

# Prediction of Partitioning Coefficients with COSMO-RS

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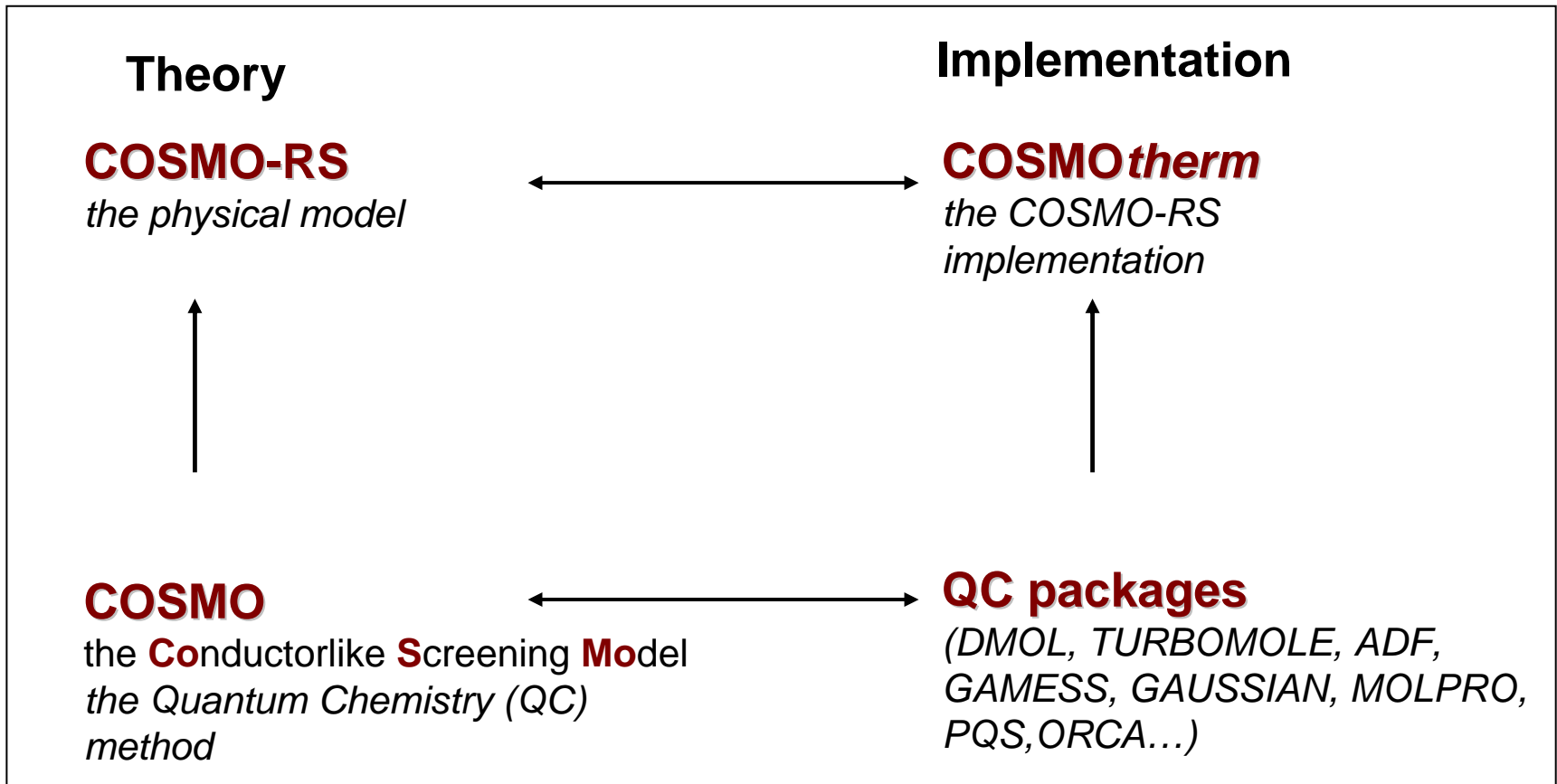
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# Outline

- Introduction: COSMO / COSMO-RS
- Partitioning (calculation via the chem. potentials)
- The  $\sigma$ -moment based QSPR models (physiological partitioning)
- Extraction using ionic liquids (ILs)

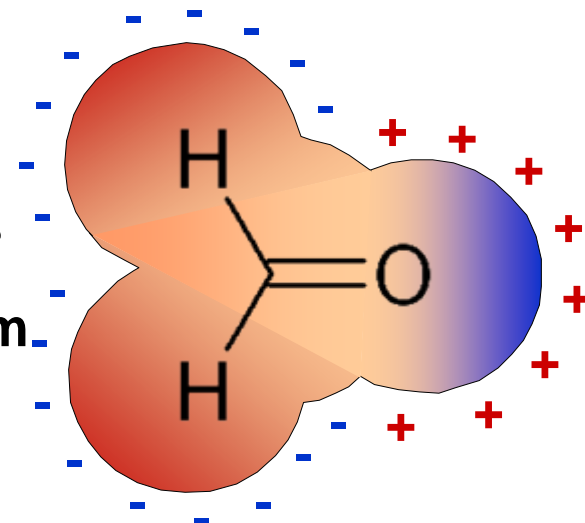
# Some definitions



# Dielectric continuum solvation models

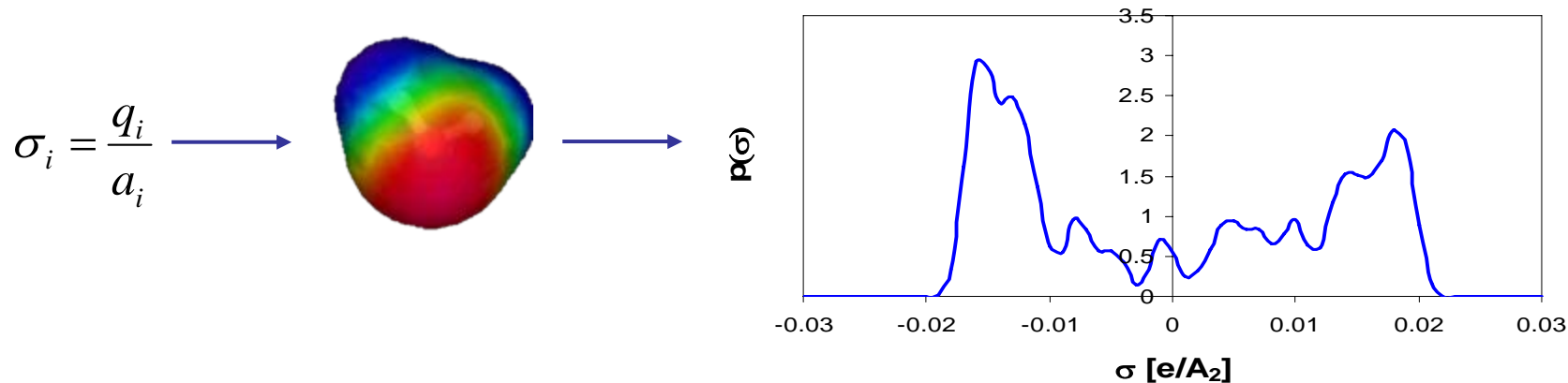
Concept for describing compounds in solution:

- Simulations using explicit solvent molecules
- Embed the molecule in a dielectric continuum



- COSMO:  $\Phi^{tot} = 0 \longrightarrow \mathbf{q} = -\mathbf{A}^{-1} \Phi^{sol}$

" $\sigma$ -profile"  $p(\sigma)$  of Water



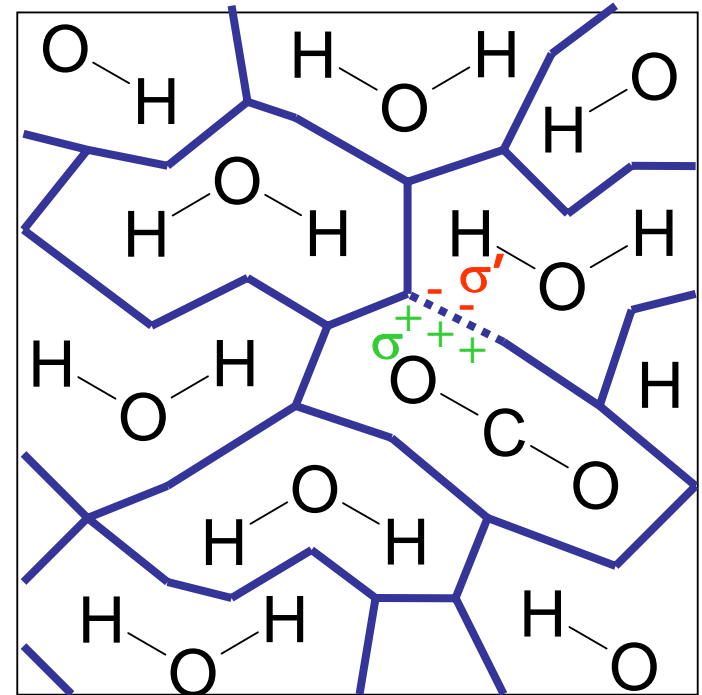
# COSMO-RS

- All surfaces are assumed to be in close contact.
- If screening charges  $\sigma$  and  $\sigma'$  on surface pairs differ, an interaction energy will result from the “*misfit*” of these charges.

$$E_{Misfit}(\sigma, \sigma') = \frac{\alpha'}{2} (\sigma + \sigma')^2$$

adjustable parameter

$E_{Misfit}$  describes electrostatic interactions between molecular surface parts of different polarity.



# COSMO-RS

Two additional interactions are incorporated into the COSMO-RS model:

- Hydrogen bond interactions between surface pieces of strongly different polarity  $\sigma \ll 0$  and  $\sigma' \gg 0$ :

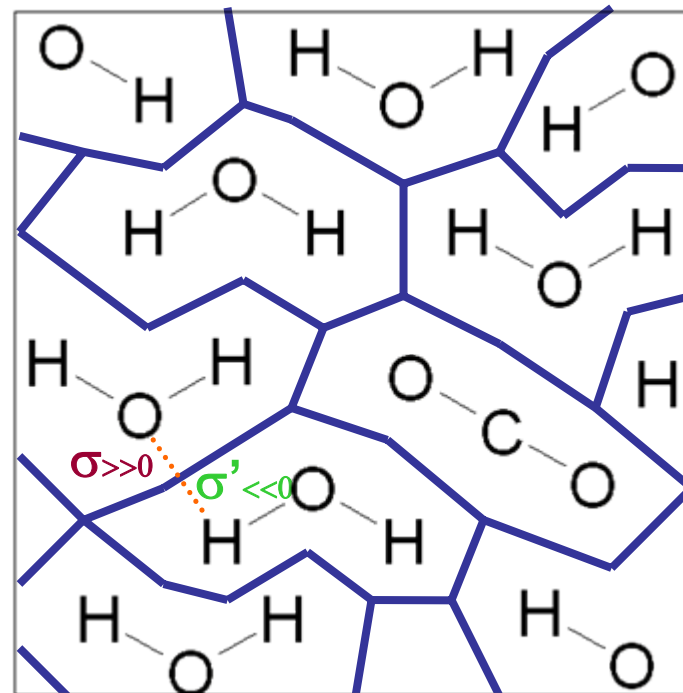
$$E_{HB}(\sigma, \sigma') = \max\{0, -c_{HB}(\sigma \cdot \sigma' + \sigma_{HB}^2)\}$$

adjustable parameter

- Spatially non-specific van der Waals interactions:

$$E_{vdW} = g_{vdW} + g'_{vdW}$$

$g_{vdW}$  are element specific adjustable parameter



- COSMO-RS interaction energy:  $E_{int} = E_{Misfit} + E_{HB} + E_{vdW}$

## COSMO-RS

- The ensemble **S** is fully characterized by the “ **$\sigma$ -profiles**”.

$$P_S(\sigma) = \sum_{i \in S} x_i P^i(\sigma)$$

- Chemical potential of a surface segment\*

$$\mu_s(\sigma) = -kT \ln \int p_s(\sigma') \exp \left\{ -\frac{E_{\text{int}}(\sigma, \sigma') - \mu_s(\sigma')}{kT} \right\} d\sigma'$$

Iterative solution

- The “ **$\sigma$ -potential**”  $\mu_s(\sigma)$  is a measure for the affinity of system **S** to a surface of polarity  $\sigma$ .
- The chemical potential of component **X** in system **S** is calculated by

$$\mu_s^X = \int p^X(\sigma) \mu_s(\sigma) d\sigma + \mu_{C,S}^X \text{ — combinatorial term (size \& shape effects)}$$

\* F. Eckert, A. Klamt, *AIChE Journal*, 48 (2002) 369-385. A. Klamt, *J. Phys. Chem.*, 99 (1995) 2224.

# COSMO-RS

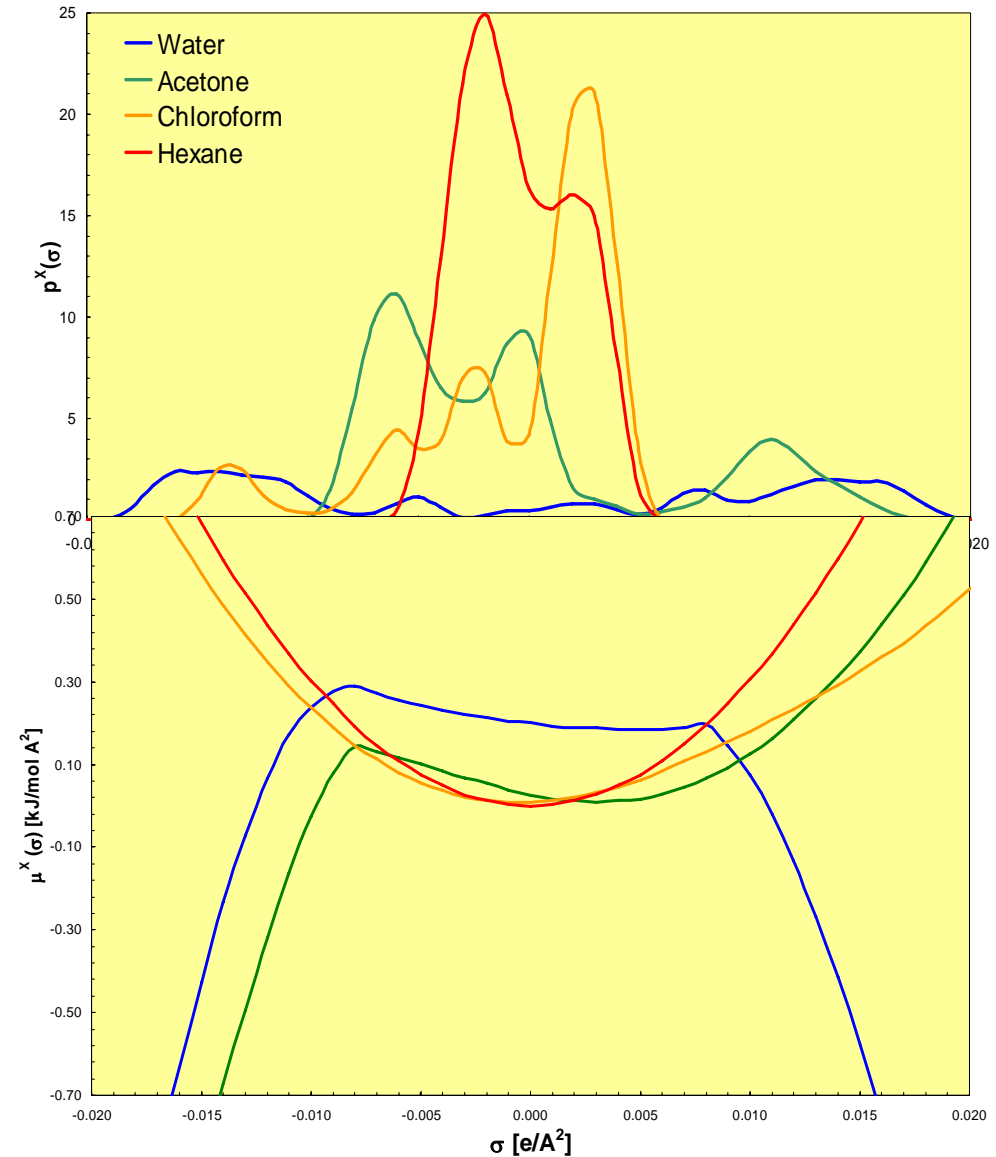
$p^X(\sigma)$  ( $\sigma$ -profile)

Screening charge density probability function for the molecular surface of a molecule X (at temperature T)



$\mu_X(\sigma; T)$  ( $\sigma$ -potential)

Chemical potential of a segment with screening charge density  $\sigma$  in a solvent X (at temperature T)



## COSMOtherm: typical errors

Due to the **generic** character of the COSMOtherm equations and parameterization, it is only possible to give an **mean expectable error** for properties !

QC-Method	Basis	$\log_{10}(\gamma)$ $\log_{10}(P_{OW})$	$\log_{10}(P_{vap})$
DMOL <sup>3</sup> BP-VWN DFT	DNP	0.35	0.3
Turbomole BP DFT (RI)	TZVP (large)	0.35	0.3
Turbomole* BP DFT (RI)	SVP (small)	0.39	0.4
Gaussian B3-LYP DFT	6-31+G(d,p) (medium)	0.42	0.4

\* MOPAC-AM1 optimization with BP-SVP-COSMO single point calculation

## Prediction of Partition Coefficients

Distribution (partition) coefficient of solute X between two solvents:

$$P_{1,2} = \frac{\text{concentration of solute in phase 1}}{\text{concentration of solute in phase 2}}$$

The calculation of the partition coefficient  $\log P_{1,2}$  is accomplished via computation of  $\mu_1^X$  and  $\mu_2^X$  in infinite dilution in the two solvents:

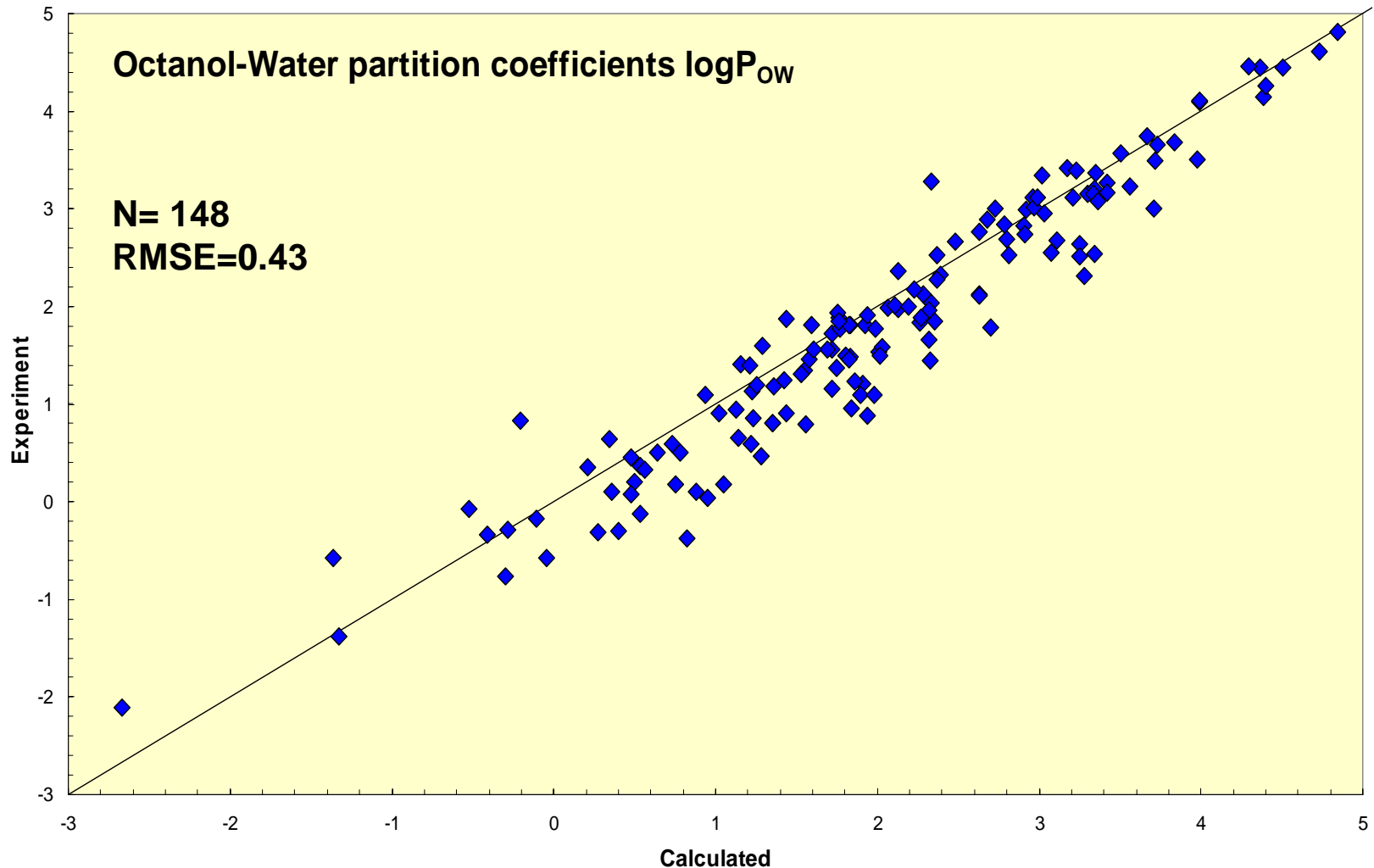
$$\log P_{ow} = \log_{10} \left[ \exp\left(\frac{\mu_2^X - \mu_1^X}{RT}\right) \frac{V_w}{V_o} \right]$$

The phases can be mixtures. E.g: Pow

Phase 1: pure water

Phase 2: 0.24 mol % water, 0.76 mol % octanole

# 1-Octanol-water partition of some organic solvents\*



\*Exp. Data: Chuman *et al.*, *Analytical Sciences*, **18**, (2002) 1015-1020.

# Air-Solvent Partition Behavior of 18 Refrigerants

$$L_S = RT\rho_S/H_S M_S$$

$H_S$  = Henry Coeff.

$M_S$  = Mol. Weight

$\rho_S$  = Density

$S$  = Solvent

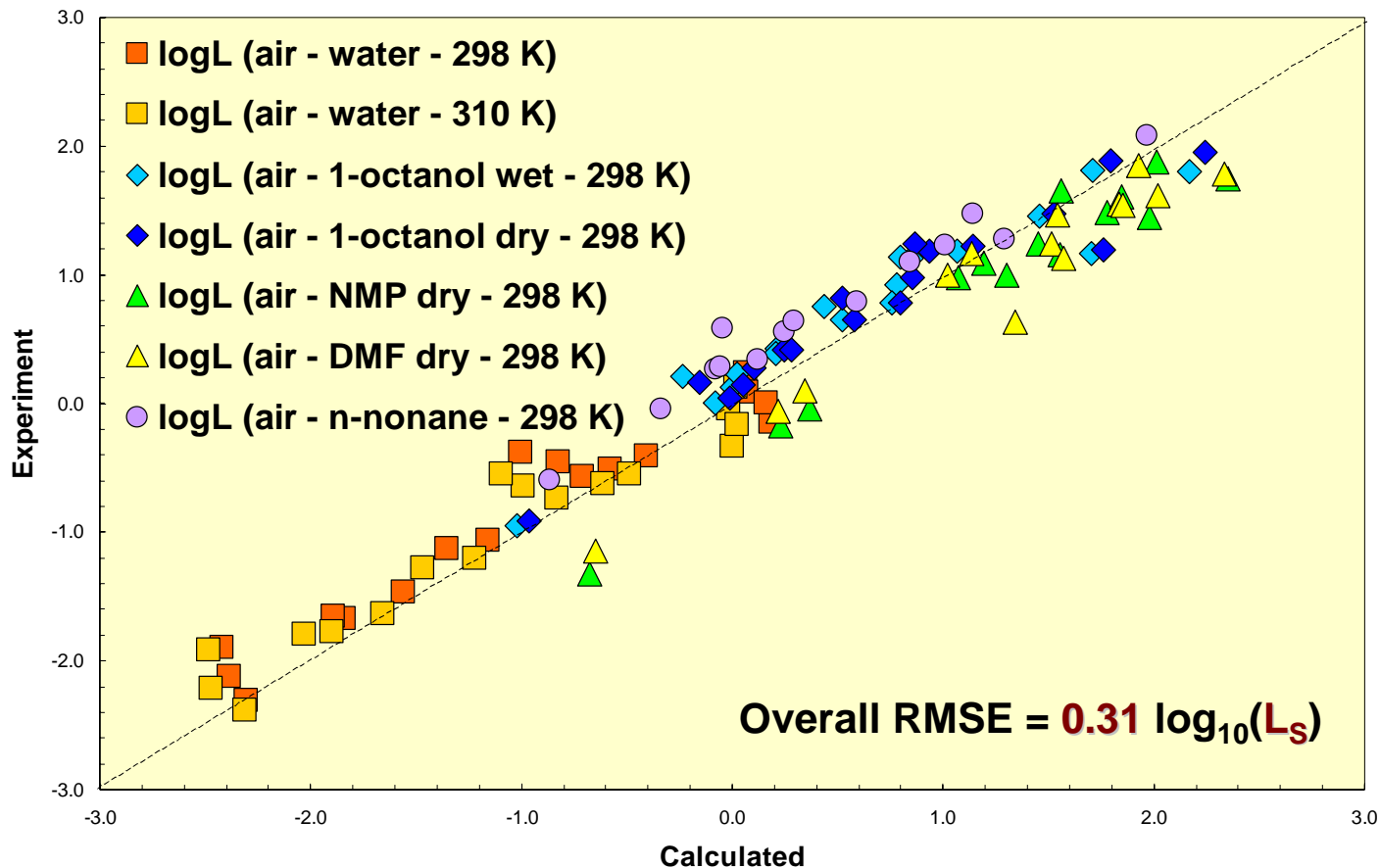
*A priori* prediction

by COSMOtherm !

No experimental

vapor pressure data

was used !



# Quantitative Structure-Property Relationship

- Treat more complicated solvents (matrices) as a pseudo liquid
- The  $\sigma$ -potential of the matrix can be approximated by a power series in  $\sigma$ :

$$\mu_S(\sigma) \cong \sum_{i=-2}^m c_S^i f_i(\sigma)$$

$$f_i(\sigma) = \sigma^i \quad \text{for } i \geq 0$$

$$f_{-2/-1}(\sigma) = f_{acc/don}(\sigma) \cong \begin{cases} 0 & \text{if } \pm \sigma < \sigma'_{hb} \\ \pm \sigma - \sigma'_{hb} & \text{if } \pm \sigma > \sigma'_{hb} \end{cases}$$

# Quantitative Structure-Property Relationship

$$\log K_{S,S'}^X = -\frac{0.4343}{RT} \left[ c_{S,S'} + \int p^X(\sigma) \{ \mu_{S'}(\sigma) - \mu_S(\sigma) \} d\sigma \right]$$

$$\log K_{S,S'}^X \cong \tilde{c}_{S,S'} + \sum_{i=-2}^m \tilde{c}_{S,S'}^i M_i^X$$

$$M_i^X = \int p^X(\sigma) f_i(\sigma) d\sigma$$

$M_0^X$  molecular area

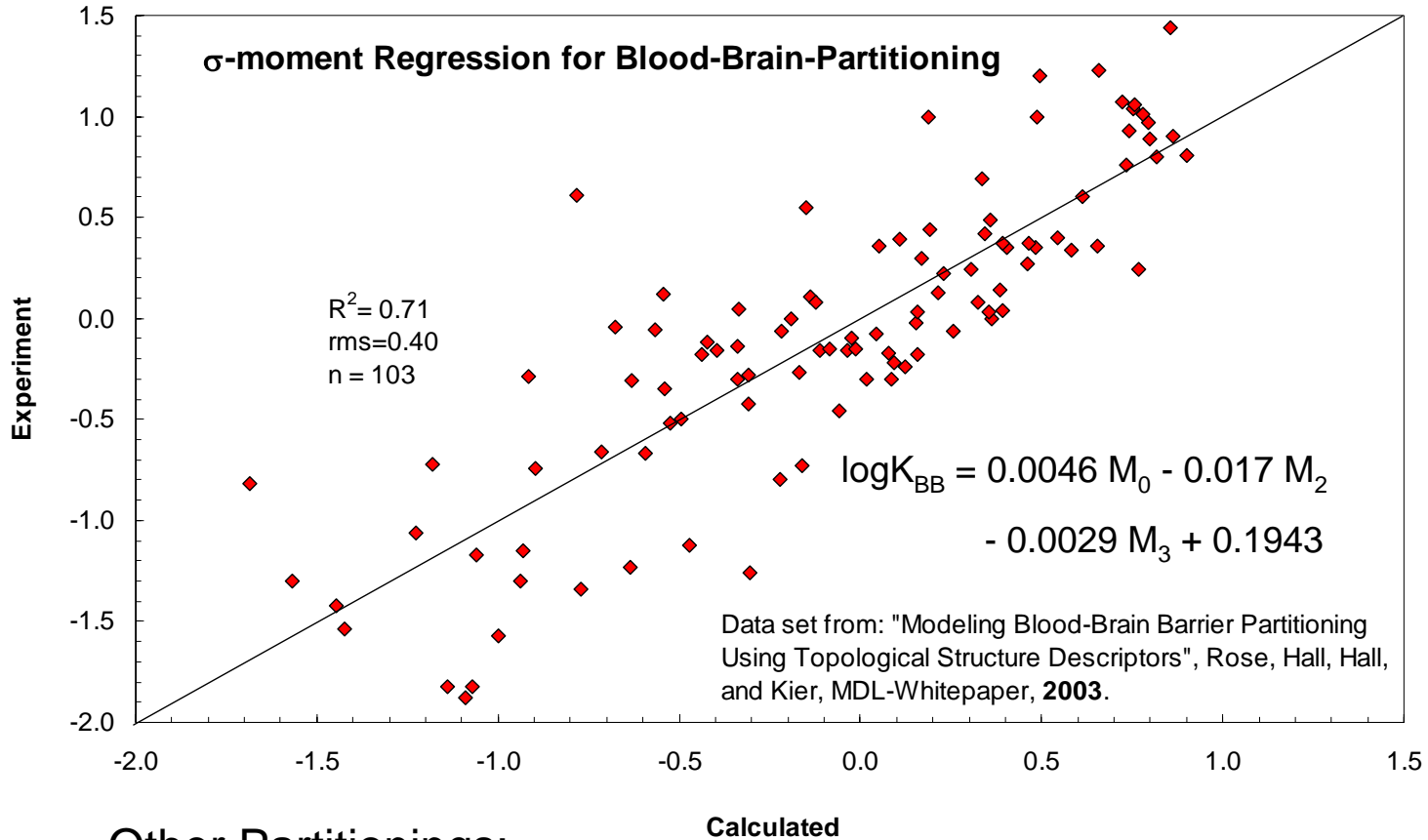
$M_1^X$  negative total charge of compound X (only neutral molecules)

$M_2^X$  correlated with the screening energy for X

$M_3^X$  kind of skewness of the profile

$M_{-1/-2}$  or  $M_{\text{don/acc}}$  are correlated with the hydrogen bond capacity

# Blood-brain partitioning $\log K_{BB}$



Other Partitionings:

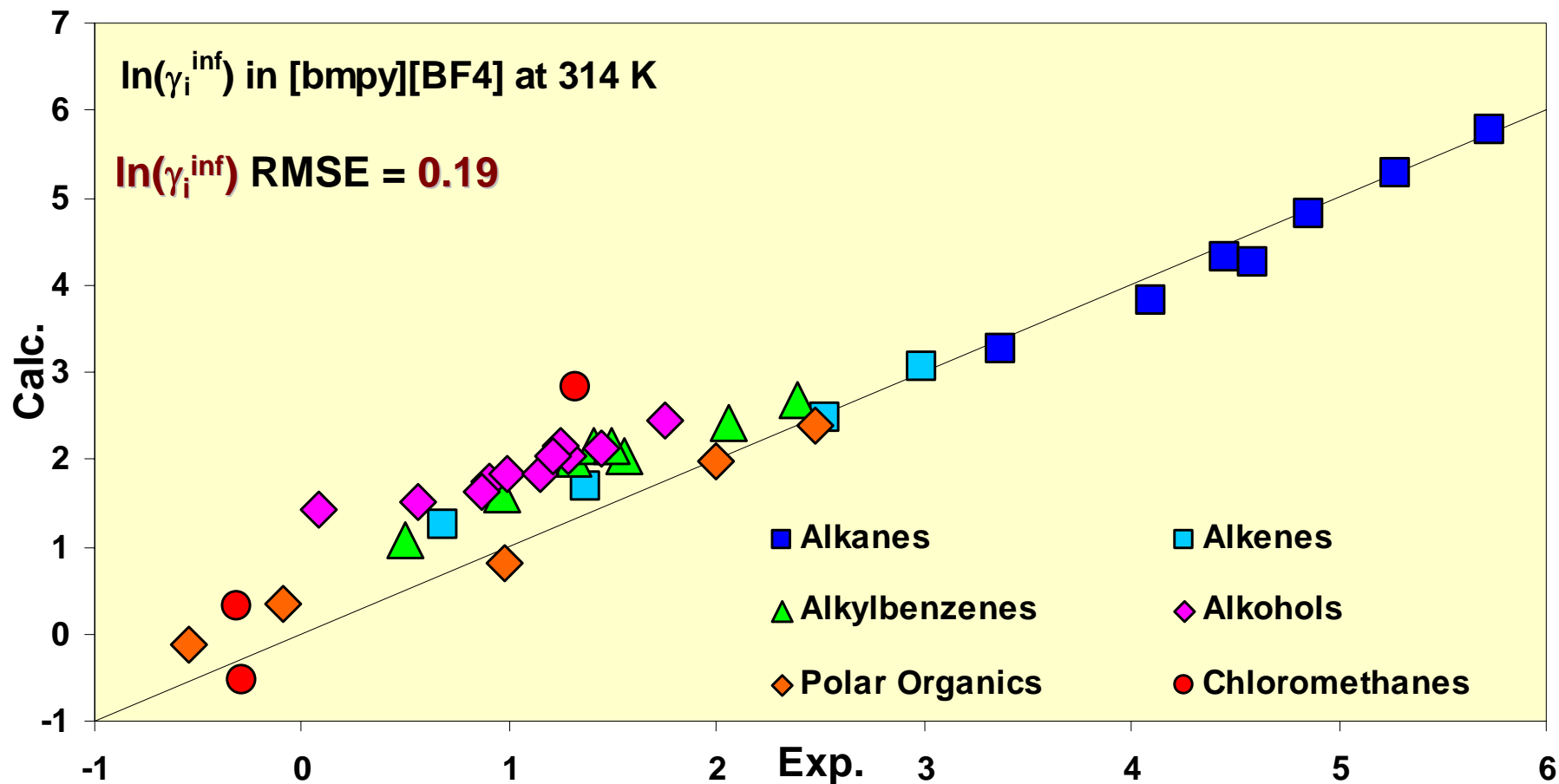
soil sorption

intestinal absorption

human serum albumine binding

# Basic Applications ILs: Activity and Partition

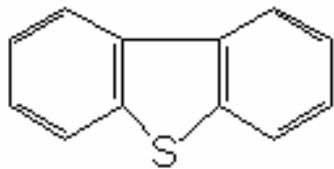
Example: Activity coefficients  $\gamma$  in solvent **Ionic Liquids**



# Desulfurization

Extraction of S-compounds from gasoline by ILs

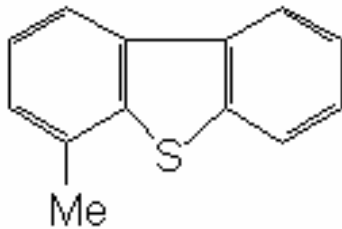
J. Eßer, P. Wasserscheid, A. Jess, *Green Chem.* **6**, 2004, 316



DBT



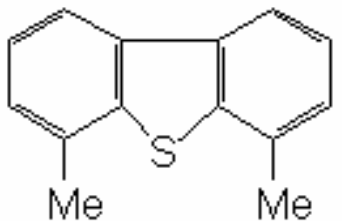
Thiophene



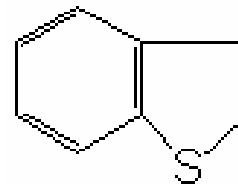
4-MDBT



Tetrahydrothiophene



4,6-DMDBT



BT

R-SH

Thiole

## Desulfurization II

$$K_N = \frac{mg(S) \text{ kg(IL)}^{-1}}{mg(S) \text{ kg(oil)}^{-1}}$$

$$K_N \approx \frac{\gamma_i^{oil}}{\gamma_i^{IL}} \frac{2M(oil)}{M(IL)}$$

### $K_N$ for **DBT** Between **IL** and **Dodecane**

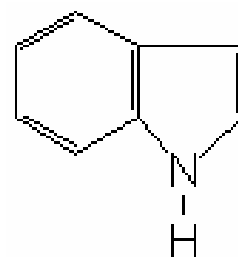
T=25°C	exp.	calc.
[BMIM][BF <sub>4</sub> ]	0.7	0.6
[BMIM][PF <sub>6</sub> ] (60° C)	0.9	0.5
[BMIM][OcSO <sub>4</sub> ]	1.9	1.1
[EMIM][EtSO <sub>4</sub> ]	0.8	2.0
[MMIM][Me <sub>2</sub> PO <sub>4</sub> ]	0.7	5.6

[BMIM]Cl/AlCl<sub>3</sub>: 4.0

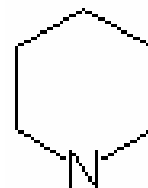
Exp.: J. Eßer, P. Wasserscheid, A. Jess, *Green Chem.* **6**, 2004, 316

# Nitrogen Partition Coefficients $K_N$ between [BMIM][OcSO<sub>4</sub>] and Dodecane

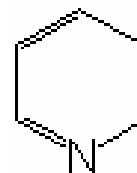
T=25°C	exp.	calc.
<b>Indole</b>	340	263.0
<b>Piperidine</b>	0.7	1.0
<b>Pyridine</b>	2.9	3.7



Indole



Piperidine



Pyridine

Exp.: J. Eßer, P. Wasserscheid, A. Jess, *Green Chem.* **6**, 2004, 316

## IL Screening $K_N^i$ between IL and a second phase

1. Provide a database of anions & cations
2. Build all possible “ILs“ as combinations of anions & cations
3. Calculate  $\gamma_i^{inf}$  and  $K_N$  of substance  $i$  in all “ILs“ and set up a hit list
4. Check the leading combinations for applicability
  - check the influence of conformers
  - check mutual solubility with the second phase
  - is it really an IL
  - stability
  - toxicity
5. Design: predict the influence of structural modifications of the leading ILs

## Summary

- Partitioning coefficients can be calculated from the COSMO-RS chemical potential for various phases and temperatures
- Ionic liquids phases can be treated
- The  $\sigma$ -moment QSPR approach can be used to model partitioning between not well defined phases.

# Acknowledgements

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Thank you !