The Synthesis and Absolute Configurations of Some Optically Active *cis*- and *trans*-1,2-Disubstituted Cyclopropanes

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Abstract: A number of *cis*- and *trans*-1,2-disubstituted cyclopropanes have been synthesized in both racemic and optically active form. Their maximum rotations and absolute configurations have been determined by chemical correlation with *trans*-2-methylcyclopropanecarboxylic acid (**6**). Application of Brewster's rules of conformational asymmetry to the compounds prepared indicates that the theory is much more satisfactory when used to predict the rotations of *trans*- rather than *cis*- 1,2-disubstituted cyclopropanes.

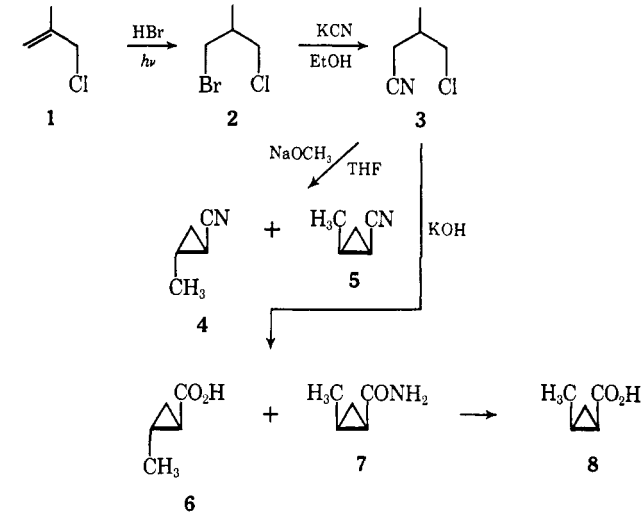
The structure of the energy surface and intermediates formed during the thermal rearrangements of cyclopropanes has an important bearing on the mechanism of carbon–carbon bond breaking and formation and on the nature of basic electrocyclic processes.[1] In an effort to examine these reactions from an intimate viewpoint, we set out to synthesize and study the thermal reactions of some optically active 1,2-disubstituted cyclopropane derivatives. This paper reports the results of these syntheses, along with an optical correlation of the compounds involved. A study of the thermal rearrangements of certain of these materials is described in an accompanying paper.[2]

Results and Discussion

Synthesis of Racemic Materials. We set as our goal the preparation of optically active *cis*-1-ethyl-2-methylcyclopropane and its *trans* isomer, also optically active. We considered attempting the preparation of these materials by asymmetric Simmons–Smith reaction;[3] however, the low optical yields of other cyclopropanes prepared by this method[3b] discouraged us and we decided instead to attempt resolution and elaboration of the 2-methylcyclopropanecarboxylic acids. The desired alkylcyclopropanes could then be obtained by homologation and reduction.

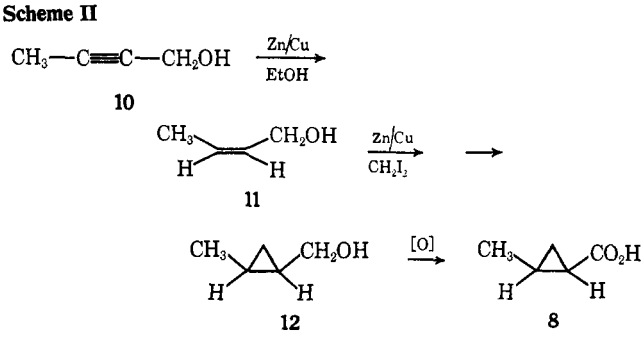
The acids **6** and **8** are available in reasonably large quantity from a synthetic route described by Applequist and Peterson[4] (Scheme I). Treatment of the chloronitrile **3** with potassium hydroxide as described by Applequist and Peterson leads to a mixture of the *trans*-acid **6** and the *cis*-amide **7**, but the reaction is extremely sensitive and small variation in reaction conditions (size of flask, speed of stirring, wetness of KOH, scale of reaction) leads to wide variation in product composition. By duplicating runs as carefully as possible, yields of 23% of pure *cis*-amide could be reproducibly obtained, along with a fraction (75% yield) that was mainly *trans*-acid **6**. In the course of this work it was found that cyclization of **3** to a mixture of **4** and **5** could be effected by using sodium methoxide in dry tetrahydrofuran. Treatment of this mixture with KOH, however, did not produce as large a percentage of amide **7** as did direct reaction of **3** with KOH.

Scheme I



Assignment of *cis* stereochemistry to the amide obtained from this reaction was made by Applequist and Peterson solely on the basis of its slower rate of hydrolysis to acid **8** compared with the rate of *trans*-amide hydrolysis.[4] We therefore felt it necessary to confirm the assignment, which we did by an independent stereospecific synthesis of *cis*-acid **8**. The route is outlined in Scheme II, and was designed to take advantage of the

Scheme II



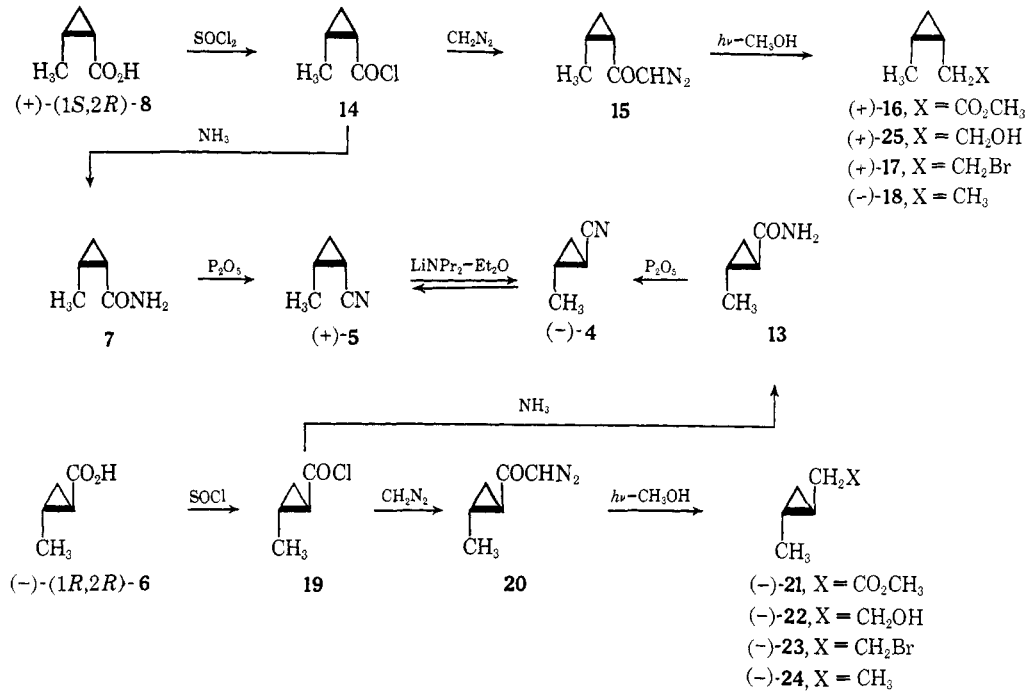
(1) (a) T. S. Chambers and G. B. Kistiakowsky, *J. Amer. Chem. Soc.*, **56**, 399 (1934); (b) R. S. Rabinovitch, E. W. Schlag, and K. B. Wiberg, *J. Chem. Phys.*, **28**, 504 (1958); (c) H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 147 (1966); (d) S. W. Benson and P. S. Nangia, *J. Chem. Phys.*, **38**, 18 (1963); (e) H. E. O'Neal and S. W. Benson, *ibid.*, **72**, 1866 (1968); (f) R. J. Crawford and A. P. Mishra, *J. Amer. Chem. Soc.*, **88**, 3963 (1966).

(2) (a) R. G. Bergman and W. L. Carter, *ibid.*, **90**, 7411 (1969). (b) A preliminary account of this work has been published: W. L. Carter and R. G. Bergman, *ibid.*, **90**, 7344 (1968).

(3) (a) H. E. Simmons and R. D. Smith, *ibid.*, **80**, 5323 (1958); (b) S. Sawada, J. Oda, and Y. Inouye, *J. Org. Chem.*, **33**, 1767 (1968); S. Sawada, J. Oda, and Y. Inouye, *ibid.*, **33**, 2141 (1968). We are indebted to Professor Inouye for informing us of his results prior to publication.

(4) D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **82**, 2372 (1960).

Scheme III



fact that 2-butyn-1-ol **10** can be stereospecifically reduced[5a] to *cis*-2-buten-1-ol **11** using zinc–copper couple in ethanol, and that the Simmons–Smith reaction to give **12** should be facilitated by the hydroxyl group adjacent to the double bond.[5b] The cyclopropylcarbinol **12** was oxidized in moderate yield to **8** using Jones reagent[6] followed by silver oxide;[7] the sample of **8** obtained in this way was identical with that obtained from deamination of amide **7**.

Once sufficient quantities of acids **6** and **8** had been obtained, a method had to be found for efficient transformation of these materials to hydrocarbons **18** and **24**. The homologation–reduction sequence decided upon was carried out in both the racemic and optically active series, and is illustrated for the optically active isomers in Scheme III. Treatment of *cis*-2-methylcyclopropanecarboxylic acid (**8**) with an equimolar quantity of thionyl chloride (no solvent) produced the acid chloride quantitatively in about 12 hr. The diazo ketone **15** could be obtained by treatment of **14** with diazomethane. As might be expected from recent work,[8] Arndt–Eistert reaction of **15** catalyzed by silver oxide gave a complex mixture of volatile products along with significant quantities of polymeric material, but photolysis of **15** in methanol (Pyrex filter) smoothly converted it to the homologated ester **16**. The photolysis was complicated somewhat by the fact that **15** underwent what appeared to be a dark reaction to give an unidentified product much less volatile than **16**. Employing a quartz rather than a Pyrex filter increased the rate of photolysis, but also enhanced the amount of polymer produced in the reaction.

The homologated ester could be readily purified by annular spinning band distillation or preparative vpc. Its nmr spectrum exhibited an ester methyl resonance at 3.6 ppm (downfield from tetramethylsilane) (3 H), methylene doublet at 2.2 ppm (J = 6 Hz, 2 H), cyclopropyl methyl signal at 1.0 ppm superimposed on other cyclopropyl absorption from 0.8 to 1.2 ppm (total 6 H), and a complex absorption at −0.2 ppm (1 H). In the infrared, the compound had strong bands at 5.73 and 8.45 μ, and its mass spectrum showed a parent peak at m/e 128, in addition to major fragments at m/e 113 (loss of CH_3), 97 (loss of OCH_3), and 69 (loss of CO_2CH_3).

Efficient transformation of the ester to the bromide **17** was achieved by lithium aluminum hydride reduction, followed by treatment of the alcohol **25** produced with triphenylphosphonium dibromide in dimethylformamide.[9] The bromide was allowed to stand in an excess of tri-*n*-butyltin hydride[10] overnight, and the hydrocarbon **18** produced was then distilled out of the reaction mixture in essentially pure form. An infrared spectrum of the bromide showed no residual hydroxyl absorption, but strong bands at 6.9, 7.91, 8.22, 9.80, and 13.50 μ. Its nmr spectrum was quite characteristic of the proposed structure, showing a triplet at 3.4 ppm (J = 6.5 Hz, 2 H), apparent quartet at 1.7 ppm (J = 6.5 Hz, 2 H), cyclopropyl methyl doublet at 1.05 ppm (J = 4 Hz, 3 H), and a broad envelope due to the remaining cyclopropyl hydrogens from 0.0 to 0.8 ppm (4 H).

An exactly similar sequence was carried out in the racemic *trans* series, starting with acid **6**, and producing hydrocarbon **24** as a final product. Details are given in the Experimental Section.

Optically Active Series. It was found after a number of trial experiments that optical fractionation of the quinine salts of both acids **6** and **8** could be achieved by recrystallization from acetone. Three recrystalliza-

(5) (a) A. J. Clarke and L. Crombie, *Chem. Ind.* (London), 143 (1957); (b) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963).

(6) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(7) R. E. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966).

(8) E. Wenkert, B. L. Mylari, and L. L. Davis, *J. Amer. Chem. Soc.*, **90**, 3870 (1968).

(9) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *ibid.*, **86**, 964 (1964).

(10) H. G. Kuivila, *Advan. Organomet. Chem.*, **1**, 47 (1964).

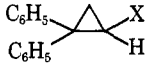
tions of the salt of **8** followed by treatment with aqueous hydrochloric acid gave acid of $[\alpha]^{25}D$ +17.9° (95% EtOH). Similarly, four recrystallizations of the quinine salt of **6** produced acid of $[\alpha]^{25}D$ −46.4° (95% EtOH) after regeneration with HCl.

The absolute configuration and maximum rotation of (−)-(1*R*,2*R*)-*trans*-2-methylcyclopropanecarboxylic acid (**6**) have been established[11] by chemical correlation with (−)-(1*R*,2*R*)-*trans*-1,2-dimethylcyclopropane (**26a**) employing (−)-*trans*-2-phenylcyclopropanecarboxylic acid (**26b**) as a relay point.[12] The dimethylcyclopropane **26a** has been similarly correlated both with (+)-S-2-methylbutanal and (+)-L-isoleucine, whose absolute configurations have been established by X-ray crystallography.[13]

(−)-(1*R*,2*R*)-**26a**, $R_1 = R_2 = CH_3$
(−)-(1*R*,2*R*)-**26b**, $R_1 = C_6H_5$; $R_2 = CO_2H$

On the basis of Sugita and Inouye's value[11] of −77.4° for the maximum specific rotation of (−)-(1*R*,2*R*)-**6**, our sample of **6** was determined to be 60.0% optically pure.

Determination of the absolute configurations and maximum rotations of the compounds in the *cis* series requires only one chemical connection between the two series, and it appeared to us that the most direct connection could be made by epimerizing the carboxyl center in the *cis*-acid **8** or one of its derivatives. Since **6** and **8** are diastereomers, such a change (inversion of only one asymmetric center) would carry the *cis* compound into a different structural series (*cis* → *trans*) but not into a different optical series. Walborsky's observation, however, that little or no epimerization of the ester group in optically active 2,2-diphenylcyclopropanecarboxylate (**27**) (which amounts to racemization in his case) occurred during 15 hr of reflux in sodium methoxide–methanol, indicated that *cis–trans* isomerization in the 2-methyl series might not be straightforward.[14] Furthermore, such an experiment would require that a method be available for preparative separation of the esters of **6** and **8**. Despite several attempts, Applequist and Peterson were unable to effect such a separation by vapor phase chromatography,[4] and their observations were amply confirmed in our laboratory.



27, X = CO_2Et
28, X = CN

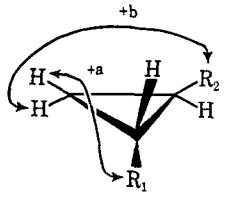
A solution to this problem was suggested by the cyclization of chloronitrile **3** to a mixture of cyclopropanenitriles **4** and **5** (Scheme I) using sodium methoxide in THF, for we had found during this experiment that **4** and **5** could be easily separated by conventional gas chromatographic techniques. Furthermore, Walborsky had reported that despite the difficulty of racemizing **27**, the corresponding nitrile **28** racemized essentially instantaneously on treatment with lithium diisopropylamide in ether.[14,15]

We therefore attempted the interconversion of **4** and **5** with lithium diisopropylamide in ether, and found that these conditions were more than satisfactory, producing about a 50:50 mixture of **4** and **5**, starting from either isomer, in a few seconds at room temperature. The optical correlation was then achieved (Scheme III) by converting optically active acid chloride **14** to amide **7** and dehydrating this material with P_2O_5 in benzene. Isomerization of the nitrile, followed by vpc purification, showed a sample of **8** of $[\alpha]^{25}D$ −12.0° had been converted to **4** of $[\alpha]^{25}D$ +44.2°. Similarly, *trans*-acid **6** of $[\alpha]^{25}D$ −46.4° could be converted through its acid chloride **19**, and amide **13** to nitrile **4** of $[\alpha]^{25}D$ −63.1°. These data were sufficient to establish that acid **8** of (1*R*,2*S*) absolute configuration had a maximum rotation of $[\alpha]^{25}D$ −28.6°.

Optically active acids **6** and **8** were then carried through the homologation–reduction sequence. Structural identity of each of the optically active compounds obtained with its racemic counterpart was established by comparison of infrared spectra. The *cis*-1-ethyl-2-methylcyclopropane (**18**) obtained from (+)-**8** was levorotatory, and had an infrared and nmr spectrum identical with those of racemic material synthesized both by the same and by an independent route.[18] Levorotatory *trans*-1-ethyl-2-methylcyclopropane ((−)-**24**) was obtained from (−)-**6**. Each optically active methylethylcyclopropane was uncontaminated (>0.5% detectable) with its stereoisomer.

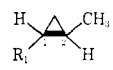
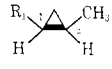
The amide interconversions described above, in conjunction with the known maximum rotation and absolute configuration of **6**, are sufficient to provide the absolute configurations and maximum rotations of each of the compounds obtained. These are as indicated in Scheme III and Table I. This assertion, of course, is predicted on the reasonable assumption that none of the chemical transformations involves loss of optical purity or inversion of configuration.

Confirmatory evidence for the assignment of absolute configurations is provided by the application of Brewster's rules of conformational asymmetry[16] to the *trans*-cyclopropanes described here. Table I gives the predicted and observed molecular rotations at the sodium D line of compounds in both series. The predictions are undoubtedly most reliable for the *trans* series, since the R ↔ H "screw pattern of polarizability" contributions (arrows), which are responsible for the optical rotation of these substances in the Brewster theory,[16] are reasonably large and exist in only one helical sense. It is probably for this reason that the agreement between predicted and observed rotation in the *trans* series is relatively good.



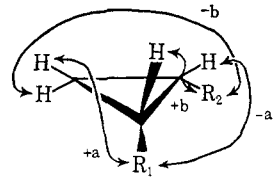
(11) T. Sugita and Y. Inouye, *Bull. Chem. Soc. Jap.*, **39**, 1075 (1966).
(12) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).
(13) W. Von E. Doering and W. Kirmse, *ibid.*, **11**, 272 (1960), and references cited therein.
(14) H. M. Walborsky and F. M. Hornyak, *J. Amer. Chem. Soc.*, **77**, 6026 (1955).
(15) H. M. Walborsky and F. M. Hornyak, *ibid.*, **78**, 872 (1956).
(16) (a) J. H. Brewster, *ibid.*, **81**, 5475, 5483, 5493 (1959); (b) J. H. Brewster in "Topics in Stereochemistry," N. H. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, pp 1–72.

Table I. Predicted and Observed Absolute Configurations and Maximum Rotations of some *cis*- and Disubstituted *trans*-1,2-Cyclopropanes[a]

Compd no.	R_1	Configuration	MW	$[M]_D^{max}$ Calcd, deg	$[M]_D^{max}$ Obsd, deg	$[\alpha]_D^{max}$ Obsd, deg
						
6	CO_2H	(1*R*,2*R*)	100	−90	−77.4	−77.4
21	$CH_2CO_2CH_3$	(1*S*,2*R*)	128	−60	−33.5	−26.2
22	CH_2CH_2OH	(1*S*,2*R*)	100	−60	−34.9	−34.9
23	CH_2CH_2Br	(1*S*,2*R*)	162	−60	−43.6	−26.9
24	CH_2CH_3	(1*R*,2*R*)	84	−60	−30.0	−35.6
4	CN	(1*R*,2*R*)	81	−160	−85	−105
						
8	CO_2H	(1*S*,2*R*)	100	0	+28.6	+28.6
16	$CH_2CO_2CH_3$	(1*R*,2*R*)	128	0	+1.20	+0.91
25	CH_2CH_2OH	(1*R*,2*R*)	100	0	+0.22	+0.22
17	CH_2CH_2Br	(1*R*,2*R*)	162	0	−10.8	−6.65
18	CH_2CH_2	(1*S*,2*R*)	84	0	−13.6	−16.2
5	CN	(1*S*,2*R*)	81	0	+8.3	+10.2

[a] Abbreviations used: MW, molecular weight; $[\alpha]_D^{max}$, specific rotation of optically pure material at the sodium D line, 25°; $[M]_D^{max}$, molecular rotation at the sodium D line, 25° ($[M]_D = MW \times [\alpha]_D/100$).

In the *cis* isomers, however, each of the right-handed R ↔ H helical contributions is balanced by a left-handed one, and so the net rotations are all predicted to be zero. Because of the cancellation of the larger first-



order contributions in the *cis* series, the signs of rotation are determined by less well understood second-order effects probably arising from chemical and conformational differences in R_1 and R_2. The rotations are therefore lower in magnitude and more erratic in sign. With these considerations in mind, the good agreement between the predicted and observed signs of rotation in the *trans* isomers, combined with the fact that none of the transformations involved a chemical change at *both* asymmetric centers, indicates that little or no over-all inversion occurred in any of the steps which were used to interconvert the compounds described here.

Experimental Section

Diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride ($LiAlH_4$) before use. Benzene was distilled and stored over molecular sieves. Optical rotations were determined on a Perkin-Elmer 141 digital readout polarimeter, nuclear magnetic resonance (nmr) spectra on a Varian Associates A-60-A spectrometer, and infrared (ir) spectra on Perkin-Elmer 137 and/or 257 instruments. Nmr chemical shifts are reported in ppm downfield from tetramethylsilane. Vapor phase chromatography (vpc) was carried out on Varian Aerograph A-90-P3 instruments, ememploying the following columns: column A; 12 ft × 1/4 in. 20% Carbowax 20M; column B, 5 ft × 1/4 in. 15% SE-30; column C, 20 ft × 3/8 in. 20% Carbowax 20M, all on 60–80 mesh Chromosorb P solid support. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-103C spectrometer. Microanalyses were performed by Spang Microanalytical Lab., Ann Arbor, Michigan.

I. *trans* Isomers, Racemic Series. (±)-*trans*-2-Methylcyclopropanecarbonyl Chloride (19). A 100-ml one-necked round-bottomed flask equipped with a magnetic stirring bar and drying tube was charged with 13.85 g of (±)-*trans*-2-methylcyclopropanecarboxylic acid **6**.[4] A total of 16.60 g of thionyl chloride was then added and the drying tube replaced; evolution of HCl began immediately. After stirring the mixture for 3 hr, infrared analysis of a small aliquot showed complete conversion to the acid chloride **19**.

(±)-*trans*-2-Methylcyclopropyldiazomethyl Ketone (20). About 400 mmol of diazomethane in ether solution was prepared from Du Pont EXR-101,[17] and distilled through an apparatus containing no ground-glass joints into a 3-l. round-bottomed flask containing a magnetic stirring bar and cooled to −5°. The entire sample of acid chloride **19** prepared as described above was dissolved in about an equal volume of ether and the solution added dropwise, with stirring and ice cooling, to the diazomethane solution. The resulting mixture was stirred for 3 hr at −5° and overnight at room temperature, and the ether removed on a rotary evaporator. The crude diazo ketone **20** contained no residual acid chloride (infrared analysis); the unstable oil exhibited strong infrared bands at 4.72, 6.10, 7.12, 7.42, 8.73, and 9.18 μ. The crude material was used immediately in the next step.

(±) Methyl 2-(*trans* 2-Methylcyclopropyl)acetate (21). The entire sample of diazo ketone prepared as described above was dissolved in 1500 ml of methanol and irradiated (Pyrex filter) with nitrogen continuously bubbled through the solution until the infrared spectrum of an aliquot worked up as described below showed no trace of diazo ketone. The methanol was distilled off (steam bath) through a Vigreux column, and the brown residue poured into a mixture of pentane and water. The phases were separated and the aqueous layer was salted heavily and extracted three times with fresh pentane. The combined pentane fractions were washed with water and saturated sodium chloride solution and dried over sodium sulfate. The pentane was distilled off through a Vigreux column on the steam bath and the brownish residue distilled at 65 mm. Vpc analysis of the major fraction (6.35 g, 36% yield over-all from acid **6**; bp 81–83° (60 mm)) on column B at 110° showed one peak, contaminated with a total of about 10% of three other products.

A small portion of this material was further purified by vapor chromatography. The nmr spectrum of the purified material (containing less than 1% impurity by vpc) exhibited an ester methyl signal (3 H) at 3.6 ppm, cyclopropyl methyl (3 H, doublet, J = 5 Hz) signal centered at 1.1 ppm, a methylene doublet (2 H, J = 6 Hz) at 2.2 ppm, and broad cyclopropyl absorption from 0.2 to 0.9 ppm (4 H). The material had strong bands in the infrared (neat film) at 3.4, 5.75, 6.96, and 8.55 μ. Its mass spectrum (70 eV) shows a parent peak at *m/e* 128, and fragmentation peaks at *m/e* 113, 97, and 69. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.85; H, 9.29.

(±)-2-(*trans*-2-Methylcyclopropyl)ethanol (22). A sample of 3.0 g of distilled ester **21** was dissolved in 20 ml of anhydrous ether and added dropwise to a well-stirred slurry of 0.5 g of $LiAlH_4$ in

(17) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

30 ml of the same solvent in a 200-ml 3-necked round-bottomed flask equipped with a reflux condenser and drying tube. The mixture was stirred for one hour at room temperature after the addition was complete, and the excess hydride destroyed by slow addition of a saturated solution of sodium sulfate in water. The white granular precipitate was filtered off, the ether removed through a Vigreux column on the steam bath, and the colorless residue distilled at 75 mm.

The alcohol (2.0 g, 86%) was obtained as a water-white oil, bp 93° (75 mm); after purification by vpc it exhibited the following nmr spectrum: methylene triplet at 3.6 ppm (2 H, J = 6 Hz), broadened O–H singlet at 2.4 ppm (1 H), methyl doublet at 1.1 superimposed on complex absorption from 1.1 to 1.7 ppm (J = 5 Hz, total 6 H), and cyclopropyl absorption from 0.1 to 0.9 ppm (3 H). Its infrared spectrum exhibited strong bands at 3.0, 3.45, 9.6, and 11.35 μ. *Anal.* Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.75; H, 12.13.

About 0.4 g of this material was allowed to stand overnight in a mixture of 3 ml of pyridine and 1.5 ml of acetic anhydride. Water was added and after standing 1 hr, the mixture salted heavily and extracted three times with pentane. The pentane extracts were combined and washed with 5% HCl and saturated brine, and dried over sodium sulfate. Concentration through a Vigreux column left a sweet smelling oil whose infrared spectrum indicated complete conversion to **(±)-2-(*trans*-2-methylcyclopropyl)ethyl acetate.** This material was purified by preparative vpc on column B. *Anal.* Calcd for $C_8H_{14}O_2$; C, 67.57; H, 9.92. Found: C, 67.83; H, 9.89.

(±)-2-(*trans*-2-Methylcyclopropyl)ethyl Bromide (23). A three-necked 100-ml round-bottomed flask equipped with a nitrogen inlet and dropping funnel was flamed out under nitrogen and charged with 1.0 g of alcohol **22**, 10 ml of dimethylformamide (DMF) (freshly distilled from calcium hydride), and 2.65 g of triphenylphosphine (fresh from storage overnight over P_2O_5 at 0.5 mm). Under a nitrogen blanket, bromine was added dropwise with rapid stirring until 2 drops produced a stable orange tint in the solution. During the addition the reaction temperature was kept below 55° by use of a water bath. A vacuum pump was then attached to the flask through a short-path distillation apparatus and all the volatile material distilled into a receiver cooled in Dry Ice–acetone. The distillation was run at 1 mm, and was continued until the temperature of the oil bath reached 80°.

The distillate was then poured into 25 ml of cold water and extracted 3 times with pentane. The pentane fractions were combined and washed 3 times with water, then with brine, and dried over magnesium sulfate. Evaporation through a Vigreux column and removal of last traces of solvent on a rotary evaporator left 1.55 g (92%) of a slightly greenish oil with prominent bands in the infrared at 3.37, 6.90, 7.92, and 8.23 μ (neat film). Its nmr spectrum exhibited a methylene triplet at 3.45 ppm (2 H, J = 6.5 Hz), apparent quartet at 1.8 ppm (2 H, J = *ca.* 6 Hz), methyl doublet at 1.05 ppm (3 H, J = 5 Hz), and complex cyclopropyl absorption from 0.1 to 0.8 ppm (4 H). Vpc analysis indicated that the crude material was contaminated with about 8% of a material having the same retention time as the *cis* isomer. After distillation it was sent for analysis.

Anal. Calcd for $C_6H_{11}Br$: C, 44.19; H, 6.79; Br, 48.9. Found: C, 44.13; H, 6.92; Br, 48.88.

(±)-*trans*-1-Ethyl-2-methylcyclopropane (24). A sample of 0.863 g of bromide **23** was mixed with 2.82 g of tri-*n*-butyltin hydride in a 100-ml round-bottomed flask. The solution was allowed to stand for 2 days; after this time, vpc analysis showed that all the bromide had been converted to a new, more volatile product. The flask was connected to an aspirator vacuum through a drying train and a trap chilled in Dry Ice–acetone. The flask was slowly warmed to 60°, and *trans*-1-ethyl-2-methylcyclopropane **(24)**[18] collected in the trap (0.366 g, 85% yield). Its nmr spectrum showed complex absorptions centered at 0.3 ppm (3 H) and 1.05 ppm (9 H), and no signals at lower field. In the infrared it had strong bands at 3.55, 7.30, 7.70, 9.32, 9.85, 10.80, 11.41, 12.55, and 13.55 μ (CS_2).

II. *cis* Isomers, Racemic Series. (±)-*cis*-2-Methylcyclopropanecarboxylic acid (8) was converted to **(±)-*cis*-1-ethyl-2-methylcyclopropane (18)** using procedures essentially identical with those used in the *trans* series. Treatment of 17.0 g of acid **8** with 18.0 g of thionyl chloride at room temperature for 12 hr produced acid chloride **14**. That these conditions were mild enough to prevent conversion of the *cis*-acid chloride **14** to its *trans* isomer **(19)**[4] was indicated by the fact that a small amount of **14** allowed to stand in contact with water for 3 hr and then extracted with ether and concentrated gave an acid whose ir was identical with that of *cis*-acid **8**.

Acid chloride **14** was converted to diazo ketone **15** with diazomethane in ether. Irradiation of 2.0 g of **15** in 100 ml of methanol (Pyrex filter) followed by work-up gave 50% yields of **(±)-methyl-2-(*cis*-2-methylcyclopropyl)acetate (16)**, but irradiation on a larger scale (20 g in 1500 ml of methanol) gave somewhat lower yields (35%), probably because a larger vessel was used with the same lamp, and the over-all rate of conversion dropped somewhat.

Twleve grams of ester **16** (bp 84° (60 mm)) was reduced with lithium aluminum hydride to give 8.0 g (85%) of **(±)-2-(*cis*-2-methylcyclopropyl)ethanol (25)**, bp 93° (75 mm). An nmr of this material (after purification on column B) showed a hydroxyl absorption at 7.2 ppm (1 H), α-methylene signal centered at 3.7 ppm (2 H), aliphatic absorption from 0.7 to 1.9 (8 H), and a broadened cyclopropyl signal at −0.2 ppm (1 H), presumably due to the cyclopropyl methylene hydrogen *trans* to the two substituents. In the infrared, it had strong bands at 3.0 and 3.45 μ, and broad absorptions with maxima at 6.92 and 9.50 μ (neat film). *Anal.* Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.49; H, 11.84. A small amount of **16** was purified by vpc on column B. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.69; H, 9.55.

A sample of 3.24 g of alcohol **25** was then converted to 3.92 g of **(±)-2-(*cis*-2-methylcyclopropyl)ethyl bromide (17)** in DMF. *Anal.* Calcd for $C_6H_{11}Br$: C, 44.19; H, 6.79; Br, 48.9. Found: C, 44.22; H, 6.74; Br, 48.94. A sample of 3.50 g of **17** (bp 83°, (70 mm)), on treatment with 2 equiv of tri-*n*-butyltin hydride, yielded 1.56 g of ***cis*-1-ethyl-2-methylcyclopropane (18).** The nmr and ir spectra of this material were identical with those of a sample synthesized by Simmons–Smith reaction on *cis*-2-pentene.[18]

Synthesis of (±)-*cis*-2-Methylcyclopropanecarboxylic Acid (8) from 2-Butyn-1-ol (10). A sample of 9.5 g of 2-butyn-1-ol[19] **(10)** was dissolved in 70 ml of 95% ethanol. Zinc–copper couple was prepared by diluting 4 ml of 20% cupric sulfate solution with 20 ml of water, adding 12 g of zinc and swirling the mixture, followed by suction filtration under a nitrogen stream. The couple was then added immediately, while still damp, to the ethanolic solution, and the mixture heated at reflux overnight under a water condenser.[5a] The solution was cooled and filtered, and the ethanol distilled off at atmospheric pressure through a Vigreux column. The residue was distilled at 50 mm; 5.0 g of material, bp 60–67°, was obtained in this way. Lowering the pressure to 20 mm yielded a fraction boiling from 70–110°, whose infrared spectrum indicated that it was mainly starting material.

Vpc analysis of the major fraction on column A showed predominantly one peak, presumably *cis*-crotyl alcohol **11** contaminated with less than 1% of the *trans* isomer and with a small amount of ethanol. Its infrared spectrum had bands at 3.0, 3.3, 3.4, 3.45, 7.0, 9.75, and 10.25 μ, consistent with an alcohol having a *cis*-double bond. An nmr spectrum showed weak signal due to ethanol, and three multiplets due to the *cis*-crotyl alcohol; one at 5.55 ppm (2 H), one at 4.10 ppm (3 H), and the third at 1.6 ppm (3 H).

A solution of iodomethylzinc iodide was then prepared from 15 g of zinc–copper couple, 44 g of methylene iodide, and 250 ml of ether, and the *cis*-crotyl alcohol **11** from the above preparation (5.0 g) added dropwise in 50 ml of ether. The mixture was stirred at reflux overnight. An aliquot was removed, worked up (*vide infra*), and subjected to vpc analysis on column A; the major constituent was a new material, but about 25% of the starting material still remained. Another 24 hr of reflux carried the conversion to 88%; further conversion could not be effected by either continued heating or addition of fresh zinc–copper couple. A solution of aqueous ammonium chloride was added, the phases were separated, and the aqueous phase was saturated with sodium chloride and extracted twice with ether. The combined ether fractions were washed three times with saturated potassium carbonate and once with brine, and dried over sodium sulfate. The ether was distilled off through a Vigreux column, leaving an orange oil which was distilled through a short-path apparatus at 19 mm. The major fraction (3.5 g) came over from 53–59°, and consisted of about 92% of the new material **12** by vpc analysis on column A. A small amount was purified on column B. *Anal.* Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.49; H, 11.84.

(18) C. S. Elliott and H. M. Frey, *J. Chem. Soc.*, 900 (1964).

(19) Obtained from Farchan Research Lab., Wickliffe, Ohio.

A sample of 0.05 g of alcohol **12** was dissolved in 5 ml of acetone and cooled to 0°. Jones reagent[6] was added until an orange color persisted in the solution, and then the mixture poured into water and extracted three times with pentane. The pentane fractions were combined and washed with water, sodium bicarbonate solution, and brine, and dried over sodium sulfate. Evaporation of the solvent through a Vigreux column on the steam bath left a light green oil, whose infrared spectrum indicated it was mainly aldehyde. This material was immediately dissolved in 5 ml of a solution of 5.0 g of silver nitrate in 30 ml of water and 50 ml of 95% ethanol[7] and treated with 20 ml of a solution of 5.0 g of sodium hydroxide in 100 ml of water dropwise. After stirring 30 min, the mixture was filtered, water added, and three ether extractions were run. Acidification of the water phase with 17% hydrochloric acid, followed by salting heavily, and extracting three times with ether gave an organic phase which was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by preparative vpc on column B; the colorless oil obtained had a vpc retention time and infrared spectrum precisely identical with those of *cis*-2-methylcyclopropanecarboxylic acid (**8**) obtained by the method of Applequist and Peterson.[4]

III. Optically Active Series. Optical Resolution of *cis*-2-Methylcyclopropanecarboxylic Acid (8). A sample of 72 g of racemic acid **8** was dissolved in 300 ml of acetone at reflux and 23 g of quinine added. A homogeneous solution formed initially, but the salt began to crystallize soon after, so acetone was added until the boiling mixture was again homogeneous. The mixture was allowed to cool to room temperature, and after standing 2 days 140 g of crystals were collected, mp 142–148°. The material collected was recrystallized twice more from fresh acetone and the crystals obtained (90 g, mp 151–154°) were shaken with a mixture of 17% hydrochloric acid and ether. The phases were separated and the aqueous solution was salted heavily and extracted twice more with ether. After washing the combined organic phases with 5% hydrochloric acid and brine, they were dried over sodium sulfate and concentrated *in vacuo*. The greenish residue was distilled (bp 98°, 20 mm) to give 18.79 g of acid **8**, whose ir spectrum was identical with that of racemic material. A sample of this material showed only one symmetrical peak by vpc on column B and had $[\alpha]^{25}D$ +17.9° (95% ethanol).

Optical Resolution of *trans*-2-Methylcyclopropanecarboxylic Acid (6). The salt of the *trans*-acid **6** was prepared from 62 g of acid and 200 g of quinine as described for the *cis* isomer. Four recrystallizations from acetone, followed by regeneration of the acid in 17% hydrochloric acid and vpc purification, gave material whose ir was identical with racemic **6**. Its rotation was $[\alpha]^{25}D$ −46.4° (95% ethanol).

The cyclopropane derivatives described below were prepared in optically active form using procedures identical with those used to synthesize the racemic materials. Structural identity of active and racemic compounds was established in each case by comparison of the infrared spectra and vapor phase chromatographic behavior of both materials.

(+)-(1*R*,2*R*)-Methyl 2-(*cis*-2-methylcyclopropyl)acetate (16) was prepared as described for the racemic material by Arndt–Eistert homologation of a sample of (+)-(1*S*,2*R*)-*cis*-2-methylcyclopropanecarboxylic acid (**8**) of rotation $[\alpha]^{25}D$ +17.9° (95% ethanol). The ester was obtained better than 98% pure by vpc; removal of the minor impurity on column A gave material of 99.5% purity whose rotation was $[\alpha]^{25}D$ +0.57°; $[\alpha]^{25}_{365}$ +12.2° ($CHCl_3$).

(+)-(1*R*,2*R*)-2-(*cis*-2-Methylcyclopropyl)ethanol (25) was obtained by reduction of the above sample of ester **16**. Vpc analysis indicated a purity of 96%; its rotation was $[\alpha]D$ +0.14°; $[\alpha]^{25}_{365}$ −1.46° ($CHCl_3$). This material was converted to **(+)-(1*R*,2*R*)-2-(*cis*-2-methylcyclopropyl)ethyl bromide (23)**, 96% pure by vpc. After purification by preparative vpc (obtained 99.0% pure), **23** had a rotation of $[\alpha]^{25}D$ −4.19°; $[\alpha]^{25}_{365}$ −16.8° (CH_3OH).

The above sample of bromide was allowed to stand in a sealed vessel with 2 equiv of tri-*n*-butyltin hydride. **(−)-(1*S*,2*R*)-*cis*-1-Ethyl-2-methylcyclopropane (18)** was distilled out of the reaction mixture better than 98% pure. The mobile colorless oil had an ir and nmr spectrum indistinguishable from those of racemic material, and showed $[\alpha]^{25}D$ −10.13°; $[\alpha]^{25}_{365}$ −34.98° (*n*-heptane).

Similarly, a sample of (−)-(1*R*,2*R*)-*trans*-2-methylcyclopropanecarboxylic acid (**6**), $[\alpha]^{25}D$ −34.8° (95% ethanol), was converted *via* the Arndt–Eistert homologation to **(−)-(1*S*,2*R*)-methyl 2-(2-methylcyclopropyl)acetate (21)**, 98% pure by vpc. Its rotation was $[\alpha]^{25}D$ −11.8° ($CHCl_3$). Lithium aluminum hydride reduction gave **(−)-(1*S*,2*R*)-2-(2-methylcyclopropyl)ethanol (22)**, 98% pure, $[\alpha]^{25}D$ −15.7° (CH_3OH). Conversion to **(−)-(1*S*,2*R*)-2-(2-methylcyclopropyl)ethyl bromide (23)**, $[\alpha]^{25}D$ −12.1° (CH_3OH) after purification on column B, was accomplished in the usual way. Tri-*n*-butyltin hydride treatment of this material gave 98% pure **(−)-(1*R*,2*R*)-1-ethyl-2-methylcyclopropane (24)**, $[\alpha]^{25}D$ −16.0°, $[\alpha]^{25}_{365}$ −47.6° (*n*-hexane). Its nmr and ir spectra were identical with those of racemic material.

Cyclization of β-Methyl-γ-chlorobutyronitrile (3). A mixture of 100 g of **3**, 48.4 g of sodium methoxide and 500 ml of THF (freshly distilled from lithium aluminum hydride) was stirred overnight in a 1-l. round-bottomed flask protected by a drying tube. Ice and water were added and the mixture was extracted three times with ether. After combining the ether phases and washing them twice with water and once with brine, they were dried over sodium sulfate. Distillation at atmospheric pressure first removed the ether and residual THF; 56 g (80% yield) of *cis*- and *trans*-2-methylcyclopropanecarbonitriles (**5** and **4**) then distilled over at 145°. Vpc analysis on column A indicated that the ratio of **4** to **5** was approximately 1.6:1.

***cis*-2-Methylcyclopropanecarbonitrile (5)** was obtained by preparative vpc on column C at 200°. Its nmr spectrum, in analogy to the other *cis* derivatives in this series, showed a one-proton multiplet at 0.6 ppm, presumably due to the cyclopropyl methylene hydrogen *trans* to both substituents, separated from the other proton absorptions grouped in a band from 0.9 to 1.5 ppm (6 H). The material showed sharp strong bands in the ir at 3.40, 4.45, 6.92, 9.08, 9.40, 9.55, 11.18, and 11.82 μ ($CHCl_3$).

***trans*-2-Methylcyclopropanecarbonitrile (4)** was obtained in the same vpc separation. It showed all its nmr signals concentrated in a broad band from 0.9 to 1.5 ppm and infrared spectrum exhibited strong bands at 3.4, 4.45, 6.92, 9.39, 10.6, 11.39, and 11.62 μ ($CHCl_3$). *Anal.* Calcd for C_5H_7N: C, 74.03; H, 8.70; N, 17.27. Found for **5**: C, 73.87; H, 8.74; N, 17.17. Found for **4**: C, 74.11; H, 8.65; N, 17.20.

IV. Optical Correlation of *cis* and *trans* Series. A sample of 3.0 g of *trans*-2-methylcyclopropanecarboxylic acid (**6**), $[\alpha]^{25}D$ −46.4° (ethanol), was converted to the corresponding acid chloride **19** and thence to 2.5 g of *trans*-2-methylcyclopropanecarboxamide[4] (**13**) by treatment with aqueous ammonia. In order to avoid optical fractionation of the crystalline amide, the entire sample was completely dissolved in methylene chloride and about half the solution removed and evaporated *in vacuo*, leaving about 1.5 g of **13** in remaining solution. To all of this material was added 15 ml of triethylamine and 30 ml of dry benzene, and the mixture was then brought to reflux under a drying tube and heated until it was homogeneous. The reaction vessel was removed from the oil bath, 6.0 g of P_2O_5 added, and the mixture stirred at room temperature for 1 hr and at reflux for a final 3 hr. It was then poured into water and the benzene phase washed with dilute hydrochloric acid, sodium bicarbonate, water, and brine. Drying and evaporation of the solvent *in vacuo* left 0.7 g of a yellow oil which showed strong nitrile absorption in the ir at 4.45 μ. A vpc of this material showed one peak, with a retention time identical with that of *trans*-2-methylcyclopropane carbonitrile prepared from **3**. After vpc purification, its rotation was $[\alpha]D$ −63.1° ($CHCl_3$). Its ir spectrum was identical with that of the racemate.

This material was stirred 6 hr with 25 ml of ether (freshly distilled from lithium aluminum hydride) and about 1.0 g of lithium diisopropylamide. Water was added and the ether phase evaporated and washed with water and brine, followed by drying over sodium sulfate. Evaporation of the ether through a Vigreux column left a brownish oil, which was distilled bulb-to-bulb at 20 mm. A vpc of the colorless oil obtained indicated that it was a 50:50 mixture of the nitriles **4** and **5**.

Similarly, a sample of *cis*-2-methylcyclopropanecarboxylic acid (**8**), $[\alpha]^{25}D$ −12.0° (ethanol), was recovered from the mother liquors of the optical resolution described earlier. This material was converted to ***cis*-2-methylcyclopropanecarbonitrile (5)** *via* the acid chloride **14** and carboxamide **7** as described for the *trans* material. This sample of **5** was treated with lithium diisopropylamide in ether at room temperature; an aliquot removed after 5 min of reaction and analyzed by vpc showed that the same mixture of nitriles **4** and **5** had been reached (50:50) that was obtained by similar treatment of *trans*-nitrile **4**. Further treatment with lithium diisopropylamide produced no change. The mixture was therefore worked up and the distilled product preparatively separated by vpc on column A. The sample of *cis*-nitrile **5** obtained had an infrared spectrum identical with that of racemic material obtained from cyclization of **3**, and showed $[\alpha]^{25}D$ −4.27° ($CHCl_3$). The *trans* nitrile obtained from the same separation also had an ir spectrum indistinguishable from the corresponding racemate, and had $[\alpha]^{25}D$ +44.2° ($CHCl_3$).

From these results, the maximum rotation of (+)-(1*S*,2*R*)-cyclopropanecarboxylic acid (*cis*-**8**) can be calculated to be

$$[\alpha]^{25}D_{max}(-12.0)\frac{(-63.1)(-77.4)}{(+44.2)(-46.4)} = +28.6^\circ \text{ (ethanol)}$$

employing the value of −77.4° (ethanol) for the maximum rotation of (−)-(1*R*,2*R*)-2-methylcyclopropanecarboxylic acid (*trans* **6**).

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Kinetics of Racemization and *cis–trans* Isomerization of the Optically Active 1-Ethyl-2-methylcyclopropanes in the Gas Phase. An Estimate of Relative Rates of Bond Rotation and Ring Closure in Diradical Intermediates[1a]

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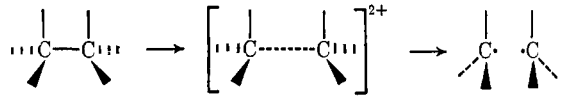
Abstract: The rates of racemization and *cis–trans* isomerization of optically active *cis*- and *trans*-1-ethyl-2-methylcyclopropane ((−)-**4C** and (−)-**4T**) have been measured at temperatures in the neighborhood of 400° in a static system in the gas phase. The rates have been analyzed to yield the unimolecular interconversion rate constants for each of the components in the system. Their similarity in magnitude indicates that an electrocyclic process proceeding through π-cyclopropane intermediates is energetically less favorable than a pathway involving stereoisomeric diradicals. A steady-state analysis of the diradical mechanism has been developed which may be solved for relative rates of rotation and cyclization of the diradicals, and these values are compared with similar numbers characteristic of diradical species which may be intermediates in other reactions already reported in the literature.

The cleavage of a carbon–carbon bond is normally assumed to occur along a reaction coordinate defined by the potential energy of the C–C stretching vibration—that is, by moving the two carbon atoms away from one another along a line coincident with the bond axis. The recent elegant discussions of carbon–carbon



bond cleavage in cyclic polyolefinic systems presented by Oosterhoff,[2] Woodward and Hoffmann,[3] Longuet-Higgins and Abrahamson,[4] Fukui,[5] Zimmerman,[6] Dewar,[7] and Salem,[8] however, have suggested that this reaction can occur more easily in some cases by rotation of the two atoms with respect to one another rather than by simply moving them apart. Thus so-called "electrocyclic" bond cleavage occurs thermally in cyclic polyolefins by rotating two carbon atoms along a coordinate with σ symmetry (the disrotatory mode[3]) when there are $4n + 2$ electrons in the open-chain π system, and along a coordinate with C_2 symmetry (the conrotatory mode[3]) when there are $4n$ electrons in the open-chain π system.

The cleavage of a carbon–carbon bond which does not have an associated π-electron framework might be considered to be the simplest electrocyclic reaction. Owing to the directional nature of the orbitals making up such a bond, the three modes of bond breaking would in principle still be available, and a transient "π bond" might be an intermediate on the route to two completely free radicals. The stereochemistry of cleavage and recombination would then be controlled only by the energetic relationships of the two orbitals, modified by weak interactions with an associated σ system present in the molecule.

This paper reports the results of stereochemical investigation of such a system, the thermal cleavage, and recombination of a bond in a substituted cyclopropane.[1b] The cyclopropane molecule was selected as an object of study because its thermal reactions were known to be clean and first order, because the presence of ring strain placed temperatures necessary to induce bond cleavage in a high but still accessible region, and in order to keep the gain in entropy for dissociation of the two radical centers as low as possible. The problem can then be restated briefly as an examination of whether stereospecific ring opening and closing of a substituted cyclopropane such as **1** (by either a conrotatory or disrotatory pathway) to produce a transient "π-cyclopropane" **2** is a higher or lower energy process than direct cleavage to give a freely rotating diradical **3**.

(1) (a) For a preliminary account of this work, see W. L. Carter and R. G. Bergman, *J. Am. Chem. Soc.*, **90**, 7344 (1968); (b) National Science Foundation Predoctoral Fellow, 1968–1969.
(2) Quoted in E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 151 (1961); see also W. Th. A. M. van der Lugt and L. J. Oosterhoff, *Chem. Commun.*, 1235 (1968).
(3) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395, 2511 (1965).
(4) H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965).
(5) K. Fukui, *Tetrahedron Letters*, 2009 (1965), and subsequent papers.
(6) H. E. Zimmerman, *J. Am. Chem. Soc.*, **88**, 1564, 1566 (1966).
(7) M. J. S. Dewar, *Tetrahedron Suppl.*, **8**, 75 (1967).
(8) L. Salem, *J. Am. Chem. Soc.*, **90**, 543, 553 (1968).