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## Review

## Transition state theory for enzyme kinetics

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## ARTICLE INFO

## Article history:

Received 6 March 2015  
and in revised form 15 May 2015  
Available online xxx

## Keywords:

Transition state theory  
Enzyme kinetics  
Quantum effects  
Tunneling  
Free energy

## ABSTRACT

This article is an essay that discusses the concepts underlying the application of modern transition state theory to reactions in enzymes. Issues covered include the potential of mean force, the quantization of vibrations, the free energy of activation, and transmission coefficients to account for nonequilibrium effect, recrossing, and tunneling.

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## Introduction

Enzyme catalysis occurs by a variety of mechanisms [1], and enzyme kineticists use a variety of levels of theory to calculate reaction rates catalyzed by enzymes. Most of these methods, in one way or another, attempt to calculate the free energy of activation, a quantity whose meaning is defined by transition state theory. Attempts to go beyond transition state theory are often cast in terms of a transmission coefficient, which corrects for the breakdown of the assumption of a separable, classical reaction coordinate in transition state theory without a transmission coefficient. Thus a transmission coefficient in principle corrects for the breakdown of the fundamental reaction–coordinate–separability assumption of transition state theory [2], but in practice it also incorporates quantum mechanics into the treatment of the reaction coordinate [3]. Since there is universal agreement that the correct description of atomic motions is quantum mechanical rather than classical mechanical, the quantum mechanical aspect of transmission coefficient is considered as an intrinsic part of the theory, not as a correction for breakdown of the theory. The transmission coefficient is an intrinsic part of the theory in an even greater sense though because the factorization of a transmission coefficient out of the total rate expression is not unique; it depends on the way that the transition state dividing surface is defined. The present essay will try to make these issues and other aspects of modern transition state theory clearer, with an explicit focus on enzyme kinetics.

It is becoming increasingly possible to use simulations in which the motion of the substrate, enzyme, cofactors, if any, and an

appreciable portion of the solvent are all represented explicitly. One can use transition state theory to extract rate constant predictions from such simulations, but this often requires going beyond textbook transition state theory and including new elements in the simulations. The present article is an essay that discusses the issues that arise in extending transition state theory to enzyme reactions.

Transition state theory was originally developed in the context of gas-phase reactions, but it was extended to condensed reactions shortly thereafter. The original formulation for condensed-phase reactions was in terms of quasithermodynamic concepts, in particular quasiequilibrium between the transition state and the reactants. I use the term quasiequilibrium for two reasons: (i) the transition state needs to be in equilibrium with the reactants, but the products states may be unpopulated; (ii) the transition state is missing one degree of freedom. For example, Evans and Polanyi [4] defined the transition state as “an infinitesimally thin layer of phase space” extending to infinity in all directions except the reaction coordinate. Thus a transition state is a mathematical entity that is like a real molecule but is missing one degree of freedom, namely the reaction coordinate. In mathematical language, we would define the transition state with a delta function for the reaction coordinate. Real equilibrium constants are one-to-one functions of free energies of reaction, and the temperature dependence of the equilibrium constant can be used to separate the free energy into an enthalpy of reaction and a term involving the entropy of reaction. Since the transition state theory rate is proportional to a the quasiequilibrium constant between the transition state (sometimes called the activated complex), the transition state rate is interpreted in terms of a generalization of the concept of free energy of reaction, namely the free energy of activation, which

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is the difference in free energy between the mathematically defined transition state and the reactants, and the temperature dependence allows us to separate this into an enthalpy of activation and an term involving the entropy of activation. These functions are quasithermodynamic because they refer to a transition state rather than a real chemical species. This conceptual framework will be used in deriving transition state theory below.

An important distinction in discussing transition state theory is the difference between a potential energy surface (also called a potential energy function) and a free energy surface (also called a potential of mean force). In applying transition state theory to gas-phase reactions, the basic input (energies, vibrational frequencies, ...) may be obtained from the Born–Oppenheimer potential energy surface, which is the electronic energy (including nuclear repulsion) of the ground electronic state as a function of nuclear coordinates. Potential energy surfaces for general gas-phase molecules with  $N$  atoms are functions of  $3N - 6$  coordinates, where  $3N$  is the number of atomic Cartesian coordinates, and we subtract 6 because the electronic energy does not depend on translating the overall center of mass or rotating the whole system in space. Reactants and products are associated with local minima on the potential energy surface, and transition states were identified with saddle points on the potential energy surface. A saddle point is a local minimum of the potential energy surface in  $3N - 7$  degrees of freedom, where now we have omitted the reaction coordinate; but it corresponds to a local maximum along the reaction coordinate. Notation: A saddle point is often called a transition structure. Calculating a rate constant by transition state theory involves calculating certain free energy quantities from the potential energy surfaces, as discussed below.

Potential energy surfaces also underlie the theory for condensed phase systems, but  $N$  is a very large number for a liquid, and it may be tens of thousands or more for realistic models of liquid-phase enzymes, but the use of free energy quantities that depend on a smaller number of degrees of freedom (for example, the number of degrees of freedom of a solute or an active site) allows one manage the complexity. For this reason, free energy surfaces are more useful for condensed-phase reactions than for gas-phase ones – both for conceptual purposes and for calculations, and yet they are often not explained well in textbooks (and sometimes not even mentioned).

Extending conventional transition state theory to reactants in a condensed phase, for example in water, in the aqueous medium of a cell, or in an enzyme which itself is in a liquid-phase medium, is not as straightforward as many textbook treatments would lead one to believe. To see this, consider a solute with  $n$  atoms. Because it is surrounded by solvent, its electronic energy is not well defined; that is, there are questions about how to partition the solute–solvent interaction energy into energy of the solute and energy of the solvent. But suppose we come up with a scheme for that. We then find that the energy is not invariant to translation or rotation of the solute if the solvent is fixed at some instantaneous configuration. The free translations and free rotations have been converted to low-energy librations by interactions with solvent. We could try to ameliorate the problem by considering a “supersolute,” by which I mean a system consisting of the solute plus many nearby solvent molecules. Now we run into another problem. The solvent, being a liquid, has many local minima of nearly the same energy. Consider water. We could have many possible networks of hydrogen bonds, and rotation of a few water molecules from one hydrogen-bonding arrangement to another gives us another local minimum. Following Stillinger, one may call these local minima of the potential energy function “inherent structures.” Stillinger proved that the number of distinguishable inherent structures of a liquid rises exponentially as a function of the number of molecules in the systems [5].

For gas-phase systems, we can proceed theoretically by finding all the low-energy minima and low energy-saddle points [6,7]. We can then carry out a complete analysis of the nuclear motion and configurations by classical mechanics (for example, vibrations might be treated by the classical mechanical harmonic oscillator approximation) or, if the system is not too large, by quantum mechanics (for example, vibrations might be treated by the quantum mechanical harmonic oscillator approximation). Clearly that is impossible for a liquid or an enzyme in solution, where it is not practical to even think about all the structures, and we are forced to use statistical mechanical sampling rather than full enumeration of structures. Using statistical mechanics, we can make firm statements even without finding all the inherent structures. The present article will attempt to explain how we do this, using the least possible amount of mathematics, although the actual calculations involve a lot of mathematics.

In section “Transition state theory in a classical world” we explain transition state theory in a classical mechanical world. By this we mean a world where *nuclear motion* follows the law of classical mechanics; as explained above, the potential energy surface that governs nuclear motion represents the electronic energy, and the electronic structure of atoms and molecules must always come from a quantum mechanical treatment (even though it might be represented by a molecular mechanics function that looks classical). The variational principle of variational transition state theory is rooted in classical mechanics and it is also explained in section “Transition state theory in a classical world”.

Classical mechanics describes many aspects of nuclear motion quite well, but for quantitative work one cannot neglect the quantum mechanical nature of nuclear motion, especially zero point energy and tunneling. Thus, in sections “Quantum mechanical nuclear motion” and “Transmission coefficient”, we explain how quantum effects are included in transition state theory.

## Transition state theory in a classical world

### Basic concepts

To provide guidance for the statistical mechanical formulation of transition state theory for condensed-phase process, we return to gas-phase systems and reconsider the meaning of the quasithermodynamic functions. In pioneering work cited above, Polanyi, Evans, and Eyring arrived at the quasithermodynamic and statistical mechanical formulation of transition state theory by considering quasiequilibrium between reactants and transition states. Since, as already pointed out, transition states are not real species, this involved a somewhat intuitive generalization of the concept of equilibrium, which they combined with one-dimensional classical models for the reactive motion (motion along the reaction coordinate) that takes a system from one side of the transition state to the other. Although these derivations gave the correct result, there were not completely satisfactory, and even as late as the 1970s, people were arguing about factors of two in the derivation [8].

A more solid foundation for transition state theory was provided by the work of Wigner. Before summarizing Wigner’s results, I briefly explain the language to be used. Phase space is the  $6N$ -dimensional space consisting of the  $3N$ -dimensional coordinate space and the  $3N$ -dimensional space of conjugate momenta. Points in phase space are called phase points; they are the “states” of a classical system. A region of phase space is said to be in local equilibrium if the relative population of states in that region satisfies a Boltzmann distribution. Note that since most phase points have nonzero momentum they are constantly moving from one position in phase space to another (from one state to another); the motion of a phase point in phase space is called a trajectory.

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