W-AM-L9

INTERACTIONS OF SMALL SOLUTES WITH MEMBRANES ((A. Pohorille, M. A. Wilson and C. Chipot)) Dept. of Pharmaceutical Chemistry, Univ. of California, San Francisco, CA 94143 and NASA-Ames Research Center, Moffett Field, CA 94035 (Spon. by L. R. Pratt)

The behavior of 15 small solutes at the water–membrane interface was investigated. The free energy of nonpolar molecules decreases monotonically from water to the membrane interior. In contrast, the free energy of solutes that exhibit some polarity has an interfacial minimum which arises from superposition of two monotonically and oppositely changing contributions: electrostatic and nonelectrostatic. Conformational preferences of flexible solutes depend on their position in the water–membrane system and, conversely, the structure and dynamics of the membrane is influence by the solutes. These results lead to a general description of interactions of small molecules with membranes helpful in understanding drug delivery across biomembranes and the mechanism of anesthetic action.

PROTEIN FOLDING

W-PM-Sym-1

THERMODYNAMICS OF PROTEIN CONDENSATIONS.
Gregorio Weber, School of Chemical Sciences, U. of Illinois.
The processes of protein subunit association and polypeptide folding (Protein condensations) are both driven by the excess entropy of the products. Contrary to a long-standing impression the changes in enthalpy and entropy with temperature are not fixed by the second law of thermodynamics but require specific thermodynamic models for their separation. One such model is that both enthalpy and entropy changes depend simply on the probability of thermal bond breaking. The free energy changes of the association of dimers and tetramers with pressure and temperature have been derived from that model and permit some general conclusions: 1: Entropy-driven reactions are only possible when the enthalpy changes of reactants and products virtually compensate each other so that $\sigma \approx 2\ \Delta H / (H_{pro.} + H_{react}) < < 1$. 2: A sufficient entropy change indispensably requires many bonds of energy less than 2 kcal/mol in the products and greater than 4 kcal/mol in the reactants. 3: The entropy increase on association depends upon conversion of the stronger protein-water (P-W) bonds into much weaker protein-protein (P-P) bonds. The conversion of P-W (hydrophobic bonds) into water-water bonds makes an insignificant contribution to the entropy change. 4: The dissociation of oligomers by hydrostatic pressure is due to the preferential destabilization by compression (Born repulsion) of the weak apolar bonds in the protein. 5: In several dimers and tetramers the enthalpy of association is approximately 25±5 kcal/mol per 1000 Å of contact surface. 6: Appreciable contributions to the entropy are limited to those bonds with breaking correlation times of less then 0.5 ns. Computations of protein folding alomg similar lines require further hypotheses concerning the relations of the entropy-driven apolar interactions and those owing to peptide dipole interactions.

W-PM-Sym-2

THE BARRIERS IN PROTEIN FOLDING. ((T. R. Sosnick, L. Mayne, S. W. Englander)) The Johnson Foundation, Department of Biochemistry and Biophysics, University of Pennsylvania, Philadelphia, PA 19104-6059.

Cytochrome c can fold rapidly, ~10 msec at 10° C, in a 2-state manner without populating intermediates. This establishes that all the required intrinsic steps in folding, including side-chain packing are inherently fast processes. These results are contrary to the current paradigm that particular steps in protein folding, including the supposedly rate-limiting molten globule to native transition, are intrinsically slow. It appears that kinetic intermediates so far characterized are trapped by barriers representing correction of misfolds formed in the initial collapse. When misfolding does not occur, our results with cyt c show that the intrinsic rate limiting step in folding is the initial collapse. Further experiments indicate that collapse is a nucleation process, limited by an energetically uphill conformational search for a relatively large scale configuration that can nucleate subsequent energetically downhill folding, perhaps through a defined sequence of intermediates, that leads to the native state.

W-PM-Sym-3

PROTEIN STRUCTURE PREDICTION BY MIMICKING FOLDING PATHWAYS. ((J. Moult)) Center for Advanced Research for Biotechnology.

W-PM-Sym-4

LINUS – A HIERARCHIC APPROACH TO PROTEIN STRUCTURE PREDICTION. ((George D. Rose and Rajgopal Srinivasan)) Johns Hopkins University, School of Medicine, Department of Biophysics and Biophysical Chemistry, 725 N. Wolfe Street, Baltimore, MD 21205. LINUS is a hierarchic procedure to predict the fold of a protein from its amino acid sequence alone. The name is an acronym for Local Independently Nucleated Units of Structure. The algorithm, which has been implemented in a computer program, ascends the folding hierarchy in discrete stages, with concomitant accretion of structure at each step. The chain is represented by simplified geometry and folds under the influence of a primitive energy function. The only accurately described energetic quantity in this work is hard sphere repulsion – the principal force involved in organizing protein conformation. Initially, LINUS was applied to large, overlapping fragments from a diverse test set of X-ray elucidated proteins, with generally accurate but rather imprecise prediction of overall fragment topology, including both secondary and supersecondary structure. Recent improvements to the program will be described.