The EC-RISM quantum solvation model for predicting tautomer ratios

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The "embedded cluster reference interaction site model" (EC-RISM) approach couples statistical-mechanical integral equation theory for predicting 3D solvent site distribution functions and quantum-chemical calculations [1]. The electronic structure of a solute is determined self-consistently with the solvent structure by mapping the continuous distribution onto a set of discrete background charges ("embedded cluster") as an additional contribution to the molecular Hamiltonian. Free energy data in solution including cavity and dispersion contributions is obtained directly from the integral equation results [2] without empirical adjustment of parameters. A particular advantage of the method is that the atomic, granular structure of the solvent is preserved which is important for the adequate treatment of directional effects such as H-bonding. Moreover, the approach is not restricted to dipolar solvent models as in continuum methods, making it suitable for modeling nonaqueous solvents such as benzene.

We outline the general framework and show that the EC-RISM method can be applied successfully to the problem of predicting tautomer free energy differences in aqueous solution that determine the species ratios. On the example of the compound set collected for the SAMPL2 prediction challenge [4] we analyze the influence of various factors on the accuracy such as the choice of the geometry (vacuum vs. solution phase), basis sets and quantum-chemical level of theory, and the parametrization of dispersive solute-solvent interactions. Without adjustments, a total r.m.s. error of ca 2 kcal mol^{-1} is achievable, while reparametrization of certain Lennard-Jones interaction terms can reduce the error to "chemical accuracy" of 1 kcal mol^{-1}.

[1] T. Kloss, J. Heil, S. M. Kast, *J. Phys. Chem. B* **2008**, *112*, 4337-4343.
[2] S. M. Kast, T. Kloss, *J. Chem. Phys.* **2008**, *129*, 236101.
[3] S. M. Kast et al., *J. Comput.-Aided Mol. Des.* **2010**, *24*, 343-353.
[4] M. T. Geballe et al., *J. Comput.-Aided Mol. Des.* **2010**, *24*, 259-279.