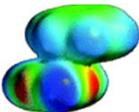©Prof. Carsten Schmuck

The InnoMol Molecular Interactions Workshop

The Pros and Cons of Electrostatic Interactions

Prof. Dr. Carsten Schmuck
University of Duisburg-Essen
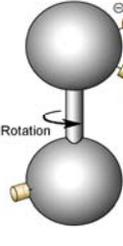Organic Chemistry
Email: carsten.schmuck@uni-due.de

1

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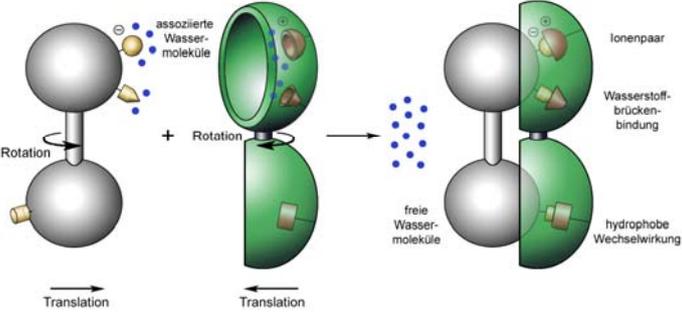
Overview: Supramolecular complex formation
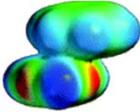

complex formation = multifaceted interplay of various different effects such as noncovalent interactions, solvent, microenvironment, rigidity etc.

2

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Strength of noncovalent bonds

- Molecules are made by the covalent connection of atoms
- Supramolecules are held together by noncovalent bonds

noncovalent bonds are typically weak (< 40 kJ/mol)

Just one noncovalent interaction is not enough!
Multiple weak, noncovalent interactions have to act in
concert to achieve binding → „Gulliver"-effect

Attn: noncovalent interactions may
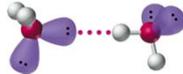influence each other!
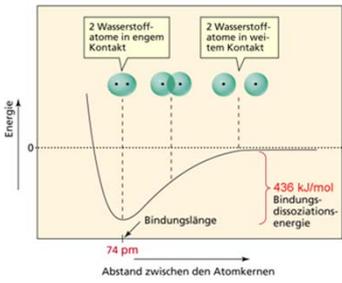
However, we also have to consider entropy which disfavors
bond formation (due to loss in translational entropy upon
bringing two particles together): $T \Delta S_{trans}$ ca. 23 kJ/mol

formation of a typical covalent bond:
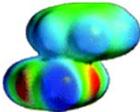H_2-molecule (BDE 436 kJ/mol)

$T \Delta S_{trans}$ << BDE

formation of a typical noncovalent bond:
H-bond (ΔE 22 kJ/mol in gasphase)

$T \Delta S_{trans} \approx \Delta E$

2 Wasserstoff-atome in engem Kontakt

2 Wasserstoff-atome in weitem Kontakt

Energie

0

436 kJ/mol
Bindungs-dissoziations-energie

Bindungslänge

74 pm

Abstand zwischen den Atomkernen

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Types of noncovalent bonds

The term "noncovalent" bonding interactions encompasses an enormous range of attractive
and repulsive forces such as:

- ion-ion
- ion-dipole
- dipole-dipole
- H-bonding (= special case of dipole dipole)
- cation-π and anion-π-interactions
- π-π-stacking interaction
- hydrophobic contacts
- dispersion interactions

stability
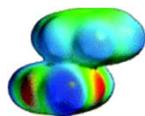
at least the general trend

Attn: It is very difficult to assign quantitative
numbers to these types of interactions as
their strength significantly depends on the
binding partners and the external conditions.

The solvent is very important for the
strength of noncovalent interactions
and hence complex stability!

Solvent affects both enthalpy and
entropy!

Each of these interactions has ist unique properties, e.g.:
- H-bonds are directional and specific, but only useful in
  nonpolar solvents and not in water
- hydrophobic contacts are stable in water but rather
  unspecific and difficult to „design"

4

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Distance dependence of noncovalent interactions

The various noncovalent interactions have different distance dependences.
- electrostatic interactions are long-ranged
- dispersion interactions work only at small distances

At very small distances repulsive forces set in

→ optimal distance and orientation

Example: interaction of two Ar atoms:
Lennard-Jones potential

$$E = B/r^{12} - C/r^6$$
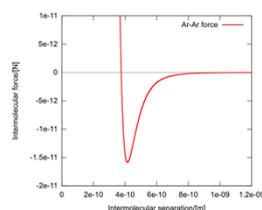
from J. N. Israelachvili, *Intermolecular and Surface Forces.*

5
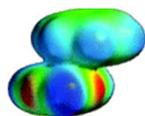
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Distance dependence of noncovalent interactions

Take home message

Type of intermolecular force	Relationship between energy and distance	
Ion-ion	$1/r$	
Ion-dipole	$1/r^2$	
Ion-induced dipole	$1/r^4$	
Dipole-dipole	$1/r^3$	
Dipole-dipole (randomly oriented)	$1/r^6$	Van der Waals Forces
Dipole-induced dipole	$1/r^6$	
Induced dipole-induced dipole	$1/r^6$	

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Electrostatic interactions

If a molecule carries a permanent charge, electrostatic interactions dominate intermolecular forces which are much larger than van der Waals forces.

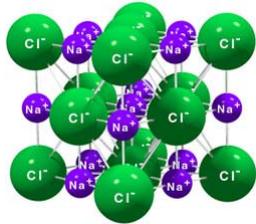- ion-ion: $E \sim 1/r$ (Coulomb law)
- ion-dipole: $E \sim 1/r^2$

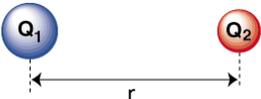by far the strongest physical force (stronger even than most covalent bonds)

at least in vacuum, in solution Coulomb interactions are extremely weakened by the solvent

NaCl crystal

ion pair formation between Na^+ and Cl^- in gasphase
$\Delta E = 500$ kJ/mol Attn: NaCl dissociates into atoms in gasphase

electrostatic interactions are strong and long ranged

Q_1 Q_2

$$E = \frac{Q_1 \cdot Q_2}{4\pi\varepsilon_0\varepsilon \cdot r}$$

r

Attn: As we are never dealing with isolated ions the „real" distance dependence of ionic interactions decays more rapidly ($E \sim 1/r^3$) than predicted by Coulomb law due to the attenuation of the electric field by the counterion nearby.

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Ion dipole interactions

= interaction between ions and polar molecules

polar

nonpolar Cl-Cl H-Cl
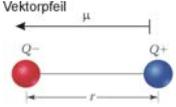
Vektorpfeil μ

dipole moment

$$\mu = Q \bullet r$$

one of the most important dipoles: the water molecule

Bindungsdipole

Example: single interaction of Na^+ with H_2O in gasphase
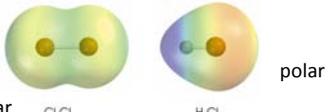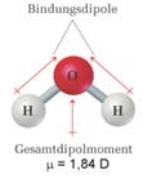
Na^+ •••• ΔE *ca.* 100 kJ/mol

Gesamtdipolmoment $\mu = 1,84$ D

Ion-dipole interactions provide the energy to dissolve salts in water

OH_2
H_2O — Na^+ — OH_2
H_2O OH_2
OH_2

solvation energy

$Na^+ + (H_2O)_m \rightarrow Na(H_2O)_6^+$

$\Delta G = -365$ kJ/mol
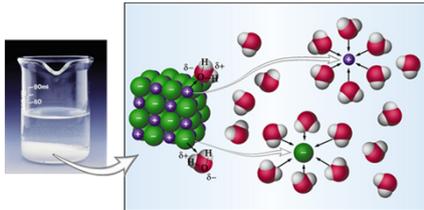
Attn: Solvation is an extremely important aspect in supramolecular chemistry, as desolvation has to take place bevor complex formation occurs.

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Quantitative description of ion dipole interaction

In contrast to Coulomb interactions between point charges which are isotropic (= not depending on the orientation), ion-dipole interactions are anisotropic and depend on the orientation of the dipole relative to the charge

$$E = -\frac{(ze) \cdot u \cdot \cos\theta}{4\pi\varepsilon_0\varepsilon \cdot r^2}$$

If possible the dipole adopts an orientation with $\theta = 0°$ (its negative end points towards a positive charge and vice versa).
The opposite orientation is repulsive.

9

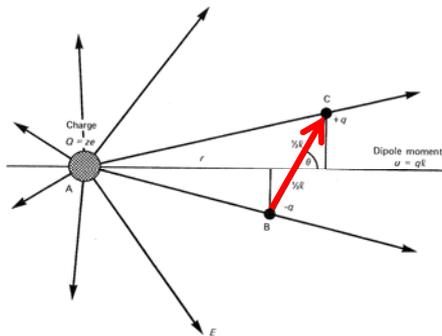©Prof. Carsten Schmuck

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Dipole-dipole interactions

$E \sim 1 / r^3$

Alignment of one permanent dipole with another can result in significant attractive forces.

two HCl molecules

two carbonyl compounds
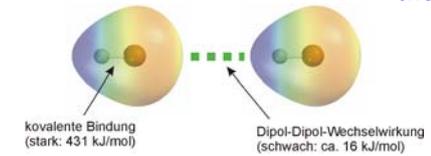
kovalente Bindung
(stark: 431 kJ/mol)

Dipol-Dipol-Wechselwirkung
(schwach: ca. 16 kJ/mol)
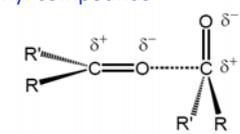
again the energy is dependent on the relative orientation of the two dipoles
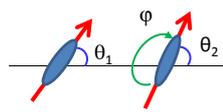
$$E = -\frac{u_1 \cdot u_2 \cdot \cos\theta}{4\pi\varepsilon_0\varepsilon \cdot r^3}[2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos\phi]$$

when the dipoles are in line:

$$E_{dipole} = -2\frac{u_1 \cdot u_2}{4\pi\varepsilon_0\varepsilon \cdot r^3}$$

Dipole-dipole interactions are rather weak and unlike ion-dipole interactions are usually not strong enough to lead to any strong mutual alignment of polar molecules in the liquid state (thermal energy kT is larger than E_{dipol}).

exception: water!

small size + large dipole
= short range association

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Freely rotating dipoles $E \sim 1 / r^6$

At large separations or in a medium of high ε dipoles can rotate more or less freely, because the dipole-dipole interaction is not strong enough to align the molecules.

- attractive orientation are occuring more often than repulsive ones (Boltzmann-distribution)
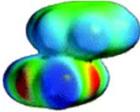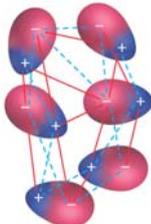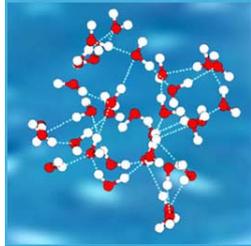- an angle-averaged attractive potential results

$$E_{orient} = -\frac{u_1^2 \cdot u_2^2}{3 \cdot (4\pi\varepsilon_0\varepsilon)^2 \cdot kT \cdot r^6} \quad \text{for } E_{dipol} < kT$$
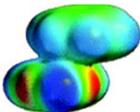
orientation interaction
Keesom interaction

one of the three parts of van der Waals forces

For small and highly polar molecules (e.g. H_2O, NH_3, HF) dipole-dipole interaction are strong enough to align neighboring molecules: short range order (so called associated liquids).

However, this also causes a decrease in entropy of the solvent!

H-bond network of liquid water

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Hydrogen bonds   First proposed by Linus Pauling in the 1930s

In principle just a special type of dipole-dipole interaction
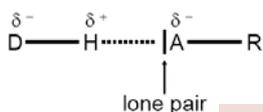
$\overset{\delta^-}{D}\!-\!\overset{\delta^+}{H}\cdots\cdots\overset{\delta^-}{|A}\!-\!R$

|
lone pair

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

2,8 Å
1,8 Å   1,0 Å
Wasserstoff-brückenbindung

- highly directional
- very specific

„master key interaction in supramolecular chemistry" (but only in nonpolar solvents)!

some gasphase data

		Distance (Å)	E (kJmol⁻¹)
[F-H-F] (semi-covalent)	anionic	F-H 1.13 (covalent: 0.92) (van der Waals 2.70) F-F 2.26 covalent: 1.42 (van der Waals 3.10)	163
HOH·····OH⁻	anionic	2.29	135
MeOH·····H⁺·····MeOH	cationic	2.39	131
DMSO·····H⁺·····DMSO	cationic	2.42	106
MeOH·····MeOH	neutral	2.70	32
HOH·····HOH	neutral	2.98	22

the strongest H-bond known, but:

$$F^- + HF \xrightarrow{H_2O} HF_2^-$$

$\Delta G = - 3.4$ kJ/mol

a all distances between oxygen atoms (except for FHF⁻)
Source: Schneider, Yatsimirsky

12
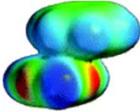
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Characteristics of H-bonds

	Strong	Moderate	Weak
A-H‑‑‑‑‑B interaction	Mainly covalent	Mainly covalent	Electrostatic
Bond energy (kJ/mol)	60 – 120	16 – 60	< 12
Bond lengths (Å)			
H‑‑‑‑‑B	1,2 - 1,5	1.5 - 2.2	2.2 - 3,2
A ‑‑‑‑‑‑B	2.2 - 2.5	2.5 - 3.2	3.2 - 4.0
Bond angles (°)	175 – 180	130 – 180	90 - 150
Relative IR Vibration (stretching symmetrical mode, cm^{-1})	25 %	10 – 25 %	< 10 %
^{1}H NMR chemical shift downfield (ppm)	14 – 22	< 14	?
Examples	Gas phase dimers with strong acids/ bases	Acids	Minor components of bifurcated bonds C—H hydrogen bonds
	Proton sponge HF complexes	Alcohols Biological molecules	O—H‑‑‑‑‑π hydrogen bonds

13
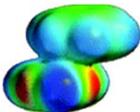
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The bifluoride ion HF$_2^-$

$$\left[F\!-\!H\!-\!F \right]^-$$

centrosymmetric triatomic anion: strongest H-bond known, with an F–H length of 114 pm and a bond strength of ca. 160 kJ mol^{-1}

distance much smaller than van der Waals radii

mainly a covalent bond: 4-electron-3-center bond

F2p   H1s   F2p
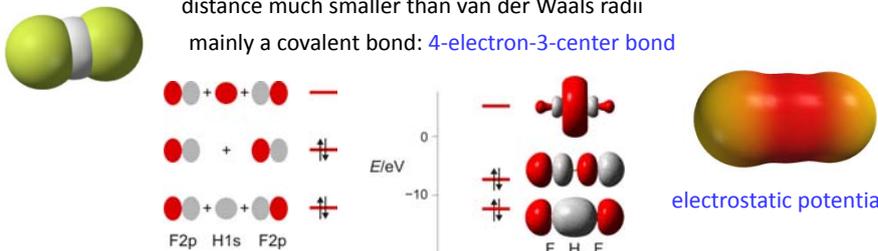
electrostatic potential

an artifical host für HF$_2^-$:

K = 5500 M^{-1} in DMSO

NMR studies

[1(FHF)]$^-$ J (H,F) = 128 Hz

(nBu$_4$N) (FHF)

19.0 18.5 18.0 17.5 17.0 16.5 16.0 15.5 15.0 14.5

δ / ppm

● F   ● N   ● O   ● C
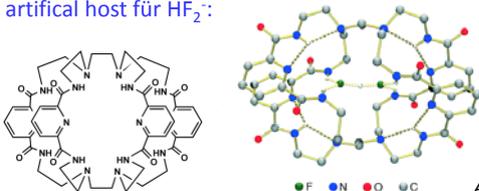
Angew. Chem. **2006**, *118*, 1955 –1959   14

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H-bonds in solution

H-bonds in solution may be significantly weakened by interactions of donor and/or acceptor with the solvent: H-bonds are only important ini nonpolar solvents but not in polar ones!

Biomimetic H-bonded complexes

Rich 1967: **12**
calc: *12.1*
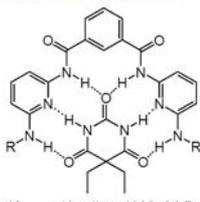
Hamilton 1988: **24.5**
calc: *24.2*
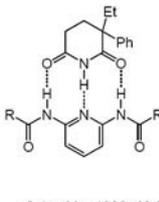
Schneider 1989: **13.0**
calc: *12.1*
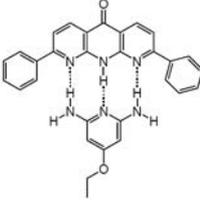
Zimmermann 1993: **10.5**
calc: *12.1*

linear correlation of Δ G with the number of H-bonds
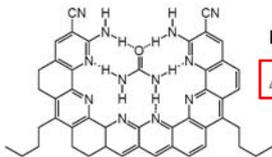
$\Delta G \sim - (5 \pm 1)$ kJ/mol per H-bond

in unpolar solvents!

Bell 1997: **29.4**

However, also the D-A-pattern influences the stability significantly (secondary effects). [15]
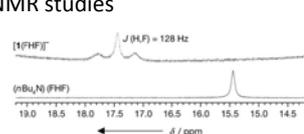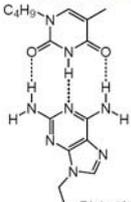

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Interplay of Interactions

Back to H-bonds
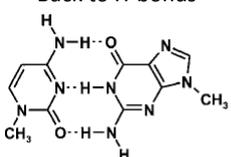
C·G
AAD·DDA
$K_{ass} \approx 10^4$ M^{-1}
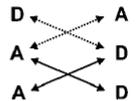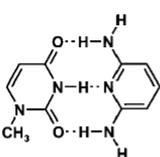
U·DAP
ADA·DAD
$K_{ass} \approx 10^2$ M^{-1}
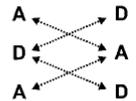
⟷ attractive secondary interaction
⤍ repulsive secondary interaction

also neighbouring H-bonds affect each other
= secondary effects
(Jörgensen et al. JACS 1991, 113, 2810)

incremental system (in CHCl$_3$)
8 kJ/mol per H-bond
+/- 3 kJ/mol per secondary interaction
Schneider et al. Chem. Eur. J. 1996, 2, 1446

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Secondary Interactions

A ‖‖‖‖ T

-ΔG (CDCl₃)   exp. 8.5
             calc. 10.0

G ‖‖‖‖ C

24.5
23.8

[kJ/mol]

Fig. 1.17. Watson-Crick base pairs with primary and secondary interactions.

➡ Secondary interactions: ~ 2.9 kJ/mol per H-bond
(repulsive or attractive)

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Matches and Mismatches

mismatch destabilizes the duplex by a factor of 40 in CHCl₃
(Gong et al. *J. Am. Chem. Soc.*, 2000, **122**, 2635)

Table 2. Binding constants (K_{ass}) and free energies of complexation (ΔG_{ass}) for receptor **2b** (picrate salt, 1.5 mM) with various amino acid carboxylates **18–22** (NMe₄⁺ salts) in water/[D₆]DMSO (40% v/v) at 25°C.

	Carboxylate	K_{ass} [M⁻¹][a]	$-\Delta G_{ass}$ [kJ mol⁻¹]
18	Ac-L-Gly-O⁻	190	13.0
19	Ac-L-Phe-O⁻	240	13.6
20	Ac-L-Val-O⁻	240	13.6
21	Ac-L-Ala-O⁻	360	14.6
22	Ac-D-Ala-O⁻	330	14.4

[a] Error limits in K were estimated as < ± 10%.

pyrrole host **1** K = 1630 M⁻¹

Schmuck et al Chem Eur J 2005, 11, 1109

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Electrostatic contributions to H-bonds

weak H-bonds are mainly electrostatic→ stability increases with increasing polarisation
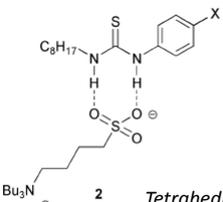
1a X=H
1b X=NO$_2$
1c X=CN
1d X=CF$_3$
1e X=CO$_2$Et
1f X=C$_6$H$_5$
1g X=OEt
1h X=NMe2

6600 M^{-1} for **1b**   K$_a$ in CDCl$_3$

ΔΔG = 16 kJ/mol

10 M^{-1} for **1h**

good correlation with σ-values
from Hammet equation

electrostatic effect!

Tetrahedron **1995**, *51*, 621

Fig. 2 Urea–sulfonate dyad studied by Wilcox and co-workers.

(a)
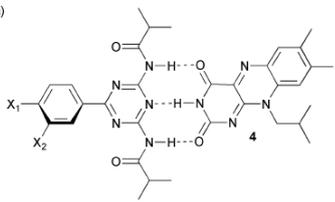
	X$_1$	X$_2$
3a	H	H
3b	Me	H
3c	NO$_2$	H
3d	CF$_3$	H
3e	H	CF$_3$
3f	OMe	H
3g	H	OMe
3h	OMe	OMe

K$_a$ in CDCl$_3$

97 M^{-1} for **3c**

ΔΔG = 5 kJ/mol

12 M^{-1} for **3h**

review article:
Chem. Soc. Rev. **2002**, *31*, 275–286

V. M. Rotello et al. *J. Org. Chem.* **1997**, *62*, 836

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Low barrier Hydrogen bonds

When the distance between the two heteroatoms within a H-bond becomes rather short
and the donor/aceptor strength are similar, a low barrier H-bond results.

The usual double well potential then
may become a single well potential.

extreme downfield
shift in the nmr
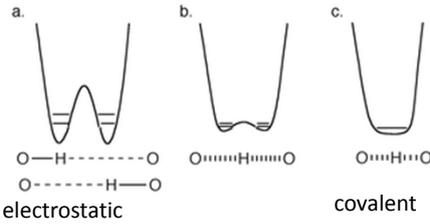
a.   b.   c.

O—H - - - - - - - O
O - - - - - - -H—O
electrostatic

O······H······O

O····H··O
covalent

90% acetone
10% water

-40 °C

Room
temperature

FIG. 2. Proton NMR spectra of the monoanion of cyclopropane-1,1-
dicarboxylic acid (6).

encircled proton   O•••O distance 2.45 Å

x-ray

JACS **2007**, *129*, 8692

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Aromatic interactions

Reviews: Chris Hunter *Chem. Soc. Rev.* **1994**, *23*, 101-109; *J. Chem. Soc., Perkin Trans. 2*, **2001**, 651-669.

quite complex interaction, lot of different factors involved
(e.g. electrostatic, induction, charge-transfer, desolvation…)

Electrostatics forces determine the geometry of the interaction, while the dispersion forces make the major contribution to the magnitude of the interaction.

simple model for electrostatic: quadrupole moment

π-cloud: negatively charged
σ-framework: positively charged

two geometries of interactions

edge to face

face to face
(but offset)

naphthalene in the solid

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Cation-π-interactions

Cation-π-interactions with transition metal ions are very common and considered to be mainly covalent involving the d-orbitals of the metal.

bisbenzenechromium(0)

Dewar-Chatt-Duncanson model

η^6-benzene

Fischer & Haffner (1955)

Zeise salt (1827)

LUMO HOMO
σ donation

HOMO LUMO
π back donation

η^2-ethylene

However, alkali- and earth alkali metal cations show much weaker interactions to π-systems and these are clearly non-covalent.

Benzene binds cations better than water!

ion	molecule	binding energy[b]	
			kcal/mol
			gasphase
Li^+	C_6H_6	38.3[c]	
Na^+	C_6H_6	28.0	
K^+	C_6H_6	19.2	80 kJ/mol
$K^+ \cdot C_6H_6$	C_6H_6	18.8	
$K^+ \cdot (C_6H_6)_2$	C_6H_6	14.5	
$K^+ \cdot (C_6H_6)_3$	C_6H_6	12.6	
K^+	H_2O	17.9	75 kJ/mol
Al^+	C_6H_6	35.2	
NH_4^+	C_6H_6	19.3	
NH_4^+	$1,3,5\text{-}C_6H_3(CH_3)_3$	21.8	

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

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Slide 1

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Origin of the Cation-π-interaction

classical electrostatic trend

M^+	Binding Energy (kcal/mol)
Li^+	38
Na^+	28
K^+	19
Rb^+	16

Dispersion forces and perhaps donor-acceptor interactions contribute to the cation-π interaction, but they are rather similar for different cations: The relative stability is mainly due to electrostatics.

e.g. for Na^+ + C_6H_6 60 % of the overall energy is electrostatic, the rest is dispersion

Binding of Na^+ to different aromatics (kcal/mol):

The more electron-rich the aromatic system the stronger the binding.

27.1   F 22.0   OH 26.9 NH_2 31.8

artifical host for cations in water

20.0   32.6

400,000   10,000

Dougherty, *JACS*, **1988**, *110*, 1983

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Slide 2

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An artificial host using cation-π-interactions

A deep cavitand binds acteylcholine and other trimethyl ammonium derivatives

ACh

Guest	NMR[b] K_a (M^{-1})	ITC[c] K_a (M^{-1})
Me_4N^+	4300 ± 600	3800 ± 600
choline	$>10^4$	25900 ± 700
acetylcholine	$>10^4$	14600 ± 1200
L-carnitine	140 ± 10	150 ± 10

in D_2O

1H-nmr

modelling studies

host   signal of the guest

Rebek *Angew. Chem. Int. Ed.* **2003**, *42*, 3150 – 3153

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Cation-π-interactions in Biology

In a survey of 33 high resolution protein crystal structures, a significant tendency is noted for cations to be in close proximity to aromatic rings (Petsko 1985).

As a general rule
- Arg binds more often than does Lys
- Trp participates more commonly than Phe, Tyr

extended cation-π-interactions in the human growth hormone receptor

binding of ACh to AChE

binding of trimethylated Lys from histone H3 to BPTF.

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Cation-π-interaction versus salt bridge

Computational study

Dougherty et al. *JACS* **2000**, *122*, 870-874

distance dependence in water

solvent	dielectric	cation−π interaction energy	salt bridge interaction energy
none	1.0	−12.5	−125.5
CCl₄	2.23	−7.8	−53.4
CH₃CO₂Et	5.99	−6.2	−19.7
CH₃CH₂OH	24.85	−5.6	−5.2
CH₃CN	37.5	−5.6	−3.8
H₂O	78.0	−5.5	−2.2

kcal/mol

x 2   x 60

- salt bridges are significantly reduced in water (large dipole of water, ε = 78)
- cation-π-interactions are hardly affected (the small water molecule is only weakly polarizable = no effect on dispersion; benzene does not need to be desolvated first)

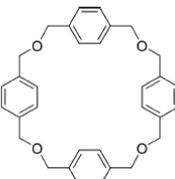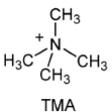cation-π-interactions are strong even in water = important for protein structure and stability!?

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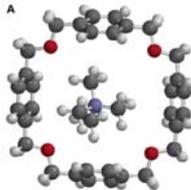The InnoMol Molecular Interactions Workshop

The effect of the counterion

The anion will of course effect the ability of the cation to participate in cation π binding (or any other type of noncovalent interaction)
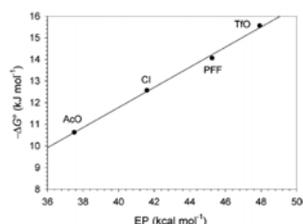
anion	K_{ass}	$-\Delta G$
Cl	165 (2)	12.57(3)
Me$_2$SnCl$_3$[g]	1004 (2)	17.01(1)
AcO	75 (2)	10.63(6)
Me$_2$Sn(OAc)Cl$_2$[h]	1068 (3)	17.16(1)
TFA	215 (2)	13.22(2)
TfO	556 (4)	15.56(1)
PFF	303 (5)	14.06(4)
Pic	458 (6)	15.08(3)

in CDCl$_3$

TMA

The counterions electrostatically inhibit the binding of the cation to a different degree.

Extrapolated energy of binding for the "free" TMA cation, i.e., in the absence of the counterion: ΔG = -44.9 kJ/mol   *JOC* **2004**, *69*, 3654.

ion pair electrostatic potential vs standard free energy of binding

Strongly associated counterions can diminish the strength of the cation binding by up to 80% in general.

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Anion-π-interactions

= noncovalent interaction of anions with electron deficient aromatics
in general, dominated by electrostatic and anion-induced polarization contributions

gas phase study: $C_6F_6 + Cl^-$ $\Delta H = -70.3$ kJ mol^{-1}

calculations on $C_6F_6 + Br^-$ $\Delta E = -65.1$ kJ/mol

- anion above the centroid
- very little charge transfer (< 0.01 e)
- purely noncovalent interaction

3.22 Å
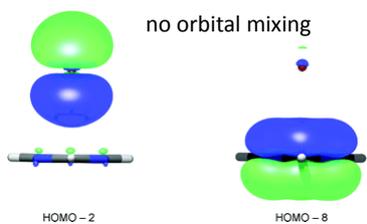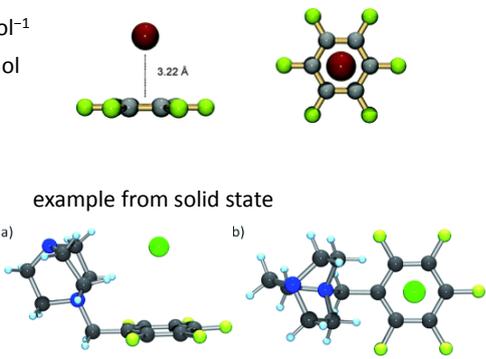
example from solid state

no orbital mixing

a)   b)

HOMO – 2   HOMO – 8

Chem. Eur. J. **2010**, *16*, 5062 – 5069

Ben J. Hay et al. *JACS* **2007**, *129*, 48; *Chem. Soc. Rev.* **2008**, 2417

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Other types of anion-π-interactions

Different types of complexes possible:
- strongly covalent σ-complexes (A)
- weakly covalent donor π-acceptor complexes (B)
- noncovalent anion-π complexes (C)

ad A)
σ-complex = Meisenheimer complex

e.g. always with F⁻

HOMO – 5

A — σ-complex
B — donor-π-acceptor
C — anion-π

covalency, charge transfer

ad B)

CN

NC   CN   + Cl⁻

2.73 Å

partial transfer of e-density

$\rho_{max} = 0.024$ e Å⁻³

Ben J. Hay et al. *JACS* **2007**, *129*, 48

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Case Study: Vancomycin Resistance

Inhibition of bacterial cell wall synthesis by reversible complexation of a specific peptide sequence.

L-Lys-*D*-Ala-*D*-Ala

$K_a \approx 10^5\text{-}10^6 \text{ M}^{-1}$

Vancomycin
drug of last hope

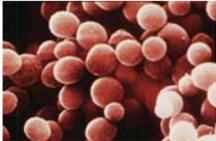---

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Case Study: Vancomycin Resistance

Inhibition of bacterial cell wall synthesis by reversible complexation of a specific peptide sequence.
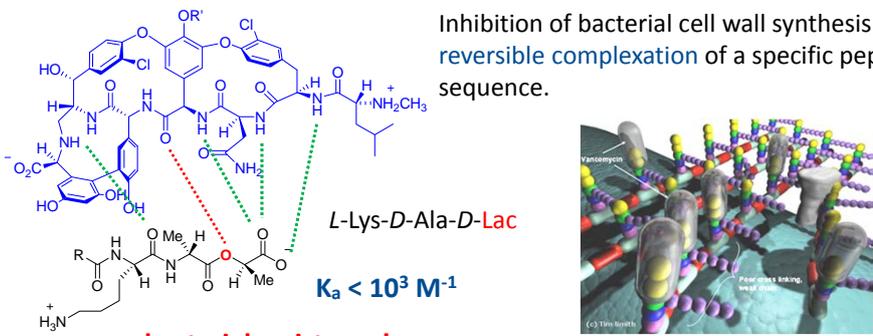
L-Lys-*D*-Ala-*D*-Lac
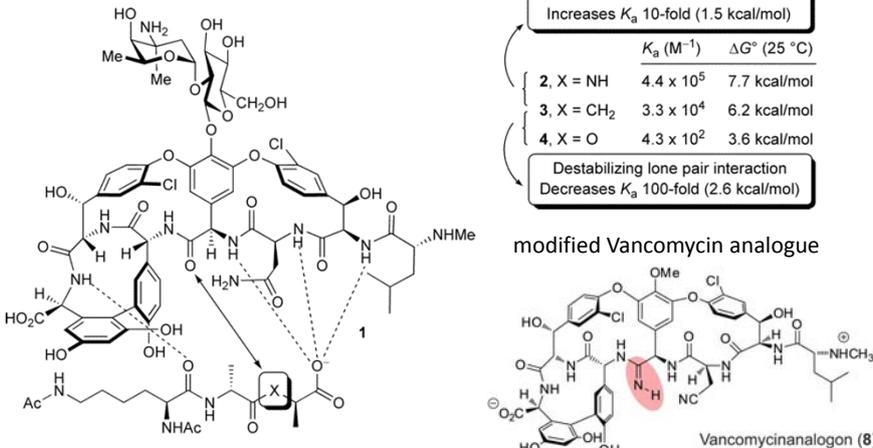
$K_a < 10^3 \text{ M}^{-1}$

bacterial resistance!

replacement of *D*-Ala by *D*-Lac
⇨ loss of one H-bond
⇨ reduces affinity by a factor of 1000

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Case Study: Vancomycin Resistance

Vancomycin resistance

H-Bond Increases K_a 10-fold (1.5 kcal/mol)		
	K_a (M^{-1})	$\Delta G°$ (25 °C)
2, X = NH	4.4 x 10^5	7.7 kcal/mol
3, X = CH$_2$	3.3 x 10^4	6.2 kcal/mol
4, X = O	4.3 x 10^2	3.6 kcal/mol
Destabilizing lone pair interaction Decreases K_a 100-fold (2.6 kcal/mol)		

modified Vancomycin analogue

Vancomycinanalogon (**8**)

similar affinity to -L-Lys-D-Ala-D-Lac and -L-Lys-D-Ala-D-Ala

D. Boger JACS **2006**, *128*, 2885; ibid **2012**, *134*, 1284.