Polar Bromination and Chlorination of Cyclopropane

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Abstract: Cyclopropane has been prepared with three deuterium atoms on the same face (**6**, cyclopropane-*cis*-1,2,3-d_3) in order to determine the mechanism of electrophilic halogenation. This labeling pattern permits determination of the stereochemistry of both electrophilic and nucleophilic attack. Bromination and chlorination proceed under polar conditions to give 1,3-dihalopropane as the predominant product. The temperature dependence of the vicinal H–H coupling constant in the unlabeled dihalopropanes confirms that the major conformer has gauche arrangements over both C–C bonds (the GG conformer). The products were stable to rearrangement under reaction conditions. The magnitude and temperature dependence of the vicinal H–H coupling constant of the labeled 1,3-dibromo- and 1,3-dichloropropanes, observed under conditions of deuterium decoupling, were uniquely consistent with a retention–inversion stereochemistry. The observed stereochemistry is consistent with initial edge halogenation with retention to form a four-membered bromonium ion, followed by nucleophilic ring opening with inversion. This initial intermediate is the most stable according to ab initio calculations.

Although cyclopropanes are far less reactive than alkenes, they may be opened by select electrophiles, including the proton, bromine, chlorine, mercury(II), and acetyl chloride.[2] Early studies assumed that traditional open carbocations were formed (**1**, E is

1 **2**

a general electrophile), but the classic experiments of Baird and Aboderin[3] demonstrated that closed or bridged carbocations are necessary intermediates for deuteration. Attack may occur either at the edge of the cyclopropane (**2**) or at the corner (**3**); moreover,

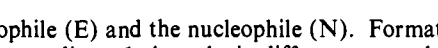
3 **4**

these intermediates must be in equilibrium. It was later realized that corner attack may result in an unsymmetrical ion **4** instead of or in addition to the symmetrical form **3**. The unsymmetrical form also may be drawn as a trigonal bipyramid.

These results with deuteration inspired the examination of other electrophiles, including bromine,[4] acetyl chloride,[5] and mercury(II) acetate.[6] In each of these studies with unsubstituted cyclopropane, the presence of bridged ions (**2**, **3**, or **4**) was inferred from the ratio of products obtained. These experiments, however, could not distinguish between edge and corner forms.

There have been numerous studies of the electrophilic ring opening of substituted cyclopropanes, particularly of polycyclic systems.[7] Wiberg and Kass[8] studied the acetolysis of alkylcyclopropanes both experimentally and theoretically. They found that the mechanism of attack depended on the substitution pattern. When only one carbon was substituted, the most stable cation was the open form (**1**, but monosubstituted). When more than one carbon was substituted, both open and bridged forms (**1**–**4**) had to be considered. Simulation of the protonation of *cis*-1,2,3-trimethylcyclopropane indicated that the stereochemistry of ring opening depends on the initial trajectory of the proton.

Because the mechanism of ring opening appears to vary with the substitution pattern, because the parent cyclopropane represents the archetype for the reaction, and because theory is most amenable for the study of cyclopropane itself, we have directed our efforts toward distinguishing which intermediates are present in the electrophilic ring opening of unsubstituted cyclopropane. The reaction, from cyclopropane to 1,3-disubstituted propane, involves at least two stereochemical events (eq 1), attachment of



(1)

the electrophile (E) and the nucleophile (N). Formation of the various intermediates **1**–**4** results in different stereochemical expectations. Therefore, we set out to demonstrate the stereochemistry of the electrophilic and nucleophilic attacks in unsubstituted cyclopropane. The minimum requirement for such a study is stereospecific isotopic labeling at two centers, as in **5**. We have

5 **6**

reported preliminary studies on bromination of this substrate.[9] Theoretical analysis of this system is complex, because the three bonds are structurally but not isotopically identical. Not only is the analysis of statistical effects confusing but also there may be differential isotope effects on attack at CHD vs CD_2. Moreover, our anlaysis[9] did not distinguish between the symmetrical and unsymmetrical forms (**3** and **4**) and did not include direct conformational analysis of the product (eq 1). To remedy these deficiencies, we have now synthesized the fully symmetrical cyclopropane-*cis*-1,2,3-d_3 (**6**), in which all three bonds are isotopically as well as structurally identical. Our synthesis was guided by the discovery of Baldwin et al. that the Wilkinson decarbonylation occurs with loss of some deuterium.[10] Also, we have performed an appropriate conformational analysis of the halogenation product of eq 1 by low-temperature NMR studies. We report herein that both bromination and chlorination occur by a retention/inversion

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(2) For a review, see: Depuy, C. H. *Fortschr. Chem. Forsch.* **1973**, *40*, 73–101.

(3) Baird, R. L.; Aboderin, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 252–255.

(4) Deno, N. C.; Lincoln, D. N. *J. Am. Chem. Soc.* **1966**, *88*, 5357–5358. Lincoln, D. N. Ph.D. Dissertation, Pennsylvania State University, 1969.

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(7) For recent results on polycyclic systems, see: Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 2988–2990. Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Org. Chem.* **1989**, *54*, 1383–1391. Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1989**, *54*, 3702–3709, and references therein.

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(9) Lambert, J. B.; Schulz, W. J., Jr.; Mueller, P. H.; Kobayashi, K. *J. Am. Chem. Soc.* **1984**, *106*, 792–793.

(10) Baldwin, J. E.; Barden, T. C.; Pugh, R. L.; Widdison, W. C. *J. Org. Chem.* **1987**, *52*, 3303–3307.

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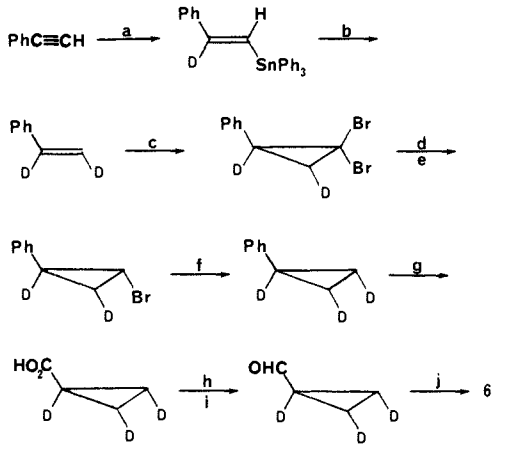
Scheme I[a]



[a](a) Ph_3SnD (87%); (b) BuLi; EtOD (60%); (c) $CHBr_3$/NaOH/BTEAB (87%); (d) Ph_3SnH (95%); (e) separation (35%); (f) BuLi; EtOD (66%); (g) O_3; H_2O_2/NaOH (56%); (h) $LiAlH_4$ (73%); (i) PCC (64%); (j) L_3RhCl (90%).

mechanism best explained in terms of the edge-halogenated intermediate **2** favored by theory.

Results

A key step in the synthesis of cyclopropane-*cis*-1,2,3-d_3 was the Wilkinson decarbonylation of cyclopropanecarbaldehyde. As originally designed, this compound had the isotopic distribution of **7**. While the synthesis was underway, Baldwin et al.[10] reported

7 **8**

significant loss of deuterium in this reaction. We carried out our own controls and confirmed that up to 40% of the deuterium is lost during the reaction. In our previous synthesis of cyclopropane-*trans*-1,1,2,3-d_4, this loss would have broadened but not destroyed the desired splitting.[9] To optimize the present study, we altered the synthesis to produce the labeling scheme of **8**, in which hydrogen rather than deuterium is lost during the decarbonylation reaction. The deuterium content and stereochemistry are unaffected by this now invisible hydrogen exchange. The final synthesis is shown in Scheme I.

The preparation of *cis*-α,β-styrene-d_2 was carried out according to the method of Baldwin and Carter.[11] Approximately 1 kg of the illustrated stannylstyrene was required to produce 2 g of the labeled cyclopropane **6**. Cyclopropanation was effected by phase-transfer catalysis with bromoform and benzyltriethylammonium bromide. Reduction with triphenyltin hydride produced a mixture of approximately 40% of the desired trans isomer of 2-bromophenylcyclopropane and 60% of the cis isomer. Separation of the isomers was accomplished by flash column chromatography, yielding the desired trans isomer in at least 98% purity.

Another key step in the synthesis was the stereospecific removal of the bromine in 2-bromophenylcyclopropane. Cyclopropyl anions normally retain their configuration, so we used a carbanionic procedure. Because proton transfer from the necessary ether solvents compromises the label, we used a solvent mixture of 13% diethyl ether and 87% hexane. The anion was generated at 0 °C by addition of 4.7 equiv of butyllithium and then quenched 15 min later with ethanol-*d*. The overall deuterium incorporation was about 96%.

The conversion of phenylcyclopropane to cyclopropanecarbaldehyde was achieved by a procedure very similar to that developed by Schulz for cyclopropane-*trans*-1,1,2,3-d_4 (**5**).[12] High resolution mass spectrometry and NMR analysis indicated that the aldehyde was more than 90% cis-d_3 and less than 10% cis-d_2.

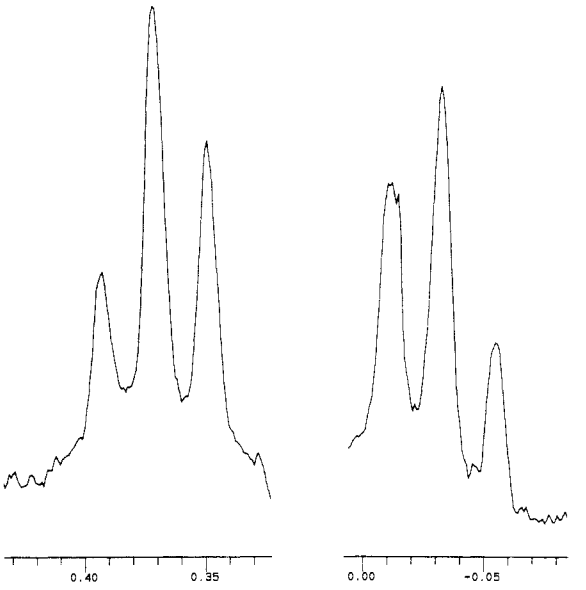


Figure 1. The ^{13}C satellites in the 400 MHz ^1H spectrum of cyclopropane-*cis*-1,2,3-d_3: $^1J(^{13}C-^1H)$ = 161 Hz, $^3J(^1H-^1H)$ = 8.8 Hz.

Cyclopropane-*cis*-1,2,3-d_3 was prepared from the stock of aldehyde as needed on a small scale just prior to reaction with the electrophile. The cis arrangement of the deuterium atoms was confirmed by the ^{13}C satellite spectrum (Figure 1). The measured cis vicinal H–H coupling of 8.8 Hz and the one-bond $^{13}C-^1H$ coupling of 161 Hz compare favorably to the literature values of 8.97 and 162 Hz (the trans coupling is 5.58 Hz).[13]

The bromination of cyclopropane in the absence of light produces 1,1-dibromopropane, 1,2-dibromopropane, and 1,3-dibromopropane in varying ratios, depending on conditions. This reaction generally is run with a catlyatic amount of iron(III) bromide.[4] Our reactions were run without solvent in a 5-mm tube on a 1.1 mmol scale of cyclopropane with a slight excess of bromine. We observed only the 1,2 (minor) and 1,3 (major) products, as the excess bromine tends to destroy some of the 1,1- and 1,2-products. To determine whether the dibromopropanes were scrambling deuterium or equilibrating under the reaction conditions, we prepared 1,3-dibromopropane-2,2-d_2 and 1,2-dibromopropane-2-*d* (see Experimental Section). After separate reaction in each case, only the respective starting dibromopropanes, without positional deuterium scrambling, were recovered.

The stereochemistry of bromination was determined by measurement of the H–H vicinal coupling constant in the product, BrCHD–CHD–CHDBr, with simultaneous irradiation at the deuterium frequency (protons at 500 MHz). The product 1,3-dibromopropane exhibited an A_2X pattern consisting of a triplet at δ 2.33 and a doublet at δ 3.53 (J = 6.2 Hz). Figure 2 shows the result of deuterium decoupling. The main byproduct, 1,2-dibromopropane, also is seen. An impurity peak obscures the upfield portion of the triplet. Cooling to −40 °C shifted the impurity peak to confirm the triplet structure. At −40 °C the coupling constant dropped to 5.9 Hz. The deuterium atoms on 1,2-dibromopropane were positionally scrambled.

Interpretation of the magnitude of the vicinal coupling in 1,3-dibromopropane-1,2,3-d_3 requires knowledge of the identity of the most stable conformer. This information was obtained from the variation of the vicinal H–H coupling constant with temperature. As Figure 3 shows, the coupling decreases with temperature in two different solvents, from about 6.2 Hz at room

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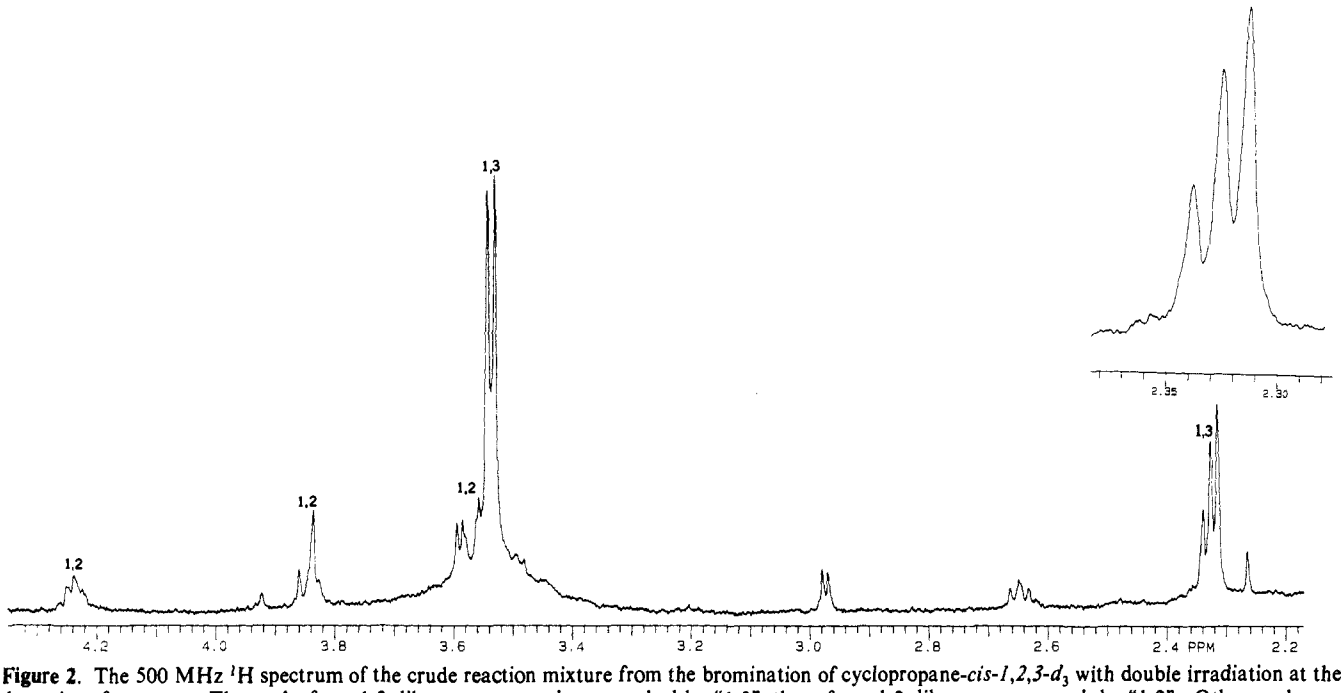

Figure 2. The 500 MHz ^1H spectrum of the crude reaction mixture from the bromination of cyclopropane-*cis*-1,2,3-d_3 with double irradiation at the deuterium frequency. The peaks from 1,3-dibromopropane-d_3 are marked by "1,3"; those from 1,2-dibromo propane-d_3 by "1,2". Other peaks are from byproducts.

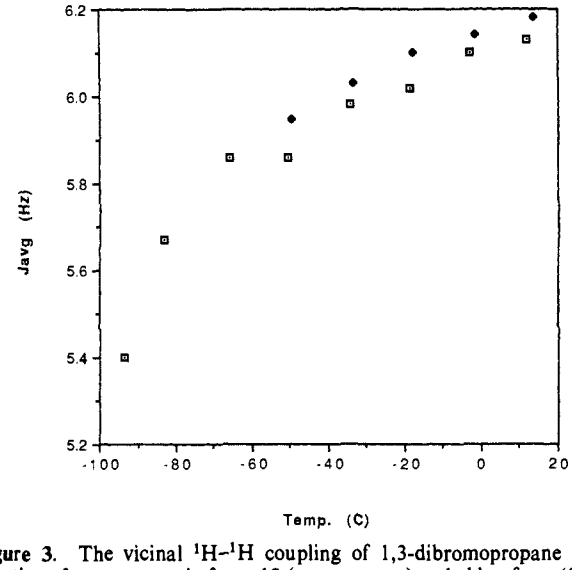

Figure 3. The vicinal ^1H–^1H coupling of 1,3-dibromopropane as a function of temperature in freon-12 (open squares) and chloroform (filled symbols), measured at 400 MHz.

temperature to 5.4 Hz at −90 °C.

Chlorination of cyclopropane was carried out in the dark in a sealed tube at 35 °C. 1,3-Dichloropropane and 1,2-dichloropropane were the major products. Again, a catalytic amount of iron was required,[4] and a slight excess of chlorine was present. The radical reaction would have produced substitution products such as 1-chlorocyclopropane and 1,1-dichloropropane,[14] which we did not observe. The 1,3-isomer showed an A_2X ^1H spectrum consisting of a triplet at δ 2.17 and a doublet at δ 3.68 (Figure 4). The vicinal H–H coupling decreased from 6.4 Hz at 30 °C to 5.9 Hz at −40 °C. The deuterium atoms on 1,2-dichloropropane were positionally scrambled.

To determine the most stable conformation of 1,3-dichloropropane in solution, we measured the vicinal coupling constant as a function of temperature for the unlabeled material (Figure 5). The coupling decreased from 6.1 Hz at 20 °C to 5.6 Hz at −90 °C.

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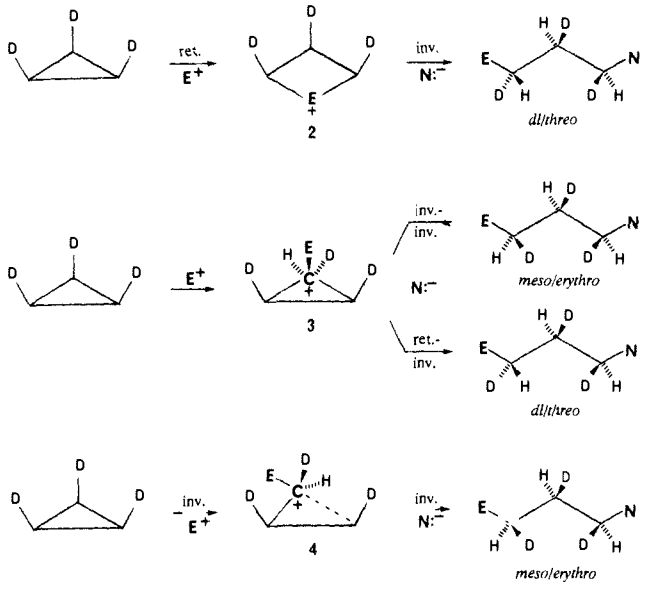
Scheme II



Discussion

Possible mechanisms leading to intermediates **2**–**4** are shown in Scheme II. For simplicity, a minimum of partial bonds is shown in the intermediates. Addition of the electrophile to the edge of the cyclopropane ring should occur with retention at both centers (**2**). Nucleophilic attack at one of these centers then would occur with inversion, leading to a retention/inversion product, shown in its anti–anti conformation in Scheme II. Because E = N for chlorination and bromination, this is a mixture of dl forms (if E ≠ N, it would be threo).

There is no clear stereochemical pathway for the formation of the symmetrical corner-halogenated intermediate **3**, since attack may occur at either basal carbon in **3**, resulting, respectively, in electrophilic inversion or retention. Calculations to be cited presently indicate that the CHDE group rotates freely anyway. Thus both pathways are shown in Scheme II, with a likely result being equal retention and inversion in the electrophilic step and all inversion in the nucleophilic step, leading to a 1/1 ratio of dl to meso (75% inversion and 25% retention overall). The unsymmetrical form **4** should be formed cleanly with inversion, as the

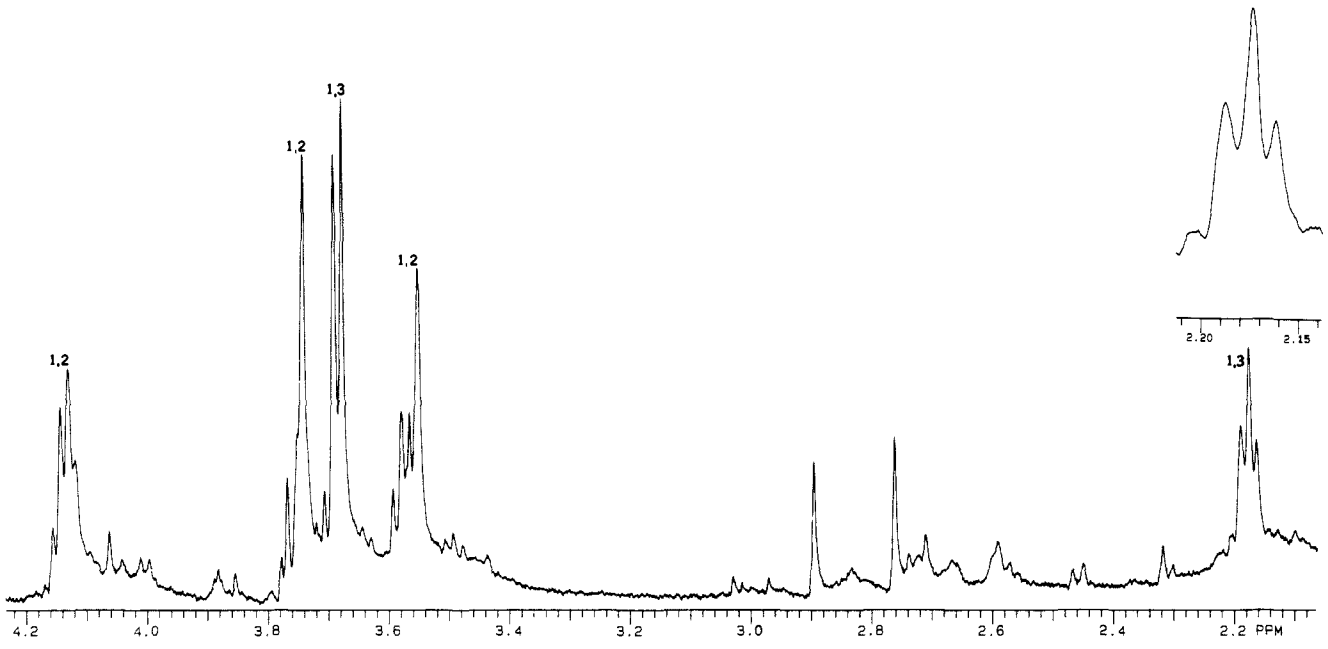


Figure 4. The 500 MHz ^1H spectrum of the crude reaction mixture from the chlorination of cyclopropane-*cis*-1,2,3-d_3 with double irradiation at the deuterium frequency. The peaks from 1,3-dichloropropane-d_3 are marked by "1,3"; those from 1,2-dichloropropane-d_3 by "1,2". Other peaks are from byproducts.

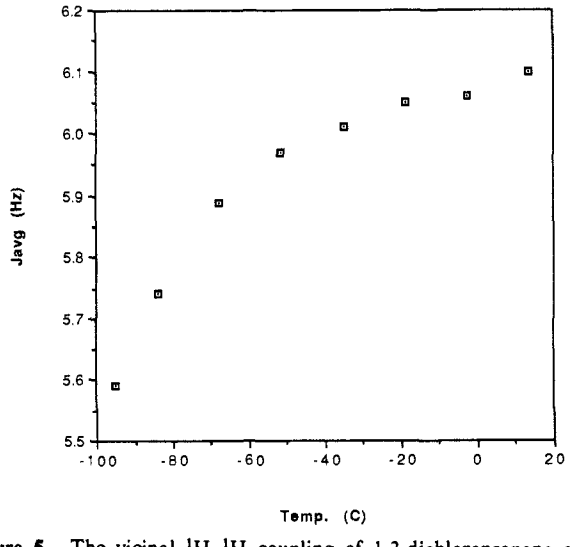


Figure 5. The vicinal ^1H–^1H coupling of 1,3-dichloropropane as a function of temperature in dichloromethane-d_2, measured at 400 MHz.

electrophile is carrying out an S_E2 displacement on the cyclopropane bond. After nucleophilic attack, the overall stereochemical result will be inversion/inversion, producing the meso form exclusively. If the unsymmetrical form can leak over to a freely rotating symmetrical form, the resulting retention/inversion pathway would give rise to some dl material.[8,15] The object of the experiments carried out in the present study was to define the mechanism through determination of the dl/meso ratio in the product, 1,3-dibromopropane.

Calculations. High level ab initio calculations have been carried out for the intermediates in the electrophilic attack on cyclopropane, particularly in the case of the proton, i.e., the $C_3H_7^+$ potential surface. Dewar and co-workers[16] found that the symmetrical (C_{2v}) corner-protonated form (**3**, E = H) is at a saddle point and that the unsymmetrical (C_s) form (**4**) is the minimum, 0.15 kcal/mol more stable. The calculations of Koch et al.[17] at the MP4(FC)/6-311G** level (on MP2 structures) with GAUSSIAN 86 found relative energies for 2-propyl, unsymmetrical corner-protonated, symmetrical corner-protonated, and edge-protonated to be 0 (as the point of comparison), 7.2, 7.3, and 8.6 kcal/mol, respectively. Moreover, they found that the CH_3^+ group is almost freely rotating in the corner-protonated forms.

Yamabe et al.[18] carried out GAUSSIAN 80 calculations for chlorination and bromination with the MIDI-1 basis set for structures and MP2 for single point energies (MP2//MIDI-1 and MP2/MIDI-1*). They found a strong preference for formation of the edge-halogenated intermediate (**2**) and suggested a novel zigzag pathway that would permit inversion–inversion stereochemistry through the edge-halogenated form.

Our own calculations used the Harris version of GAUSSIAN 82. Geometries were optimized at the RHF/3-21G level, and energies were calculated at the RHF/6-31G* or MP2/6-31G* levels. Detailed geometries and the *Z*-matrices may be found elsewhere.[19] For chlorination, we found the relative energies for the 2-propyl, edge-chlorinated, 1-propyl, symmetrical corner-chlorinated, and unsymmetrical corner-chlorinated cations to be 0, 4.8, 15.7, 25.3, and 38.0 kcal/mol. At this level, in agreement with Yamabe, the edge-chlorinated form is more stable than all other forms except the 2-propyl cation, which requires hydrogen shifts for its formation and leads to a different product.

In order to include electron correlation, we substituted the smaller fluorine atom. At the 6-31G*//3-21G level, fluorination exhibited the same trends as chlorination: 2-propyl (0 kcal/mol), edge-fluorinated (6.0), 1-propyl (16.5), symmetrical corner-fluorinated (24.6), and unsymmetrical corner-fluorinated (48.2). Inclusion of electron correlation at the MP2/6-31G*//3-21G level resulted in the following energies: edge-fluorinated (0 kcal/mol), 2-propyl (0.8), symmetrical corner-fluorinated (10.7), 1-propyl (15.2), and unsymmetrical corner-fluorinated (50.5). Although the 2-propyl form moved up in energy in comparison with the edge-fluorinated form, there were no really major changes.

Both from our calculations and those of Yamabe et al., we may conclude that the lowest energy form leading to 1,3-dihalopropane is the edge-halogenated intermediate **2**, in contrast to protonation where the corner-protonated form is slightly favored. The

(15) The importance of the unsymmetrical form has only recently been appreciated. Battiste, M. A.; Coxon, J. M. *Tetrahedron Lett.* **1986**, *27*, 517–518. Fărcaşiu, D. Private correspondence.

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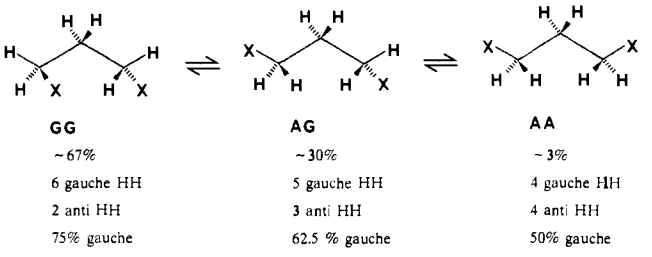
Scheme III



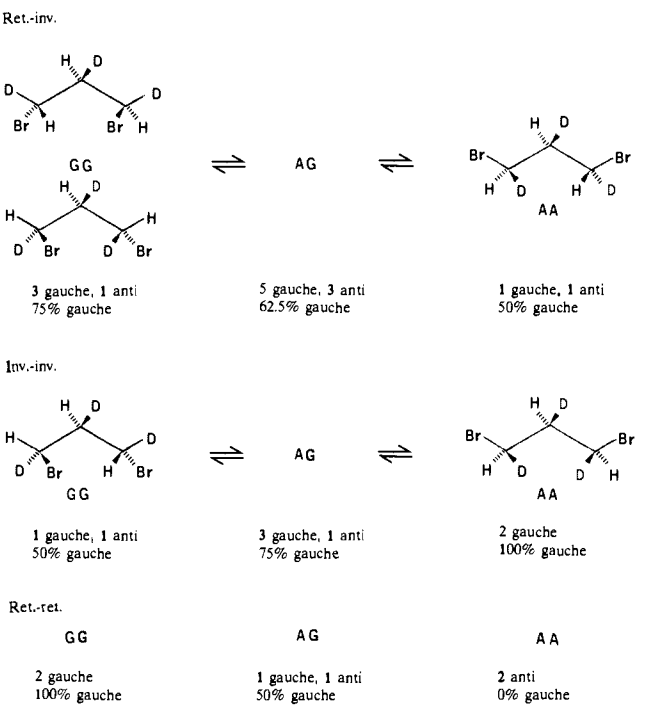
availability of the lone pair on halogen may explain this difference. Moreover, for halogenation, the unsymmetrical corner-halogenated form is less stable than the symmetrical form, also in contrast to protonation.

Bromination. In order to understand the significance of the magnitude and temperature dependence of the vicinal H–H coupling in 1,3-dibromopropane-*1,2,3-d*$_3$ formed by reaction of the labeled cyclopropane with bromine, it is necessary to look at the conformational equilibrium of unlabeled 1,3-dibromopropane (Scheme III). The gauche–gauche (GG) conformer has been found to be the only conformer present in the solid and the dominant conformer in the gas (the gas-phase proportions are given in Scheme III).[20] As the conformational equilibrium is fast on the NMR time scale, only a single signal is observed for the mixture, and the splitting is a weighted average for the three conformers, $J = p_{GG}J_{GG} + p_{AG}J_{AG} + p_{AA}J_{AA}$. Within each conformer, each of the central (2) protons has specific dihedral relationships with each of the four (1 and 3) outer protons, for a total of eight. As noted in Scheme III, there are six gauche and two anti relationships in the GG conformer, five gauche and three anti in the AG, and four gauche and four anti in the AA. Coupling over a gauche arrangement always is considerably smaller than one over an anti arrangement. The GG conformer has the largest proportion of gauche arrangements, so that the average J should be smallest for GG, intermediate for AG, and largest for AA.

As the temperature decreases, the proportion of the most stable conformer should increase. The observation (Figure 3) that J decreases with temperature means that there is a larger proportion of gauche arrangements in the preferred conformer, as expected for the GG conformer. These results confirm earlier observations in the gas phase[20] and negate the assumption of an anti–anti conformer in our preliminary report.[9]

With the knowledge that the GG conformer is the most stable, we now may proceed to analyze the results with the labeled system. Scheme IV shows the conformational mixtures for the retention–inversion (dl) and inversion–inversion (meso) results. For simplicity, the AG conformers are not shown (there are four in the case of retention–inversion and two for inversion–inversion). As the temperature decreases, the increased proportion of the GG conformer will modulate the observed J according to the relative contributions of gauche and anti dihedral relationships. For retention–inversion (dl product), the proportion of gauche relationships for the labeled system shown in Scheme IV increases from 50% for AA to 62.5% for AG to 75% for GG. In contrast, for the double inversion mechanism (meso product) the proportion of gauche relationships decreases from 100% for AA to 75% for AG to 50% for GG. Thus for the retention–inversion mechanism, the coupling constant must decrease as the temperature is lowered (as the GG conformer becomes more populated); for the double inversion mechanism, the coupling constant must increase as the temperature is lowered. The observation of a decrease from 6.2 Hz at 30 °C to 5.9 at −40 °C therefore excludes the double inversion mechanism. A double retention mechanism would have required an unknown retention stereochemistry for the nucleophilic attack. As seen in Scheme IV, double retention also would predict a decrease in J as the temperature is lowered, but the decrease should be steeper than for retention–inversion (50 to 100% gauche for double retention vs 62.5 to 75% gauche for retention/inversion for AG to GG). The relatively small decrease as the temperature is lowered is better explained by the retention–inversion mechanism, but these data do not logically exclude the double retention mode.

Scheme IV



The magnitude of the coupling constant as well as its temperature dependence provides useful information. Scheme III shows that in the unlabeled system the GG conformer contains 75% gauche relationships between the vicinal protons, the AG conformer has 62.5% gauche relationships, and the AA conformer 50%. Examination of Scheme IV shows that by coincidence these are the exact percentages resulting from the retention–inversion mechanism in the labeled system. For this and only this mechanism, the magnitude of the coupling constant should be identical for the labeled and unlabeled materials. Indeed, at 30 °C, both the unlabeled and the labeled materials showed a J of about 6.2 Hz at 30 °C and of 5.9 Hz at −40 °C. The identity of the magnitude of the coupling at both temperatures is strong evidence for the retention–inversion mechanism. The double inversion mechanism should have produced a J for the labeled material that was larger (more anti) than that of the unlabeled material, with an increasing differential as the temperature was lowered. The double retention mechanism should have produced a J for the labeled material that was smaller (more gauche) than that of the unlabeled material, again with an increasing differential as the temperature was lowered.

These experiments deal with averages. Thus we cannot exclude a small proportion of the double inversion (or of the unlikely double retention) mechanism, but we can conclude that the overwhelming preponderance of the reaction takes place via retention–inversion.

As seen in Scheme II, edge bromination is the only mechanism that results exclusively in retention–inversion. Reaction via the unsymmetrical corner-brominated intermediate **4** should take place with double inversion (the electrophile comes in opposite to the carbon–carbon bond to be broken). Reaction via the symmetrical corner-brominated form **3** (or via the unsymmetrical form if it equilibrates rapidly with the symmetrical form) should take place with 75% inversion and 25% retention. Thus corner attack results

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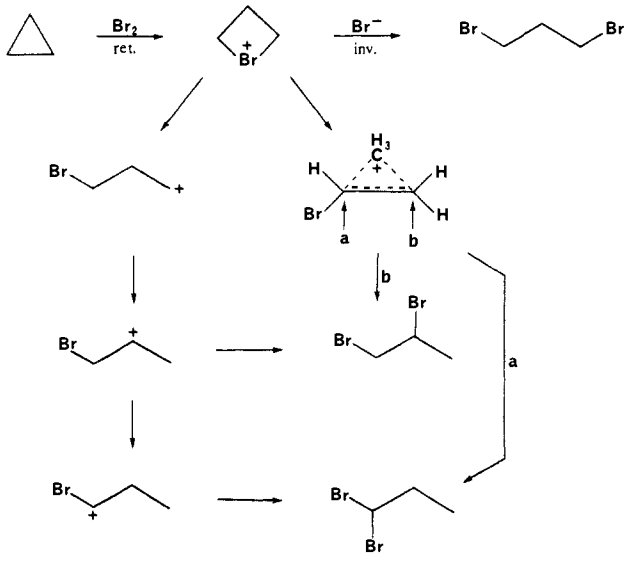
Scheme V



in 75–100% inversion, so we can exclude it as the preponderant mechanism.

These results are in agreement with the calculations, which predicted that the edge-brominated form is most stable.[18] It is not necessary to invoke the zigzag mechanism, which would have led to double inversion, now excluded. The mechanism of electrophilic bromination of cyclopropane thus parallels that of alkene bromination, with a four-membered bromonium (brometanium) ion on one hand (**2**) and a three-membered bromonium (bromiranium) ion on the other. Scheme V summarizes the mechanism. Attack occurs preponderantly with retention at the edge to form the bromonium ion, which is attacked by bromide with inversion to form 1,3-dibromopropane.

Some irreversible leakage can occur either to the classical (and more stable) 1-bromo-2-propyl cation, which could form 1,2-dibromopropane. Further rearrangement to the 1-bromo-1-propyl cation could lead to 1,1-dibromopropane. The side reaction producing 1,2-dibromopropane, however, occurs with scrambling of deuterium, which can be explained by rearrangement of the corner-brominated form possibly to a corner-protonated form, which is known to scramble deuterium. Attack by bromide at the two basal positions would lead, respectively, to the 1,1- and 1,2-dibromopropanes.

Chlorination. The analysis for chlorination parallels that for bromination. Previous studies again have shown that the GG conformer is the most stable.[20] To confirm this fact for our conditions, we examined the temperature dependence of the vicinal coupling constant in the unlabeled material (Figure 5). The observation that J decreases as the temperature is lowered confirms that the most stable conformer is GG. The value is 6.1 Hz at 20 °C and 5.9 Hz at −40 °C.

The coupling constant for 1,3-dichloropropane-*1,2,3-d*$_3$ formed by reaction of the labeled cyclopropane was observed to decrease from 6.4 Hz at 30 °C to 5.9 Hz at −40 °C. This decrease, by the same analysis as for bromination, is incompatible with the double inversion stereochemistry. Comparison of the coupling constant in the labeled and unlabeled forms confirms this conclusion. The near equivalence in magnitude at the two temperatures is incompatible with both the double inversion and the double retention stereochemistries. All observations, however, are compatible with retention–inversion.

Electrophilic chlorination, like bromination, appears to proceed via edge attack to form a chloretanium ion (**2**), in agreement with our calculations and those of Yamabe et al.[18] Thus chlorination follows the same mechanism as shown in Scheme V for bromination.

Conclusions

Electrophilic bromination and chlorination of cyclopropane yield 1,3-dihalopropane as the major product. When cyclopropane-*cis-1,2,3-d*$_3$ is the substrate, the vicinal coupling constant in the 1,3-product is diagnostic of the stereochemistry of the reaction. We observed that the 1,3-product does not interconvert with the 1,2-product under reaction conditions for both bromination and chlorination and that the label is not structurally scrambled. Analysis of the magnitude of the coupling requires knowledge of the identity of the most stable conformer of the product. The decrease in the magnitude of the vicinal coupling constant in the unlabeled 1,3-dihalopropanes shows that the GG conformer is the most stable. The magnitude and temperature dependence of the coupling constant in the labeled materials are consistent only with a retention–inversion stereochemistry. Consequently, both bromine and chlorine appear to attack cyclopropane at the edge with retention, and the resulting halonium ion then is attacked by halide ion with inversion to form the product, as shown in Scheme V. Another pathway leads to the 1,2-products with scrambling of the label. This latter result may occur via the open carbocations of Scheme V or, more likely, via the illustrated corner-protonated cyclopropane, in which rapid rotation of the hypervalent CH_3 group occurs.

Experimental Section

The deuterium-decoupled ^{1}H NMR spectra were recorded on a Varian VXR-500 spectrometer at G. D. Searle Laboratories, Skokie, IL. We are indebted to Dr. Roy Bible and Elizabeth Hajdu for obtaining these spectra. All other ^{1}H and ^{13}C NMR spectra were recorded on a Varian XLA-400 spectrometer. Mass spectra were recorded on a Hewlett-Packard Model 5985A GCMS system. High-resolution mass spectra were recorded on a VG Analytical 70-SE spectrometer. All boiling points are uncorrected. Hexane and butylbenzene were distilled from CaH_2. Diethyl ether was distilled from Na. Lithium aluminum deuteride was purchased from Cambridge Isotopes. Ethanol-*d* was purchased from Aldrich. Triphenyltin hydride was prepared by reduction of triphenyltin chloride with $LiAlH_4$. Calculations were carried out on a Harris 1000 minicomputer with the GAUSSIAN 82 program.[21]

***cis*-α,β-Styrene-*d*$_2$** was prepared according to the method of Baldwin and Carter:[11] ^{1}H NMR ($CDCl_3$) δ 5.72 (t, J_{HD} = 2.8 Hz, 1 H), 7.2–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 113.3 (t, J_{CD} = 24.5 Hz), 126.2, 127.8, 128.5, 136.4 (t, J_{CD} = 23.5 Hz), 137.5; MS, *m/z* 106 (M^+, 100), 105 (40.3), 104 (14.6), 80 (22.0), 79 (49.7), 78 (25.8).

2,2-Dibromophenylcyclopropane-*cis*-*1,3-d*$_2$. Into a 1000-mL Erlenmeyer flask was placed 29.1 g (0.275 mol) of the deuterated styrene, 1.2 g (0.0044 mol) of benzyltriethylammonium bromide (BTEAB), and 135 mL of $CHBr_3$. This mixture was cooled to 0 °C in an ice bath, and 145 mL of a 50% NaOH solution was added in one portion. The reaction was stirred at 0 °C for 3 h and then at room temperature for 1 h. The solids were removed by filtration and washed three times with ether. The layers were separated, and the organics were washed with 2 × 225 mL of brine. The combined aqueous layers were extracted with 2 × 225 mL of ether, and the combined organic portions were dried ($MgSO_4$). The ether was removed on a rotary evaporator, and $CHBr_3$ was recovered by vacuum distillation. The product was collected as a colorless oil (bp 82–90 °C, 0.4 mmHg): 60.0 g (0.216 mol, 79%); ^{1}H NMR ($CDCl_3$) δ 1.98 (br s, 1 H), 7.2–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 26.7 (t, J_{CD} = 25.6 Hz), 28.3, 35.4 (t, J_{CD} = 25.0 Hz), 127.5, 128.2, 128.8, 135.8; MS, *m/z* 280, 278, 276 (M^+, 1.1, 2.2, 1.1), 199 (19.0), 197 (20.5), 118 (79.2), 117 (100).

***trans*-2-Bromophenylcyclopropane-*cis*-*1,3-d*$_2$.** Into a flame-dried, three-necked, 500-mL, round-bottomed flask was placed 130.0 g (0.468 mol) of the dibromide. Over the course of 45 min, 165.0 g (0.470 mol) of freshly prepared triphenyltin hydride was added dropwise. The temperature of the reaction was kept below 60 °C by external cooling. The reaction was allowed to stir overnight and then was diluted with pentane. The solids were filtered off, the organics were dried ($MgSO_4$), and the solvents were removed on a rotary evaporator. The residue was distilled (bp 65–80 °C, 0.5 mmHg) to yield 88.5 g (0.445 mol, 95%) of a 1.5/1.0, cis/trans mixture. The isomers were separated by flash column chromatography by using 230–400 mesh silica gel and hexane as the eluant: ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 7.6 Hz, 1 H), 3.00 (d, J = 7.6 Hz, 1 H), 7.0–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.5 (t, J_{CD} = 25.4 Hz), 21.4, 26.4 (t, J_{CD} = 25.1 Hz), 125.9, 126.5, 128.5, 139.7; MS, *m/z* 200, 198 (M^+, 0.7, 0.6), 119 (100), 117 (29.1).

Phenylcyclopropane-*cis*-*1,2,3-d*$_3$. In a typical preparation, 10.0 g (0.050 mol) of the *trans*-bromide was placed into a flame-dried, three-necked, 500-mL, round-bottomed flask. This material was covered with 50 mL of anhydrous ether and 200 mL of anhydrous hexane. The mixture was cooled to 0 °C, and 150 mL of 1.6 M BuLi in hexane was

added over the course of 15 min. The reaction was allowed to stir for an additional 15 min, and then an excess of ethanol-*d* was added. The reaction mixture was washed with 2 × 400 mL of H_2O, the organics were dried ($MgSO_4$), and the solvents were removed on a rotary evaporator. The residues of several runs were combined and distilled (bp 65–70 °C, 20 mmHg) to yield 21.7 g (from a total of 53.9 g of bromide, 66%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 0.66 (br s, 2 H), 7.0–7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 8.7 (t, J_{CD} = 24.8 Hz), 14.8 (t, J_{CD} = 24.6 Hz), 125.3, 125.6, 128.2, 143.9; MS, *m/z* 121 (M^+, 58.2), 120 (100), 119 (40.2), 93 (52.5), 92 (43.9), 59 (43.1), 51 (41.8).

Cyclopropane-*cis*-1,2,3-d_3-carboxylic Acid. Into a 500-mL, three-necked, round-bottomed flask was weighed 21.0 g (0.174 mol) of phenylcyclopropane-*cis*-1,2,3-d_3. This material was covered with 250 mL of absolute CH_3OH, and the solution was cooled in an ice bath. Ozone generated by a Welsbach T-23 ozonator was bubbled through the solution for 29 h. Dioxygen was bubbled through the reaction for 10 min. The reaction mixture then was added dropwise to an ice-cooled solution of 200 mL of 30% H_2O_2 and 300 mL of 20% NaOH. Once addition was complete, the reaction was allowed to warm to room temperature, stir for 3 h, and reflux overnight. The CH_3OH was removed on a rotary evaporator, and the reaction mixture was acidified to pH 4 with concentrated HCl. The aqueous layer was extracted with 10 × 80 mL of ether. The ether was removed by rotary evaporation, and the residue was extracted with 5 × 100 mL of pentane. The organic layers were dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The extraction procedure was repeated, and the combined residues were distilled (80–85 °C, 20 mmHg) to yield 8.7 g (0.098 mol, 56%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 1.04 (s, 2 H), 11.8 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.7 (t, J_{CD} = 25.2 Hz), 12.5 (t, J_{CD} = 26.1 Hz), 181.8; MS, *m/z* 89 (M^+, 1.0), 88 (8.0), 72 (9.2), 61 (31.2), 44 (100).

Cyclopropyl-*cis*-1,2,3-d_3-methanol. Into a flame-dried, 500-mL, three-necked, round-bottomed flask was weighed 4.5 g (0.119 mol) of $LiAlH_4$. This material was covered with 200 mL of anhydrous ether, and the mixture was cooled in an ice bath. Over the course of 15 min, 8.3 g (0.093 mol) of cyclopropane-*cis*-1,2,3-d_3-carboxylic acid in 10 mL of anhydrous ether was added dropwise. The ice bath was removed, and the reaction was allowed to stir for an additional 3.5 h. The mixture was recooled in an ice bath, and H_2O was added to quench the reaction. The total volume of H_2O was brought up to 200 mL, and the layers were separated. The aqueous layer was extracted with 7 × 80 mL of ether, and the combined organics were dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was distilled (45 °C, 50 mmHg) to yield 5.1 g (0.068 mol, 73%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 0.18 (s, 2 H), 2.60 (br s, 1 H), 3.43 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 2.2 (t, J_{CD} = 24.8 Hz), 12.9 (t, J_{CD} = 24.5 Hz), 67.4; MS, *m/z* 75 (M^+, 0.2), 58 (7.9), 46 (9.8), 45 (100), 44 (76.5), 43 (14.8).

Cyclopropanecarbaldehyde-*cis*-1,2,3-d_3. Into an oven-dried, 250-mL, round-bottomed flask was weighed 19.18 g (0.089 mol) of pyridinium chlorochromate (PCC). This material was covered with 180 mL of freshly distilled CH_2Cl_2 (from CaH_2). The flask was fitted with a reflux condenser, and 4.5 g (0.060 mol) of cyclopropyl-*cis*-1,2,3-d_3-methanol was added in one portion. The solution turned black immediately and began to reflux gently for about 20 min. The reaction was stirred for 4.5 h, and the organics were decanted off of the black residue. The residue was washed with 5 × 100 mL of ether, and the combined organics were passed through a short silica gel column. The solvents were removed by distillation, and the fraction boiling at 80–97 °C was collected to yield 2.6 g (0.036 mol, 60%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 1.07 (s, 2 H), 8.93 (t, J_{HD} = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 6.9 (t, J_{CD} = 25.6 Hz), 22.3 (t, J_{CD} = 25.9 Hz), 201.6; MS, *m/z* 73 (M^+, 85.9), 72 (69.2), 45 (98.1), 44 (100), 41 (62.3); HRMS calcd for $C_4H_3D_3O$ 73.0607, found 73.0609; calcd for M–H 72.0528, found, 72.0527; calcd for M–D 71.0466, found 71.0469; no other 71, 72, or 73 peaks were observed.

Cyclopropane-*cis*-1,2,3-d_3. In a typical experiment, 1.87 g (2.02 mmol) of tris(triphenylphosphine)rhodium(I) chloride was weighed into an oven-dried, 10-mL, round-bottomed flask. This material was covered with 6 mL of anhydrous butylbenzene, and 0.14 g (1.92 mmol) of cyclopropanecarbaldehyde-*cis*-1,2,3-d_3 was added. The flask was sealed and heated at 75–85 °C for 7 h. The flask was cooled, and the product was vacuum transferred into a tube for immediate electrophilic ring opening. Yields were 70–78 mg (80–90%), based on recovered aldehyde: ^1H NMR (acetone-d_6) δ 0.18, J_{12} = 8.8 Hz.

Reaction of Cyclopropane-*cis*-1,2,3-d_3 with Bromine. Into a 5-mm o.d. tube were placed 8 mg of Fe filings and one drop of Br_2. Cyclopropane-*cis*-1,2,3-d_3 (approximately 0.05 g, 1.1 mmol) was vacuum transferred into the tube, which then was sealed. The tube was wrapped in aluminum foil and placed in the dark. After 23 h the tube was cooled and opened. The contents were transferred to an Erlenmeyer flask containing saturated sodium thiosulfate and $CHCl_3$. The organic layer was removed, and the aqueous layer was extracted once with $CHCl_3$. The combined organics were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The residue was taken up in $CDCl_3$ and transferred to a 5-mm NMR tube.

Reaction of Cyclopropane-*cis*-1,2,3-d_3 with Chlorine. Into a 5-mm o.d. tube was placed 1 mg of Fe fillings. Approximately one drop of Cl_2 was condensed into the tube, and cyclopropane-*cis*-1,2,3-d_3 cyclopropane (approximately 0.05 g, 1.1 mmol) was vacuum transferred into the tube. The tube was sealed, wrapped in aluminum foil, and stored at −35 °C for 16 h. The tube was opened, and the excess Cl_2 was allowed to evaporate. The remaining contents of the tube were flushed with $CDCl_3$ into a flask containing 3 mL of H_2O. The layers were separated, and the organics were dried ($MgSO_4$) and transferred to an NMR tube.

1,3-Dibromopropane-2,2-d_2 was prepared from diethyl malonate-2,2-d_2 (Aldrich) according to our earlier procedure.[22] An overall deuterium incorporation of 88% was obtained.

1,2-Dibromopropane-2-*d*. Into a flame-dried, 100-mL, three-necked, round-bottomed flask containing 1.1 g (0.045 mol) of Mg was placed 50 mL of anhydrous diethyl ether. The system was kept under an Ar atmosphere, while 5.0 g (0.041 mol) of 2-bromopropene was added dropwise. Once all of the bromide had been added, the reaction was allowed to stir for an additional 0.5 h. The reaction flask was equipped to bubble gas through a 50-mL, round-bottomed flask containing 20 mL of CH_2Cl_2 and an excess of Br_2. Deuterium oxide (2 mL) was added dropwise to the Grignard reagent. The propene-2-*d* so generated was allowed to bubble through the solution of Br_2. Excess Br_2 was quenched with a saturated solution of sodium thiosulfate. The organic layer was separated and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to yield a yellow oil. The ^1H spectrum indicated greater than 95% deuterium incorporation.