

# Accurate NMR shift calculations for species in aqueous solution at ambient and high-pressure conditions

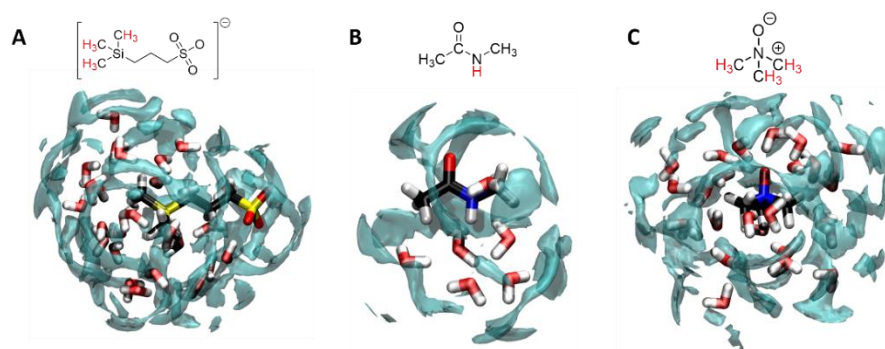
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Nuclear magnetic resonance (NMR) spectroscopy is one of the main analytical techniques to investigate chemical systems, and a broad range of conditions including high pressure ( $p$ ) can readily be investigated in NMR experiments. [1] In addition to experiments, computational methods have been employed to calculate NMR parameters and gain insight into experimentally inaccessible systems. An example for one of these systems is the effect of high- $p$  conditions on small molecules and peptide conformations in water. [2] However, reaching quantitative agreement with experiments is still a challenging task even at ambient conditions due to the high structural sensitivity of NMR calculations, especially with respect to the accurate description of the solvent influence.

Here we show the first example of joining state-of-the-art computational methodologies, *ab initio* molecular dynamics simulations (AIMD) for generating microsolvated structural ensembles and “embedded cluster reference interaction site model” (EC-RISM [3]) calculations for predicting accurate NMR response parameters for species in aqueous solution, extending a previous approach for electron paramagnetic resonance (EPR) parameters. [4] Applied to the reference compound trimethylsilylpropanesulfonate (DSS) and target molecules *N*-methylacetamide (NMA) and trimethylamine *N*-oxide (TMAO), we demonstrate that a hybrid solvent system, consisting of a limited number of explicit water molecules in an EC-RISM background, achieves quantitative accuracy for chemical shifts and is considerably more efficient than previous approaches. [5]



Using the same hybrid solvent system in classical force field molecular dynamics simulations (FFMD) reveals that the general approach to hybrid solvent systems is transferable. However, one drawback in FFMD-generated ensembles can be traced back to the inaccurate description of hydrogen bonds which need further improvement.

For high- $p$  NMR calculations we present the novel use of  $p$ -dependent geometry optimizations using EC-RISM. Despite small structural influence of pressure, the impact on  $p$ -dependent shifts matches the range of experimental changes, hence geometry change needs to be addressed.

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