

On the indirect relationship between protein dynamics and enzyme activity



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ABSTRACT

The behaviors of simple thermal systems have been well studied in physical chemistry and the principles obtained from such studies have been applied to complex thermal systems, such as proteins and enzymes. But the simple application of such principles is questionable and may lead to mistakes under some circumstances. In enzymology, the transition state theory of chemical reactions has been accepted as a fundamental theory, but the role of protein dynamics in enzyme catalysis is controversial in the context of transition state theory. By studying behaviors of complex thermal systems, we have revised the Arrhenius equation and transition state theory and our model is validated in enzymology. Formally speaking, the revised Arrhenius equation is apparently similar to a conventional Arrhenius equation, but the physical meanings of its parameters differ from that of traditional forms in principle. Within this model, the role of protein dynamics in enzyme catalysis is well defined and quantified.

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Contents

1. Behaviors of simple and complex thermal system	53
2. Transition state theory and the Arrhenius equation for chemical reactions of complex thermal systems	54
3. Alcohol dehydrogenase	55
4. Protein folding kinetics	55
5. Relation among protein dynamics and enzyme activity	56
6. Protein dynamics and abundance curve of active conformation of enzyme	57
7. The dispute about scientific concept and criteria	58
8. Conclusion	58
Acknowledgements	58
References	58

Conventional thermodynamics was developed in the study of behaviors of simple thermal systems such as the ideal gas (Schroeder, 2000). When it was fully established, the principles have been gradually applied to fields of complex thermal systems. Although great achievements have been made over time, we must bear in mind that the validation of the principles of conventional thermodynamics in the field of complex thermal systems has not been fully tested. When it occurs, different conclusions of science may be obtained by applying different research methods. As

chemical studies now target the behaviors of complex thermal systems such as biological systems and Nano-scale materials, the case becomes more and more serious (Dill and Bromberg, 2010).

Clearly, the behaviors of complex thermal systems differ from that of simple thermal systems. Currently, there are two different ways to handle these differences. Some scientists, particularly experimentalists, prefer to revise principles of conventional thermodynamics and believe that it can account for all behaviors of complex thermal systems. In another way, some believe that the behaviors of complex thermal systems differ from that of simple thermal systems in principle and new principles of physics and chemistry should be proposed. By the second way, the dynamic

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system and dissipative structure theory have been proposed (Kondepudi and Prigogine, 2014). Inspired by such approaches, we have proposed new principle of irreversible thermodynamics and protein thermodynamic structure theory (Zhao, 2009, 2013).

A fundamental task of science for both biology and physical chemistry is to reveal thermodynamic mechanisms for biological processes and expose the logical relationship between protein motion and function (Frauenfelder and McMahon, 1998; Berendsen and Hayward, 2000). In order to resolve this, one problem of science should firstly be addressed. As biological macromolecules, including proteins, enzymes, DNA and RNA, are all complex thermal systems, we should ascertain whether the thermodynamical principles for simple thermal systems are still suitable or validated in the field of complex thermal systems. If the answer is no, we should endeavor to find the right formulation of thermodynamics for complex thermal systems.

At present, studies on the relationship between protein dynamics and protein function are focusing on the relationship between protein dynamics and enzyme activity. This is currently under fierce debate. One opinion, which is held by many experimental scientists, is that there is a general relationship between protein dynamics and enzyme activity (Bhabha et al., 2011; Henzler-Wildman et al., 2007; Klinman and Kohen, 2013; Garcia-Viloca et al., 2004). Another opinion is that if there is such relationship, the effects of protein dynamics on enzyme activity should be expressed in parameters of enzyme kinetics, particularly activation energy of enzymatic reaction. There is no experimental report that the activation energy of enzymatic reaction could be influenced by a change of protein dynamics, and thus the relationship between protein dynamics and enzyme activity is often disputed (Kamerlin and Warshel, 2010a; Warshel and Ram, 2016).

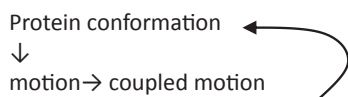
Here we show that the Arrhenius equation and transition state theory, which works well for simple chemical reactions, should be revised in the field of complex thermal systems or enzymatic-catalyzed reactions. This revised Arrhenius equation makes clear the effect of protein dynamics on enzyme activity and changes the parameters of enzymatic kinetics. In addition, our conclusion is that protein dynamics takes its role in enzyme activity by influencing thermodynamic states of protein conformation; or in other words, there is indirect relation between protein dynamics and enzyme activity.

1. Behaviors of simple and complex thermal system

Conventional thermodynamics was developed from studies of the behavior of simple thermal systems. For simple thermal systems, the motions of all the components are completely independent of each other; there are no coupled motions among the components and there is no infrastructure within the system.

However, the coupled motion or cooperativity is a common phenomenon in protein conformational change. In view of conventional theory, the behaviors of a protein show complexity (Frauenfelder, 2002; Karplus, 2000). In studies of protein thermodynamic structure theory, we have proposed the scientific definition of complex and stable thermal systems (Zhao, 2011a, 2012).

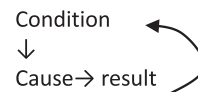
Within a protein, a logical cyclic relationship can be found.



The protein conformation modulates the range and amplitude of internal motion of components of a protein. The change of internal motion can also influence the coupled motion within a protein. The

nature of the coupled motions of a protein determines protein conformation.

A more general definition of a system could be expressed.



In this definition, a complex thermal system acts an indivisible whole in thermodynamics and represents one degree of freedom of thermodynamics.

For simple thermal system

$$E = \text{constant}$$

$$E_w = E_1 + E_2 + E_3 + \dots$$

$$N_p = \sum_i e^{-\frac{E_i}{kT}}$$

where E is energy of its components. E_i is the energy of i th component of the system. E_w is the total energy of thermal system. N_p is partition function of its components.

For complex thermal system

$$\Delta G = \Delta G^0 - F(s)$$

$$\Delta G = \Delta G^0 - B(s - s_0) \text{ (in linear area)}$$

$$E_w \leq E_1 + E_2 + E_3 + \dots$$

$$N_p = \sum_i e^{-\frac{[\Delta G_i^0 - F_i(s)]}{kT}}$$

where ΔG is the energetic level of complex system, F is a function, b is revision efficiency, s is the quantification of an environmental factor, E_w is the total energy of thermal system. N_{ps} is the partition function of the state of a complex thermal system.

Within a complex thermal system, the energy of the total system comes from coupled motion of its components; the uncoupled motion makes no contribution to the total energy of the system, and so the energy of the system is not the sum of energy of its components. The concept of the partition function of a complex thermal system makes it possible to calculate the distribution curve of thermodynamic states of complex thermal systems (Zhao, 2012, 2015).

From the equations above, we can deduce the differences between the behaviors of complex thermal systems when compared to simple thermal systems.

One major difference is that the thermodynamic state of a complex thermal system is sensitive to a change of temperature (or other types of environmental factors) and the abundance of one state can dramatically change over a small temperature range (i.e. the abundance of one state can reach close to 100%). In contrast, the abundance of one quantum state of a molecule at a high energetic level can only reach up to 50% in a broad range of temperatures. See Fig. 1 for detail.

There is a special phenomenon in the behavior of a complex thermal system, or abundance curve shift along an environmental factor (e.g. temperature). When a complex thermal system is changed, for example by a change in sequences, its properties will change also. Compared with the original system, the distribution curve of a new state of the system will appear at a different position along coordinates of an environmental factor (temperature in this

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