Prediction of aqueous acidities and tautomer ratios by embedded cluster integral equation theory

J. Heil(1), S. Ehrhart(1), T. Kloss(1), K. F. Schmidt(2), S. Güssregen(2), S. M. Kast(1)

(1) Eduard-Zintl-Institut für Anorganische und Physikalische Chemie, Technische Universität Darmstadt, Petersenstr. 20, 64287 Darmstadt, Germany
(2) Sanofi-Aventis Deutschland GmbH, R&D CAS Drug Design FFM, Industriepark Hoechst, 65926 Frankfurt am Main, Germany

The "embedded cluster reference interaction site model" (EC-RISM) approach combines statistical-mechanical integral equation theory and quantum-chemical calculations in order to predict thermodynamic data for chemical reactions in solution [1]. The electronic structure of the solute is determined self-consistently with the structure of the solvent which is described by 3D RISM integral equation theory. The coupling is achieved by mapping the continuous solvent-site distribution onto a set of discrete background charges ("embedded cluster") and using it as an additional contribution to the molecular Hamiltonian. Recent progress in the understanding of conceptual and numerical features of the integral equation approximations [2] allows computations on hundreds of compounds in a reasonable time with good accuracy.

We report results from the application of the EC-RISM methodology to the prediction of aqueous pKₐ values and of tautomer ratios for small organic molecules. We discuss critically important parameters that influence the accuracy of the approach, such as the adequate treatment of multiple conformations, the choice of the quantum-chemical level of theory, as well as the force field governing nonpolar solute-solvent interactions.

Please note that the content of the talk is also presented as a poster.
