

# Recent advances in the Embedded Cluster Reference Interaction Site Model

Patrick Kibies,<sup>1</sup> Nicolas Tielker,<sup>1</sup> Stefan Maste,<sup>1</sup> Miquel Alexandre Garcia-Ratés,<sup>2,3</sup>  
Frank Neese,<sup>2</sup> Stefan M. Kast<sup>1</sup>

<sup>1</sup>*Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund,  
44227 Dortmund, Germany*

<sup>2</sup>*Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany*

<sup>3</sup>*FAccTs GmbH, 50677 Köln, Germany*

The Embedded Cluster Reference Interaction Site Model (EC-RISM) is a well-established method to combine quantum-chemical calculations with the three-dimensional Reference Interaction Site Model (3D RISM). [1-3] This integral equation theory represents the solvent by the equilibrium distribution functions of its constituting atoms around the solute, from which thermodynamic properties such as the excess chemical potential and the partial molar volume are readily accessible. The quantum-chemical part of the EC-RISM method does not only provide the electrostatic part of solute-solvent interactions but also allows for the determination of observables from the solvent-polarized solute wave function, such as the electronic energy of the solvated molecule and spectroscopic information like infrared (IR) data, nuclear magnetic resonance (NMR) [4] and electron paramagnetic resonance (EPR) parameters. [5]

Quantitative results for the excess chemical potential have been obtained for water and organic solvents based on partial molar volume-based corrections, enabling the prediction of properties with high accuracy. In the SAMPL6 and SAMPL7 blind challenges, the acidity constants ( $pK_a$ ) of diverse sets of compounds could be predicted with consistent RMSEs of 1.15 and 0.72  $pK$  units, respectively. [6-8] Octanol-water partition coefficients ( $\log P$ ) of the challenge compounds on the other hand yielded a prediction range of 0.47-1.84, leaving room for improvement of organic phase models.

As a very recent development, the EC-RISM formalism was integrated directly into the SCF procedure of the popular quantum chemistry package ORCA. [9] In contrast to the established script-based approach, calculation of the electrostatic potential and of 3D RISM distribution functions are performed during the SCF iteration, saving considerable computational overhead. This approach also allows for the formulation of an analytic gradient enabling geometry optimizations on the EC-RISM free energy surface from which, for instance, pressure-dependent changes in molecular geometries and their influence on spectroscopic observables can be deduced. Early results indicate that the effect of small, pressure-induced changes in molecular structure on pressure-dependent NMR parameters can be significant.

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