

Intramolecular Dynamics for the Organic Chemist

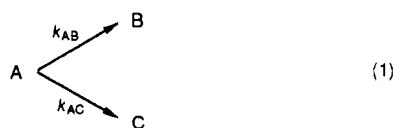
BARRY K. CARPENTER

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

Received May 14, 1992

Rigorous experimental evaluation of any new conceptual model is required before it can be incorporated into the overall paradigm of the scientific community. But once the model is accepted, a dangerous thing can happen. One can easily forget that the conceptual structure is just a model, and that it might not have applicability outside the domain in which the original tests were conducted. In this Account I will examine the possibility that undue reverence for existing models might have misled us as organic chemists into thinking about our reactions in ways that are incorrect, or at least incomplete.

The reader will be invited to re-examine such familiar diagrams as (1), and to ask "What do those arrows really mean?" and "What do k_{AB} and k_{AC} mean?" Related



questions such as "What do we mean by a reaction intermediate?" and "What do we mean by a concerted reaction?" also will be raised (if not answered!). At the heart of the matter will be the issue of whether the commonly employed models for reaction kinetics, such as transition state theory¹ (TST) and RRKM theory² are really adequate to describe all of the thermal reactions that an organic chemist might encounter.

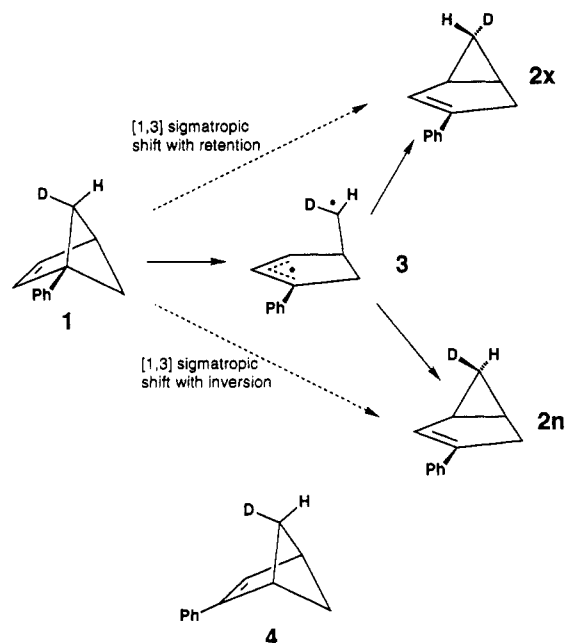
Statement of the Problem

In 1984 work from this laboratory revealed that the thermal isomerization of 1-phenylbicyclo[2.1.1]hex-2-ene-endo-5-d (1, Scheme I) to 3-phenylbicyclo[3.1.0]hex-2-ene-6-d occurred with a 10:1 preference for formation of the endo (2n) over the exo (2x) epimer of the product.³ There was no doubt that the ratio was kinetically controlled, because the products were stable to the reaction conditions. The product ratio exhibited no steric isotope effect, since a reaction run with the exo epimer of 1 gave 2n and 2x in a 1:10 ratio.

The stereochemical outcome was unremarkable: similar behavior had been seen in a methyl-substituted analogue many years earlier,⁴ and the predominant reaction occurred with inversion of configuration at the migrating carbon, as predicted by the Woodward-

Barry Carpenter was born in Hastings, England in 1949. He received the B.Sc. degree from Warwick University and a Ph.D. from University College, London (with H. M. R. Hoffmann). He came to the U.S. as a postdoctoral fellow with Jerome Berson at Yale in 1973. He joined the faculty at Cornell in 1975, and is currently Professor of Chemistry there. His research interests involve the comparison of theory and experiment in the study of reaction mechanisms.

Scheme I



Hoffmann rules. However, it did come as a surprise to discover that the product ratio exhibited no detectable temperature dependence over a range of >85 °C. One can see the problem that this poses if one views the reaction as an example of the scheme shown in eq 1. According to TST, the rate constants k_{AB} and k_{AC} can be expressed by eq 2 and 3, and hence the product ratio by eq 4. In these equations ΔH^{\ddagger}_{AB} is the activation enthalpy for conversion of A to B, and ΔS^{\ddagger}_{AB} is the activation entropy for the same conversion. One sees that (4) leads to the expectation of a temperature-dependent product ratio unless $\Delta H^{\ddagger}_{AB} = \Delta H^{\ddagger}_{AC}$. In the case of the conversion of 1 to 2n and 2x, it seemed surprising that the apparent Woodward-Hoffmann-allowed, concerted process giving 2n and the unidentified reaction giving 2x would happen to have exactly the same activation enthalpy.

(1) (a) Pelzer, H.; Wigner, E. *Z. Physik. Chem.* 1932, B15, 445. (b) Glasstone, S.; Laidler, K. J.; Eyring, H. *Theory of Rate Processes*, McGraw-Hill: New York, 1940.

(2) (a) Rice, O. K.; Ramsperger, H. C. *J. Am. Chem. Soc.* 1927, 49, 1617. (b) Rice, O. K.; Ramsperger, H. C. *J. Am. Chem. Soc.* 1928, 50, 617. (c) Kassel, L. S. *J. Phys. Chem.* 1928, 32, 225. (d) Kassel, L. S. *J. Phys. Chem.* 1928, 32, 1065. (e) Marcus, R. A.; Rice, O. K. *J. Phys. Colloid Chem.* 1951, 55, 894. (f) Marcus, R. A. *J. Chem. Phys.* 1952, 20, 359. (g) Robinson, P. J.; Holbrook, K. A. *Unimolecular Reactions*; Wiley: New York, 1971. (h) Forst, W. *Unimolecular Reactions*; Academic Press: New York, 1973.

(3) Newman-Evans, R. H.; Carpenter, B. K. *J. Am. Chem. Soc.* 1984, 106, 7994.

(4) Roth, W. R.; Friedrich, A. *Tetrahedron Lett.* 1969, 2607.

$$k_{AB} = \frac{k_B T}{h} e^{-\Delta H^\ddagger_{AB}/RT} e^{\Delta S^\ddagger_{AB}/R} \quad (2)$$

$$k_{AC} = \frac{k_B T}{h} e^{-\Delta H^\ddagger_{AC}/RT} e^{\Delta S^\ddagger_{AC}/R} \quad (3)$$

$$\frac{k_{AB}}{k_{AC}} = e^{(\Delta H^\ddagger_{AC} - \Delta H^\ddagger_{AB})/RT} e^{(\Delta S^\ddagger_{AB} - \Delta S^\ddagger_{AC})/R} \quad (4)$$

If we sought to avoid this ad hoc coincidence, by abandoning the idea of a concerted reaction, things did not get much better. The obvious biradical intermediate (3) would need a barrier to C4–C5 rotation that was higher than any barrier to product formation in order to explain the product ratio. Such a barrier would have to be purely entropic⁵ since any enthalpic component would revive the incorrect prediction of a temperature-dependent product ratio. But it did not seem plausible that any decrease in entropy accompanying interconversion of rotamers of 3 could be more significant than that for conversion of 3 to a transition state for product formation, since the latter involved the formation of a new small ring.

The only recourse seemed to be to return to the original hypothesis—that we had stumbled on a case where two pathways from reactant to products, with different transition states, happened by coincidence to have identical activation enthalpies.

Even this ad hoc explanation was rendered untenable by the discovery that 2-phenylbicyclo[2.1.1]hex-2-ene-endo-5-d (4) showed very similar behavior to that of 1.³ The products from rearrangement of 4 did interconvert under the reaction conditions, but the intrinsic rate constants for their formation could still be calculated, and their ratio showed no detectable temperature dependence over a range of 50 °C. It seemed highly implausible that the coincidental equality of activation enthalpies considered for rearrangement of 1 would occur also in rearrangement of 4. Subsequently, we discovered two completely different reactions (vide infra) that showed the same behavior—i.e. a temperature-independent ratio, differing significantly from unity, for two products related as optical or isotopic-label isomers. This allowed rejection of the “coincidence” explanation with a high degree of confidence. So what was left?

Three Scenarios for the Failure of the Statistical Models of Kinetics When Applied to Thermal Reactions of Polyatomic Molecules

It may seem like a rash intellectual leap to propose, simply on the basis of our observations of temperature-independent product ratios, that the fundamental models of kinetics needed revision, but the reasoning given above left us with no obvious alternative.

While it was already known from elegant state-selective chemistry on small molecules that statistical models could fail,⁶ it was their potential failure for the reactions of relatively large molecules under “normal”

(5) In the language of variational transition-state theory, where a transition state is a saddle point on the free energy surface, such barriers are possible (a) Garrett, B.; Truhlar, D. *Acc. Chem. Res.* 1980, 13, 440. (b) Hase, W. L. *Acc. Chem. Res.* 1983, 16, 258. See also Doubleday, C., Jr.; Camp, R. N.; King, H. F.; McIver, J. W., Jr.; Mullally, D.; Page, M. *J. Am. Chem. Soc.* 1984, 106, 447.

(6) Rizzo, T. R.; Hayden, C. C.; Crim, F. F. *J. Chem. Soc., Faraday Discuss.* 1983, 75, 223.

thermal conditions that interested us. Once forced to think about this problem, we found that we could envision two scenarios where one might expect the existing models not to work well; a third was proposed by another group.

Branching to Products after a Single Transition State. One of the reactions that we found to exhibit the problematic behavior described above was the thermal decomposition of 2,3-diazabicyclo[2.2.1]hept-2-ene-*exo,exo*-5,6-*d*₂ (5) to bicyclo[2.1.0]pentane-*exo,exo*-2,3-*d*₂ (8x), -*endo,endo*-2,3-*d*₂ (8n), and molecular nitrogen (see Figure 1).

This reaction, like the bicyclo[2.1.1]hexene rearrangement, had been studied by the group of W. R. Roth many years earlier.⁷ They discovered that 8x was formed in preference to 8n—an unusual result if one compares relative orientations of the methano bridge and the deuterium labels in the reactant and products. The products were known to interconvert under the reaction conditions, with an equilibrium constant of 1.0 within experimental error.⁸ We determined the intrinsic rate constants for the inversion reaction leading to 8x (*k*_i) and the retention leading to 8n (*k*_r), and, once again, found no detectable temperature dependence of the *k*_i/*k*_r ratio, although the errors propagated into this ratio were relatively large.

In contemplating possible mechanisms for the reaction, we took into account the persuasive experimental evidence in support of a stepwise cleavage of the two C–N bonds of 5.⁹ Since the stereochemistry would be set by the reaction(s) leading to cleavage of the remaining C–N bond in the diazenyl biradical (6), we carried out AM1-CI semiempirical molecular orbital calculations¹⁰ (and some ab initio calculations, although these are not yet complete) on this process. The results, when combined with experimental data on the heats of formation of bicyclopentane and estimates of the heat of formation of cyclopentane-1,3-diyl (7),¹¹ could be summarized in the enthalpy surface shown in Figure 1. The key feature of this surface was that it exhibited a *single* transition state followed by branching to cyclopentane-1,3-diyl and to the two products. The transition state had the necessary property of a single negative eigenvalue to its force constant matrix, but after the saddle point the surface opened onto a kind of plateau, from which each of the post-transition-state minima could be reached without further barrier.

Regardless of the detailed accuracy of the surface, the fact that one could construct it at all raised serious questions, not only about the applicability of TST but also about several concepts that had hitherto seemed relatively clear, such as the meaning of a reaction intermediate or the meaning of a concerted reaction.

(7) (a) Roth, W. R.; Martin, M. *Justus Liebigs Ann. Chem.* 1967, 702, 1. (b) Roth, W. R.; Martin, M. *Tetrahedron Lett.* 1967, 4695. For related studies, see: (c) Allred, E. L.; Smith, R. L. *J. Am. Chem. Soc.* 1967, 89, 7133. (d) Allred, E. L.; Smith, R. L. *J. Am. Chem. Soc.* 1969, 91, 6766. (8) Baldwin, J. E.; Ollerenshaw, J. *J. Org. Chem.* 1981, 46, 2116. (9) Simpson, C. J. S. M.; Wilson, G. J.; Adam, W. *J. Am. Chem. Soc.* 1991, 113, 4728. See also: Adams, J. S.; Burton, K. A.; Andrews, B. K.; Weisman, R. B.; Engel, P. S. *J. Am. Chem. Soc.* 1986, 108, 7935. Adams, J. S.; Weisman, R. B.; Engel, P. S. *J. Am. Chem. Soc.* 1990, 112, 9115. (10) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* 1985, 107, 3902.

(11) (a) Turner, B. B.; Goebel, P.; Mallon, B. J.; Doering, W. von E.; Coburn, J. F.; Pomerantz, M. *J. Am. Chem. Soc.* 1968, 90, 4315. (b) Engel, P. S. *Chem. Rev.* 1980, 80, 99. (c) Engel, P. S.; Wood, J. L.; Sweet, J. A.; Margrave, J. L. *J. Am. Chem. Soc.* 1974, 96, 2381. (d) Adam, W.; Oppenländer, T.; Zang, G. *J. Org. Chem.* 1985, 50, 3033. (e) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976.

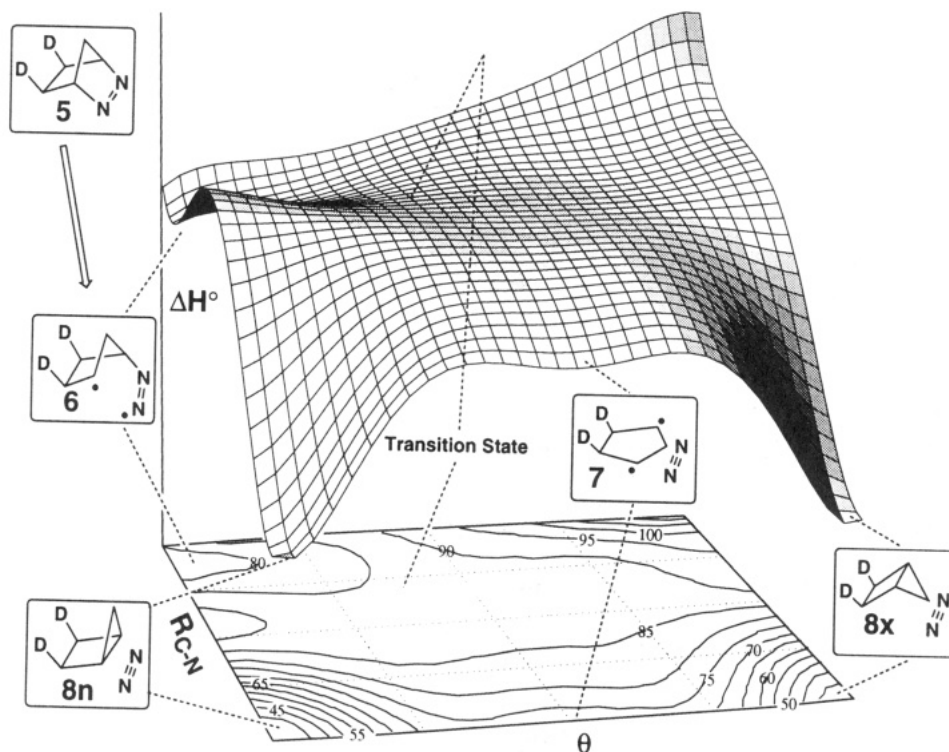


Figure 1. Semiempirical enthalpy surface for the product-forming step in the decomposition of 2,3-diazabicyclo[2.2.1]hept-2-ene-*exo,exo-d*₂. θ is the angle between the planes defined by the three- and four-membered rings of bicyclo[2.1.0]pentane. R_{C-N} is the length of the C-N bond in the diazenyl biradical. Heats of formation are in kilocalories/mole.

TST and RRKM theory cannot predict the product ratio if the reaction occurs on a surface like that shown in Figure 1. One can see from eq 4 that TST makes its prediction of rate constant ratios (and hence product ratios) on the presumed existence of two different transition states for the two processes being compared. When two products come from the *same* transition state, eq 4 ceases to apply. RRKM theory faces the same problem.

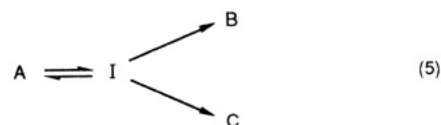
In the debate over concerted vs stepwise reactions that followed the presentation of the Woodward-Hoffmann rules, much argument centered on the definition of an intermediate. The issue under discussion almost always concerned the *depth* of the potential energy well representing the putative intermediate.¹² The surface of Figure 1 suggests that there could be another issue that is at least as important: it is the *location* of the well in the space of geometrical coordinates. If the surface in Figure 1 were qualitatively correct, would one call biradical 7 an intermediate in the conversion of 6 to the bicyclo[2.1.0]pentane stereoisomers? Some individual molecules might reside temporarily at the location of the local minimum¹³ for 7 during the reaction; some might not. It appears that the question becomes moot as soon as one draws the surface. By similar reasoning one can see that the question of whether C-N bond cleavage and C-C bond formation are concerted is almost without meaning, since it can be answered only on a molecule-by-molecule basis, and people typically do not want $\approx 10^{23}$ answers to one question!

(12) (a) Baldwin, J. E.; Fleming, R. H. *Fortschr. Chem. Forsch.* **1970**, *15*, 281. (b) Doering, W. von E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279.

(13) We have shown experimentally the unstabilized cyclopentane-1,3-diyls are local minima and not just transition states (Peterson, T. H.; Carpenter, B. K. *J. Am. Chem. Soc.* **1992**, *114*, 1496), and this conclusion has recently been supported by *ab initio* calculations (Sherrill, C. D.; Seidl, E. T.; Schaefer, H. F., III *J. Phys. Chem.* **1992**, *96*, 3712).

In even more general terms, one might ask just what was implied by those arrows of eq 1 and their associated rate constants. If we meant that there were two processes occurring via different transition states, then perhaps we were being too restrictive in our consideration of possible mechanisms. If we did not mean that, then how were we hoping to define the rate constants k_{AB} and k_{AC} ? Possible answers to the latter question will be presented in the second half of this Account.

Branching to Products from Intermediates of High Potential Energy. One perhaps might view the enthalpy surface of Figure 1 as a pathological case that constitutes a rare exception to an otherwise generally satisfactory agreement between the statistical models of kinetics and experimental observations. In fact, it is not clear just how rare the situation described in this scenario really is, but more to the point, it is also not so clear that the statistical models should work even for more "normal" reactions. Take, for example, the familiar situation of a reaction occurring via a high-potential-energy structure that serves as common intermediate leading to two or more products. In order to distinguish this case from the one discussed above (where it was not so obvious whether one should call biradical 7 an intermediate in the azo-compound reaction), let us suppose that this time the surface requires most molecules to enter the local potential energy minimum that we are identifying as our intermediate. The situation can be summarized as shown in (5):



In the RRKM picture, the conversion of A to B occurs by the following sequence of events:



In eq 6–12 M represents any collision partner; species given an asterisk are presumed to have total nonfixed energy sufficient to cross the barrier for reaction, but to have it statistically distributed among vibrations and rotations; species labeled T_{ij} represent the transition states for interconversion of i^* and j^* .

For most single-step reactions occurring under normal thermal conditions, there is no reason to believe that the RRKM model is substantially in error.¹⁴ Its extrapolation to a multistep reaction, such as the one considered here, is much less obvious, however. In particular, it is not at all clear that the energy distribution in the intermediate I will be properly described by the RRKM model.

One presumes that the energization of the reaction coordinate for a molecule occurs at the expense of the $3N - 7$ other modes. Were this not so, the total energy that one would need to supply in order to achieve reaction would depend on the number of nonreactive modes—in other words, the apparent activation energies of comparable reactions would go up as the size of the molecule increased. This does not happen in reality.

At the instant of its birth, the intermediate I has a distinctly nonstatistical distribution of nonfixed energy. The energy is localized in the reaction coordinate that formed I from A^* . The other $3N - 7$ modes are cool because of the energy drain that was required to cause reaction. We can call this nonstatistically energized intermediate I^* . The total nonfixed energy in I^* is much lower than in A^* because most of the nonfixed energy of A^* went toward raising the potential (fixed) energy of the system. There is evidence to suggest that rates of intramolecular redistribution of vibrational energy are *much* lower at low levels of energization,¹⁵ presumably because low-energy vibrations are approximately harmonic, and anharmonicity of vibrations promotes transfer of energy from one mode to another. Thus one can imagine that I^* , being born with a nonstatistical distribution of internal energy, and perhaps being able to survive in that state for a relatively long time, might behave differently from one's expectations for the I^* of the RRKM model. In particular, one could imagine that selection between the two reaction coordinates leading from I to B and C might

not be made in the way that RRKM theory would suggest. In a limiting case, imagine that the same atomic displacements that converted A to I if continued would take I to B. In that case I^* would already have its energy localized in the I to B reaction coordinate, and so the rate of formation of B, and hence the ratio of B to C formed in the overall reaction, would be higher than one might have expected on the basis of the RRKM model. In the more general case, one could imagine that the efficiency of coupling of the A-to-I reaction coordinate with the I-to-B and I-to-C coordinates might have an influence on the product ratio. Methods for estimating these coupling efficiencies will be proposed later in the Account.

It is perhaps worth contrasting the scenario described here with the one examined in the classic experiment of Rynbrandt and Rabinovitch¹⁶ in which a hexafluorobicyclopropyl was prepared with a large amount (111 kcal/mol) of internal energy that initially was nonstatistically distributed. The molecule showed branching to products (derived by difluorocarbene extrusion) that deviated from the statistical expectation by only 3.5%. The difference between Rynbrandt and Rabinovitch's experiment and ours is that, at the branch point to products, they had an intermediate with relatively low potential energy and very high nonfixed energy, whereas we have "intermediates" with relatively high potential energy and quite low nonfixed energy.

Reaction Coordinates Restricted to a Small Subset of Atoms. The groups of L. M. Raff and D. L. Thompson at Oklahoma State University have recently conducted classical trajectory calculations on the decompositions of a variety of polyatomic molecules. They have found several instances of highly nonstatistical behavior.¹⁷ In the systems that they have studied, neither of the two scenarios described above pertained. Instead, they concluded that nonstatistical behavior could be expected when the reaction coordinate did not produce large energetic changes in one or more bonds in the remainder of the molecule. Under such circumstances the reaction trajectories may cover a small region of phase space very thoroughly, but leave large regions relatively unexplored. It is important to note that this scenario would permit nonstatistical behavior even for relatively high levels of nonfixed energy.

Approximate Models for the Reaction Dynamics of Polyatomic Molecules

Modern high-performance computers have made it possible to carry out classical trajectory calculations on reactions of polyatomic molecules, provided that the potential energy surface for the reaction can be approximated with a series of functions of the type used in molecular-mechanics calculations.¹⁸ The difficulties with adopting this approach, from the point of view of an organic chemist, are (1) that the necessary potential functions are not known for most reaction transition states, and (2) that, even when the potential functions are known, the calculations themselves are

(16) Rynbrandt, J. D.; Rabinovitch, B. S. *J. Phys. Chem.* 1971, 75, 2164.

(17) (a) Raff, L. M. *J. Chem. Phys.* 1989, 90, 6313. (b) Sewell, T. D.; Schranz, H. W.; Thompson, D. L.; Raff, L. M. *J. Chem. Phys.* 1991, 95, 8089.

(18) See, for example: Sewell, T. D.; Thompson, D. L. *J. Phys. Chem.* 1991, 95, 6228.

(14) An apparent exception involves single-step reactions occurring over low barriers (Bauer, S. H.; Borchardt, D. B.; Chiu, N.-S. *Ber. Bunsen-Ges. Phys. Chem.* 1988, 92, 407. Borchardt, D. B.; Bauer, S. H. *J. Chem. Phys.* 1986, 85, 4980).

(15) Oref, I.; Rabinovitch, B. S. *Acc. Chem. Res.* 1979, 12, 166.

far from routine. Thus, while it is quite possible that, in the future, this approach will be used by organic chemists to analyze their reactions, at present it appears that more approximate procedures would be valuable. We have adopted two different approximate approaches.

Trajectory Calculations on Low-Dimensional Projections of the Potential Energy Surface. We have carried out trajectory calculations for the decomposition of the diazenyl biradical **6**, by assuming that the enthalpy surface shown in Figure 1 also serves as a projection of the potential energy surface for the reaction.¹⁹ Points on this surface were estimated from a combination of semiempirical molecular orbital calculations (AM1-CI), experimental observations, and Benson group additivites.

Clearly the surface is not of the correct dimensionality. It has only two geometrical dimensions (θ is the angle between the planes of the three- and four-membered rings in bicyclo[2.1.0]pentane, R is the length of the remaining C-N bond) instead of the proper $3N - 6 = 39$. The reduced dimensionality facilitates both the calculations and the interpretation of the results, but it obviously represents an approximation, whose severity is not easily estimated.

Approximately 50 000 trajectories were run on the surface at each temperature, and the ratio of the intrinsic rate constants for inversion and retention (k_i and k_r , respectively) determined at six temperatures between 130 and 180 °C. The rate constant ratio was found to drop from 2.30 at the lowest temperature to 2.22 at the highest. This small difference was well inside our experimental error and so appeared to be consistent with our failure to detect temperature dependence on the k_i/k_r ratio. The simulation also correctly predicted the ratio to be >1 , but it did not get the magnitude right (the observed value was 4.7 ± 0.9). Overall, though, the results of the simulation seemed to be reasonably satisfactory.

Of particular interest to us was the *reason* that the simulation had correctly predicted a preference for inversion during the decomposition of the diazenyl biradical. This was readily seen when some representative trajectories were plotted out on a contour map of the surface. The results are shown in Figure 2. For the purpose of comparison, three trajectories starting from the same point, just before the transition state, are shown; they differ only in the direction of their initial motion. One can see that trajectory a had too large a fraction of its initial kinetic energy in the R direction and hence was unable to cross the barrier to nitrogen loss. Trajectory c had too large a fraction in the θ direction and was similarly reflected back to the bound diazenyl biradical. Trajectory b had a ratio of R and θ motions that was within the relatively narrow window permitting reaction. The reaction coordinate from the diazenyl biradical to the transition state for its loss of nitrogen involves changes in both the R and θ parameters; this combination of R and θ displacements both defines the reactive trajectory b and, by conservation of momentum, mandates its continuation toward the inversion product. In more picturesque language, one can say that *there is a "beam" of trajectories that has the correct combination of R and θ motions to*

(19) Lyons, B. A.; Pfeifer, J.; Carpenter, B. K. *J. Am. Chem. Soc.* 1991, 113, 9006.

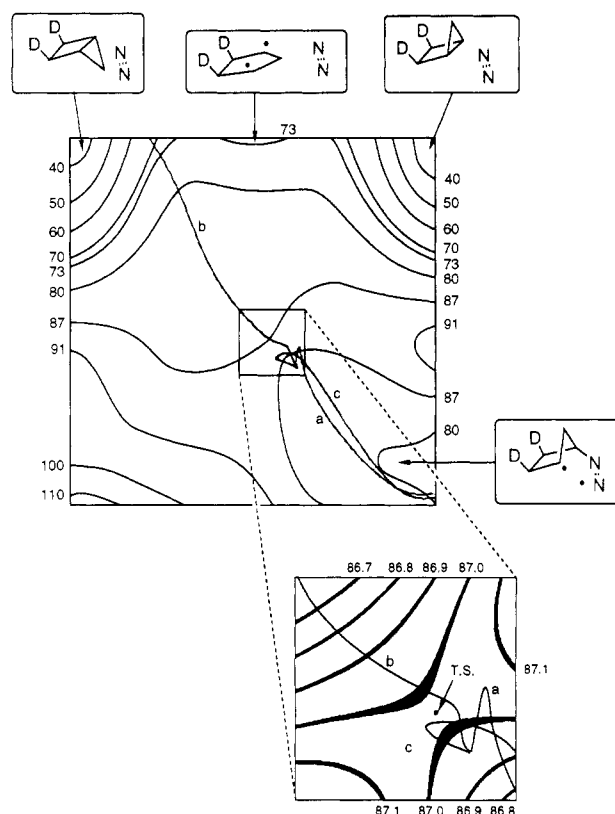


Figure 2. Representative trajectories on a contour plot corresponding to the surface shown in Figure 1.

permit loss of nitrogen, and this "beam" is pointing roughly in the direction of the inversion product. The retention product can be formed by trajectories starting from other points on the surface, or trajectories with higher initial kinetic energy, but in general the preference for the inversion product persists for the reason cited.

This explanation for the preference for inversion of configuration and for the weak temperature dependence of the stereoselectivity appeared reasonably satisfactory, but there remained concerns about the use of such a low-dimensional model for the potential energy surface. Fortunately, an alternative approach for analyzing the reaction dynamics suggested itself during the construction of this surface. This alternative model addresses the dimensionality issue, although it has other approximations that might be causes for concern.

Vectorial Decomposition of the Reaction Coordinate

Application to Thermal Decomposition of Azo Compounds.²⁰ A critical point on the potential energy surface for decomposition of **6** was obviously the transition state for cleavage of the remaining C-N bond. Molecular orbital calculations²¹ were carried out on this transition state. The vibrational analyses that were part of these computations revealed, as required, a single

(20) Peterson, T. H.; Carpenter, B. K. *J. Am. Chem. Soc.* 1992, 114, 766.

(21) Semiempirical calculations were carried out using the AM1 Hamiltonian (ref 10) with the minimal CI necessary for a proper description of a singlet biradical. Ab initio calculations used the Gaussian 88 package (Gaussian 88, M. J. Frisch, M. Head-Gordon, H. B. Schlegel, K. Raghavachari, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, E. M. Fluder, S. Topiol, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA).

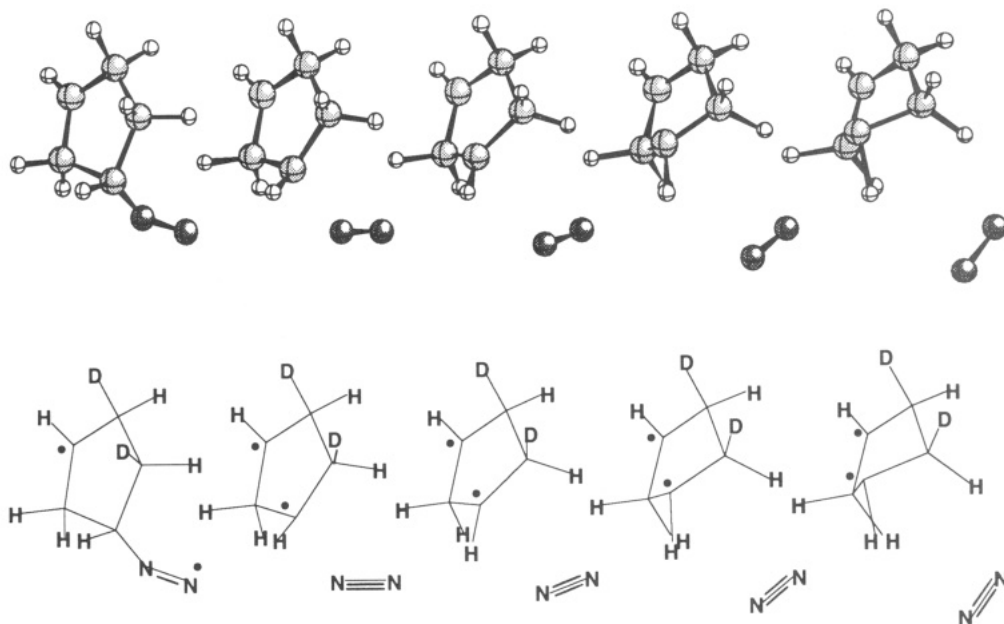


Figure 3. The AM1-CI reaction coordinate for decomposition of the singlet diazenyl biradical from 2,3-diazabicyclo[2.2.1]hept-2-ene-*exo,exo*- d_2 .

imaginary frequency. The atomic motions corresponding to the imaginary frequency define the reaction coordinate, as illustrated in Figure 3 for an AM1-CI calculation on the singlet state. UHF/6-31G* calculations on the triplet yielded a picture that looked virtually identical.

A striking feature of the reaction coordinate was the conformational change occurring in the hydrocarbon fragment as the nitrogen departed. According to the calculations, the reaction coordinate for nitrogen expulsion "imprinted" on the hydrocarbon fragment a set of atomic motions that carried it to a part of the potential energy by hypersurface where the arrangement of atoms was closer to the structure of **8x** than **8n**. For the triplet state, which would require a spin change before product formation could occur, such dynamic events may be of little consequence, but for the singlet biradical, which could presumably collapse to products very rapidly, the dynamics might provide an explanation for the experimentally observed preference for formation of **8x** over **8n**. This picture was really a restatement of the results from the previous trajectory calculations.

The pictorial representation of the reaction dynamics could be translated into a semiquantitative prediction of the product ratio.²² The Cartesian atomic displacements corresponding to the reaction coordinate represent the elements of a $3N$ -dimensional vector (where N is the number of atoms). This vector can be thought of as the center of the "beam" of reactive trajectories described earlier, except that the full-dimensional space of the problem has now been used. We hypothesized that the product ratio could be estimated by comparing components of the mass-weighted reaction-coordinate vector along directions leading to post-transition-state minima on the potential energy hypersurface.²⁰

After addressing certain technical problems, like the need to conserve total angular momentum, and the need

to allow for curved reaction paths,²⁰ the results from the AM1-CI calculations were as follows: for azo-compound **5** the calculated k_i/k_r ratio was 4.3 (the observed value is 4.7 ± 0.9). For 2,3-diazabicyclo[2.1.1]hex-2-ene-*exo-5-d*²³ the calculated value was 1.9, whereas the observed value is 1.2. The latter result showed that the close agreement with the experimental results for **5** was fortuitous, but suggested that a semiquantitative prediction might still be feasible.

It occurred to us that a useful test of the model would be to predict and then measure isotope effects on the product ratio for 2,3-diazabicyclo[2.2.1]hept-2-ene. Accordingly we compared k_i/k_r for **5** and for 2,3-diazabicyclo[2.2.1]hept-2-ene-*endo-1,4,5,6,7,7-d_6*. The calculated isotope effect (d_2/d_6) was 1.099 and the measured value was 1.10 ± 0.04 (95% confidence interval for four measurements). The calculated and observed ratios (d_1/d_2) for 2,3-diazabicyclo[2.2.1]hept-2-ene-*endo-7-d* were 0.936 and 0.93 ± 0.04 . The results were simultaneously encouraging and disappointing: the best estimates of the isotope effects were close to the predicted values, but the wide experimental error bars did not permit a convincing comparison.

Application to the Thermal Rearrangement of 1-Phenylbicyclo[2.1.1]hex-2-ene-*endo-5-d*.²⁴ As we contemplated application of the vector resolution model to other systems, it became apparent that we might have to contend with two problems. The first was that the model was inherently self-contradictory! The transition structure was identified by virtue of the *single* imaginary frequency for its normal modes of vibration. The existence of only one such frequency implies that the potential energy surface slopes down in only one direction. It cannot be possible, therefore, to branch from a transition state to several products without crossing a higher point on the potential energy surface for at least one of those products, and yet we were implying that the reaction accomplished this impossibility in our vector decomposition. In the particular

(22) Since the bicyclo[2.1.0]pentane label isomers interconvert under the reaction conditions, it is more accurate to use a ratio of phenomenological rate constants for inversion and retention (k_i/k_r) than to use the product ratio as an experimental measure to be compared with the calculations.

(23) Chang, M. H.; Dougherty, D. A. *J. Am. Chem. Soc.* 1982, 104, 1131.

(24) Carpenter, B. K. *J. Org. Chem.* 1992, 57, 4645.

cases of the azo compound deazetization, inspection of the computed potential energy surfaces revealed that this error was probably not serious because, in each case, the "channel" leading down from the transition state quickly opened out into a kind of a plateau, where the branching could occur. Since the true branch point was close to the transition structure, our assumption that it was actually at the transition structure probably did not constitute an egregious error. On the other hand, it was not obvious that this fortunate accident would occur in all reactions. The calculations on phenylbicyclo[2.1.1]hexene showed that, indeed, it did not.

The second problem that one could anticipate was that certain of the transformation vectors (as modified to take account of path curvature) might make angles with the reaction coordinate vector that were $>90^\circ$. What would this mean for the reaction dynamics? We encountered this difficulty too in the phenylbicyclo[2.1.1]hexene calculations.

The enthalpy surface for the rearrangement of 1-phenylbicyclo[2.1.1]hexene-*endo-5-d* was explored in three geometrical coordinates, R , θ , and ϕ , defined in diagram A of Figure 4, using AM1-CI.

As R was increased from its initial value of 1.591 Å, the calculated heat of formation rose, until R reached about 2.0 Å (with θ and ϕ being allowed to adopt their lowest-energy values). Beyond 2.0 Å, ΔH_f° first stayed approximately constant and then began slowly to decrease. Despite this behavior, it was apparent that the C-C bond was far from broken at $R = 2.0$ Å, as revealed by the large barrier to torsion (diagram B in Figure 3). If there was still residual bonding at $R = 2.0$ Å, why did the calculated value of ΔH_f° not rise as R increased further? A plausible explanation was that at about $R = 2.0$ Å the increase in ΔH_f° caused by further extension of the bond was just matched by a decrease in ΔH_f° caused by relief of strain in the rest of the molecule. Attempted torsion at $R = 2.0$ Å reduced the C-C bonding, but the resulting increase in ΔH_f° was not matched by a decrease due to relief of strain. This explanation was supported by the decrease in the barrier to torsion at $R = 2.2$ Å (diagram C in Figure 4). At $R = 2.4$ Å the barrier to torsion away from the initial value of ϕ was calculated to be near zero. Minima due to the products started to appear in the enthalpy surface at this stage (diagram D in Figure 4).

Given this kind of surface, the reaction could be described as follows. In the early stages, the motions of the atoms are restricted to those approximately defined by an increase in R and an increase in the pyramidal angle, θ . Once the barrier to torsion has disappeared, the selection of the *direction* of the torsional motion is presumably determined by the efficiency of coupling of the R, θ motion to the two possible ϕ motions.

Since the critical branching point this time occurred well beyond the formal transition state for the reaction, an approximate reaction coordinate at the branch point had to be determined. Accordingly, the vector of mass-weighted atomic displacements between the minimum energy structure with $R = 2.3$ Å and the critical point at $R = 2.4$ Å where the barrier to torsion is lost was used. This vector was found to make an angle of 27° with the vector describing a 10° torsion in the inversion direction, but an angle of 152° with the vector describing

a 10° torsion in the retention direction.²⁵ *The smaller angle for the inversion direction implied more efficient coupling of the initial R, θ reaction dynamics into the torsion leading to inversion, in accord with the experimental preference for formation of the inversion product.*

Interestingly, the angle between the reaction-coordinate vector and the vector describing torsion in the direction of the retention product was found to be greater than 90° . The implication was that, in order to reach the retention product, the most probable reaction trajectory would involve a *reflection* of the initial R, θ trajectory, with the product being formed on the transit back to starting material. Schematic trajectories for formation of the inversion and retention products are shown in diagram D of Figure 4. In reality such trajectories should be shown on a diagram illustrating simultaneous changes in R , θ , and ϕ , but that is hard to draw!

Since the delayed onset of torsional motion is likely to be common in the opening of other strained rings, this analysis suggests that there could be a general *dynamic* preference for inversion of configuration in such systems, if the reaction were not, in fact, a true pericyclic process.^{26,27} Whether this prediction is correct remains to be seen.

Application to the Vinylcyclopropane Rearrangement. In 1976 Andrews and Baldwin reported the first complete stereochemical analysis of a vinylcyclopropane rearrangement.²⁸ The reactant was optically active *trans*-2-methyl-*trans*-propenylcyclopropane. All four possible stereoisomers of the 3,4-dimethylcyclopentene product were observed, but the products were not racemic (as one might have expected for a biradical mechanism if one believed the statistical kinetic models).

Even though the temperature dependence of the product ratios was not known, it occurred to us that this system might be one in which there was dynamic control of the branching from a single biradical. This hypothesis was supported by the observation of temperature-independent branching in a related system.²⁹ Accordingly, we set out to apply the vector resolution model to the reaction studied by Andrews and Baldwin.

As one might have expected, AM1-CI calculations revealed the same kind of delayed onset of torsion exhibited by the 1-phenylbicyclo[2.1.1]hexene rearrangement. The barrier to torsion disappeared at a C1-C2 distance of 2.01 Å. At this point the rearrangements occurring with retention and inversion separated from each other by the sense of rotation about the C2-C3 bond (see Figure 5). The sense of rotation about the C1-C3 bond was defined by the need to bring together C2 and C5 in order to form the five-membered ring of the product. Since the reaction-coordinate vector (estimated as for the 1-phenylbicyclo[2.1.1]hexene rearrangement) made angles $<90^\circ$ with the two torsion vectors, it was possible to make a

(25) The internal rotation angles are kept small so that the atomic displacements can be approximated by linear synchronous transit vectors.

(26) Carpenter, B. K. *J. Am. Chem. Soc.* 1985, 107, 5730.

(27) It should be noted that the primary evidence in favor of a nonpericyclic mechanism for the phenylbicyclo[2.1.1]hexene rearrangement is *experimental* (the lack of temperature dependence of the product ratio).

(28) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* 1976, 98, 6705.

(29) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* 1990, 55, 695.

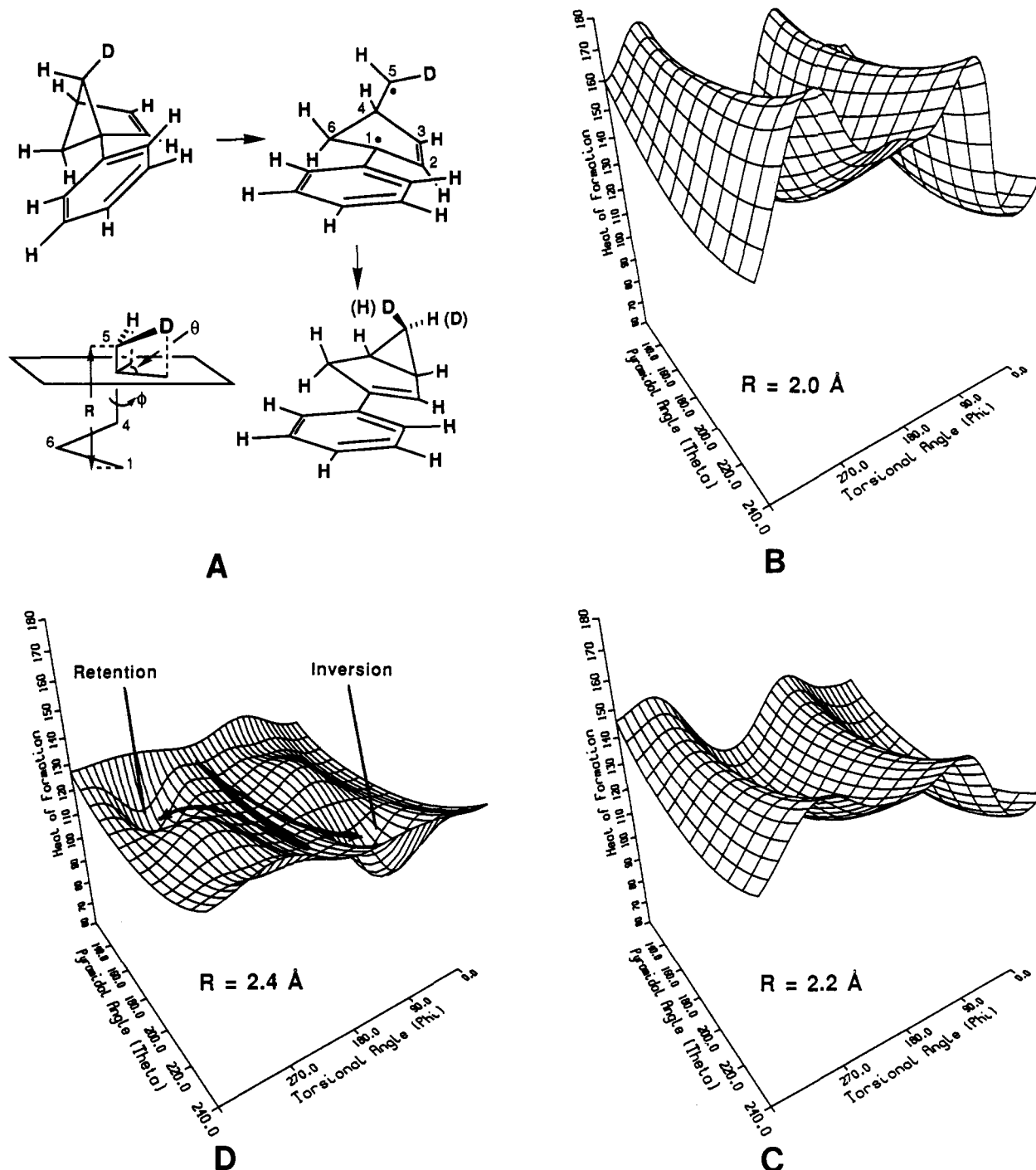


Figure 4. (A) Definition of the coordinates in which the enthalpy surface for rearrangement of 1-phenylbicyclo[2.1.1]hex-2-ene-endo-5-d was explored. (B) Enthalpy surface illustrating large barrier to torsion at $R = 2.0 \text{ \AA}$. (C) Enthalpy surface illustrating decrease in barrier to torsion with increasing R . (D) Enthalpy surface illustrating disappearance of barrier to torsion and appearance of minima due to products at $R = 2.4 \text{ \AA}$. Schematic trajectories for formation of inversion and retention products are shown on this surface.

quantitative prediction of the inversion/retention ratio: it was calculated to be 64.6% inversion and 35.4% retention. Progress down each branch of the reaction continued without significant change in calculated ΔH_f° until two new critical points were reached, those being the structures I and R in Figure 5. These structures had remarkable properties: in each, one could rotate by 90° about C4–C5 with no change in energy. Since one might have thought of C4 and C5 as being part of an allylic radical, it was initially hard to understand how this could be possible. Closer inspection of the calculations revealed that it was caused again by a balance of opposing forces. The loss of π bonding

between C4 and C5, due to 90° torsion, was exactly balanced by an increase in σ bonding between C2 and C5 at the specified C2–C5 distances.

The C4–C5 torsion now made accessible both suprafacial and antarafacial products. Again, the suprafacial/antarafacial ratios could be estimated by the vector resolution method. They were found to be 54.8% suprafacial to 45.2% antarafacial for the retention branch and 97.3% suprafacial to 2.7% antarafacial for the inversion branch.

In total, the mechanism formed a double-forked structure, as shown in Figure 5. The probability of reaching each product could now be estimated, with

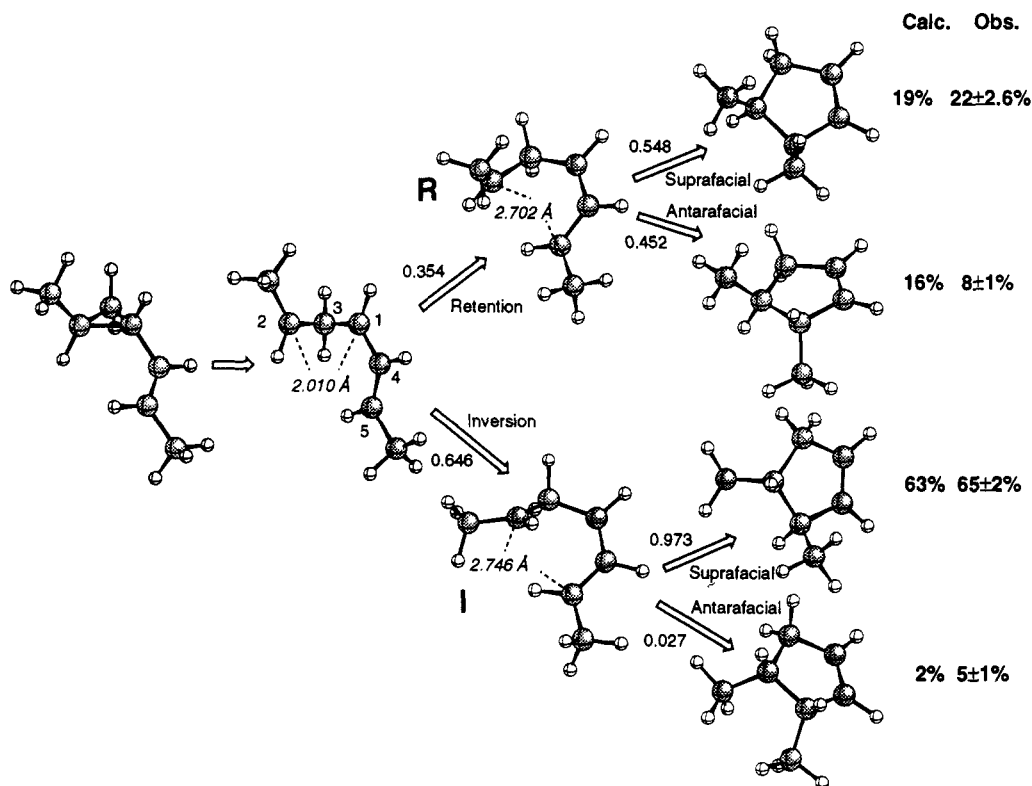


Figure 5.

the results shown in Figure 5. The computed product ratios came out to be quite close to those observed experimentally.

As in the azo-compound calculations, the agreement with experimental results turned out to be at least partly fortuitous, because similar calculations for *trans*-1-(1-ethenyl-2-*d*)-2-methylcyclopropane led to a prediction of a 25% sr:22% ar:45% si:8% ai product ratio (sr means suprafacial-retention, etc.) whereas the observed³⁰ ratio is 18:15:55:13. Worse still, we were unable to rationalize some of our own experimental results!²⁹ The ar/si ratio for *trans*-1-(*trans*-2-phenylethenyl)-2-methylcyclopropane was found experimentally to be 5.9 but calculated to be 0.7. Whether this profound disagreement represents a complete invalidation of the entire vector-resolution model or whether it is a special-case aberration of unknown origin is not yet clear.

If one accepts the mechanism for the vinylcyclopropane rearrangement that arises from the dynamic hypothesis, an interesting and perhaps disturbing corollary comes with it. The reaction involves a biradical whose equilibrium geometry is achiral, but the products are optically active. The "rule" that an optically active compound must give racemic products in a reaction occurring via an achiral intermediate appears to have been violated. Of course the issue returns us to the question of just what one means by an intermediate. There is, in fact, no requirement that the product ratios of a reaction reflect the symmetry of the potential energy surface, unless one insists on the behavior for the intermediates that is postulated in the statistical kinetic theories. As soon as that

restriction is lifted, the product ratios cease to tell one anything (or at least anything simple) about the symmetry of the potential energy surface.

Future Directions

Even if one is willing to accept the case in favor of a dynamic model for the thermal reactions of polyatomic molecules, questions still remain about its domain of applicability. When will the statistical models be adequate, and when will they not? Does one need to consider detailed dynamics for reactions in solution? If so, do ionic reactions exhibit dynamically controlled product formation? What experimental criteria can one develop to detect the occurrence of significant dynamic effects? These are all questions that we hope to address over the next several years.

I consider myself extremely fortunate to have had such talented coworkers as Rick Newman-Evans, Reyna Simon, Barbara Lyons, Debbie Bebout, Jörg Pfeifer, and Tom Peterson working on this project. I am pleased to have this opportunity to thank them in print. I am very grateful to Professors Lionel M. Raff and Donald L. Thompson for recognizing the relationship between their work and ours and for providing results prior to publication. Support for some of the experimental work came from the NIH and AFOSR. The theoretical work was 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.

(30) Baldwin, J. E.; Ghatlia, N. D. *J. Am. Chem. Soc.* 1991, 113, 6273.