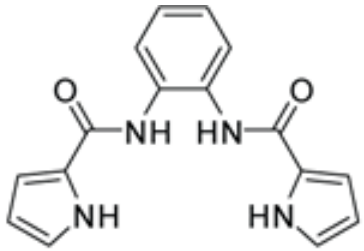


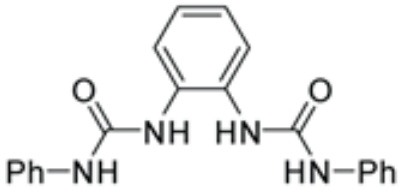


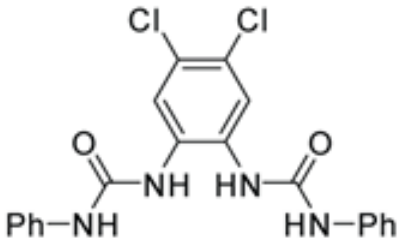


n_H	1	2	3	6	
$-\Delta G(Cl^-)$	5.7	11.6	14.2	18.2	kJ/mol
$-\Delta G(Br^-)$	4.6	7.2	12.0	12.6	kJ/mol

in DMSO
+ 0.5% water

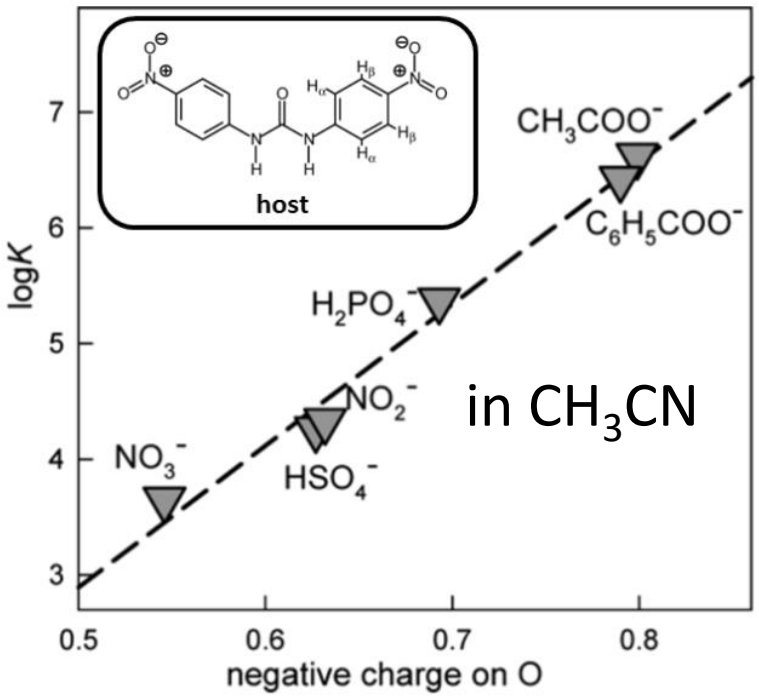




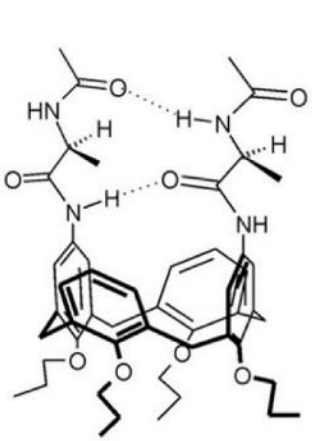


$-\Delta G(Cl^-) =$	6.1	9.2	10.3	kJ/mol
$-\Delta G(CH_3COO^-) =$	13.5	19.8	22.0	kJ/mol

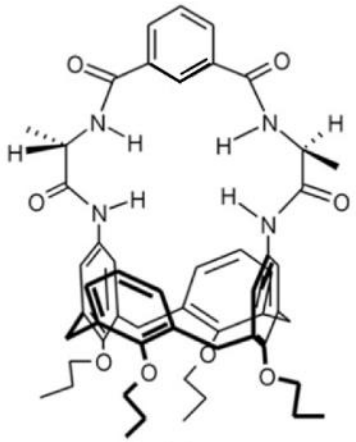
Anion-Binding through Hydrogen Bonds



The larger the negative charge density of the anion, the stronger the anion binding.



A

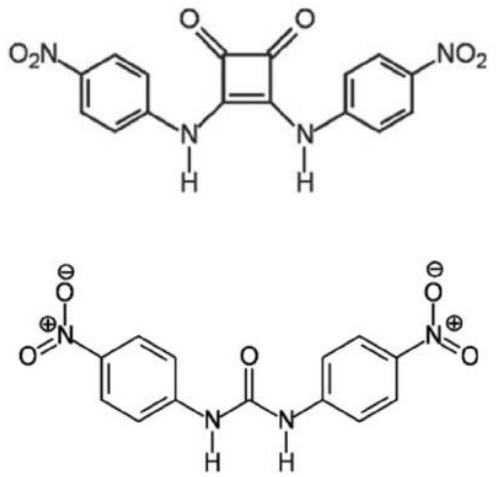


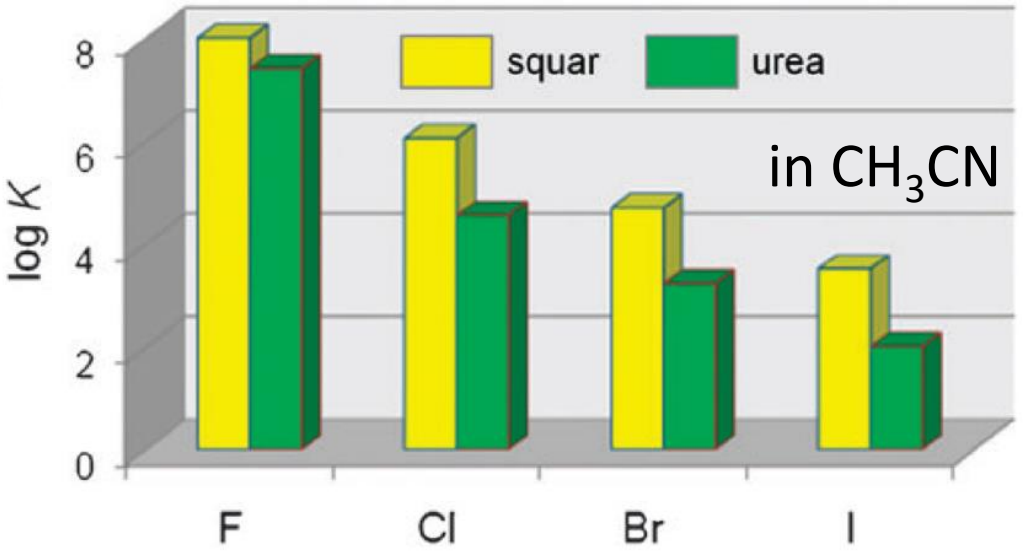
B

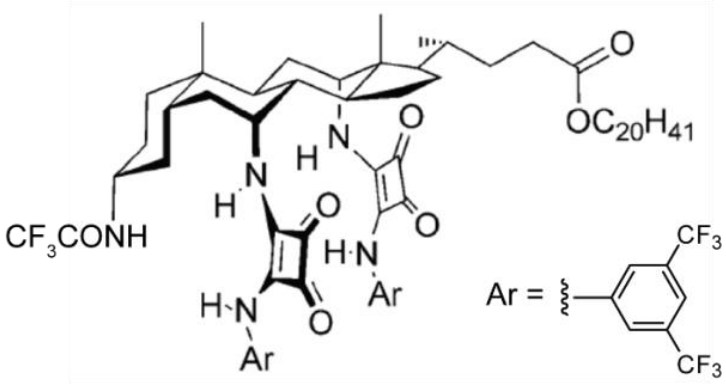
$-\Delta G(MeCOO^-) =$	14.8	kJ/mol
$-\Delta G(PhCOO^-) =$	16.3	kJ/mol

Preorganisation leads to stronger binding receptors

Record Affinities for „classical“ H-Bond Anion Binding

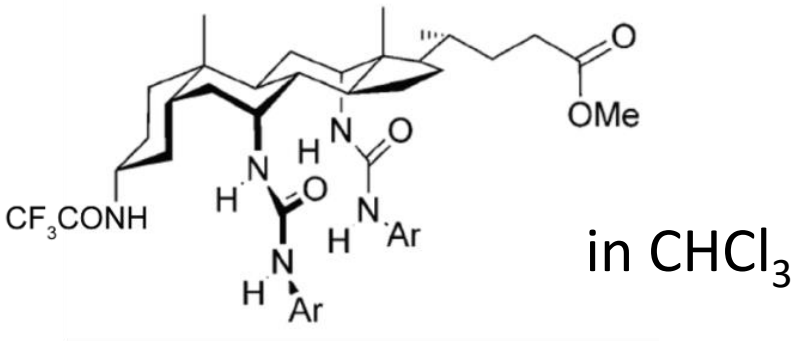






squaramide-based host

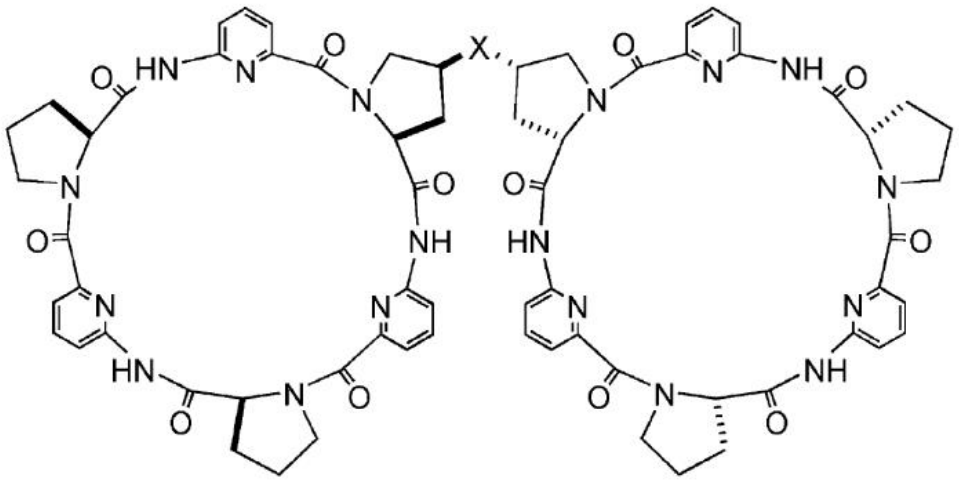
$-\Delta G(EtN_4^+Cl^-) = 82$ kJ/mol

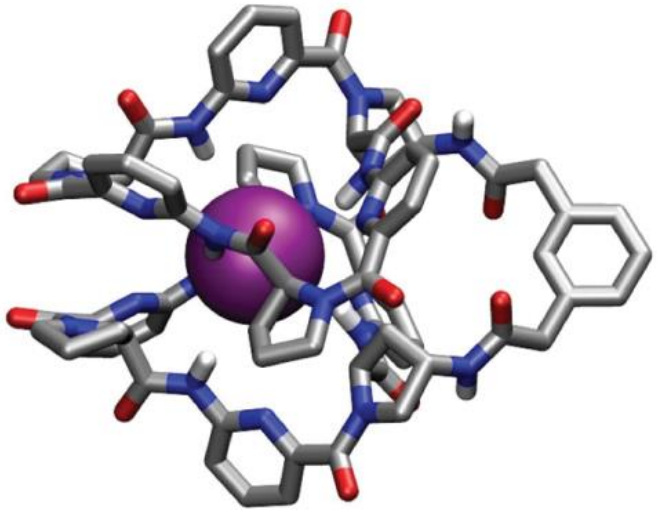


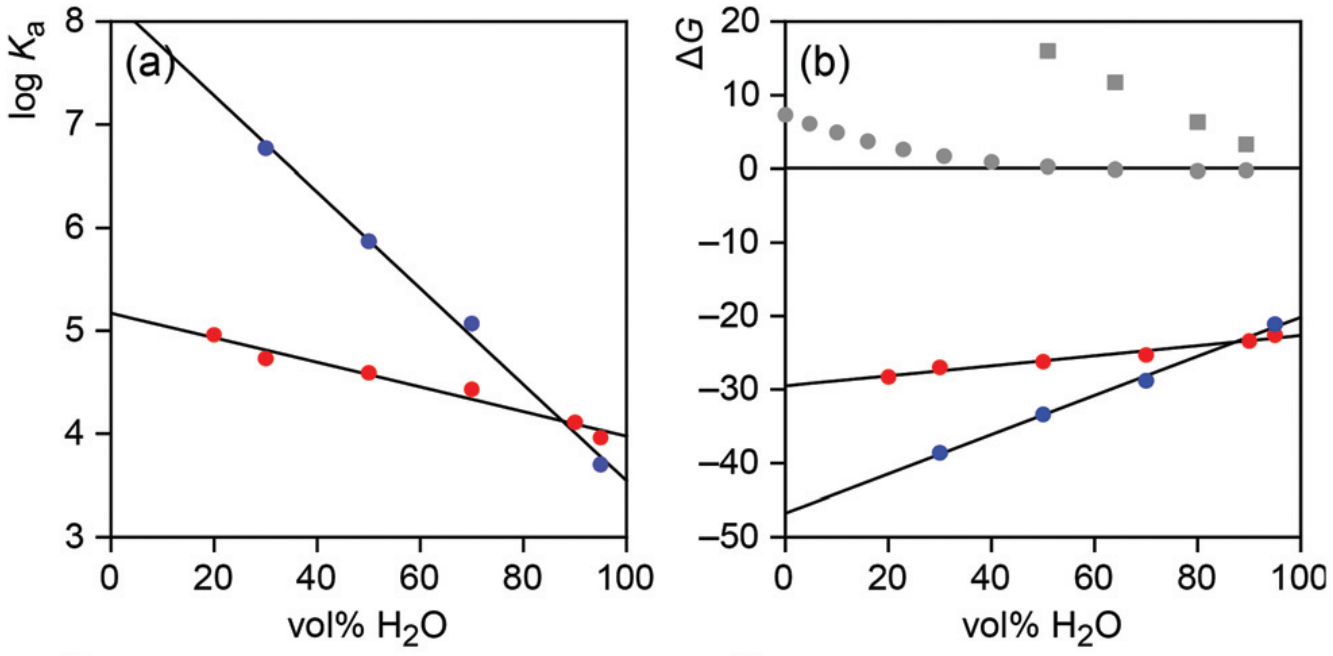
urea-based host

$-\Delta G(EtN_4^+Cl^-) = 56$ kJ/mol

Record Affinities for „classical“ H-Bond Anion Binding

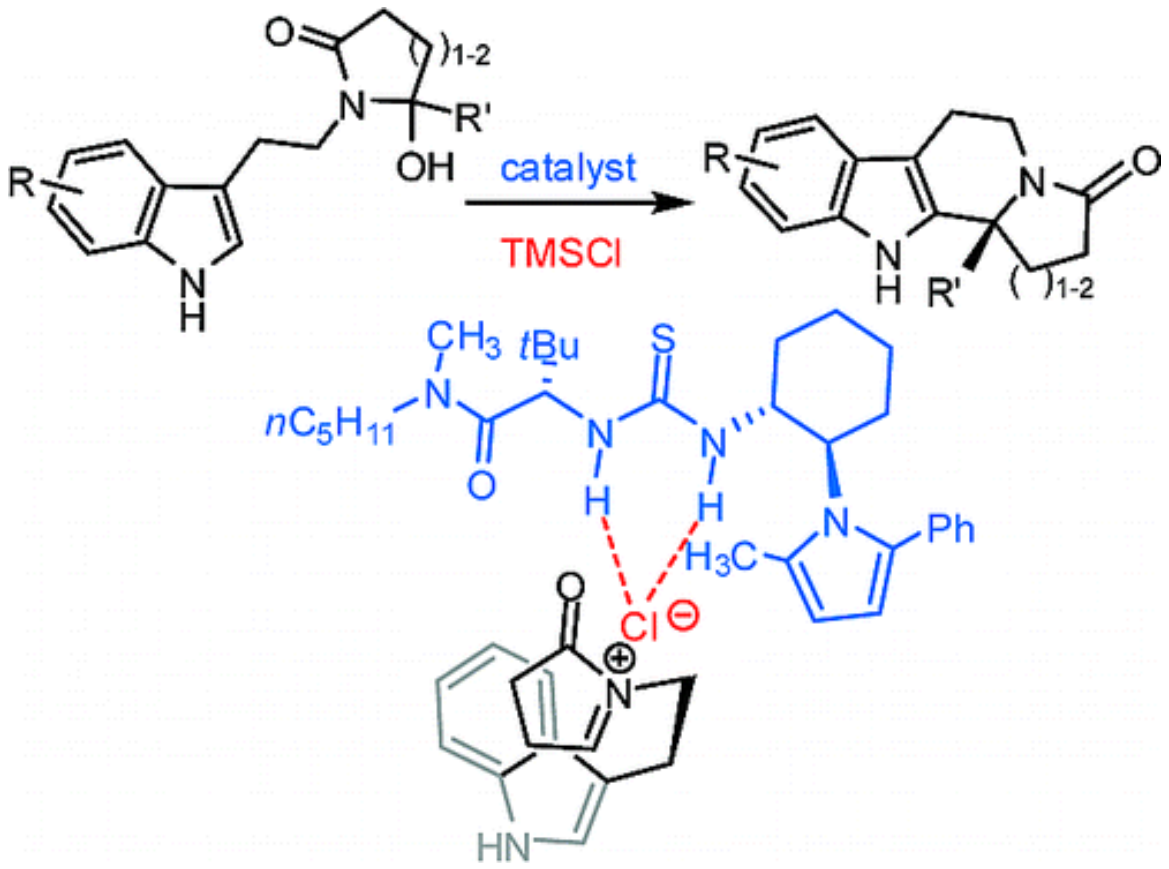






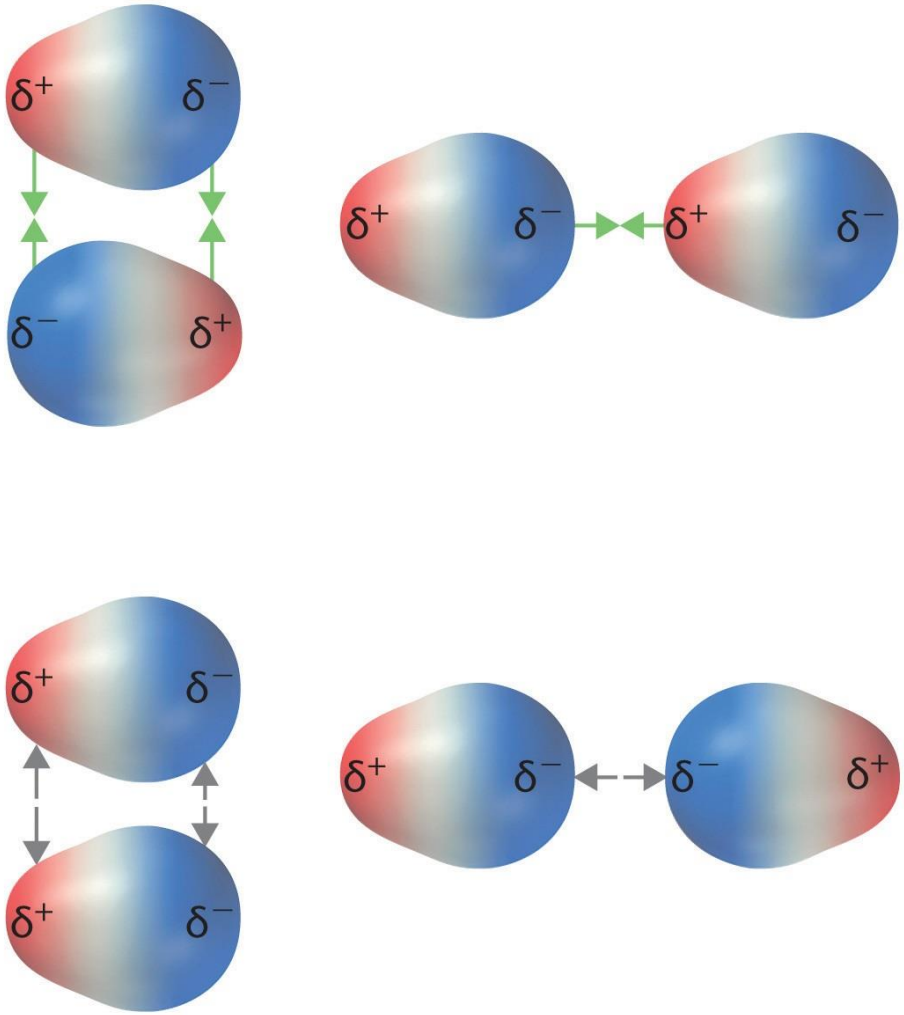
Org. & Biomol. Chem. **2014**, *12*, 8851-8860.

Chirale Anion-Bondskatalyse



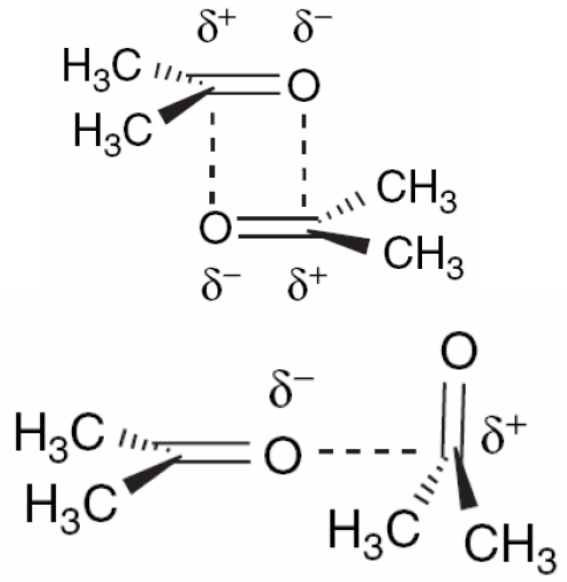
Jacobsen group*: J. Am. Chem. Soc.*, **2007**, *129* (44), pp 13404–13405

Dipole - Dipole Interactions



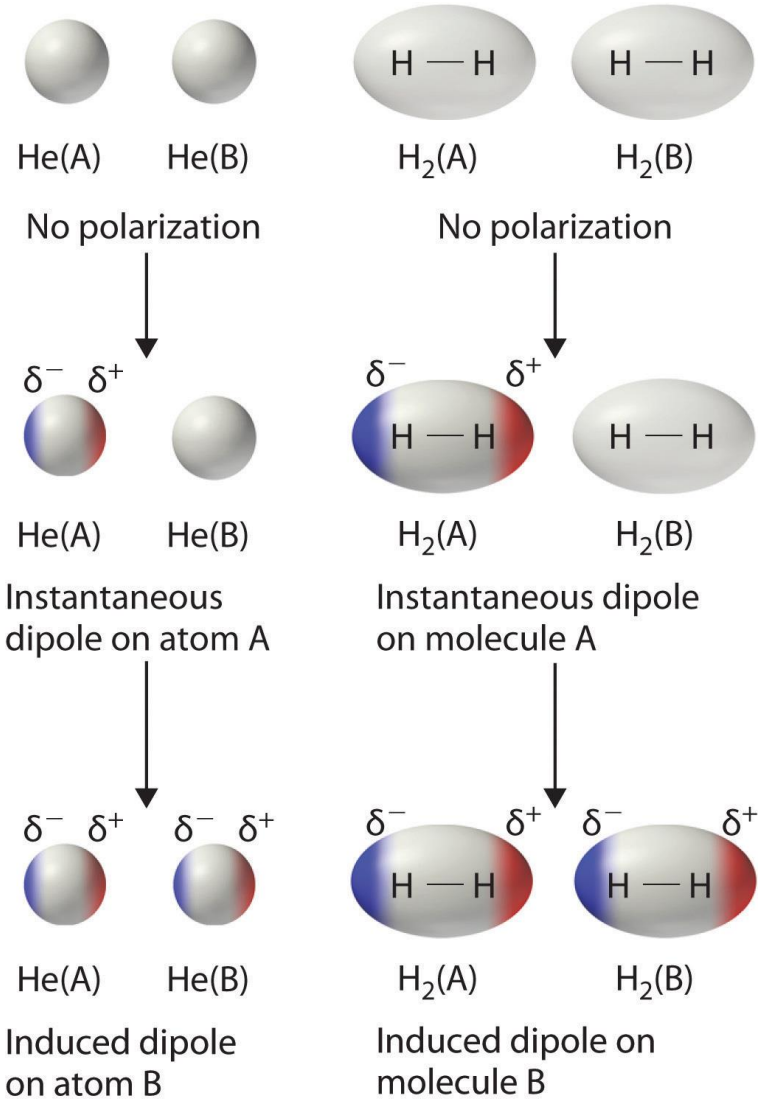
$$E = \frac{-\mu_1 \mu_2 (3\cos^2\theta - 1)}{4\pi\varepsilon\varepsilon_o r^3}$$

Energy ~ 5 bis 50 kJ/mol



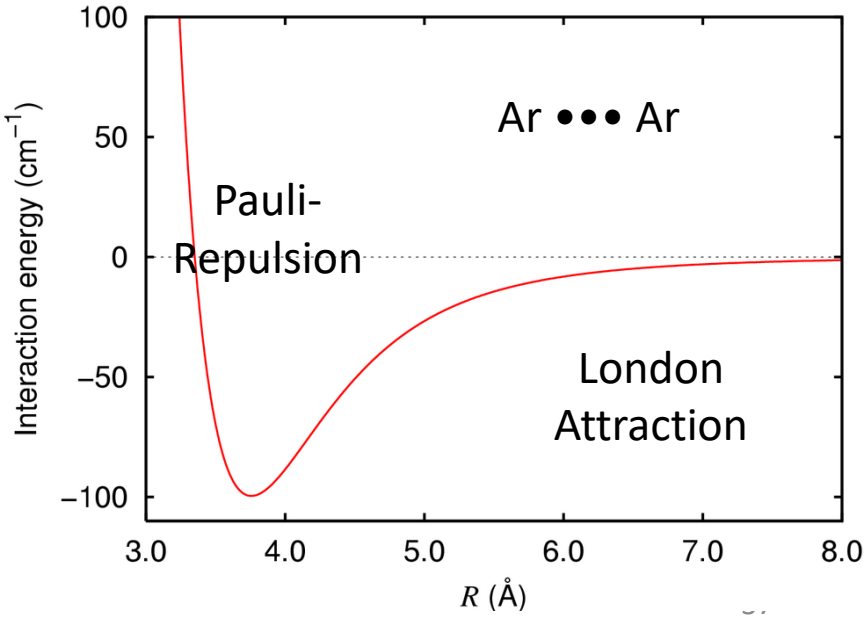
Aceton: for 0.5 nm distance
E ~ 2 kJ/mol in CH_3Cl

Dispersion Interactions



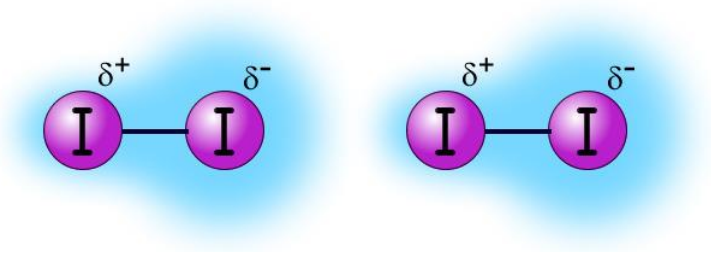
London-Dispersion-Formula:

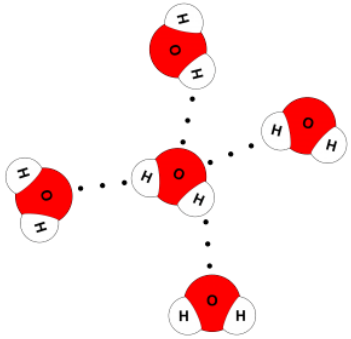
$$E_{AB}^{disp} = -\frac{3}{2}\frac{I_A I_B}{I_A + I_B}\frac{\alpha^A \alpha^B}{R^6}$$



Dispersions Energies are important!

Atom- or Molecule pair	Fraction of E_{disp} from E_{total} (%)
Ne-Ne	100
CH_4-CH_4	100
HCl-HCl	86
HBr-HBr	96
HI-HI	99
CH_3Cl-CH_3Cl	68
NH_3-NH_3	57
H_2O-H_2O	24



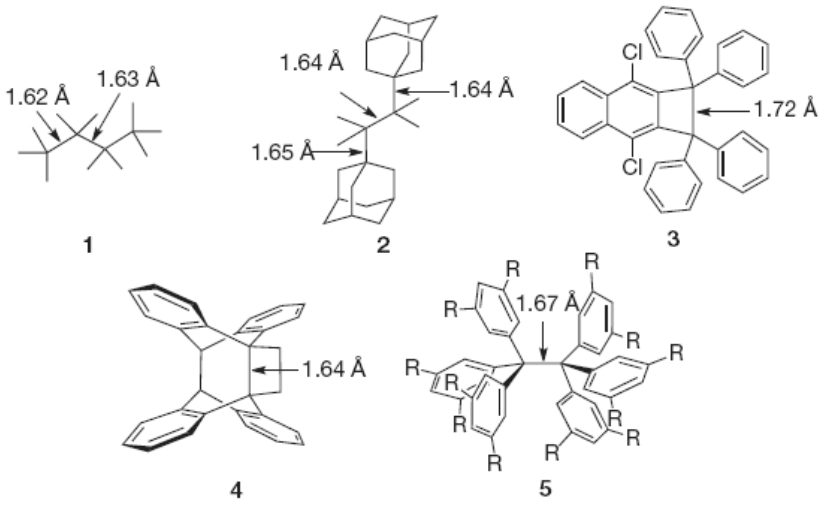


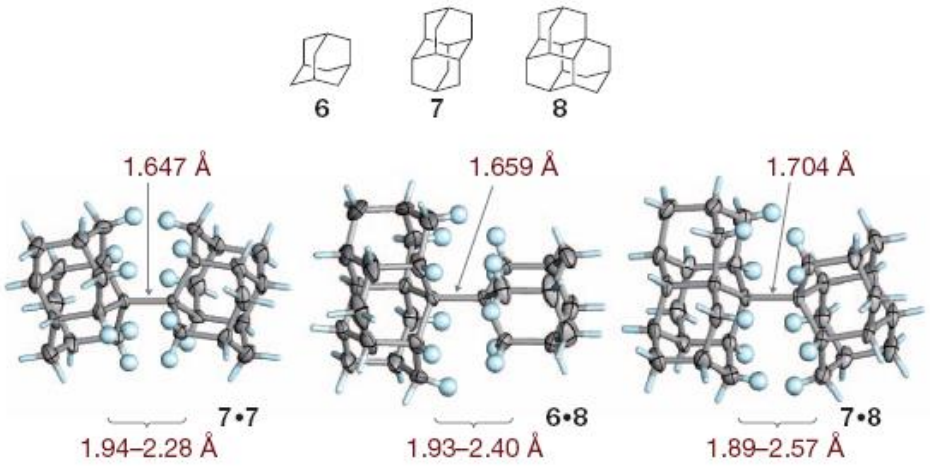
Comparison:

Sublimation enthalpy of iodine (I_2) = 62 kJ/mol.

Sublimation enthalpy of water ice = 52 kJ/mol.

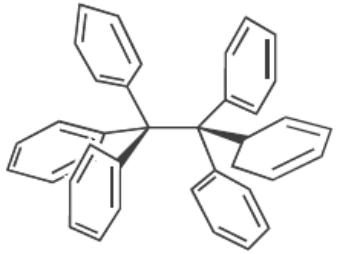
Dispersions Interations in Organic Chemistry



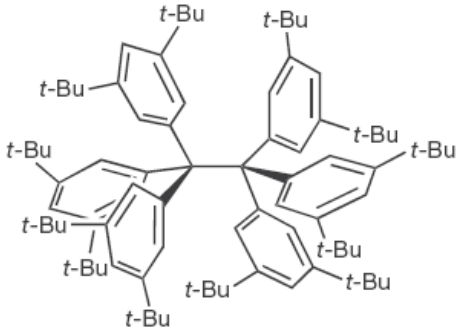


"Normal" C-C-Bond:
BDE: 350 kJ/mol = 83 kcal/mol
d = 1.54 Å

7•7



5 (R = H)



5 (R = t-Bu)

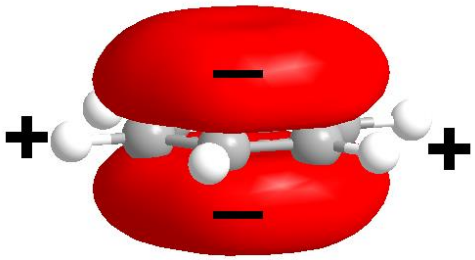
Method/quantity	BDE (kcal mol^{-1})	C–C (Å)	BDE (kcal mol^{-1})	C–C (Å)	BDE (kcal mol^{-1})	C–C (Å)
B3LYP/6-31G(d,p)	43.9	1.674	−20.9	1.730	−26.1	1.709
B3LYP-D/6-31G(d,p)	70.7	1.653	10.3	1.735	44.5	1.674
B97D/6-31G(d,p)	64.5	1.668	6.5	1.791	38.8	1.698
M06-2X/6-31G(d,p)	65.8	1.648	12.3	1.702	33.0	1.669
Experiment	—	1.647	—	—	—	1.670(3)

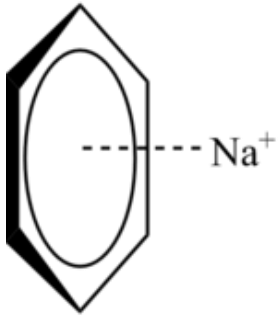
without Disp

with Disp.

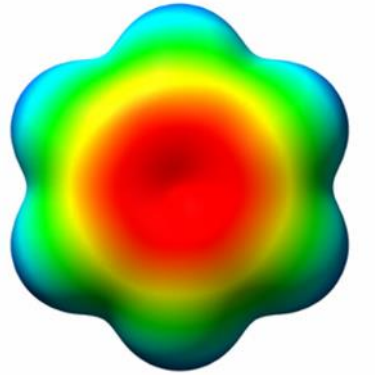
Nature **2011**, *477*, 308-311.

Cation-π Interactions

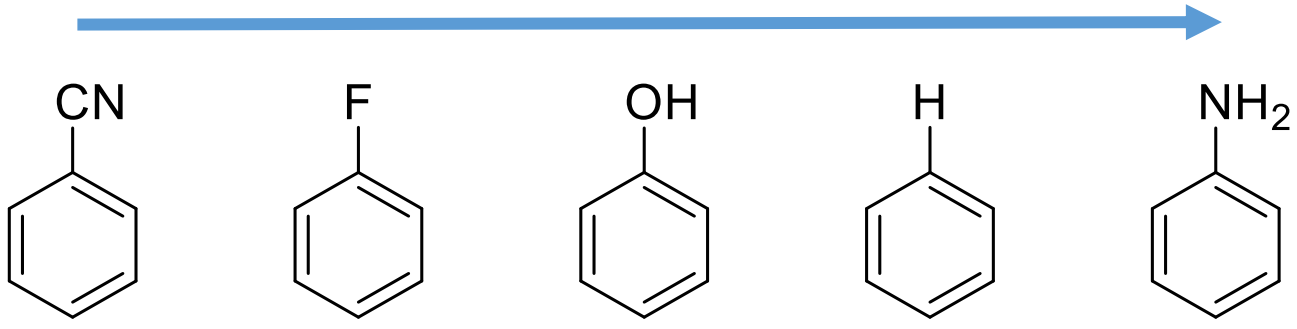




M^+	$\Delta G_{Gasphase}$ (kJ/mol)
Li^+	159
Na^+	113
K^+	79
NH_4^+	79
Rb^+	67



C_6H_6

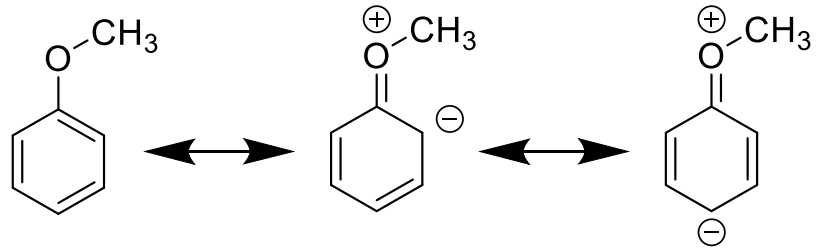


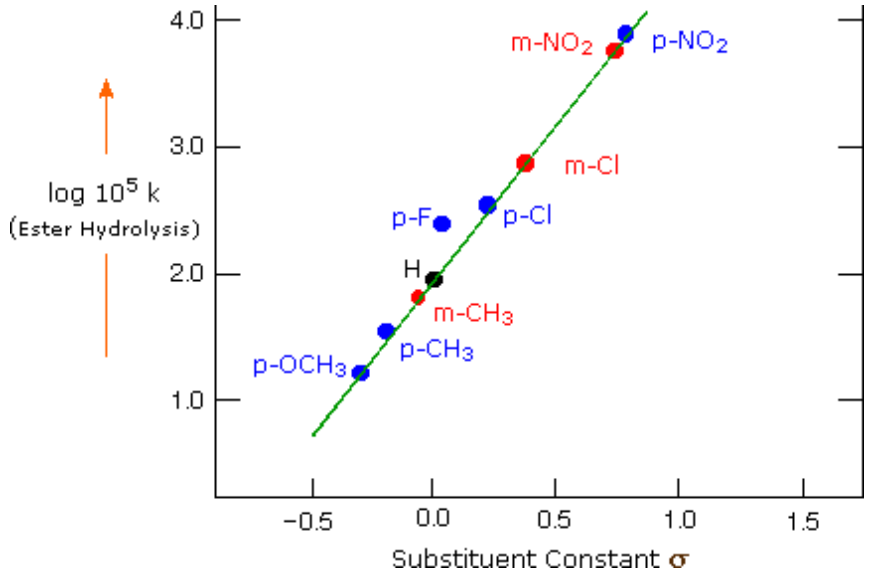
66 92 112 113 133

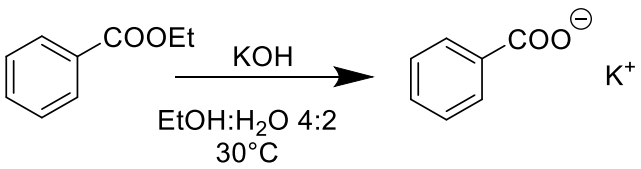
$\Delta G_{gas\ phase}$ (kJ/mol) for Na^+-complex

Cation-π Interactions: Explanation Models

Recap: Resonance & Hammett constants

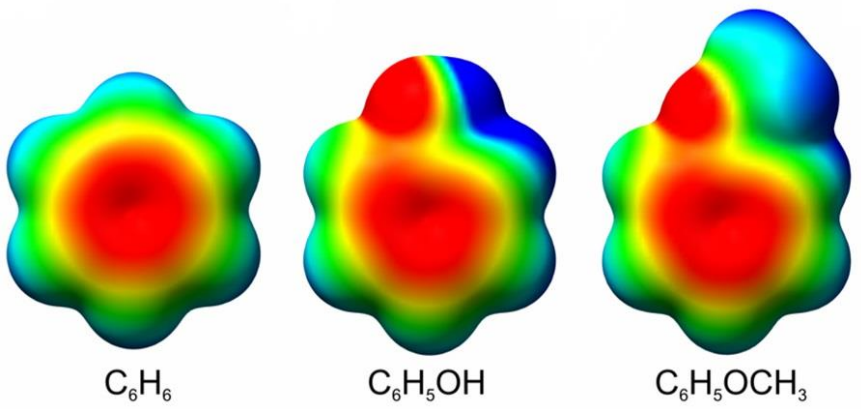






electrostatic potential

$$V(\mathbf{r}) = \sum_{\mathrm{A}}^{\text{nuclei}} \frac{Z_{\mathrm{A}}}{|\mathbf{r} - \mathbf{R}_{\mathrm{A}}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \mathrm{d}\mathbf{r}'$$

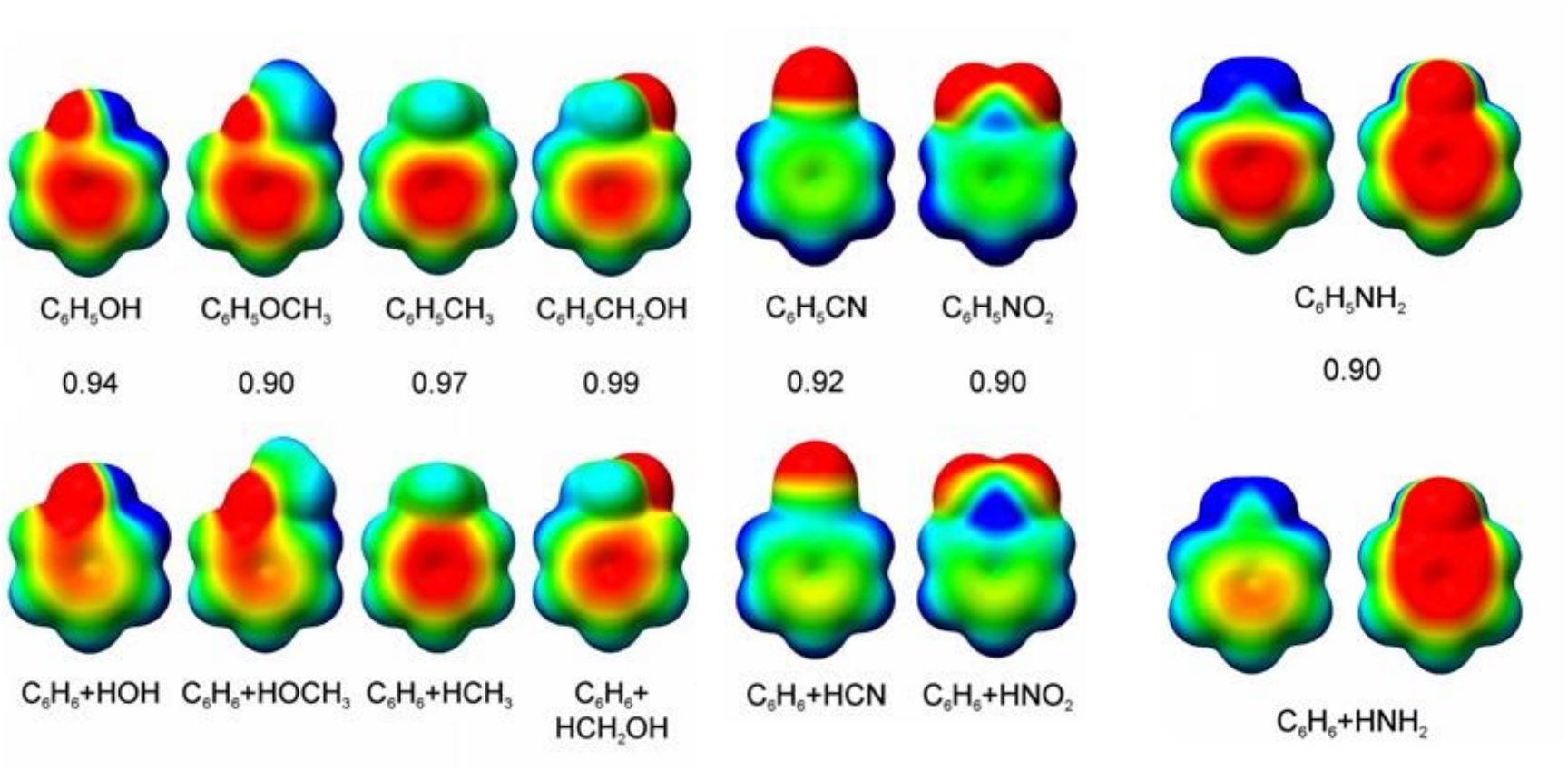


electrostatic potential (kJ/mol)

−63 0 63

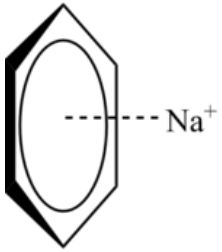
Literatur: *J. Chem. Theory Comput.* **2009**, *5*, 2301

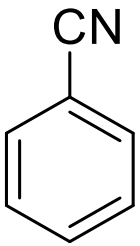
Direct Substituent-Effects instead of Resonance

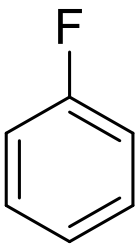


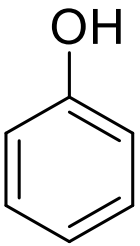
Literatur: *J. Chem. Theory Comput.* **2009**, *5*, 2301

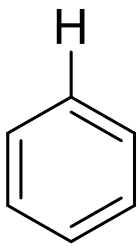
Cation-π Interactions: Experiment *vs* Theory

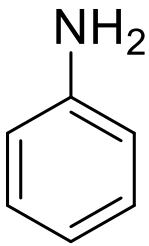






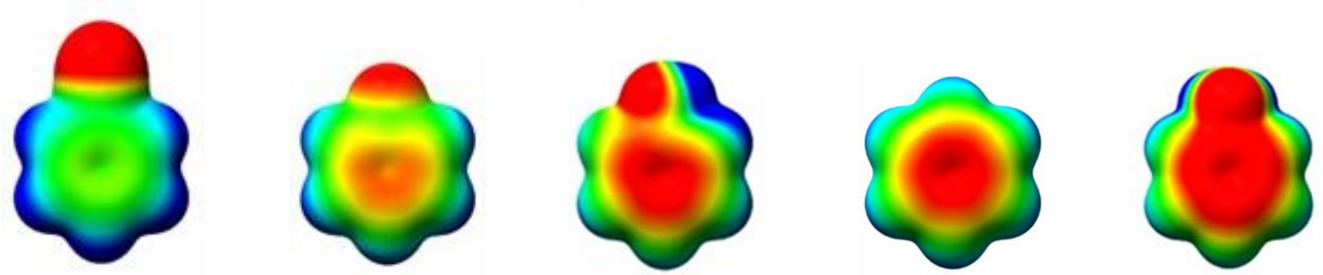






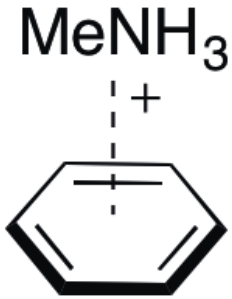
(kJ/mol)

ΔG_{gas}(Exp)	66	92	112	113	133
ΔG_{gas}(Theor-total)	67	91	111	113	133
ΔG_{gas}(Theor-Fragment)	65	75	97	113	123



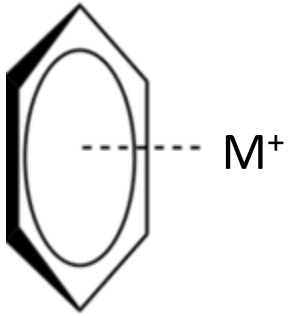
electrostatic potential (kJ/mol)

Solvent Effects on Cation-π Interactions



Medium	Interaction energy kJ/mol
gas phase	52
CCl_4	33
EtOAc	26
EtOH	23
H_2O	23

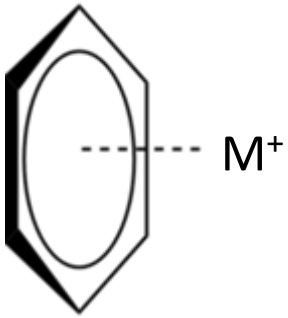
increasing solvent polarity



In the Gasphase: $Li^+ > Na^+ > K^+ > Rb^+$

water: $K^+ > Rb^+ >> Na^+, Li^+$

Solvent Effects on Cation-π Interactions



Experiment:

In the Gas phase: $Li^+ > Na^+ > K^+ > Rb^+$

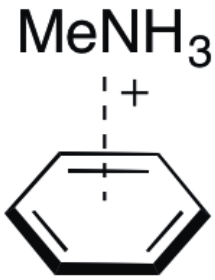
In water: $K^+ > Rb^+ >> Na^+, Li^+$

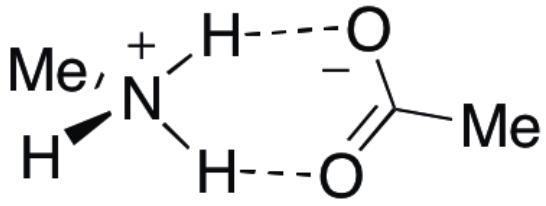
M^+	ΔG_{gas}(Cation-π) (kJ/mol)	ΔG_{hydr}(Cation) (kJ/mol)	"ΔG_{aq}(Cation-π)" (kJ/mol)
Li^+	159	510	-11
Na^+	113	410	-24
K^+	79	339	-34
NH_4^+	79	335	-33
Rb^+	67	318	-39

Very rough estimation: $\Delta G_{aq}(\text{Cation-}\pi) \approx \Delta G_{gas}(\text{Cation-}\pi) - x \cdot \Delta G_{hydr}(\text{Cation})$

x ≈ Fraction of removed solvent shell. (e.g. 1/3)

Cation-π Interaction vs. H-bonds

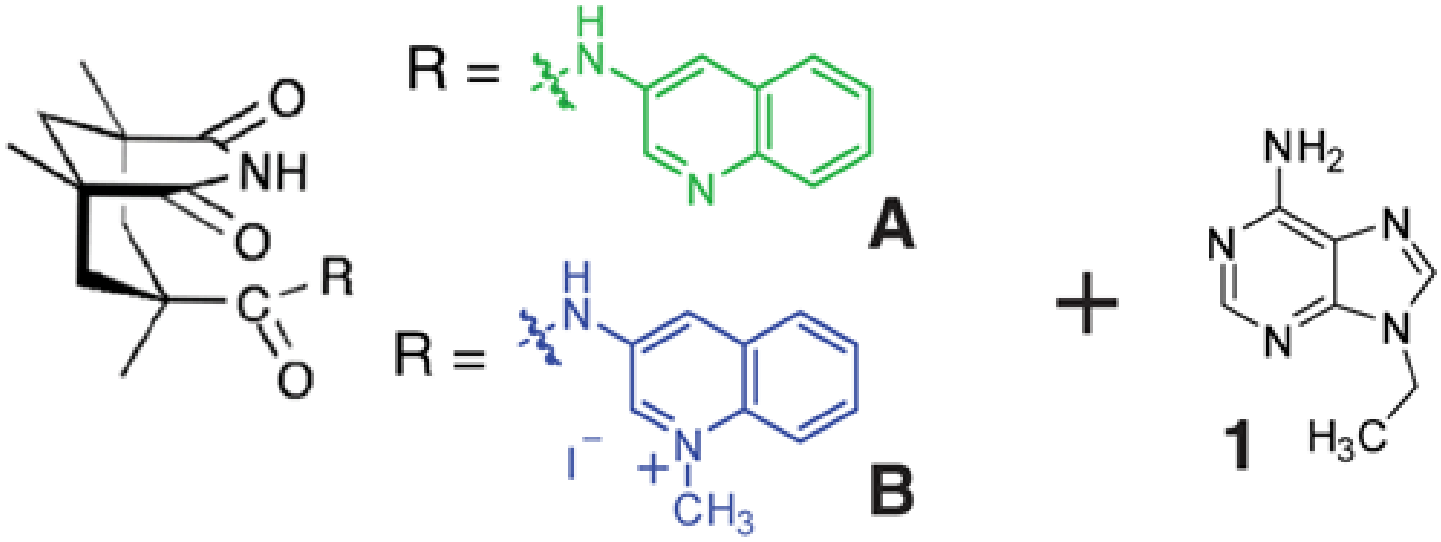


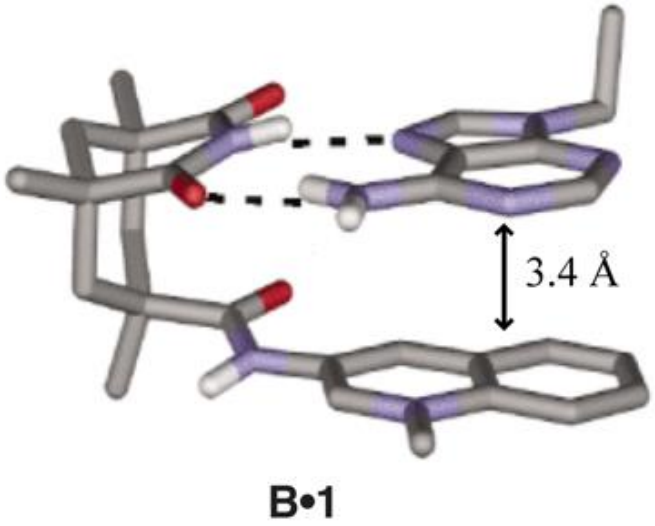


Medium	Interaction energy kJ/mol	
gas phase	52	525
EtOAc	26	82
EtOH	23	22
H_2O	23	9

Cation-π interactions often stronger than H-bonds in aqueous media!

Systems with Cation-π Bonding

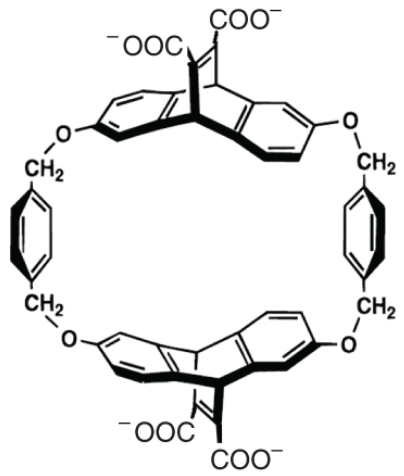




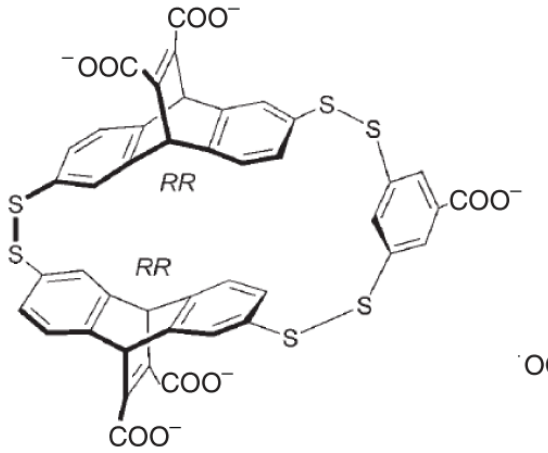
Rezeptor	$-\Delta G$ (kJ/mol)
A	10.6
B	13.0

in $(CDCl_2)_2$

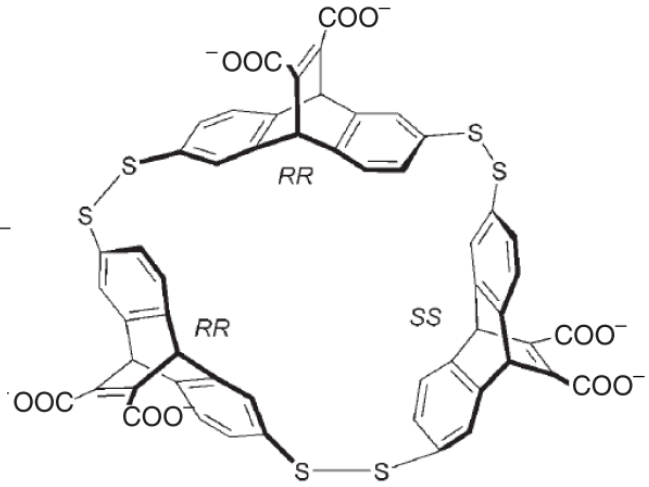
Systems with Cation-π Bonding



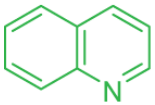
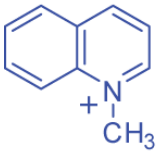
I



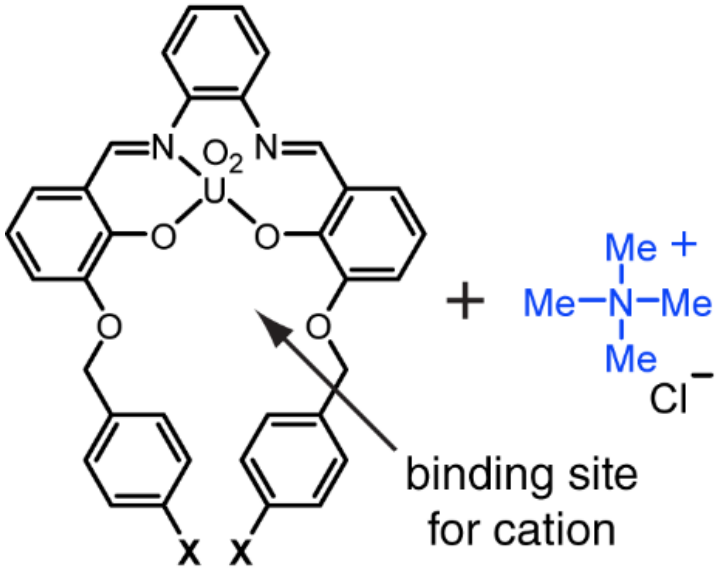
II



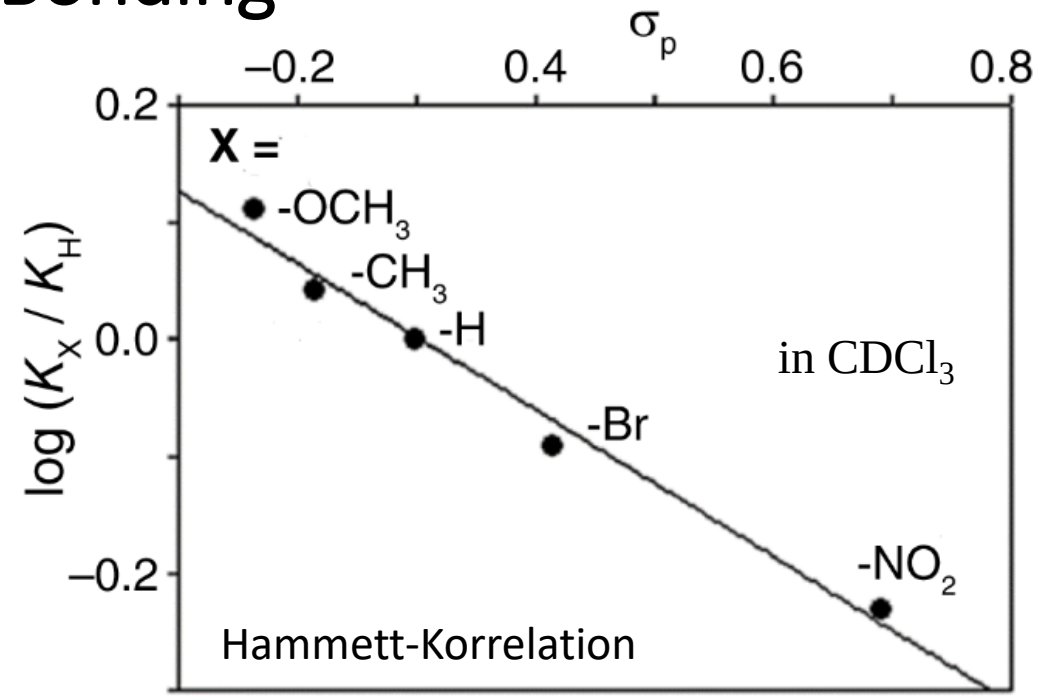
III

	22	19	19	kJ/mol
	32	30	27	kJ/mol
solvent	$CHCl_3$	H_2O	H_2O	

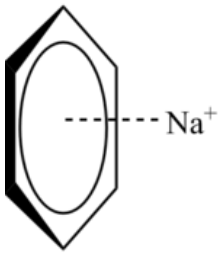
Systems with Cation-π Bonding

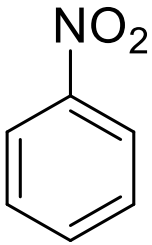


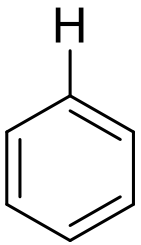
+ Me(Me)(Me)N$^+$ Cl$^-$

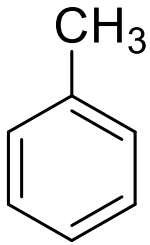


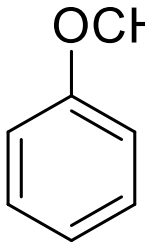
Compare::







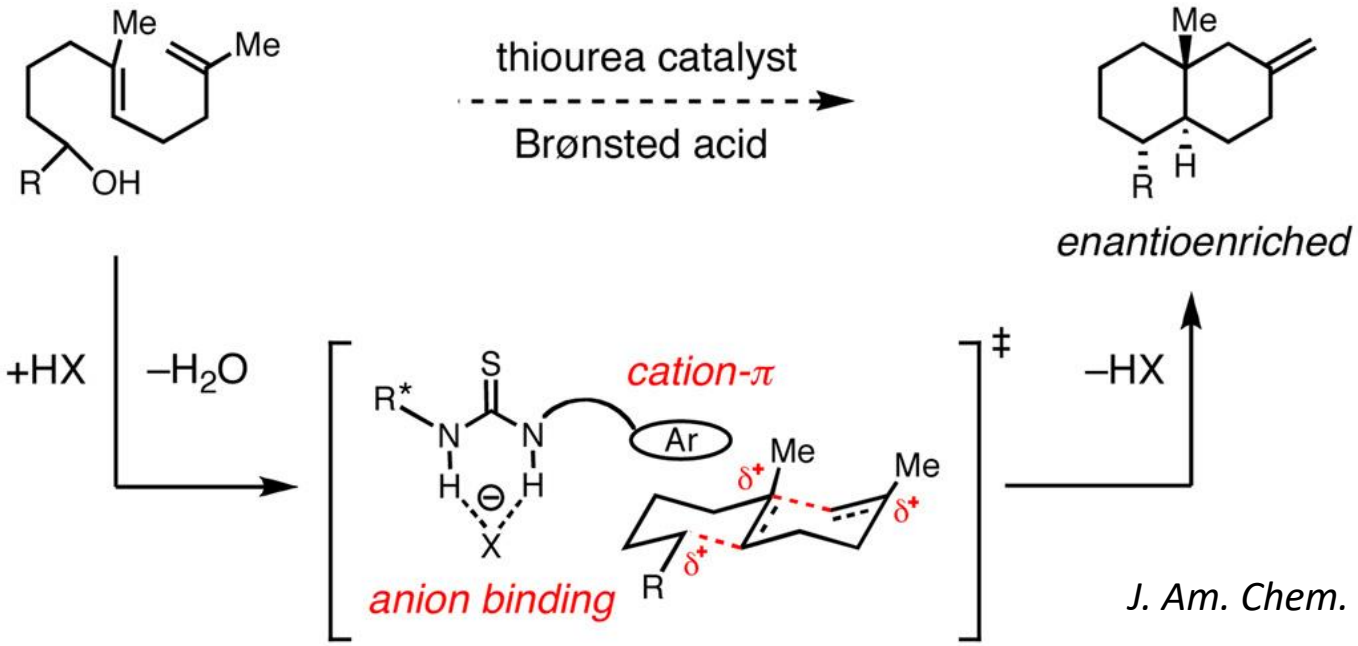




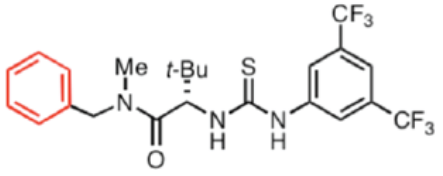
(kJ/mol)

ΔG_{gas}(Theory)	59	113	118	119

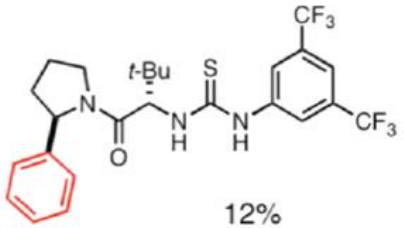
Supramolecular Catalysis with Cation-π Bonds



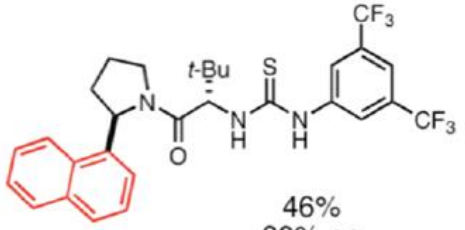
J. Am. Chem. Soc. **2010,** *132*, 5030



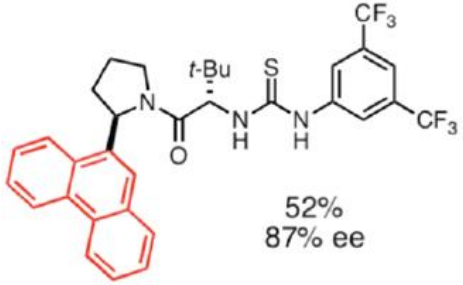
10%
9% ee



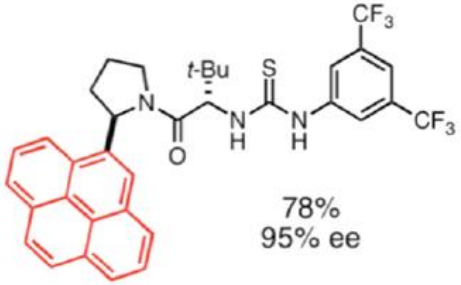
12%
25% ee



46%
60% ee

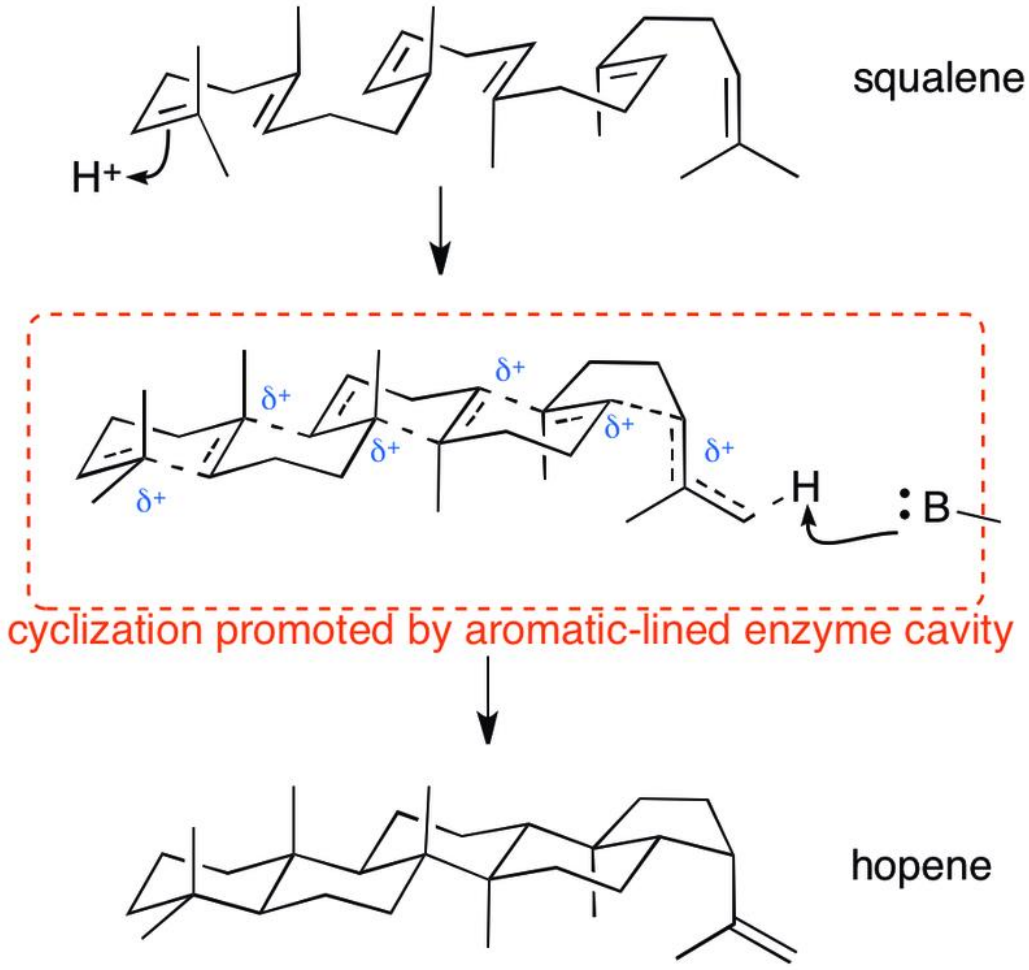


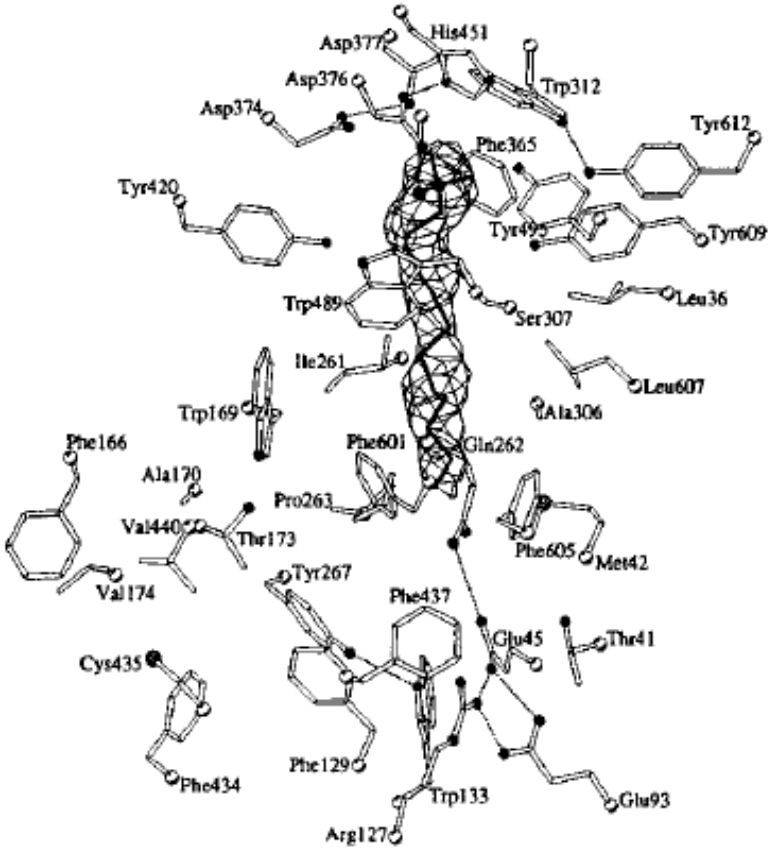
52%
87% ee



78%
95% ee

Catalysis with Cation-π Bonds in Biology

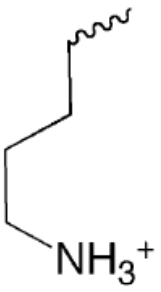




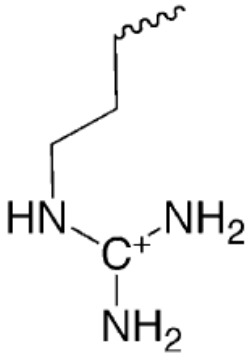
Science, **1997**, *277*, 1811

=> Cation-π are important for steroid synthesis!

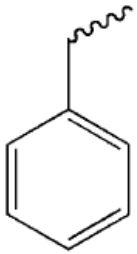
Cation-π Bonding is Widely Found



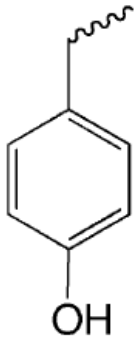
Lys



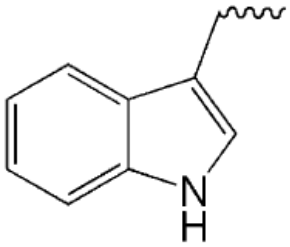
Arg



Phe



Tyr

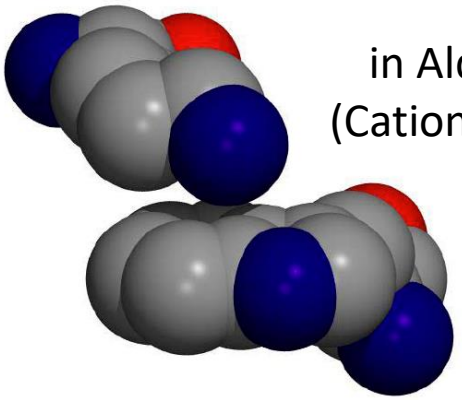


Trp

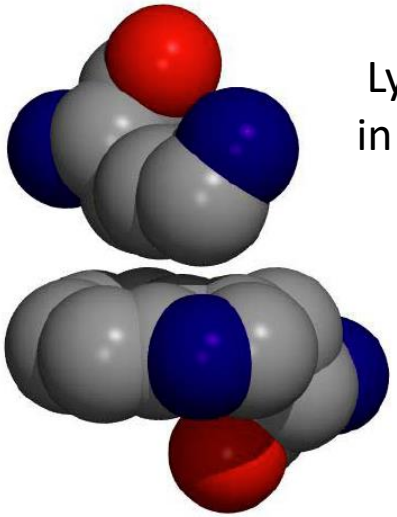
Amino acid		Total number*	Cation-π interactions‡	
K	Lys	13,446	1,006	7%
R	Arg	10,919	1,988	18%
F	Phe	9,162	915	10%
Y	Tyr	8,309	1,187	14%
W	Trp	3,412	892	26%

Proc. Natl. Acad. Sci. **1999**, *96*, 9459

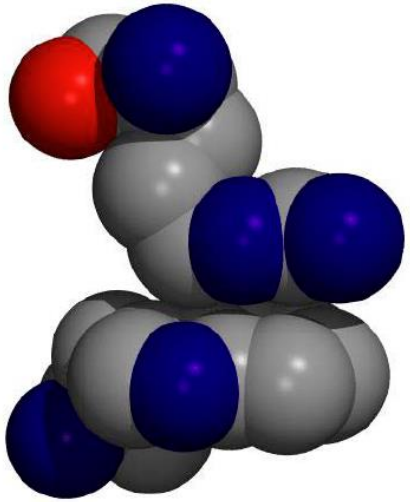
Cation-π Bonding in Proteins



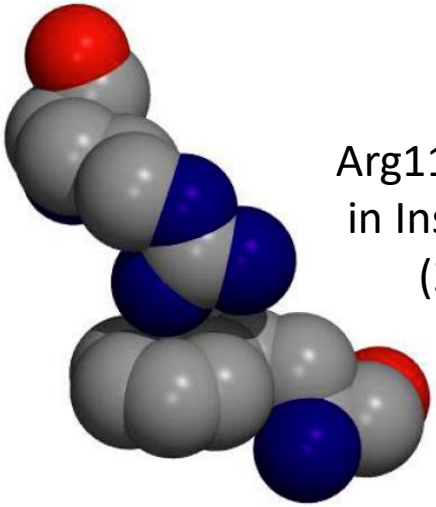
Lys248 ••Trp265
in Aldehyd-Oxidoreduktase
(Cation-π Energy ca. 37 kJ/mol)



Lys76B ••Trp58B
in Transaldolase B
(18 kJ/mol)

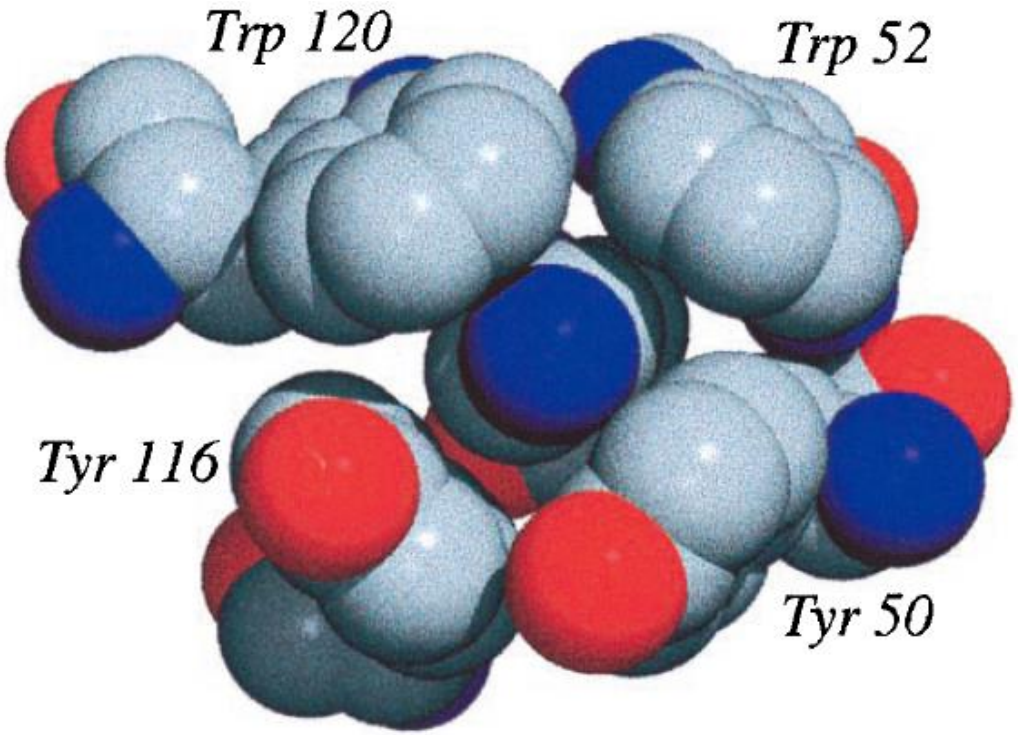


Arg77A ••Trp211A
in OppA
(35 kJ/mol)

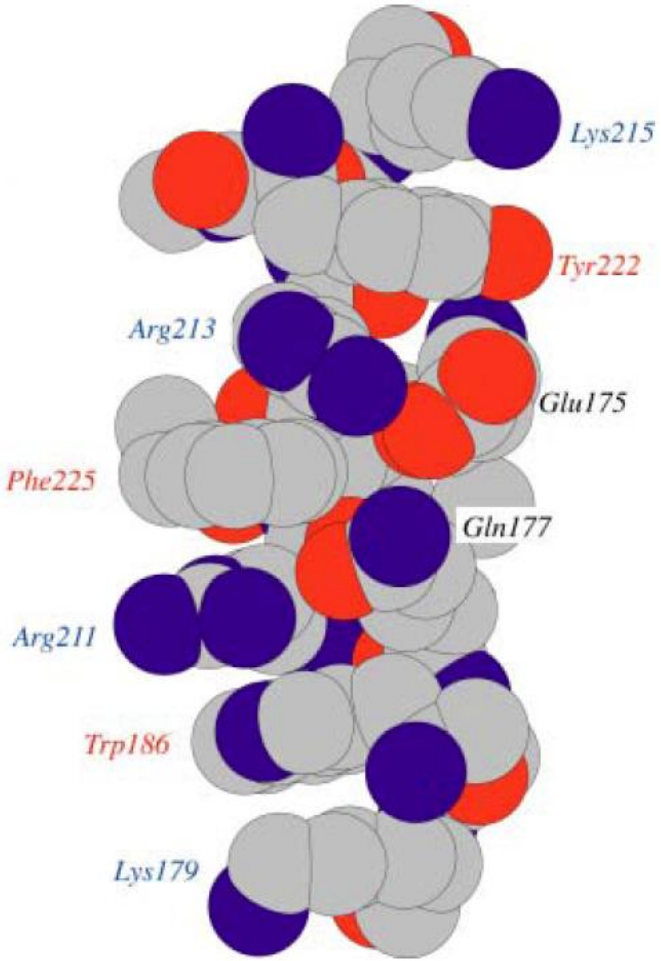


Arg1136 ••Trp1175
in Insulin Rezeptor
(28 kJ/mol)

Spektakuläre Cation-π Bondsmotive

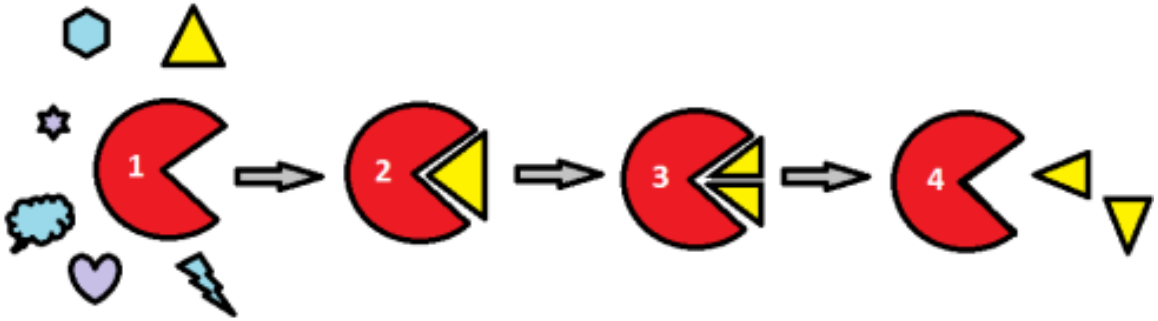


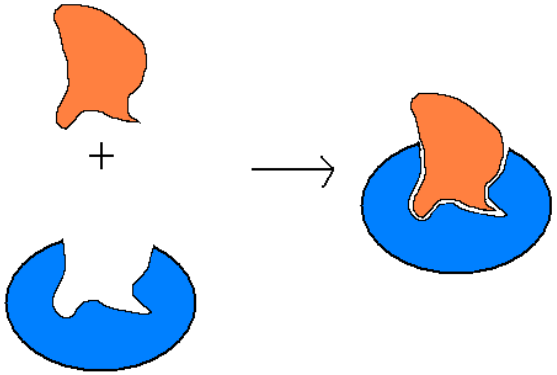
Glukoamylase
(totale Cation-π Energy ca. **92 kJ/mol**)

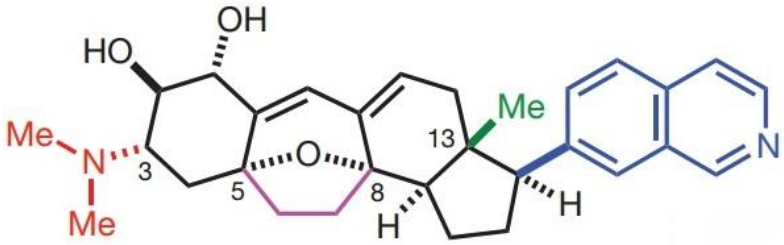


growth hormone receptor)

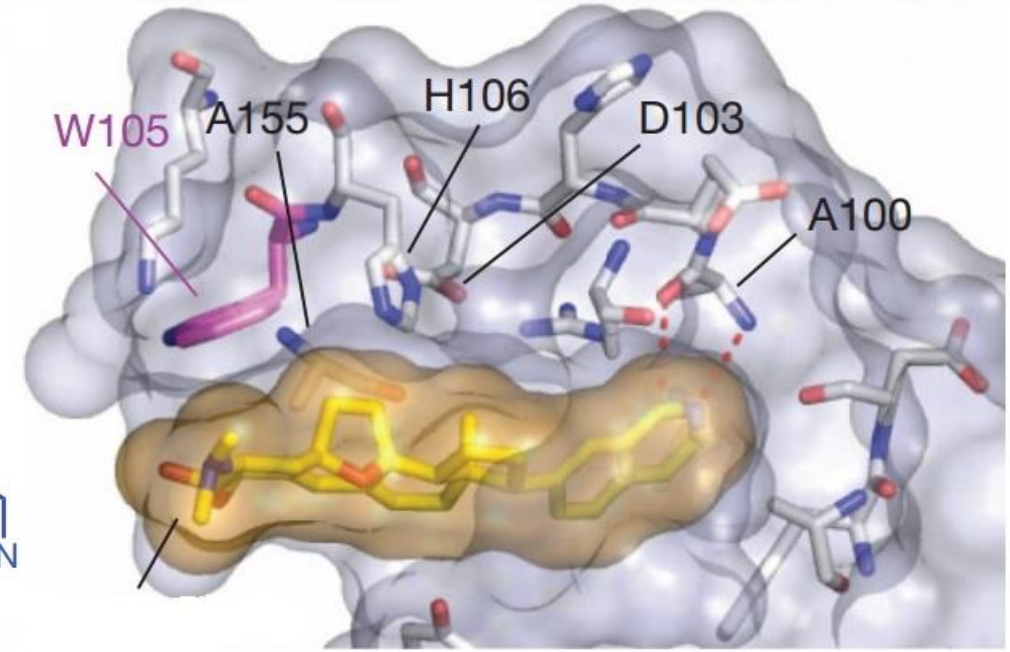
Emil Fischers Lock and Principle





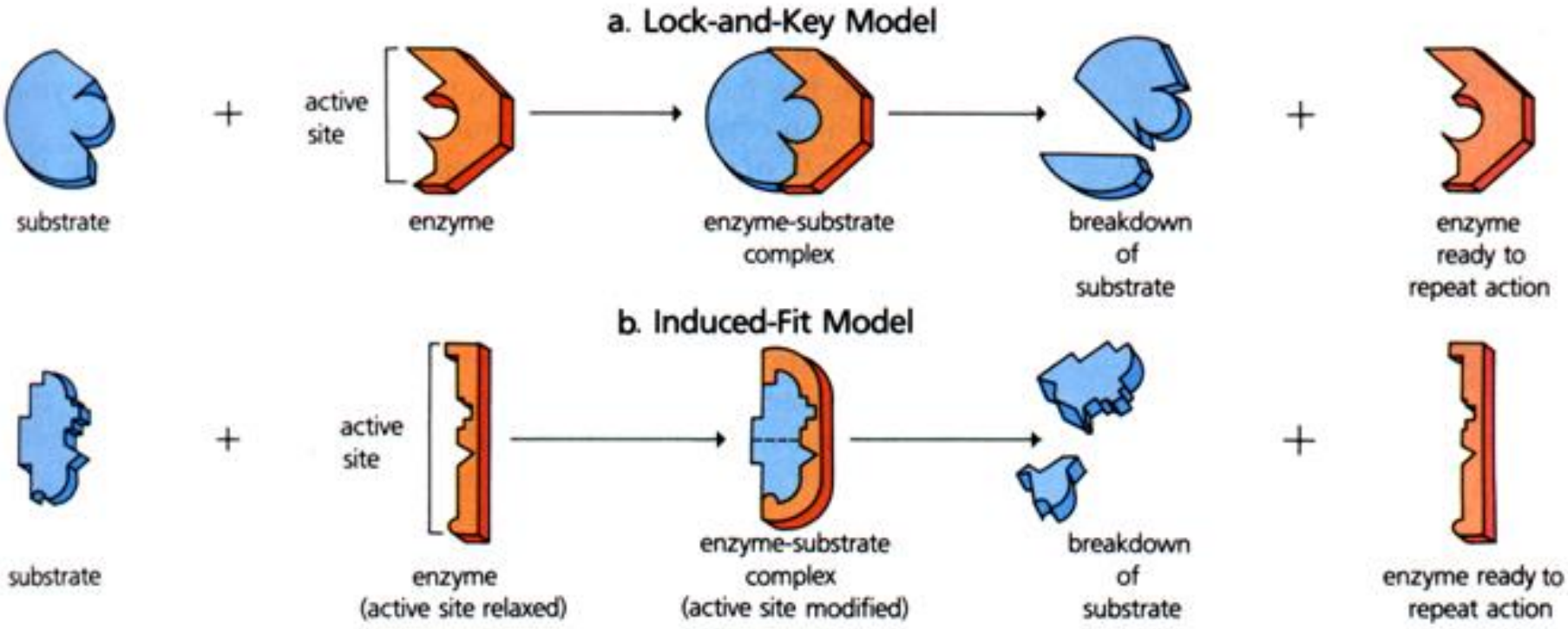


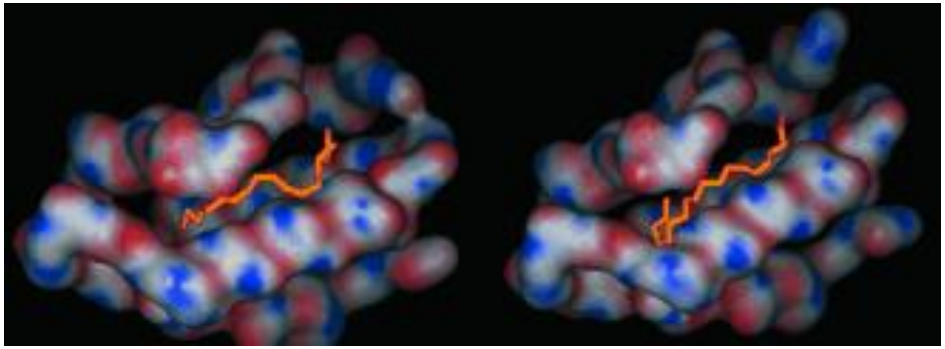
Cortistatin A



Cortistatin A • CDK8 complex

Induced-Fit Modell (Daniel E. Koshland)





nsLTP-Protein•Oleate nsLTP-Protein•Stereate

The 55% Rule

Table 1. Packing coefficients for some common organic liquids.

Organic liquid	Packing coefficient[a]
benzene	0.54
toluene	0.54
n-hexane	0.51
cyclohexane	0.56
methylene chloride	0.54
chloroform	0.53
carbon tetrachloride	0.53
diethyl ether	0.51
acetone	0.52
acetonitrile	0.53
N,*N*-dimethylformamide	0.61
methanol	0.54
ethanol	0.55
water	0.63

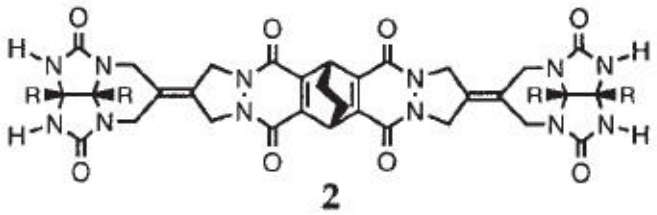
$$PC = \frac{\sum_{i=1}^{n} v_{\mathrm{w}}^{i}}{V} = \frac{V_{\mathrm{w}}}{V}$$

S. Mecozzi, J. J. Rebek, *Chem. Eur. J.* **1998**, *4*, 1016-1022.

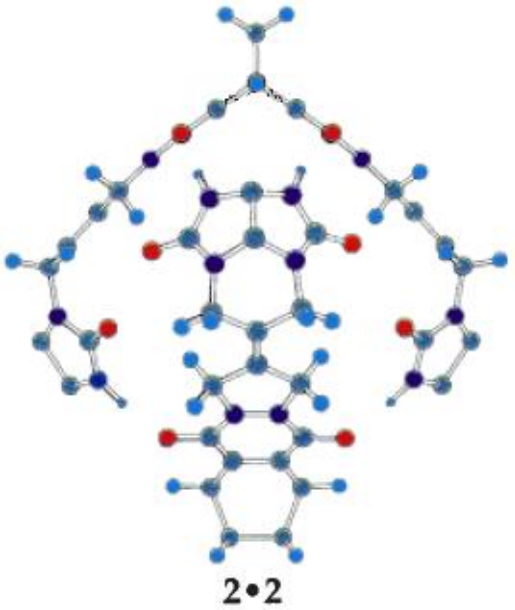
The 55% Rule

Table 4. Binding constants, volume, and packing coefficients for selected guests in capsule **2**·**2**.

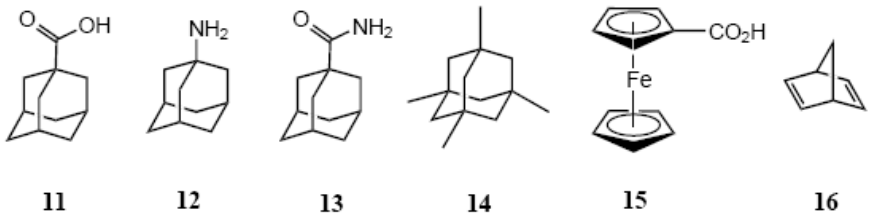
	Binding constant	Volume [Å^3]	Packing coefficient
16	12[a]	97	0.43
17	1700[b]	103	0.46
18	1800[b]	110	0.49
19	500[b]	102	0.45
20	3800[b]	125	0.56
21	5.2×10^5[b]	132	0.59
22	5.2×10^5[b]	135	0.60
23	910[a]	160	0.71
11	130[a]	154	0.68
24	510[b]	142	0.63
25	0	154	0.68
26	0	181	0.80



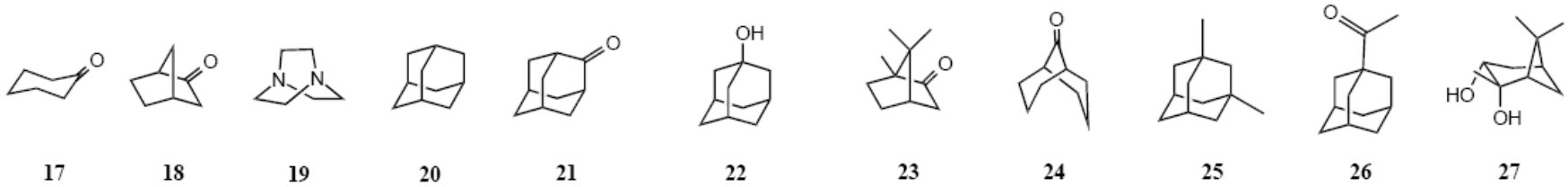
2



2•2



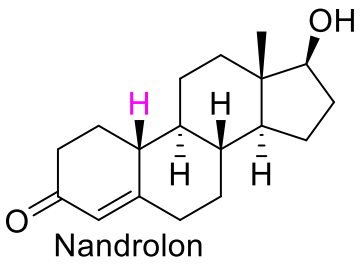
11 **12** **13** **14** **15** **16**



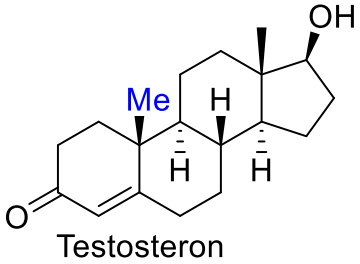
17 **18** **19** **20** **21** **22** **23** **24** **25** **26** **27**

S. Mecozzi, J. J. Rebek, *Chem. Eur. J.* **1998**, *4*, 1016-1022.

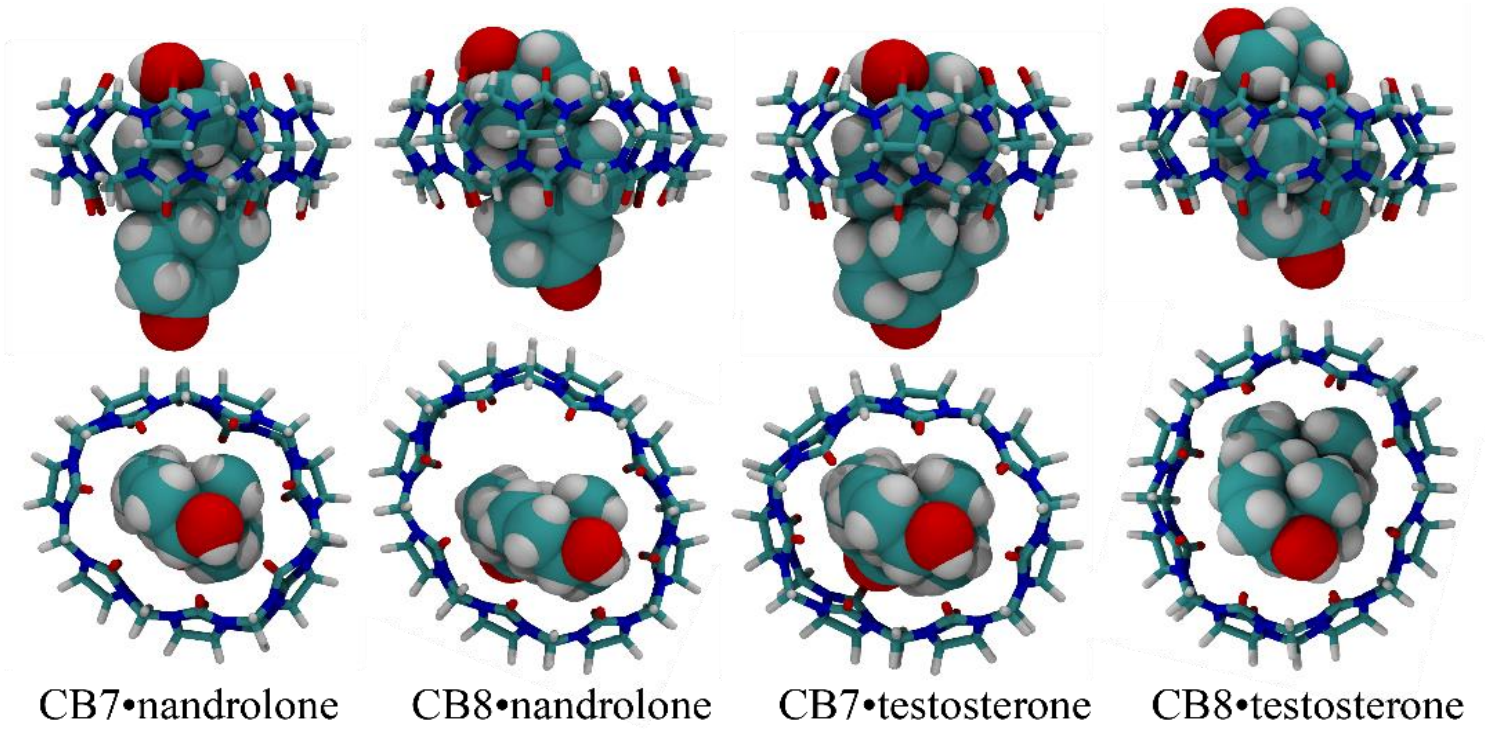
Cucurbit[*n*]urils as Steroid-Binders



Nandrolon



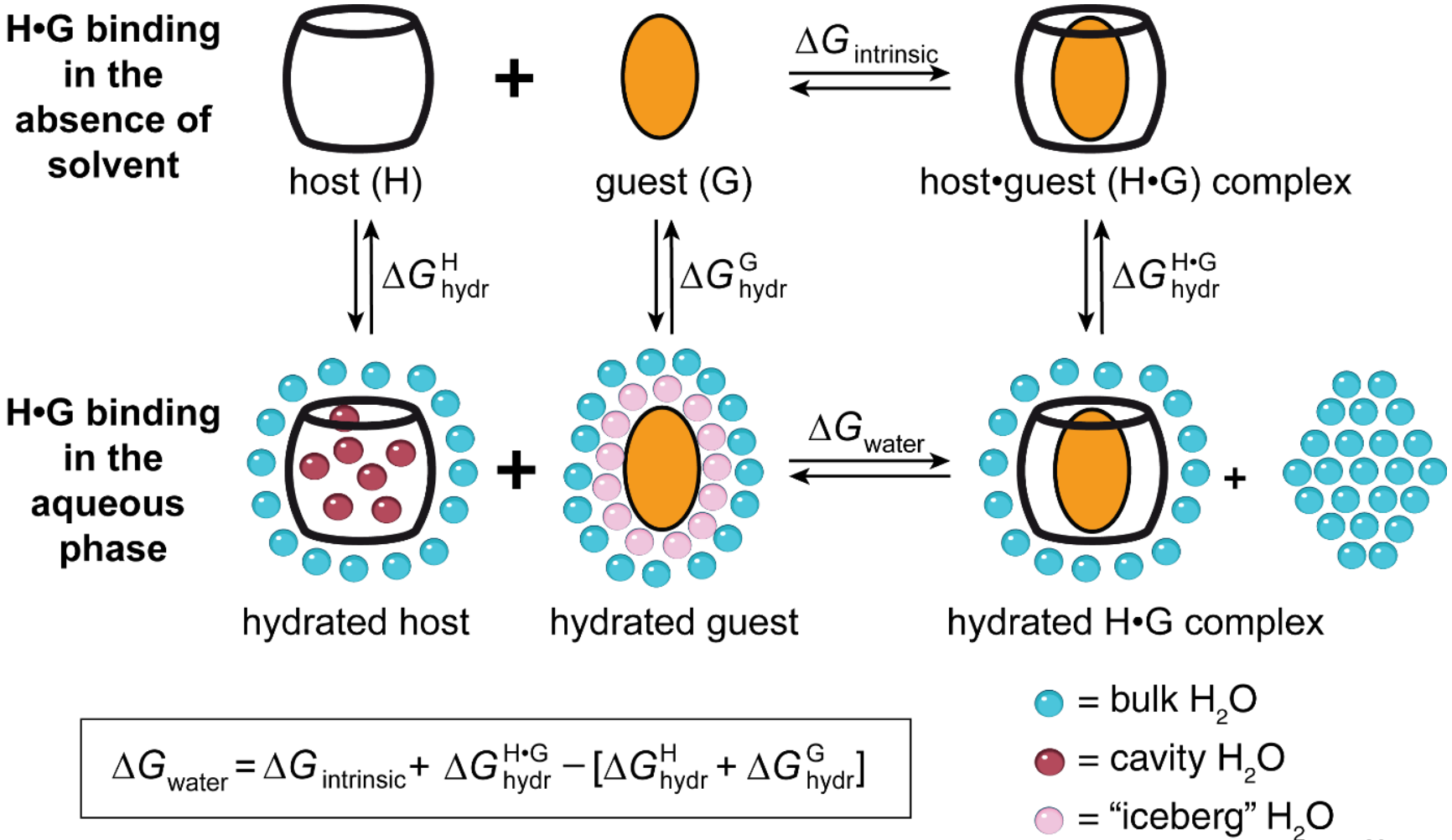
Testosteron


CB7•nandrolone CB8•nandrolone CB7•testosterone CB8•testosterone

K_a (M^{-1}) in H_2O	**$1 \cdot 10^7$**	**$2 \cdot 10^7$**	<1000	**$1 \cdot 10^8$**
ΔH (kJ/mol)	−52	−38	n.d.	−41
$-T\Delta S$ (kJ/mol)	12	−4	n.d.	−5
Packungskoeff.	**70**	**56**	**73**	**59**

J. Am. Chem. Soc., **2016**, 138, 13022

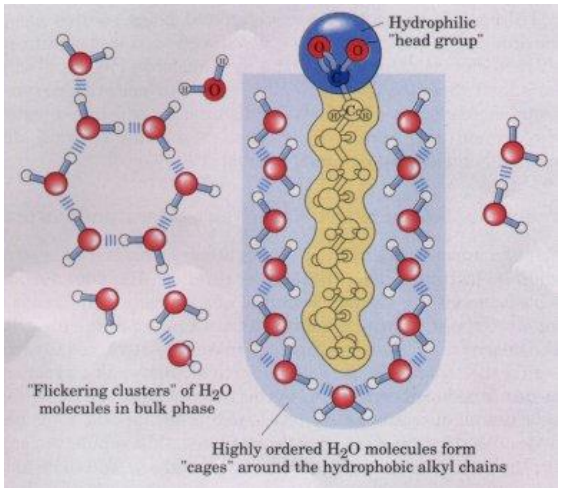
Solvent- and Hydrophobic-Effects



$$\Delta G_{water} = \Delta G_{intrinsic} + \Delta G^{H•G}_{hydr} - [\Delta G^{H}_{hydr} + \Delta G^{G}_{hydr}]$$

Konventionelle Sichtweise form hydrophobic effect

„Lehrbuch-Bild“ form hydrophobic effect



http://www.chemgapedia.de/


THE HYDROPHOBIC EFFECT: FORMATION OF MICELLES AND BIOLOGICAL MEMBRANES

1973

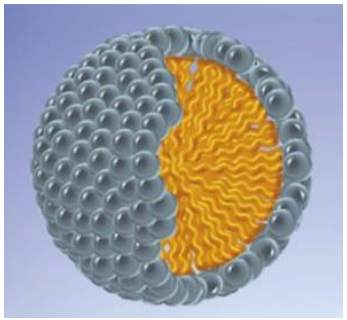
Charles Tanford (geb. Tannenbaum)

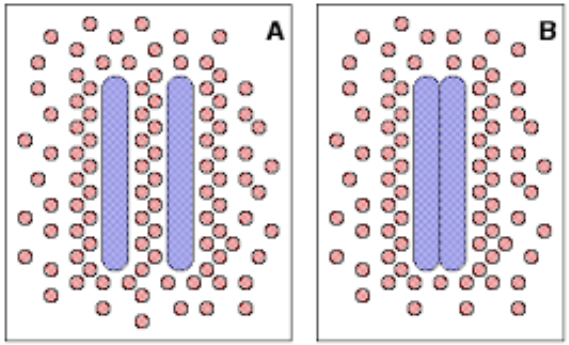
Walter J. Kauzmann

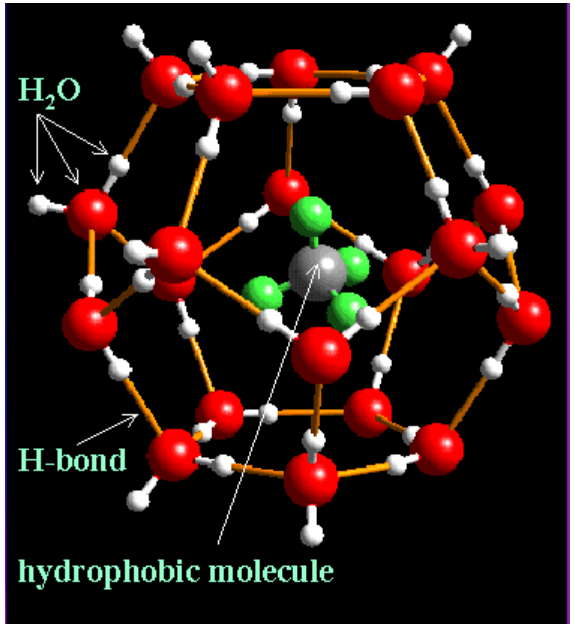
The hydrophobic effect is the observed tendency of nonpolar substances to aggregate in an aqueous solution and exclude water molecules. The word hydrophobic literally means "water-fearing", and it describes the segregation of water and nonpolar substances, which maximizes hydrogen bonding between molecules of water and minimizes the area of contact between water and nonpolar molecules. In terms of thermodynamics, the hydrophobic effect is the free energy change of water surrounding a solute A positive free energy change of the surrounding solvent indicates hydrophobicity, whereas a negative free energy change implies hydrophilicity.

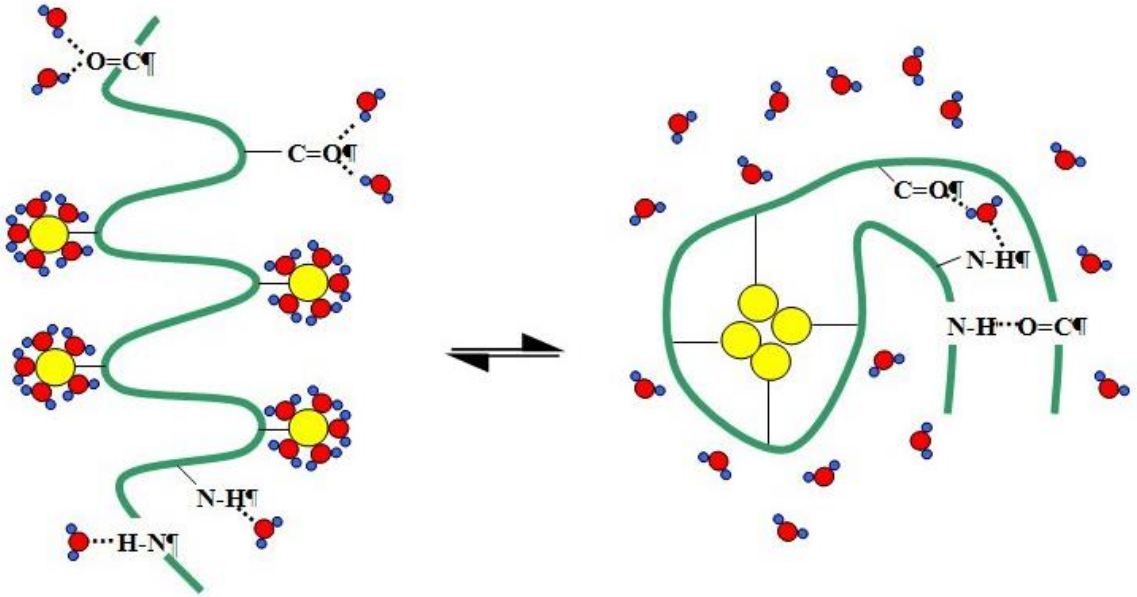
The hydrophobic effect is responsible for the separation of a mixture of oil and water into its two components. It is also responsible for effects related to biology, including: cell membrane and vesicle formation, protein folding, insertion of membrane proteins into the nonpolar lipid environment and protein-small molecule associations. Hence the hydrophobic effect is essential to life. Substances for which this effect is observed are known as hydrophobes.

Types of the hydrophobic Effect

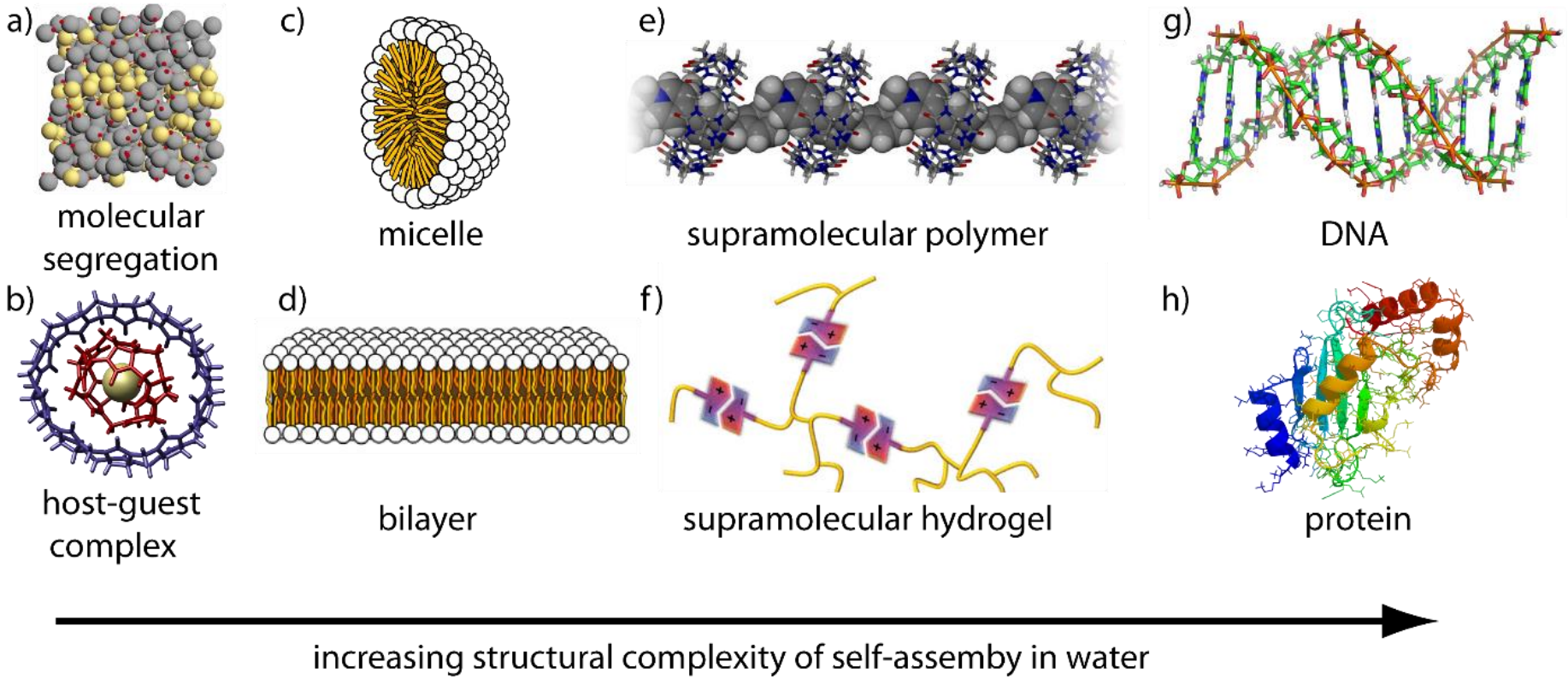








Typical Self-assembled Systems in Water



Biedermann, F. (**2017**) Self-Assembly in Aqueous Media.
In: Atwood, J. L., (ed.) Comprehensive Supramolecular Chemistry II, vol. 1, pp. 241–268. Oxford: Elsevier.

Classical view on the hydrophobic effect

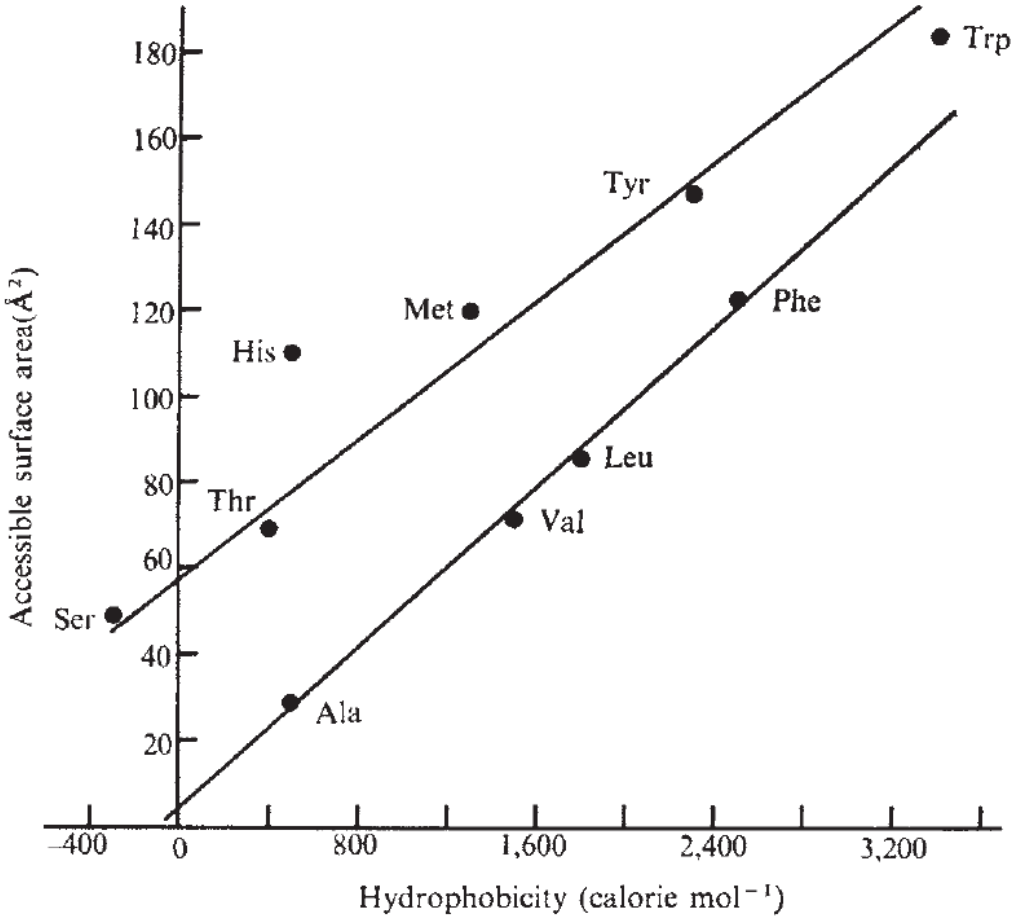


FIG. 1 Accessible surface areas of residue side chains (see text) plotted against hydrophobicity (free energy change for the transfer from 100% organic solvent to water[3]).

Standard-Equation for the hydrophobic effect

$$\Delta G_{hp} = \text{const}\ \Delta A$$

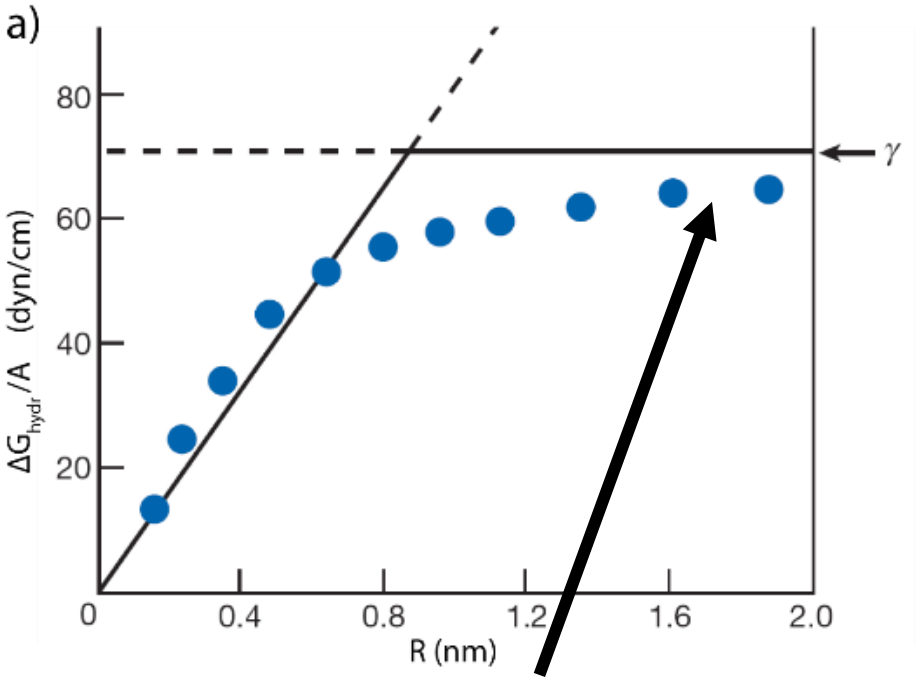
const ~ 120–200 J mol^{-1} Å^{-2}

for comparison:
Surface tension of water:
γ = 430 J mol^{-1} Å^{-2}

Chothia, C. Hydrophobic bonding and accessible surface area in proteins. *Nature* **248**, 338-339 (1974).

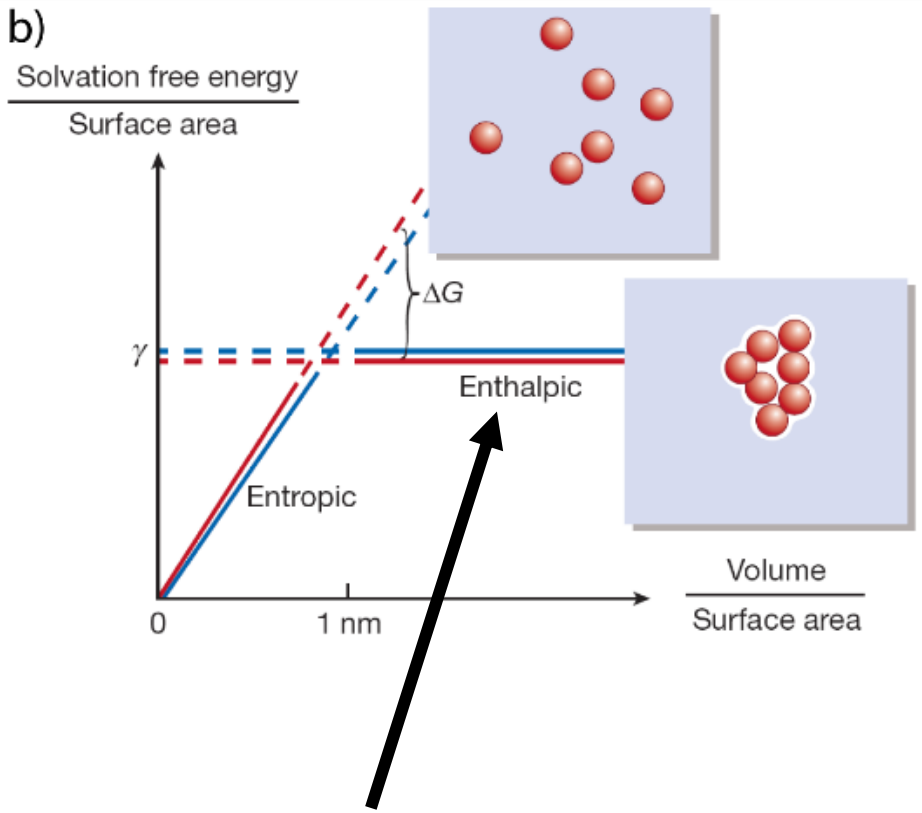
Updated Model for the Classical Hydrophobic Effect

Results from Computer-Simulations:



$$\Delta G_{hp} = \text{const}\ \Delta A$$

Standard-Equation for the hydrophobic effect reached only at larger length scales

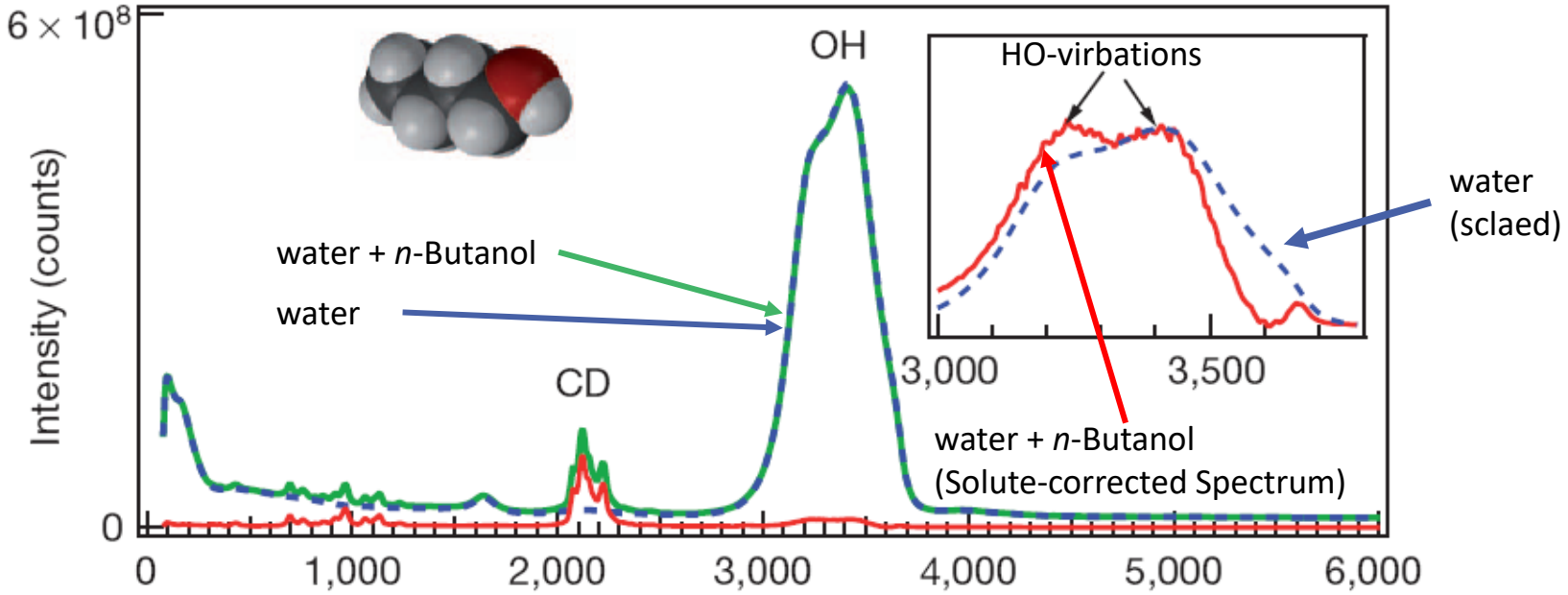


At smaller length scales, the hydrophobic effect is entropically driven.
At larger length scales, the hydrophobic effect is enthalpically driven.

Nature **2005,** 437, (7059), 640-647

Updated Model for the Classical Hydrophobic Effect

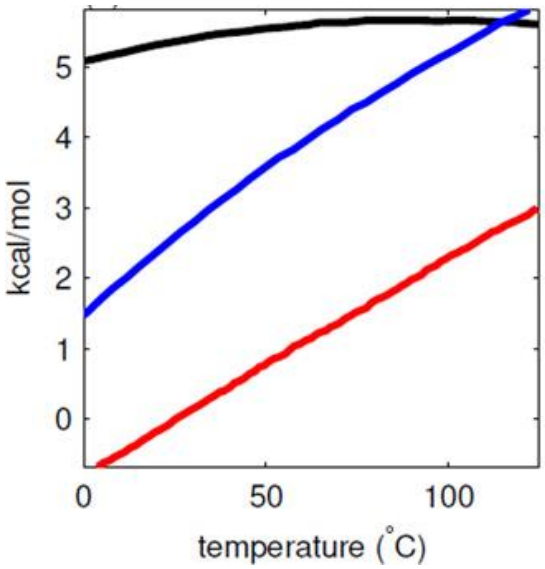
Historically, hydrophobic hydration shells were thought to resemble solid clathrate hydrates[2–4], with solutes surrounded by polyhedral cages composed of tetrahedrally hydrogen-bonded water molecules. But more recent experimental[5–8] and theoretical[9–16] studies have challenged this view and emphasized the importance of the length scales involved. Here we report combined polarized, isotopic and temperature-dependent Raman scattering measurements with multivariate curve resolution (Raman-MCR)[17–19] that explore hydrophobic hydration by mapping the vibrational spectroscopic features arising from the hydrophobic hydration shells of linear alcohols ranging from methanol to heptanol. Our data, covering the entire 0–100 °C temperature range, show clear evidence that at low temperatures the hydration shells have a hydrophobically enhanced water structure with greater tetrahedral order and fewer weak hydrogen bonds than the surrounding bulk water. This structure disappears with increasing temperature and is then, for hydrophobic chains longer than ~1 nm, replaced by a more disordered structure with weaker hydrogen bonds than bulk water. These observations support our current understanding of hydrophobic hydration, including the thermally induced water structural transformation that is suggestive of the hydrophobic crossover predicted to occur at lengths of ~1 nm



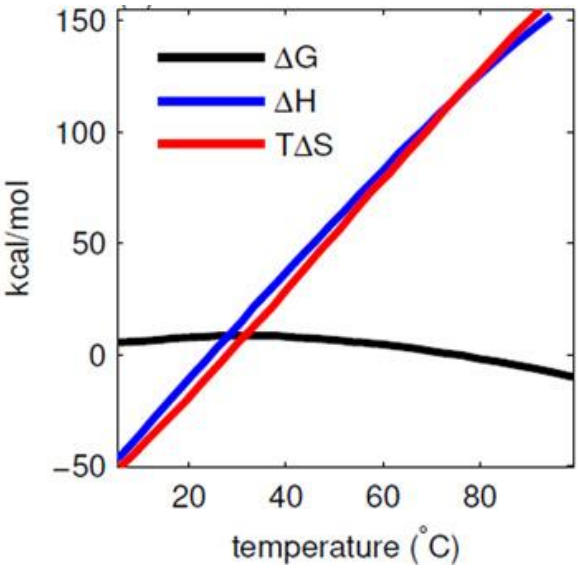
Nature **2012,** 491, (7425), 582-585.

Enthalpy-Entropy-Compensation

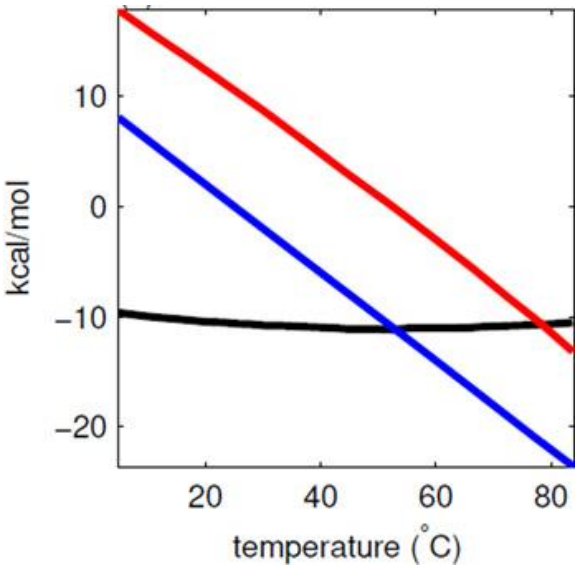
Neopentane-Transfer:
bulk -> water



Protein-unfolding
(Myoglobin)



Protein-Protein
Association

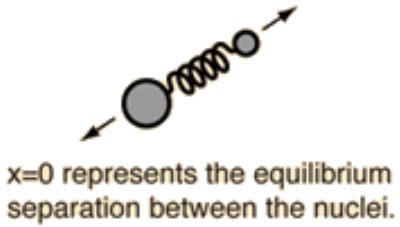


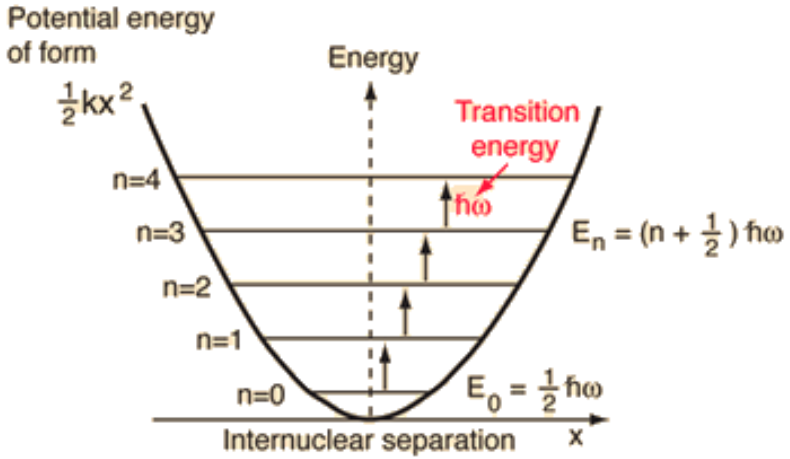
$$\Delta G = \Delta H - T\Delta S$$

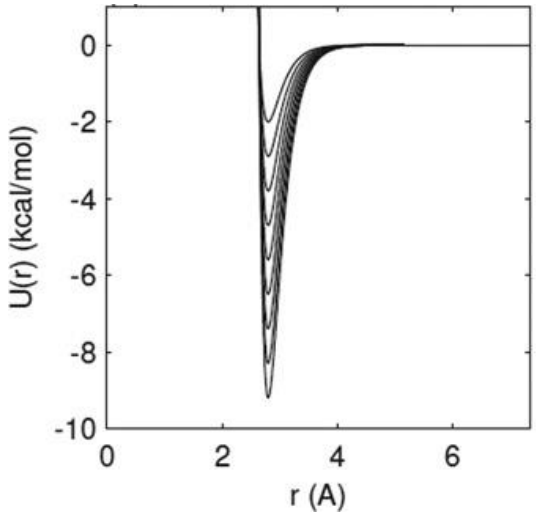
Annu. Rev. Biophys. 2013. 42:121–42

Enthalpy-Entropy-Compensation: Possible reasons:

1)

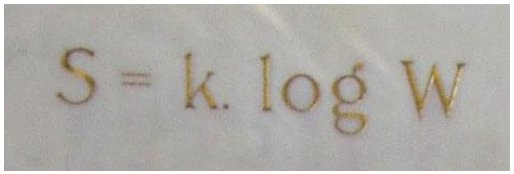






$$\omega = \sqrt{\frac{k}{m}}$$

$$E_n = \hbar\omega\left(n + \frac{1}{2}\right)$$

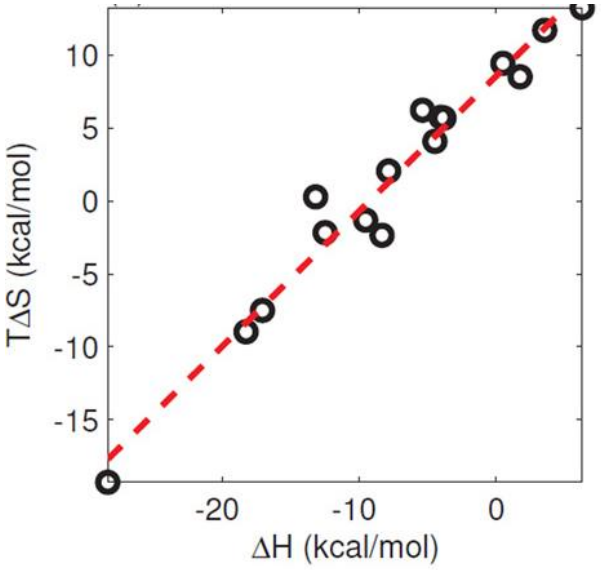


Higher Binding-enthalpy (deeper potential) leads to worse entropy

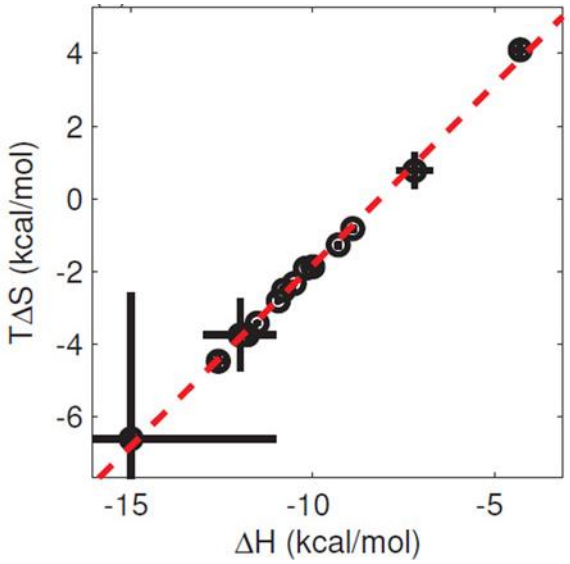
2) Entropy-enthalpy compensation due to special features of water

Annu. Rev. Biophys. 2013. 42:121–42

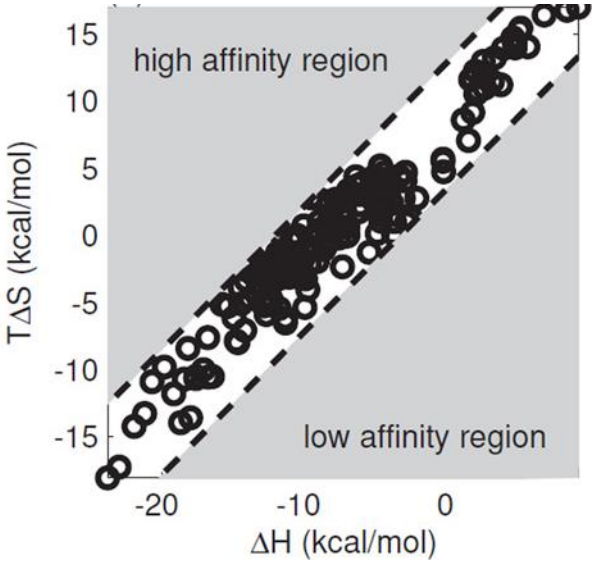
Enthalpy-entropy compensation: Is it real?



„enthalpy-entropy-comp.“ for different protein-ligand complexes



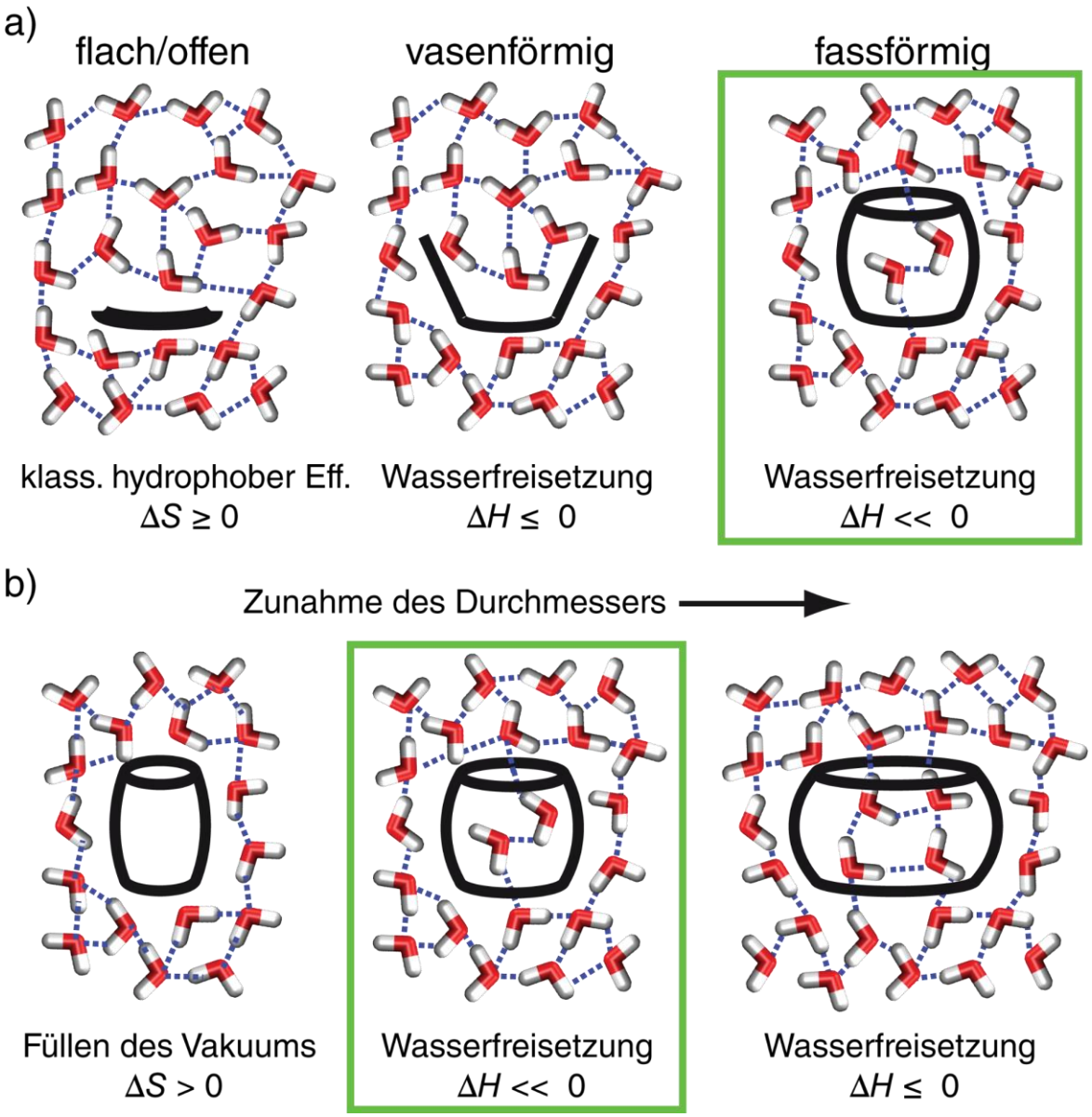
„enthalpy-entropy comp.“ for measured for identical system in different labs



coincidental selection of systems with similar affinities?

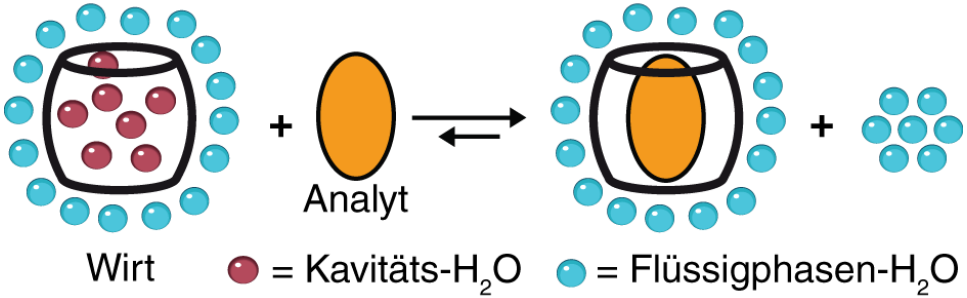
Annu. Rev. Biophys. 2013. 42:121–42

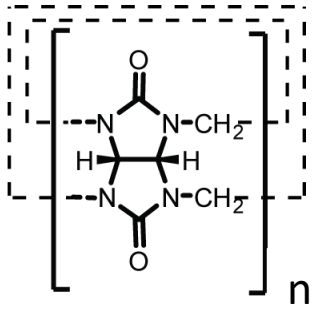
The High-energy Water Model for Cavities

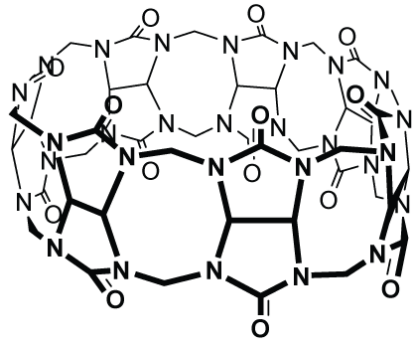


Angew. Chem. Int. Ed. **2014**, *53*, 11158

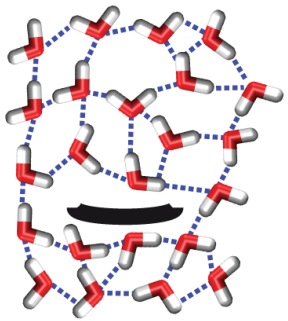
The High-energy Water Model for Cavities





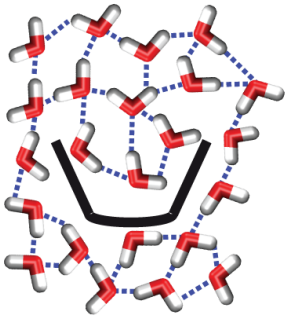


Flach/offen



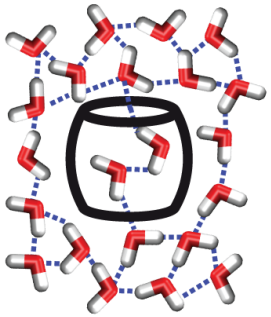
klass. hydroph. Eff.
$\Delta S \geq 0$

Vasenförmig

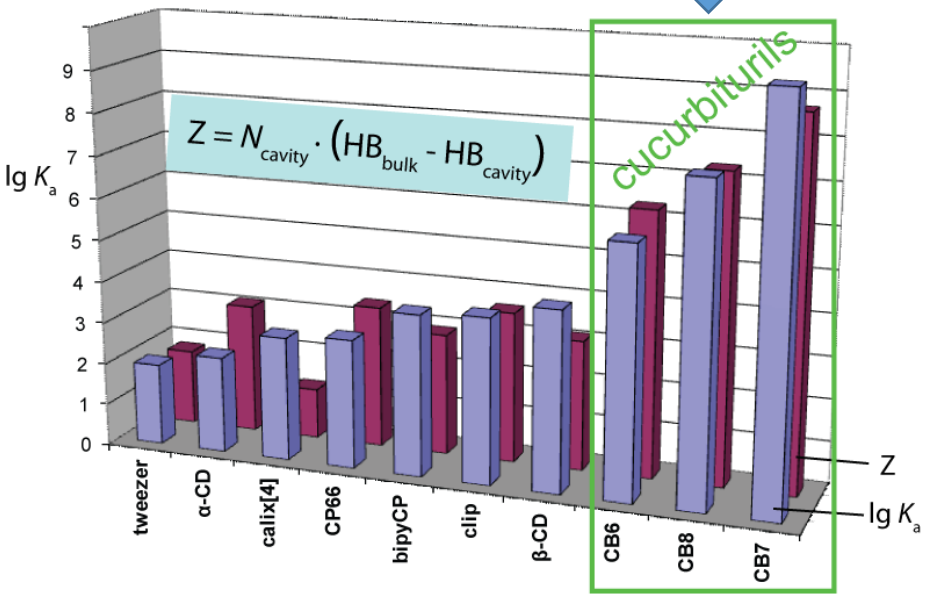


Kavitätswasserfreisetz.
$\Delta H \leq 0$

Fassförmig

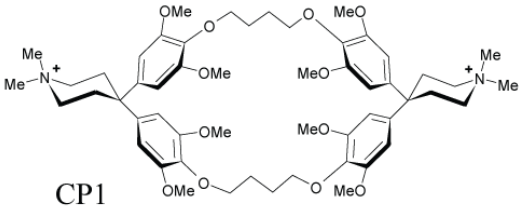


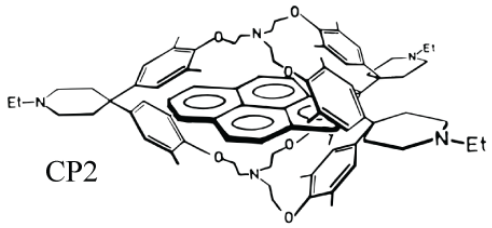
Kavitätswasserfreisetz.
$\Delta H << 0$

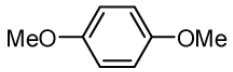
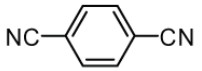
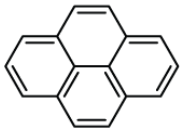


Angew. Chem. Int. Ed. **2014**, *53*, 11158

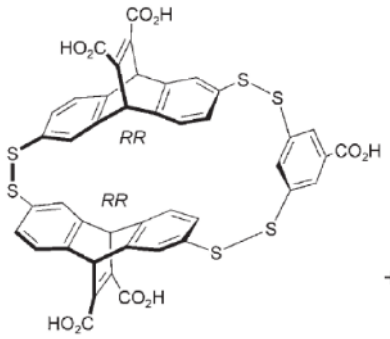
Cavity Water Release as an Enthalpic Driving Force for Host-Guests Binding



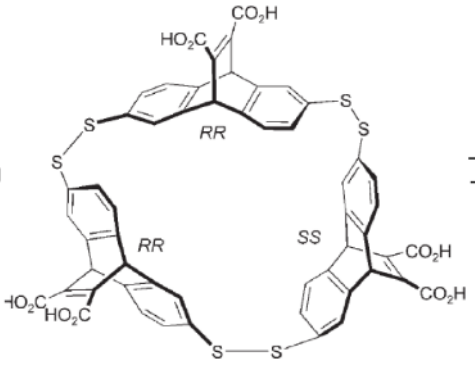


host	guest	solvent	ΔG	ΔH	$-T\Delta S$
CP1		water	–22.5	–41.8	19.3
		MeOH	–5.0	–15.5	10.5
		water	–21.8	–43.1	21.3
		MeOH	–7.8	ca. –18	- - -
CP2		water (1% DMSO)	–39.3	- - -	- - -
		MeOH	–26.7	–50.1	23.4
		$CHCl_3$	–9.6	–13.0	3.4

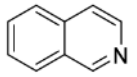
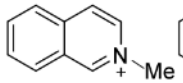
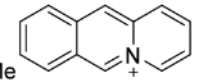
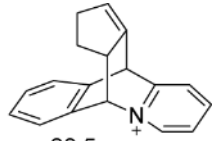
F. Diederich and coworkers, J. Am. Chem. Soc. 1990, 112, 339 & *J. Am. Chem. Soc.* **1991**, *113*, 5420



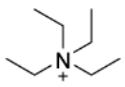
CP3

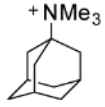


CP4

ΔH(CP3)	–22.4	–38.3	–40.6	–38.5
ΔH(CP4)	–15.1	–23.8	–23.7	–25.8
$-T\Delta S$(CP3)	3.6	8.1	7.5	6.6
$-T\Delta S$(CP4)	–4.2	–2.8	–5.4	–4.9





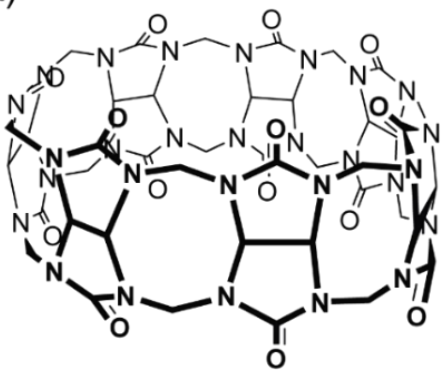
ΔH(CP3)	–30.6	–26.2	–26.5
ΔH(CP4)	–18.5	–18.8	–19.5
$-T\Delta S$(CP3)	4.9	–0.6	–1.9
$-T\Delta S$(CP4)	–8.7	–9.2	–15.0

Data from:
S. Otto and coworkers,
Chem. Eur. J. **2008**, 14, 2153
Review:
F.B. H.-J. Schneider,
Chem. Rev. **2016**, *116*, 5216

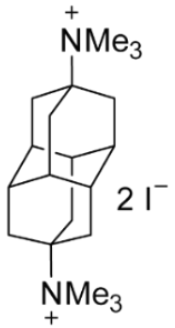
Host-guest binding in water is often enthalpically favored but entropically disfavored with $|\Delta H| \ll |T\Delta S|$

Ultra stable Host-Guest Complexes in Water

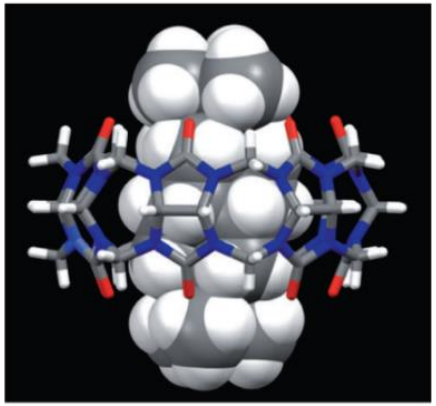
a)



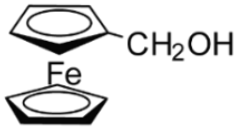
cucurbit[7]uril (CB7)



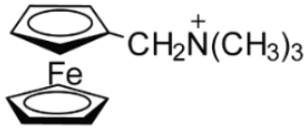
$K_a = 7 \cdot 10^{17}\ M^{-1}$



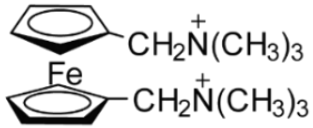
b)



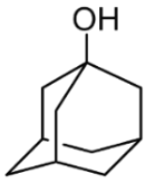
$K_a = 3 \cdot 10^{9}\ M^{-1}$
$\Delta H = -90$ kJ/mol
$-T\Delta S = 36$ kJ/mol



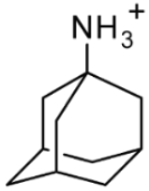
$K_a = 4 \cdot 10^{12}\ M^{-1}$
$\Delta H = -90$ kJ/mol
$-T\Delta S = 18$ kJ/mol



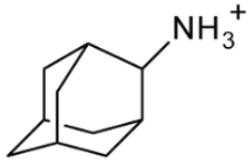
$K_a = 3 \cdot 10^{15}\ M^{-1}$
$\Delta H = -90$ kJ/mol
$-T\Delta S = 2$ kJ/mol



$K_a = 2 \cdot 10^{10}\ M^{-1}$
$\Delta H = -80$ kJ/mol
$-T\Delta S = 21$ kJ/mol



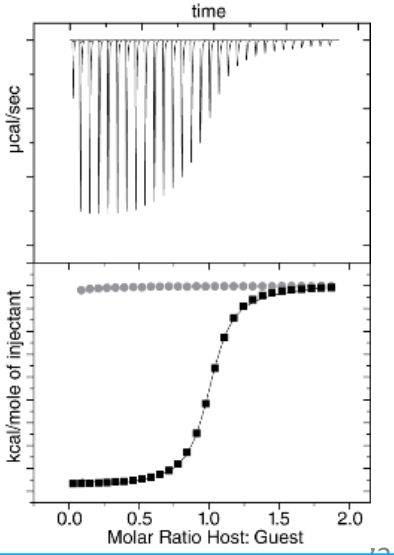
$K_a = 2 \cdot 10^{14}\ M^{-1}$
$\Delta H = -81$ kJ/mol
$-T\Delta S = 0$ kJ/mol



$K_a = 1 \cdot 10^{14}\ M^{-1}$
$\Delta H = -82$ kJ/mol
$-T\Delta S = 2$ kJ/mol

Isothermal Titration Calorimetry (ITC)

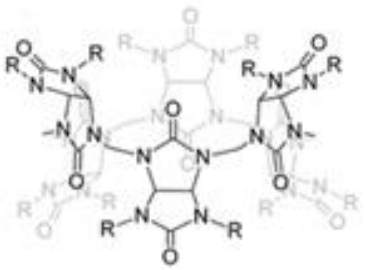
Measurement of K, ΔH, $T\Delta S$ and the stoichiometry.

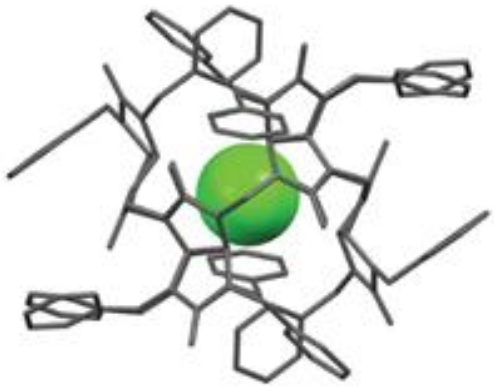


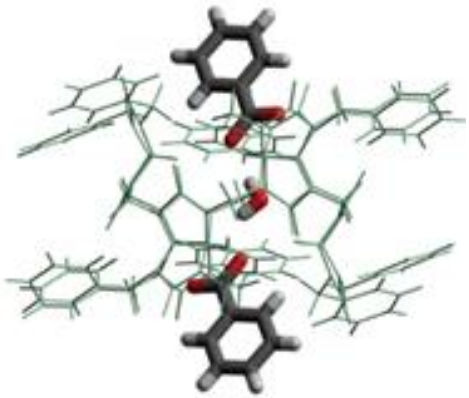
Ultra stable Host-Guest Complexes in Water

Bambus[6]uril

M. A. Yawer, ... V. Sindelar, *Angew. Chem. Int. Ed.* **2015**, *54*, 276



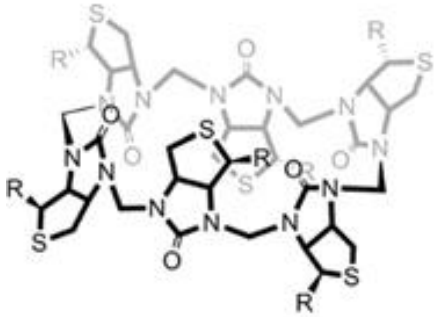


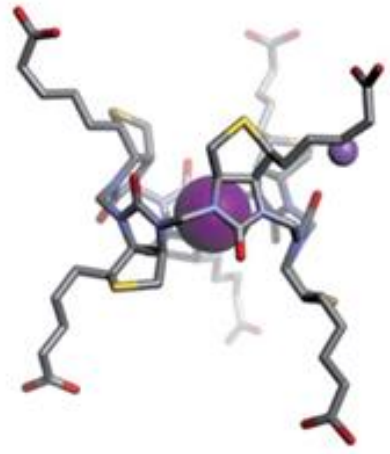


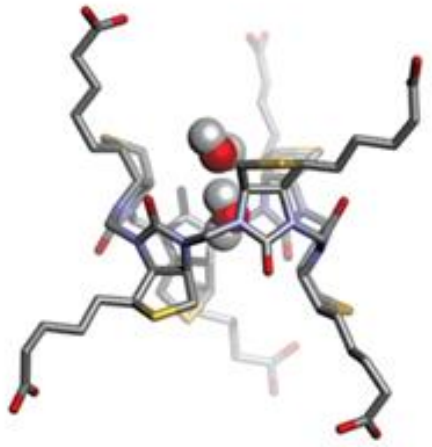
K_a(Iodid) = 2•10^6 M^{-1}
ΔH = −81 kJ/mol

Biotin[6]uril

M. Lisbjerg, ... M. Pittelkow, *Org. Biomol. Chem.* **2015**, *13*, 369-373.





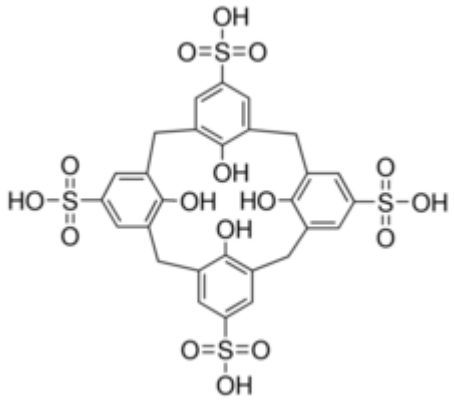


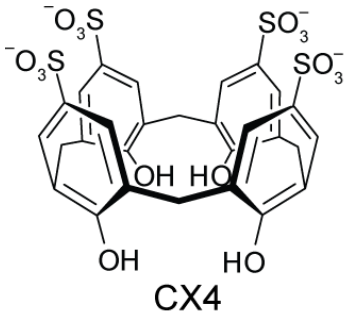
K_a(Iodid) = 5•10^3 M^{-1}
ΔH = −43 kJ/mol

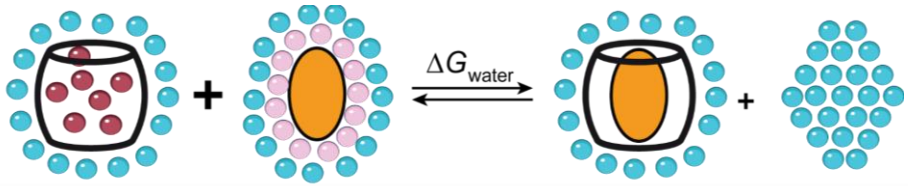
- $\Delta H << 0$ and $-T\Delta S < 0$ for alle halogenides in water
- for complexation of Br^- & I^- through Bambus[6]uril: ΔH(water) < $\Delta H(CHCl_3)$

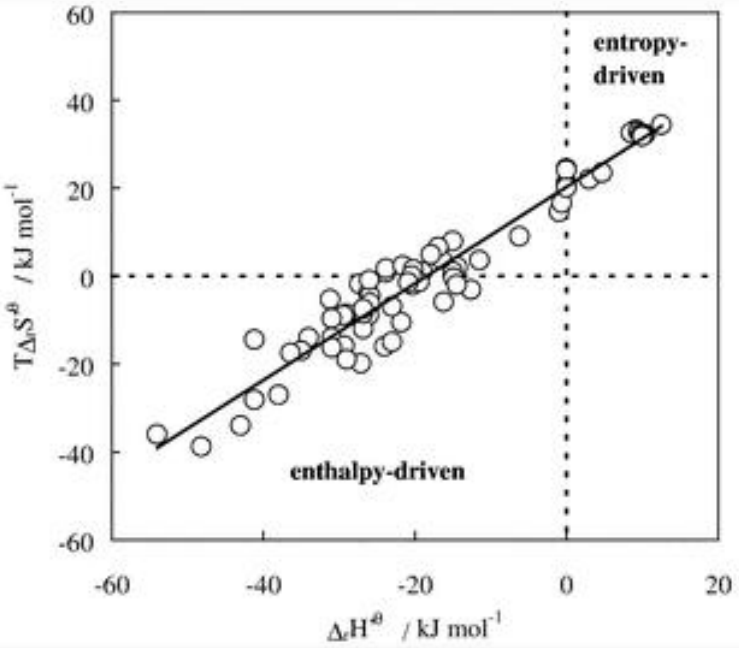
Review:
F.B. H.-J. Schneider, *Chem. Rev.* **2016**, *116*, 5216

Enthalpy-entropy-Kompensation for Host-Guest Systems

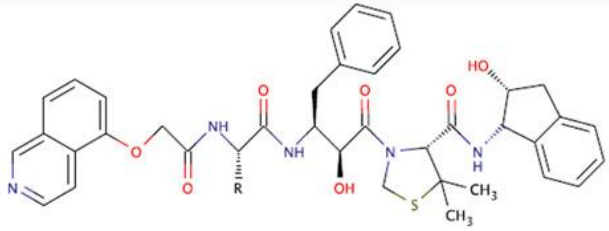






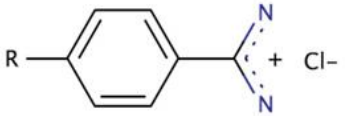


HIV-1 Protease Inhibitora



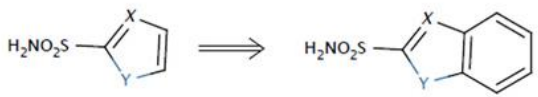
R group	kcal/mol ΔG	ΔH	TΔS
–S–CH_3	-14.87(9)	-8.2(2)	-6.67(9)
–SO_2–CH_3	-14.6(2)	-12.1(6)	-2.5(2)

Trypsin Inhibitors



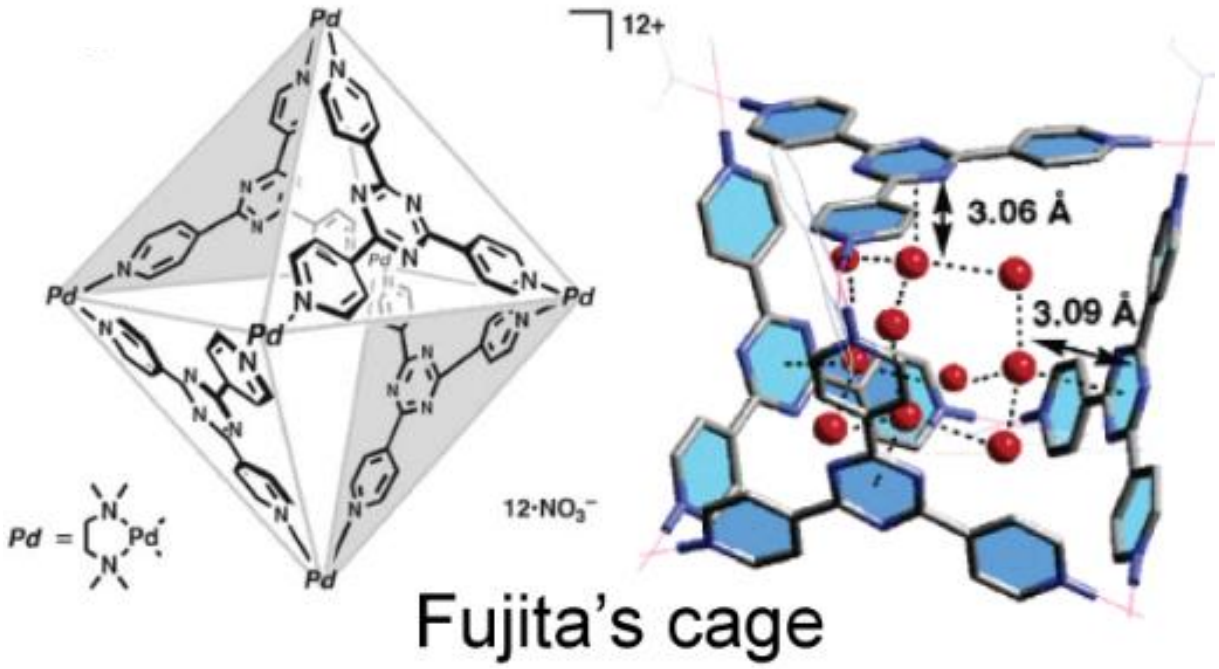
R group	ΔG	ΔH	TΔS
–H	-6.35(5)	-4.5(1)	1.8(1)
–Et	-6.07(5)	-3.3(1)	2.7(2)
–*n*-Bu	-6.26(5)	-2.4(1)	3.9(2)

Trypsin Inhibitors



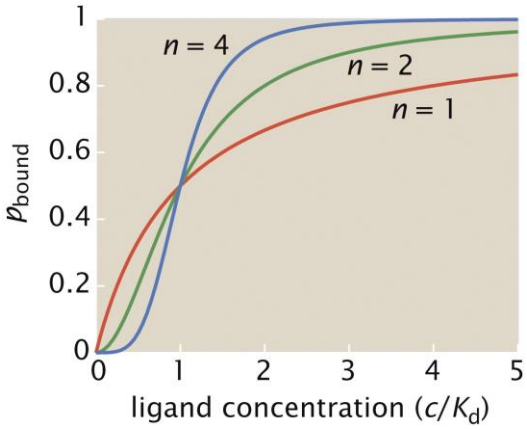
X	Y	ΔΔG	ΔΔH	TΔΔS
N	NH	1.1(2)	4.2(4)	3.1(4)

Cooperativity through hydrophobic effect(?)

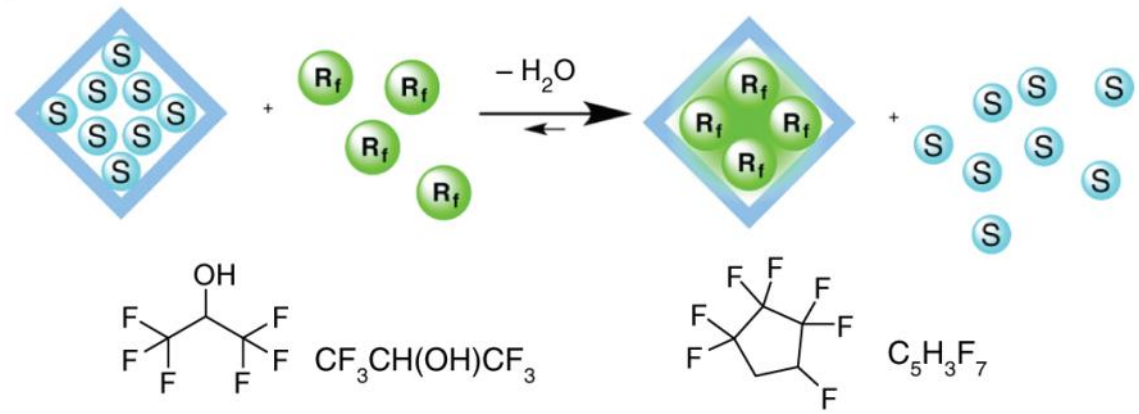


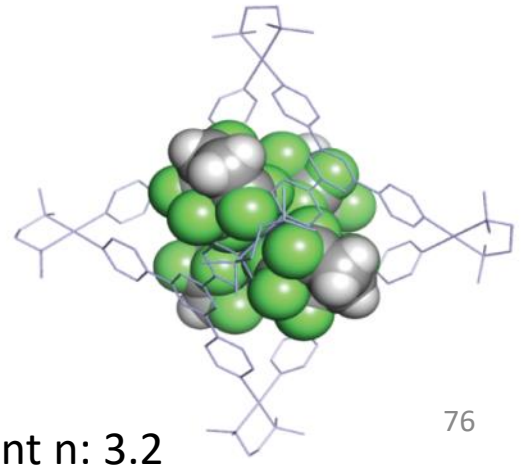
Fujita's cage

Reminder: Hill-Equation



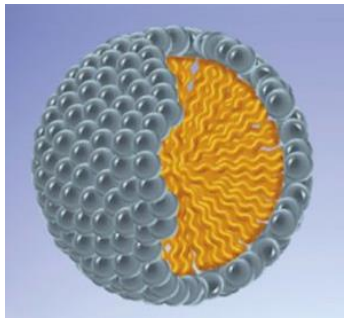
$$\theta = \frac{[L]^n}{K_d + [L]^n} = \frac{[L]^n}{(K_A)^n + [L]^n} = \frac{1}{(\frac{K_A}{[L]})^n + 1}$$

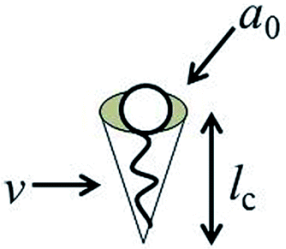




Hill-coeffizient n: 3.2

Self-Assembly of Surfactants

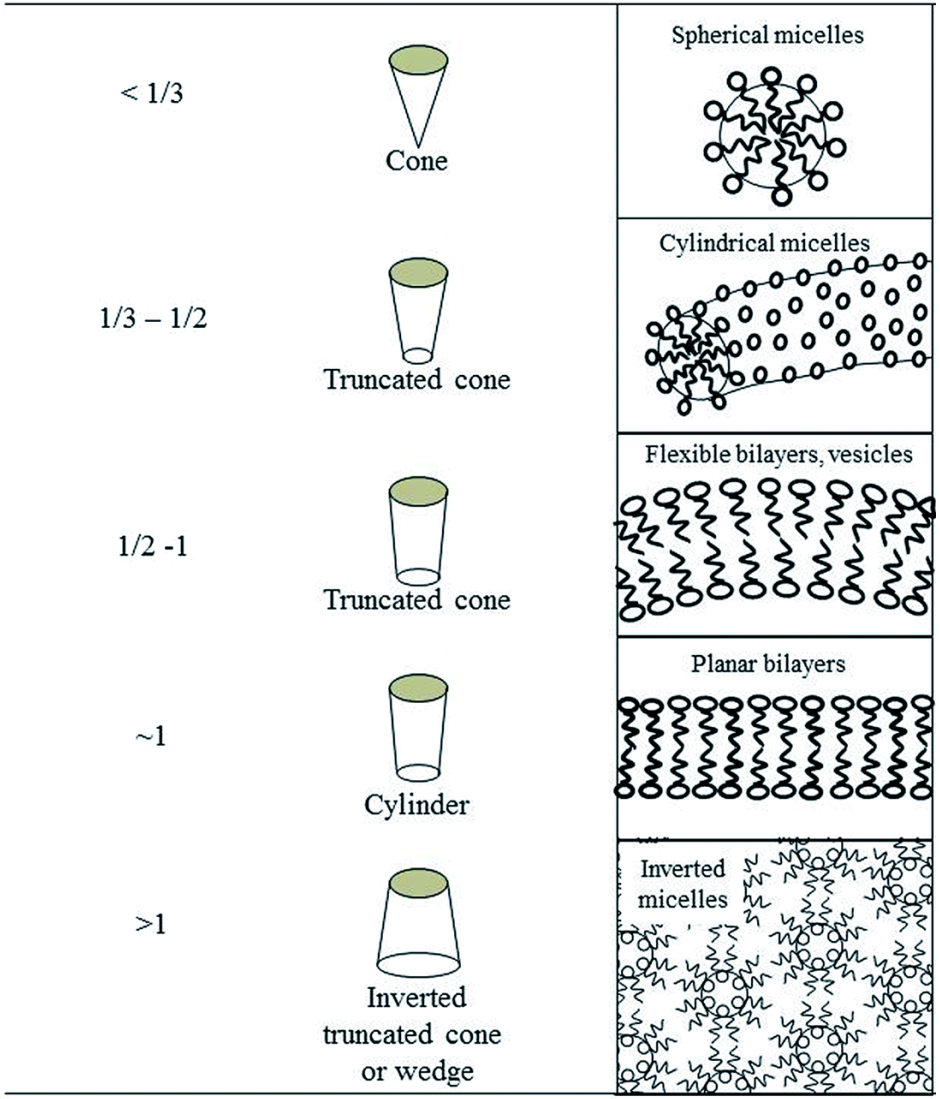




$$\text{Packing Parameter} = \frac{v}{a_o \cdot l_c}$$

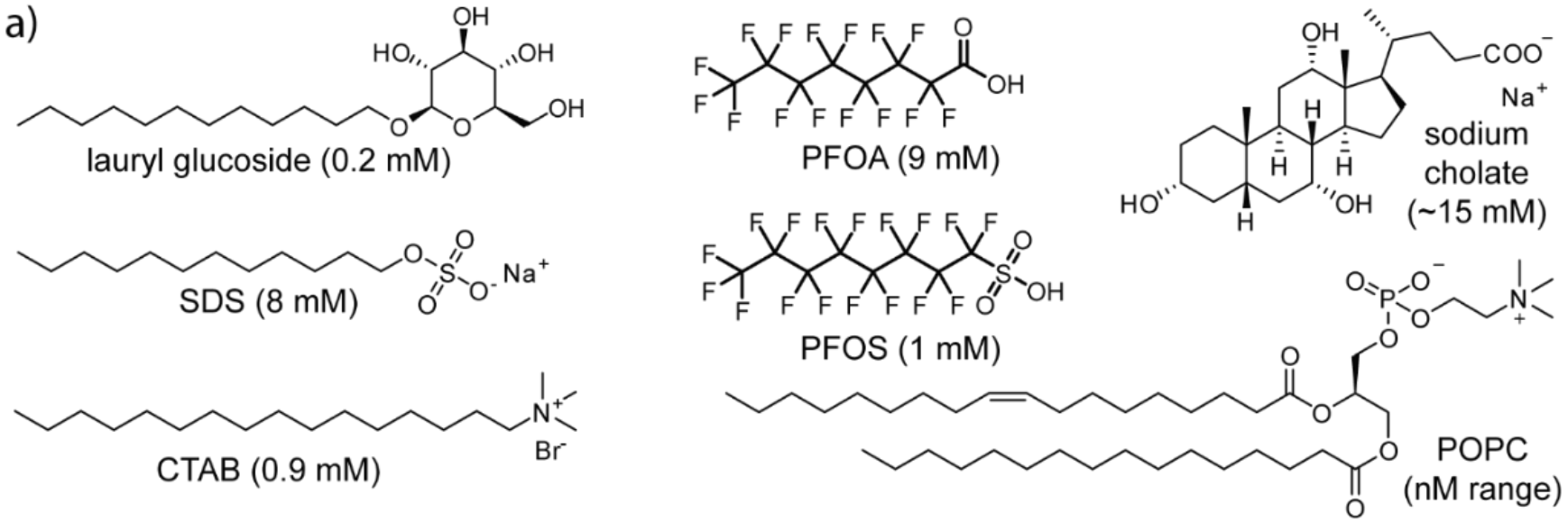
Note!

a_0 ia only an effective size, that also depends on charge and other factors



Langmuir **2002,** 18, (1), 31-38

Self-assembly of Tensiden



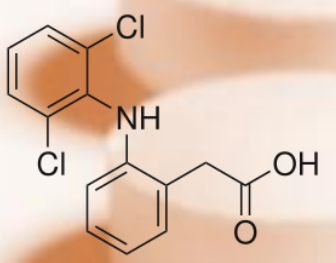
$$\Delta G_M^0 = RT\left(\frac{1}{j} + \beta\frac{i}{j}\left|\frac{z_s}{z_c}\right|\right)\ln \mathrm{CMC} + RT\left(\frac{i}{j}\left|\frac{z_s}{z_c}\right|\beta \ln\left(\frac{i}{j}\left|\frac{z_s}{z_c}\right|\right) - \frac{\ln j}{j}\right)$$

$$\Delta G_M^0 \approx RT\left(\frac{1}{j} + \beta\frac{i}{j}\left|\frac{z_s}{z_c}\right|\right)\ln \mathrm{CMC} \qquad \text{(eq. 2)}$$

Langmuir **1996,** 12, (5), 1208-1211

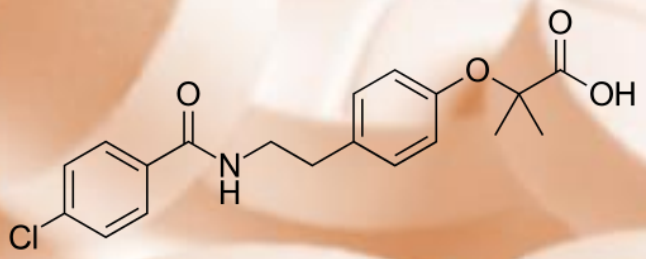
Pharmaceutical drugs as pollutants in water

Drug concentration in fresh water (ng/L)



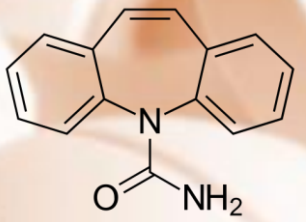
Diclofenac

150



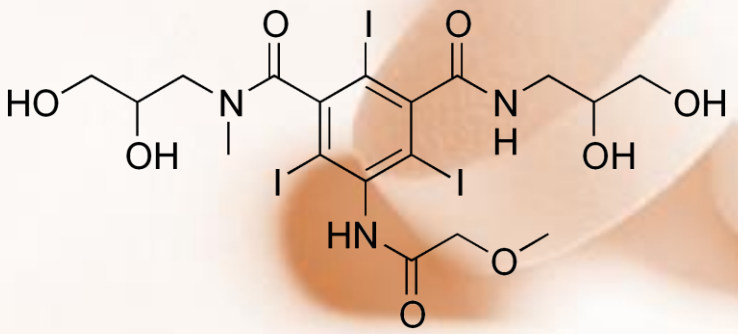
Bezafibrate

350



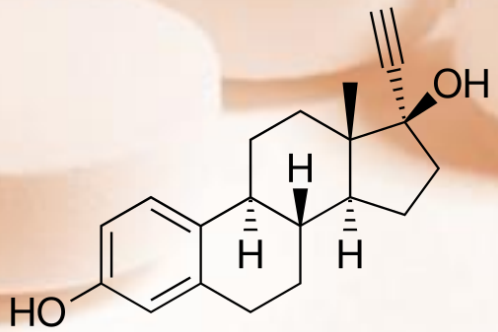
Carbamazepine

25



Iopromide

100

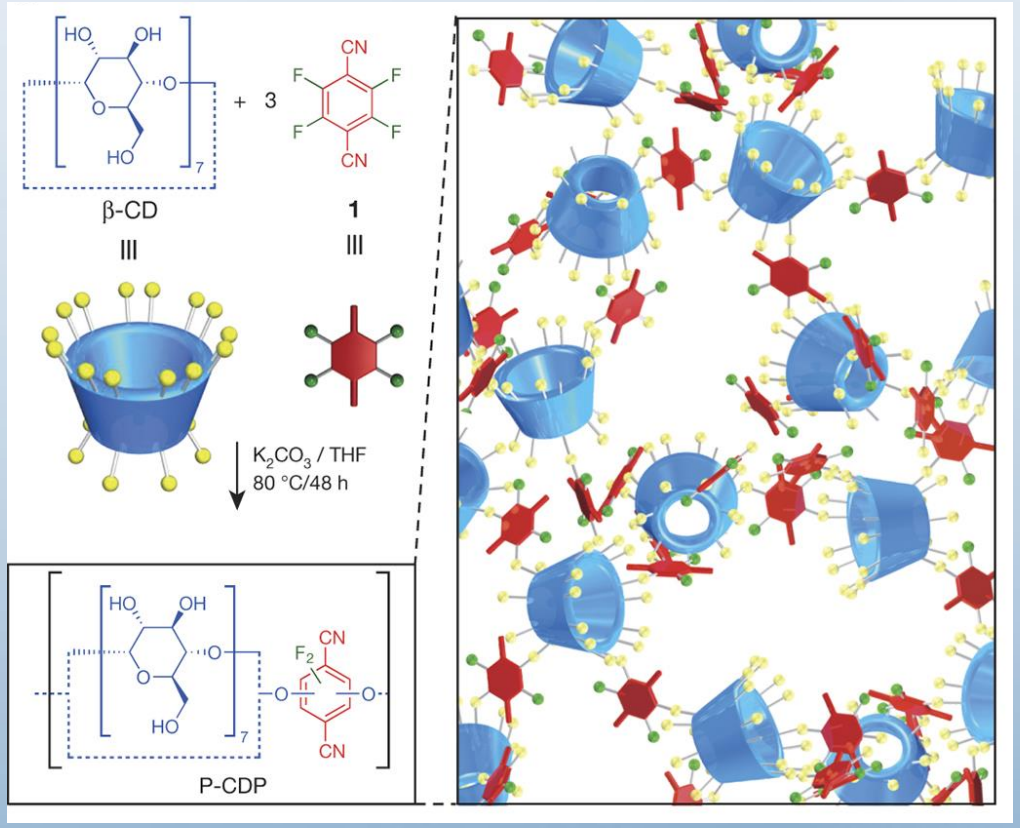


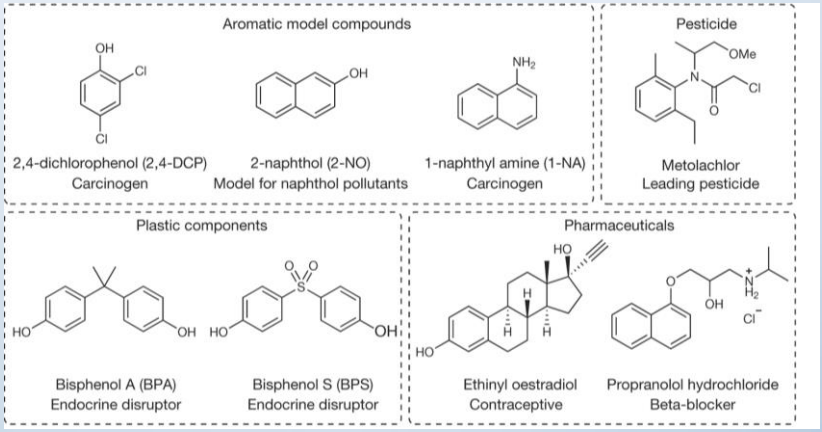
17α-Ethinylestradiol

5

Source: *World Health Organization: Pharmaceuticals in Drinking Water (2012)*

Host-Guest-Based Water Purification





Dichtel group (USA), *Nature,* **2015,** *529*, 190–194

HELMHOLTZ ASSOCIATION