

The dark energy of proteins comes to light: The role of conformational entropy in molecular recognition by proteins.

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Studies of the interaction of a series of calmodulin-binding domains with calcium-saturated calmodulin (CaM) indicated that binding could cause large and widely distributed changes in protein motion (1,2,3). A linear relationship between the entropy of binding and the change in conformational entropy (ΔS_{conf}) of CaM was indicated (2). Recently, the dynamical proxy for ΔS_{conf} used in these studies has been calibrated and the significance of the change in ΔS_{conf} quantitatively confirmed (4). We are now exploring the question of whether the relationship between the ΔS_{tot} and the ΔS_{conf} of a folded protein upon binding a ligand suggested by the CaM system is general. We have assembled NMR relaxation studies reported in the literature and measured missing corresponding binding entropies using ITC. In one case, we have repeated the NMR relaxation using more appropriate ^{13}C -based techniques. Fifteen protein-ligand interactions are included. The apparent linear relationship between ΔS_{tot} and ΔS_{conf} is maintained ($R = 0.75$). This result has significant implications for the evolution of proteins, for the thermodynamic basis for protein-ligand interactions and for rational drug design. Finally, in an effort to understand the cooperativity of motion within the protein matrix, we have carried out studies of the pressure sensitivity of internal motion in the protein ubiquitin. We find that the pressure response is heterogeneous but surprisingly clustered within the structure. These observations begin to explain the apparent incongruity of the observed pressure denaturation of proteins and those predicted by the hydrophobic nature of the protein core. Supported by the NIH, the Mathers Foundation and the Wenner-Gren Foundations.

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