

Prediction of Partitioning Coefficients with COSMO-RS

Michael Diedenhofen

Andreas Klamt

COSMOlogic GmbH & Co. KG
Burscheider Str. 515
D-51381 Leverkusen
Germany

Phone: +49-2171-731-680

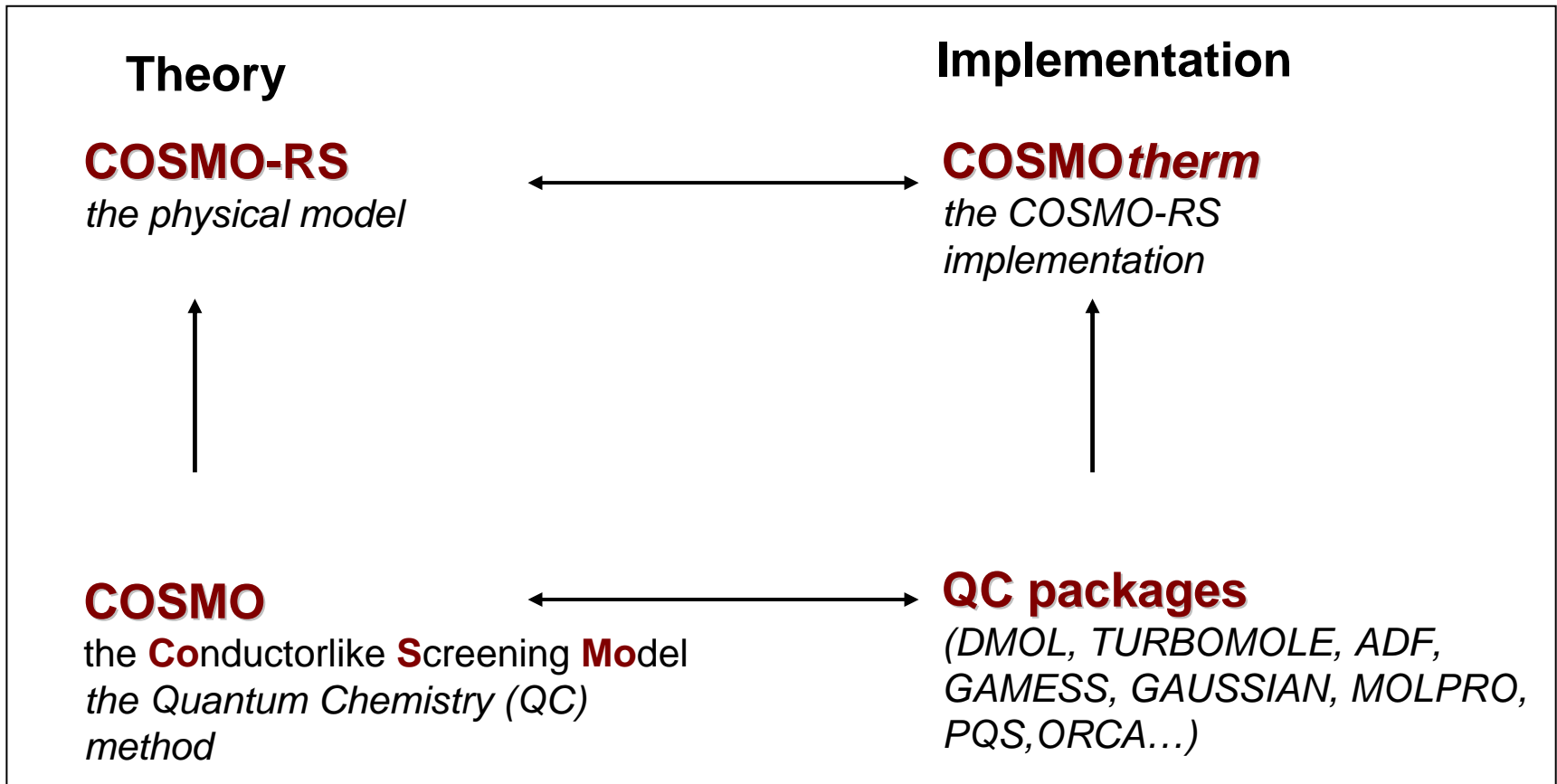
Fax: +49-2171-731-689

Web: <http://www.cosmologic.de>

Outline

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

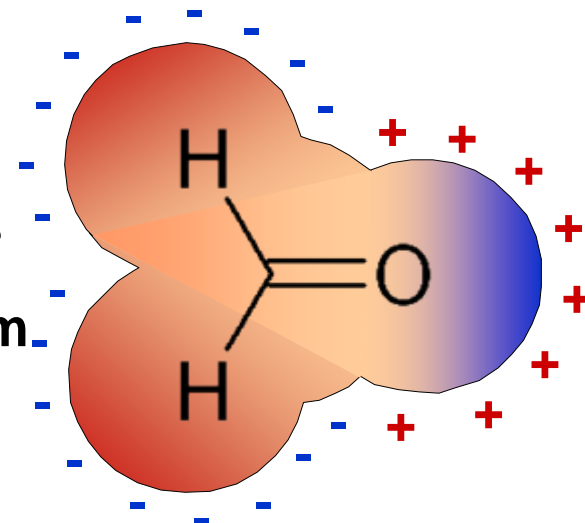
Some definitions



Dielectric continuum solvation models

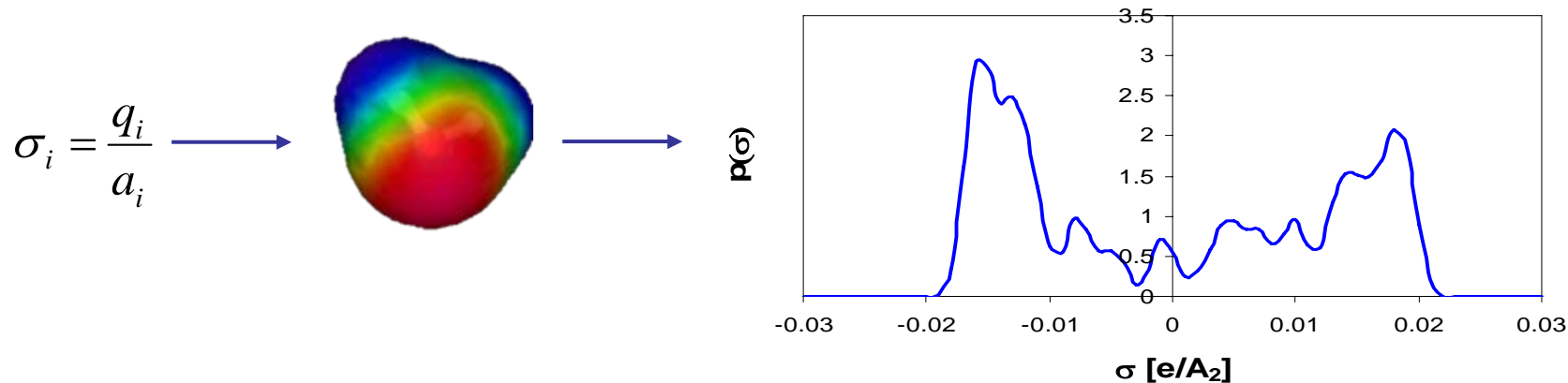
Concept for describing compounds in solution:

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



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

" σ -profile" $p(\sigma)$ of Water



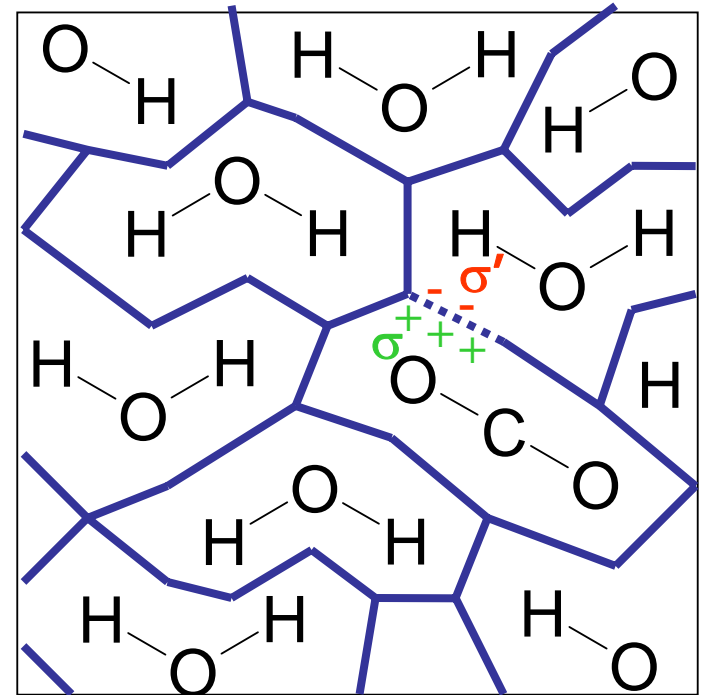
COSMO-RS

- All surfaces are assumed to be in close contact.
- If screening charges σ and σ' 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 $\sigma' \gg 0$:

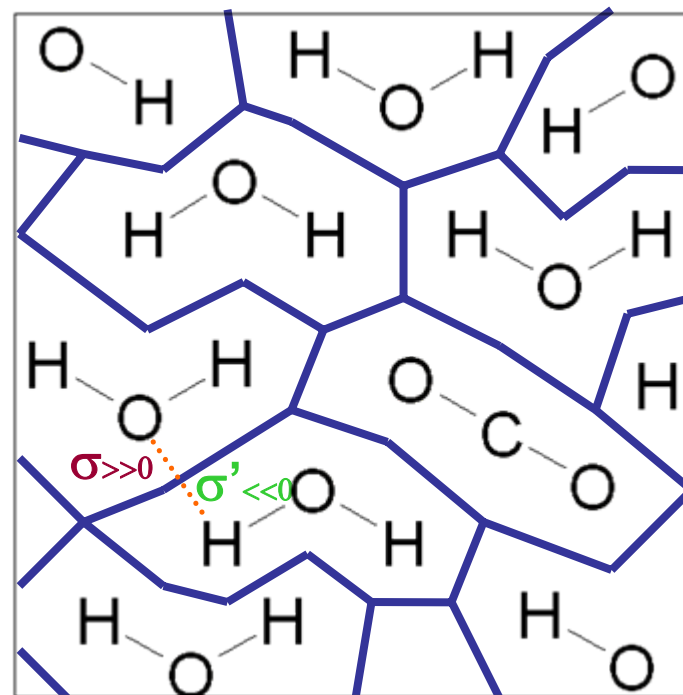
$$E_{HB}(\sigma, \sigma') = \max\{0, -c_{HB}(\sigma \cdot \sigma' + \sigma_{HB}^2)\}$$

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 “ **σ -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 “ **σ -potential**” $\mu_s(\sigma)$ is a measure for the affinity of system **S** to a surface of polarity σ .
- 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

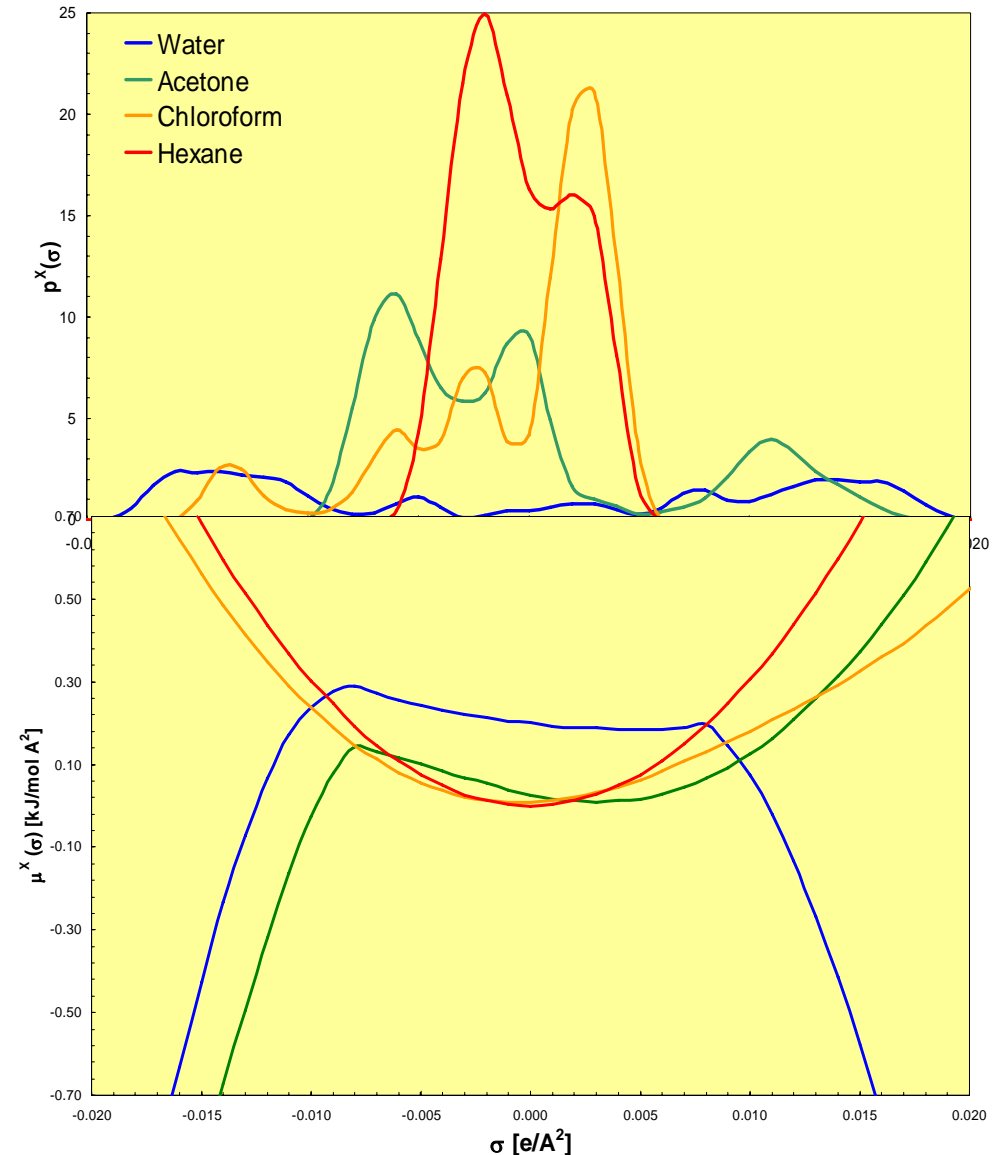
$p^X(\sigma)$ (σ -profile)

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



$\mu_X(\sigma; T)$ (σ -potential)

Chemical potential of a segment with screening charge density σ 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 ³ 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 μ_1^X and μ_2^X in infinite dilution in the two solvents:

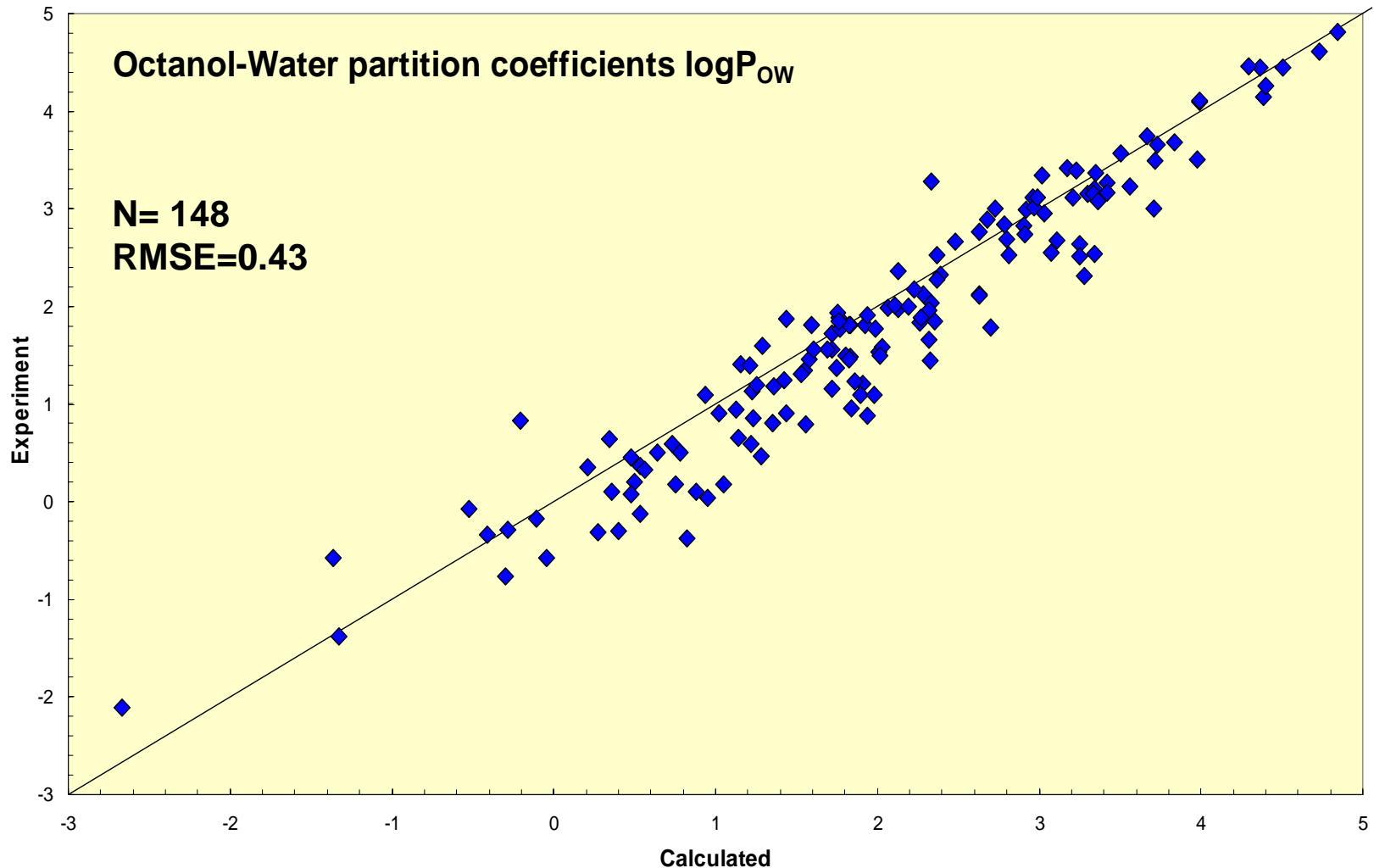
$$\log P_{ow} = \log_{10} \left[\exp\left(\frac{\mu_2^X - \mu_1^X}{RT}\right) \frac{V_w}{V_o} \right]$$

The phases can be mixtures. E.g: Pow

Phase 1: pure water

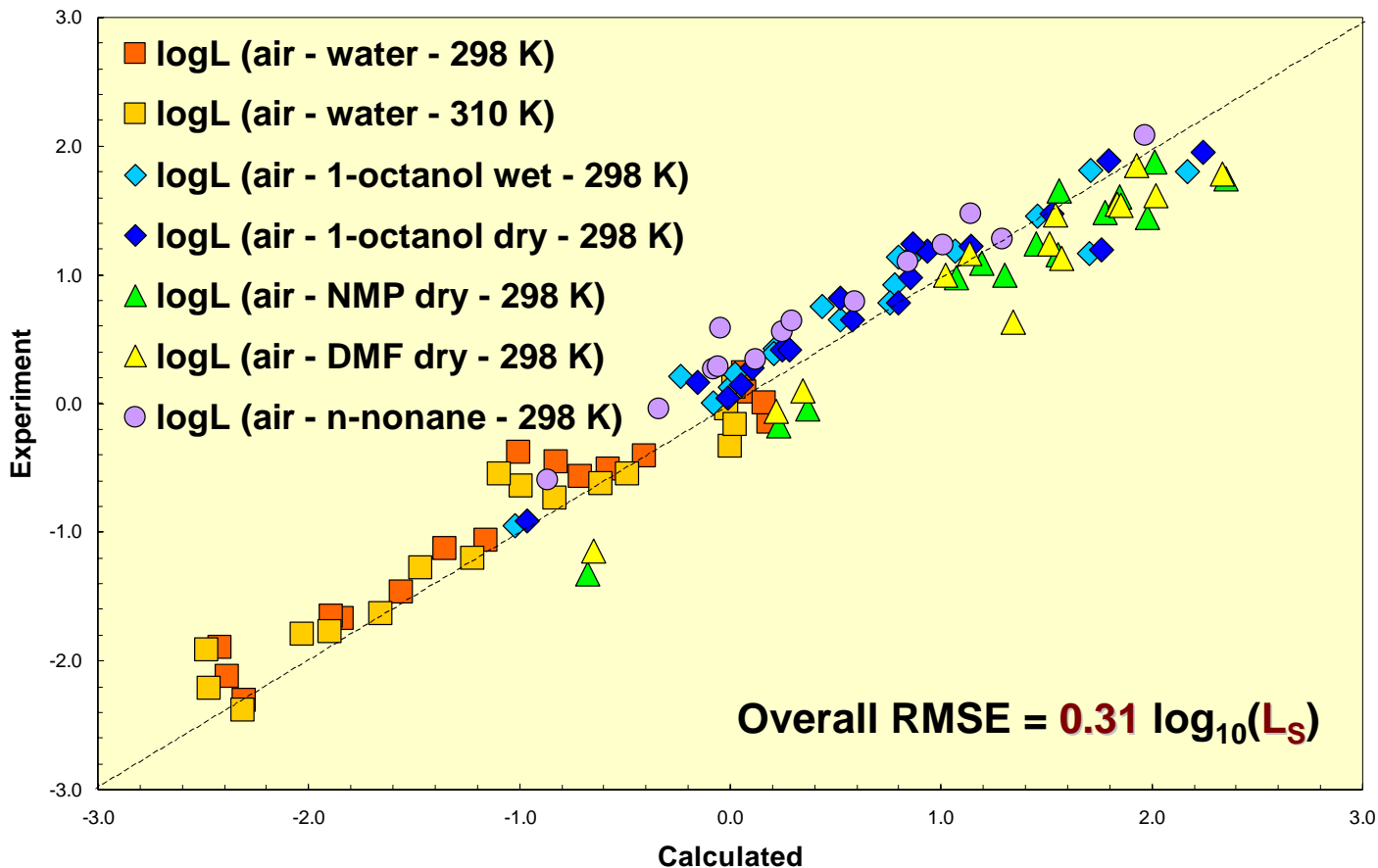
Phase 2: 0.24 mol % water, 0.76 mol % octanole

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

ρ_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 σ -potential of the matrix can be approximated by a power series in σ :

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

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

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

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

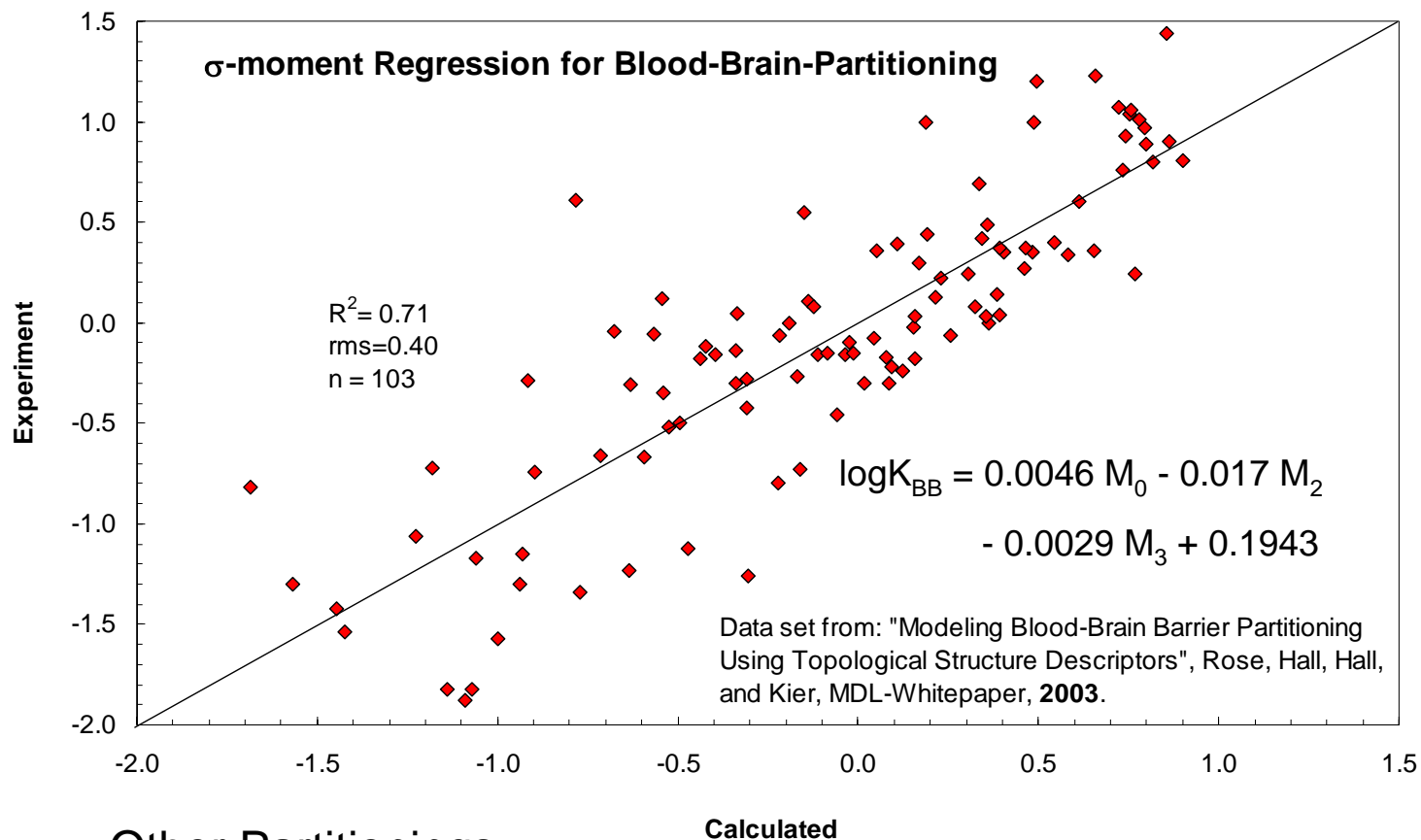
M_1^X negative total charge of compound X (only neutral molecules)

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:

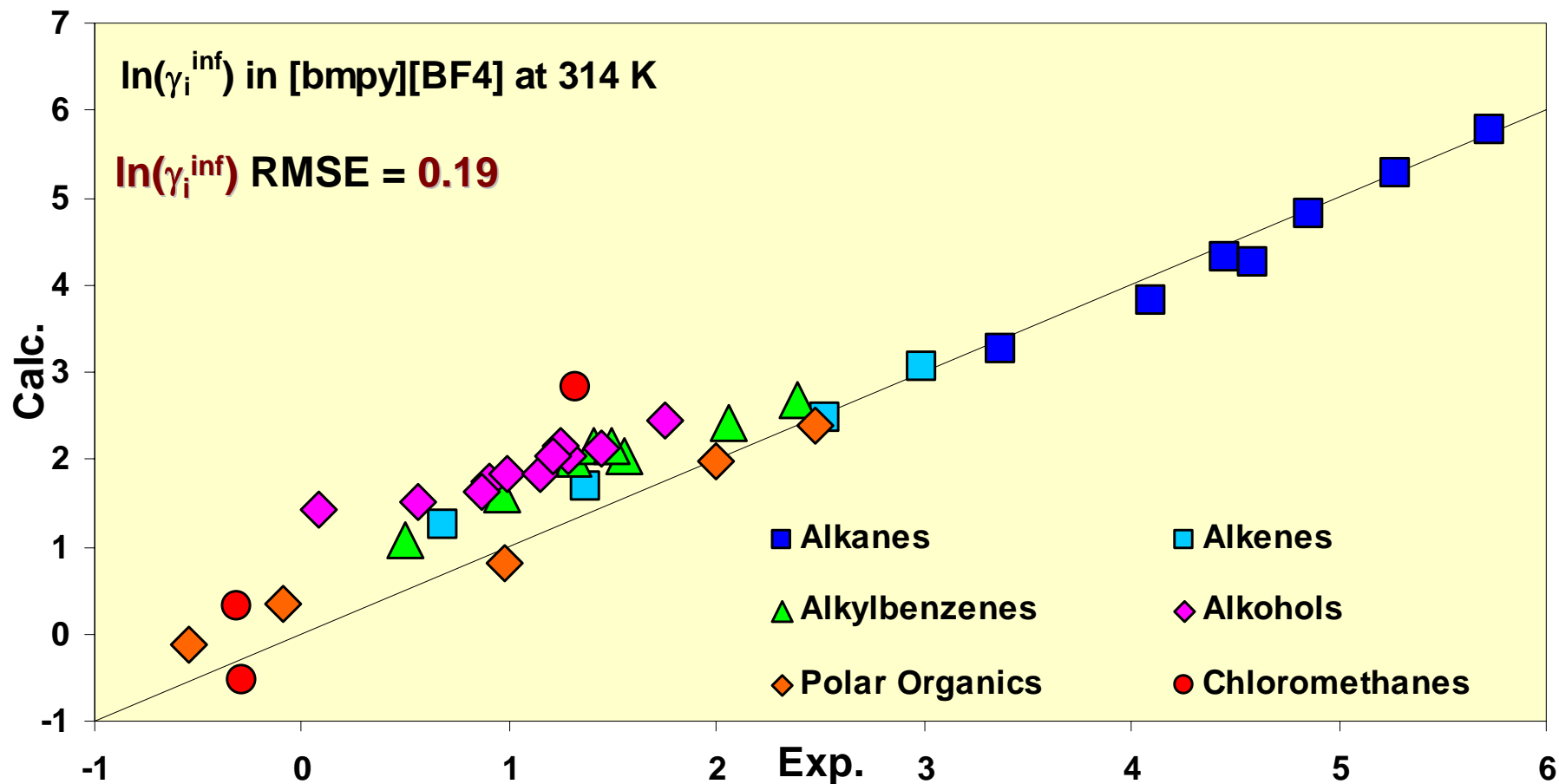
soil sorption

intestinal absorption

human serum albumine binding

Basic Applications ILs: Activity and Partition

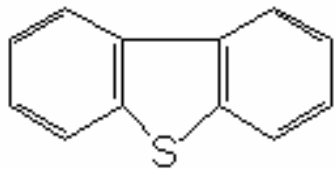
Example: Activity coefficients γ in solvent **Ionic Liquids**



Desulfurization

Extraction of S-compounds from gasoline by ILs

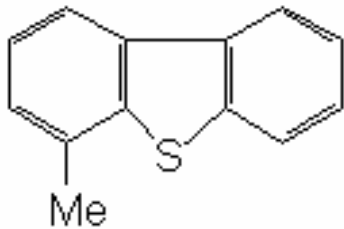
J. Eßer, P. Wasserscheid, A. Jess, *Green Chem.* **6**, 2004, 316



DBT



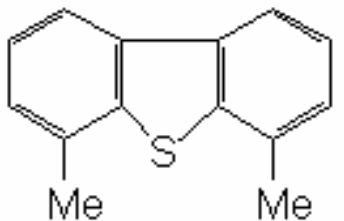
Thiophene



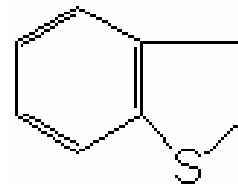
4-MDBT



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**

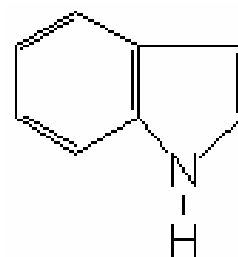
T=25°C	exp.	calc.
[BMIM][BF ₄]	0.7	0.6
[BMIM][PF ₆] (60° C)	0.9	0.5
[BMIM][OcSO ₄]	1.9	1.1
[EMIM][EtSO ₄]	0.8	2.0
[MMIM][Me ₂ PO ₄]	0.7	5.6

[BMIM]Cl/AlCl₃: 4.0

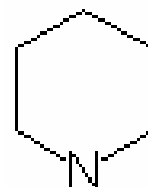
Exp.: J. Eßer, P. Wasserscheid, A. Jess, *Green Chem.* **6**, 2004, 316

Nitrogen Partition Coefficients K_N between [BMIM][OcSO₄] and Dodecane

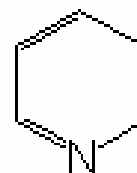
T=25°C	exp.	calc.
Indole	340	263.0
Piperidine	0.7	1.0
Pyridine	2.9	3.7



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 γ_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 σ -moment QSPR approach can be used to model partitioning between not well defined phases.

Acknowledgements

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Thank you !