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SPECIAL ISSUE

Transition State

Re-Evaluating the Transition State for Reactions in Solution

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Abstract: In this microreview we revisit the early work in the development of Transition State Theory, paying particular attention to the idea of a dividing surface between reactants and products. The correct location of this surface is defined by the requirement that trajectories not recross it. When that condition is satisfied, the true transition state for the reaction has been found. It is commonly assumed for solution-phase reactions that if the potential energy terms describing solvent-solute interactions are small, the true transition state will occur at a geometry close to that for the solute in vacuo. However, we emphasize that when motion of solvent molecules occurs on a time scale similar or longer than that for structural changes in the reacting solute the true transition state may be at an entirely different geometry, and that there is an important inertial component to this phenomenon, which cannot be described on any potential energy surface. We review theories, particularly Grote-Hynes theory, which have corrected the Transition State Theory rate constant for effects of this kind by computing a reduced transmission coefficient. However, we argue that searching for a true dividing surface with near unit transmission coefficient may sometimes be necessary, especially for the common situation in which the rate-determining formation of a reactive intermediate is followed by the branching of that intermediate to several products.

1. Introduction

Although presented under the rubric of a microreview, this article is more properly viewed as a hybrid between a review and a research paper since it contains new material in addition to the expected summary of existing work. The topic addressed is the modeling of reactions in solution. In particular, we are concerned with how solvents respond to solutes that undergo substantial changes in shape during a reaction, which is surely a common phenomenon in the reactions of complex organic molecules. There is experimental and computational evidence that the necessary solvent reorganization accompanying such a reaction (and requiring, as it typically will, whole solvent molecules to relocate) can take picoseconds to tens of picoseconds.[1] However, for the reacting molecule in the gas phase, the time required to change geometry from the transition state to the next local minimum is typically ≤ 100 femtoseconds.[2] We argue (as have others) that there are several important con-

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sequences of this timescale mismatch. In particular, we focus on relocation of the true transition state for the reaction in solution, and the fostering of transient but strongly repulsive solvent-solute interactions, whose consequences are, we believe, best understood by models that treat the solvent atomistically. In this article, we consequently review the existing models, introduce a new atomistic model in its simplest form, and discuss some of the physical insights that we believe arise from it. Finally, we discuss the prospects for applying more complex and realistic versions of the new model to real solution-phase reactions.

2. Theoretical Framework

Because chemists studying reactions in solution have usually been interested in the behavior of the solute, there has been the natural tendency to think that an appropriate model would start with the expected reaction coordinate connecting intermediates and transitions states (TSs) for the solute in vacuo, and then to perturb it on the basis of calculated solvent effects.[3] However, this approach necessarily implies that solvents can respond almost instantaneously to changes in the solute. That assumption is adopted by most implicit and explicit solvent models. The assumption may be reasonable if the principal effect of the reaction under study is a change in polarity of the solute, because such a change can usually be accommodated by moving electrons and a few key protons in the solvent, and those changes can usually occur rapidly. However, there are well-known cases, particularly involving proton transfers in the reacting solute, where the assumption of instantaneous solvent response has been recognized to be invalid,[4] and methods to deal with this situation have been developed. Those methods (which will be discussed later) have typically left the position of the TS unaffected and accounted for the effect of slow solvent motion through a reduction in the transmission coefficient, κ. There is no doubt that such an approach is currently the most practical. However, we will emphasize in this microreview that slow solvent motion causes a relocation of the TS, and that attempting to find its new location might be particularly important when one is concerned with calculating product ratios. The recognition of the TS relocation is at the root of methods such as Variational Transition State Theory (vide infra), but here we introduce a simple model that shows the effect pictorially. In principle, the new model could be extended to allow a search for the relocated TS in real chemical simulations. The methodology required for such searches is currently available only for low dimensional models, but techniques applicable to realistic systems are being developed, and are mentioned at the end of this microreview. Here, our concern is more on the question of why one might want even to try to conduct such a search.

The basis for most rate-constant calculations in chemistry is Transition State Theory (TST). However, it has been recognized for some time that simple application of TST to solution-phase reactions can lead to overestimation of the rate constant if the response of the solvent occurs on a time scale similar to or slower than that for changes in the reacting solute.[5] Early theories treated this phenomenon as a frictional drag on the reacting solute, caused by the relatively slow adjustment time of the solvent. Attempts were then made to compute the magnitude of this effect, and to incorporate it into a reduced value for the transmission coefficient of TST. Prominent among such methods was Kramers theory, but it has been superseded by Grote-Hynes (GH) Theory, which provides a more sophisticated description. In the following sections we present brief reviews of TST and GH theories. Our view is that the interaction of reacting solute and solvent is best understood in a phase-space representation. Because phase-space diagrams do not commonly appear in organic chemistry papers, we choose to introduce them first.

2.1. An Introduction to Phase Space

Most chemists are familiar these days with the concept of a potential energy surface (PES), which expresses the dependence of the potential energy of a molecule on its geometry. It is commonly believed that if one had a full, accurate PES for a reaction, one would know everything one needed to know about the reaction, but that is not really correct. Reactions are defined by change, which implies some time dependence in the description of the transformation. That time dependence can be incorporated if, in addition to specifying the relative positions in space of each atom, as one does in the construction of a PES, one also specifies their momenta. The geometry of a molecule of N atoms can be thought of as a point in a $3N$–6 dimensional space, called configuration space. In order to include information about the relative momenta of the atoms, one needs a $6N$–9.[6a] dimensional space, called phase space.[6b] The crucial property of phase space in its application to reaction dynamics is that every point in it is unique. In other words, if one knows the geometry of a molecule and the momenta of its atoms, then within the limits of classical mechanics, one knows its entire history and future with absolute certainty. By contrast, if one knows only the geometry of the molecule and its associated PE, one has to guess at its history and future by making some sort of assumption, such as TST.

Obviously, it is not feasible to depict the full $3N$–6 configuration space for a molecule on a page, and so we have become used to seeing reduced-dimensional projections, in which potential energy is plotted as a function of just one or two geometrical coordinates. A similar problem clearly exists for phase-space depictions, which have to be projections from an even higher dimensional space. Phase space projections are quite easy to understand but require a little getting used to. We begin with the phase portrait for a simple one-dimensional harmonic oscillator, shown in Figure 1. The parabolic dependence of potential energy on position (q) for this system (panel A of Figure 1) is familiar. Suppose now that we are interested in the dynamics of this oscillator at a fixed total energy, indicated by the dashed horizontal line in panel A of Figure 1. Because total energy is equal to the sum of potential and kinetic components, we can easily deduce the kinetic energy (let's call it T) of the oscillator as a function of q by subtracting the potential energy from the total energy. That will lead to an inverted parabola, as shown in panel B of Figure 1. Now that we know the kinetic energy, we also know the momentum, because the kinetic energy is equal to $p^2/2\mu$, where p is the momentum and μ is the reduced mass for the oscillator. Equivalently, we could write $p = \pm\sqrt{(2\mu T)}$, which emphasizes that momentum is a signed quantity. So, we can guess the shape of a p vs. q plot by pasting together the KE profile and PE profile (which has the same shape as the negative of the KE profile) and changing the shape a bit (because of the square root). The result is an ellipse, or, if one chooses the units on the axes appropriately, a circle, as shown in panel C of Figure 1.

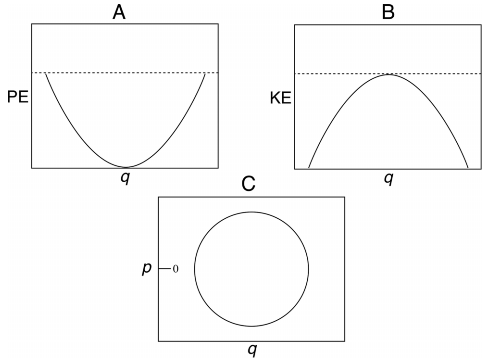


Figure 1. Depictions of how the potential energy (panel A), kinetic energy (panel B) and momentum (panel C) vary with position (q) for a one-dimensional harmonic oscillator.

This exercise becomes somewhat more interesting if one now switches to a double minimum oscillator, for which the PE profile (panel A of Figure 2) would be a familiar representation of a single-step chemical reaction.

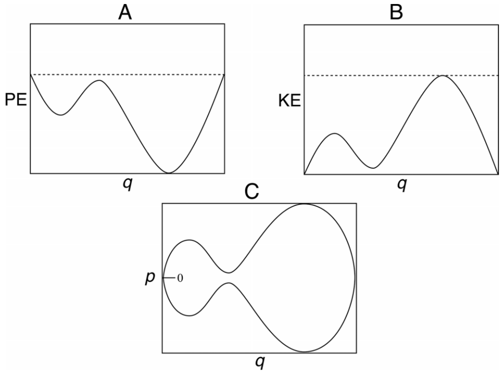


Figure 2. Depictions of how the potential energy (panel A), kinetic energy (panel B) and momentum (panel C) vary with position (q) for a one-dimensional double-minimum oscillator.

We choose the total energy to be slightly above the PE of the TS for our one-dimensional reaction, and then the mnemonic of pasting together PE and KE profiles, and distorting a bit, gives us something looking like an unsymmetrical peanut for the phase portrait (panel C of Figure 2). That object will be useful for understanding dividing surfaces, which we address below.

2.2. Transition State Theory

The first theoretical description of the dependence of the rate constant of a chemical reaction on the temperature was formulated by Arrhenius,[7] who in 1889, and following the work of van't Hoff, provided an empirical relationship between the temperature and the rate constant in an equation bearing his name. In the 1930s Wigner,[8] Eyring,[9] as well as Gwynne Evans and Polanyi[10] developed simultaneously what is now known as Transition State Theory.

TST is a classical theory that calculates the rate of the reaction as the equilibrium flux of reactive trajectories through a TS dividing surface; this dividing surface will be explained in detail below. Although there has been much discussion of quantum mechanical analogs of TST[11] we here treat only the original classical version, because the dividing surface that will form our principal focus is incompatible with quantum mechanics.

It is commonly claimed that conventional TST makes two main assumptions.[12] The first, called the equilibrium assumption, requires that the reactant state and TS be in thermal equilibrium. The maintenance of energetic equilibrium means that the thermalization maintaining this equilibrium is (at least) as fast as the rate at which these states are depopulated.[13] The equilibrium condition is usually satisfied for most gas-phase bimolecular reactions and for reactions in the liquid phase, because energy exchange between solutes and solvent is usually rapid enough to maintain the equilibrium.[14] However, there are cases where equilibrium is not maintained, even in solution.[15] In addition, for unimolecular reactions of intermediates with low barriers to product formation, it is commonly the case that most trajectories coming from the reactant state will have enough energy in a product-forming reaction coordinate to cross the second barrier as soon as they reach it.[16]

The second claimed assumption, specifies that any trajectory crossing the TS dividing surface from the reactant state is on a path towards the product state and will reach it without recrossing the dividing surface prior to the product being reached.[17] Because the rate is calculated as the flux through the TS, any non-reactive trajectory that crosses the TS dividing surface, or reactive trajectory that crosses it more than once will increase the flux through the dividing surface, thus leading to an overestimate of the rate constant. This means that TST gives us an upper limit on the true rate constant, and that if we found a dividing surface without any recrossing then TST would give the exact value of the rate constant (subject to certain caveats[18]).

In conventional TST the transition state dividing surface is located at the saddle point, which is the maximum energy point in the minimum energy path from reactants to products. However, TST is most powerful in the form of Variational Transition State Theory (VTST),[13,17,19] which is a generalization of TST that removes the restriction on the dividing surface to cross the saddle point. In VTST the dividing surface is variationally optimized to minimize the rate constant, usually by finding the maximum free energy along the reaction path. Although this surface is properly located in phase space, most of the VTST calculations assume that the TS can be found in configuration space.[16a] TST and its modern development VTST have been extensively reviewed,[3b,13,17,19,20] but here we will focus on in its application to condensed-phase reactions, its applicability and limitations when working in configuration space, and the potential of including phase space into the methodology.

In this microreview, we take a different point of view on the two supposed assumptions of TST. By treating the non-recrossing criterion for the dividing surface as an assumption, one is implying that there exists some other criterion of higher priority for locating the TS. However, in our view the location of the TS is defined solely by the satisfaction of the non-recrossing criterion. Hence, if one finds a putative TS whose associated dividing surface suffers recrossing (leading to a reduction in the TST transmission coefficient), then the TS is, strictly speaking, in the wrong place.[21] That said, there may be no problem with using such an approximate TS, as GH theory does, for computation of the overall rate constant of a single-step reaction. The potential problem arises, we suggest, when one is concerned with branching to several products after a rate-determining TS.

The supposed equilibrium assumption of TST is not really an assumption either, because it can be shown to be a consequence of the non-recrossing requirement.[22] It will be apparent, therefore, that the concept of the dividing surface and its proper location is central to the present discussion. We address these issues next.

2.2.1. The Dividing Surface and the Conventional TS

We have spoken about the dividing surface as a hypersurface that divides the full space of coordinates (the phase space) between reactant and products in a way that satisfies the non-recrossing criterion.[17,23] The phase-space diagram from Figure 2 serves to illustrate the point.

This phase portrait was derived for a one-dimensional oscillator. If the whole system were one dimensional, then trajectories could only run around the perimeter of the phase plot. However, if we consider the somewhat more realistic situation in which the reaction coordinate is one dimensional but is coupled to many more dimensions, representing unreactive motions of the atoms of a polyatomic molecule, then the trajectories in this projection could have any momentum inside the perimeter of the diagram. In Figure 3 we show in blue a schematic reactive trajectory, beginning in the reactant region on the left and terminating in the product region on the right. The question at hand is where to place our dividing surface, shown schematically as a straight red line in Figure 3, so that it satisfies the non-recrossing criterion. It will be apparent that the left-hand panel of Figure 3 represents a poor choice because it is crossed several times by the trajectory. It is also apparent, that the only place one could locate the dividing surface to guarantee no recrossing would be at the "pinch point" of the phase plot, as shown in the right-hand panel of Figure 3. If one now recalls the discussion in Section 2.1, relating the shape of the phase portrait to the shape of the PE profile, one recognizes that the place we have chosen as the ideal location for the dividing surface is the local maximum in the PE profile, which we would identify as the conventional TS. But here is the crucial caveat: *this relationship between the dividing surface and the conventional TS only holds for a one-dimensional reaction coordinate* (*except in the special case of degenerate reactions, where symmetry may dictate the location of the TS*).[24] As has been known for many years,[25] and as we will illustrate below, adding even one more dimension breaks the relationship between the two. Under these circumstances, *the dividing surface continues to define the true TS, the local maximum (or saddle point in higher dimensions) on the PES does not.*

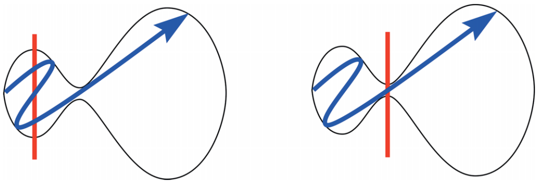


Figure 3. Illustration of poorly chosen (left) and well-chosen dividing surfaces in the phase space of a one-dimensional reaction coordinate. Activation and deactivation steps are neglected.

2.3. Solvent and Solute Coordinate Separation

There can be little argument that the fearsome complexity of organic chemistry has been successfully tamed by assuming a rough transferability of properties between similar systems. The classification of chemical reactions through the idea of the functional group, and the interpretations of infrared, ultraviolet and nuclear magnetic spectra have all benefitted enormously from this approximation. When one comes to consider reactions in solution, therefore, it seems natural to use a similar approach, and to assume that a reaction in one solvent is likely to be grossly similar to the same reaction in another solvent. This mindset leads easily to the notion that solute and solvent degrees of freedom are separable, with the former constituting a primary set, the latter a secondary set, and much of the focus becoming a proper description of the coupling between the two sets.

Once the separation is made between solvent and solute degrees of freedom, there are different ways in which solvent can be represented – either, with an implicit model, an explicit model, or a mixture between both.[26] Implicit solvation models replace solvent molecules by an electrostatic field that is equivalent to the one produced by the solvent when polarized by the solute, and may also include nonelectrostatic terms to approximate specific effects such as hydrogen bonding.[3b,3c,27] However, by their nature, purely implicit solvent models cannot represent specific solute-solvent interactions at an atomistic level. In principle, this problem can be addressed by explicit-implicit hybrid treatments in which some solvent molecules, usually the first solvation shell around the solute, are included in full atomistic representation and then everything else is treated with an implicit solvation model.[25]

Finally, there are fully explicit solvation models, in which all solvent molecules are treated at a fully atomistic level. In these models, the separation of solvent and solute coordinates has a clear computational motivation. It is an approximation that can serve to make feasible a simulation that would otherwise be intractable, because of the large number of degrees of freedom that the explicit solvent molecules introduce to the model. Typically, one tries to model the reaction as a function of a single coordinate, which has to be a combination of the degrees of freedom of the system, usually an internal coordinate that is called the Reaction Coordinate (RC). The definition of this coordinate is very important because the RC should be normal (perpendicular in many dimensions) to the dividing surface at the TS and in order to improve the definition one could include any number of degrees of freedom of the solvent. For the reasons outlined earlier, the coordinates that define the RC are considered to be the primary degrees of freedom.

Commonly, the secondary degrees of freedom in explicit solvent models are deemed to have an influence on the reaction that can be treated statistically, in some fashion. This approach is the one adopted by the Potential of Mean Force (PMF)[28] methodology to calculate the free energy profile of the reaction. The PMF is calculated from the probability density of finding the system in a given value of the RC, which is defined for the primary coordinates alone. It has consequently been argued that the PMF can consequently be viewed as a free energy function for the secondary degrees of freedom, but an ensemble-averaged potential energy profile for the primary ones.[13a] Commonly, the primary coordinates involve only atoms of the solute, but it is possible to include some explicit solvent molecules, as we discuss further below. However, if one wants to retain the dynamical properties of the system only unbiased molecular dynamics (no umbrella sampling) can be used to sample the full space of coordinates.[29]

2.4. Grote-Hynes Theory

All three classes of model outlined in the previous section rely on the assumption that solvents can respond rapidly to changes in the solute. What does one do when that is not the case? Arguably the most successful approach to dealing with this situation comes from GH theory.

GH theory is a powerful tool for calculating reaction rates in solution when solvent dynamical effects are responsible for reducing the actual rate constant (κ) from its TST approximation. It does so by calculating a prefactor (transmission coefficient) for the TST rate constant (κ_{TST}). The first stochastic approach to calculating this factor was Kramers Theory,[30] which represented solvent interactions with the solute through a combination of Brownian motion and dissipative effects, as embodied in a simple Langevin equation description.

GH theory builds on this approach by defining a free energy profile along a RC ($_x$). In the neighborhood of the barrier top ($x^{\ddagger} = 0$) the reaction barrier is assumed to be parabolic and the reactive coordinate satisfies a generalized Langevin equation (GLE):[31]

$$\ddot{x}(t) = \omega_{beq}^2\, x(t) - \int_0^t d\tau\, \zeta(t-\tau)\, \dot{x}(\tau) + F^{*}(t) \tag{1}$$

The equilibrium barrier frequency ($\omega^2{}_{\mathrm{beq}}$) depends on the curvature of the barrier and the time dependent friction [$\zeta(t)$] per solute mass (μ) is the time correlation function of the dynamic forces exerted by the solvent particles on the solute coordinate. It should be stressed that the friction just described is only valid in the vicinity of the barrier top as it can be different from the corresponding frictions relevant for reactants and products. As a matter of fact, the entire description is assumed to be valid just in the vicinity of the barrier.[32]

With these assumptions detailed above, GH theory derives the following relation between the k_{TST} and k.[31]

$$\kappa = \frac{k}{k_{TST}} = \left(\frac{\lambda}{\omega_{beq}}\right) \tag{2}$$

Thus, the transmission coefficient (k) is the ratio of the reactive frequency (λ) and the mean barrier frequency.[31,33]

$$\lambda = \frac{(\omega_{beq}^2)}{\lambda + \hat{\zeta}(\lambda)} \tag{3}$$

Here the frequency dependent friction $\zeta(\lambda)$ is the transform of the time dependent friction.

$$\hat{\zeta}(\lambda) = \int_0^\infty dt\, e^{-\lambda t}\, \zeta(t) \tag{4}$$

These two equations are the key of GH theory. They show that the transmission coefficient is determined by the reactive frequency and the reactive frequency is determined both by the barrier frequency and by the frequency component of the time dependent friction at λ.[32,33]

There are four important limits for the GH theory.[33,34] First, if the solvent adapts itself fast enough, to the scale of the reactive frequency, then the frequency dependence of $\hat{\zeta}(\lambda)$ can be ignored and the equations reduce to the Kramers Theory result.

$$\kappa_{KR} = \frac{\omega_{beq}}{\zeta} \tag{5}$$

This is the only limit in which the friction constant provides a satisfactory description of the interaction with the solvent. In general, the full dynamics description of $\zeta(t)$ is required.[32]

A second important limit occurs when the solvent dynamics are slow on the reactive timescale λ^{-1}, also called a nonadiabatic solvation, and then:

$$\hat{\zeta}(\lambda) = \lambda^{-1}\, \zeta(t=0) \tag{6}$$

In this case $\hat{\zeta}\ (t = 0)$ is the initial friction, i.e. a measure of the solute-solvent coupling frequency.[33]

$$\kappa_{GH} \rightarrow \kappa_{na} = \frac{(\omega_{bna}^2)}{\omega_{beq}^2} \tag{7}$$

$$\omega_{bna}^2 = \omega_{beq}^2 - \zeta(t=0) > 0$$

Here $\omega^2{}_{\mathrm{bna}}$ is the frequency of the nonadiabatic barrier along the reaction moves. This frequency is less than the corresponding $\omega^2{}_{\mathrm{beq}}$ as the passage occurs for fixed solvent configuration and the equilibrium solvation is not incorporated to $\omega^2{}_{\mathrm{bna}}$. In this case the absence of solvation dynamics is responsible for the deviation from equilibrium solvation assumption.

The third limit is called the “polarization cage” limit and involves the crossing of a broad reaction barrier and a strong solute-solvent coupling.[33,34]

$$\omega_{beq}^2 < \zeta(t=0) \tag{8}$$

On short time scales the solute coordinate is trapped while crossing the barrier because the solvent moves too slowly. The initial friction is too large to allow the reaction to proceed. No net passage over the barrier can occur until the solvent moves to relax this "cage" and frees the motion along the RC. In this case the solvent dynamics are essential for the reaction to occur and the transmission coefficient will reflect that, decreasing as the solvent relaxation time lengthens. In this case something more than the initial time behavior of $\zeta(t)$ will be required to characterize the influence of the non-equilibrium solvation on the reaction rate.

The fourth and final limit, called the weak solvation limit, involves a very weak solvent coupling where the barrier crossing and thus the transmission coefficient is largely insensitive to the surrounding solvent. This can be seen in the nonadiabatic limit where, if $\zeta(t = 0)$ is too small, $\kappa_{na} = 1$ and then $\kappa \rightarrow \kappa_{TST}$.[33,34]

3. Limits of the Framework

There is no question that for many reactions VTST is the way to go when calculating its rate constant. Moreover, the combination of VTST with the frictional corrections from GH theory has been proven to be a very useful tool for the calculation of rate constants of many reactions in solution.[35]

In GH theory, the friction used to modify the TST rate constant and the rate constant itself are dependent on the definition of the RC. This implies that a bad definition of the RC can lead to a low transmission coefficient without the participation of any solvent dynamical effects. Note, for example that in Section 2.1 we pointed out that the ideal location for the dividing surface was guaranteed to be identical to the location of the conventional TS only in one dimension. It has been proven that the inclusion of solvent coordinates in the calculation of the PMF can give a more complete picture of the reaction[36] and even improve the definition of the TS dividing surface to the point where the transmission coefficient is close to unity.[37] This means that, while most PMF use only the solute coordinates (i.e. those for the solute reaction in vacuo) as the primary set, some degrees of freedom of the solvent (or even all of them) can be included statistically in the primary set to account for the solvent effects, thereby improving the model of the RC. Consequently, we can say that the interaction between the solvent and the solute has a statistical component which plays a major role in many reactions[38] and those components can be modeled by the inclusion of solvent degrees of freedom into the RC. However, there are also effects that seem to be best understood with a different sort of atomistic description of the solvent,[15,39] which we discuss next.

3.1. The Inertial Barrier Created by Solvation[51]

As discussed above, the Kramers, GH and related models have dealt with the rate constant reduction by introducing a frictional effect to represent the coupling between solvent and solute dynamics. That approach has had significant success.[31–35] Here we point out two ways in which the atomistic representation of the solvent described below may give one new insights.

The first issue takes us back to the original Wigner definition for the dividing surface – namely that it should be a surface in phase space that is not recrossed by reactive trajectories.[23] Put another way, if one finds a dividing surface that is recrossed by trajectories, it is not in the right place to be a TS (although we note that the closer to unity the transmission coefficient is for such a putative TS, the better an approximation it represents to the true TS).

Consequently, we can recognize that the result of dynamical solvent effects is to relocate the TS, even if the underlying PES is unaffected. The original frictional model of Kramers accounted for the effect of this relocation on the gross rate constant but was not capable of telling us where the new TS was. The frequency-dependent friction in the GH model corrects this deficiency and allows the examination of molecular-level space and time scale effects on the rate.[35n,35o] We argue here that a different model, capable of representing atomistic interactions between solutes and nearby solvents can give additional insights. In particular, recent computational and experimental work has shown that the shell of solvent molecules around a reacting solute can present an inertial barrier to reaction rather than a frictional one.[40,41] This phenomenon is conceptually related to the polarization cage in GH theory (Section 2.4), but has two important differences. The polarization cage is identified as a strong solvent interaction with charges in the reactant state of the solute, which inhibits redistribution of charge during a reaction. The inertial phenomenon considered here does not depend on charge or on an *existing* strong interaction between solute and solvent. Instead it is a phenomenon associated with change of shape of the solute, requiring solvent molecules to move as a consequence. This can *induce* transient strong solvent-solute interactions, with potentially important consequences, as we describe below.

The relocation of the TS and the inertial solvent effect are both conveniently illustrated with a very simple physical model, shown in Figure 4. The red masses represent a solute that is capable of reaction, because the PE as a function of the distance r_1 has two unequal minima. The minimum at larger distance is lower in potential energy and hence corresponds to the product. The blue masses represent a solvent shell that has a very weak harmonic restoring force. The interaction between solute and solvent is represented by a term proportional to $(r_2 - r_1)^{-12}$, like the repulsive part of a Lennard-Jones potential. A key feature of this model is that one can find out exactly where the true dividing surface is[25] and can investigate how it responds to changes in parameters of the model. For the present discussion, it is sufficient to change only one parameter, the reduced mass of the solvent model μ_2. Figure 4 shows also the contour plot of the PES described by the coupled oscillators.

Figure 5 shows a close-up of the saddle-point region (the conventional TS) and reveals how three different dividing surfaces respond as μ_2 changes. The three dividing surfaces are defined as follows. In blue is a dividing surface based on the assumption that the reaction coordinate is defined only by the solute, i.e. the reaction coordinate is r_1. The PES projection of the dividing surface would therefore be orthogonal to r_1, in other words parallel to r_2. It is completely unaffected by changes in μ_2. The red dividing surface takes into account the influence of the model solvent on the PE profile of the solute. Its projection is orthogonal to the two-dimensional intrinsic re-

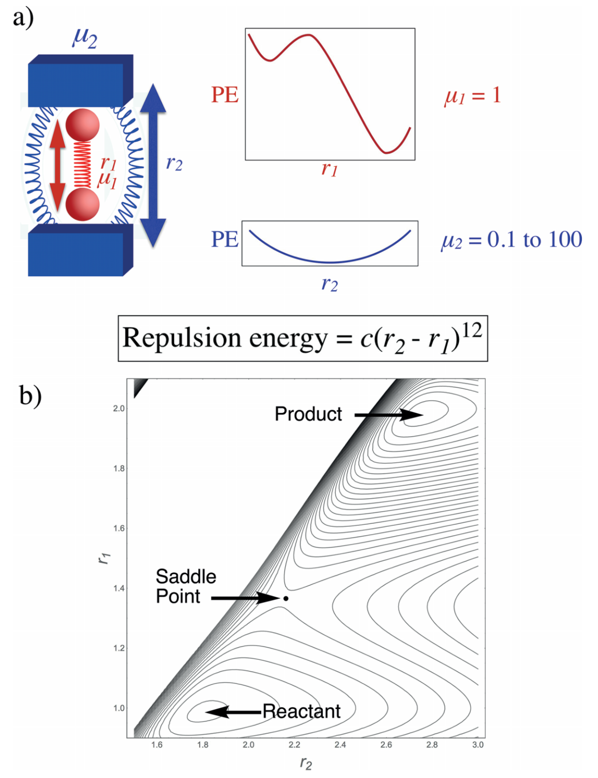


Figure 4. (a) A simple physical model for inertial solvent effects on reacting solutes. (b) Contours of the PES for the model shown in a. The small segment of the PES in the upper left corner of the contour plot corresponds to an unphysical situation with $r_1 > r_2$. However, there is an infinite barrier separating this region of the PES from that with $r_1 < r_2$ and so trajectories started in the latter region can never reach the unphysical part of the potential.

action coordinate (IRC) on the potential, but still passes through the PES saddle point. Because the IRC is defined in mass-weighted coordinates, it does change with μ_2, and the dividing surface perpendicular to it does too. Although the projected dividing surface continues to pass through the PES saddle point, it rotates with respect to the blue DS as μ_2 changes. The green line is the PES projection of the true dividing surface for this potential,[25] i.e. the one for which the non-recrossing condition is satisfied.

What the model reveals is that when μ_2 is small with respect to μ_1, the projections of the three dividing surfaces are quite close to each other, but as the relative reduced mass of the solvent model gets larger, the true dividing surface moves away from the ones that are rooted at the PES saddle point. The important point here is that, even if one could take the solvent into account properly in defining an IRC for a solution-phase reaction (which generally one cannot), a DS orthogonal to that IRC but still centered on the PES saddle point (the red line) would be incorrect.

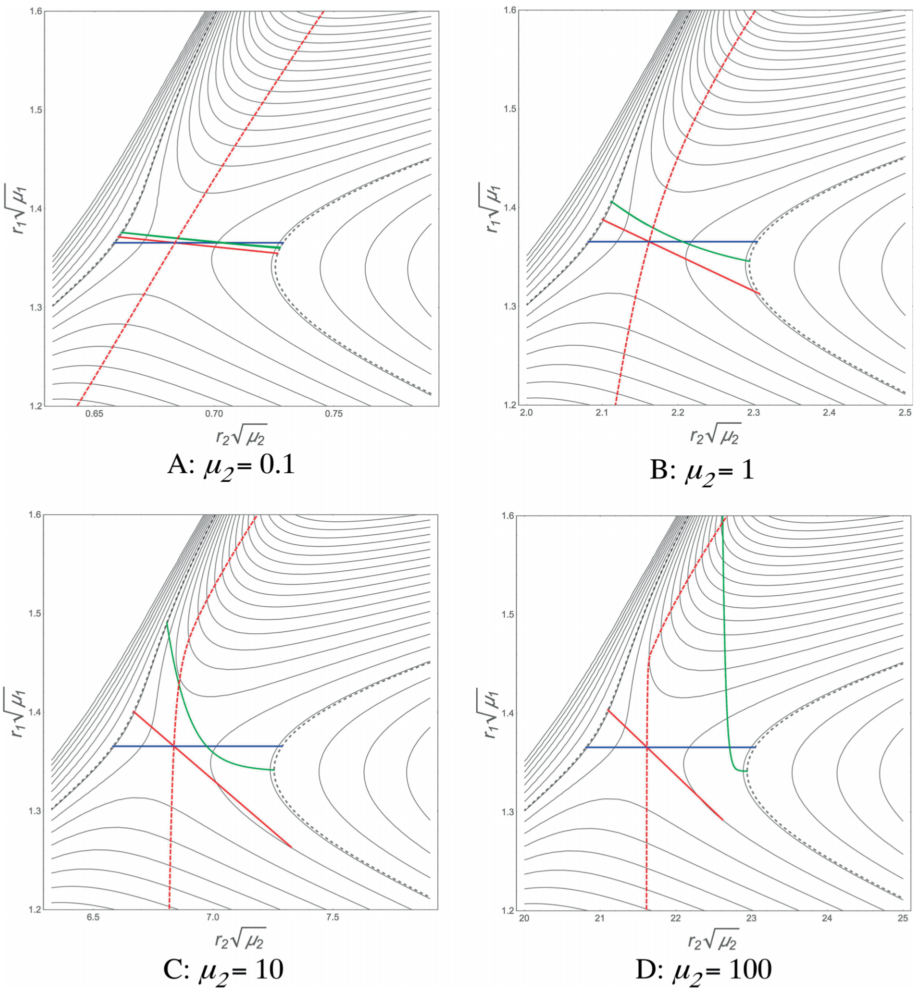
What is the effect of choosing an incorrect DS on one's understanding of the dynamics in this system? There turn out to be several effects, but let's look at just one of them here. A useful technique is to sample the initial conditions, at a constant total energy, and to explore how the time required to get from the DS to the product well on the PES varies with different initial conditions. The results are shown in Figure 6 as a comparison between the true TS (the green dividing surfaces in Figure 5) and the conventional TS (the blue dividing surface in Figure 5). Each panel of Figure 6 is an individual phase-space plot in which the momentum perpendicular to the dividing surface ($p_\perp$) is plotted against position along the dividing surface. The colors in the diagrams report how long each trajectory with those particular initial conditions took to reach the product well, with violet being the shortest times and red the longest.

Cursory comparison of the panels for true and conventional TSs in Figure 6 reveals that they are of very similar shape for $\mu_2 = 0.1$ but become increasingly different as the reduced mass of the solvent model increases. Recalling the discussion of Section 2.1, one can recognize that the shapes of the phase portraits reflect the shapes of the PE profiles that they span. All of the blue dividing surfaces in Figure 6 cover the same part of the potential, and so they all have the same shape. By contrast, the green dividing surfaces explore quite different parts of the potential, and so have quite different shapes.

The second thing to notice is that all of the phase plots for the true TS in Figure 6 are neatly divided along the $p_\perp = 0$ line, with the positive parts of the diagram all being featureless and violet, indicating short transit time to the product. This is exactly what a dividing surface is supposed to do, it separates those trajectories heading to the product from those heading to the reactant, with none of the trajectories recrossing the surface. The colored structures that one sees in the halves of the plots with $p_\perp < 0$ reveal interesting things about the dynamics in the vicinity of the reactant well, but that is not relevant to the present discussion.

By contrast with the neat division of the phase plots for the true TS, those for the conventional TS show ill-defined separation between transit times to the product for positive and negative values of $p_\perp$. There are trajectories with $p_\perp > 0$ that take a long time to reach the product, and those with $p_\perp < 0$ that get there quickly. That is because there is recrossing of our poorly chosen dividing surface. Trajectories that were initially headed to the product (i.e. have $p_\perp > 0$) but recross and go instead to the reactant are classified here as product → reactant recrossings, whereas those doing the reverse are called reactant → product recrossings. As the reduced mass of the solvent model increases, the proportion of reactant → product recrossings stays roughly constant, but the proportion of product → reactant recrossings increases substantially. This occurs because high reduced mass for the model solvent causes an inertial barrier to reaction for the model solute. The solvent oscillator cannot expand fast enough to accommodate the expanding solute, and the repulsion between the two causes the solute to contract again, i.e. to recross the DS.

These observations may be all very interesting, but the obvious question is whether the model on which they are based has any relevance to real chemical reactions in real solvents. In particular, one may wonder whether a model in which the solvent reduced mass is 100 times that of the solute is capable of telling one anything useful about a normal chemical reaction. An answer to that question comes from exploring the energetic consequences of the inertial effects outlined above. The reduction in potential energy as the solute passes from the saddle



A: μ_2= 0.1

B: μ_2= 1

C: μ_2= 10

D: μ_2= 100

Figure 5. Close-up of the PES shown in Figure 4, near the saddle point region. The dashed contours in each panel show the energy at which all calculations were done. The dashed red line is the intrinsic reaction coordinate (IRC) for the PES. The blue line is the PES projection of the dividing surface between reactant and product, if one assumes that the reaction coordinate is r_1. The red line is the dividing surface projection at the saddle point, which is locally orthogonal to the IRC. It does not look orthogonal because of the choice of axis scales. The green line is the PES projection of the true dividing surface, which satisfies the non-recrossing criterion.

point region of the PES to the product minimum causes an initial rise in kinetic energy of the solute. The coupling between solute and solvent oscillators then permits energy transfer between the two. One can track this effect as a function of time by calculating the total energy (potential plus kinetic) for the solute as each trajectory evolves. Averaging the results for all trajectories that are initially heading towards the product (i.e. have initial $p_\perp > 0$) leads to the results shown in Figure 7.

As Figure 7 shows, when the reduced mass of the solvent model is smaller than or comparable to that of the solute, the energy transfer between the two is monotonic. However, when the reduced mass of the model solvent is much higher than that of the solute, the energy transfer becomes oscillatory. This happens because the expanding solute collides with the solvent, which is unable to respond fast enough for the solute to reach the product minimum on the PES, and so the solute begins to contract again, thereby raising its potential energy. In the case of the highest mass solvent model, these collisions happen repeatedly until the solvent has had time to accommodate the increased size of the solute. This is a purely inertial phenomenon; it has nothing to do with the potential energy function for the solvent model, which is identical for the four lines in Figure 7. Interestingly, this phenomenon has been observed in a full-scale MD simulation of a solution-phase reaction. The reaction is the ring opening of the singlet carbene, shown in Figure 8.[42b] When the energy transfer to the solvent from the exothermic ring opening was tracked, exactly as described above for the simple model, the results showed clear signs of the inertial effect of the solvent, as shown in Figure 9. The non-monotonic behavior seen at ≈ 100 fs in Figure 9 is the result of inertial effects of the solvents, and is, to a good approximation independent of the nature of the solvent. The high reduced mass for the solvent in the simple model which reproduced this effect is seen to be a surrogate for the collective effect of a whole shell of solvent molecules in a real reaction. When there is a substantial change in shape of a reacting solute, it will not usually be possible to accommodate that by moving a single solvent molecule without affecting its neighbors. This is not a new discovery; like so many ideas in chemical dynamics this insight came first from Don Bunker,[41f] who was

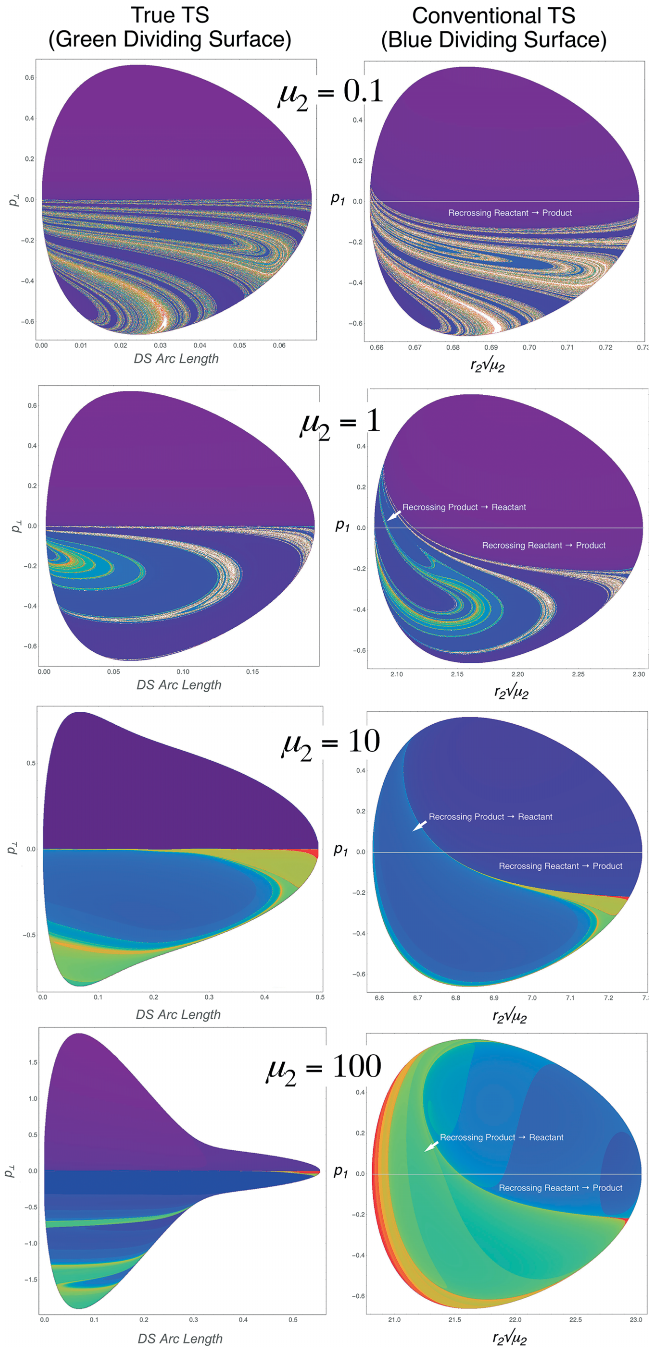


Figure 6. A comparison of trajectory transit times from the true TS (green dividing surface in Figure 6) and conventional TS (blue dividing surface in Figure 6) to the product. The color scale goes from violet for short times to red for long times. The quantity p⊥ is the momentum perpendicular to the dividing surface, with a positive sign being in the direction of the product.

simulating the solution-phase photodissociation of I_2 and wrote in 1972: "The difficulty appears to be that even though cage recombination involves a single smooth maximum in the I–I separation, there are not one but several struck solvent molecules. Thus, as we have verified by inspection of the trajectories, practically all solvents have high net momentum-carrying capacity and behave as if they were made of massive molecules."

When the energy transfer to the solvent from the exothermic ring opening was tracked, exactly as described above for the simple model, the results showed clear signs of the inertial effect of the solvent, as shown in Figure 9. The non-monotonic behavior seen at ≈ 100 fs in Figure 9 is the result of inertial

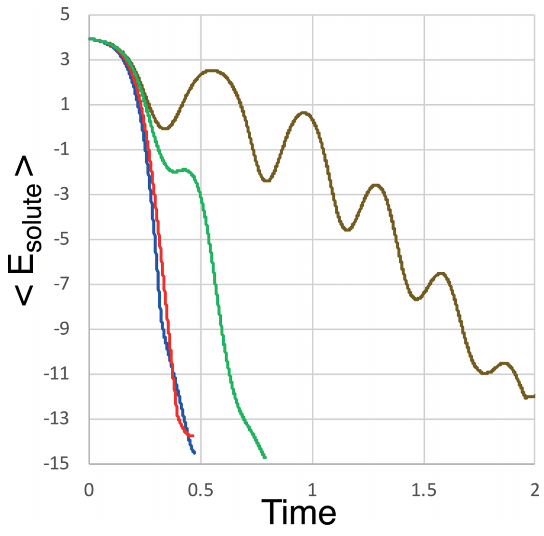


Figure 7. Total (potential + kinetic) energy of the model solute as a function of time for different reduced masses of the model solvent. The solvent reduced masses are 0.1 for the blue line, 1 for the red line, 10 for the green line, and 100 for the brown line. The reduced mass of the model solute is 1 for all lines.

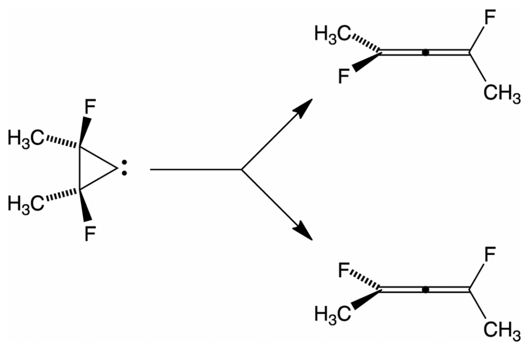


Figure 8. A carbene ring opening that has been simulated by molecular dynamics in a variety of solvents. The products are enantiomeric allenes.

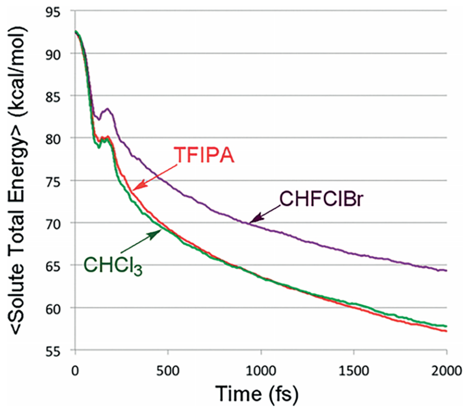


Figure 9. Total solute energy for the ring opening of the carbene shown in Figure 8 for different solvents. TFIPA is 1,1,1-trifluoroisopropyl alcohol. Reproduced from ref.[42b] with permission from the Royal Society of Chemistry.

effects of the solvents, and is, to a good approximation independent of the nature of the solvent. The high reduced mass for the solvent in the simple model which reproduced this effect is seen to be a surrogate for the collective effect of a whole shell of solvent molecules in a real reaction. When there is a substantial change in shape of a reacting solute, it will not usually be possible to accommodate that by moving a single solvent molecule without affecting its neighbors. This is not a new discovery; like so many ideas in chemical dynamics this insight came first from Don Bunker,[41f] who was simulating the solution-phase photodissociation of I_2 and wrote in 1972: "The difficulty appears to be that even though cage recombination involves a single smooth maximum in the I–I separation, there are not one but several struck solvent molecules. Thus, as we have verified by inspection of the trajectories, practically all solvents have high net momentum-carrying capacity and behave as if they were made of massive molecules."

Importantly, the transient, strong interaction between solvent and solute, caused by the solvent's inability to respond fast enough to the changes of geometry of the solute, has an influence on more than just energy transfer. As implied in Figure 8, the reaction coordinate for ring opening of the carbene bifurcates,[42a] with the two branches leading to opposite enantiomers of the allene product. The collisions between solute and solvent responsible for the anomalies in the energy transfer profiles occur just as the trajectories are approaching the bifurcation and can influence which branch of the reaction coordinate is selected. For achiral solvents, these effects average out, and so the product is racemic. However, when the solvent is chiral and optically pure the effects do not average out, and there can be a solvent induced enantiomeric enrichment. The simulations predicted that with enantiomerically pure 1,1,1-trifluroisopropyl alcohol as solvent, the enantiomeric enrichment would be about 15 %. Although modest by synthetic standards, this is nonetheless more than an order of magnitude larger than any solvent-induced enantioselectivity previously seen. It arises because the inertial solvent effect creates new barriers to reaction, which are not equivalent when the solvent is chiral.

The model that we have introduced here is designed to be scalable, which in the present case means that one can add terms to the potential energy function to represent further interactions within and between solvent and solute until, in the limit, one arrives exactly at the typical form seen for a force-field based molecular dynamics simulation of a solution phase reaction. At any level of complexity, the fact that both solute and solvent are represented atomistically means that a straightforward separation of potential energy terms into solute components, solvent components, and the coupling between them is always possible. The kinetic energies terms of the Hamiltonian can also be unambiguously assigned to solute or solvent.

Obviously, the more complex the model becomes the more accurate it should be, but the more difficult it will be to analyze the results and the more specific those results will be for the particular reaction under study. In the present article, we have restricted ourselves to the simplest possible form of the model, for which the results are expected to have the least specific accuracy but, we hope, the greatest generality. However, we note that, because the limit in complexity of our model would be a classical MD simulation, it is clear that the model cannot deal with quantum mechanical effects, and so will never supplant those models that do. More generally, we hope that the new model will be viewed as a possible addition to – not a replacement for – the extensive research into modeling of solution phase reactions that has preceded it.

We believe that attempting to find the location of the true dividing surface is particularly important when the rate-determining step of a reaction is followed by branching to more than one product, whether in a bifurcating reaction coordinate, as just illustrated, or from a transient intermediate. Again, a simple model serves to illustrate the point. Figure 10 shows the contours for a symmetrical potential of the so-called "caldera" type.[16b] This particular version has very small potential energy barriers between the intermediate and the products. The question is what the product ratio is if one starts with reactant A.

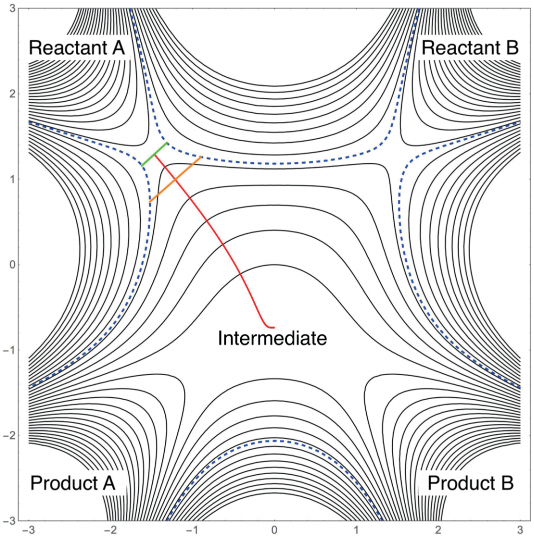


Figure 10. A symmetrical PES, linking two reactants to two products via a common intermediate. The red line is the intrinsic reaction coordinate from the upper left saddle point to the intermediate. The green line is a plausible dividing surface at the saddle point, for a total energy equal to that of the dashed contour. The orange line is another dividing surface, which might be appropriate if the reaction were subject to inertial solvent effects. See text for further discussion.

If one uses so-called statistical kinetic models, in which explicit dynamics have been averaged out, then any symmetry element on the PES must be expressed in rate constant ratios. In the case of the PES in Figure 10, this would mean that the ratio of products A:B would have to be 1:1, even if one started with pure reactant A. However, it is now widely recognized that reactions on this kind of potential are subject to a "dynamic matching" phenomenon, in which Newtonian momentum conservation favors the formation of product B from reactant A, and product A from reactant B.[43] This effect is so strong that if one samples the dividing surface at the upper left saddle point, whose projection onto the PES is shown by the green line in Figure 10, then none of the trajectories is found to give product A.

In practical (i.e. higher dimensional) examples of reactions that can be thought of as occurring on this kind of potential, the product ratio B:A will be finite. For example for the deazetization of 2,3-diazabicylo[2.2.1]hept-2-ene-*exo*,*exo*-5,6-d2, the product ratio is ≈ 5:1 in the gas phase,[44] but qualitatively the dynamic preference is still observed. Importantly for the present microreview, the ratio of products of this reaction was studied as a function of pressure in supercritical propane, and the product ratio was found to decrease as the pressure increased.[44] At the time, this was explained as collisional cooling of reacting molecules down into the central minimum on the PES. However, recent (as yet unpublished) molecular dynamics simulations of the reaction in supercritical propane suggest that the central minimum on the PES is too shallow to trap trajectories for long enough to explain the experimental observations in that way. An alternative explanation, consistent with both the MD simulations and experiment, is that the supercritical propane relocates the dividing surface in phase space, and does so in a way that is density (and hence pressure) dependent.

This effect, for the purposes of the present microreview can be illustrated on the low-dimensional PES shown in Figure 10. One can explore how the product ratio changes for different dividing surfaces. The answer is revealed in Figure 11, which shows the percentage of product B formed from reactant A, as the surface from which trajectories are initiated is moved down the reaction coordinate, towards the intermediate. Each dividing surface has a PES projection that is orthogonal to the IRC, and connects contours corresponding to the chosen total energy, such as the orange line in Figure 10. It is apparent the product ratio is strongly dependent on the correct location of the DS.

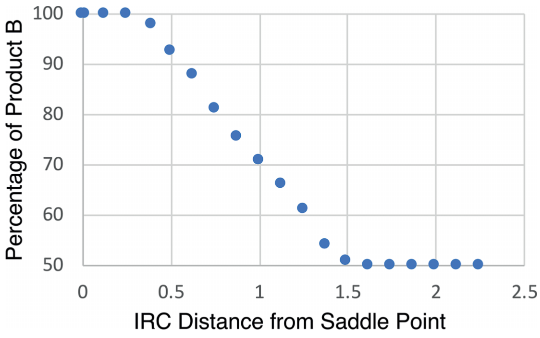


Figure 11. Consequences of relocating the dividing surface between reactant A and the intermediate on the product ratio, for the potential shown in Figure 10.

4. Conclusions and Future Prospects

In organic chemistry, a transition state is generally given a structural interpretation – essentially it is a molecule with one or more partial bonds. That picture may be modified but is not usually fundamentally changed for a reaction in solution, which is after all the medium in which almost all organic chemistry is conducted. In this microreview we have tried to emphasize that commonly occurring phenomena for reactions of organic molecules in solution can create dynamical barriers to reaction that are unrelated (or only weakly related) to this conventional picture. If projected onto the configuration space of the solute these barriers would typically not be sharply defined (because of the many possible solvent configurations of similar free energy), but importantly could occur far away from conventional transition states, even if the electronic interactions between solvent and solute were weak.

The existence of these dynamical barriers has long been recognized, and methods for calculating their effect have been developed. If one is interested in the best possible estimate of the rate constant for a single-step reaction, the rate constant for a single-step reaction, then methods such as GH theory that use a dividing surface located at an approximation to the TS and improve the TST rate constant by the calculation of the transmission coefficient may be sufficient. However, recognition that the real barrier to reaction might be far from the conventional TS (which would be signaled by a very small transmission coefficient) could be important if one were in the business of catalyst design, or more interested in product ratios than absolute magnitudes of rate constants.

We have argued for the importance of searching for the true dividing surface (or, at least a closer approximation to it), not only as a way to calculate the correct rate constant but also to adequately predict the behavior of the system after crossing the dividing surface. What we have not done, of course, is to discuss how to find the true dividing surface (or, more probably, multiple dividing surfaces for real chemical reactions in solution). This is a daunting task because the number of degrees of freedom rapidly becomes unmanageable even for the simplest systems. In fact, it has to be admitted that, at present, the methodology for extending the methods for finding the dividing surface in low-dimensional models to real, multidimensional systems does not exist. However, we still think that this is the right time to highlight the issues raised in this microreview. First, we hope that the low-dimensional model presented here serves to raise issues about the nature of transition states for solution-phase reactions. Second there is reason to be optimistic about new methods for the analysis of higher dimensional systems. Recent approaches have taken advantage of Lagrangian Descriptors (LDs) to locate the dividing surface in phase space for chemical systems.[45] LDs are a trajectory diagnostic for revealing dynamic structures in phase space. The methodology was originally developed for the study of Lagrangian transport in fluid dynamics.[46] The benefits of the methodology reside in the straightforward implementation and the evident interpretation of the data as it provides a “high resolution” method for exploring high dimensional phase space with low dimensional slices. The methodology relies on the study of the properties of trajectories to explore the phase space structures. The problem rests now in how to correctly perform the dimensionality reduction to study the system. This is a very active field of research in science and engineering, because so many physical problems rely on optimum interpretation of large, high-dimensional data sets. A good deal of progress has been made on the reduction of multidimensional configuration-space reaction coordinates to the optimal representations in two or three dimensions – see, for example, the work of Taketsugu.[47] The task for our purposes will be to extend that effort from configuration space to phase space. It seems very probable that machine learning techniques will play an important role in this research.[48]

Even if the optimum representation of the dividing surface in a reduced-dimensional phase space can be accomplished, one must admit that the result will *still* be an approximation. One might reasonably ask whether the effort involved would be worth it, given that existing methods can already give one approximate solutions to the problem.[49] Our point, is that the approach we advocate will offer a *different* approximation, and viewing complex physical problems from several different perspectives is generally a worthwhile task in the effort to gain deeper understanding.

In addition to advances in theoretical and computational methodology, there are an increasing number of experimental studies of solvent dynamics and its influence on reaction kinetics.[40,41,50] To date, most of these studies have been in polar solvents but more recently in nonpolar ones too. Of particular relevance to the understanding of thermal reactions are ultrafast studies that do not rely on the generation of electronic excited states.[41a] The combined application of ultrafast spectroscopy for experimental data molecular dynamics for the theoretical results, and now analysis methods such as LDs, holds out the hope that the proper representation of transition states for solution-phase reactions may be attainable in the not-too-distant future.

Acknowledgments

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Keywords: Transition states · Dynamic effects · Condensed phase · Kinetics · Computational chemistry

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[51] We alert the reader to a potential confusion of terminology. The term "inertial" has been used in several different ways in modeling of solution-phase reactions. It has been used to mean short time Gaussian time-dependence of the friction in GH theory, the free flight of the molecules at constant momentum, or specific short term evens in photochemistry (see, for example ref.[40]). In the present context, we are discussing thermal reactions for which initial transfer of energy from solute to solvent can be partially reversed as a result of inertial resistance of a collection of solvent molecules to change in geometry of the solute. It is this phenomenon that we refer to as an inertial barrier.

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