Protein misfolding thermodynamics

Md Mozzammel Haque[1, 2 *], Richard Bayford[2]

[1]Middlesex University, The Burroughs, London, NW4 4BT, UK

[2]ChemiScience, Ashulia, Dhaka-1344, Bangladesh

[*]mdmozzammelhaque@gmail.com

Abstract: It is known that protein misfolding is governed by the hydrophobic effect of solutes at hydrophobic amino acid side-chains. The hydrophobic force of non-aqueous solutes acts as a driving force for the spatial rearrangement of protein side-chains, whose structural transitions need to be regulated in both time and space. Smaller hydrophobic solutes exert more effect at protein side-chains, which involves the clustering of proteins into misfolded shapes. The consequences of misfolding are either loss of protein function, gain of toxic function or both. This is a physical process, whose result has been directly linked to a large number of human diseases.

Keywords: Hydrophobic effect, Hydrophobic solutes, Misfolding temperature limit,

In cells, proteins function in an aqueous solution. Electrolytes and other small molecules play important roles in the structure formation and function of proteins. A function of proteins in water can broadly be classified as hydrophilic and hydrophobic. Electrolytes and small molecules are inorganic and organic compounds (e.g. most drugs, size 1nm), which support the function of proteins[1].

Electrolytes dissociate completely in aqueous solution are strongly hydrated, which exert hydrophilic interactions (dipole-dipole, ion-dipole, and ion-ion) on hydrophilic sites (Fig. 1a). The hydrophilic force is generally the combination of electrostatic repulsion and attraction between hydrated/non-hydrated ions. The high dielectric constant of water (78.5) weakens the electrostatic interactions between two ions in solution and charged residues in biopolymers and membranes, to the level of thermal energy. At low ionic strengths, electrostatic repulsion (e.g. common ion effect) is a very long range-acting force, which dominates the hydrophobic force, destabilizes hydrophobic interactions[2] (protein unfolding). In addition, water on

hydrophobic surfaces that exhibit a hydration force (Fig. 1a), which is a strong short-range repulsive force that acts between water and non-polar molecular surfaces[3].

Protein folding in cells occurs through a delicate balance of hydration and hydrophilic forces, which are determined by a heterogeneous anisotropic lipid bilayer. For water-soluble proteins, whose folding is majorly driven by the hydrophobic force[4].

Weak electrolytes (e.g. organic and inorganic) and non-electrolytes (e.g. organometallics, biomolecules etc.) that dissolve in water as ions/molecules have a property of the hydrophobic effect rather than hydrophilic forces. These molecules/ions bind directly with hydrophobic amino acid side chains and loosen protein backbone hydrogen bonds.

The more electronegative elements hold on to their electrons more tightly, which thus are not readily polarized in water. The high charge (oxidation state) to radius ratio of elements (e.g. Al^{3+}, F^{-}), which determines its specific attraction for hydrophobic sides, is at the origin of its hydrophobic effects on proteins. The hydrophobic force is more active if all bonds in solutes are symmetrical bonds (e.g. CCl_4) that do not change dipole during the interaction.

The hydrophobic force ξ_{HP} of solutes ("wrong" metal/ions, small, large and macromolecules) can be defined by the following equation:

$$\xi_{HP} = \frac{k_B T}{\sqrt[3]{\varsigma \nabla}}$$

Interactions of such solutes at hydrophobic sites as a whole display collective motions and excitations of energy, which are in the order of thermal energy k_BT (where T= absolute temperature and k_B = Boltzmann constant). The actual hydrophobic force achieved by such solutes is the result of the optimization of shapes, which can be determined by using volume[5] ∇ (∇ = specific volume x molar mass). ς is a constant, whose value depends on solute shapes.

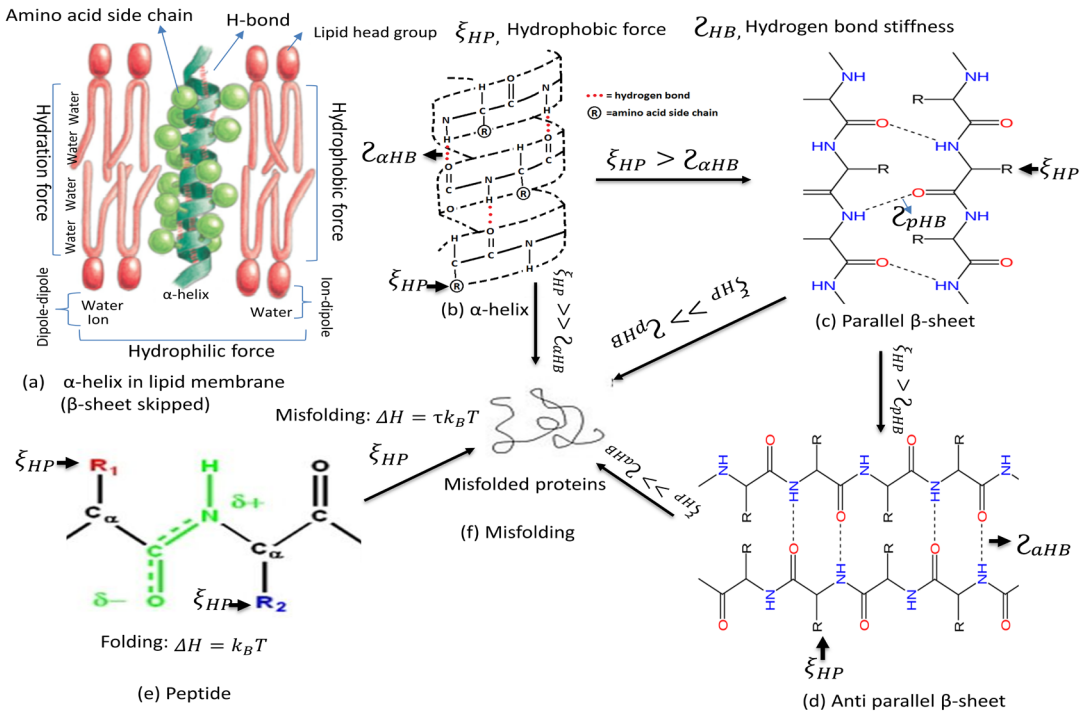

Figure 1. Protein folding (a, b, c, d, e) and misfolding (f)

The stiffness of hydrogen bonds in backbone proteins is much weaker than the hydrophobic or hydrophilic forces because hydrophobic amino acid side chains are attached to the polypeptide backbone, but this is much stronger than generic bonds between small molecules. Based on hydrogen bond lengths and their alignment, hydrogen bonds formed between every fourth amino acid in α-helices are considered slightly weaker than those found in β-sheets[6], i.e. $\wp_{aHB}>\wp_{pHB}>\wp_{\alpha HB}$. However, an anti-parallel β-sheet (Fig. 1d) is significantly more stable than a parallel structure (Fig. 1c) (distorted H-bonds) due to their well-aligned H-bonds, which are at a right angle[7].

Alteration of the protein structure is a physical process, which is driven by the hydrophobic force if $\xi_{HP}> \wp_{HB}$ (See Fig1.). The changing of protein shapes is the concept of topological chirality, which represents the formed gradient factor in the functional space of a polypeptide chain[8]. However, at all levels, the topological chirality τ is a function of the gradient vector. The gradient vector used for protein misfolding has the misfolding temperature $T_{Misfolding}$, which is the deformation temperature limit between the hydrophobic interaction[9] ΔH and the thermal energy k_BT. This defines the misfolding temperature limit, which is

$$T_{Misfolding} = \frac{\Delta H}{\kappa_B \tau}$$

In protein folding, k_BT and ΔH are equal (Fig. 1e), which sets a limit on the amount of the temperature by which the protein can be misfolded (Fig.1f). This misfolding temperature is usually much higher than the absolute temperature, which is associated with the gradient of the misfolded energy surface of a peptide that acts as a hydrophobic force within the configuration space. In addition, high ionic strength results in a larger magnitude for ΔH, and an increase in $T_{Misfolding.}$ However, the hydrophobic force that leads to protein shape-changing is entropic at low temperatures and enthalpic at higher temperatures. Therefore, the enthalpic component of the hydrophobic force contributes to protein misfolding.

Conclusions

Although the mechanism of protein misfolding is not fully understood. This paper suggests that the process of protein misfolding, the hydrophobic force of solutes (e.g. “wrong” metals/ions, “wrong” molecules) can be determined, and is higher than the stiffness of protein backbone hydrogen bonds. This force is a result of features that yield a large enthalpy on misfolding. Furthermore, the consequence of this force is the destabilization of the folded states of proteins as a function of temperature. The temperature dependence hydrophobic interactions have been determined as the misfolding temperature, which changes from protein folding to misfolding. These findings could provide a valuable insight into protein structures, which will open new opportunities for the study of the precise misfolding mechanism which is a key feature of many disorders of humans.

References

(1) Osada, H. *Protein targeting with small molecules: chemical biology techniques and applications*; John Wiley & Sons, Inc.: Hoboken, N.J., 2009.

(2) Stenner, R. S. *Protein and peptide folding, misfolding and non-folding;* John Wiley & Sons, Inc.: Hoboken, N.J., 2012.

(3) Disalvo, E. A., *Membrane hydration: the role of water in the structure and function of biological membranes*; Springer: Cham, 2015.

(4) Petsko, G. A., Ringe, D. *Protein structure and function*; Oxford University Press (1st

Ed): Oxford, 2009.

(5) Marcus, Y. *Ions in water and biophysical implications: from chaos to cosmos*; Springer: Dordrecht, 2012.

(6) Scott, R.L., Fernandez, A. *A mathematical approach to protein biophysics*; Springer: Cham, 2017.

(7) Kuriyan, J., Konforti, B., Wemmer, D. *The molecules of life: physical and chemical principles*; Garland Science: N.Y., 2012.

(8) Bruns, C. J., Stoddart, J. F. *The nature of the mechanical bond: from molecules to machines*; John Wiley & Sons, Inc.: Hoboken, N.J., 2016.

(9) Huddler, D., Zartler, E. R. *Applied biophysics for drug discovery*; John Wiley & Sons, Inc.: Chichester, West Sussex, 2017.