benzene-H), 3.72, 3.63 (ABq, 16 H, pyridine-CH_AH_B-, J = 13.2 Hz), 3.42 (s, 8 H, benzene-CH_2-); Anal. Calcd for $C_{44}H_{44}N_8 \cdot HClO_4 \cdot CHCl_3 \cdot 2H_2O$: C, 57.45; H, 5.36; N, 11.91. Found: C, 57.36; H, 5.11; N, 11.90.

Preparation of $H^+ \subset 4 \cdot OH^-$. A solution of the proton cryptate, $H^+ \subset 4 \cdot NO_3^-$, in methanol was passed through an anion exchange column (Muromac 1-X8, OH^- form). Evaporation of the eluent to dryness and recrystallization of the residue from CH_2Cl_2-MeOH gave colorless prisms: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.48, 7.46, 7.43, 7.00, 6.97 (AB_2, 18 H, pyridine-H), 3.83 (s, 24 H, $-CH_2-$).

Preparation of Water Cryptate $H_2O \subset 4$. Powder of the proton cryptate $H^+ \subset 4 \cdot OH^-$ was left to stand for half a year. The water cryptate thus generated was separated from the proton cryptate by preparative TLC on silica gel (Merck 60PF_{254}, CH_2Cl_2/MeOH = 80/20, v/v). The content of water cryptate in the powder of $H^+ \subset 4 \cdot OH^-$ was higher than that of crystallized $H^+ \subset 4 \cdot OH^-$: FAB-MS, m/z (%) 704 (M + 18, 100), 687 (M + 1, 33.4); ^1H NMR (CD_2Cl_2, 270 MHz) δ 8.59, 8.39, 8.20 (t, J = 52.7 Hz, N--H-O), 7.66, 7.63, 7.60, 7.20, 7.17 (AB_2, 18 H, pyridine-H), 3.59 (s, 24 H, $-CH_2-$).

Competition Experiment between $K^+ \subset 3$ and 18-Crown-6. A solution of 18-crown-6 (0.05 mL, 0.160 M) in DMSO-d_6 was added to a solution of $K^+ \subset 3 \cdot ClO_4^-$ (4.81 mg) in 0.55 mL of DMSO-d_6. The initial concentrations of $K^+ \subset 3 \cdot ClO_4^-$ and 18-crown-6 were 9.74×10^{-3} and 1.33×10^{-2} M, respectively. The mixture was prepared in a NMR sample tube and left to stand at room temperature. At an appropriate interval, ^1H and ^{13}C NMR were observed at 25 °C (270 MHz). After half a year, the integral of each aromatic proton signal was recorded and used for the association constant determination.

pK_a Measurement of 1·4HCl. A 10-mL aqueous methanol solution (methanol/water = 80/20, w/w) of 1·4HCl (1.63×10^{-3} M) was titrated with 0.1 N NaOH solution at 25 ± 0.1 °C. Ionic strength was kept constant at I = 0.01 by LiCl. The titration curve was analyzed by calculation, and pK_a values thus obtained were compared to the pK_a values obtained from the half neutralized points. Two sets of values were identical within an experimental error.

Picrates Extraction Experiments. Equal volumes (5 mL) of chloroform (TOKYO KASEI, spectrophotometric grade) solution of the ligand (1.0×10^{-3}-1.2×10^{-3} M) and aqueous alkali metal picrate solution ([PicH] = 1.0×10^{-3} M, [MOH] = 0.1 M, M^+ = Li^+-Cs^+) were vigorously stirred with a magnetic stirrer in a Teflon sealed vial at 20 ± 2 °C for 48 h. The extraction was complete in 24 h, but stirring was continued for an extended period of time. After centrifugation, the organic phase was carefully transferred by a syringe, and the picrate concentration was determined spectrophotometrically at 374 nm (ϵ = 1.86×10^4). The distribution ratio, D, was calculated by the following equation:

$$D = [Pic^-]_{org}/[Pic^-]_{aq}$$

Anion Inclusion. ^1H NMR spectra were recorded on a Hitachi R-20B (60 MHz) spectrometer. The compound $H^+ \subset 4 \cdot NO_3^-$ (17.8 mg, 2.37×10^{-5} mol) was dissolved in 0.28 mL of a CF_3COOD-D_2O (50/50, v/v) mixture. To this solution was added 0.019 mL of a solution of tetramethylammonium chloride in D_2O (2.6 M). Temperature-dependent ^1H NMR spectra were observed in the range of 34-74 °C. The concentration ratio, $4 \cdot nD^+/Cl^- \subset 4 \cdot nD^+$, was determined by the integration of each methylene proton signal, which was separated by a computational method. The plots of ln K versus T^{-1} were optimized by a least-squares procedure, and ΔH and ΔS were determined by the slope and the equation $\Delta G = \Delta H - T\Delta S$.

Acknowledgment. We gratefully thank the Ministry of Education, Science and Culture, Japan, for support of this work with a Grant-in-Aid for Scientific Research (No. 61470027). We also thank Miss Kayoko Ogi for the 400-MHz ^1H NMR measurements.

Mercuration of Cyclopropane

Joseph B. Lambert,*[†,1a] Erik C. Chelius,[†,1b] Roy H. Bible, Jr.,[‡] and Elizabeth Hajdu[‡]

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60208, and G. D. Searle and Company, 4901 Searle Parkway, Skokie, Illinois 60077. *Received July 2, 1990*

Abstract: Mercury(II) acetate reacts with cyclopropane to form, after treatment with bromide, $BrHgCH_2CH_2CH_2OAc$. The stereochemistry of this reaction has been determined by use of cyclopropane-*cis*-1,2,3-d_3 and comparison of the vicinal coupling constants in the unlabeled and the deuterated propane product. The temperature dependence and absolute magnitude of these couplings indicate that the terminal carbons in the labeled product have an erythro rather than a threo relationship. The erythro structure is consistent with a double-inversion mechanism, whereby both electrophilic attack by mercury and nucleophilic attack by acetate occur with inversion. This stereochemistry is most consistent with a corner-mercurated intermediate. Initial edge attack is not excluded, provided that the edge-mercurated intermediate rearranges quickly to the corner-mercurated species without alteration of stereochemistry.

Although cyclopropanes are much less nucleophilic than alkenes, they are subject to attack by reactive electrophiles such as the proton and bromine, chlorine, and mercury(II).[2] Halogenation has been particularly well studied both theoretically and experimentally. In unsubstituted cyclopropane[3] and in many substituted cyclopropanes, the electrophilic attack by Br_2 or Cl_2 occurs with retention (probably at the edge rather than the corner), and the nucleophilic attack occurs with inversion. Electrophilic attack by mercury(II) has been examined extensively with a variety of substituted cyclopropanes.[4] Although there is no exclusive stereochemical pathway for the electrophilic attack, inversion is most commonly observed, and inversion is the normal pathway as well for the nucleophilic pathway. Transition metals normally attack by edge attack with retention.[5]

Mercuration of unsubstituted cyclopropane has only recently been examined preparatively and found to give 1,3 addition

[†] Northwestern University.
[‡] G. D. Searle and Co.

(1) (a) This work was supported by the National Science Foundation (Grant CHE-8910841). (b) Fellowship recipient from the Division of Organic Chemistry of the American Chemical Society, sponsored by the Rohm & Haas Co.

(2) DePuy, C. H. *Fortschr. Chem. Forsch.* **1973**, *40*, 73-101.
(3) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, N. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156-3162.
(4) Lukina, M. Y. *Russ. Chem. Rev.* **1962**, *31*, 419-439. Nesmeyanova, O. A.; Lukina, M. Y.; Kazanskii, B. A. *Dokl. Akad. Nauk SSSR* **1963**, *153*, 114-117 (888-891 in English). Ouellette, R. J.; Robins, R. D.; South, A., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1619-1624. Sokolov, V. I.; Rodina, N. B.; Reutov, O. A. *J. Organomet. Chem.* **1969**, *17*, 477-480. Deboer, A.; DePuy, C. H. *J. Am. Chem. Soc.* **1970**, *92*, 4008-4013. Jensen, F. R.; Patterson, D. B.; Dinizo, S. E. *Tetrahedron Lett.* **1974**, 1315-1318. DePuy, C. H.; McGirk, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 2366-2367. DePuy, C. H.; McGirk, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 1121-1132. Balsamo, A.; Battistini, P. C.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1975**, *40*, 3233-3237. Coxon, J. M.; Steel, P. J.; Whittingdon, B. I. *J. Org. Chem.* **1989**, *54*, 3702-3709.

0002-7863/91/1513-1331$02.50/0

Table I. Vicinal Coupling Constants of 3-(Bromomercurio)propyl-*1,2,3-d*$_3$ Acetate and of Unlabeled 3-(Bromomercurio)propyl Acetate as a Function of Temperature in CD_2Cl_2

temp,[a] °C	J(HgCHDCHD),[b] Hz	J(AcOCHDCHD),[c] Hz	temp,[a] °C	J(HgCH$_2$CH$_2$),[d] Hz	J(AcOCH$_2$CH$_2$),[e] Hz
12.8	6.61	6.90	12.8	7.07	5.77
-3.4		7.01	-3.6	7.30	5.83
-19.5	6.80	7.01	-19.7	6.97	5.78
-35.9	7.29	7.22	-35.9	6.98	5.76
-51.6	7.77	7.01	-52.3	6.92	5.76
-67.7	8.01	7.21	-68.0	6.64	5.69
-83.8	8.22	7.30	-84.1	6.68	5.50
-94.4	8.13	7.34	-94.5	6.51	5.36

[a] Measured with an anhydrous methanol standard. [b] From the doublet (δ 1.96) due to the proton adjacent to mercury. [c] From the doublet (δ 4.08) due to the proton adjacent to oxygen. [d] From the triplet due to the protons adjacent to mercury. [e] From the triplet due to the proton adjacent to oxygen.

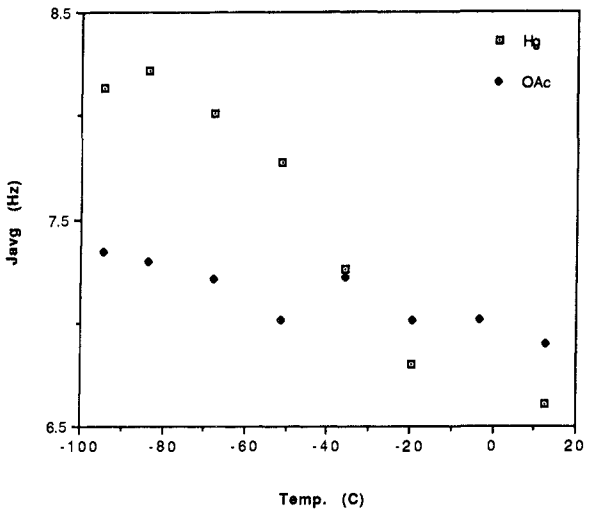


Figure 1. Temperature dependence of the vicinal ^{1}H–^{1}H coupling constants in BrHgCHDCHDCHDOAc.

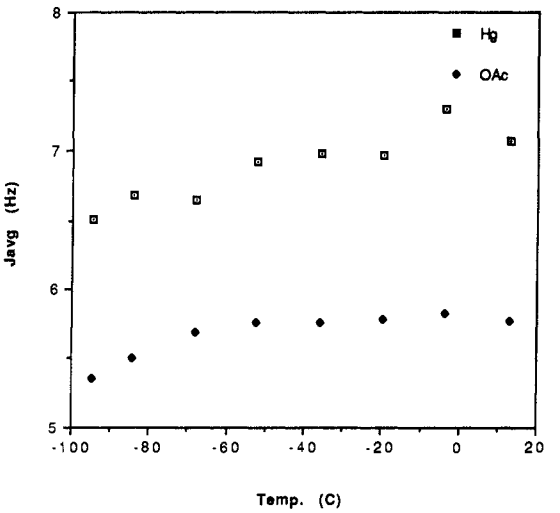


Figure 2. Temperature dependence of the vicinal ^{1}H–^{1}H coupling constants in BrHgCH$_2$CH$_2$CH$_2$OAc.

products, the major of which was 3-(bromomercurio)propyl acetate (eq 1).[6] Unsubstituted cyclopropane shares lack of regiochemical

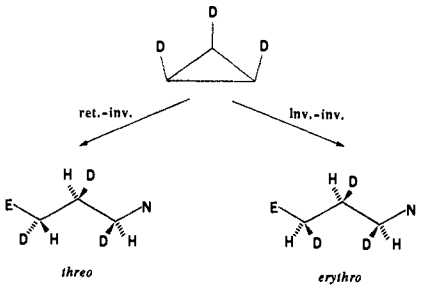
$$\triangle \xrightarrow[\text{(II) KBr}]{\text{(I) Hg(OAc)}_2,\ HClO_4} \text{BrHg–CH}_2\text{CH}_2\text{CH}_2\text{–OAc} \qquad (1)$$

bias with DePuy and McGirk's *cis,cis*-1,2,3-trimethylcyclopropane.[4] Moreover, in the unsubstituted case, open-chain carbocations are primary and hence are less likely as intermediates. Consequently. we have studied the stereochemistry and mechanism of the ring opening of unsubstituted cyclopropane with mercury(II) acetate by means of the stereochemical deuterium label recently reported for halogenation of cyclopropane.[3] By the use of all-cis trideuterated cyclopropane (cyclopropane-*cis-1,2,3-d*$_3$), the stereochemistry of both electrophilic and nucleophilic steps can be determined. Unlike bromine and chlorine but like the proton, the mercury electrophile lacks a lone pair of electrons. Mechanistic distinctions between the groups may be expected. We report herein the stereochemistry of ring opening of unsubstituted cyclopropane with mercury(II) acetate, and we suggest a mechanism that is most in consonance with the observed stereochemistry.

Results

Cyclopropane-*cis-1,2,3-d*$_3$ was available from our study of the halogenation mechanism.[3] We used a slight modification of the procedure of Bloodworth and Cooksey[6] and obtained 3-(bromomercurio)propyl acetate as the major product. Our subsequent efforts were addressed to determining the stereochemistry of the electrophilic and nucleophilic steps in the formation of this product. This objective was achieved by examining the absolute magnitude and temperature dependence of the two vicinal coupling constants

Scheme I



in the product. The protons respectively adjacent to mercury and to acetate are coupled to the proton on the middle carbon (BrHgCHDCHDCHDOAc). These two coupling constants are recorded as a function of temperature in Table I and are displayed in Figure 1.

To understand the significance of these values, it is necessary to have some knowledge of the conformer populations for 3-(bromomercurio)propyl acetate. Because no previous study has been reported, we carried out measurements of the vicinal coupling constants in the unlabeled compound (BrHgCH$_2$CH$_2$CH$_2$OAc) as a function of temperature (Figure 2).

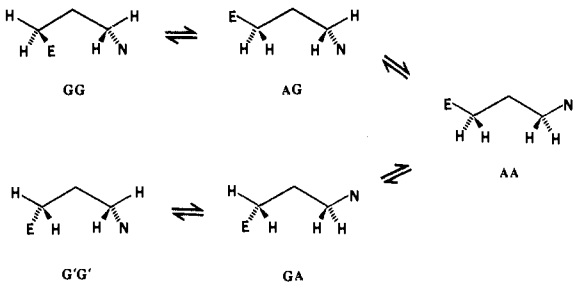
Discussion

There are four stereochemical modes for the formation of 3-(bromomercurio)propyl acetate in the mercuration reaction: inversion in both the electrophilic and nucleophilic steps, retention in both steps, inversion in the electrophilic step with retention in the nucleophilic step, and retention in the electrophilic step with inversion in the nucleophilic step. Retention at the nucleophilic step would be unprecedented, so we will set aside those two modes for the time being. A retention/inversion mechanism would produce the threo mercurio acetate, and double inversion would produce the erythro form (Scheme I) (this nomenclature refers

(5) Bäckvall, J. E.; Björkman, E. E.; Petersson, L.; Siegbahn, P.; Strick, A. *J. Am. Chem. Soc.* **1985**, *107*, 7408–7412. Lambert, J. B.; Chelius, E. K. *J. Organomet. Chem.* **1989**, *379*, 187–190.

(6) Bloodworth, A. J.; Cooksey, C. J. *J. Organomet. Chem.* **1985**, *295*, 131–135.

Scheme II



to the relative stereochemistry of the terminal carbons).

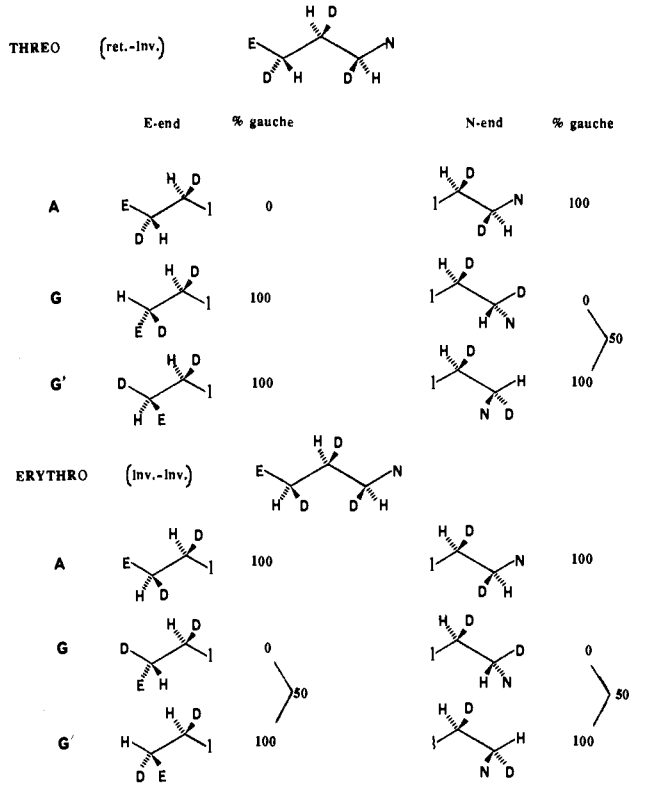
Identification of the stereochemistry of the product requires analysis of the vicinal couplings together with an understanding of the conformations of the mercurio acetate. The undeuterated molecule can exist as five conformers: both substituents anti to the carbon framework (AA), both substituents gauche to the framework (GG or G'G'), mercury anti with acetate gauche (AG), and mercury gauche with acetate anti (GA) (Scheme II). There is no previous information on distribution of conformers, but we can obtain the identity of the most stable isomer by examination of the temperature dependence of the vicinal proton–proton coupling constants in the unlabeled system. The GG and G'G' conformers have six gauche and two anti relationships between these vicinal protons (75% gauche), the AG and GA conformers have five gauche and three anti relationships (62.5%), and the AA conformer has four gauche and four anti relationships (50% gauche). The coupling between anti-related protons is at the Karplus maximum, and the coupling between gauche-related protons is close to the Karplus minimum. Therefore, coupling in GG and G'G' will be the smallest, in AA the largest, and intermediate for AG and GA. As the temperature is lowered, the equilibrium will shift toward stabler conformers. The observed decrease of both vicinal couplings (Figure 2) indicates that gauche relationships are favored over anti relationships at both ends of the molecule, so that the stablest conformation is GG or G'G'.

Determination of the stereochemistry of the reaction next requires analysis of the proportions of gauche and anti conformers in the expected labeled threo and erythro products of Scheme I. In the product shown in eq 1 and represented more generally for the deuterated species in Scheme I, distinct ^1H–^1H coupling constants may be observed for the electrophilic and nucleophilic ends of the molecule, respectively ECHD–CHD– and –CHD–CHDN (E = BrHg and N = OAc). The magnitudes of these vicinal couplings may be considered with reference to the stereochemistry only around the fragment that contains the two stereocenters on the coupling pathway. The more distant third center may be ignored. This situation contrasts with the analysis for bromination and chlorination, in which the products were symmetrical (E = N) and only one coupling constant was observable.[3] Scheme III presents the arrangements for the two ends of the molecule. These two fragments may exist in one anti or two gauche arrangements (A, G, G').

Threo Result. The retention/inversion pathway of Scheme I leads to a threo product, as was observed for bromination and chlorination. For the E–C–C–C fragment in the mercuration product, the anti conformer (anti refers to the relationship between E and the N-terminal C) contains only an anti HCCH pathway for the coupling protons. Both of the gauche conformers contain only gauche HCCH pathways. Consequently, as the temperature is lowered and more gauche conformers are populated, the coupling constant over this fragment should decrease. For the C–C–C–N pathway, the anti conformer contains only a gauche arrangement for the coupling pathway. The two gauche conformers respectively have gauche and anti pathways, for an average of 50% gauche. Therefore, as the temperature is lowered and more gauche conformers are populated, the coupling constant should increase slightly. These expectations are contrary to observation, as both vicinal couplings increase with lower temperature (Figure 1).

Erythro Result. An inversion/inversion pathway leads to an erythro product. As seen in Scheme III, for both electrophilic

Scheme III

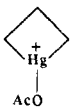


and nucleophilic fragments, the anti conformer has an entirely gauche HCCH pathway and the gauche conformers have an average of 50% gauche. Both vicinal coupling constants therefore should increase at lower temperature, because the more populated gauche conformers have a high proportion of the anti pathway. This expectation is in accord with the observations of Figure 1.

Similar arguments could be presented for the double retention and the inversion/retention pathways, but we have excluded them because there is no precedent for a nucleophilic attack with retention.

In addition to the slope of the change in these coupling constants with temperature, their absolute magnitude is influenced by the stereochemical pathway. The comparison is best made at the lowest examined temperature, so that only the double-gauche conformers (Scheme II) need be examined. In the unlabeled material, each vicinal coupling is composed of contributions from one anti and three gauche pathways, so that one may characterize the couplings as being 75% gauche. As already noted, for the labeled erythro product from the retention/inversion pathway, the electrophilic fragment is composed of 100% gauche pathways and the nucleophilic fragment of 50% gauche pathways. Thus, the labeled material should have a smaller coupling in the electrophilic fragment and a larger coupling in the nucleophilic fragment than the unlabeled product. For the threo product from the double-inversion pathway, both fragments are composed of 50% gauche pathways. This decrease from the unlabeled material implies an increase in both couplings. The observation is that the coupling over the electrophilic pathway increased from 6.6 (unlabeled) to 8.2 Hz (labeled) at −90 °C and that the coupling over the nucleophilic pathway increased from 5.4 (unlabeled) to 7.3 Hz (labeled) at −90 °C. Thus, the absolute magnitude of the couplings is in accord only with the double-inversion pathway leading to the erythro product.

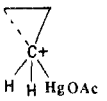
What mechanism is consonant with a double-inversion stereochemistry? The simplest mechanism would be corner attack to form unsymmetrical corner-mercurated cyclopropane. Nucleophilic attack at the backside of the weaker ring bond would then lead to the erythro product. We have already associated edge attack to form a four-membered ring (**1** or **1'**) with retention/inversion.[3] The electrophilic formation of the four-membered ring, which is a mercuretane in this case, would occur with retention,



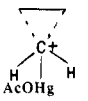
1

1'

and nucleophilic opening of the ring to form 3-(bromomercurio)propyl acetate would occur with inversion. Although we can exclude this overall pathway, it is possible that initial attack occurs at the edge, which possesses the highest electron density. Rearrangement can then occur to the unsymmetrical corner-mercurated species. Although corner attack has been appreciated since the early experiments of Baird and Aboderin,[7] the distinction between a fully symmetrical (3) and an unsymmetrical (2) form



2

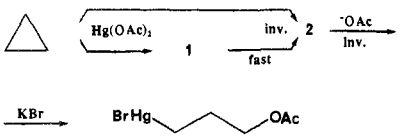


3

has only recently been appreciated.[8] The unsymmetrical nature of the cation holds the stereochemistry at the site of electrophilic attack, so that after the nucleophilic attack the final result is double inversion. These steps are summarized in Scheme IV (unlabeled). An alternative, and closely related, mechanism is the zigzag pathway suggested by Yamabe et al.[9]

These results contrast with those found for the bromination and chlorination of cyclopropane, in which retention/inversion occurs.[3] The contrast is immediately evident in the respective temperature dependences of the vicinal coupling constants for the products of halogenation and mercuration. As seen for mercuration in Figure 1, these couplings increase with lower temperature, and this result is interpreted as requiring double inversion. The deuterated products of halogenation, on the other hand, have vicinal couplings that decrease with lower temperature, and this result was interpreted as requiring retention/inversion.[3] The key difference may be the presence of lone pairs on the halogens. The proton, like mercury(II), appears to prefer the corner isomer.[8] Coxon and co-workers[4,10] have studied mercuration of substituted cyclopropanes extensively and have come to conclusions similar to ours. They explain the preferred corner attack of the proton (1s orbital) and of mercury (d_σ orbital) as resulting from the favorable interaction of these LUMOs with both the symmetric and the antisymmetric HOMOs of cyclopropane.

Scheme IV



Conclusions

Mercuration of unsubstituted cyclopropane with mercury(II) acetate occurs with inversion in both the electrophilic and the nucleophilic steps, in contrast to bromination and chlorination. This conclusion is based on the magnitude and temperature dependence of the proton–proton vicinal coupling constants in 3-(bromomercurio)propyl acetate that was formed by treatment of cyclopropane-*cis*-*1,2,3*-d_3 with mercury(II) acetate followed by potassium bromide. The double-inversion pathway may be interpreted in terms of corner attack to form an unsymmetrical corner-mercurated cyclopropane, which is opened by acetate with inversion. Alternatively, initial attack could occur along the edge, with rearrangement of mercury from the edge to the corner prior to the nucleophilic attack. This two-step pathway, or the closely related zigzag mechanism,[9] also would lead to double inversion.

Experimental Part

Reaction of Cyclopropane-*cis*-*1,2,3*-d_3 with Mercury(II) Acetate. This procedure was patterned after that of Bloodworth and Cooksey.[6] Into a 5-mm o.d. tube was placed 0.10 g of mercury(II) acetate, 0.6 mL of CH_2Cl_2, and 1 drop of 70% $HClO_4$. About 0.05 g (1.1 mmol) of cyclopropane-*cis*-*1,2,3*-d_3 was vacuum transferred into the tube.[3] The tube was sealed, wrapped in aluminum foil, and placed in the dark for 8 days. The tube was opened, and the contents were flushed with CH_2Cl_2 into an Erlenmeyer flask containing 30 mL of CH_2Cl_2 and 30 mL of H_2O. The mixture was stirred for 0.5 h, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2. The combined organics were placed in a flask containing 2.6 g of KBr and 20 mL of H_2O. This mixture was stirred for 1 h. The layers were separated, the organics were dried over $MgSO_4$, and the solvent was removed on a rotary evaporator. The resulting yellow oil was transferred to a 5-mm NMR tube for measurement of the coupling constants on a Varian XLA-400 spectrometer.

(7) Baird, R. L.; Aboderin, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 252–255.
(8) Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 988–995. Battiste, M. A.; Coxon, J. M. *Tetrahedron Lett.* **1986**, *27*, 517–518. Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, 943–945. Koch, W.; Liu, B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 3479–3480.
(9) Yamabe, S.; Minato, T.; Seki, M.; Inagaki, S. *J. Am. Chem. Soc.* **1988**, *110*, 6047–6053.
(10) Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Org. Chem.* **1989**, *54*, 1383–1391.