

Ab initio molecular dynamics for biomolecular spectroscopy

Mariana Rossi

Fritz-Haber-Institut der Max-Planck-Gesellschaft, Faradayweg 4-6, D-14195, Berlin, Germany

Accurate theoretical predictions for peptides and proteins (structure, dynamics, function) require an accurate, verified description of the underlying potential energy surface (PES). However, a completely trustworthy first-principles quality treatment that is affordable even for moderately sized systems (few hundred atoms) is arguably not yet settled. We here provide experiment-theory benchmark studies of designed polypeptides *in vacuo*, a “clean-room” environment which allows an unambiguous comparison.

We address mostly the helix-forming alanine-based Ac-Ala_{*n*}-LysH⁺ polypeptide series in the gas phase, for which experiments [1, 2] have indicated helical structures for $n \geq 8$. We explore extensively the conformational space of these molecules by performing thousands of relaxations using the van der Waals corrected [3] PBE exchange-correlation potential (PBE+vdW), as implemented in the FHI-aims program package [4]. We find that helices emerge as the preferred structure in the length range $n=4-8$ not just due to enthalpic factors (hydrogen bonds and their cooperativity, van der Waals dispersion interactions, electrostatics), but importantly also by a vibrational entropic stabilization over competing conformers at room temperature. The stabilization is shown to be due to softer low-frequency vibrational modes in helical conformers than in more compact ones, which produce significant differences in vibrational entropy [5]. This observation is in agreement with experiment [2], and with our own previous work [6], employing a quantitative comparison of calculated *ab initio* anharmonic IR spectra to experimental IR multiphoton dissociation (IRMPD) data, that show firmly α -helical structures for $n=10, 15,$ and 19 at 300 K.

As an overview, benchmark energy hierarchies for Ac-Ala₅-LysH⁺ (80 atoms) using methods beyond DFT (MP2, RPA) will be shown, and limitations of the current feasible methods will be discussed. Also, recent efforts to enhance even further the quality of the PES and include quantum nuclear effects in the IR spectra of molecules through path-integral molecular dynamics and modern flexible thermostats will be briefly discussed.

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