



Mezimolekulové interakce

Interakce molekul

- ◆ **reaktivně** – vzniká či zaniká kovalentní vazba
 - překryv elektronových oblaků, mění se vlastnosti
- ◆ **nereaktivně** – vznikají molekulové komplexy
 - slabá, nekovalentní, nechemická, fyzikální či van der Waalsova (vdW) interakce
 - molekulový komplex, vdW molekula – zachovává vlastnosti jednotlivých komponent
 - přechod mezi klasickými a vdW molekulami je spojitý
 - principiálně neexistují pro vdW komplexy žádná „partnerská“ omezení

Projevy nekovalentních interakcí

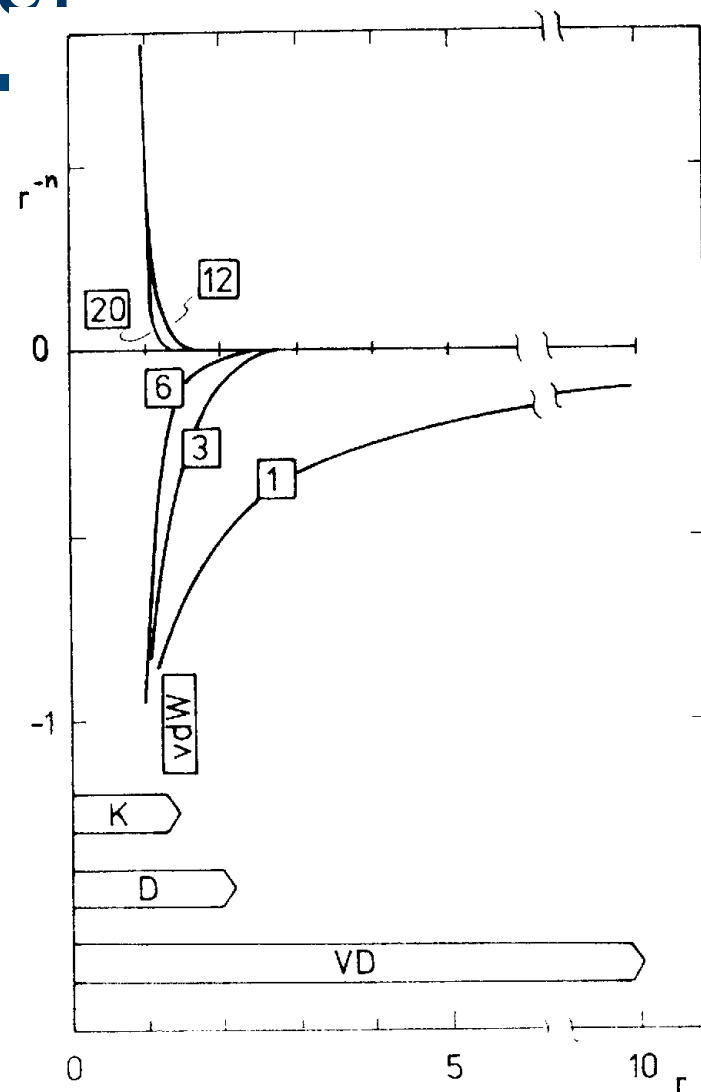
- ◆ chování reálného plynu
- ◆ Jouleův-Tompsonův jev
- ◆ existence kapalin
- ◆ biologie, existence života – párování bazí v DNA, transkripce DNA, skládání proteinů, procesy rozpoznávání, vazbu ligandů do biomolekul

Původ nekovalentních interakcí

- ◆ není v překryvu elektronových orbitalů
- ◆ elektrické a magnetické vlastnosti systémů
 - nerovnoměrné rozložení náboje v molekulách
 - multipóly – dipól, kvadrupól, ... (elektrostatická, coulombická interakce)
 - indukované multipóly (vždy pozitivní interakce – atrakce, nazývá se indukční, polarizační interakce)
 - disperzní interakce – důsledek elektronové korelace (vlnová funkce jednoho systému „respektuje“ vlnovou funkci druhého systému) př. interakce atomů vz. plynů

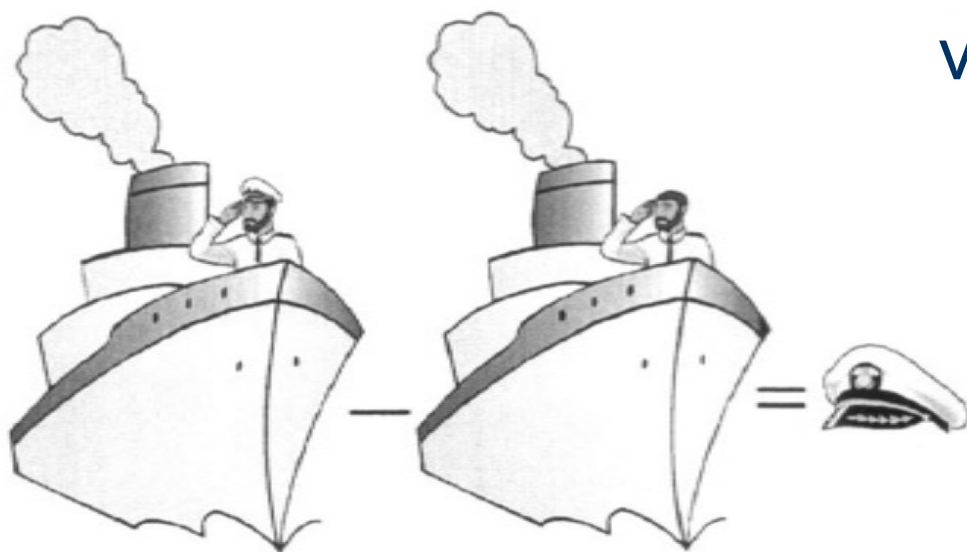
Původ nekovalentních interakcí

- přitažlivé síly
 - int. mezi multipóly
 - int. mezi multipólem a ind. multipóly (pozitivní)
 - disperzní síly (pozitivní)
- ◆ k přitažlivým silám musí existovat ještě odpudivý protějšek
 - výměně repulzí síla



Interakční energie

$$A + B \rightleftharpoons A...B \quad \Delta E = E(A...B) - (E(A) + E(B))$$
$$\Delta E \ll E(X)$$

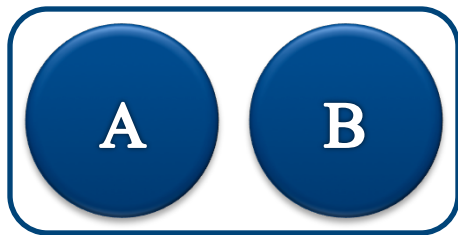


velmi náročné na
kvalitu výpočtu E

Interakční energie

- ◆ Přesnost – velké báze, zahrnutí el. korelace např. CCSD(T)/CBS
- ◆ Při použití konečných bází – basis set superposition error (BSSE)
 - při popisu komplexu je báze větší než báze fragmentů
 - Counterpoise (CP) – u fragmentů počítá s kompletní bází (ostatní fragmenty jsou tzv. ghost atoms)
 - S rostoucí velikostí báze klesá BSSE chyba, při CBS je nulová!

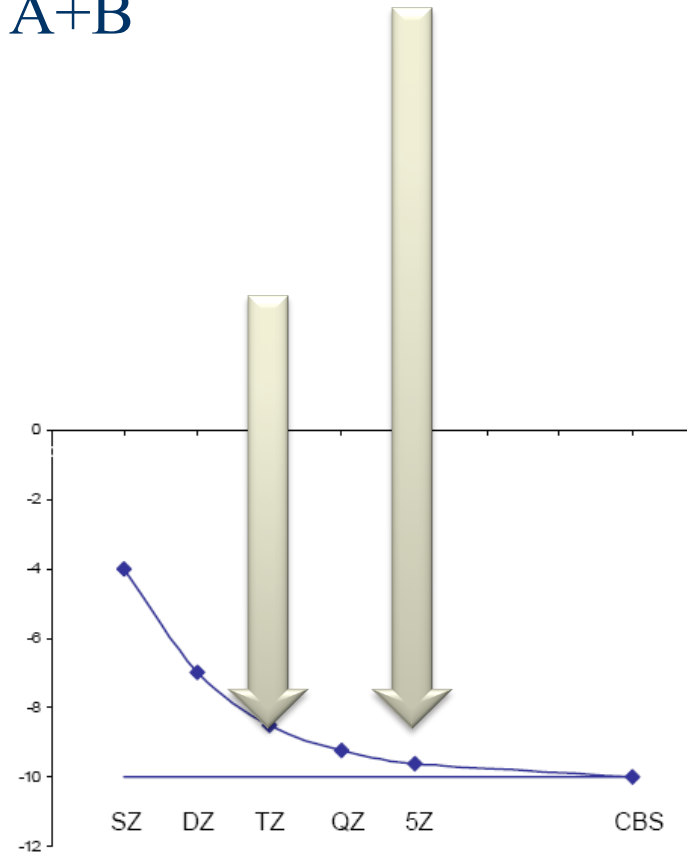
Bez BSSE korekce



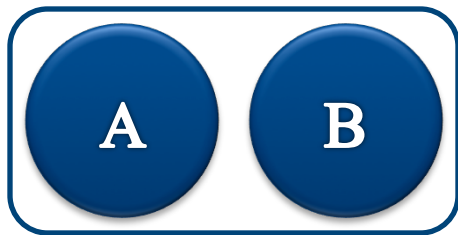
$E(A...B)$ v bázi $A+B$

$E(A)$ v bázi A

$E(B)$ v bázi B



S BSSE korekcí



$E(A...B)$ v bázi A+B



$E(A)$ v bázi A+B



$E(B)$ v bázi A+B

Přesné interakční energie

◆ CCSD(T)/CBS

- přímé výpočty v CCSD(T) a extrapolace např. cc-VTZ - >cc-VQZ jsou téměř nemožné

was fitted in their original work. Herein we have used the aug-cc-pVDZ → aug-cc-pVTZ extrapolation.

$$E_X^{HF} = E_{CBS}^{HF} + Ae^{-\alpha X} \quad (11)$$

$$E_X^{CORR} = E_{CBS}^{CORR} + BX^{-3} \quad (12)$$

Given that higher-order correlation-energy contributions cannot be neglected, we have approximated the CCSD(T)/CBS interaction energies according to the following scheme:

$$\Delta E_{CBS}^{CCSD(T)} = \Delta E_{CBS}^{MP2} + (\Delta E^{CCSD(T)} - \Delta E^{MP2}) \Big|$$

Deformační energie

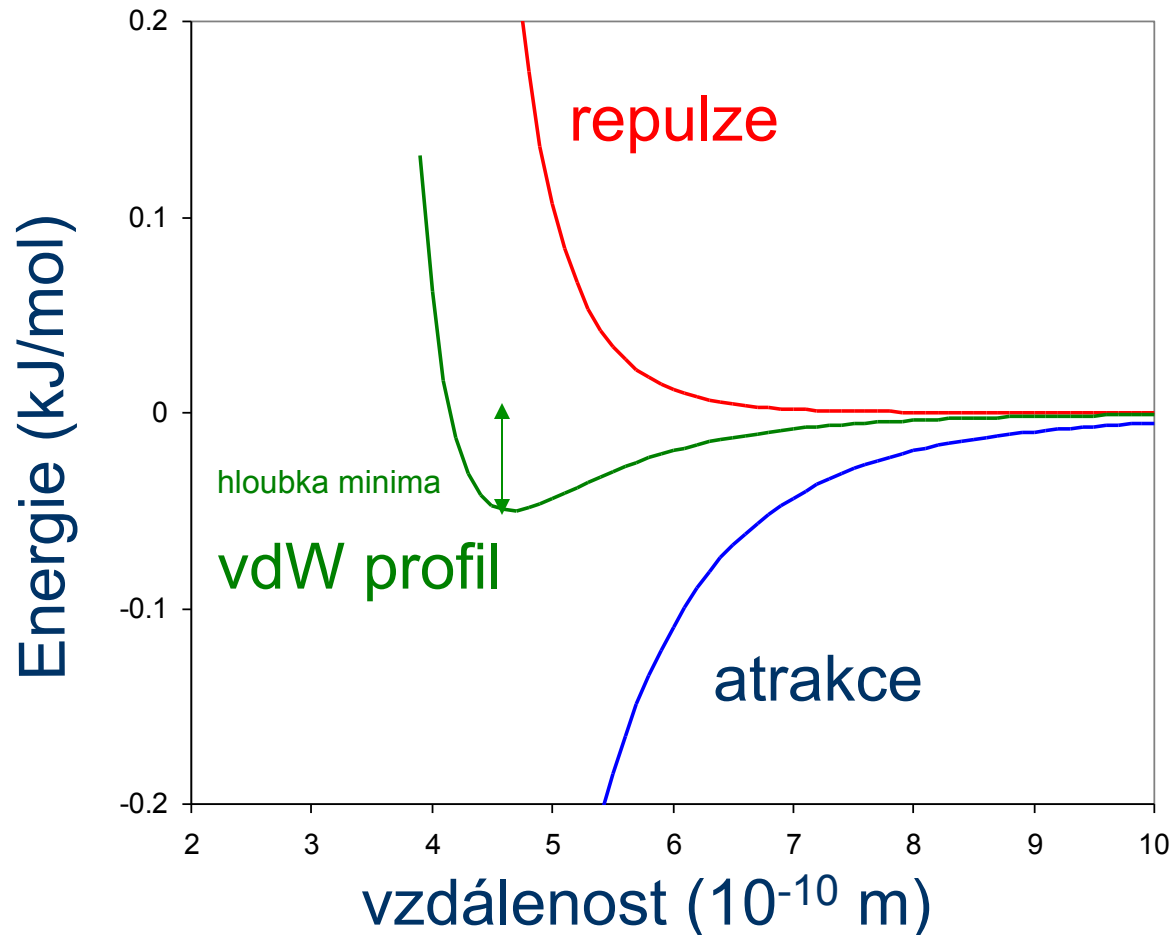
- ◆ Pokud jsou energie fragmentů počítány pro geometrie z komplexu, je interakční energie, zatížena chybou – deformační energie
- ◆ Odstranění této chyby znamená výpočet energií pro geometricky relaxované komplexy

Interakční energie

$$E = E_{coul.(els.)} + E_{pol.} + E_{disp.} + E_{rep.}$$

- Coulombická (elektrostatická)
 - Polarizační (indukční)
 - Disperzní (Londonovy síly) – někdy zaměňována s van der Waals
 - Repulzní (Pauliho repulze)
-
- Existují alternativní rozdělení, zejména biochemie používá zvláštní zoologii interakcí (vod. vazby, solné můstky, vdW síly, π -interakce, hydrofóbní interakce atp.)

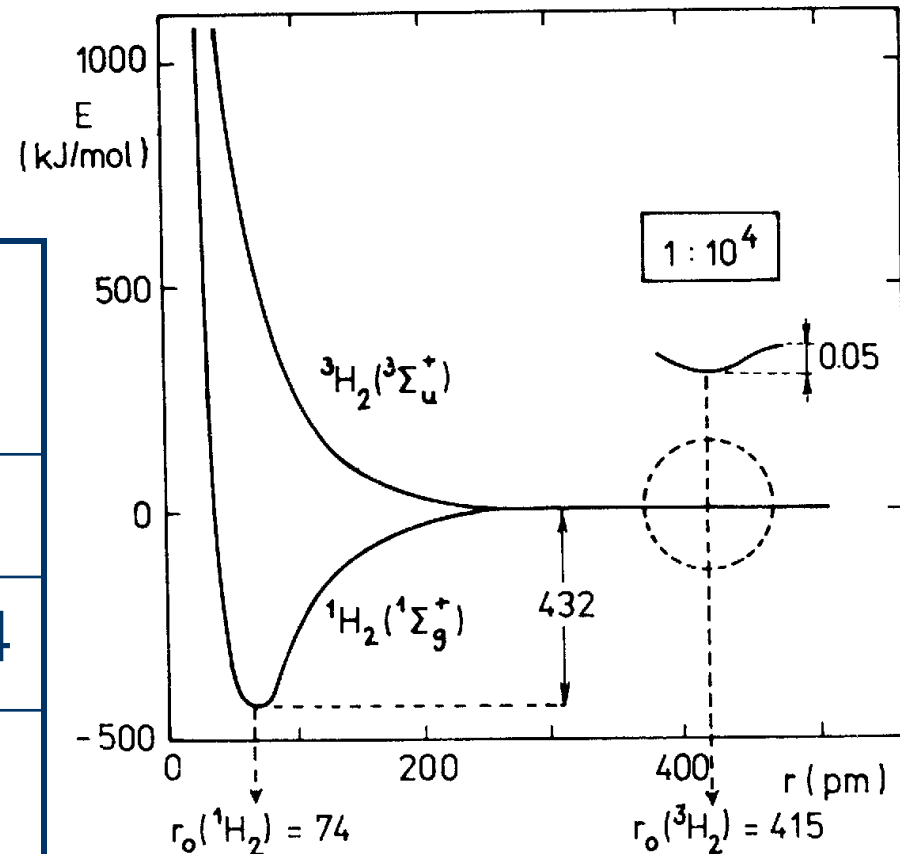
Nekovalentní komplex



$^3\text{H} \dots \text{H}$ komplex

vdW molekula $^3\text{H}_2$ vs. $^1\text{H}_2$

charakter.	$^1\text{H}_2$ ($^1\Sigma_g^+$)	$^3\text{H}_2$ ($^3\Sigma_u^+$)
D (pm)	74.09	415.4
E_D kJ/mol	432.0	0.0514
Multipl. sp.	singlet	triplet



Stabilita nekovalentních komplexů

- ◆ hloubka minima – stabilita nekov. komplexu
 - 4-20 kJ/mol slabé (hlavně disperzní síly)
 - 12-40 kJ/mol silnější, zejména díky vodíkovým vazbám
 - až 100 kJ/mol iontové komplexy
 - je-li en. < 10.5 kJ/mol pak je za normální teploty vdW molekula velmi nestabilní

$$\Delta E = E(A..B) - (E_A + E_B)$$

Stabilita nekovalentních komplexů

- ♦ při asociaci molekul klesá entropie, $-T\Delta S > 0$
- ♦ u vdW komplexů hraje entropie významnou roli

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

Gibbsova energie
(volná energie)

entalpie

entropie

$$\Delta H = \Delta U + \Delta(PV)$$

$$\Delta U = \Delta E + \Delta ZPVE$$

Stabilizační energie (kJ/mol)

He...He	0.089	HF...H ⁺	548.1
Ar...Ar	1.116	H ₂ O...H ⁺	756.5
HF...HF	27.1	NH ₃ ...H ⁺	923.8
HF...H ₂ O	42	HF...Li ⁺	124.3
H ₂ O...H ₂ O	29.2	H ₂ O...Li ⁺	170.3
H ₂ O...NH ₃	31.0	H ₂ ...H ₂	0.433
NH ₃ ...NH ₃	16.8	N ₂ ...N ₂	1.208

SAPT

- ◆ Symmetry Adapted Perturbation Theory
 - Pro WFT, velmi náročná
 - Pro DFT dostupná i pro „středně“ velké systémy

$$E_{\text{int}} = E_{\text{pol}}^{(1)} + E_{\text{ex}}^{(1)} + E_{\text{ind}}^{(2)} + E_{\text{ex-ind}}^{(2)} + E_{\text{disp}}^{(2)} + E_{\text{ex-disp}}^{(2)} + \delta HF \quad (6)$$

$$E_{\text{elec}} = E_{\text{pol}}^{(1)} \quad (7)$$

$$E_{\text{ind}} = E_{\text{ind}}^{(2)} + E_{\text{ex-ind}}^{(2)} \quad (8)$$

$$E_{\text{disp}} = E_{\text{disp}}^{(2)} + E_{\text{ex-disp}}^{(2)} \quad (9)$$

$$E_{\text{exch}} = E_{\text{ex}}^{(1)} \quad (10)$$

vdW molekuly

- ◆ váží se jinou nežli chemickou vazbou
 - iontové komplexy
 - komplexy s vodíkovou vazbou
 - přenosové (charge-transfer) komplexy
 - pravé vdW komplexy (dominuje disperzní energie)

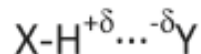
vdW forces

- ◆ The attractive or repulsive forces between molecular entities (or between groups within the same molecular entity) other than those due to bond formation or to the electrostatic interaction of ions or of ionic groups with one another or with neutral molecules. The term includes: dipole–dipole, dipole-induced dipole and London (instantaneous induced dipole-induced dipole) forces. The term is sometimes used loosely for the totality of nonspecific attractive or repulsive intermolecular forces. IUPAC Gold Book

What Is the Covalency of Hydrogen Bonding?

Sławomir Janusz Grabowski^{*†‡}

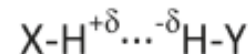
Hydrogen Bond



Lewis acid Lewis base

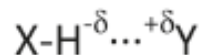
Brønsted acid Brønsted base

Dihydrogen bond



Lewis acid Lewis base

Hydride Bond



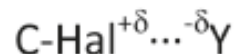
Lewis base Lewis acid

Agostic bond



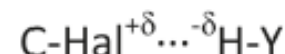
Lewis base Lewis acid

Halogen Bond



Lewis acid Lewis base

Halogen-hydride bond



Lewis acid Lewis base

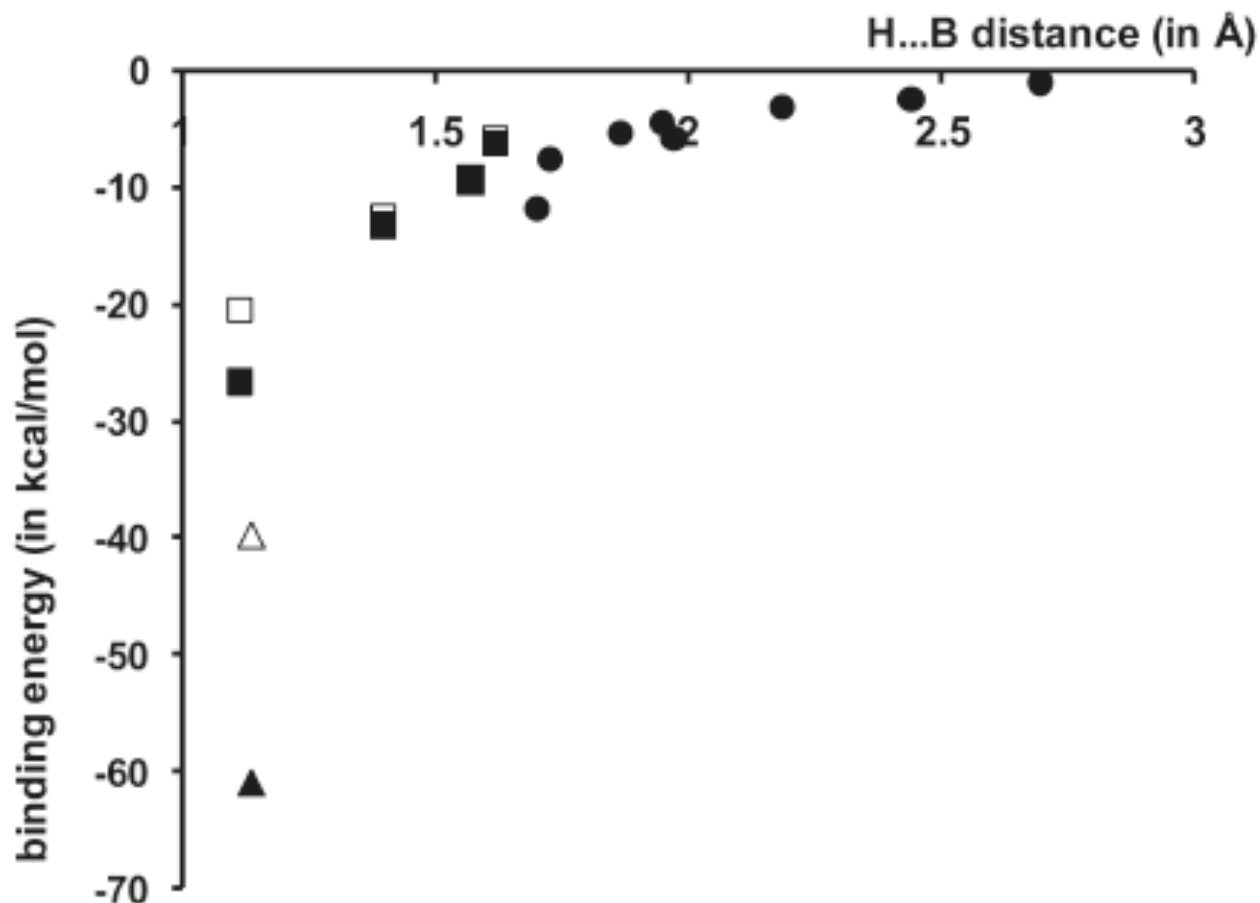
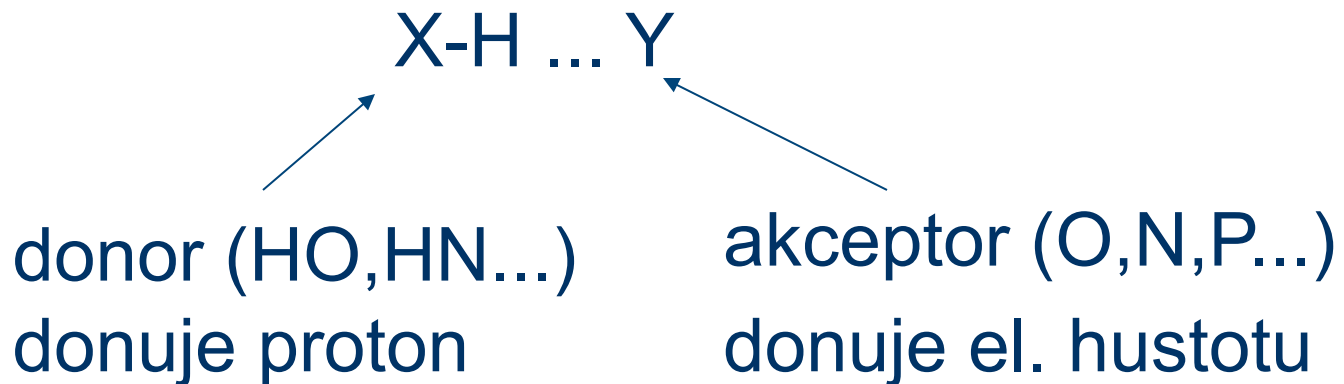


Figure 5. Relationship between the proton–acceptor distance (in Å) and the binding energy (kcal/mol) for complexes of Table 1. Squares correspond to the dihydrogen bonds, triangles to the $(\text{FHF})^-$ system, and circles to the other complexes. Open symbols correspond to the binding energies calculated in such a way that the deformation energy is taken into account, and closed symbols correspond to supermolecular approach where deformation energy is not included. Reprinted with permission from ref 101. Copyright 2005 Wiley Interscience.

Vodíková vazba

- ♦ pomezí mezi nekov. a chemickou vazbou



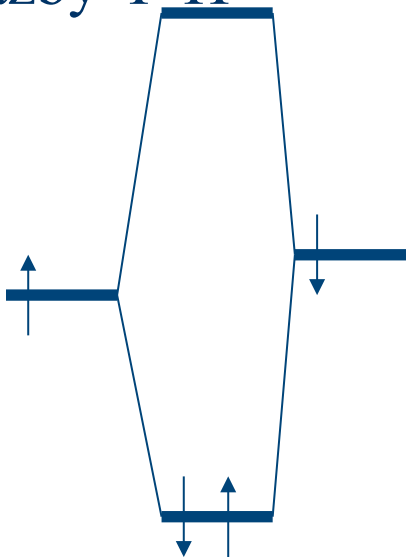
prodloužení X-H vazby, červený posun v IR

$$R(\text{X-H}\dots\text{Y}) \sim r_{\text{vdW}}(\text{X}) + r_{\text{vdW}}(\text{Y})$$

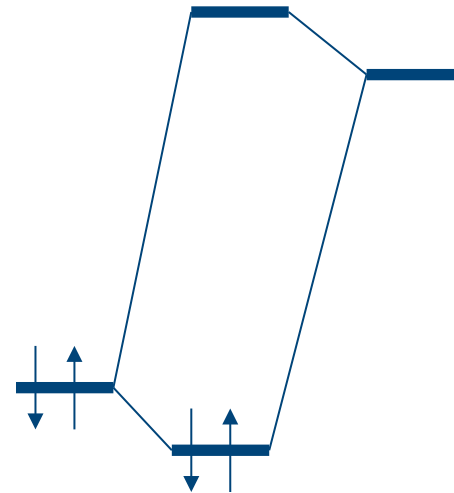
Vodíková vazba

Chemická vazba

elektronová hustota atomu X je donorována do σ^* orbitalu vazby Y-H



Vodíková vazba



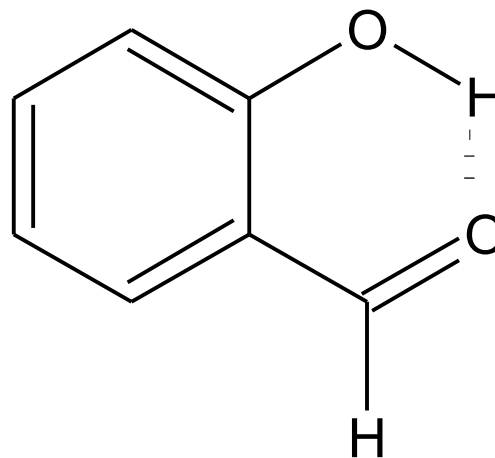
Vodíková vazba

Tabulka 5.2: Interakční příspěvky (v $\text{kJ}\cdot\text{mol}^{-1}$) k nevazebné interakci ve dvou nekovalentních komplexech s vodíkovou vazbou a v jednom s halogenovou vazbou.

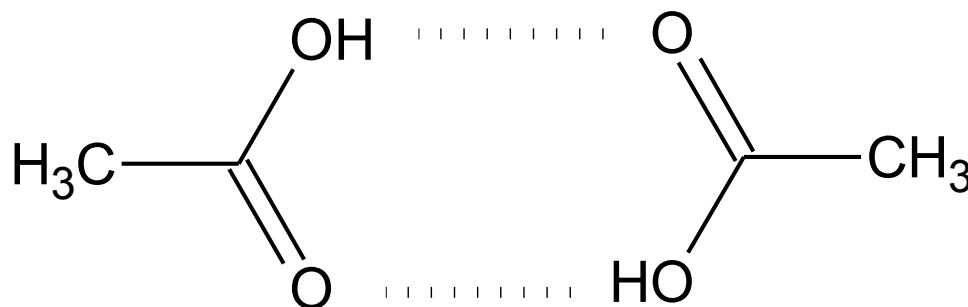
Interakce	$\text{H}_2\text{O}\cdots\text{H}_2\text{O}$	$\text{FH}\cdots\text{FCl}$	$\text{HF}\cdots\text{ClF}$
elektrostatická	-25.8	-10.3	-14.2
indukční	-4.5	-4.5	-2.5
disperzní	-9.2	-4.4	-6.9
repulzní	21.3	10.6	13.6
přenos náboje	-3.7		
celková	-21.9	-8.6	-10.1

Vodíková vazba

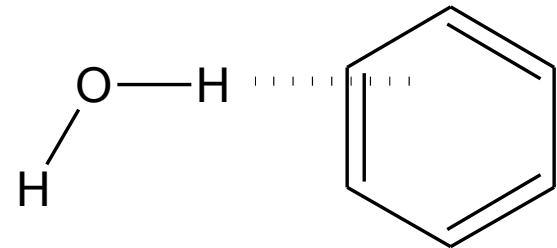
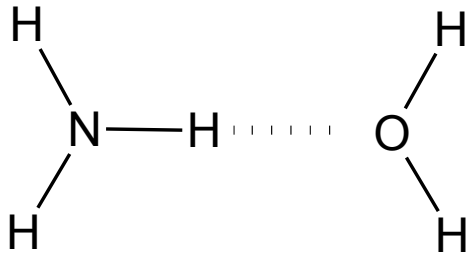
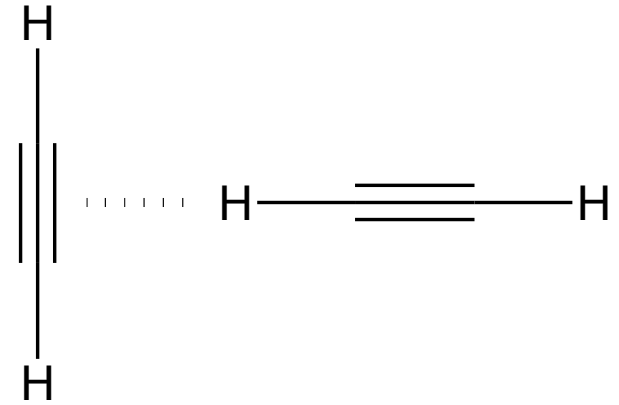
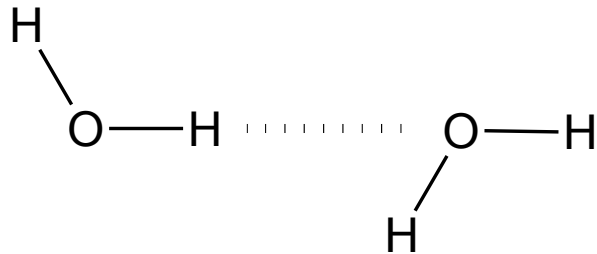
- ◆ intramolekulární



- intrermolekulární

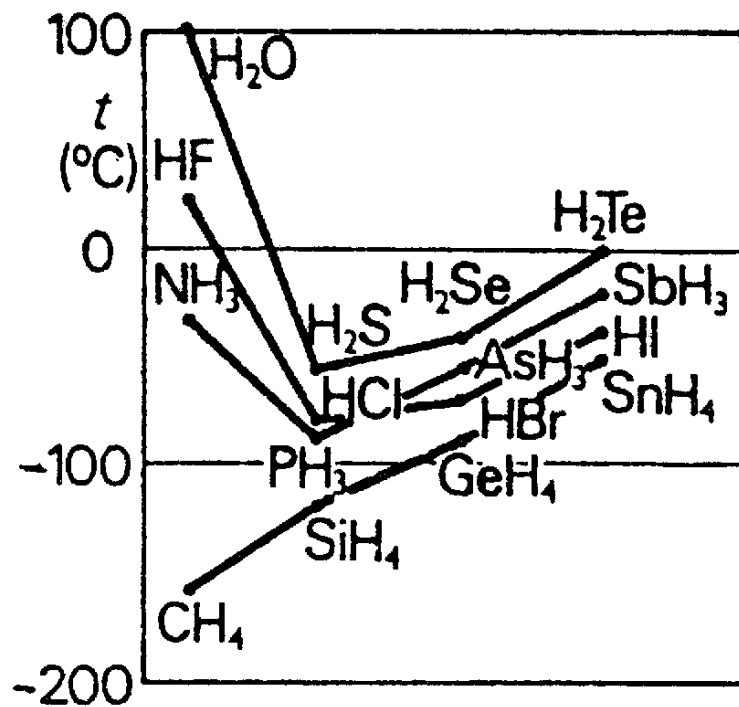
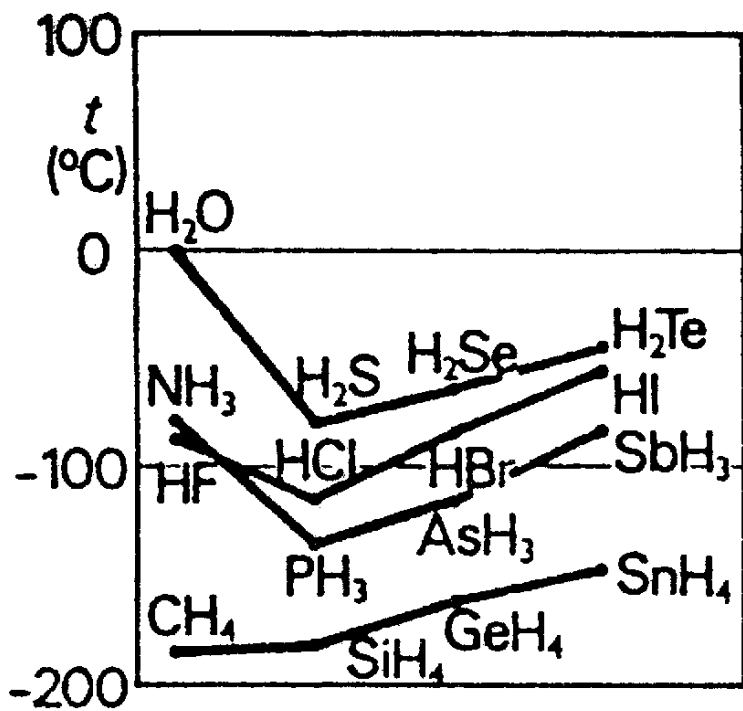


Vodíková vazba



Voda, amoniak a fluorovodík

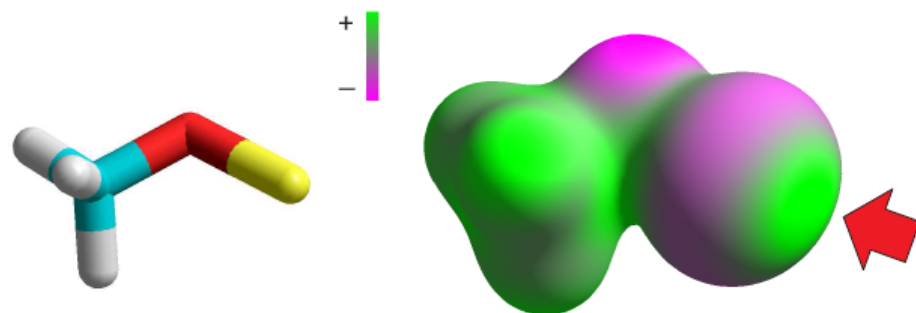
- ◆ anomální teploty tání a varu



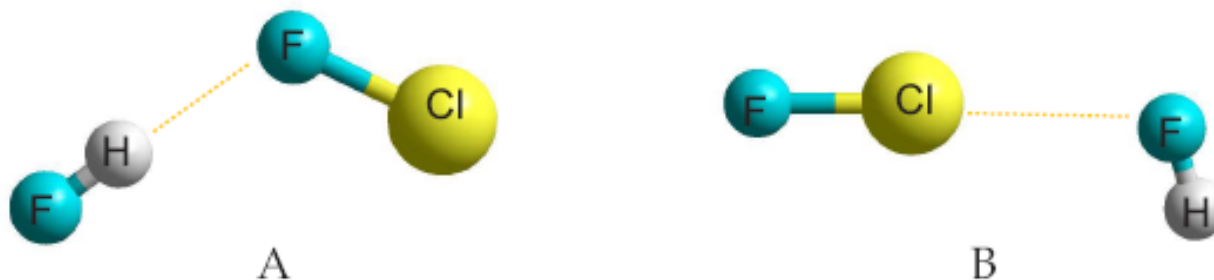
Halogenová vazba

D-X ... Y
X - halogen

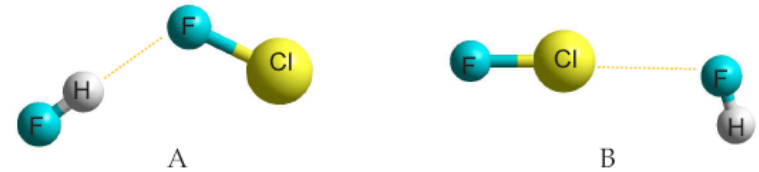
Obrázek 5.6: Molekula CH_3OCl a její elektrostatický potenciál, σ -hole je označena červenou šipkou.



Obrázek 5.7: Dva mezimolekulové komplexy HF s ClF , komplex A se váže vodíkovou vazbou a komplex B halogenovou vazbou.



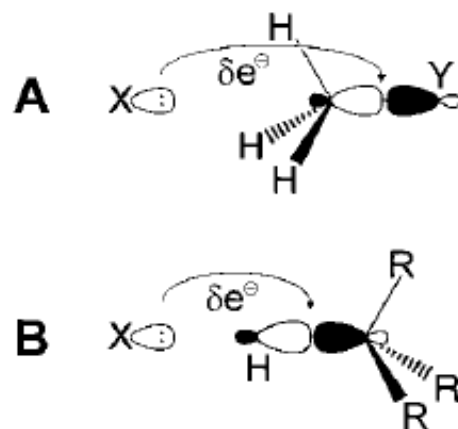
Halogen



Tabulka 5.2: Interakční příspěvky (v $\text{kJ}\cdot\text{mol}^{-1}$) k nevazebné interakci ve dvou nekovalentních komplexech s vodíkovou vazbou a v jednom s halogenovou vazbou.

Interakce	$\text{H}_2\text{O}\cdots\text{H}_2\text{O}$	$\text{FH}\cdots\text{FCl}$	$\text{HF}\cdots\text{ClF}$
elektrostatická	-25.8	-10.3	-14.2
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přenos náboje	-3.7		
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Nepravá vodíková vazba Blue-Shifting H-bond



Chem. Rev. **2000**, *100*, 4253–4264

Blue-Shifting Hydrogen Bonds

Pavel Hobza^{*,†,‡} and Zdeněk Havlas^{‡,§}

Figure 9. Schematic pictures of the electron density transfer (δe^-) in (A) improper, blue-shifting hydrogen-bonded complex and in (B) classical hydrogen-bonded complex. In the former case (A), the main electron density transfer goes from the electron lone pair of X to the C–Y σ^* antibonding orbital, while in the latter case (B), the electron density transfer goes to σ^* antibonding orbital of the C–H bond which is involved in the hydrogen bonding.

Nepravá vodíková vazba

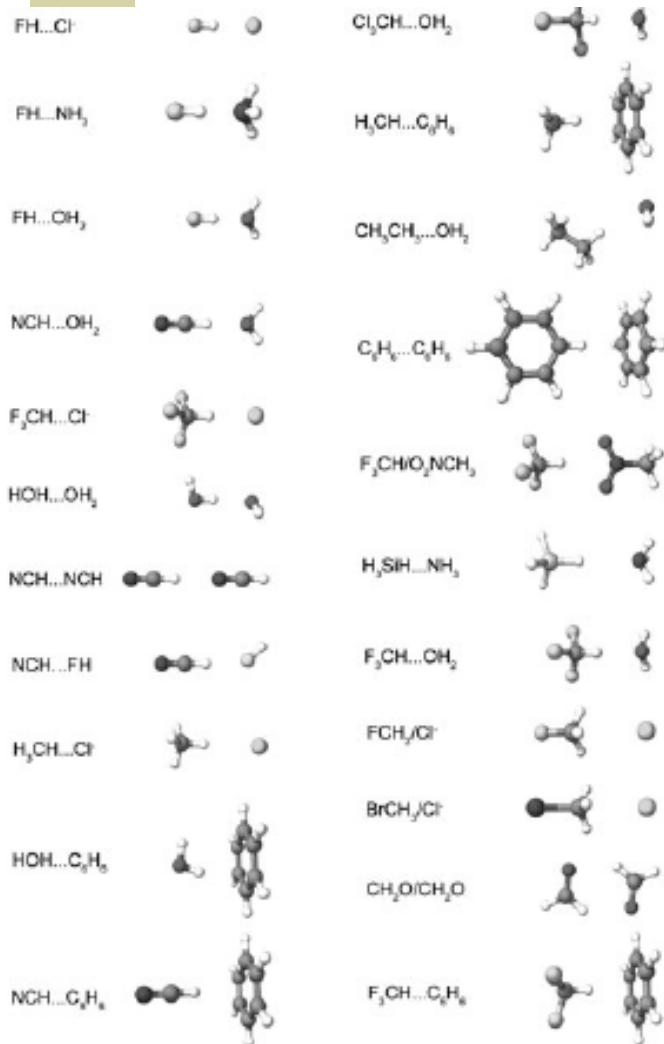
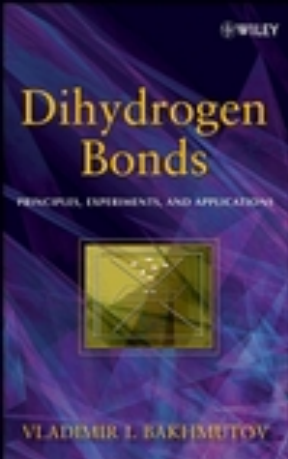


Table 1. Changes of the bond length $\Delta R(X-H)$ [Å] and frequency of stretching vibration $\Delta \nu(X-H)$ [cm^{-1}] in full complexes and in an inhomogeneous electric field in comparison with corresponding data for monomers calculated at the MP2/6-31G(d,p) level.

	Full complex		Electrostatic + polarization effects Electric field		Non-electrostatic effects Full-electric		NE/E ⁰⁰ index g
	$\Delta R(X-H)$	$\Delta \nu(X-H)$	$\Delta R(X-H)$	$\Delta \nu(X-H)$	$\Delta \Delta R(X-H)$	$\Delta \Delta \nu(X-H)$	
	a	b	c	d	e	f	
FH...Cl	0.0372	-774	0.0122	-263	0.0250	-511	2.1
FH...NH ₃	0.0240	-535	0.0046	-143	0.0194	-392	4.2
FH...OH ₂	0.0132	-281	0.0031	-96	0.0101	-185	3.3
NCH...OH ₂	0.0088	-142	0.0036	-65	0.0052	-57	1.4
F ₃ CH...Cl	0.0064	-104	-0.0057	41	0.0121	-145	-2.1
HOH...OH ₂	0.0061	-75	0.001	-16	0.0051	-59	4.3
NCH...NCH	0.0055	-75	0.0013	-25	0.0042	-50	3.2
NCH...FH	0.0036	-48	0.0012	-26	0.0024	-22	2.0
H ₃ CH...Cl	0.0047	-44	0.0011	-13	0.0036	-31	3.3
HOH...C ₆ H ₆	0.0015	-15	0.0009	-9	0.0006	-6	1.5
NCH...C ₆ H ₆	0.0017	-16	0.0016	-15	0.0001	-1	0.1
Cl ₃ CH...OH ₂	-0.0002	8	-0.0023	22	0.0021	-14	-0.9
H ₃ CH...C ₆ H ₆	-0.0005	12	0.0004	-1	-0.0009	13	-2.3
CH ₃ CH ₃ ...OH ₂	-0.0010	8	0.0005	-1	-0.0015	9	-3.0
C ₆ H ₆ ...C ₆ H ₆	-0.0032	49	-0.0006	13	-0.0026	36	4.3
F ₃ CH/O ₂ NCH ₃ ^{(0), (c)}	-0.0037	58	-0.0023	29	-0.0014	29	0.6
H ₃ SiH...NH ₃	-0.0039	18	-0.0033	16	-0.0006	2	0.2
F ₃ CH...OH ₂	-0.0040	55	-0.0045	54	0.0005	1	-0.1
FCH ₃ /Cl ^(d)	-0.0042	59	-0.0047	59	0.0002	0	-0.1
BrCH ₃ /Cl ^(d)	-0.0043	62	-0.0020	28	-0.0023	34	1.15
CH ₃ O/CH ₃ O	-0.0046	54	-0.0046	44	0.0000	10	0.0
F ₃ CH...C ₆ H ₆	-0.0052	86	-0.0024	29	-0.0028	57	1.2

Figure 1. Structures of investigated complexes which display red shifts (left column) and blue shifts (right column).



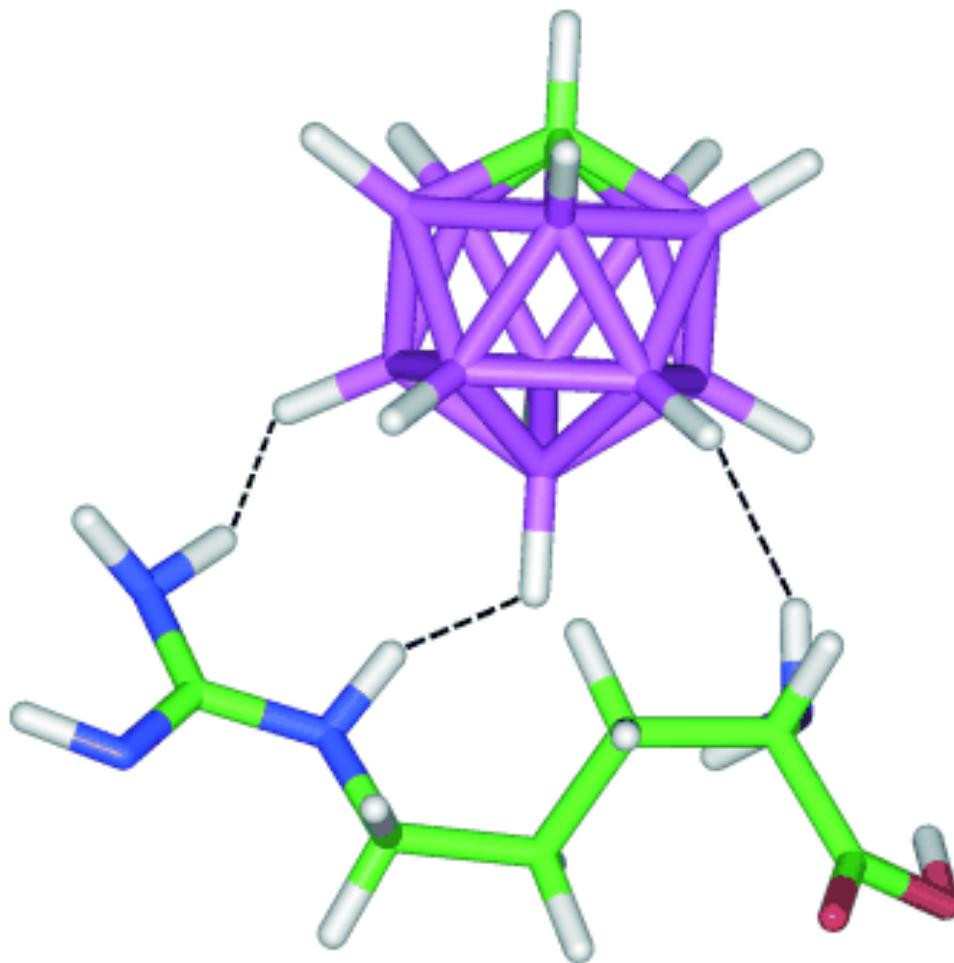
Dvojvodíková vazba Dihydrogen bond

Among the various nonconventional hydrogen bonds, dihydrogen bonds are the most unusual and intriguing. These bonds are formed between two hydrogen atoms, the first positively charged and acting as a proton-donor component, the second negatively charged and acting as a proton-acceptor site:

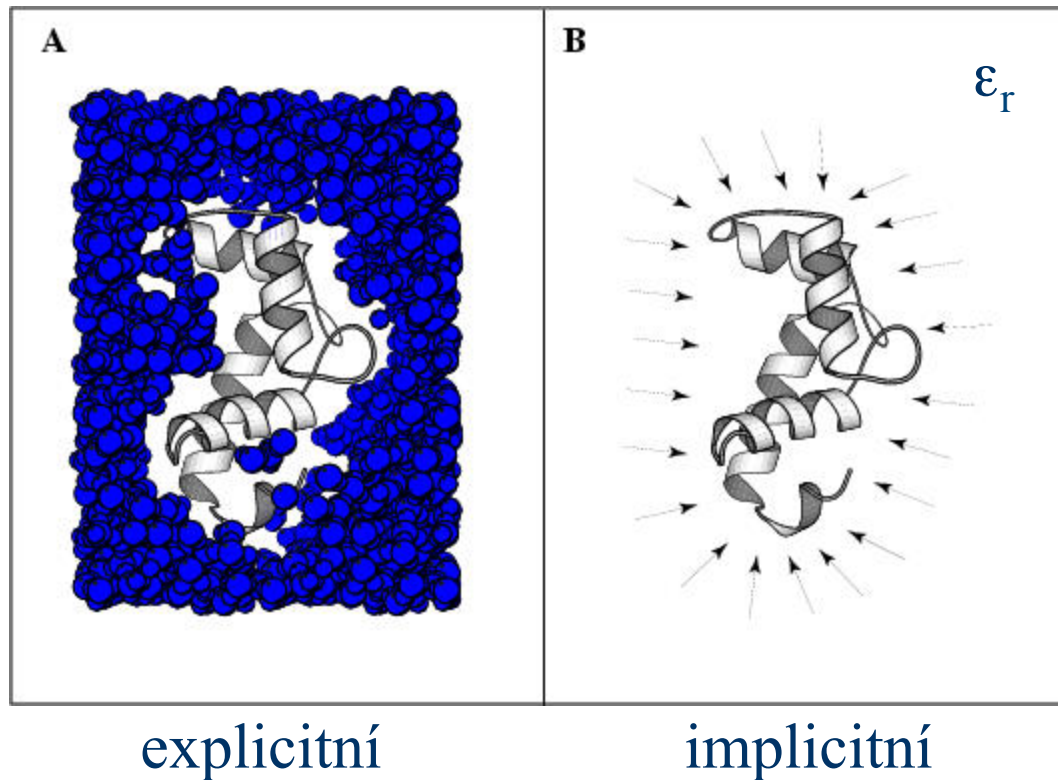


The first reliable data on the existence of such bonds within crystal structures came from the mid-1990s [9], when Wessel and co-workers reported on the unusually-short intermolecular contacts $\text{B}-\text{H} \cdots \text{H}-\text{N}$. Nowadays, studies in this fast-developing field involve a large number of chemical elements participating in the bonding quartet $\text{X}-\text{H} \cdots \text{H}-\text{Y}$. It is clear now that this unusual bonding plays an important role as an organizing interaction in molecular architecture (intramolecular dihydrogen bonds), in molecular aggregations (intermolecular dihydrogen bonds), and in the reaction ability of molecules.

Dvojvodíková vazba



Solvatace



Definice povrhu

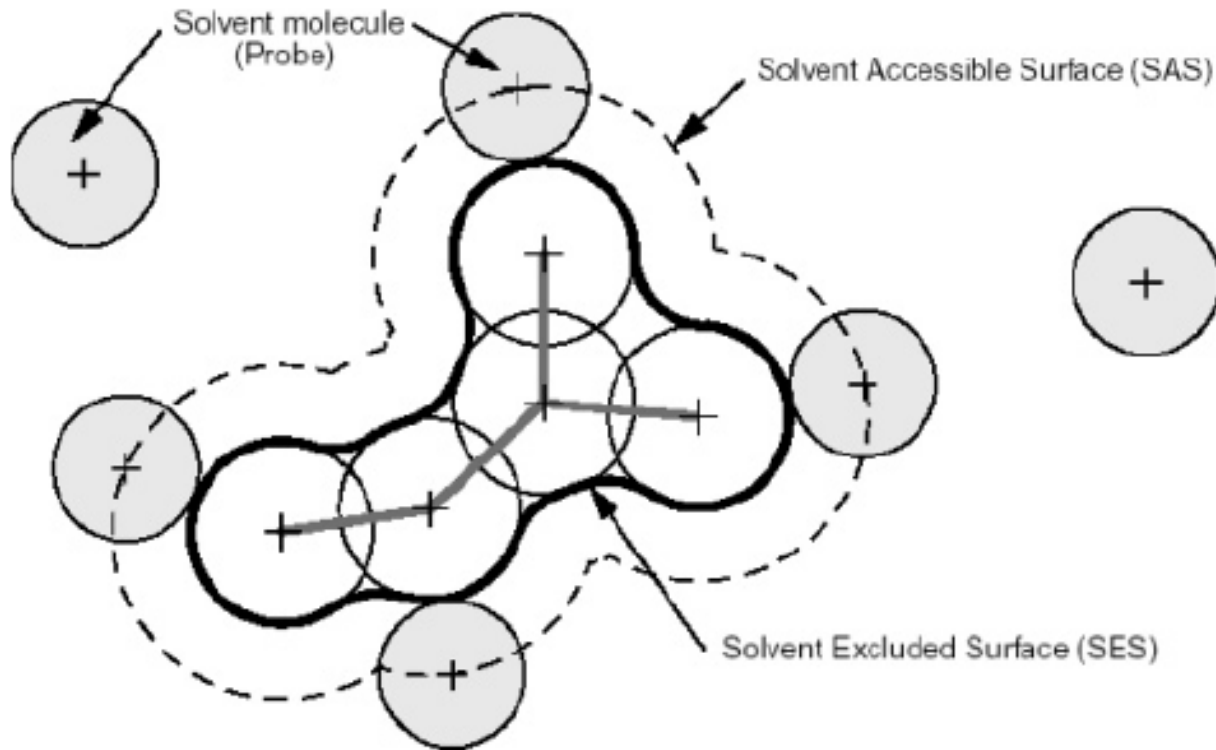


Figure 1. Solvent accessible surface (SAS) traced out by the center of the probe representing a solvent molecule. The solvent excluded surface (SES) is the topological boundary of the union of all possible probes that do not overlap with the molecule.

Implicitní modely

- ◆ Implicit models treat the solvent as a continuous medium having the average properties of the real solvent, and surrounding the solute beginning at the van der Waals surface.
- ◆ The generalized Born (GB), Surface Area (SA) model is very popular.
- ◆ In the GB/SA model, the total solvation free energy G_{solv} is given as the sum of a solvent-solvent cavity term (G_{cav}), a solute-solvent van der Waals term (G_{vdW}), and a solute-solvent electrostatics polarization term (G_{pol})

$$G_{solv} = G_{cav} + G_{vdW} + G_{pol} \quad G_{cav} + G_{vdW} = \sum_{k=1}^N ASP(k)ASA(k)$$

where $ASA(k)$ is the total solvent accessible surface area of atom k and $ASP(k)$ is an empirically determined atomic solvation parameter.

$$G_{pol} = -166.0 \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{\sqrt{r_{ij}^2 + b_i b_j} \exp\left(-\frac{r_{ij}^2}{4b_i b_j}\right)}$$

where the double sum runs over all pairs of atoms (i and j). q_i and q_j are the partial charges of i and j , respectively, and r_{ij} is the i,j th atom pair separation. ϵ is the dielectric constant of the medium. b_i and b_j are the so-called Born radius of atom i and j , respectively.

Implicitní modely - QM

- ◆ Neporušený systém

$$E_{\text{HF}}^0 = \langle \Psi_{\text{HF}} | \hat{H}^0 | \Psi_{\text{HF}} \rangle$$

- ◆ Se solvatací

$$G_{\text{HF}}^{\text{S}} = \left\langle \Psi_{\text{HF}} \left| \hat{H}_{\text{eff}} - \frac{1}{2} \hat{V}_{\text{int}} \right| \Psi_{\text{HF}} \right\rangle$$

Chem. Rev. 2005, 105, 2999–3093

Quantum Mechanical Continuum Solvation Models

Jacopo Tomasi,^{*,†} Benedetta Mennucci,[†] and Roberto Cammi[‡]

Ukázka z Gaussianu

Self-consistent PCM results
=====

```
<psi(f) | H |psi(f)> (a.u.) = -99.577537 (A)
<psi(f) |H+V(f)/2|psi(f)> (a.u.) = -99.584002 (B)
(Polarized solute)-Solvent (kcal/mol) = -4.06 (C)
```

Partition over spheres:

Sphere	on Atom	Surface	Charge	GE1	GCav	GDR
1	H1	15.27	-0.157	-2.36	0.00	0.00
2	F2	32.58	0.157	-1.70	0.00	0.00

Predicted energy value for external iteration and state-specific SRCF calculations

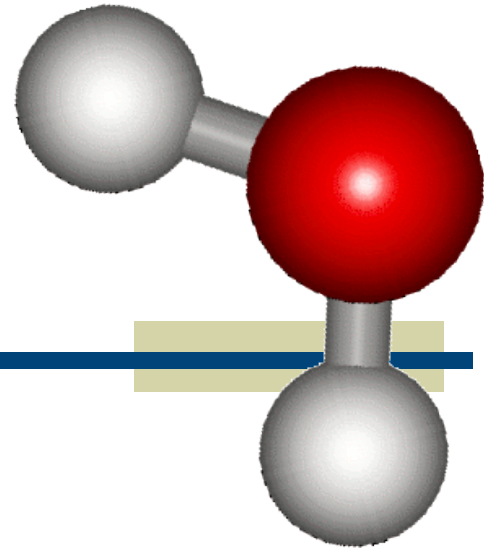
After PCM corrections, the energy is -99.5840023899 a.u.

Line (A) reports the energy computed using the polarized solute wavefunction and the gas phase Hamiltonian, line (B) reports energy computed using the polarized solute wavefunction and the Hamiltonian in solution, line (C) reports the interaction energy between the polarized solute and the solvent, which corresponds to the integral $\langle \Psi(f) | V(f)/2 | \Psi(f) \rangle$ (in kcal/mol), and the final line reports the predicted energy incorporating all PCM corrections.

Explicit models

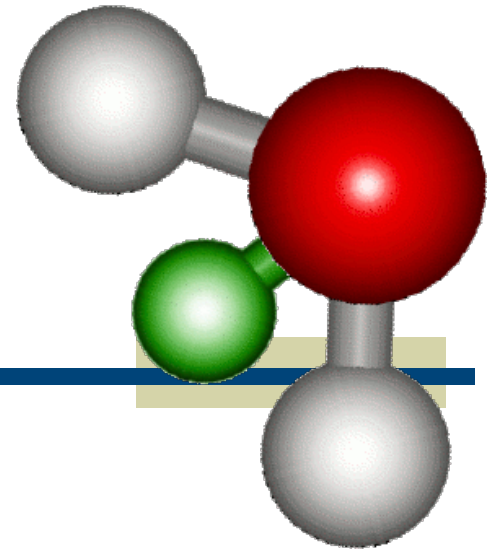
- ◆ rigid models (fixed atom positions)
- ◆ flexible models (include bond stretching & angle bending)
- ◆ polarizable models (include explicit polarization term)
- ◆ planar
- ◆ steric

3-SITE



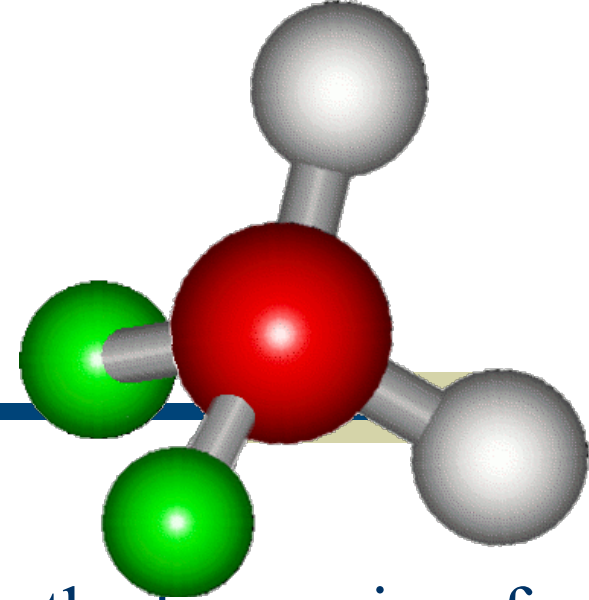
- ◆ planar & rigid
- ◆ three interaction sites
- ◆ each atom gets assigned a point charge
- ◆ TIP3P (Jorgensen, 1983)
- ◆ SPC/E (Berendsen, 1987)
- ◆ POL3 (Caldwell & Kollman, 1995)

4-SITE



- ◆ planar & rigid
- ◆ the negative charge near the oxygen along the bisector of the HOH angle
- ◆ TIP4P (Jorgensen, 1983)

5-SITE



- ◆ the negative charge representing the lone pairs of the oxygen atom
- ◆ tetrahedral & rigid
- ◆ TIP5P (Jorgensen & Mahoney, 2000)

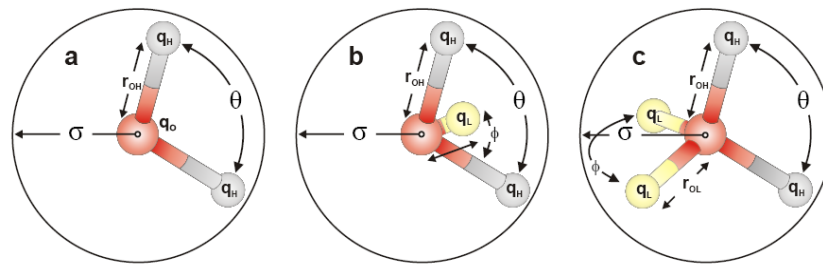
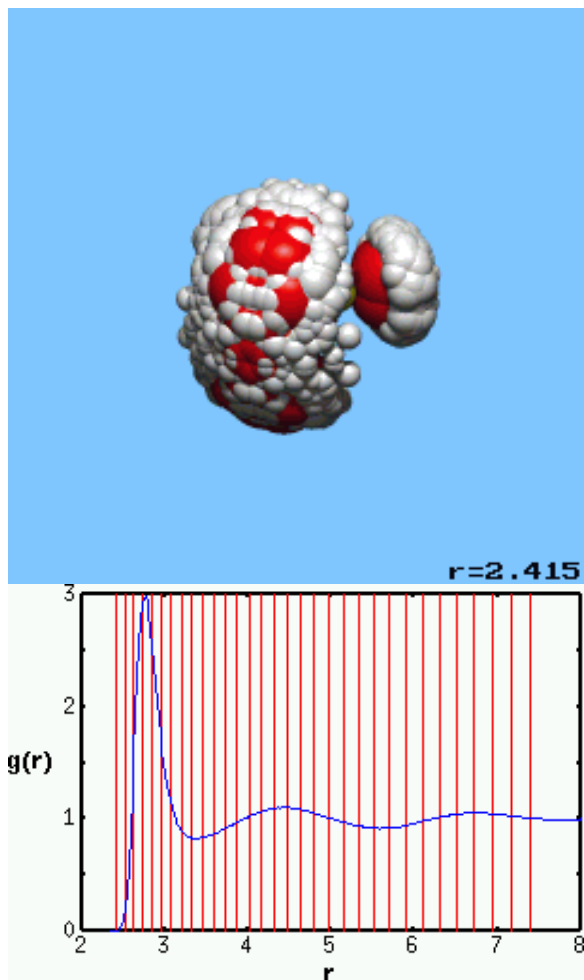


Table 1. Parameters of the explicit water models studied, as used in the AMBER package (*cf* Figure 1).

Parameter (units)	TIP3P	TIP4P	TIP5P	SPC/E
q_H^a (e)	0.417	0.520	0.241	0.424
q_O^b (e)	-0.834	0.0	0.0	-0.848
q_L^c (e)	-	-1.040	-0.241	-
r_{OH}^d (Å)	0.9572	0.9572	0.9572	1.0
r_{OL}^e (Å)	-	0.15	0.70	-
Θ_{HOH}^f (deg)	104.52	104.52	104.52	109.47
Φ_{LOL}^g (deg)	-	-	109.47	-
ϵ^h (kcal/mol)	0.1521	0.155	0.16	0.1554
σ_O^i (Å)	3.15061	3.15365	3.12	3.1656

^{a, b, c} q_H , q_O , q_L are charges on hydrogen, and oxygen atoms and on the lone-pair sites (L), respectively. ^{d, e} r_{OH} , r_{OL} are distances between the oxygen and hydrogen, and between oxygen and L, respectively. ^{f, g} Θ_{HOH} , Φ_{LOL} the angles “formed” between hydrogen, oxygen, and hydrogen, and between L, oxygen, and L, respectively. ^{h, i} ϵ , σ are the Lennard-Jones parameters.

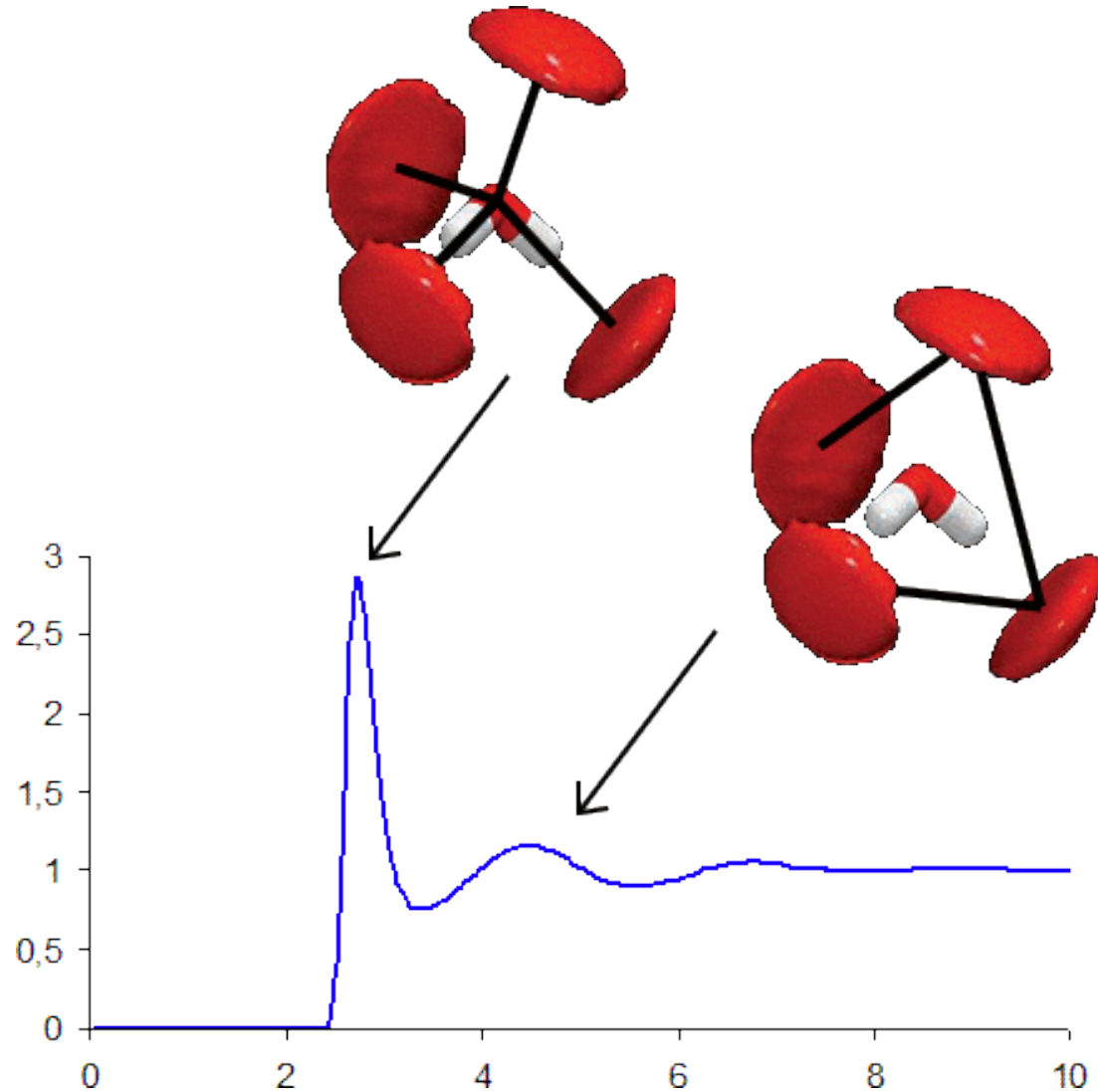
Analýza – co je RDF?



Bunches of red oxygens and white hydrogens show the probability that a water molecule at certain distance r from the fixed (blue and yellow) molecule will have given relative position and orientation. The animation is thus an attempt to visualize the full pair correlation function. This function is six-dimensional: one distance r and five angular variables. We have measured this function during a 300 ps simulation of 500 TIP4P water molecules at $T=25^\circ\text{C}$ and ambient density.

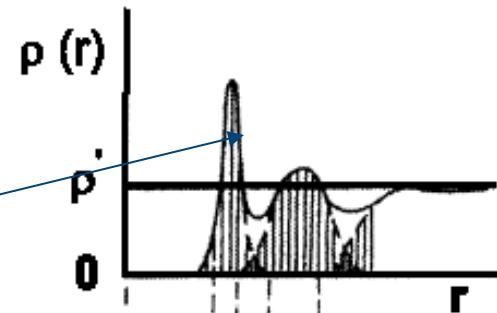
The histograms were taken by 15° in each angular variable (with the exception of regions close to the poles). The r -coordinate is identified with time, i.e., each frame corresponds to a selected distance (shown in red in the graph of the O-O pair correlation function). For this distance, one molecule from the pair is fixed, and around it 8000 positions of water molecules with highest probability are drawn with diameters proportional to the probability. See also the [water page](#).

Radial distribution function

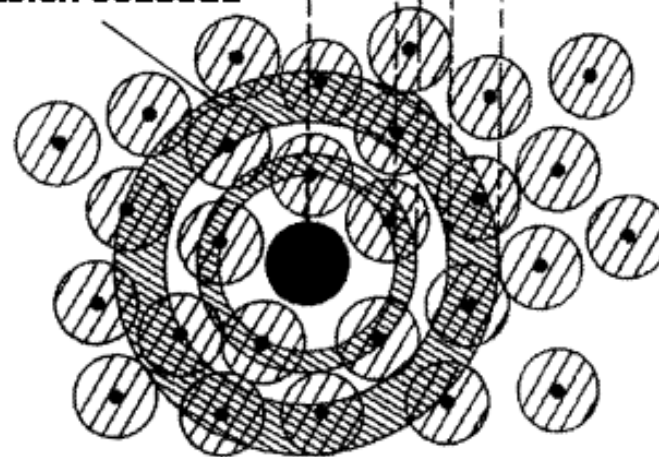


Radiální Distribuční Funkce

v systému solut-solvent – první solvatační sféra

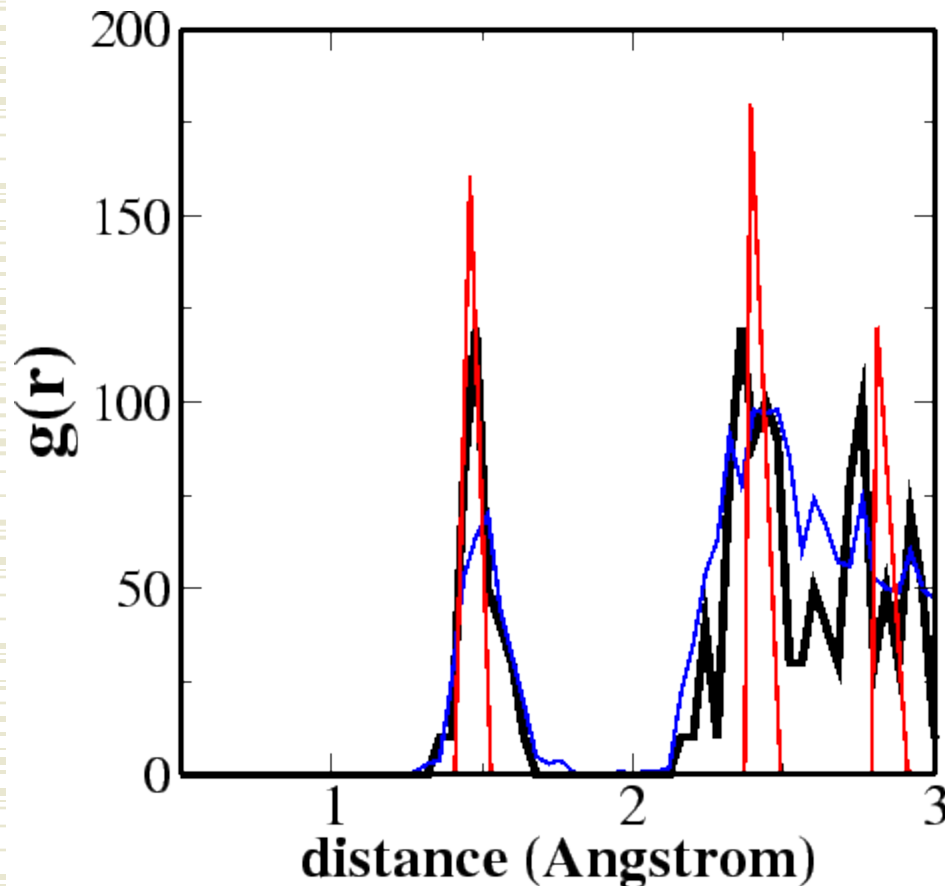


vrstvy nejbližších sousedů



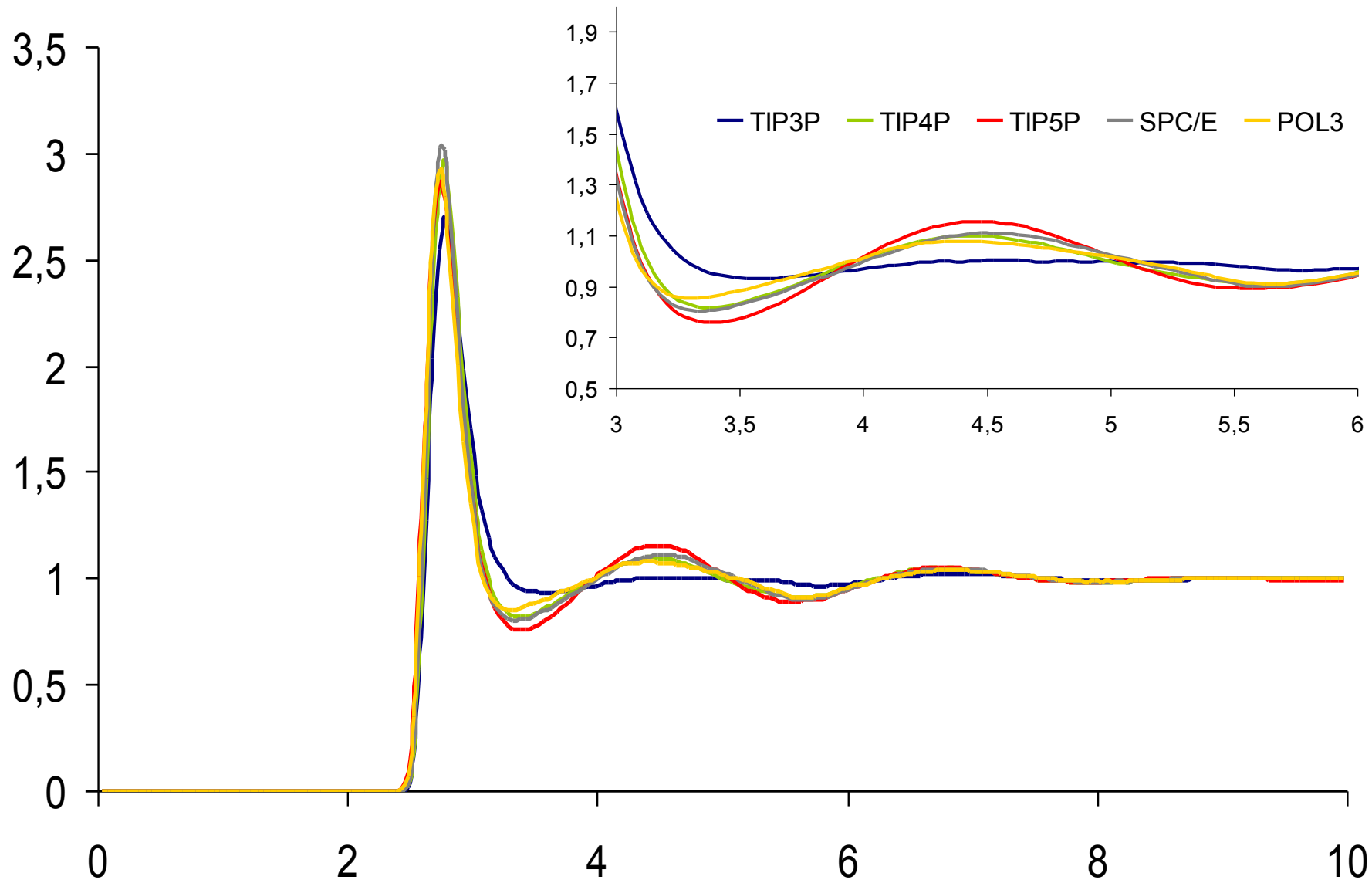
strukturní faktor je spojen s Fourierovou transformací RDF

RDF - crystal



Radial distribution function of the diamond cluster (black line) compared with the radial distribution functions of a **pure diamond crystal** (red line) and of amorphous carbon (blue line).

Radial distribution function – 1 atm



Explicit water models

	Dipole moment	Dielectric constant	Self diffusion [10 ⁻⁵ cm ² /s]	Density maximum [°C]	Melting temperatures [°C]
SPC/E	2.4	71	2.5	-38.0	-58.2
TIP3P	2.4	82	5.2	-91.0	-127.6
TIP4P	2.2	53	3.3	-25.0	-40.7
TIP5P	2.3	81.5	2.6	+4.0	0.8
Expt.	2.95	78.4	2.3	+3.984	0

TIP3P byl parametrizován pro cutoff, při použití PME se zvyšuje D, reparametrizaci navrhl Brooks (J. Chem. Phys. 121 (20), 10096, **2004**)

Cost of computation

- ◆ TIP3P 100%
- ◆ SPC/E ~101%
- ◆ TIP4P ~140%
- ◆ TIP5P ~240%
- ◆ POL3 ~1230%



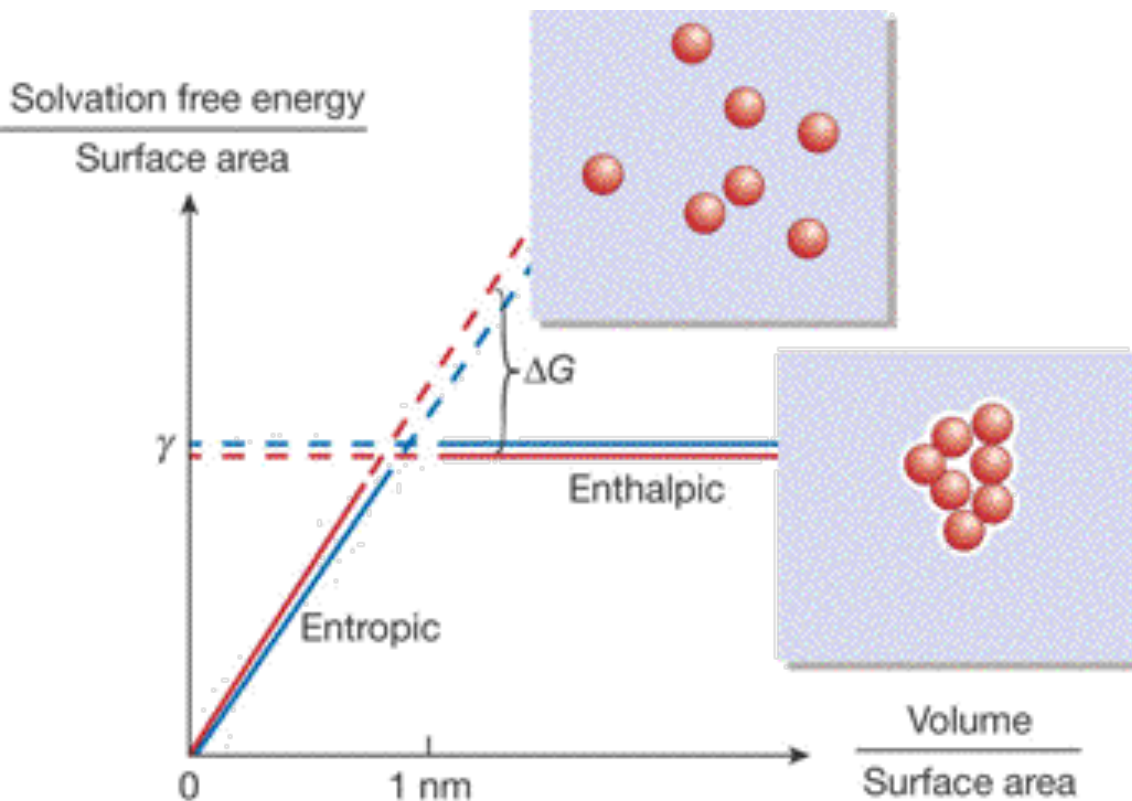
Hydrofóbní efekt



Hydrophobic effect

- ◆ The hydrophobic effect is fundamentally based on the tendency of (polar) water molecules to exclude non-polar molecules.
- ◆ At the molecular level, the hydrophobic effect is an important force that drives protein folding, formation of the lipid bilayer, insertion of membrane proteins to the nonpolar lipid environment and protein-small molecule interactions.

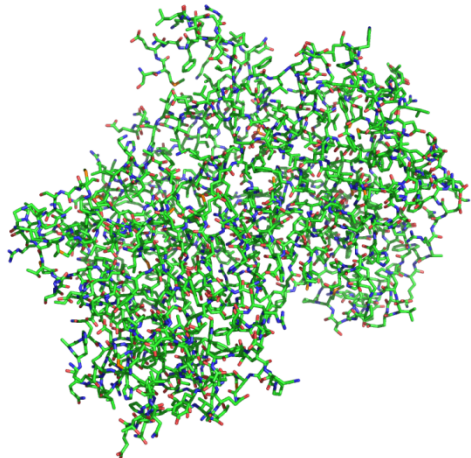
Hydrofóbní efekt



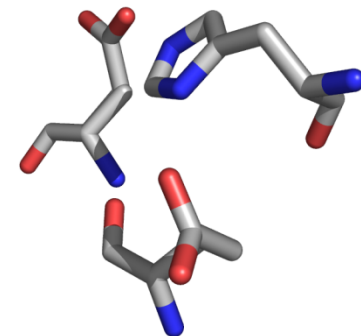
For large enough clusters, ΔG is a favourable driving force. The horizontal and sloping lines indicate the behaviour of the solvation free energy for the assembled and disassembled cluster, respectively. Red lines indicate the free energies at a higher liquid temperature; blue lines indicate the free energies at a lower temperature. The liquid–vapour surface tension is indicated by γ . 'Volume' and 'surface area' denote the volume excluded to water, and the solvated surface area of that volume, respectively. (Adapted from Chandler, D., "Insight Review: Interfaces and the driving force of hydrophobic assembly" Nature 437, 640-647 (2005).)

Studium nekovalentních interakcí

- ◆ Vyžaduje velmi přesné metody kvantové chemie
- ◆ Co dělat v případě biomolekul?
 - Hybridní metody (QM/MM)
 - Semiempirické výpočty
 - Empirické potenciály
- ◆ Aplikace: např. drug design



Kompromis



MM

LDA

GGA

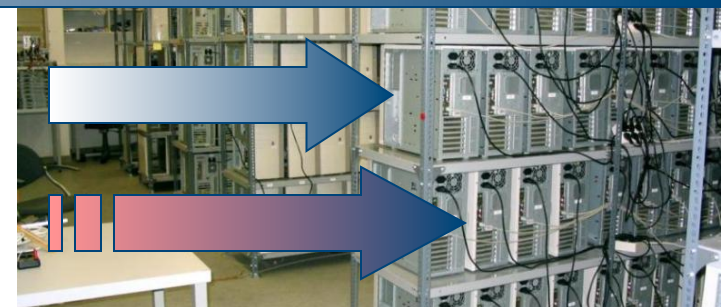
hybridní DFT

MP2

CCSD(T)

spolehlivost metody

výpočetní nároky metody



100.000

10.000

1.000

100

10

dostupná velikost modelu

**reprezentativní model
velmi aproximativní metoda**

**nevhodný model
velmi spolehlivá metoda**

Kenneth M. Merz, Jr.*

Termodynamický cyklus

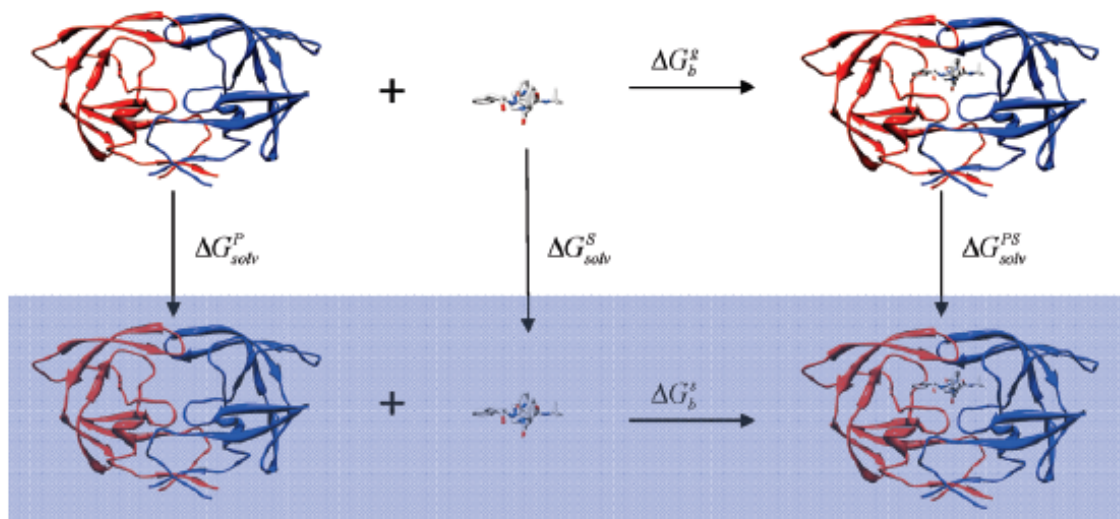


Figure 1. Thermodynamic cycle to estimate the free energy of binding of a drug molecule to a protein receptor. P = Protein, S = small molecule/substrate, and PS = protein-small molecule/substrate complex.

Protein–Ligand Binding Free Energies. Consider the standard thermodynamic cycle shown in Figure 1.^{15,18} Using this, we can write the following standard expressions:

$$\Delta G_b^s = \Delta G_b^g + \Delta G_{solv}^{PS} - \Delta G_{solv}^P - \Delta G_{solv}^S \quad (2)$$

where ΔG indicates free energy changes in the gas-phase (ΔG^g) or solution (ΔG^s), and the subscript b denotes binding. Terms associated with changes in the solvation free energy are also indicated by solv. What we want to do next is to

Termodynamický cyklus

briefly outline below. Expanding out the free energy of binding in the gas-phase term and consolidating the solvation free energies, we can write:

$$\Delta G_b^s = (E_{\text{total}}^{\text{PS}} + H_{\text{corr}}^{\text{PS}}) - TS^{\text{PS}} - ((E_{\text{total}}^{\text{P}} + H_{\text{corr}}^{\text{P}}) - TS^{\text{P}} + (E_{\text{total}}^{\text{S}} + H_{\text{corr}}^{\text{S}}) - TS^{\text{S}}) + \Delta\Delta G_{\text{sol}} \quad (3)$$

where the E_{total} terms are the individual electronic energies, H_{corr} are the individual enthalpy correction terms to the electronic energies, and the S terms are the respective the entropies. The latter two terms can be computed using the rigid-rotor harmonic approximation.^{19,20} $\Delta\Delta G_{\text{sol}}$ is given as:

$$\Delta\Delta G_{\text{sol}} = \Delta G_{\text{solv}}^{\text{PS}} - \Delta G_{\text{solv}}^{\text{P}} - \Delta G_{\text{solv}}^{\text{S}} \quad (4)$$

and the individual terms can be obtained from explicit or implicit solvation models or experiment.^{21,22} Rearranging and collecting terms together that represent the change in the total energy, enthalpy, and entropy, respectively, we obtain:

$$\Delta G_b^s = (E_{\text{total}}^{\text{PS}} - (E_{\text{total}}^{\text{P}} + E_{\text{total}}^{\text{S}})) + (H_{\text{corr}}^{\text{PS}} - (H_{\text{corr}}^{\text{P}} + H_{\text{corr}}^{\text{S}})) - (TS^{\text{PS}} - (TS^{\text{P}} + TS^{\text{S}})) + \Delta\Delta G_{\text{sol}} \quad (5)$$

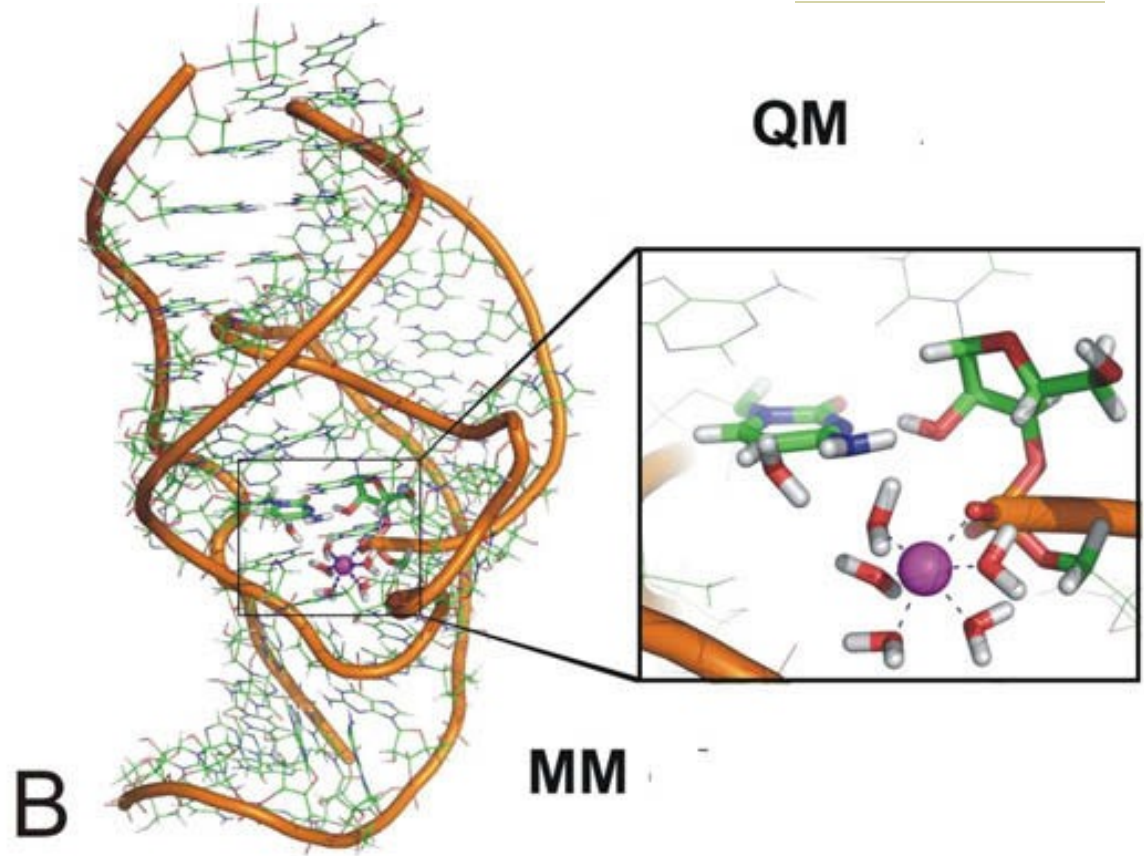
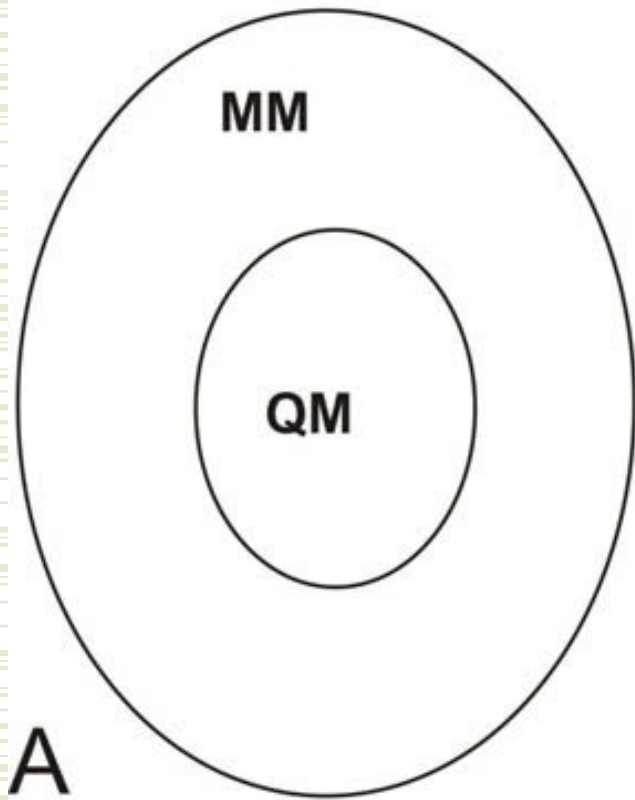
which, when consolidated, leads us to a compact representation²³ of the four key terms we have to evaluate in order to obtain the free energy of binding of a ligand to a protein in aqueous solution:

$$\Delta G_b^s = \Delta E_{\text{int}}^{\text{PS}} + \Delta H_{\text{corr}}^{\text{PS}} - T\Delta S^{\text{PS}} + \Delta\Delta G_{\text{sol}} \quad (6)$$

where the first three of the individual terms are defined as:

$$\begin{aligned} \Delta E_{\text{int}}^{\text{PS}} &= E_{\text{total}}^{\text{PS}} - (E_{\text{total}}^{\text{P}} + E_{\text{total}}^{\text{S}}) \\ \Delta H_{\text{corr}}^{\text{PS}} &= H_{\text{corr}}^{\text{PS}} - (H_{\text{corr}}^{\text{P}} + H_{\text{corr}}^{\text{S}}) \\ T\Delta S^{\text{PS}} &= TS^{\text{PS}} - (TS^{\text{P}} + TS^{\text{S}}) \end{aligned} \quad (7)$$

QM/MM



QM/MM

◆ aditivní vs. subtraktivní schéma

known as additive and subtractive approaches. In the additive scheme, the total energy of the system is represented as a sum of the QM energy of the QM core, E_{QM} , the MM energy of the MM region (without the QM core), E_{MM} , and the interaction between both regions, $E_{QM/MM}$:

$$E_{tot} = E_{QM} + E_{MM} + E_{QM/MM}, \quad (2)$$

The subtractive scheme [31–33] was originally called integrated molecular-orbital molecular mechanics (IMOMM) but is more frequently known as ONIOM (abbreviated from the original name: Our own N-layered Integrated molecular Orbital + molecular Mechanics) scheme. It divides the system into layers and subtracts double counted energies of the smaller layer as follows:

$$E_{tot} = E_{real}^{MM} + E_{model}^{QM} - E_{model}^{MM}, \quad (3)$$

where E_{real}^{MM} represents energy of the whole real system (containing both the QM and MM regions) as calculated by the lower-level method, typically MM, E_{model}^{QM} is energy of the QM core calculated at a higher level, typically a QM method, and E_{model}^{MM} is the energy of the QM core calculated at the lower MM level. Subtractive and additive schemes are in principle equivalent, differing just in the technical details of their implementation.

Calculation of free energy barrier

- ◆ Empirical potentials (MM)
 - Empirical valence bond (EVB), pioneered by Warshel and Weiss (JACS 1980, 102, 6218)
 - broadly used
 - parametrization

$$k = \gamma \left(\frac{k_B T}{h} \right) \exp \left(- \frac{\Delta G^\ddagger}{k_B T} \right)$$

- ◆ Nonempirical potentials (QM)
 - Now, impractical
 - Future, RI-DTF+D
- ◆ Combined QM/MM
 - Warshel and Levitt (JMB 1976, 103, 227)

QM/MM

- ◆ QM
 - HF, RI-MP2, CC
 - DFT
 - RI-DFT (LSDA, GGA)
 - Hybrid B3LYP, MPW1K
- ◆ MM
 - AMBER – parmXY
 - Explicit water molecules (TIP3P, SPC/E)
- ◆ QM-MM
 - QM – capping (-H)
 - QM-MM: mechanical, electronic embedding

QM/MM – Free energies

- ◆ Robust sampling
 - Umbrella sampling
 - Free energy perturbation
- ◆ Classical dynamics on QM/MM potential
- ◆ Hand-in-Hand evolution
 - CPMD
 - ADMP