JOC Perspective

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On the Stereochemical Characteristic of the Thermal Reactions of Vinylcyclobutane

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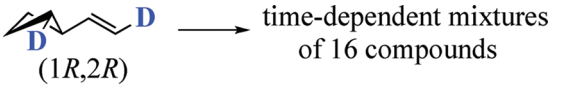


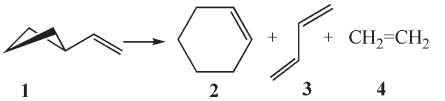
This Perspective outlines the stereochemical and mechanistic complexities inherent in the thermal reactions converting vinylcyclobutane to cyclohexene, butadiene, and ethylene. The structural isomerization and the fragmentation processes seem, at first sight, to be obvious and simple. When considered more carefully and investigated with the aid of deuterium-labeled stereochemically well-defined vinylcyclobutane derivatives there emerges a complex kinetic situation traced by 56 structure-to-structure transformations and 12 independent kinetic parameters. Experimental determinations of stereochemical details of stereomutations and [1,3] carbon sigmatropic shifts are now being pursued and will in time contribute to gaining relevant evidence casting light on the reaction dynamics involved as flexible short-lived diradical intermediates trace the paths leading from one d_2-labeled vinylcyclobutane starting material to a mixture of 16 structures.

Introduction

The thermal chemistry exhibited by vinylcycloalkanes has evolved over the past 50 years, providing both serious challenges and valuable mechanistic insights. Substituted vinylcyclopropanes and vinylcyclobutanes attracted more attention than larger homologues, for ring strain facilitated reactions leading to structural isomerizations through [1,3] carbon shifts and other varieties of transformations at relatively modest temperatures. Similar types of thermal reactions shown by vinylcyclopentanes, vinylcyclohexanes, vinylcycloheptenes, and larger homologues and thermal reactions leading to these structures from cycloheptene, cyclooctene, cyclononene, and larger cycloalkenes are well-known, and of considerable interest, but not as thoroughly investigated.[1]

Vinylcyclopropane appeared in the literature in 1896 as Gustavson reported preparing this hydrocarbon from pentaerythritol tetrabromide, $C(CH_2Br)_4$.[2] The major product formed through his synthetic efforts turned out to be spiropentane, and vinylcyclopropane itself was secured in 1922 by Demjanow and Dojarenko.[3] The structural assignments and even the possible existence of both of these C_5H_8 isomers remained contested for several decades; even some preeminent organic chemists such as Christopher K. Ingold, the first recipient of the ACS James Flack Norris Award in 1965, and Frank C. Whitmore, a giant among organic chemists in midcentury, thought and declared in print (in 1923 and 1937) that these hydrocarbons did not exist and were not capable of existence.[4] These errors in judgment were in due course corrected as an abundance of structural detail for both isomers provided sure corroborations. No one today need be influenced or limited by the pronouncements of these authorities and others convinced by them at one time that the hydrocarbons were only hypothetical structures, not real entities.

The thermal isomerization of vinylcyclopropane to cyclopentene was discovered in 1960 by Vogel and his colleagues and by Overberger and Borchert.[5] The first example of a similar isomerization of a vinylcyclobutane was reported 1963: isopropenylcyclobutane was converted to 1-methylcyclohexene and isoprene plus ethylene.[6] The thermal reactions of vinylcyclobutane (**1**) leading to cyclohexene (**2**) and butadiene (**3**) plus ethylene (**4**) were first studied in 1978 and 1980.[7]



By the late 1960s, the generally espoused view of the reaction mechanisms responsible for the isomerizations of vinylcyclopropanes and vinylcyclobutanes accomplished

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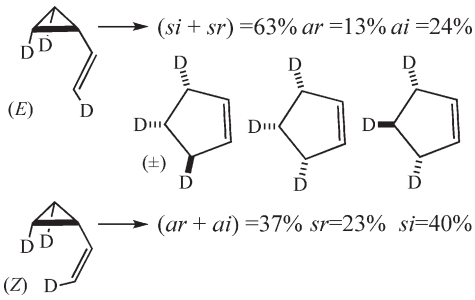
by [1,3] carbon shifts, and fragmentations of vinylcyclobutanes, involved cleavages of the C(1)−C(2) bond of a ring to form a diradical intermediate which in turn led to a ring expansion or a fragmentation.[8] This generalization prompted some serious reflections as to how such a diradical intermediate might be envisaged, or if diradicals should be considered apparitions of transition structures or real intermediates having real lifetimes.[9]

Vinylcyclopropanes and later vinylcyclobutanes also exhibited thermal stereomutations, as in the relatively rapid interconvertion of cis and trans isomers of 1-vinyl-2-*d*-cyclopropanes.[10] Again, processes based on diradical intermediates seemed the appropriate mechanistic rationale.

When orbital symmetry theory was introduced in 1965 and sigmatropic reactions were defined and generalized, [1,3] carbon shifts were not mentioned.[11] Vinylcyclopropane and isopropenylcyclobutane thermal chemistry and mechanistic accounts involving diradical intermediates rationalizing the transformations observed were not considered. But within a few years, such thermal reactions became of considerable importance as they emerged as isomerizations possibly relevant to the principle of conservation of orbital symmetry. The stereochemistry of the [1,3] carbon shift converting 6-*endo*-acetoxy-7-*exo*-*d*-bicyclo[3.2.0]hept-2-ene to 2-*exo*-acetoxy-3-*exo*-*d*-bicyclo[2.2.1]hept-5-ene reported by Berson and Nelson in 1967 reflected a process involving a suprafacial shift with inversion at the migrating −CHD group, a telling demonstration of the predictive power of orbital symmetry considerations.[12] When "The Conservation of Orbital Symmetry" was published first in *Angewandte Chemie* in 1969 and then as a separate brochure in book form,[13] the stereochemical course of the [1,3] carbon sigmatropic shift found for the 6-*endo*-acetoxy-7-*exo*-*d*-bicyclo[3.2.0]-hept-2-ene reactant was taken as a reliable indication that the reaction involved "a concerted symmetry-allowed suprafacial [1,3] shift, *with inversion at the migrating center*." The product formed was taken as a validation of the mechanism. Further, but with suitable caution, Woodward and Hoffmann considered it worthwhile to reflect about the stereochemical consequences of concerted processes for the vinylcyclopropane-to-cyclopentene reaction. They rightly pointed out that only two of the four possible stereochemical paths were consistent with symmetry-allowed processes, and prefigured experimental tests of stereochemical outcomes that could be accessed through making and studying isomerizations shown by maximally labeled reactants.

Their intriguing deliberations provided challenging speculations, but long before experimental work ascertained reaction stereochemistry for thermal isomerizations of (substitituted) monocyclic vinylcyclopropanes to (substituted) cyclopentenes the vinylcyclopropane-to-cyclopentene isomerization was in many quarters framed mechanistically as a conceptual absolute. It was accepted as a sure and spectacular example of the power and reach of the principles underlying the conservation of orbital symmetry concept. Many ignored the clear admonitions of Woodward and Hoffmann that "a given symmetry-allowed concerted reaction need not necessarily represent the manner in which reacting molecules will actually comport themselves. Quite possibly another path, involving reactive intermediates of relatively low energy, may be followed...."

SCHEME 1. Stereochemical Paths for Vinylcyclopropane-to-Cyclopentene Isomerizations



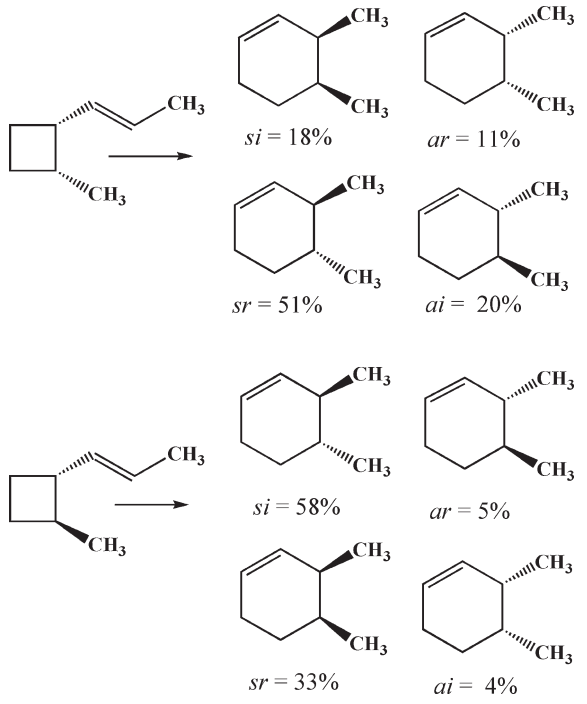
From 1970 to about 2005, the issues related to the stereochemistry of vinylcyclopropane thermal chemistry were investigated in depth in several laboratories, and a clear picture emerged. Substituents larger than deuterium bias stereochemical outcomes. When two larger-than-deuterium substituents adorn a reactant the more thermodynamically stable isomeric products are favored. When both stereomutation and [1,3] carbon shift gas-phase reactions starting from 1-(*E*)-*d*-ethenyl- or 1-(*Z*)-*d*-ethenyl-2,3-*endo*-d_2-cyclopropane were followed, the product mixtures of labeled vinylcyclopropanes and cyclopentenes were analyzed and the quantitative distributions of isomers at a constant temperature and various reaction times provided relative reaction rate constants for each of the four possible [1,3] shift paths. The experimentally estimated distribution of paths favor, very slightly, the orbital-symmetry "allowed" paths, 40% *suprafacial,inversion* (*si*) and 13% *antarafacial, retention* (*ar*), or 53% in all. The "forbidden" paths lead to 23% *suprafacial,retention* (*sr*) and 24% *antarafacial,inversion* (*ai*) outcomes (Scheme 1).[14]

Extensive computational work to define the reaction surface by Davidson and Gajewski and Houk and coworkers,[15] and reaction dynamics calculations following 34000 trajectories achieved by Doubleday,[16] gave the theory-based distribution of paths to be 42% *si,* 10% *ar,* 30% *sr,* 18% *ai*, in fair agreement with the experimental results.

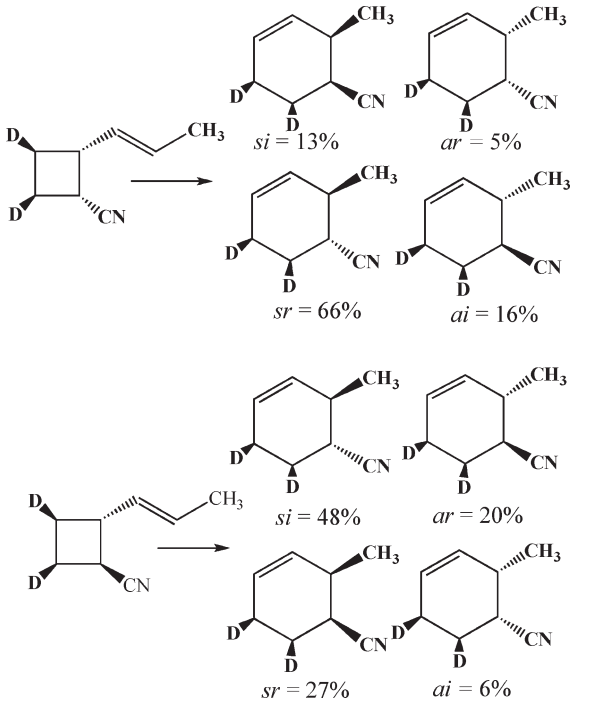
Much of importance relating to the vinylcyclopropane story is simply left out here. A detailed summary in *Chemical Reviews* in 2003 provides a more extensive account and more ample literature citations.[17]

While considerable experimental and computational work on the thermal chemistry of vinylcyclopropane systems has been invested and served well to distinguish the critical difference between concerted and orbital symmetry allowed mechanistic understandings versus others dependent on short-lived diradical reactive intermediates, the reactions of vinylcyclobutanes have not been so extensively studied. Thermal reactions of vinylcyclobutanes could have provided kinetic data for stereomutations and [1,3] carbon shifts and fragmentations, and they could have impinged more generally on fundamental mechanistic questions. Are diradical intermediates involved in all three types of reactions? Are diradical intermediates also of importance in cyclohexene-to-vinylcyclobutane reactions and ethylene plus butadiene-to-cyclohexene additions? Are Diels−Alder and retro-Diels−Alder reactions surely concerted and orbital symmetry controlled?[18] Reams of experimental data and mounds of computer-generated output confirm the largely accepted or

SCHEME 2. Stereochemical Paths for 1(*E*)-Propenyl-2-methylcyclobutane-to-3,4-Dimethylcyclohexene Isomerizations



SCHEME 3. Stereochemical Paths for d_2-Labeled 1(*E*)-Propenyl-2-cyanocyclobutane-to-3-Methyl-4-cyanocyclohexene Isomerizations



even unquestioned conviction that these reactions are concerted. Nonconcerted mechanistic options for Diels–Alder reactions have been considered, rarely, but they have not gained much attention.

This topic is gaining some traction, slowly, as experimental data and theory-based models have provided grounds for reconsideration.[19] Such matters must be set aside here so as to concentrate on the stereochemical issues leading from a vinylcyclobutane to other vinylcyclobutanes and to cyclohexenes.

In 1981, Doering and Mastrocola reported a study following both stereomutations and [1,3] carbon shifts of the four stereoisomers of 1-cyano-2-vinylcyclobutane and providing an early recognition that the reactions were not obviously concerted; concertedness was simply undiscernible.[20]

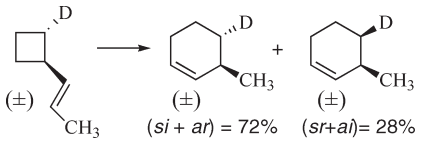
In 2001, a full stereochemical account of the stereomutations and [1,3] shifts of stereoisomeric 1(*E*)-propenyl-2-methylcyclobutanes[21] (Scheme 2) made clear that the isomerizations leading to specific 3,4-dimethylcyclohexenes were not governed by orbital symmetry rules. Starting from one enantiomer of the cis reactants, the *trans*-3,4-dimethylcyclohexenes were dominant (71%), though they were reached by "forbidden" *sr* and *ai* paths. Starting from one of the trans starting materials, the dominant [1,3] carbon shift products were enantiomeric *trans*-3,4-dimethylcyclohexenes (63%), corresponding to "allowed" *si* and *ar* transformations.

A second example was soon provided by Doering and coworkers utilizing 1(*E*)-propenyl-2-cyano-3,4-*cis*-d_2-cyclobutanes.[22] The deuterium-labeling allowed tracing stereochemical details of stereomutations and [1,3] carbon shifts without a need to follow optically active isomers: the stereochemical dispositions of (*E*)-propenyl and cyano and methyl groups relative to the deuterium substituents in cyclobutane and cyclohexene structures revealed the paths traversed as specific 3,4-disubstituted cyclohexenes were formed (Scheme 3).

The two studies[21,22] led to very similar results: the patterns of stereochemical preferences for the four possible paths leading from the 2-substituted 1(*E*)-propenylcyclobutanes to 3,4-dimethylcyclohexenes or 3-methyl-4-cyanocyclohexenes proved to be remarkably consistent. The cis reactants favor trans products and forbidden/allowed paths by 71:29 and 82:18; the trans reactants favor the trans products and allowed/forbidden paths by 63:37 and 68:33. More stable diastereomeric trans products prevail in all four product mixtures (Schemes 2 and 3), whether or not orbital symmetry sanctioned stereochemical paths may be invoked. Both cis reactants favor stereochemical paths in rank order $sr > ai > si > ar$. Both trans starting materials favor the stereochemical paths in rank order $si > sr > ar > ai$, though the *ar* and *ai* paths from the trans hydrocarbon reactant are not very different. Still, the overall resemblance of stereochemical outcomes from the experimental findings recorded by the two groups are striking. The [1,3] carbon shifts in both systems take place by way of short-lived diradicals that have sufficient conformational flexibility within a caldera region of the potential energy surface to favor exit channels leading to diastereomers of greater thermodynamic stability. The isomerizations from these disubstituted vinylcyclobutanes to 1,2-disubstituted cyclohex-3-enes are not orbital symmetry conserved concerted reactions.

The racemic cis and trans isomers of 1(*E*)-propenyl-2-*d*-cyclobutane equilibrated and gave 3-methyl-4-*d*-cyclohexenes with [1,3] shifts showing a $k(si + ar)/k(sr + ai)$ ratio of 72:28 (Scheme 4).[23] The isomerizations to 3-methyl-4-*d*-cyclohexenes could not have been biased by thermodynamic preferences. Stereomutations, while modestly faster than [1,3] shifts, did not seriously limit following the isomerizations to [1,3]

SCHEME 4. 1(*E*)-Propenyl-2-*d*-cyclobutane Isomerizations to 3-Methyl-4-*d*-cyclohexenes



shift products. The four isomers of 3-methyl-6-*d*-cyclohexene products were formed and analyzed but could not provide information on the *r* or *i* stereochemistry of the -CH_2 [1,3] shifts involved.

Thermal Chemistry of Deuterium-Labeled Vinylcyclobutanes

The experimental findings summarized above, and similar experimental determinations involving other careful studies of different systems exhibiting stereomutations and [1,3] carbon sigmatropic isomerizations,[24] lead one to anticipate that the thermal chemistry of the parent hydrocarbon, vinylcyclobutane itself, would show qualitatively similar behaviors. To secure quantitatively reliable data on stereochemical preferences for thermal reactions of suitable deuterium-labeled vinylcyclobutanes would most probably find similar stereochemical patterns. Securing that data might seem a weakly justified exercise leading to just another example of an established pattern of stereochemical proclivities.

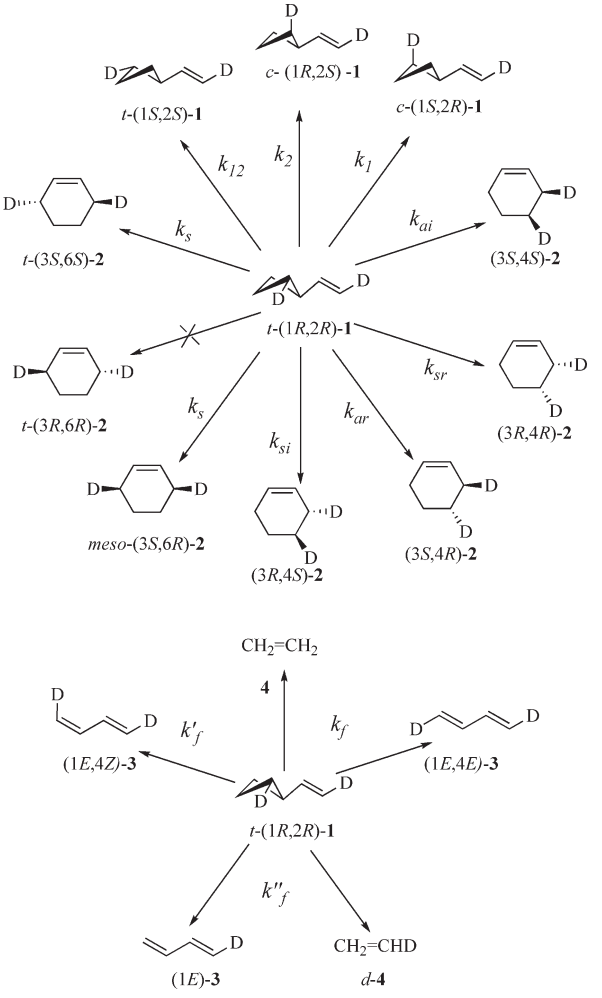
Two clear justifications for electing to aim at gaining a full stereochemical account of vinylcyclobutane thermochemistry may be propounded: the experimental data would provide a valuable or even an essential foundation for theoretical work leading to a delineation of the time-dependent dynamic evolutions of the diradical conformers involved, a challenging aspiration still beyond current capabilities.[25] The experimental work would of necessity require novel methods to attain its objectives, thus establishing one or more new utilitarian approaches applicable when addressing similar challenges.

Were one to prepare a suitable specific stereoisomer of 1(*E*)-*d*-ethenyl-2-*d*-cyclobutane (d_2-**1**) and follow the time-dependent thermal reaction mixtures it would generate, the stereochemical picture could be well-defined. The practical difficulties inherent in completing the investigation would be substantial but well worth the effort. Several single stereoisomers of d_2-**1** would need to be prepared in ample quantities, purified, and well characterized. A single stereoisomer could then be subjected to thermal reactions in the gas phase for defined reaction times at a constant temperature.

Each reaction mixture would include 16 distinct structures to be condensed and separated into collections of four structural classes (vinylcyclobutanes, cyclohexenes, butadienes, and ethylenes) (Scheme 5). Assignments of absolute stereochemistry and quantitative analytical data for the four stereoisomers of d_2-**1** and of all four stereoisomers of 3,4-d_2-**2** would need to be secured. The requisite data reductions would then follow, and rate constants for thermal stereomutations and [1,3] carbon shifts leading to 3,4-d_2-**2** isomers would be calculated. All four rate constants for these [1,3] shifts starting from a single d_2-**1** isomer, the $k(si)$, $k(ar)$, $k(sr)$, and $k(ai)$ rate constants, could be obtained.

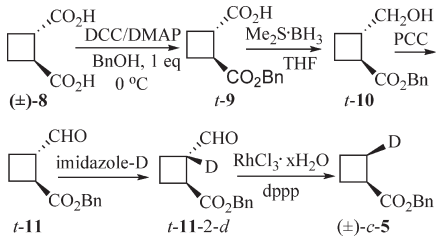
Each reaction mixture could be mapped by connecting relationships between one d_2-**1** stereoisomer and 14 of the 15

SCHEME 5. Product Mixtures Derived from Any One d_2-1 Stereoisomer of 1(*E*)-*d*-Ethenyl-2-*d*-cyclobutane (*t*-(1*R*,2*R*)-1**, *t*-(1*S*,2*S*)-**1**, *c*-(1*R*,2*S*)-**1**, or *c*-(1*S*,2*R*)-**1**)**



different compounds that would come into existence through the thermal reactions. Each of the four d_2-**1** isomers could react to give three other vinylcyclobutanes, six of the seven different d_2-cyclohexenes, three butadienes, and two ethylenes. These multiple reaction options reflect only 12 independent kinetic parameters: there are 12 rate constants involved in the kinetic scheme for stereomutations, but only three independent kinetic parameters (k_1, k_2, and k_{12}); each d_2-**1** isomer would lead to four 3,4-d_2-cyclohexenes through rate constants $k(sr)$, $k(si)$, $k(ar)$, and $k(ai)$. Each d_2-**1** isomer would have only two options for making 3,6-d_2-cyclohexenes by rate constant*s* $k(s)$ and $k(a)$, for the migrating $C(4)H_2$ group would have no retention versus inversion stereochemical option. The *trans*-d_2-**1** isomers would lead to *meso* product by $k(s)$ and *t*-(3*S*,6*S*)-**2** by $k(a)$. The two *cis*-d_2-**1** isomers would convert to *meso* 3,6-d_2-cyclohexene using $k(a)$ and *t*-(3*R*,6*R*)-**2** structures by way of $k(s)$. The five fragmentation products involve only 3 kinetic parameters. One fragmentation rate constant, k(f), would lead from *t*-(1*R*,2*R*)-**1** to (1*E*,4*E*)-**3** and to ethylene (**4**) in equal amounts; a second independent kinetic parameter, k'(f), would give (1*E*,4*Z*)-**3** and ethylene (**4**) in equal amounts; the third, k''(f), would provide (1*E*)-**3** and *d*-**4** in equal amounts.

SCHEME 6. Racemic Benzyl *cis*-2-*d*-Cyclobutanecarboxylate



The kinetic complexity is not as overwhelming as one might imagine at first glance. Were one to concentrate on the stereomutations and [1,3] carbon shifts leading to 3,4-d_2-cyclohexenes, only seven independent kinetic parameters would be needed to gain the detailed stereochemical characteristics of these conversions, a manageable objective if the necessary synthetic and analytical capabilities could be effectuated.

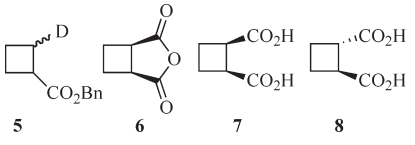
Starting with another d_2-**1** stereoisomer, rather than the *t*-(1*R*,2*R*)-**1** example featured in Scheme 5, different dispositions of rate constant parameters leading to specific products would need to be redistributed appropriately.

The three independent kinetic parameters accounting for [1,3] carbon shifts leading to 3,6-d_2-cyclohexenes could be determined, but not easily. Obtaining these parameters and those for the fragmentations are now being postponed for another day, for they are not essential to the primary objective of this study.

Syntheses of Specific Stereoisomers of 1(*E*)-*d*-Ethenyl-2-*d*-cyclobutane

Preparations of specific stereoisomers of 1(*E*)-*d*-ethenyl-2-*d*-cyclobutane were accomplished through several approaches. Much has been learned in the process, though optimal synthetic schemes are still being sought.

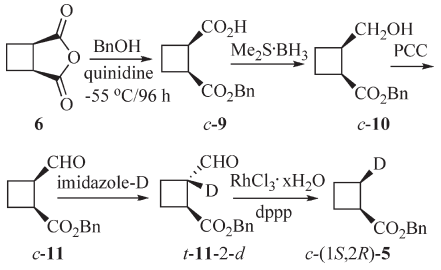
Stereoisomers of 2-*d*-labeled benzyl cyclobutanecarboxylates (**5**) were projected as convenient synthetic intermediates, and *cis*-cyclobutane-1,2-dicarboxylic anhydride (**6**), *cis*-cyclobutane-1,2-dicarboxylic acid (**7**), and racemic *trans*-cyclobutane-1,2-dicarboxylic acid (**8**) were recognized as appropriate and interconvertible starting materials for making various versions of **5**.



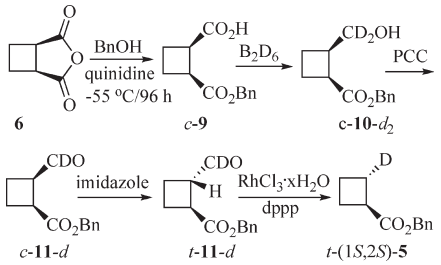
Commercial sources now command prices from about \$500−\$1000 for 5 g of **6**, **7**, or **8**. The racemic trans diacid **8** is listed as \$876/5 g in the current Aldrich catalog. How times have changed! In 1968, Aldrich offered the diacid **8** at \$23/100 g.[26] In the early1970s, Windhorst followed through on his thesis research and synthesized (+)-(1*S*,5*S*)-bicyclo-[3.2.0]heptane-3-one starting from 550 g of commercial diacid **8**.[27] Synthetic work at this scale is hardly imaginable today in an academic setting!

Racemic benzyl *cis*-2-*d*-cyclobutanecarboxylate was prepared from the racemic trans diacid ((±)-**8**) as represented in Scheme 6. An unexceptional monoesterification gave benzyl

SCHEME 7. Benzyl *cis*-(1*S*,2*R*)-2-*d*-Cyclobutanecarboxylate



SCHEME 8. Benzyl *trans*-(1*S*,2*S*)-2-*d*-Cyclobutanecarboxylate



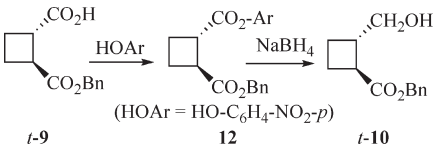
ester *t*-**9**; the monoester led through a reduction product (*t*-**10**) to benzyl *trans*-2-formyl-cyclobutanecarboxylate (*t*-**11**). The introduction of the deuterium label with imidazole-D[28] left the trans formyl substituent stereochemically unaltered, almost. Some epimerization intruded, reflecting a trans/cis equilibrium favoring the trans diastereomer (*t*-**11**-2-*d*). The decarbonylation reaction employing 4% catalytic $RhCl_3 \cdot xH_2O$ and 1,3-diphenylphosphinopropane (dppp)[29] provided the *cis*-2-*d*-cyclobutanecarboxylate ((±)-*c*-**5**) in 60% yield. The ^{2}H NMR spectrum reflected the 94:6 ratio of cis (δ 2.33) and trans (δ 2.22) isomers (Scheme 6). Another decarbonylation protocol of a *trans*-2-formylcyclobutanecarboxylate employing 5% $RhCl(CO)(PPh_3)_2$ and dppp in toluene at reflux proved far less satisfactory.

Benzyl *cis*-(1*S*,2*R*)-2-*d*-cyclobutanecarboxylate was made starting from anhydride **6**. A highly asymmetric ring-opening by benzyl alcohol in the presence of quinidine at −55 °C over 96 h, as reported by Bolm and co-workers, afforded product *c*-**9** in 97% yield and 96% ee (Scheme 7).[30] Reduction of the acid with $Me_2S \cdot BH_3$ gave benzyl (1*S*,2*R*)-2-(hydroxymethyl)-cyclobutanecarboxylate (*c*-**10**) in 80% yield. A PCC oxidation to *give c*-**11** followed by an imidazole-D promoted epimerization in THF at reflux for 24 h provided the *cis*-2-*d*-*trans*-2-formyl product, *t*-**11**-2-*d*. A catalytic decarbonylation using $RhCl_3 \cdot xH_2O$ and dppp in diglyme at reflux overnight gave *c*-(1*S*,2*R*)-**5** in 60% yield. The ^{2}H NMR ($CHCl_3$) spectrum showed absorptions at δ 2.22(6%, trans isomer) and δ 2.33 (94% cis isomer) (Scheme 7).

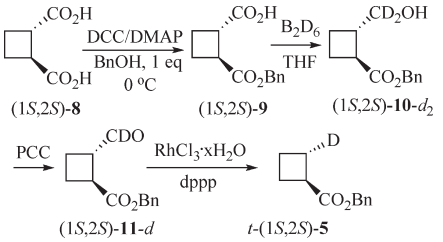
Benzyl *trans*-(1*S*,2*S*)-2-*d*-cyclobutanecarboxylate (*t*-(1*S*,2*S*)-**5**) was obtained following the steps used previously with slight modifications (Scheme 8). Reduction of the acid ester was done with B_2D_6;[31] the conversion of *c*-**10**- d_2 to *c*-**11**-*d* to *t*-**11**-*d* was done using unlabeled imidazole for the penultimate step. The catalytic decarbonylation reaction afforded *c*-(1*S*,2*S*)-**5** in 71% yield. The ^{2}H NMR spectrum of the product showed absorptions at δ 2.22 (95%, trans isomer) and δ 2.33 (5%, cis isomer).

Even though B_2D_6 proved an excellent reagent providing in this case the $-CD_2OH$ substituent in 92% yield, it was in

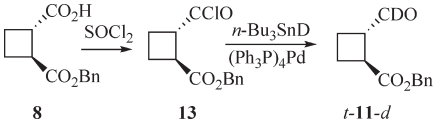
SCHEME 9. Selective Reduction of *p*-Nitrophenyl Ester in the Presence of a Benzyl Ester Substituent



SCHEME 10. Benzyl *trans*-(1*S*,2*S*)-2-*d*-Cyclobutanecarboxylate from (1*S*,2*S*)-8



SCHEME 11. Deuterioformyl from Carbonylchloride Substituent



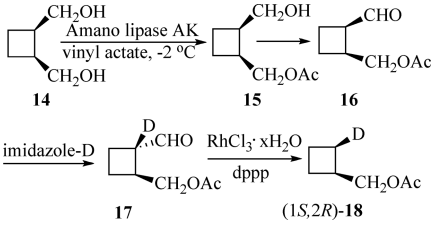
some respects awkward to generate in situ, and another reaction sequence was considered, using *trans*-2-(benzyloxycarbonyl)cyclobutanecarboxylic acid (*t*-**9**) as a trial substrate (Scheme 9). It was condensed with *p*-nitrophenol using DCC in CH_2Cl_2. The mixture of diesters (**12**) obtained in 84% yield was reduced with $NaBH_4$ in THF to give benzyl *trans*-2-(hydroxymethyl)cyclobutanecarboxylate) (*t*-**10**) in 73% yield. Were $NaBD_4$ used, the CD_2OH variant would have been made. A single unoptimized trial cannot be a conclusive indicator, but this selective two-step reduction of *t*-**9** to give *t*-**10** without reducing the benzyl ester substituent might prove a practical alternative to the B_2D_6 option.[32]

Two alternatives to suppress unwanted epimerizations introduced with imidazole leading to equilibrations of formyl substituents have been considered and still seem attractive. One would depend on a single enantiomer of the trans diacid as a starting material. Reactions used above without an imidazole step could lead from (1*S*,2*S*)-**8** to *t*-(1*S*,2*S*)-**5** (Scheme 10).

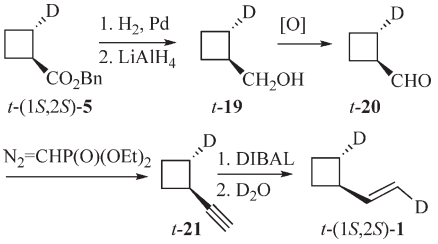
This approach could be adjusted by avoiding the B_2D_6 reduction in favor of the *p*-nitrophenyl ester reduction alternative or by converting **8** to the related acid chloride (**13**) and then preparing the deuterioformyl substituted compound (***t*-11**-*d*) otherwise, as achieved by Fedé in a related system (Scheme 11).[23]

Another approach to securing a specific 2-*d*-labeled cyclobutanecarboxylate is provided by chemistry reported by Alexandre and Huet and co-workers.[33] The enzymatic acetylation of the *cis*-cyclobutane-1,2-dimethanol **14** (readily prepared from **7**) takes place with remarkable efficiency and selectivity to afford **15** in 99% yield and >99.9% ee in less than 14 h at −2 °C. The 1-acetoxymethyl-2-*d*-cyclobutane ((1*S*,2*R*)-**18**) formed in four steps from the meso dialcohol by way of **16** and **17** as outlined below (Scheme 12) could be converted easily to the corresponding stereoisomer of 1(*E*)-*d*-ethenyl-2-*d*-cyclobutane, *c*-(1*S*,2*R*)-**1**.

SCHEME 12. (1*S*,2*R*)-1-Acetoxymethyl-2-*d*-cyclobutane



SCHEME 13. *t*-(1*S*,2*S*)-1-(*E*)-*d*-Ethenyl-2-*d*-cyclobutane



These various routes to stereochemically well-defined 2-*d*-labeled benzyl cyclobutanecarboxylic esters are serviceable but are still not perfected. Additional work toward better procedures for making such synthetic intermediates is in progress.

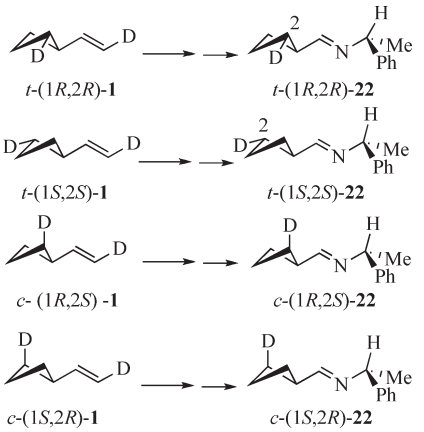
(1*S*,2*S*)-1(*E*)-*d*-Ethenyl-2-*d*-cyclobutane, the stereoisomer here abbreviated as *t*-(1*S*,2*S*)-**1**, could be made from the corresponding benzyl 2-*d*-cyclobutanecarboxylate, *t*-(1*S*,2*S*)-**5**, without risking an epimerization at C(1) (Scheme 13). Catalytic hydrogenation followed by a $LiAlH_4$ reduction would lead to the hydroxymethylcyclobutane (**19**), which could easily give aldehyde **20** without epimerization through an oxidation by a oxoammonium tetrafluoroborate salt.[34] The aldehyde could be transformed under mild conditions to the ethynylcyclobutane **21** by reaction with (diazomethyl)-phosphonic acid diethyl ester.[35] The ethynyl function could be reduced with DIBAL, followed by D_2O,[36] to give the *trans*-(1*S*,2*S*) stereoisomer of the vinylcyclobutane, *t*-(1*S*,2*S*)-**1** (Scheme 13).

Quantitative Analyses of the Four Isomers of 1(*E*)-*d*-Ethenyl-2-*d*-cyclobutane

The cis and trans stereoisomers of 1(*E*)-*d*-ethenyl-2-*d*-cyclobutane are diasteriomers, while the two cis and the two trans structures are pairs of enantiomers. The enantiomeric pairs cannot be distinguished through NMR spectroscopy without being modified effectively through some chirotopical influence, such as a chiral solvent or a chiral lanthanide shift reagent or a chiral liquid crystal environment. After numerous attempts with such options proved inadequate for our objectives a simple structural alteration to achieve the necessary adjustment was employed successfully.

Oxidation of d_2-vinylcyclobutanes with OsO_4, $NaIO_4$, and 2,6-lutidine in dioxane/H_2O would give the corresponding aldehydes without epimerization at C(1).[37] Condensation of the aldehyde or mixture of aldehydes with (*R*)-(+)-α-methylbenzylamine gives an imine, or mixture of imines (Scheme 14). All four possible diastereomers formed were observable as distinct absorptions by $^{13}C\{^1H,^2H\}$ NMR spectroscopy.[38]

SCHEME 14. Conversion of 1-(*E*)-*d*-Ethenyl-2-*d*-cyclobutanes to Stereochemically Related (*R*)-(+)-α-Methylbenzyl Imines



The pseudoequatorial deuterium substituents of trans isomers perturb the ^{13}C(2) and ^{13}C(4) chemical shifts upfield less than the pseudoaxial deuterium substituents of cis isomers, by 23 ppb. The chirotopical influence of the (*R*)-(+)-α-methylbenzyl imine function contributes more shielding of *pro-R* ^{13}C(2) and ^{13}C(4) atoms than for *pro-S* ^{13}C(2) and ^{13}C(4) carbons; the larger upfield shift advantage of *pro-R* over *pro-S* carbons is 52 ppb. Thus, the four isomers viewed by ^{13}C{^{1}H,^{2}H} NMR in the window including ^{13}C(2)DH resonances of the derived imines are distinctively spaced at relative chemical shifts of 0, 23, 52, and 75 ppb. Spectra of two mixtures of the four isomeric imines are reproduced in Figure 1. This analytical tactic allows one to quantify the relative proportions of all four diastereomeric imines obtained from the thermal product mixture collected from a kinetic run.[38]

Quantitative Analyses of the Four Isomers of 3,4-d_2-Cyclohexene

The mixture of cyclohexenes generated in thermal reactions of d_2-**1** isomers will have contributions from seven different isotopomers (d_2-**2**; Scheme 5) and an analytical method for gaining quantitative assessments for all four 3,4-d_2-cyclohexenes in the presence of the three 3,6-d_2-**2** stereoisomers requires some unusual tactics. The best options were seen to be ones concentrating on C(4)HD structural features, for complications from C(3)HD contributions to NMR spectral data reflecting a composite of seven d_2-**2** compounds were anticipated to be hard to deconvolute. The trick required was to find some means to observe the isomeric signature of all four 3,4-d_2-**2** isomers at C(4)HD under conditions disclosing the stereochemical details of a C(4)HD−C(3)DH pair in each discrete 3,4-d_2-**2** isomer. The objective was attained through a structural modification of the cyclohexenes and then by exercising ^{13}C{^{1}H,^{2}H} NMR spectroscopy.

A given mixture of d_2-cyclohexenes (d_2-**2**; Scheme 5) may be converted into a mixture of d_2-labeled cyclohexene oxides (d_2-**23**) through an epoxidation, and then a highly asymmetric hydrolysis[39] affords a mixture of (1*R*,2*R*)-d_2-cyclohexane-1,2-diols (d_2-**24**). The mixture may then be condensed with 2,3-butanedione and trimethyl orthoformate to provide conformationally defined dispositions of 3,4-d_2- and 3,6-d_2-derivatives (d_2-**25**; Scheme 15).[40]

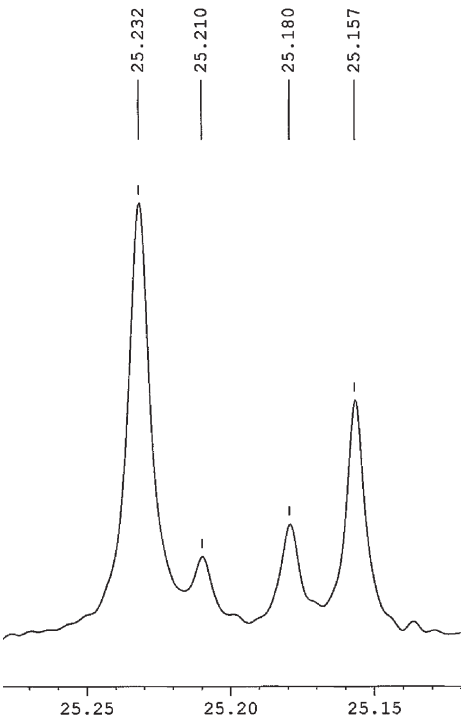
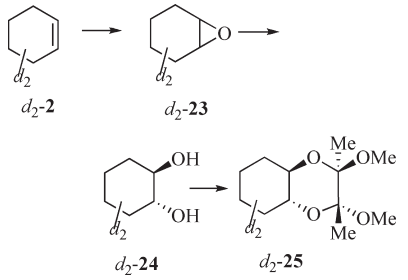


FIGURE 1. ^{13}C{^{1}H,^{2}H} NMR absorptions recorded for a mixture of the four diastereomers of d_2-**22** (Scheme 14) rich in *t*-(1*S*,2*S*)-**22**, in the upfield C(2)HD region. The absorptions (left to right) are for *t*-(1*S*,2*S*)-**22**, *c*-(1*S*,2*R*)-**22**, *t*-(1*R*,2*R*)-**22**, and *c*-(1*R*,2*S*)-**22** in the proportions 54, 8, 12, and 26%.[38]

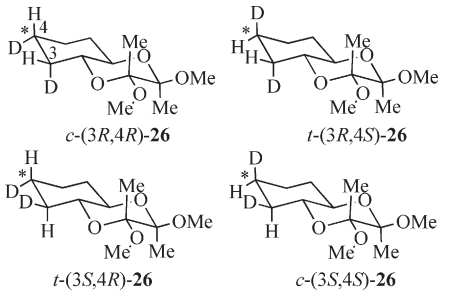
SCHEME 15. 3,4- and 3,6-d_2-Labeled (1*R*,2*R*)-Cyclohexane-1,2-diols and Conversions to 3,4- and 3,6-d_2-Labeled Octahydro-2,3-dimethoxy-2,3-dimethyl-1,4-benzodioxins



From all seven d_2-**2** isomeric cyclohexene products a mixture of eight d_2-labeled diacetals would be obtained, four having 3,4-d_2-**26** structures (Scheme 16) as well as four 3,6-d_2-**26** isomers. But only the 3,4-d_2-labeled isotopomers would be registered in the ^{13}C(4)HD{^{1}H,^{2}H} NMR absorption spectrum window recorded for the eight component mixture (Scheme 16).[41]

The ^{13}C(4) chemical shifts in unlabeled diacetals are distinct from those assigned to ^{13}C(3) nuclei, and each isomeric version of the four diacetals reflects two determinants of deuterium perturbations of the ^{13}C(HD) chemical shifts. When the deuterium is in a axial position the $^{1}\Delta$ upfield perturbation is 54 ppb larger than for the shift induced from a equatorial deuterium at C(4). In the C(4)HD−C(3)HD vicinal combination the $^{2}\Delta$ upfield deuterium perturbation on the ^{13}C(4) chemical shift is larger for the equatorial D than for the axial D, by 11 ppb. Thus, the

SCHEME 16. Four Stereoisomeric 3,4-d_2-26 Diacetals Prepared from 3,4-d_2-Labeled Cyclohexenes



progression of relative chemical shifts for $^{13}C\{^1H,^2H\}$ in the $^{13}C(4)HD$ region is 0, 11, 54, and 65 ppb, corresponding to the sequence of isomers *t*-(3*R*,4*S*)-**26**, *c*-(3*S*,4*S*)-**26**, *c*-(3*R*,4*R*)-**26**, and *t*-(3*S*,4*R*)-**26**. A window of the $^{13}C(4)\{^1H,^2H\}$ NMR spectrum from δ 23.85 to 23.7 ppm is shown in Figure 2.

Perspective, Conclusions, and Prospective

This Perspective recounts in outline form developments over the past 50 years relevant to the thermal chemistry of vinylcyclopropanes and vinylcyclobutanes. The mechanistic uncertainties along the way have been largely resolved thanks to experimental work providing information on heats of formation, activation energies, and reaction stereochemical details and to theory-based contributions defining potential energy surfaces and reaction dynamic trajectories. The reactions involve thermal stereomutations and [1,3] carbon sigmatropic shifts; vinylcyclobutane and substituted vinylcyclobutanes also give fragmentation products.

Both vinylcyclopropanes and vinylcyclobutanes furnished with methyl, phenyl, cyano, and deuterium substituents exhibit reaction stereochemical outcomes that make plain key mechanistic insights. The reactions are not governed by theory based on the concept of the conservation of orbital symmetry. The theory justifiably affirms that *orbital symmetry is conserved in concerted reactions* and the reactions displayed by vinylcyclopropanes and vinylcyclobutanes are not concerted. They take place through interventions of short-lived conformationally flexible diradical intermediates. The patterns of stereochemical preferences uncovered for specific substituted vinylcyclopropanes and vinylcyclobutanes are sensitive to the substituents and to the stereochemistry of reactants. The substituents (larger than deuterium) influence reaction paths leading on to the transition structure space and the conformational adjustments in the diradical space, or caldera region, influence the preferences for one over another exit channel.[42] When different diastereomeric products reached by [1,3] carbon shifts are options, the more thermodynamically stable choices are favored.

The paths for vinylcyclopropane-to-cyclopentene isomerizations when only deuterium-labeled reactants are followed provided a strong basis for detailed computational investigations and dynamic calculations.[14−17] The experimental and theory-based contributions meshed wonderfully, and the contending mechanistic perceptions of a few years ago simply coalesced, providing a well-supported consensus.

The stereochemical paths for thermal reactions available to the parent vinylcyclobutane structure, were it adorned

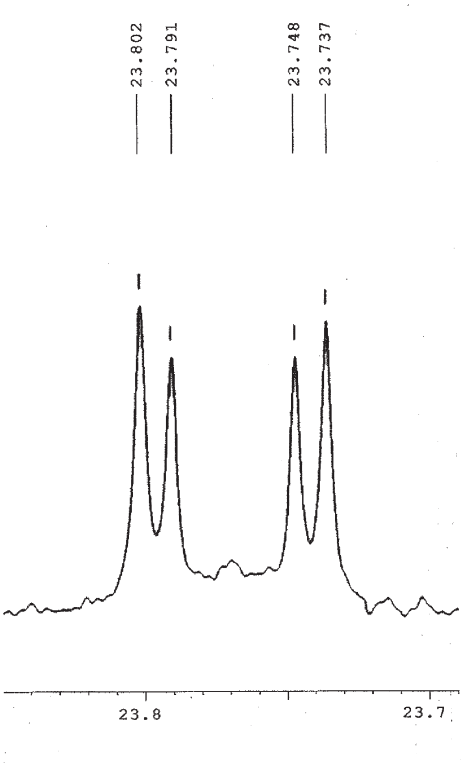


FIGURE 2. $^{13}C\{^1H,^2H\}$ NMR absorptions recorded for a mixture of the four stereoisomers of *3,4-d_2*-**26** (Scheme 16).[41]

with suitable stereochemically well placed deuterium labels, would define the details of vinylcyclobutane stereomutations, [1,3] carbon shifts leading to cyclohexenes, and fragmentations. Were a specific d_2-labeled vinylcyclobutane stereoisomer such as *t*-(1*S*,2*S*)-**1** synthesized and then thermally reacted to give time-dependent mixtures of the 16 structures isolated and separated and subjected to quantitative analyses, and stereochemical details of the reactions could be uncovered.

That venturesome quest is still a work in progress; it might be viewed as a quixotic aspiration, an unreachable ideal, an aspiration without much regard to practicality. Nevertheless, it is being pursued. The overall strategy of the projected work and some of the synthetic sequences and analytical methods developed to date have been outlined. Current retrospective and prospective views lead directly to optimistic prospective anticipations. With time and good fortune, the mechanistic questions raised by the thermal chemistry of vinylcyclobutane will be answered. When the results are in, a compatible conjoining of experimental stereochemical data for stereomutations and [1,3] carbon shifts with theory-based models of multidimensional reaction surfaces and reaction dynamics calculated trajectories could well be attained. May such an outcome be achieved as it has been realized for the vinylcyclopropane system!

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