A small change in composiiton - a large change in dynamics?

Infrared-Spectra of NFGAIL and it's Flourinated Analogues

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Kurzgefasst

- Scaling cascades in protein dynamics
- Infrared signatures of peptide conformations
- REactive modes

Introduction

The conformational dynamics of proteins and peptides is a hierarchical process which involves characteristic time scales ranging from 10^{-12} seconds to 10^{0} seconds.

The physical models of the conformational dynamics consist predominantly of *local* interactions. Hence long-range interactions and dynamics on all time scale levels are mediated by a chain of local interactions.

Small, local, changes in the underlying potential as can be chemically realised by substitution of atom group, or replacing a single hydrogen atom by a halogen, can alter the dynamics of the peptide and hence its propensity to fold. For the hexa-peptide NFGAIL (Asn-Phe-Gly-Ala-Ile-Leu) 1, which is part of a human amyloid peptide, small chemical perturbations have been shown to drastically alter the process of fibril formation [1–3]. Aggregation of (misfolded) oligopeptides is a molecular processes present in Alzheimer's disease.

As a part of project B05 in the CRC1114 "scaling cascades in complex systems", a spectroscopic experiment in which vibrational modes are selectively excited such that the dynamics along a chosen reaction coordinate (RC) are sped up is being built in the group of Karsten Heyne. They aim for changing the conformational dynamics of the halogenated NFGAIL monomers by directly exciting âreactive modesâ along the numerically derived RCs. A reactive mode is a vibrational mode that points along the RC. Selectively exciting this mode by an IR pump pulse should trigger a conformational change, which subsequently can be read out by an IR probe pulse.

First principles calculations of vibrational spectra In order to link IR experiments to simulation data we will compute IR spectra of different conformers of the NFGAIL peptide and its fluorinated counterpart. To this end we will apply density functional theory molecular dynamics simulations allowing us to explicitly account for anharmonic effects, solvent and finite temperature.

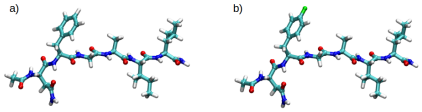

Abbildung 1: *The hexa-peptide a) NFGAIL and b) its fluorinated analoge 4Phe-NFGAIL*

Although, due to the computational demands of first principle simulations, only time-scales on the order of tens of picoseconds are directly accessible, this data will be of additional value by serving as a reference to evaluate the short time-scale behaviour of the classical simulations. In particular, all interactions with the solvent will be modelled explicitly, including polarisation effects, enabling us to directly analyse the coupling of solute-solvent interactions with the internal motions of the solute peptides. IR spectra can be computed from first principles molecular dynamics simulations via the Fourier transform of the autocorrelation function of the dipole moments along the trajectory.

Reactive modes We will use classical molecular dynamics simulations so as to explore the conformational dynamics of the hexapeptide. Beside the probabilities of the different conformations, these simulations will provide a model for the time scales and transition vectors for the conformational transitions. These information needs to be related to motions that can be excited by IR light so as to stimulate transitions. To this end, the high-dimensional transition vectors will be projected onto the vibrational modes obtained from the first-principles simulations. The best match that also has a significant intensity, according t the computed spectra can then be tested experimental and validated with respect of acceleration (or slowing down of) the (mis)-folding transitions.

WWW

`http://www.sfb1114.de`

Weitere Informationen

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