Apolar-polar Competition for Water of Hydration Drives Protein Function

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Thesis: *According to the old adage, "Oil and water don't mix!" But oil-like and vinegar-like side chains, constrained by the amino acid sequence of a protein, are forced to interact, and the physico-chemical forces controlling waters of hydration provide the basis for protein function in biology.* The key aspect to the interactional forces arises from the hydration of oil-like (hydrophobic) and vinegar-like (e.g., charged) side chains as well as other bound functional groups. Of course, the well-appreciated hydration of charged (polar) groups is exothermic; ΔE(charge hydration) is negative. As shown in 1937 by Butler, however, the hydration of hydrophobic (apolar) groups is exothermic, that is, ΔE(hydrophobic hydration) is also negative! Yet with addition of too many hydrophobic groups solubility is lost, because the $(-T\Delta S)$-term of the Gibbs free energy for solubility, $\Delta G(\text{solubility}) = \Delta E - T\Delta S$, is positive. With too many hydrophobic groups resulting in too much hydrophobic hydration, the positive $(-T\Delta S)$-term dominates the negative ΔE-term; solubility is lost, and hydrophobic association (insolubility) results. Even so, the common exothermic reaction on hydration of hydrophobic and charged groups results in a competition for hydration, described as an apolar-polar repulsive free energy of hydration and designated as ΔG_{ap}.

The inverse temperature transition (ITT) is a phase separation that occurs on raising the temperature of aqueous solutions of amphiphilic polymers, such as proteins, which have the proper balance of apolar and polar groups). The ITT is endothermic on association of hydrophobic groups as the reverse occurs wherein hydrophobic hydration becomes less ordered bulk water. At temperatures above that of the ITT, too much hydrophobic hydration develops during a fluctuation toward hydrophobic dissociation and re-association recurs. If a charged species should appear near the fluctuation toward hydrophobic dissociation, however, the newly formed charged group recruits nascent hydrophobic hydration for its own charge hydration; too much hydrophobic hydration does not occur, and the dissociation stands. Thus, the changing state of a functional group such as a carboxyl with two states of polarity ($-COOH$ and $-COO^-$) controls hydrophobic association/dissociation. This mechanism utilizes all amino acid side chains and prosthetic groups capable of presenting a changed state of polarity as the result of an input energy to the system.

Coupled to the hydrophobic association/dissociation and/or the change in ΔG_{ap} resulting from a change in functional state is an elastic deformation, and the combination result in protein function. Examples are given using the crystal structure data from the Protein Data Bank of the 1) Complex III/Reiske Iron Protein for mitochondrial coupling of electron transport to proton translocation, 2) of the mitochondrial F_0- and F_1-motors of ATP synthase that produces most of the ATP that performs the work required to sustain living organisms, 3) of the myosin II motor of muscle contraction, 4) of kinesin motor of microtubular transport, 5) of the calcium-gated K-channel, and so on.

In short, by this perspective the principal role of water in biology resides in the competition for hydration between hydrophobic groups and polar groups of changeable polarity, which change results in a ΔG_{ap} that effects elastic deformation and drives biological function.