Title: COSMOsim3D for drug-similarity, alignment, and COSMOsar3D for molecular field analysis

Christoph Loschen, ACS, San Diego, CA, March 26, 2012, 1:35PM to 2:10PM

Abstract Body: By the practical success of the COSMO-RS fluid phase thermodynamics model [1] in many areas of chemistry, the COSMO polarization charge densities σ have been proven to be excellent descriptors for the quantification of the most important kinds of molecular interactions in the liquid phase, as polar interactions, hydrogen bonding and hydrophobicity.

Since the same intermolecular interaction modes, which govern fluid phase thermodynamics, are also responsible for binding of ligands to receptors, it is most plausible that a σ-based description of ligand-receptor interactions should be very promising. Initial approaches in this direction [2] mostly have disregarded the spatial distribution of surface polarities. Only recently we have achieved a 3D-representation of the surface polarization charges by forming generating local σ-profiles on a regular grid. A 3D σ-similarity of two molecules can be defined as the sum of the σ-similarities on the grid points and by optimizing this similarity through rotation and translation of the probe molecule versus the target. This method is introduced here as COSMOsim3D.

The same technique can be used for subsequent molecular field analysis, for which we introduce the name COSMOsar3D. First validation studies have proven that COSMOsar3D, yields very promising results and seems to be superior compared to traditional MFA approaches not only regarding prediction quality, but also with respect to model robustness.

[1] (a) Klamt, A. J. Phys. Chem. 1995, 99, 2224-2235. (b) Klamt, A. COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamic and Drug Design; Elsevier: Amsterdam, 2005.

[2] Thormann, M., Klamt, A., Hornig, M., Almstetter, M. COSMOsim: Bioisosteric Similarity Based on COSMO-RS σ Profiles , J. Chem. Inf. Model., 2006, 46 (3), pp 1040–1053.

Title: **New developments in prediction of solid-state solubility and cocrystallization**

Christoph Loschen, ACS, San Diego, CA, March 29, 2012, 10:15AM to 10:45AM

Abstract Body: Due to its ability to treat mixtures at variable temperatures and to compute accurate solvation energies based on first-principles, the fluid phase thermodynamics theory COSMO-RS has become very useful in chemical engineering and in wide areas of physical and medicinal chemistry. Only recently it could be shown that COSMO-RS[1] as implemented in the COSMOtherm software package can be used for efficient screening of cocrystal forming compounds (coformers). The excess enthalpy H_{ex} of an active pharmaceutical ingredients (API) - coformer mixture reflects the tendency of those two compounds to form a cocrystal. Other applications of this approach are solvent selection during drug processing and estimation of solubilities. We will also demonstrate that in combination with our COSMObase library and the COSMOfrag software tool[2] efficient and accurate cocrystal and solubility screenings without a prior costly quantum chemical calculation can be performed on a large set of molecular data. Eventually some recent applications of COSMO-RS theory towards the description of crystal surface morphologies will be presented (COSMOhkl).

[1] A. Klamt, *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 2011, **1** , 699.

[2] M. Hornig and A. Klamt, *J. Chem. Inf. Model.*, 2005, **45** , 1169.