

Description of explicit solvation by automated water placement based on free energy

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Although many chemical reactions occur in solution, the elucidation of the involved solvated structures still presents a considerable challenge.

Quantum chemistry enables us to study the impact of an environment on the electronic structure. While continuum solvation models improve the description, they lack the ability to predict structural changes originating from explicit interactions with solvent molecules. Microsolvation, i.e., incorporation of few solvent molecules, improves the description of the structure in solution, but also implicates three major challenges.

The required number of solvent molecules, their location, and the relevant conformations of the solute in solution are often unknown.

We resolve these issues with a combined Molecular Dynamics (MD) and Grid Inhomogeneous Solvation Theory (GIST) [1] approach to analyze the solvent density around the solute. Our algorithm, Free Energy Based Identification of Solvation Sites (FEBISS), samples the phase space of the solute, locates favorable water positions and allows the user to select a sufficient number of water molecules to obtain a reliable physically sound microsolvation.

This methodology was applied to a variety of different systems. Our determined water positions are highly similar to ab-initio MD reference data [2] and neutron scattering data [3] and for a B₁₂ antivitamin we observe a significant structural change going from gas phase to solution, which was predicted by NMR spectroscopy [4] and not observed with implicit solvation. This work highlights the general applicability of our approach to systems of varying orders of magnitude and its capability to determine the number and position of water molecules for microsolvation studies.

[1] Nguyen, C. N. et al., J. Chem. Phys., 2012

[2] Weiss, A. K. et al., Mol. Biosyst. 2013

[3] Fabris, F. et al., Org. Biomol. Chem. 2012

[4] Tollinger, M. et al., Helv. Chim. Acta, 1999