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Solvent viscosity effects on the conformational dynamics of a helical hexapeptide

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Solvent Viscosity Effects on the Conformational Dynamics of a Helical Hexapeptide

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We have used ^{13}C dynamic NMR spectroscopy to determine the rate constants for the conformational dynamics of a 3_{10} helical hexameric peptide, Z-$(Aib)_6$-OtBu (Aib = residue of alpha-aminoisobutyric acid). Because the strongly helix-promoting Aib residue is achiral, oligomers of Aib will form left- and right-handed helices with equal probability. Furthermore, these helices interconvert, through a large number of single bond rotations, between left- and right-handed helical forms on a timescale that is measurable via ^{13}C dynamic NMR. We have measured rate constants for this interconversion in a series of solvents of varying viscosities, including small, 1-, 2-, and 4-carbon alcohols, measured at temperatures between ~ 3°C and ~43 °C. Our work is in contrast to the studies that seek to quantify the role of solvent viscosity using viscogens such as glycerol, ethylene glycol, and glucose added to dilute aqueous solutions of biopolymers. We have observed that, at low temperatures, the solvent viscosity limits the rate of the conformational dynamics of this peptide in a 1/eta fashion, consistent with Kramers' diffusional model of reaction dynamics in a viscous medium. At higher temperatures, the rate constants do not appear to adhere to a 1/eta-type dependence. Our poster will interpret the measured rate constants within Kramers' theory and alternative theories of condensed-phase conformational dynamics.

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Unharmonicity And Self-Similarity Of The Free Energy Landscape Of Protein G

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Unprecedented insight into the organization of the near-native free energy landscape of protein G is obtained from 0.4 micro seconds long atomistic molecular dynamics simulations in explicit solvent. Novel models and frameworks are used to assess the time-dependence of salient thermodynamical features. While the quasi-harmonic character of the free energy is found to degrade in a few ns, the slow modes display a very mild dependence on the trajectory duration. This property is shown to originate from a striking self-similarity of the free energy landscape embodied by the consistency of the principal directions of its local minima and of the ``virtual jumps" connecting them.

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Molecular dynamics studies on the closed to open transition of the SHP-2 N-SH2-domain phosphotyrosine-peptide binding cleft

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The N-terminal SH2 domain (N-SH2) of the non-receptor tyrosine phosphatase SHP-2 is involved in localization of SHP-2 by recognition of phosphotyrosine (pY) peptides as well as self-inhibition of SHP-2 phosphatase activity through the formation of a protein-protein interface with the phosphatase domain. Mutations that disrupt this interface can increase both SHP-2 phosphatase activity and pY-peptide binding affinity, and are associated with pediatric leukemias and the congenital condition Noonan syndrome. We have applied explicit-solvent molecular dynamics simulations to study the closed to open transition of the N-SH2 pY-peptide binding cleft so as to better characterize the molecular process involved in N-SH2 pY-dependent binding. The simulations show that changes in the backbone conformation of a single residue, Tyr66, can control this transition by inducing loop motion. The existence of stable conformations in the left-handed helical and the extended regions of Tyr66 phi/psi space prevent rapid interconversion of the backbone and create a conformational switch. Additionally, in the open conformation, sidechain-sidechain interactions serve to pin the Tyr66 sidechain to the surface of the protein and away from the binding cleft entrance, unlike in the closed conformation where this sidechain partially occludes the cleft. The conformational properties of the Tyr66 backbone and sidechain suggest a mechanism for pY-peptide binding, and the structurally well-defined binding cleft conformations resulting from the