Automated Exploration of the low-energy Chemical Space with fast Quantum Chemical Methods

Stefan Grimme

Mulliken Center for Theoretical Chemistry

Efficient schemes for the in silico sampling of the molecular chemical space by semiempirical tightbinding methods combined with a meta-dynamics driven search algorithm are described. The focus is set on the generation of proper thermodynamic ensembles at a quantum chemical level for conformers, but similar procedures for protonation states, tautomerism and non-covalent complex geometries are also discussed. The ensembles consisting of all significantly populated minimum energy structures normally form the basis of further, mostly DFT computational work, e.g. with composite methods like PBEh-3c or B97-3c as the next step.
By using basic quantum chemical methods, electronic effects or possible bond breaking/formation are accounted for and a very reasonable initial energetic ranking of the candidate structures is obtained. Due to the huge computational speedup gained by the fast low-cost quantum chemical methods, overall short computation times even for systems with hundreds of atoms (typically drugsized molecules) are achieved. Furthermore, specialized applications, such as sampling with implicit solvation models or constrained sampling for transition states, metal-, surface-, or non-covalently bound complexes as well as application to 1H-NMR spectroscopy is discussed. The procedures have been implemented in a freely available computer code called CREST, that makes use of the fast and reliable GFNn-xTB methods.