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Theoretical Investigation of Solvent-Driven Dynamic Stereochemistry

VCD (vibrational circular dichroism) spectroscopy is established as a common and reliable method for investigating the absolute configuration of small molecules.1 However, in order to obtain a detailed understanding of the preferred conformation, suitable computer-assisted methods are necessary to enable a reliable conformational search and predict the experimental spectrum.1 Yet, the experimental and theoretical methods reach their limits or become more difficult once solvent effects become relevant and thus have to be taken into account as solvation can modulate conformational ensembles. More polar solvents, such as DMSO, can result in strong interaction with the investigated molecule, necessitating consideration of explicit microsolvation.1 To overcome this problem, a new approach using the EC-RISM solvation theory (Embedded Cluster Reference Interaction Site Model)2 was investigated. EC-RISM combines quantum mechanical calculations with the statistical mechanics-based 3D RISM solvation model in an iterative and self-consistent process and can be used for the direct determination of relative conformer free energies and their populations in solution. This approach provides added value over implicit solvation theories such as PCM (Polarizable Continuum Model) due to consideration of solvent site density correlation and distribution functions around a molecule of interest.3,4,5 Furthermore, a spatially resolved solvation free energy density is accessible that allows for assigning the contribution of certain solvent regions to the overall solvation effect.6 According to the most densely populated positions the relevant interactions between the solvent and solute can be predicted and applied for the placement of explicit solvent molecules. To evaluate this approach, two different compounds (Fig. 1) were analyzed in DMSO and chloroform solution, emphasizing solvent-driven conformational changes as well as the competition between intra- and intermolecular interactions.7,8

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Primary author(s) : Ms. TAN, Dilber (Ruhr-Universität Bochum)

Co-author(s) : Dr. TIELKER, Nicolas (Technische Universität Dortmund); Prof. KAST, Stefan (Technische Universität Dortmund); Prof. MERTEN, Christian (Ruhr-Universität Bochum)

Presenter(s) : Ms. TAN, Dilber (Ruhr-Universität Bochum)