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Fate of Diradicals in the Caldera: Stereochemistry of Thermal Stereomutation and Ring Enlargement in *cis*- and *trans*-1-Cyano-2(*E*)-propenylcyclopropanes

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Abstract: This study of thermally induced stereomutation and ring enlargement in *both* (−)-*trans*-1-cyano-2(*E*)-propenylcyclopropane [(−)-*trans*-**1**] and (+)-*cis*-1-cyano-2(*E*)-propenylcyclopropane [(+)-*cis*-**1**] to cyclopentenes definitively contraindicates the usefulness of Woodward−Hoffmann rules of orbital symmetry as a theoretical basis for predicting the stereochemistry of the products. From both diastereomers, the *same* (+)-*trans*-4-cyano-3-methylcyclopentene [(+)-*trans*-**2**] is the major product among the four diastereomeric products, "allowed" and formally the result of a single internal rotation of the cyano-bearing carbon atom from (−)-*trans*-**1**, "forbidden" and the result of zero internal rotations from (+)-*cis*-**1**. Stereomutation and ring enlargement are discussed in detail in terms of rotational propensity, thermodynamic preference, and the possible role of diradicals in transit and diradicals as intermediates in a caldera.

Introduction

Vinylcyclopropanes undergo thermally induced ring enlargements to cyclopentenes, and stereomutations to configurational isomers (see Figure 1).[1] Although the products of ring enlargement are formed kinetically much more slowly than the products of stereomutation, they are thermodynamically "massively favored at equilibrium".[1c] As a consequence ring enlargement has seen significant application in synthetic organic chemistry, while stereomutation has been the object only of mechanistic experimentation and speculation. Investigation into the stereochemistry of the ring enlargement begins with Mazzochi and Tamburin,[2] continues with Doering and Sachdev[3] and Andrews and Baldwin,[4] and extends to this work by Barsa.[5] Both ring enlargement and stereomutation are illuminated more brightly when *cis* and *trans* educts can be compared side by side as here and in Sachdev.[6]

The early 1970s were characterized by widespread hope that the theory of orbital symmetry of Woodward and Hoffmann would provide the basis for a useful prediction of the stereochemical outcome of not obviously concerted, possibly diradical intermediated reactions. In that pursuit, the thermal rearrangement of vinylcyclopropanes played a prominent role.[1c] Contemporary experimentation was limited to *trans*-1,2-disubstituted cyclopropanes,[7] and led to agreement that the major paths of

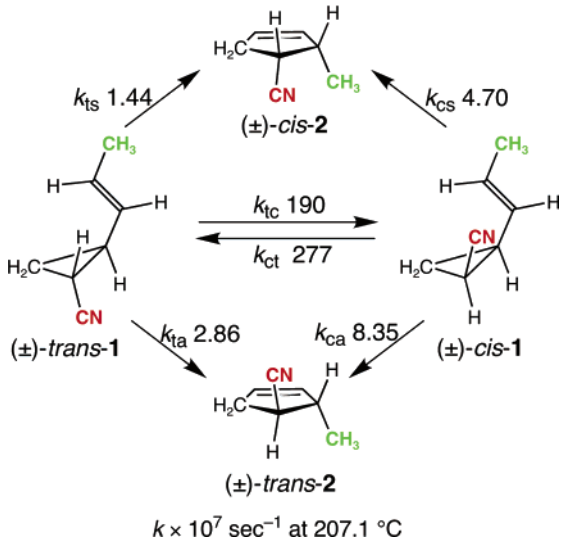


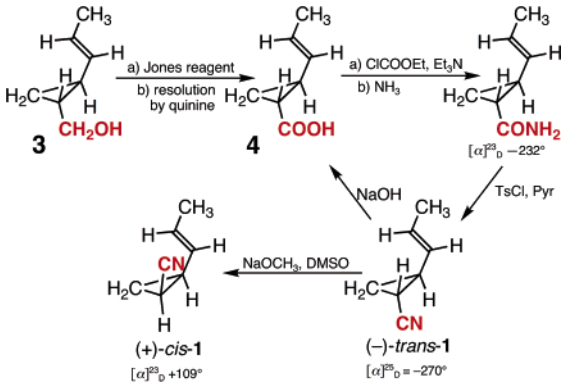
Figure 1. Interconversions of racemic *trans*- and *cis*-1-cyano-2(*E*)-propenylcyclopropane (*trans*-**1** and *cis*-**1**; k_{tc} and k_{ct}) and their ring enlargements to *cis*- and *trans*-4-cyano-3-methylcyclopentene (*trans*-**2** and *cis*-**2**; k_{ts} and k_{ta} , and k_{cs} and k_{ca}). Specific rate constants at 207.1 °C in the gas phase are given in units of 10^{-7} s^{-1}.

ring enlargement to cyclopentenes from vinylcyclopropanes were Woodward−Hoffmann *allowed* processes, suprafacial in the cisoid allyl group (*s*) and "with inversion" at the secondary radical (*i*). Coincidentally it was also a period strongly under the spell of Benson's dubious ∼9 kcal mol^{-1} as the energy of activation for reclosure of 1,3- and 1,4-diradicals,[8,9] widespread,

(1) Reviews: (a) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; pp 81−87 among others. (b) Baldwin, J. E. *J. Comput. Chem.* **1998**, *19*, 222−231. (c) (Especially advised) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197−1212.
(2) Mazzochi, P. H.; Tamburin, H. *J. Am. Chem. Soc.* **1970**, *92*, 7220−7221; **1975**, *97*, 555−561.
(3) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* **1975**, *97*, 5512−5520.
(4) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6705−6706.
(5) Barsa, E. A. Ph.D. Dissertation, Harvard University, 1976; *Diss. Abstr. Int. B* **1977**, *37*, 5077 (order no. 77-9303).
(6) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* **1974**, *96*, 1168−1187.
(7) In many of the early examples, a methyl group, used as the second substituent, precluded observation of stereomutation and ring enlargement of the *cis* isomers by preemption by a faster homoretroene reaction.
(8) Doering, W. v. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279−5283.
(9) Isborn, C.; Hrovat, D. A.; Borden, W. T. *J. Phys. Chem.* **2004**, *108*, 3024−3029.

10.1021/ja0305961 CCC: $27.50

Scheme 1



uncritical acceptance of which encouraged a classical conceptual scheme for the transition region.

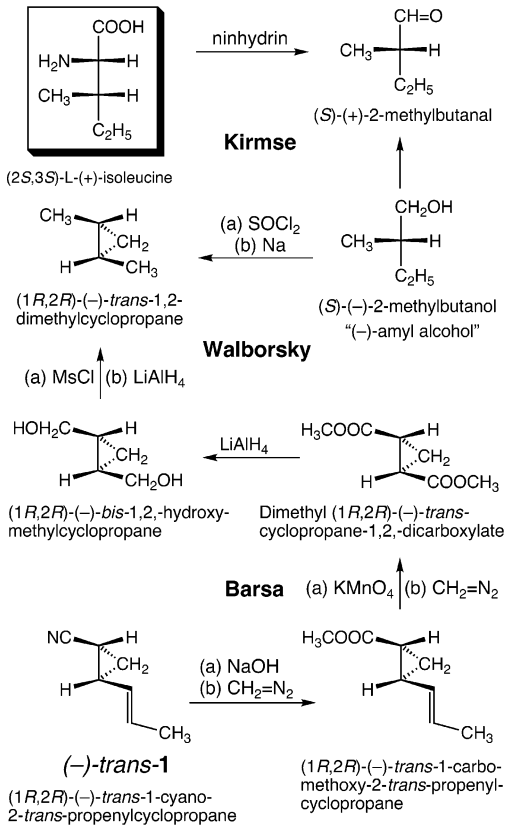
Publication of this portion of Barsa's extensive mechanistic work so long after that of Andrews and Baldwin[4] on *trans*-1-methyl-2(*E*)-propenylcyclopropane not only complements the recent appearance of two studies of a similarly substituted pair of cyclobutanes,[10,11] but provides the only direct comparison of both the *cis* and *trans* isomers of a *cyclopropane*. Barsa's goal was the full set of 14 specific rate constants that describe thermal interconversion among the pairs of enantiomers of *cis*- and *trans*-1-cyano-2(*E*)-propenylcyclopropanes (*cis*-**1** and *trans*-**1**), and their irreversible ring enlargements to the enantiomers of the diastereomeric 4-cyano-3-methylcyclopentenes (*trans*-**2** and *cis*-**2**; Figure 1 shows the racemic pair). Whereas a methyl group *cis* to the propenyl group, as in the analogous example of Andrews and Baldwin, undergoes a more rapid homoretroene cleavage effectively to the exclusion of ring enlargement, the cyano-substituted analogue is free of that frustrating complication, and possessed of other often extolled advantages.

Preparation of Materials

Preparation of (−)-*trans*-**1** and (+)-*cis*-**1** began with *trans*-1-hydroxymethyl-2(*E*)-propenylcyclopropane (**3**; Scheme 1).[12] Optical activity was introduced by resolution of the quinine salt of *trans*-2(*E*)-propenylcyclopropane-1-carboxylic acid (**4**). The question of optical purity and absolute configuration was addressed by transformation to dimethyl cyclopropane-1,2-dicarboxylate, the optical purity of which had occupied the attention of Walborsky et al.[13] and Sachdev.[6] In the kinetic calculations, (−)-*trans*-**1** of $[\alpha]^{25}_{365} = -916.5°$ was assumed to be 100% optically pure and was confidently ≥97%.

The products of ring enlargement, *trans*-**2** and *cis*-**2**, were prepared from dihydrosarkomycin, itself prepared following a sequence owed to Newman and McPherson.[14] Dihydrosarkomycin was resolved by fractional crystallization of its brucine salt from ethyl acetate following the procedure of Shemyakin et al.[15] The specific rotation reported by Hooper for dihydrosarkomycin, $[\alpha]^{25}_{D} = +66.7°$, was taken as that of optically pure material on the assumption that sarkomycin, its precursor, having been of natural origin, was likely optically pure.[16]

Scheme 2



Interrelation of Configurations

Interrelating the relative chiralities of the cyclopropanes and the cyclopentenes has been accomplished through the device of absolute configurations in the absence of direct chemical interrelations. The absolute configuration of the cyclopropanes is based on the relation of active (*S*)-(−)-amyl alcohol to (2*S*,3*S*)-L-(+)-isoleucine as the key reference compounds,[17] and to Kirmse's establishment thereby of the (1*R*,2*R*) configuration for (+)-*trans*-dimethylcyclopropane.[18] By chemical connection to this compound, Walborsky et al. have assigned an absolute configuration to dimethyl (1*R*,2*R*)-(−)-*trans*-cyclopropane-1,2-dicarboxylate. In the present work, (−)-*trans*-**1** has in turn been related to Walborsky's (1*R*,2*R*)-(+)-*trans*-dimethylcyclopropane (for depiction and details, see Scheme 2).

The absolute configuration of the cyclopentenes depends first on the relation of (*R*,*S*)-(+)-dihydrosarkomycin (**5**$_s$; Scheme 3) to (*R*)-(+)-3-methylcyclohexanone (**6**) of known absolute configuration as established by Hill et al.[19] and on the relation of (*S*,*R*)-(−)-dihydrosarkomycin (**5**$_r$) to (+)-*trans*-**2** by way of methyl 3-methylcyclopentene-4-carboxylate (**7**$_r$), and of **7**$_s$ to methyl 1-methylcyclopentane-2-carboxylate (**8**$_s$) as the connecting compounds. Establishing the relation to (+)-*cis*-**2** is trivial.

(10) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2002**, *67*, 3249−3256.
(11) Doering, W. v. E.; Cheng, X.-h.; Lee, K.-w.; Lin, Z.-s. *J. Am. Chem. Soc.* **2002**, *124*, 11642−11652.
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(16) Hooper, I. R.; Cheney, L. C.; Cron, M. J.; Fardig, O. B.; Johnson, D. A.; Johnson, D. L.; Palermiti, F. M.; Schmitz, H.; Wheatley, W. B. *Antibiot. Chemother*. **1955**, *5*, 585−595.
(17) Trommel, J.; Bijvoet, J. M. *Acta Crystallogr., B* **1954**, *7*, 703−709.
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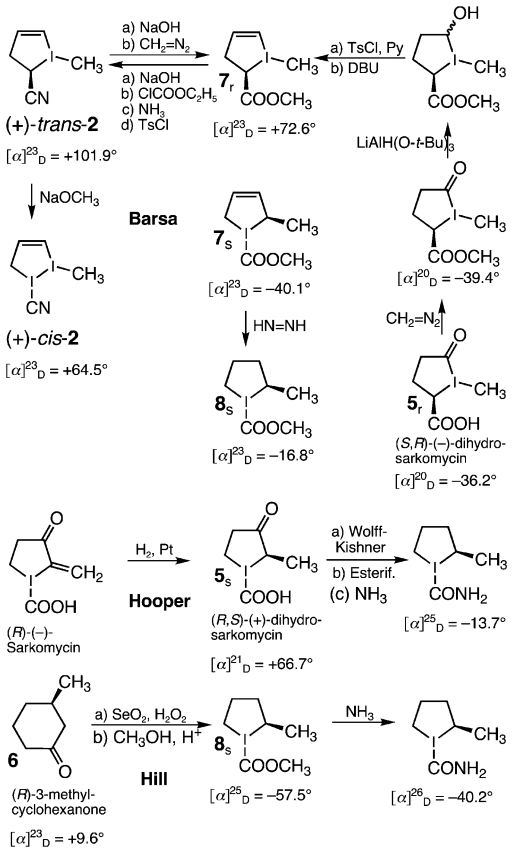
(19) Hill, R. K.; Foley, P. J., Jr.; Gardella, L. A. *J. Org. Chem.* **1967**, *32*, 2330−2335.

Scheme 3



Kinetics

With the configurational relation of (−)-*trans*-**1** to (+)-*cis*-**1**, and of (+)-*trans*-**2** to (+)-*cis*-**2**, and the relation of each set to the other firmly in hand, elucidation of the kinetics of the complete system could be undertaken. The study began with the kinetics of the racemic system in Figure 1, the data bearing on which are found in the Supporting Information, Table SI-1. Its six specific rate constants fell into two distinct sets differing considerably in magnitude. The two constants describing the interconversion of *trans*- and *cis*-**1**, k_{tc} and k_{ct}, were easily determined with acceptably high precision, while the four describing the ring enlargements to *trans*-**2** (k_{ta} and k_{ca}) and *cis*-**2** (k_{ts} and k_{cs}) (Figure 1), being smaller by almost 2 orders of magnitude, could still be measured simultaneously with the faster two interconversions, but at low conversion and correspondingly at a substantially lower level of precision. Optimization of the six specific rate constants was accomplished in the usual fashion by application of the Runge−Kutta method to the set of four partial differential equations involving the six rate constants. While our earlier program produced the same values as a later program created by Roth and Fink,[20] only the latter incorporated the method of Marquardt[21] for the evaluation of the individual uncertainties (recorded at 3σ, the 95% confidence level). A more accurate determination of the sums of the rate constants $k_3 + k_4$ and $k_5 + k_6$ (Figure 2) could have been obtained by starting from equilibrium concentrations of *trans*- and *cis*-**1** and operating at higher temperatures to higher degrees of conversion, but without adding any improvement in the ratios within the pairs.

(20) Roth, W. R.; Fink, R. Unpublished results.
(21) Marquardt, D. W. *J. Soc. Ind. Appl. Math.* **1963**, *11*, 431−441.

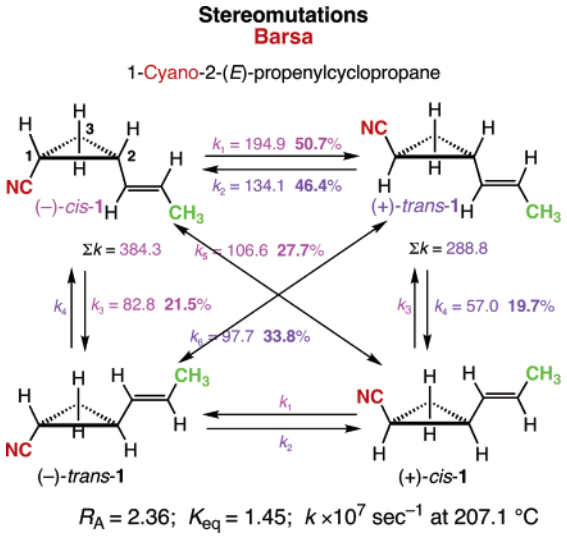


Figure 2. Six specific rate constants in units of 10^{-7} s^{-1} for stereomutations among enantiomeric and diastereomeric *cis*- and *trans*-1-cyano-2(*E*)-propenylcyclopropanes at 207.1 °C in the gas phase. The enantiomers of the educts actually used are depicted for the sake of consistency with other similar schemes.

Table 1. First-Order Specific Rate Constants at 207.1 °C for the Thermally Induced Stereomutations and Ring Enlargements of *cis*- and *trans*-Cyano-2(*E*)-propenylcyclopropanes (*cis*-**1** and *trans*-**1**, Respectively)

reaction	$k \times 10^{-7}$, s^{-1}
trans-**1** → *cis*-**1** (k_{tc})[a]	190 ± 3
cis-**1** → *trans*-**1** (k_{ct})[a]	277 ± 6
trans-**1** → *cis*-**2** (k_{ts})[a]	1.44 ± 0.03
trans-**1** → *trans*-**2** (k_{ta})[a]	2.86 ± 0.08
cis-**1** → *cis*-**2** (k_{cs})[a]	4.70 ± 0.13
cis-**1** → *trans*-**2** (k_{ca})[a]	8.35 ± 0.25
(+)-*cis*-**1** → (−)-*trans*-**1** (k_1)[b]	194.9 ± 6.5
(−)-*trans*-**1** → (+)-*cis*-**1** (k_2)[b]	134.1 ± 3.3
(+)-*cis*-**1** → (+)-*trans*-**1** (k_3)[b]	82.8 ± 2.5
(−)-*trans*-**1** → (−)-*cis*-**1** (k_4)[b]	57.0 ± 1.5
(+)-*cis*-**1** → (−)-*cis*-**1** (k_5)[b]	106.6 ± 6.0
(−)-*trans*-**1** → (+)-*trans*-**1** (k_6)[b]	97.7 ± 2.0
(−)-*trans*-**1** → (−)-*trans*-**2** (k_7)[c]	0.56
(−)-*trans*-**1** → (+)-*trans*-**2** (k_8)[c]	2.31
(−)-*trans*-**1** → (−)-*cis*-**2** (k_9)[c]	0.97
(−)-*trans*-**1** → (+)-*cis*-**2** (k_{10})[c]	0.48
(+)-*cis*-**1** → (+)-*trans*-**2** (k_{11})[c]	5.72
(+)-*cis*-**1** → (−)-*trans*-**2** (k_{12})[c]	2.66
(+)-*cis*-**1** → (−)-*cis*-**2** (k_{14})[c]	1.82
(+)-*cis*-**1** → (+)-*cis*-**2** (k_{13})[c]	2.89

[a] Values for the same rate constants calculated by the program of Roth and Fink (see the text) are recorded in Figure 1. [b] Also reported in Figure 2. [c] Also reported in Scheme 6 (as the enantiomeric set for consistency with other schemes).

Dissection of the specific rate constants of the racemic compounds is accomplished in our usual manner from estimation of the ratio of enantiomers at zero time. The specific rate constants derived from the kinetic data are collected in Table 1, Figure 2, and Scheme 6.

Mechanistic Models

The conceptual scheme propounded for thermal rearrangements in small ring compounds consists of three, long obvious, superficially simple elements of bond-breaking, internal rotations, and bond-making, the reverse of bond-breaking. The ultimate goal is the identification of factors that will allow the effect of constitutional and configurational perturbations to be predicted—at least qualitatively.

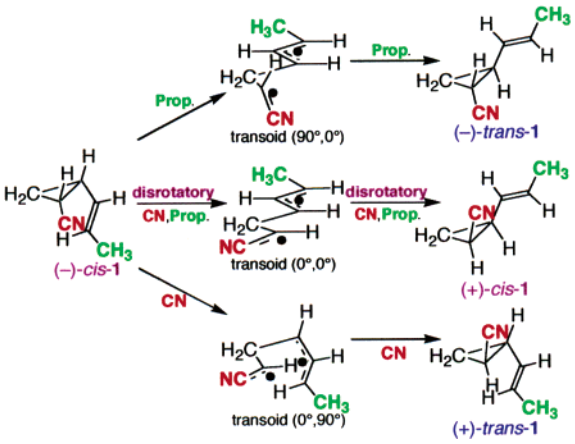


Figure 3. Stereomutation modeled by dynamically controlled diradicals in transit proceeding from (−)-*cis*-**1** by a continuous, disrotatory (both outward; three other modes not shown), double rotation to (+)-*cis*-**1**, and each by single-rotational processes to (−)-*trans*-**1** (propenyl rotation) and (+)-*trans*-**1** (cyano rotation).

In the first, bond-breaking phase—which may be designated as a collection of entry channels into the caldera—an excitation energy, equivalent to that which would be required to break the covalent bond in an analogously substituted *acyclic* example less any ring strain released, is acquired in the usual manner by collisions, and then concentrated into the apposite stretching mode by the reverse of intramolecular vibrational relaxation (ivr). In contrast to the acyclic instance where two radicals can then be generated by bond dissociation, in the cyclic instance vibrational excitation can be carried to ever higher vibrational levels without accomplishing bond-breaking. Coupling with a torsional mode and its conversion to an internal rotation are required to effect bond-breaking and generation of an (unexcited) diradical.

At this point a bifurcation is visualized. By conservation of the torsional momentum involved in the bond-breaking, the diradical may continue on to its predestined product. In this process the diradical is not an intermediate, but is perhaps more informatively described as a "diradical in transit". It does not pause in the caldera to explore its own internal torsional modes, but rather proceeds on without further intervention to bond-making. There being several appropriate torsional modes in cyclic organic molecules of any realistic size and substitution, several stereochemically distinct paths to bond-breaking may comprise a collection of entrance channels and their corresponding exit channels. In the three examples discussed in this paper, these modes may include two single-rotational processes, and four double-rotational processes leading to (0°, 0°) transoid conformations (only one of two disrotational processes is shown in Figure 3), each corresponding to a distinct diradical in transit.

Alternatively, the diradical may be diverted to the status of an intermediate by ivr, that is, to another of the several shallow conformational minima accessible to the diradical. The diradical may now be described as a "diradical as intermediate" able to explore its various conformations by conversions of apposite torsional modes into internal rotations. Among these will be the conformation from which return to the activated state of the cyclic educt without stereochemical change is a viable if not observable process. The extreme expression of this alternative is the establishment of an equilibrium among available conformational minima at a rate substantially faster than that of exit to products.

Stereomutations

Interconversions among the stereoisomeric cyclopropanes are markedly favored *kinetically* if not *thermodynamically* over ring enlargements: 98.6% faster from (−)-*trans*-**1**, 96.7% from (+)-*cis*-**1**. Stereomutation and ring enlargement are *formally* accomplished by homolysis of the weakest carbon−carbon bond (here the C1−C2 bond) to a diradical, rotation about the C1−C3 bond (hereafter referred to as "cyano rotation") or about the C2−C3 bond ("(*E*)-propenyl rotation") by single rotation (or both, by double rotation), and reclosure to stereoisomers of cyclopropanes or cyclopentenes (Figure 2 and Scheme 6, respectively). Hidden from view are the "identity" reactions of reclosure to educt of unchanged stereochemistry! Taking the sum of the three rate constants for stereomutation for each isomer to be 100%, the two processes of single rotation account for 72.2% from (−)-*cis*-**1**, and 66.1% from (+)-*trans*-**1**. Even more strikingly, single rotation by cyano is favored over (*E*)-propenyl rotation: 50.7% as (+)-*trans*-**1** versus 21.5% as (−)-*trans*-**1** from (−)-*cis*-**1**, and 46.4% as (−)-*cis*-**1** versus 19.7% as (+)-*cis*-**1** from (+)-*trans*-**1**. This observation is yet another example of rotational propensity favoring the slender cyano group.

In a circle of reversible reactions of this type,[22] the ratio of the specific rate constants for formation of the products of single rotation about one carbon atom vis-à-vis that of another is a constant, whether starting from (+)-*trans*-1 or (−)-*cis*-**1**. This constant, dubbed rotational propensity (R_A),[3] here defines the ratio of rotation of the cyano-bearing carbon atom to that of the (*E*)-propenyl-bearing carbon atom (notation cyano/(*E*)-propenyl). This ratio, 2.36, may be compared to values reported for other cyclopropanes: 2.20 for cyano/isopropenyl,[3] 2.47[23] and 2.30[24] for cyano/phenyl, 1.76 for cyano/phenylacetylenyl,[23] and 0.90 for cyano/methyl.[25] Parenthetically, the similarity of rotational propensities in related cyclobutanes is noteworthy: most appositely, 2.41 for cyano/(*E*)-propenyl (Figure 4), but also 1.93 for cyano/(*Z*)-propenyl[11] and 1.48 for cyano/vinyl.[26]

As a relevant diversion, we note that substitution at the formally uninvolved, third carbon atom of the cyclopropane ring (C3) is a factor in determining the magnitude of R_A, and is not to be ignored. As an illustration, the influence of the methyl group at C3 in 1-cyano-2(*Z*)-propenyl-3-methylcyclopropane is strongly reflected in four values for R_A, which range from 1.04 to 4.86.[27] (The effect of disubstitution at C3, e.g., in an appropriate derivative of chrysanthemic acid, has not appeared in the literature.) Rotational propensities are perhaps better notated with a subscript indicating the nature of the substitution at C3, e.g., as $(R_A)_{CHH}$ in the present example, $(R_A)_{CHMe}$ in those cited immediately above, and $[(R_A)_{CMeMe}]$ in a hypothetical 3,3-dimethyl example.

That most of the available experimental evaluations of R_A have cyano in common is not meant to imply that this group

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(23) Doering, W. v. E.; Barsa, E. A. *Tetrahedron Lett.* **1978**, 2495−2498.
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(27) Doering, W. v. E.; Barsa, E. A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *79*, 2355−2357.

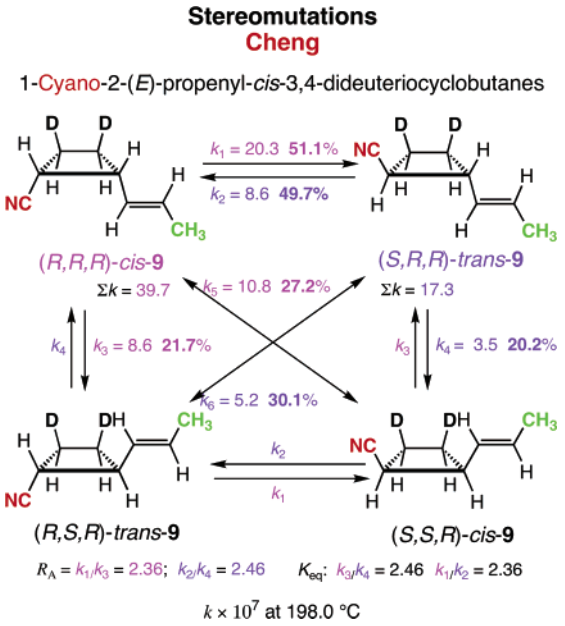


Figure 4. Six specific rate constants in units of 10^{-7} s^{-1} for stereomutations among enantiomeric and diastereomeric *cis*- and *trans*-1-cyano-2(*E*)-propenyl-*cis*-3,4-dideuteriocyclobutanes at 198.0 °C in the gas phase, along with values of the rotational propensity (R_A) and equilibrium constant.

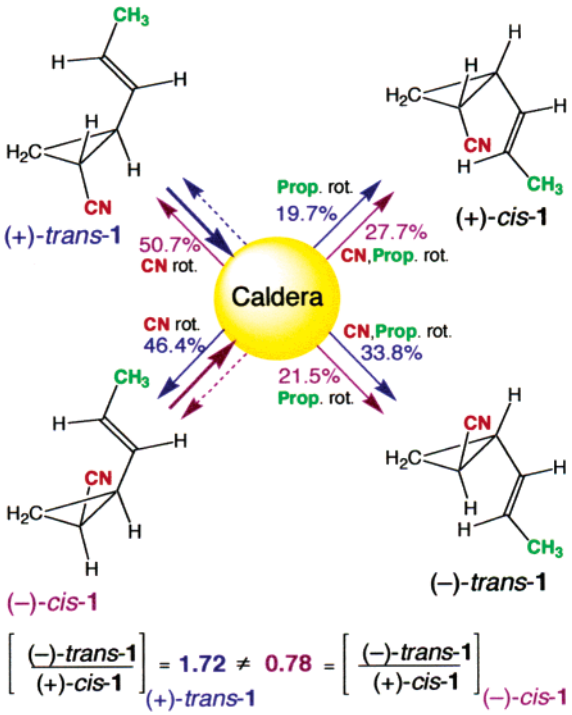


Figure 5. Entry into a hypothetical caldera with an equilibrated intermediate in common, followed by exit by two single-rotational processes, a double-rotational process, and a zero-rotational (the "identity" reaction) process for educts (+)-*trans*-**1** (blue arrows) and **(−)**-*cis*-**1** (mauve arrows).

constitutes or should constitute a reference standard. Note for instance methyl/ethyl ($R_A = 1.17$)[28] (but see Baldwin and Seldon for a newer value of $R_A \approx 1.0$)[29] and isopropyl/phenyl ($R_A = 1.27$).[23] Indeed, it is problematic whether it makes sense to seek an intrinsic factor for each individual group since interactions among the substituents at all three carbon atoms appear to determine the observed rotational propensities.

Disubstitution at one of the *rotating* carbon atoms is exemplified by methyl 1,2-diphenylcyclopropane-2-carboxylate as uncovered by Chmurny and Cram[30] and examined in more detail by Doering, Robertson, and Ewing.[31] These compounds show a very high value of $R_A = 18 \pm 3$ (phenyl,hydrogen/carbomethoxy,phenyl). Replacement of the carbomethoxy group by cyano returns R_A to an unexceptional value, 2.21 (phenyl, hydrogen/cyano,phenyl). Note also the unexceptional values of $R_A = 1.69$ shown by methyl 1-phenylcyclopropane-2-carboxylate (carbomethoxy,hydrogen/phenyl,hydrogen), 2.30 shown by cyano,hydrogen/phenyl,hydrogen, and 1.37 for cyano,hydrogen/cyano,methyl.[32]

Between the two extremes of hypothetical mechanistic schemes for stereomutation, a continuum of the ratio of reclosure to internal rotation from very large—diradical in transit (dint)—to very small—diradical as intermediate (dasi)—can be discerned. Distinction between the two extremes becomes possible only when data from *both cis* and *trans* educts are available. Under the operation of dasi, the same distribution of products would be expected regardless of the stereochemistry of the educts; that is, the ratios of the two products in common, (−)-*trans*-**1** and (+)-*cis*-**1** from *either* (+)-*trans*-**1** or (−)-*cis*-**1**, should be identical (Figure 5). The experimental ratios being 1.72 and 0.78, respectively, this criterion seems *not* to be satisfied. The possibility that these ratios might in reality be identical can be assessed by estimating the changes in relative rates of formation that would be required to bring about identity. Calculation (for example, to a common value of 0.94, which slightly favors the *trans* educt over the *cis* educt) reveals that these changes would have to amount to 18−32% of their experimental values, values that do not appear credibly to fall within our estimate of experimental uncertainties.[33] In a superficially more forgiving examination, the average of the two values from (+)-*trans*-**1** and (−)-*cis*-**1** for the stereoisomers resulting from cyano rotation, (*E*)-propenyl rotation, and double rotation are, respectively, 48.6 ± 2.1%, 20.6 ± 1.1%, and 30.8 ± 3.0% (from Figure 5). The apparent uncertainties in these values are perhaps small enough to be more supportive of equilibration within the caldera. What is missing is a set of three or more repetitions of the kinetics that would have provided a better grip on experimental uncertainties. The hypothesis of product distribution coming from equilibration within the caldera gains in credibility from a consistency with the other two examples in the literature. Relative contributions from the same three rotational components from the *cis*- and *trans*-1-methyl-2(*E*)-propenylcyclobutanes are 45.8 ± 1.3%, 32.9 ± 1.0%, and 22.0 ± 2.1%, respectively (Figure 6),[10] while from *cis*- and *trans*-1-methyl-2(*E*)-propenyl-*cis*-3,4-dideuteriocyclobutane these contributions are 50.4 ± 0.7%, 21.0 ± 0.8%, and 28.6 ± 1.5%, respectively (Figure 4).[11] Within possibly acceptable limits of uncertainties, a credible case can be made for the distribution of the stereomutational products being *independent* of the stereochemistry of the educt, or nearly so. The rub is in "nearly so". The conclusion would be stronger were experiments of higher

(28) Carter, W. L.; Bergman, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 7411−7425.
(29) Baldwin, J. E.; Seldon, C. B. *J. Am. Chem. Soc.* **1993**, *115*, 2239−2248.
(30) Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4237−4244.
(31) Doering, W. v. E.; Robertson, L. R.; Ewing, E. E. *J. Org. Chem.* **1983**, *48*, 4280−4286.
(32) Doering, W. v. E.; Horowitz, G.; Sachdev, K. *Tetrahedron* **1977**, *33*, 273−283.

(33) Arithmetically expressed, $(19.7 + c_t)/(33.8 - c_t) = 0.94$ when $c_t = 6.2$ while $(27.7 - c_c)/(21.5 + c_c) = 0.94$ when $c_c = 3.9$ is the result.

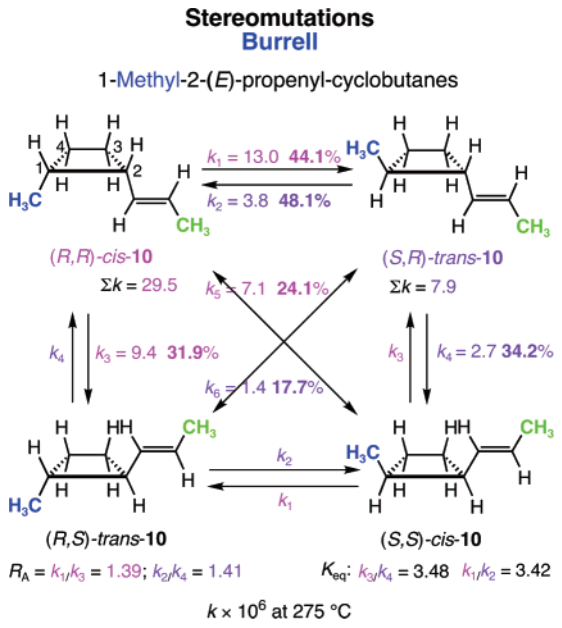


Figure 6. Six specific rate constants (in units of 10^{-6} s^{-1} and numbered as in Figure 3) are given for stereomutations among enantiomeric and diastereomeric *cis*- and *trans*-1-methyl-2(*E*)-propenylcyclobutanes at 275 °C in the gas phase, along with values of the rotational propensity (R_A) and equilibrium constant.

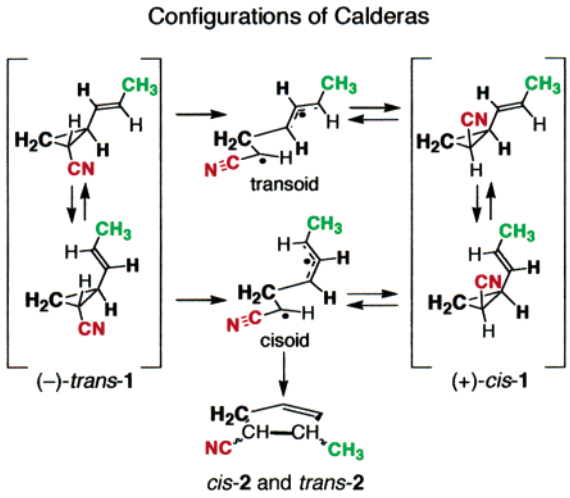
precision and accuracy to confirm the complete independence of product distribution of the stereochemistry of the educt.

Under the operation of dint, the ratios among the various bond-breaking modes determine the distribution of stereoisomers in stereomutation; that is, product distributions are *dependent* on the stereochemistry of the educt. Only by coincidence could the product distribution coincide with that expected of dasi and thus appear to be independent. A believable model is essential for comparison with experiment, but such a model eludes us. Even about a possible difference between disrotatory double rotation from (−)-*cis*-**1** (Figure 3) and conrotatory double rotation from (+)-*trans*-**1** (Figure SI-1) we know nothing, although it is hard to believe the two processes should be as nearly identical in magnitude as would appear.

Validation of the dint extreme may be forthcoming only through theoretical calculations of the dynamic trajectory type. Analysis of the paths or trajectories followed from entry into, and through exit from, the multidimensional potential energy "surface" of a large number of molecules excited to the total energy level of a diradical can in principle, and increasingly in practice, lead to the correct prediction of the ratios among products emerging from the caldera. This purely calculational approach promises to generate highly reliable quantitative predictions of rate constants on an ad hoc basis, but probably at the cost of not bringing to light qualitative factors influencing the distribution among entrance channels and therefore among products. A timely, detailed, and sympathetic overview with references is given in sections 6 and 7 of Baldwin's review.[1c]

Some hope may be attached to an experimental comparison of sterically more disparate pairs, such as *cis*- and *trans*-1-*tert*-butyl-2(*E*)-propenylcyclopropane (cyclobutane) or *cis*- and *trans*-1-phenyl-2(*E*)-propenylcyclopropane (cyclobutane), among others imaginable. But in this endeavor the point may have been reached where the multiplicity of variables is too great to expect qualitatively useful factors or correlations to emerge.

Scheme 4



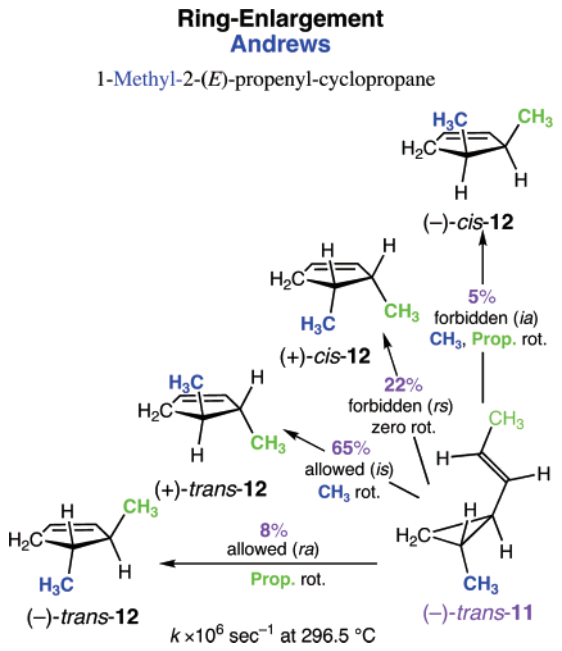
Ring Enlargements

Before beginning discussion of the minor, products of ring enlargement, we note that a *single* caldera is not an acceptable conceptual scheme where two or more noninterconverting calderas may be involved.[34,35] In the three examples cited, entry can lead to transoid and cisoid configurations of the caldera, neither being likely to interconvert within the short lifetime of the individual calderas (see Scheme 4). Exit from the presumably major transoid caldera may lead only to products of stereomutation, while exit from the minor cisoid set can lead in addition to ring enlargement (in an unknown ratio). This latter process amounts to no more than ∼2.5% stereomutation. The relative distribution among the three cyclopropanes from the cisoid caldera—or from the transoid for that matter—is not known. Neither are the ratios of the two configurations starting from (−)-*cis*-**1** or (+)-*trans*-**1**. If it be assumed that the ratios are quite similar in magnitude, the hypothesis of two calderas common to both remains acceptable, otherwise not.

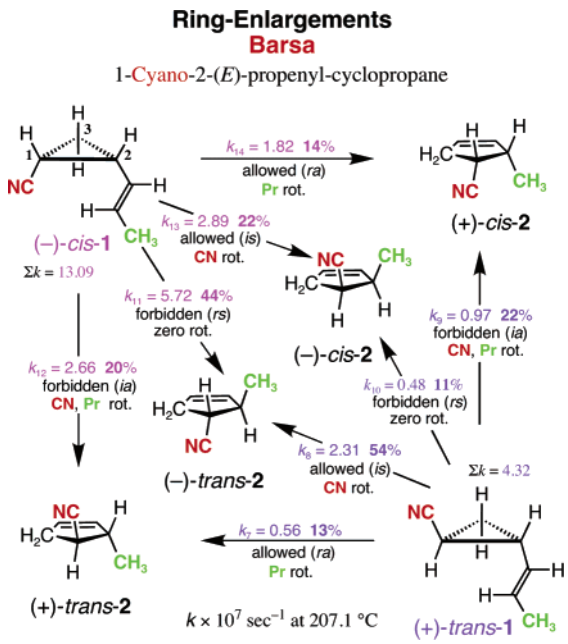
Although ring enlargements are the least prominent kinetically among the thermal rearrangements of vinyl-substituted cyclopropanes, they have attracted a disproportionate amount of attention because their stereochemistry can be analyzed in terms of the rules of Woodward−Hoffmann orbital symmetry.[36] Several studies on *trans*-2-methylcyclopropanes variously substituted by 1-substituted vinyl groups were quite uniformly distinguished by strong favoring of the two Woodward−Hoffmann allowed processes. During this period, observation of the role of the corresponding *cis* isomers was completely thwarted by their predilection for a homoretroene reaction so much faster than stereomutation or ring enlargement that no relevant signals could be detected (see, for example, the reaction investigated by Andrews and Baldwin in Scheme 5).[4] Once the offending methyl group had been replaced by a group such as cyano, the retroene reaction was, of course, completely eliminated, and the role of the *cis* isomers could then be observed (Scheme 6).[5,6]

(34) Thermal interconversion within a caldera between the two sets requires *cis*−*trans* isomerization of allylic radicals, and is rendered highly improbable within the lifetime of a caldera by an enthalpy of activation estimated to be ∼16 kcal mol^{-1}.
(35) Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483−4489.
(36) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970; p 121.

Scheme 5

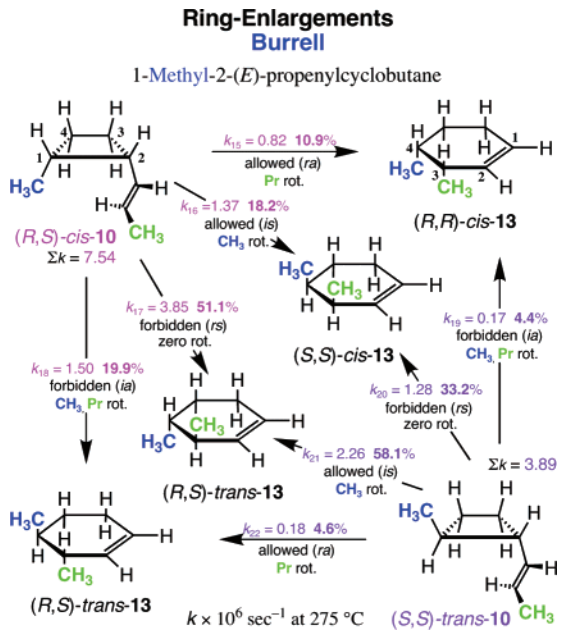


Scheme 6

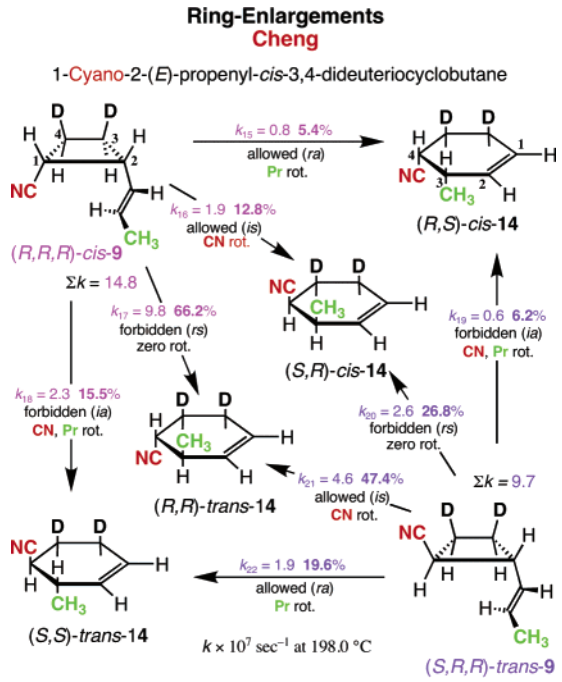


Ring enlargements of the type for **(+)**-*trans*-**1** and (−)-*cis*-**1** to *cis*- and *trans*-4-cyano-3-methylcyclopentenes (*cis*- and *trans*-**2**) look superficially more amenable to a mechanistic understanding in that they may occur only through the family of cisoid configurations of the continuous or intermediary diradicals (Scheme 4). However, they amount kinetically to no more than 1.4% and 3.3% of the kinetic fates of (+)-*trans*-**1** and (−)-*cis*-**1**, respectively (inevitably in neglect of the unknowable identity reactions). As a consequence the stereochemistry of the cyclopentenes obtained as final products in good yield (owing to the highly favorable thermodynamics) has been so highly compromised that it is of little theoretical interest or synthetic value. No matter. The specific rate constants of their formation remain mechanistically interesting.

Scheme 7



Scheme 8



That ring enlargements of cyclopropanes should be so much slower than stereomutation is uncontroversially explained by the adverse steric interactions inherent in generating the apposite diradical in the obligatorily cisoid configuration (Scheme 4). In the cyclobutanes, ring enlargement competes comfortably with stereomutation. The contrast finds no facile explanation (cf. Figure 4 and Scheme 8, or Figure 6 and Scheme 7).

That *trans* isomers should be favored is consistent with the difference in steric energy of 0.6 kcal mol^{-1} estimated by MM2 calculations of isomeric *cis*- and *trans*-**2**, but correct analysis must be in terms of kinetic control. At the much higher temperature of 387.4 °C, the rates of formation of *trans*-**2** are compressed somewhat to 60% and 59%, respectively, but are certainly not notably temperature-dependent. The close similarity

to the *trans*-1-methyl-2(*E*)-propenylcyclopropane investigated by Andrews and Baldwin is shown in Scheme 5.[4] A similar preponderance is observed in several other studies of *trans*-1,2-disubstituted cyclopropanes (64−79%; see Table 1 in Baldwin's review).[1c]

In striking contrast to the *trans* isomers, the favored processes in the ring enlargement of the *cis* isomers formally follow Woodward−Hoffmann forbidden pathways. Thus, the two enantiomers of *trans*-**2** from (+)-*trans*-**1** are produced by formally *allowed* processes to the extent of 67%, and from (−)-*cis*-**1** by *forbidden* processes to the extent of 64% (Scheme 6). Similar behavior is seen in the two cyclobutanes. Thus, Baldwin and Burrell have made the same observation in their heroic study of the 1-methyl-2(*E*)-propenylcyclobutanes: (*S*,*S*)-*trans*-**10** leads to 63% *trans*-**13** in allowed processes, while (*R*,*S*)-*cis*-**10** leads to 71% *trans*-**13** in forbidden processes (Scheme 7).[10,37] In the parallel study of 1-cyano-2(*E*)-propenyl-*cis*-3,4-dideuteriocyclobutanes (Scheme 8),[11] (*S*,*S*)-*trans*-**9** favors ring enlargement to *trans*-**14** seemingly by Woodward−Hoffmann *allowed* processes (67%), while (*R*,*S*)-*cis*-**9** favors the *same trans*-**14** by Woodward−Hoffmann *forbidden* processes (82%). These observations, acquired by extensive, painstaking, and critical experimental work, have laid to rest any predictive value in the application of the Woodward−Hoffmann rules to ring enlargements in these vinyl-substituted cyclopropanes and cyclobutanes.

Closer inspection of the distribution of enantiomers in the favored *trans* isomers reveals a striking excess of the *same* enantiomeric cyclopentene, (−)-*trans*-**2**, from either (+)-*trans*-**1** as the educt (54%) or (−)-*cis*-**1** (44%). The other *trans* component, (+)-*trans*-**2**, is a minor product (13% and 20%, respectively) even though equally favored thermodynamically. Its contributions, incidentally, represent the maximum that a necessarily achiral (0°, 0°) diradical as intermediate could play in the caldera.

The relative ease of the rotational element associated with the production of each of the four cyclopentenes may be a factor. The major stereoisomer, (−)-*trans*-**2**, from (+)-*trans*-**1** (54%) is formally the result of a single, cyano rotation, and the result of a zero rotational process from (−)-*cis*-**1** (44%). The minor *trans* component, (+)-*trans*-**2**, requires a single internal rotation of the (*E*)-propenyl group starting from (+)-*trans*-**1**, or a double rotation, that of the cyano group *and* the (*E*)-propenyl group, from (−)-*cis*-**1**. In stereomutation, it may be recalled that the rotational propensity (R_A) is the ratio of rotation of the cyano-bearing carbon atom vis-à-vis that of (*E*)-propenyl, and has the value 2.36. In the ring enlargement of (+)-*trans*-**1** to (−)- and (+)-*trans*-**2**, cyano rotation is favored over rotation of the (*E*)-propenyl group by a factor of 4.1. In the ring enlargement of (−)-*cis*-**1**, the same rotations are in a ratio of 1.6, but lead to the thermodynamically less favored *cis* isomers (−)-*cis*-**2** and (+)-*cis*-**2**. Much the same picture can be seen in the rearrangements of cyclobutanes, Schemes 7 and 8.

Conclusions

In stereomutation the equivalent of a diradical as intermediate common to (+)-*trans*-**1** and (−)-*cis*-**1** as educts appears to be closely approached. It is also strongly indicated in the behavior of the two cyclobutanes (Figures 4 and 6). The fastest reaction is interconversion of the two educts by internal rotation of the cyano group, an outcome consistent with the R_A value. Beyond that, double rotation is somewhat favored over a single rotation of the (*E*)-propenyl group in the present example, but not in that of Baldwin and Burrell (Figure 6).

In ring enlargement, very much the minor reaction kinetically, the *same* product, (−)-*trans*-**2**, predominates regardless of the educt—by cyano rotation from (+)-*trans*-**1**, by zero internal rotation from (−)-*cis*-**1**. From each educt, the minor product, (+)-*trans*-**2**, requires an internal rotation of the (*E*)-propenyl group, the slower rotating group in stereomutation, by single and double rotation, respectively.

As long as attention is focused only on *trans* educts, a favoring of Woodward−Hoffmann "allowed" paths (*is* and *ra*) has been sustained. But any imputed, more general predictive value evaporates when it is recognized that the *cis* isomers favor the "forbidden", *rs* and *ia* paths! This behavior has been confirmed not only in the comparable cyclobutane, but also in the more recent examples of *cis*-1-phenyl-2(*E*)-propenylcyclopropanes[38] and *cis*-1-phenyl-2(*E*)-styrylcyclopropanes.[39] It is not amiss to restate the usefulness of application of the Woodward−Hoffmann rules: reactions that follow allowed paths *may* be concerted in mechanism, while reactions that follow forbidden paths are *not* concerted.

The favoring of *trans* isomers in ring enlargement is consistent with a thermochemical advantage, but the substantial favoring of one enantiomer over its mirror image appears to originate in the dynamics of internal rotations. The model of a diradical as intermediate, *fully* equilibrated in the caldera, is not supported in ring enlargement, although the similarity in distribution of products from both educts suggests a partial approach to equilibrium within the caldera prior to exit.

Each of the three related examples of the behavior of both *cis* and *trans* educts has required a notable amount of exacting work, and has been more than justified by having provided a definitive answer to the long-standing issue of the role of the Woodward−Hoffmann rules in not obviously concerted thermal rearrangements. A better understanding of the centrally important internal rotational component may involve examination of more disparately substituted examples, but other still arcane aspects may well demand new experimental and theoretical tactics beyond those utilized here.

Experimental Section

General Procedures. NMR spectra were recorded on Varian T-20 and A-60 spectrometers in $CDCl_3$ unless otherwise stated. Chemical shifts and coupling constants (*J*) are reported in parts per million (δ) from tetramethylsilane and hertz (Hz), respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer model 337 grating spectrophotometer, and are reported in reciprocal centimeters (cm^{-1}). Optical rotations were determined on a Perkin-Elmer 141 digital-readout polarimeter in a 1 dm quartz cell at the reported temperatures ± 0.5 °C, and recorded in grams per 100 mL of solution. Uncertainties in specific rotations are estimated to be no more than ±2%. Preparative separations by HPLC were effected on a Waters Associates ALC instrument with an M-6000 pump. Quantitative analyses were made on a Perkin-Elmer model 990 instrument, relative areas being measured by a Digital Integrator Autolab model 6300-01. Purification and separation of larger samples was

(37) Relatively, the retroene reaction has been slowed enough in this cyclobutane system to allow observation of the stereochemistry of ring enlargement from the *cis* isomer despite the presence of the methyl group at C2.

(38) Baldwin, J. E.; Boncorsi, S. J. *J. Org. Chem.* **1994**, *59*, 7401−7409.
(39) Ascuncion, L. A.; Baldwin, J. E. *J. Am. Chem. Soc.* **1995**, *117*, 10672−10677.

accomplished by means of an Aerograph model A90-P3 instrument employing the following columns: column A, 13 ft × 0.25 in., 10% Carbowax 20M on Anakrom ABS 70/80; column B, 10 ft × 0.25 in., 5% OV 22 on Anakrom ABS 50/60. Exact masses were determined with an AEI model MS-9 double-focusing mass spectrometer. Melting points were determined without correction in a Hershberg apparatus.

(−)-*trans*-2(*E*)-Propenylcyclopropane-1-carboxylic Acid. To a 4.8 g sample of *trans*-1-hydroxymethyl-2(*E*)-propenylcyclopropane (**3**),[12] in 100 mL of acetone, was added 30 mL of 2.67 M Jones reagent (from 26.7 g of CrO_3, 23 mL of concentrated H_2SO_4, and water to bring the volume to 100 mL) over a period of 1 h at 10−15 °C with stirring. After an additional 1 h of being stirred, the mixture was poured onto ice−water, and extracted twice with methylene chloride. This extract was washed with water, dried over $MgSO_4$, and concentrated to a residue. Distillation in vacuo gave 2.6 g of a slightly yellow liquid: ^{1}H NMR spectrum identical with that reported.[40]

A solution of 21 g of this acid and 54.4 g of anhydrous quinine in 140 mL of acetone was allowed to crystallize at 25 °C for 6 h and then at −5 °C for an additional 12 h. Filtered and washed with 100 mL of 1:2 acetone/petroleum ether, this material (21 g) was recrystallized from 50 mL of acetone (6 h at 25 °C; 12 h at −5 °C). After three more recrystallizations, 8.5 g of quinine salt was obtained. Recovered in the usual way, 2.1 g of crude acid was obtained: $[\alpha]^{25}_{578}$ −190° (*c* 0.60, EtOH).

(−)-*trans*-1-Cyano-2(*E*)-propenylcyclopropane [(−)-*trans*-1]. A solution of 4.0 g of crude optically active acid as prepared above and 4.44 mL of triethylamine in 40 mL of methylene chloride was added dropwise at −25 °C under nitrogen over 20 min to a solution of 3.1 mL of ethyl chloroformate in 30 mL of methylene chloride. After an additional period of stirring for 1.5 h at −20 to −5 °C, ammonia was bubbled through the mixture for 20 min. After being stirred further at 25 °C for 1.5 h, the mixture was filtered to remove salts. Concentration left a solid residue, which was crystallized from water to give 2.6 g of (−)-*trans*-2(*E*)-propenylcyclopropane-1-carboxamide: mp 121−122 °C; $[\alpha]^{25}_{D}$ −232° (*c* 0.60, EtOH); ^{1}H NMR (acetone-d_6) 7.5−6.0 (s, 2H), 5.65 (qd, J = 5 and 16 Hz, 1H), 5.1 (dd, J = 7 and 16 Hz, 1H), 2.2−0.6 (m, 4H), 1.6 (d, J = 5 Hz, 3H).

A solution of 1.8 g of *p*-toluenesulfonyl chloride (TsCl) in 2 mL of pyridine was added at 5 °C over a 15 min period to a solution of 1.2 g of the (−)-amide above in 1.5 mL of dry pyridine. After being stirred for 8 h at 10−22 °C, the mixture was diluted with 50 mL of ether. The salts were separated by filtration and washed three times each with 20 mL of ether. The combined ether solutions were washed with cold 0.5 M HCl and water, then dried over $MgSO_4$, and concentrated by distillation to an oil. Separation of the major product by GC (column A, 140 °C; retention time 30 min) from a minor product (2%; retention time 40 min) afforded 0.8 g of (−)-*trans*-**1**: bp 175 °C; ^{1}H NMR (CCl_4) 5.7 (qd, J = 6 and 16 Hz, 1H), 5.0 (dd, J = 7 and 16 Hz, 1H), 2.2−1.7 (m, 1H), 1.7 (d, J = 6 Hz, 3H), 1.5−0.9 (m, 3H); $[\alpha]^{23}_{D}$ −270.2°; $[\alpha]^{23}_{578}$ −280.9°, $[\alpha]^{23}_{365}$ −916.5° (*c* 1.062, EtOH); MS *m*/*z* calcd for C_7H_9N 107.0771, found 107.0732.

(+)-*cis*-1-Cyano-2(*E*)-propenylcyclopropane [(+)-*cis*-1]. A 0.9 g sample of the (−)-*trans*-**1** prepared immediately above was epimerized in 10 mL of dimethyl sulfoxide (DMSO) containing 1 g of sodium methoxide for 20 min at 25 °C. Workup in the usual way (water, ether extraction, washing, drying, concentration by distillation) afforded an oil, which was separated by GC on column A at 140 °C into a fraction (retention time 30 min) of (−)-*trans*-**1** of unchanged specific rotation ($[\alpha]^{23}_{365}$ −916.5°) and one of (+)-*cis*-**1** (retention time 40 min): $[\alpha]^{23}_{D}$ +108.9°; $[\alpha]^{23}_{365}$ +434.9° (*c* 0.699, EtOH); ^{1}H NMR (CCl_4) 5.8 (qd, J = 6 and 15 Hz, 1H), 5.2 (dd, J = 7 and 15 Hz, 1H), 1.8 (d, J = 6 Hz, 3H), 2.2−0.8 (m, 4H). Anal. Calcd for C_7H_9N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.44; H, 8.54; N, 13.12 The ratio of (−)-*trans*-**1** to (+)-*cis*-**1** after equilibration was 50.3:49.7.

Dimethyl (−)-*trans*-1,2-Cyclopropanedicarboxylate. A mixture of 0.4 g of a sample of (−)-*trans*-**1** ($[\alpha]^{23}_{365}$ −199.9° (*c* 0.729, EtOH; ≤21.8% (199.9/916.5) optical purity), 10 mL of 10 M sodium hydroxide, and 10 mL of ethanol was boiled under reflux for 8 h. The solution was extracted with ether, acidified with concentrated aqueous HCl at 0 °C, and extracted with two 50 mL portions of ether. Washed with 10 mL of water, dried over $MgSO_4$, and concentrated, the ethereal extract gave an oil which was treated with an excess of ethereal diazomethane at 0 °C. The usual workup was followed by isolation by GC on column A at 125 °C to give 0.3 g of methyl (−)-*trans*-2(*E*)-propenylcyclopropane-1-carboxylate: $[\alpha]^{23}_{D}$ −55.0°, −54.9°; $[\alpha]^{23}_{365}$ −193.4° (*c* 0.863, 0.815, respectively, CH_3OH); ^{1}H NMR (CCl_4) 5.6 (qd, J = 6 and 16 Hz, 1H), 5.0 (dd, J = 7 and 16 Hz, 1H), 3.6 (s, 3H), 1.65 (d, J = 6 Hz, 3H), 2.1−0.6 (m, 4H).

To a solution of this sample in 40 mL of 80% aqueous *tert*-butyl alcohol was added a solution of 20 mg of potassium permanganate and 2 g of sodium periodate ($NaIO_4$) in 50 mL of water. The pH of the solution was kept between 8 and 9 by the addition of portions of potassium carbonate. After 0.5 h of standing, *tert*-butyl alcohol was removed in vacuo. The resulting aqueous suspension was acidified with concentrated HCl at 0 °C and extracted three times with 50 mL portions of ether. Dried over $MgSO_4$ and concentrated, the resulting solution was treated with excess ethereal diazomethane at 0 °C. The product of the usual workup was separated into major components by GC on column B at 120 °C. The second component had the same retention time and IR spectrum as an authentic sample of dimethyl (−)-*trans*-1,2-cyclopropanedicarboxylate and specific rotations of $[\alpha]^{27}_{D}$ −51.2° and −50.8° and $[\alpha]^{27}_{568}$ −52.9° and −52.6° (*c* 0.635 and 0.724, respectively, CH_3OH) (corresponds to $[\alpha]^{27}_{D} \geq -234°$ for optically pure material).

Resolution of Dihydrosarkomycin. Racemic dihydrosarkomycin (*trans*-2-methyl-3-oxocyclopentanecarboxylic acid) was prepared following the procedure of Newman and McPherson and purified by crystallization from ether: mp 90 °C (lit.[14] mp 94 °C); ^{1}H NMR ($CDCl_3$) 12.0 (s, 1H), 2.8−2.1 (m, 6H), 1.2 (d, J = 6 Hz, 3H). Contrary to the published results, the brucine salt of the (+)-acid was first to crystallize at 37 °C, while the salt of the (−)-acid crystallized from the mother liquor at −20 °C. The (−)-acid from this salt was recrystallized from ether: mp 93.0−94.5 °C after drying in vacuo (lit.[15] mp 98.0−99.5); $[\alpha]^{20}_{D}$ −36.0°, −36.4°; $[\alpha]^{20}_{365}$ −300.9°, −303.9° (*c* 1.124, 1.188, respectively, distilled water) (lit.[15] $[\alpha]^{26}_{D}$ −68.0°).

A sample of this (−)-acid was converted in the usual manner to its methyl ester by diazomethane. Purification of methyl (−)-*trans*-2-methylcyclopentan-3-one-1- carboxylate was effected on column B at 120 °C: $[\alpha]^{22}_{D}$ −39.4°, −39.4°; $[\alpha]^{22}_{365}$ −354.6°, −358.0° (*c* 1.037, 1.752, respectively, EtOH); ^{1}H NMR (CCl_4) 3.7 (s, 3H), 2.8−1.95 (m, 6H), 1.1 (d, J = 6 Hz, 3H).

Methyl (+)-*trans*-3-Methylcyclopentene-4-carboxylate. A solution of 3.0 g of the ester above in 20 mL of tetrahydrofuran (THF) was added at 0 °C over a 5 min period to a solution of 10.0 g of LiAlH-$(OC(CH_3)_3)_3$ in 25 mL of anhydrous THF. After resting at 0 °C for 1 h, the mixture was poured into 100 mL of cold, 5% aqueous acetic acid and extracted twice each with 75 mL of ether. The ethereal solution was washed with 20 mL of saturated aqueous potassium bicarbonate, dried over $MgSO_4$, and concentrated to an oil, which was not explored further but was carried directly to the next step.

A 1 M excess of TsCl was added to a solution of 1.2 g of these alcohols in 25 mL of pyridine. After 34 h at 5 °C, this mixture was poured onto 40 mL of ice−water and extracted twice with 50 mL portions of ether. The ether extract was washed successively with cold 6 M HCl and 10 mL of water until acidic, dried over $MgSO_4$, and concentrated to a crude, solid tosylate.

An 8.0 g sample of the tosylate in 10 mL of THF containing 12 g of diazabicycloundecane (DBU) was heated at 85−90 °C for 8 h under

(40) Lishanskii, I. S.; Pomerantsev, V. I.; Illarionova, N. G.; Khachaturov, A. S.; Vakorina, T. I. *J. Org. Chem. USSR* **1971**, *7*, 1870−1875; *Zh. Org. Khim.* **1971**, *7*, 1803−1810.

nitrogen. Poured onto 20 mL of ice−water, the mixture was extracted twice with 50 mL portions of ether. The combined ether extracts were washed successively with 15 mL of dilute HCl, 15 mL of saturated aqueous sodium bicarbonate, and water, then dried over $MgSO_4$, and concentrated to a solution, which was separated by GC on column A at 120 °C into four components. The first (45%) was identified as methyl (+)-*trans*-3-methylcyclopentene-4-carboxylate: ^{1}H NMR (CCl_4) 5.6 (s, 2H), 3.7 (s, 3H), 3.2−2.4 (m, 4H), 1.2 (d, J = 6 Hz, 2H); $[\alpha]^{23}_D$ +72.9°; $[\alpha]^{23}_{365}$ +244.3° (*c* 0.752, CH_3OH).

(+)-*trans*-4-Cyano-3-methylcyclopentene [(+)-*trans*-2]. The following four steps were effected without isolation of intermediate products. The unseparated mixture of methyl esters immediately above was saponified with 10% aqueous NaOH overnight at 40 °C. The usual workup afforded ∼1 g of carboxylic acids, which were converted to a mixture of acid chlorides by the ethyl chloroformate procedure described above, thence to the amides (without isolation to avoid altering the optical purity), and finally by treatment with TsCl to a mixture of cyano compounds. Separation by GC on column A at 130 °C gave as the first major peak ∼0.2 g [7% overall from dihydrosarkomycin, $[\alpha]^{20}_D$ −36.2° (*c* 1.124, distilled water)] of (+)-*trans*-**2**: ^{1}H NMR (CCl_4) 5.63 (s, 2H), 3.2−2.3 (m, 4H), 1.22 (d, J = 7 Hz, 3H); $[\alpha]^{23}_D$ +101.9°, +101.6°; $[\alpha]^{23}_{365}$ +337.8°, +338.5° (*c* 0.576, 0.615, cyclohexane); MS *m*/*z* calcd 107.0771, found 107.0730.

A 150 mg sample of (+)-*trans*-**2**, $[\alpha]^{23}_{365}$ +337.0° (*c* 1.013, cyclohexane), was boiled under reflux for 10 h in a solution of 5 mL of 10 M NaOH and 5 mL of ethanol. The cooled, two-phase mixture was treated with 6 mL of water, extracted with ether, acidified at 0 °C with concentrated HCl, and extracted three times with 15 mL each of ether. The dried ($MgSO_4$) ethereal extract was concentrated and treated with ethereal diazomethane as described above. Collected by GC, the methyl (+)-*trans*-3-methylcyclopentene-4-carboxylate had $[\alpha]^{23}_{365}$ +244.0° (*c* 0.990, CH_3OH).

(+)-*cis*-4-Cyano-3-methylcyclopentene [(+)-*cis*-2]. To a solution of a 150 mg sample of the **(+)-*trans*-2** above in 1 mL of DMSO was added 100 mg of sodium methoxide at 25 °C under nitrogen. After standing for 20 min, the mixture was treated with 8 mL of water, and worked up in the usual manner. Separation by GC on column A gave recovered (+)-*trans*-**2** [62.3%; $[\alpha]^{23}_{365}$ +337.0° (*c* 0.656, cyclohexane)] and **(+)-*cis*-2** (37.7%): ^{1}H NMR (CCl_4) 5.76 (s, 2H), 3.4−2.6 (m, 4H), 1.2 (d, J = 8 Hz, 3H); $[\alpha]^{23}_D$ +64.4°, +64.9°, +64.2°; $[\alpha]^{23}_{365}$ +224.6°, +225.0°, +223.4° (*c* 0.817, 0.663, 0.457, respectively, cyclohexane); MS *m*/*z* calcd 107.0771, found 107.0717.

Reduction of Methyl (−)-*trans*-3-Methylcyclopentene-4-carboxylate to Methyl (−)-*trans*-2-Methylcyclopentane-1-carboxylate. To 0.8 g of yellow potassium azodicarboxylate in 5 mL of dioxane (distilled from sodium; stored over molecular sieves) under nitrogen was added 200 mg of methyl (−)-*trans*-3-methylcyclopentene-4-carboxylate {$[\alpha]^{23}_D$ −40.1°, $[\alpha]^{23}_{365}$ −134.5° (*c* 0.927, cyclohexane)}, followed by 100 mg of glacial acetic acid in 2.0 mL of dioxane in 0.2 mL portions at intervals of 1.5 h until the yellow salt had been consumed. Extraction with ether, filtration, washing with 5 mL of dilute sodium bicarbonate, washing twice with 10 mL of water, drying over $MgSO_4$, and concentration afforded a crude product from which 100 mg of methyl (−)-*trans*-2-methylcyclopentane-1-carboxylate was isolated by GC on column A at 115 °C: ^{1}H NMR (CCl_4) 3.8 (s, 3H), 2.5−1.0 (m, 8H), 1.1 (br d, J = 7 Hz, 3H); $[\alpha]^{25}_D$ −16.6°, −16.9°, −16.8°; $[\alpha]^{25}_{365}$ −51.2°, −51.1°, −51.3° (*c* 1.036, 0.865, 0.542, respectively, CCl_4).

A solution of 100 mg of methyl (±)-*trans*-3-methylcyclopentene-4-carboxylate in 1 mL of ethyl acetate containing 30 mg of 10% Pd on carbon was shaken under hydrogen for 5 h at 25 °C. The filtered solution was subjected to GC on column A at 115 °C to yield methyl (±)-*trans*-2-methylcyclopentane-1-carboxylate as its major component (80%). The minor product is likely the *cis* isomer: ^{1}H NMR (CCl_4) 3.8 (s, 3H), 3.1−2.6 (m, 1H), 2.5−1.2 (m, 7H), 0.95 (d, J = 7 Hz, 3H).

General Method for Kinetics. Thermal rearrangements in the gas phase or in solution were effected in sealed Pyrex ampules (100 × 4 mm i.d.) suspended in the vapors of boiling tetralin at 207.1 °C in a 1 L Pyrex flask fitted with a 46 × 5 cm neck. These ampules had been prepared beforehand by first soaking in aqueous ammonia (20%) overnight, rinsing with water and acetone, drying, then treating with dichlorodimethylsilane (20% in benzene), rinsing with benzene and acetone, and drying. The lower 36 cm of the bath was insulated with several layers of asbestos and a final wrapping of Fiberglas. The uncovered upper portion of the neck served as an air-cooled condenser. The temperature of the vapors was measured with an iron−constantan thermocouple and a Leeds and Northrop no. 8686 millivolt potentiometer. In no runs did temperature fluctuation exceed 0.3 °C. Samples were purified before use by GC, and transferred by microsyringe to the ampules, which were then sealed under reduced pressure (∼10^{-4} mmHg), and suspended in the boiling vapors by means of a wire hook. The time lag to thermal equilibrium was ∼1 min.

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Supporting Information Available: A figure complementing Figure 6 and three tables of kinetic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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