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Fate of the Intermediate Diradicals in the Caldera: Stereochemistry of Thermal Stereomutations, (2 + 2) Cycloreversions, and (2 + 4) Ring-Enlargements of *cis*- and *trans*-1-Cyano-2-(*E* and *Z*)-propenyl-*cis*-3,4-dideuteriocyclobutanes

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Abstract: This paper addresses the decades-old problem of gaining a measure of intellectual control over the fate of the diradical intermediate in not-obviously-concerted thermal rearrangements. It focuses mainly on the stereochemistry of the thermal rearrangement of *cis*- and *trans*-1-cyano-2-*trans*-propenylcyclobutane to the related ring-enlarged products, 4-cyano-3-methylcyclohexenes. The complete stereochemical profile is revealed by the incorporation of a pair of cis deuterons to serve as a stereochemical lighthouse. The striking result (besides providing a further example of the inapplicability of the orbital symmetry rules of Woodward and Hoffmann to not-obviously-concerted reactions) is the predominance of the *same* stereoisomer regardless whether starting from the cis or trans educt. This preference is rationalized by a simple conceptual scheme based on two premises of the behavior of the diradical as intermediate: removal of the diradical from the caldera of rotationally labile conformations occurs whenever the two radical centers come within bonding distance in an appropriate orientation of orbitals; relative internal rotational rates are in the order, cyanomethyl faster than methallyl, faster than internal rotation about the backbone.

Introduction

The class of “diradical” thermal reorganizations is divided into concerted and not-obviously-concerted subclasses on the basis of the criterion of energy of concert. The former strictly obey the Woodward−Hoffmann rules of orbital symmetry and follow stereochemical paths under full intellectual control. Enthalpies of activation in the second class are under modest intellectual control, but stereochemistry is anything but. Most of the studies in the second class have involved cyclopropanes and cyclobutanes, the strain energies of which bring the reactions into a manageable range of temperatures. This work is no exception and is concerned with the stereochemistry of three modes of reaction of a suitably substituted cyclobutane.

Cyclobutanes undergo a variety of purely thermal reactions, the rates of which are influenced almost exclusively by temperature and pressure alone (“no-mechanism”, “not-obviously-concerted” thermal reorganizations). Their study has been an exemplar of the productive interaction of mechanistic organic chemists, earlier with statistical kineticists[1] and later with calculational organic chemists.[2]

From the first studies of unlabeled cyclobutane, which revealed the single exit channel of fragmentation [(2 + 2) cycloreversion] to two molecules of ethylene, through studies of labeled derivatives to reveal stereomutation, and finally the introduction of vinyl groups to add ring-enlargement, the number of exit channels brought under observation has increased dramatically. These developments may be followed in a sequence of references.[3] Coupled with comparable developments in cyclopropanes, these works have intensified an awareness of the rudimentary level of our intellectual control over the distribution and stereochemistry of products in multichanneled, not-obviously-concerted thermal reorganizations. Meanwhile calculational control has advanced rapidly in parallel with extraordinary advances in computer power.

About twenty years ago, we began to examine the systems *cis*- and *trans*-1-cyano-2-(*cis*-propenyl)cyclobutane (**1** and **2**) and *cis*- and *trans*-1-cyano-2-(*trans*-propenyl)cyclobutane (**5** and

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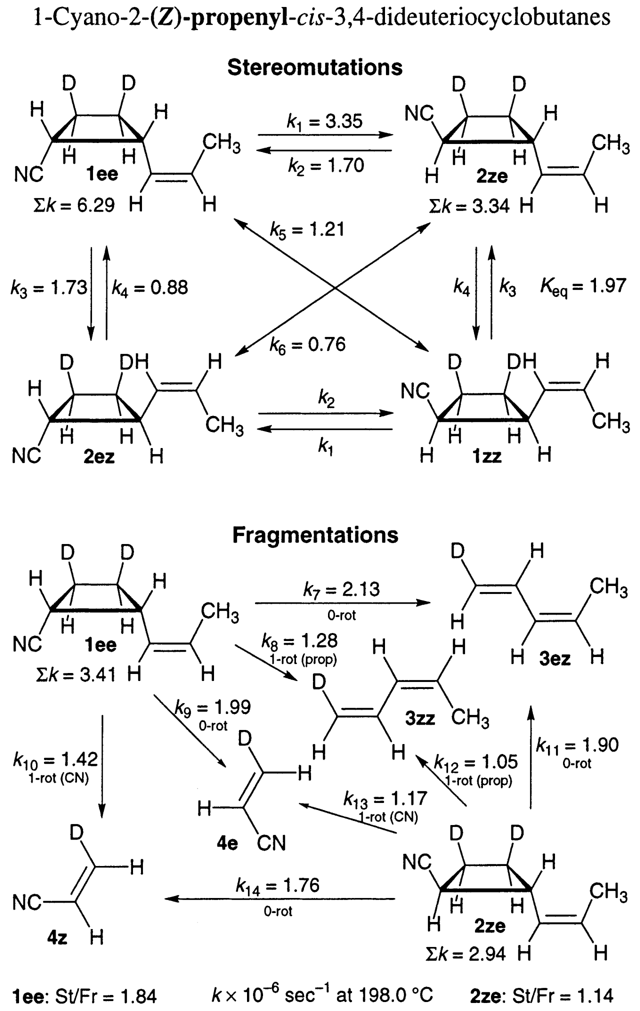


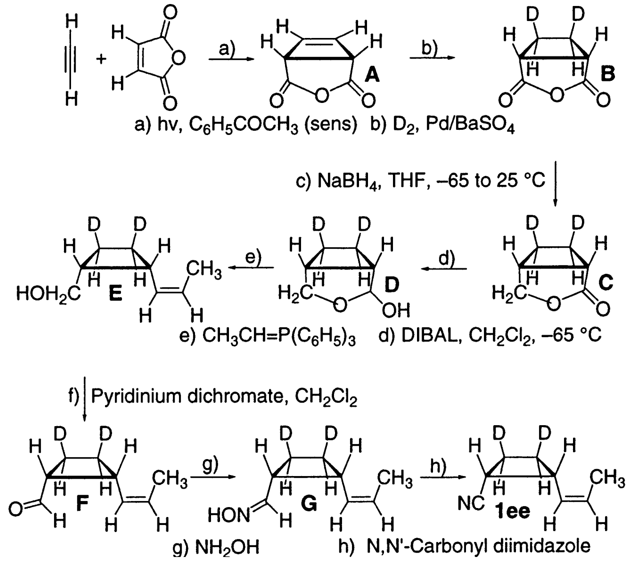
Figure 1. Specific rate constants at 198 °C for stereomutation and fragmentation of **1** and **2** (10^{-6} s^{-1}). Designations **e** and **z** refer to the relation of cyano (first) and *cis*-propenyl (second) to the pair of cis deuterons as reference.

6),[4] in an extension of the work of Sachdev on 1-cyano-2-isopropenylcyclopropane[5] and that of Mastrocola on 1-cyano-2-vinylcyclobutane.[6]

To render visible all internal rotational possibilities, first, optical activity with disappointing results, and later, two cis deuterium atoms as the chiral element have been employed (transformation "of interrelations among enantiomers into interrelations among diastereomers"). Although deuterium has long been used as a probe of the stereochemistry of fragmentation,[7] it has not been used in this way as a probe for stereomutation or ring-enlargement.[8]

Reactions of the (*Z*)-propenyl system are limited to stereomutation and to fragmentation to piperylene (**3**) and acrylonitrile (**4**), ring-enlargement being thwarted by steric inhibition of the generation of the apposite allyl radical in the necessarily *cis*-configuration required for generation of a strain-free cyclohexene ring (Figure 1). The (*E*)-propenyl system additionally may undergo ring-enlargement to the 4-cyano-3-methylcyclohexenes, **7** and **8** of Figure 2.

Scheme 1



Structure of Educts and Products. Although this section is presented in considerable detail because the structure of the cyclobutanes is critically important to the reliability of the conclusions, a trusting reader may pass over it and proceed directly to the Thermal Reorganizations section. The preparation of *cis*-1-cyano-2-(*cis*-propenyl)-3,4-dideuteriocyclobutane, **1ee**, is accomplished by the sequence of reactions in Scheme 1 (experimental details are given only for the dideuterium compounds, although identical procedures were first developed for the nondeuterated compounds). Preparation of the corresponding *trans*-1-cyano-2-(*cis*-propenyl)-3,4-dideuteriocyclobutane, **2ze**, was effected by base-catalyzed equilibration of **1ee**. Conversion of the *cis*-propenyl group in **1ee** into its corresponding *trans*-propenyl isomer **5ee** was accomplished photochemically. A fourth isomer, **6ze**, was prepared from **5ee** by base-catalyzed equilibration. As was to be expected, the trans isomers, **2ze** and **6ze**, were favored at equilibrium by a factor of ~3 (Figure 3).

Identification of H-1, H-2, H-7, H-8, and H-9 in the ^{1}H NMR spectra of all four stereoisomers follows in a straightforward manner from chemical shifts, integrated areas, coupling patterns, and decoupling experiments. Identification of the cis and trans configuration of the propenyl groups is based on the coupling constants of H-7 and H-8: ~10 Hz for **1**, **1ee**, **2**, and **2ze**; ~16 Hz for **5**, **5ee**, **6**, and **6ze**. Identification of the remaining hydrogen atoms and assignments of stereochemistry are based on lanthanide induced shifts (LIS) with reagent, Eu(fod)$_3$.[9] We find relative bound shifts, as extensively developed independently by Davis et al.,[10] in practice more convenient to use than absolute bound shifts.[11]

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(4) Of the several advantages offered by the cyano group—acidifying effect, LIS-friendliness—not the least is its low steric value: Vögtle, F.; Neumann, P.; Zuber, M. *Chem. Ber.* **1972**, *105*, 2955–2962.

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(7) See for example: Srinivasan, R.; Hsu, J. C. N. *J. Chem. Soc., Chem. Commun.* **1972**, 1213–1214. Wang, Y.-s.; Chickos, J. S. *J. Org. Chem.* **1987**, *52*, 4776–4781.

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(9) Tris(1,1,1,2,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)europium.

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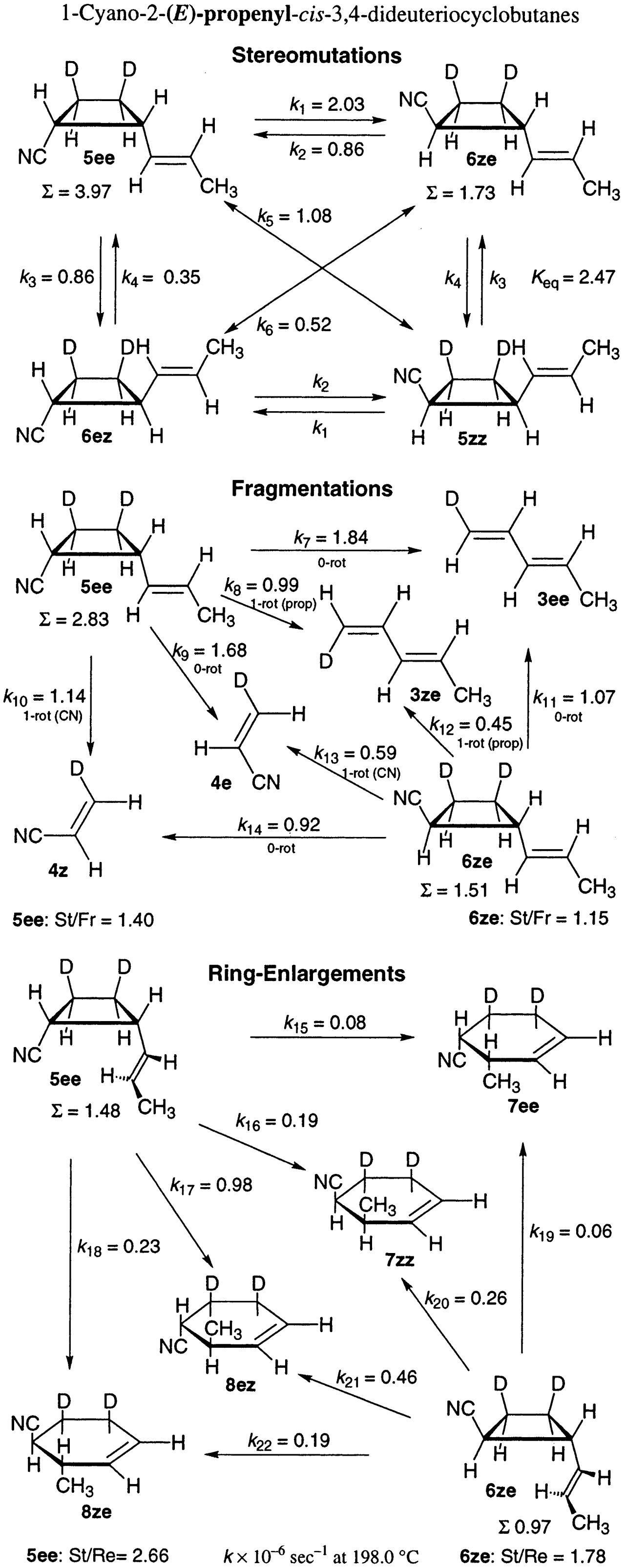
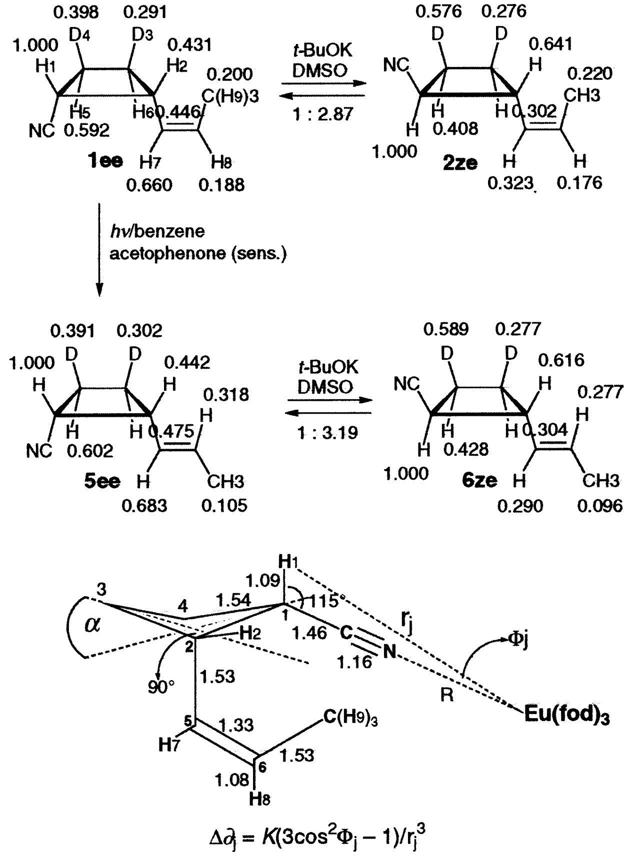


Figure 2. Specific rate constants at 198 °C for stereomutation, fragmentation, and ring-enlargement of **5** and **6** (10^{-6} s^{-1}). Designations **e** and **z** refer to the relation of cyano (first) and *trans*-propenyl (second) to the pair of cis deuterons as reference.



$$\Delta\delta_j = K(3\cos^2\Phi_j - 1)/r_j^3$$

Figure 3. Interactions among the four cyanopropenylcyclobutanes in this work. Relative responses in chemical shifts to the lanthanide shift reagent, Eu(fod)$_3$, (H-1 = 1.000) of the hydrogen atoms in the nondeuterated compounds **1**, **2**, **5**, and **6** (see also Table 1) are indicated. At the bottom is drawn the average geometry assumed for the nitrile−europium coordinate bond and the parameters in the McConnell−Robertson equation governing pseudocontact shifts (distances in Å).

Chemical shifts of all hydrogen atoms in compounds **1**, **2**, **5**, and **6** were recorded at 11, incrementally increased concentrations of the shift reagent. The data were plotted as the differences in chemical shifts of H-1 through H-8 against H-9, which was well separated in all the spectra. Linear regression afforded slopes that define the relative response of each type of hydrogen atom to the shift reagent. The intercepts at zero concentration of shift reagent are differences between the conventional chemical shifts and that of H-9 and provide a source of the few chemical shifts that are otherwise obscured by unresolved overlaps. These latter values are recorded in italics in Table 1. In the next step, the relative response factors vis-à-vis H-9 were normalized against H-1, the most responsive of the hydrogen atoms, being set equal to 1.000. These "experimental" factors, Δ_{ex}, are given in both Figure 3 and Table 1.

As might be expected intuitively, the hydrogen atoms next closest to the coordinating cyano group after H-1 all show large response factors ranging from 0.576 (H-4 in **2ze**) to 0.683 (H-7 in **5ee**). The stereochemical relation of the cyano and propenyl groups is indicated not only by the response factors for H-7 (larger, 0.660 and 0.683, in the cis compounds, **1ee** and **5ee**, respectively; smaller, 0.323 and 0.290, in the trans compounds, **2ze** and **6ze**, respectively) but also from the response factors for H-2 (smaller, 0.431 and 0.442, in **1ee** and **5ee**, respectively; larger, 0.641 and 0.616, in **2ze** and **6ze**, respectively).

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Table 1. NMR Chemical Shifts and Lanthanide Induced Shifts ($Eu(fod)_3$) in $CDCl_3$ of Cyanopropenyl Cyclobutanes

		1ee	**1**	**2ze**	**2**	**5ee**	**5**	**6ze**	**6**
H-1	δ^a	3.27	3.29	2.77	2.77	3.22	3.24	2.72	2.76
	$\Delta_{ex}{}^b$	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	$\Delta_{cl}{}^c$		1.000		1.000		1.000		1.000
H-2	δ	3.49	3.51	3.55	3.56	3.16	3.17	3.14	3.18
	Δ_{ex}	0.424	0.431	0.643	0.641	0.440	0.442	0.618	0.616
	Δ_{cl}		0.410		0.605		0.416		0.603
H-3	δ		*2.30*[d]		*2.19*		*2.21*		*2.10*
	Δ_{ex}		0.291		0.276		0.302		0.277
	Δ_{cl}		0.306		0.278		0.309		0.278
H-4	δ		*2.34*		*2.25*		*2.32*		*2.19*
	Δ_{ex}		0.398		0.576		0.391		0.589
	Δ_{cl}		0.410		0.605		0.416		0.603
H-5	δ	2.22	*2.24*	2.20	*2.23*	2.16	2.17	2.12	*2.16*
	Δ_{ex}	0.578	0.592	0.413	0.408	0.592	0.602	0.430	0.428
	Δ_{cl}		0.604		0.427		0.622		0.423
H-6	δ	2.03	2.07	1.84	1.86	*2.11*	2.13	1.83	1.87
	Δ_{ex}	0.438	0.446	0.305	0.302	0.466	0.475	0.308	0.304
	Δ_{cl}		0.445		0.298		0.470		0.293
H-7	δ	5.72	5.72	5.36	5.36	5.71	5.71	5.44	5.44
	Δ_{ex}	0.661	0.660	0.325	0.323	0.664	0.683	0.279	0.290
	Δ_{cl}		0.650		0.310		0.671		0.304
H-8	δ	5.61	5.62	5.50	5.49	5.57	5.57	5.54	5.54
	Δ_{ex}	0.188	0.188	0.175	0.176	0.315	0.318	0.248	0.277
	Δ_{cl}		0.188		0.171		0.306		0.277
H-9	δ	1.59	1.60	1.66	1.66	1.72	1.73	1.66	1.67
	Δ_{ex}	0.198	0.200	0.221	0.220	0.095	0.105	0.103	0.096
	Δ_{cl}		0.193		0.227		0.109		0.096

[a] Chemical shifts in parts per million with reference to tetramethylsilane. [b] Sensitivity of H−j to LIS relative to H-1 = 1.000. [c] In those instances where the chemical shift could not be extracted from the normal NMR spectrum, a value in italics was estimated by extrapolation of the LIS data to zero concentration of the shift reagent (see Figure 3).

Further analysis involves a quantitative comparison of the experimental values theoretically calculated by the McConnell-Robertson equation (eq 1),[12] which evaluates the pseudocontact LIS of hydrogen atoms in terms of two variables, Φ_j, the angle between the line connecting H−j with the principle magnetic axis of the substrate−metal complex, and r_j, the distance between H−j and the lanthanide atom. The lanthanide is generally assumed to be collinear with the C−CN group and is here taken to have a nitrogen−lanthanide separation R of 2.5 Å (see Figure 3).[10d,11] For each H−j, values of Φ_j and r_j are estimated from Dreiding-stereochemical models in which the four-atom system, H-2, C-2, C-4, and C-6, is maintained coplanar; that is, C−H-2 and the olefinic group are eclipsed. Cyclobutane being nonplanar, each of the four stereoisomers may exist in two conformations. The angle, α, is assumed equal to 20°. The resulting absolute values obtained by application of eq 1, $\Delta\delta_j$, are then converted to values relative to H-1, $\Delta_{j(calc)}$, by eq 2. When these values are plotted against the corresponding

$$\Delta\delta_j = K(3\cos^2\Phi_j - 1)/(r_j)^3 \tag{1}$$

$$\Delta_{j(calc)} = [(3\cos^2\Phi_j - 1)/(r_j)^3]/[(3\cos^2\Phi_1 - 1)/(r_1)^3] \tag{2}$$

$$\Delta_j{}' = \mathbf{a}[\Delta_{j(calc/conformation\ \alpha)}] + \mathbf{b}[\Delta_{j(calc/conformation\ \beta)}] + \mathbf{c} \tag{3}$$

experimental values, Δ_{ex}, all but two of the hydrogen atoms fall on a straight line. The first exception is H-1, which appears too responsive. This discrepancy is likely due to a contact shift superimposed on the pseudocontact shift calculated by the McConnell−Robertson equation. As a consequence, H-1 is not included in the subsequent calculation. The second discrepancy involves H-3 and arises from the existence of two conformations of the cyclobutane ring. Experimental values, Δ_j, are therefore compared to an optimized combination of the calculated theoretical values. This combination is made by the linear regression of eq 3, H-1 being omitted. The results are shown in Table 1, while values of $\Delta_j{}'$ are given in Table 2.

Table 2. Correlations in the *cis*-Propenyl Compounds, 1 and 2, and in the *trans*-Propenyl Compounds, 5 and 6, of Calculated Values of LIS Response Factors of the Pairs of Conformations with Experimental Values

correlation[a]	**a**[b]	**b**[b]	**c**[b]	σ	σ_a	σ_b	r[c]
eqax1/axeq1[d] vs **1**[e]	0.188	0.578	0.010	0.014	0.003	0.003	**0.997**
eqax1/axeq1 vs **2**	0.714	−0.256	0.150	0.136	0.331	0.311	0.654
eqeq2/axax2 vs **2**	0.795	−0.019	0.005	0.022	0.008	0.007	**0.993**
eqeq2/axax2 vs **1**	0.213	0.257	0.177	0.150	0.391	0.345	0.587
eqax5/axeq5 vs **5**	0.142	0.662	−0.002	0.019	0.005	0.005	**0.996**
eqax5/axeq5 vs **6**	0.545	−0.060	0.115	0.148	0.308	0.284	0.623
eqeq6/axax6 vs **6**	0.784	0.003	−0.004	0.011	0.002	0.002	**0.998**
eqeq6/axax6 vs **5**	0.344	0.146	0.184	0.159	0.385	0.386	0.585

[a] Correlation by eq 3 ($\Delta_j{}' = \mathbf{a}(\Delta_{j(calc)/conformation\ \alpha}) + \mathbf{b}(\Delta_{j(calc)/conformation\ \beta}) + \mathbf{c}$). [b] Best fit values by least squares linear regression. [c] The correlation coefficient, *r*. [d] Calculated values, $\Delta_{j(calc)}$. [e] Experimental values, Δ_{exp} (from Table 1).

Examination of Table 2 reveals far higher correlation coefficients for the assigned structures than for their alternatives. Compare, for example, **eqeq2/axax2** versus **2** and versus **1**. Further to be noted is the essentially exclusive favoring of the equatorial−equatorial conformation over the axial−axial in compounds **2** and **6**: **a** = 0.795 and **b** = −0.019, and **a** = 0.784 and **b** = 0.003, respectively. It seems justified also to conclude that both conformations contribute to the equilibrium structure of **1** and **5**, for which **a** = 0.188 and **b** = 0.578, and **a** = 0.142 and **b** = 0.662, respectively.[13] The advantage in having the propenyl group equatorial is correspondingly 75% in *cis*-propenyl and 82% in *trans*-propenyl. This bias is fully consistent with the narrower profile of the cyano group.

Thermal Reorganizations. The kinetics of the various thermal transformations were brought to light by heating samples in the gas phase in sealed ampules. The kinetics were determined at four temperatures, 192.0, 198.0, 207.2, and 217.8 °C. Analyses of products were by GC, the relative areas being converted into relative concentrations by application of independently determined response factors. Samples of undeuterated **1** and **2** were used to determine specific rate constants for stereomutation and fragmentation to acrylonitrile (**4**) and *cis*-piperylene (**3**). The ratio of these latter two rates should have been equal, but was generally ~0.8, presumably owing to some polymerization of acrylonitrile that we were unable to eliminate. In the final calculations of specific rate constants, those for formation of acrylonitrile ($k_9 + k_{10}$) were adjusted to equal the values for *cis*-piperylene ($k_7 + k_8$); that is, the ratio was assumed to be 1.00 (Figures 1 and 2). Otherwise recoveries were 100% within experimental uncertainties. The double rotational processes, for example of **1ee** to **1zz**, cannot be distinguished explicitly from two-step processes such as **1ee** to either **2ze** or **2ez**, then to **1zz**. However, if the two direct interconversions (k_5 and k_6 of Figure 1) were omitted from the kinetic model, agreement between calculated values of ($1 - e^{-kt}$) and

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(12) Seux, R.; Morel, G.; Foucand, A. *Tetrahedron Lett.* **1972**, 1003−1006.

(13) For a successful application to conformational equilibria in some acyclic nitriles, see ref 12a; and in cyanocyclohexane, ref 15.

Table 3. Molar Percent Concentrations of Products from Thermal Reorganizations of **1ee** and **2ze** at 198.0 °C

time[a]	1ee	1zz	2ze	2ez	3ez	3zz	4e	4z	“5ee”[d]
0.0[b,c]	97.42 ± 0.76	1.46 ± 0.16	0.42 ± 0.32	0.21 ± 0.32	0.33 ± 0.34	0.17 ± 0.21	0.31 ± 0.30	0.20 ± 0.23	0.00 ± 0.08
1.0	94.64	1.89	1.37	0.71	0.91	0.48	0.84	0.54	0.00
2.0	90.81	2.23	2.52	1.35	1.95	1.05	1.80	1.20	0.10
4.0	85.81	2.62	4.30	2.43	2.91	1.69	2.70	1.90	0.23
6.0	78.46	3.55	5.89	3.46	5.12	3.11	4.74	3.49	0.43
8.0	73.08	3.69	8.09	4.09	5.71	3.76	5.37	4.10	0.69
0.0[b,c]	0.66 ± 0.22	0.33 ± 0.20	90.40 ± 0.71	7.93 ± 0.08	0.00 ± 0.29	0.00 ± 0.53	0.00 ± 0.45	0.00 ± 0.36	
3.0	2.42	1.25	84.72	8.21	1.90	0.97	1.75	1.11	
6.0	3.40	1.83	80.41	8.46	3.45	1.93	3.21	2.17	
9.0	4.63	2.60	74.48	8.67	5.62	3.44	5.27	3.79	
12.0	5.20	3.06	69.41	8.74	7.69	5.42	7.41	5.70	

[a] Time in hours. [b] Calculated by linear extrapolation to zero time of the data. [c] Standard deviation by linear least squares regression. [d] Identity supported by GC retention time alone.

Table 4. Calculated Specific Rate Constants at 198.0 °C of Stereomutation and Fragmentation of 1-Cyano-2-(*Z*)-propenyl-*cis*-3,4-dideuteriocyclobutanes, **1ee**, **2ze**, **1zz**, and **2ez** (Figure 1)

stereomutation		fraction	fragmentation	
k_1[a]	3.35 ± 0.42	0.348	k_7	2.13 ± 0.29
k_3	1.73 ± 0.29	0.180	k_8	1.28 ± 0.19
			k_9	1.99 ± 0.28
			k_{10}	1.42 ± 0.18
k_2	1.70 ± 0.15	0.177	k_{11}	1.90 ± 0.23
k_4	0.88 ± 0.07	0.091	k_{12}	1.05 ± 0.31
k_5	1.21 ± 0.18	0.126	k_{13}	1.17 ± 0.23
k_6	0.76 ± 0.05	0.079	k_{14}	1.76 ± 0.22

[a] Specific rate constants in units of 10^{-6} s^{-1}.

experimental concentrations was much poorer than when optimized values for k_5 and k_6 were included. We believe the resulting values of k_5 and k_6 to be the least accurate in this work.

Quantitative analysis by NMR of purified samples of the products from **1ee** and **5ee** allowed dissection of the specific rate constants from the nondeuterated materials into diastereomeric pairs. The ratios of **3ze** to **3ee** are complicated by some subsequent rearrangement of deuterium in an otherwise degenerate 1,5-hydrogen shift (in *cis*-piperylene but not in *trans*-piperylene). The resulting perturbation in chemical shift of the relevant vinyl hydrogen atoms by deuterium appears as shoulders on the peaks of the terminal vinyl hydrogen atoms. Details of the correction for this complication are available in the dissertation of Cheng, as are all other parts of the experimental work.[14] A sample of data from the rearrangements of **1ee** and **2ze** at 198.0 °C is given in Table 3. The complete set of data is available in Cheng's dissertation.[14]

The derived specific rate constants are given in Table 4 and Figure 1. The precision we were able to attain at four temperatures, 192.0, 198.0, 207.2, and 217.8 °C, was insufficient to allow the temperature coefficients to be determined with an accuracy sufficient to warrant dissection of the ratios of the exit channels into differences in enthalpy and entropy. The results, which are not discussed here in detail but are available,[14] are in unexceptional agreement with the values expected of stabilization in cyanomethyl and allyl radicals. Arrhenius parameters for the disappearance of **1ee** are $E_a = 38.1 \pm 1.1$ kcal mol^{-1} and log $A = 12.6 \pm 0.5$, and of **5ee** are $E_a = 38.9 \pm 1.2$ kcal mol^{-1} and log $A = 12.8 \pm 0.5$.

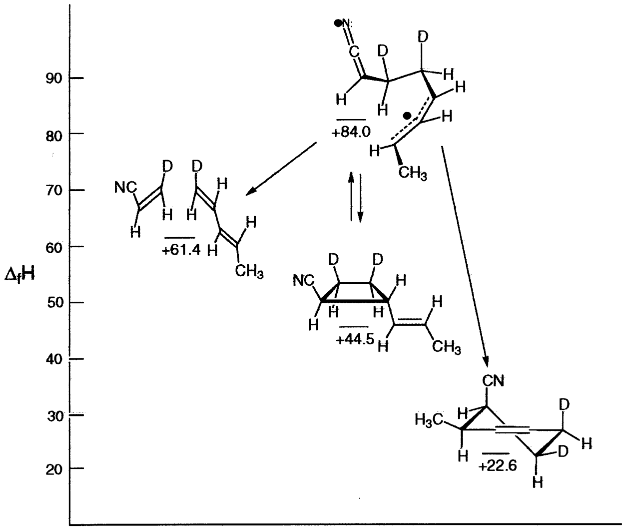

Figure 4. Estimated enthalpies of formation of the cyclobutane educt, products, and diradical transition region for *trans*-1-cyano-2-*trans*-propenylcyclobutane (**6**) in kcal mol^{-1}.

Table 5. Calculated Specific Rate Constants at 198.0 °C of Stereomutation, Fragmentation, and Ring-Enlargement of 1-Cyano-2-(*E*)-propenyl-*cis*-3,4-dideuteriocyclobutanes, **5ee**, **6ze**, **5zz**, and **6ez** (Figure 2)

stereomutation		fraction	fragmentation		ring-enlargement	
k_1[a]	2.03 ± 0.24	0.348	k_7	1.84 ± 0.22	k_{15}	0.08 ± 0.01
k_3	0.86 ± 0.08	0.180	k_8	0.99 ± 0.12	k_{16}	0.19 ± 0.03
			k_9	1.68 ± 0.20	k_{17}	0.98 ± 0.15
			k_{10}	1.14 ± 0.11	k_{18}	0.23 ± 0.01
k_2	0.82 ± 0.04	0.177	k_{11}	1.07 ± 0.21	k_{19}	0.06 ± 0.01
k_4	0.35 ± 0.04	0.091	k_{12}	0.45 ± 0.05	k_{20}	0.26 ± 0.01
k_5	1.08 ± 0.17	0.126	k_{13}	0.59 ± 0.07	k_{21}	0.46 ± 0.04
k_6	0.52 ± 0.04	0.079	k_{14}	0.92 ± 0.13	k_{22}	0.19 ± 0.01

[a] Specific rate constants in units of 10^{-6} s^{-1}.

Ring-enlargement is a third mode among the reactions of **5ee** and **6ze**. The resulting 4-cyano-3-methylcyclohexenes are identified by comparison with samples prepared by the Diels−Alder reaction of acrylonitrile and *trans*-piperylene, a reaction that *cis*-piperylene does not undergo. The structure including stereochemistry of the dideuterium analogues is assured by analysis of the LIS spectra (for details, see Cheng[14]). The kinetics are followed in the same manner as described above. The resulting specific rate constants are given in Table 5 and Figure 2.

Discussion

The three modes of reaction, stereomutation, fragmentation, and ring-enlargement, are initiated by cleavage of the 1,2-bonds, the weakest, to the corresponding conformationally labile

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(14) Cheng, X.-h. Ph.D. Dissertation, Harvard University, 1988; *Diss. Abstr. Int. B* **1990**, *50*, 3472.

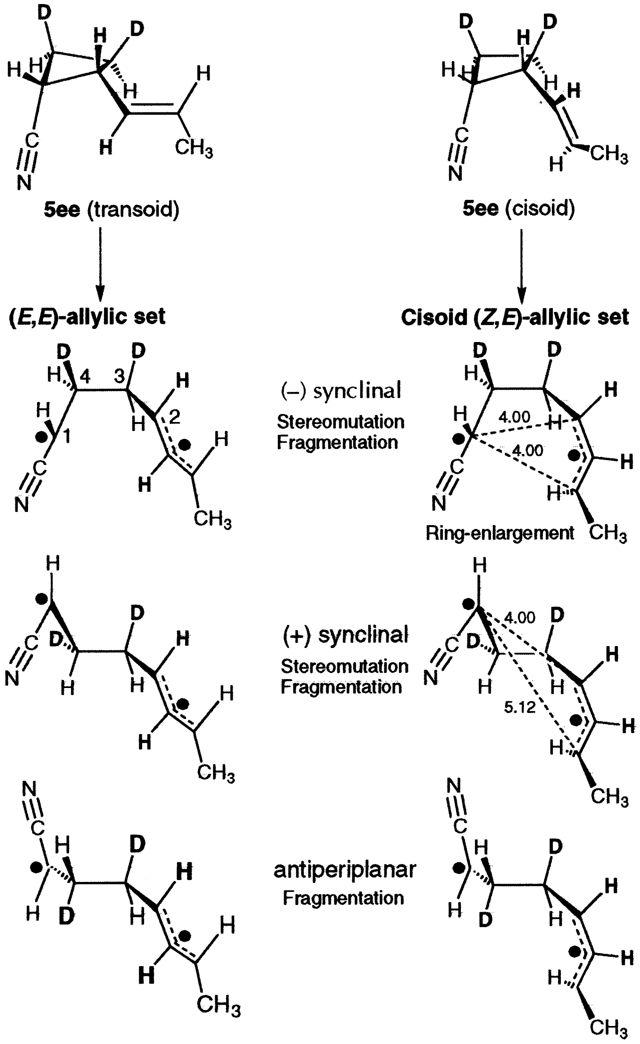
diradicals in the caldera. The thermochemistry among the products (Figure 4) varies markedly.[15−17] The products of fragmentation, acrylonitrile and piperylene, lie ∼23 kcal mol^{-1} below the enthalpy of formation estimated for the generic diradical, while the products of stereomutation have estimated enthalpies of formation ∼40 kcal mol^{-1} below. The cyanomethylcyclohexenes resulting from ring-expansion are the most stable, lying some 61 kcal mol^{-1} below. A glance at Figure 2 shows that these three exit channels comprise 34%, 48%, and 18% of the reaction of **5ee** and 42%, 36%, and 23% of **6ze**, respectively. We conclude that distribution among the three modes is not correlated in any recognizable way to the thermochemistry. Although fragmentation may be favored by entropy, this factor seems also not to dominate the outcome.

Stereomutation and fragmentation comprise 65% and 35%, respectively, of the reaction of **1ee** and 53% and 47%, respectively, of the reaction of **2ze**. The system does not participate in ring-enlargement to a significant degree owing most likely to adverse steric repulsions between the *cis*-methyl group and the ethano link in the necessarily cisoid ("tucked under") conformations required for generation of a *cis*-cyclohexene. In contrast, *cis*- and *trans*-1-methyl-2-*cis*-propenylcyclobutanes have been found first by Jordan[3g] and most recently in full detail by Baldwin and Burrell[3h] to give a small amount of ring-enlargement: 2.8% from the cis isomer and 3.3% from the trans isomer. The failure of the *cis*-propenyl compounds **1ee** and **2ze** may be due to an unfavorable thermochemistry. This factor has been examined by molecular mechanical estimations of the relative steric energies of cisoid and transoid conformations of the proximate, coplanar allylic radicals. On the assumption that the differences in heats of formation of the transition regions parallel the differences among the selected conformations, the *cis*-propenyl group in its cisoid orientation is 3.78 and 2.80 kcal mol^{-1} higher in steric energy than in its transoid orientation in the (*E*,*Z*) and (*Z*,*Z*) diastereomers, respectively. By contrast, the differences in the *trans*-propenyl systems, **5ee** and **6ze**, are 1.08 and 0.98 kcal mol^{-1}, respectively (Table 5).

The calderas of diradicals can be divided into two noninterconvertible subsets differing in configuration of the allylic radical (Scheme 2; illustrated for **5ee** only). One is composed of (*Z*,*E*)-1,3-disubstituted allylic radicals, the other, of (*E*,*E*)-1,3-disubstituted allylic radicals. Thermal interconversion within the caldera between the two sets requires cis−trans isomerization of the allylic radicals and is rendered highly improbable within the lifetime of the caldera by an enthalpy of activation estimated to be ∼16 kcal mol^{-1}.[18] As a consequence, crossing between systems **1**/**2** and **5**/**6** is not observed.[19]

Each of these two subsets is comprised of three conformations staggered about the C-3−C-4 bond and interconnected by rotation about that bond by a barrier presumed to be ∼3 kcal mol^{-1}, the barrier to rotation in butane. Although no direct, observable consequence stems from these three "backbone" conformations, each differs in the modes of exit available to it. The antiperiplanar set may engage only in fragmentation, while the (+) synclinal set may also engage in stereomutation.[20] Ring-enlargement is precluded in the (*E*,*E*) (+) synclinal set by the thermochemical improbability of generating a *trans*-cyclohexene and in the (*Z*,*E*) (+) synclinal set by the longer separation [reducible by internal rotation about the C-3−C-2 bond (vide infra)]. In the (−) synclinal set, the cis conformation can engage in all three modes of exit, while ring-enlargement remains barred to the trans set.

Scheme 2



Stereomutation among the cyclobutanes **1** and **2**, and **5** and **6**, is governed by Onsager's demonstration that (at equilibrium) $k_1 \times k_4 \times k_1 \times k_4 = k_3 \times k_2 \times k_3 \times k_2$, whence $k_1/k_2 = k_3/k_4 = K$, the equilibrium constant, and $k_1/k_3 = k_2/k_4 = R_a$, the relative rotational propensities of cyano versus (*Z*)- and (*E*)-propenyl.[21] In the systems **1**/**2** and **5**/**6**, the equilibrium constants, *K*, have the values 1.97 and 2.47 at 198.0 °C, respectively, corresponding to $\Delta\Delta G = -0.63$ and -0.85 kcal mol^{-1}, respectively. These values are in good agreement with those differences in steric energy between isomers **1** and **2**, and **5**

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(15) Heats of formation of **3**, **4**, cyclobutane, and 3-methylcyclohexene are taken from Pedley, Naylor, and Kirby. Replacement of hydrogen by cyano is estimated following ref 16 in Doering and Wang.

(16) Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd ed; Chapman and Hall: London, 1986.

(17) Doering, W. v. E.; Wang, Y.-h. *J. Am. Chem. Soc.* **1999**, *121*, 10967−10975.

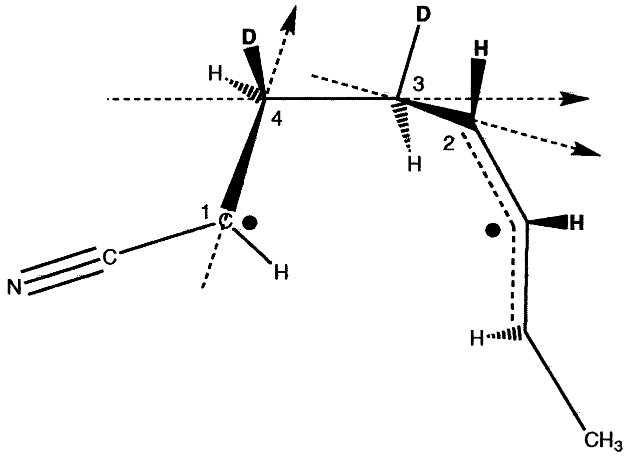
(18) Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483−4489.

(19) The small amount of material questionably suggested to be **5ee** from **1ee** in Table 3 is supported by GC retention time only.

(20) In connection with synclinal (gauche), (−) and (+) designate helicity about the back, C-3−C-4, bond.

(21) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* **1974**, *96*, 1168−1187.

Scheme 3



and **6**, calculated by Allinger's MM2 program for conformations of lowest energy: −0.38 and − 0.57 kcal mol^{-1}, respectively.[22]

The relative rotational propensities, R_a, have the values 1.94 and 2.35 in the systems **1**/**2** and **5**/**6**, respectively. These values are comparable to those found in 1-cyano-2-vinylcyclobutane (1.48),[6] 1-cyano-2-isopropenylcyclopropane (2.20),[5] and 1-cyano-2-*trans*-propenylcyclopropane (2.36)[23] and somewhat larger than the rotational propensity of methyl versus *trans*-propenyl, 1.41, elucidated by Baldwin and Burrell in the system 1-methyl-2-*trans*-propenylcyclobutane.[3h] Although there is no theoretical reason k_1/k_2 should be equal to k_1/k_3, the near identity of their values may simply be coincidental or an indication that the relevant channels of exit from the caldera reflect the differences in the thermochemical stability of the products. The double rotational processes make smaller contributions to stereomutation (zero rotational processes not being measurable).

The "diradical" as a mechanistic conceptual scheme for the not-obviously-concerted reactions consists of a rate-determining entry of the educt into a caldera, rapid conformational changes, and the sudden death of the diradical by covalent bond formation, leading to exit channels that determine the structure and relative proportion of products. Entry into the caldera is achieved by bond-breaking to noninteractive singlet diradicals. This step is considered not to be achieved simply by reaching a higher level stretching vibration that corresponds in energy to that of the incipient diradical. Such an excited vibrational state is still one of the educt and only becomes a state of the diradical when coupled to some further motion such as an internal rotation that destroys any residual bonding between C-1 and C-2. At that point, orbital overlap vanishes and with it rule by Woodward and Hoffmann. An example, shown in Scheme 3, is that from **5ee** in the (−) synclinal conformation. The cyano group has rotated to an extent that the saturated hydrogen atom at C-1 is facing the sp^2 orbital of C-2, which may also be orthogonal to the sp^2 orbital of C-1. The propenyl group has remained in a cis conformation without further rotation. (Its rotation simultaneous with the readjustments required to accommodate the planarity of the allylic radical seems less attractive.) Subsequent rotation of the cyano group in either direction leads to the reestablishment of a bonding relation between C-1 and C-2 and either to the stereoisomeric cyclobutane (**5ee** to **6ze**) or to a nonreaction (**5ee** to **5ee**).

In the diradical conceptual scheme, nonreactions of the cyclobutane involving ring-opening and ring-closing without leaving an observable trace inevitably contribute to the full picture of the exit channels accessible from the caldera and the conformational gyrations of the diradical leading to them. Although not observable as a stereomutation of a cyclobutane, the nonreaction can be observed in principle in the reverse, the cyclodimerization of (*E*)- or (*Z*)-deuterioacrylonitrile and (*E*)- or (*Z*)-deuterio-*cis*-piperylene to the corresponding cyclobutanes. Although such a study has not been made, in the related, more symmetrical system, the thermal dimerization of *cis*-dideuterioacrylonitrile, the two processes involving no internal rotations prior to closure of the intermediate diradicals to the dicyanocyclobutanes amount to 38% of the stereochemical outcome, despite being Woodward−Hoffmann forbidden![3c]

The zero rotational processes become observable, if not in stereomutation, at least in principle in ring-enlargement and fragmentation. The latter mode of reaction might appear to offer a favorable opportunity, but, as can be seen in Figure 5, the desired $k_{0-\mathrm{rot}}$ is not separately observable because it is composed of both k_{10} and k_7, two uncorrelated rate constants each of which also consists of two components, $k_{0-\mathrm{rot}}$ and $k_{\mathrm{Pr-rot}}$, and $k_{0-\mathrm{rot}}$ and $k_{\mathrm{CN-rot}}$, respectively. There is no way of circumventing this limitation, although, as noted previously, relevant insight into all six processes can be obtained from the reverse reaction of cyclodimerization. However, values for ($k_0 - k_2$) and ($k_{\mathrm{CN}} - k_{\mathrm{Pr}}$) can be extracted (Figure 5). These are positive in all instances. We are struck by the preponderance of the individual (as opposed to coupled) products that have involved no rotation prior to cleavage. Thus, of the piperylenes formed from **1ee** and **2ze**, 62% and 64%, respectively, have resulted from no internal rotation prior to cleavage. The comparable values from **5ee** and **6ze** are 65% and 71%, respectively. A similar result is seen in the acrylonitrile half of the fragmentation: **1ee** and **2ze**, 60% and 61%, respectively; **5ee** and **6ze**, 58% and 60%, respectively. Strictly, these values pertain not just to zero rotations but to an even number of rotations generally.

If a statistical model is explored in which the set is restricted to zero, single, and double rotations prior to cleavage, their relative contributions are given by

$$(1 - x)^2 + 2x(1 - x) + x^2$$

where x is the chance of a single rotation, and $(1 - x)$ is the chance of no rotation. In the case of piperylene, the mean of the four values, now construed as the sum of the fractions of zero and double rotations, 0.657, corresponds to a value of $(1 - x) = 0.78$ ($x = 0.22$), whereas with respect to acrylonitrile, the mean value 0.597 corresponds to $(1 - x) = 0.72$ ($x = 0.28$). In this model cyano rotation again appears to be favored over propenyl, but by a small factor of only 1.27.

Ring-enlargements present a further example where application of Woodward−Hoffmann rules leads to discordant predictions of the major products. Both **5ee** and **6ze** lead to **8ez** as the major product, the more so from cis isomer **5ee** by a forbidden process *rs* than from the trans isomer **6ze** by an allowed process *is*. In toto, **6ze** leads to the four possible products in the order **8ez**, allowed-*si* (47%) as the major product, **7zz**, forbidden-*sr* (27%), and **8ze**, allowed-*ar* (20%) in com-

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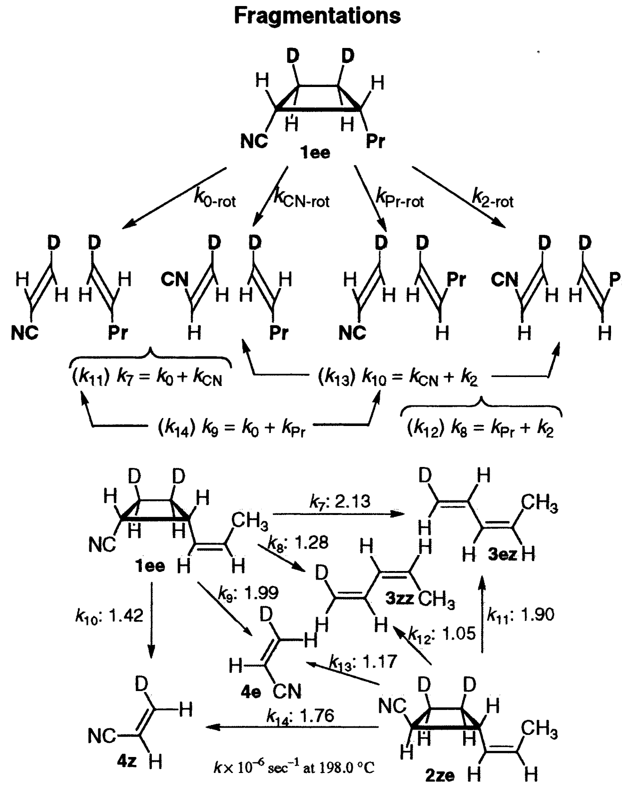
[22] Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8132 (As made available in Cambridge Chem 3D plus 6.0).

[23] Barsa, E. A. Ph.D. Dissertation, Harvard University, 1976; *Diss. Abstr. Int. B* **1977**, *37*, 5077 (pp 99−132).



1ee

$$2(k_0 - k_2) = (k_9 + k_7) - (k_{10} + k_8) = 4.12 - 2.70;\ k_0 - k_2 = 0.71$$

$$2(k_{CN} - k_{Pr}) = (k_{10} + k_7) - (k_9 + k_8) = 3.55 - 3.27;\ k_{CN} - k_{Pr} = 0.14$$

2ze

$$2(k_0 - k_2) = (k_{14} + k_{11}) - (k_{13} + k_{12}) = 3.66 - 2.22;\ k_0 - k_2 = 0.72$$

$$2(k_{CN} - k_{Pr}) = (k_{13} + k_{11}) - (k_{14} + k_{11}) = 3.07 - 2.81;\ k_{CN} - k_{Pr} = 0.13$$

5ee

$$2(k_0 - k_2) = (k_9 + k_7) - (k_{10} + k_8) = 3.52 - 2.13;\ k_0 - k_2 = 0.70$$

$$2(k_{CN} - k_{Pr}) = (k_{10} + k_7) - (k_9 + k_8) = 2.98 - 2.67;\ k_{CN} - k_{Pr} = 0.15$$

6ze

$$2(k_0 - k_2) = (k_{14} + k_{11}) - (k_{13} + k_{12}) = 1.99 - 1.03;\ k_0 - k_2 = 0.48$$

$$2(k_{CN} - k_{Pr}) = (k_{13} + k_{11}) - (k_{14} + k_{12}) = 1.66 - 1.36;\ k_{CN} - k_{Pr} = 0.15$$

Figure 5. Internal rotations involved in the four paths for fragmentation for **1ee**. Their relation to the experimental rate constants are then indicated. At the bottom, the only analytical conclusions give the differences in rate constants (10^{-6} s^{-1} at 198 °C) between the zero and double rotational processes ($k_0 - k_2$) and the cyano and propenyl processes ($k_{CN} - k_{Pr}$) from the educts, **1ee**, **2ze**, **5ee**, and **6ze**.

parable amount, and **7ee**, forbidden-*ai* (6%) as the minor product, while the cis isomer **5ee** leads to **8ez**, forbidden-*sr* (66%), **7zz**, allowed-*si* (13%), **8ze**, forbidden-*ai* (16%), and **7ee**, again the minor product, allowed-*ar* (5%) (see Figure 5). The fact is both educts show much the same distribution of products within likely experimental uncertainties without regard to any *dictat* by orbital symmetry rules of Woodward and Hoffmann.

This disregard is also apparent in the major products of ring-enlargement of optically active *cis-* and *trans*-1-cyano-2-propenylcyclopropane,[23] which closely parallel the cyclobutane results of this paper. More satisfying are the closely similar results obtained by Baldwin and Burrell in their awesome resolution of the system of *cis-* and *trans*-1-methyl-2-propenylcyclobutanes by means of optical activity as the informant.[3h] These are reproduced in Figure 6 in parentheses. The small differences from the cyano results are trivial in comparison to the overall agreement. The indicated compression seems not unreasonable in light of the smaller rotational propensity of methyl and the higher temperature of reaction (275.0 versus 198.0 °C).

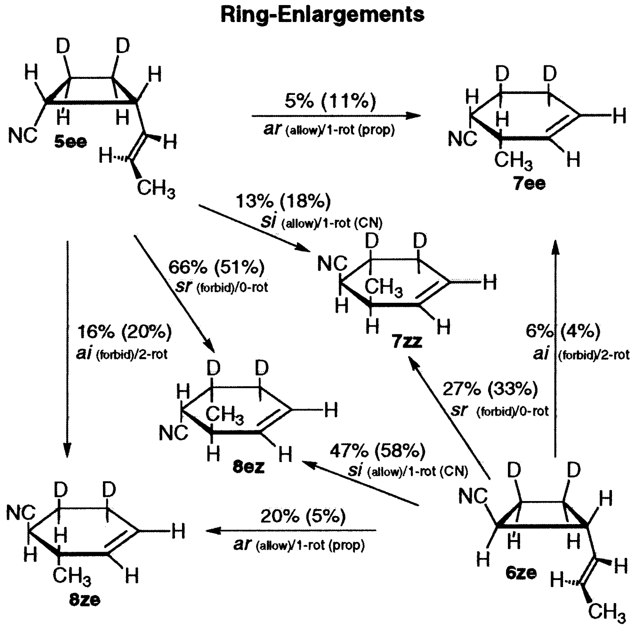


Figure 6. Distribution of products in % from 1-cyano-2-*trans*-propenylcyclobutane (this paper; 198 °C; NC) and 1-methyl-2-*trans*-propenylcyclobutane (Baldwin and Burrell; 275 °C; H_3C in parentheses; D = H).[3h]

Of the three modes of reaction open to the cyclobutanes, ring-enlargement is the simplest in the sense that only cisoid (*Z*,*E*) diradicals can participate, as noted above (Scheme 2). Both cisoid and transoid conformations are competent to engage in stereomutation and fragmentation, but having no way of examining the behavior of the two conformations independently, and being at a loss to understand the relative distribution among the three modes of reaction, we focus a detailed exploration of the diradical conceptual scheme on ring-enlargements.

The striking features of the ring-enlargement are the predominance of a single stereoisomer as noted above and the favoring of the thermodynamically *trans*-cyanomethylcyclohexenes and *trans*-dimethylcyclohexenes over *cis-* in our system and that of Baldwin and Burrell, respectively,[3h] and also in the cyclopropane series.[23]

The qualitative aspects of ring-enlargement find reasonable accommodation within the framework of the diradical hypothesis outlined above. (In what follows, the text and figures are a feeble substitute for models in hand.) The initial entry into the caldera by breaking bond C-1−C-2 in **5ee** and **6ze** is seen as a further progression of the torsion already inherent in the C-3−C-4 bonds of the nonplanar cyclobutanes. The cisoid conformation of lower enthalpy of formation, ax.eq of **5ee** (−) leads to the cis (*Z*,*E*)-diradical, (−) synclinal-**1**, of Figure 7. To the extent that some further internal rotation in the direction of (−) synclinal-**1/2** is required to reach a nonbonded diradical—a sufficient condition for loss of Woodward−Hoffmann control—that of the cyano group is preferred to that of the methallyl group in recognition of the widely documented observation of its greater rotational propensity, and in the guess that the propenyl group is fully occupied in becoming the coplanar allyl radical responsible for the reactions occurring at these lower temperatures. This is not to say that rotation of the propenyl group during the bond-breaking process to a similar synclinal diradical does not occur, only that it is a less likely play.

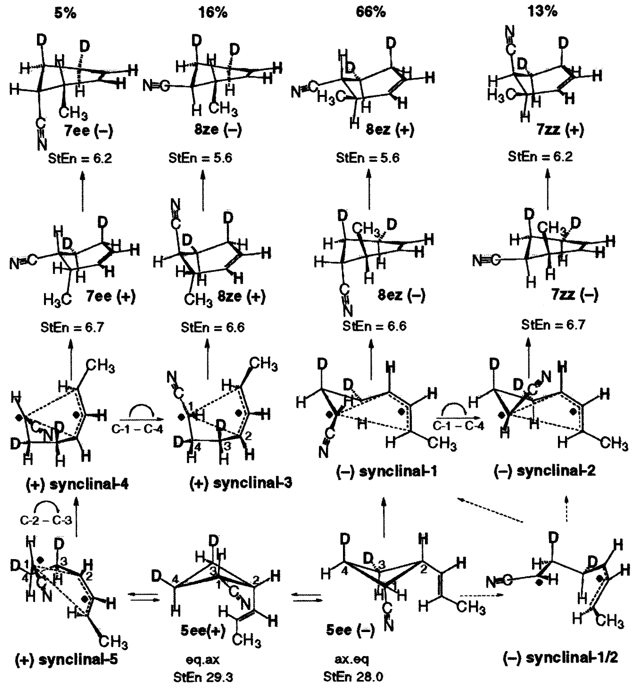


Figure 7. Four of a large number of paths for the formation of the four 1-cyano-2-methylcyclohexenes from the two conformations of *cis*-1-cyano-2-*trans*-propenylcyclobutane **5ee**. The designations (−) and (+) refer to the helical chirality of the conformations, not optical chirality. Steric energies (StEn) from molecular mechanical calculations are in kcal mol^{-1}.

It is a quality of the (−) synclinal diradicals that the cyanomethyl radical is more or less equally well situated to form a four-membered or a six-membered ring by bonding to one or the other of the terminal atoms of the methallyl radical. Proceeding without further internal rotations beyond the torsions needed to accommodate the formation of the six-membered ring (in its higher energy, ax.ax conformation) leads to the thermodynamically more stable product, **8ez** (+). The minor product, **7zz** (+), is not only the thermodynamically less stable, but requires for its formation an internal rotation of the cyanomethyl group by way of (−) synclinal-**2** and **7zz** (−).

Breaking the weakest bond in the higher energy conformation, eq.ax, of **5ee** (+) leads to cis, (*E*,*E*)-diradical, (+) synclinal-**5** and gains entry to the minor pair, **8ze** (−) and **7ee** (−). In contrast to (−) synclinal diradicals, (+) synclinal diradicals have a substantially longer separation between the cyanomethyl radical and the terminal atom of the methallyl radical, bonding between which is required for formation of six-membered rings. As a consequence, internal rotations are required in order to come within bonding distance. Shortening is achievable by a 180° rotation of the methallyl radical about the C-2−C-3 bond (rotation about the backbone returns the system to the major (−) synclinal set, in which no such rotation is required). The result is (+) synclinal-**4**. Proceeding with no further rotation via **7ee** (+) as indicated in Figure 7 leads to the thermodynamically less favored **7ee** (−). To reach the thermodynamically more favored **8ze** (−) via **8ze** (+), a further rotation, that of the cyanomethyl group, to (+) synclinal-**3** is required. But note that, according to the premised ordering of internal rotations, the cyanomethyl group will already have undergone 180° rotation to a significant extent prior to the required 180° rotation of the methallyl group to (+) synclinal-**4**.

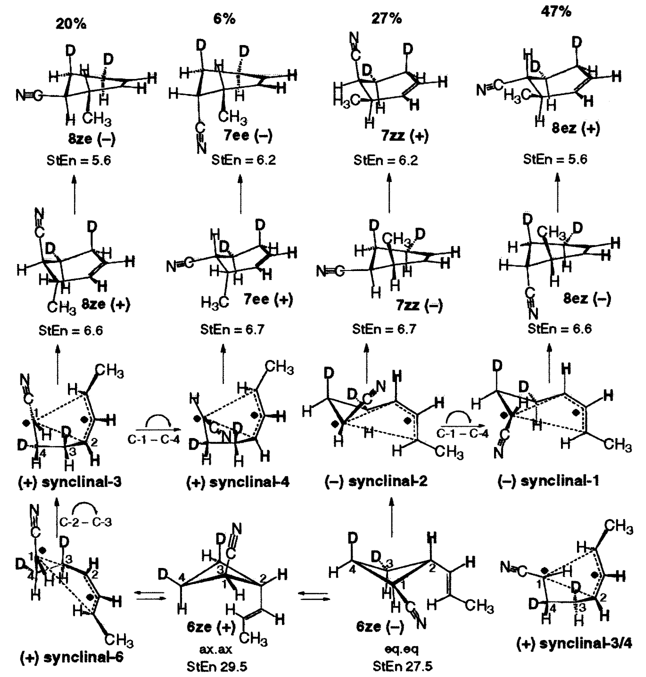


Figure 8. Four of a large number of paths for the formation of the four 1-cyano-2-methylcyclohexenes from the two conformations of *trans*-1-cyano-2-*trans*-propenylcyclobutane **6ze**. The designations (−) and (+) refer to the helical chirality of the conformations, not optical chirality. Steric energies (StEn) from molecular mechanical calculations are in kcal mol^{-1}.

In similar fashion, the lower energy conformation, eq.eq, of **6ze** (−) leads preferentially to the cis (*Z*,*E*)-diradical, (−) synclinal-**2** (Figure 8), which, in contrast to **5ee** (−), requires a rotation of the cyanomethyl group to produce (−) synclinal-**1**, and then the thermodynamically more stable **8ez** (+). The higher energy conformation, ax.ax, of **6ze** (+) similarly requires an internal rotation, but the less favorable one of the methallyl group, and then leads directly without a further internal rotation of the cyanomethyl to the more stable product **8ze** (−).

Were (−) synclinal-**1/2** an intermediate in common from both **5ee** (−) and **6ze** (−), and the sole way to **8ez** (+) and **7zz** (+), the ratio of these two products would be the same from both educts. That this ratio is larger (5.1) from **5ee** and smaller (1.74) from **6ze** is qualitatively ascribable to the path from **5ee** to the thermodynamically favored trans **8ez** (+) being direct, whereas that from **6ze** requires a full 180° rotation of the cyanomethyl group about the C-1−C-4 bond. The opposite is true for the generation of **7zz** (+). Here a C-1−C-4 rotation is required of (−) synclinal-**1** from **5ee** and leads to the thermodynamically higher energy, cis configuration of the cyanomethylcyclohexene, whereas the path from **6ze** (−) is direct. The change in ratio of **8ez** (+) to **7zz** (+) from 5.10 (66/13) starting from **5ee** (−) to 1.74 (47/27) starting from **6ze** (−) can be translated into free energy values of 1.82 and 0.62 kcal mol^{-1}, respectively. Simplistically, they can then be separated into a thermodynamic favoring of 1.22 kcal mol^{-1} and the disfavoring factor of a cyanomethyl rotation of 0.60 kcal mol^{-1}.

We view this attempt to understand the stereochemistry of ring-enlargement as a plausible, possibly misguided beginning, but believe it is based on reasonable premises: the life of a diradical is terminated whenever the two radicals come within apposite bonding distance and orientation; internal rotational gyrations make some stereochemical exploration possible within the limits of the lifetime of any particular diradical; and the likelihood of internal, product-altering rotations is in the decreasing order cyanomethyl > methallyl > backbone. Under this scheme, products are determined by a principle of least rotational involvement. The larger the number of internal rotations (and the slower their rates) required of an initial diradical to reach a conformation appropriate to collapse to a designated product, the longer will have been the lifetime of the diradical and the smaller its contribution to the total distribution among products. The scheme makes clear why random distribution from a common caldera is not seen in these types of rearrangement. It focuses as does the theoretical analysis of Doubleday on internal rotations as the decisive factor in reactions with a common diradical as intermediate. It may perhaps be generously described as a poor man's trajectory analysis!

Experimental Section

General Methods. NMR spectra were recorded on JEOL-270, Bruker AM250, and Bruker WM300 and -500 spectrometers in $CDCl_3$ unless otherwise stated. NMR chemical shifts and coupling constants (J) are reported in ppm (δ), from tetramethylsilane, and hertz (Hz), respectively. Infrared spectra (IR) were recorded on a Perkin-Elmer model 337 grating spectrophotometer and reported in reciprocal centimeters (cm^{-1}). KBr sample plates were used for all the measurements. Quantitative gas chromatographic analysis (GC) was effected on a Perkin-Elmer model 990 instrument with an Autolab model 6300-01 digital integrator. Preparative GC employed a Gelmac 300 instrument. The following columns were used in the purification and separation of samples: Column A: Carbowax 20M on Anakrom ABS 59/60, 2m × 0.25 in.; Column B: 20% DBTCB on Chromsorb P 60/80, 3m × 0.25 in.; Column C: 20% TCEPE on Chromsorb P 60/80, 3m × 0.25 in.; Column D: 20% Carbowax 20M on Chromsorb P 60/80, 3m × 0.25 in. Melting points (mp) are measured with a Hershberg apparatus; boiling points (bp) are uncorrected.

General Method of Kinetics. Samples were transferred by microsyringe and sealed at 10^{-3} mm in dimethyldichlorosilane-treated Pyrex ampules, with an equal volume of tridecane as internal standard and 2% of diphenylamine as inhibitor of polymerization. For heating, the ampules were suspended in the vapors of pure compounds boiling under reflux as previously described.[21] Temperatures were monitored with an iron−constantan thermocouple and a Leeds and Northrop No. 8686 millivolt potentiometer. The temperature gradient was found to be less than 0.3 °C across the section of the heating bath where the ampules were suspended, while temperature fluctuation during any run was less than 0.3 °C. The time lag between the insertion of the ampules and the attainment of the final vapor temperature was ∼1 min. Four sets of reactions were run at 192.0, 198.0, 207.2, and 217.8 °C.

After specified intervals of time, ampules were removed and analyzed quantitatively by capillary GC for the areas of products relative to tridecane. These were converted to relative concentrations by application of predetermined GC response factors. The products were separated and isolated by preparative GC and analyzed quantitatively by NMR to determine the ratios among the pairs of diastereomers. Concentrations were converted to molar percent concentrations for purposes of calculation. Samples of undeuterated **1** and **2** were used to determine specific rate constants for stereochemical interconversion and fragmentation to *cis*-piperylene and acrylonitrile. The further dissection of these rate constants was accomplished by partitioning between the pairs of diastereomers by NMR as a function of reaction time and extrapolation of the resulting linear change in the ratios to zero time.

(*R*)-1-Cyano-*cis*-2-(*cis*-propenyl)-*trans*-3,*trans*-4-dideuteriocyclobutane (1ee) (see Figure 1). **(a) Cyclobut-3-ene-1,2-dicarboxylic Acid Anhydride (A).** Into a 3000 mL immersion-well photolysis flask with two sidearms were placed 49.0 g (0.50 mol) of freshly sublimed maleic anhydride, 19 mL (14.0 g, 0.12 mol) of acetophenone, and 2600 mL of ethyl acetate (both dried with a 4 Å molecular sieve). One of the sidearms was fitted with a calcium sulfate drying tube; the other, with a gas inlet tube attached to an acetylene tank. Acetylene was purified by passing it through two traps, one packed with anhydrous sodium hydroxide pellets, the second filled with concentrated sulfuric acid. The photolysis flask was cooled in a dry ice/acetone bath to −65 °C. The lamp housing was cooled by circulating methanol that was maintained at −10 °C by a FLEXI-COOL refrigerator. The reaction solution was degassed by bubbling nitrogen through for 30 min, then saturated with acetylene by passing the gas through the solution for 1 h. The solution was irradiated with a 700 W, high-pressure Hanovia mercury lamp. After the lamp was turned on, the flow of acetylene was kept around 10 psi, and a moderate flow of nitrogen maintained efficient stirring of the reaction mixture. The reaction was monitored by removing small portions of the reaction mixture at hourly intervals, evaporating the solvent, and measuring the ^1H NMR spectrum in $CDCl_3$. After 26 h of irradiation, there was no further increase in the ratio of signal intensities of the product and maleic anhydride. Removal of the solvent by rotary evaporator left 52.0 g of a yellow solid, which was recrystallized from chloroform to yield 25.4 g (0.205 mol) of colorless leaflets of **A** (41%): mp 86−88 °C; ^1H NMR 6.48 (s, 1H), 4.04 (s, 1H).

(b) *trans*-3-*trans*-4-Dideuteriocyclobutane-1,2-dicarboxylic Acid Anhydride (B). Deuteration was performed in a hydrogenation apparatus at atmospheric pressure. A mixture of 0.40 g of 5% palladium on barium sulfate, 42.0 g of **A**, and 150 mL of ethyl acetate (distilled from calcium hydride) was stirred under deuterium at atmospheric pressure and room temperature. Uptake of deuterium was complete after 8 h (3000 mL). Filtration followed by removal of solvent gave a colorless solid residue which was recrystallized from chloroform to give 39.5 g (0.309 mol) of **B** as colorless leaflets (88%): mp 78−80 °C; ^1H NMR 3.51 (s, 1H), 2.39 (d, 1H). No cis-deuterated product being detectable by ^1H or ^2H NMR analysis, a stereoisomeric purity of ∼99% was indicated for the deuterated product.

(c) *trans*-3-*trans*-4-Dideuterio-*cis*-2-hydroxymethylcyclobutanecarboxylic Acid Lactone (C). Into a 250 mL, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel and a nitrogen gas inlet tube were placed 3.9 g (0.103 mol) of sodium borohydride and 50 mL of tetrahydrofuran (THF; distilled from $LiAlH_4$). The flask was cooled in a dry ice/acetone bath at −65 °C. Under nitrogen atmosphere and with stirring, a solution of 13.0 g (0.10 mol) of **B** in 100 mL of dry THF was added over a period of 30 min. The cooling bath was removed, and the mixture was continuously stirred for a further 2 h at room temperature. The reaction was treated by slow addition of 1.0 M HCl until all the solid had dissolved. The mixture was extracted three times with chloroform (100, 70, and 50 mL portions, respectively). The combined organic layers were washed with saturated aqueous NaCl, dried with anhydrous $NaSO_4$, and concentrated. Distillation of the residue under reduced pressure gave 6.5 g (0.057 mol) of **C** as a colorless liquid (57%): bp 65−66 °C/0.7 Torr; ^1H NMR δ 4.28 (m, 2H), 3.11 (s, 1H), 2.12 (s, 2H).

(d) *trans*-3-*trans*-4-Dideuterio-*cis*-2-hydroxymethylcyclobutanecarbaldehyde Hemiacetal (D). A 500 mL, three-necked flask, equipped with a pressure-equalizing dropping funnel, a magnetic stirrer, and a gas inlet tube, was flame-dried with nitrogen before use. A solution of 10.0 g (0.088 mol) of **C** and 100 mL of methylene chloride (distilled from CaH_2) was introduced, degassed, and cooled to −65 °C in a dry ice/acetone bath. Under a nitrogen atmosphere and with stirring, 100 mL of 1.0 M isobutylaluminum hydride (DIBAL) in hexane was added from the dropping funnel to the lactone over a period of 2 h. Stirring was continued for a further 3 h at −65 °C. The reaction was monitored by thin-layer chromatography (TLC: silica gel plate; ether/hexane = 4:1, detected by 20% $SbCl_6$ in CCl_4). At −65 °C, a solution of 1.0 M HCl was added slowly to terminate the reaction and dissolve the solid. The aqueous layer was separated and extracted with two 50 mL portions of methylene chloride. The combined organic layers were neutralized with aqueous $NaHCO_3$, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Fractional distillation of the residue afforded 7.0 g of **D** as a colorless liquid (69%): bp 80−82/0.5 Torr; ^{1}H NMR 5.33 (s, 1H), 3.87 (m, 2H), 2.89 (m, 2H), 1.66 (d, 2H).

(e) *trans*-3-*trans*-4-Dideuterio-*cis*-2-(*cis*-propenyl)cyclobutylmethanol (E). A Wittig reagent was prepared from 30.0 g of ethyltriphenylphosphonium iodide suspended in 150 mL of THF at −65 °C and a 1.0 M solution of *tert*-butyllithium in hexane. Forced by a gentle stream of nitrogen, a degassed solution of 7.0 g of **D** in 10 mL of dry THF was added to the freshly prepared Wittig reagent through a stainless steel needle. After completion of the addition, the mixture was stirred for 8 h at room temperature, cooled again to −65 °C, and acidified with aqueous 1.0 M HCl. Separated solid was extracted twice with ether, as was the aqueous filtrate. The combined ether solutions were neutralized with saturated $NaHCO_3$, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Distillation of the residue under reduced pressure gave 4.9 g of **E** as a colorless liquid (64%): bp 43−50 °C/0.4 mmHg; ^{1}H NMR 5.57 (m, 2H), 3.69 (m, 2H), 3.40−3.55 (m, 1H), 2.65 (m, 1H), 1.70 (m, 1H), 1.60 (d, 3H).

(f) *trans*-3-*trans*-4-Dideuterio-*cis*-2-(*cis*-propenyl)cyclobutane Carbaldehyde (**F**). A solution of 4.9 g (0.038 mol) of **E** in 10 mL of CH_2Cl_2 (freshly distilled from CaH_2) was added dropwise to a mixture of 19.6 g (0.052 mol) of pyridinium dichromate and 40 mL of CH_2Cl_2 at room temperature over a period of 20 min. After having been stirred for 16 h, the reaction mixture was treated with 20 mL of water and extracted with 20 mL portions of ether and pentane. After removal of solid material by filtration, the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, then dried over anhydrous $MgSO_4$. The concentrated residue was distilled in vacuo to give 3.9 g (0.031 mol) of **F** as a colorless liquid (yield 81%): bp 37−45 °C at 1.5 mmHg; ^{1}H NMR 9.75 (s, 1H), 5.50 (m, 2H), 3.60 (m, 1H), 3.30 (m, 1H), 2.30 (m, 1H), 1.80 (m, 1H), 1.70 (d, 3H).

(g) *trans*-3-*trans*-4-Dideuterio-*cis*-2-(*cis*-propenyl)cyclobutanecarbaldehyde Oxime (G). To a mixture of 3.9 g of **F** and 4.3 g of hydroxylamine hydrochloride in 50 mL of water was added 21.5 g of 40% aqueous K_2CO_3 with stirring that was continued for 2 days. Concentration, extraction with two 20 mL portions of ether, washing with brine, drying over anhydrous $MgSO_4$, and concentration gave 2.5 g of crude oxime **G**, used further without purification: ^{1}H NMR 8.60 (br m, 1H), 5.52 (m, 2H), 3.20 (m, 2H), 2.00 (m, 2H), 1.80 (d, 3H).

(h) (*R*)-1-Cyano-*cis*-2-(*cis*-propenyl)-*trans*-3,*trans*-4-dideuteriocyclobutane (1ee). To a solution of 3.2 g of *N*,*N*-carbonyldiimidazole in 30 mL of CH_2Cl_2 (freshly distilled from CaH_2) was added over a period of 20 min a solution of 2.5 g of crude oxime **G** in 5 mL of CH_2Cl_2. After being stirred for 2 h, the mixture was concentrated to a residue, three ether extractions (100 mL each) of which were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated to 3.1 g of a pale yellow liquid. Analysis by GLC (column A, 150 °C) revealed three components, **1ee** (90%), **5ee** (10%), and a mixture of **2ze** and **6ze** (<1%): ^{1}H NMR (sample of **1ee** purified by GLC) 5.72 (m, 1H, $J = 10$), 5.61 (m, 1H, $J = 10$), 3.49 (t, 1H), 3.27 (t, 1H), 2.22 (t, 1H), 2.03 (t, 1H), 1.59 (d, 3H); ^{2}H NMR 2.32 (overlapping peaks); IR 3010(s), 2960(s), 2230(s), 2200(m), 1660(m), 975(m), 920(m), 720(s).

(*R*)-1-Cyano-*trans*-2-(*cis*-propenyl)-*cis*-3,*cis*-4-dideuteriocyclobutane (2ze). To a solution of 2.3 mg (0.20 mmol) of freshly sublimed potassium *tert*-butylate in 1.0 mL of dimethyl sulfoxide (dried over CaH_2), cooled to 15 °C, was added slowly by syringe a twice degassed sample (50 μL) of **1ee**, purified by GC (column A, 120 °C), under nitrogen and with stirring. After 15 min of stirring, 5 μL of water was injected to quench the reaction. After a further 5 min of stirring, 1 mL of water and 2 mL of pentane were added. The separated aqueous layer was extracted three times with 1.0 mL portions of pentane. The combined organic extracts were washed with water until neutral, dried over anhydrous Na_2SO_4, and concentrated to a residue, which was purified by vacuum transfer at 0.001 mmHg. Analysis by capillary GC indicated an equilibrium ratio of **2ze** to **1ee** of 2.87 ± 0.05 (four runs). The mixture was separated and each isomer was purified by preparative GC (column D, 130 °C). **2ze**: ^{1}H NMR 5.50 (m, 1H, $J = 10$), 5.36 (m, 1H, $J = 10$), 3.55 (t, 1H), 2.27 (t, 1H), 2.20 (t, 1H), 1.87 (t, 1H), 1.66 (d, 3H); ^{2}H NMR 2.20 (overlapping peaks); IR 3010(s), 2980(s), 2240(s), 2230(s), 2200(m), 1650(w), 1450(m), 1300(m), 970(m), 930(m), 900(m), 720(s).

The equilibrium ratio obtained with nondeuterated **2/1** is 2.97 ± 0.06, while that from **2ze**/**1ee** effected in DMSO-d_6 (quenching with D_2O showed incorporation of deuterium exclusively at C^1 as expected) is 3.37 (one run).

(*R*)-1-Cyano-*cis*-2-(*trans*-propenyl)-*trans*-3,*trans*-4-dideuteriocyclobutane (5ee). A 30 mL Pyrex test tube with outlet attached to a drying tube was loaded with 75 μL of GLC-purified **1ee**, 140 μL of acetophenone, and 25 mL of benzene (both dried with 3 Å molecular sieves). Clamped next to the water-cooled lamp-housing of a 450 W, high-pressure Hanovia mercury lamp, the reaction mixture was irradiated until monitoring by capillary GC indicated the beginning of a decline in the concentration of **5ee**, at which time the ratio **5ee**/**1ee** was 3−4. (Extrapolation to infinite time gave a ratio of 6.5−7.0.) Removal of benzene followed by separation and purification on column D at 130 °C gave pure **5ee** as a colorless liquid: ^{1}H NMR 5.71 (m, 1H, $J = 16$), 5.57 (m, 1H, $J = 16$), 3.22−3.16 (m, 2H), 2.17−2.10 (m, 2H), 1.72 (d, 3H); ^{2}H NMR 2.23 (s, 1H), 1.86 (s, 1H); IR 3020(m), 2970(s), 2240(s), 2210(s), 1665(w), 965(s), 920(w).

(*R*)-1-Cyano-*trans*-2-(*trans*-propenyl)-*cis*-3,*cis*-4-dideuteriocyclobutane (6ze). The procedure for epimerization of **1ee** to **2ze** described above applied to **5ee** led to an equilibrium mixture, **6ze**/**5ee** = 3.19 ± 0.04 (nondeuterated analogue, 3.05 ± 0.04). **6ze**: ^{1}H NMR 5.54 (m, 1H, $J = 16$), 5.44 (m, 1H, $J = 16$), 3.14 (t, 1H), 2.72, (t, 1H), 2.12 (t, 1H), 1.83 (t, 1H), 1.66 (d, 3H); ^{2}H NMR 2.15 (overlapping peaks); IR 2980(s), 2950(s), 2230(s), 2200(m), 1660(w), 1450(m), 970(s), 930(w).

(*R*)-1-Cyano-*cis*-2-methylcyclohex-3-ene (7) and (*R*)-1-Cyano-*trans*-2-methylcyclohex-3-ene (8) (see Figure 8). A solution of 0.77 g of hydroquinone, 5.5 g of acrylonitrile (purified by fractional distillation), and 50 mL of piperylene (Aldrich, 65−70% purity) was placed in a 200 mL, high-pressure reactor equipped with a heater and mechanical stirrer. Having been heated and stirred for 14 h at 125 °C, the reaction mixture was washed with 10% aqueous NaOH, neutralized with 10% aqueous HCl, washed with brine, and dried over anhydrous Na_2SO_4. Fractional distillation afforded 11.8 g (97% based on acrylonitrile) of a colorless liquid (bp 39 ± 2 °C at 0.12 mmHg). Analysis by capillary GC revealed **7** (40%), **8** (47%), and two minor products. Separation and purification by GC (column C, 140 °C) afforded **8** (retention time (t_R), 56 min) and **7** (t_R, 70 min). **7**: ^{1}H NMR 5.71 (m, 1H), 5.49 (m, 1H), 2.92 (m, 1H), 2.47 (m, 1H), 2.25 (m, 1H), 2.10−2.00 (m, 2H), 1.85 (m, 1H), 1.18 (d, 3H). **8**: ^{1}H NMR 5.69 (m, 1H), 5.49 (m, 1H), 2.45 (m, H), 2.32 (m, 1H), 2.13−2.06 (m, 3H), 1.84 (m, 1H), 1.17 (d, 3H).

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