First principles sampling and representation of a reduced molecular potential energy surface

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Flexible organic molecules can adopt a variety of conformations that can interconvert. Here we describe our efforts to employ first principles to study the dynamics of such conformational ensemble and to investigate the potential energy surface (PES) of a well-characterized synthetic peptide γα [1].
We utilize a genetic algorithm based search for sampling the conformational space of the γα peptide. We combine the conformers found by the algorithm with reference conformers [1] and create a conformational ensemble of 73 conformers with a relative energy below 0.3 eV. A transition between two conformers can be direct, with a single barrier, or indirect, i.e. combined from multiple direct transitions. We assume that pairs of conformers connected by a direct transition are geometrically similar and interconvert via a limited number of rotations around single bonds. We construct a similarity matrix by calculating torsional RMSD for all conformer pairs. Subsequently, we remove all values exceeding a threshold of 0.3 rad and convert the matrix to a network, where the nodes represent conformers and the edges their distance in torsion angle space. We employ the shortest path Dijkstra algorithm in order to connect the 10 energetically lowest conformers to obtain a reduced network. For each of the pairs of conformers from the reduced network we suggest a transition path. The paths are optimized by the aimsChain routine that implements the string method and the corresponding transition states are identified. We present the results in form of a barrier tree and in form of a disconnectivity graph. Furthermore we use the obtained information to verify the conformational coverage of the global search. In addition we investigate the relation between the alternatives to the torsional RMSD as a similarity metric and the composition of the reduced network.
Our approach does not only provide a reduced and meaningful representation of the PES, it also provides an ideal starting point to refer to experiments and towards generation of free energy surfaces by biased molecular dynamics techniques.

[1] R. Kusaka, D. Zhang, P. S. Walsh, J. R. Gord, B. F. Fisher, S. H. Gellman, T. S. Zwier, *J. Phys. Chem. A,* **2013**, *117*, 10847–10862.