

Insights into Chemistry through the Computation of Free Energy Hot-Spots

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Predicting free energies is one of the key challenges in modern quantum chemistry [1]. For small, unimolecular systems this is usually done via a frequency analysis of the molecule using quantum mechanics (QM) calculations. For large systems, usually free energy differences computed from sampled energies are considered by applying, e.g., Bennett's acceptance ratio method [2]. The interpretation of free energy results is in most cases not straightforward, because it is not possible to distinguish different contributions [3] and, therefore, to understand the underlying effects (e.g., bond weakening, sterical clashes, new non-covalent interactions) causing the free energy to change. Based on an approach originally introduced by Berens *et al.* [4] to estimate quantum corrections to thermodynamic properties, we present a method [5,6] that calculates the vibrational part of the free energy from the vibrational density of states function and locates changes in the potential energy surface. Those are the so-called hot-spots, which we interpreted as the locations causing the overall free energy change. We show the performance of our method for two examples. The first uses classical mechanics to describe the binding of a protein and an inhibitor, where our method identifies all relevant interactions between protein and inhibitor. The second example uses quantum mechanics to identify all atoms affected by the anomeric effect in glucose. We expect, our method to be generally applicable for visualizing and understanding changes between two states within molecular transformations.

References

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