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Research Article

Organic chemical reaction mechanisms clarified for deuterium- and carbon-13-labeled hydrocarbons†

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Abstract: Questions bearing on just how organic chemical structures are converted to other compounds can be addressed in numerous ways through syntheses and studies of appropriately designed stable–isotope-labeled analogs. Most of the examples in the present review summarize studies of various thermal isomerizations and fragmentations that have provided information on mechanistic details, determinations of reaction stereochemistry, tests for possible interventions of short-lived reaction intermediates, and relevant checks of theory-based predictions and rationalizations. Such work serves either to reinforce generally accepted conceptual constructs for posited reaction mechanisms or to prompt reinterpretations of imperfect mechanistic understandings, as the experimental findings may require. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: deuterium- and carbon-13-labeled hydrocarbons; degenerate isomerizations; thermal stereomutations; sigmatropic rearrangements; cycloadditions; skeletal inversions; isomerization of cyclopropane to 1-propylidene

Introduction

The great strides in the scientific understandings now associated with the appellation 'physical organic chemistry' were initially unnoticed, but in 1940–1960 they emerged into full view. By 1960 the foundations that permitted and stimulated further impressive progress in the next few decades had been established.[1–3] The knowledge base at hand in 1960 was then conjoined with new technical capabilities in spectroscopy, other realms of instrumentation, electronics and computers, breakthrough intellectual achievements, and greatly expanded opportunities for securing chemicals of all varieties from commercial sources. The rich potential inherent in using isotopic labeling approaches to testing organic chemical reaction mechanistic understandings had already been demonstrated impressively by 1960,[4] and further applications of labeled compounds in this area of inquiry grew rapidly in number and scope.

Mechanistic distinctions could be formulated and then tested in new ways utilizing the distinctive capacities of isotopic labeling experiments. Such work only became more relevant as computational chemistry suggested preferred mechanistic options, options to be tested, not necessarily accepted without efforts to evaluate them relative to alternative rationales and anticipated experimental outcomes. For comparisons with results secured through semi-empirical or *ab initio* calculations, simple hydrocarbons offered distinct advantages: the calculations could be undertaken at higher levels of theory, and could be anticipated to be closer to reality, for the compounds of interest were relatively small and composed of relatively light atoms. The related experimental findings would be less convoluted with major electronic or steric substituent effects. This opportunity to gain better understandings of reaction mechanisms through experiments stimulated by theory or by reported experimental findings led, perhaps ineluctably, to work with isotopic labeling.

Part of our launch in this direction followed from early exposures to the impressive mechanistic distinctions related to benzyne chemistry and cyclopropylcarbinyl–cyclobutyl–allylcarbinyl cations reported by Roberts and his colleagues.[4] Another was provided through gaining some practical guidance on dealing with isotopes in Nystrom's Radiocarbon Laboratory at

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the University of Illinois. While some investigations in our laboratory have depended on ^{3}H, ^{14}C, and ^{35}S radioisotopes, many more have relied on ^{2}H and ^{13}C. A few reports have been pertinent to structural issues, as in the validation of the cyclic structure for cyclopropanone through microwave spectroscopy of the parent ketone and deuterium-labeled analogs,[5] but most have been concerned with experiment-based mechanistic distinctions.

The present review summarizes a representative sampling of our mechanistic inquiries depending on ^{2}H and ^{13}C labeling. They include a substantial range of subjects and types of experimentation, from simple tracer-based distinctions, measurements of primary and secondary deuterium kinetic isotope effects, reaction stereochemical determinations for simple conversions and for complicated sets of kinetically competitive transformations, and situations where simultaneous labeling with deuterium and carbon-13 seemed essential and proved effective.

Isotope dilution and dynamic isotope dilution approaches have been used, but are not included in this review. The flexibility provided by the wide range of isotope-based experimental protocols and analytical options, and the great diversity of synthetic transformations that can be marshaled to prepare just the right isotopically labeled version of the molecule to be used to investigate the reaction one wishes to study in detail, are apparent. Their contributions to mechanistic organic chemistry continue to be essential.

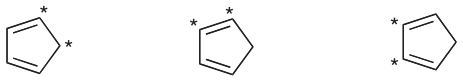
Results of isotopic labeling experiments

The examples of isotopic labeling experiments gathered here exemplify the questions we have found intriguing, or even baffling, and the experimental findings and implications they have provided. Neither the examples nor the listing of references is exhaustive. Additional references may be traced easily through those cited.

Photoisomerizations and phototranspositions of carbon atoms in cyclopentadiene

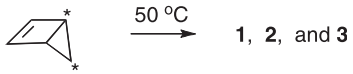
The photoisomerization of cyclopentadiene to bicyclo[2.1.0]pent-2-ene is an electrocyclic reaction,[6,7] one that can be followed without recourse to isotopic labels. For examining mechanistic issues, however, isotopic labels can be of great benefit. A study intended to distinguish between thermal isomerization of bicyclo[2.1.0]pent-2-ene to cyclopentadiene through cleavage of C(1)–C(4)[8] or through a convoluted process linking C(1) with C(4) and C(2) with C(5) was pursued. More immediate approaches to the mechanistic ambiguity were thwarted by facile thermal [1,5] hydrogen shifts characteristic of cyclopentadienes.[9]

Vicinally disposed $^{13}C_2$-isotopomers of cyclopentadiene (**1–3**) seemed an ideal starting point for the investigation. They were prepared from barium [^{13}C]-carbonate through an efficient six-step reaction sequence.[10]



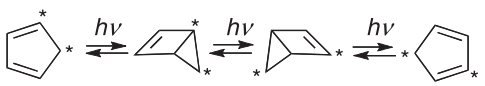
1 **2** **3**

Photochemical activation of these cyclopentadienes led to vicinal $^{13}C_2$-isotopomers of bicyclo[2.1.0]pentene such as **4**. When they rearranged thermally, the carbon atoms remained vicinally related, thus confirming the simple disrotatory, orbital-symmetry-forbidden valence isomerization.[11] The clear mechanistic distinction was not obscured by rapid [1,5] hydrogen shifts available to vibrationally excited 'hot' cyclopentadienes as they crossed the activation barrier.



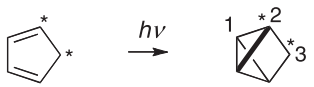
4

In the course of the investigation processes that were totally unexpected and most probably would never have been detected in the absence of the isotopic labels were uncovered. The reaction mixture formed through photolysis of the vicinal $^{13}C_2$-cyclopentadienes contained the vicinal $^{13}C_2$-bicyclo[2.1.0]pent-2-enes and also non-vicinal $^{13}C_2$-bicyclo[2.1.0]pent-2-enes and $^{13}C_2$-labeled tricyclo[2.1.0.$0^{2,5}$]pentanes.[10] Degenerate photochemical [1,3] carbon shifts in bicyclo-pentenes, as in the equilibrium between **4** and **5**, and the overall phototransposition of carbon atoms in cyclopentadienes such as **1** and **6**, were unanticipated transformations.



1 **4** **5** **6**

A further surprise was the formation of tricyclo[2.1.0.$0^{2,5}$]pentane, as in the isomerization of **1** to **7**, a conversion similar to the photoisomerization of benzene to benzvalene. The relative positions of ^{13}C labels in the hydrocarbon isotopomers were clearly evident thanks to ^{13}C NMR and analyses of ^{13}C–^{13}C spin–spin couplings. The very minor tricyclic component discovered in photochemical reaction mixtures might well not have been detected and characterized without the tell-tale data provided by the ^{13}C spectra.



1 **7**

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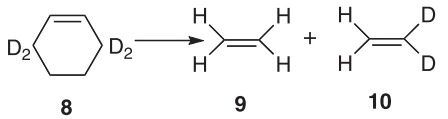
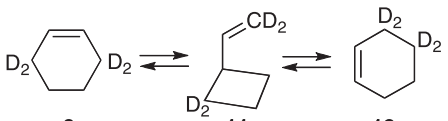
Diels–Alder and retro-Diels–Alder reactions

Diels–Alder reactions command a towering and fully deserved reputation in synthetic organic chemistry for great reliability, versatility, and stereochemical predictability. They have also been given special status as the prototypical concerted cycloaddition reaction. From a mechanistic perspective, there are good reasons to accept this position of prominence for the Diels–Alder reaction, at least on a provisional basis. There are also reasons to speculate whether there might be some reactants leading to products that satisfy the Diels–Alder paradigm, reactions interrelating a diene and an olefin with a corresponding cyclohexene, but which might not take place in a concerted fashion.[12]

The simplest possible Diels–Alder system is butadiene plus ethylene to give cyclohexene. In the forward direction, the gas-phase reaction provides a product mixture that includes minor amounts of vinylcyclobutane, a structure that might well stem from a 1-hexen-3,6-diyl diradical intermediate. When 3,3,6,6-d_4-cyclohexene (**8**) is heated under shock-tube conditions to obviate complications from surface-catalyzed reactions, the products include both ethylene (**9**) and 1,1-d_2-ethylene (**10**), from 3.4% (at 1077 K) to 5.4% of the ethylenes formed at 1195 K. An equilibrium involving 2,2,2′,2′-d_4-vinyl-cyclobutane (**11**) and 3,3,4,4-d_4-cyclohexene (**12**) serves well to rationalize these findings.[13,14]

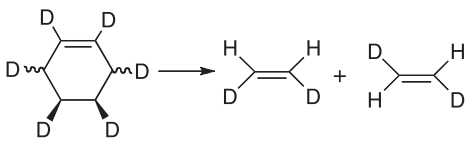


8 **9** **10**



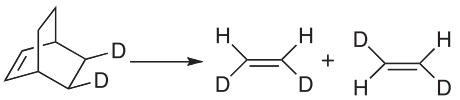
8 **11** **12**

Birch reduction of benzene-d_6, followed by a reduction of the labeled 1,4-cyclohexadiene intermediate with diimide gave a d_6-cyclohexene having *cis*-5,6-deuterium labels (**13**). Under shock-tube reaction conditions it gave 5.1% (at 1094 K) and up to 9.3% (at 1180 K) of the stereochemically non-conservative *trans*-d_2-ethylene product (**15**). Again, this experimental observation is consistent with some participation of a 1-hexen-3,6-diyl diradical intermediate.



13 **14** **15**

cis,exo-5,6-d_2-Bicyclo[2.2.1]hept-2-ene undergoes a retro-Diels–Alder reaction in a highly stereochemically conservative way, giving the cis isomer of 1,2-d_2-ethylene exclusively, to within experimental uncertainty.[15,16] *cis,exo*-5,6-d_2-Bicyclo[2.2.2]oct-2-ene (**16**), however, reacts thermally in a single-pulse shock tube at 1017 K (for 800 μs) to produce ethylene (**9**) and both isomers of 1,2-d_2-ethylene, as identified and quantified by tunable diode laser spectroscopy. The trans isomer **15** accounts for a minimum of 6.3% of the d_2-ethylenes in the product mixture.[17]



16 **14** **15**

Complete conservation of stereochemical integrity is observed in the retro-Diels–Alder reaction of bicyclo[2.2.1]hept-2-ene, but not in the retro-Diels–Alder reactions of cyclohexene and bicyclo[2.2.2]oct-2-ene. The reasons for the differing stereochemical characteristics of these reaction of simple hydrocarbon homologs remain to be understood.

Occasionally Diels–Alder reactions that seem indicative of non-concerted mechanisms are reported.[18] Recent femtosecond real-time studies of retro-Diels–Alder reactions of cyclohexene and bicyclic homologs have provided support for non-synchronous bond cleavages.[19,20] The potential energy surfaces for the vinylcyclobutane-to-cyclohexene thermal rearrangement and the Diels–Alder reaction of ethylene with butadiene merge in some common areas, according to a DFT theoretical study and complete active space calculations.[21] One senses that the complete realm of stereochemically non-conservative, or non-concerted Diels–Alder and retro-Diels–Alder reactions, remains to be mapped.

Degenerate skeletal inversions in bicyclo[2.1.0]pentanes

In recent decades, it has become more and more apparent that the stereochemical and kinetic characteristics of a thermal isomerization may be sensitive to substituent effects. Even the 'simple' replacement of a hydrogen with a methyl, to serve as a stereochemical marker, may alter a reaction's stereochemical preferences and activation parameters. To avoid or at least to minimize substituent effects, isotopic labeling appropriate for detecting an isomerization, revealing stereochemical out-comes, and defining activation parameters may serve to clarify mechanistic details most valuably. They also maximize opportunities to compare experimental data on prototytical thermal

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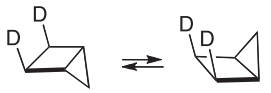
reactions and theory-based computational results. When the two approaches agree closely, one gains confidence in both, and in the interpretations of the chemical transformations reached through mutually supporting evidence of such different types.

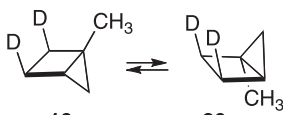
A simple example is afforded by the 'ring-flip' isomerization interconverting the exo and endo isomers of 2-methylbicyclo[2.1.0]pentane, first reported by Chesick in 1962.[22] The activation parameters for the gas-phase approach to thermal equilibrium were found to be $\log A = 14.45$ and $E_a = 38.9$ kcal/mol.

When *cis*,*exo*-2,3-d_2-bicyclopentane (**17**) was thermally equilibrated with the endo isomer **18** in the gas phase in the temperature range 153–208 °C the activation parameters for the skeletal inversion were found to be $\log A = 13.9$ and $E_a = 37.8$ kcal/mol.[23] The differences are small, yet potentially of significance. The theoretical estimations of E_a and of the putative intermediate or transition structure, the cyclopentan-1,3-diyl diradical, have been advanced from a number of laboratories. The differences are 'in reasonable agreement' but not in a very exact agreement with the experimental E_a value, a discrepancy that awaits clarification.[24,25]



17 **18**

A methyl at C(2) or C(5) of bicyclopentane increases E_a for the thermal equilibration of exo and endo isomers by 1.1 and 1.4 kcal/mol.[23] Interestingly, a methyl substituent at C(1) of bicyclopentane does not change the E_a parameter for skeletal inversion significantly: the experimental E_a value for the approach to equilibrium between **19** and **20** is 38.0 kcal/mol.



19 **20**

These isomerizations do not have stereochemical options: only subtle methyl substituent effects on activation parameters may vary. Just how these effects contribute to variations in energies for ground states and transition structures remains to be sorted out.

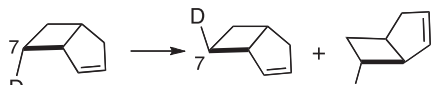
Skeletal inversions and thermal epimerizations in bicyclo[3.2.0]hept-2-ene and bicyclo[4.2.0]oct-2-ene

Another bicyclic 'ring-flip' isomerization has been uncovered in bicyclo[3.2.0]hept-2-ene. This fascinating hydrocarbon was known to fragment to ethylene and cyclopentadiene, undergo a retro-[2 + 2]-addition to give 1,3(*Z*)-6-heptatriene, and to isomerize through a [1,3] carbon shift to form norbornene.[26] Further scrutiny, made possible by utilizing deuterium-labeling strategies, led to the discovery and kinetic characterization of two additional degenerate thermal rearrangements, a skeletal inversion and an epimerization at C(7).

Bicyclo[3.2.0]hept-2-ene labeled with an endo deuterium at C(6) (**21**) might isomerize to an *exo*-*d*-bicyclo[3.2.0]hept-2-ene (**22**) through a skeletal inversion. A simple one-center epimerization made possible by cleavage of C(5)–C(6) or C(6)–C(7) would hardly be likely.

21 **22**

endo-7-*d*-Bicyclo[3.2.0]hept-2-ene (**23**) could give enantiomeric *exo*-7-*d* isomers **24** and **25**, the first through a one-center epimerization, one that could be facilitated by a relatively easy thermal cleavage of C(1)–C(7), and the second through a skeletal inversion achieved through cleavage of C(1)–C(5) and overall epimerizations at both carbons.[27]



23 **24** **25**

Gas-phase reaction kinetic studies at 275 °C defined the rate constants for these two isomerizations. Starting with the *endo*-6-*d* substrate **21**, the one-way rate constant for the ring-flip process, k_f, was found to be $3.6 \times 10^{-8}\ s^{-1}$. Starting with the *endo*-7-*d* substrate **23**, the one-way reaction to give **24** and **25** occurred with rate constant $(k_f + k_{7e}) = 5.35 \times 10^{-7}\ s^{-1}$. The rate constant k_{7e} for the epimerization process was then $5.0 \times 10^{-7}\ s^{-1}$; the epimerization at C(7), the migrating carbon in the [1,3] shift, is 11 times slower than the [1,3] carbon migration leading to norbornene, and the ring-flip is slower still.[27]

Similar experiments with deuterium-labeled bicyclo[4.2.0]oct-2-enes were performed at 300 °C. Analysis of product mixtures with ^{2}H NMR revealed no detectable increase in *exo*-7-*d* product from starting material containing 82.7% endo;17.3% exo 7-*d* isomers, **23**:**24**. The ratio of the two isomers stayed constant over six kinetic runs for times up to 30 h. The ring-flip process in this case seems just too slow to be observed under these reaction conditions.[28,29]

26 **27**

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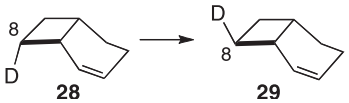
For the *endo*-8-*d* starting material (**28**), the thermal epimerization to form **29** was relatively rapid. The one-way epimerization rate constant was about seven times faster than the rate constant for the [1,3] carbon shift giving 5-*d*-bicyclo-[2.2.2]oct-2-enes. In this case the intermediate diradical seems to have ample opportunity to rotate about the C(7)–C(8) bond and then reclose the C(1)–C(8) bond before the downhill [1,3] shift takes place irreversibly.



28 **29**

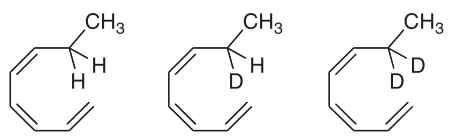
In the homologous bicyclo[3.2.0]hept-2-ene, the balance of options for the diradical is skewed the other way: the choice between net epimerization at C(7) and [1,3] shifts favors the sigmatropic process significantly.

Antarafacial [1,7] hydrogen shifts

Today antarafacial [1,7] hydrogen shifts are recognized as unexceptional thermal reactions, but when first encountered they were somehow extraordinary. Over the years they have received less experimental and theoretical attention than the more commonly seen suprafacial [1,5] hydrogen shifts.

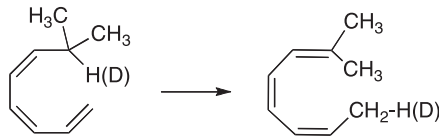
In 1979, the primary kinetic k_H/k_D isotope effect for the [1,7] hydrogen shift converting vitamin D_3 to previtamin D_3 was found to be ≈ 45. This very large value was considered to be appropriate for the antarafacial shift and a linear and symmetrical transition structure.

Later kinetic studies of deuterium kinetic isotope effects for [1,7] sigmatropic rearrangements of d_0, 7-*d*, and 7,7-d_2-*cis*,*cis*-1,3,5-octatrienes (**30**,**31**,**32**) provided very different estimations. The primary k_H/k_D ratios determined for the isomerizations giving both cis,cis,cis, and cis,cis,trans isomers of 2,4,6-octatriene at three temperatures ranged from 6.4 to 7.7.[30]



30 **31** **32**

More precise data were accessible through kinetic studies of d_0- and 7-*d*-*cis*,*cis*-7-methyl-1,3,5-octatriene (**33**,**34**), which can each give only single products (**35**,**36**) through a [1,7] shift of hydrogen or deuterium. The primary effects measured from 60 to 115°C were 4.6–7.0 in a regular progression: the $\ln(k_H/k_D)$ versus $T(K)^{-1}$ correlation gave a linear plot with slope $(E_a^D - E_a^H)/R$, which led to $(E_a^D - E_a^H) = 2.0$ kcal/mol. The data are consistent with the [1,7] hydrogen shift having a linear transition structure and being considerably facilitated by tunneling.[31]

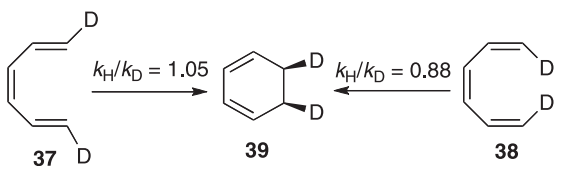


33 (**34**) **35** (**36**)

Electrocyclic isomerization of *cis*-1,3,5-hexatriene

When one concentrates on gaining stereochemical and kinetic information on thermal pericyclic reactions of minimally substituted hydrocarbons, utilization of stereospecifically positioned deuterium labels to probe reaction sterechemistry is an obvious tactic. Such work also makes one increasingly sensitive to the fact that pairs of hydrogen related enantiotopically in starting material or product may be diastereotopic in the transition structure, and could then reflect distinct k_H/k_D kinetic isotope effects.

The first demonstration of diastereotopically distinct k_H/k_D kinetic isotope effects depended on preparing and then following the thermal electrocyclic reactions of unlabeled *cis*-1,3,5-hexatriene and its *trans*,*trans*- and *cis*,*cis*-1,6-d_2-isotopomers, **37** and **38**.[32] Competitive gas-phase isomerizations at 140°C of unlabeled triene and **37** or **38** to *cis*-5,6-d_2-cyclohexadiene (**39**) followed by mass spectral m/z 80/82 ratios showed that the k_H/k_D values are very d_2-triene dependent. For the *trans*,*trans*-1,6-d_2 triene **37**, k_H/k_D is 1.05 ± 0.03, while for the *cis*,*cis*-1,6-d_2 triene **38**, k_H/k_D is inverse, 0.88 ± 0.02. Theory-based calculations gave k_H/k_D values of 1.00 and 0.87, or 1.01 and 0.88 when a correction for tunneling was included, in fine agreement with the experimental observations.[32]



Electrocyclic isomerization of cyclobutene

Similar issues were at play in experiments looking for diastereotopically distinct isotope effects in the cyclobutene to butadiene thermal isomerization, but quite a different experimental plan had to be implemented. Cyclobutene, 1-*d*-cyclobutene, and 3-*d*-cyclobutene

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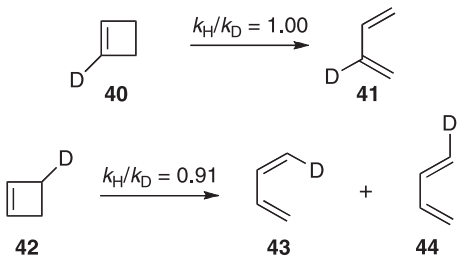
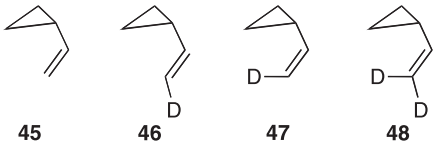
were prepared and purified. Competitive isomerizations in the gas phase at 140°C of unlabeled reactant and 1-*d*-cyclobutene (**40**) as they were converted to butadiene and 2-*d*-butadiene (**41**) were followed by determining the GC/MS *m*/*z* 54/55 ratio for the cyclobutene mixture. It remained constant as the isomerizations progressed over two half-lives, demonstrating that the secondary k_H/k_D effect at C(1) in **40** is negligible. Competitive isomerizations of **40** and 3-*d*-cyclobutene (**42**) were then followed by ^{2}H NMR over more than two half-lives. The k (**42** → **43** + **44**)/k (**40** → **41**) rate constant ratio. From the relative rates of overall isomerizations and the relative proportions of 1-*d*-butadiene stereoisomers **43** and **44** formed (52.4 and 47.6%, respectively), the secondary k_H/k_D values could be calculated. For the isomerization of **42** to *cis*-1-*d*-butadiene (**43**), $k_H/k_D = 1.04 \pm 0.03$; for the conversion of **42** to *trans*-1-*d*-butadiene (**44**), $k_H/k_D = 1.15 \pm 0.03$.[33]



The ground state for cyclobutene and the conrotatory transition structure were defined computationally and vibrational frequencies were found for unlabeled and the several isotopically labeled variants. The semiclassical secondary deuterium kinetic isotope effects computed were 1.12 and 1.05, in excellent agreement with the values found experimentally. These demonstrations of diastereotopically specific second deuterium kinetic isotope effects gained from both experimental and theory-based approaches reinforce one's confidence in the geometrical details of the calculated transition structures and *ab initio* force constants provided by theory.

Thermal isomerization of vinylcyclopropane to cyclopentene

Another demonstration of diastereotopically specific secondary k_H/k_D effects was secured for 2′-*d*-substitutions in vinylcyclopropanes. Both olefinic methylene hydrogens at C(2′) are very much involved in the transition structure, for there is a substantial k_H/k_D effect observed when both are replaced with deuterium, a mechanistically significant fact first reported by Chickos.[34] When these hydrogens are replaced individually, the k_H/k_D ratios are quite different.[35] Syntheses of vinylcyclopropanes **45**, **46**, **47**, and **48** were accomplished. The kinetics of thermal isomerizations to the corresponding cyclopentenes were conducted in a static gas-phase reactor at 341°C and were followed for more than three half-lives by GC.



The k_H/k_D ratios found were 1.15 ± 0.3 for **46**, 1.08 ± 0.05 for **47**, and 1.21 ± 0.03 for the d_2-reactant (**48**). The product $(1.08 \pm 0.05) \times (1.15 \pm 0.03) = (1.24 \pm 0.05)$ is in fair agreement with the k_H/k_D ratio found for isomerizations of d_2- versus d_0-vinylcyclopropanes, (1.21 ± 0.03).[35] In the transition structure, the involvements of the 2′ diastereotopic hydrogens at the migration terminus are distinct geometrically and electronically. They both interact substantially and discretely with the migrating group as the [1,3] carbon-shift process attains the transition structure.

Stereochemistry of the vinylcyclopropane-to-cyclopentene isomerization

Complexity in thermal reactions comes in many guises. In the case of the vinylcyclopropane-to-cyclopentene isomerization, two loom large. First, stereochemically well-defined dispositions of deuteriums (or other substituents) at C(2) and C(3) of the cyclopropyl ring of a reactant lose stereochemical integrity much faster than [1,3] shifts to give cyclopentene products take place.[36,37] Thus, the prospects for a stereochemically informative tracking of a specific starting material to each of several stereoisomers in a product mixture seem unpromising. Second, deuterium labels at C(2), C(3), and C(2′), even if positioned with perfect stereochemical exactitude, and even if somehow relatively rapid thermal stereomutations did not complicate matters, cannot give rise to four stereoisomeric products. Hence one could not deduce the relative importance of all four possible paths, the *si*, *ar*, *sr*, and *ai* options, through quantifying all individual reaction products, even if the rapid stereomutations of the starting material were not an issue.

In the example shown, the *syn*,*cis*-2,3-(*E*)-2′ isomer of d_3-vinylcyclopropane (**49**) could in theory be converted through four distinct [1,3] carbon-shift paths of both 'allowed' (*si*, *ar*) and 'forbidden' (*sr*, *ai*) varieties. But only three distinct products would be formed.

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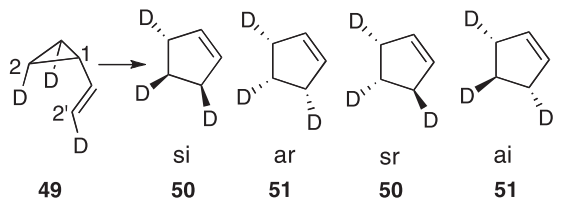
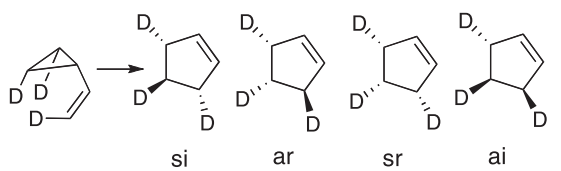
The cis, trans isomer **50** would be formed as a racemate, for both C(1)–C(2) and C(1)–C(3) bond cleavages would initiate reactions, at equal rates. The all cis isomer **51** and the trans,trans isomer **52** are meso compounds and could be quantified separately. Thus, one could get measures of the relative importance of (*si* + *sr*) paths and of the *ar* and *ai* paths.



49 **50** **51** **50** **51**

Can one overcome this limitation by resorting to a chiral substrate? A chiral *trans*-2,3-(*E*)-2′-d_3-vinylcyclopropane could be prepared and isomerized but there would still be only three observable products. One would have equal rates of bond cleavage for C(1)–C(2) and C(1)–C(3), and again the cis,trans isomers in the product mixture would be racemic. The cis,trans isomers stemming from just one of the two enantiotopic bonds broken to initiate the rearrangement would be just one enantiomer, but they would be counterbalanced exactly by the mirror-image-related cis,trans product derived from cleaving the other enantiotopic bond.

Fortunately, this awkwardness is easily obviated by running reactions on reactants labeled in two ways at C(2′). From *syn,cis*-2,3-(*E*)-2′-d_3-vinylcyclopropane (**49**) one can determine the relative importance of (*si* + *sr*), *ar*, and *ai* paths. From *syn,cis*-2,3-(*Z*)-2′-d_3-vinylcyclopropane (**53**), as shown in the equation below, there would still be only three discrete labeled cyclopentenes in each product mixture. The racemic cis,trans product **50** would be reached through both the *ar* and *ai* stereochemical paths; the *sr* path would lead to **51** and the *si* path would give **52**. Combining the product stereochemistry data from isomerizations of both starting materials, the complete stereochemical distribution could be derived – if the fast stereomutation reactions of the starting materials could somehow be overcome.



53 **52** **50** **51** **50**

This challenge proved difficult, but not impossible.[38] Product distributions and the extent of time-dependent stereomutations in labeled vinylcyclopropanes were determined at very short structural isomerization reaction times – times corresponding to from 1.0 to 2.7% conversion of labeled vinylcyclopropanes to cyclopentene products. The d_3-cyclopentene product distributions were determined by high-resolution ^{1}H NMR at 500 MHz, with broad-band ^{2}H and olefinic ^{1}H decoupling. Stereochemically sensitive deuterium-induced differences in chemical shifts of the three different types of C(4)–H absorptions in labeled products were exploited. The expected C(4)–H absorptions for the three isomers were observed and then modeled through best-fit calculations and theory-defined spin–spin coupling patterns (Figure 1). The NMR spectra of product mixtures led to estimations of product distributions, which then could be used with the time-weighted distributions of isomeric d_3-vinyl-cyclopropanes to calculate rate constants for the four stereochemically distinct reaction paths.

Figure 2 shows one example of experimental data and a best-fit calculated spectrum. From the relative proportions of stereoisomers in d_3-cyclopentene product mixtures and the time-weighted average relative concentrations of all three possible isomeric forms of each starting material one may calculate the relative importance of each of the four possible stereochemically distinct paths from vinylcyclopropane to cyclopentene.

The experimental estimates of the relative rate constants associated with the four paths turned out to be 40% *si*, 23% *sr*, 13% *ar*, and 24% *ai*, all $\pm$ 2–3%. These stereochemical findings reinforced earlier stereochemical

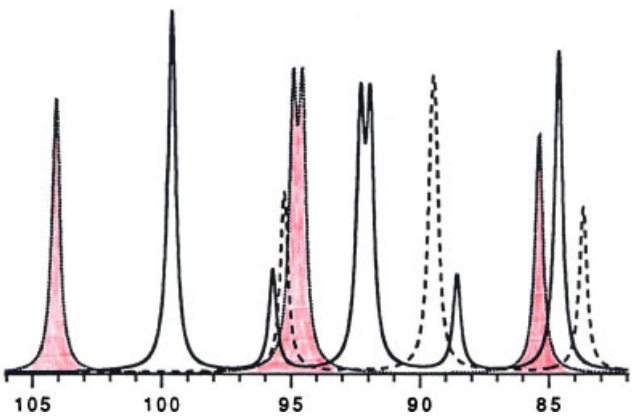


Figure 1 Homoallylic hydrogens (C(4)–H hydrogens) in 3,4,5-d_3-cyclopentenes **50**, **51**, and **52**, parts of AB_2, ABX, and AB_2 three-spin systems, as calculated based on the parameters giving the best fits for the transitions observed for the equilibrium mixture of isomers.

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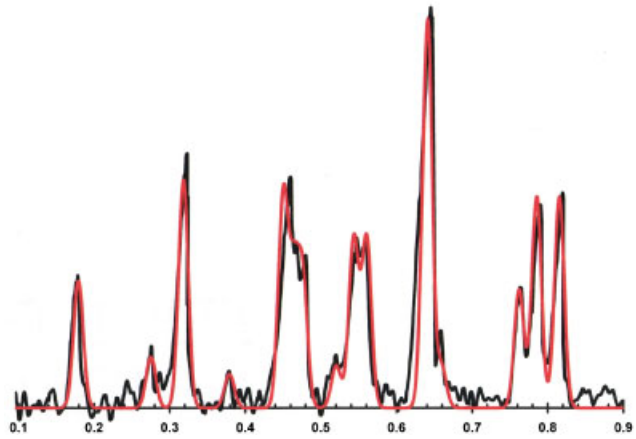


Figure 2 Experimental (dark) and calculated (light) ^{1}H NMR spectra for the C(4)–H absorptions of 3,4,5-d_3-cyclopentene isomers **50**, **51**, and **52**, formed from thermal isomerizations starting from *syn,cis*-2,3-(*E*)-2′-d_3-vinyl-cyclopropane (**53**). Under the reaction conditions (300°C, 48 min) there was a 1% conversion to cyclopentenes; the product distribution was 41% **50**, 23% **51**, and 36% **52**. This figure is available in colour online at www.interscience.wiley.com/journal/jlcr

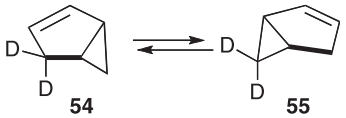
studies,[39,40] which had determined that all four paths, both 'allowed' and 'forbidden' stereochemical paths, do participate in vinylcyclopropane-to-cyclopentene isomerizations. They also prompted serious computational efforts to understand the potential energy surface for the [1,3] carbon shifts[41,42] and to follow through with major-league dynamic calculations.

These efforts led to model-based calculated distributions of relative paths in fine agreement with experimental observations. The first such effort was based on dynamics calculations for 569 trajectories; the results were 45% *si*, 28% *sr*, 12% *ar*, and 16% *ai*.[43] More extensive dynamics calculations based on 34 000 trajectories found the participations of the four paths to be 42% *si*, 30% *sr*, 10% *ar*, and 18% *ai*.[44]

Experimental and theory-based stereochemical results indicate that 47 or 48% of the isomerizations utilized 'forbidden' paths. Both experimental findings and reaction dynamics calculations have *si* > *sr* and *ai* > *ar*. One cannot sustain, in light of these concordant results from such different vantage points, a mechanistic view featuring some prominent role for orbital symmetry as a controlling factor in these [1,3] carbon-shift isomerizations.

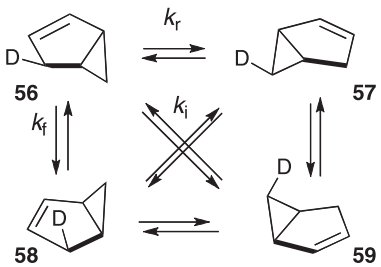
Degenerate isomerizations of bicyclo[3.1.0]hex-2-ene

That bicyclo[3.1.0]hex-2-ene can execute a degenerate isomerization through a [1,3] carbon migration was demonstrated as early as 1963 by Doering and Grimme through the interconversion of **54** and **55**.[45]



Further studies with more substituted analogs as well as other deuterium-labeled systems provided further insights.[46–48] The [1,3] carbon-shift takes place both with *ai* and *sr* stereochemical characteristics, and the sigmatropic shifts are kinetically competitive with another process, the skeletal inversion or 'ring-flip' isomerization involving simultaneous one-center epimerizations at C(1) and C(5).

More extensive kinetic experiments led to rate constants and activation parameters for interconversions of the four possible 4-*d*- and 6-*d*-labeled racemic stereoisomers.[49] Over the temperature range 225–255°C the relative rate constants did not vary significantly (48:36:16 for $k(sr) = k_r$, $k(\text{flip}) = k_f$, and $k(ai) = k_i$). The derived activation parameters were essentially identical for all three reaction types ($\log A = 14.1$, 14.2, 14.1 and $E_a = 43.8$, 44.3, and 44.8 kcal/mol). All three paths share the same rate-determining step, providing a short-lived diradical intermediate on a relatively flat potential energy surface leading to alternate exit channels and isomeric products. Interestingly, all three observed paths are orbital symmetry 'forbidden'.



Detailed theoretical work on these degenerate isomerizations, including the dynamic aspects of trajectories on the transition region surface, or 'caldera,' modeled the observed partitionings among the three paths.[50] The agreement between experiment and theory could hardly have been more satisfactory, for the dynamics calculations following trajectories at 498 and 528 K predicted the relative rate constants $k_r = (47 \pm 1.7)\%$, $k_f = (38 \pm 1.7)\%$, and $k_i = (15 \pm 1.3)\%$.

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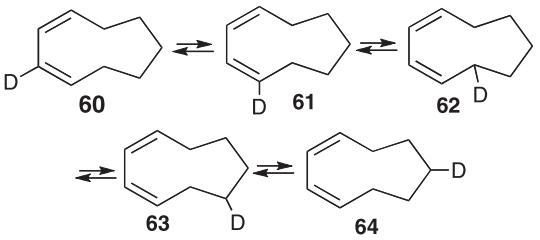
[1,5] Hydrogen shifts in *cis,cis*-1,3-cyclononadiene

The thermal [1,5] shifts of hydrogen in *cis,cis*-cyclononadiene feature aspects of complexity that are not related to stereochemical subtleties. These hydrogen shifts are degenerate. To follow them kinetically would require some isotopic labeling approach, and, following the pioneering work of Winstein and co-workers of [1,5] hydrogen shifts in *cis,cis*-1,3-cyclooctadiene, deuterium labeling was the obvious choice.[51,52] There was every reason to expect the shifts to be concerted and suprafacial.

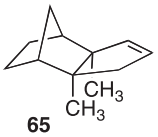


Yet complexities remain. For the kinetic analysis of data gained by following the interconversions of the five possible d_1-labeled cyclononadienes (**60–64**) one must deal properly with the statistical issues and the various conformational isomers included among ground states and transition structures.[53] It turned out, according to DFT calculations, that for *cis,cis*-cyclononadienes there are 11 ground-state conformational isomers separated by ten transition structures. For the [1,5] shifts there are five transition structures that may be reached by eight of the ground state conformers; three cannot be excited to a transition structure directly. Two can get directly to two different transition structures. These complexities were handled through a generalized formulation of the Winstein–Holness equation,[54] and the linear algebra necessary for solving the relevant set of five differential equations was managed with the aid of Maple software. In the end, the experimental E_a value for the [1,5] hydrogen shifts was found to be 37.1 ± 0.8 kcal/mol, while the theory-based calculated value for E_a was 37.5 kcal/mol.[52]

Synthesis and absolute configuration of (−)-albene

Literature reports on the synthesis of the novel hydrocarbon natural product (-)-albene and assignment of its absolute stereochemistry prompted mechanistic concerns and led to a labeling study utilizing both ^{13}C and deuterium. Sorting things out in this specific instance was worthwhile, though the mechanistic ambiguities did not directly involve reactions of hydrocarbons. The mechanistic questions were resolved, and the experience led indirectly to three further studies based on both ^{13}C and deuterium labeling, as summarized below.

(−)-Albene, isolated in 1962 from *Petasites albus*, a medicinal plant called White Butterbur in the UK and Weiße Pestwurz in Germany,[55] is now known to be the (*1S,2S,6S,7R*) enantiomer of 2-*endo*-6-*endo*-dimethyltricyclo[5.2.1.$0^{2,6}$]dec-3-ene (**65**).



Synthetic chemistry reported to give the authentic natural product included a reaction featuring an *endo*-3,2-methyl shift in a 2-norbornyl cation system, a rarity of some interest. One thing led to another: an efficient total synthesis of racemic albene,[56] a demonstration of the absolute stereochemistry of (-)-albene, which forced a reversal of the earlier assignment bolstered by a total syntheses,[57] and then a labeling experiment to test for an *endo*-3,2-methyl shift in the chloro annelation reaction along the earlier reported synthetic path and for possible rearrangements through *exo*-3,2-methyls shifts, Wagner–Meerwein rearrangements, and 6,2-hydride shifts in norbornyl cation intermediates.[58] Finally, two reinterpretations of degradation chemistry reported for albene were advanced.[59]

Two labeled versions of the requisite synthetic intermediate were prepared for the mechanistic study,[58] one labeled with a single ^{13}C and the second with that label as well as *exo*-d_2 substitution at C(5),C(6) (**66**). Careful analysis of ^1H, ^2H, and ^{13}C NMR spectra of the tricyclic ketone formed (**73**) proved that no *endo*-3,2-methyl shift had been involved in any step in the overall reaction. Rather, the data were consistent with the multi-step rationale shown (in a formal 'stop-frame' depiction of the reaction sequence), one involving a proton transfer to hydroxyl, heterolytic bond cleavage to form a cation (**67**) and water, an *exo*-3,2-methyl shift to give **68**, a Wagner–Meerwein rearrangement converting **68** to **69**, a 6,2-deuterium shift to form **70**, another Wagner–Meerwein rearrangement providing **71**, a stereoselective intramolecular electrophilic addition of the tertiary cation on its exo face to the chloro olefin substituent to produce **72**, and finally hydrolysis of

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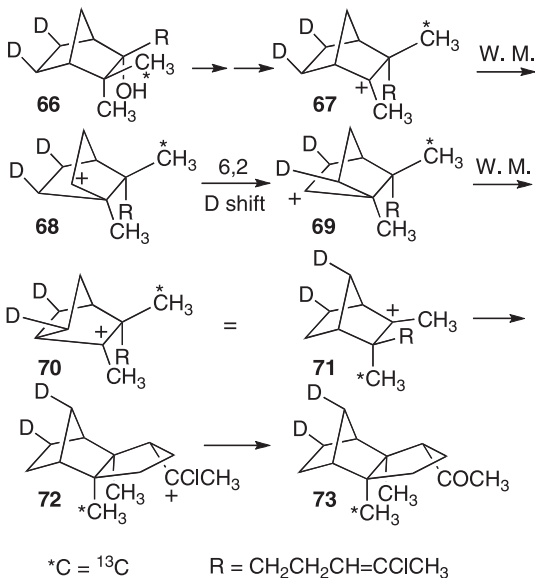
the chloro-substituted cationic intermediate to provide the ketone **73**. This sequential series of molecular rearrangements in norbornyl cationic intermediates may seem lengthy, but every step has well-known precedents; no first-of-a-kind reaction needs to be invoked to account for the overall synthetic conversion.

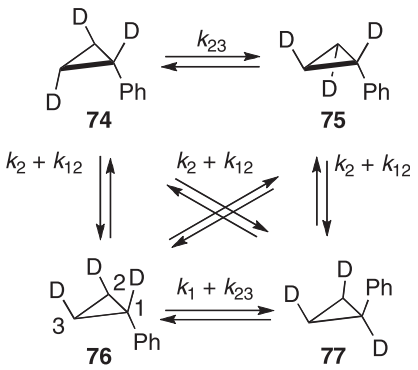


Thermal stereomutations of phenylcyclopropane

Quite a different motivation instigated a complete analysis of the thermal stereomutation reactions of labeled phenylcyclopropanes. This system could suffer C(1)–C(2) and C(1)–C(3) bond cleavages at equal rates, or homolytic rupture of C(2)–C(3) at a presumably much slower rate. The diradicals could collapse to reform cyclopropane bonds to give either starting material or stereoisomers differing by either one or two net epimerizations. The diradical model would anticipate both stereochemical outcomes. Were the overall stereomutations to be the result of two-centered epimerizations, they could well be viewed as formed through concerted conrotatory processes without the intervention of diradical intermediates.

A phenylcyclopropane bearing one or more deuterium labels on the cyclopropyl ring – deuterium substituents taken to be unperturbing stereochemical markers – could give stereomutation reactions defined by four rate constants: k_1 for a one-center epimerization at C(1), $k_2 = k_3$ for a one-center epimerization at C(2) or at C(3); k_{12} for the two-center reversal of stereochemistry at C(1) and C(2) simultaneously, and k_{23}.

Unfortunately, the thermal stereomutations of a single enantiomer of 2-*d*-phenylcyclopropane, or of 2,3-d_2-phenylcyclopropane, cannot lead to these four rate constants. One can get partial results, but not the four rate constants necessary to make the distinction between stereomutations more plausibly rationalized through a diradical model or one based on orbital symmetry considerations and concerted conrotatory two-center epimerizations. The kinetic scheme shown immediately below is appropriate for stereomutations starting with any one of the 1,2,3-d_3-phenylcyclopropanes shown. Note that all eight rate constants leading from **74** or **75** to **76** or **77** (and vice versa) are identical! Direct interconversions at 309.3°C of the two meso structures **76** and **77** and (**74** + **75**), the racemic stereoisomer, monitored by Raman and ^{1}H NMR spectroscopies, led to the rate constants $(k_1 + k_{23}) = 0.36 \times 10^{-5}\,s^{-1}$ and $(k_2 + k_{12}) = 1.07 \times 10^{-5}\,s^{-1}$. When racemic (**74** + **75**) is the starting material, the direct enantiomerization reaction cannot be followed for k_{23} is not observable.[60]



Following the time evolution of the four isomers starting with the (2*R*,3*R*) – (+) stereoisomer **74** provided three rate constants; for k_{23}, $(k_1 + k_{23})$, and $(k_2 + k_{12})$.[61] The rate constants deduced were $k_1 = 0.36 \times 10^{-5}\,s^{-1}$, $k_{23} = 0$, and $(k_2 + k_{12}) = 1.07 \times 10^{-5}\,s^{-1}$, not a surprising clarification, but still an incomplete outcome, since only three kinetic parameters, not four, had been secured.

This limitation was overcome by preparing and then following the kinetics of stereomutations starting with (1*R*,2*S*,3*R*)-2-^{13}C-1,2,3-d_3-phenylcyclopropane (**78**).[61] This chiral ^{13}C,d_3-labeled reactant allows one to distinguish between k_2 and k_{12} processes, as in the example shown. Rate constant k_2 and constant k_{13}, which equals k_{12}, lead from the starting material **78**, chiral only by virtue of the ^{13}C label, to different

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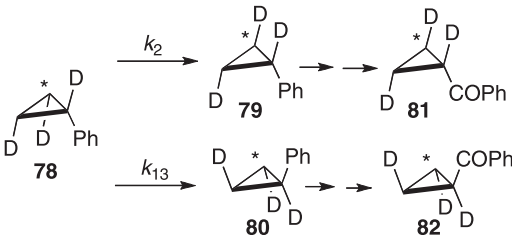
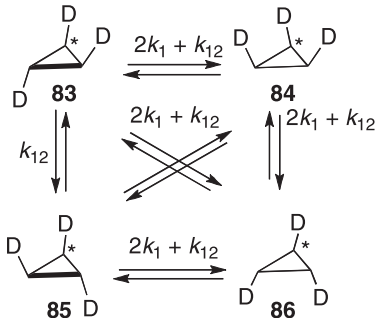
structures related as enantiomers, **79** and **80**. These enantiomers can be quantified through ^{1}H NMR: after the phenyl substituents had been converted to carboxylic acids and then to benzoyl derivatives **81** and **82**, the enantiomeric forms could be quantified in the presence of a suitable chiral shift reagent, Eu(hfc)$_3$.



The rate constants uncovered were $k_2 = 0.87 \times 10^{-5}$ s^{-1} and $k_{12} = 0.20 \pm 0.01 \times 10^{-5}$ s^{-1}. One-center epimerizations, $k_1 = 0.36 \times 10^{-5}$s^{-1} and $k_2 = 0.87 \times 10^{-5}$ s^{-1}, are of prime importance in these stereomutations; the two-center epimerization $k_{12} = 0.20 \pm 0.01 \times 10^{-5}$ s^{-1} is the minor contributor, and k_{23} contributes not at all. The experimental findings are fully consistent with a mechanistic understanding based on the involvement of short-lived non-statistical 1-phenyl-1,3-trimethylene diradical intermediates.[61] Confirmatory evidence gathered in a related but independent study reinforced the mechanistic conclusion.[62]

Thermal stereomutations of cyclopropane

The same limitations, inherent in any attempt to define more independent kinetic parameters than there are independent experimental observables accessible, thwarted early efforts to gain rate constants for one-center and two-center thermal epimerizations in deuterium-substituted cyclopropanes. 1,2-d_2-Cyclopropanes allow for only three isomeric forms and the determination of only two of the three possible mechanistically significant rate constants. A complete analysis of rate data, however precise and accurate the data might be, would not provide a complete set of rate constants. They would not allow one to distinguish between an observed one-center event at C(1) or C(2) leading from a cis to a trans isomer and a two-center epimerization at C(1) and C(3) or C(2) and C(3)! There are only two geometrical isomers of 1,2,3-d_3-cyclopropane and one accessible rate constant for thermal stereomutations. They too would fail to overcome the challenge and settle the mechanistic question. The conundrum was solved by preparing and studying the stereomutations of a chiral ^{13}C-labeled 1,2,3-d_3-cyclopropane.[63–65]



The kinetic situation is simple, though the synthetic and analytical chemistry requirements are not. There are only two independent kinetic parameters thanks to the distribution of one deuterium on each carbon atom. Each of the three C–C bonds in the ^{13}C,d_3-labeled cyclopropanes will cleave and lead to one-center and two-center epimerization events at equal rates. Ten of the relevant rate constants in the kinetic scheme are equal and given by $(2k_1 + k_{12})$. Only the rate constants directly interconverting the chiral isomers **83** and **85** are different; they are equal to k_{12}. By following the loss of optical activity using vibrational circular dichroism spectroscopy, and the equilibration of the two geometrical forms **84** and (**83**, **85**, and **86**) using both FTIR and tunable diode laser spectroscopic analyses of gas-phase reaction mixtures, the k_1 and k_{12} rate constants were found to be essentially equal. At 407°C, they were $k_1 = (0.38 \pm 0.02) \times 10^{-5}$ s^{-1} and $k_{12} = (0.40 \pm 0.03) \times 10^{-5}$ s^{-1}, and hence $k_1/k_{12} \approx 1$.[63–65] The rate constants point toward a diradical mechanism, and away from any mechanism requiring the exclusive or nearly exclusive involvement of k_{12} processes. The experiments have led to fresh theory-based assessments of cyclopropane stereomutations, and the discrepancies between theory and experiment have been substantially reduced.[66] The precise k_1/k_{12} ratio remains under scrutiny, but it seems clear to all that both one-center and two-center epimerizations contribute to thermal stereomutations of cyclopropanes to comparable, or roughly comparable, extents.

Isomerization of cyclopropane to 1-propylidene

Another instance where both deuterium and ^{13}C labeling proved efficacious involved a test for the possibility that cyclopropane (**87**) might isomerize

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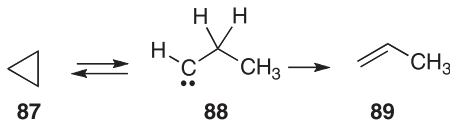
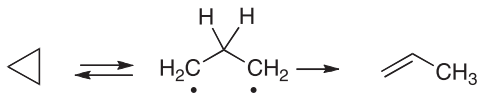
thermally to 1-propylidene (**88**), which could then form propylene (**89**) with very little activation energy.



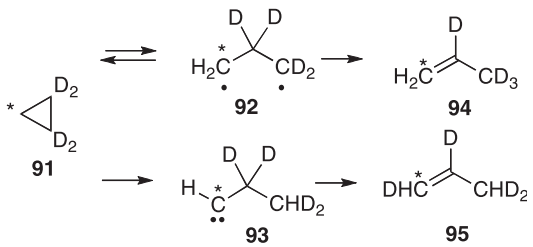
87 **88** **89**

This hypothetical reaction (**87** → **88**) was at first discounted as a realistic possibility when theoretical calculations projected an exorbitantly high activation energy, but as theory and computational power grew ever more powerful, the prospects seemed brighter – or at least less totally gloomy. By 1999 high-level computational definitions of the C_3H_6 isomers, cyclopropane (**87**), 1-propylidene (**88**), and propylene (**89**), concluded that the carbene pathway might compete energetically with the path from cyclopropane to propylene involving a trimethylene diradical intermediate (**90**), the consensus mechanism for the overall isomerization.[67] The calculated $\Delta\Delta E_a$ was only 2.4 kcal/mol, which at a reaction temperature of say 435°C would not be too daunting. Were that the real $\Delta\Delta E_a$ value, the propylidene mechanism should be competitive enough to be detected!



87 **90** **89**

To test the possibility that the 1-propylidene route might actually participate in the cyclopropane-to-propylene isomerization – the oldest recognized thermal isomerization of a hydrocarbon[68] – a sample of 1-^{13}C-2,2,3,3-d_4-cyclopropane (**91**) was prepared and studied.[69] This labeled reactant presents no complications associated with various cyclopropane thermal one-centered and two-centered stereomutations, for there are no cyclopropane stereoisomers accessible.



The starting material **91** was isomerized to labeled propylenes at 435°C in the gas phase with cyclopentane as a bath gas for times ranging from 20 to 42 h. The reaction mixtures were analyzed by ^{13}C NMR, concentrating attention on the olefinic methylene carbon region near 116 ppm for *C(1)H2 or possible *C(1)HD absorptions. Were the isomerization to take place exclusively through the trimethylene diradical, the ^{13}C label at C(1) of the diradical **92** would not be deuterium labeled, nor would the propylene product **94** be deuterium labeled at C(1). If, however, the 1-propylidene intermediate labeled with ^{13}C at C(1) (**93**) were to contribute to the overall reaction, the propylene formed would be labeled with ^{13}C and with one deuterium at C(1) (**95**). The ^{13}C NMR spectra recorded at 151.2 MHz with inverse gated proton decoupling showed a strong singlet for *C(1)H2, consistent with the mechanism based on trimethylene diradical intermediates such as **92**, and, centered 0.69 ppm upfield, a 1:1:1 triplet split by 24 Hz from J_{13C-D} coupling, confirming the participation of the 1-propylidene intermediate and the production of product **95**.[69] No scrambling of labels was evident in recovered starting material.

In this case the combination of both ^{13}C and deuterium labeling, assembled in accord with the analytical strategy elected, provided a clear-cut answer to the question posed by theory: the trimethylene route is dominant, but the path through a 1-propylidene intermediate is a distinct participant in the overall isomerization, as predicted by theory.

Conclusion

The thermal fragmentation and isomerization reactions of relatively simple hydrocarbons provide attractive opportunities for experimental and computational chemists to aim for deeper understandings of reaction mechanisms, and to challenge and develop their intellectual and technical approaches to the questions that arise. Work in this area has provided more detailed grounds for comparing and contrasting the methods and outcomes experimentalists and theoreticians contribute to the common enterprise. Studies dependent on specific deuterium- and carbon-13-labeled hydrocarbons, in the examples reviewed here and many more reported by other laboratories, have supported these developments. The experimental work has been contingent on suitable strategies, applications of the power of synthetic organic chemistry, and utilizations of a substantial range of analytical tools and data reduction methodologies. Progress has been apparent. More difficult problems can now be considered tractable and worth investing time and energy in pursuing than was the case just a few decades ago. And more mechanistic problems, of more subtle aspect, await our attention.

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