

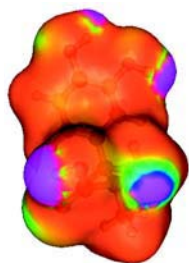
## COSMOtherm for drug research

### ...validated applications

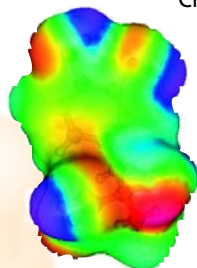
- drug solubility in water
- solubility in any solvent / solvent screening
- general partition coefficients between any solvents
- special partition properties: logBB, intestinal absorption, Human Serum Albumin Binding

### ...further potential applications

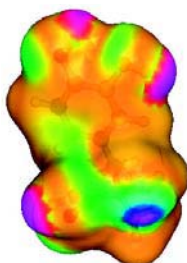
- unified interaction model of electrostatics, H-bonds, and lipophilicity
- valuable for molecular field analysis (MFA)
- extension to membrane modelling
- localisation of interaction sites
- solvent influence on morphology
- surely many other applications



Methyldopamin colored by Intestinal Absorption



Methyldopamin colored by  $\sigma$



Methyldopamin colored by Blood-Brain Partition Coefficient

## COSMOlogic Products

- > COSMOtherm: Software for Life Science and Fluid Phase Thermodynamics
- > COSMObase: Database of 3200 DFT/COSMO-files for common solvents and compounds
- > TURBOMOLE: Fast Quantum Chemical Program (Prof. R. Ahlrichs, Univ. of Karlsruhe, Redistribution and Support by COSMOlogic)
- > COSMOfrag: Software for rapid screening and HTS applications with COSMOtherm

## COSMOlogic Services

- > Consulting in Computational Chemistry and Fluid Phase Thermodynamics
- > Contract Calculations in the Context of COSMOtherm
- > Contract Research, Development, and Programming in Computational Chemistry related Areas
- > General Programming of Interfaces and Tools for Chemistry and Chemical Engineering

# COSMOtherm

A novel access to solubility, partitioning, and molecular interactions for drug design and development

**COSMOlogic** GmbH & Co. KG

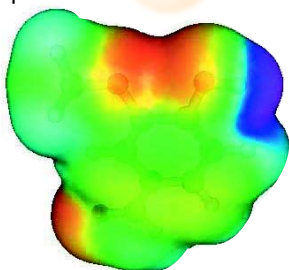
Your Competent Partner for  
Computational Chemistry and Fluid Thermodynamics

Burscheider Str. 515  
D-51381 Leverkusen  
Tel.: 49 (0) 2171 73168 0  
Fax: 49 (0) 2171 73168 9  
E-mail: [info@cosmologic.de](mailto:info@cosmologic.de)  
Web: <http://www.cosmologic.de>  
CEO: Dr. Andreas Klamt

CAChe Research, USA [cacheresearch.com](http://cacheresearch.com) [cosmo@cacheresearch.com](mailto:cosmo@cacheresearch.com)

Cosmotherm – It's Physics, not just QSAR!

COSMOtherm (originally COSMO-RS) derives the thermophysical behavior of liquids from the information provided by unimolecular quantum chemical calculations (DFT) on the compounds of interest. In these calculations each molecule is handled as if it was embedded in a conductor (COSMO-approximation). As a result, the screening charge density  $\sigma$  is available on each part of the molecular surface, as it is illustrated by vanillin on the right.

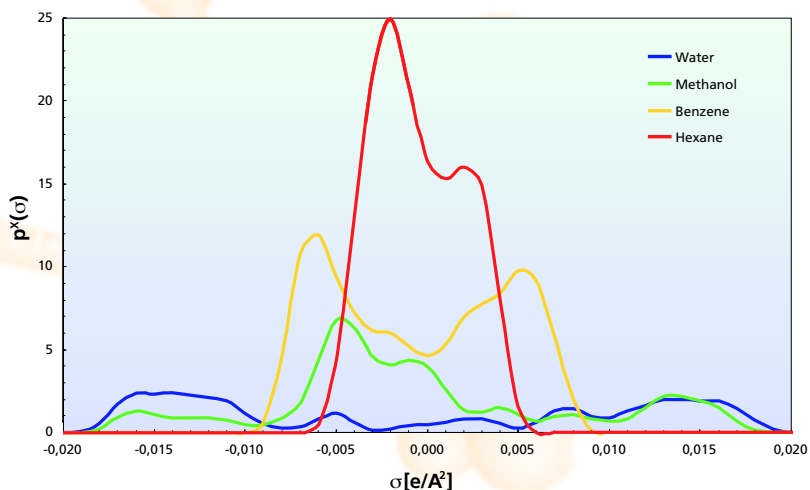


As a second step all interactions of molecules in liquids are described as contact interactions of molecular surfaces, and the interaction energies are quantified using the screening charge densities  $\sigma$  and  $\sigma'$  of the two interacting surface pieces. This results in the expressions

$$E_{hb}(\sigma, \sigma') = a_{eff} e_{hb}(\sigma, \sigma') = a_{eff} c_{hb} \min\{0, \sigma\sigma' + \sigma_{hb}^2\}$$

$$E_{misfit}(\sigma, \sigma') = a_{eff} e_{misfit}(\sigma, \sigma') = a_{eff} \frac{\alpha'}{2} (\sigma + \sigma')^2$$

for the electrostatic misfit and for the hydrogen bonding energy, respectively. The few parameters appearing in these formulae have been carefully adjusted to experimental data.

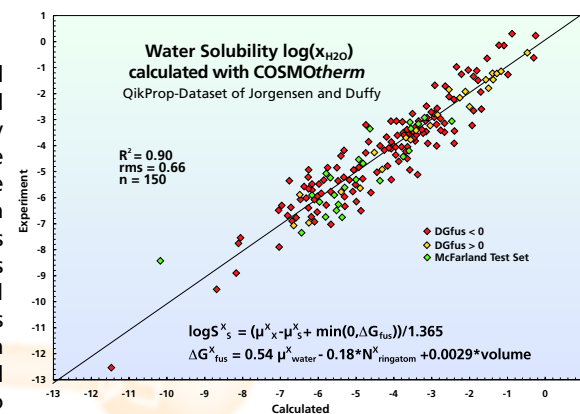


For an efficient statistical thermodynamics calculation the molecular surfaces are virtually split into small pieces of size  $a_{eff}$ , and contacts of such pieces are considered as independent. This approach (which is similar to the assumption of interacting surfaces in group contribution methods) corresponds to a reduction of the spatial screening charge distribution to a one-dimensional histogram, which we call  $\sigma$ -profile. As illustrated below  $\sigma$ -profiles  $p^x(\sigma)$  are characteristic for each compound X.

It is important to note, that the  $\sigma$ -profile  $p_S(\sigma)$  of a mixture S is simply given by the weighted sum of the  $\sigma$ -profiles of the components. Now the statistical thermodynamics of the system S of interacting surface pieces is calculated by an efficient and exact algorithm, ending up with a chemical potential of each component X. At this point, activity coefficients and many other thermophysical properties of the system (e.g. excess enthalpy and entropy and even vapor pressure) are readily available. This novel statistical thermodynamics is more exact than the algorithm used in group contribution methods, avoiding any mean-field assumption and hence being as reliable in the limit of infinite dilution as it is with finite concentrations.

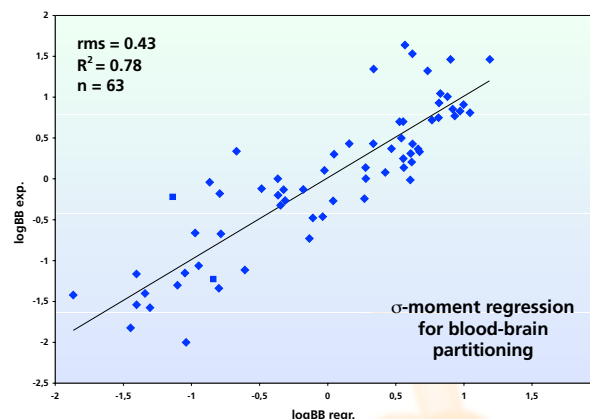
## Calculation of Solubility

Solubility of any liquid compound X in pure and mixed solvents and especially in water is readily calculated by COSMO-RS making use of the chemical potentials of X in the solvent and in its pure liquid state. In order to be able to predict solubilities of solid compounds,  $\Delta G_{fusion}$  has been fitted by physically meaningful regression using only 3 descriptors from COSMOtherm. As shown on a test set of pesticides, this method is very predictive even if applied to very different drugs and pesticides.



## Partition Coefficients

Partition coefficients between well-known solvent systems like octanol-water are available by COSMOtherm since the chemical



potential of each compound in the two phases can be calculated. The chemical composition of biological systems often is unknown and in addition the phases may be inhomogeneous. In these cases the  $\sigma$ -moment approach allows for the set up of QSPR models. Several ADME properties successfully have been calculated, such as: blood brain partition, intestinal absorption and human serum albumin binding.

## Efficiency Aspects

The quantum chemical density functional (DFT) COSMO calculations based on semi-empirical geometries can nowadays be run in about 8min for typical drug compounds even on normal PC-processors. COSMOtherm itself only takes milliseconds for a calculation and is able to run on any Windows or UNIX/LINUX computer. For rapid screening and HTS applications a shortcut of COSMOtherm (COSMOfrag) is available which derives  $\sigma$ -profiles from precalculated similar molecules. COSMOfrag calculations take only a few seconds per compound and thus allow for COSMOtherm usage in HTS projects.

## References:

- ♦ A. Klamt, J. Phys. Chem. 99 (1995) 2224.
- ♦ F. Eckert, A. Klamt, AIChE J. 48 (2002) 369.
- ♦ A. Klamt, F. Eckert, M. Hornig, M. Beck, T. Bürger, J. Comp. Chem. 23 (2002) 275.
- ♦ R. Jones, P. C. Conolly, A. Klamt, M. Diedenhofen, J. Chem. Inf. Model. 45 (2005) 1337.
- ♦ K. Wichmann, M. Diedenhofen, A. Klamt, J. Chem. Inf. Model. 47 (2007) 228.