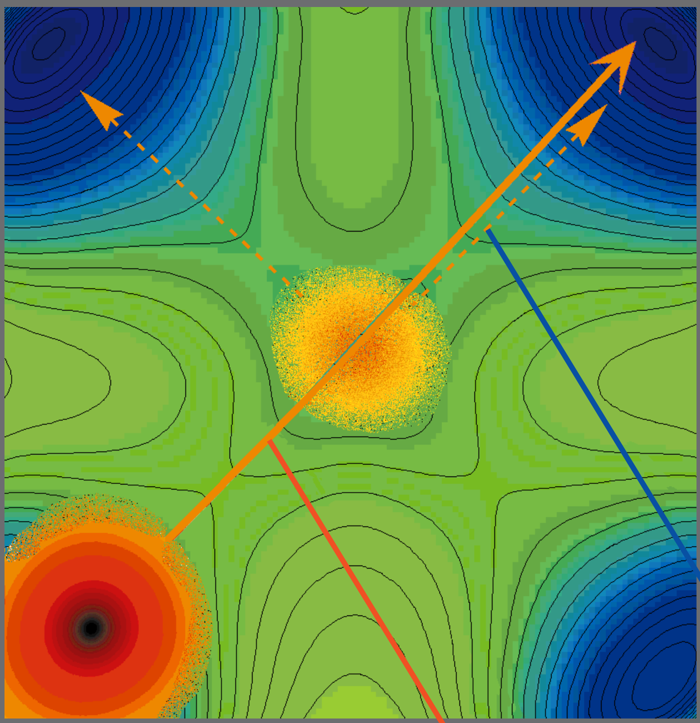
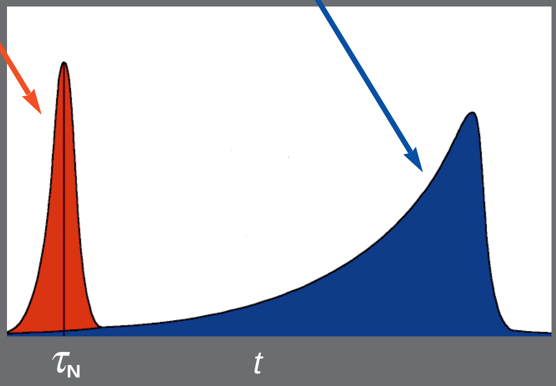


MD simulations suggest that thermally generated intermediates sometimes undergo rapid reactions along “direct” trajectories, which may pass through or near the intermediate region on the potential energy surface, but are not influenced by the symmetry of the underlying energy surface. Such reactions are wrongly assigned as concerted.

ANGEWANDTE
CHEMIE
©WILEY-VCH

The bimodal distribution of lifetimes *t* for the intermediate that will result when direct and statistical trajectories coexist can be probed by experiments conducted in supercritical fluids. Studies of this type can lead to experimental estimates for the lifetime τ_N of the nonstatistical population of intermediates, which can be compared directly with MD simulation results.



Dynamic Behavior of Organic Reactive Intermediates

Barry K. Carpenter*

Although organic chemists have traditionally relied on the so-called statistical models of kinetics, notably transition state theory (TST) and its microcanonical analogue, RRKM theory, to interpret their experiments, research conducted over the last few years has revealed that these models may be inadequate to describe the behavior of reactive intermediates generated in the course of normal, organic chemistry experiments. This review summarizes recent theoretical and experimental results, primarily from the author's laboratory, of studies that have concentrated on circumstances where the deviation from TST behavior is particularly marked. These are reactions involving high-potential energy intermediates that are capable of leading to more than one product.

Keywords: computer chemistry · diradicals · kinetics · molecular dynamics · supercritical fluids

1. Introduction

Research conducted over the last few years[1] has revealed that two of the statistical kinetic models intensively used—namely transition state theory[2] (TST) and its microcanonical analogue, RRKM theory[3]—by organic chemists to describe the behavior of reactive intermediates may be inadequate. It is a central feature of these models—indeed it is what makes them statistical models—that the redistribution of excess kinetic energy within molecules (principally vibrational energy) be assumed to occur much faster than chemical events, namely bond cleavage or formation. A corollorary to this assumption is that preparation of a set of molecules with a nonstatistical distribution of kinetic energy, say localized in a particular normal mode of vibration, should have no effect on the rate of reaction when compared to the reference rate for molecules with the same amount of energy statistically distributed. This is because the presumed fast redistribution would make the nonstatistical population into a statistical population before reaction could occur. The near universal failure of early experiments that were designed to divert the course of a thermal reaction by excitation of particular vibrational modes of the reactant with an infrared laser[4] led many people to the conclusion that the statistical approximation is a good one.

Researchers in the chemical physics community who are knowledgeable about the limitations of the statistical approximation might, if asked, have offered warnings about applying it to multistep reactions, especially those that involve intermediates with high potential energy. Nevertheless, most organic chemists have relied on kinetic models, TST or RRKM theory, that are based on the statistical approximation to analyze just such reactions. This review presents some reasons for thinking that incautious use of the statistical kinetic models might have led to a misinterpretation of some organic reaction mechanisms.

2. Direct Trajectories

A moment's thought can cause one to question the universal applicability of the statistical approximation. The physical mechanisms by which redistribution of vibrational energy and (unimolecular) chemical reaction occur are not very different. If a chemical event—bond cleavage or formation—were to take place within the period of a few molecular vibrations, it would necessarily occur on a timescale comparable to, or perhaps even faster than, redistribution of vibrational energy. The organic chemist's chemical intuition may lead him or her to conclude that for a reaction to be that fast it would either have to be essentially barrierless, or the reacting molecule would have to have excess energy far above the threshold value. However, such intuitive deductions merely serve to show how deeply entrenched the statistical models are in our thinking. Through association of the rates of reaction only with barrier heights and total energy content of the reacting molecules one has implicitly accepted the statistical approximation. Molecular dynamics simulations

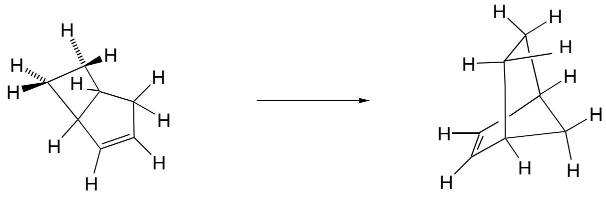
---

[*] Prof. B. K. Carpenter
Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, NY 14853-1301 (USA)
Fax: (+1) 607-255-4137
E-mail: bkc1@cornell.edu

1433-7851/98/3720-3341 $ 17.50+.50/0

suggest that molecules can undergo very fast reactions even when there is a significant energy barrier, and when the total energy is only slightly above the threshold for crossing that barrier.[5a]

A striking example of this behavior occurred in a simulation of the nominal [1,3] sigmatropic rearrangement that interconverted bicyclo[3.2.0]hept-2-ene (**1**) and bicyclo[2.2.1]hept-2-ene (norbornene, **2**).[5b,c] This reaction was studied by the so-called direct dynamics technique, in which the calculation of the molecular potential energy, and the derivatives of that quantity with respect to all geometrical coordinates, are calculated "on the fly" for each trajectory as it evolves.[6] This technique has the great advantage of circumventing the extremely difficult procedure of mapping out the full potential energy surface (PES) for a reaction. Its biggest disadvantage is that it necessarily requires some relatively fast method for computing the potential energy and its derivatives. Typically, that means high-level ab initio calculations cannot be used, at least for molecules of a size of interest to organic chemists. In the present case of **1**→**2** the AM1[7] and PM3[8] semiempirical molecular orbital methods were employed.[9]



1 **2**

As revealed in the potential energy profile shown in Figure 1, the two models agree that the reaction occurs in a nonconcerted fashion via the biradical **3**, which is situated at a local minimum on the PES. However, the methods disagree about the depth of the potential-energy well that corresponds to **3**. At this point one must confront the fact that the fast semiempirical models, which make the direct dynamics simulation feasible, may not be giving accurate descriptions of the underlying PES. However, rather than enter the contentious debate about the reliability of semiempirical molecular orbital methods, I would prefer simply to ask "What if..?" What if the reaction did involve an intermediate biradical; what evidence for its existence might one expect to see experimentally?

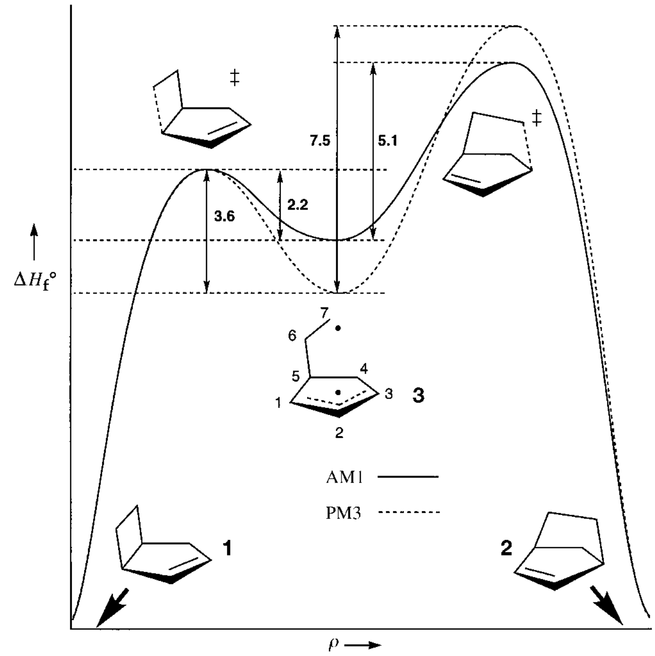
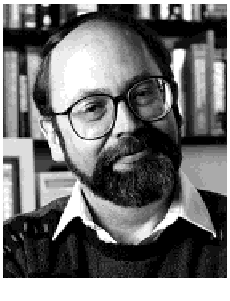


Figure 1. Variation in the enthalpy of the reaction Δ_f^0 in kcal mol^{-1} along the reaction coordinate ρ for the interconversion of **1** and **2**, according to AM1 and PM3 semiempirical molecular orbital calculations.

An answer might come from studying the stereochemistry of the reaction at the migrating carbon atom. If the barrier to internal rotation about the C6–C7 bond were smaller than the barrier to bond formation in the biradical (and both AM1 and PM3 claim that it is) then one might expect to see considerable loss of stereochemical integrity. If there were any stereoselectivity at all, one would expect it to correspond to retention of configuration, since, in a standard kinetic analysis, whatever stereoselectivity there may be could arise only from a failure of the biradicals to reach equilibrium among the rotamers prior to reaction. The experimental fact, first revealed in the classic experiments of Berson and Nelson[10] on an acetoxy derivative of **1**, is that there is a strong preference for inversion of configuration at the migrating carbon atom. Later studies with just deuterium labels revealed a somewhat lower stereoselectivity, but still with inversion preferred.[11] The latter experiments also



Barry K. Carpenter was born on February 13 1949 in Hastings, UK. He completed his B. Sc in Molecular Sciences at Warwick University (1970) before moving to the University College London where he completed his Ph D in organic chemistry in 1973. Between 1973–75 he was a NATO postdoctoral fellow with J. A. Berson at Yale University. Since 1975 he has been in the Department of Chemistry at Cornell University, first as an Assistant Professor (1975–1981), then as an Associate Professor (1981–1985), and since 1985 as Professor. Outside of research and teaching he has been a consultant to many companies, and has participated in many capacities in the organization of journals and conferences. He has received a number of awards which include: Elected Fellow of the American Association for Advancement of Science (1989), Alexander von Humboldt Senior Scientist Award (1990), ACS Cope Scholar Award (1997). His research interests are all in the field of reaction mechanisms.

revealed that the stereoselectivity appeared to exhibit a strange temperature dependence: 76:24 inversion:retention at 276 °C[11a] but 89:11 at 312 °C.[11b] Rarely do reactions show higher stereoselectivity at higher temperature. A possible explanation for this observation will be presented below.

Since the preference for inversion seems inexplicable by the biradical mechanism, and since inversion of configuration is exactly what the Woodward–Hoffmann rules predict for a concerted pericyclic mechanism,[12] there would appear to be persuasive evidence that, as feared, the semiempirical models are giving an incorrect description of the PES, and that the reaction is really a concerted process that involves no biradical intermediate at all.

Nevertheless, we decided to run molecular dynamics (MD) simulations on the AM1 and PM3 surfaces. The procedure involved starting the trajectories in the vicinity of the higher transition structure, allowing them to pass throught the region of the biradical, and then checking to see whether they crossed the lower barrier. This actually corresponds to running the reaction backwards from the way that it goes in reality, but microscopic reversibility allows one to draw useful conclusions anyway. Kinetic energy was supplied in a quantized fashion to the normal modes of the starting structures, with every mode having at least zero-point energy, and some (the lower frequency ones) having higher vibrational excitation. The distribution of energy was chosen to represent a sample from a population at a temperature of 300 °C. It was only feasible to run 100 trajectories on each surface because the calculations are very computationally intensive. This is not a large enough number to represent a statistically valid sample from which quantitative conclusions could be drawn. Nevertheless, the qualitative results were quite informative.

Four of the trajectories run on the PM3 surface passed through the region of the biradical intermediate and formed the closed-shell bicyclo[3.2.0]heptene in about 250–300 fs. The other 96 approached the geometry of the transition structure for C–C bond formation, but did not cross the barrier, and appeared instead to remained "trapped" in the region of the biradical. The feature that differentiated the molecules that reacted promptly from those that became trapped at the intermediate was not the total available energy—several of the "trapped" molecules actually had higher total energies than those that reacted promptly. The proportion of molecules that reacted rapidly was greater on the AM1 surface, with 10 of the 100 trajectories showing this behavior. Some of the trajectories of the trapped species were followed for 2 ps. On neither the AM1 nor the PM3 surface did any of them exit to a closed-shell product.

If one assumes that the "trapped" trajectories correspond to molecules for which the statistical approximation would work reasonably well then one can estimate their lifetimes in the region of the local minimum by RRKM calculation.[3] The results are summarized in Figure 2, where the lifetime of each trajectory in the region of the biradical is summarized in two histograms, one for the PM3 surface and one for the AM1 surface. On average, the molecules that reacted promptly underwent C–C bond formation about 300 times faster than the RRKM model estimates should have been possible.

But there was another feature of the rapidly reacting molecules that was at least as remarkable as their short sojourn in the region of the intermediate: all of them underwent C–C bond formation with a stereochemistry that corresponded to an inversion of configuration at the migating carbon atom. It seems reasonable to assume that the trapped trajectories would lose their "memory" of how they entered the region of the biradical and so would eventually exit to the products in a way that reflected the symmetry of the potential energy surface—that is, with a 50:50 probability of selecting the exits that corresponded to retention or inversion. However, this symmetry was apparently not "seen" by the promptly reacting molecules.

The claimed existence of the promptly reacting molecules, following what I will call from now on *direct trajectories*,[13] is clearly the feature of this dynamics simulation that distinguishes it from the predictions of any statistical model. The fact that the direct trajectories correspond to nonstatistical behavior is confirmed both by their brief duration and by their failure to conform to the symmetry of the underlying PES. But, these are symptoms of nonstatistical behavior; what is its cause?

If it is not total energy that distinguishes direct, nonstatistical trajectories from the trapped, statistical ones, it must be the distribution of the available energy among the

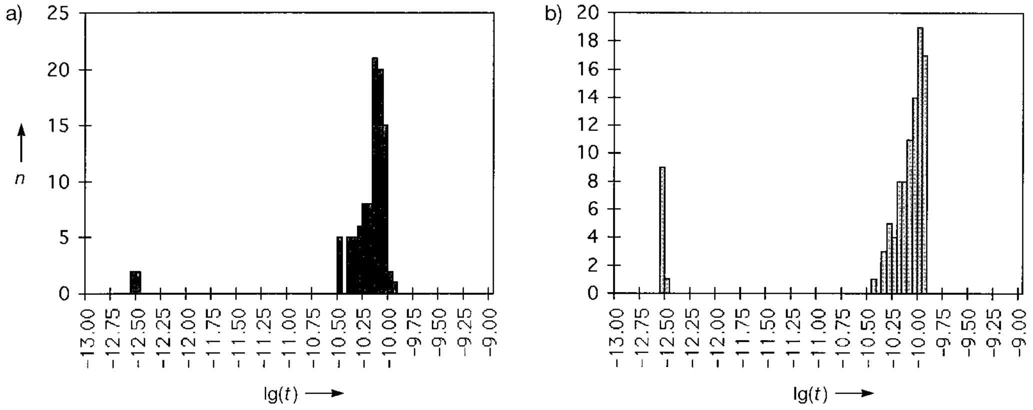


Figure 2. Lifetime (t, in seconds) distributions for the biradical **3** from a) PM3 and b) AM1 dynamic simulations. n = number of trajectories. See text for further discussion.

vibrational modes of the molecule. Indeed, inspection of the direct trajectories reveals that to be true. All of them had a distribution of vibrational energy that caused internal rotation about the C–C bond to the migrating carbon atom at about the same rate, and all with the same sense. Remarkably, the sense of this internal rotation had been deduced by Berson and Nelson from cleverly designed experiments back in 1970.[14] The promptly reacting molecules in our simulation behaved as if they had read the 1970 paper![*] In order to understand what these molecules are doing it is useful to remind ourselves of what would happen if the statistical approximation really were valid throughout the course of the reaction.

3. The Statistical Models

The RRKM picture of a thermal unimolecular reaction[3] is that molecules become energized by collisions, and that eventually a few will have enough total energy to cross the barrier to reaction. However, while possession of total energy above the threshold value is a necessary condition for reaction, it is not a sufficient one. The excess energy must be localized in the set of atomic motions that we call the reaction coordinate if chemical transformation is to occur. Thus, within the small set of molecules that possess sufficient total energy to react is an even smaller subset that has the energy localized in the right vibrational modes to cross the barrier. One could think of the transition–structure region on the potential energy surface as acting like a phase–space[15] filter that allows through only those few molecules that meet certain well-defined conditions. In the RRKM picture one can identify the conditions for passage through this filter and compute the fraction of molecules that meet the conditions by relatively straightforward statistical methods. For reactions in which the barrier height is much greater than kT, this model seems to work very well. However, it is not yet a complete description of what we are interested in. We have only considered crossing the first barrier. If we have defined our reaction to be one that involves an intermediate there must, by definition, be another barrier to be crossed before the reaction is complete. It is in the second step that dynamically interesting things can happen.

4. Dynamic Matching

At first sight there may be no obvious reason why crossing the second barrier would be any different from crossing the first. However, a little more thought allows one to recognize that the reactant molecules for this second step have rather different characteristics from those for the first step. Most importantly, they belong to the elite group that was allowed to pass through the first phase–space filter. In other words they must, at the moment they first attain the geometry of the intermediate, have a rather specialized distribution of their internal energy. Of course, if the statistical models were universally applicable, this special initial distribution of internal energy would have no consequence, because the information that it represented (essentially a history of formation of the intermediate) would be lost before the second reaction occurred. However, this is the point at which the statistical approximation can fail. For the original reactant molecules, which are energized far above their lowest vibrational states, the assumption of very rapid intramolecular redistribution of energy is probably a good one, because many of the vibrational modes will act quite anharmonically, and anharmonicity serves to transfer energy between vibrational modes. However, for a thermally generated intermediate of high potential energy most of the vibrational energy has been drained out of nonreactive modes in order to energize the reactant coordinate for its formation, and so the nonreactive modes can be expected to exhibit near harmonic behavior and consequent weak intermode coupling. Furthermore, the density of vibrational states of the nonreactive modes will typically be much lower than for a highly energized "normal" reactant, and this too can be expected to reduce the rates of energy redistribution.[3g]

If the statistical approximation did apply to the intermediate the small amount of excess vibrational energy that it possessed would become statistically scrambled among the accessible modes. One would then have to wait for sufficient kinetic energy to accumulate in the reaction coordinate for crossing the second barrier before the chemical transformation could be completed. This waiting period is the principal contributor to the lifetime of the intermediate, according to the statistical models. If, on the other hand, the statistical approximation did not apply one could conceive of a situation in which some of the newly created intermediates would find that they already possessed sufficient energy in the second reaction coordinate to sail right on over the second barrier. Those that satisfied this condition would exhibit lifetimes for the intermediate that would be much shorter than the statistical models could understand, since the reacting molecules would have bypassed the scrambling and relocalization of internal energy that such models assume to be necessary.

In order for the hypothesized nonstatistical behavior to occur it is clear that the reaction coordinate for crossing the first barrier must involve similar atomic motions to that for crossing the second. Under such circumstances there can exist efficient "dynamic matching"[5a] between the entrance and exit to the region of the local minimum in the PES that corresponds to the intermediate. In other words, reacting molecules can follow direct trajectories over the first barrier, through the region of the intermediate, and over the second barrier without experiencing the kind of redistribution of internal energy that unthinking application of the statistical kinetic models would seem to require. However, not all molecules can be expected to show such behavior in a thermal reaction. Although the first transition–structure region acts as a quite selective filter, it is not selective down to a single state. There may be molecules in many different states—which differ, for example, in the phase angles between the nonreactive modes—that would be granted entrance to the

---

[*] An animation of a direct and a trapped trajectory is found under http://www.chem.cornell.edu/~bkc1/dynamics.html.

intermediate. A mode that is effectively nonreactive for the first reaction coordinate may be of more importance for the second one, and so not all molecules admitted to the intermediate region may be allowed to exit on the first attempt. If the local minimum has any significant depth it is unlikely that those molecules that fail to make it out on the first try will succeed in doing so on the second. They will become the "trapped" species that the statistical models assumed should be representative of all reacting molecules. They will indeed have to redistribute their internal energy and wait for it to become localized in the second reaction coordinate.

The fraction of molecules that follow direct trajectories will be determined in large measure by the strength with which the dynamics for entrance to and exit from the region of the intermediate are coupled. In simple cases we have shown that the strength of coupling can be estimated by a vectorial analysis.[16] In more complex cases it has so far proven hard to make that estimate without doing a full dynamic simulation. However, one thing is clear: if there are several entrances to and exits from the region of the intermediate on the PES it is quite unlikely that a particular entrance will be dynamically coupled with equal strength to all exits, even when the symmetry properties of the PES would appear to make the exits equivalent. As shown in the simple contour plot of Figure 3 the vertical mirror plane that makes the two transition structures equivalent by symmetry for exit from the intermediate is not "seen" by direct trajectories that enter from just one reactant. If one thinks of the reaction coordinates for passage over each transition structure as simple vectors then it is apparent that the entrance vector makes very different angles with the two exit vectors. This is the reason why the direct trajectories in our simulation of the nominal [1,3] sigmatropic rearrangement did not lead to the two stereoisomeric products with equal probability. Only those trajectories that roll around the intermediate region for some time—the statistical trajectories—can be expected to take the two exits with equal probability.

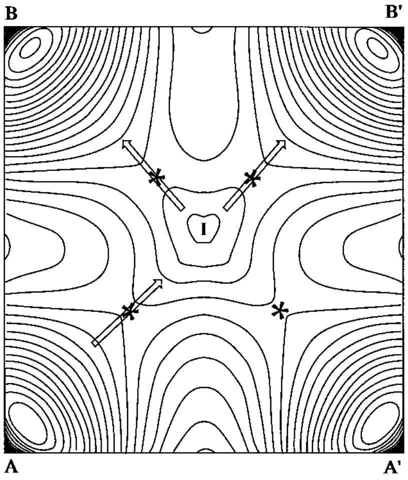


Figure 3. Contour plot of an arbitrary twofold-symmetric PES with a symmetrical intermediate. The reactants are **A** and **A′**, the products **B** and **B′**, and the transition structures are indicated by *. The arrow pointing towards the intermediate **I** symbolizes the reaction coordinate for its formation. The other two arrows symbolize the reaction coordinates for conversion of the intermediate into the products.

It seems likely that the higher proportion of direct trajectories found on the AM1 surface for the [1,3] shift is related to the fact that the intermediate PE well is shallower on that surface than on the PM3 one. It is in the nature of the topology of smooth surfaces that shallower minima tend to have "wider" exit channels. This means that the second phase–space filter becomes looser in its acceptance criteria as the local minimum becomes shallower, and so there is a higher probability that molecules will be able to traverse entrance and exit barriers in a single pass.

While it could not be hoped that the MD simulations could reproduce quantitative experimental data—the semiempirical PE surfaces are too unreliable for that—one might be concerned that the small proportions of direct trajectories seen in the simulations do not seem even qualitatively consistent with the experimental stereoselectivities. However, there is an experimental fact about the rearrangement of compound **1** that has not yet been mentioned. Only about 1–2% of the product is **2**. The remaining 98–99% is cyclopentadiene plus DHC=CHD. Some of these products arise from retro-Diels–Alder decomposition of the product, but if the [1,3] rearrangement really did involve biradical **3** one could expect that some of the fragmentation products could come directly from it too. In fact, a recent femtosecond spectroscopy study has been interpreted as providing experimental evidence for just such a reaction of biradical **3**,[17] although it should be pointed out that the biradical in that case was generated photochemically and consequently had much higher excess internal energy than one would expect for the thermally generated intermediate.

No direct trajectories for fragmentation were seen in the simulations. While this negative result might be attributed to the small sample of trajectories and/or the poor quality of the molecular orbital methods employed, another explanation seems plausible. Fragmentation of **3** presumably requires excitation of modes with C5–C6 stretching components. There is no obvious reason why such modes should contribute significantly to the formation of **3** (in fact, Horn et al.[17] postulate that excitation of this stretch will lead to concerted retro-Diels–Alder fragmentation of norbornene, bypassing **3** altogether) and so dynamic matching between the formation of **3** and its fragmentation is expected to be weak; in other words there should be very few direct trajectories for such a reaction. In the biradical model of the reaction the only source of the rearrangement product with retention of configuration is the statistical population of **3**, and so reducing the contribution from this population, by bleeding it off in a fragmentation reaction, will increase the overall stereoselectivity. Furthermore, if the population of **3** that leads to fragmentation and to the component of **2** that has retained stereochemical configuration really is well described by statistical models, then one would be justified in using TST to analyze the temperature dependence of this competition. The fragmentation of **3** presumably would have a positive activation entropy, whereas the ring closure of **3** to **2** would presumably have a negative one. Consequently, raising the temperature can be expected to increase the proportion of fragmentation, and hence increase the proportion of inversion in **2**. Perhaps this is the source of the unusual temperature dependence of the stereoselectivity that was cited earlier.

5. Stepwise and Concerted Reactions

For decades chemists, especially physical organic chemists, have concerned themselves with distinguishing stepwise from concerted reactions.[18] While there are undoubtedly some reactions that fall neatly into one category or the other, for many reactions the distinction is meaningless. In an earlier review[1] classes of PES were described for which it was not possible to determine whether a local minimum should or should not be called an intermediate in a particular reaction. Here the focus will be on another phenomenon that serves to make the mechanistic distinction moot.

Suppose for the moment that the results of the simulations on the [1,3] shift were qualitatively correct—the reaction really did occur with two dynamically distinct populations of a biradical intermediate. How would such a result be interpreted within the framework of a statistical kinetic model such as TST? The population that gave the two products with equal probability, and involved a relatively long-lived intermediate, would appear to be a "stepwise" component to the reaction. The population that gave just one product and involved something that, if it were an intermediate at all, lasted only for a few molecular vibrations, could well be assigned to the "concerted" category (an assignment bolstered in this case by the coincidental agreement of the observed major product with that predicted by the Woodward–Hoffmann rules[12]). However, concerted reactions are supposed to occur on a part of the PES where there is no local minimum that corresponds to an intermediate; the direct trajectories in the simulations all passed through exactly the same local minimum in which the statistical trajectories became trapped. Rather than there being two different mechanisms, stepwise and concerted, which occur on different parts of the PES, the simulation suggested that there are two different dynamic populations that occupy the same region of the PES.

This phenomenon, if generally applicable, would serve to resolve a long-standing problem. For many supposedly concerted reactions thermochemical estimates of the enthalpy barrier to the alternative stepwise reaction reveal little or no "energy benefit of concert."[19] This apparently coincidental equality of activation barriers for the two supposedly different mechanisms is revealed, in the present interpretation, not to be a coincidence at all, since the two "mechanisms" occur in the same region of the PES.

6. Dynamic Matching versus Barrier Height: Cyclopropane Stereomutation

One of the characteristics of molecules that follow direct trajectories is that they need not conform to the symmetry of the PES in the way that we have come to expect. Thus it is theoretically possible (and, perhaps, experimentally observed in reactions such as the vinylcyclopropane rearrangement[20]) for an optically active reactant to pass through an intermediate with an achiral minimum-energy structure and yet still give optically active products.

An even more stringent test would be to examine reactions for which the exit channel that experiences the best dynamic match to the entrance has a higher barrier to product formation than others that are only weakly dynamically coupled. TST on such a surface would make the clear prediction that the product corresponding to the lowest (free energy) barrier should be kinetically favored. Nonstatistical dynamics might give the preference to a higher barrier channel! It appears that cyclopropane stereomutation occurs on a PES for which such effects might come into play.

The stereomutation (interconversion of optical isomers and *cis*/*trans* isomers) of substituted cyclopropanes is an apparently simple reaction for which there are hidden mechanistic subtleties. Perhaps the feature that has commanded most attention over the many years of study of this reaction has been the prediction by Hoffmann[21] that the process for cyclopropane itself should occur by conrotatory ring opening to give a trimethylene biradical and, of course, conrotatory closure back to cyclopropane. Interestingly, the relative sense of the double methylene group rotation (conrotatory or disrotatory), which was really the essence of Hoffmann's prediction, has not yet been subjected to experimental scrutiny. Rather, the focus has been on the implicit prediction that correlated double rotation should be favored over single rotation of the terminal methylene groups of the trimethylene biradical. Had the trimethylene biradical sat in a relatively deep potential well on the PES one might have expected random rather than correlated rotations of the methylene groups.[22]

Experiments have been carried out on optically active [1,2-D_2]cyclopropane[23] and on optically active [^{13}C-1,2,3-D_3]cyclopropane.[24] In each case the kinetic studies afford two phenomenological rate constants: k_α, the rate constant for loss of optical activity, and k_i, the rate constant for approach to equilibrium of the geometrical isomers. The ratio k_i/k_α can be converted into a ratio of mechanistic rate constants for rotation of one or both methylene groups, k_1 and k_{12}, respectively. In the case of the doubly labeled cyclopropane the conversion requires an assumed value for a secondary H/D isotope effect; in the case of the quadruply labeled molecule it requires only the reasonable assumption that the ^{12}C/^{13}C isotope effect be negligible.

Sadly, these conceptually elegant and experimentally demanding investigations have come to conflicting conclusions. There is no plausible value of the H/D isotope effect that can make the results of the independent studies consistent, and hence no answer on which all researchers agree about whether double methylene group rotation really is favored over single rotation.

If one were willing to trust the predictions of modern electronic structure theory for a molecule as small as cyclopropane it would appear that a clear answer might come from that quarter. However, here too there are pitfalls for the incautious. All modern, high-level, ab initio calculations[25] agree that the lowest energy transition structure for cyclopropane stereomutation is that for conrotatory ring opening, just as Hoffmann had predicted from his extended Hückel calculations. However, the energy differences between conrotatory and disrotatory, or between conrotatory and monorotatory pathways are found in the modern calculations to be much smaller than the extended Hückel model had suggested—small enough that little selectivity between the pathways would be expected at the greater than 400 °C temperatures required for the reaction to occur at a reasonable rate.

Microscopic mechanisms exist for stereomutations that occur only via transition structures corresponding to correlated double rotation and yet wind up as net single-rotation events. These pathways apparently further reduce any preference for correlated double rotation. They are paths in which the trimethylene biradical is formed by disrotation and closes by conrotation, or vice versa.[25] Such reactions do not, as one might think, violate the principle of microscopic reversibility, since that principle tells one only about requirements for reactions that follow the lowest energy pathway. Molecules opening or closing the ring via a disrotatory transition structure would not be following the lowest energy pathway. Nevertheless, such paths might make significant contributions to the overall reaction if, as the modern calculations suggest, the energy differences between conrotatory and disrotatory transition structures were small.

In collaboration with the group of Professor W. T. Borden at the University of Washington we have recently completed a molecular dynamics study on the stereomutation of [1,2-D_2]cyclopropane.[26] The calculations involved fitting an analytical function to points from ab initio electronic structure calculations at the GVB/6-31G* and CASPT2N/6-31G* levels of theory. A projection of the resulting surface is shown in Figure 4. With the vicinities of the key stationary points (the conrotatory and disrotatory transition structures, and the monorotatory second-order stationary point) used as the starting points, 12 000 trajectories were run on the surface. The ratio of double to net single rotations was computed, and compared with the predictions from TST. The difference was striking. As the qualitative analysis outlined above would lead one to expect, TST predicted a ratio of double to net single rotations of only 1.18. However the MD calculations on the same PES found a ratio of 4.73 ± 0.11 (with the uncertainty arising from sampling error).

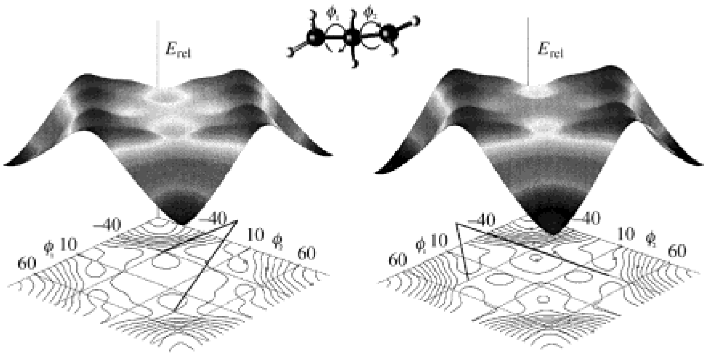


Figure 4. Projections of the analytical PES for the trimethylene biradical used in the MD simulation of cyclopropane stereomutation. The two geometrical coordinates in each graph are the dihedral angles for internal rotation of the terminal methylene groups. The graphs differ in the value of the C-C-C angle. The conrotation and disrotation transition states are shown on the left and right, respectively. E_{rel} is the relative potential energy.

The principal source of the difference is that the molecular dynamics reveal most of the trimethylenes formed by disrotation also reclose by disrotation, and not conrotation as the TST model would seem to imply. The reason is closely related to the phenomenon of conservation of angular momentum, which is applied in this case to the rotating methylene groups. Thus most of the trimethylenes formed by disrotation choose to return to cyclopropane by a path with a higher barrier than necessary. This constitutes a clear example of nonstatistical behavior, and hence a warning flag to those of us who have previously assumed TST-like kinetics for our reactive intermediates.

One must always wonder how sensitive the results of a MD simulation are to the assumptions involved—most particularly the approximation to the PES for the system. In the particular case of cyclopropane stereomutation there exists some information on that point. Concurrent with the simulation described above was one conducted by Doubleday, Bolton, and Hase using the direct dynamics technique.[27] Although their PES was somewhat different from ours, the results were similar. TST on their surface predicted double rotation to be favored over single rotation by 1.5:1, whereas their MD simulations gave a ratio between 2.9:1 to 3.5:1. Thus one can have some confidence that the difference between MD and TST models is not a result of some quirk in the calculations.

7. Experimental Evidence for Mechanistically Significant Direct Trajectories

The preceding discussion has had as a principal theme the claim that direct trajectories are of mechanistic significance because they can mimic behavior expected for a concerted reaction, that is a process occurring on a part of the PES where there is no local minimum that corresponds to an intermediate. In particular, the direct trajectories can lead to product ratios that fail to conform to the symmetry of the PES. It becomes important, therefore, to distinguish when a reaction really occurs by competitive mechanisms that explore different parts of the PES and when it occurs with coexistence of nonstatistical and statistical dynamic populations of a common "intermediate." We have recently developed an experimental technique that may allow such a distinction to be drawn.

The strategy behind the experiment is to try to intercept the putative direct trajectories by collision of the "intermediate" with a chemically unreactive partner. For a direct trajectory, redistribution of internal energy as a result of the collision would correspond to a deflection from the ballistic path to product, and might convert it into a trapped, presumably statistical, trajectory. This should result in a change in the product ratio. The situation can be modeled kinetically as shown in Figure 5b. In this scheme the PES is assumed to possess an effective symmetry element such that statistical trajectories will lead to the two products **P** and **Q** with equal probability. The direct trajectories are assumed to give only

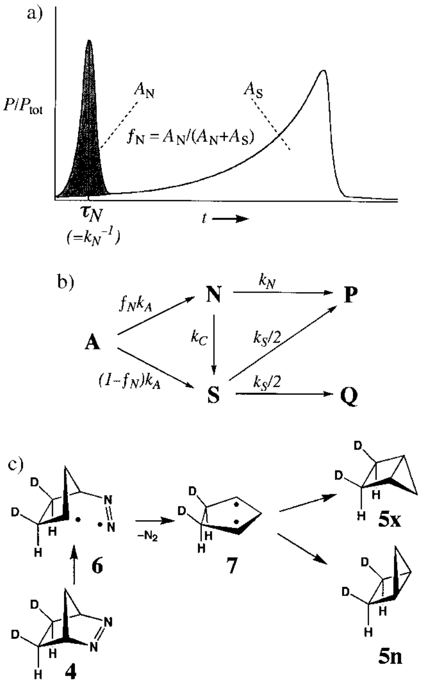


Figure 5. Kinetic representation of the supercrtical-fluid experiment described in the text. a) Schematic representation that generalizes the simulation results shown in Figure 2; P/P_{tot} = relative probability of the intermediate having a lifetime t, A_N/A_S = the proportion of the non-statistical/stastical population; b) the kinetic scheme; c) the particular reaction studied in the experiment.

one product (in this case **P**), for reasons discussed above. The phenomenological rate constants k_P and k_Q, for the formation of **P** and **Q**, respectively, from **A**, can be related to the microscopic rate constants of the mechanistic scheme by applying the usual steady-state approximation to the biradical populations **N** and **S** as shown in Equation (1). As expected,

$$\frac{k_P}{k_Q} = \frac{k_C + (1 + f_N)k_N}{k_C + (1 - f_N)k_N} \tag{1}$$

the ratio of phenomenological rate constants depends on the collision frequency k_C, on the fraction of trajectories that are nonstatistical f_N, and on the rate constant k_N, with which the nonstatistical population proceeds on to its product.

To intercept the direct trajectories it is clear that k_C has to be of similar magnitude to k_N. The simulations described earlier in this review have given values for the average lifetime of the nonstatistical populations of singlet biradicals ($\tau_N = k_N^{-1}$) in the range 100 to 300 fs.[5,26,27] That means one needs collision frequencies in the range of 10^{12} to 10^{13} s^{-1}. Such high collision frequencies are not easily attained in the gas phase, but are accessible in supercritical fluids.[28] In such a medium the density, and hence effective collision frequency, can be adjusted over a wide range by changing the pressure.[28,29] As shown by Equation (1) the dynamic model leads one to expect that the product ratio should approach unity as the pressure, and hence collision frequency, increases. This expectation stands in contrast to that from the competitive-mechanisms model, as illustrated by consideration of the specific reaction studied in the present work.

The azo compound **4** has long been known to give the stereoisomeric biyclopentanes **5x** and **5n** (Figure 5c) in a ratio that favors the *exo* isomer by about 3:1 in the gas phase.[30] Correction for the interconversion of the products during the reaction allows one to derive the intrinsic ratio (k_P/k_Q), which turns out to be constant at (4.7 ± 0.9):1 over a temperature range from 130 to 180 °C.[16] One mechanism for explaining the preferential formation of **5x** would be to invoke a concerted C–C bond formation and C–N bond cleavage from the biradical **6**, which is now generally agreed to be the first-formed intermediate.[31] If this concerted reaction occurred with inversion of configuration at the carbon center from which N_2 was departing, the result would indeed give **5x**.[30] In order to explain the source of **5n** one might invoke a competitive process in which C–N bond cleavage occurred prior to C–C bond formation to afford cyclopentane-1,3-diyl, which could give both stereoisomers of the bicyclopentane.

An alternative explanation for the stereochemistry has arisen from a combination of experiments[16] and molecular dynamics simulations[16,32] on the reaction. In this mechanism cleavage of the second C–N bond always precedes formation of the C–C bond. Some fraction (f_N) of the population of the resulting cyclopentane-1,3-diyl closes to product **5x** before it has had time to randomize its internal energy. The preference for formation of **5x** over **5n** in such a picture can be ascribed to better dynamic matching between the entrance channel to cyclopentane-1,3-diyl and the exit channel for inversion.[16]

As described above, the dynamic model leads one to expect that k_P/k_Q should decrease with increasing pressure if the reaction were run in a supercritical fluid. By contrast, one might expect from the competitive-mechanisms model that the product ratio would increase with increasing pressure. This expectation is because the only influence from a change in pressure that one might expect in the latter model would arise from differences in the activation volume for the two pathways. It is well known that activation volumes for uncharged systems are related to numbers of bonds being made and broken in the rate-limiting transition structure.[33,34] By this criterion, the activation volume for the putative concerted pathway should be smaller than that for the stepwise one, and so the former should be favored at higher pressure, and lead to an increase of k_P/k_Q (although it should be noted that the range of pressures explored here is smaller than that used in studies where such effects have been detected.[33]) This difference in expected outcomes from the two models is not specific to the reaction studied here. It is generally true that the dynamic model will lead to predictions of lower product ratios with increasing pressure whereas the competitive-mechanisms model will predict the opposite (at least for the common situation in which the mechanisms in competition are stepwise and concerted versions of the same transformation).

The experimental results are shown in Figure 6.[35] The lines through the data points correspond to best fits of an isolated-binary collision (IBC) model (solid line),[36] and of a Troe-type model (dashed line) in which the collision frequency in the supercritical propane is related to the inverse of the self-diffusion coefficient.[37] It is clear that the ratio of pheno-

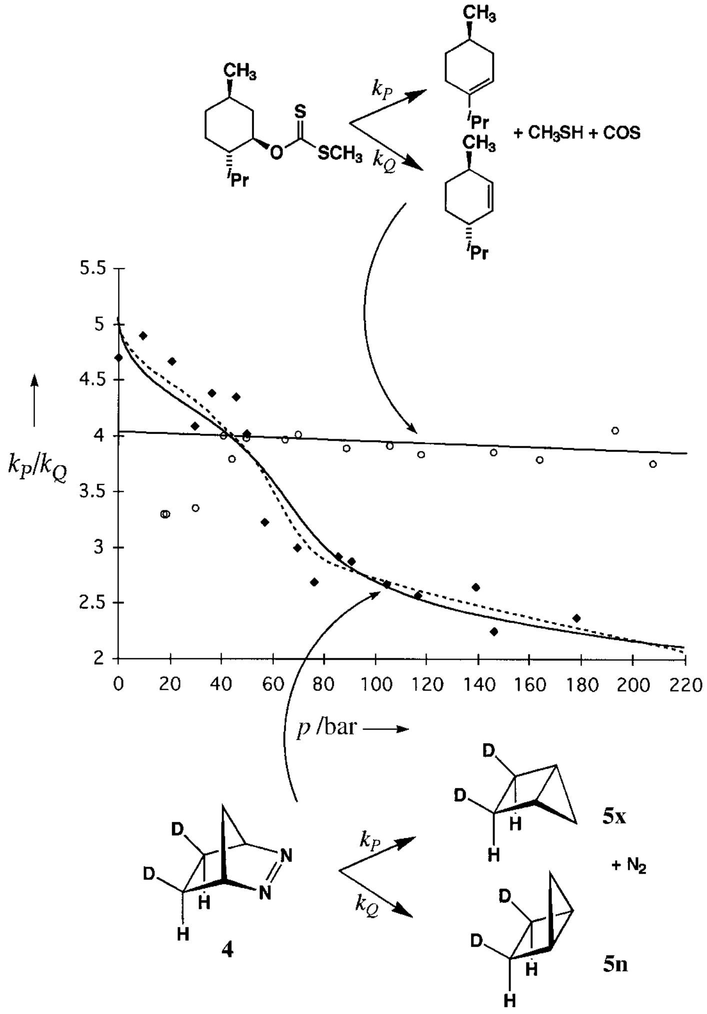


Figure 6. Experimental results for the ratio of phenomenological rate constants as a function of pressure in supercritical propane at 140 °C. The curves through the azo-compound data are from the IBC model (solid line) and the Troe model (dashed line).

menological rate constants decreases with increasing pressure, as expected for the dynamic model. The data smoothly interpolate between previously determined gas-phase and solution-phase values of k_P/k_Q.[16] Furthermore the best-fit values of the adjustable parameters for the IBC and Troe models seem physically reasonable.[35] Of special interest are the fraction (f_N) of reactions that occur via direct, nonstatistical trajectories, which turned out to be 0.67 for both models, and the lifetime ($\tau_N = k_N^{-1}$) of the nonstatistical population, which was found to be 130 ± 22 fs by the IBC model and 103 ± 13 fs by the Troe model.[35]

Also shown in Figure 6 (top) are results for a control reaction in which the products really do come from two competitive mechanisms. The competitive pathways for the control are both believed to be concerted reactions,[38] and in accord with that, one sees little dependence of product ratio on pressure in the region where the reactant is miscible with the supercritical fluid (above about 40 bar).[35] The azo compound can be shown to be miscible with the propane throughout the pressure range of the experiment.[35]

It appears that the study of reactions in supercritical media may be of general value for distinguishing dynamically controlled reactions from those that occur by genuinely different mechanisms. In the cases where the former appears to be the better description, such studies can also afford values for critical parameters that can be compared with simulation results.

8. Summary and Outlook

In this review the focus has been on the significant deviations from TST-like behavior that can be expected for some reactive intermediates. The work to date has concerned itself primarily with the behavior of singlet-state biradicals, but there is no obvious reason why other intermediates shouldn't show similar nonstatistical dynamics. In fact, the author's research group is examining, both experimentally and theoretically, reactions of radical pairs and singlet carbenes for which some preliminary results already suggest that similar behavior is being exhibited.

In a significant departure from the work to date we have also begun, in collaboration with Professor M. N. Paddon-Row at the University of New South Wales, to examine the role of molecular dynamics in intramolecular electron transfer. Here, attention is being paid to the role that molecular vibrations can have in promoting the electron-transfer event. This promises to provide an interesting complement to earlier studies that have sought to identify particular structural motifs that may facilitate the reaction.

As increasing computational power makes dynamic simulation of large molecules more feasible, it should be possible to expand the application of MD techniques to a wide range of organic transformations. The use of more accurate methods for computing the underlying PES is becoming feasible as computers become faster. Work along these lines is currently following three tracks. In one approach, semiempirical methods are recalibrated against the results of high-level ab initio models for specific reactions,[6] while in another, density functional theory with the local-density approximation is used to derive the potential energy and its derivatives.[39] In the third approach, hybrid quantum mechanical and molecular mechanics methods are employed.[40] All three methods have been used with good results.

If the work so far completed is any guide, such studies may reveal that the simple kinetic and structural models that we in the organic chemistry community have been forced to use in the past may not always have served us as well as we had hoped.

The experimental testing of the computational predictions is particularly challenging. The supercritical-fluid experiments described in this review promise to provide some useful insights, as well as quantitative data that can be compared with simulation results. However, there is certainly plenty of room for mechanistic chemists to devise other techniques that can probe the role of dynamics in reactions run under the conditions of the typical organic chemistry laboratory. This is a new kind of task for the physical organic chemist, and one that the author hopes some readers may choose to take on.

In the end, one probably doesn't want to be forced to carry out a full molecular dynamics simulation for every reaction in order to find out whether deviations from statistical behavior are to be expected. It is to be hoped that the community of organic chemists may be able to do for molecular dynamics what it did quite successfully for electronic structure theory, namely to derive simple, qualitative or semiquantitative rules that capture the essence of the full theory. We are currently rather far from that goal, and probably will remain so until enough full-scale simulations and experiments have been conducted for the community to begin to perceive the patterns of behavior of reactive intermediates.

The author would like to thank the National Science Foundation for support of the work described herein. He also owes a considerable debt of gratitude to the graduate students and postdoctoral associates who work on the experimental testing of the new theoretical models. The collaboration with Dr Borden's group and the congenial interaction with Drs Doubleday and Hase on the cyclopropane stereomutation calculations were much appreciated and are gratefully acknowledged. Finally, the author expresses his thanks for use of the facilities of the University of New South Wales, and for the kind hospitality of his host there, Prof. Michael Paddon-Row, during the sabbatical leave in which he wrote most of this review.

Received: January 20, 1997 [A270IE]
German version: *Angew. Chem.* **1998**, *110*, 3532–3543

---

[1] B. K. Carpenter, *Acc. Chem. Res.* **1992**, *25*, 520–528.

[2] a) H. Pelzer, E. Wigner, *Z. Phys. Chem. Abt. B* **1932**, *15*, 445–471; b) S. Glasstone, K. J. Laidler, H. Eyring, *Theory of Rate Processes*, McGraw-Hill, New York, **1940**.

[3] a) O. K. Rice, H. C. Ramsperger, *J. Am. Chem. Soc.* **1927**, *49*, 1617–1629; b) O. K. Rice, H. C. Ramsperger, *J. Am. Chem. Soc.* **1928**, *50*, 617–620; c) L. S. Kassel, *J. Phys. Chem.* **1928**, *32*, 225–242; d) L. S. Kassel, *J. Phys. Chem.* **1928**, *32*, 1065–1079; e) R. A. Marcus, O. K. Rice, *J. Phys. Colloid Chem.* **1951**, *55*, 894–907; f) R. A. Marcus, *J. Chem. Phys.* **1952**, *20*, 352–368; g) P. J. Robinson, K. A. Holbrook, *Unimolecular Reactions*, Wiley, New York, **1971**; h) W. Forst, *Unimolecular Reactions*, Academic Press, New York, **1973**.

[4] For an interesting discussion of this topic, see K. L. Kompa, R. D. Levine, *Acc. Chem. Res.* **1994**, *27*, 91–93.

[5] a) R. D. Kay, L. M. Raff, *J. Phys. Chem. A* **1997**, *101*, 1007–1017; b) B. K. Carpenter, *J. Am. Chem. Soc.* **1995**, *117*, 6336–6344; c) B. K. Carpenter, *J. Am. Chem. Soc.* **1996**, *118*, 10329–10330.

[6] For an example and key references, see Y.-P. Liu, D. Lu, A. Gonzalez-Lafont, D. G. Truhlar, B. C. Garrett, *J. Am. Chem. Soc.* **1993**, *115*, 7806–7817.

[7] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

[8] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209–264.

[9] Calculations were carried out with Revision 2 of the MOPAC93 package (J. J. P. Stewart, Fujitsu Limited, Tokyo, Japan, **1993**).

[10] J. A. Berson, G. L. Nelson, *J. Am. Chem. Soc.* **1967**, *89*, 5503–5504.

[11] a) J. E. Baldwin, K. D. Belfield, *J. Am. Chem. Soc.* **1988**, *110*, 296–297; b) F.-G. Klärner, R. Drewes, D. Hasselman, *J. Am. Chem. Soc.* **1988**, *110*, 297–298.

[12] R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, **1970**.

[13] a) M. J. Davis, S. K. Gray, *J. Chem. Phys.* **1986**, *84*, 5389–5411; b) M. J. Davis, *J. Chem. Phys.* **1987**, *86*, 3978–4003; c) M. Simonson, K. S. Bradley, G. C. Schatz, *Chem. Phys. Lett.* **1995**, *244*, 19–26; d) A. A. C. C. Pais, A. I. Voronin, A. J. C. Varandas, *J. Phys. Chem.* **1996**, *100*, 7480–7487; e) S. R. Vande Linde, W. L. Hase, *J. Am. Chem. Soc.* **1989**, *111*, 2349–2351; f) W. L. Hase, *Science* **1994**, *266*, 998–1002.

[14] J. A. Berson, G. L. Nelson, *J. Am. Chem. Soc.* **1970**, *92*, 1096–1097.

[15] For a lucid review on the concept of phase space, see R. Q. Topper in *Reviews in Computational Chemistry, Vol. 10* (Eds.: K. B. Lipkowitz, D. B. Boyd), VCH, New York, **1997**.

[16] a) T. H. Peterson, B. K. Carpenter, *J. Am. Chem. Soc.* **1992**, *114*, 766–767; b) B. A. Lyons, J. Pfeifer, T. H. Peterson, B. K. Carpenter, *J. Am. Chem. Soc.* **1993**, *115*, 2427–2437.

[17] B. A. Horn, J. L. Herek, A. H. Zewail, *J. Am. Chem. Soc.* **1996**, *118*, 8755–8756.

[18] See, for example R. E. Lehr, A. P. Marchand in *Pericyclic Reactions, Vol. 1* (Eds.: A. P. Marchand, R. E. Lehr), Academic Press, New York, **1977**, chap. 1.

[19] W. von E. Doering, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 5279–5283.

[20] J. E. Baldwin, *J. Comput. Chem.* **1997**, *19*, 222–231, and references therein.

[21] R. Hoffmann, *J. Am. Chem. Soc.* **1968**, *90*, 1475–1485.

[22] S. W. Benson, H. O'Neal, *J. Phys. Chem.* **1968**, *72*, 1866–1887.

[23] a) L. D. Pedersen, J. A. Berson, *J. Am. Chem. Soc.* **1975**, *97*, 238–240; b) J. A. Berson, L. D. Pedersen, B. K. Carpenter, *J. Am. Chem. Soc.* **1976**, *98*, 122–143; c) S. J. Cianciosi, N. Ragunathan, T. R. Freedman, L. A. Nafie, J. E. Baldwin, *J. Am. Chem. Soc.* **1990**, *112*, 8204–8206.

[24] S. J. Cianciosi, N. Ragunathan, T. R. Freedman, L. A. Nafie, D. K. Lewis, D. A. Glenar, J. E. Baldwin, *J. Am. Chem. Soc.* **1991**, *113*, 1864–1866.

[25] a) S. J. Getty, E. R. Davidson, W. T. Borden, *J. Am. Chem. Soc.* **1992**, *114*, 2085–2093; b) J. E. Baldwin, Y. Yamaguchi, H. F. Schaefer III *J. Phys. Chem.* **1994**, *98*, 7513–7522; c) C. Doubleday, Jr. *J. Phys. Chem.* **1996**, *100*, 3520–3526.

[26] D. A. Hrovat, S. Fang, W. T. Borden, B. K. Carpenter, *J. Am. Chem. Soc.* **1997**, *119*, 5253–5254.

[27] C. Doubleday, Jr., K. Bolton, W. L. Hase, *J. Am. Chem. Soc.* **1997**, *119*, 5251–5252.

[28] T. W. Randolph, J. A. O'Brien, S. Ganapathy, *J. Phys. Chem.* **1994**, *98*, 4173–4179, and references therein.

[29] For an early experiment in which the influence of a similar phenomenon on the overall magnitude of the phenomenological rate constant was investigated, see M. L. Dutton, D. L. Bunker, H. H. Harris, *J. Phys. Chem.* **1972**, *76*, 2614–2617.

[30] a) W. R. Roth, M. Martin, *Justus Liebigs Ann. Chem.* **1967**, *702*, 1–7; b) W. R. Roth, M. Martin, *Tetrahedron Lett.* **1967**, 4695–4698; c) E. L. Allred, R. L. Smith, *J. Am. Chem. Soc.* **1967**, *89*, 7133–7134.

[31] a) C. J. S. M. Simpson, G. J. Wilson, W. Adam, *J. Am. Chem. Soc.* **1991**, *113*, 4728–4732; b) J. S. Adams, K. A. Burton, B. K. Andrews, R. B. Weisman, P. S. Engel, *J. Am. Chem. Soc.* **1986**, *108*, 7935–7938; c) J. S. Adams, R. B. Weisman, P. S. Engel, *J. Am. Chem. Soc.* **1990**, *112*, 9115–9121.

[32] D. C. Sorescu, D. L. Thompson, L. M. Raff, *J. Chem. Phys.* **1995**, *102*, 7910–7924.

[33] F.-G. Klärner, B. Krawczyk, V. Ruster, U. K. Deiters, *J. Am. Chem. Soc.* **1994**, *116*, 7646–7657.

[34] For lucid general descriptions of the physical basis for pressure effects on elementary reactions, including some cautionary notes on interpretation of activation volumes, see a) J. A. Montgomery, Jr., D. Chandler, B. J. Berne, *J. Chem. Phys.* **1979**, *70*, 4056–4066; b) J. Troe, *J. Phys. Chem.* **1986**, *90*, 357–365; c) W. L. Hase, *J. Phys. Chem.* **1986**, *90*, 365–374.

[35] M. B. Reyes, B. K. Carpenter, *J. Am. Chem. Soc.* **1998**, *120*, 1641–1642.

[36] K. E. Schultz, D. J. Russell, C. B. Harris, *J. Chem. Phys.* **1992**, *97*, 5431–5438.

[37] a) B. Otto, J. Schroeder, J. Troe, *J. Chem. Phys.* **1984**, *81*, 202–213; b) H. Hippler, V. Schubert, J. Troe, *J. Phys. Chem.* **1984**, *81*, 3931–3941; c) G. Maneke, J. Schroeder, J. Troe, F. Voss, *Ber. Bunsen-Ges Phys. Chem.* **1985**, *89*, 896–906.

[38] H. R. Nace, *Org. React. (N.Y.)* **1962**, *12*, 57–100.

[39] R. Car, M. Parrinello, *Phys. Rev. Lett.* **1985**, *55*, 2471–2474.

[40] F. Bernardi, M. Olivucci, M. A. Robb, *J. Am. Chem. Soc.* **1992**, *114*, 1606–1616.