Chem. Rev. **2003,** *103,* 1197−1212

Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes

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Received July 10, 2002

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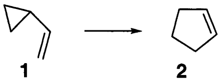
1. Introduction

Vinylcyclopropane was introduced to the chemical world through Gustavson's reported synthesis of the hydrocarbon late in the 19th century.[1] The preparation from $C(CH_2Br)_4$ gave mostly spiropentane; the major olefinic isomer was thought to be vinylcyclopropane, or "vinyltrimethylene" in the nomenclature of the day, but it proved to be 1-methylcyclobutene.[2] Authentic vinylcyclopropane was secured by Demjanov and Dojarenko in 1922.[3]

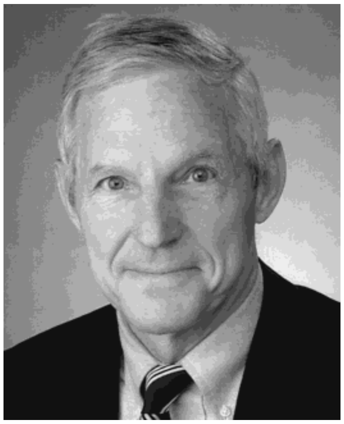
This clarification of the literature and secure route to vinylcyclopropane were greeted with considerable reserve. Even as late as 1937 a leading American organic chemist could assert that vinylcyclopropane was "*incapable of existence*".[4] Physical methods finally provided conclusive evidence for the structural assignment. Today the structure of vinylcyclopropane is known in considerable detail[5] and has been scrutinized in any number of theoretical investigations.

The thermal conversion of vinylcyclopropane (**1**) to cyclopentene (**2**) was reported independently in 1960 by Vogel[6] and by Overberger and Borchert.[7] Vogel also noted the more facile isomerization of 1-phenyl-1-vinylcyclopropane to 1-phenylcyclopentene. One year earlier Neureiter uncovered the first example of this type of rearrangement when he observed that 2,2-dichloro-1-vinylcyclopropane (**3**) was converted initially to 4,4-dichlorocyclopentene (**4**).[8] The regiochemistry reflected migration of the C2 carbon and cleavage of the weakest cyclopropyl bond.



1 **2**

3 **4**



John Baldwin, now a distinguished professor and chair of the department of chemistry at Syracuse University, graduated summa cum laude from Dartmouth College in 1959 and completed Ph.D. studies at the California Institute of Technology in chemistry and physics in 1962 working with John D. Roberts. He started teaching at the University of Illinois in 1962, where he was recognized through an Alfred P. Sloan Fellowship, Associate Membership of the Center for Advanced Study at the University of Illinois, and a John Simon Guggenheim Memorial Foundation Fellowship. He served on the faculty of the University of Oregon as professor of chemistry from 1968 to 1984 and as dean of the college of arts and sciences from 1975 to 1980, following a year in Hamburg and Munich as a Senior U.S. Scientist Awardee of the Alexander von Humboldt Foundation. Other visiting appointments have been spent in Heidelberg, Wroclaw, Stockholm, and Göteborg. Since moving to Syracuse in 1984, his research has concentrated on experimental determinations of reaction stereochemistry for thermal rearrangements, often utilizing isotopically labeled reactants and novel analytical strategies for following the time evolution of complex reaction mixtures.

The activation energy for the vinylcyclopropane-to-cyclopentene thermal reaction (the vinylcyclopropane rearrangement)[9−11] proved to be about 13 kcal/mol lower than E_a for the cis,trans equilibration of the 1,2-d_2-cyclopropanes,[12,13] a difference remarkably similar to the resonance energy of the allyl radical. These observations led promptly to an appreciation of the vinylcyclopropane rearrangement as a diradical-mediated reaction, one involving thermal homolytic cleavage of the C1−C2 cyclopropane bond to generate an allylic stabilized diradical intermediate, a 2-(*Z*)-pentene-1,5-diyl diradical (**5**).[14−17] The stereo-

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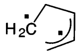
isomeric 2-(*E*)-pentene-1,5-diyl diradical (**6**) would as well be accessible, but would not lead to cyclopentene product.



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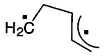

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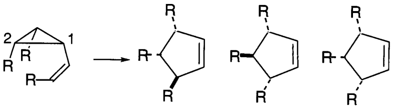
The excellent match between the observed E_a for the vinylcyclopropane rearrangement and what one might expect from simple thermochemical considerations and a putative diradical mechanism was given careful consideration in 1969 when Woodward and Hoffmann used the vinylcyclopropane rearrangement to exemplify [1,3] sigmatropic reactions.[18,19] They noted that a two-step nonconcerted path for the isomerization by way of a diradical intermediate would not be thermodynamically unreasonable. They also drew attention to the stereochemical consequences of orbital-symmetry-controlled concerted paths for the vinylcyclopropane-to-cyclopentene reaction. They noted that *antarafacial, retention* (*ar*) and *suprafacial,inversion* (*si*) paths would be symmetry allowed, while the *sr* and *ai* isomerization products could not be produced through symmetry-allowed processes. They stated truisms based on the principle of the conservation of orbital symmetry theory: if the rearrangement were an orbital-symmetry-allowed concerted conversion, then the reaction stereochemistry would be as predicted. They did not make a mechanistic or stereochemical prophecy.

Their representational example was a vinylcyclopropane substituted with three R groups (**7**) rearranging with C1−C2 bond cleavage to give three stereoisomeric cyclopentenes. The first product (**8**), reached through an *ar* [1,3] shift, and the second (**9**), from a *si* shift, would be symmetry allowed. The third isomer (**10**) would stem from a *sr* process; it could not be produced in a symmetry-allowed manner.



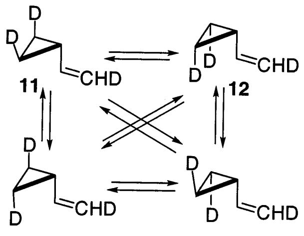
7 **8** **9** **10**

Closer scrutiny of the possibilities leads to a recognition that **8** could be reached through either *ar* or *ai* paths, or both. The enantiomer of the (*ar* + *ai*) product would be formed through cleavage of the C1−C3 cyclopropyl bond and (*ar* + *ai*) shifts. Thus the stereochemical options—three products through four distinct paths—encouraged one to think about how one might determine the participation of *ar* and *ai* paths separately.

The special attention directed toward the vinylcyclopropane rearrangement by Woodward and Hoffmann no doubt contributed to an enhanced interest in the reaction. Their recognition that either a two-step diradical mechanism or an orbital-symmetry-allowed concerted mechanism might be envisaged seemed to call for an experimental determination of reaction stereochemistry. After all, given the sure correlation between reaction stereochemistry and predictions of reaction stereochemistry based on orbital symmetry theory, one might clarify the mechanistic issue at once, in favor of an orbital-symmetry-controlled process or the alternative, the thermodynamically not unreasonable stepwise, diradical-mediated isomerization.

To achieve a definition of reaction stereochemistry for a suitably substituted vinylcyclopropane proved to be a very challenging goal, for kinetically competitive reactions camouflaged the target. *cis*-2-Methyl-1-vinylcyclopropane and similarly substituted vinylcyclopropanes give 1,4-(*Z*)-hexadiene and similar acyclic diene products, through homodienyl [1,5] hydrogen shifts, and relatively small yields of cyclopentene products.

Thermal stereomutation reactions tend to scramble stereochemical distinctions in substituted vinylcyclopropanes much faster than rearrangements lead to cyclopentene products. These rapid homodienyl [1,5] hydrogen shifts and stereomutations were recognized in the mid-1960s.[20−22] Isomers **11**−**14** of the parent system labeled only with three deuterium atoms interconvert rapidly while d_3-cyclopentene products form relatively slowly.[23,24]



13 **14**

Thus, by 1970, the vinylcyclopropane rearrangement was well-established and had gained considerable attention. The sterechemistry and mechanism of the rearrangement were not known. The importance of the reaction as the simplest known [1,3] carbon sigmatropic shift and the substantial challenges the reaction presented to both experimentalists and computational chemists were reflected in several early reviews, and further reviews have continued to appear regularly.[16,17,25−35]

The present contribution concentrates on the stereochemical and mechanistic aspects of the vinylcyclopropane rearrangement. A small sampling of related rearrangements and synthetic applications is included as a reminder that mechanistic concerns cover just one facet of the rich chemistry exhibited by vinylcyclopropanes and various closely related structures.

2. Reaction Kinetics

The vinylcyclopropane rearrangements of many substituted systems have been followed kinetically to establish rate constants and activation parameters. These most valuable contributions toward understanding the reaction have been thoroughly reviewed[16,17,27,28] and need not be recapitulated in detail here. Taken together, they are completely consistent with the proposition that cleavage of a cyclopropyl C1−C2 bond is rate limiting and that substitution so as to lead to a more stable diradical intermediate structure lowers the activation energy for the rearrangement. One can formulate this generalization in several ways, such as by plotting $\Delta G^{\ddagger}$(rearrangement) versus $\Delta G^{\ddagger}$(cis,trans-stereomutation) values for a series of substituted vinylcyclopropanes;[35−37] a good linear correlation is seen. Substituents exerting a radical-stabilizing effect facilitate cis,trans-stereomutations and vinylcyclopropane rearrangements in parallel fashion; $\Delta\Delta G^{\ddagger}$ is 3−4 kcal/mol, with rearrangements slower than stereomutations.

Our best current experimental estimate for activation parameters for the parent hydrocarbon are $E_a = 51.7$ kcal/mol and $\log(A,\mathrm{s}^{-1}) = 14.3$.[11] Gas phase heats of formation for cyclopentene and vinylcyclopropane are 8.7 ± 0.3 and 30.4 ± 0.3 kcal/mol, respectively.[11] Cyclopentene is more stable by 21.7 kcal/mol and is massively favored at equilibrium.

3. Substituent Effects

Simpson and Richey determined that a methoxy substituent at C1 of a vinylcyclopropane lowered the activation energy for rearrangement by about 5 kcal/mol, whereas at the *trans*-C2 position it lowered E_a by a far more substantial 11 kcal/mol.[38] Subsequent kinetic work has explored in greater depth the rearrangement-facilitating effects of alkoxy and similar substituents, most recently in a thorough study including $SiMe_3$ and SMe examples.[39] At C1, the measured or cited literature E_a values for Me, $SiMe_3$, SMe, OMe, and OEt substituents are 49.4, 48.1, 47.2, 44.7−45.7, and 45.1 kcal/mol, modest but not trivial effects, considered consistent with a diradical mechanistic formulation.[39] For *trans*-C2 substituted systems (Me, SMe, OMe, OEt, and NMe_2), the E_a values are 48.7, 41.5, 38.7, 38.4, and 31.2 kcal/mol, respectively.

This detailed, carefully secured kinetic information may be interpreted in various ways. If one accepts the proposition that there is well-documented evidence elsewhere in the literature for concertedness in the vinylcyclopropane rearrangement, then one may postulate a mechanism involving concerted processes with different degrees of transition-state stabilization. If one interprets the data through a diradical mechanistic model, they suggest that the SMe and OMe groups are better at stabilizing an adjacent radical center when initially at C2 than at C1. The $-CH_2CH_2\bullet$ to $-CH_2(MeS)CH\bullet$ or $-CH_2(MeO)CH\bullet$ conversion, according to this view, is more exothermic than conversion of $-CH_2(H_2C{=}CH)CH\bullet$ to $-CH_2(H_2C{=}CH)C\bullet(SMe)$ or $-CH_2(H_2C{=}CH)C\bullet(OMe)$. There could also be important differential substituent effects on ground-state stabilities.

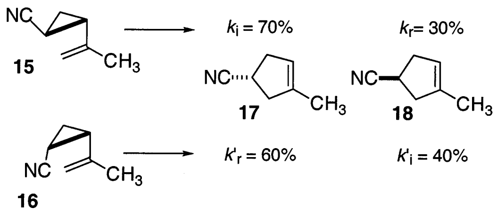
Donor−acceptor-substituted vinylcyclopropanes provide ready access to a wide variety of functionalized cyclopentene derivatives.[40] The reactions take place in competition with stereomutations of reactants and with various degrees of stereoselectivity. Both stereomutations and [1,3] shifts seem to involve stepwise mechanisms proceeding through intermediate, highly stabilized 1,3-zwitterionic species.[41,42] While the great synthetic utility of such reactions is unquestionable, the diradical versus 1,3-zwitterion formulation of intermediates remains problematic. Some theory suggests that a given system may favor one or the other electronic structural variant in response to changes in solvent.[43] Other calculations find that transition structures for the rearrangements retain diradical character, even when a donor substituent (hydroxyl) and an acceptor substituent (cyano) are positioned here or there; the transition structures resemble two weakly interacting connected radical substructures.[44] The calculated activation energies for rearrangements of the disubstituted systems reflect the radical-stabilizing capacities of the substituents.

4. Reaction Stereochemistry

Mazzocchi and Tamburin in 1970 found that different diastereomers of 1-(*E*)-propenyl-2-ethoxycarbonyl-3-methylcyclopropane rearranged to *different* mixtures of diastereomeric cyclopentene products.[45,46] Thus, both complete stereochemical scambling of starting materials prior to rearrangement, and intervention of completely efficient stereorandomizing diradical intermediates could be ruled out. The rearrangements did occur with some sterechemical selectivity; it only remained to gain quantitative information on all stereochemically competitive paths.

Doering and Sachdev approached this challenge by studying optically active 2-cyano-1-isopropenylcyclopropanes **15** and **16**.[47,48] The cyano substituent, being a fair radical-stabilizing group, facilitated the reaction, it contributed essentially no steric bulk, and it obviated the homodienyl [1,5] hydrogen shifts most 2-alkyl substituents would have contributed.

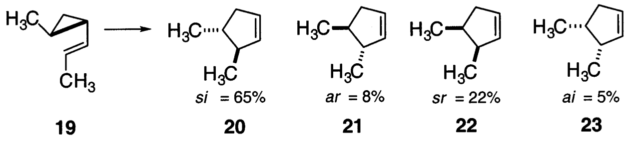
They were able to define experimentally the reaction-time-dependent mole percent concentrations and optical activities of the cis and trans isomers of starting materials and of the 4-cyano-1-methylcyclopentene products **17** and **18**. From these data they were able to calculate the rate constants leading from any one of the four isopropenylcyclopropane isomers to the two enantiomers of product. For one enantiomer of the trans reactant (**15**), the rate constants for migration with inversion, k_i, and with retention, k_r, are equivalent to the combinations ($k_{si} + k_{ai}$) and ($k_{sr} + k_{ar}$), for no stereochemical marker was positioned at C2′. (The reaction rate constants here and elsewhere in this review are identified by subscripts corresponding to stereochemical outcomes, or stereochemical relationships between one vinylcyclopropane and one cyclopentene, whatever the mechanism.) From the trans substrate the k_i:k_r balance was 70:30; migration with inversion was favored. From the cis substrate (**16**), the ratio of rate constants k'_i:k'_r was 40:60, with retention at the migrating carbon predominating.



Clearly the stereochemical disposition of the cyano substituent in these examples has a major influence on the reaction stereochemistry, even though the alternative products are of equal energy.

Andrews took advantage of the fast conversion of *cis*-2-methyl-1-alkenylcyclopropanes to acyclic dienes to simplify the kinetic situation for his stereochemical study of a vinylcyclopropane rearrangement.[49] Without that competing reaction, the kinetic outline would have been a composite of stereomutations and of four sets of reactions linking one stereoisomer of the starting material with all four possible [1,3] carbon shift products.

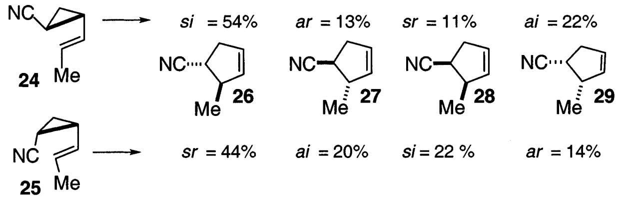
Since the cis enantiomers react to form 1,4-(*Z*)-heptadiene orders of magnitude faster than they revert to trans diastereomers, the kinetic situation becomes far more tractable. Only two rather than four sets of isomerizations can lead to cyclopentene products. Reaction-time-dependent data on the mole percent concentrations and ee values of trans enantiomers of the substituted vinylcyclopropane, and of *cis*- and *trans*-3,4-dimethylcyclopentenes, may be transformed through straightforward calculations to the four rate constants linking one *trans*-2-methyl-1-(*E*)-propenylcyclopropane (**19**) to each of the four 3,4-dimethylcyclopentenes (**20**−**23**).



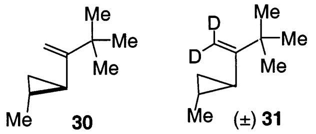
The relative rate constants at 296.5 °C were k_{si} = 65%, k_{ar} = 8%, k_{sr} = 22%, and k_{ai} = 5%. Four paths were in evidence; the orbital-symmetry-allowed *si* and *ar* routes were favored, but not dramatically (73:27). Both "allowed" and "forbidden" products retained substantial optical purity. The reaction was viewed as proceeding through four energetically concerted processes, two "allowed" and two "forbidden" according to the dictates of orbital symmetry theory, with the possible intervention of a planar π-vinylcyclopropane intermediate.[49]

This experimental study, the first to report rate constants for all four stereochemically distinct paths for the rearrangement of an unconstrained monocyclic vinylcyclopropane, was followed by Barsa's similar work on optically active 2-cyano-1-(*E*)-propenylcyclopropanes (**24**, **25**).[50] The technical demands of his investigations were extremely challenging, but rate constant data could be extracted from observables gained through careful kinetic and stereochemical experiments. The results are summarized below. For the trans reactant at 207 °C, the pattern of relative rate constants found was very similar to the one observed by Andrews, but for the reversed importance of *sr* and *ai* paths.

The rearrangement of the trans isomer (**24**) favors "allowed" paths leading to trans products **26** and **27** (67:33), while the cis reactant (**25**) favors "forbidden" paths over the "allowed" options (64:36).[50] Both diastereomers favor formation of the more thermodynamically stable trans diastereomers of 3-methyl-4-cyanocyclopentene.



In 1984, Gajewski and Warner reported on the rearrangements of (−)-(*R*,*R*)-*trans*-1-(1′-(*tert*-butyl)-vinyl)-2-methylcyclopropane (**30**) at 280 °C.[51] Two thoughtful considerations prompted this choice of substrate. First, the bulky *tert*-butyl substituent could be anticipated to favor access to the 2-*tert*-butyl-2-(*Z*)-hexene-1,5-diradical, were it involved, and thus favor [1,3] shifts relative to stereomutations leading to formation of an acyclic diene product by way of cis enantiomers. Second, the two [1,3] shift products would not be biased thermochemically, for they would be related as enantiomers. In earlier stereochemical work,[49] product stability factors might have favored the formation of trans rather than cis 3,4-disubstituted cyclopentenes through such a bias. Parallel work with the 1′-(*tert*-butyl)-2′,2′-d_2-vinyl analogue [(±)-**31**, 80% deuterated] provided information on secondary deuterium kinetic isotope effects.[52−55]



The [1,3] shift rate constants reflected an isotope effect of 1.125 ± 0.04 at 280 °C; a rotational isotope effect was evident at the product-determining stage of the transformation. The unlabeled and d_2-labeled systems were reported to isomerize to cyclopentene products with modest and yet distinct degrees of net retention, 7.1 ± 1% and 4.1 ± 1.5%, respectively, in stark contrast to the 40% net inversion seen in vinylcyclopropane rearrangements reported for a dimethyl-substituted vinylcyclopropane by Andrews and Baldwin.[49] A nonconcerted diradical mechanism was suggested.

A second experimental study provided a further contradiction to the stereochemical characteristics found for the vinylcyclopropane rearrangements uncovered in earlier studies.[47−50] Careful kinetic work by Carpenter and co-workers published in 1990 provided good evidence in favor of a diradical-mediated mechanism for the vinylcyclopropane rearrangement of *trans*-(1*R*,2*R*)-1-((*E*)-styryl)-2-methylcyclopropane to 3-phenyl-4-methylcyclopentenes.[56] The dominant trans products were formed in a (5.9 ± 0.3):1 ratio, a fact consistent with a diradical intermediate that lives such a short time that it fails to reach an equilibrium nuclear configuration, or mixture of conformational forms.

The absolute stereochemical assignments made for the trans enantiomeric products led to the conclusion that, in this case, the *ar* pathway was strongly favored over the *si* route, in contrast to the $k_{si} > k_{ar}$ preference seen for *trans*-1-(*E*)-propenyl-2-methylcyclopropane.[49] Unfortunately, kinetically controlled product ratio information on the *cis*-3-phenyl-4-methylcyclopentene enantiomers could not be secured.[56]

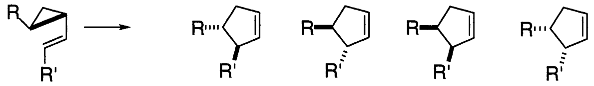
These markedly conflicting stereochemical results served as an encouragement to undertake more comprehensive experimental efforts, to uncover the factors responsible for the stereochemical discrepancies and to learn how different substituents influenced stereochemical preferences.

From 1991 to 1996 six additional vinylcyclopropane systems substituted variously with deuterium or methyl or phenyl were synthesized and subjected to experimental studies leading to definitions of reaction stereochemistry.[57−64] Five systems having substitutents at 2′-(*E*) and 2-trans positions were secured in high enantiomeric excess and with known absolute stereochemistry. The absolute stereochemical assignments for all products were established. The parent vinylcyclopropane labeled with deuterium atoms at 2′, 2, and 3 positions was prepared in two distereomeric meso variants. The thermal rearrangements of these vinylcyclopropanes were followed kinetically, with explicit, analytical exact deconvolutions of raw kinetic and stereochemical data to take full account of stereochemical contributions contingent on competitive stereomutations.

The obvious complexities associated with the thermal stereomutations characteristic of vinylcyclopropanes have at times led to overly pessimistic and erroneous conclusions. The assertion sometimes encountered that experimental work attempting to determine reaction stereochemistry for the vinylcyclopropane rearrangement must of necessity be invalid, because vinylcyclopropane starting materials, however carefully designed and synthesized to carry out this type of study, suffer parallel and more rapid enantiomerization and diastereomerization processes, is simply wrong. Quite valid stereochemical information on [1,3] shifts can be obtained despite rapid kinetically competitive enantiomerization and diastereomerization processes. One only has to treat the kinetic situation in detail, exactly, secure the requisite data, and deconvolute it properly to obtain the kinetically controlled rate constants for specific [1,3] carbon shifts.

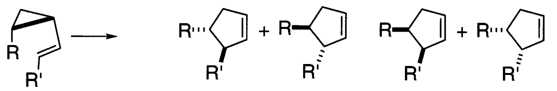
The experimental work invested to meet these demands encompassed a range of substrates and reaction temperatures, relied on different investigators, and utilized a variety of analytical methods and data-reduction protocols. Yet the stereochemical outcomes were qualitatively completely consistent. The pattern of stereochemical preferences observed provides a reasonable basis for stereochemical generalizations.

Table 1. Kinetically Controlled Reaction Stereochemistry for Vinylcyclopropane-to-Cyclopentene Rearrangements of *trans*-2,2′-(*E*)-Disubstituted Reactants



R	R′	*si* (%)	*ar* (%)	*sr* (%)	*ai* (%)	ref
D	D	40	13	23	24	59
Me	D	55	15	18	13	57
CN	Me	54	13	11	22	50
Me	Me	65	8	22	5	49
Me	Ph	60	10	19	11	58
Ph-d_5	D	58	8	24	10	62
Ph	Me	44	20	25	11	60
Ph	Ph	67	12	17	4	63

Table 2. Kinetically Controlled Reaction Stereochemistry for Vinylcyclopropane-to-Cyclopentene Rearrangements of *cis*-2,2′-(*E*)-Disubstituted Reactants



R	R′	(*sr* + *ai*) (%)	(*si* + *ar*) (%)	ref
Ph-d_5	D	52	48	62
CN	Me	64	36	50
Ph	Me	90	10	60
Ph	Ph	91	9	63

All of the eight fully stereochemically defined vinylcyclopropane rearrangements of unconstrained, monocyclic systems—seven hydrocarbon examples as well as the *trans*-1-(*E*)-propenyl-2-cyanocyclopropane studied by Barsa and Doering[50] (Table 1)—occur through all four possible stereochemically distinct paths, in proportions varying with substituents). For trans reactants, migration with inversion is somewhat favored, as is utilization of the allylic unit in a suprafacial sense. The inequality $k_{si} > k_{ar}$ holds even for the deuterium-labeled parent system.

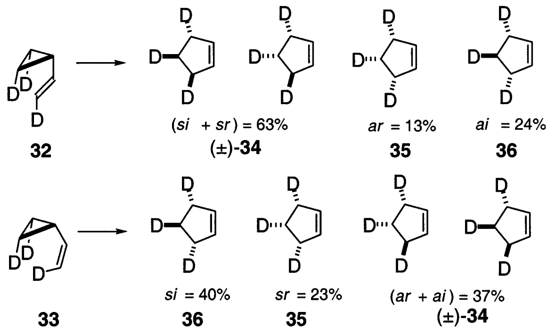
All three systems having a trans methyl group at C2 follow the same kinetic format.[49,57,58] Two-centered stereomutations leading to racemization of the trans starting material may be followed while all one-centered epimerizations forming cis enantiomers continue on irreversibly to afford acyclic dienes. The time-dependent mole percents of both trans enantiomers and of the four stereoisomers of the corresponding cyclopentene products can be used to calculate the kinetically controlled direct rate constants for isomerizations from one enantiomer of starting material to each of the four cyclopentene products. The analysis is simple; it involves nothing more complicated than asking a least-squares program to find best parameters for theoretical integrated rate equations appropriate to the kinetic situation. One, of course, needs many more experimental (time, mole percent) data points than parameters!

For the vinylcyclopropanes studied having a phenyl substituent at C2,[60,62,63] stereomutations led to all four stereoisomeric versions of substrate, and the kinetic situation became somewhat more complicated, for cis isomers also reacted to form cyclopentene products. Nevertheless, the translation of raw time-dependent kinetic data for the isomers of starting materials and products could be carried through, explicitly, using the exact, theory-dictated analytical expressions to fit data and find kinetically controlled rate constants.

The rate constant ratios found for the cis isomers of the 2-phenyl systems (Table 2) contrast in most interesting fashion with those seen for the related trans isomers.[58,60,63] The experimental studies concentrated on trans reactants; racemic samples of cis isomers of starting materials were used to get good values of ($k'_{si} + k'_{ar}$) and ($k'_{sr} + k'_{ai}$), but no cis starting materials of high ee were prepared and studied separately.

The cis isomers formed through stereomutations of optically active trans substrates were in all three cases essentially racemic, and thus only combinations of rate constants could be extracted. For the reactions leading to 3,4-diphenyl and 3-methyl-4-phenylcyclopentenes, the [1,3] shift rate constants strongly favored formation of the trans isomers: ($k'_{sr} + k'_{ai}$):($k'_{si} + k'_{ar}$) values were found to be 91:9 and 90:10, that is, with the “forbidden” paths leading to thermochemically favored products strongly advantaged. For the reactions leading to 3-*d*-4-phenylcyclopentenes, the racemic *cis*-vinylcyclopropane formed through stereomutations of the optically active starting trans isomer formed products with ($k'_{sr} + k'_{ai}$):($k'_{si} + k'_{ar}$) = 52:48. An important influence of product thermochemical stability was evident in these three examples. It clearly trumps the dictates of orbital symmetry theory, whatever the detailed mechanism may be.

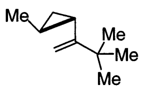
The stereochemistry of the parent (deuterium-labeled) vinylcyclopropane system was secured through thermal rearrangement studies of both *syn*-2,3-(*E*)-2′-d_3 and *syn*-2,3-(*Z*)-2′-d_3 labeled versions of the parent hydrocarbon.[59,61] Both were necessary, for each can form but three distinct products: the *E* isomer (**32**) leads to racemic 3,4,5-d_3-cyclopentene ((±)-**34**) through *si* and *sr* paths and to the all-cis and trans,trans meso isomers **34** and **36** by *ar* and *si* routes, respectively. The *Z* starting material gives trans,trans and all-cis isomers through *si* and *sr* paths, respectively, and the racemic diastereomer through *ar* and *ai* reactions. Thus, combining stereochemical findings from runs from both starting materials can provide rate-constant information for all four paths.



Given the extremely fast competitive stereomutation reactions, the kinetic work tracked reactant and product stereochemistry over the first 1.0−2.7% of vinylcyclopropane rearrangement, periods short enough so that stereochemical scrambling of starting substrates could not proceed to a debilitating extent before products could be isolated and defined stereochemically. The relevant linear equations relating observed product distributions as functions of reaction-time-averaged mole percent concentrations of the three isomers of each d_3-vinylcyclopropane substrate allowed one to secure experimental rate constants for the four [1,3] shift paths.[59]

For vinylcyclopropanes substituted only with three deuterium atoms, the suprafacial routes are favored 63:37 and the inversion paths are favored 64:36. The breakdown among all four paths is 40% *si*, 13% *ar*, 23% *sr*, and 24% *ai*. The estimated uncertainties of these values, from averages over five kinetic runs, were 2−3%.[59]

In hindsight, the two stereochemical studies that seemed in conflict with Andrew’s pioneering work[49] turned out to be flawed. The first case was a preliminary communication.[51] Careful reevaluation of the experimental work that formed the basis of this communication was undertaken by Gajewski and Squicciarini.[65] They discovered that the (*R*) isomer of 1-*tert*-butyl-4-methylcyclopentene has an $[\alpha]^{25}_{365}$ rotation of only −2.4 ± 0.4 in cyclohexane, rather than 150.4 as previously reported.[51] The problem followed from incomplete separation of chiral 3-methyl and 4-methyl isomers from a synthetic product mixture. New kinetic and stereochemical work using the (1*S*,2*S*) isomer **37** demonstrated a high preference for migration with inversion, rather than migration with net retention: ($k_{si} + k_{ai}$):($k_{sr} + k_{ar}$) = 85:15.[65]



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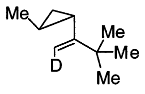

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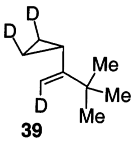
A racemic sample of *trans*-1-(1′-(*tert*-butyl-2′-(*E*)-*d*-vinyl)-2-methylcyclopropane [(±)-**38**, 81% deuterated] was also followed; the 1-*tert*-butyl-4-methyl-5-*d*-cyclopentene product mixture showed a preference for trans product: trans:cis = 86:14. Thus, although the two ratios of rate constants determined did not allow one to calculate the relative rates for the four distinct paths, the ranges of possibilities consistent with the incomplete data appeared comparable: they were calculated to be 72−86% *si*, 14−0% *ar*, 0−14% *sr*, and 14−0% *ai*. The pattern is similar but of course not identical to the one seen earlier for the dimethyl-labeled vinylcyclopropane studied by Andrews and Baldwin.[49]

Later studies of a similar reaction found that the thermal vinylcyclopropane rearrangement of *cis*-2,3-d_2-*trans*-(1′-*tert*-butyl-2′-(*Z*)-*d*-vinyl)cyclopropane (**39**)



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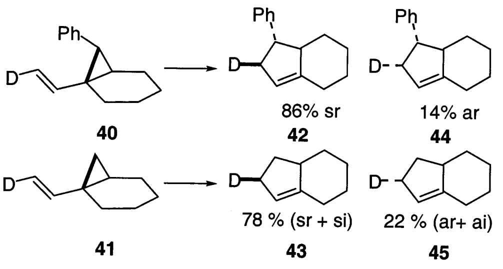
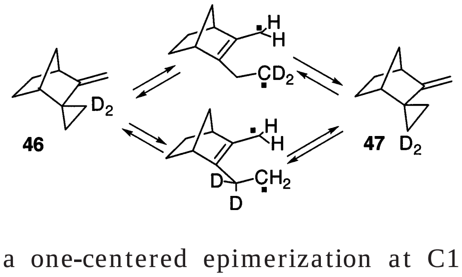
takes place with high stereoselectivity favoring the *si* path.[66,67] It appeared from NMR spectral analyses and simulations to be greater than 70% stereoselective, even before corrections for incomplete deuterium labeling and some cis,cis isomer in the starting material (together amounting to 15% of the sample of **39** employed) and for loss of stereochemical integrity of the starting material during the thermal reaction caused by stereomutations. Further analysis, spectral fittings, and corrections implied about 90% stereoselectivity. The isomerization was viewed as a sterically unbiased concerted reaction in which the orbital-symmetry-controlled *si* pathway is dominant.

In the second case of apparent conflict,[56] an experimental problem was also uncovered. An inadvertent reversal of sign for an optical rotation led to a corresponding reversal of absolute stereochemistry assignments for the *trans*-3-phenyl-4-methylcyclopentenes.[58] With this simple error corrected, the two studies were brought into excellent agreement. The favored kinetically controlled stereochemistry is *si* rather than *ar*, by (59 ± 3):10 according to the revised reading of Carpenter's data[56] or by 60:10 according to Bonacorsi's later study.[58]

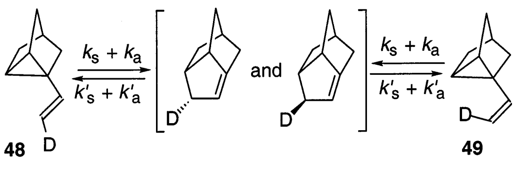
Further stereochemical work has probed how added geometrical constraints influence stereochemical preferences for vinylcyclopropane rearrangements. Two substituted 1-vinylbicyclo[4.1.0]heptanes (**40** and **41**) were rearranged to bicyclo[4.3.0]non-1(9)-ene products: both suprafacial (**42**, **43**) and antarafacial migration products (**44**, **45**) were observed.[68,69] 1-Vinyl-6-*exo*-dimethylaminobicyclo[4.1.0]heptane has been converted efficiently to 7-*exo*-dimethylaminobicyclo-[4.3.0]non-1(9)-ene.[70]



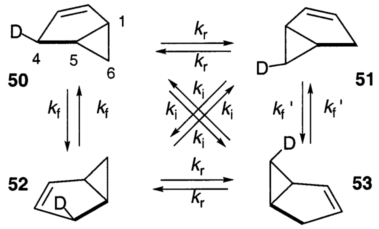
Heating a deuterium-labeled analogue of 2-methylene-3-spirocyclopropanebicyclo[2.2.1]-heptane (**46**) led to a one-centered epimerization at C1 of the vinylcyclopropane substructure and an equilibration between **46** and **47**. This outcome demonstrates that a 2-(*Z*)-pentene-1,5-diyl diradical can pass through an all-carbons-planar or nearly planar conformational form. Access to a 2-(*E*)-pentene-1,5-diyl diradical is not required for epimerization at C1.[71]



The deuterium-labeled 1-vinylnortricyclene **48** forms **49** reversibly without loss of deuterium label in the gas phase at 413−446 °C; the observed reaction may be interpreted as involving transient formation of relatively unstable tricyclo[4.2.1.0^{3,7}]non-3-ene isomers through both *sr* and *ar* paths.[72] According to a theoretical estimate, the hypothetical tricyclononene structure that contradicts Bredt's rule is only 15.5 kcal/mol above 1-vinylnortricyclene.[72]

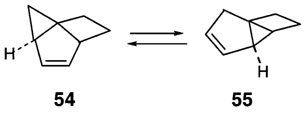


The degenerate interconversions of stereochemically labeled substituted bicyclo[3.1.0]hex-2-enes through [1,3] carbon shifts have been known since 1962.[14] Detailed stereochemical work using chiral and deuterium-labeled substrates showed that three kinetically competitive processes contribute to the overall chemistry observed, a "ring-flip" skeletal inversion and both *sr* and *ai* 1,3 shifts.[73−75] After a hiatus of some 25 years, the kinetic issues were readdressed by Keliher in 2002 for the parent system. Careful gas-phase kinetic work was done starting with both 4-*exo*-*d*-bicyclo[3.1.0]hex-2-ene (**50**) and the 6-*exo*-*d* analogue (**51**).[76] The three processes designated by rate constants k_r, k_f, and k_i have essentially identical activation energies, 43.8, 44.3, and 44.8 kcal/mol. The relative rates are temperature independent and in the proportions k_r:k_f:k_i = 48:36:16.

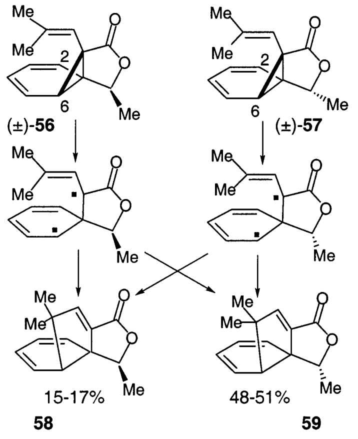


This interconversion of degenerate vinylcyclopropane isotopomers must have four isometric and isotopomeric transition structures corresponding to entry into and exiting from a high-energy plateau over which conformational modifications of diradical entities may take place. The symmetry of the situation is unusual, insofar as the 4-fold potential energy surface accommodates both [1,3] shifts and the ring-flip stereomutation process.

Tricyclo[4.2.0.0^{1,3}]oct-4-ene (**54**), a novel structure containing a bicyclo[3.1.0]hex-2-ene substructure with a 4,5-ethano bridge, may be thermally equilibrated with isomer **55** through a *sr* [1,3] shift at 180−200 °C.[77] For the forward reaction, $E_a \approx 31$ kcal/mol, a relatively low barrier associated no doubt with the substantial strain energy of the reactant.



The vinylcyclopropane rearrangements exhibited by a pair of diastereomeric 7-*endo*-vinylnorcaradienes (**56**, **57**) proved indicative of a diradical-mediated process. The racemic samples of **56** and **57** isomerized through cleavage of a cyclopropyl bond to afford the same racemic [4.5]spirocyclic diradical; it led on to racemic mixtures of [1,3] shift products **58** and **59** in essentially identical product ratios (16 ± 1% **58**, 49.5 ± 1.5% **59**), as well as to the Cope rearrangement product.[78,79]



5. Computational Studies of the Rearrangement

The initial attempts to uncover the mechanism of the vinylcyclopropane rearrangement through computational approaches did not fare particularly well, for the semiempirical and ab initio methods used and the computational limitations at that time were ill-suited to open-shell diradical structures. One early MINDO/3-theory-based effort predicted a strong preference for isomerization with *sr* stereochemistry,[80] a prediction soon found to be incorrect.[81] Yet this pioneering work did find a diradical transition structure, one having a C1−C5 distance of 3.407 Å, a geometrical attribute not far from the best contemporary values.

When the AM1 semiempirical method was exercised on this rearrangement in 1990, it indicated that the vinylcyclopropane rearrangement occurred in a "concerted allowed" way.[82] On the RHF-AM1 hypersurface only one stationary point, a saddle-point, was found to link vinylcyclopropane and cyclopentene. It was taken as the transition state corresponding to the *si* concerted process. The distance separating the two carbon atoms to be joined through the rearrangement to cyclopentene was only 2.648 Å. The calculated activation energy for the isomerization was 63.6−63.8 kcal/mol.[82,83]

In the 1990s the challenge to computational chemistry posed by the vinylcyclopropane rearrangement, and by other [1,3] carbon sigmatropic shifts, continued to attract persistent attention. In a 1992 review on hydrocarbon pericyclic reactions, the vinylcyclopropane rearrangement was still considered to be geometrically constrained to be suprafacial on the allyl system, while having an option of either retention or inversion at the migrating carbon.[84] A transition structure for the "allowed" *si* shift, with a clearly evident allylic π-system substructure, was located. The geometry and energy of the transition structure were extremely dependent on the level of theory employed. The reaction barrier at the RHF/6-31G* level was 84 kcal/mol, and the C1−C5 distance was 2.555 Å. The CASSCF/3-21G calculations gave a lower value for the activation barrier, and the structure became even more diradical in nature: the C1−C5 distance was 3.381 Å, a distance permitting little interaction between radical components. A stepwise, diradical-mediated reaction mechanism seemed a definite possibility.

This mechanistic possibility for the vinylcyclopropane rearrangement seemed to be set aside in 1995, when the notion that some pericyclic reactions might be viewed as stepwise processes was termed "obsolete" in another review of pericyclic reactions.[85] Thus conceptual orthodoxies and mechanistic possibilities for the vinylcyclopropane rearrangement contended mightily not so long ago! But by 1997 one could consider without embarrassment the possibility that there could be competing concerted and stepwise mechanisms for pericyclic reactions,[86] a view not far from a recognition that some pericyclic reactions may take place entirely through stepwise paths.

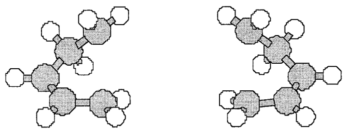
Further studies using a variety of computational methods found consistently that calculated activation energies for stepwise vinylcyclopropane rearrangements were lower by 10 kcal/mol or more compared with E_a values for concerted rearrangements.[87] Other theoretical work on [1,3] carbon shifts has served to clarify mechanistic options in various systems.[88−90]

In 1997, two groups provided dramatic new computational insights on the rearrangement, insofar as the results had direct relevance to reaction stereochemistry. Davidson and Gajewski[91] and Houk and co-workers[92] used CASSCF and DFT calculations to probe the potential energy surface. A diradical transition structure was located and ascribed to the *si* path. Stereochemical scrambling was associated with diradical species deviating from the "concerted" pathway at minimal energetic cost. Excellent figures portrayed correlations between net intrinsic reaction coordinate paths and energy, and between bond lengths for breaking and forming bonds as the reaction progressed. The work found several transition structures mediating low activation energy conformational isomerizations between diradical species, isomerizations which could lead eventually to isomeric products.

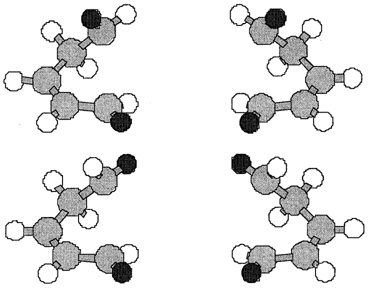
The 2-(*Z*)-pentene-1,5-diyl diradical transition structure for the vinylcyclopropane rearrangement has more recently been calculated at the UB3LYP level; the imaginary frequency corresponds predominantly to the terminal methylene group torsion about the C4−C5 bond.[93]

A more expansive theoretical effort for substituted vinylcyclopropanes made clear that structures in the transition region are essentially purely diradical in character and outlined how substituents can influence overall reaction stereochemistry through modulating conformational isomerizations among alternative diradical species.[94]

The insights of such computational results have been reformulated with the recognition that there must be two transition structures for the C_5H_8 system, related as enantiomers.[35]



For a system labeled with deuterium at the migrating carbon or, as illustrated in the ball-and-stick representations below, with two deuterium atoms, there had to be four transition structures, related as stereoisomers.[35] All four would be "isometric", in Mislow's sense of the term,[95] but distinct stereochemically. Thus a complete potential energy surface for thermal rearrangements of a suitably isotopically labeled vinylcyclopropane would include four isoenergetic transition structures leading to four stereoisomeric cyclopentenes. The relatively flat region central to the four transition structures might well allow dynamic factors, entropy, and other influences unknown to standard transition state theory to dictate overall reaction stereochemistry.



Suhrada and Houk have employed (U)B3LYP/6-31G* and (4,4)CASPT2/ 6-31G* calculations to map the potential energy surface for the three competitive reactions among isomeric bicyclohexenes.[96] The surface features four isotopomeric transition structures, identical geometrically but for absolute stereochemistry and the location of the deuterium label. The subtle details of the energetic nuances of the surface as well as dynamic effects sensitive to the vibrational modes excited and the relative phases of key vibrational modes are now being addressed through dynamic calculations. These results should be highly illuminating for the specific bicyclohexene system examined, which features one type of stereomutation and two distinct [1,3] carbon shifts on a C_{2v}-symmetric potential energy surface. They should as well provide every incentive for parallel work leading to adequate graphical depictions of the more complicated stereomutations and rearrangements of deuterium-labeled vinylcyclopropanes. Here the relatively flat potential energy surface will feature two sets of four exit (or entry) ports, four leading to and from vinylcyclopropanes and four to cyclopentenes.

Computational studies of the vinylcyclopropane-to-cyclopentene isomerization facilitated by electron-transfer catalysis may provide insights complementary to those attained for the uncatalyzed thermal reaction.[97,98] An acyclic radical cation intermediate structure is implicated, though a "concerted" *si* path could well be energetically competitive: the respective transition structures disfavor the "concerted" path according to both ab initio and density functional calculations by 2.7 and 5.4 kcal/mol, respectively. Here, as in the thermal reaction, the hypersurface is relative flat, and dynamic effects could be influential determinants of product ratios.

In rigid bicyclic systems, vinylcyclopropane radical cations have delocalized ring-closed structures.[99] Vinylcyclopropane rearrangements in suitably substituted systems are well-known;[100−102] in other cases, intermolecular or intramolecular competitive reactions can predominate.[103,104]

6. Reaction Dynamics

While concerns about the limitations of transition state theory and the possible contributions to "concertedness" of reaction dynamics compared with those associated with a potential energy surface have long been pondered, as long as adequate computational tools for exploring the issue were not at hand, little progress could be made. The question posed by Andrist in 1973, for instance, could not be pursued toward a resolution of the uncertainty.[105] Slowly, the computational limitations receded.

As early as 1985, Carpenter used simple trajectory calculations to probe the limitations of transition state theory for reactions involving a 4-fold symmetric potential energy surface.[106] The conservation of momentum effects were evident and recognized to have implications for [1,*n*] sigmatropic shifts. This concern for the likely importance of dynamic effects on sigmatropic shifts generally and the vinylcyclopropane rearrangements specifically was expressed in further detail in 1990.[56] There is a strong tendency for nuclei in structures passing through the transition region for a particular set of vinylcyclopropane rearrangements to conserve linear and angular momentum. Accordingly, the final observed product distribution *"need not reflect the symmetry of the equilibrium nuclear geometry of the intermediate"*. The reaction may occur with dynamic control of branching ratios.[56]

A full development of these insights in 1990 was harshly restricted by practical considerations, for full-scale trajectory calculations, even with the powerful capabilities of modern supercomputers, could not at that time be contemplated for molecules large enough to be of interest to organic chemists.

In 1992, this line of inquiry was pursued through an attempt to approximate reaction trajectory calculations though a more computationally tractable vector resolution model and AM1-CI calculations.[107] According to the model, applied to the reactions of *trans*-1-(*E*)-propenyl-2-methylcyclopropane, the predicted stereochemical outcomes of the vinylcyclopropane rearrangement were 63% *si*, 16% *ar*, 19% *sr*, and 2% *ai*, not that different from the experimental figures, 65% *si*, 8% *ar*, 22% *sr*, and 5% *ai*.[49] Given the likely experimental uncertainties and a clear recognition that the fair agreement had to be at least partly fortuitous, the outcome was still striking. A conformationally evolving diradical was formed through cleavage of a cyclopropyl C−C bond: rotation at C2 could lead to inversion or there could be more conformational twisting at C1 to finish breaking C1−C2 and allowing stereochemistry at C2 to be retained. On each of the two paths, a second bifurcation directed the suprafacial versus antarafacial outcomes, favoring suprafacial:antarafactial ≈55:45 along the inversion branch and ≈97:3 on the retention path. Thus a plausible dynamic model was proposed and subjected to a simple calculational test run. The conceptual gain more than offset the limitations associated with the restricted computational tools at hand.

Over the past decade, the critical role dynamic factors may play in [1,3] sigmatropic rearrangements and other organic reactions has continued to be explored conceptually and through modeling studies. Important inferences have been gained, despite limited computational resources arrayed against the gigantic challenges posed by the requirements of full-fledged dynamics simulations for large molecules.

Reaction stereochemistry may well be dictated by reaction trajectories and dynamic outcomes, rather than by models based on competitive, parallel reactions. Neither Woodward−Hoffmann rules nor any other construct for explanation involving a one-to-one mapping of different transition structures each leading to a stereochemically distinct product may be an adequate guide to mechanistic understanding.[108] The competitive issues may be settled by various trajectories between one starting material and various products linked by a common transition region.

The stereochemistry of the bicyclo[3.2.0]hept-2-ene isomerization to norbornene with mostly inversion but some retention of configuration at the migrating carbon is dictated by dynamics. The favored *si* path is orbital-symmetry-“allowed”, but the experimentally observed preference for the *si* stereochemical outcome has nothing to do with conservation of orbital symmetry.[109,110] A diradical intermediate is clearly implicated. The diradical selects exit channels from the transition region in a nonstatistical fashion in ways sensitive to distributions of vibrational energy and phase relationships. The dynamic model is simply different from a traditional transition-state theory or RRKM formulation; dynamic outcomes rather than competitive parallel pathways and alternative transition states account for reaction stereochemistry. Further work in this direction, especially on [1,3] shifts and on the classic conversion of 2,3-diazabicyclo-[2.2.1]hept-2-ene to bicyclo[2.1.0]pentane by way of the cyclopentane-1,3-diyl diradical,[111−113] has served to extend this message.[114,115]

During the past decade, traditional unimolecular transition state theory has been ever more carefully considered, revised, and appreciated for all it can do well, even as its significant limitations are becoming more generally recognized.[116−120] New theory and applications of theory to rate constant and chemical dynamic calculations, especially to relative large unimolecular systems, are testing, extending, and challenging current understandings and limits.[121−129] The ever greater power of higher level theory for defining the geometry and energy of stationary point species is prompting new approaches toward efficient interpolations and calculations of minimum energy paths, inclusion of quantum and nonequilibrium solvation effects, and other computational alternatives to gain reliable potential energy hypersurfaces suitable for reaction dynamics calculations.[130−139]

Direct dynamics studies for reactions of molecules not long ago considered too large for such investigations are appearing more and more frequently. Calculated energy and product distributions often compare well with experimental findings.[140−144]

The thermal stereomutations of isotopically labeled cyclopropanes provide an apt case in point. The mechanistic problem has attracted serious work for some 40 years, and with the advent of ever better computational methods for defining open-shell systems, the characteristics of the singlet trimethylene diradical became reasonably well defined. There followed impressive direct dynamics studies of the thermal stereomutations of deuterium-labeled cyclopropanes,[145−149] work that served to clarify the key mechanistic issues still associated with this long-standing problem.[37]

7. Reaction Dynamics for the Vinylcyclopropane Rearrangement

More recently Doubleday and co-workers have addressed the vinylcyclopropane rearrangement with similar tactics. A preliminary study followed quasi-classical trajectories on a potential energy surface provided by ab initio calculations including dynamical electron correlation, fitted by AM1 with specific reaction parameters (AM1-SRP).[150] With this approach it was possible to predict product distributions and thus reaction stereochemistry by following trajectory counts. While the outcomes varied slightly with different sampling schemes, the averaged percent yields from the 569 trajectories connecting d_3-vinylcyclopropanes with d_3-cyclopentenes were $si:ar:sr:ai = 45:12:28:16$, with estimated uncertainties of 3−4%.

More thorough direct dynamics trajectory studies gave similar results.[151] Three diradical transition state structures with various isomeric dispositions of three deuterium labels (eight diastereomeric transition states) were initialized quasiclassically with a Boltzmann normal mode sampling at 573 K, and 34 000 trajectories were followed. The computed product ratios were found to be $si:ar:sr:ai = 42:10:30:18$, values but little different from those found in the preliminary study. Each initial diradical transition structure gave all four possible stereochemical outcomes, suggesting that product distributions are entirely under dynamic control. The isomerization mechanism is one involving diradical structures traversing four competing direct reaction paths. These product ratios calculated by direct dynamics methods are quite close to experimental estimates of the product ratios, $si:ar:sr:ai = 40:13:23:24$.[59]

Further investigations of the unimolecular dynamics characteristic of the diradical region of the potential energy surface found that diradicals giving products within about 600 fs did so with stereochemical outcomes strongly dependent on the initial transition structure and the vibrational modes excited.[152] The small proportion of longer lived diradicals led to products in a more stereorandom fashion.

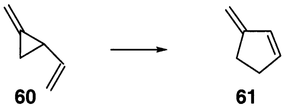
While this level of agreement between theory and experiment is extremely gratifying, it may be well to keep in mind that theory-based definitions of all aspects of a potential energy surface for diradical species remain limited by methods and basis sets and computational investments. Tetramethylene is a case in point: the potential energy surface has been probed and defined through ever deeper theoretical studies by Doubleday for more than a decade, most recently using a 44CAS-MCSCF (four-electron−four-orbital complete active space multiconfigurational self-consistent field) wave function with cc-pVTZ on carbons and cc-pVDZ on hydrogens (180 contracted basis functions) computed with multireference CI with all single and double excitations—very serious calculations indeed.[153] Yet at still higher levels of theory the relative energies of two key stationary point structures were altered, and some features of the calculated potential energy surface needed to be revised.[154] While the wonderfully successful applications of direct dynamics calculations to the vinylcyclopropane rearrangement may be greeted with happy confidence, the future still lies ahead.

8. Related Reactions

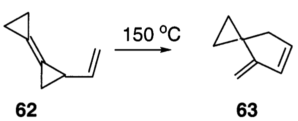
Beyond the small world preoccupied with mechanistic aspects of the vinylcyclopropane rearrangement, there is a much larger sphere of activity devoted to synthetic objectives and novel reactions. The reactions may correspond to the vinylcyclopropane−cyclopentene retrosynthetic template[155] but have no need to be limited to thermal reaction conditions or uncatalyzed processes or some limited palette of atoms from the periodic table. Such activity continues to achieve new objectives in the specialized realm of natural product syntheses.[30,34,156] The boundaries limiting further developments of these efforts are not yet in sight.

New syntheses of vinylcyclopropane continue to be of interest,[157−160] and numerous new methodologies for preparing substituted vinylcyclopropanes for specific applications, or to develop asymmetric protocols, have appeared.[161−168]

Vinylcyclopropane systems having additional elements of unsaturation show similar reactivity. 1-Methylene-2-vinylcyclopropane (**60**) is converted smoothly to 3-methylenecyclopentene (**61**).[169] While the reaction might be formulated as a Cope process, rather than as a [1,3] shift, kinetic and stereochemical evidence suggests that the [1,3] carbon shift path is dominant. The reaction has recently been confirmed to proceed by way of the cross-conjugated 4-methylene-2-(*Z*)-pentene-1,5-diyl diradical.[170] Yet 1-cyclopropylidene-2-vinylcyclopropane (**62**) is isomerized at 150 °C to afford 4-methylenespiro[2.4]hept-5-ene (**63**) in 95% yield.[171] Cyclopropylallenes rearrange thermally to 3-methylenecyclopentenes,[80] and cyclopropylketenes isomerize to 2-cyclopentenones.[172]

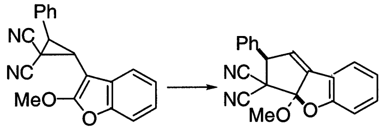


60 **61**

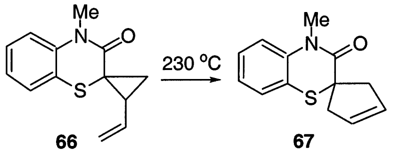


62 **63**

Efficient preparations of novel complex structures anticipated to have pharmacological interest can be achieved through vinylcyclopropane rearrangements. Specific recent examples suggest that the rearrangement can be effected successfully even with reasonably complex polyfunctional systems, as in the isomerization of **64** to **65**,[173] and in a variety of heteroatom-rich analogues, as in **66** to **67**.[174−178]



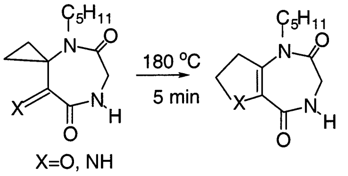
64 **65**



66 **67**

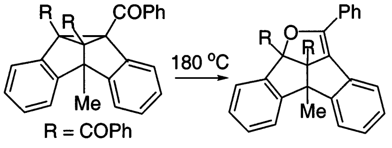
Additional examples attest to the synthetic utility of various transition-metal-catalyzed vinylcyclopropane rearrangements,[179] as well as conversions of alkynyl and allenylcyclopropanes to cyclopentene structures![180−182]

The well-known carbonylcyclopropane-to-dihydrofuran thermal rearrangement, and the related rearrangement of cyclopropylketimines, have recently provided fast routes to dihydropyrrole- and dihydrofuran-fused bicyclic diazepine-2,5-diones (**68** to **69**).[183]

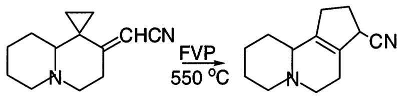


68 **69**

Another recent thermal rearrangement leading to dihydrofuran **71** from the isomeric carbonylcyclopropane **70** involves a dibenzobarrelene system.[184−186] Other applications include cyclopentene annellation applications,[187] such as the isomerization of **72** to **73**.[188]

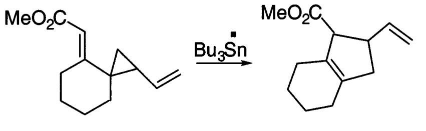


70 **71**



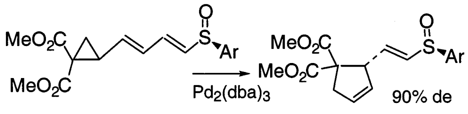
72 **73**

Heating a *trans*-1,2-divinylcyclopropane system will ordinarily but not invariably[189] cause thermal isomerization to the cis isomer, which continues on through a facile Cope process to form a 1,4-cycloheptadiene.[79,190,191] The divinylcyclopropane **74** instead gives the vinylcyclopropane rearrangement product **75** when exposed to the tributyltin radical.[192] The conversion probably involves addition of the radical to the $-CH{=}CH_2$ group, fragmentation of the three-membered ring, formation of the five-membered ring, and homolytic cleavage of a C−Sn bond to afford product **75** and to regenerate the catalyst. Other exploitations of radical-mediated vinylcyclopropane ring-opening reactions have appeared in the synthetic literature.[193−196]



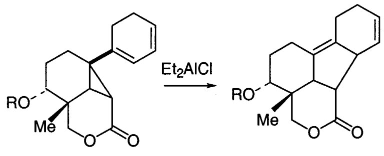
74 **75**

A similar outcome has been achieved in a different way, using a butadienylcyclopropane and tri(dibenzylideneacetone) dipalladium(0) catalytically. Again, an addition, fragmentation, bond-formation to give the five-membered ring, and elimination sequence can account for the product observed. The chiral sulfinyl functionality leads to product with high diastereoselectivity.[197]

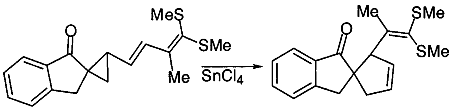


76 **77**

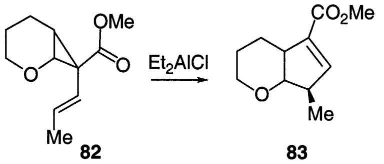
The same basic sequence of steps leading from a vinylcyclopropane to a cyclopentene product may be instigated for appropriate systems using Lewis acid catalysts. The examples shown[198−201] could be multiplied many times over.



78 **79**

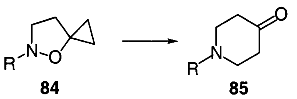


80 **81**



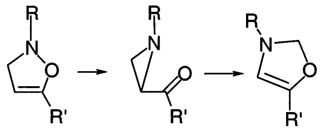
82 **83**

The Brandi reaction of a spiro[cyclopropane-1,5′-isoxazolidine] (**84** to **85**) may be viewed as analogous to vinylcyclopropane rearrangements, though the mechanistic details could well be different: homolytic cleavage of the relatively weak N−O bond initiates the conversion.[202] The isomerization of spiropentane to methylenecyclobutane may be considered of the same type. Other examples in which a weak single bond connected to a cyclopropane, rather than vinylcyclopropane, rearranges with the same topography will presumably be recognized, engineered, and demonstrated.



84 **85**

Other more exotic heterocyclic systems provide examples of novel rearrangements that most probably involve interconversion of heteroatom-substituted vinylcyclopropanes and cyclopentenes, as in the sequence leading from isoxazolidine **86** to intermediate **87** to oxazoline **88**.[203] A similar transient formation of an aziridinylcarbonyl structure is probably involved in the well-known thermal isomerization of 2-ethyl-4,4-dimethyloxazoline to *N*-allyl-*N*-methylpropionamide.[204,205]



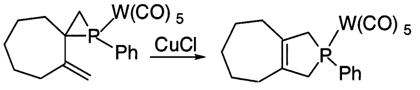
86 **87** **88**

The parent C_5H_8 hydrocarbon system strongly favors reaction from vinylcyclopropane to cyclopentene, though the reaction in reverse, the cyclopentene to vinylcyclopropane conversion, has been detected and studied with the aid of carbon-13 labeling and shock-tube kinetic techniques.[206] The preferred direction of the rearrangement is reversed in systems favoring the vinylcyclopropane moiety for other thermochemical reasons, as in the isomerization of bicyclo[2.1.1]hex-2-ene (**89**), a 3,5-methano-bridged cyclopentene, to bicyclo[3.1.0]hex-2-ene (**90**).[207]

89 **90**

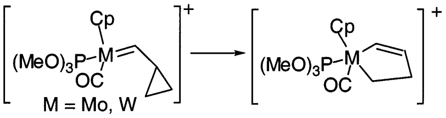
This rearrangement could as well be considered as one involving a [1,3] carbon migration in a vinylcyclobutane. A recent gathering of information on thermal [1,3] carbon sigmatropic rearrangements of vinylcyclobutanes emphasizes the many stereochemical and mechanistic similarities between vinylcyclopropane and vinylcyclobutane rearragements.[208] While experimental information on vinylcyclobutane rearrangements in unconstrained monocyclic systems is more limited, all examples studied in detail point toward a similar mechanistic pattern: isomerizations take place by way of diradical intermediates and give all four possible stereochemical outcomes, in different proportions.[209−215] Reaction stereochemistry is not constrained by orbital symmetry rules.

The isomerization of vinylaziridines and cyclopropylketimines are well-known, and *N*-cyclopropylimines rearrange nicely photochemically to 1-pyrrolines.[216] Other cyclopropylimines give 1-pyrrolines thermally, unless homodienyl [1, 5] hydrogen shifts predominate.[217] In other heteroatom-substituted systems as well, homodienyl [1, 5] hydrogen shifts can be the strongly preferred reaction,[218,219] just as they can be in hydrocarbon systems. Vinylphosphiranes rearrange as well,[220] as do the related tungsten pentacarbonyl complexes (**91** to **92**).[221,222]



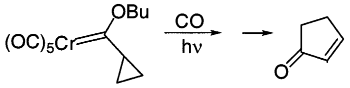
91 **92**

Organometallic analogues of the vinylcyclopropane rearrangement with transition metals incorporated directly in the basic five-atom template are known, as in the molybdenum and tungsten cationic systems reported by McElwee-White (**93** to **94**).[223] The initial



93 **94**

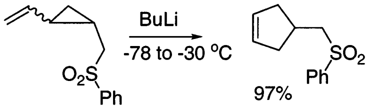
products react further to afford 2-cyclopentenone. A probably similar synthesis was reported in 1989 for a chromium carbene complex (**95** to **96**).[224] This paper



95 **96**

includes a remarkable characterization of vinylcyclopropane rearrangements as “thermally forbidden ($_{\pi}2_s + _{\sigma}2_s$) transformations”, a view fairly representative of some schools of thought at that time.

One limitation of the thermal rearrangement often mentioned relates to the temperatures required. High temperatures are needed in some cases, so the reaction may not be suitable in the context of synthetic sequences including fragile thermally labile functionalities. The point is well taken, but many clever strategies for achieving vinylcyclopropane rearrangements at modest temperatures have evolved and been reduced to practice. Special note should be made of oxyanion- and carbanion-accelerated rearrangements, as exemplified in Danheiser's early work,[225–228] including the **97** to **98** conversion by way



97 **98**

of the anion. By now such variants of the rearrangement have an extensive review literature.[229,230] 1-Trialkylsilyloxy substituents also exert a powerful rate-enhancing effect on the rearrangement.[231,232]

9. Summary

The still growing importance of vinylcyclopropane rearrangements in synthetic applications attests to the power of adaptation within the synthetic organic chemistry community. The retrosynthetic transform gives the conceptual model, and clever choices of substituents and reaction conditions provide substituted cyclopentene reaction products. Hydrocarbon systems and heteroatom-substituted analogues show the same patterns of reactivity.

The impressive synthetic developments and exploitations of the rearrangement achieved since the 1960s have been accompanied by sustained attempts to sort out the mechanistic issues. By now the kinetic, stereochemical, and mechanistic aspects of the vinylcyclopropane rearrangement have been reasonably well defined, but for a few rhetorical concerns.

The rearrangement is initiated through cleavage of C1–C2. The rate constants for stereomutations resulting from reclosure of diradicals such as **5** and **6** and for conversions to cyclopentene products correlate quite well with the radical stabilizing characteristics of substituents. The stereochemical preferences of rearrangements are system dependent. In the parent system, and in all other cases where the relative importances of all four possible paths have been quantified, they are all evident, to different extents (Table 1). These experimental facts are consistent with conformational flexibility allowing some but not complete conformational evolution within a family of diradical structures on a relatively flat potential energy surface before one meets and matches the prerequisites of an exit channel. The rearrangements are consummated when a diradical attains the appropriate limited region of phase space with geometry and vibrational modes phased to pass through the exit path toward product. Modeling of the vinylcyclopropane rearrangement for the parent system based on this view with quasiclassical trajectory calculations gives product distributions in fine agreement with experimental values.

Other models derived from conceptual schemes linked to orbital symmetry theory and to a dual mechanism hypothesis have at times been entertained. According to these formulations, the vinylcyclopropane rearrangement may take place by either or both two-step diradical and orbital-symmetry-controlled pericyclic mechanisms. Here one should note that “pericyclic mechanisms” and “pericyclic reactions” are sometimes considered as synonyms, and sometimes as very different categories. The balance between these alternatives may vary from case to case. With this mechanistic scheme, any stereochemical result can be accommodated! Products formed through *si* and *ar* paths are read as indicative of concerted reactions, while *sr* and *ai* products signal the intrusion of diradical-mediated two-step processes. With this construct, one may interpret reactions taking place with high preference for a *si* stereochemical outcome as evidence in favor of a concerted mechanism. Other reactions with just as high a preference for “forbidden” *sr* and *ai* paths (Table 2) are then indicative of stepwise diradical reactions. Reactions that give a mixture of products derived from all four possible paths are of course denotative of both two-step diradical and orbital-symmetry-controlled pericyclic mechanisms operating simultaneously and competitively.

To sustain these models one must assume that “allowed” stereochemical outcomes must be controlled by the dictates of orbital symmetry theory, rather than by any other factors. Possible substituent effects on the contortions required to break a C1–C2 bond through bond elongations and torsional displacements about C3−C1 and C3−C2 are just neglected. Possible steric interactions or ponderal effects influencing which end of the C1−C2 bond will exert the major torsional contribution to bond rupture are ignored. The lack of a perceptible energy of concert (a lower $\Delta H^{\ddagger}$) for vinylcyclopropane rearrangements that do take place with a high degree of stereochemically "allowed" outcomes is conveniently disregarded.

In "two remarkable contributions",[233] Doering has recently discussed in depth another reaction long considered to involve a continuum of mechanistic possibilities: the Cope rearrangement.[234,235] The responses of the reaction to substituent effects may reflect a transition region framed by a relative flat potential energy surface and features appropriate to "aromatic" and to cyclohexa-1,4-diyl diradical extremes, or to a system-specific balance between these extremes.

In two equally remarkable papers Doering has extended earlier work of Doubleday by considering the extent to which competitive thermal stereomutation and fragmentation reactions of cyclobutane, and of a wide range of substituted cyclobutanes, may be controlled by entropy.[236,237] The concerns are common to other reactions involving diradical intermediates having limited lifetimes on relatively flat potential energy surfaces. To provide a vivid descriptor or "sobriquet" giving a mental image of the situation, he has dubbed the high-energy, flat potential energy domain a caldera. Now a caldera is a geologic structure, a featureless crater formed through collapse of a volcanic cone, rimmed by infacing scarps. Beyond the edges of a caldera, passing the angular reentrants, steeply sloping escarpments lead to lower elevations. A diradical intermediate structure on the generally smooth plane of a potential energy surface surrounded by a number of possible exit channels, like a geologist positioned on a caldera, may egress from the height in several ways. The lip of a geologic caldera may be trivially elevated over the floor; the exit from a figurative caldera may challenge a diradical intermediate with an energy demand comparable to $k_{\mathrm{B}}T$, an indecisive factor. Momentum and entropy may then dictate the product-determining aspects of the reaction.

This conceptual and visually accessible model extends the insights of computational work discussed above, as it helps one weigh the factors that may contribute to reaction mechanism for processes that are not obviously concerted and may involve diradical intermediates.

The vinylcyclopropane rearrangement involves a short-lived family of diradical conformational forms on a caldera-like potential energy surface. Further experimental and theoretical studies, especially trajectory calculations and direct dynamic simulations for diradical intermediates, are likely to extend this picture and test when it may be applied fittingly in other reactions. Thorough stereochemical work on the vinylcyclobutane-to-cyclohexene rearrangement and determinations of lifetimes for diradicals such as **5** and **6** seem like obvious, important, and timely new challenges.

10. Acknowledgments

Support from the National Science Foundation for work on the thermal reactions of simple hydrocarbons at Syracuse University, most recently through Grants CHE 9902184 and CHE 0211120, is gratefully acknowledged. Thanks are due as well to Professor Phyllis A. Leber of Franklin & Marshall College and two anonymous referees for making valuable suggestions based on an earlier version of this review.

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CR010020Z