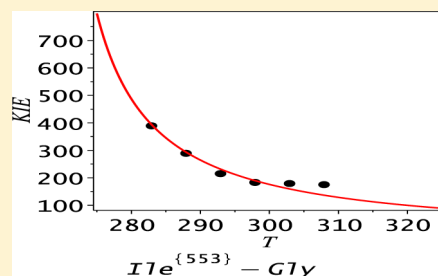


Quantum Variational Transition State Theory for Hydrogen Tunneling in Enzyme Catalysis

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ABSTRACT: Experiments in recent years have shown that there is a large kinetic isotope effect in the rate of transfer of hydrogen or deuterium in enzymatic reactions of soybean lipoxygenase-1. The kinetic isotope effect (KIE) is only weakly temperature dependent but varies significantly in the presence of mutants whose functional groups are located rather far from the reaction center. In this paper we suggest that variational transition state theory as applied to dissipative systems, above the crossover temperature between deep tunneling and thermal activation, may be used as a paradigm for understanding the dynamics of these reactions. We find that the theory fits the experimental data rather well. The effects of different mutants are readily interpreted in terms of the friction they exert on the reaction center. Increasing the distal functional group increases the friction and thus lowers the kinetic isotope effect.



I. INTRODUCTION

The past two decades have seen the accumulation of a large body of experimental evidence that nonclassical mechanisms dominate hydrogen atom transfer in enzyme catalysis.^{1–4} Detailed temperature dependent measurement of isotope effects in soybean lipoxygenase-1 (SLO) revealed a large kinetic isotope effect.² The transfer rate of hydrogen is typically 2 orders of magnitude larger than that of deuterium. Arrhenius plots of the isotope effect lead to an activation energy which is far too small to account for the large isotope effect, which is almost temperature independent.³ This almost immediately suggests that the hydrogen transfer mechanism is dominated by tunneling. As is well understood, tunneling rates are exponentially sensitive to the mass of the tunneling particle. The larger the mass, the smaller the rate.

Measurements, on a series of mutants, where the mutant itself is quite far away from the reaction center showed that mutants can significantly alter the temperature dependence and magnitude of the kinetic isotope effect in one case by a factor of almost 4.⁴ This sensitivity is perhaps an additional indication that the transfer process is dominated by tunneling. Indeed, the “standard” interpretation of the experimental results has been in terms of Marcus like^{5–8} outer sphere electron transfer reactions,^{9–11} curve crossing theories, in which the hydrogen jumps through nonadiabatic coupling from the diabatic reactants’ force field to that of products.^{4,12,13} Although Marcus theory is usually applied to electron transfer reactions, the mass of the hydrogen atom is sufficiently small to suggest that it could also be applicable to hydrogen transfer.⁹ Curve crossing is a nonclassical process, and it is also exponentially sensitive to the mass of the transferred particle. This nonadiabatic coupling theory approach has been applied to the experimental data by various authors.^{4,10,12,13} A central feature is that the effect of mutants on the isotope effect is to change the distance between the reactants and products, thus affecting the kinetic isotope effect.^{12,13}

Edwards et al.¹³ in a detailed analysis conclude that the more bulky the residue in the distal mutation is, so the larger the distance between the reactant and product states, leading to a lowering of the kinetic isotope effect. They also undertook detailed molecular dynamics simulations; however, these were inconclusive; they could not corroborate that the distance really changes by the amounts needed to fit the theory to the experimental rates.

The role of the enzyme in hydrogen transfer catalysis is itself a topic of debate. Antoniou et al.¹⁴ argued that the enzyme tends to make the barrier thinner thus facilitating hydrogen transfer. In later work from the same group^{15,16} it was suggested that the role of the enzyme was to enable a stochastic search of the conformation space so as to minimize a barrier to reaction. Tunneling was considered to be less important, and the extent of tunneling remained unclear from their analysis.

Another aspect which has been discussed extensively in the literature is the idea of vibrational promoting modes as a key toward understanding the role of the enzyme in the catalysis. Hay and Scrutton¹⁷ have recently reviewed some of the experimental and theoretical evidence which suggests that such promoting modes are a key to the catalytic process. At the same time, recent theoretical studies, first by Boekelheide et al.¹⁸ and then by Dametto et al.,¹⁹ who studied barrier crossing in dihydrofolate reductase, seem to indicate that vibrational promoting modes are not of great importance. Miller and co-workers,¹⁸ using quantized molecular dynamics simulations, have also concluded that nonequilibrium dynamical coupling between protein residues and the intrinsic reaction vanishes at distances which are larger than 4–6 Å from the transferring hydride.

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In this paper, we suggest a somewhat different framework for the description and analysis of the kinetic isotope effect (KIE). Guided by the qualitative observations, we suggest that the reaction is dominated by tunneling through a barrier on the ground electronic state force field. However, this tunneling process is affected by the interaction of the tunneling particle—hydrogen—with its surroundings, considered to be the bath. The effect of the bath on the tunneling dynamics may be considered, to zeroth order, as a frictional force on the tunneling particle. Changing distal functional groups may then be thought of as changing the frictional force.

The employment of the dissipative system as a model for studying tunneling in enzymatic reactions is not new in itself. Kanaan et al.²⁰ used the classical version of variational transition state theory to account for frictional effects on the transfer reaction. Schwartz and co-workers have used this approach for a long time;²¹ however, they have incorporated it within the framework of nonadiabatic transitions when studying the SLO system.

The theory of dissipative tunneling—that is, tunneling in the presence of frictional forces, has been worked out in the 1980s. Wolynes²² was the first to obtain an expression for the tunneling rate through a parabolic barrier.²³ This was then extended to anharmonic potentials and very low temperatures (down to $T = 0$) in a series of papers, of which perhaps the seminal one is that of Caldeira and Leggett.²⁴ A review of the theory of dissipative tunneling may be found in ref 25. A few years later, Pollak demonstrated that the dissipative tunneling theories may be understood in the framework of a quantum variational transition state theory.^{26,27} In this theory, the friction changes the reaction coordinate, which becomes a collective mode, that is, a linear combination of the original reaction coordinates and the modes of the surrounding bath. This also creates a change in the potential of mean force along the reaction coordinate. Increasing the friction leads to a softer force field, or equivalently to a lower barrier frequency, so that tunneling becomes exponentially smaller as predicted by the instanton based theories. For the purpose of the present analysis, we note that Pollak demonstrated that Wolynes's theory is identical to a harmonic variational transition state theory, in which one considers only the parabolic barrier vicinity of the barrier and the harmonic vicinity of reactants.²⁷ The rate is given by the ratio of the quantum flux through the variational barrier and the density of the reactants.

The central theme of the present paper is to show that the measured KIEs for SLO and its mutants may be accounted for using the harmonic VTST. The large KIE is due to tunneling through the barrier; changing the mutants changes the frictional force felt by the tunneling particle. The larger the distal functional group, the larger the frictional force and so the smaller the KIE.

In section II we review the harmonic VTST for dissipative systems. It is then applied to the experimental data obtained for SLO and its mutants in section III. We end with a Discussion of the implications of these results and consider possible strategies for future work to verify whether the very simple approach presented in this paper is really viable.

II. VTST FOR DISSIPATIVE TUNNELING AT TEMPERATURES ABOVE CROSSOVER

We assume that the dynamics of the tunneling particle, whose mass is M , coordinate and momentum q and p respectively is given by the dissipative Hamiltonian

$$\hat{H} = \frac{\hat{p}^2}{2M} + V(\hat{q}) + \sum_{j=1}^N \left[\frac{\hat{p}_j^2}{2m_j} + \frac{m_j \omega_j^2}{2} \left(\hat{x}_j - \frac{c_j}{m_j \omega_j^2} \hat{q} \right)^2 \right] \quad (2.1)$$

where the hats denote operators, the bath modes are characterized by masses m_j , frequencies ω_j , and coupling coefficients to the system c_j and $V(\hat{q})$ is the potential.

It is well-known that, in the classical limit,²⁸ the classical dynamics of the particle is governed by the equivalent generalized Langevin equation (GLE)

$$M\ddot{q} + \frac{dV(q)}{dq} + M \int_0^t dt' \gamma(t-t')\dot{q}(t') = F(t) \quad (2.2)$$

with the identification that the frictional force may be expressed in terms of the properties of the dissipative bath and the coupling to it as

$$\gamma(t) = \frac{1}{M} \sum_{j=1}^N \frac{c_j^2}{m_j \omega_j^2} \cos(\omega_j t) \quad (2.3)$$

It is important to discuss the mass dependence of the frictional force. A zeroth order rule of thumb is that the effect of the medium should be independent of the mass of the test particle. Thus, in eq 2.2 the product of the particle mass and the friction function should be a property of the medium, but not of the system. This would then imply that the magnitude of the friction is inversely proportional to the mass of the particle. This same assumption was used in a previous study of the isotope effect in the diffusion of H and D atoms on a surface.²⁹ The random force is

$$F(t) = \sum_{j=1}^N c_j \left[\left(x_j(0) - \frac{c_j}{m_j \omega_j^2} q(0) \right) \cos(\omega_j t) + \frac{p_j(0)}{m_j \omega_j} \sin(\omega_j t) \right] \quad (2.4)$$

and we note that when averaged over the thermal distribution $\exp(-\beta H)$ (with $\beta = 1/(k_B T)$) it vanishes and that its time correlation function is proportional to the friction.

We further assume that the potential is characterized by a harmonic well located at q_a with frequency ω_a and a parabolic barrier located at q^\ddagger with barrier frequency ω^\ddagger and barrier height V^\ddagger :

$$V(q) = \begin{cases} \frac{1}{2} M \omega_a^2 (q - q_a)^2; & q \sim q_a \\ V^\ddagger - \frac{1}{2} M \omega^\ddagger^2 (q - q^\ddagger)^2; & q \sim q^\ddagger \end{cases} \quad (2.5)$$

The quantum partition function of the reactant around the harmonic well is then given by

$$Z_b = \text{Tr}[\exp(-\beta \hat{H})] = \frac{1}{2 \sinh\left(\frac{\hbar \beta \omega_a}{2}\right)} \prod_{j=1}^N \frac{1}{2 \sinh\left(\frac{\hbar \beta \omega_j}{2}\right)} \quad (2.6)$$

When considering the barrier dynamics, one replaces the full potential with its parabolic barrier approximation. The dissipative Hamiltonian is then a quadratic form which may

be diagonalized such that the resulting normal mode Hamiltonian has the form

$$\hat{H} = \frac{\hat{p}_\rho^2}{2} + V^\ddagger - \frac{1}{2}\lambda^\ddagger(\hat{\rho} - \rho^\ddagger)^2 + \sum_{j=1}^N \left[\frac{\hat{p}_{y_j}^2}{2} + \frac{\lambda_j^2 \hat{y}_j^2}{2} \right] \quad (2.7)$$

where the renormalized barrier frequency is given in terms of the system parameters and friction by the Kramers–Grote–Hynes equation^{30–32} (with $\hat{\gamma}(s) = \int_0^\infty dt \exp(-st)\gamma(t)$ denoting the Laplace transform of the time dependent friction).

$$\lambda^\ddagger + \hat{\gamma}(\lambda^\ddagger)\lambda^\ddagger = \omega^\ddagger \quad (2.8)$$

The renormalized mass weighted barrier coordinate ρ and the stable mode mass weighted coordinates y_j are linear combinations of the system coordinate q and bath coordinates x_j . Further details on the normal mode transformation may be found for example in ref 33.

By its nature, the normal mode form of the dissipative Hamiltonian (eq 2.7) in the region of the barrier is separable, so that the thermal flux through the parabolic barrier is given by the product of the thermal flux through the one-dimensional barrier and the partition functions of the stable modes in the barrier region. The VTST estimate for the rate is then given by the ratio of the thermal flux through the barrier and the density of reactants:

$$\Gamma_{\text{VTST}} = \frac{\lambda^\ddagger}{\omega^\ddagger} \Xi \Gamma_{\text{TST}} \quad (2.9)$$

where the “standard” TST estimate for the rate is

$$\Gamma_{\text{TST}} = \frac{\omega_a}{2\pi} \exp(-\beta V^\ddagger) \quad (2.10)$$

and the Wolynes factor Ξ is readily seen to be

$$\Xi = \frac{\omega^\ddagger}{\omega_a} \frac{\sinh\left(\frac{\hbar\beta\omega_a}{2}\right)}{\sin\left(\frac{\hbar\beta\lambda^\ddagger}{2}\right)} \prod_{j=1}^N \frac{\sinh\left(\frac{\hbar\beta\omega_j}{2}\right)}{\sinh\left(\frac{\hbar\beta\lambda_j}{2}\right)} \quad (2.11)$$

The tunneling through the parabolic barrier is reflected through the function $\sin(\hbar\beta\lambda^\ddagger/2)$ appearing in the denominator. It diverges at the so-called crossover temperature T_c defined by the relation^{25,34}

$$\hbar\beta\lambda^\ddagger = 2\pi \quad (2.12)$$

Above the crossover temperature the rate is dominated by transmission through the parabolic barrier; below the crossover temperature the rate is dominated by “deep” tunneling through the anharmonic barrier. The divergence is a well-known artifact of the parabolic barrier; it is due to the fact that the parabolic barrier extends down to $-\infty$ while, in any real situation, the potential is bounded from below. All that it means is that the VTST estimate based on the parabolic barrier approximation is invalid for temperatures in the vicinity of the crossover temperature and below it. Extensions of the theory of dissipative tunneling which cover the whole range of temperatures are reviewed in ref 25 but are irrelevant for the purposes of the systems to be studied in the next section.

The Wolynes factor as written in eq 2.11 is not yet amenable to practical computations. As shown in ref 27, using the product representation of the \sinh function and some

properties of the normal mode transformation allows one to rewrite the factor in terms of the Laplace transform of the friction function as originally derived by Wolynes:

$$\Xi = \prod_{k=1}^{\infty} \frac{\omega_a^2 + \nu^2 k^2 + \nu k \hat{\gamma}(\nu k)}{-\omega^\ddagger{}^2 + \nu^2 k^2 + \nu k \hat{\gamma}(\nu k)} \quad (2.13)$$

and ν is the Matsubara frequency

$$\nu = \frac{2\pi}{\hbar\beta} \quad (2.14)$$

Equations 2.9, 2.10, and 2.13 are the practical working equations to be used in the next section.

It is useful to consider some of the properties of the quantum VTST. One notes that in the classical limit the Wolynes prefactor reduces to unity and the classical prefactor of the rate expression $((\lambda^\ddagger/\omega^\ddagger)(\omega_a/2\pi))$ is independent of the temperature. To reduce the number of parameters needed to determine the rate we will employ ohmic friction, that is, the friction function is given as

$$\gamma(t) = 2\gamma\delta(t) \quad (2.15)$$

where γ is the friction coefficient and $\delta(t)$ the Dirac “delta” function. This form implies that the Laplace transform of the time dependent friction for any s is $\hat{\gamma}(s) = \gamma$. As already noted above, the friction coefficient is inversely dependent on the mass. This implies that, if the friction is moderate such that $\gamma/\omega^\ddagger \leq 1$, then the reduced barrier frequency $\lambda^\ddagger/\omega^\ddagger$ is almost independent of the mass. In the strong damping limit it would scale as the inverse of the square root of the mass. This in turn implies that isotopic substitution from H to D will reduce the prefactor by at most a factor of $\sqrt{2}$. A KIE which is larger can only come through the Wolynes factor, or in other words is a result of tunneling through the parabolic barrier.

The use of an ohmic friction function is an approximation. One would expect that typically the force autocorrelation function on the reaction coordinate would have a memory time which is of the order of a period of a “typical” vibrational frequency. One may generalize the theory by introducing memory friction and obtaining the Wolynes factor in the presence of memory. It is well understood that memory time tends qualitatively to lower the effect of the friction. In practical terms this means that the introduction of memory friction would mainly lead to the conclusion that the friction parameter (now defined as the zero Laplace component of the time dependent friction function) would be somewhat larger as compared to the friction parameter obtained with ohmic friction. In other words, introduction of memory friction will change the details but not the qualitative picture. Given the simplicity of the approach presented here, it seems quite reasonable to employ the ohmic picture instead of introducing some additional fitting parameters for the memory.

III. VTST FOR THE ENZYMATICALLY CATALYZED HYDROGEN TRANSFER

To apply the theory to the reactions of the SLO family, one needs to determine four parameters. These are the well and barrier frequencies, the friction coefficient, and the barrier height to reaction. Actually, it is not the full barrier height that one needs, only the difference in the barrier height for the reaction with H and D atoms. In principle the bare barrier height on the ground state Born–Oppenheimer potential energy surface is independent of the mass, but the reaction is

also not a one-dimensional one. The reacting hydrogen has three degrees of freedom, one C–H stretch vibration, which is the reaction degree of freedom, and two bending degrees of freedom, which are “spectators”. The isotopic substitution of the H atom directly affects also the dynamics of these “spectator” modes. Foremost, their frequencies change and this may appreciably affect the reaction rate. As a result, their zero point energy is larger for H than for D, and this implies that the barrier to reaction should be larger for D than for H. The zero point energy at the barrier is typically lower than in the reactant region, since a barrier is usually accompanied with a weakening of bonds. Moreover, if the motion through the barrier is fast as compared with the time scale of the perpendicular vibrations, then at the barrier these “spectator” modes are not necessarily quantized, and so at the barrier, in this sudden limit, one may ignore their zero point energies. This sudden limit then implies that the difference in the zero point energies in the reactant region of the perpendicular vibrations translates into an increase of the effective barrier height for the D transfer as compared to the H atom transfer.

As also noted in the experimental papers, an Arrhenius plot of the experimental KIE reveals an added barrier height for the D transfer of the order of 1–2 kcal/mol. Such an added barrier height contributes a factor of 24–35 in the experimental temperature range of 280–315 K and is insufficient to characterize KIEs, which lie typically between 100 and 200. However, the added barrier height induced by the zero point motions of the vibrations which are perpendicular to the reaction coordinate must be part of the story.

As is well-known from many examples, typical C–H stretch frequencies for alkanes lie in the range of 2850 to 3000 cm^{-1} while the bend frequencies lie in the range of 1350–1480 cm^{-1} . We therefore chose the stretch frequency to be 2925 cm^{-1} and the bend frequency to be 1400 cm^{-1} for the H reaction and a factor of $\sqrt{2}$ lower for the D reaction. This then implies a barrier for the D transfer which is 1400 $(1 - 1/\sqrt{2}) = 410$ cm^{-1} larger than for the H atom transfer. This contributes a KIE factor which ranges from 8.2 to 6.5 in the temperature range of 280–315 K. We stress that this change in the barrier height and the stretch frequency were taken to be the same for all the KIEs of all mutants of the reaction presented below.

The only parameters that need to be fit then are the barrier frequency and the friction coefficients. The barrier frequency is one parameter which remains the same for all SLO reactions. The only remaining parameter which is fit separately to each mutant is the friction coefficient. This is consistent with the heart of the theory, which is that changing the mutant changes the friction felt by the particle being transferred. We also note that in practice this means that the VTST theory needs half as many fit parameters as the Marcus based approach,¹³ since in the latter case one fits two parameters for each mutant, a distance and a frequency.

The barrier frequency used to fit all the data for the hydrogen transfer was 1308 cm^{-1} for H and $1308/\sqrt{2} = 925$ cm^{-1} for D. It should be stressed that this value is a fit, it is not based on any force field computations. Qualitatively, it is a reasonable number, considering that one is dealing with a light atom transfer process. Moreover, it is rather sensitive to the KIE; increasing it would give a much too large KIE, while decreasing it would give a rather small KIE. However, at the end of the day, it is a fit, which should be verifiable using other means based on molecular dynamics and force field computations.

Finally we denote the reduced friction coefficient as $\alpha = \gamma/\omega^\ddagger$ and note that it is a factor of $\sqrt{2}$ larger for H as compared to D, since, as detailed in the previous section, the friction coefficient scales inversely with the mass. The resulting fits to the experimental data for the different mutants on the 553 site and the reduced friction coefficients used for each data set for the D atom transfer are shown in Figure 1. The different residues for

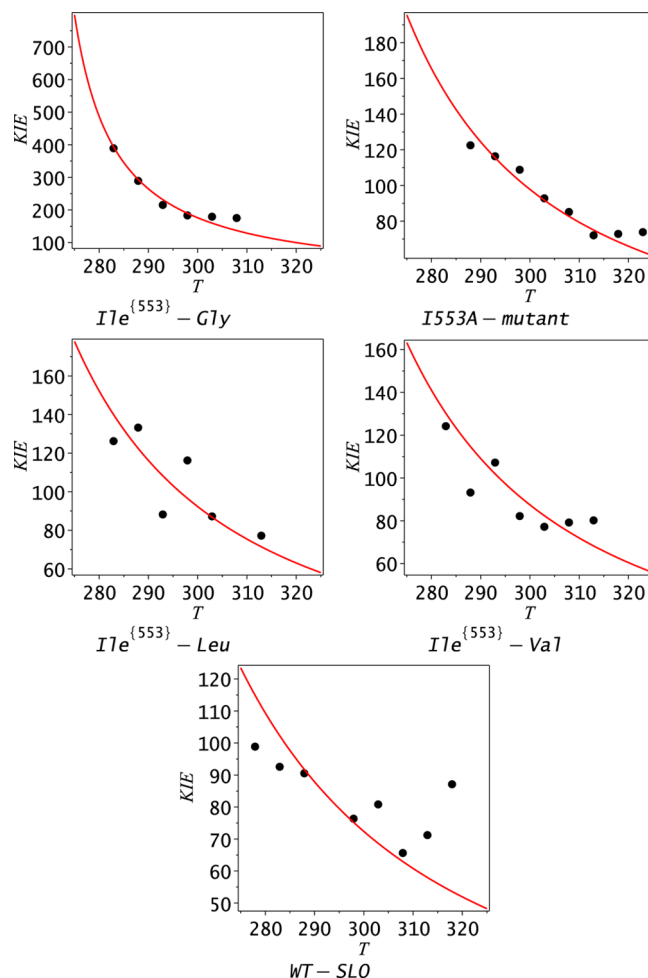


Figure 1. VTST fits to the KIE of different mutants of the enzymatically catalyzed H transfer reaction of SLO at the 553 site of the wild type. The solid lines are the fits, and the solid circles are the experimental results as reported in ref 4. For further details, see the text.

each of these are shown schematically in Figure 2. From this figure one notes that the four fitted friction coefficients increase from 0.165 for Ile⁽⁵⁵³⁾-Gly to 0.43 for Ile⁽⁵⁵³⁾-SLO providing a clear correlation between the size and complexity of the residue and the friction coefficient. We also note that the reduced

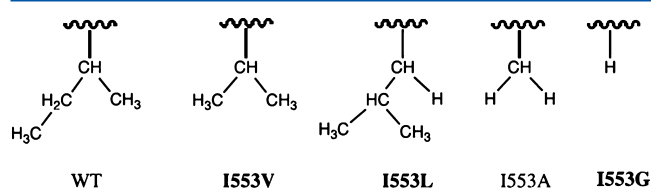


Figure 2. Schematic diagrams of SLO mutants studied in Figure 1. The figure is adapted from ref 4.

friction coefficient of 0.33 for Ile^{553}-Val is larger than that of either I^{553}-A or Ile^{553}-Gly. These results indicate that the size and complexity of the mutant can be correlated with the effect of friction on the tunneling of the H or D atom through a parabolic barrier. Increasing the size and complexity of a distal mutant can create small changes in strain on the backbone leading to subtle but measurable changes in the force correlation function felt at the reaction center. In this respect one should note that the changes in the value of the friction coefficient needed to fit the experimental data are not very large, consistent with such subtle effects.

In Figure 3 we show the fit to two additional mutants but at two different sites. Since the sites are different, it is difficult to

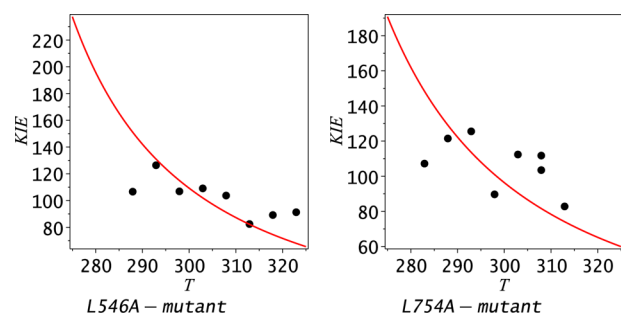


Figure 3. VTST fits to the KIE of different mutants of the enzymatically catalyzed H transfer reaction of SLO at the 546 and 754 sites. The solid lines are the fits, and the solid circles are the experimental results as reported in ref 4. For further details, see the text.

compare the two, except to note that the magnitude of the reduced friction coefficient is similar to the magnitude found for the 553 site.

To complete the discussion, we note that, with the barrier frequencies chosen, the crossover temperatures between deep tunneling and thermal activation (see eq 2.12) are all significantly below the experimental temperature range, as shown in Table 1.

Table 1. Fitted (Reduced) Friction Parameters, Resulting Renormalized Barrier Frequencies, and Crossover Temperatures for the Different Mutant Reactions^a

mutant	$\alpha(\text{D})$	$\lambda^\ddagger/\omega^\ddagger(\text{D})$	$\lambda^\ddagger/\omega^\ddagger(\text{H})$	$T_c(\text{D})$	$T_c(\text{H})$
I553-G	0.165	0.921	0.890	195	267
I553-A	0.31	0.857	0.805	181	241
I553-L	0.33	0.849	0.794	180	238
I553-V	0.35	0.840	0.783	178	234
WT	0.43	0.808	0.741	171	222
L546-A	0.275	0.872	0.824	185	247
L754-A	0.315	0.855	0.802	181	240

^a $T_c(\text{D})$ and $T_c(\text{H})$ are the crossover temperatures for the friction coefficients given in the table for D and H respectively, given in kelvins. All other notation is as defined in the text.

IV. DISCUSSION

In a recent review²¹ Schwartz states, “The simple one-dimensional view of a reaction coordinate with a free energy barrier to reaction is far too simplistic, the actual surface is highly complex with thousands of ‘hills and valleys.’ A single reactive event will not elucidate the nature of the reaction.”

This statement is based on the experience of many in simulating the classical dynamics of the large molecular systems involved, using semiempirical force fields. The purpose of the present paper is not to make the presumptuous statement that the tunneling process may be described merely by a simple one-dimensional barrier tunneling dynamics. The analysis has shown though that the experimental data may all be fit reasonably well using the simple minded VTST theory of tunneling. It has made some reasonable order in the effect of mutants on the kinetic isotope effect, showing that different functional groups could be considered as changing the frictional force felt by the tunneling particle.

Our analysis should help in guiding future detailed molecular dynamics studies of these complex systems. It should provide a reasonable baseline which could then aid in interpreting the very complicated molecular dynamics of the systems involved. In this context we note that the barrier frequency we fit to the experimental data is rather large, indicative of a potential barrier which is not dissimilar to the adiabatic barrier which may be found by considering the nonadiabatic coupling between two adiabatic potentials. It also implies that the time scale for crossing the barrier is very fast, as also noted by various molecular dynamics studies.¹⁶ Perhaps though the most important aspect of the analysis is that it is consistent with the assumption that the hydrogen transfer is dominated by tunneling. We also note that one could model the friction on the reaction coordinate by using classical molecular dynamics and a computation of the force autocorrelation function for the different mutants. Given their rather large distance from the reaction center one would expect that the resulting force autocorrelation functions would not change drastically, in qualitative agreement with the rather small change in the friction coefficients needed to fit the experimental data. Such additional computational studies are necessary to verify the mechanism considered in this paper.

The theory presented uses a minimal amount of parameters to account for the kinetic isotope effect. The assumptions made are rather elementary: tunneling through a parabolic barrier at temperatures above the crossover temperature, the lack of participation of bending modes in the reaction, and modeling the effect of the surroundings in terms of a frictional force. Interestingly, the frictional forces themselves are not very strong, as evidenced by reduced friction coefficients which are unity or less; this too may be considered as consistent with the fact that the different mutants are rather distant from the reaction center so that their effect is not very large. This is very different from the tunneling dynamics of a hydrogen atom on a surface, where the same VTST model used here was able to fit the experimental data but based on rather strong frictional coupling to the surface.²⁹

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Notes

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