

# 22 Variational Transition-State Theory and Multidimensional Tunneling for Simple and Complex Reactions in the Gas Phase, Solids, Liquids, and Enzymes

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## I. INTRODUCTION

The theory of absolute reaction rates, or transition-state-theory, forms the basis of almost all of our discussions of isotope effects in chemical reactions.<sup>1</sup>

This is as true now as it was 25 years ago, except that now we have a much better appreciation of the high accuracy afforded by transition-state theory in its modern form. This chapter is concerned with modern transition-state theory, which differs from that in use 25 years ago in two key ways:

- Consistent incorporation of variational effects
- Inclusion of multidimensional corner-cutting tunneling contributions

By variational effects we mean the use of variational transition-state theory<sup>2-6</sup> to optimize the transition state dividing surface. By multidimensional tunneling we mean, at a minimum, accounting for the change in vibrational frequencies of modes perpendicular to the reaction coordinate.<sup>7</sup> For quantitative accuracy though, we know that tunneling calculations must allow for the possibility of corner cutting, that is the tendency of the dominant tunneling paths to lie on the concave side of the minimum energy path.<sup>8-12</sup> The incorporation of tunneling is usually accomplished by a transmission coefficient, which can also be used for other purposes, as discussed in Section IV.A. The consistent inclusion of quantization effects, especially zero-point energy, on perpendicular vibrations is implicit in the above description, and in fact for quantitative calculations of reaction rates and even for qualitative discussions of kinetic isotope effects (KIEs), purely classical variational transition state theory<sup>2-4</sup> is only of historical and heuristic importance.

The above discussion of quantum effects and classical transition-state theory prompts a few comments on definitions, notation, and some conceptual issues. First of all we use *transition-state theory* as a generic name for both conventional transition-state theory and generalized transition-state theories, such as variational transition-state theory; however, in the present chapter, I restrict the acronym TST to mean conventional transition-state theory. Transition-state theory assumes that one can identify a hypersurface in phase space, separating reactants from products and called the transition-state dividing surface, that serves as a dynamical bottleneck (as discussed in more detail in Section IV.A). Conventional transition-state theory<sup>13,14</sup> is the special case where the transition-state dividing surface passes through the saddle point, and the transmission coefficient is taken as unity (thus tunneling is neglected). The transition-state dividing surface is often just called the transition state, although that term is used by some workers, especially electronic structure theorists who are not dynamicists, to denote a saddle point on the potential energy surface (PES). Conventional transition-state theory and conventional transition states are also denoted by the widely used double-dagger symbol ( $\ddagger$ , also called a double cross), which dates back to Eyring's secretary, Miss Lucy D'Arcy.<sup>15</sup> We often use \* or TS to denote a variational transition state. Transition states that are not located at saddle points are sometimes called generalized transition states (abbreviated GT or TS) to emphasize their nonconventional character. Variational transition-state theory (VTST) in which the transition state is optimized for a canonical ensemble is called canonical VTST or, for short, canonical variational theory (CVT).<sup>16</sup> Usually, in both TST and CVT, vibrations are quantized on the whole reaction path (including reactants and transition states), but rotation and reaction-coordinate motion are not. We call this quasiclassical (QC), by analogy to *quasiclassical trajectories* in which vibrations are initially quantized, but everything else is classical. (In our older papers, we sometimes said *hybrid* rather than *quasiclassical*.) Here is the first big disconnect: the isotope effect community tends to call this *semiclassical*. However, we (and a large number of chemical physicists) use the word semiclassical for WKB-like treatments of quantum phenomena such as tunneling<sup>9-12,17-19</sup> [or, in other contexts, for methods where classical and quantal equations of motion are integrated in tandem]; thus when we say semiclassical we mean including tunneling, but when the isotope effect community says semiclassical they mean excluding tunneling. For that reason, we will not use the overworked and confusing word semiclassical in the

rest of this chapter, except in references and at the end of Section III, where it has the chemical physics meaning, i.e., approximate quantal dynamics (not neglect of tunneling).

There is another language issue which it is good to clarify at the outset, namely differences between barrier height, activation energy, activation free energy, and related terms. The potential energy surface (PES, really a hypersurface, and also called potential energy function) is the sum of the Born–Oppenheimer electronic energy and the nuclear repulsion. Chemical reactions, except barrierless ones (which are not considered in this chapter) have one or more saddle point on the PES between reactants and products. The energy difference between the lowest-energy saddle point and the energy of the reactant is called the classical barrier height or zero-point exclusive barrier height, denoted  $V^\ddagger$ . Technically, if there could possibly be any confusion, this would be called the forward  $V^\ddagger$  to distinguish it from the reverse  $V^\ddagger$ , which is the potential energy of the saddle point minus the potential energy of products. The smaller of the forward and reverse  $V^\ddagger$  is called the intrinsic  $V^\ddagger$ . The energy of the products minus the energy of reactants is called the energy of reaction, denoted  $\Delta E$ . Thus the intrinsic  $V^\ddagger$  is  $V^\ddagger$  in the direction in which  $\Delta E$  is negative.

Zero-point-inclusive barrier heights are obtained by adding in zero-point energy, recalling that the reaction coordinate has no zero-point energy at the saddle point (this coordinate is missing in the transition state) or at reactants for a bimolecular reaction (because it is a relative translational mode there), but the zero-point energy of the reaction coordinate is not zero at reactants for a unimolecular reaction. Adding zero-point energy converts  $V^\ddagger$  to the vibrationally adiabatic ground-state potential at the saddle point, which is called  $V_a^{\ddagger G}$ . Subtracting the zero-point energy of reactants then yields  $\Delta H_0^{\ddagger,0}$  where  $H$  denotes enthalpy, the subscript denotes a temperature of 0 K, and the 0 in the superscript denotes standard state. Note that some workers write  $\Delta^\ddagger H_0^0$  instead of  $\Delta H_0^{\ddagger,0}$ . The addition of product zero-point energy to  $\Delta E$  and the subtraction of reactant zero-point energy converts it to  $\Delta H_0^0$ . Evaluating  $V^\ddagger$  and  $\Delta H_0^{\ddagger,0}$  at the canonical variational transition state instead of the conventional one converts them to  $V^{\text{CVT}}$  and  $\Delta H_0^{\text{CVT},0}$ , which can also be written as  $V^*$  and  $\Delta H_0^*$ . Both  $\Delta H_0^{\ddagger,0}$  and  $\Delta H_0^{\text{CVT},0}$  are enthalpies of activation; technically though we should call these quasithermodynamic enthalpies of activation for three reasons. First of all, the use of thermodynamic language to discuss transition states is an analogy, not real thermodynamics. This is worthy of elaboration: Transition states are dividing surfaces in phase space; they are assumed to be in statistical mechanical equilibrium with forward-moving trajectories originating at reactants, but since the dividing surface has the wrong number of dimensions to correspond to a real molecule (the reaction coordinate  $z$ , is missing), this is not thermodynamic equilibrium. Following others,<sup>14</sup> we call it *quasiequilibrium*, and the associated free-energy difference is the (quasithermodynamic) free energy of activation. Although the quasiequilibrium language is well established, many workers omit the quasi.<sup>20</sup> Second, the quasiequilibrium does not necessarily apply to transition state phase points originating at products (which are not present in equilibrium amounts when forward rates are measured).

There is a third reason why it is important to use the word quasithermodynamic. This is the use of transition-state language to express experimental results. The transition-state theory rate constant at temperature  $T$  may be written in the form

$$k = (C^\circ)^{1-n} \gamma(T) \frac{k_B T}{h} \exp[-\Delta G_T^{\text{TS},0}/RT] \quad (22.1)$$

where  $C^\circ$  is the standard-state concentration,  $n$  is the molecularity (2 for bimolecular, 1 for unimolecular),  $\gamma$  is the transmission coefficient,  $k_B$  is Boltzmann's constant,  $h$  is Planck's constant,  $\Delta G_T^{\text{TS},0}$  is the quasithermodynamic standard-state molar free energy of activation at temperature  $T$ , and  $R$  is the gas constant. However, when experimentalists express rate data in thermodynamic language (which is very common in the enzyme kinetics community, but also seen often in physical organic chemistry papers), they use

$$k = (C^\circ)^{1-n} \frac{k_B T}{h} \exp[-\Delta G_{\text{act}}^\circ(T)/RT] \quad (22.2)$$

Clearly  $\Delta G_T^{\text{TS},o}$  (and its special cases  $\Delta G_T^{\text{CVT},o}$  and  $\Delta G_T^{\ddagger,o}$ ) and  $\Delta G_{\text{act}}^o$  are different quantities. We call the former the quasithermodynamic standard-state free energy of activation and the latter the phenomenological free energy of energy. Of course one often shortens the notation; for example, "standard-state free energy of activation" becomes "activation free energy." (When  $n = 1$ , the dependence on choice of standard state is often smaller than experimental error.)

The transmission coefficient is often far from unity. Even when  $\gamma$  is included in a calculation, theory can predict the phenomenological free energy of activation. Comparing Equation 22.1 and Equation 22.2 yields

$$\Delta G_{\text{act}}^o = \Delta G_T^{\text{TS},o} - RT \ln \gamma(T) \quad (22.3)$$

Furthermore we have

$$\Delta G_{\text{act}}^o = \Delta H_{\text{act}}^o(T) - T\Delta S_{\text{act}}^o(T) \quad (22.4)$$

$$\Delta G_T^{\text{TS},o} = \Delta H_T^{\text{TS},o} - T\Delta S_T^{\text{TS},o} \quad (22.5)$$

The Gibb–Helmholtz equation also has analogies for the quasithermodynamic and phenomenological quantities. Thus

$$\Delta H_{\text{act}}^o = -T^2 \frac{d(\Delta G_{\text{act}}^o/T)}{dT} \quad (22.6)$$

$$\Delta H_T^{\text{TS},o} = -T^2 \frac{d(\Delta G_T^{\text{TS},o}/T)}{dT} \quad (22.7)$$

Clearly, just as in Equation 22.3, all the phenomenological activation quantities have two contributions — one from the quasithermodynamic part of Equation 22.1 and one from the transmission coefficient. Another language that has been used for these contributions is *substantial* for the part of the former (quasithermodynamic) that can be calculated with a single temperature-independent definition of the TS and *nonsubstantial* for the rest.<sup>21</sup> This is a useful computational distinction, but it depends on the definition used for the TS (and the choice of temperature); see Section IV.C.2.

Finally we come to activation energy, by which we mean the Arrhenius activation energy, denoted  $E_a$ . This is defined by replacing Equation 22.2 with the much simpler equation:

$$k = A(T)\exp(-E_a(T)/RT) \quad (22.8)$$

where

$$E_a \equiv -R \frac{d \ln k}{d(1/T)} \quad (22.9)$$

Thus this too is a phenomenological quantity. However, perhaps surprisingly, Tolman showed that  $E_a$  has a very simple interpretation. It is the average energy of molecules that react minus the average energy of all possible reactants in the system.<sup>22,23</sup> This provides insight into the temperature dependence of  $E_a$ ,<sup>24</sup> which usually leads to a concave Arrhenius plot, that is,  $E_a$  increases as  $T$  increases.

Much confusion has been engendered by confusing  $V^\ddagger$ ,  $\Delta H_0^{\text{TS},o}$ ,  $\Delta H_T^{\text{TS},o}$ ,  $\Delta G_T^{\text{TS},o}$ ,  $\Delta G_{\text{act}}^o$ , and  $E_a$  in various combinations or by neglecting the temperature dependences of the last four of these quantities. A good illustration of the danger is provided by the gas-phase reaction of O(<sup>3</sup>P) with H<sub>2</sub> to form OH and H. Computing  $E_a$  from Equation 22.9 by using average slopes over various  $T$  ranges,

one obtains 14 kcal/mol at 1400–1900 K, 8 kcal/mol at 318–471 K, and 6 kcal/mol at 250–300 K,<sup>25–27</sup> but  $V^\ddagger$  is estimated to be 13 kcal/mol.<sup>25,27,28</sup>

## II. PREVIOUS REVIEWS

Variational transition state theory with multidimensional tunneling has been reviewed several times, and it might be useful to provide a guide to some of these reviews that could be most useful to the present readers.

A historical and conceptual overview<sup>6</sup> has already been referenced; additional overviews of the current status of transition state theory were given in the Henry Eyring Memorial Issue of *JPC*<sup>29</sup> and the Centennial Issue of *JPC*.<sup>30</sup>

An introductory and conceptual overview is available in *Accounts of Chemical Research*<sup>5</sup> followed by an even shorter introduction,<sup>31</sup> a more complete attempt at a self-contained derivation and explanation of the foundations is given in a NATO Advanced Study Institute volume,<sup>32</sup> which is recommended reading for all new students of VTST. Other pedagogical chapters are available in the *Techniques of Chemistry* series<sup>33</sup> and the *Encyclopedia of Computational Chemistry*.<sup>34</sup> A handbook-style article that gives full details for gas-phase calculations (except for the final details of the corner-cutting tunneling methods, which were improved later) is also available.<sup>35</sup>

The above reviews are focused on fundamental theory and gas-phase applications. Reviews of condensed-phase applications are also available: vacuum–solid state interfaces,<sup>30,36</sup> reactions in liquids,<sup>29,30,37</sup> and reactions catalyzed by enzymes.<sup>38,39</sup>

A review specifically addressed to KIEs is also available.<sup>40</sup>

## III. VALIDATION AGAINST ACCURATE QUANTUM MECHANICAL DYNAMICS

A key attribute of VTST with multidimensional tunneling (VTST/MT) is that it has been well validated against quantum mechanical dynamics calculations. This is important because the uncertainties in the potential energy surface cancel out when one compares converged quantum dynamics to approximate dynamics (VTST/MT) for a given PES, whereas attempts to validate the theory by comparison to experiment always raise questions about the PES. An early review of the validations against accurate quantal dynamics was provided,<sup>41</sup> and a very complete review of validations for 74 three-body reactions (collinear and three-dimensional) for which accurate quantal rate coefficients are available has also been written.<sup>42</sup> The latter article includes a number of isotopically substituted reactions.

A key issue in making the tunneling calculations reliable is to allow for sufficient corner cutting. We have developed two approximations, to be discussed in more detail below. One, called the small-curvature tunneling (SCT) approximation<sup>43</sup> is valid when the curvature of the minimum-energy path (MEP) is small; in such a case the tunneling paths are close enough to the MEP that the potential energy along the optimum tunneling paths may be represented semiquantitatively (i.e., as well as for calculating transition state-zero-point energies) by harmonic expansions centered on the MEP. The other, called the large-curvature tunneling (LCT) approximation,<sup>44</sup> which is required when the curvature of the MEP is large, involves tunneling in a broad region of coordinate space called the reaction swath, and in particular it requires information about the potential energy in regions too far from the MEP to be well represented in MEP-based coordinates. By microcanonically (i.e., at each energy) optimizing the tunneling path from among these two approximations, we obtain a method called optimized multidimensional tunneling (OMT) or microcanonical OMT ( $\mu$ OMT).<sup>44</sup>

To illustrate the kind of accuracy that may be obtained with this method, we may consider, as an example from the review<sup>42</sup> mentioned above, the (real three-dimensional) reactions of  $O(^3P)$  with

H<sub>2</sub>, with HD to produce OH, with HD to produce OD, and with D<sub>2</sub> at 300 K. Conventional transition state theory is in error by factors of 0.05, 0.08, 0.15, and 0.14, respectively, which would give errors of up to a factor of 3 in kinetic isotope effects. VTST with multidimensional tunneling that neglects corner cutting reduces the errors, and the factors become 0.16, 0.20, 0.38, and 0.36, which would reduce the maximum error in a KIE to a factor of 2.4. Including corner-cutting tunneling by the same microcanonically optimized MT method,  $\mu$ OMT, that is practical for (and has been applied to) reactions in large systems such as polyatomic molecules and enzymes, reduces the error further, resulting in factors of 1.16, 1.16, 1.47, and 1.29 (the errors are reduced because the factors are closer to unity), which would give a maximum error in KIEs of 1.27. This is a typical example of the improvement afforded by VTST with optimized multidimensional tunneling.

Validation against accurate quantum dynamics for larger systems is precluded in most cases by the lack of accurate quantal results for systems with more than three atoms. However such comparisons are available for H + CH<sub>4</sub> and O(<sup>3</sup>P) + CH<sub>4</sub> and they show similar agreement to what we found for atom-diatom reactions.<sup>45-47</sup>

For condensed-phase systems, we do not have comparisons to accurate quantal results, but we do have comparisons to other completely different semiclassical methods that show good agreement for hydrogen site hopping on rigid and non-rigid Cu surfaces, as reviewed elsewhere.<sup>30</sup> Comparison has been made to accurate quantal dynamics for an Eckart barrier linearly coupled to a harmonic bath (which is a model of reaction in liquid solution); the calculations agree well with each other.<sup>48,49</sup>

## IV. THEORY

### A. GAS PHASE

The theory of VTST with multidimensional tunneling is most straightforward for gas-phase bimolecular reactions, and an understanding of this case provides a good foundation for understanding the condensed phase. The key historical references for the treatment we now use are as follows:

- VTST<sup>16,50,51</sup>
- more general reaction coordinates<sup>52-54</sup>
- consistent incorporation of multidimensional tunneling<sup>7,55,56</sup>
- small-curvature tunneling<sup>43,57</sup>
- large-curvature tunneling<sup>44,58,59</sup>
- optimized multidimensional tunneling<sup>44,59</sup>

The fundamental assumption of transition-state theory is the existence of a dynamical bottleneck. Consider a reaction



with a rate coefficient  $k$  defined by

$$-\frac{d[A]}{dt} = k[A][B] \quad (22.11)$$

where  $t$  denotes time, and  $[X]$  is the concentration of X. Technically, transition-state theory replaces  $k$  by a one-way flux coefficient corresponding to the rate of passage of phase points (i.e., trajectories) through a hypersurface in phase space that separates reactants from products. The hypersurface is the transition state, and often it is just called the dividing surface. If reactants are in local equilibrium, and all trajectories passing through the dividing surface in the direction

of products originated at reactants and will proceed fully to products without ever returning to the dividing surface, then TST is exact in a classical mechanical world. Otherwise it overestimates the rate. Therefore, in VTST<sup>2-6,16,29-35,41,42,60</sup> one optimizes the location of the dividing surface to minimize the rate. The optimized dividing surface is called the variational transition state or the dynamical bottleneck. In practice, one quantizes the vibrational motions, which involves replacing classical partition functions, which are phase space integrals, by quantal ones, which are sums over states; because of quantum effects such as this the upper bound no longer strictly applies. Nevertheless the variational optimization of the dividing surface at this stage is still justified on physical grounds. As a final step, one may add a transmission coefficient ( $\gamma$ ) to account for tunneling ( $\gamma > 1$ ) or for trajectories that recross the transition state ( $\gamma < 1$ ), or both. We have found that the accuracy of VTST is typically very good<sup>42,45,46</sup> even if we do not correct for recrossing; therefore in most of our work we include a transmission coefficient only to correct for tunneling, except that we also correct for nonclassical reflection whenever we correct for tunneling. (Nonclassical reflection is the wave phenomenon of diffraction by the barrier top, which means that particles with more than enough energy to surmount the barrier are nevertheless partially reflected by it. This is the obverse of tunneling, and it partly cancels the enhancement due to tunneling, but because tunneling occurs at energies with larger Boltzmann factors than nonclassical reflection, tunneling almost always dominates — except for very small intrinsic barriers.)

In general we can write  $\gamma$  approximately as a product:

$$\gamma = \kappa(T)I(T)g(T) \quad (22.12)$$

where  $\kappa(T)$  accounts for tunneling (technically, in light of nonclassical reflection, for the net effect of treating the reaction coordinate quantum mechanically),  $I$  for classical or quasiclassical reflection, and  $g$  for the breakdown of the equilibrium assumption. In general for gas-phase reactions we have set  $I = g = 1$ ; then  $\gamma = \kappa$ . We shall discuss the transmission coefficient further below.

We place the trial transition states at trial positions  $z_0$  along the reaction coordinate, and we specify the geometry (shape) and orientation of the dividing surface by  $\Omega$ . Without tunneling, the VTST rate constant (see Equation 22.11) for a bimolecular reaction at temperature  $T$  may then be written as

$$k^{\text{VTST}} = (C^{\circ})^{-1} \frac{k_{\text{B}}T}{h} \exp\{-[G^{\text{GT},\circ}(T, z_*, \Omega_*) - G^{\text{R},\circ}(T)]/RT\} \quad (22.13)$$

$$= \frac{k_{\text{B}}T}{h\Phi^{\text{R}}(T)} \min_{z_0, \Omega} Q^{\text{GT}}(T, z_0, \Omega) e^{-V_{\text{RP}}(z_0)/RT} \quad (22.14)$$

where GT (as already stated) is a synonym for TS, R denotes reactants (including their relative translation),  $\Phi^{\text{R}}(T)$  is the reactants' partition function per unit volume,  $z_0$  is the value of the reaction coordinate at which the dividing surface crosses the reaction path,  $\Omega$  denotes the shape and orientation of the TS,  $Q^{\text{GT}}$  is the partition function of the generalized transition state (with its zero of energy on the reaction path),  $V_{\text{RP}}$  is the molar potential energy on the reaction path, and  $z_*$  and  $\Omega_*$  are the values of  $z_0$  and  $\Omega$  that minimize the calculated rate constant. (The overall translation of the entire system has no effect on the rate and is omitted in all quantities.) Here we include symmetry numbers in partition coefficients, although in most of our previous papers, we collected the symmetry numbers as a separate factor.

If the nuclear motions were governed by classical mechanics, Equation 22.13 and Equation 22.14 would provide an upper bound to the accurate rate constant.<sup>4,16,32,61</sup> If one completely optimized the dividing surface not just in coordinate space but as a function of all coordinates and momenta (that is, in phase space), one would obtain the exact local-equilibrium rate constant in a classical world. This is a rigorous result, but impossible to achieve. Anyway the real world is quantum mechanical, and we assume that all vibrational partition functions in Equation 22.14 are quantized. This makes the theory less rigorous but more relevant to real molecules.

By comparing Equation 22.13 and Equation 22.14 to each other we see that minimizing the calculated rate constant is equivalent to maximizing the free energy of activation. The VTST free energy of activation may be written

$$\Delta G^{\text{CVT},o}(T) = \max_{z_0, \Omega} G^{\text{GT},o}(T, z_0, \Omega) - G^{\text{R},o}(T) \quad (22.15)$$

We could also label  $\Delta G^{\text{CVT},o}$  as  $\Delta G^*$ .

The concept of reaction coordinate plays an important role in the theory. In fact, there is more than one reaction coordinate. Globally the reaction coordinate is defined as the distance  $s$  along the reaction path. This coordinate plays a critical role in tunneling calculations. Locally the reaction coordinate is the degree of freedom (called  $z$ ) that is missing in the generalized transition state. Even locally, this may differ from  $s$ .

A good general prescription for the reaction path is the steepest descent path in isoinertial coordinates or, more technically, the union of the steepest descent path from the saddle point to the reactants with the one from the saddle point to products.<sup>7,8,62</sup> Isoinertial coordinates are coordinates where every direction of motion is associated with the same reduced mass. There are two essentially equivalent ways to obtain isoinertial coordinates, mass scaling and mass weighting. Spectroscopists prefer mass-weighted coordinates defined by<sup>63</sup>

$$x_{\alpha\beta} = m_{\alpha}^{1/2} R_{\alpha\beta} \quad (22.16)$$

where  $R_{\alpha\beta}$  is the Cartesian coordinate ( $\beta = x, y, \text{ or } z$ ) of atom  $\alpha$ , and  $m_{\alpha}$  is the mass of atom  $\alpha$ . These coordinates have units of  $\text{mass}^{1/2}$  length, e.g.,  $\text{amu}^{1/2} \text{ \AA}$ . In these coordinates all directions of motion have a unitless reduced mass of unity (which I find confusing). I prefer mass-scaled coordinates defined by

$$x_{\alpha\beta} = (m_{\alpha}/\mu)^{1/2} R_{\alpha\beta} \quad (22.17)$$

where  $\mu$  is an arbitrary constant with units of mass. In this coordinate system, coordinates have units of length, and all directions of motion have a reduced mass of  $\mu$ . If one sets  $\mu = 1 \text{ amu}$ , then  $x_{\alpha\beta}$  in units of  $\text{\AA}$  has the same numerical value as  $q_{\alpha\beta}$  in units of  $\text{amu}^{1/2} \text{ \AA}$ . If one sets  $\mu$  equal to the mass of whatever atom dominates the polyatomic motion of interest, then  $x_{\alpha\beta}$  has a numerical value of approximately the same magnitude as the actual distance moved by that atom, which is convenient for thinking about lengths of tunneling paths. Further discussion of these coordinates is provided in a recent comment.<sup>64</sup> It can easily be shown that the steepest descent path is the same in all isoinertial coordinate systems;<sup>50</sup> one special case is the "intrinsic" reaction path (usually abbreviated IRC) used by Fukui.<sup>65</sup> We denote the steepest descents path in isoinertial coordinates<sup>7,8,62</sup> by minimum-energy path (MEP). Note that at the saddle point the MEP is parallel to the imaginary-frequency normal mode. Elsewhere it is curved, and the curvature is physically meaningful because of the mass scaling; this is useful for understanding corner-cutting tunneling.<sup>10,66</sup>

The transition-state dividing surface is defined by the MEP only on the reaction path itself. The full definition of the transition-state dividing surface requires a global definition (a definition that is valid off the MEP as well as on it) of the reaction coordinate  $s$  or  $z$ ,<sup>67</sup> after which the one-parameter sequence of dividing surfaces (with parameter  $s_0$  or  $z_0$ ) is defined by  $s = s_0$  or  $z = z_0$ . In our original work<sup>16,51</sup> we took the dividing surface to be locally a plane orthogonal to the MEP in isoinertial coordinates, but we approximated the partition functions in a way<sup>50,51,61</sup> that provided physical results even when this surface is unphysical beyond a certain distance from the MEP. This procedure leads to a reaction coordinate  $z$  that is rectilinear, e.g., it is the distance along a straight line in both Cartesian and isoinertial coordinates.

In later work we defined the dividing surface at locations displaced from the MEP in terms of curvilinear coordinates,<sup>52</sup> in particular the valence coordinates used in spectroscopic force fields.



Such valence coordinates<sup>63</sup> are the collection of bond stretches, valence angle bends, and bond torsions, and they are often redundant (which complicates the treatment<sup>68</sup>). For this kind of dividing surface, the reaction coordinate  $z$  is curvilinear, i.e., not the distance along a straight line.

A further advance involves the optimization of the orientation of the dividing surface so that it need not be locally perpendicular to the reaction path. Our algorithms for doing this are called reorientation of the dividing surface (RODS)<sup>53,69,70</sup> and variational reaction path (VRP).<sup>54</sup> Since the reaction coordinate  $z$  is locally defined as the distance along a normal to the dividing surface, this corresponds to optimizing the definition of the reaction coordinate. In the context of association reactions, an algorithm in which the reaction coordinate definition is optimized along with the position of the dividing surface along a one-parameter sequence of paths is called "variable reaction coordinate" (VRC) variational transition-state theory.<sup>71,72</sup> Thus the RODS, VRP, and VRC algorithms are instances of a more general variational prescription. One key difference, however, is that the RODS and VRP algorithms are used with quantized partition functions (a plus compared to VRC) but (a minus) have no simple way to include vibration-rotation coupling (which is handled by classical mechanics in the VRC algorithm). There are also differences in the treatment of anharmonicity and vibrational mode-mode coupling as well as the kinds of reactions to which the methods are well suited. Because quantization of the vibrational partition functions on the dividing surface is very important for simple barrier reactions with tight transition states, the formalism we have developed is well suited to such reactions. 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. By using the RODS algorithm one can calculate rate constants for several isotopic versions of a reaction from a single reaction path,<sup>70</sup> which is more efficient than using the MEP, which changes upon isotopic substitution or isotopic scrambling.

In the last few years there has also been tremendous progress in the treatment of barrierless association reactions with strictly loose transition states. A strictly loose transition state is defined as one in which the conserved vibrational modes are uncoupled to the transition modes and have the same frequencies in the variational transition state as in the associating reagents.<sup>73,74</sup> (Conserved vibrational modes are modes that occur in both the associating fragments and the association complex, whereas transition modes 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 that is missing in the transition state<sup>71-77</sup> and elegant derivations of rate expression for these successive improvements.<sup>75-78</sup> The recent variational implementation of the multifaceted dividing surface (MDS) variable reaction coordinate (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. Although some refinements (e.g., the flexibility of pivot point placement for cylindrical molecules like O<sub>2</sub><sup>77</sup>) would still be welcome, the dynamical formalism is now very well developed. However this formalism is probably less interesting for KIEs because the most interesting KIEs seem to be associated with reactions that have tight transition states.

There is some work that suggests that VTST rate constants can be calculated accurately for low-barrier<sup>79-81</sup> and even no-barrier associations<sup>82-84</sup> with reaction-path methods such as those that we have employed for tight transition states. This requires further study.

We now return to the transmission coefficient. Let the transition state (the dividing surface that yields the minimum in Equation 22.14) value of any quantity be denoted  $*$ . Then, multiplying Equation 22.14 by the transmission coefficient to account for multidimensional tunneling (MT) yields

$$k^{\text{VTST/MT}} = \kappa(T) \frac{k_B T}{h} \frac{Q^*(T)}{\Phi^R(T)} e^{-V_{\text{RP}}^*/RT} \quad (22.18)$$

In a tunneling region, at least one component of the nuclear momentum is imaginary and is associated with a negative contribution to the kinetic energy. As mentioned in Section III, in multidimensional systems this leads to a negative centrifugal effect — also called the negative bobsled effect or the quantum bobsled effect.<sup>8,10</sup> We usually call it corner cutting; the physical picture is that the tunneling path is not on the MEP but rather is on its concave side.

In practice, as already mentioned in Section III, we have developed two very useful approaches to the multidimensional tunneling problem. In both of these we estimate  $\kappa$  by a multidimensional WKB-like approximation as a function of tunneling energy, and the temperature-dependent transmission coefficient in Equation 22.18 is obtained by averaging the tunneling probabilities calculated for a set of tunneling energies and tunneling paths. In a more complete theory (for example, Ref. 12 or 17), one would optimize the tunneling paths; the optimum tunneling paths minimize WKB imaginary action integrals, which in turn maximizes the tunneling probabilities. We have found<sup>42</sup> that sufficiently accurate results can be obtained by a simpler criterion<sup>44</sup> in which, for each energy, we choose the maximum tunneling probability from two approximate results: one, called small-curvature tunneling (SCT),<sup>43,57</sup> calculated by assuming that the curvature of the reaction path is small, and the other, called large-curvature tunneling (LCT),<sup>6,31-33,35,44,57-59,85</sup> calculated by assuming that it is large. The result is called microcanonically optimized multidimensional tunneling ( $\mu$ OMT) or, for short, optimized multidimensional tunneling (OMT). The resulting VTST/OMT rate constants have been carefully tested against accurate quantum dynamics,<sup>42,45,46</sup> and the accuracy has been found to be very good.

The SCT, LCT, and OMT tunneling calculations differ from one-dimensional models of tunneling in two key respects: (i) These approximations include the quantized energy requirements of all the vibrational modes along the tunneling path; since the vibrational frequencies are functions of the reaction coordinate, this changes the shape of the effective potential for tunneling. (ii) These approximations include corner-cutting tunneling. Corner cutting has the effect that the tunneling path is shorter than the minimum-energy path. Therefore the optimum tunneling paths involves a compromise between path length and effective potential along the path. As a consequence, the optimum tunneling paths occur on the concave side of the minimum energy path, i.e., they cut the corner.<sup>8-12,31,32,66,85-91</sup>

The considerations summarized above have important implications. In order to calculate the VTST rate constant we must not only know the geometry, energy, and frequencies at the saddle point, but also we must know the reaction path, reaction-path potential, and vibrational frequencies over a wide enough range of  $s_0$  to find the minimum in Equation 22.3. Calculating tunneling contributions requires even more information about the potential energy surface because tunneling occurs over a wider region than the region where the variational transition state occurs. This is easy to understand if one recognizes that the variational transition state approximately corresponds to the maximum of the effective potential for tunneling in the small-curvature limit. To calculate the whole barrier we need potential energy surface information over a wider range than is required to find the maximum of the barrier. When reaction-path curvature is large, corner cutting becomes extensive and one needs to know potential energy surface information not just on the reaction path but also over a broad swath on its concave side; this is called the tunneling swath.<sup>87,91</sup> In recent work,<sup>92</sup> we made the LCT tunneling calculation more efficient by developing an interpolation scheme that yields the required information about the PES in the large-curvature reaction swath with a much smaller number of electronic structure calculations than were required by the previous algorithm. The algorithm can be further improved<sup>93</sup> by interpolating not only along each tunneling path but also from path to path. The improved algorithms mean that LCT calculations now involve much less work, compared to SCT calculations, than they used to, and these savings are important for applying high levels of electronic structure theory to complex reactions.

A function that plays a key role in the tunneling calculations is the ground-state (G) vibrationally adiabatic potential curve  $V_a^G(s)$ , which is defined by

$$V_a^G(s) = V_{RP}(s) + \varepsilon_1^G(s) \quad (22.19)$$

where  $s$  is distance along the reaction path,  $V_{RP}$  is the potential energy along the reaction path, and  $\varepsilon_1^G$  is the ground-state energy (zero-point energy) of the vibrational modes perpendicular to the reaction path. This is called vibrationally adiabatic because the vibrational quantum numbers are conserved (they all remain zero) as one proceeds along the reaction path.

A critical aspect of including a transmission coefficient is that it must be consistent with VTST. We have solved this problem by using the ground-state approximation<sup>5,55,56</sup> for the transmission coefficient. In this approximation, the transmission coefficient is the ratio of an approximate quantum mechanical thermally averaged transmission probability for reaction in the ground state to the thermally averaged transmission probability implied for ground-state reaction in VTST. The transmission probability implied for ground-state reaction by VTST is a Heaviside step function at a total energy of  $V_a^G(s)$  where  $V_a^G$  is defined in Equation 22.19. One can treat the threshold region even more accurately by a method we call improved canonical variational theory (ICVT).<sup>35,56,94</sup> For most reactions, the results are almost identical to CVT. Hence we usually just report the simpler CVT results, which is easier for readers to understand.

Note that "probability of reaction in the ground state" in the previous paragraph refers to being in the ground state as one passes through the transition-state region. In general, vibrational quantum numbers are not conserved all the way from reactants to products. However we find that for small-curvature of the reaction path one can calculate accurate transmission coefficients by considering  $V_a^G(s)$  as a global effective potential for tunneling because, at the low energies where tunneling is important, the reactive flux in the transition-state region is primarily associated with the vibrational ground state although many low-energy vibrational and rotational states of the reactant and product may contribute to this flux.<sup>95-100</sup> In comparison, the LCT case is more complicated in two respects: (i) We need nonadiabatic effective potentials for a variety of tunneling paths exhibiting extreme corner coming. (ii) On the low-energy side of the transition state we must connect the tunneling path to vibrationally excited states (of the product for an exoergic or symmetric reaction and of the reactant for an endoergic one).<sup>58,86,88-90</sup> Pictures of tunneling paths for tunneling into vibrationally excited states are given elsewhere.<sup>44,86,89,90</sup> Even when the tunneling proceeds formally into the ground state, the large-curvature algorithm involves a vibrationally nonadiabatic effective potential in the tunneling region.

Note that we use the ground-state approximation for the transmission coefficient at all  $T$ . At low  $T$  (where tunneling is important) it is justified by the fact that the system passes through the transition region either in the ground state (at least on the high side of the transition state) or in an energetically similar state. At high  $T$ ,  $\kappa$  tends to unity for any reasonable choice of effective tunneling potential so the ground-state approximation remains acceptable.

Another point to be emphasized here is the separability of the reaction coordinate. An intrinsic aspect of transition state theory without a transmission coefficient is the separability of the reaction coordinate. (A coordinate is called separable if there are no cross terms in the Hamiltonian that couple it or its conjugate momentum to other coordinates or their conjugate momenta.) A truly separable reaction coordinate would not exhibit recrossing, and so a transmission coefficient that corrects for recrossing is also a correction for nonseparability. Corner-cutting tunneling is also a manifestation of nonseparability. Thus VTST/MT can be much more accurate than a theory with a separable reaction coordinate. At temperatures where  $\kappa > 2$ , the reaction is dominated by tunneling, and the nonseparable tunneling dynamics is a larger contributor to the calculated rate than the overbarrier part calculated with a separable reaction coordinate.

Now we return to the consideration of the other factors,  $\Gamma$  and  $g$ , in Equation 22.12. First consider  $\Gamma$ . Recrossing of the TS dividing surface can in principle invalidate the use of

transition-state theory, but in our experience this effect is usually small for simple barrier reactions in the gas phase if the TS is variationally optimized. The effect is expected to become more important as temperature increases,<sup>41,42,61</sup> and our extensive tests against accurate quantum mechanics show that VTST tends to overestimate rate constants by about 25–30% at 1500–2400 K.<sup>42</sup> It is hard to estimate the effect for polyatomic reactions because accurate quantal results are not generally available at high  $T$ . Furthermore it is not clear whether we can believe estimates based on classical or quasiclassical trajectory calculations because they tend to overestimate recrossing due to not enforcing quantization conditions at the dynamical bottleneck.

Unimolecular reactions in the gas phase require an additional consideration, namely the competition between preferential reaction of the more energetic molecules in the reactant ensemble and replenishment of the equilibrium distribution by energy transfer. Gas-phase unimolecular reactions are well known to suffer a fall-off from the high-pressure limit, and there is general agreement that this is due to vibrational nonequilibrium.<sup>101,102</sup> In fact, more often than not, the reaction cannot be studied at high enough pressure to actually observe the full high-pressure plateau, which corresponds to equilibrium conditions. For this reason we will not consider gas-phase unimolecular reactions in this chapter. In contrast, nonequilibrium effects are generally assumed to be negligible for gas-phase bimolecular reactions, although detailed evidence for this is not as complete as one would like. There have been many studies of translational nonequilibrium, and they agree that that effect is small, although not totally missing for the most quantitative work.<sup>103</sup> Vibrational nonequilibrium could be more of a problem given that vibrational spacings are large,<sup>104</sup> but one careful study found that the effect is small, even for fast reactions,<sup>105</sup> although further work with more general assumptions about the state-to-state transition probabilities is required for a definitive statement. Nevertheless, for reactions with free energies of activation of several  $RT$  or higher, the most credible evidence from studies of gas-phase reactions is that it is a good approximation to assume reactant equilibrium — with one exception: vibrational nonequilibrium is well known to be large for one very special class of bimolecular reactions: diatomic dissociation. This has been studied by many workers,<sup>106–111</sup> and it is explained by the fact that vibrational relaxation is slow in a molecule with only one vibrational degree of freedom.

## B. REACTIONS IN THE SOLID STATE AND AT SOLID SURFACES

The gas-phase methods discussed above have been extended to reactions at crystalline surfaces<sup>36</sup> by the embedded-atom method.<sup>112–115</sup> The same formalism applies to solid-state reactions. The system is separated into a primary subsystem (cluster) and a secondary one (lattice), with the former embedded in the lattice. The lattice is frozen, while the atoms of the cluster are allowed to vibrate. For an  $N$ -atom cluster, the system has  $3N$  degrees of freedom and the generalized transition states have  $3N - 1$  degrees of freedom. This differs from a nonlinear gas-phase system where the corresponding numbers are  $3N$  and  $3N - 7$ , respectively; the reason for this difference is that the fixed lattice removes translations and rotations from the problem.

Consider the case of a reactive solute (i.e., a reactive guest molecule, e.g., an isomerizing complex) in a solid host. The cluster can be just the solute or even a portion of the solute, but the spirit of the method is that the cluster also includes a reasonable number (20–100) of host atoms, with the rest of the host serving as the lattice. As one carves a larger and larger cluster out of the fixed lattice, the method (in principle) converges.

A simpler way to treat reactions in solids is just to ignore the host.<sup>116,117</sup> This replaces three low-frequency lattice vibrations by substrate rotations, and the effect of this on rate predictions has not been systematically tested. Other approximations that one makes in this approach may be more important; namely, one neglects the effect of the lattice on the reaction path and on the potential energy profile and solute vibrations along the reaction path. If one includes the effect of the host as a static field, one recovers the special case of the embedded cluster method where the solute is the cluster and the host is the lattice.

Usually, in calculating the tunneling contributions, one averages over a continuous distribution of tunneling energies in the reaction coordinate. This makes sense because at the saddle point, the reaction coordinate is an unbound vibration with a continuous spectrum. At reactants, the reaction coordinate becomes a relative translational mode for a bimolecular reaction or a collision of a reactive species with a solid surface, but it becomes a bound vibration for a unimolecular reaction. Unimolecular reactions in solids and at solid surfaces are sometimes studied at very low temperatures where the discreteness of the reactant's reaction-coordinate energy distribution must be considered. In such cases the integral over tunneling probabilities as a function of tunneling energy is replaced by a sum over tunneling probabilities at discrete energies.<sup>113,117,118</sup> At low enough temperature, the reaction rate constants and KIEs become independent of temperature because all reaction occurs out of a single state (the ground state). In practice, this  $T$ -independent limit may be approached as follows. First, as  $T$  is lowered, the rate constant becomes almost independent of  $T$  as the guest molecule is cooled to its ground state, but a small temperature dependence will remain due to thermal excitation of low-frequency lattice vibrations (low-frequency phonon modes).<sup>117</sup> Then, as  $T$  is lowered further, even the lattice-state distribution tends to a single state. There has been some discussion in the literature of coherent quantum processes at low temperature, but when phenomenological rate constants have been observed they seem to be well described by the same kind of formalism that we use at higher  $T$ . One does need to reexamine the equilibrium assumption though, just as discussed for liquids in the next section.

## C. REACTION IN LIQUIDS

### 1. Solute-Solvent Separation

Reactions in liquids<sup>29,30,33,37,119-123</sup> or amorphous solids are more complex than those in the gas phase or in well-ordered crystalline environments. Two types of transition-state theory treatments may be distinguished. In explicit solvent models, all solute and solvent molecules are treated on an equal footing, at least from the point of view of dynamics (one might still use hybrid methods to obtain the potential energy surface). In implicit solvent treatments<sup>33,37</sup> the solute is treated explicitly and the solvent is treated by a continuum-solvation model; a special case would be to include only the solvent reaction field. However, there are many treatments that fall on the boundary between explicit solvent and implicit solvent. For example, one might freeze certain degrees of freedom of either the solute or the solvent in one or more steps of the calculation. For another example, in implicit solvent treatments, one sometimes singles out a few solvent molecules in the first solvation shell to be treated on the same footing as the solute; this yields the so called mixed discrete-continuum models.

Methods for reactions in liquids can also be applied to amorphous solids and even crystalline solids, although I shall just say liquids in this section. Section IV.B discussed methods that take advantage of the ordered structure of a crystalline host. In the gas phase, in crystalline solids, and in approximations that take advantage of a solute-solvent separation with implicit solvent, the reactive molecule or solute often has only one saddle point or a small number of saddle points whose contributions can be treated individually and added. For example, the gas-phase reaction of OH with propane to make  $n$ -propyl radical and H<sub>2</sub>O proceeds through two transition states, *gauche* and *trans*.<sup>124</sup> Similarly the aqueous Menshutkin reaction of NH<sub>3</sub> with CH<sub>3</sub>Br passes through a single saddle point if only the solute is explicit.<sup>125</sup> However, if we add explicit solvent there are innumerable saddle points differing from one another in the arrangement of solvent hydrogen bonds and in torsions around hydrogen bonds, not just in the first solvation shell but throughout the liquid. The key new issue that occurs in liquid-phase transition-state theory that does not occur in gases or in crystalline environments is the intrinsically statistical character of the medium. Unless one uses statistical methods (Monte Carlo or molecular dynamics) to average over the myriad of solvent configurations, one may miss the essence of the problem (at worst) or at least

miss important quantitative contributions to the enthalpy and entropy of activation. In principle, continuum models, because they directly approximate the free energy of solvation (not just the solute-solvent interaction energy) include even the entropic contribution of the changing number of low-energy solvent configurations as the system proceeds along the reaction path (the free energy of solvation includes the change in internal free energy of the solvent<sup>126</sup>). However, in practice one cannot always be confident that the first solvation shell is well represented by a continuum model. That is the motivation for mixed discrete-continuum models. However, adding even a few (three or more) solvent molecules to the explicit subsystem greatly increases the number of floppy degrees of freedom so that statistical averaging becomes difficult again. In other words, even a small cluster consisting of a solute molecule and a small number of solvent molecules may require, for a proper treatment, the same kinds of statistical mechanical averaging that one requires to treat the whole liquid statistically.

## 2. Reaction Coordinates and Nonequilibrium Solvation

For transition-state theory calculations on reactions in solution and solids, we must revisit the question of nonequilibrium effects, i.e., the magnitude of the  $g$  factor in Equation 22.12. There is one class of liquid-phase reactions where nonequilibrium effects are well known to be important. That is outer-sphere electron transfer (also called weak overlap electron transfer) where nonequilibrium bath contributions are a critical part of Marcus' theory.<sup>127,128</sup> For other reactions in liquids, the conventional assumption is that liquid reactions are at equilibrium, i.e., like the high-pressure limit in gases. Like many assumptions that work quite well in practice, this assumption is often accepted without examining its basis, but there is work available that is relevant to the question of reactant disequilibrium in reactions with nuclear motion in the reaction coordinate. In seminal work,<sup>129</sup> Kramers identified three regimes for liquid-phase reactions: weak solute-solvent coupling, intermediate solute-solvent coupling, and strong solute-solvent coupling. An extreme limit of weak coupling of a molecule to its surroundings would be a gas, but for liquids the weak-coupling regime is associated with a low-viscosity solvent. Strong coupling would be a high-viscosity solvent, where the "frictional" effect of solvent is sometimes associated with small-scale spatial diffusion across the transition state region — since diffusion involves a lot of back and forth motion to accomplish small net motion, it leads to recrossing of the transition state, and this is what is meant when one says that friction decreases a rate.

First we consider the limit of weak solute-solvent coupling, sometimes thought of as energy-diffusion.<sup>130,131</sup> In the energy-diffusion regime, energy flow within the solute (or into the solute) cannot keep up with reaction, and the rate slows down. This is the analog of the nonequilibrium effect that is well established for gas-phase unimolecular reactions. Can one observe this in liquids? Perhaps the only example where the interpretation is detailed enough to merit serious concern is the cyclohexane isomerization. This interpretation is based on the pressure dependence of the rate and it is not definitive, although it does provide caution about accepting the local equilibrium assumption uncritically.<sup>132-134</sup> At the same time, one must also be cautious about invoking disequilibrium on the basis of an inadequate appreciation of transition state theory. For example, it is important to realize that even though some modes may be more effective at causing reaction than other modes are, TST fully includes this kind of effect. Thus, for example, an argument that tunneling or classical barrier recrossing is promoted by some particular vibration of the reactants is not a disequilibrium effect.

Next we consider the nonequilibrium effect associated with strong solute-solvent coupling. This effect is sometimes called nonequilibrium solvation, but this term is often misunderstood. To sort out the issues it is important to recall the quasiequilibrium discussion in Section I. One might say that the fundamental assumption of transition state theory is that one can calculate the reaction rate by calculating the one-way flux toward products of an ensemble of trajectories in a transition state that is in quasiequilibrium with reactants. Now if the reactant states are in local

equilibrium<sup>104</sup> with each other, these states, by Liouville's theorem<sup>135</sup> of statistical mechanics, will evolve into an equilibrium distribution in the transition-state region. Label a sequence of trial dividing surfaces by  $z = z_i$  with reactants at large negative  $z$ , products at large positive  $z$ , and  $z_i < z_{i+1}$ . Suppose that  $z = z_2$  is a perfect dynamical bottleneck, that is, all species with  $z = z_2$  that are moving toward products came directly from reactants without ever having had  $z = z_2$  before, and they will proceed to products without ever having  $z = z_2$  again. Then transition-state theory will be perfect if we put the TS at  $z = z_2$ . However, if we put the TS at  $z = z_1$ , the TS ensemble will include some nonreactive trajectories moving toward  $z_2$  that turn around before they get there and recross the  $z = z_1$  dividing surface toward reactants. I would say that transition-state theory overestimates the rate constant because it counts those nonreactive recrossing trajectories. However, you could also identify those phase points (a phase point is a point in phase space, that is, it is a point on a trajectory) at  $z = z_1$ , that are moving toward large  $z$  but will recross the  $z = z_1$  dividing surface and remove them from the TS ensemble. The resulting ensemble is missing some phase points that are present in the equilibrium ensemble, and so you might say that the error in the transition-state calculation is due to the fact that it uses the equilibrium ensemble — you would call the error a nonequilibrium effect. This would be correct if you define your terms, but it is not the language used here. It is more informative to recognize that the ensemble at  $z = z_1$  really is equilibrated to a good approximation ( $g \approx 1$ ) but some members of the ensemble are points on recrossing trajectories ( $\Gamma < 1$ ).

Another way to correct the calculation with  $z = z_1$  is to calculate how much the actual rate is reduced relative to the transition-state theory one (calculated at  $z = z_1$ ) because of the recrossing trajectories and to multiply the transition-state theory rate constant by a transmission coefficient  $\Gamma$ , which is less than unity. Then the calculation at  $z_1$ , with  $\Gamma < 1$ , and the calculation at  $z = z_2$ , with  $\Gamma = 1$ , give the same answer. However, the division of the free energy of activation (see Equation 22.2) into quasiequilibrium and nonsubstantial contributions (as defined in Section I) will change. Thus this division is actually a description of a particular calculation that was done with a particular definition of the transition state, and one should be careful not to attribute a deeper significance to it. When one hears the statement that  $\Gamma \approx 1$ , the true meaning is that somebody has found a transition state definition that is good enough to set  $\Gamma \approx 1$ . However, one finds that if  $\Gamma \ll 1$ , it does not prove that transition-state theory breaks down for this reaction; rather it means that transition-state theory breaks down with that particular definition of the TS. Defining the TS is equivalent to defining the reaction coordinate  $z$  since the TS dividing surface is the mathematical surface with  $z = z_i$ .

Suppose that *all* surfaces defined by  $z = z_i$  include some recrossing trajectories. Then variational transition-state theory cannot be perfect with  $z$  chosen as the reaction coordinate. Suppose, however, that one can define a new coordinate  $s$  by

$$s = z + u \quad (22.20)$$

where  $u$  is some other coordinate, such that  $s = s_*$  does define a perfect transition state. Then I would say that  $s$  is the best choice for reaction coordinate and that coordinate  $u$  participates in the reaction coordinate.

The discussion above has particular relevance to reactions in solution. In particular suppose that  $z$  is a solute coordinate, and  $u$  is a solvent coordinate. Then I would say that the solvent participates in the reaction coordinate. The equilibrium ensemble that I would calculate without considering the solvent ( $u$ ) cannot describe the rate process in a transition state sense. This is called *nonequilibrium solvation*. In other words nonequilibrium solvation is the participation of solvent coordinates in the reaction coordinate.

If the solvent coordinates that participate in the reaction coordinate are manageable, for example the atomic coordinates that are necessary to describe the length of some solute-solvent hydrogen bond, then the most direct way to proceed is to allow these coordinates to explicitly

participate in the reaction coordinate. Our experience has been that if those solvent molecules that participate in the reaction coordinate are included in the explicit degrees of freedom, and the reaction coordinate is identified with the path of steepest descents through the explicit degrees of freedom in isoinertial coordinates, i.e., the MEP, this procedure will "automatically" generate a reaction coordinate that includes the relevant degrees of freedom in the reaction coordinate. In other words it seems that one can take  $\Gamma \approx 1$  if one uses the MEP as the reaction coordinate. Sometimes, however, it is not practical to do this. For example, for weak-overlap electron transfer, the best reaction coordinate seems to be a solvent electric polarization coordinate.<sup>127,128</sup> Because of the long-range nature of electrostatic forces, the calculation of the electric field exerted on the reactive molecule by the solvent requires knowing the Cartesian coordinates of a large number of solvent molecules. Suppose this number is a hundred. Including all these solvent molecules in the explicit system would greatly increase the number of saddle points and hence the number of steepest descent paths. Furthermore the steepest descent paths might not all be independent, that is, there might be only small barriers separating the valleys surrounding each of these paths so that one cannot just sum and average over their independent contributions calculated with the harmonic approximation for vibrations perpendicular to the path. When we are unable to find a good enough reaction coordinate to make  $\Gamma \approx 1$  because of difficulty in identifying the collective solvent motions that participate in the reaction coordinate, we say that solvent friction is responsible for slowing down the rate process. The treatment of this kind of effect in terms of friction and collective solvent coordinates is discussed elsewhere.<sup>29,30,37,119,121,122,126,136-146</sup>

In light of these complexities, there is more than one practical way to proceed, as discussed next. We will divide the methods into two categories: (i) those based on an MEP<sup>33,37,121,140,141,143-145,147-149</sup> or a small number of MEPs whose fluxes are additive and (ii) a method based on a potential of mean force and an ensemble of MEPs.<sup>38,39,150-152</sup> The first category includes summing over a small number of transition states with differing conformations, if necessary (see the hydroxyl plus propane example mentioned above), and it is especially suitable for implicit-solvent methods; whereas the second category is designed to handle the case of an uncountable number of saddle points as arise in explicit-solvent treatments of liquid-phase reactions. Furthermore the methods in the first category may be subclassified into implicit bath models and reduced-dimensional bath models. We consider two implicit bath methods, in particular separable equilibrium solvation (SES)<sup>148</sup> and equilibrium solvation path (ESP),<sup>33,121,147,148</sup> and we consider one reduced-dimensional-bath model, which is called the nonequilibrium solvation (NES) method.<sup>141,143</sup> Finally we consider one ensemble-based method, called ensemble-averaged variational transition-state theory with multidimensional tunneling (EA-VTST/MT).<sup>38,151</sup> Note that the EA-VTST/MT method was originally developed for enzyme reactions, but it is general enough to apply to any kind of reaction.

### 3. VTST/MT Methods for Condensed-Phase Reactions

#### a. *Implicit Bath*

In these methods the system consists of a primary system and a bath, and the reaction coordinate depends only on the coordinates of the primary system. The primary system includes the reactive solute for a unimolecular reaction and the reacting solutes for a bimolecular reaction; in addition it can include one or more solvent molecules. The solvent may be treated by a continuum solvent model or a discrete one, although if one makes the solvent discrete, the explicit solvent model of Section IV.C.3.b can also be used and may in fact be required.

In the implicit solvent models we let  $\mathbf{x}$  denote the  $3N$  coordinates of the  $N$ -atom explicit subsystem (primary system). Then the multidimensional potential of mean force (PMF) is written as

$$W(\mathbf{x}) = V(\mathbf{x}) + \Delta G_S^{\circ}(\mathbf{x}, T) \quad (22.21)$$



where  $V$  is the gas-phase potential energy surface of the primary system, and  $\Delta G_S^0$  is the standard-state free-energy<sup>37</sup> of solvation of the rigid solute at temperature  $T$ . Note that  $W(\mathbf{x})$  is obtained by averaging over a thermal distribution of the implicit molecules of the solvent. At thermal equilibrium, the mean force of the implicit molecules on the  $3N$  coordinates of the explicit ones is the negative of the gradient of  $W$ .<sup>153</sup>

In the separable equilibrium solvation (SES) method, we find the MEP and vibrational frequencies on the surface  $V$ , then add the second term of Equation 22.21 for geometries along the MEP. This gives VTST without tunneling. Tunneling can no longer be approximated with the ground-state approximation of Section IV.B since information about the liquid solvent is only available at finite  $T$ , and the system does not remain a liquid all the way to temperatures where only the ground state is populated. Furthermore the available information ( $\Delta G_S^0$ ) about the solvent is thermally averaged, but the strictly correct procedure would be to tunnel through an unaveraged effective potential, then average the tunneling probabilities, not tunnel through a free-energy profile (it is physically incorrect to treat the entropic contribution to the free-energy as a potential energy that can be tunneled through). However, if the temperature dependence of  $\Delta G_S^0$  is not too large, one can derive an approximation,<sup>147,148</sup> called the zero-order canonical mean shape approximation (CMS-0), to the correct tunneling average that involves  $W(\mathbf{x})$  as the effective potential. In the SES approximation we use the CMS-0 approximation for both SCT and LCT tunneling calculations. As in the gas phase, care is taken<sup>147</sup> to insure that the transmission coefficient is consistent with VTST so that it becomes unity if quantum effects on the tunneling coordinate motion are neglected.

The equilibrium solvation path (ESP) approximation is the same as the SES one except that the MEP and vibrational frequencies are computed from  $W$  rather than from  $V$ . This can be very important because the low-energy region of the best liquid-phase variational transition state might be quite different from any geometry in the sequence of geometries along the gas-phase MEP.<sup>154</sup> Another example of when it would be very important to use a reaction path optimized in liquid solution would be when the very nature of the transition state depends strongly on solvent.<sup>155</sup> Extreme examples are when the reaction does not occur in the gas phase or occurs in a different way (or by a different mechanism), when the reactants or products are unstable in the gas phase, or when the reaction is barrierless in the gas phase but not in the liquid.

### b. Reduced-Dimensionality Bath

Rather than treat all solvent degrees of freedom implicitly one may single out one or a few solvent coordinates to be included in the explicit coordinate set. If these coordinates consist of the atomic Cartesians of one or a few solvent molecules, then this yields a mixed discrete-continuum model<sup>156-159</sup> that can be treated just as in Section IV.C.3.a and requires no further discussion. Another possibility, though is to use one or more *collective* solvent coordinates, which represent collective motion of the solvent. Collective solvent coordinates were already mentioned in Section IV.A in conjunction with electron transfer reactions. An especially broad class of collective solvent coordinates is based on energy gaps; we have recently provided a critical analysis of this kind of solvent coordinate and compared it to coordinates based on valence coordinates.<sup>145</sup> Sometimes very useful collective solvent coordinates can be defined by using a specific model for the reaction, such as charge transfer.<sup>137,140,160</sup>

The formulation<sup>141,143</sup> of NES theory that we have used is more general, and it does not assume a specific form for the solvent coordinate. For the case of a single solvent coordinate, one adds the following solvent Hamiltonian to the Hamiltonian of the  $3N$  atoms of the primary system for a generalized transition state at a location  $s$  along the reaction path:

$$H_{\text{solvent}} = \frac{p_y^2}{2\mu} + \Delta G_S^0(\mathbf{x}, T) + \frac{1}{2}F[y - C(\mathbf{x} - \mathbf{x}^\ddagger)]^2 \quad (22.22)$$

where  $p_y$  is the momentum conjugate to collective solvent  $y$ ,  $\mu$  is the scaling mass of Equation 22.17,  $F$  is the force constant,  $C$  is the solute-solvent coupling vector,  $\mathbf{x}$  (as before) is a vector of coordinates of the primary system, and  $\mathbf{x}^\ddagger$  is the geometry of the saddle point of  $W$ . All vectors in Equation 22.22 are of order  $3N$ . When  $C$  is a null vector, the solvent is equilibrated to the primary system; alternatively, if  $y$  were constrained to have the value

$$y_{\text{eq}} = C \cdot (\mathbf{x} - \mathbf{x}^\ddagger) \quad (22.23)$$

the theory would also reduce to ESP theory. In the NES model, though,  $y$  is allowed to vibrate around its equilibrium position.

One can obtain values for the new parameters  $F$  and  $C$  from specific solvent models or from general considerations involving general quantities like solvent viscosity, diffusion coefficients, and solvent relaxation times. After the parameters are fixed, the calculations proceed just as in the ESP case except that there are  $3N + 1$  coordinates instead of  $3N$ .

In transition-state theory, the partition functions and quasithermodynamic free energy of the transition state are actually surrogates for a dynamical quantity, the one-way flux through the transition-state dividing surface. The reactant partition functions and free energy are, however, true equilibrium thermodynamic quantities. Thus nonequilibrium solvation enters the theory for the transition state but not the reactant, and  $C$  is nonzero for generalized transition states but  $C = 0$  for reactants. (Reactant disequilibrium is something different and, if present, enters through  $g$ , not  $F$  and not Equation 22.22.)

### c. Explicit Bath

The theory for an explicit bath is called ensemble-averaged variational transition state with multidimensional tunneling (EA-VTST/MT). It was originally developed<sup>38,151</sup> for reactions catalyzed by enzymes, and implementation details<sup>151,152,161</sup> were also worked out in that context, but it is also applicable to other condensed-phase reactions. We review it here in the liquid-phase language of Section IV.C.3.a.

The EA-VTST/MT model has two stages. In stage one, all atoms of the system are treated on an equal footing. In practice one would treat from  $10^2$  to  $10^5$  atoms with periodic or stochastic boundary conditions. The first step is to calculate a one-dimensional potential of mean force  $W(z)$  where  $z$  is the stage-one reaction coordinate. A one-dimensional PMF is very similar to the multidimensional PMF considered above except that only one coordinate is fixed (and all the rest averaged over) instead of fixing  $3N$  coordinates. The coordinate  $z$  is fixed in the sense that  $W(z)$  corresponds to a particular value of  $z$ . It can also be fixed at a sequence of values along the reaction path in simulations used to compute  $W(z)$ ;<sup>162-171</sup> simulations with fixed  $z$  are called constrained- $z$  simulations. An alternative to constrained dynamics is restrained dynamics or restrained Monte Carlo in which one calculates  $W(z)$  from simulations in which  $z$  not fixed but varies freely.<sup>163,172-179</sup> To improve the statistics one applies a bias potential (restraining potential) that ideally would be the negative of the true PMF. Furthermore it is convenient to break the simulation into a series of *windows*, in each of which one applies a harmonic restraining force whose purpose is to force the system to spend more time in a particular region near the minimum of the associated harmonic potential. After the simulation the probability distribution is corrected to remove the artificial bias(es), and the PMF is calculated from the unbiased distribution. This procedure is called umbrella sampling or multistage importance sampling. In the description in stage 2 below, we will assume that molecular dynamics calculations with umbrella sampling were used in stage 1. During the umbrella sampling run, configurations are saved at well-spaced time intervals for possible later analysis. A subset of these configurations will also be used in stage 2.

Standard methods for calculating  $W(z)$  are purely classical mechanical. Our first goal, however, is to calculate a quasiclassical  $W(z)$  in which the vibrations that are strongly coupled to  $z$  are quantized. We have developed a procedure to do this,<sup>150</sup> based on projected instantaneous normal-mode analysis.

From  $W(z)$  we can calculate a free energy of activation profile  $\Delta G_T^{GT,o}(z)$ . If  $z$  is a rectilinear coordinate, one simply needs to subtract the free energy of the reaction coordinate of the reactant and adjust the zero of energy. If  $z$  is not rectilinear, there is also a Jacobian term to be added;<sup>180</sup> for  $z$  coordinates that are simple functions of valence coordinates, the Jacobian term is usually less than  $RT$  (and can be neglected in all but the most precise work) although if  $z$  is a collective solvent coordinate, the Jacobian term could be large. Maximizing  $\Delta G_T^{GT,o}(z)$  with respect to  $z$  yields  $\Delta G^{CVT}(T)$ . Putting this into Equation 22.1 with  $\gamma = 1$  yields a stage-1 approximation  $k^{(1)}$  to the rate constant. This approximation is quasiclassical.

In stages 2 and 3 we continue to use the stage-1 quasiclassical value of  $G^{CVT}(T)$  as part of the calculation, but we no longer assume that the transmission coefficient is unity. These two stages differ in the way that the field exerted by the secondary zone is included in the primary-zone dynamics calculations.<sup>151</sup> In either stage, the transmission coefficient  $\gamma$  is the average over a large number of transmission coefficients  $\gamma_i$  calculated for various possible reaction paths of the primary system corresponding to transition-state configurations  $i$  selected from the variational transition-state window of stage 1 (or other nearby windows — see next paragraph). Each of these  $\gamma_i$  consists of two factors,  $\gamma_i = \Gamma_i \kappa_i$ , with one factor  $\Gamma_i$  accounting for dynamical recrossing<sup>4,29,33,35,136,181</sup> and the other factor  $\kappa_i$  accounting for the increase in the rate due to quantum mechanical tunneling contributions. The latter factor is defined by extending the definitions of a consistent CVT transmission coefficient that were used earlier in the gas phase,<sup>7,56</sup> in embedded clusters in solids,<sup>113</sup> and in liquid solution.<sup>147</sup>

The reaction coordinate used in stage 1 may be inaccurate, and the transmission coefficient is designed to make up for that inaccuracy as well as to include tunneling. In stage 2, one samples the transition-state ensemble determined in stage 1. In particular, one selects the  $L$  saved configurations from stage 1 that have  $z$  values closest to the value  $z_i^{(1)}$  at which the quasiclassical  $W(z)$  of stage 1 has its maximum at the temperature of the simulation. In practice  $L$  might, for example, be in the range from 5 to 20. This selection process is sometimes called rare-event sampling; a difference of what is done here from the standard method<sup>181–185</sup> is that in our case the PMF is quasiclassical with many of the vibrations perpendicular to the reaction coordinate being quantized.<sup>150</sup> This is particularly important for quantitative work and for the calculation of KIEs.

For each of the  $L$  selected members of the transition-state ensemble, one calculates a transmission coefficient  $\gamma_i^{(2)}$ , where  $i = 1, \dots, L$ . This is called the stage-2 transmission coefficient or the static-secondary-zone (SSZ) approximation to the transmission coefficient. During stage 2, the system is divided into a primary zone and a secondary zone.<sup>151,179,186</sup> The partition of atoms into one zone or another can be done in various ways, similar to the primary system/bath partition in Section IV.C.3.a. Then, for each configuration  $i$  of the entire system, selected from the transition-state ensemble as specified in the previous paragraph, one performs the following steps: (a) Freeze the secondary zone with its coordinates for this ensemble member. (b) Optimize the primary zone coordinates to the nearest saddle point. (c) Find the MEP of the primary zone in the field of the fixed secondary zone. (d) Carry out a VTST calculation without tunneling. This yields a new quasiclassical rate constant, and one defines a quasiclassical transmission coefficient by

$$\Gamma_i \equiv \frac{k^{CVT}(T, i)}{k^{(1)}(T)} \quad (22.24)$$

(e) Add multidimensional tunneling, still with the secondary zone frozen. This yields another transmission coefficient:

$$\kappa_i \equiv \frac{k^{\text{CVT/MT}}(T, i)}{k^{\text{CVT}}(T, i)} \quad (22.25)$$

One then repeats this  $L$  times, after which one can calculate the stage-2 quasiclassical rate constant by

$$k_{\text{QC}}^{(2)} = \Gamma^{(2)}(T)k^{(1)}(T) \quad (22.26)$$

where

$$\Gamma^{(2)} = \frac{1}{L} \sum_{i=1}^L \Gamma_i \quad (22.27)$$

and the final stage-2 rate constant, including tunneling, by

$$k^{(2)} = \gamma^{(2)}(T)k^{(1)}(T) \quad (22.28)$$

where

$$\gamma^{(2)} = \frac{1}{L} \sum_{i=1}^L \Gamma_i \kappa_i \quad (22.29)$$

Notice that each of the  $L$  stage-2 calculations is essentially an embedded cluster calculation of the type described in Section IV.C.2. However, although the secondary zone is static for each of these calculations, it varies from calculation to calculation. For a given  $i$  the reaction coordinate is the optimum one for that fixed secondary zone. Furthermore the reaction coordinate dependence on the secondary zone coordinates is not neglected, as in Section IV.C.3.a, but is built in by the dependence of the MEP on  $i$ . Thus the averaging of the transmission coefficient over the TS ensemble is a practical way to allow the secondary zone coordinates to participate in the reaction coordinate.

Just as in Section IV.A and Section IV.C.3.a, care is taken<sup>151</sup> to insure that the transmission coefficients of Equation 22.24 and 22.25 are consistent so that  $\Gamma_i$  becomes unity if there is no variational effect, and  $\kappa_i$  becomes unity if quantum effects on the reaction coordinate are neglected.

In many (maybe even most) cases, it is probably sufficient to use the SSZ approximation. In fact, Hynes and coworkers concluded that what they call the nonadiabatic solvation limit, in which  $\Gamma$  is governed by frozen-solvent configurations at the transition state, often provides an excellent description of the barrier passage.<sup>138,142</sup> Nevertheless, we have developed a stage-3 procedure<sup>151,161</sup> that can be used to include bath relaxation along each MEP. In this stage, the primary-zone atoms are held fixed at a sequence of geometries on a stage-2 MEP, and, for each structure in the sequence, the secondary zone is equilibrated to the primary zone to obtain the relative change in free energy of the bath (recall that the secondary zone is already equilibrated to the primary zone at the stage-1 variational transition state). Adding the change in secondary-zone free energy to the effective potential along the path gives new values of  $\Gamma_i$  and  $\kappa_i$ . The former is averaged to obtain  $\Gamma^{(3)}$ , and the product  $\Gamma_i \kappa_i$  is averaged to obtain  $\gamma^{(3)}$ . Then, a stage-3 quasiclassical rate constant and final rate constant are obtained by

$$k_{\text{QC}}^{(3)} = \Gamma^{(3)}(T)k^{(1)}(T) \quad (22.30)$$

and

$$k^{(3)} = \gamma^{(3)}(T)k^{(1)}(T) \quad (22.31)$$

respectively.

In stage 3, the effective potential includes the change in free energy of the secondary zone along the primary-zone reaction coordinate in an average way, by assuming that the bath is equilibrated to the primary system. Consequently, the transmission coefficient in stage 3 is called the equilibrium secondary zone (ESZ) approximation.<sup>151</sup> One could imagine an even more sophisticated treatment in which the secondary zone motion is included but without assuming it is equilibrated. Such a treatment is available,<sup>145</sup> but so far it has not been widely applied nor presented in completely general way. Such a treatment would be required to allow the secondary-zone atoms or the polarization of distant parts of the bath to participate explicitly in the reaction coordinate, rather than effectively through the ensemble average. However the evidence to date is that the EA-VTST/MT method is adequate even for at least some systems in which secondary-zone motions play an important role in promoting reaction.<sup>187</sup>

It is worth emphasizing that in the SSZ approximation, the secondary zone is only static for a given  $i$ . Since it varies from  $i$  to  $i$  it is effectively not static. Similarly in the ESZ approximation, the secondary zone is equilibrated for a given  $i$ , but differently equilibrated for each  $i$ . Thus this approach includes nonequilibrium solvation, despite its name, which refers only to a given member of the TS ensemble.

#### D. REACTIONS IN ENZYMES

Reactions in enzymes are intermediate between those in the liquid phase and those in a crystalline solid phase. In the implicit bath methods of Section IV.C.3.a, liquid-phase reactions are treated by the separable equilibrium solvation (SES) and equilibrium solvation path (ESP) approximations. Both of these approximations take advantage of the clear separation between solute and solvent. However there is no such clear-cut separation in enzyme kinetics unless we treat the whole enzyme, coenzyme (if any), and substrate as a solute, which is impractical. Therefore we use a somewhat arbitrary separation into primary subsystem and secondary subsystem,<sup>151,179,186</sup> which is similar to the separation described in Section IV.B for processes at gas-crystal interfaces.<sup>114</sup> When we do this, the nature of typical enzyme activation sites leads to a more structured environment for the primary system (substrate or part of substrate plus nearby of the protein and perhaps all or part of a prosthetic group) than we have when we carve a primary system consisting of a solute and a few solvent molecules out of a liquid. Aside from that the EA-VTST/MT method is applied to enzymes in the same way as already explained. In fact, as already stated, this method was originally developed in the context of enzymes.<sup>38,151,152,161</sup>

Enzyme reactions also have unique aspects that require special considerations not involved in modeling simple reactions. Foremost among these is the enzyme itself. As compared to a small solute or substrate, the enzyme, despite having well defined secondary, tertiary, and quaternary structure, can be floppy enough to make significant configurational entropic contributions to the free energy of activation, and the individual physical contributions to each stage of the calculation may be quite different than for liquids.

One further comment specific to enzyme kinetics is that we must distinguish the kind of dynamical disequilibrium discussed in Section IV.C.2 (disequilibrium in the state space of the reactants of an elementary reaction step) from mechanistic disequilibrium. One might say that an enzyme reaction that has two fast steps that are not cleanly separated kinetically has some of the latter, which is often called kinetic complexity. However, we see no strong evidence in any enzyme mechanism we have studied of nonequilibrium distributions in the dynamical sense, and this does

not surprise us based on the experience with nonbiological reactions summarized above. Thus we expect that such effects are small.

## V. APPLICATIONS TO KIEs

Variational transition state theory with multidimensional tunneling (VTST/MT) has been widely applied, and in several cases KIEs have been computed. This section gives a brief summary of some of these applications. Our notation is that  $X/Y$  denotes the ratio of the rate constants for  $X$  and  $Y$ . In addition to discussing TST (conventional transition-state theory), CVT (canonical variational transition-state theory), CVT/SCT (CVT with small-curvature tunneling), and CVT/OMT (CVT with optimized multidimensional tunneling), which are all explained above, we sometimes compare to CVT/ZCT where ZCT denotes zero-curvature tunneling. Zero-curvature tunneling calculations are the same as SCT except that reaction-path curvature is neglected. As a consequence this level of theory is the same as CVT/SCT and CVT/OMT with the one exception that it does not allow corner cutting in the tunneling.

### A. GAS PHASE

Comparison to accurate quantal results for KIEs in  $O + H_2$  and isotopomers was already mentioned in Section III. For polyatomic reactions though we do not have accurate quantum mechanical KIEs for comparison.

The [1,5] sigmatropic hydrogen shift in *cis*-1,3-pentadiene has an experimental KIE of 5.2 at 470 K.<sup>188</sup> Dewar et al.<sup>189</sup> proposed that this occurs by tunneling but calculated a KIE of 146 at 498 K. Although an accurate PES is not known, Austin Model 1 (AM1) gives a reasonable PES, and we used it to study this reaction. For  $^1H$ ,  $\kappa$  is 4.2 in the ZCT approximation but 6.5 with OMT. For D, these values are 2.5 and 3.0, respectively. Our calculated KIEs<sup>43</sup> are 2.25 without tunneling, 3.7 with ZCT, and 4.9 with SCT (which is the same as OMT in this case).

Note that the PES in the above calculation (and in most of our work since then) is implicit, not an analytic function. In particular the calculation was carried out by direct dynamics,<sup>43,44,87,190-193</sup> which means that whenever we require the potential energy or its gradient or Hessian, we perform an electronic structure calculation. Thus the PES is defined implicitly by the level of electronic structure theory that is chosen.

The experimental KIE for  $CF_3 + CD_3H \rightarrow CF_3H/CF_3D$  is 3.2 at 627 K.<sup>194</sup> We studied<sup>44</sup> this reaction by using specific reaction parameters<sup>44,192,193,195</sup> in AM1; the resulting implicit PES<sup>44</sup> is called AM1-SRP-2. The KIE is 2.1 without tunneling, about 2.6 with ZCT tunneling, and 3.0 with OMT tunneling.<sup>44</sup> The effects are much larger at 300 K where the KIE is 5.5 at the CVT level, 7.7 with CVT/ZCT, and 16 with CVT/OMT.

For the reaction of H with  $CH_4$  and the  $S_N2$  reactions of  $Cl^-$ ,  $Cl(H_2O)^-$ , and  $Cl(H_2O)_2^-$ , with  $CH_3Cl$ , we carried out a factor analysis of the vibrational partition functions to show which modes contribute to the secondary KIEs. We found non-negligible contributions to the KIEs from high-frequency modes, mid-frequency modes, and low-frequency modes. This work is reviewed elsewhere.<sup>40,196</sup>

We studied the reaction of OH with  $CH_4$ ,  $CD_4$ , and  $^{13}CH_4$ .<sup>197</sup> We found that even without tunneling, VTST predicts quite different KIEs than TST. Thus these reactions provide a good illustration of a key difference between TST and VTST. In TST the geometry of the lowest-energy point in the TS is the same for all isotopic variations because that point is the saddle point of the PES, which is independent of isotopic substitution. Not only the geometry of the saddle point but also its force constant matrix (Hessian) is invariant to isotopic substitution. Much of the beauty of the classic TST formulation of KIEs<sup>1</sup> follows from this fact. However, in real reactions, the dynamical bottleneck can depend on the isotopic constitution of the reagents. A measure of the difference in geometries is the difference in  $V_{MEP}(S_*)$ , i.e., the potential energy on the reaction

path at the variational transition state. For OH + CH<sub>4</sub> the PES used in our study has  $V^\ddagger = 7.37$  kcal/mol. The value of  $V_{\text{MEP}}(s^*)$  for OH + CH<sub>4</sub> varies from 7.15 to 7.03 kcal/mol as  $T$  increases from 250 to 2400 K, whereas for OH + CD<sub>4</sub> it varies from 7.28 to 7.17 kcal/mol, and for OH + <sup>13</sup>CH<sub>4</sub> it varies from 7.19 to 7.10 kcal/mol. The Boltzmann factor of this energy difference contributes as much as a factor of 1.31 to the CH<sub>4</sub>/CD<sub>4</sub> KIE and a factor of 1.08 to the CH<sub>4</sub>/<sup>13</sup>CH<sub>4</sub> KIE. For CH<sub>4</sub>/CD<sub>4</sub> the contributions from high-, mid-, and low-frequency vibrations differ from unity by as much as 0.88, 0.57, and 6.40, respectively; the corresponding numbers for CH<sub>4</sub>/<sup>13</sup>CH<sub>4</sub> are 1.002, 0.970, and 0.889. The calculation of heavy-atom KIEs requires high precision. For CH<sub>4</sub>/<sup>13</sup>CH<sub>4</sub> our calculated overall KIE of 1.005 at 273–353 K agrees with the experimental value<sup>198</sup> at those temperatures. For CH<sub>4</sub>/CD<sub>4</sub>, the only experimental value<sup>199</sup> was 1.1 at 416 K, and we calculated 4.5 at that temperature. However, after our paper was submitted, a new experimental value of 4.0 was reported.<sup>200</sup> Further analysis of these KIEs was reported by other workers.<sup>201–203</sup> A quasithermodynamic-type<sup>21</sup> analysis of the perprotio case by Masgrau et al.<sup>204</sup> is particularly informative in understanding the temperature dependence and magnitude of the OH + CH<sub>4</sub> rate constant.

We also calculated CH<sub>4</sub>/CD<sub>4</sub> and CH<sub>4</sub>/<sup>13</sup>CH<sub>4</sub> KIEs, as well as CH<sub>4</sub>/CH<sub>3</sub>D KIEs, for Cl + CH<sub>4</sub>. A direct dynamics study<sup>205</sup> gave good agreement with experiment<sup>206–210</sup> whereas a later study<sup>211</sup> based on an analytic PES was less accurate. The CH<sub>4</sub>/CD<sub>4</sub> KIEs were also calculated for O(<sup>3</sup>P) + CH<sub>4</sub>,<sup>212</sup> but no experiment is available. At room  $T$ , the CVT/OMT KIE is 4.0 times larger than the TST value because of tunneling, whereas at 2400 K it is 7% lower. Further analysis of the KIE is available.<sup>213,214</sup>

For the S<sub>N</sub>2 reaction of F(H<sub>2</sub>O)<sup>−</sup> with CH<sub>3</sub>Cl, three experimental KIEs were reported<sup>215</sup>: H<sub>2</sub>O/D<sub>2</sub>O = 0.65, CH<sub>3</sub>Cl/CD<sub>3</sub>Cl = 0.85, and [F(H<sub>2</sub>O)<sup>−</sup> + CH<sub>3</sub>Cl]/[F(D<sub>2</sub>O)<sup>−</sup> + CD<sub>3</sub>Cl] = 0.56. We<sup>216</sup> calculated 0.65, 0.83, and 0.54, respectively. We showed that these KIEs are dominated by the high-frequency stretching mode of the microsolvating water molecule, which is consistent with some,<sup>217–219</sup> but not all, previous interpretations of bulk solvent isotope effects. The key to the interpretation is that the hydrogen bond to water is weaker at the transition state than at the reactant due to charge delocalization away from the ion. A review<sup>220</sup> is available. In later work, the solute and solvent KIEs for methyl chloride solvolysis were studied with upto 13 explicit water molecules.<sup>221</sup>

We predicted the OD and ND<sub>3</sub> KIEs for the OH + NH<sub>3</sub> reaction,<sup>222</sup> but so far they have not been measured.

The experimental CH<sub>3</sub>X/CD<sub>3</sub>X KIEs of the Cl<sup>−</sup> + CH<sub>3</sub>Br, Cl<sup>−</sup> + CH<sub>3</sub>I, and Br<sup>−</sup> + CH<sub>3</sub>I S<sub>N</sub>2 reactions at 300 K are  $0.79 \pm 0.05$ ,  $0.84 \pm 0.02$ , and  $0.76 \pm 0.03$ , respectively.<sup>223–225</sup> We calculated  $0.94 \pm 0.03$ , 0.91, and  $0.94 \pm 0.02$ .<sup>226</sup> It is encouraging that we correctly predicted the inverse nature of these KIEs, but the errors are disconcertingly large. The inverse character of the KIEs was attributed to high- and low-frequency modes, offsetting a normal contribution from mid-frequency modes. Kato et al.<sup>225</sup> agreed that our neglect of third-body collisions is reasonable under the experimental conditions and concluded that further theoretical work is required to fully understand the KIEs.

We calculated C<sub>2</sub>H<sub>5</sub>Cl/C<sub>2</sub>D<sub>5</sub>Cl KIEs for the competitive E2 and S<sub>N</sub>2 gas-phase reactions of ClO<sup>−</sup> with C<sub>2</sub>H<sub>5</sub>Cl as functions of  $T$ .<sup>227</sup> The treatment required additional assumptions beyond VTST to predict the branching ratio. The KIE for the S<sub>N</sub>2 reaction is predicted to decrease with  $T$ , whereas the KIE for the E2 reaction is predicted to be very small at low  $T$ , then to increase with  $T$ .

Experimental<sup>228–230</sup> and calculated<sup>231</sup> KIEs for various isotopic substitutions in Cl + H<sub>2</sub> → HCl + H are listed in Table 22.1 (when there is more than one experiment we compare to the average). The trends are all well reproduced by theory. As a follow up we calculated the accurate quantum mechanical rate constant for the <sup>1</sup>H<sub>2</sub> case for this potential energy surface and found that it agreed with our transition-state theory rate constants within 16% over a factor of 7.5 in  $T$ .<sup>232</sup>

**TABLE 22.1**  
**Kinetic Isotope Effects for Cl + H<sub>2</sub>**

KIE	T (K)	Experiment	Theory
H <sub>2</sub> /D <sub>2</sub>	245	13 ± 2	15
	300	8 ± 1	10.5
	345	7 ± 1	8.3
H <sub>2</sub> /T <sub>2</sub>	275	34	51
	345	18	26
H <sub>2</sub> /HD <sup>a</sup>	245	3.4	4.4
	345	2.5	3.1
H <sub>2</sub> /HT <sup>b</sup>	245	6.5	7.5
	345	4.1	6.0
H <sub>2</sub> /DT <sup>b</sup>	275	21	26
	345	12	15
HD → HCl/DCI	300	1.8	2.1
	445	1.4	1.8

<sup>a</sup> sum of production of HCl and DCI.

<sup>b</sup> sum of production of HCl and TCl.

Experiments are available for the reaction of OH with C<sub>3</sub>H<sub>8</sub>, C<sub>3</sub>H<sub>6</sub>D<sub>2</sub>, C<sub>3</sub>H<sub>5</sub>D<sub>3</sub>, C<sub>3</sub>H<sub>3</sub>D<sub>5</sub>, and C<sub>3</sub>H<sub>2</sub>D<sub>6</sub>, and C<sub>3</sub>D<sub>8</sub>.<sup>233</sup> Because of multiple sites, and conformations, simulating these experiments requires 22 rate calculations. The results<sup>124</sup> exhibit some striking features. For example, the CVT rates are factors of 2–3 lower than the TST ones for C<sub>3</sub>H<sub>8</sub> and 10–30% lower than TST for C<sub>3</sub>D<sub>8</sub>; the errors of conventional TST for different isotopologs do not largely cancel, and the KIEs decrease by a factor of 2 when the variational effects are included. Abstraction of H from a secondary carbon has a classical barrier of only 2.2 kcal/mol, and  $\kappa$  is actually greater for D than for H. This effect (that tunneling decreases the KIE) cannot be predicted by one-dimensional tunneling methods, but it is easy to see how it arises in multidimensional models. In particular, the zero-point-inclusive barrier is much smaller for H, and this eliminates most of the tunneling for H, but not for D. Thus at 295 K, the H/D KIE for a secondary site reaction is 5.6 with TST, 2.7 with CVT, and 2.6 with CVT/OMT. For the *trans* primary-site reaction these values are 6.6, 3.1, and 6.6, whereas for the *gauche* primary-site reaction they are 6.6, 4.4, and 5.0. In all three cases the CVT/ $\mu$ OMT KIE is less than the TST one.

The deuterium KIEs for the association reaction of H with C<sub>2</sub>H<sub>4</sub> presented a great challenge to theory. The very poor agreement of theory with experiment raised questions about the assumptions of TST and even about the validity of the Born–Oppenheimer approximation.<sup>234–236</sup> An even greater challenge to theory was provided by the muonium + C<sub>2</sub>H<sub>4</sub> experiments of Garner et al.<sup>237</sup> We calculated a more accurate PES and applied VTST/MT to the high-pressure rate constants<sup>79–81</sup> and obtained good agreement with experiment for a large number of KIEs. Although the barrier is low, ~1.7 kcal/mol, tunneling is very important for calculating reliable KIEs for this reaction. The location of the variational transition state depends significantly on both isotopic composition and temperature.

We also studied Mu KIEs with H<sub>2</sub> and D<sub>2</sub>,<sup>238,239</sup> HBr,<sup>240,241</sup> and CH<sub>4</sub>.<sup>242</sup> Muonium KIEs are extremely challenging because of the very large zero-point energy associated with bonds involving Mu and the concomitantly large anharmonicity and because the very light mass of Mu makes the tunneling very quantal, but we successfully predicted<sup>238</sup> the reaction rate for Mu + D<sub>2</sub> before it was measured.



In addition to  $\text{Mu} + \text{CH}_4$ , we studied ten other isotopic variants of the  $\text{H} + \text{CH}_4$  and  $\text{CH}_3 + \text{H}_2$  reactions.<sup>242</sup> Since one of the implicit PESs we used should be quite accurate the calculations provided a good test of the dynamical methods or of experiment, and indeed some of the experiments do seem to merit reexamination. An earlier paper on  $\text{H} + \text{CD}_3\text{H}$ <sup>243</sup> employed an older, less accurate version of the multidimensional tunneling approximation that somewhat overestimates the effect of reaction-path curvature when it couples more than one perpendicular mode to the reaction coordinate (the current version of the SCT<sup>43,57</sup> and OMT<sup>44,58,59</sup> approximations were introduced later). Nevertheless the reader is referred to the earlier paper for a historical discussion of coupled-motion tunneling and its effects on secondary KIEs. A key point made in that discussion is that it is important to consider coupling due to reaction-path curvature along the whole portion of the MEP in the tunneling region, not just the mixing of various coordinates in the imaginary-frequency normal mode of the saddle point. Furthermore, because tunneling is often delocalized over a large region, one should almost always avoid the parabolic approximation, unless one uses an effective frequency that takes account of the nonquadratic character of the barrier<sup>244</sup> and the curvature of the reaction path.<sup>245</sup>

## B. KIEs IN LIQUID PHASE

The  $\text{H}^-/\text{D}^-$  KIEs for liquid-phase hydride transfer reactions, in particular bimolecular hydride transfer between  $\text{NAD}^+$  analogs<sup>88</sup> and unimolecular hydride migration in a polycyclic hydroxy ketone<sup>246</sup> were calculated in the SES approximation, the former using reduced-dimensionality analytic surfaces and the latter by dual-level direct dynamics with 81 vibrational degrees of freedom explicitly participating in the tunneling calculation. The bimolecular case is dominated by large-curvature tunneling and the unimolecular case by small-curvature tunneling.

The reaction of H with methanol to produce  $\text{H}_2$  and  $\text{CH}_2\text{OH}$  in water was studied in the SES,<sup>148,247</sup> ESP,<sup>121,148,247</sup> and NES<sup>141,143</sup> approximations. The  $(\text{H} + \text{CH}_3\text{OH})/(\text{D} + \text{CH}_3\text{OD})$  secondary KIE is calculated to be 0.48, 0.51, and 0.37 in these three approximations,<sup>143,247</sup> respectively, in comparison to an experimental value<sup>248</sup> of 0.7. The  $(\text{H} + \text{CH}_3\text{OH})/(\text{H} + \text{CD}_3\text{H})$  primary KIE was calculated to be 21.3, 20.2, and 19.5, respectively, in comparison to an experimental value<sup>249</sup> of 20. In both cases we assumed a solvent relaxation time of 10 fsec. The solute-solvent coupling strengths were predicted by a model based on diffusion coefficients. The primary KIE is relatively insensitive to this solute-solvent coupling strength, but the secondary KIE is predicted to be larger, in particular to be 0.44 (and hence in slightly better agreement with experiment) if we arbitrarily decrease the solute-solvent coupling strength by a factor of two. It is not clear though if the treatment of the nonequilibrium solvation effect is the largest error in the theory (the gas-phase potential energy surface and the free energy of solvation surface are also uncertain). This aqueous free radical reaction is a very interesting test case for theory because the solvation effects are smaller and apparently more subtle than those in ion reactions. Clearly more work is needed.

## C. ENZYMES

Many enzyme reactions involve proton or hydride transfer in the chemical step, and we know from experience with simpler reactions that multidimensional treatments of the tunneling process are essential for quantitative accuracy and sometimes even for qualitative understanding. Our experience with gas-phase reactions showed that we can obtain good accuracy for reactions dominated by tunneling including corner-cutting tunneling paths, but enzyme reactions bring in new issues such as the possible need for more complicated reaction coordinates.

We have now used the EA-VTST/OMT method reviewed above to calculate KIEs for several enzyme-catalyzed reactions<sup>38,39,151,152,161,179,186,250-252</sup> and the comparison of these results to experiment<sup>253-265</sup> provides a test of whether the gas-phase theory can be successfully

**TABLE 22.2**  
**Enzyme Systems for which KIEs have been Calculated by EA-VTST/OMT**

Enzyme	Coenzyme	H <sup>±</sup>	D	A	QPES	N <sub>1</sub>	N <sub>tot</sub>	L
Enolase	Mg <sup>2+</sup>	H <sup>+</sup>	C	N	AM1	25	8863	1
LADH	NADH, Zn <sup>2+</sup>	H <sup>-</sup>	C	N	AM1 + SEVB	21	5506	18
MADH	TTQ	H <sup>+</sup>	C	O	PM3 - SRP	25	11025	6
Xyl	Mg <sup>2+</sup>	H <sup>-</sup>	C	C	PM3 + SVB	32	25317	5
SCAD	FAD	H <sup>-</sup>	C	N	AM1 + SVB	43	23277	15
DHFR	NADPH	H <sup>-</sup>	C	C	AM1 + SVB	40	21468	13

*Notation:* H<sup>±</sup>, transferred ion; D, donor; A, acceptor; QPES, method used for quantum mechanical part of potential energy surface; N<sub>1</sub>, number of atoms in primary zone for the tunneling calculations; N<sub>tot</sub>, total number of atoms; L, number of systems averaged in transition state ensemble. *Abbreviations:* LADH, liver alcohol dehydrogenase; MADH, methylamine dehydrogenase; Xyl, xylose isomerase; SCAD, short-chain acyl CoA dehydrogenase; DHFR, dihydrofolate reductase; NADH, reduced nicotinamide adenine dinucleotide; TTQ, tryptophan tryptophylquinone; FAD, flavin adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; AM1, Austin model 1; SEVB, semiempirical valence bond; SRP, specific reaction parameters; SVB, simple valence bond.

extended to complex reactions in solution. (The enolase calculations<sup>179</sup> use a simpler version of the theory, but we expect that a calculation with the later EA-VTST/OMT formalism would give similar results.) The enzyme systems studied are summarized in Table 22.2, and the theoretical results are compared to the experimental ones in Table 22.3. The reader is referred to the original papers for discussion of such critical issues as pH, temperature of the experiments, mutations, and kinetic complexity. We simply note here that all the theoretical calculations are at 300 K and that these comparisons of theory to experiment have all the usual complications one finds in enzyme kinetics (for example, the intrinsic KIE may be higher than the experimental value due to kinetic complexity), but I hope that these details are not needed in an overview of the results.

**TABLE 22.3**  
**Experimental and Calculated KIEs for Enzyme Systems**

Enzyme	KIE	Experiment	Stage	TST	EA-VTST	EA-VTST/OMT
Enolase	Primary H/D	3.3	SSZ	4.7	3.7	3.5
	Secondary H/D	n.a. <sup>a</sup>	SSZ	0.89	0.96	0.96
LADH	Primary H/T	7-8	ESZ	6.6	6.7	6.9
			ESZ		6.6	7.5
	Secondary H/T	1.36	SSZ	1.08	1.09	1.27
			ESZ		1.09	1.36
MADH	Primary H/D	17	SSZ	5.9	5.9	18
Xyl	Primary H/D	3-4	SSZ	1.8	1.8	3.8
SCAD	Primary H/D	7-53	SSZ	3.5	3.2	4.1
			ESZ		3.7	70
DHFR	Primary H/D	3	SSZ	2.7	2.5	2.8
	Secondary H/D	1.13	SSZ	1.00	1.03	1.13 <sup>b</sup>

<sup>a</sup> n.a. denotes not available

<sup>b</sup> Published in Ref. 252 before the experiment was reported in Ref. 265.

Next I give a few comments on the various cases.

The enolase case<sup>179</sup> is very interesting because it shows a significant variational effect on the KIE. The breaking C–H bond distance is 0.18 Å longer at the variational transition for proton transfer than at that for deuteron transfer. This lowers the predicted primary KIE by 21%, which is essential for obtaining good agreement with experiment.

The LADH case<sup>151,186</sup> is a very significant one because previous models<sup>266</sup> were unable to simultaneously fit the primary and secondary KIEs except by making assumptions about the force constants that eventually turn out to be incorrect. The problem is dissected in detail in our first paper on this enzyme<sup>186</sup> and in a review;<sup>39</sup> the conclusion that one draws is that multidimensional corner-cutting tunneling is essential to understanding the origin of the KIEs. The LADH case shows only a small effect of including secondary-zone entropy effects on the transmission coefficient, i.e., the SSZ and ESZ KIEs are similar, although the more complete ESZ theory does agree better with experiment.

The MADH case<sup>251</sup> is interesting because of the large amount of tunneling and the very large KIE. Tunneling increases the rate of proton transfer by a factor of 75, which lowers the phenomenological free energy of activation by 2.5 kcal/mol. The good agreement of the EA-VTST/OMT KIE with experiment is very encouraging.

The xylose isomerase case<sup>152,250</sup> is important because the hydride transfer is strongly coupled to Mg<sup>2+</sup> motion. Nevertheless our treatment with the simple difference-of-bond-lengths reaction coordinate gives a picture of the reaction that is very consistent with experiment. The tunneling in this reaction has also been studied by Nicoll et al.<sup>267</sup>

The SCAD reaction has the complication that the hydride transfer is strongly coupled to a proton transfer. Our calculations<sup>161</sup> predict a nonconcerted mechanism, but the experimental situation is unclear. The extremely large effect of relaxing the secondary zone along the reaction path in the calculation of the transmission coefficient is probably an indication that we need a larger primary zone for this case.

The DHFR case<sup>252</sup> is interesting because, as for xylose isomerase, the hydride motion is strongly coupled to the structural changes in the protein. It is very interesting that for DHFR our results are in good agreement with those of Hammes–Schiffer and coworkers,<sup>268,269</sup> who used a collective reaction coordinate depending on the atomic coordinates of all the atoms of the substrate and enzyme. The secondary deuterium KIE was a prediction published before the experiment was available.

## VI. SOFTWARE

Software for carrying out VTST/OMT and EA-VTST/OMT calculations is available at <http://comp.chem.umn.edu/truhlar>.

## VII. CONCLUDING REMARKS

This article has focused on the assumptions underlying the formalism that is available for practical calculations of the rate constants and KIEs of complex systems, with a special emphasis on conceptual and operational issues, such as the quasiequilibrium approximation, the reaction coordinate, quantization of vibration, the treatment of tunneling, the coupling of a primary system to a bath, and the different ways of putting the components of the calculations together for reactions in the gas phase, in liquids, and in enzymes. We also provided a brief review of some calculations of KIEs. One subject that is not covered is the use of quantum mechanical scattering theory to study the quantized energy levels of the transition state. This subject, reviewed elsewhere,<sup>97,99</sup> has provided a look at the transition states, including their lifetimes and state-specific decay probabilities, with the finest level of detail allowed by the uncertainty limitations of quantum mechanics. The picture provided by this computational transition-state spectroscopy is fully

consistent<sup>270</sup> with the way that we use variational transition states and tunneling probabilities to calculate reaction rates, and in fact it provides deep support for the theory.

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## GLOSSARY

The following is a glossary of acronyms used in this paper, except for those explained in Table 22.2, which are not repeated here:

CVT	canonical variational theory (same as canonical VTST)
DS	dividing surface
EA	ensemble-averaged
ESP	equilibrium solvation path
GT	generalized TS
ICVT	improved CVT
IRC	intrinsic reaction coordinate (same as MEP)
JPC	Journal of Physical Chemistry
KIE	kinetic isotope effect
LCT	large-curvature tunneling
MDS	multifaceted DS
MEP	minimum energy path (assumed to be in isoinertial coordinates)
MT	multidimensional tunneling
NATO	North Atlantic Treaty Organization
NES	nonequilibrium solvation
OMT	optimized MT
PES	potential energy surface (really a hypersurface) — same as potential energy function
PMF	potential of mean force
RODS	reorientation of the DS
QC	quasiclassical
SCT	small-curvature tunneling
SES	separable equilibrium solvation
S <sub>N</sub> 2	bimolecular nucleophilic substitution
SSZ	static secondary zone (refers to the configuration of the secondary zone during the calculation of the transmission coefficient for a single member of the TS ensemble)
TS	transition state
TST	TS theory ( <i>in this chapter</i> the acronym TST always means conventional TST, although the words "transition-state theory" are often used to include generalized transition-state theory including variational transition-state theory, with or without tunneling)
VRC	variable reaction coordinate
VRP	variational reaction path
VTST	variational TS theory
WKB	Wentzel-Kramers-Brillouin

ZCT zero-curvature tunneling  
 $\mu$ OMT microcanonically optimized MT (often just called OMT)

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