

Article

Protein Folding and the Minimum Rate of Entropy Production

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Abstract

Protein folding displays a very narrow range of stability energy as measured by the ΔG° value associated with the process of protein folding from the unfolded sequence of amino acids defining a particular protein. We have recently reported the Gaussian distribution of ΔG° values obtained from a Data Base, constituted by more than five hundred data points from protein folding processes. An average value of $\Delta G^\circ = -30.9$ kJ/mol was obtained. Considering that a protein solution may include thousands of hydrogen bonds in water solution, this is an extremely low value, approximately equivalent to two hydrogen bonds. The enthalpy–entropy compensation has been repeatedly used as the main empirical mechanism, based in classical thermodynamics, to explain the low energy involved in stabilizing proteins. I present here a different approach, based on the thermodynamics of steady states in open systems, in an attempt to complement the achievements obtained through the EEC. The main conclusions explain the narrow range of ΔG° values reported previously as a consequence of environmental conditions, such as the protein solubility, and the plausible concentration, “in vivo,” of both protein forms, folded and unfolded. Particularly relevant is the condition of increasing the entropy of irreversible processes inside adiabatic systems. It is also worth noting the observation that, according to the results obtained from the theoretical model used, any protein could be folded with slightly different stability values of ΔG° , following the theorem of minimum entropy production rate.

Keywords: protein folding; minimum rate of entropy production; open systems

1. Introduction

Protein stability can be measured by the ΔG° value corresponding to the transformation of a protein synthesized in the ribosome as a random coil, *A*, into a folded and functional protein in possession of a well-defined structure, *B*:



We have recently reported the Gaussian distribution of ΔG° values for a set of 583 protein folding processes, as calculated by using the Gibbs–Helmholtz equations and the thermodynamic information from a Data Base [1]. The average value obtained was -30.9 ± 0.9 kJ/mol with a standard deviation $SD = 21$ kJ/mol. This value is surprisingly low when compared to the corresponding values of ΔH° and $T\Delta S^\circ$: 173 kJ/mol ($SD = 206$) and 142 kJ/mol ($SD = 193$). The enthalpy–entropy compensation (EEC) has been the main argument used to explain this small range of ΔG° values in stabilizing protein structures [1–13]. In this contribution I present a model system based on the thermodynamics of steady states in open systems, following the formulation described by Denbigh [14], in an attempt to complement the achievements obtained through the EEC.



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The main conclusions derived from the application of the model suggest that the narrow range of ΔG° values reported previously [1] could be the consequence of environmental conditions, such as the protein solubility, the plausible concentration of both protein forms, folded and unfolded “in vivo”, the size and form of the biological systems, as well as the condition of increasing the entropy of irreversible processes inside adiabatic systems. It is also worth highlighting that the results obtained from the theoretical model suggest that any protein could be folded with slightly different stability values of ΔG° , following the theorem of minimum rate of entropy production [15].

2. Methods

To look for the origin of the narrow range of ΔG° values associated with protein stability within the framework of thermodynamics, we postulate a model composed of a simple chemical transformation such as the process of protein folding contained within an open system under a steady state condition. First, we will consider the chemical reaction taking place inside a closed system:



where A stands for the denaturized protein and B stands for the folded functional protein. At constant values of pressure, p , and temperature, T , a change in the entropy of the closed system, dS_s , as a consequence of a change in the concentration of any of the reaction components, will be given by:

$$dS_s = \frac{dH_s}{T} - \frac{dG_s}{T} \quad (2)$$

where dH_s and dG_s stand for the corresponding changes in enthalpy and Gibbs free energy. Following the formulation of Denbigh, the change in entropy created in the universe will be given by:

$$dS_u = dS_s + dS_e \quad (3)$$

where dS_u , dS_s and dS_e stand for the entropy changes of the universe, the closed system, and the environment respectively, considering the universe as the adiabatic system formed by the sum of the system plus the environment. At constant values of pressure and temperature, and in the absence of irreversible processes, the environment acts as a heat reservoir; therefore, its change in entropy, dS_e , will be:

$$dS_e = -\frac{dH_s}{T} \quad (4)$$

Substituting Equations (2) and (4) in (3), we obtain:

$$dS_u = \frac{dH_s}{T} - \frac{dG_s}{T} - \frac{dH_s}{T} = -\frac{dG_s}{T} \quad (5)$$

Finally, according to the second law, the entropy creation in the universe, considered as an isolated system, must increase in any irreversible change associated with a decrease in the Gibbs free energy of the closed system.

The change in Gibbs free energy associated with changes in the concentration of the reaction components of Equation (1), at constant values of pressure and temperature, is given by:

$$dG_s = (\mu_b - \mu_a)VdCb \quad (6)$$

where μ_b and μ_a stand for the chemical potentials of A and B respectively, and dCb stands for an infinitesimal change in the concentration of B . Assuming that the reaction (1) is of first order in both directions:

$$\frac{dCb}{dt} = k_aCa - k_bCb \quad (7)$$

where ka and kb stand for the first order rate constant for the left-to-right and the reverse reaction (1) respectively.

Substitution of (7) in (6) gives:

$$dGs = (\mu_b - \mu_a)V(kaCa - kbCb)dt \quad (8)$$

$$-\frac{1}{V} \frac{dGs}{dt} = (\mu_b - \mu_a)(kbCb - kaCa) \quad (9)$$

Substituting (5) in (8) we obtain:

$$\frac{1}{V} \frac{TdSu}{dt} = (\mu_b - \mu_a)(kbCb - kaCa) \quad (10)$$

Equation (10) represents the rate of entropy creation per unit volume due to the chemical reaction taking place in the closed system. Assuming an ideal behavior, $\mu_b - \mu_a$ in Equation (10) becomes:

$$\mu_b - \mu_a = \Delta G^\circ + RT \ln \left(\frac{Cb}{Ca} \right) \quad (11)$$

In the true equilibrium, Cb and Ca are equal to the equilibrium concentration, Cbe and Cae ; under that condition, $\mu_b - \mu_a = 0$ and the rate of entropy creation per unit volume is zero. Let now a fluctuation in the open system displacing the equilibrium concentration of B , Cbe , while maintaining constant that of A , Cae .

From the equilibrium constant we have $Cae = Cbe/K = Cbe kb/ka$, and after substituting in (10) we obtain:

$$\frac{1}{V} \frac{TdSu}{dt} = (\Delta G^\circ + RT \ln Cb - RT \ln Cbe + RT \ln K)(kbCb - kbCbe) \quad (12)$$

Finally, following the nomenclature of Denbigh [14], the rate of entropy creation per unit volume, θ , is defined as:

$$\theta \equiv \frac{1}{V} \left(\frac{dSu}{dt} \right) \quad (13)$$

and substituting (13) in (12) we obtain:

$$T\theta(react.) = RT \ln \left(\frac{Cb}{Cbe} \right) kb(Cb - Cbe) \quad (14)$$

Equation (14) gives the rate of entropy production per unit volume created by the chemical transformation (1) taking place in the closed system as long as the reaction is slow enough for the concentration Cb to acquire well-defined values.

The closed-system model considered above may be composed of at least two phases separated by a diathermic and permeable wall. One of the phases hosts the chemical reaction to which Equation (14) applies, thus acting as an open system. The passage of matter through the walls separating the distinct phases of the system also contributes to the change in the Gibbs free energy of the whole system. The environment is in thermal and mechanical equilibrium with the system, acting, therefore, as a heat reservoir. The contribution of the transference of component B from Equation (1) is given by:

$$dG = \mu_b dn_b + \mu_b' dn_b' \quad (15)$$

where μ_b and μ_b' stand for the chemical potential of B inside the system and outside the system respectively; dn_b and dn_b' stand for the infinitesimal changes of moles of B from inside to outside the system. Since $dn_b = -dn_b'$, we have:

$$dG = (\mu_b - \mu_b') dn_b$$

and, from the last,

$$-\frac{1}{V} dG = (\mu_b' - \mu_b) dCb \quad (16)$$

To introduce the time in Equation (16) we need a flow equation relating dCb to the gradient of chemical potential between the inside and outside of the system. Following Onsager, we have chosen the gradient of chemical potential so that its product with the flow is equal to the rate of entropy production per unit volume, Θ :

$$(\mu_b - \mu_b') \left(\frac{dCb}{dt} \right) = T\Theta \quad (17)$$

Accordingly, we will express the flow, dCb/dt , as proportional to the gradient of chemical potential:

$$-\frac{dCb}{dt} = rb(\mu_b - \mu_b') \quad (18)$$

where rb is a constant related to the diffusion properties of B , the geometric properties of the system, and also the plausible existence of physiological channels facilitating permeability between system and environment.

Substituting (18) in (16) we have:

$$-\frac{1}{V} \left(\frac{dG}{dt} \right) = rb(\mu_b' - \mu_b)^2 \quad (19)$$

The same Equation (18) can be used for describing the diffusion of the component A of the chemical transformation (1):

$$-\frac{1}{V} \left(\frac{dG}{dt} \right) = ra(\mu_a' - \mu_a)^2 \quad (20)$$

The sum of Equations (19) and (20), together with Equation (5) and identity (13) give the rate of entropy creation as a consequence of the diffusion of the reaction components in (1), A and B :

$$T\Theta(dif) = ra(\mu_a' - \mu_a)^2 + rb(\mu_b' - \mu_b)^2 \quad (21)$$

Assuming, as above, an ideal behavior of the reaction components, and the same value for the standard chemical potentials, $\mu^\circ_a = \mu^\circ_{a'}$ and $\mu^\circ_b = \mu^\circ_{b'}$, we obtain:

$$T\Theta(dif) = ra \left(RT \ln \left(\frac{Ca'}{Ca} \right) \right)^2 + rb \left(RT \ln \left(\frac{Cb'}{Cb} \right) \right)^2 \quad (22)$$

Finally, the total rate of entropy creation due to the chemical reaction plus the diffusion processes is given by:

$$T\Theta = RT \ln \left(\frac{Cb}{C_{be}} \right) kb(Cb - C_{be}) + ra \left(RT \ln \left(\frac{Ca'}{C_{ae}} \right) \right)^2 + rb \left(RT \ln \left(\frac{Cb'}{Cb} \right) \right)^2 \quad (23)$$

This equation gives the rate of entropy creation as a function of the B concentration, C_b , after a fluctuation in the open phase, displacing the equilibrium concentration of B , C_{be} , while maintaining constant that of A , C_{ae} . The equation has been obtained under

the assumption that dC_b/dt across the walls limiting the phase hosting the chemical transformation (1) is proportional to the gradient of chemical potential, $\mu_b' - \mu_b$ and $\mu_a' - \mu_a$. However, the flow of concentration due to the chemical reaction, dC_b/dt , is proportional to the gradient of molar concentration (Equation (7)) but not to the gradient of chemical potential. Only in close proximity to the equilibrium can we expect the flow of B , expressed as dC_b/dt , to be proportional to the gradient of chemical potential.

Coming back to Equation (14) and assuming an ideal behavior:

$$T\theta_{(react.)} = RT \ln\left(\frac{C_b}{C_{be}}\right) kb(C_b - C_{be})$$

$$\begin{aligned} kb(C_b - C_{be}) &= kbC_{be}\left(\frac{C_b}{C_{be}} - 1\right) = \\ &= kbC_{be}\left(\exp\left(\frac{\mu_b - \mu_{be}}{RT}\right) - 1\right) \end{aligned}$$

Expanding the last equation for values of $\mu_b - \mu_{be}$ sufficiently small we have:

$$kbC_{be}\left(\exp\left(\frac{\mu_b - \mu_{be}}{RT}\right) - 1\right) = kbC_{be}\left(\frac{\mu_b - \mu_{be}}{RT}\right) = kbC_{be} \ln\left(\frac{C_b}{C_{be}}\right) \quad (24)$$

After substitution of (24) into (14) we obtain:

$$T\theta_{(react.)} = RTkbC_{be}\left(\ln\left(\frac{C_b}{C_{be}}\right)\right)^2 \quad (25)$$

Finally, the sum of Equations (21) and (25) will give:

$$T\theta = RTkbC_{be}\left(\ln\left(\frac{C_b}{C_{be}}\right)\right)^2 + ra\left(RT \ln\left(\frac{C_a'}{C_{ae}}\right)\right)^2 + rb\left(RT \ln\left(\frac{C_b'}{C_b}\right)\right)^2 \quad (26)$$

Equation (26) gives the rate of entropy creation in the proximity of equilibrium, after a fluctuation in the open phase, displacing the equilibrium concentration of B , C_{be} , while maintaining constant that of A , C_{ae} .

The steady state condition implies that both A and B forms of the protein remain invariant over time. Following Equations (7) and (18), the rate of change in B concentration will be given by:

$$dC_b/dt = kb(C_{be} - C_b) + rb\left(RT \ln\left(\frac{C_b'}{C_b}\right)\right) \quad (27)$$

Similarly to the exponential expansion conducted to arrive at Equation (24), Equation (27) becomes:

$$\frac{dC_b}{dt} = kbC_{be} \ln\left(\frac{C_{be}}{C_b}\right) + rbRT \ln\left(\frac{C_b'}{C_b}\right) \quad (28)$$

By setting Equation (28) equal to zero, we can obtain the C_b value corresponding to the steady state, $C_b(ss)$:

$$C_b(ss) = \exp\left(\frac{\ln C_b'}{1 + \left(\frac{kbC_{be}}{rbRT}\right)} + \frac{\ln C_{be}}{1 + \left(\frac{rbRT}{kbC_{be}}\right)}\right) \quad (29)$$

An Excel spreadsheet from Microsoft 365 (Microsoft Corporation) was used for all calculations (Supplementary Material).

3. Results and Discussion

Figure 1A shows, as an example, the behavior of the model system described under Methods, satisfying the theorem of minimum rate of entropy creation, according to which the system constituted by the transformation of A into B (1) reaches a steady state in which the rate of entropy production acquires a minimum positive value. As can be seen in the figure, the equilibrium concentration of B in the closed system is $2.4 \mu\text{M}$ (gray curve in Figure 1A). This is an equilibrium state under which no concentration changes in B can be observed and the rate of entropy creation, $T\Theta$, is equal to zero. However, when the closed system becomes an open phase, with an external concentration different from that inside the phase hosting the chemical transformation, the inward or outward flow increases (discontinuous curve in the same figure), thus producing an entropy creation curve (thick black curve) displaying a minimum at the same concentration of B at which a steady state for which dC_b/dt is zero is observed (indicated by an arrow).

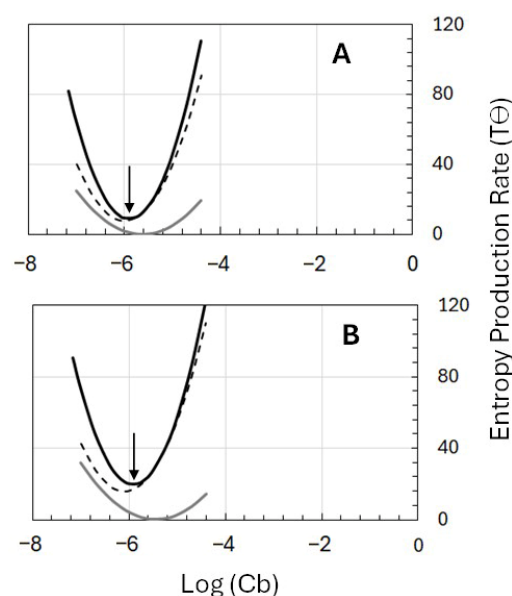


Figure 1. Rate of entropy production. Calculation of the entropy production rate, $T\Theta$, as a function of the concentration of the B form of a protein (in logarithmic form), following Equation (26). Values of parameters used in both parts (A,B): $r_a = r_b = 10^{-6}$, $k_b = 10^7/K$, $C_{ae} = 10^{-10}$. Part (A): $C_b' = 1 \mu\text{M}$, $C_a' = 0.3 \text{ nM}$ and $\Delta G^\circ = -25 \text{ kJ/mol}$. Part (B): $C_b' = 0.8 \mu\text{M}$, $C_a' = 0.5 \text{ nM}$ and $\Delta G^\circ = -26.25 \text{ kJ/mol}$. Continuous curves in “black” correspond to the entropy production rate at the steady state and were obtained following Equation (26). Discontinuous curves correspond to the entropy production rate due to diffusion and were obtained following Equation (22). Continuous gray curves correspond to the entropy production rate due to the chemical reaction and were obtained following Equation (25). The arrows indicate the C_b concentration of the steady state as calculated by using Equation (29).

In the case of the simple model described here, changes in the permeability of the wall enclosing the distinct phases composing the system, r_b and r_a , or changes in the environmental C_b' concentration can induce changes in the rate of entropy production, $T\Theta$. Figure 1B shows the same example of Figure 1A but with slightly different external concentrations of both forms of the protein, A and B , and with a different value corresponding to the free energy of folding, ΔG° . As can be observed, the new steady state of the system is producing B with a higher rate of entropy production, $T\Theta$. However, the steady state is reached at the same concentration as in the previous case described above.

The number of unknown variables needed to evaluate the model is obviously large. It is difficult to combine them into a simple physical model. This difficulty is not helped by the complex reality of the organelles formed by the ribosome attached to the membrane

of the endoplasmic reticulum. However, this should not be an impediment to proposing approaches analogous to those that have been traditionally made with the thermodynamics of equilibrium, the conceptual usefulness of which is beyond doubt. The concentration of the two forms of the protein folded and unfolded, C_a and C_b , have been selected within a range of concentrations from about 1 mM, considering the limitations of protein solubility, to about 0.1 nM, to allow for the capability of their interaction with other biological macromolecules; the rate constant values, k_a and k_b , have been selected according to the equilibrium constant values; and finally the diffusion coefficients, which are related to surface, volume, and the general physical properties determining the wall permeability between the system and the environment have been assigned numerical values approximately related to the diffusion coefficients of proteins.

Figure 2 shows a summary of the different values of entropy production rate obtained from the model described above. I have plotted different values of ΔG° against the rates of entropy creation for different external conditions, in this case the external concentration of B , represented by each of the curves. The same could have been done with any other parameter related to the external environment of the phase hosting the transformation. The resulting values of ΔG° obtained agree with those previously reported [1], and correspond to the Gibbs free energy associated with the protein folding at 25 °C. As can be observed, most of the ΔG° values obtained are within the range of about -10 to -40 kJ/mol.

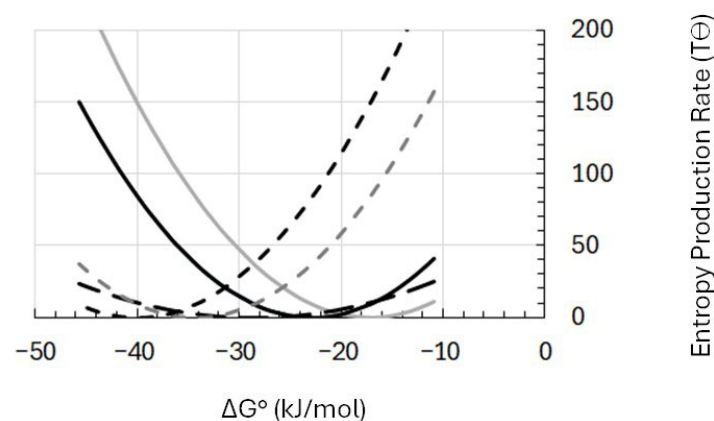


Figure 2. Rate of entropy production. Each curve on the graph corresponds to the rate of entropy production (J t dm^{-3}) in the folding of a protein at the steady state, as a function of its ΔG° value of the folding process (in logarithmic form) and for a particular concentration of B , Cb' in the environment: continuous gray curve, 0.1 μM ; continuous black curve, 1 μM ; discontinuous black curve, 1 mM; discontinuous gray curve, 0.1 mM; discontinuous (long segments) black curve, 10 μM .

The model described here serves as a qualitative framework rather than a predictive biological description. The results obtained from the model, shown in Figure 2, admit at least three critical readings: First, the rate of entropy creation depends on the external conditions of the system. Second, many interesting reports may be found contributing to the understanding of the narrow range of ΔG° values for the folding of proteins, particularly those suggesting that a low stability may provide greater plasticity to perform its function [16–21]. The simple model used here, based on the thermodynamics of open systems in steady state conditions, agrees with the narrow range of ΔG° values reported previously [1] from a different point of view. It seems that the range of ΔG° values may be associated with environmental conditions such as the protein solubility, the minimal protein concentration needed to interact with other proteins or any other macromolecules, the concentration of both protein forms, folded and unfolded, outside the system, the size and form of the system, as well as the permeability of the system wall, and indeed the condition of increasing the entropy of irreversible processes inside adiabatic systems.

Third, it is worth of noting that, according to these results, any protein could be folded with slightly different stability values of ΔG° , following the theorem of minimum rate of entropy production [22]. The two examples displayed in Figure 1 correspond to two slightly different ΔG° values associated with slightly different external conditions (the external concentrations of Cb' and Ca'). The concentration of B at the steady state is the same in both cases, although the rate of entropy creation is larger in the case described in part B of Figure 1. This could be interpreted as a slightly different folding of the same protein resulting from changes in the environment.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/biophysica6010014/s1>

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