Localization and decomposition of free energies in solution

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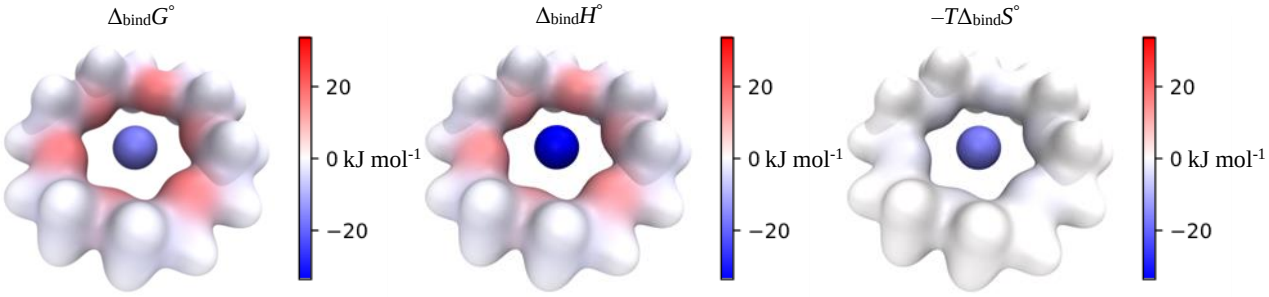
The Gibbs free energy is the relevant thermodynamic quantity to understand the direction and outcomes of chemical reactions or biophysical processes. It is directly associated with partition coefficients, solubilities, or binding constants for host-guest and protein-ligand complexes. Therefore, several experimental and computational methods are established to determine binding free energies. However, these methods only yield macroscopic quantities and offer no insight into individual contributions of the system's components. Interpreting these macroscopic quantities can be especially challenging, for instance, when the reaction Gibbs energy is relatively small due to underlying counteracting processes. [1]

In order to get a better insight into the reaction thermodynamics we here present approaches to decompose and localize free energy contributions using both classical force field (FF) and quantum mechanical (QM) methods. Both methods employ the decomposition of the reaction Gibbs free energy into energetic and entropic proportions, and furthermore split these into solvation and gas phase contributions.

In the QM approach, free energy decomposition is achieved by combining the embedded reference interaction site model (EC-RISM) for solvation thermodynamics with a normal mode analysis (NMA) calculation to obtain gas phase contributions. Moreover, to not only decompose but also localize the free energy contributions, we use the three-dimensional reference interaction site model (3D RISM) in the FF approach. Local solvation (free) energies and entropies can then be mapped onto individual molecular sites or groups. [2,3] Local energetic components are calculated using molecular dynamics simulations, while local vibrational entropy contributions can be obtained via NMA or density of states integration (DSI). [4,5]



With these novel approaches we can combine both the decomposition and localization aspects, as atom-wise contributions are not only calculated for the binding free energy but also for its thermodynamic components. These atom-local values can then be visualized and used to identify "hot spots" in terms of reaction sites or protein regions for, e.g., ligand binding. [4] Furthermore, major energetic and entropic contributions to the driving force can be identified. Exemplary applications include crown ether complexes and solvent-controlled supramolecular cage formation.

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