Invited Lecture
Inter-Disciplinary Explorations in Chemistry (I-DEC 2018)

Studying Protein Conformational Dynamics

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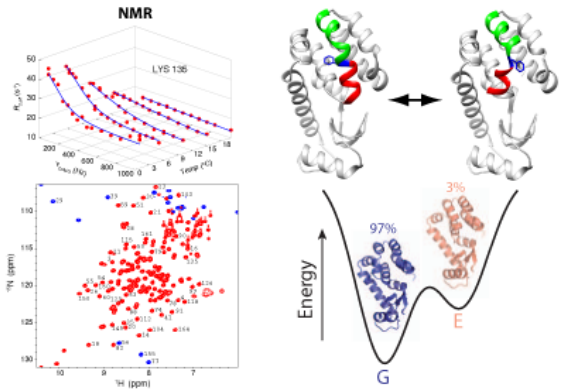
Abstract:
At ambient temperature protein molecules populate different conformational states in solution. Exchange is normally between a dominant ground state and different minor states that are populated to only a few percent and are invisible to all traditional biophysical techniques. However these 'invisible' minor conformers can be detected by modern NMR techniques so long as they are populated to ~0.5% and have lifetimes in the microsecond to 50 millisecond range [1]. CPMG type relaxation dispersion experiments can be used to study exchange occurring on the millisecond timescale. These new methods have been used to understand the conformational dynamics of cavity mutants of T4 lysozyme and have shown that the protein interconverts on the millisecond timescale between two conformations termed 'buried' and 'exposed'. In the 'buried' form Phe114 is buried in the core of the protein and exposed to solvent in the 'exposed' form [2]. A combination of experimentally guided MD simulations show that the activation barrier for the interconversion is a very modest ~5 k_BT [3]. New multiquantum CPMG experiments that are more sensitive to conformational exchange have been developed [4,5] and are providing insights into how the protein molecule gets activated to make the transition.



References and Notes:

1. NMR paves the way for atomic level descriptions of sparsely populated, transiently formed biomolecular conformers. *PNAS*, **110**, 12867-12874 (2013)
2. Solution structure of a minor and transiently formed state of a T4 lysozyme mutant. *Nature.* **477**, 111-114 (2011).
3. Atomistic Picture of Conformational Exchange in a T4 Lysozyme Cavity Mutant: An Experiment-Guided Molecular Dynamics Study. *Chem Sci.* **7**, 3602-3613 (2016)
4. Enhancing the Sensitivity of CPMG Relaxation Dispersion to Conformational Exchange Processes by Multiple-Quantum Spectroscopy. *Angew Chem Int Ed Engl.* **55**, 11490-11494 (2016)
5. Measuring the signs of the methyl ^{1}H chemical shift differences between major and 'invisible' minor protein conformational states using methyl ^{1}H multi- quantum spectroscopy. *J. Biomol. NMR.* **70**, 187-202 (2018)

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Bio-Sketch of Speaker

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Research Interests:
1) Studying Conformational Dynamics of Biomolecules.
2) Developing new NMR methods to study the conformational dynamics of biomolecules.