# Portable Models for Entropy Effects on Kinetic Selectivity

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**ABSTRACT:** Differences in entropies of competing transition states can direct kinetic selectivity. Understanding and modeling such entropy differences at the molecular level is complicated by the fact that entropy is statistical in nature; i.e., it depends on multiple vibrational states of transition structures, the existence of multiple dynamically accessible pathways past these transition structures, and contributions from multiple transition structures differing in conformation/configuration. The difficulties associated with modeling each of these contributors are discussed here, along with possible solutions, all with an eye toward the development of portable qualitative models of use to experimentalists aiming to design reactions that make use of entropy to control kinetic selectivity.

"...the incorporation of the entropy concept into chemistry was anything but smooth. Its assimilation was slow and met with much resistance, overt and otherwise."<sup>1</sup>

# KINETIC SELECTIVITY

The concept of controlling kinetic selectivity by lowering the free energy of a transition state leading to a desired product relative to that of a transition state leading to an undesired product is well established.<sup>2</sup> Why then is it so difficult to rationally control, i.e., predict, kinetic selectivity for many reactions? Here the contribution of an ever-present factor that is difficult to quantify—entropy—is examined. Difficulties with handling entropy are faced not only by those looking for back-of-the-envelope predictions but also by those carrying out state-of-the-art computations on reaction mechanisms.

# DISORDERLY CONDUCT

While describing entropy as disorder is generally frowned upon in the world of physical chemistry (and by the author), that concept is applied broadly. In the realm of selectivity control of organic reactions, it often manifests as more conformationally flexible transition states being entropically preferred. Of course, this factor also can be described in the language of accessible microstates, more conformationally flexible species possessing more of them. To me, the key distinction between these descriptions is that the former is often abstract (think handwavy), while the latter involves counting (Figure 1). I often think of enthalpy as "how much" and entropy as "how many".

Nowadays, we are excellent at computing relative enthalpies using quantum chemistry,<sup>3,4</sup> but counting how many is more difficult—why is that? As noted in a recent essay by Grimme and Schreiner on "expected developments and challenges [in computational chemistry] for the next 25 years [starting in 2018]", "a [...] problem of [...] enormous complexity is the accurate computation of entropy for which basically no routine methods exist."<sup>4</sup> Some of the problems that hamper applied theoretical chemists pursuing portable,<sup>5</sup> predictive models of



**Figure 1.** Graphic for a t-shirt created by the author showing a subset of the possible microstates created by combining the letters in the word "entropy."

kinetic selectivity are described here, along with some possible solutions. The focus here is on the reacting molecules. Of course, for many reactions of interest, these molecules are surrounded by solvent molecules. The pitfalls associated with modeling contributions to entropy from solvation have been discussed elsewhere,<sup>6</sup> and Plata and Singleton's discussion of these issues in the context of modeling a typical organic reaction provides an excellent jumping-off point for interested parties.<sup>7</sup>

# PROCEED WITH CAUTION

Focusing only on electronic energy or enthalpy is, of course, dangerous. Two classic cases where neglecting entropy leads to erroneous mechanistic conclusions are highlighted in Figure 2. In Figure 2a is shown a scenario where, in terms of enthalpy, a reaction is barrierless but, in terms of free energy, has a barrier. This scenario is not uncommon for bimolecular addition

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**Figure 2.** Comparison between reaction coordinate curves without (red, bottom) and with (blue, top) entropy included for (a) a reaction with a barrier due only to entropy and (b) a reaction with an entropic intermediate.

reactions where bonds are made and not broken, for example, the carbene addition shown in Figure 3a,b.<sup>8</sup> Since two molecules are coming together, entropy is reduced. In Figure 2b is shown a scenario where, in terms of enthalpy, a reaction is concerted, but, in terms of free energy, has an intermediate. Since this intermediate results from the entropic component of free energy rather than the enthalpic, it is termed an "entropic intermediate".<sup>9</sup> An example of an entropic intermediate relevant to an organocatalyzed cycloaddition is shown in Figure 3c,d.<sup>10a</sup> Evidence for entropic intermediates can be obtained through ab initio molecular dynamics (AIMD; also called direct or on-thefly dynamics) simulations,<sup>11</sup> where relatively long lifetimes are observed for structures without enthalpic barriers to proceed toward products.<sup>9</sup> Whether or not an entropic intermediate is actually formed, AIMD simulations can be used to characterize slowing due to unfavorable entropic effects associated with favorable enthalpic effects, a phenomenon referred to (when the favorable enthalpic effects are electrostatic in nature) as "electrostatic drag" (Figure 4).<sup>12</sup> While electrostatic drag occurs at very short time scales, entropy-enthalpy compensation pervades chemistry and should never be forgotten: whenever one does something to help enthalpically, one must consider the entropic consequences.<sup>126</sup>

These discussions focused on the vertical axis of a reaction coordinate diagram, i.e., energy. The presence or absence of the entropic part of free energy also affects what is going on in the horizontal dimension. For example, as shown by the dashed line in Figure 2b, the structure (position along the horizontal axis) of the highest energy point along the reaction coordinate also can



Figure 3. (a) Reaction without an enthalpy barrier that possesses a free energy barrier. (b) Reaction coordinate diagram for reaction in (a) where reaction coordinate is defined as distance for one of the forming C–C bonds. Adapted from ref 8. Copyright 1984 American Chemical Society. The size of some labels was increased for clarity. (c) Reaction with an entropic intermediate. (d) Reaction coordinate diagram for reaction in (c). Reprinted from ref 10a. Copyright 2012 American Chemical Society.



Figure 4. Example of electrostatic drag from ref 12a.

change when entropy is taken into accounted. This change in structure can be important when designing a catalyst, for example, or when deciding how to initiate downhill AIMD simulations. The highest point in free energy is called the "variational transition state" and is associated with minimal dynamical recrossing.<sup>13</sup> In Figure 2b, for example, if one initiated AIMD trajectories from the transition structure on the potential energy surface (PES) and ran them toward the reactant, one would expect to get a large amount of recrossing because the variational transition state would be uphill from the starting point.

A few words about "transition state" versus "transition structure". While these terms are often applied fairly loosely, PATHWAY WIDTH

As described above, the curvature of a PES in a direction orthogonal to a reaction coordinate is related to entropy. As stated eloquently by Campbell and co-workers, "An enthalpy change is associated with a change in the energy of a minimum and maximum in the potential-energy surface for the reaction, whereas an entropy change reflects only a change in the curvature of that potential-energy surface about a maximum or minimum (i.e., the freedom of motion of that species)."<sup>21</sup> How might this factor be expressed in AIMD simulations for competing reactions?

Consider the case shown schematically in Figure 6a, in which the reaction coordinate leading to one product is (approx-



**Figure 6.** (a) PES for a reaction with two transition structures of equal potential energy/enthalpy but different entropy. (b) Reaction possessing such a PES.

imately) orthogonal to that leading to a competing product and the transition structures have (approximately) the same energies on the reaction's PES. Selectivity here then should be related to the width of the pathway to each product. Measuring this width is not straightforward, e.g., at which height should one measure? But one can run AIMD trajectories initiated at the reactant (uphill) and see how many make it to each product. More are expected to reach the product via the wider pathway, since there are more ways (counting again) to get through the transition state region.<sup>22</sup> This type of scenario was described recently for the reaction shown in Figure 6b, where the two approximately orthogonal reaction coordinates corresponded primarily to formation of the  $C_a - C_b$  and  $C_a - C_c$  bonds and a greater number of uphill AIMD trajectories were found for passage through the wider transition state region.<sup>23</sup> This viewpoint connects PES shape to dynamic behavior to entropy. In doing so, it provides an avenue for both rationalization and design based on entropy if the structural changes associated with PES shape can be readily assessed (not always the case!).

# PES PROBLEMS

Visualizing a PES for all but the simplest reactions can be exceedingly difficult. What makes a reaction "simple" here? A small molecular size, symmetry, conformational rigidity—all characteristics not possessed by many reactions of interest. Why does the absence of these features complicate construction of a PES? The answer is simple: degrees of freedom. Molecules have

they are used here as recommended by Tuñón and Williams (and others).<sup>14</sup> Transition structure is used to describe a firstorder saddle point on a PES. Transition state is used to describe the collection of structures encountered near a transition structure. While an intrinsic reaction coordinate (IRC)<sup>15</sup> is on a PES and passes through a transition structure, AIMD trajectories are not and do not. As a bundle, they comprise a transition state when they pass through the "dividing surface" that separates reactants from products (and minimizes recrossing).

# LOCAL FLEXIBILITY

So, if one wishes to associate a free energy with a point on a PES, one must account for entropy. How does one obtain this local entropy correction?<sup>16</sup> Doing so involves accounting for the vibrational states of the stationary point (including zero-point energy), leading to the (ro)vibrational entropy. For a transition structure, these would not include the reaction coordinate (imaginary vibration). The problem generally encountered here is that these vibrations are anharmonic, but modeling them as such is prohibitively expensive. To do so requires mapping out the local region of the PES with respect to all degrees of freedom–a daunting task for all but the smallest molecules (*vide infra*). Consequently, harmonic potentials are generally used as approximations (Figure 5), and the quality of these approx-



**Figure 5.** (Left) Typical depiction of the portion of a PES leading to a transition structure (marked with ‡). The IRC is highlighted in red. (Right, top) Anharmonic potential curve orthogonal to the IRC from the PES at left with vibrational energy levels indicated. (Right, bottom) Harmonic approximation of this potential curve.

imations is translated directly into the quality of the estimate of the entropy contribution to free energy. Note that not only the shape of the potential curve differs in harmonic and anharmonic treatments but also the spacing between vibrational levels, i.e., the vibrational density of states.

What can be done to improve this situation? First, the harmonic approximation is generally worse for low frequency vibrational modes (a low frequency is associated with a flat slice of the PES).<sup>17</sup> Consequently, some recommend setting all frequencies less than 100 cm<sup>-1</sup> to 100 cm<sup>-1</sup> (the quasi-harmonic approximation).<sup>18</sup> Others recommend the rigid-rotor-harmonic-oscillator (RRHO) approach (and its extensions), where low-lying vibrations (<100 cm<sup>-1</sup>) are treated as internal rotations.<sup>19</sup> As mentioned above, one also could model the relevant region of the PES explicitly,<sup>20</sup> although this approach is not feasible for molecules with more than a few degrees of freedom. Others recommend making no corrections.

many (3N-6 internal degrees of freedom, if not linear, where N =number of atoms), but we, as humans, can generally only handle visualizing one or two plus energy, as in the PES plots shown above. So the aim is to create reduced/low-dimensional plots. In some cases, one or two degrees of freedom dominate the structural changes that occur along a reaction coordinate-say, the lengths of two forming C-C bonds in a Diels-Alder reaction or the forming and breaking  $\sigma$ -bonds in an S<sub>N</sub>2 reaction-but often more than two degrees of freedom are important.<sup>24</sup> What does one do in the latter case? One could use all three Cartesian axes for different degrees of freedom and code energy with color, but that requires a different way of wrapping one's mind around PES landscapes and only gets us one additional degree of freedom. One could construct multiple plots highlighting subsets of the important degrees of freedom, but then connections between them are lost. One could combine degrees of freedom into "collective variables," but this again obscures connections between degrees of freedom. This third approach is taken to the extreme in an IRC plot in which all structural changes are boiled down into a single "reaction coordinate" variable.

How does one determine which degrees of freedom are most "important"? Importance here is subjective and often defined based on the intuition of the researchers carrying out a study. One suspects, for example, that changes to a particular degree of freedom might correlate with changes to selectivity and then pursues that hypothesis. Recently, Carpenter and co-workers described an alternative, unbiased, approach in which principal component analysis (PCA) was used to determine "the reduced dimensional space that captures the most structural variance in the fewest dimensions".<sup>25</sup> Their software, called *PathReducer*, can be applied to both IRCs and MD trajectories.<sup>26</sup>

Even if one can identify key degrees of freedom, it can be difficult to construct useful PESs. A typical approach involves carrying out a series of constrained structural optimizations for various values of those key degrees of freedom. In some cases, however, discontinuities in such plots arise, as other degrees of freedom change dramatically during such optimizations (e.g., Figure 7; in addition, discontinuities can arise from changes to



**Figure 7.** Two PESs (from the author's group) for which discontinuities were encountered during construction. Some of these discontinuities are highlighted.

the number of real frequencies). In these cases, one sometimes constrains other degrees of freedom, but that of course introduces other approximations of which one must be conscious when interpreting results. Methods involving interpolation between well-chosen points on PESs have shown promise, but these can be prohibitively expensive if extensive coverage of a PES is desired.<sup>27</sup>

#### FREE ENERGY LANDSCAPES

One might ask if it is meaningful to construct free energy surfaces if entropy *is* curvature/width on a PES. It is done. One can compute an entropy contribution to free energy for any point (i.e., geometric and electronic structure) on a PES and thus can arrive at a single free energy value for that point, so why not combine those into a surface? Personally, this practice causes me some cognitive dissonance,<sup>28</sup> but I still make use of it.

If one wants to turn an IRC into a free energy reaction coordinate (Figures 2 and 3), there are options.<sup>29</sup> The first approach is easily implemented, but, some would say, fraught with peril: run frequency calculations at points along the IRC and add the resulting corrections to obtain free energies for each point. This leads to a new reaction coordinate curve whose maximum (in free energy) may have a different structure than that on the IRC. This approach also assumes that the minimum free energy reaction path does not deviate from the IRC. And, to top it off, this process breaks one of the "rules" taught to aspiring computational chemists: frequency analysis is only meaningful at stationary points.<sup>30</sup> There are better approaches. For example, one can use more involved techniques for treating PES curvature along an IRC, as implemented in *Polyrate/Gaussrate.*<sup>31</sup>

Another method, which has not yet received much traction among modelers of synthetic organic reactions, is metadynamics.<sup>32,33</sup> In this approach, free energy is related to (and computed from) probabilities of particular values of collective variables encountered during a simulation. Again, one must deal with the problem of choosing meaningful collective variables, making sure that these have different values in all minima (metastable states) and transition states. Doing so again generally involves chemical intuition or trial and error, although automated approaches, some based on machine learning, are being developed.<sup>32</sup> It is important to note that metadynamics simulations involve classical entropy rather than quasiclassical entropy, the latter accounting for zero point energy (which is usually included in AIMD simulations).

A third approach, called entropic path sampling, makes use of AIMD simulations.<sup>34</sup> In this approach, a bundle of trajectories is run and then snapshots from these are divided into ensembles characterized by shared structural features (based on ranges defined by the user). Again, how best to choose these structural features amounts to the same problem we keep encountering. For each ensemble, configurational entropy is then calculated based on probabilities for degrees of freedom. These entropies can then be plotted against the structural features used to create the snapshot ensembles, for example.

# COUNTING CONFORMATIONS

Besides accounting for local flexibility, one must account for separate transition states leading to the same products. This is an issue of separate stationary points—transition structures—corresponding to separate variational transition states, i.e., nonlocal flexibility or conformational entropy. Often multiple pathways to a given product differ in conformation (or configuration, if, for example, a metal is involved).<sup>35</sup> Such a scenario is shown schematically in Figure 8 for a case where five transition states, all of which have the same free energy, lead to two competing products. In this case, the product formed via the greater number of transition states will predominate. Again, counting is important. In some cases, these different transition state conformations/configurations will be equivalent by symmetry, but in many cases they will not.



**Figure 8.** Diagram emphasizing that there can be multiple transition states of the same or similar free energies leading to the same product and the number leading to each of two competing products need not be the same.

In most cases, the multiple transition states leading to a given product will not have the same energy. Often, kinetic selectivity in that case is rationalized or predicted by comparing the energy of the lowest energy transition state leading to one product with the lowest energy transition state leading to the other product. Instead, however, a Boltzmann weighted average based on the energies of all transition states should be used (assuming Curtin—Hammett conditions),<sup>36</sup> so that the contribution from each at a given temperature is captured, i.e., there is an ensemble of transition state conformations/configurations/etc. (which can be thought of as microstates) leading to a given product.<sup>37</sup>

## DYNAMICAL DIVERSIONS

The concepts described above were presented with the assumption that transition state theory and related statistical theories are sufficient for describing the kinetically selective reactions one desires to examine.<sup>13</sup> There are some reactions for which that assumption is not valid. Aside from complications due to quantum mechanical tunneling,<sup>38</sup> some reactions are subject to "non-statistical dynamic effects," i.e., effects due to the momentum possessed by atoms when they pass transition states.<sup>11</sup>

A prime example is the class of reactions whose pathways to products involve "post-transition state bifurcations" (PTSBs)<sup>39</sup> In such reactions, a single transition structure is connected directly to two product minima on a PES via paths that monotonically decrease in energy (shown schematically in Figure 9a; complications particular to constructing PESs for systems with PTSBs were described recently, and a potential solution to these problems was proposed, by Hsu and coworkers<sup>40</sup>). Since separate transition structures for each product do not exist, one cannot compare the free energies of their associated transition states to arrive at a selectivity prediction. Consequently, product selectivity must be controlled by nonstatistical effects. Luckily, one can still run AIMD trajectories to see which product is preferred.

An example of a reaction with a PTSB is shown in Figure 9b, where addition of dichloroketene to an alkene occurs asynchronously, with formation of the new C–C bond involving the carbonyl carbon preceding formation of the other C–C bond, via a transition structure with a perpendicular arrangement of alkene and carbonyl  $\pi$ -bonds.<sup>10a</sup> In this case, selectivity results from a difference in the distribution of atomic masses (i.e., there is a kinetic isotope effect), emphasizing the importance of momentum. However, it was shown that this reaction actually involves an entropic intermediate—while it has a PTSB on the PES it is actually stepwise in terms of free energy (which also has implications for recrossing).



**Figure 9.** (a) Portion of a PES, from the transition structure forward, for a reaction with a PTSB. (b) Reaction with a PTSB.

Not surprisingly, the caveats mentioned above are still relevant: one should consider variational transition states, one should inquire as to the presence of entropic intermediates, curvature and width of the pathways to products matters,<sup>41</sup> and multiple transition states (each with or without PTSBs) may contribute.

Another type of reaction where nonstatistical dynamic effects are key is shown schematically in Figure 10a. In this case, the transition structures leading to competing products are connected to each other by a relatively flat region of the PES that is similar in energy to them. In this scenario, trajectories initially heading toward one transition state may approach it but then wander (roam,<sup>42</sup> leak) toward the other. This sort of intertransition state communication is not accounted for in standard models. While it has been proposed for reactions such as the competing water loss/1,2-alkyl shift processes shown in Figure 10b,<sup>43</sup> it is not yet clear how common such a scenario is. That being said, this scenario is related to a much-studied class of reactions involving flat regions of PESs with multiple exit channels rather than simple transition states separating reactants from products-so-called "calderas," "mesas," "para-intermediates," or "twixtyls".<sup>44</sup> Such flat regions of PESs, if flat enough, correspond to entropic intermediates.9

# IMPLICATIONS FOR REACTION DESIGN

How do we apply these concepts to the design of kinetically selective reactions? Consider the three reactions shown in Figure 11, all of which are selective as a result of entropy, not enthalpy, differences between transition states.<sup>45</sup> While the selectivities in these systems are small and comparable to errors expected in many sorts of quantum chemical calculations (on the order of 1 kcal/mol), qualitative models would be of value



**Figure 10.** (a) PES (as a 2D contour map with energy coded by color) for a reaction with an inter-transition state roaming region. Adapted from ref 43. Copyright 2021 American Chemical Society. (b) Reaction possessing a PES akin to that shown in (a).



**Figure 11.** Three reactions for which kinetic selectivity is controlled by entropy rather than enthalpy.

for both rationalization of results and forward design. For some of the systems shown, changes to selectivity based on solvent and changes to catalysts or substrates were reported, providing further touchpoints for qualitative models.

Perhaps the entropic discrimination in these systems results from drag<sup>12</sup>—due to specific electrostatic or dispersion interactions. This effect would be visible and quantifiable, perhaps using entropic path sampling (if enough trajectories can be obtained), in AIMD simulations. But are these simulations feasible for systems of this complexity–complexity commonly encountered in modern synthetic organic chemistry?

The systems shown in Figure 11a,b are large, too large to obtain large numbers of AIMD trajectories with DFT. While this practical impediment may soon disappear, meaningful results also might be obtained using recently developed semiempirical methods,<sup>46</sup> which could be benchmarked on the background reactions without catalysts for which DFT trajectories are reasonable. And these semiempirical methods open the door to including large numbers of explicit solvent molecules, allowing one to compare and contrast gas phase, continuum, microsolvation, and bulk solvent effects.<sup>47,48</sup>

The system shown in Figure 11c involves a photochemical reaction. While all of our entropy models should be applicable to reactions on excited state surfaces, there are complications with modeling such reactions. First, getting electronic structures correct for most excited states generally requires methods that are much more time-consuming than DFT, i.e., multiconfigurational approaches.<sup>49</sup> Second, that makes running AIMD trajectories impractical for all but the smallest model systems. Third, photochemical reactions involve switching between electronic states, e.g., initial excitation to S1 followed by conversion back to S0. However, determining where on a PES the switch occurs (e.g., at a conical intersection; is that conical intersection near a transition structure on the S0 PES?) can be difficult, especially if one wishes to allow for such "surface hopping" during AIMD trajectories such that one can see how the momentum before the hop affects posthop behavior.<sup>50</sup>

# OUTLOOK

Where does this leave us? I am left with both trepidation and resolve. I am trepidatious, since a reliable recipe for modeling entropy effects on selectivity for reactions of complex organic molecules is not yet readily available. But I am resolved to chip away at the problem with all the tools available, in pursuit of portable models, useful for designing future experiments. For, as stated long ago by Price and Hammett (in the context of a study on carbonyl reactivity):

"The present results emphasize the complete hopelessness of any general theory of the effect of structure on reactivity which is based upon considerations of potential energy alone."<sup>51</sup>

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#### REFERENCES

(1) Kragh, H.; Weininger, S. T. Sooner Silence than Confusion: The Tortuous Entry of Entropy into Chemistry. *Hist. Stud. Phys. Biol. Sci.* **1996**, *27*, 91–130.

(2) Lewis, D. E. A Future History of Selectivity in Organic Chemistry: Whence, Where and Whither? *Bull. Hist. Chem.* **2022**, *47*, 62–76.

(3) Bursch, M.; Mewes, J.-M.; Hansen, A.; Grimme, S. Best Practice DFT Protocols for Basic Molecular Computational Chemistry. *ChemRxiv* 2022, DOI: 10.26434/chemrxiv-2022-n304h.

(4) Grimme, S.; Schreiner, P. R. Computational Chemistry: The Fate of Current Methods and Future Challenges. *Angew. Chem. Int. Ed.* **2018**, *57*, 4170–4176.

(5) Hoffmann, R. Qualitative thinking in the age of modern computational chemistry—or what Lionel Salem knows. J. Mol. Struc. THEOCHEM **1998**, 424, 1–6.

(6) (a) Nagaoka, M.; Okuyama-Yoshida, N.; Yamabe, T. Origin of the Transition State on the Free Energy Surface: Intramolecular Proton Transfer Reaction of Glycine in Aqueous Solution. J. Phys. Chem. A **1998**, 102, 8202–8208. (b) Ho, J.; Klamt, A.; Coote, M. L. Comment on the Correct Use of Continuum Solvent Models. J. Phys. Chem. A **2010**, 114, 13442–13444. (c) Garza, A. J. Solvation Entropy Made Simple. J. Chem. Theory Comput. **2019**, 15, 3204–3214. (d) Conquest, O. J.; Roman, T.; Marianov, A.; Kochubei, A.; Jiiang, Y.; Stampfl, C. Calculating Entropies of Large Molecules in Aqueous Phase. J. Chem. Theory Comput. **2021**, 17, 7753–7771. (e) Gorges, J.; Grimme, S.; Hansen, A.; Pracht, P. Towards understanding solvation effects on the conformational entropy of non-rigid molecules. Phys. Chem. Chem. Phys. **2022**, 24, 12249–12259.

(7) Plata, R. E.; Singleton, D. A. A Case Study of the Mechanism of Alcohol-Mediated Morita Baylis–Hillman Reactions. The Importance of Experimental Observations. *J. Am. Chem. Soc.* **2015**, *137*, 3811–3826.

(8) Houk, K. N.; Rondan, N. G. Origin of Negative Activation Energies and Entropy Control of Halocarbene Cycloadditions and Related Fast Reactions. J. Am. Chem. Soc. **1984**, *106*, 4293–4294.

(9) Yang, Z.; Jamieson, C. S.; Xue, X.-S.; Garcia-Borràs, M.; Benton, T.; Dong, X.; Liu, F.; Houk, K. N. Mechanisms and Dynamics of Reactions Involving Entropic Intermediates. *Trends Chem.* **2019**, *1*, 22–34.

(10) (a) Gonzalez-James, O. M.; Kwan, E. E.; Singleton, D. A. Entropic Intermediates and Hidden Rate-Limiting Steps in Seemingly Concerted Cycloadditions. Observation, Prediction, and Origin of an Isotope Effect on Recrossing. J. Am. Chem. Soc. 2012, 134, 1914-1917. (b) A related example in solid-state chemistry: Schön, J. C.; Wevers, M. A. C.; Jansen, M. 'Entropically' stabilized region on the energy landscape of an ionic solid. J. Phys. Cond. Mat. 2003, 15, 5479-5486. (11) (a) Ma, X. Y.; Hase, W. L. Perspective: Chemical dynamics simulations of non-statistical reaction dynamics. Philos. Trans. R. Soc. A 2017, 375, 20160204. (b) Lourderaj, U.; Park, K.; Hase, W. L. Classical trajectory simulations of post-transition state dynamics. Int. Rev. Phys. Chem. 2008, 27, 361-403. (c) Carpenter, B. K. Dynamic behavior of organic reactions. Angew. Chem. Int. Ed 1998, 37, 3340-3350. (d) Carpenter, B. K.; Harvey, J. N.; Orr-Ewing, A. J. The study of reactive intermediates in condensed phases. J. Am. Chem. Soc. 2016, 138, 4695-4705. (e) Carpenter, B. K. Intramolecular Dynamics for the Organic Chemist. Acc. Chem. Res. 1992, 25, 520-528. (f) Yang, Z.; Houk, K. N. The Dynamics of Chemical Reactions: Atomistic Visualizations of Organic Reactions, and Homage to van't Hoff. Chem.-Eur. J. 2018, 24, 3916-3924. (g) Tantillo, D. J. Beyond Transition State Theory - Non-statistical Dynamic Effects for Organic Reactions. Adv. Phys. Org. Chem. 2021, 55, 1-16.

(12) (a) Xing, Y.-Y.; Chen, S.-S.; Chen, D.-Z.; Tantillo, D. J. Effects of electrostatic drag on the velocity of hydrogen migration – pre- and post-transition state enthalpy/entropy compensation. *Phys. Chem.* 

Chem. Phys. 2020, 22, 26955–26960. (b) Houk, K. N.; Leach, A. G.; Kim, S. P.; Zhang, X. Binding Affinities of Host–Guest, Protein– Ligand, and Protein–Transition-State Complexes. Angew. Chem. Int. Ed. 2003, 42, 4872–4897.

(13) Bao, J. L.; Truhlar, D. G. Variational transition state theory: theoretical framework and recent developments. *Chem. Soc. Rev.* 2017, 46, 7548–7596.

(14) Tuñón, I.; Williams, I. H. The transition state and cognate concepts. *Adv. Phys. Org. Chem.* **2019**, *53*, 29–68.

(15) (a) Fukui, K. The Path of Chemical Reactions - The IRC Approach. Acc. Chem. Res. **1981**, 14, 363–368. (b) Maeda, S.; Harabuchi, Y.; Ono, Y.; Taketsugu, T.; Morokuma, K. Intrinsic Reaction Coordinate: Calculation, Bifurcation, and Automated Search. Int. J. Quantum Chem. **2015**, 115, 258–269. (c) Deng, L.; Ziegler, T. The Determination of Intrinsic Reaction Coordinates by Density Functional Theory. Int. J. Quantum Chem. **1994**, 52, 731–765. (d) Gonzalez, C.; Schlegel, H. B. Reaction Path Following in Mass-Weighted Internal Coordinates. J. Phys. Chem. **1990**, 94, 5523–5527.

(16) Note that additional corrections are needed if the number of molecules changes during a reaction.

(17) Bootsma, A. N.; Wheeler, S. Popular Integration Grids Can Result in Large Errors in DFT-Computed Free Energies. *ChemRxiv* **2019**, DOI: 10.26434/chemrxiv.8864204.v5.

(18) (a) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J. Phys. Chem. B* **2011**, *115*, 14556–14562. (b) Another common approach is to scale frequencies; see, for example: Scott, A. P.; Radom, L. Harmonic Vibrational Frequencies: An Evaluation of Hartree–Fock, Møller–Plesset, Quadratic Configuration Interaction, Density Functional Theory, and Semiempirical Scale Factors. *J. Phys. Chem.* **1996**, *100*, 16502–16513.

(19) (a) Ayala, P. Y.; Schlegel, H. B. Identification and treatment of internal rotation in normal mode vibrational analysis. *J. Chem. Phys.* **1998**, *108*, 2314–2325. (b) Spicher, S.; Grimme, S. Single-Point Hessian Calculations for Improved Vibrational Frequencies and Rigid-Rotor-Harmonic-Oscillator Thermodynamics. *J. Chem. Theory Comput.* **2021**, *17*, 1701–1714. (c) Besora, M.; Vidossich, P.; Lledós, A.; Ujaque, G.; Maseras, F. Calculation of Reaction Free Energies in Solution: A Comparison of Current Approaches. *J. Phys. Chem. A* **2018**, *122*, 1392–1399. (d) Watson, L. A.; Eisenstein, O. Entropy Explained: The Origin of Some Simple Trends. *J. Chem. Educ.* **2002**, *79*, 1269–1277. (e) Grimme, S. Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem.—Eur. J.* **2012**, *18*, 9955–9964.

(20) (a) Piccini, G.; Sauer, J. Effect of Anharmonicity on Adsorption Thermodynamics. J. Chem. Theory Comput.h 2014, 10, 2479–2487.
(b) Piccini, G.; Sauer, J. Quantum Chemical Free Energies: Structure Optimization and Vibrational Frequencies in Normal Modes. J. Chem. Theory Comput. 2013, 9, 5038–5045. (c) Li, Y.-P.; Bell, A. T.; Head-Gordon, M. Thermodynamics of Anharmonic Systems: Uncoupled Mode Approximations for Molecules. J. Chem. Theory Comput.h 2016, 12, 2861–2870.

(21) Stegelmann, C.; Andreasen, A.; Campbell, C. T. Degree of Rate Control: How Much the Energies of Intermediates and Transition States Control Rates. *J. Am. Chem. Soc.* **2009**, *131*, 13563.

(22) (a) De Leon, N.; Berne, B. J. Intramolecular rate process: Isomerization dynamics and the transition to chaos. J. Chem. Phys. **1981**, 75, 3495. (b) Lee, S.; Goodman, J. M. VRAI-selectivity: calculation of selectivity beyond transition state theory. Org. Biomol. Chem. **2021**, 19, 3940–3947. (c) Leffler, J. E.; Grunwald, E. Rates and Equilibria of Organic Reactions As Treated by Statistical, Thermodynamic and Extrathermodynamic Methods; Wiley: New York, 1963.

(23) Bai, M.; Feng, Z.; Li, J.; Tantillo, D. J. Bouncing off walls – widths of exit channels from shallow minima can dominate selectivity control. *Chem. Sci.* **2020**, *11*, 9937–9944.

(24) Czakó, G.; Gyö ri, T.; Papp, D.; Tajti, V.; Tasi, D. A. First-Principles Reaction Dynamics beyond Six-Atom Systems. *J. Phys. Chem. A* **2021**, *125*, 2385–2393. (25) Hare, S. R.; Bratholm, L. A.; Glowacki, D. R.; Carpenter, B. K. Low dimensional representations along intrinsic reaction coordinates and molecular dynamics trajectories using interatomic distance matrices. *Chem. Sci.* **2019**, *10*, 9954–9968.

(26) A related approach: Tsutsumi, T.; Ono, T.; Taketsugu, T. Reaction Space Projector (ReSPer) for Visualizing Dynamic Reaction Routes Based on Reduced-Dimension Space. *Top. Curr. Chem.* **2022**, 380, 19.

(27) Kwon, H.-Y.; Morrow, Z.; Kelley, M. C. T.; Jakubikova, E. Interpolation Methods for Molecular Potential Energy Surface Construction. J. Phys. Chem. A 2021, 125, 9725–9735.

(28) Tantillo, D. J. Dynamic effects on organic reactivity—Pathways to (and from) discomfort. J. Phys. Org. Chem. **2021**, 34, No. e4202.

(29) Sun, Q.; Lu, X.; Tantillo, D. J. Dynamic Effects in Intramolecular Schmidt Reactions: Entropy, Electrostatic Drag, and Selectivity Prediction. *ChemPhysChem* **2021**, *22*, 649–656.

(30) https://gaussian.com/freq/ (accessed 2022-04-27).

(31) (a) Zheng, J.; Bao, J. L.; Meana-Pañeda, R.; Zhang, S.; Lynch, B. J.; Corchado, J. C.; Chuang, Y. Y.; Fast, P. L.; Hu, W.-P.; Liu, Y.-P.; Lynch, G. C.; Nguyen, K. A.; Jackels, C. F.; Fernandez Ramos, A.; Ellingson, B. A.; Melissas, V. S.; Villà, J.; Rossi, I.; Coitiño, E.-L.; Pu, J.; Albu, T. V.; Ratkiewicz, A.; Steckler, R.; Garrett, B. C.; Isaacson, A. D.; Truhlar, D. G. *Polyrate 17*; University of Minnesota: Minneapolis, 2017.
(b) Zheng, J.; Zhang, S.; Corchado, J. C.; Meana-Pañeda, R.; Chuang, Y.-Y.; Coitiño, E.-L.; Ellingson, B. A.; Truhlar, D. G. *Gaussrate 17*; University of Minnesota: Minneapolis, MN, 2017.

(32) Bussi, G.; Laio, A. Using metadynamics to explore complex freeenergy landscapes. *Nature Rev. Phys.* **2020**, *2*, 200–212.

(33) (a) Related methods: Giese, T. J.; Ekesan, Ş.; York, D. M. Extension of the Variational Free Energy Profile and Multistate Bennett Acceptance Ratio Methods for High-Dimensional Potential of Mean Force Profile Analysis. J. Phys. Chem. A 2021, 125, 4216–4232.
(b) Kim, B.; Snyder, R.; Nagaruju, M.; Zhou, Y.; Ojeda-May, P.; Keeton, S.; Hege, M.; Shao, Y.; Pu, J. Reaction Path-Force Matching in Collective Variables: Determining Ab Initio QM/MM Free Energy Profiles by Fitting Mean Force. J. Chem. Theory Comput.h 2021, 17, 4961–4980.

(34) (a) Qin, Z.-X.; Tremblay, M.; Hong, X.; Yang, Z. J. Entropic Path Sampling: Computational Protocol to Evaluate Entropic Profile along a Reaction Path. *J. Phys. Chem. Lett.* **2021**, *12*, 10713–10719. (b) For a related approach, see ref 19c.

(35) Lu, T.; Porterfield, M. A.; Wheeler, S. E. Explaining the Disparate Stereoselectivities of *N*-Oxide Catalyzed Allylations and Propargylations of Aldehydes. *Org. Lett.* **2012**, *12*, 5310–5313.

(36) (b) Seeman, J. I. The Curtin-Hammett principle and the Winstein-Holness equation: new definition and recent extensions to classical concepts. *J. Chem. Educ.* **1986**, *63*, 42–48. (c) Seeman, J. I. Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin-Hammett Winstein-Holness kinetics. *Chem. Rev.* **1983**, *83*, 83–134. (a) Williams, I. H. Gibbs energies of activation for reacting systems with multiple reactant-state and transition-state conformation. *J. Phys. Org. Chem.* **2022**, DOI: 10.1002/poc.4312s.

(37) (a) Recent examples and additional detailed discussions: Romero-Téllez, S.; Cruz, A.; Masgrau, L.; González-Lafont, A.; Lluch, J. M. Accounting for the instantaneous disorder in the enzyme-substrate Michaelis complex to calculate the Gibbs free energy barrier of an enzyme reaction. Phys. Chem. Chem. Phys. 2021, 23, 13042-13054. (b) Viegas, L. P. Simplified Protocol for the Calculation of Multiconformer Transition State Theory Rate Constants Applied to Tropospheric OH-Initiated Oxidation Reactions. J. Phys. Chem. A 2021, 125, 4499-4512. (c) Masgrau, L.; Truhlar, D. G. The Importance of Ensemble Averaging in Enzyme Kinetics. Acc. Chem. Res. 2015, 48, 431-438. (d) Pracht, P.; Grimme, S. Calculation of absolute molecular entropies and heat capacities made simple. Chem. Sci. 2021, 12, 6551-6568. (e) Grimme, S.; Bohle, F.; Hansen, A.; Pracht, P.; Spicher, S.; Stahn, M. Efficient Quantum Chemical Calculation of Structure Ensembles and Free Energies for Nonrigid Molecules. J. Phys. Chem. A 2021, 125, 4039-4054. (f) Zhao, Q.; Hsu,

H.-H.; Savoie, B. M. Conformational Sampling for Transition State Searches on a Computational Budget. *J. Chem. Theory Comput.* **2022**, DOI: 10.1021/acs.jctc.2c00081. (g) Vitek, A. K.; Jugovic, T. M. E.; Zimmerman, P. M. Revealing the Strong Relationships between Ligand Conformers and Activation Barriers: A Case Study of Bisphosphine Reductive Elimination. *ACS Catal.* **2020**, *10*, 7136–7145. (h) Guan, Y.; Ingman, V. M.; Rooks, B. J.; Wheeler, S. E. AARON: An Automated Reaction Optimizer for New Catalysts. *J. Chem. Theory Comput.* **2018**, *14*, 5249–5261.

(38) (a) Schreiner, P. R. Quantum Mechanical Tunneling Is Essential to Understanding Chemical Reactivity. *Trends Chem.* **2020**, *2*, 980–989. (b) McMahon, R. J. Chemical Reactions Involving Quantum Tunneling. *Science* **2003**, *299*, 833–834.

(39) (a) Hare, S. R.; Tantillo, D. J. Post-Transition State Bifurcations Gain Momentum – Current State of the Field. *Pure Appl. Chem.* **2017**, *89*, 679–698. (b) Rehbein, J.; Carpenter, B. K. Do we fully understand what controls chemical selectivity? *Phys. Chem. Chem. Phys.* **2011**, *13*, 20906–20922. (c) Ess, D. H.; Wheeler, S. E.; Iafe, R. G.; Xu, L.; Çelebi-Ölçüm, N.; Houk, K. N. Bifurcations on potential energy surfaces of organic reactions. *Angew. Chem., Int. Ed* **2008**, *47*, 7592–7601. (d) Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. I. Evolution of the Diels–Alder Reaction Mechanism since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions. *Angew. Chem. Int. Ed* **2021**, *60*, 12660– 12681.

(40) Chuang, H.-H.; Tantillo, D. J.; Hsu, C.-P. Construction of Two-Dimensional Potential Energy Surfaces of Reactions with Post-Transition-State Bifurcations. J. Chem. Theory Comput. **2020**, 16, 4050–4060.

(41) Hare, S. R.; Pemberton, R. P.; Tantillo, D. J. Navigating Past a Fork in the Road: Carbocation– $\pi$  Interactions Can Manipulate Dynamic Behavior of Reactions Facing Post-Transition-State Bifurcations. J. Am. Chem. Soc. **2017**, 139, 7485–7493.

(42) (a) Bowman, J. M.; Suits, A. G. Roaming reactions: the third way. *Phys. Today* **2011**, *64*, 33–37. (b) Townsend, D.; Lahankar, S. A.; Lee, S. K.; Chambreau, S. D.; Suits, A. G.; Zhang, X.; Rheinecker, J.; Harding, L. B.; Bowman, J. M. The roaming atom: straying from the reaction path in formaldehyde decomposition. *Science* **2004**, *306*, 1158–1161.

(43) Feng, Z.; Tantillo, D. J. Dynamic Effects on Migratory Aptitudes in Carbocation Reactions. J. Am. Chem. Soc. **2021**, 143, 1088–1097.

(44) (a) Carpenter, B. K. Nonstatistical Dynamics in Thermal Reactions of Polyatomic Molecules. *Annu. Rev. Phys. Chem.* 2005, 56, 57–89. (b) Hoffmann, R.; Swaminat, S.; Odell, B. G.; Gleiter, R. Potential Surface for a Nonconcerted Reaction-Tetramethylene. *J. Am. Chem. Soc.* 1970, 92, 7091–7097. (c) Doering, W. V.; Ekmanis, J. L.; Belfield, K. D.; Klarner, F. G.; Krawczyk, B. Thermal Reactions of Antiand Syn-Dispiro[5.0.5.2]tetradeca-1,8-Dienes: Stereomutation and Fragmentation to 3-Methylenecyclohexenes. Entropy-Dictated Product Ratios from Diradical Intermediates? *J. Am. Chem. Soc.* 2001, *123*, 5532–5541. (d) Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. Mechanism of the Vinylcyclobutane Rearrangement of Sceptrin to Ageliferin and Nagelamide E. *Angew. Chem. Int. Ed* 2006, *45*, 4126–4130.

(45) (a) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. Stereodivergent, Diels–Alder-initiated organocascades employing  $\alpha,\beta$ unsaturated acylammonium salts: scope, mechanism, and application. *Chem. Sci.* **2017**, *8*, 1511–1524. (b) Garzan, A.; Jaganathan, A.; Marzijarani, N. S.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. Solvent-Dependent Enantiodivergence in the Chlorocyclization of Unsaturated Carbamates. *Chem.*—*Eur. J.* **2013**, *19*, 9015–9021. (c) Nagasaki, K.; Inoue, Y.; Mori, T. Entropy-Driven Diastereoselectivity Improvement in the Paternò–Büchi Reaction of 1-Naphthyl Aryl Ethenes with a Chiral Cyanobenzoate through Remote Alkylation. *Angew. Chem. Int. Ed* **2018**, *57*, 48804885.

(46) Bannwarth, C.; Caldeweyher, E.; Ehlert, S.; Hansen, A.; Pracht, P.; Seibert, J.; Spicher, S.; Grimme, S. Extended tight-binding quantum chemistry methods. *WIREs Comp. Mol. Sci.* **2021**, *11*, No. e1493.

(47) López, C. S.; Faza, O. N. Solvation. In *Applied Theoretical Organic Chemistry*; Tantillo, D. J., Ed.; World Scientific, 2018; Chapter 4.

(48) Nieves-Quinones, Y.; Singleton, D. A. Dynamics and the Regiochemistry of Nitration of Toluene. J. Am. Chem. Soc. 2016, 138, 15167–15176.

(49) Szalay, P. G.; Müller, T.; Gidofalvi, G.; Lischka, H.; Shepard, R. Multiconfiguration Self-Consistent Field and Multireference Configuration Interaction Methods and Applications. *Chem. Rev.* **2012**, *112*, 108–181.

(50) (a) Examples: Mignolet, B.; Curchod, B. F. E.; Martínez, T. J. Rich Athermal Ground-State Chemistry Triggered by Dynamics through a Conical Intersection. *Angew. Chem. Int. Ed* **2016**, *55*, 14993–14996. (b) Li, J.; Lopez, S. A. Multiconfigurational Calculations and Nonadiabatic Molecular Dynamics Explain Tricyclooctadiene Photochemical Chemoselectivity. J. Phys. Chem. A **2020**, *124*, 7623–7632.

(51) Price, F. P., Jr.; Hammett, L. P. Effect of Structure on Reactivity of Carbonyl Compounds; Temperature Coefficients of Rate of Formation of Several Semicarbazones. *J. Am. Chem. Soc.* **1941**, *63*, 2387–2393.

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# Abstract

Differences in entropies of competing transition states can direct kinetic selectivity. Understanding and modeling such entropy differences at the molecular level is complicated by the fact that entropy is statistical in nature; i.e., it depends on multiple vibrational states of transition structures, the existence of multiple dynamically accessible pathways past these transition structures, and contributions from multiple transition structures differing in conformation/configuration. The difficulties associated with modeling each of these contributors are discussed here, along with possible solutions, all with an eye toward the development of portable qualitative models of use to experimentalists aiming to design reactions that make use of entropy to control kinetic selectivity.

