PROTEIN ELECTROSTATICS: Experimental insights that CHALLENGE THE COMPUTATIONAL PARADIGM

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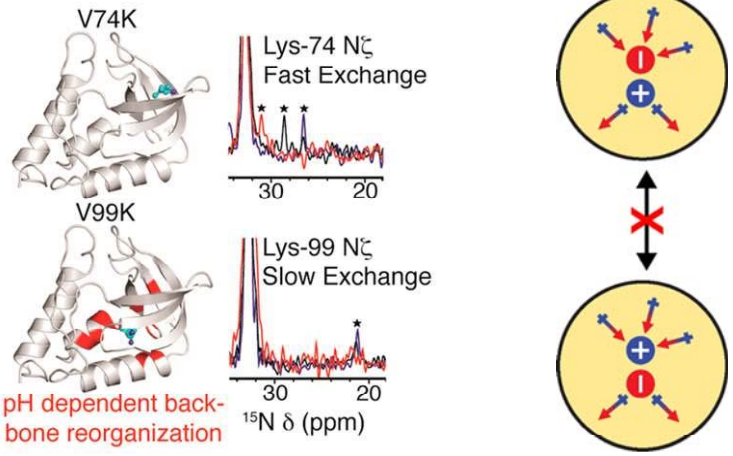
Proteins: Structure, Function and Genetics

Seminar Details:

Date: March 18
Time: 4:00 pm
Venue: Chemistry Department Committee Room (MS710)



ABSTRACT

I will give a brief introduction on protein electrostatics followed by a summary of the properties of surface ionizable residues. Most ionizable residues (Asp, Glu, Lys, His, Arg) are found on the surface of proteins, where their charged moieties can have unrestricted access to water. The properties of these residues are governed by their unlimited access to water. In contrast, a few ionizable residues are buried below the protein-water interface. Although relatively rare, these internal ionizable residues are essential for H^+ transport, e^- transfer, catalysis, and all other forms of biological energy transduction performed by proteins. Because the charged forms of these residues are incompatible with the dry and hydrophobic character of the protein interior, the pK_a values of buried Asp, Glu, Lys and His can shift, always in the direction that favors the neutral state, often dramatically (e.g. pK_a > 10 for Asp and Glu, pK_a < 5 for Lys). These shifts in pK_a render the stability of the folded state highly pH sensitive. I will describe past results from an ongoing, systematic study of buried ionizable residues; we have measured pK_a values of Asp, Glu, Lys, His and Arg at 25 internal positions in staphylococcal nuclease and of Lys at 10 internal positions in ribonuclease H. The microenvironments of buried ionizable groups were characterized with crystal structures. NMR spectroscopy was used to examine conformational changes coupled to the ionization of buried groups. Structural reorganization of widely different amplitudes has been observed (local, partial, sub-global and global unfolding). These structural transitions govern the pK_a values of these buried groups and they are extremely difficult to reproduce with structure-based calculations. I will describe recent work showing that buried groups with anomalous pK_a values can be used to engineer pH switch proteins that respond with a large conformational change to small changes in pH in the physiological range. This approach will be useful to engineer protein therapeutics (e.g. toxins and antibodies) that take advantage of the known differences in pH in cancerous and normal tissues.

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