

SUPRAMOLECULAR BINDING THERMODYNAMICS

By Dispersion-Corrected Density Functional Theory

Computing accurate binding free energies is a fundamental challenge to molecular modeling. Where the binding free energies of 29 ligands to the host CB7 were reproduced with an RMSE of 1.9 kcal/mol using PM6-DH+, though this involved fitting of the solvation free energy change.

In this study Grimme presents a computational methodology that reproduces binding free energies of 13 *chemically diverse* host-guest complexes with a MAD of 2.1 kcal/mol. Though the accuracies of the two studies are similar there are many differences between the two approaches.

The gas phase interaction energies are computed using dispersion corrected DFT calculations. Practically, this means that, unlike the study by Muddana and Gilson, no conformational averaging is performed. The dispersion correction includes a three-body term that is shown to contribute up to 4.6 kcal/mol to the gas phase interaction energy. The similar three-body terms also contribute to the vibrational free energy contributions (see below) and together with the gas phase contributions lower the MAD by 1.3 kcal/mol compared to experimental binding free energies.

Similarly, **the solvation free energy** is computed using DFT and COSMO and, unlike the Muddana and Gilson paper, is not corrected empirically. This may be due to the fact that the DFT/COSMO calculations (including the radii used to define the surface) already has been carefully calibrated while the PM6/COSMO calculations have not.

The **vibrational free energy corrections** are computed in the gas phase using dispersion and hydrogen-bond corrected PM6 and DFTB (PM6-D3H and DFTB-D3H, respectively). These corrections were developed as part of this study based on the S66 data set and implemented in an external program interfaced with the MOPAC and DFTB codes (Grimme, personal communications).

The **vibrational entropy contribution increases exponentially with decreasing vibrational frequency** and this can introduce numerical unstable binding free energies for these systems as low vibrational frequencies are common. Grimme deals with this problem by introducing a hybrid function where the vibrational entropy is smoothly replaced (using a switching function) with a corresponding free-rotor entropy for low frequency modes. As computed in his study, the free-rotor entropy increases much less steeply as the vibrational frequency decreases and produced binding free energies that are in better agreement with experiment.

However, computing numerically stable vibrational frequencies for low frequency modes remains a challenge for these systems and may require manual intervention (Grimme, personal communications).

Source: <http://www.compchemhighlights.org/2013/02/supramolecular-binding-thermodynamics.html>