

CHAPTER 5

Variational transition state theory

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Abstract

We present an overview of variational transition state theory from the perspective of the dynamical formulation of the theory. This formulation provides a firm classical mechanical foundation for a quantitative theory of reaction rate constants, and it provides a sturdy framework for the consistent inclusion of corrections for quantum mechanical effects and the effects of condensed phases. A central construct of the theory is the dividing surface separating reaction and product regions of phase space. We focus on the robust nature of the method offered by the flexibility of the dividing surface, which allows the accurate treatment of a variety of systems from activated and barrierless reactions in the gas phase, reactions in rigid environments, and reactions in liquids and enzymes.

5.1 INTRODUCTION

Transition state theory (TST) is a theoretical framework for calculating and interpreting rate constants of chemical reactions. TST was formulated nearly 70 years ago [1–3] with the goal of providing a computational tool for predicting rate constants from a knowledge of the potential energy surface (PES) controlling the reaction. However, this goal was not attained until much later because theoretical chemists were unable to calculate the PES with sufficient accuracy. Thus, for many years, TST was used primarily for correlating and interpreting rate constants, including kinetic isotope effects, and that aspect of its use continues and will be discussed briefly. The major focus of this article, however, is on the more recent use of TST as a computational tool for predicting rate constants. It is a testament to the utility of TST that its development has continued over an unusually long period of time. For historical perspectives on TST, we refer the reader to previous reviews and perspectives [4–6]. In this work, we review variational transition state theory

(VTST) with multidimensional tunneling (MT) contributions and its implementation for calculating rate constants for chemical reactions in gaseous and condensed phases.

5.2 GAS PHASE REACTIONS

TST provides a means to evaluate the equilibrium rate constant, that is the rate constant for an equilibrium ensemble of reactants described by a Boltzmann distribution of states [7]. The method also assumes that the reaction is electronically adiabatic so that the reaction dynamics of the system can be described by motion of the atoms on a single PES [8]. TST is most easily described in its classical mechanical form, because when classical mechanics is valid, TST can be derived by making a single approximation, the so-called fundamental dynamical assumption [3]. We first review classical TST and the justification for the variational form [9] of the theory before discussing approximate methods for including quantum mechanical effects into the theory.

Our starting point for describing the computational approach to rate constant calculations is to define the Hamiltonian H for a reaction of N atoms with masses m_i , $i = 1, \dots, N$, and Cartesian coordinates $R_{i\zeta}$, $i = 1, \dots, N$, $\zeta = x, y, z$, and conjugate momentum $P_{i\zeta}$, $i = 1, \dots, N$, $\zeta = x, y, z$, which can be reduced to the compact form

$$H(\mathbf{q}, \mathbf{p}) = \frac{\mathbf{p}^2}{2\mu} + V(\mathbf{q}) \quad (1)$$

by introducing the mass-scaled coordinates

$$q_{i\zeta} = \sqrt{\frac{m_i}{\mu}} R_{i\zeta} \quad (2)$$

and momenta

$$p_{i\zeta} = \sqrt{\frac{\mu}{m_i}} P_{i\zeta} \quad (3)$$

where μ is a reduced mass that is chosen for convenience, and $V(\mathbf{q})$ is the PES as a function of the mass-scaled coordinates.

5.2.1 Classical mechanical theory

Exact classical equilibrium rate constants for electronically adiabatic reactions are obtained by evaluating the flux of reactive trajectories through a dividing surface separating the reactant and product regions of phase space (\mathbf{q}, \mathbf{p}) . The dividing surface plays an important role in TST and its variational formulation, and it is worthwhile being explicit about how it is defined and used. For a system of N atoms, the total phase space, excluding overall translation and rotation, has $6(N - 2)$ degrees of freedom. The dividing surface is then a $6N - 13$ degree of freedom hypersurface that is defined by the constraint $Z(\mathbf{q}, \mathbf{p}) = 0$. We consider only those dividing surface that separate reactants from products, where by

convention $Z(\mathbf{q}, \mathbf{p})$ is a function that is negative for reactant-side regions and positive for product-side regions of phase space. The flux of trajectories through the dividing surface at phase point (\mathbf{q}, \mathbf{p}) on the dividing surface is given by

$$\left. \frac{dZ}{dt} \right|_{Z=0} = \left(\frac{\partial Z}{\partial \mathbf{q}} \frac{d\mathbf{q}}{dt} - \frac{\partial Z}{\partial \mathbf{p}} \frac{d\mathbf{p}}{dt} \right) \Big|_{Z=0} = \left(\frac{\mathbf{p}}{\mu} \frac{\partial Z}{\partial \mathbf{q}} - \frac{\partial V}{\partial \mathbf{q}} \frac{\partial Z}{\partial \mathbf{p}} \right) \Big|_{Z=0} \quad (4)$$

The reactant rate constant is then obtained by the proper averaging of this flux through a dividing surface. The dividing surface can be defined to be in the interaction region (e.g. near the saddle point of the reaction) as well as in the reactant region. The question that arises is what weighting of phase points to use in this averaging for arbitrary choices of dividing surface, and there are two parts to this question. One is the correct statistical weight and the other is the weight that should be used to select only reactive trajectories. For the choice of dividing surface in the reactant region, the correct statistical weight to obtain an equilibrium rate constant is an equilibrium distribution of states. For example, the correct statistical weight for a canonical rate constant is just the Boltzmann factor, $\exp(-\beta H)$ [7]. Liouville's theorem of classical mechanics [10] shows that an equilibrium distribution of reactant states will evolve into an equilibrium distribution at the dividing surface and products [11]. Thus, the correct statistical weight for any choice of dividing surface is an equilibrium distribution.

Now we turn to the question of the proper weight to select reactive trajectories. First, note that the flux given by Eq. (4) can be both positive and negative. Averaging the flux over an equilibrium distribution with no additional weighting will include all trajectories, that is, those that cross the dividing surface in both directions, including nonreactive as well as reactive trajectories, so that the equilibrium average is zero. Stated another way, the principle of detailed balance insures that the equilibrium average of the total flux at the dividing surface vanishes. The *total forward flux* is obtained by giving nonzero weight to those phase space points on the dividing surface for which dZ/dt is positive. However, some of these phase space points may actually lie on trajectories that recross the dividing surface or are nonreactive or both (this includes trajectories that originate in the products region and recross the dividing surface one or more times, reactive trajectories that originate in the reactants region and cross an odd number of times, and nonreactive trajectories that originate in the reactants region and cross an even number of times). The *total one-way reactive flux* of reactants toward products is obtained by projecting out only those phase space points that lie on trajectories originating in reactants and ending up in products. For this choice of weighting, a reactive trajectory that recrosses the dividing surface multiple times will have multiple contributions to the averaged flux. The *net one-way reactive flux* of reactants to products is obtained by counting each of these trajectories only at its first crossing, even if it crosses more than once. The latter two are much harder to calculate because they require following trajectories to make sure they are reactive. (The fundamental assumption of TST, as we shall see, is that the latter *net one-way reactive flux* equals the former *forward flux*.) A compact expression for the *net one-way reactive flux* through the dividing surface is written as

$$F_Z(\mathbf{q}, \mathbf{p}) = \delta(Z) \left(\frac{\mathbf{p}}{\mu} \frac{\partial Z}{\partial \mathbf{q}} - \frac{\partial V}{\partial \mathbf{q}} \frac{\partial Z}{\partial \mathbf{p}} \right) \chi(\mathbf{q}, \mathbf{p}) \quad (5)$$

where the Dirac delta function $\delta(Z)$ restricts the phase space to the hypersurface dividing reactants from products (i.e. $Z = 0$). The characteristic function $\chi(\mathbf{q}, \mathbf{p})$ projects out the net contribution from reactive trajectories and therefore requires following trajectories from phase points on the dividing surface forward and backward in time to make sure they originated in reactants and finished in products and that only the first crossing is counted. With these definitions, the exact classical rate constant for a canonical ensemble at temperature T is obtained from a phase-space average of the reactive flux

$$k_C(T) = \frac{1}{\Theta(T)(2\pi\hbar)^{3N}} \int d\mathbf{q}d\mathbf{p} \exp(-\beta H) F_Z \quad (6)$$

where $\hbar = h/2\pi$, h is Planck's constant, $\beta = 1/k_B T$, k_B is Boltzmann's constant, and $\Theta(T)$ is a normalization factor appropriate for the type of reaction (unimolecular or bimolecular). For a unimolecular reaction the normalization factor is given by

$$\Theta(T) = \frac{1}{(2\pi\hbar)^{3N}} \int d\mathbf{q}d\mathbf{p} \exp(-\beta H) \theta(-Z) = q_{CM}^T(T) Q_C^R(T) \quad (7)$$

where the Heaviside step function [$\theta(x)$ is zero for $x < 0$ and 1 for $x > 0$] restricts the phase-space average to the reactant region, $Q_C^R(T)$ is the vibrational-rotational partition function of the reactant species, and $q_{CM}^T(T)$ is the translational partition function for the center-of-mass motion of the system. For bimolecular reactions $\Theta(T)$ takes the form

$$\Theta(T) = q_{CM}^T(T) \Phi_C^R(T) \quad (8)$$

where $\Phi_C^R(T)$ is the reactant partition function per unit volume and includes the translational partition function per unit volume for the relative motion of the two reaction species. The center-of-mass translational partition function in the normalization term cancels an identical factor in the phase space average in the numerator of Eq. (6).

The fundamental dynamical assumption of TST [3] approximates the reactive flux through the dividing surface by the forward flux of all trajectories (reactive and nonreactive). If the reaction coordinate were truly separable, then there would be no reversals in the reaction coordinate, as long as the potential energy has a negative second derivative along the reaction coordinate, so the fundamental assumption may be restated as an assumption that the reaction coordinate is separable and the effective potential along the reaction coordinate is convex. In this case the characteristic function is replaced by the TST approximation

$$\chi^{\text{TST}}(\mathbf{q}, \mathbf{p}; Z) = \theta\left(\frac{\mathbf{p}}{\mu} \frac{\partial Z}{\partial \mathbf{q}} - \frac{\partial V}{\partial \mathbf{q}} \frac{\partial Z}{\partial \mathbf{p}}\right) \quad (9)$$

and the reactive flux is approximated by

$$F_Z^{\text{TST}}(\mathbf{q}, \mathbf{p}) = \delta(Z) \left(\frac{\mathbf{p}}{\mu} \frac{\partial Z}{\partial \mathbf{q}} - \frac{\partial V}{\partial \mathbf{q}} \frac{\partial Z}{\partial \mathbf{p}}\right) \theta\left(\frac{\mathbf{p}}{\mu} \frac{\partial Z}{\partial \mathbf{q}} - \frac{\partial V}{\partial \mathbf{q}} \frac{\partial Z}{\partial \mathbf{p}}\right) \quad (10)$$

In this approximation it is assumed that trajectories with positive flux at the dividing surface (i.e. those with $\chi^{\text{TST}}(\mathbf{q}, \mathbf{p}; Z) > 0$) are reactive, and there is no need to follow trajectories of phase points forward and backward in time. The exact classical rate

constant is independent of the definition of the dividing surface, since every reactive trajectory must cross any dividing surface separating reactants from products. The generalized TST expression is not independent of the choice of arbitrary dividing surface and is written as a explicit function of Z

$$k_C^{\text{GT}}(T, Z) = \frac{1}{(2\pi\hbar)^{3N} \Theta(T)} \int d\mathbf{q}d\mathbf{p} \exp(-\beta H) F_Z^{\text{TST}}(\mathbf{q}, \mathbf{p}) \quad (11)$$

TST counts all forward crossings as reactive (each reactive trajectory must cross the dividing surface with positive flux at least once), and errs by counting as reactive nonreactive trajectories that cross the dividing surface an even number of times and overcounting reactive trajectories that recross the dividing surface. Therefore, the classical TST rate constant is always greater than or equal to the exact classical equilibrium rate constant, and this fact is the basis for variational TST (VTST) in which the dividing surface is optimized to minimize the rate constant and thereby give the best upper bound to it [6,9].

In our most straightforward implementation of VTST for gas-phase reactions, rather than allow arbitrary orientations of the dividing surface, we consider a one-parameter sequence of dividing surfaces that are defined in terms of a reaction path [12,13]. This procedure is applicable to complex problems, and it immediately provides a practical improvement over the conventional choice of placing the dividing surface at the saddle point. A robust choice for the reaction path is the minimum energy path (MEP), that is, the path of steepest descent in the mass-scaled coordinates [14]. The coordinates on this path are denoted $\mathbf{q}^{\text{MEP}}(s)$ as a function of a progress variable s , and the path is defined by

$$\mathbf{q}'(s) \equiv \frac{d}{ds} \mathbf{q}^{\text{MEP}}(s) = - \left. \frac{\partial_{\mathbf{q}} V}{|\partial_{\mathbf{q}} V|} \right|_{\mathbf{q}=\mathbf{q}^{\text{MEP}}(s)} \quad (12)$$

This equation is integrated along the reaction coordinate s from the saddle point at $s = 0$ with an initial step along the eigenvector for the unbound mode into the product region ($s < 0$) and reactant ($s > 0$) region. Generalized transition-state dividing surfaces are constrained to be hyperplanes that are orthogonal to the reaction path and are defined by their location s along the reaction coordinate. Given the vector, $\mathbf{q}'(s)$, tangent to the MEP at point s , the dividing surface orthogonal to this tangent vector is defined by

$$Z_s(\mathbf{q}, \mathbf{p}) = \mathbf{q}'(s)[\mathbf{q} - \mathbf{q}^{\text{MEP}}(s)] = 0 \quad (13)$$

For s not equal to 0, a dividing surface is called a generalized transition state (to distinguish it from the conventional transition state where the gradient is zero). With this choice of dividing surface the generalized TST rate expression given by Eq. (11) reduces for a bimolecular reaction to

$$k_C^{\text{GT}}(T, s) = k_C^{\text{GT}}(T; Z_s) = \sigma \frac{k_B T}{h} \frac{Q_C^{\text{GT}}(T, s)}{\Phi_C^{\text{R}}(T)} \exp[-\beta V^{\text{MEP}}(s)] \quad (14)$$

where $V^{\text{MEP}}(s)$ is the potential evaluated on the MEP at s , the zero of energy of the potential is defined to be the reactant equilibrium geometry (i.e. $V^{\text{MEP}}(s)$ at reactants is zero), and $Q_C^{\text{GT}}(T, s)$ is the classical mechanical generalized transition state partition

function for the bound modes orthogonal to the reaction path at s . Note that this partition function is defined with its zero of energy at the local minimum of the potentials for the bound modes orthogonal to the reaction coordinate. The symmetry factor σ accounts for the fact that the generalized transition state partition function is computed for one reaction path, and for reactions with equivalent reaction paths, this partition function needs to be multiplied by the number of equivalent ways the reaction can proceed. For example, in the reaction $D + H_2 \rightarrow DH + H$, D can react with either H atom, so there are two equivalent pathways and $\sigma = 2$. The symmetry factor does not occur in the more general expression for the rate constant given in Eq. (11) because the phase space average includes all equivalent configurations that lie in the dividing surface. The interested reader is directed to a more detailed discussion of symmetry factors in TST by Pechukas [15]. The canonical variational theory (CVT) rate constant is obtained by minimizing Eq. (14) with respect to s

$$k_C^{\text{CVT}}(T) = \min_s k_C^{\text{GT}}(T, s) = k_C^{\text{GT}}[T, s_C^{\text{CVT}}(T)] \quad (15)$$

where $s_C^{\text{CVT}}(T)$ is the location of the dividing surface that minimizes Eq. (14) at temperature T . Eq. (14) provides a quantitative framework for discussing activation energy and steric effects, with the former originating mainly in the exponential term and the latter mainly in the partition function of the transition state.

The expression in Eq. (14) can be recast into a thermodynamic formulation as [13]

$$k_C^{\text{GT}}(T, s) = \frac{k_B T}{h} K^0 \exp[-\Delta G_C^{\text{GT},0}(T, s)/RT] \quad (16)$$

in which K^0 defines the standard state and $\Delta G_C^{\text{GT},0}(T, s)$ is the standard state free energy of formation of the generalized transition state. Minimizing the canonical rate constant as in Eq. (15) is equivalent to maximizing the free energy of activation with respect to the location of the dividing surface [13,16].

Throughout this section, all rate constant expressions have had a subscript C to denote classical mechanics. Consistent with notation used in previous work, no subscript is used when quantum mechanical effects are included.

5.2.2 Inclusion of quantum mechanical effects

For many reactions, especially those including light atoms, such as reactions involving the transfer of a hydrogen atom, proton, or hydride ion, classical mechanics is not sufficient, and quantum mechanical effects on the motion of the atoms must be included. The inclusion of quantum mechanical effects can also be important when zero-point energies for modes with high vibrational frequencies change along the reaction coordinate. High-frequencies can result from heavy-atom vibrations with large force constants, as well as vibrational modes dominated by light atom motion. In addition quantum effects may be smaller, but not necessarily negligible, for rearrangements dominated by motions of heavier atoms. A rigorous quantum mechanical formulation of TST that employs the fundamental assumption as its only

approximation has been discussed [17] with the conclusion that no rigorous quantum version of TST exists that does not require a solution of the full multidimensional reaction dynamics [18]. Therefore, additional approximations are needed to include quantum mechanical effects into TST. The standard approach is an *ad hoc* procedure [1,19] that replaces classical partition functions by approximate quantum mechanical ones and then includes correction factors for quantum mechanical effects (such as tunneling) on the reaction coordinate motion. Replacing the classical partition functions in Eq. (14) by quantum mechanical ones results in a quantized generalized transition state rate constant given by

$$k^{\text{GT}}(T, s) = \sigma \frac{k_{\text{B}}T}{h} \frac{Q^{\text{GT}}(T, s)}{\Phi^{\text{R}}(T)} \exp[-\beta V^{\text{MEP}}(s)] \quad (17)$$

The classical phase-space averages for bound modes in Eq. (11) are replaced by quantum mechanical sums over states. If one assumes separable rotation and uses an independent normal mode approximation, the potential becomes decoupled, and one-dimensional energy levels for the bound modes may be conveniently computed. In this case, the quantized partition function is given by the product of partition functions for each mode. Within the harmonic approximation the independent-mode partition functions are given by an analytical expression, and the vibrational generalized transition state partition function reduces to

$$Q_{\text{HO}}^{\text{GT}}(T, s) = \prod_m \frac{1}{2 \sinh[\hbar \omega_m(s) \beta / 2]} \quad (18)$$

where $\omega_m(s)$ is the harmonic frequency for mode m at location s along the MEP. When low frequency modes are present, the harmonic approximation is very often not valid, and methods for including anharmonicity must be considered [20].

Harmonic frequencies for bound modes at stationary points on the PES (i.e. locations where $\partial V / \partial \mathbf{q} = \mathbf{0}$) are obtained by diagonalizing the matrix of second derivatives (properly mass-weighted or mass-scaled), which is denoted the Hessian matrix. Frequencies for modes at other locations along the reaction coordinate require special attention since the first derivatives are not zero, and diagonalization of the Hessian would mix the reaction coordinate mode with bound vibrations. Determination of the bound modes orthogonal to the reaction coordinate can be accomplished in a straightforward manner by working in a space normal to the tangent to the reaction path [12] or by projecting out the reaction coordinate motion from the Hessian matrix [21]. The latter method often has the unsatisfactory characteristic that transitional modes (those that correspond to translations or rotations of the reactants or products in an asymptotic region but that evolve into or from a hindered rotation or bending vibration in the interaction region) can have unphysical imaginary frequencies (corresponding to negative eigenvalues of the Hessian matrix) along the reaction coordinate [22]. The use of curvilinear internal coordinates is an attractive alternative that helps with this problem [23].

The quantized generalized transition state rate constant equation (17) is a hybrid expression in which the bound modes are treated quantum mechanically but the reaction

coordinate motion is treated classically. Consistent quantum mechanical treatments of reaction coordinate motion rely on the fact that the adiabatic theory of reactions [24,25] is equivalent to one form of VTST (microcanonical VTST) when the reaction coordinate is treated classically [13,26]. In the adiabatic theory of reactions, coordinates orthogonal to the reaction coordinate are treated as ‘fast’ variables. Reaction probabilities $P^A(\mathbf{n}, E)$ for a state defined by quantum numbers \mathbf{n} at total scattering energy E are obtained by considering the dynamics on the one-mathematical-dimensional vibrationally adiabatic potential. In the harmonic approximation the vibrationally adiabatic potential is written

$$V^A(s, \mathbf{n}) = V^{\text{MEP}}(s) + \sum_m \hbar \omega_m(s) \left(n_m + \frac{1}{2} \right) \quad (19)$$

where the sum is over the bound modes of the generalized transition state at s , and the energy level for state n_m of mode m at location s along the reaction coordinate is given by the harmonic approximation. The reaction probabilities $P^A(\mathbf{n}, E)$ are then thermally averaged to yield the rate constant. When reaction coordinate motion is treated classically, the adiabatic theory of reactions yields an expression for the thermal rate constant which is equivalent to that obtained from microcanonical variational theory even though the approximations in the two theories are very different [13,26]. Since the one-dimensional scattering problem can be treated quantum mechanically, a multiplicative tunneling correction factor for the adiabatic theory of reactions can be obtained, and the equivalency of microcanonical VTST and adiabatic theory makes it consistent to use the same correction factor to account for the quantization of reaction coordinate motion in the variational theory.

The adiabatic approximation is made in a curvilinear coordinate system, and although the potential energy term is simple, the kinetic energy term is complicated by factors dependent upon the curvature of the reaction path [21,25,27]. As shown by Skodje et al. [28], the most successful methods for including the multidimensional effect of the reaction path curvature in the adiabatic calculations of the reaction probabilities specify a tunneling path that ‘cuts the corner’ and shortens the tunneling length. Marcus and Coltrin [29] found the optimum tunneling path for the collinear $\text{H} + \text{H}_2$ reaction by finding the path that gave the least exponential damping. General multidimensional tunneling (MT) methods, applicable to polyatomic reactions, have been developed that are appropriate for systems with both small [28,30] and large [12,31,32] reaction path curvature, as well as more general methods that optimize tunneling paths by a least-imaginary-action principle [31,33]. In practice it is usually sufficient to optimize the imaginary action from among a small set of choices by choosing either the small-curvature tunneling approximation, or the large-curvature tunneling approximation, which gives more tunneling at a given tunneling energy; this is called microcanonical optimized multidimensional tunneling (μOMT), or, for short, optimized multidimensional tunneling (OMT) [32,34].

The quantum mechanical CVT rate constant with the tunneling correction factor, $\kappa^{\text{MT}}(T)$, included is given by [35]

$$k^{\text{CVT/MT}}(T) = \kappa^{\text{MT}}(T) k^{\text{CVT}}(T) \quad (20)$$

Rather than compute the tunneling through all adiabatic potentials that contribute significantly to the tunneling correction factor, the tunneling correction factor is approximated by tunneling through just the ground-state potential [35]

$$\kappa^{\text{MT}}(T) = \frac{\int_0^\infty dE e^{-\beta E} P^{\text{MT}}(\mathbf{n} = 0, E)}{\int_0^\infty dE e^{-\beta E} P_C(\mathbf{n} = 0, E)} \quad (21)$$

where $P^{\text{MT}}(\mathbf{n} = 0, E)$ is the multidimensional tunneling approximation to the probability for tunneling through the ground-state adiabatic potential at total energy E and $P_C(\mathbf{n} = 0, E)$ is the classical analog, which is zero for total energy E below the maximum of the adiabatic barrier and one for energy above it. At low temperatures where tunneling corrections are most important, quantized systems tend to be in the ground state, and this approach provides a good approximation. As temperature increases, tunneling through excited-state adiabatic potentials would contribute relatively more, but tunneling becomes less important and the correction factor decreases until at sufficiently high temperatures it tends to unity. The ground-state method gives the correct high temperature limit, and for intermediate temperatures, the tunneling through excited-state adiabatic potentials is approximated (implicitly) by the tunneling probabilities for the ground-state potential with the energy scale shifted by the difference in the excited-state and ground-state energies at the ground-state maximum.

After including variational and quantum effects, the quasithermodynamic variables of TST, like entropy of activation and energy of activation, may be decomposed into ‘substantial’ contributions that derive from formulas analogous to those of statistical thermodynamics [36] and ‘nonsubstantial’ contributions deriving from the transmission coefficient [37].

5.2.3 Improved prescriptions for the reaction coordinate and dividing surface

The formalism summarized above is well suited for bimolecular reactions with tight transition states and simple barrier potentials. In such cases we have found that the variational transition state can be found by optimization of a one-parameter sequence of dividing surfaces orthogonal to the reaction path, where the reaction path is defined as the MEP. However, although dividing surfaces defined as hyperplanes perpendicular to the tangent to the MEP (as described in Section 5.2.2) are very serviceable, a number of improvements have been put forth.

It is important to emphasize, in describing these improvements, that the generalized transition-state dividing surface is defined by the MEP only on the reaction path itself. The full definition of the transition state dividing surface for VTST calculations is usually specified by starting with a global definition of a reaction path, after which a one-parameter sequence of dividing surfaces is defined by the location at which the dividing surface crosses the path. In our original work [12,38] we took the dividing surface to locally be a plane orthogonal to the MEP in isoinertial coordinates, but we approximated

the partition functions in a way [13,26] that provided physical results even when this surface is unphysical beyond a certain distance from the MEP. The first important improvement is to use curved dividing surfaces defined in terms of nonredundant [22,23] or redundant [39] internal coordinates. Because the neglect of anharmonic bend–stretch interactions is less serious in curvilinear internal coordinates than in rectilinear coordinates [15,40], a dividing surface defined in curvilinear internal coordinates is much more physical, and the harmonic frequencies calculated this way provide much better harmonic approximations to the bound motions in the dividing surface and hence to $Q^{\text{GT}}(T, s)$.

A next higher level of refinement is to *optimize* the orientation of the dividing surface rather than assume that it is normal (in either rectilinear or curvilinear coordinates) to the MEP [40–42]. This variational optimization should in principle improve the rate, just as optimizing the location at which the dividing surface intersects the MEP improves the rate. Even more significantly though it allows one [40,42] to carry out VTST calculations without calculating (or without converging) an MEP, which is often expensive (because it requires small step sizes to follow it) and/or hard to converge.

The use of curvilinear coordinates and optimization of the orientation of the dividing surface are important for quantitative calculations on simple barrier reactions, but even more flexibility in the dividing surfaces is required to obtain quantitative results for very loose variational transition states such as those for barrier-less association reactions or their reverse (dissociation reactions without an intrinsic barrier).

In the context of association reactions, an algorithm in which the reaction coordinate definition is optimized along with the dividing surface along a one-parameter sequence of paths is called ‘variable reaction coordinate’ (VRC) variational transition state theory [43,44]. In the last few years there has been considerable progress in optimizing VRCs for barrier-less association reactions with strictly loose transition states. A strictly loose transition state is defined as one in which the conserved vibrational modes are uncoupled from the transitional modes and have the same frequencies in the variational transition state as in the associating reagents [45,46]. Conserved vibrational modes are modes that occur in both the associating fragments and the association complex, whereas transition modes (already mentioned above) include overall rotation of the complex and vibrations of the complex that transform into fragment rotations and relative translations upon dissociation of the complex. Progress has included successively refined treatments of the definition of the dividing surface and of the definition of the reaction coordinate (the coordinate that is missing in the transition state) [43,46–48], and elegant derivations of rate expression for these successively improved reaction coordinates [48,49]. A guiding principle in the choice of reaction coordinate in all these methods is to make the reaction coordinate correspond to a physical motion that is relatively uncoupled from the motions orthogonal to it, because the assumption of a separable reaction coordinate is a key aspect of the fundamental assumption of TST, as mentioned above. The recent variational implementation of the multifaceted dividing surface (MDS) VRC version of VTST seems to have brought the theory to a flexible enough state that it is suitable for application to a wide variety of practical applications to complex barrier-less association reactions of polyatomic molecules [50].

5.2.4 Spectroscopy of the transition state

The quantization of transition state energy levels is not simply a mathematical device to add quantum effects to the partition functions. The quantized levels actually show up as structure in the exact quantum mechanical rate constants as functions of total energy [51]. The interpretation of this structure provides clear evidence for quantized dynamical bottlenecks, both near to and distant from the saddle points, as reviewed elsewhere [52]. Quantized variational transition states have also been observed in molecular beam scattering experiments [53]. Analysis of the reactive flux in state-to-state terms from reactant states to transition state levels to product states provides the ultimate limit of resolution allowed by quantum mechanics [53,54]. Quantized energy levels of the variational transition state have been used to rederive TST using the language of quantum mechanical resonance scattering theory [55].

5.2.5 Applications

Recent applications of VTST/MT to polyatomic gas-phase reactions that illustrate the power of the theory include the reactions of chlorine atoms with hydrogen molecules [56] and the reactions of hydrogen atoms with ethylene [57,58] and methane [59], including kinetic isotope effects.

5.3 REACTIONS IN CONDENSED PHASES

Compared to gas-phase reactions, those in condensed-phase systems are more difficult to treat because of the close proximity of other atoms and molecules to the reacting species; interactions with the surroundings affect both the energetics and dynamics of a reaction. Short-range effects, due to atoms and molecules in the immediately vicinity of the reacting species, can be treated using an embedded cluster approach in which the reacting species and a finite number of surrounding atoms are included explicitly in calculations of reaction energies and dynamics using standard approaches used in gas-phase calculations. A major challenge for condensed-phase reactions arises from the fact that long-range interactions of the reacting species with atoms or molecules, which are not directly participating in the reaction, can affect both the energetics and dynamics of reactions thus requiring calculations on much larger systems than the embedded cluster models. Sometimes such effects can be included by continuum solvent models [60] or by the use of collective reaction coordinates [61,62], or both.

We first consider the case of a condensed-phase environment in which the atoms have well defined equilibrium geometries and the fluctuations around these geometries are small compared to the interatomic distances (e.g. solids). In this type of rigid environment the long-range effects of the environment are restricted to the reaction energetics and the dynamics, to the extent that dynamics may be separated from energetics, can be treated accurately using an embedded cluster model. We then discuss two approaches to treating reactions in an environment in which the atoms and

molecules have many local equilibrium structures that are interconnected by small barriers (i.e. ones that can be easily surmounted by thermal fluctuations). In this type of fluid environment both the energetic and dynamic effects of anharmonicity and perhaps also long-range interactions need to be considered.

The average environment that the reacting species encounter in gas phase and condensed fluid environments is isotropic and translationally invariant. This is not true for rigid environments with well-defined lattice sites, e.g. the average environment that a reacting species sees near a lattice site is very different from that near an interstitial site.

5.3.1 Reactions in rigid environments and application to reactions in crystals or at crystal–vapor interfaces

Solid-state reactions, at least in a crystal, are characterized by the need to consider only one or a few environments for the reacting subsystem. The reacting subsystem may interact with this environment by a variety of interactions, including electrostatic and dispersion forces, hydrogen bonding, and dielectric screening of intramolecular Coulomb interactions due to the electric field lines passing through the environmental medium. These effects must be included in the Hamiltonian. One also needs to consider effects such as relaxation of the lattice around the reacting subsystem or reconstruction of a surface in absence and presence of the reacting subsystem. These considerations also apply to the calculation of equilibrium properties in the solid state, but a question that arises only when one considers dynamics is the inclusion of medium degrees of freedom in the dividing surface, or medium participation in the reaction coordinate.

As mentioned above, these effects can all be included by an embedded cluster approach [63]. In this method one starts with a large but finite rigid lattice representing the crystal and adds the reacting substance as a substitutional impurity, defect, or interstitial in the solid (absorbate) or on its surface (adsorbate). The origin is defined in some convenient way to be at or near the center of the reacting substance. All lattice atoms within a distance R_0 of the origin are fully included in the Hamiltonian, that is, they are treated dynamically on an equal footing with the atoms of the absorbate or adsorbate.

The other atoms in the lattice are held rigid. As such they enter the Hamiltonian and they help to enforce the macroscopic habit on the environment of the reacting substance, but they do not participate dynamically. In principle, both the size of the lattice and the value of R_0 are increased until the results converge.

This kind of treatment requires only minor changes in a VTST computer program. The most significant changes are that there are no translational or rotational partition functions or coordinates to project out of the Hessians. Reactants have $3N$ vibrations, rather than $3N - 6$, and transition states have $3N - 1$ vibrations rather than $3N - 7$.

Examples of applications that have been studied by this method are surface diffusion of hydrogen atoms on metal surfaces [63–66], bulk diffusion [64,66], subsurface-to-surface transport [66], and dissociative chemisorption [67].

5.3.2 Reactions in fluid environments with a single reaction coordinate

The prescription for using VTST for gas-phase and solid-state reactions relies on locating saddle points and reaction paths. For reactions in fluids, there are many saddle points that are close in energy and that differ significantly only in the configuration of solvent molecules [68]. Similarly, the PESs of large clusters often have multiple minima, often separately by low barriers [69], and when a molecule reacts on or with a large cluster, these minima lead to multiple saddle points. The multiple saddle points may be considered to result from the large anharmonicity of the solvent (i.e. of the liquid-phase solvent or the large-cluster microsolvant), and their treatment requires special consideration. As in the case of solid-state reactions, VTST including quantum mechanical effects can be applied to an embedded cluster model, which contains solvent molecules as well as the reacting subsystem; however, unlike the solid-state case where the remainder of the system is fixed in a rigid configuration, it is important to sample over configurations of the remainder of the solvent or to use a mean-field representation that includes an average over solvent configurations.

To generalize the procedures of Sections 5.2 and 5.3.1 to the liquid phase, one can start from the full microscopic description of the system. The Hamiltonian for the whole system is partitioned into a gas-phase component, as given in Eq. (1), for a reactive embedded molecule or embedded cluster (note: an embedded cluster is often called a supermolecule) in the absence of the solvent, and a solvent component that includes coupling between the solvent and reactive subsystem:

$$H(\mathbf{q}, \mathbf{p}, \mathbf{x}, \mathbf{p}_x) = \frac{\mathbf{p}^2}{2\mu} + V_C(\mathbf{q}) + \frac{\mathbf{p}_x^2}{2\mu} + V_S(\mathbf{x}, \mathbf{q}) \quad (22)$$

where \mathbf{q} and \mathbf{p} are coordinates and conjugate momentum of the embedded molecule or cluster (henceforth called the solute), \mathbf{x} and \mathbf{p}_x are the solvent coordinates and conjugate momentum, $V_C(\mathbf{q})$ is the PES for the isolated solute, and $V_S(\mathbf{x}, \mathbf{q})$ is the PES for the solvent including the solvent interactions with the solute. We first consider the classical mechanical expression for the rate constant for this model

$$k_C^{\text{GT}}(T; Z) = \frac{1}{(2\pi\hbar)^{3N+3N_s} \Theta(T)} \int d\mathbf{q}d\mathbf{p} \int d\mathbf{x}d\mathbf{p}_x \exp(-\beta H) F_R^{\text{TST}}(\mathbf{q}, \mathbf{p}, \mathbf{x}, \mathbf{p}_x) \quad (23)$$

where $3N_s$ is the number of degrees of freedom of the solvent, and the normalization factor $\Theta(T)$ includes the partition function for both the solute and solvent. The reactive flux is explicitly written as a function of solvent coordinates as well as those of the solute. However, if the dividing surface is only a function of the solute coordinates and momentum, Eq. (23) takes on a simpler form

$$k_{\text{C.ES}}^{\text{GT}}(T; Z) = \frac{1}{(2\pi\hbar)^{3N} \Theta(T)} \int d\mathbf{q}d\mathbf{p} \exp\left[-\beta\left(\frac{\mathbf{p}^2}{2\mu} + W(\mathbf{q})\right)\right] F_R^{\text{TST}}(\mathbf{q}, \mathbf{p}) \quad (24)$$

where the potential of mean force (PMF) [36] $W(\mathbf{q})$ is defined by

$$\exp[-\beta W(\mathbf{q})] = \frac{1}{(2\pi\hbar)^{3N_s}} \int d\mathbf{x}d\mathbf{p}_x \exp\left[-\beta\left(\frac{\mathbf{p}_x^2}{2\mu} + V_C(\mathbf{q}) + V_S(\mathbf{q}, \mathbf{x})\right)\right] \quad (25)$$

The normalization factor can also be rewritten in terms of the PMF

$$\Theta(T) = \frac{1}{(2\pi\hbar)^{3N}} \int d\mathbf{q}d\mathbf{p} \exp\left[-\beta\left(\frac{\mathbf{p}^2}{2\mu} + W(\mathbf{q})\right)\right] \theta(-Z) \quad (26)$$

so that the rate constant takes the form of the gas-phase expression with an effective, solvent-averaged potential. Classically, the only approximation is the fundamental dynamical assumption of TST, with the restricted choice of dividing surface to not include any of the solvent coordinates or momentum. We use the subscript ES on the rate constant to denote an equilibrium solvation model, in which the only influence of the solvent is to modify the interaction potential. It has long been realized that the effect of equilibrium solvation can be included in TST using the PMF [5,70–74]; however, most previous calculations of equilibrium solvation contributions to the TST rate constant express the PMF as a function of a single coordinate—the reaction coordinate. Eq. (24) differs by the fact that the rate constant is written as a function of a multidimensional equilibrium solvation PES.

Although $W(\mathbf{q})$ may be defined entirely in terms of condensed-phase averages, as in Eq. (25), it can also be defined with reference to gas-phase calculations, in which case it equals the gas-phase free energy of activation plus the free energy of solvation [60, 74–77]. Thus, the equilibrium solvation rate constant given in Eq. (24) takes the thermodynamic form for the rate constant (as given in Eq. (16) for the gas phase)

$$k_{C,ES}^{GT}(T, s) = \frac{k_B T}{h} K^0 \exp[-\Delta G_{C,ES}^{GT,0}(T, s)/RT] \quad (27)$$

where the equilibrium-solvation standard-state free energy of activation is expressed as

$$\Delta G_{C,ES}^{GT,0}(T, s) = \Delta G_C^{GT,0}(T, s) + \Delta G_{\text{solv}}^{GT,0}(T, s) - \Delta G_{\text{solv}}^{R,0}(T) \quad (28)$$

and $\Delta G_{\text{solv}}^{GT,0}(T, s)$ and $\Delta G_{\text{solv}}^{R,0}(T)$ are the free energies for solvating the generalized transition state at s and reactants, respectively.

If the reaction path and dividing surface are optimized in the gas phase, but the rate constant is calculated with the equilibrium solvation Hamiltonian, the resulting rate constant is called separable equilibrium solvation (SES) [57]. However, if the reaction path and dividing surface are optimized with the equilibrium solvation potential, the result is labeled equilibrium solvation path (ESP) [57,78].

The assumption of equilibration of the solvent at all geometries of the solute neglects the coupling of solvent dynamics with solute dynamics. For example, if the solute dynamics are rapid with respect to the solvent motion, the solvent will not have time to equilibrate as the solute rearranges. Fluctuations of solvent molecules can induce recrossings of the dividing surface and a breakdown of the fundamental dynamical

assumption of TST. This type of influence of the liquid on the reaction rate is often referred to as a nonequilibrium or dynamical solvent effect [5,70,71,73,79].

Formulating TST in terms of an approximate flux through a dividing surface reveals a means to mitigate the effects of this breakdown. Variational optimization of a dividing surface that is a function of solvent coordinates as well as the coordinates of the embedded cluster will minimize the recrossings induced by solvent reorganization. However, this procedure leads to more complicated calculations of the ensemble averages in Eq. (23) because they are constrained to configurations lying on the dividing surface. Evaluations of averages over solvent degrees of freedom for fixed configurations of the solute, as required when the dividing surface is a function of only solute coordinates, are standard in PMF calculations [75], whereas evaluations of ensemble averages for more general dividing surfaces are much more complicated. (The formulation of classical TST for arbitrary dividing surfaces [80] is related to the formulation of potentials of mean force for constrained molecular dynamics [81] and to PMF calculations for more complicated reaction coordinates [82].)

This use of arbitrary reaction coordinates also allows [62] inclusion of nonequilibrium solvation effects in VTST by using the solvent energy-gap reaction coordinate that first arose [83] in weak-overlap charge-transfer theory. In electron transfer kinetics, nonequilibrium effects are often studied by a spin boson model [84] in which two diabatic states of the electronic wave function are linearly coupled to a harmonic bath. The coupling constant is a parameter of the model. A more general model, the generalized Langevin treatment [71,85], also involves a linearly coupled harmonic bath, but it has the advantage that the friction coefficient is related by the fluctuation-description theorem [86] to the time autocorrelation function of the force exerted on the system by the bath. In classical mechanics, the time autocorrelation function can be obtained from a molecular dynamics simulation, and one can use this kind of friction estimate to model nonequilibrium solvation [87,88]. This is accomplished by describing solvent frictional effects by a collection of harmonic oscillators that are linearly coupled to the solute degrees of freedom. In the limit of a continuum of oscillators, the classical dynamics for this model are equivalent to the generalized Langevin equation for solute dynamics [89]. When the reaction is treated as a reaction coordinate coupled to a harmonic bath, harmonic TST with a dividing surface at the saddle point that includes dependence on the harmonic solvent coordinates yields the Kramers [90] and Grote-Hynes [91] theories, as reviewed elsewhere [92,93]. This simple model of a reaction in solution is surprisingly robust for describing dynamical solvent effects, even for systems for which the reaction dynamics appear to be controlled by anharmonic solvent reorganization [94]. In an attempt to develop a widely applicable practical scheme for estimating the conditions under which nonequilibrium solvent effects are important and to increase physical insight, the friction has also been further approximated in terms of effective diffusion constants [78,95]. This has the advantage that it neither assumes the validity of classical mechanics nor requires large-scale simulations. We have presented VTST treatments of multidimensional embedded cluster models linearly coupled to harmonic solvent coordinates, including variationally optimizing the dividing surface (including both harmonic solvent and embedded cluster coordinates) and quantum mechanical effects [73,87,95]; and these treatments can be viewed as a generalization of

Grote–Hynes theory to include multidimensional, anharmonic (in the embedded cluster coordinates), and quantum mechanical effects.

The treatment of quantum mechanical effects, particularly tunneling, is especially challenging for reactions in liquids. Comparisons of calculations using VTST methods including multidimensional tunneling corrections for gas-phase reactions, as outlined in Section 5.2.2, with benchmark calculations for a model reaction in solution (a reaction coordinate linearly coupled to a harmonic bath) have shown that the methods are capable of quantitative accuracy for these types of systems and that the largest deficiencies arise from the approximate treatment of anharmonicity, not tunneling [96]. A general prescription for treating tunneling in the presence of a bath, based upon a multidimensional tunneling approximation using the PMF, has been given [97] and applied [76,95,98]. VTST has been used to study the effect of nonequilibrium solvation on quantum mechanical tunneling in models of hydrogen addition to benzene [78] and hydrogen abstraction from methanol [95] and to examine the importance of multidimensional tunneling for a model of a proton transfer reaction in explicit solvent [88].

5.3.3 Reactions in fluid environments with an ensemble of reaction coordinates

For some reactions in solution, it may be necessary to include a large number of saddle points and reaction paths. These reaction paths might differ primarily in the conformation of the bath. One can always attempt to model this situation, as in Section 5.3.2, by using a single reaction coordinate and a mean field representation of the bath, but this will not always be valid, and it requires considerable physical insight to properly include solvent motion in the reaction coordinate, when that is necessary.

In order to treat this kind of system more reliably, ensemble-averaged VTST [99–101] has been developed. In this method, the calculation is divided into two stages. In stage one, one uses a predefined chemical reaction coordinate z to calculate a one-dimensional PMF. The maximum value of this PMF defines the stage-1 free energy of activation,

$$\Delta G^{(1)} = \Delta G^{\ddagger,0}(z_*) \quad (29)$$

at location z_* . In carrying out this calculation, we quantized the vibrations perpendicular to z by a new method developed for this purpose [102]. Because of this quantization, the resulting free energy is not completely classical and we call it quasiclassical. In the process of calculating this stage-1 quasiclassical free energy of activation we sample a large number of systems with $z_* - \delta_z \leq z \leq z_* + \delta_z$, where δ_z is a small numerical tolerance (in principle δ_z should be zero). The equilibrium ensemble corresponding to this small range of z is called the stage-1 transition state ensemble.

In stage 2, one calculates a transmission coefficient for the stage-1 rate constant. This transmission coefficient is calculated by an ensemble average over CVT/ μ OMT calculations for various reaction paths (labeled $\alpha = 1, 2, \dots, N_\alpha$) that pass through N_α samples from stage-1 transition state ensemble. In particular, the final ensemble-averaged

VTST with multidimensional tunneling (EA-VTST/MT) rate constant is given by

$$k(T) = \gamma(T) \frac{k_B T}{h} K^0 \exp(-\Delta G^{(1)}/RT) \quad (30)$$

where

$$\gamma(T) = \frac{\sum_{\alpha=1}^{N_\alpha} \kappa_\alpha(T) \Gamma_\alpha(T)}{N_\alpha} \quad (31)$$

In stage 1, all atoms are treated on an equal footing. However in stage 2, the system is divided into N_1 primary-zone atoms and N_2 secondary-zone atoms. For each α , the N_2 secondary-zone atoms are frozen and the N_1 primary-zone atoms are optimized to the nearest saddle point, then a MEP is calculated, again with N_2 atoms frozen. In both steps, the secondary-zone atoms are not neglected; they provided an effective potential field that is included in the Hamiltonian. Continuing in this fashion, we calculate a free energy of activation profile $\Delta G_\alpha(T)$ for the primary subsystem in the effective field of the secondary subsystem; this is reminiscent of the method in Section 5.3.1. Then

$$\Gamma_\alpha(T) = \exp\{ - [\Delta G_\alpha(T) - \Delta G^{(1)}(T)]/RT \} \quad (32)$$

Finally one calculates a transmission coefficient $\kappa_\alpha(T)$ that accounts for tunneling and nonclassical reflection, and we use this in Eq. (31) to calculate the overall transmission coefficient $\gamma(T)$.

Some points should be noted about this treatment. The first is that the transmission coefficient and the quasithermodynamic free energy of activation are not independent. If we choose a poor reaction coordinate for stage 1, then the Γ_α values in stage 2 may be very small. The second is that the procedure used for step 2 allows the secondary subsystem to participate in the reaction coordinate. In other words, since each conformation of the secondary subsystem has its own reaction path, the reaction path does depend on the coordinates of the secondary subsystem.

It is also possible to include a third stage in which the secondary zone is relaxed as a function of s for each α [99]. Although this is more expensive, it is not necessarily more accurate because the transition state passage might be well modeled by an ensemble average of essentially fixed secondary-zone structures [93].

EA-VTST/OMT has been applied successfully to several enzyme reactions, as reviewed elsewhere [100,103].

5.4 SUMMARY AND CONCLUSIONS

“It is no criticism of a chemical theory to call it ‘approximate’ or ‘limited’. The value of a theory is measured by the strength of its predictions within its restricted range of applicability” [104]. TST is an approximate theory with a very broad range of applicability, covering elementary reaction rate constants for virtually all kinds of chemical reactions, provided that the reactants are in local thermal or microcanonical

equilibrium, and it can even be extended to certain questions in state-selected chemistry. It provides a language for discussing and analyzing activation energy, steric effects, and solvent and other environmental effects. When the transition state is variationally optimized and quantum effects, especially vibrational zero point energy and tunneling, are included, it provides a quantitative theory as well. It seems unimaginable that it can ever become obsolete, and we expect that research on its application to more and more complex processes will continue to abound.

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