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**Fast Events in Protein Folding following Ultrarapid Mixing** LISA LAPIDUS, KIMBERLY COOPER, EMILY TUBMANN, Michigan State U., DAVID HERTZOG, Stanford U. & LLNL, JUAN SANTIAGO, Stanford U., OLGICA BAKAJIN, LLNL — A continuous flow microfluidic mixer fabricated out of fused silica was used to study microsecond time scales of protein folding by monitoring natural tryptophan fluorescence. This mixer uses hydrodynamic focusing and diffusion to lower the concentration of the initial denaturant, inducing the protein to fold. The mixing time can be as fast as 8 $\mu$s and allows access to times that are inaccessible in conventional mixers. Using a confocal microscope we observe the UV fluorescence spectrum from naturally occurring tryptophans in 3 well-studied proteins, cytochrome c, apomyoglobin and lysozyme, as a function of time after rapid mixing. Single value decomposition of the time dependent spectra reveal two separate processes: 1) a spectral shift which occurs within the mixing time and 2) a fluorescence decay occurring between 100 and 300 microseconds. We attribute the first process to hydrophobic collapse and the second process the formation of the first tertiary contacts. While the slower rate obviously depends on the details of the folding trajectory of each protein, we note that all three measured rates anti-correlate well with the fraction of secondary structure formed. This work demonstrates that hydrophobic collapse is much faster than had been estimated with slower mixing methods and is in good agreement with measured rates of intramolecular diffusion in unstructured peptides.

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