

## Extra Seminar

Tuesday, September 7, 2010

10h00, HL 214

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### **“Nanomechanics at the single molecule level”**

Understanding the molecular mechanisms that confer mechanical stability to well-defined biological systems is a major challenge in modern physics, chemistry and biology. For example, while cell mechanics is known to play a decisive role in determining cell shape and also in endo- and exocytosis, the chemical origin of the membrane mechanical resistance remains largely unknown. Using force-spectroscopy AFM, we demonstrate that the overall mechanical stability of the lipid bilayer results from a complex and fine mechanochemical balance, where the chemical composition of both the headgroup and tail has a crucial effect. At the single molecule level, force-clamp spectroscopy allows us to monitor for the first time the conformational dynamics of a single protein along its route to the fold. Contrary to previous belief, we demonstrate that the acquisition of the protein's native conformation occurs after dynamic maturation of an ensemble of collapsed states that are mechanically labile and structurally heterogeneous. These results support the validity of statistical mechanics models in describing the folding of a small protein on biological timescales. Remarkably, the existence of such newly discovered ensemble of collapsed states that hold the key to explaining how an extended polypeptide folds while regaining its mechanical stability is likely to have profound implications on the onset of conformational diseases, occurring at the level of a single molecule. Finally, mechanical force provides an alternative means to heat or electricity to activate chemical reactions. However, the full reconstruction of the potential energy surface governing a chemical reaction under force remains still largely incomplete. Using a combination of protein engineering techniques with single molecule force-clamp spectroscopy we examined the influence of force on the rate at which a protein disulfide bond is reduced by nucleophiles in a bimolecular substitution reaction ( $S_N2$ ). Our experiments directly identify a reactivity switch occurring at  $\sim 500$  pN, resulting from a force-induced conformational change in the ground state of the disulfide bond. The single protein data is providing a new view that will help guide the development of theories on the statistical dynamics of folding and *ab-initio* studies of a chemical reaction while placed under a stretching force; of common occurrence in nature.

Coffee/tea will be available at 09h50