Stereochemistry of the Electrophilic Ring Opening of Cyclopropanes. 2. Reaction of *cis*- and *trans*-1,2,3-Trimethylcyclopropane with D^+

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Abstract: The stereochemistry of the attack of D^+ in a number of solvents on *cis*- and *trans*-1,2,3-trimethylcyclopropane has been determined. In the cis isomer all carbons are identical, and the reaction proceeds with 68% retention and 32% inversion of configuration by the attacking D^+, and with 95% or greater inversion by the nucleophile (forming the acetate, trifluoroacetate, bromide, or methyl ether). Stereochemical analysis was carried out by NMR analysis, either by examining the deuterium NMR or, in the case of the methyl ethers, by means of a long-range deuterium isotope effect on the absorption position of the methoxyl protons in the presence of $Eu(fod)_3$. In the trans isomer there is one unique carbon, that bearing the trans methyl group, and this carbon is completely symmetrical to electrophilic attack. At this carbon D^+ attacks also with twice as much retention as inversion. Attack at the other two carbons can occur from either of two sides. It is shown that attack from the side of the cis methyls occurs three times more often than attack from the side of the trans methyls. By combining two different isotope effects on the europium shifted NMR spectra it was possible to determine the stereochemistry of attack from the cis side (5:1 retention to inversion) and trans side (1:2 retention to inversion). The results are interpreted in terms of an unsymmetrical corner-protonated cyclopropane.

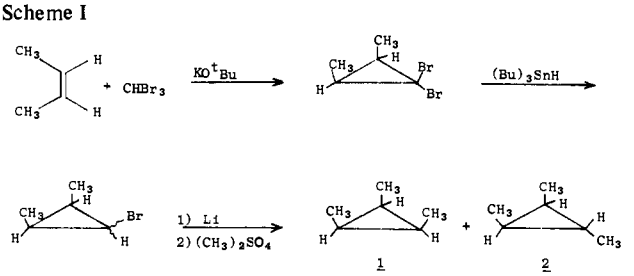
Cyclopropanes readily undergo ring cleavage upon treatment with acids, and the nature of the intermediate or intermediates which may be formed in this electrophilic cleavage reaction remains one of the most intriguing unanswered questions in small-ring chemistry. The reaction is of special interest because it remains one of the few in which a carbon–carbon single bond is broken by a proton, and while several investigations have been made into the mechanism of these reactions, numerous ambiguities remain. In this paper we report the results of a study of the stereochemistry of the electrophilic attack on *cis*- and *trans*-1,2,3-trimethylcyclopropane by D^+ in several solvents, and discuss the implication of these results to the mechanism of electrophilic cleavage of cyclopropanes.

Results and Discussion

A number of previous studies of the stereochemistry of ring opening of cyclopropanes have been carried out.[1] In a large majority of these cases the electrophile has been shown to enter with retention of configuration, but examples of reaction with inversion and with a mixture of retention and inversion are also known. However, we have shown that in unsymmetrically substituted cyclopropanes the nature and stereochemistry of the substituent can control the direction of attack on the ring and hence the stereochemistry of the ring opening.[1e]

In order to eliminate any possible stereochemical bias we decided to begin by investigating the completely symmetrical *cis*-1,2,3-trimethylcyclopropane (**1**). The synthetic sequence we used is given in Scheme I, and has some advantages for our

Scheme I

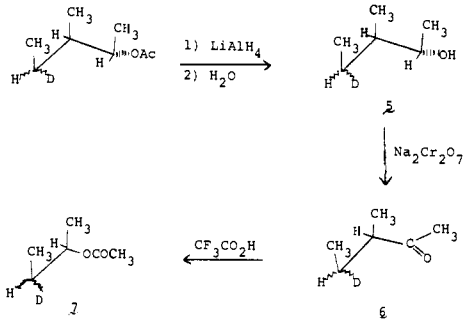


purposes over other reported methods for the synthesis of this compound.[2] Yields of a mixture of the monobromo compounds[3] from olefin averaged about 60%, while methylation occurred in approximately 50–60% yield to give a mixture of cis (**1**) and trans (**2**) isomers with the latter predominating (60:40). These isomers can be separated by spinning-band distillation or preparative gas chromatography.

***cis*-1,2,3-Trimethylcyclopropane.** Cyclopropane **1** reacts very rapidly with pure CF_3COOD at room temperature, or upon heating with CH_3COOD/D^+ or $CH_3O^+D_2$, to give ring-opened products. In Figure 1 we illustrate the four products of stereochemical interest which could arise from acetolysis (**3** and **4**). These are indeed the main products, together with some tertiary acetate resulting from hydrogen migration.[4] We note immediately that the acetates resulting from nucleophilic inversion belong to the threo series (**3**)[5] while those resulting from nucleophilic retention are erythro acetates (**4**).[6] These two isomers can be separated and analyzed by gas chromatography and nucleophilic inversion (threo acetate) is found to predominate by a 95:5 ratio.

Our next task was to determine the stereochemistry of the deuterium within both the threo and erythro acetates. The procedure is shown in Scheme II. First we collected pure

Scheme II



samples of each isomer by preparative GC. The pure acetates were then each converted to alcohols ($LiAlH_4$) and oxidized to the corresponding ketone (**6**) with $Na_2Cr_2O_7$ in aqueous ether under experimental conditions which have been reported not to epimerize an adjacent chiral center.[7,8] Mass spectral analysis of this ketone showed it to contain only a single deuterium atom (>95% d_1).

The NMR spectrum of an undeuterated sample of **6** in the presence of europium shift reagent [$Eu(fod)_3$] is shown in

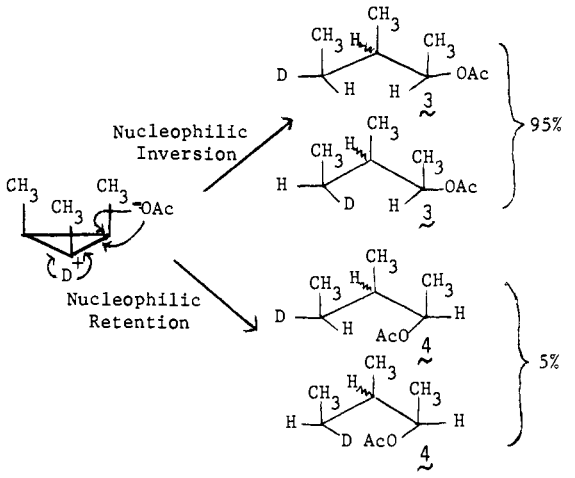


Figure 1. Products from the reaction of *cis*-1,2,3-trimethylcyclopropane with D^+ in deuterioacetic acid.

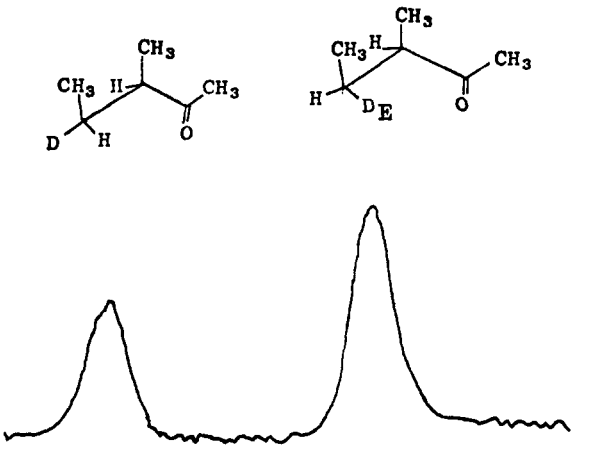


Figure 3. ^2H NMR spectrum of 4-deuterio-3-methyl-2-pentanone [24 mg of ketone + 120 mg of $Eu(fod)_3$ in 450 μL of $CCl_4/CFCl_3$, 1:1]: mixture of the erythro isomer (68%) and the threo isomer (32%).

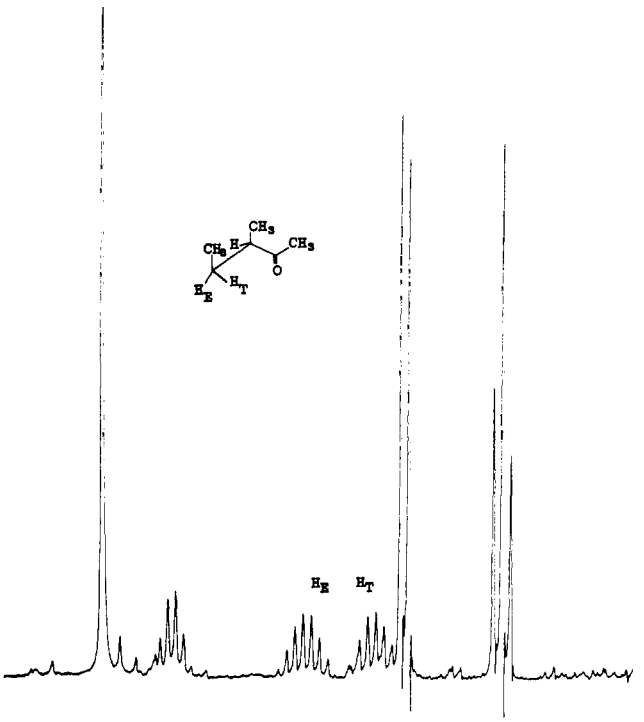


Figure 2. 90-MHz ^1H NMR spectrum of 3-methyl-2-pentanone in the presence of $Eu(fod)_3$.

Figure 2. Note the two diastereotopic protons (H_E and H_T) whose replacement by deuterium indicates retention or inversion, respectively, in the ring-opening reaction. (The proton assignment is justified below.) In theory the amount of deuterium in each position could be determined by integration of the proton spectrum, but this is difficult to carry out quantitatively because of the partial overlap of H_T with the methyl protons. This difficulty disappears in the deuterium magnetic resonance (^2H NMR) spectrum (see Figure 3) since the methyl group contains no deuterium.

The ^2H NMR spectrum clearly shows that the product resulting from ring opening with retention of configuration by D^+ predominates over that with inversion by a 68:32 ratio, and identical stereochemical results within experimental error were obtained from both threo and erytheo acetate indicating that the stereochemistry of electrophilic attack is independent of the stereochemistry of nucleophilic attack.

All that remains is to verify our assignments of the absorption positions for H_E and H_T in **6** (and simultaneously, of course, the ^2H NMR absorptions for the corresponding D_E and D_T). To accomplish this, the ketone was oxidized under Baeyer–Villiger conditions[9] with peroxytrifluoroacetic acid to a mixture of *threo*- and *erythro*-3-deuterio-2-butyl acetate (**7**) followed by reduction with lithium aluminum hydride to a mixture of the diastereomeric 3-deuterio-2-butanols. The ^2H NMR spectrum of this mixture showed a 68:32 ratio of absorptions with the major peak being identified as the erythro diastereomer through NMR comparisons with authentic samples of *threo*- and *erythro*-3-deuterio-2-butanol prepared by independent lithium aluminum deuteride reductions of the *cis*- and *trans*-2-butene oxides, respectively.[10]

An analogous series of experiments was carried out using CF_3COOD as the solvent and electrophilic reagent. In this case the ring-opened trifluoroacetates and rearranged tertiary acetate were formed in a 55:45 ratio. This mixture was hydrolyzed to a mixture of the corresponding alcohols, a portion of which was purified by preparative GC. The 3-methyl-2-pentanol was identified as the threo isomer[1] showing that within the limits of our analytical method in this case (NMR analysis: ±5%) the nucleophile enters with complete inversion of configuration. Mass spectral analysis of the rearranged tertiary alcohol, 3-methyl-3-pentanol, showed it to be highly deuterated (up to d_7) presumably because the tertiary trifluoroacetate undergoes facile elimination addition reactions. Pure ketone **6**, resulting from oxidation of the 3-methyl-2-pentanol, was shown to consist of 34% d_0, 63% d_1, and 3% d_2 species, and we ascribe the much larger amounts of d_0 species found in this reaction as compared to the acetolysis (>95% d_1) to be due to preferential attack by the protons released during the exchange reaction of the tertiary trifluoroacetate.

Stereochemical analysis was again carried out on the ketone **6** by both ^1H and ^2H NMR, and the results were, within experimental error, the same as with acetic acid/D^+ at 90 °C, namely, 68% retention of configuration, 32% inversion by the deuterium.

Next we carried out ring opening of **1** by heating in CH_3OD containing D^+. A mixture of three ethers was obtained, as indicated by GPC analysis, and these were identified as the threo ether (80%), erythro ether (4%), and rearranged tertiary ether (16%) by comparison with authentic samples prepared from commercially available alcohols with the assumption that the threo ether (formed by nucleophilic inversion) predominates over the erythro isomer. This latter assumption was also justified by the NMR spectra of the two ethers. The stereochemistry of the deuterium within the threo methyl ether could

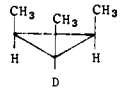
Figure 4. Splitting of the methoxyl peaks in the threo and erythro ethers in the presence of Eu(fod)$_3$.

be determined by ^{2}H NMR analysis directly on the ether itself, and it proved to be the same, within experimental error, as that from ring opening by acetic or trifluoroacetic acid, namely, 68% erythro deuterium (opening by electrophilic retention) and 32% threo deuterium (32% electrophilic inversion). In preparing these samples we also recorded the ^{1}H NMR spectrum and we noted (Figure 4) that the methoxyl protons of the threo ether were split in this same 68:32 ratio, indicating a deuterium isotope effect on the europium-induced chemical shift.[11]

The methoxyl peak of that threo ether isomer containing threo deuterium absorbs further downfield than the isomer containing erythro deuterium. Separations of about 6 Hz between the two peaks can be induced at high europium concentrations. The erythro methyl ether also shows a similar but smaller (3 Hz) splitting of its methoxyl signal so that the stereochemistry of the deuterium within each isomer could also be determined easily from the ^{1}H NMR. It showed the same approximately 2:1 retention:inversion ratio of D^+ attack.

In order to investigate the stereochemistry of ring opening in as nonpolar a medium as possible we next reacted **1** with deuterium bromide in methylene chloride solution. The ring-opened bromides were converted to acetates by reaction with tetramethylammonium acetate in acetone under reaction conditions favoring S_N2 displacement. The main product was the erythro acetate, indicating a threo configuration for the bromide and hence that in this case also the nucleophile enters with inversion. ^{2}H NMR analysis on the acetate showed the same 68:32 retention to inversion ratio for electrophilic attack as found for the reactions in the other solvent systems.

As a final check we prepared 1-deuterio-*cis*-1,2,3-trimethylcyclopropane (**8**) and carried out ring-opening reactions



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with H^+ under various conditions. In these cases the proton entered with the same 2:1 retention to inversion ratio as was found for deuterium in the protonated cyclopropane system, ruling out an isotope effect as the source of the stereochemical results.

***trans*-1,2,3-Trimethylcyclopropane.** Electrophilic ring opening of the trans isomer, **2**, can occur by attack on the unique carbon holding the trans methyl group, or on either of the carbons holding the cis methyls. If we assume complete inversion by the nucleophile (95% or greater inversion was found in the cis isomer) then attack at the former carbon (C_T) leads to the formation of threo ethers or acetates while attack at either of the latter carbons (C_C) leads to erythro ethers or acetates. This is illustrated in Figure 5.

Note that electrophilic attack on C_T is unbiased since the two bonds joining this carbon to the ring are identically substituted. Attack from either side gives threo ether, and the

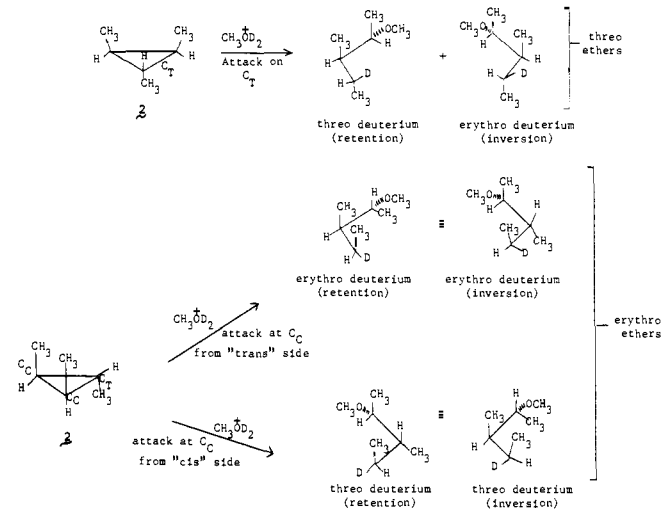


Figure 5. Possible products from the reaction of *trans*-1,2,3-trimethylcyclopropane with D^+ in CH_3OD assuming complete inversion by the nucleophile.

stereochemistry of the deuterium within this ether gives the stereochemistry of electrophilic attack. This can be determined directly from the methoxyl protons in the ^{1}H NMR spectrum, by integration of the ^{2}H NMR spectrum, and, in the case of acetolysis, by hydrolysis to the corresponding alcohol, oxidation to the ketone, and ^{2}H NMR analysis as described earlier (see Scheme II). All of these methods agree in showing the same stereochemical results for attack on C_T as for attack on the carbons of the cis isomer, namely, 2:1 retention to inversion (68% threo deuterium, 32% erythro deuterium).

Electrophilic attack on *trans*-1,2,3-trimethylcyclopropane occurs approximately equally at each carbon, so that $\frac{1}{3}$ threo and $\frac{2}{3}$ erythro esters or acetates are formed. As Figure 5 shows, attack on C_C from the "trans" side leads to the same deuterium stereochemistry (erythro deuterium) no matter whether the electrophile attacks with retention or inversion, while the opposite deuterium stereochemistry results from either electrophilic retention or inversion from attack on the "cis" side. If we examine the stereochemistry of the deuterium in the erythro ethers we get, not the stereochemistry of the ring-opening step, but rather the relative ease of attack of D^+ on C_C from the "trans" and "cis" sides. We find that the ratio of threo to erythro deuterium within the erythro ethers is 75:25 showing that "cis" attack occurs three times more often than "trans" attack. We had previously shown that mercuric salts attacked cyclopropanes more readily on cis-substituted bonds than on trans-substituted bonds[1] and this same effect, presumably a steric one, is found for D^+ attack. We can clearly see all the experimental results for the methanolysis of the trans isomer in the Eu(fod)$_3$ shifted methoxyl region of the mixture of threo and erythro ethers obtained directly from the reaction mixture. The ratio of the two ethers is 2:1 erythro:threo showing the statistical attack on these carbons. Within the threo ether we can see a 2:1 ratio of threo to erythro deuterium showing a 2:1 retention to inversion ratio by D^+ while within the erythro ether we can see a 3:1 threo:erythro deuterium ratio, showing a 3:1 preference for cis vs. trans attack. These results have been confirmed by GPC analysis of the ethers and acetates (from acetolysis) and by ^{2}H NMR analysis.

1-Deuterio-*trans*-1,2,3-trimethylcyclopropane. Still to be determined was the stereochemistry of attack of electrophile on C_C from the cis and trans direction. Because of the peculiar symmetry of the *trans*-trimethylcyclopropane system electrophilic retention and inversion give the same product. In order to determine these stereochemistries we prepared the 1-deuterio isomer of *trans*-trimethylcyclopropane (**9**) by

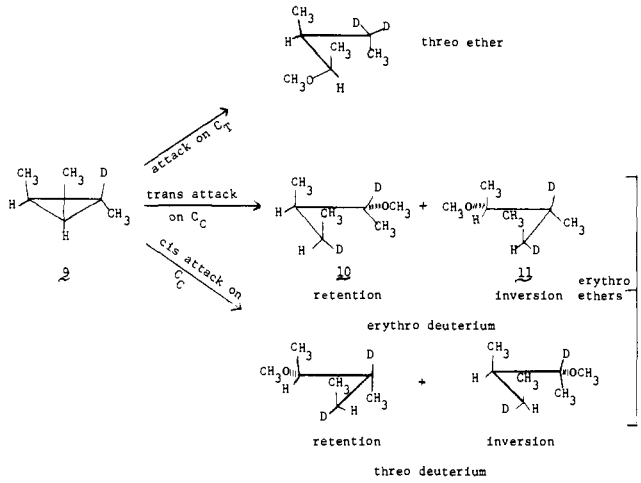


Figure 6. Products from the reaction of 1-deuterio-*trans*-1,2,3-trimethylcyclopropane with D^+ in CH_3OD.

carrying out the reduction of the dibromide (Scheme I) with tributyltin deuteride. After methylation a mixture of monodeuterated cis and trans isomers was obtained and separated. Results from ring opening of the cis isomer were reported above.

The deuterated trans isomer was opened by reaction in $CH_3O^+D_2$ in accordance with the scheme in Figure 6. As before a 2:1 ratio of erythro to threo ethers was formed, but now these ethers each contained two deuterium atoms per molecule. The ^1H NMR was run in the presence of a large amount of $Eu(fod)_3$ shift reagent. What should we expect to see in the methoxy region of such a spectrum?

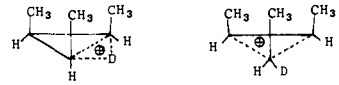
First the methoxyl peak of the threo ether should be unchanged in position, but now occurs as a singlet because it is not a mixture of deuterium diastereomers. Its absorption position can be verified by the addition of a sample of authentic threo ether. The methoxyl region of the erythro ethers, on the other hand, should be more highly split because substitution by deuterium α to an oxygen results in a greater degree of complexation by the shift reagent and hence a downfield shift for the resonances in the deuterated as compared to the protonated molecule.[12] Consider the case of trans attack on C_C. Attack of D^+ with retention leads to erythro ether with the methoxyl group on the same carbon as a deuterium atom (**10**). The methoxyl peak in this molecule will absorb downfield from the methoxyl peak in **11**, the isomer resulting from trans attack on C_T with inversion by D^+ in which the methoxyl group is on the same carbon as a hydrogen atom and does not shift appreciably from its monodeuterio analogue. Thus the isomers with erythro deuterium will be split into two peaks, one from electrophilic retention and one from electrophilic inversion. Similarly the erythro ether with threo deuterium will be split into two peaks, the downfield peak now corresponding to inversion, the upfield one to retention. The threo ether appears as expected, as a single peak, unchanged in position from its monodeuterio analogue. But the original 75:25 mixture of erythro isomers is now split into four peaks, two (those with the second deuterium β to the methoxyl) essentially unchanged in position and two new peaks from the isomers with deuterium α to the methoxyl groups. A pure sample of the mixture of erythro ethers was isolated by preparative GPC and its spectrum also determined. Expansion and integration allows a reasonably good estimate of the stereochemistry of attack on C_C from both the cis side (5:1 retention to inversion) and from the trans side (1:2 retention:inversion) to be obtained.

The stereochemical results we have found in this study are summarized in Figure 7. In the cis isomer, and in attack at C_T in the trans isomer, we have shown that the stereochemistry

Figure 7. Retention:inversion ratios for D^+ attack on trimethylcyclopropanes. The nucleophile attacks with >95% inversion.

is the same within experimental error in several solvent systems. For attack on C_C the reaction has been studied only in methanol as solvent.

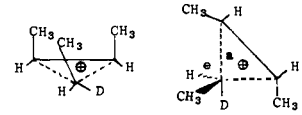
The first and most important conclusion from these studies is that the activation energies for inversion and retention by electrophile are very nearly the same, and yet the reaction does not occur by way of a completely symmetrical intermediate which would lead to a 50:50 mixture of products. Two types of protonated cyclopropanes have been considered previously, edge-protonated (**12**) and corner-protonated (**13**).[13,14] It is easy



12 **13**

to see how deuterium could enter with retention of configuration from an edge-protonated intermediate. However, in order to get electrophilic inversion from **12** a great deal of molecular motion and change in bonding would have to occur, and certainly the structure of an edge-protonated cyclopropane as usually drawn does not make it obvious why the inversion and retention pathways should have nearly the same energy. On the other hand, in the symmetrical corner-protonated intermediate retention and inversion pathways are identical (except for isotopic substitution) in energy. We do not find a 50:50 mixture of products, and our isotope studies have ruled out an isotope effect as an explanation for the results. Next we considered the possibility that ring-opened products arise from both an edge- and a corner-protonated intermediate, with the former leading to complete electrophilic retention, the latter to an equal mixture of retention and inversion. Of course, by choosing the proper mixture of the two pathways many stereochemical results can be accommodated. Yet two lines of argument can be brought against such a mixture of mechanisms. In the first place it would be extremely surprising if the relative amounts of the two independent pathways would remain constant over a wide range of experimental condition. Yet we find that the retention:inversion ratio for the cis isomer is unchanged within experimental error whether the reaction is carried out in acetic acid, trifluoroacetic acid, methanol, or methylene chloride. Secondly, one would not expect that the two independent paths would give exactly the same amount of nucleophilic inversion and retention. Yet in reactions of **1** we find the same D^+ stereochemistry within the 5% erythro product (from nucleophilic retention) as we do within the 95% threo product from inversion. Taken together these two arguments seem to us to be most compatible with a single intermediate which gives rise to products. In order to accommodate our results, this intermediate must be unsymmetrical, but only slightly so. We suggest that the electrophile enters (probably by way of an edge-protonated species) in the plane of the ring and remains there in the intermediate which leads to ring opening.

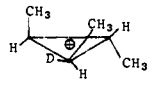
We might draw an analogy here to a trigonal bipyramidal structure (**15**), with the electrophile attacking axially.[15] One



14 **15**

bond of the three-membered ring would be axial, the other equatorial so as to accommodate the small ring. Nucleophilic attack on the equatorial carbon would then lead to retention by D^+, and attack on the axial carbon would lead to inversion by D^+. The carbons are not identical in such an intermediate and an exact 50:50 ratio of products would not be expected. Of course ring opening must occur more rapidly than pseudorotation, which interchanges H and D.

Is this picture able to account for the stereochemical results of attack on C_C from the "cis" and "trans" sides? In a general way, yes. In a completely symmetrical case, as in the cis isomer or on reaction at C_T in the trans isomer, retention is favored over inversion by 2:1. For attack at C_C we must superimpose an additional factor on this 2:1 ratio. We suggest that methyl–methyl repulsions will speed up bond breaking on the ring bond between two cis methyls. This factor will increase the amount of retention upon attack on C_C from the cis side (**16**) and will increase the amount of inversion upon attack on C_C from the trans side (**17**), in accord with experimental observation.



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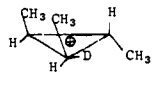

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Finally it should be emphasized that we are dealing here with the intermediate which leads to products and not necessarily to the intermediate which is formed in the rate-determining step. In fact we believe that the formation of an edge-protonated cyclopropane is probably rate determining, with the proton moving along the edge into the corner. We will give evidence on this point in later papers.

Experimental Section

Boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. ^1H NMR spectra were obtained on Varian A-60A, EM-360, and HA-100 instruments with $CDCl_3$ or CCl_4 as solvents and tetramethylsilane as internal standard. ^{13}C and ^2H NMR spectra were recorded on a JEOL Model PFT-100 Fourier transform instrument. Mass spectra were measured on Varian M-66 and MAT CH-7 spectrometers. Shift reagent concentrations are reported as molar ratios.

GLPC analyses and preparative separations were performed on F & M Model 700 and Varian Aerograph Model 200 gas chromatographs employing the following columns: (A) 3.0 m × 6 mm 20% SE-30 on non-acid-washed Chromosorb W; (B) 1.5 m × 6 mm 20% SE-30 on non-acid-washed Chromosorb W; (C) 1.5 m × 6 mm 20% UCON 550X on non-acid-washed Chromosorb P; (D) 3.5 m × 6 mm 20% Carbowax 20M on non-acid-washed Chromosorb W; (E) 15 m × 3 mm 3% Carbowax 20M on non-acid-washed Chromosorb W; (F) 10 m × 6 mm 10% Carbowax 20M on non-acid-washed Chromosorb W.

Acetic acid-*O-d* was prepared from equimolar amounts of acetic anhydride and D_2O (99% isotopic purity).

Deuterium bromide was prepared following the procedure of Caple et al.[16] The gas was stored in the freezer as a solution in methylene chloride.

Tri-*n*-butyltin deuteride was prepared according to the procedure described by Lahournere and Valade.[17] Starting from 154.3 g of tri-*n*-butyltin hydride, the deuterated compound was obtained in 80% yield (bp 87–88 °C (0.7 mm)).

Preparation of the Deuterated Cyclopropane (8 and 9). The same procedure as for the nondeuterated compounds was employed. Instead of tri-*n*-butyltin hydride, tri-*n*-butyltin deuteride was used as the reducing agent.

1,1-Dibromo-*cis*-2,3-dimethylcyclopropane. The reaction between *cis*-2-butene, bromoform, and potassium *tert*-butoxide[18] was conducted as outlined by Skell and Garner,[3] bp 64–69 °C (14 mm, under nitrogen), yield 81%. GLC analyses were conducted on column A at 135 °C.

1-Bromo-*cis*-2,3-dimethylcyclopropane. The reduction of 1,1-dibromo-*cis*-2,3-dimethylcyclopropane with freshly prepared tri-*n*-butyltin hydride[19] was carried out exactly as described by Seyferth and co-workers.[23] *syn*- and *anti*-1-bromo-*cis*-2,3-dimethylcyclopropane: bp 60–70 °C (150 mm, under nitrogen); yield 71%. GLPC analyses were carried out on columns A and B at 100 °C.

Table I. Natural Abundance ^{13}C NMR Spectra

Cyclopropane	Chemical shift[a]	Multiplicity	J^b ^{13}C–H	Assignment
1	182.4	d	170	C-1,2,3
1	186.7	q	120	C-Methyl
2	172.2	d		C-3
2	174.6	d		C-1,2
2	175.7	q		C-3 methyl
2	181.0	q		C-1,2 methyls

[a] Values in parts per million from internal CS_2. [b] Coupling constants for those protons attached directly to the carbon in question.

1,2,3-Trimethylcyclopropane (1 and 2).[2b] A three-neck round-bottom flask was fitted with a dry ice condenser, a self-leveling addition funnel, Ar inlet and outlet, and a mechanical stirrer. The entire apparatus was flamed out under dry Ar, cooled to room temperature, and then charged with 60 mL of anhydrous ether and 2.86 g (415 mmol) of Li wire previously washed free of grease with dry hexane. At −10 °C in an acetone bath (utilizing dry ice as coolant) with mechanical stirring under dry Ar was added 24.0 g (161 mmol) of 1-bromo-*cis*-2,3-dimethylcyclopropane in 10 mL of diethyl ether and 6 mL of tetrahydrofuran. The addition required 1 h; reaction was evident from the developing gray-black coloration. After stirring for an additional 0.5 h, the reaction vessel was cooled to −80 °C and 16 mL (21.2 g, 160 mmol) of dimethyl sulfate in 40 mL of diethyl ether was added dropwise over 1 h with mechanical stirring under Ar. After the reaction mixture was allowed to warm to room temperature over 8 h, the reaction was quenched through the addition of 100 mL of saturated aqueous NH_4Cl at 0 °C. This mixture was stirred and warmed to room temperature over 0.5 h. The products were isolated by extraction with ether (3 × 10 mL). The ethereal extracts were washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and distilled on a spinning band column: trans isomer **2**, bp 52–55 °C (635 mm); cis isomer **1**, bp 60–62 °C (635 mm); combined yield 39% (cis:trans 40:60). All spectra and ring-opening reactions were carried out on 98–99% purity material as judged by GLC analysis on column A at 75 °C. The structures of **1** and **2** were confirmed by spectral data including natural abundance ^{13}C NMR spectra (see Table I).

Trifluoroacetolysis. A 250-mL three-neck round-bottom flask which had been oven dried and cooled under dry Ar was fitted with a reflux condenser, mechanical stirrer, self-leveling addition funnel, and Ar inlet. The outlet of the inert gas system was attached to a $CaSO_4$ drying tube mounted on the condenser. In this vessel was placed 4.25 g of D_2O. After cooling in an ice–water bath, 44.50 g of freshly distilled [bp 37–40 °C (635 mm)] trifluoroacetic anhydride was added dropwise under Ar over 15 min. An aliquot was removed for NMR analysis of isotopic purity with $CHCl_3$ as internal standard.

To this CF_3CO_2D solution was added 2.00 g of cyclopropane **1** at room temperature over 5 min with stirring under an inert gas atmosphere. The reaction mixture was then stirred at room temperature for 1 h. After analysis of an 0.5-mL aliquot by NMR, the reaction mixture was poured into a solution of 20 g of NaOH in 60 mL of H_2O at 0 °C. This mixture was stirred magnetically for at least 24 h at room temperature. The products were isolated by ether extraction (5 × 25 mL) followed by washing of the organic phase with saturated NaCl (2 × 20 mL). After drying ($MgSO_4$), the products were concentrated by distillation (30-cm glass-helices column) and then distilled pure (10-cm tantalum helices column): **5** and **4**-OH, bp 75–93 °C (160 mm); yield 100%. The alcohols were collected by GLC on column C (115 °C, 60 mL min^{-1}) and then analyzed mass spectrometrically (**5**, principally d_1; **4**-OH, up to d_7).

Chromic Acid Oxidation of 5. In a 100-mL three-neck round-bottom flask were placed 1.416 g (13.7 mmol) of **5** and 10 mL of anhydrous ether. The solution was cooled to 0 °C for 15 min. After the reaction flask was fitted with a reflux condenser, addition funnel, and mechanical stirrer, 7 mL of Brown's reagent,[7] which had been precooled to 0 °C, was added dropwise over 5 min with stirring. A second batch of 7 mL of precooled Brown's reagent was added over 5 min. Stirring was continued for 5 min after all of the oxidant had been added.

The reaction mixture was immediately extracted with ether (4 × 25 mL). (Initial extracts were quite black and, thus, the surface tension of the effluent from the separatory funnel was the best guide to the layer separation.) The ether extracts were washed with 5% K_2CO_3 (3 × 15 mL) and H_2O (4 × 10 mL) followed by drying ($MgSO_4$). The product (**6**) was purified by vacuum distillation, and was found to be identical with authentic material except for substitution by deuterium (mass spectral analysis: 34% d_0, 63% d_1, 3% d_2). **6:** bp 63–65 °C (110 mm); yield 0.782 g (56%). ^1H and ^2H NMR analyses in the presence of $Eu(fod)_3$ [15:85 $Eu(fod)_3$:substrate] in CCl_4 revealed a 68:32 ratio of diastereomers. Identical results were obtained in a separate ring-opening experiment.

Control Experiment for the Oxidation of 5. Brown's reagent[7] was prepared from 5.768 g of anhydrous $Na_2Cr_2O_7$ in 15 mL of D_2O followed by the addition of 3.85 mL (6.9 g) of D_2SO_4 and enough D_2O to make exactly 25 mL of solution in a volumetric flask. After thorough mixing, this "deuterated Brown's reagent" was cooled in an ice–water bath.

3-Methyl-2-pentanol-*O-d* was prepared by washing 3 g of unlabeled alcohol with D_2O (3 × 10 mL) in a separatory funnel, drying ($MgSO_4$), and distilling: bp 125–129 °C (635 mm); yield 2.372 g (80%). NMR analysis revealed complete O-deuteration.

The deuterated alcohol (2.372 g) was oxidized exactly as described above for **5** except that Brown's reagent and H_2O washes were replaced with "deuterated Brown's reagent" and D_2O washes. The product ketone was isolated by GLPC on column C and analyzed by mass spectrometry: 89% d_0, 11% d_1, 0% d_2. Therefore, no more than 5.5% and most probably less than 1.4% (25% of 5.5%) of the inversion product could have been generated during oxidation of **5.**

3-Deuterio-2-butyl Acetate (7) from the Baeyer–Villiger Oxidation of 6. The exact procedure of Emmons and Lucas[9] was followed with 600 mg of **6. 7:** bp 72–76 °C (105 mm); yield 0.541 g (80%).

3-Deuterio-2-butanol (7-OH) from the Lithium Aluminum Hydride Reduction of 7. The product from the Baeyer–Villiger oxidation (**7**, 0.541 g, 4.7 mmol) was stirred magnetically for 1 h with 1.5 g of $LiAlH_4$ in 20 mL of ether in a 50-mL round-bottom flask at 0 °C. The reaction mixture was worked up with 1.5 mL of aqueous Na_2SO_4, 1.5 mL of 15% NaOH, followed by 4.5 mL of aqueous Na_2SO_4 until a granular precipitate resulted. The ether layer was separated, dried ($MgSO_4$), filtered, and concentrated by distillation, and the alcohol was collected by GLC on column C at 125 °C. Analysis of 7-OH by ^1H and ^2H NMR in the presence of $Eu(fod)_3$ [15:85 $Eu(fod)_3$:substrate] in CCl_4 followed by comparisons with authentic diastereomers revealed a 68:32 ratio of *erythro-* to *threo*-3-deuterio-2-butanol. Identical results were obtained in a separate experiment involving ring opening and subsequent degradation and analysis.

Authentic *erythro-* and *threo*-3-Deuterio-2-butanol. The exact procedure of Pasto, Cumbo, and Hickman[10] was employed.

Acetolysis. *cis*-1,2,3-Trimethylcyclopropane (440 mg) and 4 mL of acetic acid-*O-d* containing 0.3% (by volume) D_2SO_4 were placed in a thick-wall tube. The tube was sealed and the mixture was heated for 1 h at 90 °C. The resulting colorless solution was poured into ice-cold diluted sodium hydroxide solution and the water phase was extracted with pentane. The pentane layer was washed with water and saturated sodium bicarbonate solution and dried over magnesium sulfate. Most of the solvent was removed by distillation over a small Vigreux column. GLC analysis of the remaining oil on column E showed, besides some olefins, a mixture of three acetates (increasing retention times): 3-methyl-3-pentyl acetate **18** (2%), *erythro*-3-methyl-2-pentyl acetate **4** (4%), and *threo*-3-methyl-2-pentyl acetate **3** (94%).

These products could be isolated by preparative GLC on column F yielding 12 mg of compound **18**, 11 mg of compound **4**, and 320 mg of **3.** Peak assignment was made by comparison with the authentic acetates. The composition of the original mixture of the diastereomeric acetate could also be determined by NMR spectroscopy. In the presence of $Eu(fod)_3$ the resonance of the carbomethoxy protons of the erythro isomer occurs at lower field compared to that of the threo isomer. The same ratio as in the GLC analysis is observed.

Conversion of the Acetate 3 to 3-Methyl-*4-d*-2-pentanol. In a 25-mL two-neck round-bottom flask, fitted with a reflux condenser, magnetic stirrer, and addition funnel with nitrogen inlet, were placed 75 mg of lithium aluminum hydride and 5 mL of anhydrous ether. To the stirred mixture was added 260 mg of *threo*-3-methyl-*4-d*-2-pentyl acetate dissolved in 5 mL of anhydrous ether. After stirring for 30 min the mixture was cooled in an ice bath and treated with 0.5 mL of 10% ammonium chloride solution. The resulting precipitate was filtered and washed with ether. After drying with magnesium sulfate most of the ether was removed by distillation through a small Vigreux column. The pure *threo*-3-methyl-*4-d*-pentanol was then collected by preparative GLC on column D yielding 148 mg (75%) of a colorless oil.

Chromic Acid Oxidation of 3-Methyl-*4-d*-2-pentanol. The procedure described above was used for this oxidation. From 110 mg of alcohol, 56 mg (52%) of pure 3-methyl-*4-d*-2-pentanone (**6**) was collected by preparative GLC on column D. Mass spectral analysis shows more than 95% d_1 species; no higher deuterated product could be detected.

Methanolysis of 1. *cis*-1,2,3-Trimethylcyclopropane (**1**, 455 mg) and 6 mL of methanol-*O-d* containing 7.5% (by volume) D_2SO_4 were placed in a thick-wall tube. The tube was sealed and heated for 1 h at 87 °C. The same workup procedure as for the acetolysis was employed. GLC analysis of the resulting mixture on column D showed, besides some olefins, the following composition (increasing retention times): *erythro*-3-methyl-2-methoxypentane-*4-d* (3.8%); *threo*-3-methyl-2-methoxypentane-*4-d* (80.1%); and 3-methyl-3-methoxypentane (16.1%). The two major products were isolated by preparative scale GLC on column D and identified by comparison with authentic material. *erythro*-3-Methyl-2-methoxypentane-*4-d* was further analyzed by recording the ^1H NMR and ^2H NMR spectra in presence of $Eu(fod)_3$ indicating 68% *erythro-4-d* and 32% *threo-4-d.*

Ring Opening with DBr. *cis*-1,2,3-Trimethylcyclopropane (**1**, 368 mg) was dissolved in 12 mL of methylene chloride containing 600 mg of deuterium bromide. This solution was allowed to stand at room temperature for 50 min. The organic phase was then washed with water and saturated sodium bicarbonate solution and dried over magnesium sulfate. Most of the solvent was removed by distillation through a small column filled with glass helices. The concentrated reaction mixture was then dissolved in 5 mL of acetone. After 2 g of tetraethylammonium acetate[24] was added the solution was refluxed for 4 h. About half of the acetone was removed by distillation through a glass helix column and the concentrated reaction mixture diluted with water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and most of the solvent removed by distillation. GLC analysis on column D showed, besides some unchanged bromide (5%), *erythro-* and *threo*-3-methyl-2-pentyl acetate (46 and 10%, respectively) and two further products (9 and 30%) that were not identified. The erythro isomer was collected by preparative scale GLC on column D. Reduction with lithium aluminum hydride and oxidation with Brown's reagent leads to 10 mg of pure 3-methyl-2-pentanone-*4-d* (**6**).

Ring Opening of *trans*-1,2,3-Trimethylcyclopropane (2). Acetolysis. Cyclopropane **2** (420 mg) and 4 mL of acetic acid-*O-d* containing 0.3% (by volume) D_2SO_4 were heated for 1 h at 90 °C in a sealed tube. The same workup procedure as for the cis compound was employed. GLC analysis on column E of the reaction mixture showed besides some olefinic products a mixture consisting of 3-methyl-3-pentylacetate (5%), *erythro*-3-methyl-2-pentyl acetate (63%), and *threo*-3-methyl-2-pentyl acetate (32%). The two isomeric secondary acetates could be isolated each in pure form by preparative GLC on column F. About 2 h retention time was required for a separation. The isolated compounds were then converted into 3-methyl-2-pentanone (**6**) as described above.

Methanolysis. Cyclopropane **2** (574 mg) and 6 mL of methanol-*O-d* containing 7.5% (by volume) D_2SO_4 were heated in a sealed tube for 1 h at 87 °C. The same workup procedure as for the cis compound **1** was employed. GLC analysis on column D indicated a mixture of *erythro*-3-methyl-2-methoxypentane (59%), *threo*-3-methyl-2-methoxypentane (28%), and 3-methyl-3-methoxypentane (13%). A preparative separation of the two isomeric secondary ethers was achieved on column F.

Ring Opening Reactions with the Deuterated Cyclopropanes 8 and 9. The same workup procedures and analysis technique were employed as for the nondeuterated species.

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(6) *erythro*-3-Methyl-2-pentyl acetate (**4**) was obtained by acetylation of a nearly 1:1 diastereomeric mixture of commercially available 3-methyl-2-pentanol. Both the erythro and the threo isomer of the resulting acetates could be isolated in pure form by preparative scale GC (see Experimental Section).
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The Crystal and Molecular Structures of *S*-(+)-2,2-Diphenylcyclopropanecarboxylic Acid and of *R*-(+)-2,2-Diphenyl-1-methylcyclopropanecarboxylic Acid. A Study of the Environments of Gas–Solid Reactions That Exhibit Anisotropic Behavior

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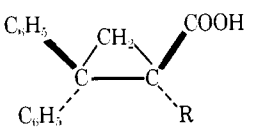
Abstract: The crystal structures of *S*-(+)-2,2-diphenylcyclopropanecarboxylic acid (I) and of *R*-(+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid (II) have been determined to examine the environment of some gas-solid reactions. The crystals of I are monoclinic, $a = 14.657(5)$, $b = 6.238(2)$, $c = 7.967(3)$ Å and $\beta = 117° 15'(2')$; there are two molecules of I in the space group $P2_1$. The structure was refined to an *R* factor of 0.043 on 1066 independent nonzero reflections. The crystals of II are orthorhombic, $a = 18.199(5)$, $b = 6.309(1)$, and $c = 11.796(2)$ Å; there are four molecules in the space group $P2_12_12_1$. The structure has been refined to an *R* factor of 0.037 on 1261 independent nonzero reflections. The molecular structures of I and II are very similar and the bond lengths in the cyclopropane ring show the influence of the exocyclic unsaturated substituents. Both structures exhibit linear chains or catemers formed by hydrogen bonding of the carboxylic acid groups along the *b* direction. In the crystal of I the *b* axis is polar and all the chains run in the same direction, whereas in II chains run in alternate directions along *b*. In both structures, the polar groups in the chains are well insulated from these groups in adjacent chains by nonpolar hydrocarbon groups, thus explaining the observed *ditropic* attack of ammonia gas on single crystals of I and II.

In studies[1-5] of the reactions of crystalline acids with ammonia and with gaseous amines the enantiomeric cyclopropane acids I and II are of particular interest. Whereas most acids



R-(−)-I, R = H
R-(+)-II, R = CH_3

crystallize as cyclic hydrogen-bonded dimers,[6] the enantiomeric acids I and II had been thought[7,8] to crystallize as hydrogen-bonded chains, or catemers.[6] A preliminary communication[4] reported the crystal structure and reaction of single crystals of the methyl acid II with ammonia gas, a reaction found to be ditropic, that is to proceed primarily along the two directions parallel to the hydrogen-bonded chains. The structure reported in preliminary form[4] has subsequently been discussed by Leiserowitz[6] in relation to the structures of other carboxylic acids. A second preliminary communication[5] has described the use of the acid I in a study of the selective reaction of gaseous optically active phenylethylamine with crystals of a single enantiomeric form of I.

This paper presents the crystal structures of resolved forms of the acids I and II on which the preliminary communications[4,5] were based, and also provides additional information about these solid-gas reactions. The x-ray structural work was