Conformational Entropy in Protein Structure Changes; Instrumental and Computational Analysis

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Abstract

Entropy is a thermodynamic quantity representing the unavailability of a system. Proteins also undergo structural changes through various processes such as folding, unfolding, intermolecular interactions, and etc. resulting in changes in the rate of disorder or entropy. Conformational entropy is the entropy associated with the number of conformations of a molecule. A conformational entropy is usually defined for the backbone and the side chain of residues of the protein.

Calculation of the probable states for backbone dihedral angles and side chain rotamers is one of the computational methods for conformational entropy analysis. These properties are used to define the degree of freedom. These variables can express the amount of conformational entropy with the Boltzmann equation. On the other hand, the only empirical method capable of measuring conformational entropy is NMR relaxation.

The amount of conformational entropy associated with a protein structure, such as α-helix, fold or unfold state, depends on the probability of its formation. The entropy of a random coil and denatured structure is significantly greater than the folded state. The side chain conformational entropy appears to play an important role in stabilizing the energy level in the denatured state, thereby inhibiting protein folding. However, recent studies have shown that the side chain conformational entropy is able to stabilize the Native structure of a protein against other folded structures. In this study, in addition to introducing structural entropy and its measurement methods, we discuss the role of this phenomenon in protein structure and dynamics.

Keywords: Conformational entropy, dihedral angle, rotamer, Boltzmann equation, NMR relaxation

Conformational entropy

Conformational entropy is the entropy associated with the number of conformations of a molecule. The concept is most commonly applied to biological macromolecules such as proteins. In proteins, backbone dihedral angles and side chain rotamers are commonly used as parameters. These characteristics are used to define the degrees of freedom.

When a protein folds, entropic effects from changing its configuration can arise from two sources: First, there will be a change in the number of conformations (essentially rotamers) populated (ΔS_{conf}). Second, the width of an allowed potential energy corresponds to the bond being restricted to a smaller range of dihedral angles and results in a loss of vibrational entropy (ΔS_{vib}; Fig 1). The sum of both these effects is configurational entropy ($\Delta S_{config} = \Delta S_{conf} + \Delta S_{vib}$)

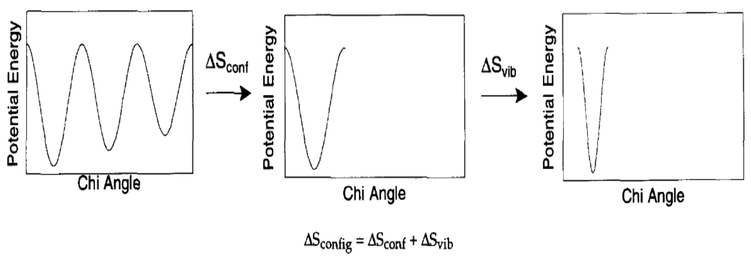

Fig 1. A reduction in the number of rotamers populated (ΔS_{conf}) and the restriction of torsional vibrations about an energy minimum (ΔS_{vib}).

NMR relaxation

In NMR spectroscopy, the term relaxation describes how signals change with time. The deterioration reflects the fact that the NMR signal, which results from nuclear magnetization, arises from the over-population of an excited state. Relaxation is the conversion of this non-equilibrium population to a normal population.

H NMR, 2D NMR, and NOE should be used for calculation of conformational entropy. Order parameter of NMR (S2) is the spatial restriction of internal motion. The order parameter by definition ranges from zero to one, corresponding to complete isotropic disorder and complete rigidity of the NMR interaction vector within the molecular frame, respectively.

Relationship between entropy (S) and NMR order-parameter (S2NMR) can be seen in below equation.

$$S = K_B M[A + Bf(1 - S^2_{NMR})]$$

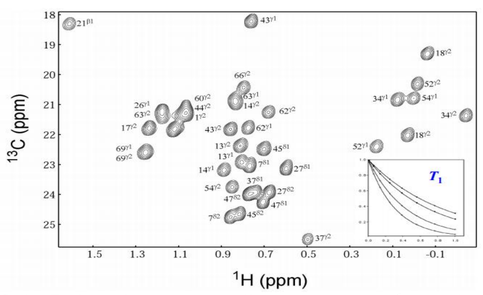

Fig 2. Spin-Relaxation, a more direct measure of protein dynamics

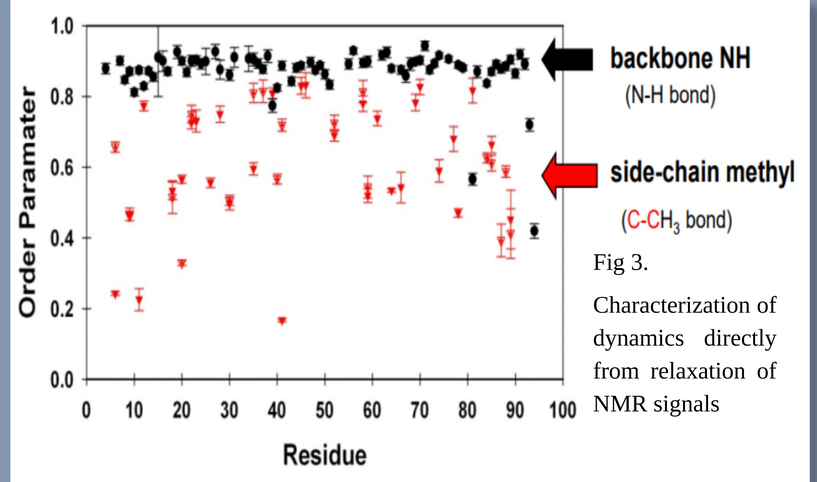

Fig 3.

Characterization of dynamics directly from relaxation of NMR signals

Conclusion

In the folded state, a rotatable x angle is merely restricted to fewer states. Although The major force opposing protein folding is loss of conformational entropy but The conformational entropy associated with the random-coil state significantly contributes to its energetic stabilization.

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Boltzmann equation

The most straightforward method uses the Boltzmann equation directly to calculate entropy:

$$\Delta S_{conf} = -R \ln W$$

W is the number of different conformations adopted in the unfolded state. This can be taken to be 3 for each sp3-sp3 single bond if it is assumed that each rotamer is populated equally in the unfolded state (i.e., each bond is 33% *gauche+*, 33% *gauche-*, and 33% *trans)*. The simplest method is therefore to estimate ΔS_{conf} as -R In 3 (-2.2 ca1.K-l mol-1) per rotatable bond.

A more sophisticated approach is to take into account that the rotamers in the unfolded state are not equally populated. A more accurate approach is to use Equation 2, where pI is the fractional population of each rotamer state in the unfolded state.

$$\Delta S_{conf} = -R \sum_i P_i \ln P_i$$

The populations of each rotamer in the unfolded state cannot yet be observed directly. Instead, Pickett and Sternberg (1993) assumed that the conformations adopted by side chains in protein crystal structures are representative of unfolded conformations (Table 1).

Table 1. Changes in side-chain conformational entropy (TΔS) *on protein folding at 300 K (kcal.mol^{-1})*

		$T\Delta S_{conf}$[a]						
Residue	Number χ angles	Pickett and Sternberg	Abagyan and Totrov	Koehl and Delarue	Blaber et al.	Creamer and Rose	Lee et al.	Mean
Ala	0	0	0	0	0	0	0	0
Arg	4	−2.03	−2.13	−1.21			−2.13	−1.88
Asn	2	−1.57	−0.81	−0.75			−0.99	−1.03
Asp	2	−1.25	−0.61	−0.65			−0.60	−0.78
Cys	2	−0.55	−1.14	−0.63			−1.06	−0.85
Gln	3	−2.11	−2.02	−1.29			−1.51	−1.73
Glu	3	−1.81	−1.65	−1.31			−1.06	−1.46
Gly	0	0	0	0			0	0
His	2	−0.96	−0.99	−0.92	−0.89		−1.00	−0.95
Ile	2	−0.89	−0.75	−0.94	−0.79	−0.67	−0.52	−0.76
Leu	2	−0.78	−0.75	−0.94	−0.69	−0.58	−0.49	−0.71
Lys	4	−1.94	−2.21	−1.63			−1.76	−1.89
Met	3	−1.61	−1.53	−1.24		−1.53	−1.37	−1.46
Phe	2	−0.58	−0.58	−0.65	−0.61	−0.87[c]	−0.42	−0.62
Pro	0	0	0	−0.30			0	−0.06
Ser	2	−1.71	−1.19	−0.43			−1.10	−1.11
Thr	2	−1.63	−1.12	−0.57			−0.99	−1.08
Trp	2	−0.97	−0.97	−1.14	−0.88	−1.16	−0.82	−0.99
Tyr	3	−0.98	−0.99	−1.07		−1.76[c]	−0.83	−1.13
Val	1	−0.51	−0.50	−0.62	−0.46	−0.42	−0.04	−0.43
Total	41	−21.88	−19.94	−16.29				−18.92
Mean	2.05	−1.09	−1.00	−0.81				−0.95