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Kinetics and Thermodynamics of Peptide (pHLIP) insertion and folding in a lipid bilayer OLEG ANDREEV, ALEXANDER KARABADZHAK, DHAMMIKA WEERAKKODY, Physics Department, URI, VLADISLAV MARKIN, Department of Neurology, UT Southwestern Med. Cent., DONALD ENGELMAN, Department of Mol. Biophys. & Biochem., Yale Univ., YANA RESHETNYAK, Physics Department, URI — We study spontaneous insertion and folding across a lipid bilayer of moderately polar membrane peptide pHLIP - pH Low Insertion Peptide. pHLIP has three major states: soluble in water or bound to the surface of a lipid bilayer as an unstructured monomer, and inserted across the bilayer as a monomeric α-helix. We used fluorescence spectroscopy and isothermal titration calorimetry to calculate the transition energies between states. The free energy of binding to a surface of lipid bilayer is about -7 kcal/mol and the free energy of insertion and folding across a lipid bilayer at low pH is nearly -2 kcal/mol. We performed stopped-flow fluorescence and CD measurements to elucidate molecular mechanism of pHLIP insertion and folding within a lipid bilayer and to calculate the activation energy of formation of transmembrane helix. pHLIP also has utility as an agent to target diseased tissues and translocate molecules through the membrane into the cytoplasm of cells in environments with elevated levels of extracellular acidity, as in cancer and inflammation. We plan to discuss a number of related kinetics and thermodynamic parameters from our measurements.

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