CHAPTER ONE

Beyond transition state theory—Non-statistical dynamic effects for organic reactions

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Contents

Abstract

Transition state theory (TST) is applicable to most reactions in most environments. However, some reactions do not adhere to its tenets. That does not mean is a bad model of reactivity, but rather that it is incomplete and therefore should not be wielded indiscriminately. Here, limitations of TST are outlined and general guidelines are given that should help one decide whether worry about applying TST is warranted for a given reaction.
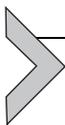
1. Introduction

1.1 Transition state theory (TST)

Transition state theory (TST) relates barriers of chemical reactions to their rates. It is generally applied to ground state reactions,[1] and those will be the focus here. For excellent reviews on TST, see references 2–5. TST and its relatives and variants (e.g., variational TST [VTST], Rice–Ramsperger–Kassel–Marcus [RRKM] theory and its extensions) are statistical theories, and the purpose of this review is to highlight *non-statistical behavior* in organic reactions, i.e., cases where currently available flavors of TST are not sufficient to rationalize or predict behavior. While the incorporation of tunneling is not covered here, it can be important for understanding reaction rates and can incorporated into both TST and non-TST models.[2–6]

1.2 Assumptions that are not always valid

Several assumptions associated with TST have been shown to be invalid for some organic reactions.

First, TST models generally assume that a *transition state* can be associated with a surface that separates reactants from products, a so-called *dividing surface*, whose position is such that recrossing is minimized (zero in classical TST, minimal in VTST). *Recrossing* is a term for a reaction *trajectory* that crosses a dividing surface more than once, e.g., a (reactant → product side of dividing surface → reactant side of dividing surface) trajectory. While recrossing is not forbidden in VTST, it is generally assumed that it does not play a significant role in most organic reactions. In some cases, however, it does.

Second, TST models assume that when a reaction trajectory approaches a minimum, it thermally equilibrates before exiting the minimum and proceeding to product. This concept can be restated as *intramolecular (internal) vibrational energy redistribution (IVR)* at a minimum being rapid. However, in cases where barriers out of a minimum toward a product are low (i.e., the energy surface is relatively flat), progression toward product might be faster than equilibration/IVR if the vibrations leading to a particular product are coupled to those involved in forming the minimum (i.e., momentum favors departure from the minimum). This phenomenon is called *dynamic matching*.[5]

Third, TST models are based on the idea that behavior of trajectories between transition states and products (post-transition state behavior) does not affect rates of product formation. This assumption leads to (usually applicable) models of *kinetic selectivity* where the relative free energies of two competing transition states are related directly to the distribution of the two products to which they are connected. However, some reactions have been shown to involve *post-transition state bifurcations (PTSBs)*,[7,8] i.e., potential energy surface (PES) pathways that connect a single *transition structure* to two products without intermediate minima. Such a scenario is not accounted for by TST.

1.3 When should one suspect that TST is not sufficient?

When should one expect that TST is not sufficient for describing a reaction? Based on the ever-growing body of examples of reactions for which non–TST (non-statistical) behavior has been shown to be important, some features of reactions that should at least prompt one to look for non–TST behavior can be noted. First, unexpected products, or unexpected relative amounts of expected products, can arise because of non–TST effects. While both may arise from effects covered by TST, one should not assume that TST holds all the answers. Second, when a reasonable mechanistic proposal (reasonability is, of course, subjective) for a reaction involves an intermediate, but barriers for conversion of this intermediate to products are likely very low, the lifetime of the intermediate may be shorter than the time required for thermal equilibration, allowing dynamic matching to play an important role. Third, when an intermediate is expected to reside on a flat region of a PES, because, for example, large structural (often conformational) changes are likely facile, momentum effects may dominate, since barriers large enough to lead to thermal equilibration are not present.

What types of observations from laboratory experiments might hint at non–TST behavior? Usually, non–TST behavior is postulated when experimental observations are not in line with computed results. But what types of discrepancies might be encountered? Experimental ratios of competing products not matching those predicted based on computed relative free energies of transition states is the most common sort of discrepancy. But one should be cautious in jumping to the conclusion that this disagreement between experiment and theory indicates important non-TST effects. First, one should be sure that the level of theory used for computing free energies

is appropriate based on benchmarking.[4,9] Second, one must consider whether or not solvent (assuming one is examining a reaction occurring in solution) is adequately treated; how best to do so is an active area of research.[10] Third, one must make sure that all relevant conformations of the competing transition structures are accounted for (located via conformational searching and weighted based on their free energies).[11] Fourth, one should consider whether transition structures located by PES exploration, i.e., in terms of electronic energies, might not be good representations of "real" transition states, i.e., free energy should be accounted for. Doing so with standard methods built into quantum chemical software packages can be dangerous,[12] and various methods for calculating *variational transition states (VTSs)*[3] and correcting for problems with the use of harmonic vibrational frequencies are known.[13,14] Fifth, one must remember that the practice of comparing free energies of transition state structures is only valid when barriers for the reaction steps in question are relatively high (c.f., the Curtin-Hammett principle);[15] if not, then more complex kinetic modeling, still based on TST, may resolve the discrepancy.[15,16] Once this gauntlet has been run, one can feel more (but not completely) confident that non–TST effects play a role.

1.4 Entropic intermediates

As noted by Houk et al. in an account describing the history of *entropic intermediates*, "An entropic intermediate is defined as a free energy minimum that is not a potential energy minimum; the favorable entropy in this region of the potential surface is responsible for the increased lifetime of this species."[17] Given this definition, such species tend to reside on relatively flat regions of PESs, since such regions are associated with approximately constant enthalpy, thereby allowing entropy differences to have important effects. Consequently, the entropic intermediate concept can explain dynamic behavior, e.g., unusually long residence times for structures that have no potential energy barrier restricting their motion. This effect can result in large amounts of recrossing and can affect how reacting molecules navigate post-transition state bifurcations, both of which are described below.

2. Characterizing non-TST effects
2.1 Ab initio molecular dynamics (AIMD)

How then, does one characterize non-TST effects? The most common approach is to run *ab initio molecular dynamics (AIMD) simulations*. In these simulations, trajectories are propagated in time using classical mechanics

and forces computed with quantum chemistry.[18,19] While a *minimum energy path (MEP)* or *intrinsic reaction coordinate (IRC)* captures a pathway on a PES, i.e., how energy changes as a structure morphs from reactant to product, it does not capture the time taken to traverse such a path nor does it capture deviations from that path due to molecular vibrations that are activated at a given temperature.[20,21] AIMD simulations capture these, and in doing so, allow momentum effects to be expressed. Of course, AIMD simulations can capture dynamic effects that are in line with TST as well as those that are not. While technical details of running AIMD simulations can be found elsewhere,[18,19] several general principles are discussed here.

In running AIMD simulations, one can include (quasiclassical) or neglect (classical) zero point energy.[22–24] One can initiate trajectories at a transition state (downhill dynamics) or at a minimum (uphill dynamics). The former approach is faster, but requires one to have located a transition state (based on optimization of a first-order saddle point on the PES, a VTS, etc.) that is thought to be relevant. The latter approach can be run without bias toward a particular type of mechanism, but doing so generally leads to unfeasible simulation times, since bond-making and -breaking events are rare. Various methods for accelerating uphill dynamics simulations are available,[25–27] but these introduce bias toward particular mechanisms. The two most popular MD approaches used to study organic reactions are Born–Oppenheimer MD (BOMD) and Car–Parrinello MD (CPMD). In the former, a wavefunction is solved for at every time step,[18,19] while in the latter, the wavefunction is propagated dynamically.[28]

2.2 Simulation results

What is one looking for in AIMD results? The following observations are common: (1) Progress through the region of a postulated intermediate in a short ($< \sim 100$ fs) time is an indication that complete IVR has not occurred and therefore dynamic matching may play a role. In some cases, two distinct populations of trajectories are found, one where product formation is fast and another where it is slow, the former generally corresponding to dynamically matched trajectories. (2) Given that most trajectories remain in the vicinity of an IRC, observation of trajectories that do not indicates that momentum effects are likely moving reacting molecules away from minimum energy paths. (3) If one suspects that a PTSB exists, then the two products expected from the PTSB should be formed in subsets of the ensemble of trajectories initiated from the single transition state region. (4) Lingering near a particular structure when no barrier to continue forward is expected

can indicate that the structure in question is an entropic intermediate. While the presence of entropic intermediates sometimes is predicted without AIMD simulations, e.g., using VTST,[3] they are more commonly found using MD. Note also that the presence of an entropic intermediate does not necessarily indicate non-TST behavior, so looking for such species could be included with the list of things to check before jumping to conclusions. (5) AIMD calculations readily allow one to estimate the amount of recrossing in a reaction simply by counting how often trajectories pass from the product side of a transition state region to the reactant side. If a large ($> \sim 10\%$) percentage of recrossing is observed, then non-TST behavior might be playing a large role. A large percentage of recrossing also may indicate, however, that trajectories were not initiated from the correct region (e.g., the PES transition structure used to initiate trajectories differs considerably from the associated VTS).

It is important to remember that, in all of these cases, the confidence with which one proposes a non–TST effect is related to the number of trajectories obtained—the more trajectories the better, but AIMD calculations can be very expensive in terms of human time and computational resources. To be safe, one should run enough trajectories that the results converge, i.e., adding more trajectories does not change one's conclusions. That means that different numbers of trajectories are required to arrive at quantitative rather than qualitative conclusions. For many organic reactions, $\sim 10^2$ trajectories are enough for the latter, but 10^3–10^4 trajectories can be required for the former. In addition, one should carefully examine geometric/electronic changes along trajectories in detail if one cares about the origins of non-TST effects. While this may seem obvious, it is non-trivial to compare structures from hundreds of trajectories, each involving hundreds of time points. It is also not trivial to present such data. Consequently, many different approaches have been used for both.[17,29,30]

2.3 The relationship between experiment and theory

What about laboratory experiments? In general, AIMD results that reproduce laboratory results when statistical models do not are taken as strong (although not necessarily definitive) support for non-TST effects. Predictions from AIMD simulations on reactions not yet tried in the lab can readily be made and put to the test, if experimentalists are up for synthesizing the necessary reactants and running the reactions. As noted above, the results in question are usually ratios of products obtained under kinetic conditions.
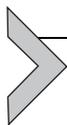
3. Representative examples

3.1 Dynamic matching

The seminal example of dynamic matching in organic chemistry comes from the work of Carpenter on the formal [1,3]–sigmatropic rearrangement that interconverts norbornene and bicyclo[3.2.0]hept-2-ene (Fig. 1).[31] The results of MD simulations on this reaction indicated that, although this reaction involved a minimum on the PES corresponding to a biradical, inversion of configuration at the migrating carbon (C1′) predominated. This preference was associated with two distinct types of MD trajectories: slow trajectories that lingered at the biradical long enough for IVR to occur and fast (direct) trajectories that spent little time at the biradical. The latter result from momentum that carries the reacting species on to product without significant IVR. As stated by Carpenter, "A substantial fraction of biradicals are prepared with internal energy already localized in the reaction coordinate for the next step, and so they pass very rapidly through the region of the local minimum on the potential energy surface. It is perhaps helpful to use the term "dynamic matching" to describe what is occurring in the fast inversion trajectories. The implication of this phrase is that some molecules enter the biradical region on the potential energy surface with intramolecular dynamics matched to the reaction coordinate for their exit." Dynamic matching is the key concept applied in most studies to understand non–statistical dynamic effects, although it can be difficult to characterize the distribution of energy in a reacting molecule and pin down the vibrations that are "matched."

A more subtle example of the importance of dynamic matching is found in studies of alkene hydroboration (Fig. 2). Various models have been applied to explain the origins of the experimentally observed selectivity for this reaction,[4,32,33] and those models that are most predictive (retro- or prospectively) incorporate both fast reacting/direct (non–statistical) trajectories that proceed rapidly past intermediates, since their excess energy
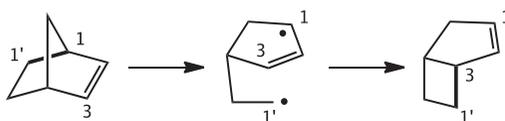

Fig. 1 The [1,3]-sigmatropic rearrangement that interconverts norbornene and bicyclo[3.2.0]hept-2-ene. The bonds broken (1–1′) and formed (3–1′) are bold.
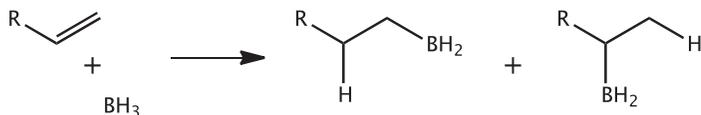
Fig. 2 Alkene hydroboration. Alkyl groups (R) of various sizes and shapes were studied.

can be used for dynamic matching, as well as slower (statistical) trajectories that are not dynamically matched and can therefore undergo IVR and/or energy transfer (cooling) with solvent before proceeding to products. In the case of alkene hydroboration, the non-statistical trajectories decrease selectivity, to varying degrees depending on the size and shape of the attached alkyl group, consistent with the fact that conventional TST models overestimate experimentally observed selectivity in this case.

3.2 Post-transition state bifurcations (PTSBs)

The product selectivity for a reaction with a transition structure followed by a bifurcating pathway to two products, i.e., possessing a PTSB, is controlled by dynamic effects.[7,8] This principle assumes, however, that, in addition to the fact that the PES for the reaction lacks minima between the transition structure and the two products (thereby marking the transition structure as *ambimodal*), there are also no entropic intermediates. It also assumes, of course, that the approximations employed in the modeling that revealed the PTSB (e.g., basis set, treatment of solvent, etc.) are reasonable. Three representative examples of reactions with PTSBs follow—one relevant to synthetic organic chemistry, another relevant to natural products biosynthesis, and another relevant to polymer chemistry—highlighting both that reactions with PTSBs are widespread and that MD simulations accounting for momentum can effectively predict product distributions for such reactions.

The reaction shown in Fig. 3, modeled by Burns and Boittier, is an example of a *bispericyclic* reaction.[34] A single transition structure is connected to products of both $(4+3)$ and $(5+2)$ cycloadditions (these two products can interconvert via a [3,3] sigmatropic shift).[35] AIMD simulations on this system indicated a very slight preference for the $(4+3)$ product, consistent with experimental results. This theoretical study also highlighted the value of considering secondary orbital interactions (SOI) when predicting whether or not PTSBs are likely for pericyclic reactions.[36,37] Houk et al. have done extensive work on this topic as well, culminating in a recent report postulating that *endo* higher order cycloadditions generally have ambimodal transition structures.[38]
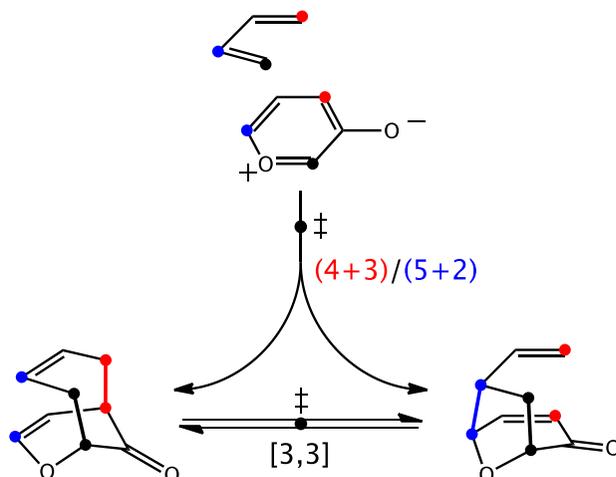
Fig. 3 A bispericyclic reaction. Black dots indicate the atoms that conjoin en route to both products, while blue and red dots indicate where bonds will form in one or the other product following the PTSB.

The reaction shown in Fig. 4 has been postulated to occur during the biosynthesis of the diterpene natural product abietadiene.[39–41] The presence of a PTSB for this reaction was proposed on the basis of PES calculations in which a region of the IRC following the initial transition structure was flat (i.e., roughly constant energy). A second transition structure that interconverts the two products shown was located by searching in this flat region.[39] Subsequently, AIMD calculations provided further support for the presence of a PTSB and showed that there exists an inherent (substrate alone, no solvent or enzyme present) dynamical preference for formation of the product that has the carbocyclic skeleton present in abietadiene, rather than the alternative product, whose carbon skeleton has not yet been reported in a natural product. This dynamical preference was associated with torsional motion around the C_{sp2}–C_{sp3} bond in the reactant. A wide variety of other biosynthetic reactions have since been shown to involve PTSBs, including many bispericyclic reactions.[8,42]

The fragmentation reaction shown in Fig. 5, a truncated model of the force-induced "unzipping" of polyladderane polymers, was studied experimentally by Burns, Xia and co-workers and modeled by Martinez and co-workers.[43] Force-modified PESs were examined, and increasing applied force led from a PES with a shallow bis-allyl radical intermediate to a PES with a PTSB. AIMD simulations for the bifurcating reaction predicted that
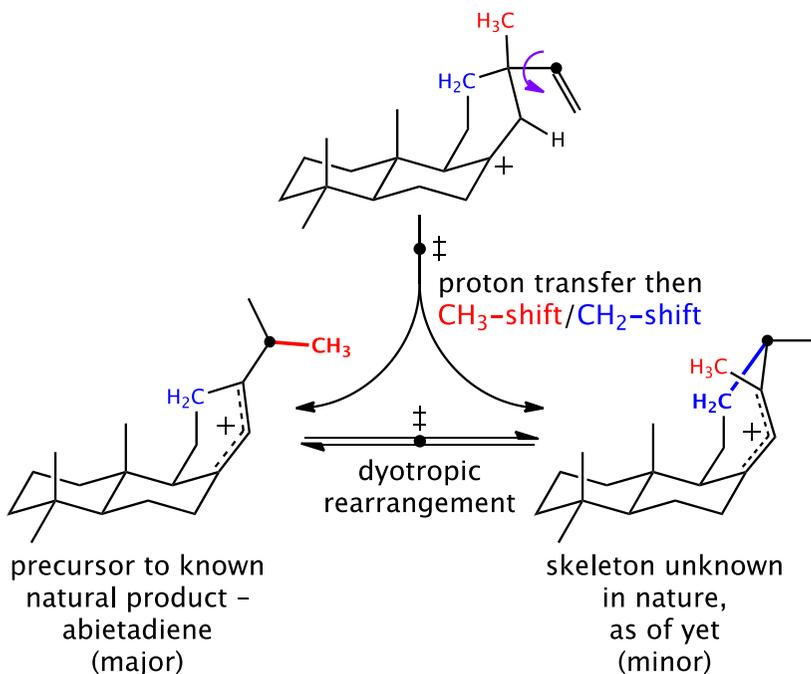
Fig. 4 A biosynthetic reaction with a PTSB. One of the blue and red groups migrate one either side of the PTSB. Torsional motion around the purple bond is key to which product is formed.
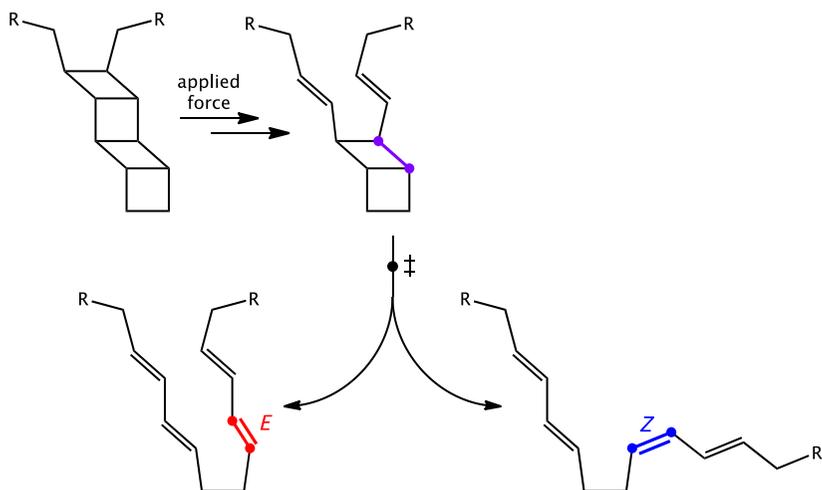

Fig. 5 A PTSB involved in force-induced ladderane fragmentation. Torsional motion around the purple bond is key to which product is formed. A transition structure for product interconversion was not described in this case.

the E alkene product should predominate over the Z alkene product (ratios near 3:1, depending on the specific force applied), consistent with experimental observations. This preference was ascribed, in part, to momentum associated with rotation around the C—C bond that becomes the E or Z double bond.

3.3 Recrossing

A classic example of the importance of recrossing comes from Singleton and coworkers' study of ketene/alkene cycloadditions (Fig. 6).[44] This reaction involves asynchronous formation of the two new C—C bonds. A $^{12}C/^{13}C$ kinetic isotope effect (KIE) was observed for this reaction that indicated that the heavier carbon isotope preferentially ended up α rather than β to the carbonyl group in the product. KIEs calculated using the PES transition structure did not reproduce this result. Careful examination of the PES for this reaction at various levels of theory led to the proposal that a PTSB was involved, with one branch leading to the product with ^{13}C α to the carbonyl and the other branch leading to the product with ^{13}C β to the carbonyl. However, the majority of trajectories initiated from the transition structure recrossed the transition structure region and headed back toward reactants. In terms of free energy, an entropic intermediate (with only one new C—C bond [largely]
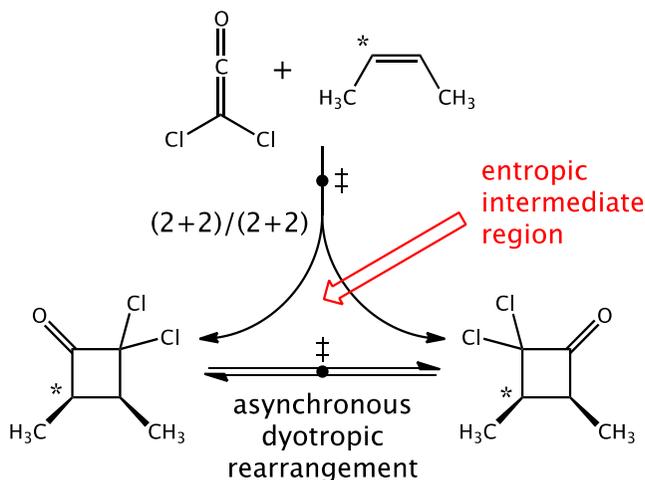

Fig. 6 A PTSB involved in dichloroketene + *cis*-2-butene cycloaddition. The isotopically labeled carbon atom in the laboratory experiments is indicated by an asterisk. An entropic intermediate was revealed when free energy rather than potential energy was considered.

formed) was found, blocked from direct formation of either product by barriers arising from entropy rather than enthalpy. The observed KIE was consistent with dynamic matching that selectively enhanced escape from the entropic intermediate toward one product over the other. In summary, a large amount of recrossing pointed to the possibility of an entropic intermediate, not itself in conflict with TST, but the amount of recrossing was determined by a non-statistical dynamic effect.

In a recent study on the Schmidt reaction (Fig. 7), differences in the amount of recrossing predicted for closely related transition states was described.[45] Although the total amount of recrossing decreased when VTSs, rather than PES transition structures were used to initiate AIMD trajectories, a difference in recrossing percentages persisted, indicating that differential dynamical tendencies to recross can impact kinetic selectivity in cases not involving PTSBs.

3.4 Roaming

Roaming is a non-statistical dynamic effect generally associated with unimolecular dissociation reactions.[46] When a molecule fragments, the two resulting pieces possess momenta. While the momenta often lead to
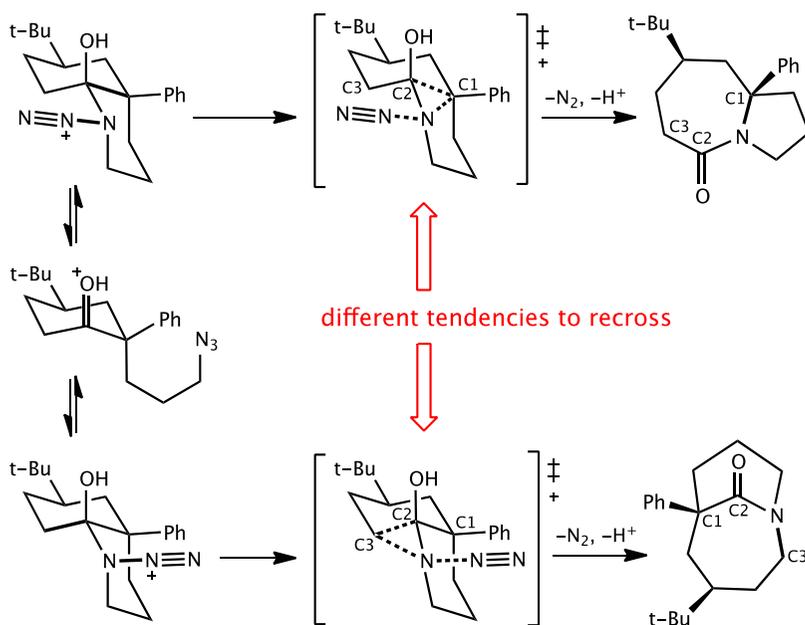

Fig. 7 Competing Schmidt reactions for which different tendencies to recross were observed in AIMD simulations for competing transition states.
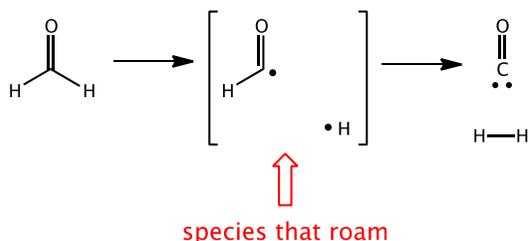
species that roam

Fig. 8 Roaming in formaldehyde fragmentation.

dissociation, in some cases, the two pieces "roam" around for a long time and then come back together. The seminal example of roaming involves fragmentation of formaldehyde (Fig. 8), studied by Moore, Suits, Bowman and co-workers.[47] In this case, homolytic dissociation of a C—H bond leads to two radicals that ultimately come together in a reaction that forms CO and H_2. While roaming does not predominate, it does make a significant contribution to the product distribution. Roaming is most significant for gas phase reactions,[46] since solvent molecules are not present to damp vibrations of the fragments, but conceptually similar models are relevant to solution reactions involving flat energy surfaces.[48]
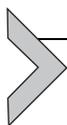
4. Concluding remarks

While TST is applicable to most organic reactions, some reactions are not adequately described by TST, including reactions with PTSBs and flat PESs. In such cases IVR is too slow to squelch momentum effects. Characterizing such reactions through AIMD simulations is becoming ever more common, but this approach is sometimes not straightforward to implement and converting results to meaningful, useful models of reactivity and selectivity is challenging. Still, a *phase space view of organic reactivity*, i.e., one that includes momentum effects,[5,10] has already proven useful in rationalizing and predicting reaction outcomes.

Acknowledgments

Glossary
Ab initio molecular dynamics (AIMD) simulations Simulations in which trajectories are propagated in time using classical mechanics and forces computed with quantum chemistry.

Ambimodal Denotes a transition structure preceding a PTSB.

Bispericyclic Denotes a pericyclic reaction involving a PTSB.

Dividing surface A surface whose position is such that recrossing is minimized (zero in classical TST, minimal in VTST).

Dynamic matching The coupling of vibrations leading to a particular product with those involved in forming the minimum that precedes it.

Entropic intermediate A minimum in terms of free energy but not in terms of enthalpy alone.

Intramolecular (internal) vibrational energy redistribution (IVR) Process by which energy is redistributed within a molecule between vibrational states.

Intrinsic reaction coordinate (IRC) MEP from a transition structure toward minimum, in mass-weighted coordinates.

Kinetic selectivity Selectivity arising from the difference in the relative free energies of two competing transition states.

Minimum energy pathway (MEP) Steepest descent pathway from a transition structure toward a minimum.

Non-statistical behavior Behavior not that cannot be rationalized or predicted with available flavors of TST.

Phase space view of organic reactivity Framework for discussing reaction trajectories that includes momentum effects.

Post-transition state bifurcations (PTSBs) PES pathways that connect a single transition structure to two products without intermediate minima.

Recrossing When a reaction trajectory crosses a dividing surface more than once.

Roaming When dissociation leads to recombination after a long time.

Trajectory The motion of a molecule, here from reactant to transition state to product.

Transition state Collection of structures at a dividing surface. In many cases also used (for better or worse) to describe a transition structure when thermal and entropy corrections to its potential energy have been added.

Transition structure First-order saddle point on a PES.

Variational transition state structure (VTS) The structure along a reaction coordinate that is highest in free energy.

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