J. Am. Chem. Soc. **1995,** *117,* 6336–6344

Dynamic Matching: The Cause of Inversion of Configuration in the [1,3] Sigmatropic Migration?

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Received February 23, 1995[⊗]

Abstract: Direct dynamics calculations using the PM3 semiempirical molecular orbital method are carried out on the formal [1,3] sigmatropic migration that interconverts bicyclo[3.2.0]hept-2-ene and norbornene. Methylated analogs are also investigated. It is shown that, despite the existence of a 5 kcal/mol local minimum corresponding to a biradical intermediate on the PM3 potential energy surface for the reaction, the transformation still occurs with a preference for inversion of configuration at the migrating carbon. This stereoselectivity is dynamic in origin and has nothing to do with conservation of orbital symmetry. It can be overcome with a suitably placed methyl substituent, as is observed experimentally. The calculations result in movies that the reader can find on the World Wide Web (http://www.chem.cornell.edu/~bkc1/Sigmatropy.html). The implications of the calculations for the mechanisms of nominal [1,*n*] sigmatropic shifts of carbon are discussed.

Kinetic models for the behavior of unobserved transient intermediates are crucial for the analysis of mechanisms in a wide variety of chemical reactions. Many examples can be found in the literature on pericyclic reactions, where, for a given transformation, one can imagine a truly pericyclic mechanism, involving simultaneous making and breaking of bonds in a process that converts reactant(s) to product(s) in a single event, or a stepwise mechanism (sometimes more than one is possible), involving the formation of a transient intermediate. Many studies on the stereochemistry of nominally pericyclic reactions have been conducted in order to try to differentiate between these mechanisms.[1] The stereochemical outcome to be expected for the pericyclic mechanism is generally unambiguous, provided one demands adherence to the rules for conservation of orbital symmetry.[2] The stereochemistry expected for the stepwise mechanism is not necessarily so obvious, however. Typically, a kinetic model has been assumed in which transient species, such as biradicals or zwitterions, that would be capable of losing stereochemical information by internal rotation about single bonds or pyramidal inversion at tricoordinate carbon will in fact lose that information, and that mechanisms involving such species will therefore be characterized by a lack of stereoselectivity.[1] It is this latter assumption that is the focus of the present paper.

The work presented herein consists of a numerical experiment in which classical molecular dynamics are studied on a potential energy surface computed by semiempirical molecular orbital theory. The procedure used is one sometimes called "direct dynamics", in which the necessary part of the potential energy surface is computed for each individual trajectory during the course of the dynamics calculation.[3] The potential energy surface in this paper describes a nominal [1,3] sigmatropic shift, but follows a mechanism in which there is a distinct singlet-state biradical intermediate, as judged by the existence of a 5 kcal/mol local potential-energy minimum in the region of the biradical structure. The results are used both to question the assumption of nonstereoselectivity of reactions involving singlet biradicals and to suggest the possible future development of a dynamic selection rule that might eventually be used to identify favorable reaction stereochemistry in a variety of thermal reactions, including (but not limited to) nominally pericyclic ones.

One of the early experimental tests of the rules for conservation of orbital symmetry was the classic series of experiments on thermal [1,3] sigmatropic migrations in bicyclo[3.2.0]hept-2-ene derivatives carried out by Berson and Nelson.[4] These studies showed preference for inversion of configuration at the migrating carbon, as predicted[2] for a pericyclic [1,3] migration that is constrained to be suprafacial. An exception to this general conclusion was found when an *endo* methyl substituent was attached to the migrating carbon. Its presence—presumably its steric influence—caused the migration now to occur with a preference for retention.[5]

More recently, the thermal rearrangement of bicyclo[3.2.0]-heptene has been reinvestigated, using only deuterium labels for the stereochemical interrogation. The principal conclusion remained qualitatively unchanged—inversion is preferred. However, it is worth noting that there was an apparently unusual temperature dependence observed, with the reaction seeming to become more stereoselective as the temperature increased (76% inversion at 276 °C,[6] and 89% inversion at 312 °C[7]). The results of all of these studies are summarized in Scheme 1. The study has very recently been extended to include heteroatom analogues.[8]

In another nominal [1,3] rearrangement—that of 1-phenylbicyclo[2.1.1]hex-2-ene-5-*d*,[9] an alternative to the orbital sym-

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[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1995.

[1] See, for example: *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. 1, Chapter 1.

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

[3] (a) See Liu et al. (Liu, Y.-P.; Lu, D.; Gonzalez-Lafont, A.; Truhlar, D. G.; Garrett, B. C. *J. Am. Chem. Soc.* **1993**, *115*, 7806) for a recent example and for key references. (b) The present calculations used the dynamic reaction coordinate procedure that is part of the MOPAC 7.0 and MOPAC 93 packages.[11]

[4] Berson, J. A.; Nelson, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 5502.

[5] Berson, J. A.; Nelson, G. L. *J. Am. Chem. Soc.* **1970**, *92*, 1096.

[6] Baldwin, J. E.; Belfield, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 296.

[7] Klärner, F.-G.; Drewes, R.; Hasselman, D. *J. Am. Chem. Soc.* **1988**, *110*, 297.

[8] Klärner, F.-G.; Yaslak, S.; Drewes, R.; Gesenberg, C.; Peter, M. In preparation.

[9] (a) Newman-Evans, R. H.; Carpenter, B. K. *J. Am. Chem. Soc.* **1984**, *106*, 7994. (b) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695.

[10] Carpenter, B. K. *J. Org. Chem.* **1992**, *57*, 4645.

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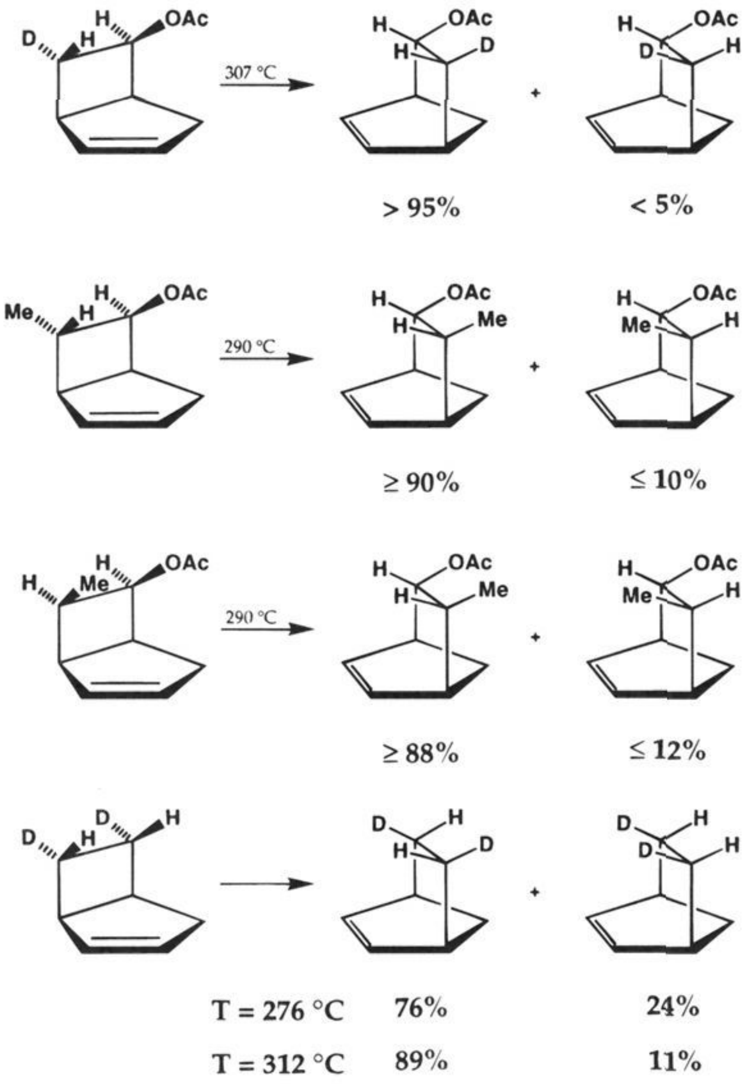
Scheme 1



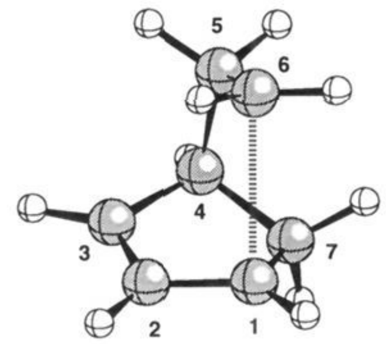
metry rules has been explored[10] in an attempt to explain the apparent lack of temperature dependence of the stereoselectivity found in this case. The analysis examined a possible role to be played by intramolecular dynamics in determining the reaction stereochemistry. Qualitative arguments were put forward, using as their basis the few geometrical coordinates of the problem presumed to be most important for the reaction.

The present study also focuses on reaction dynamics, but it uses a different computational approach. The work reported in this paper involved direct classical dynamics calculations on the bicyclo[3.2.0]hept-2-ene system, in the full multidimensional space of the problem, using the PM3 semiempirical molecular orbital procedure[11] to provide the underlying potential energy surface.[12] The results suggest that the experimentally observed preference for inversion in the rearrangement of this molecule cannot be considered definitive support for a pericyclic mechanism, since a similar result might be expected for a reaction involving a distinct biradical local minimum on the potential energy surface. They further suggest that some of the elements of the earlier qualitative analysis[10] may be correct, whereas others need modification. Calculations have been carried out on methylated and non-methylated substrates, in order to assess the steric effect of a methyl group on the migrating carbon. The results of the calculations in these two series will be presented and discussed separately, and then put in a more general context in a concluding section of the paper.

Bicyclo[3.2.0]hept-2-ene/Norbornene Interconversion

Results. The PM3 model, using the minimal CI necessary for description of a singlet biradical,[13] does not exactly reproduce the experimental thermodynamics of the bicyclo[3.2.0]hept-2-ene to norbornene rearrangement. In reality, the reaction is probably somewhat exothermic, whereas the calculations make it slightly endothermic. This error does not necessarily invalidate the use of the method for the qualitative purposes described herein, but it does have an impact on the way that the calculations were carried out.

Table 1



Mode	Frequency (cm^{-1})	Description of Principal Components
1	306.3*i*	C1-C6 stretch; out-of-plane H bends at C1 and C6.
2	174.5	C4-C5 and C5-C6 torsions.
3	313.9	C3-C4-C5 angle bend, plus ring flex.
4	336.1	C5-C6 torsion, plus ring flex.
5	383.2	C5-C6 torsion, plus ring flex.
6	444.3	Out-of-plane H bends at C2 and C3, plus ring flex.
7	518.9	Out-of-plane H bends at C2 and C3, plus ring flex.
8	643.4	Out-of-plane H bends at C1 and C6.

The PM3 model finds a distinct biradical minimum, with separate transition states leading to the bicyclo[3.2.0]heptene and norbornene closed-shell minima. The apparent error in overall thermodynamics is reflected in the relative energies of the transition structures—with the one linking the biradical to norbornene being higher in energy by about 4 kcal/mol. This probable artifact made it easier to run the trajectories in the reverse direction from those corresponding to the real reaction—i.e., toward bicyclo[3.2.0]heptene. The principle of microscopic reversibility should still allow one to draw conclusions about the real reaction from such an analysis.

As a prelude to the dynamics studies, a normal-mode analysis was carried out on the transition structure linking the biradical and norbornene. The first eight vibrational modes (in order of increasing calculated frequency) are characterized in Table 1.

All trajectories were started from this transition structure. Kinetic energy exactly equal in magnitude to the computed zero-point energy was supplied to each of the 44 modes of real frequency. The mode of imaginary frequency was supplied with 2 kcal/mol of kinetic energy, making a total of 92.9 kcal/mol of total kinetic energy in the starting state. With the particular relative phases selected for the initial vibrational modes, the molecule left the starting structure and completed formation of bicyclo[3.2.0]heptene in a little over 250 fs. Interestingly, it did so with an approximately 180° counterclockwise rotation about the C5−C6 bond, corresponding to product formation with inversion of configuration at C6.

By choosing a stationary point on the potential energy surface as the starting structure, one has selected only those initial states in which all vibrational modes are simultaneously at their positions of minimum potential energy. Nevertheless, there are still a large number (2^{45}) of relative phases that can be defined for the vibrations. The different phase combinations define

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[11] (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Calculations were carried out using MOPAC 7.0 on an IBM RS/6000 computer. Some checks were made using MOPAC 93 on a Power Macintosh 8100/80AV. While small differences between MOPAC 7.0 and 93 were found, none affected the conclusions of this paper.

[12] Since the PM3 calculations give heats of formation rather than potential energies of all species, the relative enthalpy was used in place of relative potential energy.

[13] Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92.

trajectories with different initial directions on the potential energy surface, but with identical starting geometries (and hence identical potential energies) and identical kinetic energies. All such trajectories should be equally probable. Since calculation of each trajectory takes between 1 and 6 h of CPU time on an IBM RS/6000 workstation, it is not feasible to investigate any significant fraction of these possible starting states. In the present study, 35 different trajectories have been studied.

Changing the relative phase of vibrational modes higher in frequency than the first eight had no significant effect on the outcome in any of the trajectories studied. Bicyclo[3.20]heptene was still formed with inversion of configuration and on a very short time scale. Changing phases of some of the first eight vibrations did have an effect, however. In particular, reversing the phase of mode 4, such that the initial rotation about the C5−C6 bond was in the clockwise sense, led to the formation of a relatively long lived (>1 ps) biradical, rather than to the rapid formation of bicyclo[3.2.0]heptene seen previously. The true lifetime and eventual fate of this biradical could not be determined because calculations of long-time trajectories are computationally too intensive, and anyway tend to be unreliable—in part because of accumulated rounding errors.

Before proceeding to a discussion of the reason for the strong dependence of the dynamic behavior on the initial phase of mode 4, it is necessary to deal with another issue. It has long been recognized that there is a potentially serious flaw in all simulations of molecular dynamics based on classical mechanics. The problem is the improper treatment of zero-point energy (ZPE).[14] Since ZPE is fundamentally quantum mechanical in origin, it is difficult to handle in a classical simulation. Of particular concern is the fact that a classical harmonic oscillator can have a kinetic energy that is lower than $h\nu/2$—indeed, it can be zero—whereas a quantum mechanical oscillator cannot. In a classical trajectory calculation it is therefore possible for ZPE to "leak out" of the modes to which it was initially assigned and to become available for exploration of parts of the potential energy surface that would not really be accessible to the true, quantized system. This ZPE leakage is of special concern in polyatomic molecules like the ones discussed in the present paper, because the total ZPE is so large—over 90 kcal/mol for the example discussed above. If this kinetic energy were somehow to accumulate in a local vibrational mode it would be enough to cause a C−C bond to break! Such an accumulation is statistically improbable, but less dramatic deviations from the true behavior of a quantized system may be much more likely.

Several methods for dealing with this problem have recently been proposed,[15] but most of them potentially add significantly to the computation time of the trajectory calculation. A less rigorous but computationally faster way of addressing the issue is to explore the behavior of a system in which only the lowest few vibrational modes are energized. That way, the total kinetic energy can never be very large, and exploration of unrealistic geometries cannot occur. In the present case, trajectories were examined in which only the first 8 modes were energized. Mode 1 had 2 kcal/mol of initial kinetic energy, as before, while each of the next 7 was excited to the level of its ZPE. The total kinetic energy in such a system is 6.2 kcal/mol. The results were essentially exactly the same as before; most trajectories having the initial phase of mode 4 corresponding to counterclockwise rotation about the C5-C6 bond led quickly to formation of bicyclo[3.2.0]heptene with inversion of configuration at C6, whereas those with the initial phase of mode 4 corresponding to clockwise rotation invariably led to the "long-lived" biradical. Two trajectories representative of each class are shown pictorially in a series of frames in Figures 1 and 2. The similarity in behavior of these low-energy trajectories to that observed for trajectories corresponding to excitation to the full ZPE of the molecule suggests that ZPE leakage cannot be a serious problem on the time scale of the simulations studied here. It also suggests that the higher frequency modes are relatively weakly coupled to the reaction coordinate for the [1,3] migration. Of particular interest is the fact that, whether full ZPE was used or not, several trajectories were discovered that led very quickly to the bicyclo[3.2.0]heptene with inversion of configuration, whereas none was discovered that led directly to this compound with retention of configuration.

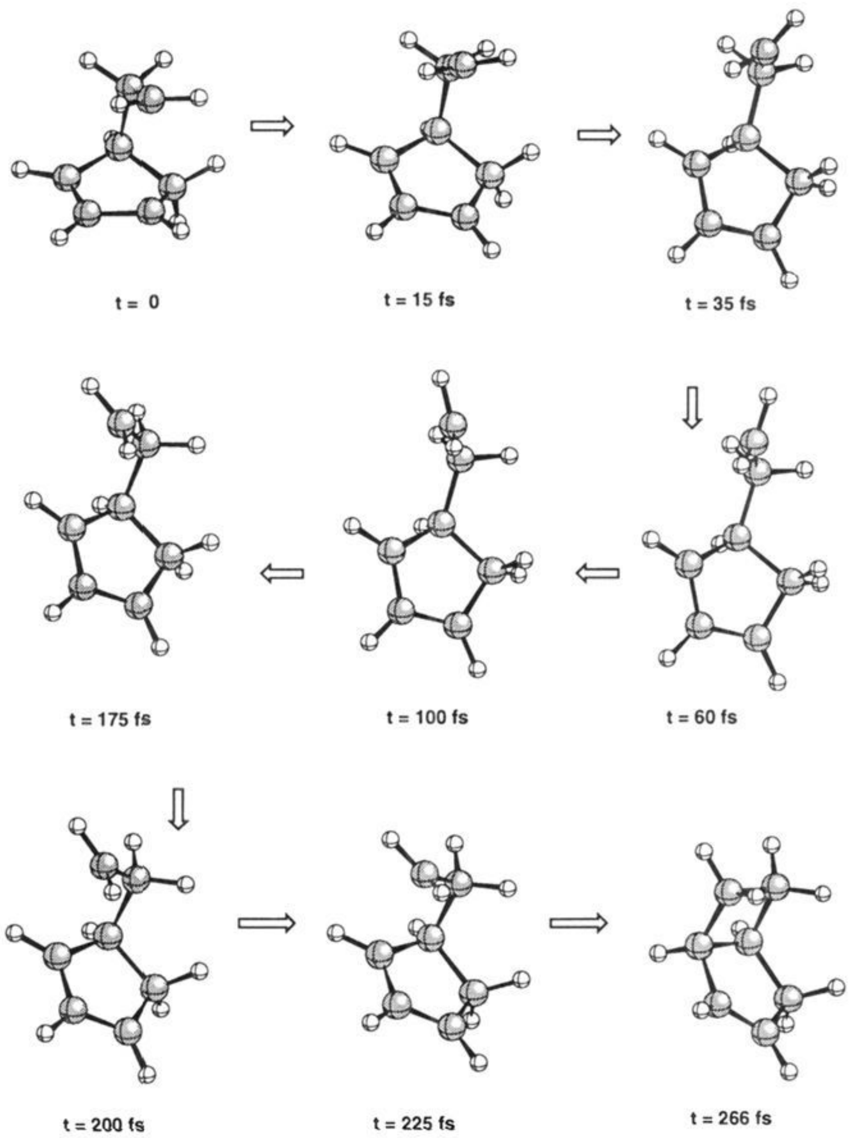

Figure 1. Snapshots from a low-energy trajectory with counterclockwise rotation of the migrating methylene.

Also worth noting is the very rapid formation of the inversion product by molecules starting out with the counterclockwise methylene rotation. An RRKM calculation carried out on the biradical,[16] using vibrational frequencies, relative energies, and moments of inertia from the PM3 calculations, resulted in a microcanonical rate constant of $1.2 \times 10^{10}\ s^{-1}$ for the conversion of the biradical to bicyclo[3.2.0]heptene at a total energy of 10.5 kcal/mol above zero-point—the internal energy predicted for a biradical formed under the conditions specified in the trajectory calculations. This rate constant, which would be an upper limit on the "true" RRKM unimolecular rate constant, implies a lifetime of at least 80 ps for the biradical—over 300 times longer than that found in the classical dynamics simulation for the inversion trajectories. The average RRKM lifetime for a thermalized population of biradicals would be longer because most of them would have total energies lower than that explored in the present calculations.

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(14) Marcus, R. A. *Discuss. Faraday Soc.* **1967**, *44*, 76.

(15) (a) Peslherbe, G. H.; Hase, W. L. *J. Chem. Phys.* **1994**, *100*, 1179. (b) Varandas, A. J. C. *Chem. Phys. Lett.* **1994**, *225*, 18. (c) Ben-Nun, M.; Levine, R. D. *J. Chem. Phys.* **1994**, *101*, 8768. (d) Lim, K. F.; McCormack, D. A. *J. Chem. Phys.* **1995**, *102*, 1705.

(16) Hase, W. L.; Bunker, D. L. *QCPE* **1975**, No. 234 (1975).

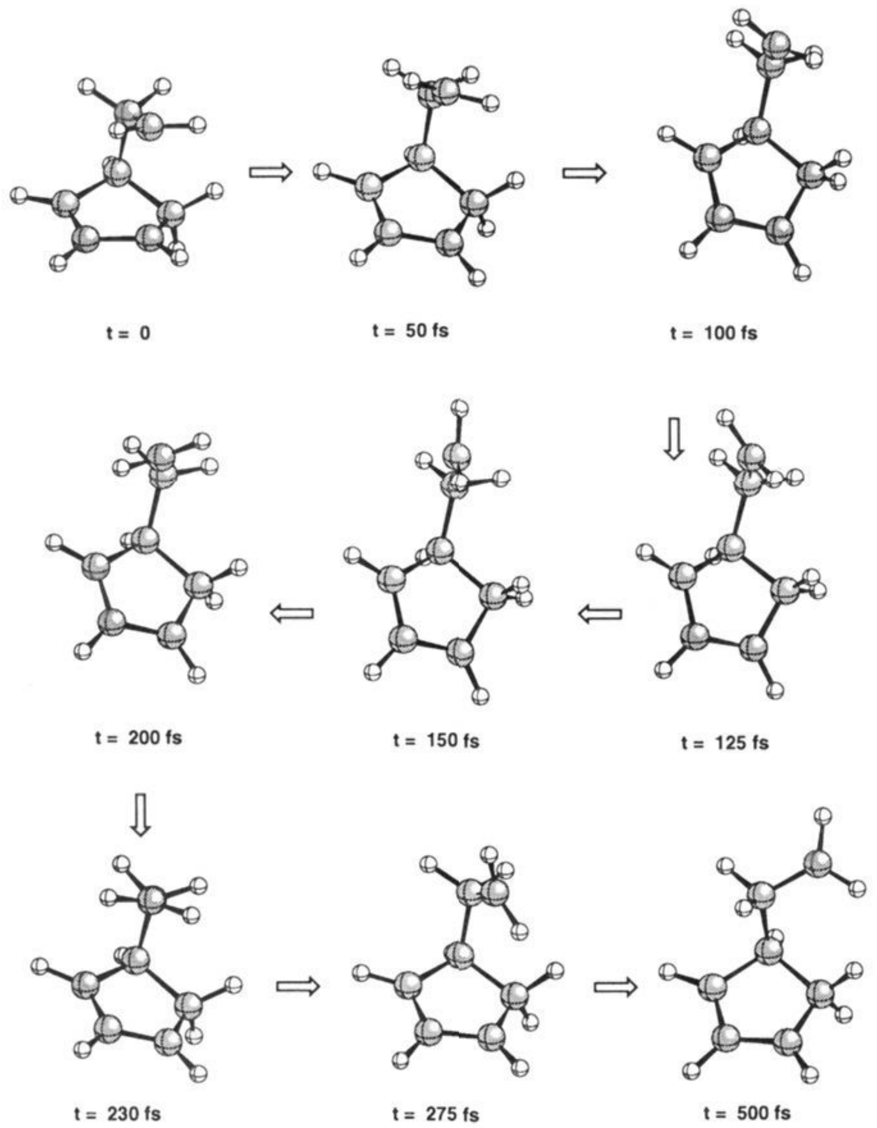


Figure 2. Snapshots from a low-energy trajectory with clockwise rotation of the migrating methylene.

Interested readers can find animations of two full-ZPE trajectories—one with clockwise methylene rotation, and one with counterclockwise rotation—on the World Wide Web. The URL is http://www.chem.cornell.edu/~bkc1/ Sigmatropy.html.

Discussion. Several questions can be raised about the results of the simulation. (1) Why were no trajectories found that would lead to direct formation of bicyclo[3.2.0]heptene with retention of configuration at the migrating carbon, whereas several were found that would form this compound with inversion of configuration? (2) Why does the initial phase of mode 4 in the starting transition structure apparently have such a profound impact on the outcome of the reaction? (3) Why do some of the reactive trajectories lead to the bicyclo[3.2.0]heptene over 300 times faster than the upper limit predicted by RRKM theory? (4) What would be the eventual fate of the "long-lived" biradical formed by molecules whose trajectories did not lead quickly to bicyclo[3.2.0]heptene? These issues will be discussed in turn.

Since only a small number of initial conditions were investigated for these trajectory calculations, and since these starting states in no way represented a sample from a thermal distribution, it is possible that the discovery of fast, reactive inversion trajectories, but not of their retention counterparts, was simply a statistical fluke resulting from improper sampling of initial conditions. However, there is reason to believe that this is not the case. The fast inversion trajectories involve an approximate 180° rotation about the C5−C6 bond. As will be discussed in detail later, this internal rotation is expected to have a very low barrier at geometries corresponding to the biradical intermediate. In the region of the biradical, the sense and rate of the rotation is therefore determined simply by conservation of angular momentum—the sense providing some "memory" of the phase of the corresponding motion (principally mode 4) in the initial state. In order to form bicyclo[3.2.0]heptene with retention in a similar direct fashion, one would appear to have three choices. The migration could, in principle, occur with no rotation at all about the C5−C6 bond; it could occur with rotation in one sense to form the biradical from the starting transition structure, and then in the opposite sense to close the biradical to the four-membered ring (Figure 3), or it could occur with rotations in integral multiples of 360° around the C5−C6 bond. In reality, it is likely that none of these choices is favorable. Migration with no rotation would require a coincidental balancing of opposing forces in the starting state that is simply statistically improbable. For example, since modes 4 and 5 of the starting transition structure each involve torsion about the C5−C6 bond, one might think that assigning them appropriate relative phases could lead to a destructive interference, and migration with no rotation. However, the proportions with which the C5−C6 torsion and the ring flex are mixed in modes 4 and 5 are different—mode 4 is mostly torsion and mode 5 mostly ring flex—so assignment of zero-point kinetic energy to each mode with opposite phases of the torsional component does not lead to cancellation of the rotation. This could be accomplished only by exciting these modes above $v = 0$, and with a larger number of quanta in mode 5 than mode 4. While a few molecules would have such an internal energy assignment in a thermal distribution, they would constitute only a tiny fraction of the total.

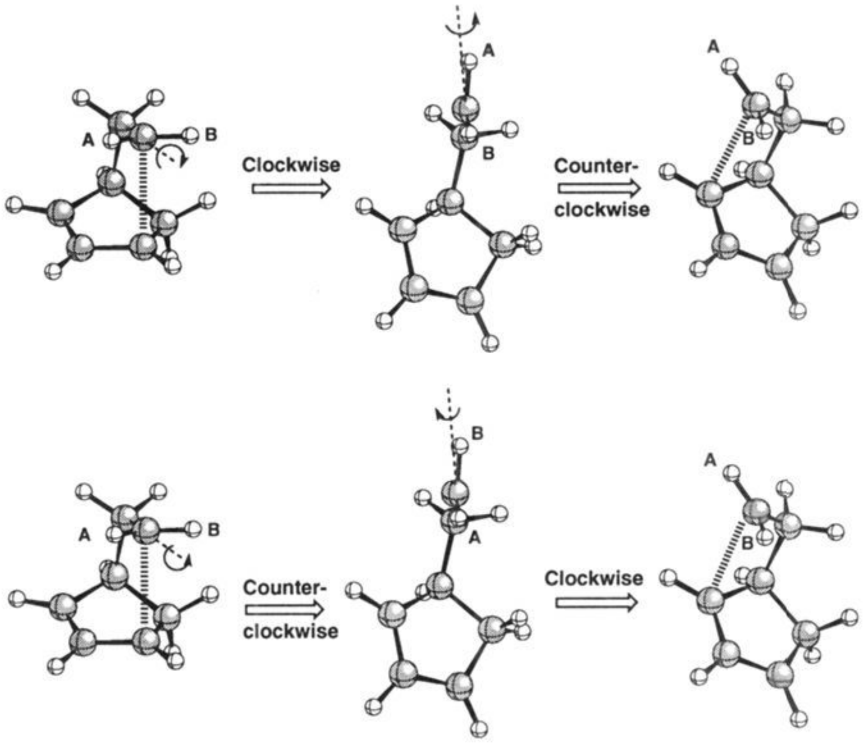


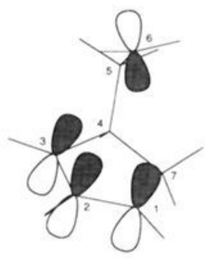
Figure 3. Interconversion of norbornene and bicyclo[3.2.0]heptene with retention of configuration requires reversal of the initial sense of methylene rotation unless multiple rotations occur (see text).

Changing the sense of the initial internal rotation part way through the trajectory is disfavored because such a reversal fails to conserve angular momentum. The most promising strategy for directly forming the retention product might therefore seem to be to execute counterclockwise C5−C6 internal rotation in multiples of 360°. One can recognize that, since this would require initial excitation of mode 4 above its zero point, such states would be disfavored by the Boltzmann factor over those with only the ZPE in each mode, but there is also another reason why this strategy fails. As pointed out in the qualitative analysis of the phenylbicyclohexene rearrangement,[8] the early stages of C−C cleavage in a strained ring are unlikely to include much torsional motion, because torsion breaks bonds without relieving angle strain. Stretching also breaks bonds, but simultaneously relieves angle strain in the rest of the molecule, and hence presents a lower-energy path for ring opening. These arguments about ring opening modes must apply also to ring formation. The trajectory that leads successfully to cyclobutane formation in the present case must be the time reverse of a low-energy trajectory that would have successfully broken open the ring. Approach of a rapidly rotating methylene to the migration terminus cannot result in bond formation because the dynamics do not correspond to the time reverse of an energetically accessible trajectory for the cyclobutane ring opening. This is a key concept that will be expanded in the later discussion. In accord with the expectations of this analysis, trajectories started with sufficient quanta in mode 4 to cause multiple internal rotations during the reaction failed to lead directly to bicyclo[3.2.0]heptene, regardless of the initial phase selected.

In summary, zero-rotation trajectories are statistically unlikely, trajectories corresponding to reversal of the sense of internal rotation part way through the reaction violate the law of conservation of momentum, and multiple-rotation trajectories cannot form any product directly because of their failure to conform to time-reversal symmetry. Only 180°-rotation trajectories giving the inversion product are likely to allow direct and rapid interconversion of norbornene and bicyclo[3.2.0]hept-2-ene.

The importance of the role played by mode 4 of the starting transition structure is attributable to the fact that the initial phase of this mode (with respect to the phase of mode 1—the mode of imaginary frequency) is primarily responsible for determining the sense of rotation of the migrating methylene during the reaction. As will be discussed below, it also has an influence on the rate of the internal rotation. In order to see why, it is necessary to recognize that at the transition structure there is residual bonding between C1 and C6. Provided one follows the direction of the formal reaction coordinate—a nearly pure stretching motion of the erstwhile C1−C6 bond—the residual bonding is invisible because the relief of ring strain that accompanies an increase in the C1−C6 distance beyond its value at the transition structure more than compensates for the increase in potential energy that would have been expected upon breaking even a partial bond. The existence of the residual bond is revealed only when one attempts torsion about the C5−C6 axis. This action fails to relieve ring strain, and then the potential energy does indeed increase, as expected.

During the 1,3 migration, the C4−C5 torsion (mostly mode 2 of the starting transition structure) that serves to slide the migrating methylene across the face of the five-membered ring can combine with counterclockwise C5−C6 rotation in a way that maintains residual C1−C6 bonding as long as possible, and therefore represents a relatively low-energy reaction path. Clockwise rotation, on the other hand, breaks the partial bond too quickly and causes a rapid rise in potential energy. This can be illustrated by structures **1** and **2**, which differ only in the sense of the C5−C6 rotation. The orbitals on C1 and C6 in structure **1** are much better aligned for bonding than those in structure **2**.



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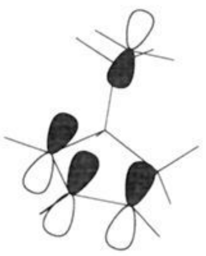

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Trajectories with an initial clockwise sense of the C5−C6 rotation consequently exhibit this rotation much later in the trajectory, when the C1−C6 bond has already been effectively broken by the stretching motion of mode 1. The difference in time of onset of the rotational motion can be seen by comparing Figures 1 and 2. Figure 1 reveals that the counterclockwise trajectory has executed approximately 90° C5−C6 internal rotation within 60 fs, whereas the clockwise trajectory (Figure 2) attains this degree of internal rotation only after about 150 fs. Once the clockwise C5−C6 internal rotation begins, however, it occurs very rapidly, because the motion of the migrating methylene away from the five-membered ring that was initiated by mode 1 of the starting transition structure is now beginning to reverse. The trajectory has reflected off a potential energy "wall" created by the CCC angle deformation at C4 and C5. The migrating methylene, which began by moving away from the five-membered ring, is by now starting to approach it again, and structures in which the C5-C6 rotation is "caught" at the 90° point will find that their potential energy rises rapidly unless the internal rotation speeds up and provides relief from the incipient steric interaction between the five-membered ring and one of the methylene hydrogens. This speeding up of the internal rotation can be seen in Figure 2—the rotation from 0 to 90° took 150 fs, whereas that from 90° to 180° takes only about 80 fs. Now we are in a situation that has been previously discussed—the migrating methylene is approaching the site at which bond formation should occur, but with rapid C5−C6 internal rotation. Since this does not represent the time-reverse of a low-energy trajectory for cyclobutane cleavage, bond formation cannot occur; the methylene simply "bounces" away from the migration terminus, and the trajectory heads off to form the extended-conformation, "long-lived" biradical.

The fact that several inversion trajectories were found leading directly to bicyclo[3.2.0]heptene with effective rate constants that are over 300 times greater than should have been possible according to RRKM theory is a good indication of "nonstatistical" behavior of the biradical. In RRKM theory, internal energy is assumed always to be statistically distributed; only the small fraction of energized molecules having their energy localized in the reaction coordinate can proceed on to product formation. In the present reaction, the energized molecule is a biradical that is prepared with a highly nonstatistical initial disposition of its internal energy, by virtue of having been filtered through the preceding transition state. A substantial fraction of biradicals are prepared with internal energy already localized in the reaction coordinate for the next step, and so they pass very rapidly through the region of the local minimum on the potential energy surface. It is perhaps helpful to use the term "dynamic matching" to describe what is occurring in the fast inversion trajectories. The implication of this phrase is that some molecules enter the biradical region on the potential energy surface with intramolecular dynamics matched to the reaction coordinate for their exit. Those molecules spend much less time in the vicinity of the local minimum than would have been expected given the depth of the potential-energy well. Trajectories involving relatively slow counterclockwise C5−C6 rotation can behave in this way. They give the bicyclo[3.2.0]-heptene with inversion of configuration. Others lead to the "long-lived", extended-conformation biradical.

What happens, then, to this extended-conformation biradical? Presumably some such biradicals would eventually find their way back to conformations from which ring closure could occur. The ring closure could give the starting material, partly epimerized, or the product. Why some recovered reactants experimentally exhibit epimerization[5] while others do not[4,6,7] is unclear, and not easily addressed in the present calculations, since to answer the question would require tracking very long trajectories. It seems likely that product formation from the extended-conformation biradical would occur with equal probability of the formal inversion and retention stereochemistries

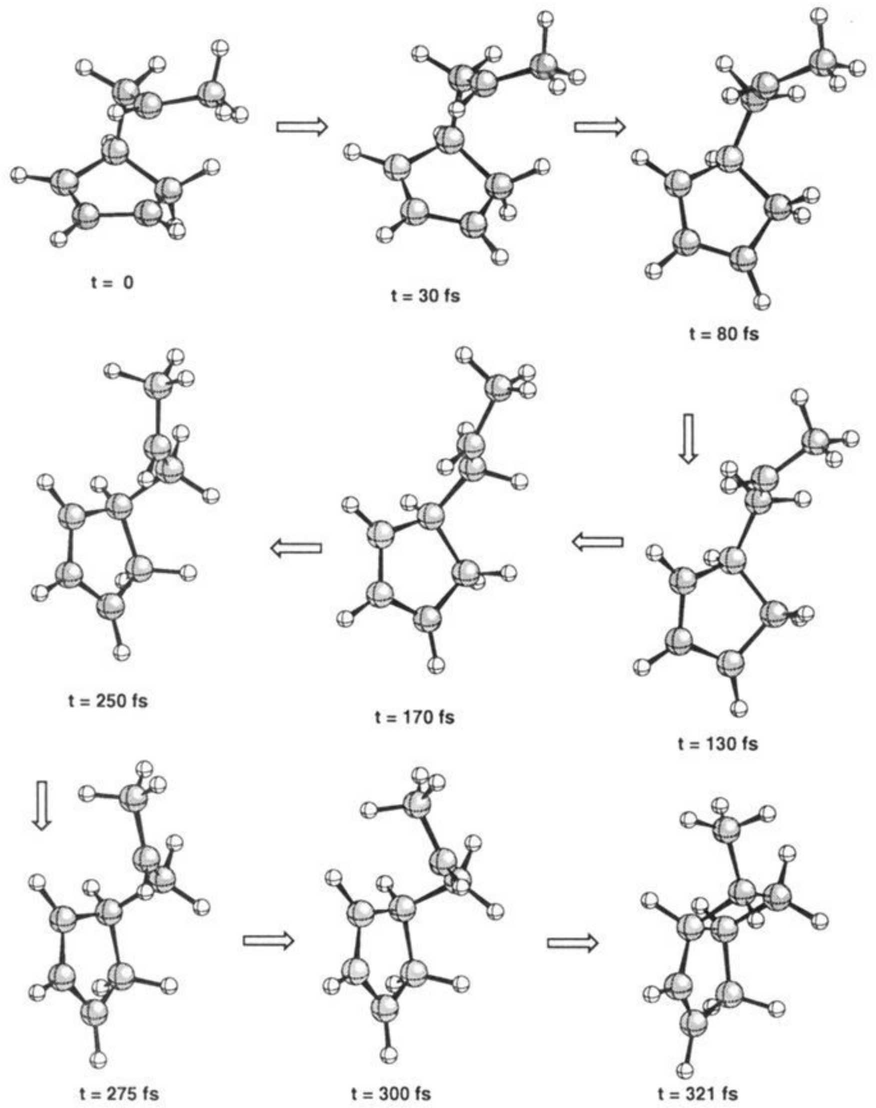

Figure 4. With an *exo*-methyl substituent, the inversion trajectory looks similar to that for the unsubstituted molecule.

(if deuterium labels were used and isotope effects were negligible), since the relatively long lifetime of the biradical would allow a redistribution of internal energy that would constitute a loss of "memory" of the stereochemistry. There is another possible fate for the biradical. As pointed out by both groups working on the deuterium-labeled bicyclo[3.2.0]heptene rearrangement,[6,7] the labeled norbornene constitutes only 1−2% of the overall product. Most of the reaction products appear in the form of ethylene-d_2 and cyclopentadiene. Some of these fragments undoubtedly come from retro-Diels−Alder reaction of the norbornene, but some could also arise by C−C cleavage of the biradical.[6] If such a process were occurring in competition with ring closure, one would expect the ratio of fragmentation to closure to be temperature dependent, since the two pathways would have identical activation enthalpies only by coincidence. Furthermore, since the activation entropy of fragmentation would presumably be positive, while that for cyclization would likely be negative, the proportion of fragmentation should increase as the temperature increased. Such a "bleeding off" of the extended-conformation biradical would tend to increase the proportion of the inversion observed in the cyclization product, since some of this product would be coming from the direct pathway, which is not susceptible to the fragmentation. An effect of this kind might explain the unusual experimental observation of increasing stereoselectivity with increasing temperature.

Methylbicyclo[3.2.0]heptene/Methylnorbornene Interconversion

Results and Discussion. If the present simulations are to be considered as candidates for reasonable models for the real systems, they should be able to explain the preference for retention of stereochemistry seen in the Berson and Nelson experiment in which the reactant had an *endo*-methyl substituent on the migrating carbon.[5] An exact simulation of the experimental study is not attempted, in part because the present calculations do not include an acetoxy substituent on C5, and in part because the trajectories are explored in the reverse direction from the actual experiment. Thus, Berson and Nelson detected the preference for retention in the formation of an excess of an *exo*-methylnorbornene from an *endo*-methylbicyclo[3.2.0]heptene.[5] In the simulation, the corresponding process would convert *endo*-methylnorbornene to *exo*-methylbicyclo[3.2.0]heptene. Presumably the issues involved in the determination of stereochemical preference for these two reactions would be similar.

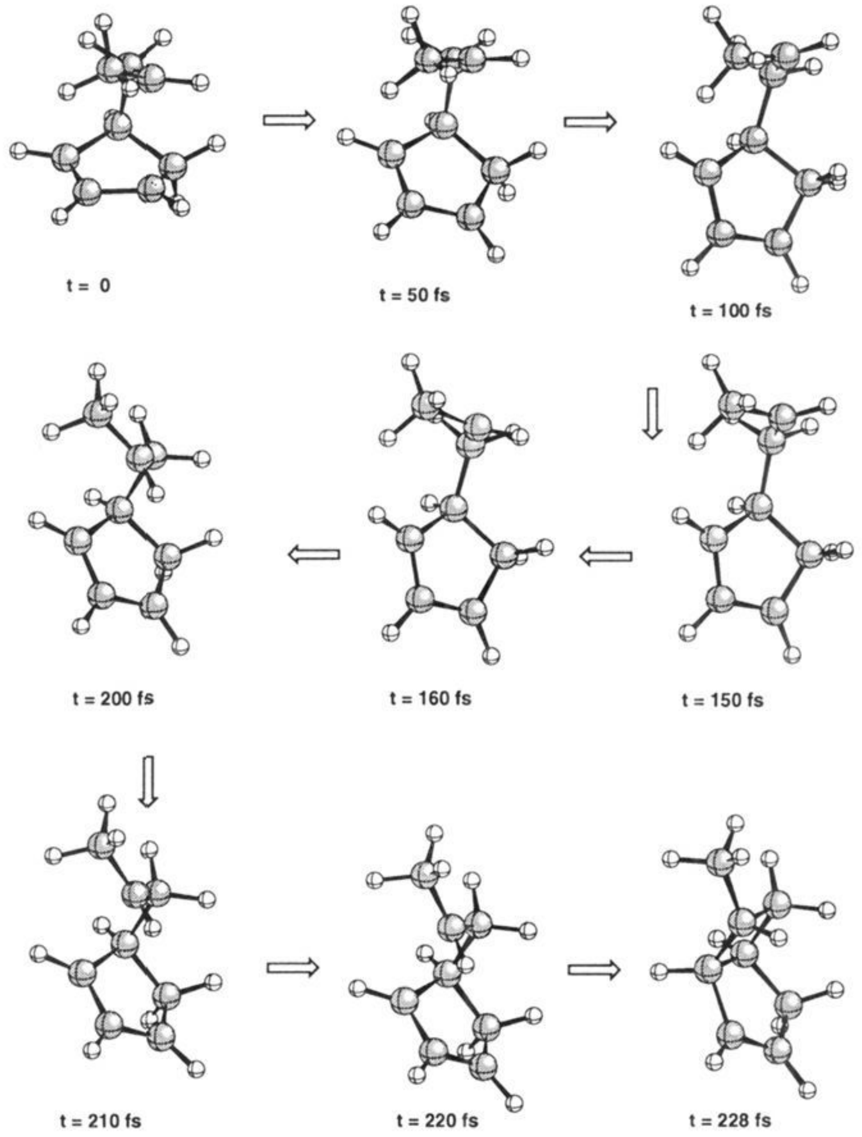

Figure 5. With an *endo*-methyl substituent, a direct formation of the product with retention of configuration can be seen.

The analysis begins with an inversion trajectory interconverting *exo*-methylnorbornene and *exo*-methylbicyclo[3.2.0]heptene. As shown in Figure 4, the dynamic picture is not very different from that found for the inversion of the parent system (Figure 1). Again, the use of low-energy classical trajectories (like that shown in Figure 4) or trajectories with all modes executing zero-point motion gave essentially identical results.

The attempted interconversion of *endo*-methylnorbornene and *endo*-methylbicyclo[3.2.0]heptene along an inversion trajectory is quite different from anything discussed heretofore. As shown in Figure 5, the early stages of the trajectory look like a normal inversion process. However, once the reflex motion of the connecting bridge begins, a steric interaction between the methyl group and the five-membered ring occurs. This is, of course, exactly the steric interaction that Berson and Nelson had in mind when they designed their experiment.[5] Its effect is to stop and then reverse the internal rotation that had been an integral part of the inversion trajectory. This can be seen by comparing the 150 and 160 fs frames in Figure 5. Essentially, the steric effect of the methyl group has converted what used to be an internal rotation into a torsional vibration with a restoring force. The beginning of the trajectory constitutes one phase of the torsional vibration and the end constitutes the return or opposite phase. Now there are two important reflexive events—the usual extension and return of the connecting tether, and this time a torsion and return of the migrating CHMe group.

Interestingly, the requirement for time-reversal symmetry implies that, if the dynamic picture presented here is correct, some of the small amount of *endo*-methylnorbornene detected by Berson and Nelson from the rearrangement of their *exo*-methylbicyclo[3.2.0]heptene would have come from a direct retention trajectory. Thus, according to this model, even *exo*-methyl substitution of the reactant is not stereochemically innocent; while it has relatively little effect on the inversion trajectory, it permits a direct retention trajectory that had not been available to the deuterium-labeled molecule. This would imply that *exo*-methyl bicyclo[3.2.0]heptene should give a lower preference for inversion than the corresponding deuterium-labeled substrate; the experimental data are permissive of this being correct,[4] but do not demonstrate it unambiguously.

General Discussion

There are several caveats that must be attached to the dynamic analysis described in this paper. They will be discussed in what the author believes to be the order of increasing importance. First, the PM3 potential energy surface for this reaction is obviously wrong in at least some respects. However, these errors may not invalidate the final qualitative conclusions. The philosophy adopted in this work has been to use the PM3 model to create a kind of "virtual reality" in which the dynamics can be explored. Arguments extrinsic to these calculations will be used (*vide infra*) to address the relationship, if any, of this model universe to the real one. It is important to emphasize that the question of the relevance of the calculations to the experimental observations does not require an *a priori* assumption of accuracy of the PM3 prediction of a biradical mechanism. If the computational results had been found to be inconsistent with the experimental data, they would obviously have been of no relevance to the real world. Since they apparently turn out to be consistent, they need to be given consideration as possible models for the real-world behavior.

A second caveat to the present calculations is the improper handling of zero-point energy. Some attempts have been made to address this issue, and they suggest that it is not a source of significant error, but it would be highly desirable to use one of the proposed methods for handling the zero-point energy problem[15] to redo the calculations reported here. This will constitute a major computational enterprise, since most methods for handling the zero-point energy more reasonably add considerably to the time required to calculate each trajectory.

The third caveat to the conclusions involves improper sampling of initial conditions. A rigorous classical trajectory simulation must begin with a representative sample ensemble of starting states.[17] No attempt has been made to do that in this work. All trajectories have been started from the same point—that being the first-order stationary point linking the norbornene and the biradical. Only a few different vibrational phase combinations, corresponding to different starting directions of the trajectories, have been explored. Calculation of a truly representative ensemble would be a rather significant (although not impossible) computational undertaking. Of particular interest would be to explore initial relative phase angles other than 0° or 180° for the normal modes. However, this requires starting at geometries that do not correspond to stationary points on the potential energy surface, and where the usual normal-mode analysis therefore cannot be carried out. Techniques for dealing with this problem have been developed,[18] but they have not been explored in the present work. The consequence of the improper sampling for the present calculations is that no quantitative conclusions can be drawn about inversion/retention ratios. More importantly, this shortcoming does leave open the possibility that a true thermal ensemble of starting states would exhibit different behavior from that seen in the present limited study. It is hoped that the general physical arguments presented in the paper go some way toward addressing this problem.

In the absence of the much more extensive calculations that would be required to handle both initial-condition sampling and zero-point energy properly, the author believes that some useful, if tentative, conclusions can be drawn from the classical-trajectory simulations reported herein.

First, one can see that some features of the earlier qualitative attempt[10] to describe the dynamics of a [1,3] migration receive support in the present analysis, whereas others now appear incorrect. Supported is the idea that bond breaking in strained rings begins with stretching, and involves significant torsion only later. That idea, in reverse, plays a crucial role in explaining the difficulty of bond formation by intermediates experiencing fast internal rotation of the groups attempting to become connected. Also supported is the idea of an important part to be played by reflected trajectories. Reflexive motions of the connecting bridge and, in the case of the methyl-substituted reactants, of the CHMe torsional vibration are central to the present analysis. What is not supported by the work reported here is the role assigned earlier to the out-of-plane bend of the groups attached to the migrating carbon. This idea arose by extrapolation from the dynamics of azo compound fragmentation, where it does seem to be the dominant contributor to the overall reaction stereochemistry.[19] In the [1,3] shift, however, it now appears that internal rotation is more important than this out-of-plane bend in influencing the stereochemical outcome of the reaction.

A more general conclusion from the present simulation studies is that the experimental observation of a preference for inversion of configuration at the migrating group in a suprafacial [1,3] sigmatropic shift probably should not be taken as definitive evidence against a biradical mechanism. The present calculations reveal an apparent preference for inversion of configuration in a hypothetical reaction for which the potential energy surface has a very distinct local minimum corresponding to a biradical. That the origin of this preference is not merely a camouflaged version of the Woodward–Hoffmann rules is revealed by the rotation barrier about the C5–C6 bond in structure **3** at the midpoint of the migration with inversion. This barrier is plotted out in Figure 6, and compared with the PM3 calculation for the rotation barrier in the propyl radical.[20] The close similarity of the two reveals that there cannot be any significant bonding of C6 to C1 or C3 in structure **3**, according to the PM3 model.

Given that the semiempirical calculations cannot be trusted to give chemically accurate potential energy surfaces for reactions of the kind studied here, it would be indefensible to claim that the results, by themselves, have disproven the pericyclic mechanism of the [1,3] sigmatropic shift. However, one can say that the observed stereochemistry for the reaction

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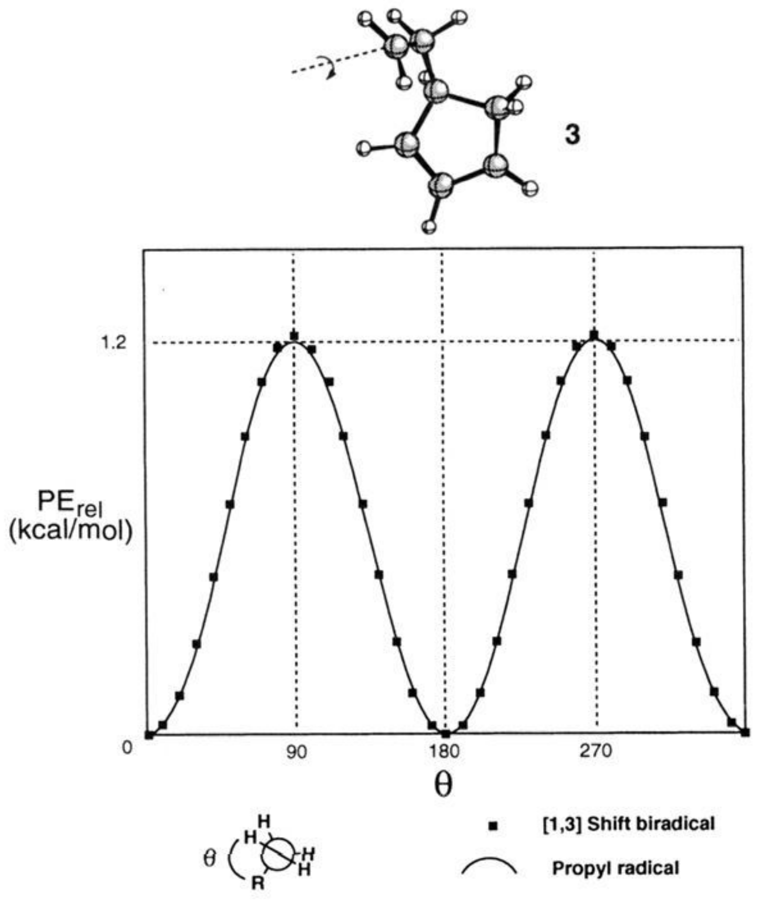

Figure 6. Comparison of barriers to internal rotation about C5−C6 in the [1,3] shift biradical and in the propyl radical.

probably should no longer be accepted as evidence against a biradical mechanism. Since this was one of the principal pieces of evidence favoring the pericyclic over the biradical mechanism, it then becomes worthwhile to reexamine all of the available information in order to assess the merits of the opposing models.

One can, in principle, probe the viability of a biradical mechanism for a nominal pericyclic reaction by comparing the experimental heat of formation for the transition state with the heat of formation computed for the putative biradical.[1] Commonly, the calculation of the latter quantity relies on methods such as the Benson group-additivity scheme,[21] with corrections for strain energy typically coming from molecular mechanics estimates. It has recently been pointed out that group-additivity methods can give erroneous results for biradicals in which there is a large energy difference between lowest singlet and triplet electronic states.[22] However, in the reactions considered here, the large distance between the "radical" sites suggests that singlet and triplet states should be close in energy, and that group additivity methods should probably give acceptable results. The comparison has been carried out for the nominal [1,3] sigmatropic shift of bicyclo[3.2.0]hept-2-ene, and it has been concluded that the biradical should have a heat of formation that is 1.3 kcal/mol below that of the rate-determining transition state.[7] Similar calculations for other formal [1,3] sigmatropic migrations suggest that the corresponding biradicals are mechanistically viable.

A clear distinction between the dynamic and pericyclic models can be found in the predicted stereochemistry, not for the [1.3] shift on which they agree, but for the [1,5] shift, on which they make opposite predictions. At least in its simplest form, the dynamic model discussed here would continue to predict a preference for inversion at the migrating carbon in a suprafacial [1,5] migration, whereas the pericyclic model clearly predicts retention.[2] The actual experimental facts are less clear cut. To the knowledge of the author, there have been studies of the stereochemistry at the migrating carbon in four different versions of the nominal [1,5] sigmatropic migration. Of these four, only one shows the large preference for retention of configuration predicted by the pericyclic mechanism. It is the rearrangement of a methyl-substituted spiro[4.4]nona-1,3-diene, studied by Kloosterziel and co-workers.[23] When the thermochemical criterion discussed above is applied to this reaction, one finds that the rate-limiting transition state for rearrangement of unsubstituted spiro[4.4]nona-1,3-diene is some 15−20 kcal/mol below the estimated heat of formation of the biradical intermediate. This reaction seems to meet all of the criteria for a truly pericyclic mechanism.

Of the other three nominal [1,5] sigmatropic shifts, one shows mixed stereochemistry with an apparent preference for retention,[24] whereas the other two show a strong preference for inversion at the migrating carbon.[25,26]

Thus the stereochemical data on the [1,5] sigmatropic shift do not fall 100% into one mechanistic camp or the other. It clearly would not be satisfactory to say that sometimes one mechanism is right and sometimes the other, unless there were sufficiently transparent criteria to predict ahead of time which would be likely to operate. That may be possible. It seems likely, to this author at least, that what makes the spiro[4.4]-nonadiene favor a pericyclic mechanism is that, in addition to being a [1,5] sigmatropic migration, it is also a 1,2 migration. The vicinal relationship between migration origin and migration terminus makes it possible to maintain simultaneous bonding of these centers to the migrating group, as is required for the transition state of a truly pericyclic reaction. In [1,n] sigmatropic shifts with $n > 2$, this maintenance of simultaneous bonding is much more difficult to achieve. One could draw the analogy with carbocation rearrangements, in which 1,n alkyl shifts are very rare whereas 1,2 shifts are ubiquitous.[27] It is possible (and, in the author's opinion, likely) that no nominal [1,n] sigmatropic migration of carbon with $n > 2$ follows a truly pericyclic mechanism.

Of course, since the simplest version of the dynamic model would appear to predict a preference for inversion of configuration in all nonpericyclic 1,n migrations, one must then be able to explain why the nominal [1,5] rearrangement of substituted bicyclo[6.1.0]nona-2,4,6-trienes studied by Klärner and coworkers[24] showed an apparent preference for retention. Interestingly, while this reaction has been cited as an example of a [1,5] sigmatropic migration,[28] the original authors recognized that formal [1,5] and [1,3] shifts can give the same products in the bicyclo[6.1.0]nonatriene system. Of particular significance for the present question is the fact that the product of a nominal [1,5] shift with retention is identical to that from a nominal [1,3] shift with inversion, in the absence of ring labels. It is thus possible that the observed rearrangement does occur with a preference for inversion. This issue is being investigated with the same kind of simulation techniques used for the present study, but a complete answer is not yet at hand.

The third conclusion to be drawn from the simulations reported here is the most general, and potentially most important. Bearing in mind the caveats mentioned earlier, there appear to exist trajectories that can pass through a region corresponding

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to a local minimum of significant depth on a potential energy surface, without spending much time (only a few hundred femtoseconds) in that region. One can schematize the situation as:

$$\mathbf{A}^* \rightarrow \mathbf{A}^\ddagger \rightarrow \mathbf{I} \rightarrow \mathbf{B}^\ddagger \rightarrow \mathbf{B}^*$$

where $\mathbf{A}^*$ is an energized reactant, **I** is the structure corresponding to the local potential-energy minimum, $\mathbf{B}^*$ is an energized product, and $\mathbf{A}^\ddagger$ and $\mathbf{B}^\ddagger$ are transition structures, with $\mathbf{B}^\ddagger$ the lower of the two in potential energy. Of the several trajectories that can take $\mathbf{A}^*$ through or near $\mathbf{A}^\ddagger$ to **I**, those that approach $\mathbf{B}^\ddagger$ with dynamics corresponding to the time reverse of a low-energy $\mathbf{B}^* \rightarrow \mathbf{I}$ trajectory will lead to rapid formation of $\mathbf{B}^*$. In a reaction where **I** has several exit channels to possible products, it may be that some channels permit such dynamic matching easily while others do so only with difficulty, or not at all. In this case there could be a dynamic preference for one product over another, even when the static potential energy surface reveals no such preference. According to the present simulations, this may be what is happening in at least some nominal [1,*n*] sigmatropic migrations. More importantly, similar considerations may lead to the development of a dynamic selection rule that would allow one to make predictions of preferred stereochemistry for thermal reactions outside the domain of nominally pericyclic processes.

The apparent existence of the short-duration trajectories discussed in this paper serves to emphasize once more[29] the hazards associated with partioning of mechanisms into "stepwise" and "concerted" categories. By any reasonable energetic criterion, the PM3 version of the [1,3] migration reported here would fit the usual description of a stepwise reaction, but it is hard to see what importance to attach to such a description if a significant fraction of the reactive trajectories can complete their passage through the region of the local minimum in about a quarter of a picosecond.

Acknowledgment. The author extends his thanks to Professors Roald Hoffmann and Joseph Gajewski for providing constructive criticism of an early version of this manuscript and to Professor Frank-Gerrit Klärner for helpful comments and for providing a copy of ref 8 prior to publication. Special thanks are due to Professor Jerome Berson for the considerable effort that he has put into thoughtful criticism of this work. The calculations were conducted using the Cornell National Supercomputer Facility, a resource Center for Theory and Simulations in Science and Engineering (Cornell Theory Center), which receives major funding from the National Science Foundation and IBM corporation, with additional support from New York State and members of the Corporate Research Institute. Finally, support of this work by the National Science Foundation (Grant No. CHE 9222587) is gratefully acknowledged.

JA950624I

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