Can continuum solvation models describe solvation?

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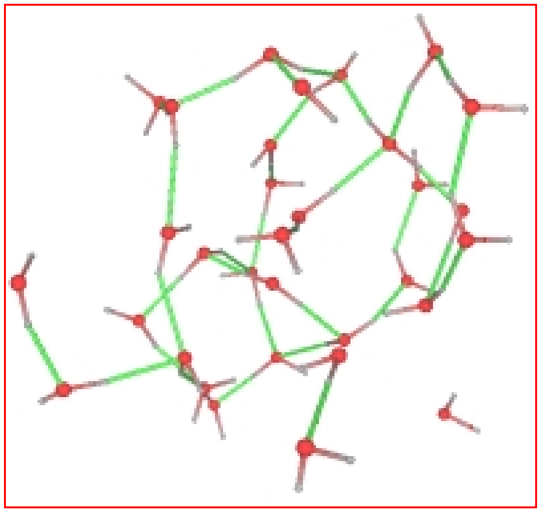
From isolated molecules to condensed phases: a different complexity

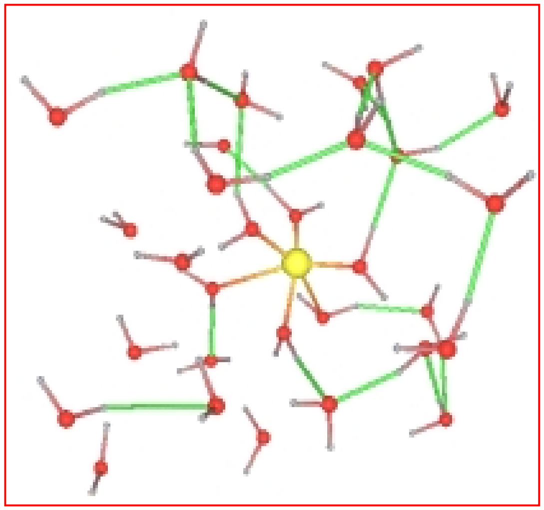
Isolated molecule → In the condensed phase

accurate QM approaches → approximate models

From condensed phases to solvated molecules: a step back in the degree of complexity



A condensed phase



A solvated molecule

Molecules in solution: which approach?

Discrete models

Dimension? → Force Fields ⇔ Necessity of parameterization; often non polarizable; problems with long-range interactions

Average? → Explicit ⇔ Time consuming

Continuum models

Dimension? → Same as in gas-phase

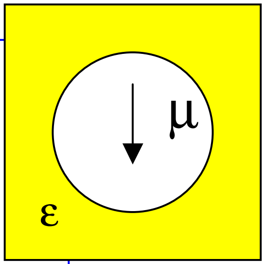
Average? → Implicit

⇔

- ✓ No force fields
- ✓ Polarizable
- ✓ Complete inclusion of long-range interactions
- ✓ Computationally cheap

The origin of continuum approaches: The Onsager Model

- A dipole (the solute) at the center of a sphere in a continuum dielectric.
- The dipole polarizes the surrounding medium which induces back an electric field inside the sphere (reaction field).



Solvent reaction

$$\phi_{RF} = \frac{2(\varepsilon - 1)\mu}{(2\varepsilon + 1)a^3}$$

Electrostatic free energy of solvation

$$\Delta G_{elec} = \frac{-\phi_{\mathrm{RF}}\mu}{2} = -\frac{(\varepsilon - 1)\mu^2}{(2\varepsilon + 1)a^3}$$

Limitations:

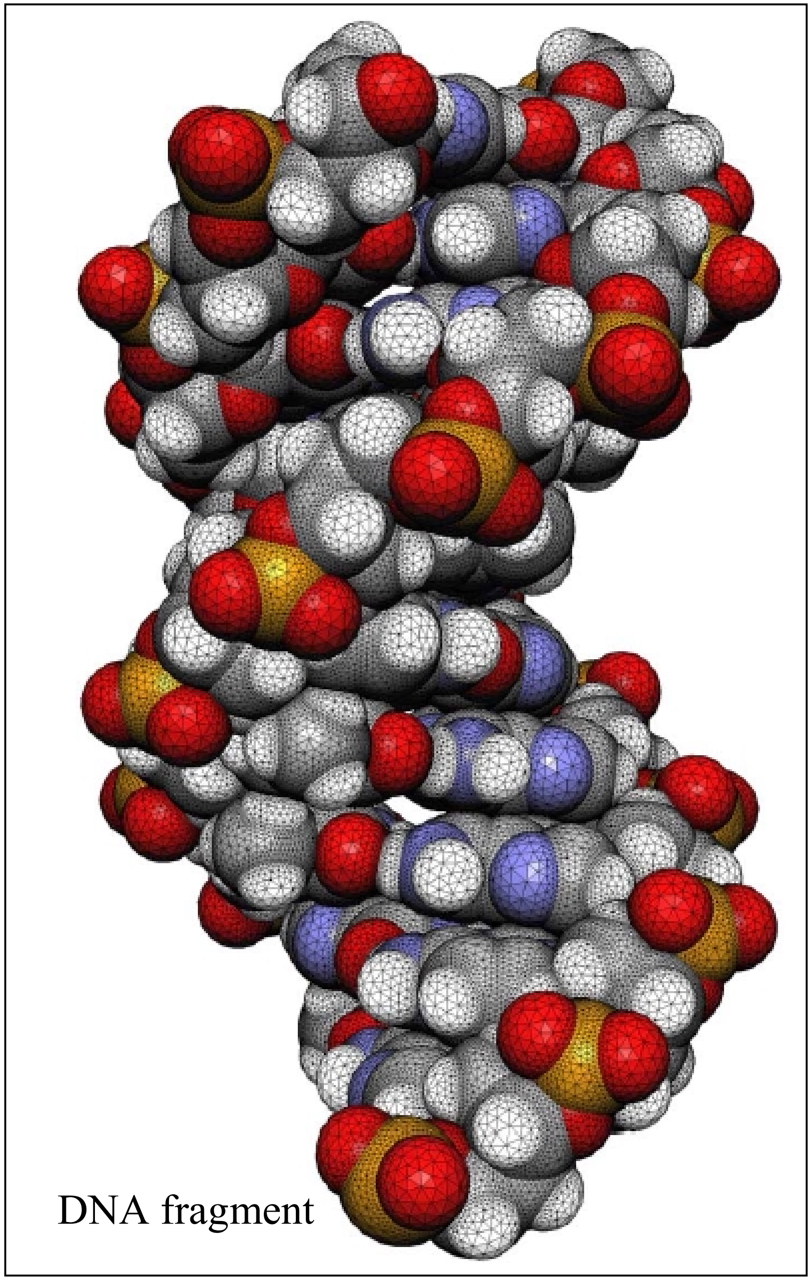
1. Simplified cavity (sphere or ellipse)
2. Dipolar representation of solute
3. Homogeneous and isotropic solvents only

Towards a more realistic approach: the molecular cavity

A realistic cavity should be modeled on the 3D structure of the solute system

⬇

Overlapping spheres centered on the nuclei forming the solute

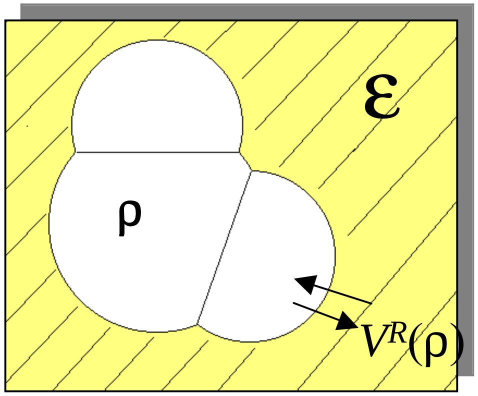


DNA fragment

Towards a more realistic approach: the Polarizable Continuum Model (PCM)

A general charge density ρ in a cavity within a continuum medium with permittivity ε:

$$\begin{cases} -\Delta V = 4\pi\rho & \text{inside} \\ -\mathrm{div}(\varepsilon\cdot\nabla V)\, V = 0 & \text{outside} \\ \quad + \text{ boundary conditions} & \end{cases}$$



The system is solved introducing a **potential** V^R representing the solvent reaction:

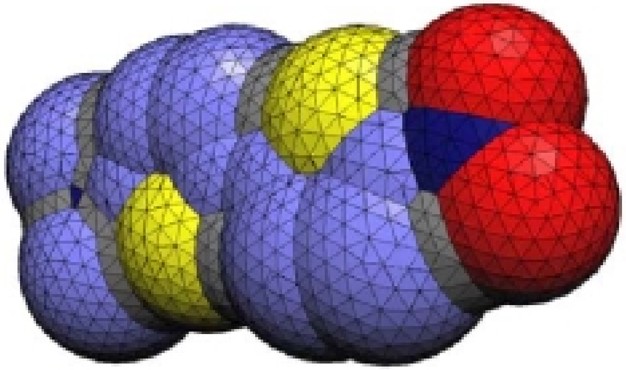
$$\begin{cases} V(x) = V^0(x) + V^R(x) \\ V^R(x;\rho) = \int_\Sigma \dfrac{\boxed{\sigma(y;\rho)}}{|x-y|}\,dy \end{cases}$$

Apparent surface charge (ASC)

describes the electrostatic response of the dielectric to the solute charge density ρ

Free energy: $G = \int \rho(x) V^0(x)\,dx + \frac{1}{2}\int \rho(x) V^R(x)\,dx$

The numerical solution



Partition of the cavity surface into N finite elements (tesserae) of know area (Boundary Element Method, BEM)

1. Discretization of the apparent surface charge
   into point-like charges

1. Reformulation of the integral operator V^R into a simple operator
   expressed as sum over tesserae

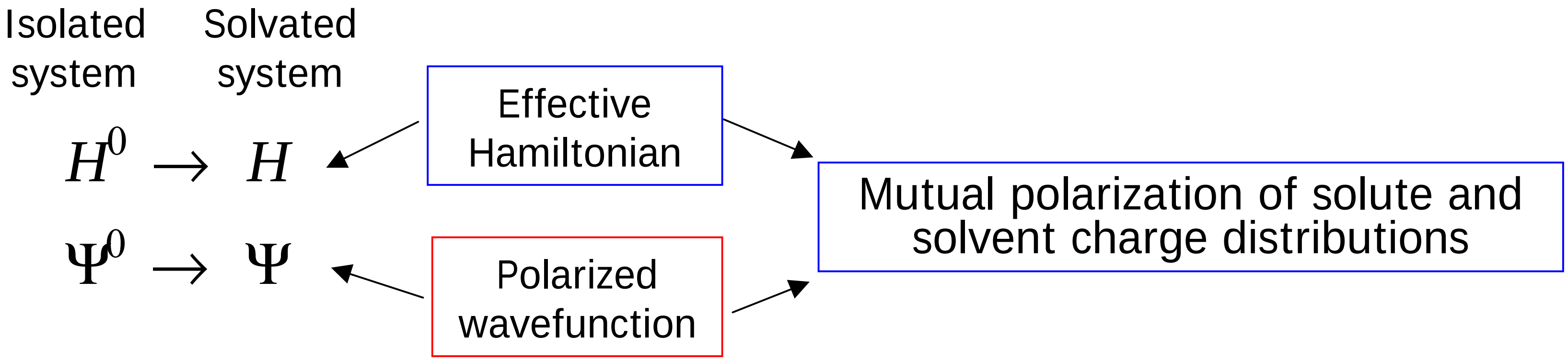
The same formalism applies to different environments: isotropic and anisotropic dielectrics, liquid/gas or liquid/metal systems with sharp and smooth boundaries ....

QM Theory of continuum solvation

Solute-solvent interactions

Proper surface operators which depend on the solute charge density

$$H\Psi = \left[H^0 + V^R \right]\Psi = E\Psi$$



Isolated system

Solvated system

$$H^0 \rightarrow H$$

$$\Psi^0 \rightarrow \Psi$$

Effective Hamiltonian

Polarized wavefunction

Mutual polarization of solute and solvent charge distributions

The solute wavefunction is affected by the solvent through well defined operators which can be formulated within different QM formalisms and extended to derivative approaches and response equations

J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 105, 2999 (2005)

The free energy of solvation

$\Delta G_{sol} \Rightarrow$ the free energy change to transfer a molecule from vacuum to solution.

$$\Delta G_{sol} = \Delta G_{cav} + \Delta G_{elec} + \Delta G_{rep/dis}$$

Cavitation: work required to form the solute cavity

Electrostatics

Repulsion and dispersion

Need to introduce interactions of different nature which require different representations (Classical or Quantum-Mechanical):

PCM:
Electrostatic (QM)

↔

- ✓ cavitation (C)
- ✓ repulsive (C)
- ✓ dispersive (C)

Excitation energies in solutions

Solvent dielectric response

Frequency dependent permittivity

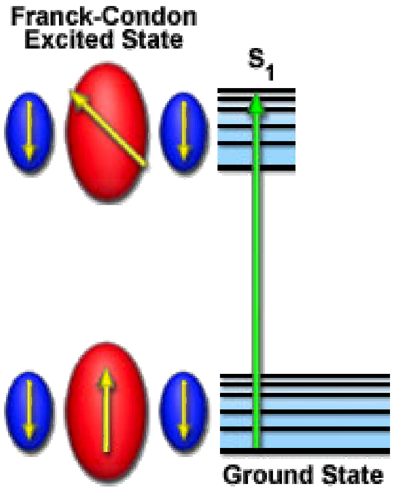
relaxation

$$\varepsilon(\omega) = \varepsilon(\infty) + \frac{\varepsilon(0)-\varepsilon(\infty)}{1+i\omega\tau_D}$$

Fast (electronic) response

nonequilibrium

equilibrium



A solute in a polar solvent

Nonequilibrium PCM

Partition of the solvent charges into fast ($q_f(\varepsilon(\infty))$ with $\varepsilon(\infty) << \varepsilon(0)$) and slow terms

$$\boxed{q(\rho^{exc}) = q_f(\rho^{exc}) + q_s(\rho^{GS})}$$

From ground state calculation

In a vertical electronic transition only the fast component will be in equilibrium with the excited state

Is the continuum model the solution?

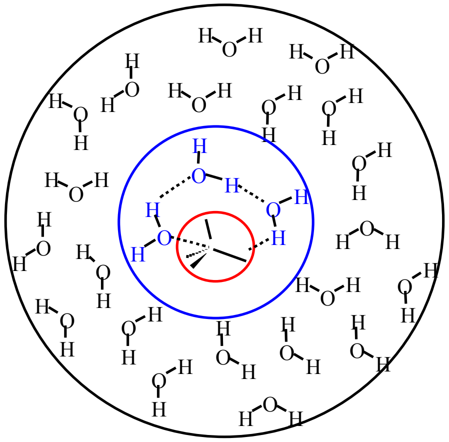
In solvents not specifically interacting with the solute

Bulk (averaged) effects

In solvents showing specific interactions with the solute

Local (specific) effects

Macro- and micro-solvation

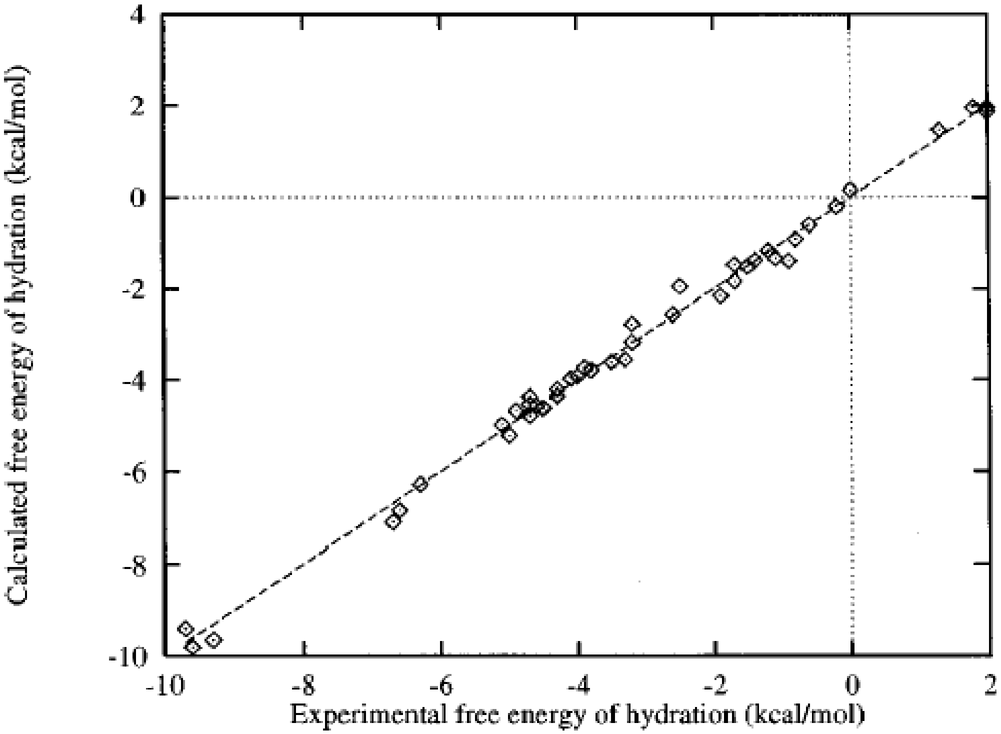


Hydration Free Energies with PCM

$$\Delta G_{sol} = \Delta G_{cav} + \Delta G_{elec} + \Delta G_{rep/dis}$$

Solutes

CH_4
CH_3CH_3
$CH_3CH_2CH_3$
CH_2CH_2
CHCH
C_6H_6
H_2O
CH_3OH
CH_3OCH_3
CH_3CH_2OH
C_3H_7OH
C_4H_9OH
CH_2OH-CH_2OH
Ph$-$OH
NH_3
CH_3NH_2
$(CH_3)_2NH$
$(CH_3)_3N$
$CH_3CH_2NH_2$
Ph$-NH_2$
pyridine
pyrrole
$NH_2=NH_2$
H_2CO
CH_3CHO
CH_3COCH_3
Ph$-$CHO
HCN
CH_3CN
CH_3COOH
CH_3COOCH_3
CH_3CONH_2
CH_3SH
$(CH_3)_2S$
Ph$-$SH
CH_3F
CH_3Cl
CH_3Br
CH_2I_2
Ph$-$Cl
Ph$-$Br
Ph$-$I
Ph$-NO_2$

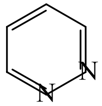
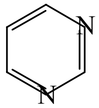
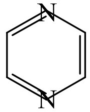


No larger errors are found, for H-bonding solutes!

V. Barone, C. Cossi, J. Tomasi, J. Chem. Phys. 107, 3210, 1997

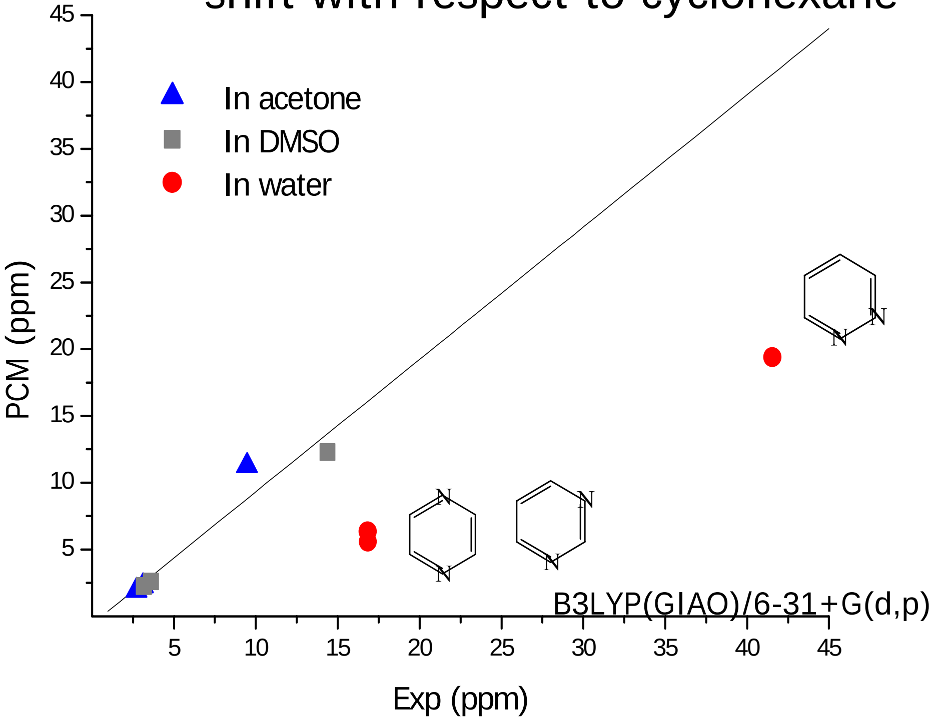
Diazines in solution

$n\rightarrow\pi^*$ absorption energies (in eV):
shift with respect to isoctane

	In acetonitrile		In water	
	PCM	Exp	PCM	Exp
	0.28	0.25	0.29	0.56
	0.13	0.12	0.14	0.37
	~ 0.0	~ 0.0	~ 0.0	0.21

TDDFT: B3LYP/6-31+G(d,p)

^{15}N nuclear shieldings:
shift with respect to cyclohexane



In water both the PCM absorption energies and the nuclear shieldings are smaller than what observed:

a part of the solvent effect is clearly missing.

B. Mennucci, J. Am. Chem. Soc. (2002), 124 1506

Global versus local

Solvation free energies on the one hand, and n-π*
transitions and nuclear shieldings on the other hand,
respond differently to bulk and specific solvent effects

✓ Solvation energies are “globally sensitive”:

they are properly described by a continuum model

✓ Nuclear shieldings and n-π^* transitions are “locally sensitive”:

they cannot be properly described by a continuum model when the solvent acts locally

A possible strategy: the Supermolecule

Supermolecule = Solute surrounded by some solvent molecules

The supermolecule properly accounts for short-range effects.

How can we correctly include long-range effects?

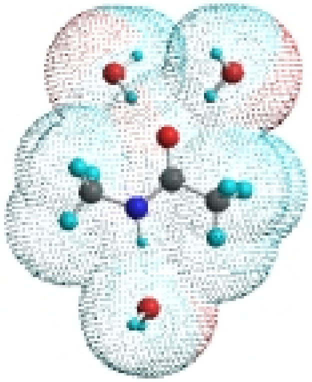
- Enlarging the dimension of the supermolecule:

  it needs explicit averages: difficult and computationally expensive

- Adding an “external” continuum:

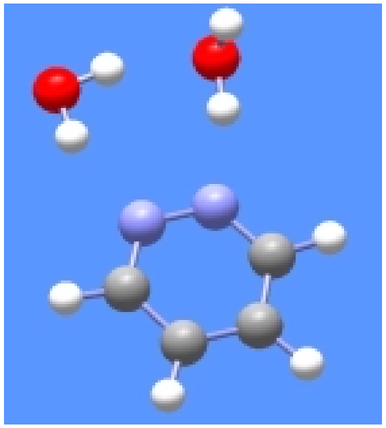
  it implicitly accounts for averages (simple and computationally cheap)

the solvated supermolecule



The supermolecule approach

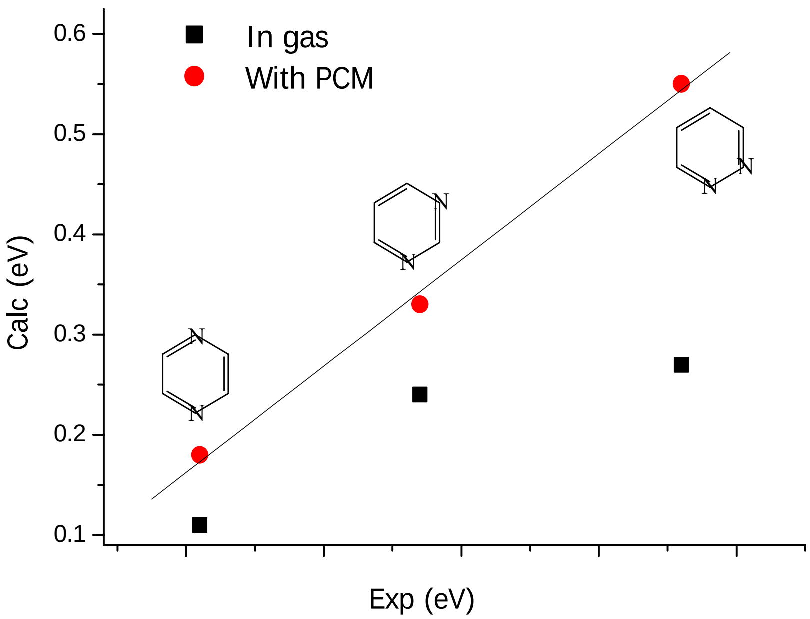
Diazines
+
2 water molecules



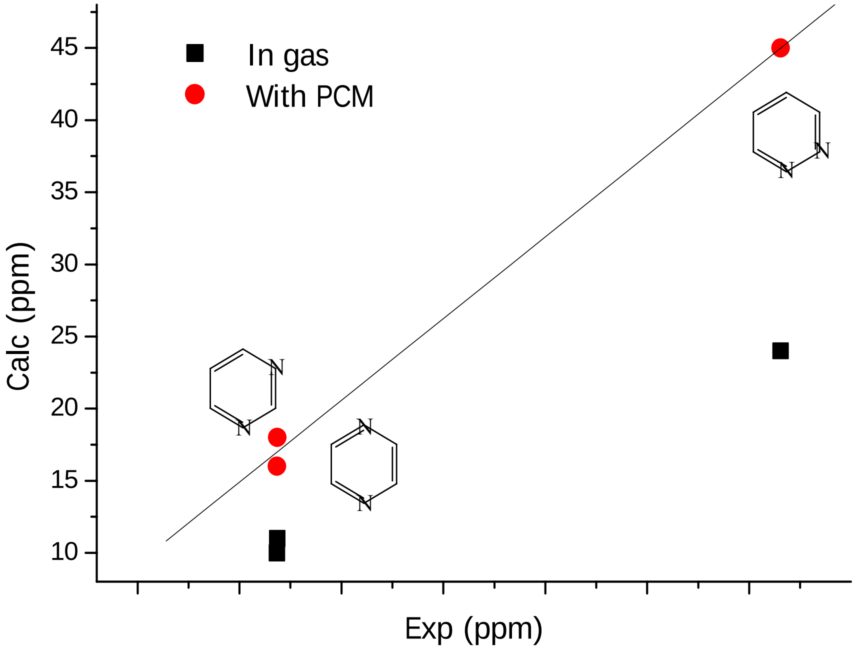
In gas

With PCM

Shift on n→π* absorption (eV)



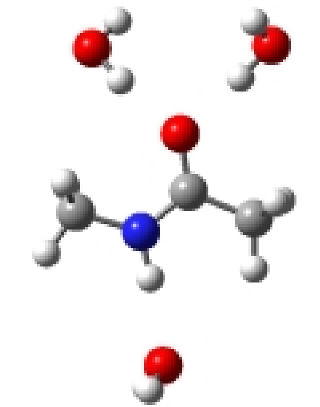
Shift on ^{15}N shielding (ppm)



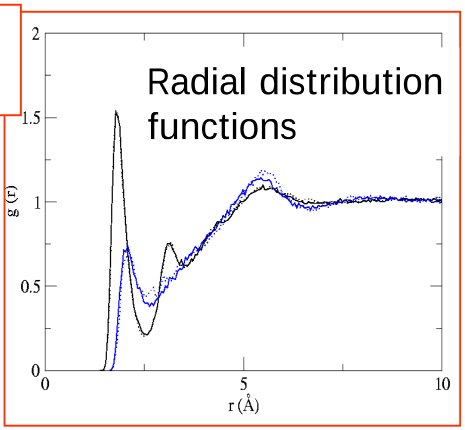
The Supermolecule: not a “black box” approach

How many solvent molecules are needed?

From the chemical analysis of the system



From MD simulations



Radial distribution functions

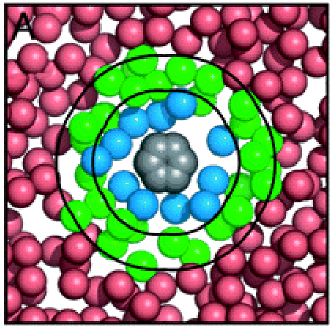
Which configuration?

- ◊ <u>From QM geometry optimizations</u>: the most stable configuration

  Proper description for strongly interacting solute-solvent systems giving rise to stable clusters.

- ◊ <u>From MD or MC simulations</u>: clusters extracted from different snapshots

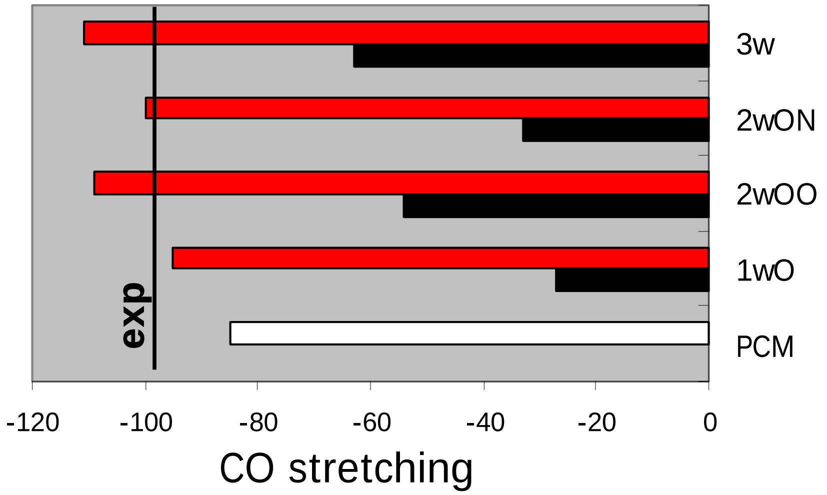
  Better for weak interacting solute-solvent described by a more dynamic situation.

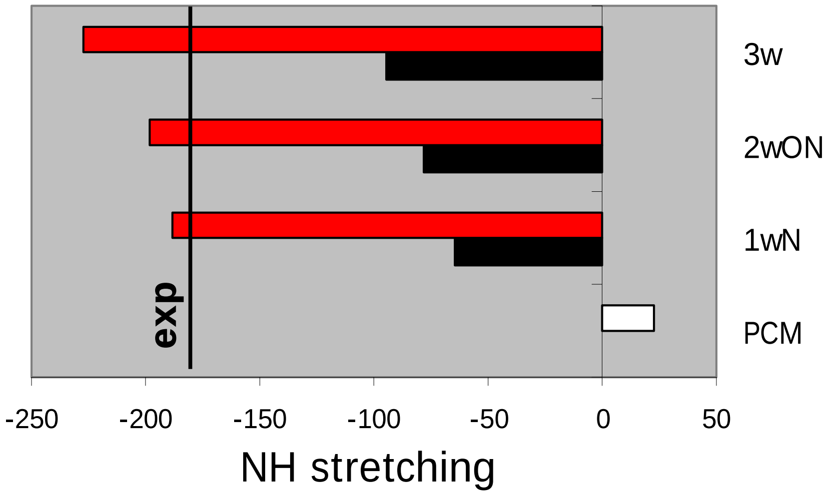


N-Methyl acetamide (NMA) in water

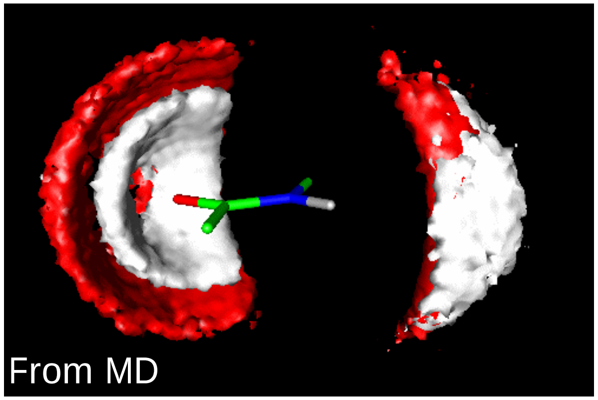
Vibrations: Shift in the frequency (cm^{-1}) with respect to gas-phase

PCM-only (white) and isolated (black) and solvated (red) <u>QM supermolecules</u> (NMA+nw)



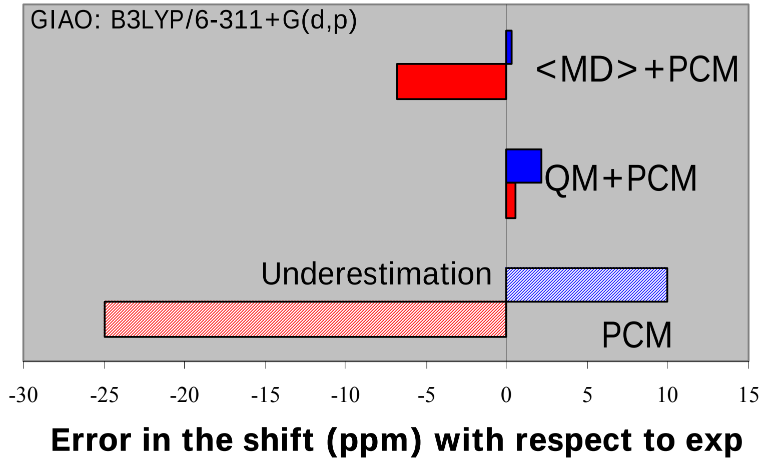


Nuclear shieldings: ^{17}O (red) and ^{15}N (blue)



<MD>:
average on
MD structures

QM:
QM NMA+nw



B. Mennucci, J.M. Martinez, J. Phys. Chem. B, 109, 9830 (2005)

N-Methyl acetamide in water

- Gas-phase clusters account only for a part of the “observed” shift.
  The total shift is recovered by introducing the additional mean-field (or continuum) effect.

- QM and MD clusters (when solvated by the continuum) give equivalent results.
  H-bonded waters are strongly linked to the solute

Hydration of NMA is represented in terms of two types of waters:

- a more mobile (or free) water: properly accounted for by a continuum description
- a much more static (or rigid) water: to be explicitly described at a molecular level.

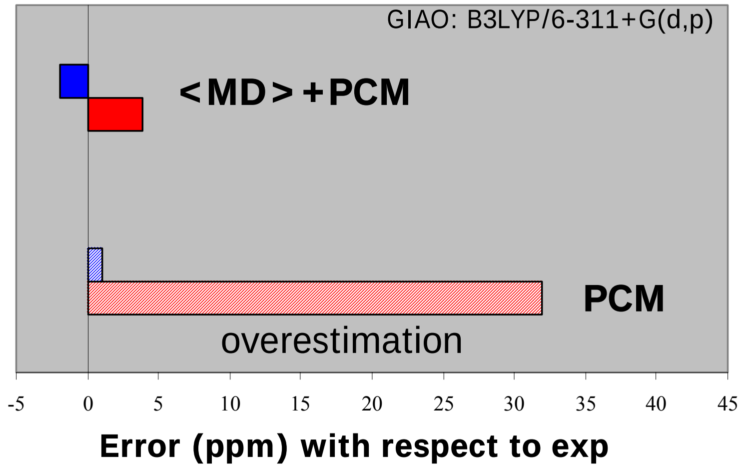
B. Mennucci, J.M. Martinez, J. Phys. Chem. B, 109, 9830 (2005)

NMA in acetone

Nuclear shieldings: ^{17}O (red) and ^{15}N (blue)

<MD>+PCM:
averages on MD
clusters+continuum

PCM :
Only continuum



For **nitrogen** both PCM-only and solvated supermolecules give equivalently correct descriptions

For **oxygen** PCM-only overestimates the solvent effects.

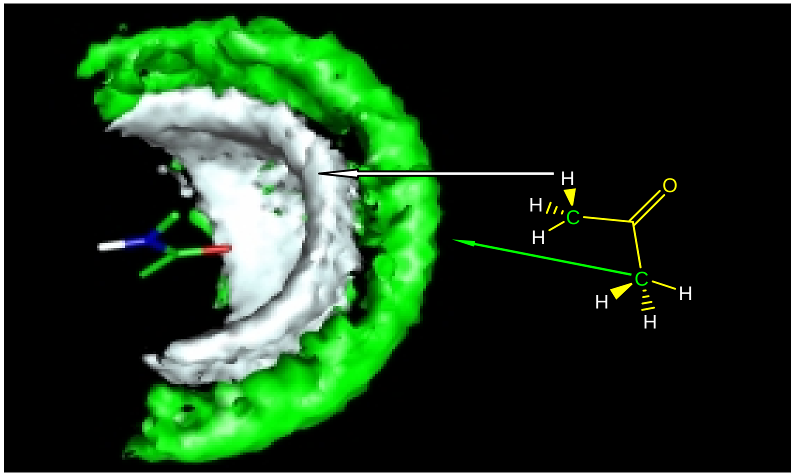
The correct picture is given by an average on different NMA-solvent clusters extracted from MD simulation + continuum

B. Mennucci, J.M. Martinez, J. Phys. Chem. B, 109, 9830 (2005)

NMA in acetone

From MD simulation:

an homogeneous sphere-like distribution of methyl groups is found around the C=O group of NMA



Spatial Distribution Function (SDF)

Methyl groups create a cage which prevents the polar part of the acetone molecule to be in close contact to NMA.

Bulk effects introduced by the continuum model must be taken into account at longer distances than usual otherwise an excessive polarization is induced on oxygen.

B. Mennucci, J.M. Martinez, J. Phys. Chem. B, 109, 9830 (2005)

Summary &....

Solvation is an intrinsically dynamic and long-range phenomenon: statistical treatments involving averaging and fluctuations from averages are thus important.

To understand solvation at the molecular scale, some main questions need to be addressed:

✓ How does solvation at the surface differ from that of bulk solvent?

✓ Are there local rigid structures of solvent at the surface?

✓ What are the time scales for solvent dynamics at the solute surface?

Choice of the proper model

Conclusions (1)

The choice of the theoretical (and computational) model has to be determined by the specific problem under study, for example:

- ➡ globally sensitive properties: continuum models are generally enough
- ➡ locally sensitive properties: hybrid approaches are generally necessary

A useful simplification for “locally sensitive” properties:

distinction between labile and persistent interactions, based on their characteristic residence time.

- ➡ the effects of labile interactions must be averaged
- ➡ the effects of persistent interactions can be taken as they are

Conclusions (2)

Persistent interactions:

QM optimized supermolecules can be used but only if the effects of outer-shell molecules are also included by the continuum model.

Labile interactions:

QM optimized supermolecules are not representative of the real situation; structures extracted from MD simulations are to be preferred.

Necessity to introduce a double average on the solvent molecules:

- for the first shell: average on different MD clusters
- for the outer shells: an implicit average through the continuum

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PCM group

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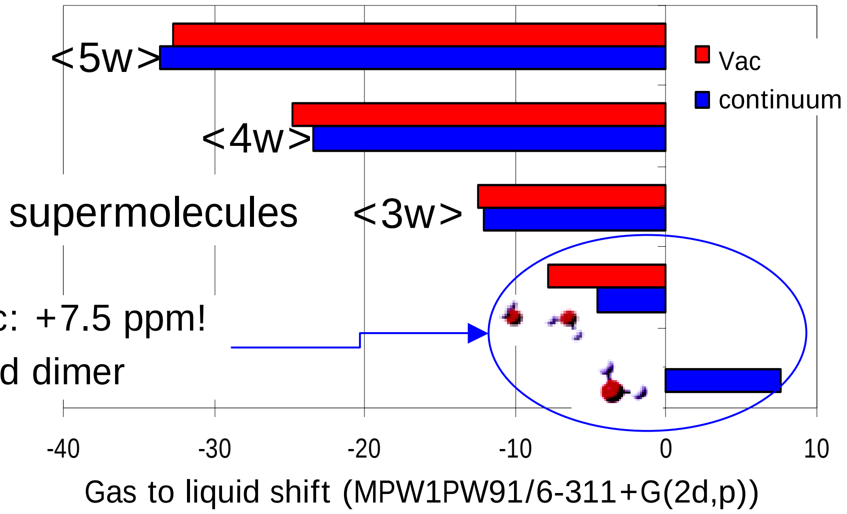
- Gaussian Inc.

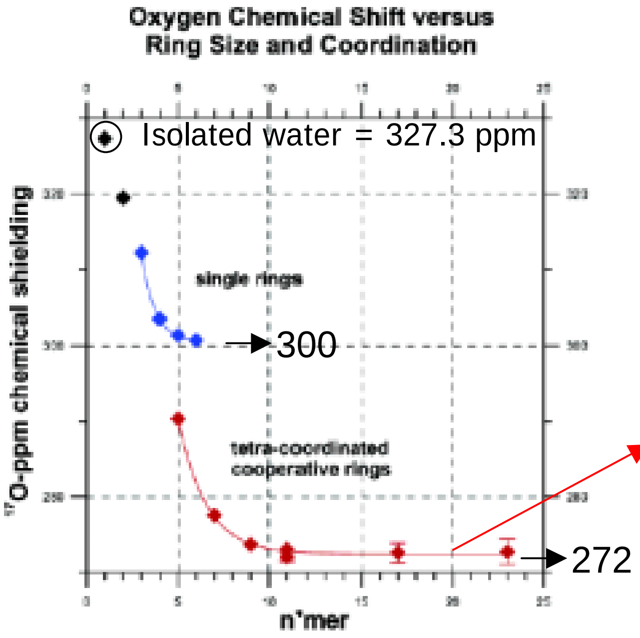
But........^{17}O-NMR shielding of water in water

Experiments:

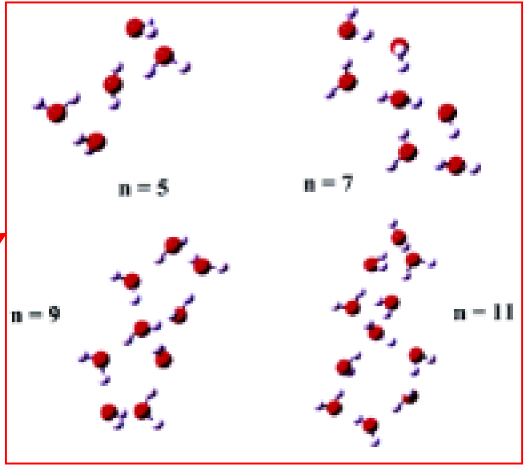
From gas phase to liquid phase = -36.1 ppm
From 100 C to 0 C = -4.35 ppm
From liquid at 0 C to ice = -8 ppm



A single water in a continuum dielectric: +7.5 ppm!
A solvated dimer worse than an isolated dimer



Four-coordinated oxygen,
in a two ring system showing
donor-acceptor cooperativity.



Large and
cooperative
H-bonded system

Failure of continuum
models

Klein, Mennucci, Tomasi, J. Phys. Chem. A, 2004

The apparent surface charge: IEF-PCM

$$A \cdot \sigma = -g \cdot V^M$$

$$A = \left(\frac{I}{2} - D_e\right) \cdot S_i + S_e \cdot \left(\frac{I}{2} + D_i^*\right)$$

$$g = \left[\left(\frac{I}{2} - D_e\right) - S_e \cdot S_i^{-1} \cdot \left(\frac{I}{2} - D_i\right)\right]$$

Integral operators defined in terms of the Green functions

$$(S_k \cdot u)(x) = \int_\Sigma G_k(x,y)u(y)dy$$

$$(D_k \cdot u)(x) = \int_\Sigma \partial G_k(x,y)u(y)dy$$

$-\Delta V = 4\pi\rho$ (in the cavity) + :

- isotropic dielectric:

$$\begin{cases} -\varepsilon\Delta V = 0 \\ \left(\frac{\partial V}{\partial n}\right)_i - \varepsilon\left(\frac{\partial V}{\partial n}\right)_e = 0 \end{cases}$$

$$G_e = \frac{1}{\varepsilon r}$$

$$\boxed{G_i(x,y) = \frac{1}{|x-y|} = \frac{1}{r}}$$

- anisotropic dielectric:

$$\begin{cases} -\mathrm{div}(\boldsymbol{\varepsilon} \cdot \nabla V) = 0 \\ \left(\frac{\partial V}{\partial n}\right)_i - (\boldsymbol{\varepsilon} \cdot (\nabla V))_e \cdot n = 0 \end{cases}$$

$$\boldsymbol{\varepsilon} = \begin{pmatrix} \varepsilon_{xx} & 0 & 0 \\ 0 & \varepsilon_{yy} & 0 \\ 0 & 0 & \varepsilon_{zz} \end{pmatrix}$$

$$G_e = \frac{1}{\sqrt{\det \boldsymbol{\varepsilon}}\sqrt{(\boldsymbol{\varepsilon}^{-1} \cdot \mathbf{r}, \mathbf{r})}}$$

- ionic solution : linearized Poisson-Boltzmann

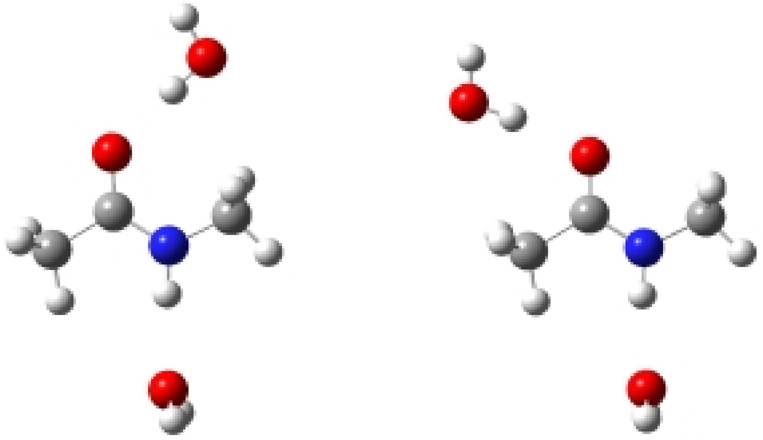
$$\begin{cases} -\varepsilon\Delta V + \varepsilon\kappa^2 V = 0 \\ \left(\frac{\partial V}{\partial n}\right)_i - \varepsilon\left(\frac{\partial V}{\partial n}\right)_e = 0 \end{cases}$$

$$\kappa^2 = 8\pi I F^2 / \varepsilon R T$$

$$I = \frac{1}{2}\sum_i c_i z_i^2$$

$$G_e = \frac{1}{\varepsilon r} e^{-\kappa r}$$

2wON



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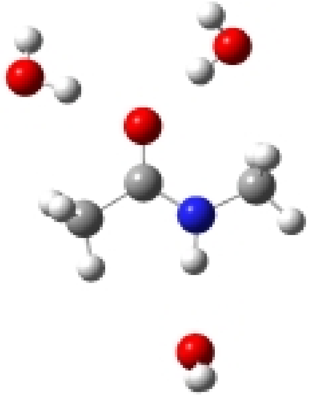
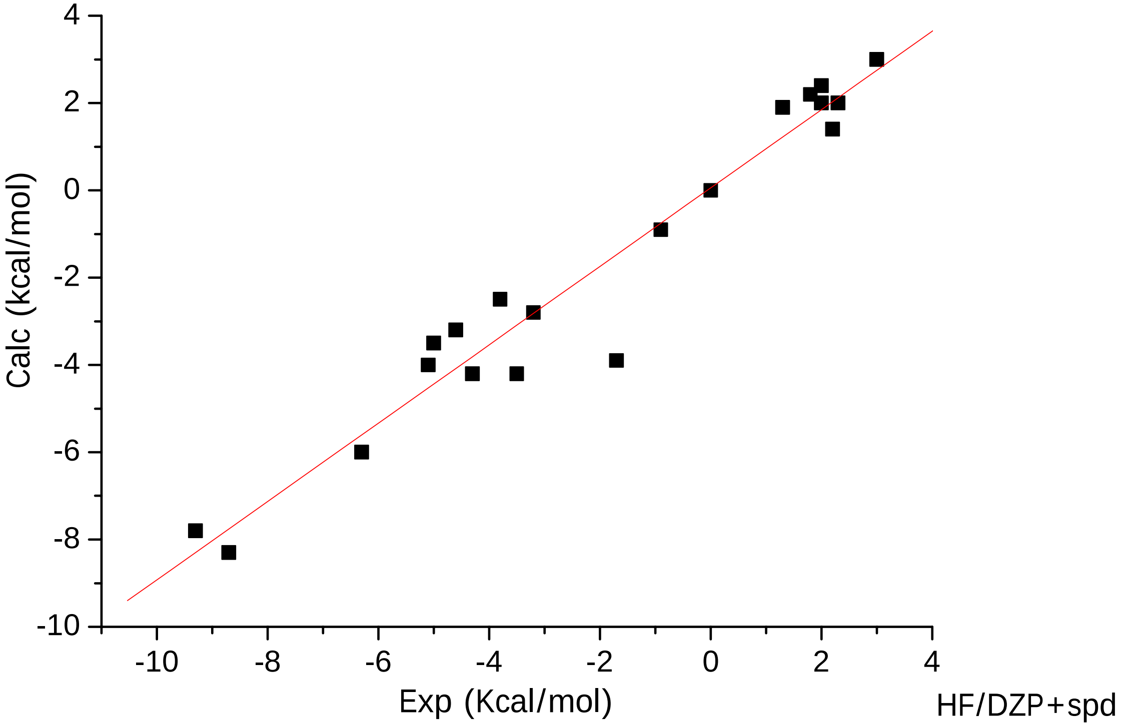


Solvation Free Energies of Different Solutes in Water at 298 K

Solutes

- H_2O
- NH_3
- H_2O_2
- N_2
- CH_4
- CO
- HCHO
- HCN
- N_2H_4
- CH_3OH
- C_2H_2
- C_2H_4
- CH_3NH_2
- C_2H_6
- CH3CHO
- C2H5OH
- C3H8
- CH3COCH3
- C6H6

$$\Delta G_{sol} = \Delta G_{cav} + \Delta G_{elec} + \Delta G_{rep/dis}$$



No significative errors are found, neither for H-bonding solutes!