Thermal Stereomutations of 1-Ethyl-2-methyl-1,2,3-trideuteriocyclopropanes

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Abstract: (−)-(1*R*,2*R*,3*S*)-1-Ethyl-2-methyl-1,2,3-trideuteriocyclopropane and (−)-(1*S*,2*R*,3*R*)-1-ethyl-2-methyl-1,2,3-trideuteriocyclopropane were synthesized and heated at 380 °C in the gas phase; the thermal stereomutations shown by these substrates were followed as a function of time by gas chromatography, ^{1}H NMR spectroscopy, and polarimetry. From the rate constants measured it was found that one-center epimerizations at C(3) are kinetically competitive and inferred that, for the trans (1*R*,2*R*,3*S*) substrate, $(k_1 + k_2):k_{12} \approx 2:1$. For the thermal stereomutations interconverting the eight isomeric 1-ethyl-2-methyl-1,2,3-trideuteriocyclopropanes, the most substituted bond hypothesis is not valid and two-center epimerizations corresponding to concerted electrocyclic processes are not kinetically dominant.

Introduction

Ever since 1958, when Rabinovitch, Schlag, and Wiberg[1] discovered the thermal interconversion of the cis and trans isomers of 1,2-dideuteriocyclopropane, there have been repeated attempts to elucidate the mechanism of such isomerizations and to understand the role possibly played by trimethylene diradical transition structures and intermediates.[2]

Despite this sustained theoretical and experimental activity, no general mechanistic model able to rationalize the relative significance of one-center and two-center epimerization processes for all substituted cyclopropane systems examined kinetically has emerged and gained widespread acceptance. That the relative magnitudes of one-center (k_j) and two-center (k_{jl}) rate constants are the key to experimentally based probes of mechanism was recognized clearly in 1964 by Setser and Rabinovitch,[3] but these rate constants in many cases have been quite difficult to measure. For the 1-methyl-2,3-dideuteriocyclopropane isomers, for example, synthetic and analytical limitations restricted kinetic experiments to such an extent that only a single rate constant, one governing approach to the equilibrium mixture of geometrical isomers, could be determined.[3] In terms of one-center and two-center rate constants, this experimentally observed kinetic parameter equals $(k_1 + k_2 + k_{13} + k_{23})$, and the contribution made by each of the four mechanistically significant k_j and k_{jl} processes remained[3] and remains unknown.

In 1968 Bergman and Carter[4] progressed toward meeting these limitations through undertaking kinetic studies on chiral versions of the cis and trans isomers of 1-ethyl-2-methylcyclopropane. They followed stereomutation kinetics for geometric isomerization by gas chromatography and for racemization of the system of isomers by polarimetry. To interpret the experimental data, two assumptions were employed: that the cis product formed from a chiral trans reactant was essentially racemic, and that all stereomutations dependend on cleavage of the C(1)–C(2) bond of a cyclopropane reactant, the "most substituted bond hypothesis". These assumptions, supported by some experimental observations and by thermochemical estimates, reduced the number of kinetics unknowns for the trans isomer from six (k_1, k_2, k_3, k_{12}, k_{13}, k_{23}) to two ($k_1 = k_2$, and k_{12}) and enabled Bergman and Carter to deduce that k_1 and k_{12} were nearly equal between 377.2 and 438.7 °C; thus there was no indication that an electrocyclic process plays any significant role in the mechanism, for it would have required $k_{12} \gg k_1$.[4]

These two studies with deuterium-labeled methylcyclopropanes[3] and chiral 1-ethyl-2-methylcyclopropanes[4] were admittedly incomplete, but they nevertheless contributed important results, defining the essential problems to be faced experimentally and providing an early indication that two-center epimerizations are not kinetically dominant in the thermal stereomutations of the isomeric 1-ethyl-2-methylcyclopropanes. In the years since these pioneering investigations were published no other kinetics studies of the thermal stereomutations interconverting isomeric isotopically labeled monoalkyl- or 1,2-dialkylcyclopropanes have appeared.

For representative *trans*-1,2-disubstituted cyclopropanes having at least one reasonably effective radical stabilizing substituent,[5] and for isotopically labeled versions of phenylcyclopropane,[6] kinetic studies have established that $(k_1 + k_2)$ is equal to or larger than k_{12}. For one isotopically labeled version of an otherwise unsubstituted cyclopropane,[7] the same pattern has been observed experimentally, but for the isomeric 1,2-dideuteriocyclopropanes, it has been[8] and is still being argued[9] that $k_{12} \gg k_1$.

The present work returns to the stereomutations of chiral 1-ethyl-2-methylcyclopropanes, introducing deuterium labeling at C(3) to permit a check for thermally induced stereochemical changes at that center and thus a test for the "most substituted bond hypothesis" applied to this system. Deuterium labels at C(1) and C(2) are incorporated to simplify the ^{1}H NMR spectra of C(3) epimers. A synthetic strategy allowing reasonably facile access to a variety of alkyl-substituted and multiply deuteriated cyclopropanes was developed and used. The kinetic results obtained show that the C(3)DH groups in (−)-(1*R*,2*R*,3*S*)- and (−)-(1*S*,2*R*,3*R*)-1-ethyl-2-methyl-1,2,3-trideuteriocyclopropane do epimerize at competitive rates, and thus that stereomutations depending on C(1)–C(3) and C(2)–C(3) bond cleavages contribute to the stereomutation events observed. The "most substituted bond hypothesis" applied by Bergman and Carter[4] to enable their kinetics analysis is accordingly not appropriate, and yet their essential experimental finding and mechanistic insight have been confirmed: the one-center and two-center epimerization rate constants for the trans substrate, k_1 and k_{12}, are of comparable magnitude, and there are no experimental grounds for invoking a kinetically

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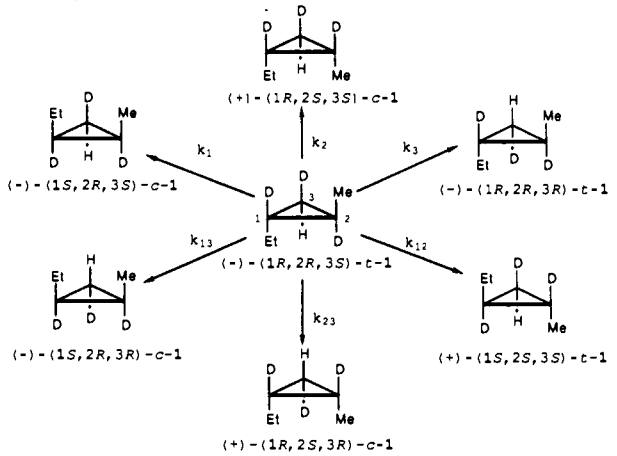
Scheme I



preemptive electrocyclic two-center epimerization process.

The thermal stereomutations interconverting the eight isomers of 1-ethyl-2-methyl-1,2,3-trideuteriocyclopropane were followed, starting from one trans and from one cis substrate, the trideuteriated and chiral 1-ethyl-2-methylcyclopropanes (−)-(1*R*,2*R*,3*S*)-*t*-**1** and (−)-(1*S*,2*R*,3*R*)-*c*-**1**.

(−)-(1*R*,2*R*,3*S*)-*t*-**1** (−)-(1*S*,2*R*,3*R*)-*c*-**1**

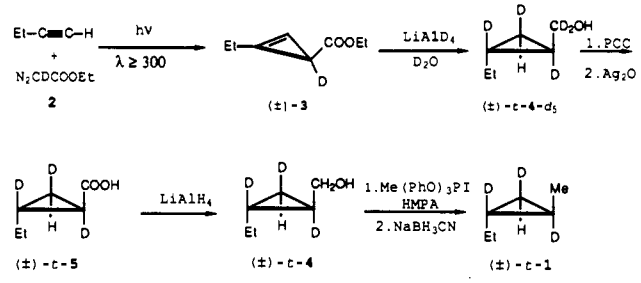
The deuterium label at C(3) in these substrates creates a chiral center without causing any significant perturbation in the cis,trans equilibrium constant, and it permits one to measure the rates of one-center epimerization at C(3). The ethyl and methyl groups, which would be expected to contribute relatively small stabilization energies in dialkyl-substituted trimethylene diradicals, provide for a meaningful test of the validity of the "most substituted bond hypothesis" in a 1,2-dialkylcyclopropane system.

The complex kinetics situation describing the stereomutation processes to be analyzed is outlined in Scheme I; with (−)-(1*R*,2*R*,3*S*)-*t*-**1** as reactant, the relationships between rate constants k_j and k_{jl} and the corresponding isomeric products are illustrated. Fortunately, no additional experimental complications arise through the formation of significant amounts of side products under the reaction conditions employed; the stereomutations are uncomplicated by the much slower structural isomerizations to olefins. For any single isomer of the set of eight stereoisomers of **1**, there are three one-center and three two-center epimerization paths available. Each one of these pathways results in a unique stereoisomer. The only isomer out of the set of eight omitted in Scheme I is the optical antipode of (−)-(1*R*,2*R*,3*S*)-*t*-**1**, which could be formed directly only through a simultaneous three-center process (k_{123}), a formal possibility unsupported by any experimental data or theoretical model.

For each one of the eight isomers there are six possible stereomutation pathways; thus 48 rate constants are needed to describe the time evolution of isomers in this system of trisubstituted cyclopropanes. With one deuterium at C(3) as a stereochemical marker, this kinetic complexity reduces to manageable proportions, for there are only nine independent variables, eight rate constants and one equilibrium constant. Four rate constants define the reactions leading from each trans to the four cis isomers (k_1, k_2, k_{13}, k_{23}); two describe the conversion of one trans isomer to other trans isomers (k_3, k_{12}), and two more describe the isomerizations converting one cis stereoisomer to other cis stereoisomers (k'_3, k'_{12}). All other rate constants can be derived from these eight rate constants and the equilibrium constant, thanks to microscopic reversibility.

The set of differential equations describing this kinetics situation of eight interconverting isomers may be solved exactly in integrated form. A computer program, utilizing a simplex optimization procedure,[10,11] uses this mathematical solution together with values for the independent parameters described above to calculate the concentrations of individual isomers as a function of time. Calculated and experimental concentration values are compared as the rate constants are varied systematically by the simplex program to optimize the match between experimental data sets and calculated concentrations. The experimental data required for this approach are secured through GC analyses of thermolysis reaction mixtures to determine the cis to trans isomer ratios, separation of cis and trans isomer sets by preparative GC, and analysis of these by ^{1}H NMR spectroscopy and by polarimetry.

Scheme II



Results

Syntheses. The racemic *trans*-1-ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane isomer (±)-*t*-**1** was synthesized through the sequence of reactions depicted in Scheme II. The photolytic addition of ethyl α-deuteriodiazoacetate (**2**)[12] to a large excess of 1-butyne gave 1-ethyl-3-ethoxycarbonyl-3-deuteriocyclopropene (**3**) as the major product. There are reports that low yields of cyclopropene adducts from such additions to terminal alkynes may result from competing insertion processes,[13] but in this case (ethoxycarbonyl)cyclopropene **3** was secured in satisfactory yield: according to capillary GC estimates, 79% of the photolysis product mixture was adduct **3**, with 5% of unreacted diazoester **2** and only 16% of three unidentified side products present. Deuterium incorporation at C(3) was nearly quantitative, according to a ^{1}H NMR spectroscopic estimation.

The subsequent reduction of cyclopropene ester **3** with lithium aluminum deuteride, followed by a quench with deuterium oxide,[14] gave the deuterium-labeled alcohol (±)-*t*-**4**-d_5 (37% overall, from diazoester **2**, after distillation).

The oxidation of (±)-*t*-**4**-d_5 to carboxylic acid (±)-*t*-**5** was accomplished in two steps. Alcohol (±)-*t*-**4**-d_5 was first oxidized with pyridinium chlorochromate in methylene chloride at room temperature to the corresponding aldehyde,[15] which was treated immediately with silver(I) oxide and aqueous sodium hydroxide to give *trans*-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic acid ((±)-*t*-**5**) in an overall yield of 56%.[16] This acid was then

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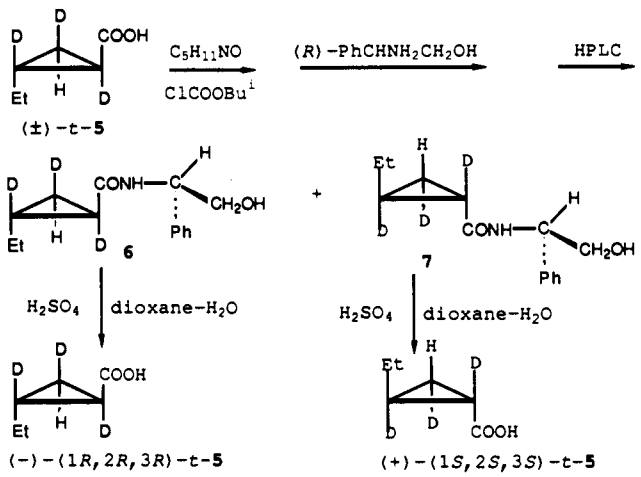
Scheme III



reduced with lithium aluminum hydride in ether to give *trans*-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanemethanol ((±)-*t*-**4**).[17]

Several routes for the conversion of alcohol (±)-*t*-**4** to the desired *trans*-1-ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((±)-*t*-**1**) were explored. For some of the (±)-*t*-**1** prepared, the alcohol was esterified with methanesulfonyl chloride in pyridine, and the relatively unstable mesylate was reduced in situ with lithium aluminum hydride[18] to give hydrocarbon (±)-*t*-**1** in 17% yield after purification and isolation by preparative gas chromatography. A simple and convenient two-step, one-pot process[19] proved to be a more efficient approach. Primary alcohol (±)-*t*-**4** was transformed first into the corresponding iodide with methyltriphenoxyphosphonium iodide in HMPA; then sodium cyanoborohydride was added, and the reaction mixture was stirred at temperatures up to 70 °C for up to 3 h. The product could be simply trapped in a cooled glass coil after the application of aspirator vacuum to the heated reaction flask. The GC isolated *trans*-1-ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((±)-*t*-**1**, 42% yield) was 100% structurally homogeneous, according to capillary GC estimations. The ^{1}H NMR spectrum of this hydrocarbon showed the expected signals for ethyl, methyl, and one C(3)H hydrogen, at δ 0.12 ppm. There was also apparent a much less intense signal, a doublet at δ 0.09, ascribable to C(3)H trans-to-ethyl from a $C(3)H_2$ contaminant from incomplete deuterium incorporation.

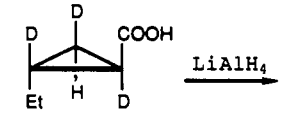
Racemic carboxylic acid (±)-*t*-**5** was resolved by way of diastereomeric amide derivatives (Scheme III).[20] Acid (±)-*t*-**5** was first converted to a mixed anhydride using *N*-methylmorpholine and isobutyl chloroformate,[21] and the anhydride was combined with (-)-(*R*)-2-phenylglycinol to afford the (1*R*,2*R*,3*R*) and (1*S*,2*S*,3*S*) diastereomers of *N*-(2-hydroxy-(1*R*)-phenylethyl)-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxamide, **6** and **7**.

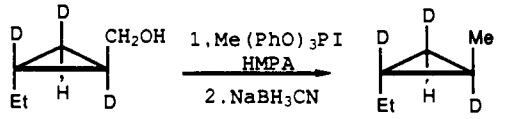
Initially, one-third of the mixture of diastereomers was separated by flash column chromatography. Due to the relatively large quantities of sample loaded on the column per elution, complete base-line separation was not achieved, and only the earlier eluting, less polar amide **6** was isolated diastereomerically pure; the later eluting fractions rich in amide **7** contained some of the diastereoisomer **6**.

Most of the 50:50 mixture of diastereomeric amides and the mixture enriched in the more polar amide **7** were resolved to secure the individual isomers through preparative HPLC on a Nucleosil column, using 7:3 ethyl acetate isooctane and a flow rate of 15 mL/min; the resolution was excellent, and large quantities of the amides could be separated easily and completely. The collected fractions of **6** and **7** were shown by chromatography on an analytical HPLC column to be diastereomerically pure.

The earlier eluting amide **6** was subjected to an acidic hydrolysis by heating it at reflux overnight in a solution of 3 N sulfuric acid in dioxane/water (1:1). Resolved (-)-(1*R*,2*R*,3*R*)-*trans*-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic acid was isolated in 94% yield. After GC purification it had $[\alpha]_D$ -73.8° (EtOH).

The last three steps to the desired chiral hydrocarbon (-)-(1*R*,2*R*,3*S*)-*t*-**1** were carried out as described above for the racemic compound. The GC-isolated (-)-(1*R*,2*R*,3*S*)-*t*-**1**, identical in ^{1}H NMR spectroscopic characteristics and by analytical GC to the racemic analog (±)-*t*-**1**, had $[\alpha]_D$ -39.0° and $[\alpha]_{365}$ -114° (*n*-heptane).





The preparation of (-)-(1*S*,2*R*,3*R*)-*cis*-1-ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((-)-(1*S*,2*R*,3*R*)-*c*-**1**) is outlined in Scheme IV. The more polar second-eluting amide **7** derived from racemic carboxylic acid (±)-*t*-**5** and (*R*)-phenylglycinol (Scheme III) was hydrolyzed with 3 N H_2SO_4 in dioxane/water to give (+)-(1*S*,2*S*,3*S*)-*trans*-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic acid, $[\alpha]_D$ +75.6° (EtOH). Treatment of carboxylic acid (+)-*t*-**5** with thionyl chloride gave the corresponding acid chloride; the crude acid chloride was diluted with ether, and ammonia was bubbled through the solution until all of the chloride was consumed to yield (1*S*,2*S*,3*S*)-*trans*-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxamide.[22]

Dehydration of this amide with phosphorus pentoxide in dry benzene at reflux in the presence of dry triethylamine provided the desired (1*S*,2*S*,3*S*)-*trans*-1-cyano-2-ethyl-1,2,3-*cis*-trideuteriocyclopropane (*t*-**9**).[23] The nitrile *t*-**9** was subjected to a base-catalyzed epimerization, using potassium *tert*-butoxide in *tert*-butyl alcohol-OD, followed by a quench with deuterium oxide. This procedure gave a 1:1 mixture of nitriles *t*-**9** and *c*-**9**, which were (imperfectly) separated by preparative GC. A second epimerization of recovered *t*-**9** was carried out to secure more *c*-**9**.

Hydrolysis of nitrile (1*R*,2*S*,3*S*)-*c*-**9** with sodium deuteroxide in deuterium oxide under reflux, followed by acidification of the product mixture by addition to a mixture of concentrated sulfuric acid and crushed ice,[24] gave (-)-(1*R*,2*S*,3*S*)-*cis*-2-ethyl-1,2,3-*trans*-trideuteriocyclopropanecarboxylic acid ((-)-*c*-**5**). The GC purified cis acid had $[\alpha]_D$ -58° (EtOH). Reduction of acid (-)-*c*-**5** with lithium aluminum hydride afforded (1*R*,2*S*,3*S*)-*cis*-1-

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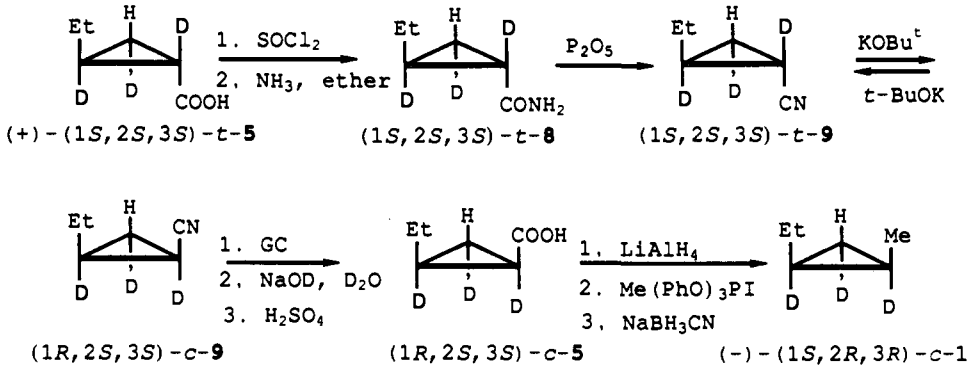
Scheme IV



hydroxymethyl-2-ethyl-1,2,3-*trans*-trideuteriocyclopropane, which upon conversion to the corresponding iodide with methyltriphenoxyphosphonium iodide in HMPA and subsequent in situ reduction with sodium cyanoborohydride finally gave (−)-(1*S*,2*R*,3*R*)-*cis*-1-ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((−)-(1*S*,2*R*,3*R*)-*c*-**1**).

Suitable preparative GC parameters for complete separation of chiral *t*-**1** and *c*-**1** samples were established using mixtures of (±)-*t*-**1** and racemic *cis*-1-ethyl-2-methylcyclopropane secured from the American Petroleum Institute. Purification of the crude product mixture from the methyltriphenoxyphosphonium iodide and sodium cyanoborohydride reactions by preparative GC under identical conditions afforded (−)-(1*S*,2*R*,3*R*)-*c*-**1** uncontaminated by any trans isomer, but, unexpectedly, there were three other products eluting together with the cis product peak, amounting to 15.5, 4.0, and 0.5% of the material collected, according to capillary GC analyses. Further purification by preparative GC at a much lower column temperature yielded (−)-(1*S*,2*R*,3*R*)-*c*-**1** in 93.3% purity. The two impurities still present amounted to 2.0 and 4.7%, respectively, of the GC purified material.

Mechanistic considerations, as well as ^{1}H NMR spectroscopic indications, led to possible identifications of these two side products as deuterium-labeled versions of *n*-propylcyclopropane and ethylcyclobutane; neither would be expected to have a substantial rotation. The 93.3% pure (−)-(1*S*,2*R*,3*R*)-*c*-**1** had $[\alpha]_D$ −20.0° and $[\alpha]_{365}$ −67.4°, or $[\alpha]_D$ −21.5° and $[\alpha]_{365}$ −72.5° ($CDCl_3$) after correction.

Kinetic Data and Data Reduction. Three versions of 1-ethyl-2-methyl-1,2,3-trideuteriocyclopropane were employed as reactants in these studies of stereomutation kinetics: (±)-*t*-**1**, (−)-(1*R*,2*R*,3*S*)-*t*-**1**, and the chiral cis isomer (−)-(1*S*,2*R*,3*R*)-*c*-**1**. Each thermolysis run was conducted in a static gas-phase reactor at 380.0 °C at pressures ranging from 103 to 122 Torr, well within the high-pressure region for these hydrocarbons.[25] All eight kinetic runs for trans reactants were carried out with neat material, while the single run using cis starting material used pentane as an inert bath-gas, for only a small amount of sample was available. Vacuum line transfer techniques were used to introduce each sample into the reactor and to collect it after a kinetic run.

Each thermolysis reaction mixture was analyzed by capillary GC to give the ratio of all cis to all trans isomers. Three analyses were done for each kinetic run, and integrated area percent data were averaged and normalized. Calculations based on the linear dependence of $\ln\{1 - (1 + K_{eq})\chi_{cis}\}$ versus time for this reversible approach to cis, trans equilibrium starting from a trans isomer, and of $\ln\{1 - (1 + 1/K_{eq})\chi_{trans}\}$ starting from a cis isomer, with K_{eq} = [trans]/[cis] at equilibrium, gave K_{eq} = 2.67 and the rate constant $k_i = (k(t \rightarrow c) + k(c \rightarrow t)) = 2.58 \times 10^{-5}$ s^{-1}; hence $k(t \rightarrow c) = (k_1 + k_2 + k_{13} + k_{23}) = 0.70 \times 10^{-5}$ s^{-1}. The observed and calculated mol % concentrations of the *t*-**1** and *c*-**1** isomer sets as a function of time are listed in Table I.

Next, the thermolysis mixtures were separated into two subsets of cis and trans stereoisomers by preparative GC. Under the conditions employed the geometric isomers *t*-**1** and *c*-**1** were readily separated, for the retention time difference was about 6 min.

(25) Elliot, C. S.; Frey, H. M. *J. Chem. Soc.* **1964**, 900–902.

Table I. Calculated[a] and Observed[b] Mol % Concentrations of *t*-**1** and *c*-**1** from Thermal Stereomutations at 380.0 °C of (±)-*t*-**1**, (−)-(1*R*,2*R*,3*S*)-*t*-**1**, and (−)-(1*S*,2*R*,3*R*)-*c*-**1**

reactant	time (min)	*t*-1	*c*-1
(±)-*t*-1	0	100	0
	277	90.1 (90.5)	9.9 (9.5)
	583	83.8 (83.8)	16.2 (16.2)
	1104	77.4 (77.7)	22.6 (22.3)
	4052	72.8 (72.8)	27.2 (27.2)
(1*R*,2*R*,3*S*)-*t*-1	0	100	0
	120	93.7 (95.4)	6.3 (4.6)
	240	89.5 (91.5)	10.5 (8.5)
	486	83.8 (85.6)	16.2 (14.4)
	720	80.6 (81.7)	19.4 (18.3)
(1*S*,2*R*,3*R*)-*c*-1	0	0	100
	180	21.9 (17.7)	78.1 (82.3)

[a] Calculated values are in parentheses; these values were calculated using K_{eq} = 2.67 and $k_i = 2.58 \times 10^{-4}$ s^{-1}. [b] Analytical GC area % data.

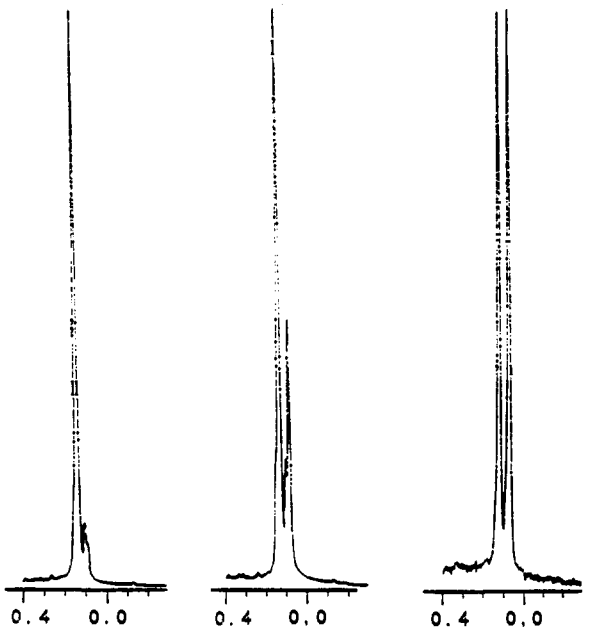


Figure 1. ^{1}H NMR spectra for the C(3)H signals of (−)-(1*R*,2*R*,3*S*)-*t*-**1** (left), the *t*-**1** isomer set after thermolysis of (−)-(1*R*,2*R*,3*S*)-*t*-**1** for 1104 min at 380.0 °C, isolated by preparative GC (center), and the *t*-**1** isomer set after thermolysis of (−)-(1*S*,2*R*,3*R*)-*c*-**1** for 180 min at 380.0 °C, isolated by preparative GC (right).

Proton NMR spectroscopy was employed to determine the relative proportions of the two stereochemical possibilities at C(3) in cis and trans isomers, which are the data needed to determine the magnitudes of the four independent rate constant sums between the paired sets of enantiomerically related stereoisomers shown in Scheme V. The hydrogen atom at C(3) in all four enantiomerically related pairs of **1** isomers appears as a distinct singlet:

Scheme V

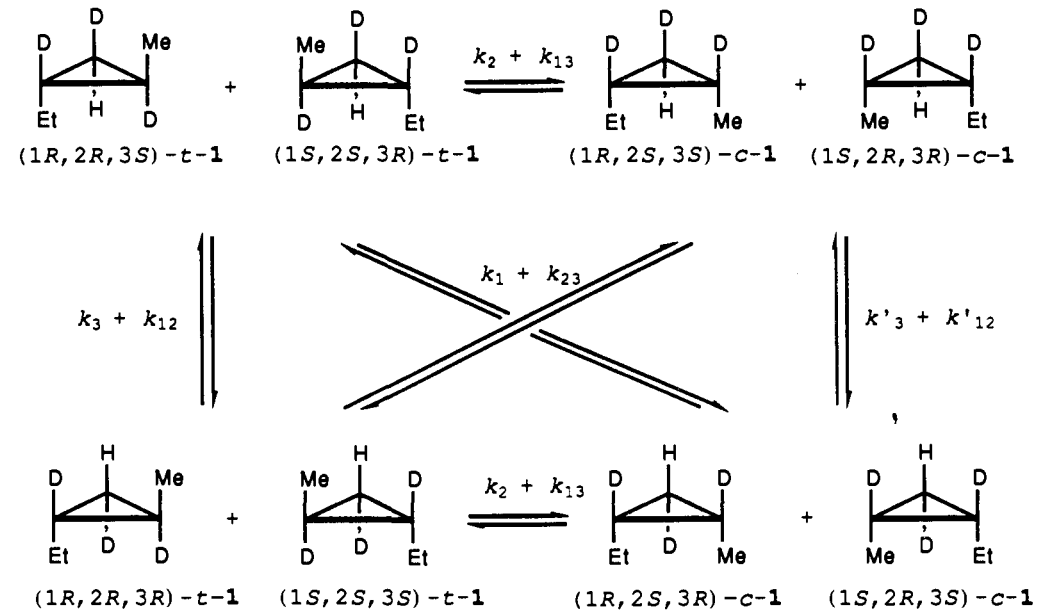


Table II. Calculated[a] and Observed Mol % Data for Curve-Fitted ^1H NMR Specta for C(3)H in Thermolysis Product Mixtures

time (min)	((1*R*,2*R*,3*S*)+(1*S*,2*S*,3*R*))-*t*-**1**	((1*R*,2*R*,3*R*)+(1*S*,2*S*,3*S*))-*t*-**1**	((1*R*,2*S*,3*S*)+(1*S*,2*R*,3*R*))-*c*-**1**	((1*R*,2*S*,3*R*)+(1*S*,2*R*,3*S*))-*c*-**1**
From Thermolyses of (−)-(1*R*,2*R*,3*S*)-*t*-**1**				
0	100	0	0	0
120	–[b] (91.1)	–[b] (4.3)	2.3 (2.3)	2.3 (2.3)
240	81.3 (83.5)	10.2 (8.0)	4.3 (4.2)	4.3 (4.2)
486	70.3 (71.1)	15.3 (14.5)	7.2 (7.2)	7.2 (7.2)
720	62.7 (62.4)	19.0 (19.4)	9.2 (9.1)	9.2 (9.1)
From Thermolyses of (±)-*t*-**1**				
1104	54.4 (52.6)	23.3 (25.2)	11.2 (11.1)	11.2 (11.1)
4053	37.0 (36.9)	35.8 (36.0)	13.6 (13.6)	13.6 (13.6)
From Thermolyses of (−)-(1*S*,2*R*,3*R*)-*c*-**1**				
0	0	0	100	0
180	8.9 (8.8)	8.9 (8.9)	74.5 (74.5)	7.8 (7.8)

[a] Calculated mol % entries based on $K_{eq} = 2.67$, $(k_1 + k_{23}) = (k_2 + k_{13}) = 0.35 \times 10^{-5}$ s^{-1}, $(k_3 + k_{12}) = 0.63 \times 10^{-5}$ s^{-1}, and $(k'_3 + k'_{12}) = 0.94 \times 10^{-5}$ s^{-1}. [b] No relative intensity data available.

Table III. Observed and Calculated[a] Mol % Concentrations of the Isomer Pairs in Scheme VI

time (min)	((1*R*,2*R*,3*S*)+(1*R*,2*R*,3*R*))-(−)-*t*-**1**	((1*S*,2*S*,3*S*)+(1*S*,2*S*,3*R*))-(+)-*t*-**1**	((1*R*,2*S*,3*S*)+(1*R*,2*S*,3*R*))-(+)-*c*-**1**	((1*S*,2*R*,3*S*)+(1*S*,2*R*,3*R*))-(−)-*c*-**1**
From Thermolyses of (−)-(1*R*,2*R*,3*S*)-*t*-**1**				
0	100	0	0	0
240	87.6 (87.8)	3.9 (3.7)	4.3 (4.2)	4.3 (4.3)
480	78.3 (78.3)	7.3 (7.4)	7.2 (7.1)	7.2 (7.2)
720	70.8 (70.6)	10.9 (11.0)	9.2 (9.2)	9.2 (9.2)
From Thermolyses of (−)-(1*S*,2*R*,3*R*)-*c*-**1**				
0	0	0	0	100
180	8.9 (8.9)	8.9 (8.9)	7.3 (7.2)	75.0 (75.0)

[a] Calculated mol % entries based on $K_{eq} = 2.67$, $(k_1 + k_{13}) = 0.35 \times 10^{-5}$ s^{-1}, $(k_2 + k_{23}) = 0.35 \times 10^{-5}$ s^{-1}, $k_{12} = 0.24 \times 10^{-5}$ s^{-1}, and $k'_{12} = 0.85 \times 10^{-5}$ s^{-1}.

Table IV. Experimentally Determined Rate Constants at 380.0 °C for Stereomutations Defined in Schemes V and VI

sums of rate constants[a]	individual rate constants[a]
$(k_1 + k_{13}) = 0.35$	$k_{12} = 0.24$
$(k_2 + k_{13}) = 0.35$	$k'_{12} = 0.85$
$(k_1 + k_{23}) = 0.35$	$k_3 = 0.39$
$(k_2 + k_{23}) = 0.35$	$k'_3 = 0.09$

[a] All $\times 10^{-5}$ s^{-1}.

for the trans isomers they are relatively close together, at δ 0.12 and 0.09 (Figure 1), and for the cis isomers (Figure 2) they are well separated, at δ −0.38 in (1*S*,2*R*,3*R*)-*c*-**1** and at δ 0.53 in a C(3) epimer, relative to the residual proton signal of $CDCl_3$ at δ 7.26.

All ^1H NMR spectra collected for the kinetics analyses were curve fitted with sums of Lorentzian-type curves, and isomer ratios were derived from relative intensity data provided by the curve-fitting software.[26] The asymmetry visible on the low-field side of peaks in the experimental spectra is apparently related to instrumental artifacts rather than incomplete isotopic substitution, for it was seen in NMR spectra of unlabeled samples as well.

The experimental values for the mol % concentrations of isomers from these spectra were based on the previously determined best total trans and cis isomer values and on the relative intensities of the two NMR singlets shown by C(3)H in trans and in cis isomers. An optimal fit to the experimental data using a computer program based on the exact solution to the differential equations describing this kinetics situation[10,11] afforded the values $K_{eq} = 2.67$ and the rate constants sums $(k_1 + k_{23}) = 0.35 \times 10^{-5}$ s^{-1}, $(k_2 + k_{13}) = 0.35 \times 10^{-5}$ s^{-1}, $(k_3 + k_{12}) = 0.63 \times 10^{-5}$ s^{-1}, and $(k'_3 + k'_{12}) = 0.94 \times 10^{-5}$ s^{-1}. Calculated and experimental mol % concentration data for Scheme V are collected in Table II.

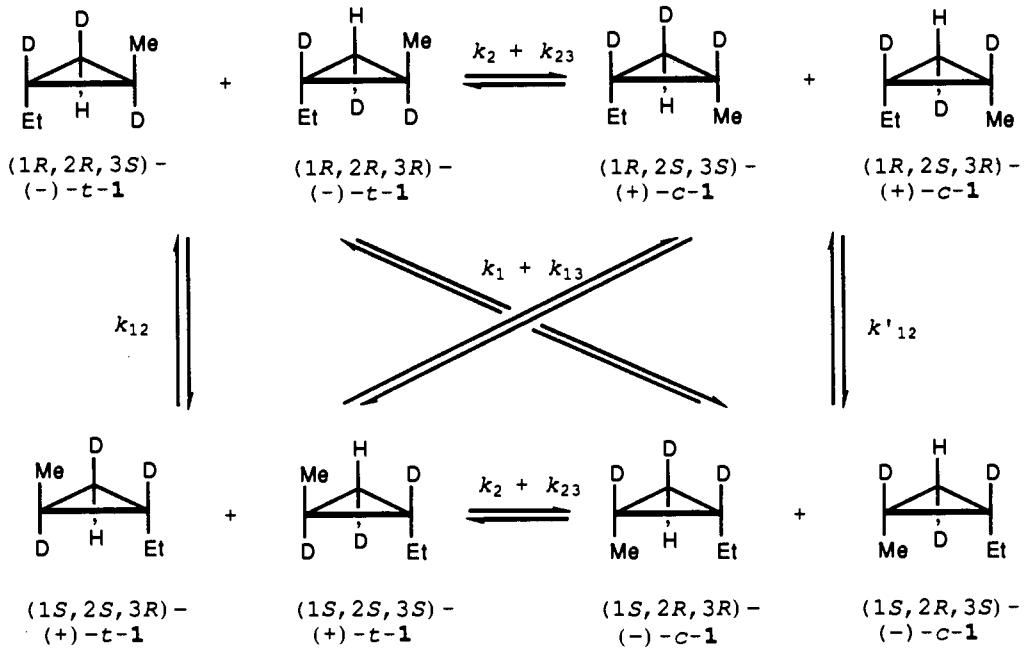
The subset of stereoisomers illustrated in Scheme VI was analyzed by means of polarimetric measurements on the cis and trans samples isolated by preparative GC. Kinetic Scheme VI is similar to Scheme V, but the criteria for pairing stereoisomers are different. Each pair of isomers now has the same absolute stereochemistry at C(1) and C(2); the contribution of deuterium at C(3) to the observed optical rotations of the samples was taken to be negligible.[27] The rotational measurements for each set of trans and cis isomers from the kinetics runs were made with $CDCl_3$ solutions, the same solvent used for ^1H NMR spectroscopic analyses.

The data needed to analyze the stereomutations according to Scheme VI was derived by combining the total cis and total trans isomer ratios determined earlier and the $[\alpha]_{365}$ values determined for the GC purified kinetics samples. Simplex optimization then gave $(k_2 + k_{23}) = 0.35 \times 10^{-5}$ s^{-1}, $k_{12} = 0.24 \times 10^{-5}$ s^{-1}, $(k_1 + k_{13}) = 0.35 \times 10^{-5}$ s^{-1}, and $k'_{12} = 0.85 \times 10^{-5}$ s^{-1}. The observed

(26) *Lab One NMR1*; New Methods Research, Inc.: Syracuse, NY, 1987; Release 3.8.

(27) Runge, W. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Part 1, Chapter 2.

Scheme VI



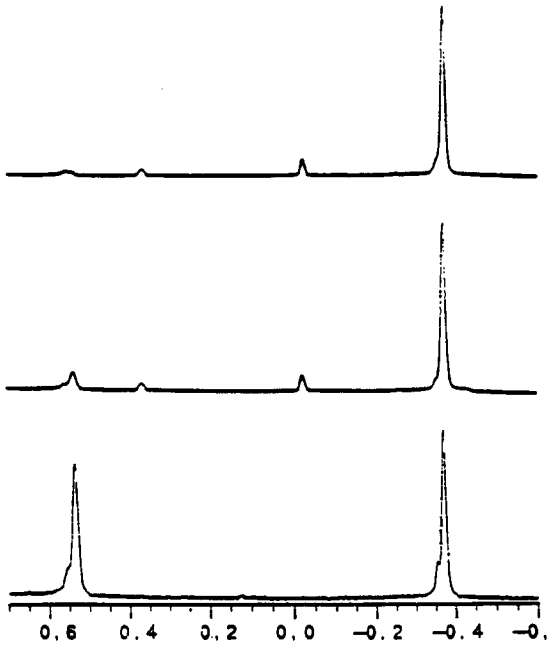


Figure 2. ^{1}H NMR spectra for the C(3)H signals of (-)-(1*S*,2*R*,3*R*)-*c*-**1**, showing as well absorptions assigned to impurities (top); of the *c*-**1** isomer set after thermolysis of (-)-(1*S*,2*R*,3*R*)-*c*-**1** for 180 min at 380.0 °C, isolated by preparative GC (middle); and of the *c*-**1** isomer set from the product mixture formed through thermolysis of (±)-*t*-**1** for 1104 min, isolated by preparative GC (bottom).

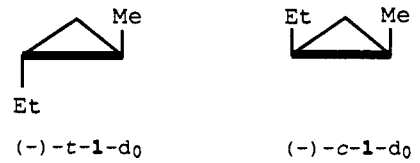
and calculated mol % concentrations corresponding to Scheme VI are given in Table III.

All cis isomer mixtures isolated from kinetic points which started with chiral trans material displayed no residual optical activity and were totally equilibrated at C(3) (Figure 2), and the trans isomer set isolated after pyrolysis of (-)-(1*S*,2*R*,3*R*)-*c*-**1** showed no measurable optical activity and was also fully equilibrated at C(3) (Figure 1); the stereomutation paths for geometrical isomerization convert a chiral substrate stereospecifically deuterium labeled at C(3) to racemic product totally stereochemically equilibrated at C(3).

Table IV summarizes the kinetics results, segregating pairs of mechanistic rate constants determined as sums and individual rate constants. The sums are not linearly independent and may not be converted into the individual rate constants without an investment of additional experimental data.

Discussion and Conclusions

Absolute stereochemical assignments for the chiral 1-ethyl-2-methyl-1,2,3-trideuteriocyclopropanes prepared are based on the known absolute stereochemistry and specific rotations of the corresponding unlabeled (-)-(1*R*,2*R*)-*trans*- and (-)-(1*S*,2*R*)-*cis*-1-ethyl-2-methylcyclopropanes, (-)-*t*-**1**-d_0 and (-)-*c*-**1**-d_0.[4]



These compounds were prepared by Bergman and Carter from (-)-(1*R*,2*R*)-2-methylcyclopropanecarboxylic acid, thought then to have a maximum specific rotation of $[\alpha]_D$ -77.4° (EtOH). More recent work[28] has rasied this value to -95.8° (EtOH), and the corresponding maximum rotations for (-)-(1*R*,2*R*)-*trans*-1-ethyl-2-methylcyclopropane ((-)-*t*-**1**-d_0) and (-)-(1*S*,2*R*)-*cis*-1-ethyl-2-methylcyclopropane ((-)-*c*-**1**-d_0) are accordingly recalculated to be $[\alpha]_D$ -44.1° and -20.1° (*n*-hexane).

For (-)-(1*R*,2*R*,3*S*)-*t*-**1** were observed specific rotations of $[\alpha]_D$ -39.0° (*n*-heptane) and -36.1° ($CDCl_3$); the specific rotation recorded for the mirror image form, (+)-(1*S*,2*S*,3*R*)-*t*-**1**, was +40.4° ($CDCl_3$). The three absolute values, ignoring possible solvent effects on the rotations, agree to 6% relative error, an uncertainty quite consistent with expectations. For the (-)-(1*S*,2*R*,3*R*)-*c*-**1** isomer, $[\alpha]_D$ was -21.5° ($CDCl_3$). For the synthetic chiral trans and cis trideuterio versions of 1-ethyl-2-methylcyclopropane, the specific rotations are in fair agreement with the recalculated maximum rotations for (-)-*t*-**1**-d_0 and (-)-*c*-**1**-d_0.[4,28]

Measured values for the sums of rate constants summarized in Table IV require that $k_1 = k_2$. The result rests on analytical data secured by NMR spectroscopy on seven sets of geometrical isomers formed in kinetic runs (Table II) and by polarimetry on four sets (Table III). The implication is that the "rotational propensity" of the ethyl group equals that of the methyl group in this cyclopropane system, an implication that conflicts with any

(28) Baldwin, J. E.; Löliger, J.; Rastetter, W.; Neuss, N.; Huckstep, L. L.; De La Higuera, N. *J. Am. Chem. Soc.* **1973**, *95*, 3796-3797. Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6705-6706.

simple correspondence between relative rotational propensities and moments of inertia of the CHEt or CHMe functions. The point has already been made experimentally by Doering and Barsa by securing kinetic data on thermal stereomutations for sets of deliberately selected, apposite 1,2-disubstituted cyclopropanes.[29] It may be that the molecular distortions dictating whether a k_1 or k_2 event results are not associated with substantial single rotations; one might have a trans reactant forming a very short-lived substituted edge-to-edge trimethylene diradical (π-cyclopropane) intermediate through a conrotatory process, followed by a disrotatory closure[30] to give the two cis isomers, the k_1 and k_2 products, at equal rates.

Bergman and Carter[4] reported that one isomerization of (−)-(1*R*,2*S*)-*c*-**1**-d_0 gave (+)-(1*S*,2*S*)-*t*-**1**-d_0 with no detectable rotation at the sodium D line and only a very small rotation, $[\alpha]^{25}_{365}$ +4°, at a higher wavelength. They calculated that this rotation corresponded to about 8% retention of optical purity, or a 54:46 preference for k'_2:k'_1, with one-center epimerization at the methyl-substituted carbon slightly more rapid than epimerization at the ethyl-substituted carbon of the cis substrate. Yet they recognized that the probable uncertainty of the experiment was such that one could conclude only that the antipodes of the trans isomer were produced in essentially racemic form, and thus that $k_1 \approx k_2$.[4]

The kinetic results secured in the present work do not provide a complete specification of all nine parameters needed to define the time evolution of relative concentrations for the eight isomers interconverting though thermal stereomutations. One has the equilibrium constant, four individual rate constants, and four sums of two rate constants (Table IV). The sums are not linearly independent and hence cannot be manipulated algebraically to give values for k_1, k_2, k_{13}, and k_{23} individually. Yet the two main objectives of this study were attained through this kinetic information, for it does test the most substituted bond hypothesis and it does provide an estimate of the relative significance of one-center $(k_1 + k_2)$ versus two-center (k_{12}) epimerization rate constants.

The experimental finding that $k_3 = 0.39 \times 10^{-5}$ s^{-1} demonstrates a kinetically significant one-center epimerization process at C(3) attendant upon cleavage of C(1)–C(3) and C(2)–C(3). The value found for k'_3, 0.09×10^{-5} s^{-1}, the rate constant for C(3)H one-center epimerization relating two *c*-**1** isomers, is smaller and not too precisely known, for only a small amount of (−)-(1*S*,2*R*,3*R*)-*c*-**1** was available for the kinetic work, and the experimental determinations of $(k'_3 + k'_{12})$ and k'_{12} were based on only one kinetic run. It may be that the steric strain associated with the *cis*-1,2-dialkyl-substituted *c*-**1** isomers, reflected in $K_{eq} = 2.67$ favoring the trans isomers, may contribute to the inequality $k_3 > k'_3$; when C(1)–C(3) breaks in a cis isomer, both k'_{13} and k'_1 events have a thermodynamic advantage over a k'_3 epimerization, and partitioning of a 1,2-dialkyltrimethylene intermediate to give three possible epimerization products might thus tend to diminish the observed value for k'_3.

The relative magnitudes of $(k_1 + k_2)$ and k_{12} may be estimated from the kinetic findings and an established empirical correlation. Since $(k_1 + k_{13}) = (k_2 + k_{13}) = 0.35 \times 10^{-5}$ s^{-1} (Table IV), $(k_1 + k_2 + 2k_{13}) = 0.70 \times 10^{-5}$ s^{-1}. The relative kinetic significance of k_{12} and k_{13} according to the most substituted bond hypothesis is that $k_{13}/k_{12} = 0$, and $(k_1 + k_2):k_{12}$ would be $0.70/0.24 \approx 2.9$. An empirical correlation[5] of two-center epimerization rate constants for *trans*-1,2-disubstituted cyclopropanes suggests that *trans*-1-ethyl-2-methylcyclopropane at 380.0 °C should have $k_{13}/k_{12} \approx 0.46$. Since $k_{12} = 0.24 \times 10^{-5}$ s^{-1}, k_{13} would then be about 0.11×10^{-5} s^{-1}. It follows that $(k_1 + k_2) \approx 0.48 \times 10^{-5}$ s^{-1}, and $(k_1 + k_2):k_{12} \approx 2:1$. The two-center epimerization rate constant k_{12} is not kinetically dominant, just as Bergman and Carter[4] concluded in 1968. This significant finding is not vulnerably dependent on an unwarranted application of the "most substituted bond hypothesis" to the stereomutations of the 1-ethyl-2-methylcyclopropanes. Experimental evidence gained with 1-ethyl-2-methyl-1,2,3-trideuteriocyclopropanes forces one to reject the "most substituted bond hypothesis", yet the primary conclusion advanced by Bergman and Carter remains valid. There is no experimental justification for postulating that a concerted electrocyclic two-center epimerization process is the kinetically dominant mechanism for the stereomutations.

Further work will be needed before a complete solution to the kinetic schemes outlined above may be secured and k_1, k_2, k_{13}, and k_{23} may be determined directly through appropriate experiments and analytical methods. Even now, though, the essential characteristics of the thermal stereomutation reactions shown by the system of eight isomers seem unmistakable: the alkyl substituents do not offer enough added stabilization to a 1,3-dialkyltrimethylene diradical, relative to a 1,2-dialkyltrimethylene diradical, to completely channel thermal stereomutation chemistry through processes involving cleavage of the C(1)–C(2) bond only, and the balance between one-center and two-center epimerizations is consistent with the pattern seen in all other 1,2-disubstituted cyclopropanes, $(k_1 + k_2) \geq k_{12}$.

Experimental Section

Unless noted otherwise, reactions were run under a nitrogen atmosphere with magnetic stirring in flame- or oven-dried glassware. Solvents were dried and distilled under nitrogen prior to use: ether and THF were dried over sodium and benzophenone, CH_2Cl_2 was dried over P_2O_5, benzene was dried and distilled from NaH, triethylamine was distilled from sodium, and hexamethylphosphoramide (HMPA) was freshly dried and distilled from CaH_2.

Preparative gas chromatography was performed on a Varian Aerograph A90·P3 or a Perkin-Elmer PE-900 gas chromatograph using various packed 4.83 mm i.d. aluminum and stainless steel columns and helium as carrier gas. Analytical GC was conducted two-dimensionally on a Hewlett-Packard (HP) 5790 gas chromatograph equipped with one injection port, two flame ionization detectors, two HP 25 m × 2 mm × 0.33 μm ultraperformance capillary columns (cross-linked methyl silicone and cross-linked 5% phenyl methyl silicone), and two reporting integrators (HP 3390A and HP 3392A), with helium as carrier gas. Mass spectra were determined on a HP 5970 mass-selective detector interfaced with a HP 5890 gas chromatograph using a HP 25 m × 2 mm × 0.33 μm ultraperformance cross-linked methyl silicone column and a HP 59970B workstation. Routine ^{1}H NMR spectra were obtained in $CDCl_3$ solutions at 300 MHz on a General Electric QE-300 spectrometer. Selected ^{1}H NMR spectra were recorded on a General Electric QN-500 instrument. Chemical shifts are reported in ppm relative to Me_4Si at 0.0 ppm. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 (Na) and 365 (Hg) nm, using a 1-mL, 100-mm path length glass microcell. Analytical HPLC was performed on a HP 1090 liquid chromatograph, equipped with a filter-photometric detector and a HP 3393A computing integrator, and also on a Rainin HPLC system, incorporating two Rainin Rabbit HBX pumps, a Gilson 112 UV/vis detector, and an Apple Macintosh Plus computer, using a 4 mm × 20 cm Machery-Nagel Nucleosil 50-5 column. Preparative liquid chromatography was conducted on a flash column (6 cm × 31 cm, Merck Li-Chroprep Si 60, 15–25 μm) and on the Rainin HPLC system described above, using a custom-made 20 mm × 25 cm Nucleosil 50-5 column (Machery-Nagel, Düren, Germany). Fractional distillations were carried out using B/R Instrument Corporation spinning band distillation systems, a B/R 800 Micro still or a B/R 36T with B/R 8500 microprocessor controller.

The standard workup protocol for product mixtures after lithium aluminum hydride reductions called for addition of *n* mL of water to the cooled (ice bath) reaction mixture, followed by *n* mL of 15% aqueous NaOH, and finally 3*n* mL of water for each *n* g of $LiAlH_4$ used.

Ethyl α-Deuteriodiazoacetate (2). Ethyl diazoacetate (92 mL) was combined with CH_2Cl_2 (130 mL) and D_2O (100 mL, 99.8 atom % D) in a 1-L Morton flask. About 2 mL of 10% NaOD in D_2O and the phase-transfer catalyst hexadecyltrimethylammonium bromide (0.5 g) were added, and the orange solution was vigorously stirred for 2 days at room temperature. The two layers were separated, the aqueous layer was washed twice with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The solution was filtered and carefully concentrated by rotary evaporation at room temperature. This procedure was repeated two to three more times, each time using fresh D_2O, until ^{1}H NMR analysis indicated that deuterium incorporation at C(α) was >99% by comparing the residual NMR C(α)H signal at δ 4.73 to the methylene quartet at δ 4.24–4.18. The D_2O used for the last two exchanges was 100 atom % D (Aldrich).

(29) Doering, W. von E.; Barsa, E. A. *Tetrahedron Lett.* **1978**, 2495–2498.
(30) Yamaguchi, Y.; Schaefer, H. F., III; Baldwin, J. E. *Chem. Phys. Lett.* **1991**, *185*, 143–150.

1-Ethyl-3-ethoxycarbonyl-3-deuteriocyclopropene (3). 1-Butyne (~60 mL, bp 8 °C, Wiley) was condensed into the reaction chamber of a low-temperature photochemical apparatus immersed in a dewar filled with dry ice, and ethyl α-deuteriodiazoacetate (**2**, 20 mL) was added; acetone was added to the dry ice of the outer dewar, a double-cylindrical water condenser was installed, and a medium-pressure mercury lamp (Hanovia, 450 W) was placed inside the condenser. Irradiation of the reactants was carried out for periods of 22–45 h, depending on the tint of the diazoester; the photoreaction was monitored occasionally by analytical GC. When the reaction was over (3:2, 97:3), excess 1-butyne was carefully removed by simple distillation at room temperature. The crude product mixture was taken up in ether, dried, and concentrated, and ester **3** was isolated in pure form by preparative GC using a 30.5 cm × 6.35 mm 20% SE-30 on 60/80 mesh Chromosorb AW DMCS HP column in series with a 3.05 m × 6.35 mm 20% DEGS on 60/80 mesh Chromosorb AW DMCS HP column. ^{1}H NMR: δ 6.31 (s, 1 H), 4.17–4.09 (m, 2 H), 2.55–2.47 (q, J = 7.3 Hz, 2 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H).

***trans*-1-(Hydroxydideuteriomethyl)-2-ethyl-1,2,3-*trans*-trideuteriocyclopropane (*t*-4-d_5).** The concentrate of cyclopropene ester **3** prepared immediately above was dried, filtered, diluted with dry ether, and added dropwise over 1 h to a slurry of $LiAlD_4$ (10 g; 99 atom % D, ICN) in ether, an addition rate sufficient to maintain a gentle reflux. Stirring was continued after the addition for 3.5 h at room temperature, and then the reaction mixture was cooled to 0 °C and was quenched with 13 mL of 100 atom % D D_2O. The mixture was stirred at room temperature for 1 h, and then 10 mL of 15% aqueous NaOH and 27 mL of water were added. The ethereal solution was washed, dried, filtered, and concentrated by distillation, and the product was purified via Kugelrohr distillation under aspirator vacuum, yielding 7.4 g of alcohol *t*-4-d_5 (37.3% based on **2**): ^{1}H NMR δ 1.68 (br s, 1 H), 1.31–1.23 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.29 (s, 1 H); mass spectrum m/e 87 (3.9), 86 (4.4), 72 (16.4), 71 (16.9), 70 (16.6), 62 (18.2), 61 (100), 60 (40.2), 43 (55.0), 42 (42.0).

***trans*-2-Ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic Acid (*t*-5).** Alcohol *t*-4-d_5 (3 g, 28.5 mmol) dissolved in CH_2Cl_2 was added rapidly via syringe at room temperature to a solution of pyridinium chlorochromate (12.9 g, 60 mmol) in CH_2Cl_2, and the resulting dark solution was stirred for 4 h at room temperature; ether was added, stirring was continued for a few minutes, and then the reaction solution was decanted from the dark viscous residue. The residue was washed twice with ether; the combined ether extracts and the product solution were filtered through a 17 cm × 2 cm Florisil column, which was washed liberally with ether. Concentration of the filtrate and washings by distillation at atmospheric pressure gave a single product, according to GC analyses. The crude aldehyde was poured into a vigorously stirred aqueous solution of water (80 mL), sodium hydroxide (6.84 g, 171 mmol), and silver(I) oxide (3.96 g, 17.1 mmol). Stirring was continued at room temperature overnight, ether was added, and the solution was cooled in an ice bath and acidified with concentrated HCl. The phases were separated, and the organic phase was extracted with ether (4×); the combined extracts were dried, filtered, and concentrated under reduced pressure, leaving 1.87 g (56% based on *t*-4-d_5) of acid *t*-5: ^{1}H NMR δ 10.4–11.8 (br s, 1 H), 1.40–1.24 (m, 2 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.76 (s, 1 H); mass spectrum m/e 117 (M^+, 2.9), 102 (20.6), 75 (93.4), 57 (49.0), 43 (100), 42 (51.2).

***trans*-1-(Hydroxymethyl)-2-ethyl-1,2,3-*cis*-trideuteriocyclopropane (*t*-4).** An ethereal solution of carboxylic acid *t*-5 (1.43 g, 12.2 mmol) was added dropwise to a suspension of $LiAlH_4$ (0.91 g, 24 mmol) in ether at a rate sufficient to maintain gentle reflux. The solution was stirred at room temperature for 5 h and then subjected to the standard workup. Concentration of the crude product solution was achieved first by distillation at atmospheric pressure and was completed by micro-spinning band distillation under aspirator vacuum; 1.02 g (82%) of alcohol *t*-4 was isolated: ^{1}H NMR δ 3.43 (s, 2 H), 1.59 (br s, 1 H), 1.26 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.29 (s, 1 H); mass spectrum m/e 103 (M^+, 0.1), 85 (4.1), 70 (18.3), 69 (24.1), 60 (100), 59 (51.1), 58 (56.3), 45 (47.0), 43 (86.2), 42 (62.9).

(±)-*trans*-1-Ethyl-2-methyl-1,2,3-*cis*-trideuteriocyclopropane (*t*-1). Methyltriphenoxyphosphonium iodide (9.05 g, 20 mmol) was added at once to a stirred solution of alcohol *t*-4 (1.0 g, 9.7 mmol) in HMPA (35 mL) at room temperature in a darkened fume hood; the resulting dark solution was stirred for 1 h, then sodium cyanoborohydride (2.514 g, 40 mmol) was added quickly in one portion. The solution was heated to 70 °C for 3 h, and the product mixture was allowed to cool to room temperature. The product hydrocarbon (±)-*t*-1 was isolated from the HMPA solution by simple distillation under aspirator vacuum over a 30-min period. The reaction flask was heated briefly up to 90 °C, and the product was collected in a glass coil trap equipped with two vacuum stopcocks, immersed in a dry ice/acetone bath. The 0.6 g of crude product (70–80% in (±)-*t*-1 by GC analysis) obtained was subsequently purified by preparative GC on a 4.6-m 20% SP-2100 on 60/80 mesh Chromosorb-W HP column at room temperature to afford 0.355 g of pure (±)-*t*-1 (42% based on (±)-*t*-4): ^{1}H NMR δ 1.26–1.12 (m, 2 H), 0.99 (s, 3 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.12 (s, 1 H); mass spectrum m/e 87 (M^+, 25), 72 (23), 71 (11), 58 (65), 57 (52), 56 (27), 44 (58), 43 (100), 42 (60), 40 (48), 39 (24).

(1*R*,2*R*,3*R*)- and (1*S*,2*S*,3*S*)-*N*-(2-Hydroxy-(1*R*)-phenylethyl)-2-ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxamide (6 and 7). To a well-stirred solution of carboxylic acid (±)-*t*-5 (3.19 g, 27.3 mmol) in dry THF (130 mL) were added dropwise at −20 °C (dry ice/2-propanol bath) *N*-methylmorpholine (3.0 mL, 27.3 mmol) followed by isobutyl chloroformate (3.76 mL, 29 mmol). After 5 min, (−)-(*R*)-2-phenylglycinol (3.98 g, 29 mmol, Aldrich, 98%; $[\alpha]_D$ −31.7° (*c* 0.75, 1 N HCl)) was added, and stirring was continued for 15 min at −20 °C. The solution was allowed to warm to room temperature, and the solvent was removed by rotary evaporation under aspirator vacuum. The light yellow solid residue was taken up in 85:15 ethyl acetate/CH_2Cl_2, and the organic solution was washed succesively with water, aqueous $NaHCO_3$, 2 N HCl, and water (100 mL each). It was dried, filtered, and concentrated to afford the crude diastereomeric amides **6** and **7** as a colorless crystalline material.

Approximately one-third of this material was subjected to preparative flash column chromatography on silica gel with 7:3 EtOAc/hexanes and flow rates of 15–25 mL/min; a differential refractometer detector (Waters Associates R403) and an HP 3390A integrator were employed. With samples ranging from 1 to 5 g dissolved in minimum volumes of hot ethyl acetate loaded on the column, and with elution times for both diastereomers as long as 5 h, complete base-line separation could not be achieved. Only the earlier eluting, less polar amide **6** was isolated diastereomerically pure using this methodology.

The remaining two-thirds of the mixture of amides was separated by HPLC on the Rainin system using 7:3 EtOAc/isooctane and the preparative Nucleosil 50–5 column, using a UV (254 nm) detector, a flow rate of 15 mL/min, and a 5-mL sample loading loop. Analytical HPLC examination of the collected fractions demonstrated that both amides were obtained diastereomerically pure.

A total of 24.6 g of carboxylic acid (±)-*t*-5 was converted in several runs to the mixture of amides **6** and **7**. Resolution by HPLC yielded 10.067 g of amide **6** and 10.5 g of **7**. Amide **6**: ^{1}H NMR (in DMSO-d_6) δ 8.41–8.38 (d, J = 8.2 Hz, 1 H), 7.28 (s, 5 H), 4.90–4.81 (m, 1 H), 3.54 (t, J = 5.8 Hz, 2 H), 1.41–1.15 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.45 (s, 1 H). Diastereomer **7**: ^{1}H NMR (in DMSO-d_6) δ 8.39–8.36 (d, J = 8.2 Hz, 1 H), 7.30 (s, 5 H), 4.84–4.80 (m, 1 H), 3.51 (t, J = 5.5 Hz, 2 H), 1.40–1.15 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H), 0.50 (s, 1 H).

(−)-(1*R*,2*R*,3*R*)-*trans*-2-Ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic Acid ((−)-*t*-5). A mixture of diastereomerically pure amide **6** (10.07 g) and 150 mL of 3 N H_2SO_4 in 1:1 dioxane/water was heated to reflux overnight. Analysis by TLC demonstrated complete hydrolysis of the amide. The reaction mixture was diluted with water and extracted with ether; the ethereal solution was dried, filtered, and concentrated by distillation, initially at atmospheric pressure and finally under aspirator vacuum, to afford 4.68 g (94%) of crude (−)-*t*-5. After GC purification on a 3.8 m 10% FFAP on 60/80 mesh Chromosorb G column at 105 °C, (−)-*t*-5 had $[\alpha]_D$ −73.8° (*c* 0.5, EtOH). ^{1}H NMR: δ 1.43–1.25 (m, 2 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.76 (s, 1 H).

(1*R*,2*R*,3*R*)-*trans*-1-(Hydroxymethyl)-2-ethyl-1,2,3-*cis*-trideuteriocyclopropane (*t*-4). An ethereal solution of carboxylic acid (−)-*t*-5 (4.68 g, 40 mmol) was added dropwise to a suspension of $LiAlH_4$ (2.85 g, 75 mmol) in ether at a rate sufficient to maintain gentle reflux. The solution was stirred at room temperature overnight and then subjected to the standard workup. Concentration of the product solution by distillation gave 3.88 g (37.7 mmol, 88%) of crude alcohol *t*-4. ^{1}H NMR: δ 3.43 (s, 2 H), 1.30–1.20 (m, 2 H), 0.95 (s, J = 7.3 Hz, 3 H), 0.28 (s, 1 H).

(−)-(1*R*,2*R*,3*S*)-*trans*-1-Ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((−)-(1*R*,2*R*,3*S*)-*t*-1). Methyltriphenoxyphosphonium iodide (34.1 g, 75.4 mmol) was added to a stirred solution of chiral alcohol *t*-4 (3.88 g, 37.7 mmol) in 190 mL of HMPA at room temperature in a darkened fume hood; the resulting dark solution was stirred for 1 h, then sodium cyanoborohydride (9.47 g, 151 mmol) was added, and the reaction mixture was heated to 70 °C for 1.5 h. It was allowed to cool to room temperature, and hydrocarbon (−)-(1*R*,2*R*,3*S*)-*t*-1 was isolated by distillation under aspirator vacuum as the reaction mixture was warmed to 90 °C. The product was trapped in a glass coil equipped with two vacuum stopcocks, cooled in a dry ice/acetone bath. The collected material, 2.67 g of a mixture of low-boiling products, contained 70% of (−)-(1*R*,2*R*,3*S*)-*t*-1 (57% yield); it was purified by preparative GC on a 4.6-m 20% SP-2100 60/80 Chromosorb-W HP column at room temperature to provide 100% pure hydrocarbon, according to analytical GC: $[\alpha]_D$ −39.0°, $[\alpha]_{365}$ −114° (*c* 1.27, *n*-heptane); $[\alpha]_D$ −36.1°, $[\alpha]_{365}$ −108°

Table V. Polarimeter Measurements for Products from Kinetic Runs

starting material	time (min)	product	weight (mg)	*c*	obsd α_D	obsd α_{365}	sp rotation $[\alpha]_D$	sp rotation $[\alpha]_{365}$
(−)-*t*-**1**	0	trans	10.3	0.94	−0.340	−1.016	−36.1	−108
	240	cis	1.3	0.11	0.000	0.000	0.0	0.0
	240	trans	24.6	2.10	−0.690	−2.074	−32.8	−98.7
	480	cis	2.4	0.21	0.000	0.000	0.0	0.0
	480	trans	27.4	2.30	−0.695	−2.057	−30.3	−89.6
	720	cis	2.9	0.25	0.000	0.000	0.0	0.0
	720	trans	19.8	1.73	−0.462	−1.369	−26.7	−79.1
(−)-*c*-**1**	0	cis	9.6	0.80	−1.160	−0.539	−20[a]	−67[a]
	180	cis	11.8	0.97	−0.163	−0.549	−16.8[b]	−56.6[b]
	180	trans	3.0	0.25	0.000	0.000	0.0	0.0

[a] Uncorrected values for 93% pure material; corrected specific rotations: $[\alpha]_D$ −21.5° and $[\alpha]_{365}$ −72.5°. [b] Uncorrected values for 95% pure material; corrected specific rotations: $[\alpha]_D$ −17.7° and $[\alpha]_{365}$ −59.6°.

(*c* 0.94, $CDCl_3$); ^1H NMR δ 1.27–1.11 (m, 2 H), 0.99 (s, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H), 0.12 (s, 1 H).

(+)-(1*S*,2*S*,3*S*)-*trans*-2-Ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxylic Acid ((+)-*t*-**5**). A mixture of the purified more polar amide **7** (10.5 g) and 150 mL of 3 N H_2SO_4 in 1:1 dioxane/water was heated to reflux for 6.5 h. Analysis by TLC confirmed the quantitative hydrolysis of the amide. The reaction mixture was allowed to cool to room temperature and was extracted with ether (5×); the ethereal material was dried, filtered, and concentrated by distillation to leave 5.15 g (44 mmol, 99%) of the crude carboxylic acid (+)-*t*-**5**. After GC purification on a 3.8-m 10% FFAP on 60/80 mesh Chromosorb G column, (+)-*t*-**5** had $[\alpha]_D$ + 75.6° (*c* 1.43, EtOH). ^1H NMR: δ 1.43–1.25 (m, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.76 (s, 1 H).

(1*S*,2*S*,3*S*)-*trans*-2-Ethyl-1,2,3-*cis*-trideuteriocyclopropanecarboxamide (*t*-**8**). To a round-bottomed flask equipped with a reflux condenser and a drying tube containing carboxylic acid (+)-*t*-**5** (5.065 g, 43.3 mmol) was added thionyl chloride (9.78 g, 82.3 mmol) via a syringe in one portion. The reaction mixture was stirred at room temperature for 5.5 h. Analysis by GC demonstrated quantitative conversion to the acid chloride. The product solution was kept overnight at room temperature without stirring, and then excess $SOCl_2$ was removed under aspirator vacuum for 30 min; the remaining crude acid chloride was diluted with ether, and anhydrous ammonia was bubbled into the solution at room temperature via a 4 mm i.d. glass tube for 4 h. GC analysis showed that all of the acid chloride had been consumed and that the desired amide was the dominant product. The reaction mixture was diluted with CH_2Cl_2 and filtered, and the filter cake was washed well with hot CH_2Cl_2. The solvent was removed from the filtrate under aspirator vacuum; the residue was taken up in pentane and concentrated, and amide *t*-**8** was isolated by suction filtration. After the residue was washed with pentane 3.93 g (78%) of (+)-*t*-**5** was obtained as a colorless solid. ^1H NMR: δ 5.70–5.20 (broad absorption centered about d 5.43, 2 H), 1.36–1.28 (q, *J* = 7.4 Hz, 2 H), 0.97 (t, *J* = 7.4, 3 H), 0.63 (s, 1 H).

(1*S*,2*S*,3*S*)-*trans*-1-Cyano-2-ethyl-1,2,3-*cis*-trideuteriocyclopropane (*t*-**9**). Amide *t*-**8** (3.93 g) was dissolved in a mixture of 100 mL of dry benzene and 43 mL of dry triethylamine, and ca. 13 g of P_2O_5 was added. The reaction mixture was heated to reflux for 6.5 h, allowed to stand at room temperature overnight, and then diluted with water. Organic and aqueous phases were separated, the aqueous layer was extracted with ether (2×), and the combined organic material was washed successively with dilute HCl, aqueous $NaHCO_3$, water, and brine. The nitrile product solution was dried, filtered, and concentrated by simple distillation and finally by micro-spinning band fractional distillation (pot temperature up to 110 °C); the concentrate was 4.356 g of a solution containing 63% of *t*-**9** (by analytical GC; estimated yield 82%). ^1H NMR: δ 1.36–1.29 (q, *J* = 7.4 Hz, 2 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 0.78 (s, 1 H).

(1*R*,2*S*,3*S*)-*cis*-1-Cyano-2-ethyl-1,2,3-*trans*-trideuteriocyclopropane (*c*-**9**). Commercial *t*-BuOD (98 atom % D, Aldrich) was dried thoroughly by heating it over sodium for 2 h to reach gentle reflux and then distilled from sodium into a flask containing freshly activated powdered 3A molecular sieves. Small pieces of potassium (1.65 g, 42.2 mmol) were added to 27 mL of the dry *t*-BuOD under reflux; 20 h at reflux was required to convert all of the potassium to *t*-BuOK. (The alcohol tended to solidify in the reflux condenser; the reaction was monitored frequently, and a heat gun in the lower region of the condenser was used occasionally. The freshly prepared solution of *t*-BuOK in *t*-BuOD had to be kept slightly above room temperature to prevent it from solidifying.) A 63% solution of chiral nitrile *t*-**9** in benzene (4.131 g of solution, containing ca. 26.6 mmol of *t*-**9**) was added via a syringe to the warm solution of *t*-BuOK in *t*-BuOD. The solution turned dark red; after the mixture was stirred for 30 min under reflux, a small amount of the reaction solution was combined with water, organic materials were extracted with ether, and the ethereal solution was examined by analytical GC. The anticipated 1:1 cis:trans ratio of nitriles was confirmed. The reaction mixture was allowed to cool to room temperature and was quenched with 3.2 mL of D_2O (100 atom % D). The quenched product solution was stirred for 10 min and then diluted with ether; the phases were separated, the aqueous phase was extracted twice with ether, and the ethereal material was dried, filtered, and concentrated by distillation. Nitriles *c*-**9** and *t*-**9** were isolated by preparative GC on a 3.2-m 10% Carbowax 20M on 60/80 mesh Chromosorb G column. Base-line separation was not achieved. The later eluting cis fraction amounted to 0.6014 g; it contained 93% of *c*-**9** and 7% of *t*-**9**. The trans fraction that was collected (0.7677 g) consisted of 84% of *t*-**9** and 16% of *c*-**9**. The trans fraction was diluted with ether, dried over $MgSO_4$, filtered, concentrated, and combined with a solution of *t*-BuOK in *t*-BuOD (1.0 g potassium, 20 mL dry *t*-BuOD); the reaction mixture was heated for 10 min, monitored by analytical GC, allowed to cool to room temperature, and quenched with 2 mL of D_2O. Separation of the cis and trans nitriles by preparative GC gave a cis fraction totaling 0.750 g (88:12 *c*/*t*). ^1H NMR of *c*-**9**: δ 1.62–1.48 (m, 2 H), 1.09 (t, *J* = 7.4, Hz, 3 H), 0.75 (s, 1 H).

(−)-(1*R*,2*S*,3*S*)-*cis*-2-Ethyl-1,2,3-*trans*-trideuteriocyclopropanecarboxylic Acid ((−)-*c*-**5**). A solution of NaOD in D_2O (100 atom % D) was prepared by carefully adding 4.0 mL of D_2O dropwise and very slowly via a syringe to a 10-mL round-bottomed flask, equipped with a stirring bar, a septum, and a nitrogen inlet and containing 0.350 g (15.2 mmol) of sodium. When all of the sodium had reacted, 0.673 g (6.9 mmol) of *c*-**9** was added quickly by syringe, and a reflux condenser was installed. The reaction mixture was heated to reflux and monitored by analytical GC; after 18 h it was allowed to cool to room temperature and poured into a mixture of concentrated H_2SO_4 and crushed ice. Carboxylic acid *c*-**5** was extracted with ether; the ethereal solution was dried, filtered, concentrated, and distilled under aspirator vacuum (Kugelrohr, pot temperature up to 115 °C) to give 0.638 g (79%) of *c*-**5**. A sample purified by preparative GC on a 30% SE-30 scrubber followed by a 3.8-m 10% FFAP on 60/80 mesh Chromosorb G column at 170–180 °C had $[\alpha]_D$ −58° (*c* 0.05, EtOH). ^1H NMR: δ 1.68–1.47 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

(1*R*,2*S*,3*S*)-*cis*-2-Ethyl-1,2,3-*trans*-trideuteriocyclopropanemethanol (*c*-**4**). A solution of carboxylic acid *c*-**5** (0.638 g, 5.45 mmol) in ether was added dropwise to a slurry of $LiAlH_4$ (0.455 g, 12 mmol) and ether at a rate sufficient to maintain gentle reflux. After 30 min the addition was complete; the reaction was stirred at room temperature overnight and then subjected to a standard workup. The ethereal product solution was concentrated by distillation to give 0.477 g (85%) of crude *c*-**4**; a sample was purified by preparative GC on a 3.2-m 10% Carbowax on 60/80 mesh Chromosorb G column at 120 °C: ^1H NMR δ 3.66–3.55 (broad q, *J* = 11.6 Hz, 2 H), 1.47–1.20 (m, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H), −0.06 (s, 1 H); mass spectrum *m*/*e* 85 (M^+ − 18, 12), 70 (31), 69 (34), 60 (100), 59 (61), 58 (56), 57 (26), 45 (50), 43 (89), 42 (61).

(−)-(1*S*,2*R*,3*R*)-*cis*-1-Ethyl-2-methyl-1,2,3-*trans*-trideuteriocyclopropane ((−)-(1*S*,2*R*,3*R*)-*c*-**1**). Methyltriphenoxyphosphonium iodide (4.16 g, 9.2 mmol) was added at once to a stirred solution of alcohol *c*-**4** in HMPA (25 mL) at room temperature in a darkened fume hood; the resulting dark solution was stirred for 1 h, and then sodium cyanoborohydride (1.16 g, 18.4 mmol) was added quickly in one portion. The reaction solution was heated to ca. 90 °C for 3 h and then allowed to cool to room temperature. The product hydrocarbon (−)-(1*S*,2*R*,3*R*)-*c*-**1** was isolated from the HMPA solution by distillation and collected in a glass coil trap. The crude product mixture was analyzed by capillary GC: the ratio of (+)-(1*S*,2*R*,3*R*)-*t*-**1** to (−)-(1*S*,2*R*,3*R*)-*c*-**1** was 24:76. Preparative GC purification of this product mixture on a 4.6-m 20% SP-2100 60/80 Chromosorb-W HP column at room temperature (retention time: 28 min) resulted in (−)-(1*S*,2*R*,3*R*)-*c*-**1** free of contamination by the trans

isomer but only 80% pure. Further purification by preparative GC employing the same column but with the GC oven chamber cooled with dry ice to temperatures ranging from -30 to -15 °C (retention time: 100 min) gave 35 mg of (-)-(1*S*,2*R*,3*R*)-*c*-**1** (93.3% pure by analytical GC; two impurities, 2.0 and 4.7%, possibly ethylcyclobutane-d_3 and *n*-propylcyclopropane-d_3[31]): ^{1}H NMR δ 1.32-1.24 (q, J = 7.3 Hz, 2 H), 1.00 (s, 3 H), 0.97 (t, J = 4.8 Hz, 3 H), -0.37 (s, 1 H); uncorrected specific rotations $[\alpha]_D$ -20.5°, $[\alpha]_{365}$ -67.4° (*c* 0.8, $CDCl_3$); corrected specific rotations $[\alpha]_D$ -21.5°, $[\alpha]_{365}$ -72.5° (*c* 0.8, $CDCl_3$); mass spectrum *m/e* 87 (M^+, 33), 72 (28), 71 (14), 59 (20), 58 (77), 57 (59), 56 (29), 44 (65), 43 (100), 42 (57), 41 (34), 40 (41).

The small amount of (+)-(1*S*,2*S*,3*R*)-*t*-**1** material present in the crude product mixture was collected from the same GC runs (at room temperature) in a purity of >98.5%: $[\alpha]_D$ +40.4°, $[\alpha]_{365}$ +121° (*c* 0.62, $CDCl_3$).

Thermal Isomerizations of (±)-*t*-1, (-)-(1*R*,2*R*,3*S*)-*t*-1, and (-)-(1*S*,2*R*,3*R*)-*c*-1. All kinetics runs were carried out in a static gas-phase reactor at 380 °C. Thermolyses using (±)-*t*-**1** and (-)-(1*R*,2*R*,3*S*)-*t*-**1** were run with neat samples. The pressure in the reactor during these runs was between 103 and 122 Torr, while the sample amount per run ranged from 55.4 to 65.9 mg. Due to the small amount of sample available, the kinetic run with (-)-(1*S*,2*R*,3*R*)-*c*-**1** included added pentane as an inert bath-gas to attain the desired pressure in the kinetic bulb. About 26 mg of (-)-(1*S*,2*R*,3*R*)-*c*-**1** combined with 27 mg of pentane resulted in a pressure of 109 Torr in the bulb. The pentane used was purified by treatment with aqueous potassium permanganate solution to remove traces of olefins, followed by heating at reflux over sodium and then by distillation from sodium; preparative GC of the distilled material gave pentane with a purity of 100%, according to capillary GC analyses.

All reactants were subjected to two freeze-thaw cycles prior to introduction into the vacuum line to ensure correct pressure readings and efficient vacuum transfers. Capillary GC analyses of the recovered thermolysis product mixtures were carried out for each kinetic point by performing three 1-μL injections of neat material. The products were then separated into their cis and trans isomer sets by preparative GC on a 4.6-m 20% SP-2100 on 60/80 Chromosorb-W HP column at room temperature; the separate sets of geometric isomers were analyzed by ^{1}H NMR in $CDCl_3$ solutions (99.8 atom % D, containing no Me_4Si), as exemplified in Figures 1 and 2. The cis and trans products resulting from kinetic runs with chiral starting materials were further characterized by polarimetric measurements. For each of these determinations, a neat sample from preparative GC collections was drawn into a microsyringe and delivered to a 1-mL volumetric flask. The weight of sample transferred to the flask was measured, and the sample was diluted with $CDCl_3$ to give the 1-mL solution used for the polarimetry. The relevant data are gathered in Table V. Given uncertainties in sample weights of ±0.1 mg and in observed rotations of ±0.001°, specific rotations for very small samples showing very low rotations have significant relative uncertainties. Analyses for the thermolysis products from (±)-*t*-**1**, (-)-(1*R*,2*R*,3*S*)-*t*-**1**, and (-)-(1*S*,2*R*,3*R*)-*c*-**1** are summarized in Tables I, II, and III.

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The Type 2 Intramolecular Imino Diels-Alder Reaction. Synthesis and Structural Characterization of Bicyclo[*n*.3.1] Bridgehead Olefin/Bridgehead Lactams

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Abstract: The type 2 imino Diels-Alder cycloaddition was used for the synthesis of a homologous series of bridgehead olefin/bridgehead lactams. The X-ray crystal structures of three members of this series, including the highly strained 2-carbomethoxy-8-oxo-2-azabicyclo[3.3.1]non-4-ene, were obtained. An analysis of the structural data permits evaluation of the responses of the bridgehead double bond and bridgehead amide linkages to similar torsional distortions.

Introduction

Bridgehead olefins **1** represent one class of molecules that contain a distorted double bond.[1] The topologic constraints of bridged bicyclic molecules force a double bond emanating from the bridgehead position to deviate from the preferred planar geometry. One result of the distortion is reduced overlap of the p-orbitals comprising the π-bond. The key substructural unit of a bridgehead olefin is the *trans*-cycloalkene. As the size of the *trans*-cycloalkene ring is reduced, the olefin becomes more distorted.

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Chemists have been interested in bridgehead olefins since Bredt studied a series of naturally occurring bicyclic terpenes in the 1920s and concluded that it was not possible to locate an olefin at the bridgehead position.[2] Despite "Bredt's Rule", many bridgehead olefins have been synthesized. However, relatively few have been structurally characterized so that the details of the double bonds' distortions could be understood.

Bridgehead lactams **2** are another class of anti-Bredt molecules.[3] The bridgehead imine bond of the zwitterionic resonance form

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