

# $pK_a$ prediction for small organic molecules in dimethyl sulfoxide (DMSO)

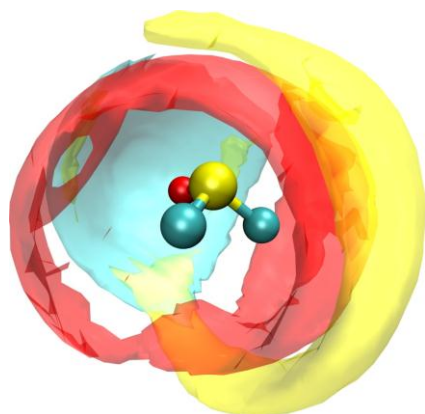
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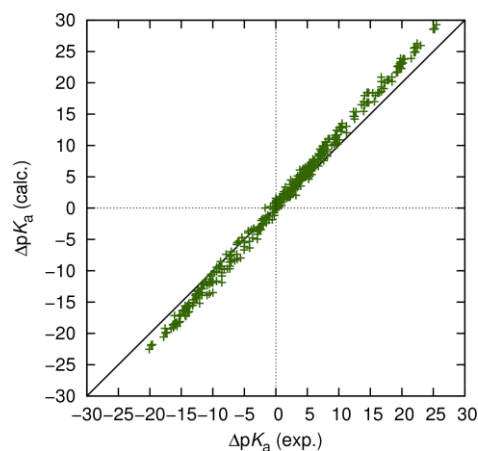
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The embedded cluster reference interaction site model (EC-RISM) approach combines statistical-mechanical integral equation theory and quantum-chemical calculations in order to predict thermodynamic data for chemical reactions in solution [1]. The electronic structure of the solute is determined self-consistently with the structure of the solvent which is described by 3D-RISM integral equation theory. 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. The EC-RISM method proved for instance useful for determining the tautomer state of small molecules in the context of the SAMPL2 challenge [3]. In comparison with typically employed dielectric continuum models the 3D-RISM methodology properly accounts for the molecular details of the solvent species.

Here we use EC-RISM to predict the acidity of small organic molecules in pure dimethyl sulfoxide (DMSO) solution. We critically discuss the influence of different solvent force field models and compare the performance of the EC-RISM method with results computed using the established polarizable continuum model (PCM). The results reveal significant improvements for various classes of compounds.



**Fig. 1.** Isosurfaces of distribution functions from calculations with 3D-RISM/HNC with the Liu model for DMSO solvent and solute [4], yellow/light: sulphur, red/dark: oxygen, blue/middle: methyl groups.



**Fig. 2.** Calculated vs. experimental  $pK_a$  shifts for phenole, aniline and thiophenole derivatives from B3LYP/6-311+G(d,p)/PCM//MP2/6-311+G(d,p)/EC-RISM/PSE-2(Liu) calculations.

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[4] H. Liu, F. Müller-Plathe, W. F. van Gunsteren, *J. Am. Chem. Soc.* **1995**, *117*, 4363.