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PERSPECTIVE

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Dynamic effects on organic reactivity—Pathways to (and from) discomfort

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Abstract

Recent computational studies highlighting the importance of accounting for dynamic effects on organic reactivity are discussed, accompanied by descriptions of the factors that led the author to pursue these projects.

KEYWORDS

bifurcation, dynamics, entropy

> "Part of creativity is thinking about, figuring out, being comfortable, and accepting of all the things we do not know, and not feeling that you have to know everything. Because that's when you start to explore..." Ma[1]

1 | THE DISCOMFORT OF OTHERS

Might personal discomfort promote discovery? Many chemists certainly have ventured into new, unfamiliar territory in pursuit of greater understanding. Two classic examples are described briefly here. Although it is not my place to say what was and was not going on in the minds of those involved, it is clear that puzzlement led to new approaches and new discoveries in both cases.

Take, for example, the following tale related by Frank Westheimer that involves facing up to things that one does not understand but wishes to apply to a problem of interest (here, the treatment of electrostatic effects)[2]:

> "I was greatly puzzled by this, and could not resolve the problem. However, in 1937, J. G. Kirkwood came to the University of Chicago ... the one year he spent at Chicago provided me with a wonderful opportunity. I had seen some of Kirkwood's papers on electrostatic effects, but could not understand them. When he arrived in Chicago in 1937, I took him my problem, which was just down his alley. He gave me Byerly's book on Fourier's series and spherical harmonics and told me to master it and come back ... Then we adapted the equations he had previously published – the ones I had not understood – to my problem of electrostatic effects in organic chemistry."

Famously, "bafflement" also was involved in R. B. Woodward's co-development of the principles of orbital symmetry conservation.[3] As stated by Woodward[3b]:

> "In 1960, I rather felt that, by and large, I had a good understanding of organic reactions – at least in my own perhaps idiosyncratic terms. But whenever I was tempted to become too complacent, there arose in my mind the spectre of these four mysterious reactions. However much I thought about them, they remained for me a true source of bafflement."

The four reactions in question turned out to be examples of pericyclic reactions (specifically cycloadditions and electrocyclizations) whose outcomes were only rationalized successfully when orbital symmetry considerations were applied. And there was a fifth reaction, an electrocyclization encountered during the synthesis of vitamin B12, that also caused discomfort[3b]:

> "Here was a real dilemma. I had analysed the situation very carefully in the light of what I regarded as the best contemporary theoretical principles, and I had reached an absolutely wrong conclusion. I was appalled ... To make matters worse, this was not simply a case which I found baffling; it was a reaction which I thought I had understood; now it was abundantly clear that I did not."

And Woodward also considered the possibility that his lack of expertise in the details of quantum chemistry might have been advantageous[3b]:

> "I raise the question: Is it possible that my own relative naïveté in quantum chemistry was a positive advantage in relation to the events to come? ... Perhaps the relatively remote and unsophisticated observer is sometimes the better able to see the forest for the trees? I do not answer this question; I only raise it."

2 | MY COMFORT ZONE

Applied computational organic chemistry has, in recent times, seen an expansion toward the modeling of dynamic effects on organic reactivity. In addition to modeling minima (reactants, products, and intermediates) and transition state structures (TSSs)—stationary points on potential energy surfaces (PESs)—and the intrinsic reaction coordinates (IRCs)[4] that connect them, an increasing number of studies describe the results of direct ab initio molecular dynamics (AIMD) simulations, which include kinetic, in addition to potential, energy and capture the effects of momentum of nuclei (a phase space perspective).[5] The details of reactivity uncovered through such studies have been both of fundamental interest and of utility in reaction development.

This is the field in which I work. Below, I describe several examples of dynamic effects on organic reactions, with a focus on the reactivity models derived from their analysis and the implications of these models for the design of subsequent experiments. The chemistry is explained so that the personal pathways that led me to the study of each system and the interpretation of results can be highlighted, with the specific goal of reminding students (and others) that meaningful discoveries need not be made only by the most experienced of practitioners.

3 | CONFESSIONS

I am an organic chemist, by training and at heart. I do not develop theoretical methods, I apply them, and I am comfortable with that (I have not always been). My comfort levels with math and physical chemistry, however, are both low. But the slow speed of my drift toward physical chemistry has been beneficial. I used to do synthetic organic chemistry with my own hands (through my first year of graduate school). That was a long time ago, and I did it very poorly, but it gave me a sense for what it means to do such research, a sense that has been invaluable in collaborating with synthetic organic colleagues. While avoiding physical chemistry, I also developed a love of arrow-pushing[6] and synthetic strategy, both interests that influence my choice of projects to pursue. I have come back to physical chemistry but done so against my will but with determination, as a result of a fascination with aspects of organic reactivity that I do not understand.

I have a compulsion to make, but I lack the hands and associated self-confidence to make *molecules*. Instead, making *models* of reactivity is my craft. My heroes in the world of physical/mechanistic/theoretical organic chemistry are those that excel at making such models, models that are useful and predictive[7]: Ken Houk, Roald Hoffmann, Paul Schleyer, Barry Carpenter, and Dan Singleton. I hope to show how facing up to my discomfort with physical chemistry concepts and methods has led me to refine the reactivity models of others and construct my own. It took me a long time to be comfortable with leaving my comfort zone,[8] but finally I accept that the process of leaving it → learning new principles and skills and thereby creating an expanded comfort zone → leaving the new comfort zone, and so on, can be immensely fulfilling, despite the associated insecurity and imposter syndrome.[9] Below I describe several aspects of research into dynamic effects on organic reactions, each accompanied by the sources of discomfort that led me to pursue them.

4 | STUCK ON A PITCHFORK—POST-TRANSITION STATE BIFURCATIONS

Source of discomfort #1. While a postdoc, Caramella's paper on the discovery that dimerization of cyclopentadiene was bispericyclic was published and I read it out of fundamental interest (Figure 1).[10a] A bispericyclic reaction is one in which two pericyclic processes have merged into a single reaction where an initial TSS (now called ambimodal[10b]) is followed by a pathway downhill in potential energy that bifurcates, without the intervention of an intermediate minimum, to two products, which themselves are interconvertible by a separate TSS for a pericyclic reaction. Cyclopentadiene dimerization is an example of what has come to be called a reaction with a post-transition state bifurcation (PTSB), a reaction whose pathways to products resemble a two-tined pitchfork.[11] In this specific case, cycloaddition is merged with a product-interconverting Cope rearrangement. At the time of its publication, I simply *did not believe that such a scenario was possible*. I emailed Ken Houk (my PhD advisor) about it, and he assured me that there was nothing wrong with the work. I filed all that away in the back of my head, not wholly cured of my disbelief.

Later, while computing mechanistic pathways for terpene-forming carbocation cyclization/rearrangement reactions early in my independent career, my coworker Young Hong and I encountered a reaction that, at first, was puzzling in that it did not lead to the products we expected based on IRC calculations.[12] After being confused for some time, it occurred to me that this reaction might involve a PTSB (Figure 2)—that realization immediately caused me to get excited and that excitement led to several studies on PTSBs in natural products biosynthesis, including one describing a reaction network that involves multiple sequential PTSBs that allow access to nine PES minima from a single TSS without intervening minima.[13] We also have encountered PTSBs, accidentally, while studying synthetically relevant organic and organometallic reactions, including a case where a PTSB is the source of unwanted side products (Figure 3).[14] We are now even in the business of rationally designing reactions with PTSBs.[15] My stored away discomfort prepared me to make sense of confusing results years later and ultimately push our work toward design.

Source of discomfort #2. To rationalize product selectivity for reactions with PTSBs, I had to face up to another source of discomfort. I knew that to predict

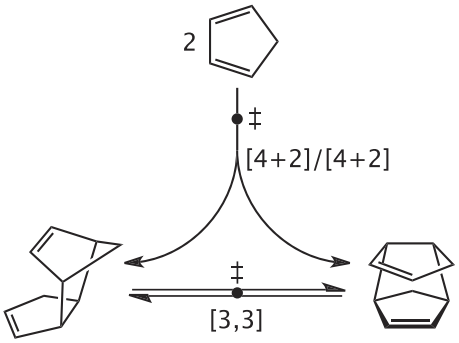

FIGURE 1 A bispericyclic reaction described by Caramella and coworkers, a reaction with a post-transition state bifurcation (PTSB)

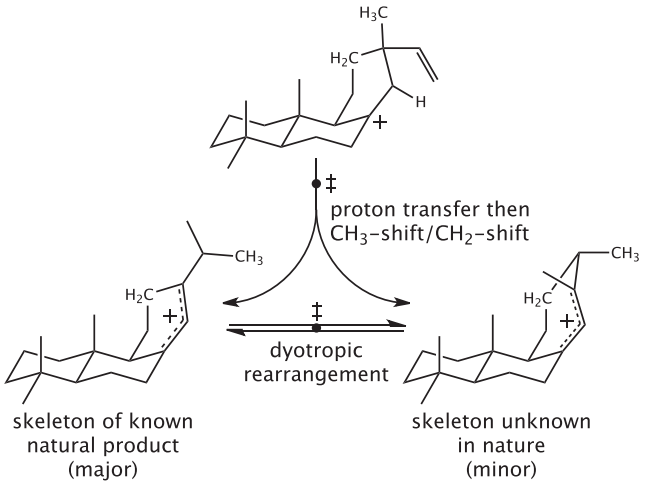

FIGURE 2 Post-transition state bifurcation (PTSB) in terpene biosynthesis. "Major" and "minor" were determined by gas phase dynamics simulations, but the major product is observed in nature while the minor is not (as of yet)

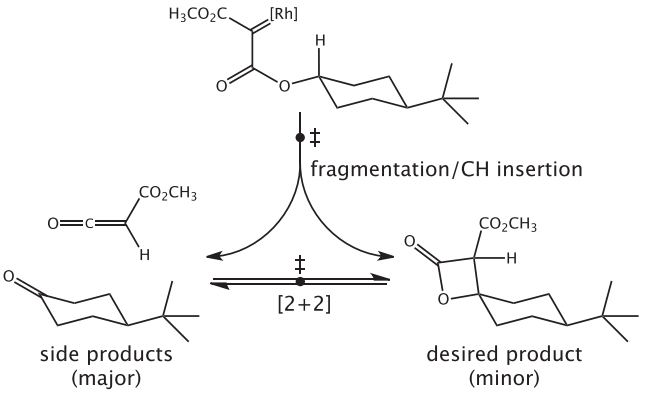

FIGURE 3 Post-transition state bifurcation (PTSB) with one branch leading to unwanted side products. "Major" and "minor" were determined by gas phase dynamics simulations, but match experimental results

product distributions for such reactions, one needed to carry out AIMD calculations.[3] I also knew that *I did not know how to do such work*. I remembered hearing about dynamics simulations and non-statistical dynamic effects from Barry Carpenter when I was a postdoc sitting in on his group meetings, but I did not grasp at all the nature of such calculations nor their importance. I was not alone—Barry was far ahead of his time. So, what to do about our PTSBs? Collaborate. I discussed this problem with Bill Hase from Texas Tech, a master of molecular dynamics simulations, during his seminar visit to UC Davis. He graciously volunteered to work with us on this problem and encouraged us to learn how to carry out such simulations on our own. Together, we published two papers describing the results of AIMD simulations for the first PTSB we discovered (Figure 2),[16] which showed that there is an inherent dynamical preference for formation of one product over the other and the dynamically preferred product was the one observed in nature; that is, without an enzyme chaperon, even in the gas phase, the known natural product skeleton was predicted to form preferentially. We have since spent many hours examining inherent dynamical tendencies and arguing that these should not be ignored even for biological reactions.[17] Ultimately, Ryan Pemberton, a PhD student who had learned to carry out AIMD simulations in Ken Houk's group, arrived at UC Davis and promptly taught my students how to carry out AIMD simulations—the flood gates were opened and such simulations are now a routine part of our work. We are not alone in applying this powerful tool on a regular basis. Figure 4 shows selected recent examples from others; the range of reactions shown highlights the general importance of dynamic effects (note, e.g., the involvement of radicals, carbocations, transition metals, enzymes, and sonication).[18]

Source of discomfort #3. Running a group that is running AIMD simulations is not free of discomfort. In particular, it has taken me years to grasp (and still not fully) *what a non-statistical dynamic effect really is*. I have had to face up to the fact that transition state theory (TST; a statistical rate theory, there are several variations of TST) is built on assumptions that are not always valid.[19] These include minimal recrossing, post-transition state behavior not mattering for rates of product formation, and rapid internal vibrational energy redistribution (IVR)—all physical chemistry concepts that are not, generally, in the wheelhouse of one with an organic heart. The work of Don Truhlar and Dan Singleton, including their disagreements (e.g., they have evaluated and debated the validity of a variety of statistical and non-statistical models for rationalizing the regioselectivity of hydroboration reactions; Figure 4, bottom right),[20] has been key to improving my understanding in this area. In particular, I learned from Truhlar that if you implement TST correctly, much purported non-statistical behavior actually is accounted for,[19] and from Singleton that, even so, non-statistical behavior does have important

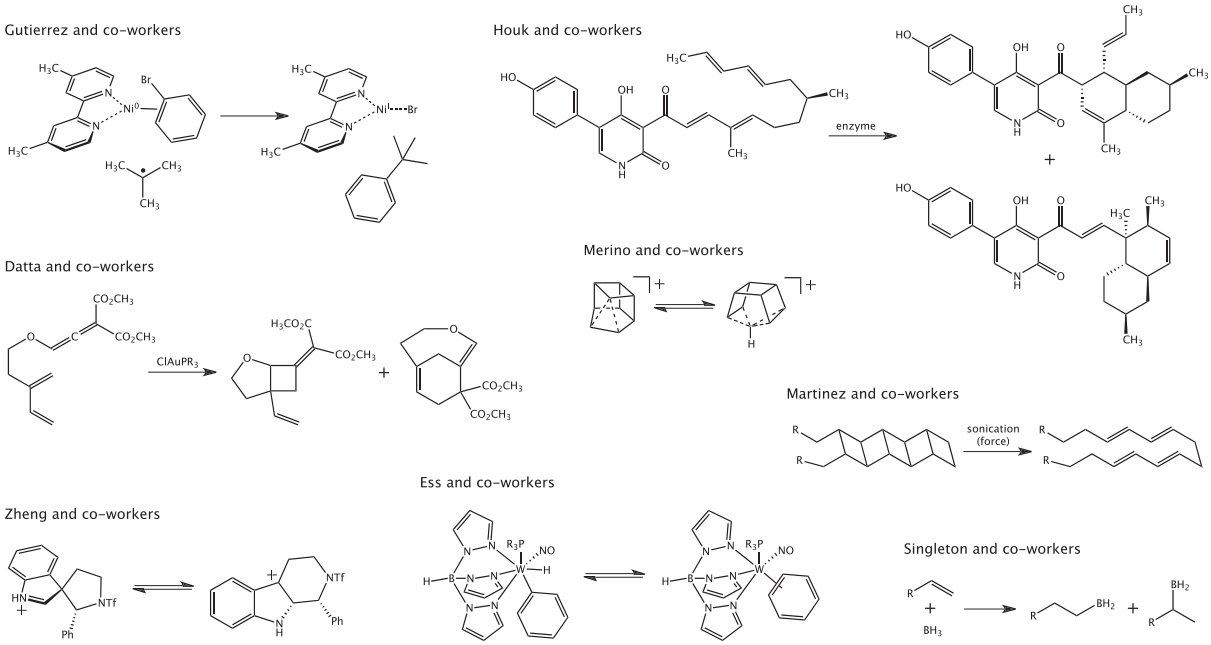

FIGURE 4 A sampling of reactions for which ab initio molecular dynamics (AIMD) simulations were used to uncover dynamic effects that modulate reactivity and/or to discover new mechanistic pathways

implications for organic reactivity. Both also have been generous in sharing their software.[21]

Working in this field also has forced me to come to terms with the limitations of humans in visualizing multiple dimensions with respect to PESs. We frequently struggle with constructing meaningful low-dimensional (low compared to all the degrees of freedom of a given molecule) PESs that capture enough features to allow us to draw useful conclusions about reactivity (e.g., Figure 5a).[22] Several approaches to addressing this issue have been described and two are mentioned here. In one, developed by Hsu and coworkers, PESs for reactions with PTSBs are constructed by interpolating between IRCs for initial ambimodal TSSs and TSSs that interconvert the two products of bifurcations (e.g., Figure 5b); this is a nontrivial endeavor![23] In the second, developed by Hare, Carpenter and coworkers, principal component analysis (PCA) is used to tease out the degrees of freedom that have the largest impact on reactivity and reaction paths are plotted on graphs constructed using these principal components (PCs) as dimensions (e.g., Figure 5c; the software developed to accomplish these tasks is called *PathReducer*).[24] Both approaches have tremendous potential to help practitioners make sense of the results of AIMD calculations.

5 | FROZEN BY INDECISION—ENTROPY EFFECTS ON SELECTIVITY

Source of discomfort #4. Like many organic chemists, I was trained to focus on the effects of enthalpy, rather than entropy, when comparing two related structures; for example, this TSS has a hydrogen-bond while that TSS does not (a focus on enthalpic "goodness"), this TSS has more steric crowding than does that one (a focus on enthalpic "badness"). Yes, organic chemists are aware of entropy, but rarely do entropic arguments enter into discussions of selectivity. Entropy effects are, of course, always relevant, but, in my experience, enthalpy arguments are generally considered first and entropy arguments only secondarily.

That approach was true for my group as well, until we encountered a system where enthalpy arguments failed (Figure 6).[25] In trying to rationalize endo/exo selectivity for the Diels–Alder reaction shown (part of a Diels–Alder/lactonization [DAL] reaction), in collaboration with the Romo group, we showed that enthalpy differences between the relevant competing TSSs were negligible; that conclusion did not depend on the level of theory used. However, predicted free energy differences

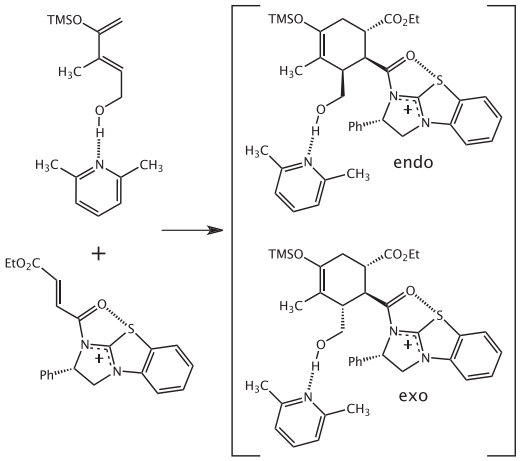

FIGURE 6 Romo's Diels–Alder reaction for which endo/exo selectivity is controlled by entropy rather than enthalpy

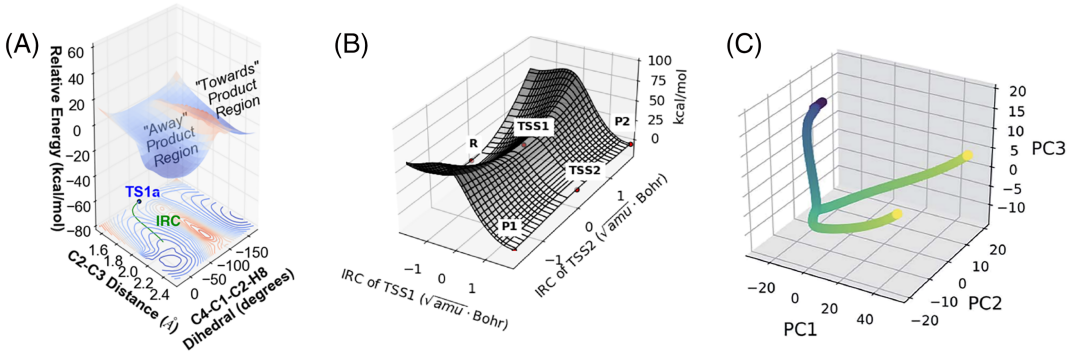

FIGURE 5 Different approaches to capturing essential features of post-transition state bifurcations (PTSBs). (a) Two representations (a three-dimensional surface and a two-dimensional projection below it) of a potential energy surface (PES) constructed from a series of constrained optimizations; the two non-energy axes (energy is also coded by color) correspond to specific degrees of freedom (reproduced with permission from Hare et al.[22]). (b) A PES constructed from the combination of two intrinsic reaction coordinates (IRCs), which correspond to the two non-energy axes (reproduced with permission from Chuang et al.[23]). (c) A *PathReducer* plot where all axes correspond to principal components (reproduced with permission from Hare et al.[24])

between the two TSSs varied significantly from level to level. There are well-known difficulties in computing entropy contributions to TSS free energies,[26] but we were not equipped at the time to confidently address that issue. Nonetheless, we were confident that enthalpy differences were not the source of selectivity and therefore suggested to our collaborators that entropy was the key. Experiments (the insensitivity of %de to temperature) bore out this conclusion. But that left me with the worry that *entropy-controlled selectivity might be more widespread than I had realized*. With encouragement from Scott Denmark, gently offered at a professional meeting where I discussed this work, I became better acquainted with the history of this problem.[27] Better late than never.

Source of discomfort #5. Now I was interested in *why* the entropies of those two competing TSSs were different. It was not at all clear from examining the structures, although I wondered if it might be related to the amount of surface area buried for each, that is, the noncovalent contacts between aromatic rings in one seemed to involve a larger contact area than in the other, which might lead to reduced flexibility. This course of thought led me to question *whether or not I knew what entropy really was*. I was aware of the problems with simply thinking of entropy as disorder and that a better description involves the number of accessible microstates (I think of enthalpy as "how much" and entropy as "how many"), but how might I make use of that knowledge? Yes, I could connect available microstates to flexibility, but would a PES picture suffice to capture that effect? AIMD simulations would be better. Scared by the size of the system involved in the DAL reaction and fearing that a relatively high level of theory might be needed to capture dispersion effects associated with π–π interactions,[28] we put this system on the backburner. Two recent lines of investigation have brought it to the forefront of our work again, though.

Both of the concepts we are fleshing out arose from our initial study on how relatively weak noncovalent interactions might modulate inherent dynamical tendencies for reactions with PTSBs.[22] The particular reaction we chose to study is shown in Figure 7. Through examinations of PESs and extensive AIMD simulations, we showed that allowing a carbocation facing a PTSB to interact with a nearby π-system, through space rather than through covalent bonds (here, a benzene interacting with the carbocation in different orientations), could enhance, reduce, or even switch product selectivity. Why? Ultimately, we converged on the idea that these noncovalent interactions modulated the *width* of the two exit channels to the products and more trajectories were able to escape the transition state region through the wider exit. This was not a new idea,[29] but it was new to us.

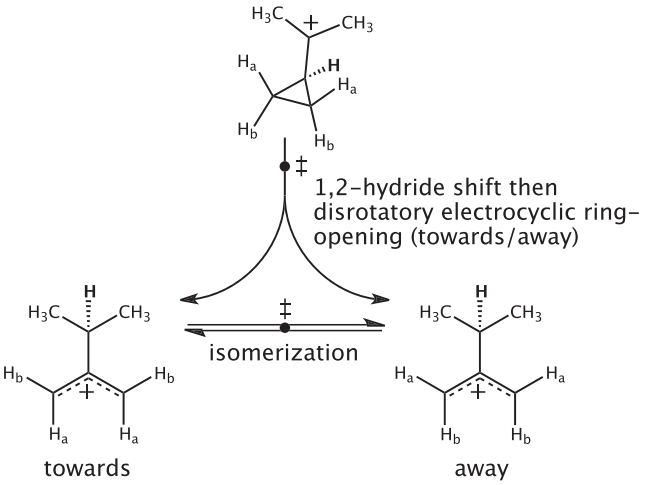

FIGURE 7 Hiscotropic reaction with a post-transition state bifurcation (PTSB) whose selectivity can be modulated by noncovalent interactions involving the face of a nearby π-system (a potential energy surface [PES] for this reaction is shown in Figure 5a)

In a subsequent study on a different carbocation reaction (Figure 8),[30] we again demonstrated the importance of pathway width in controlling product distribution, here for a reaction with a relatively flat PES but no PTSB. When we originally submitted this work for publication, we were reminded (surprisingly gently) by referees that we ought to cast our discussion in terms of entropy, that is, while height on a PES is related to enthalpy, width reflects entropy—wider paths allow more ways through them. We missed the boat on making that connection in our original submission and the work was, appropriately, rejected as too preliminary (it had other problems, too). After revising the work in response to the nudges from the original referees, the story became much stronger.

The other key concept that came out of our analysis of the reaction in Figure 7 was the recognition of the importance of something we call "electrostatic drag." We noticed that systems with the benzene molecule near to the migrating hydrogen took longer to form product and ascribed this effect to a stickiness between the migrating hydrogen, which bears some positive charge, and the benzene quadrapole,[31] that is, the electrostatic attraction imparted drag on the hydrogen. Carpenter has discussed a related type of drag imposed by solvent.[32] The drag effect is, of course, related to the concept of enthalpy/entropy compensation.[33] The stronger the electrostatic attraction (the better the enthalpy of interaction), the less flexible is the system (the worse is the entropy). Now we are applying these concepts to try to tease out the details of the entropy controlled

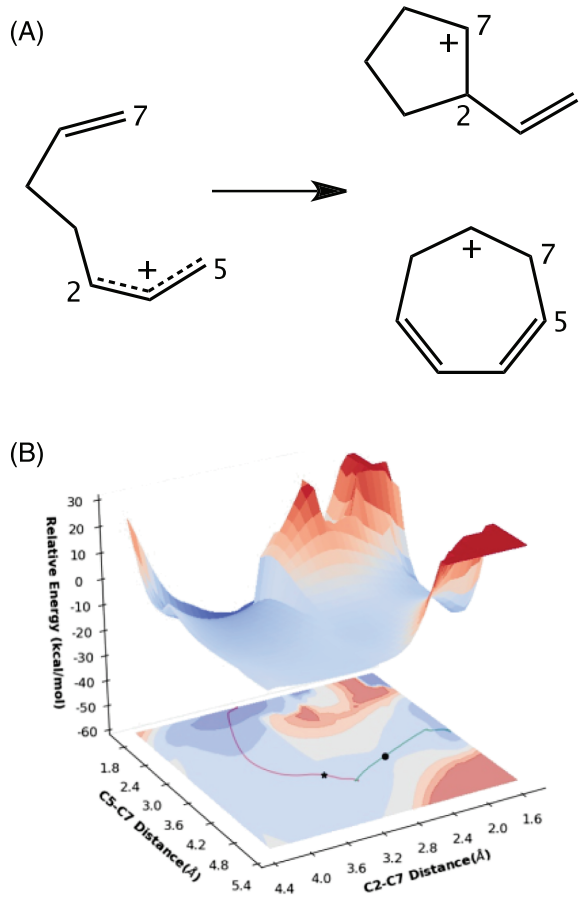

FIGURE 8 (a) Cationic cyclization for which potential energy surface (PES) pathways to products have distinctly different widths. (b) PES with transition state structures (TSSs) and intrinsic reaction coordinate (IRC) paths marked on the two-dimensional projection. Colors are used to indicate relative electronic energies

selectivity for the DAL reaction discussed above and other systems, with an eye again toward employing these concepts in reaction/catalyst design efforts.

6 | AFRAID TO GET EXCITED—ORGANIC PHOTOCHEMISTRY

Source of discomfort #6. The discomfort in my immediate future will likely center on how to model *photochemical reactions that do not involve the lowest lying triplet states of excited organic molecules*. While there has been extensive work in this area,[34] there remain unanswered questions, especially with regard to the dynamical behavior of complex organic molecules undergoing reaction. We are currently aiming to determine the best (compromise of accuracy and affordability) methods for mapping out excited state energy surfaces and predicting where molecules cross between surfaces. We are most interested in determining when during a reaction a given molecule falls back to the ground state and how the momentum of the reacting excited molecule is converted into the momentum in the ground state that determines product selectivity. We are particularly inspired in this area by classic work from Tully, Truhlar, Martinez, and Curchod and recent work by Lopez.[35] Photochemistry is another area that fascinates me but pushes on the boundaries of my understanding and comfort. And digging into it provides an opportunity to see how well the reactivity/selectivity models we have developed for ground state dynamics translate to the world of organic photochemistry.

7 | EXPLICIT CONTENT AHEAD—DISCRETE SOLVENT MOLECULES

Source of discomfort #7. Another area in which we are actively engaged is accounting for solvent effects on organic reactivity using AIMD simulations with explicit solvent. This is again an area with a long history,[36] but one where it is not clear which methods can and should be used for complex reactions of complex organic molecules, despite some fascinating studies.[37] We are driven to pursue this area for two main reasons.

1. We have encountered several reactions where we suspect that solvent cage effects are modulating dynamic behavior and thereby modulating selectivity. For example, in the reaction mentioned above in which a side product is formed via a PTSB (Figure 3), we consistently overestimate the percentage of side product formed when using implicit solvent models; the exit channel leading to this product involves fragmentation (the other exit channel does not), which may well be discouraged by surrounding solvent. Inspirational work in this area on small systems has been carried out again by Carpenter.[32]
2. We wonder how the time needed for solvent reorganization during a reaction is connected to the outcome of trajectories. When using implicit solvent models, the solvent field effectively adjusts at each step of the trajectory (1-fs steps are typical). But is this approximation valid? The answer is almost certainly system dependent. The larger the change in charge distribution during reaction, the more the solvent will need to reorganize in response, the less valid the approximation is likely to be. Work by Truhlar has indicated that the approximation is valid for relatively nonpolar systems,[38] but the jury is out on more polar reactions.[37] The impacts of relatively slow solvent reorganization on photochemical reactions where electronic excitation changes charge distributions of solute are well known[39]—another connection between my current discomforts.

8 | PERSONAL PATHWAYS—THE GOOD AND BAD

Venturing outside of my comfort zone has allowed me to learn new skills and discover unexpected details of organic reactions. This is not surprising in light of published research on the relationship between discomfort and learning.[40] But have I been creating models that are really new or have I just been applying existing models in new ways and/or to new systems? One could make an argument for either and I am fine with either. Is there added value, which I equate here with creation (making) in the application? To me, yes, but to others, I do not really know. In that regard, I have largely resigned myself to letting the audience for my work decide, despite the discomfort associated with that (think criticisms of papers and grant proposals), and pursue things I find interesting (This essay may similarly put me at risk of disapproval.).

There is, of course, value in showing that a model appreciated by one group is useful to another group and that generally requires translation and illustrative examples considered relevant to the new group; the degree to which such translation is valued is a personal issue. I do not consider myself an expert member of many of the communities with which I interact—physical chemists, synthetic organic chemists, organometallic chemists, photochemists, natural products isolation chemists, and biosynthetic chemists—and there is danger associated with that—for me, my students, my audience—but also tremendous opportunities for mutual learning and model creation.[7,41]

> "Anyhow, when you are doing something in a recurring way to diminish risk or doing it in the same way as you have done it before, it is clear why professionalism is not enough. After all, what is required in our field, more than anything else, is the continuous transgression. Professionalism does not allow for that because transgression has to encompass the possibility of failure and if you are professional your instinct is not to fail, it is to repeat success. So professionalism as a lifetime aspiration is a limited goal." Glaser[42]

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