Bromination of Cyclohexa-1,3-diene and (*R*,*S*)-Cyclohexa-3,5-diene-1,2-diol

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The configuration of 1,2,3,4-tetrabromocyclohexane (mp 90 °C), **5a**, has been established as 1,2*t*,3*t*,4*c* by an X-ray crystallographic determination. The structures of two of three dibromocyclohexenes (**3a**, **3b**, and **3c**) have been reassigned on the basis of NMR evidence and an X-ray crystallographic determination of the structure of **3b** (*trans*-3,6-dibromocyclohexene). The structures of the two major isomers of 3,4,5,6-tetrabromocyclohexane-1,2-diol obtained by bromination of *cis*-cyclohexa-3,5-diene-1,2-diol also were established by X-ray crystallographic determinations of their monobenzoate esters. Studies of their formation indicate that the mechanism of bromination of 1,3-cyclohexadiene and *cis*-cyclohexa-3,5-diene-1,2-diol are similar. Addition of 1 equiv of bromine occurs rapidly by anti 1,2-addition, which is followed by rearrangements to form products of conjugation addition. A second equivalent of bromine adds to afford mostly the 1,2*t*,3*t*,4*c*-tetrabromo compounds at −70 °C and, with cyclohexadiene, the 1,2*t*,3*c*,4*t*-tetrabromo compound at higher temperature.

Introduction

Our studies[1,2] on the photochemistry of 1,3-cyclohexadiene (**1**) led to an interest in preparation of derivatives starting with cyclohexa-3,5-diene-1,2-diol (**2**). Initial protection of the double bonds is helpful, as the diol readily dehydrates to phenol. Bromination[3,4] is one method of protecting the double bonds of alkenes.[5,6] However, reports of electrophilic bromination of **1** have led to conflicting results concerning the products formed.[7−9] Therefore, we have investigated the bromination of **1** and **2** in order to determine the usefulness of this reaction in protecting the double bonds of these dienes.

We report here the results of our studies on the electrophilic bromination of **2**, including X-ray crystallographic structure determinations of two tetrabromocyclohexanediol derivatives in order to establish stereochemistry. Reactions with **1** also were performed as a model and to compare the effects of the hydroxyl groups on the course of the reaction. X-ray determinations establish the structures of the thermodynamic dibromocyclohexene and the major tetrabromocyclohexane formed at low temperature, the stereochemistry of which previously had been misassigned.[10]

Experimental Section

Chemicals. 1,3-Cyclohexadiene (Aldrich) was distilled before use. *cis*-3,5-Cyclohexadiene-1,2-diol (Aldrich, 20 wt % solution) was freed of ethyl acetate by careful concentration under a stream of dry nitrogen and crystallization at −20 °C. Pyridine (Aldrich), dichloromethane, and carbon tetrachloride were reagent grade and were dried before use.

Dibromination of 1,3-Cyclohexadiene (1). A three-neck round-bottom flask fitted with an addition funnel, $CaCl_2$ drying tube, and magnetic stirbar was charged with 1 mL (10.5 mmol) of 1,3-cyclohexadiene in 25 mL of carbon tetrachloride. The flask was lowered into a dry ice−ethanol bath, and the temperature was maintained at −15 to −20 °C. The flask was protected from room light, the stirrer was started, and a solution of 1 mL (21 mmol) of bromine in 10 mL of carbon tetrachloride was added dropwise from the addition funnel. When the addition of bromine was complete, the flask was removed from the cooling bath and allowed to warm to room temperature. The reaction was filtered by vacuum to afford 1.07 g of colorless product, and another 2.95 g of product was obtained by evaporation of the filtrate under reduced pressure. The solids were combined to afford 3.0 g of crude product. Recrystallization from ethanol afforded 2.1 g (83% recovery) of **5b** as a colorless solid. Mp: 140 °C (lit.[7] mp 141 °C). ^{1}H NMR: 4.19 (dd, 2H, 7.7, 2.9 Hz), 4.07 (m, 2H), 2.5 (dd, 2H, 4.0,d 10.6 Hz), 2.0 (apparent dd, 2H, 2.8, 11.3 Hz). ^{13}C NMR: 60.5, 51.9, 37.0.

Low-Temperature Dibromination of 1 Using Excess Bromine. The reaction apparatus was set up as described in the preceding section. The flask was charged with 85 μL (0.89 mmol) of 1,3-cyclohexadiene and 67 μL of pyridine in 10 mL of carbon tetrachloride and 10 mL of dichloromethane. The flask was lowered into a dry ice−ethanol bath with a temperature of −70 °C. The flask was carefully protected from exposure to light. A solution of 0.30 mL (5.3 mmol) of bromine in 5 mL of carbon tetrachloride and 5 mL of dichloromethane was added dropwise from the addition funnel. A solid formed in the bottom of the flask by the time the addition of bromine was complete. The reaction was stirred for several hours at −70 °C and then overnight, during which period it gradually warmed to room temperature and the solid redissolved. The solvent was stripped off under reduced pressure to afford an oily residue, which was dissolved in CH_2Cl_2 and washed with dilute hydrochloric acid and then water. The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated using a stream of dry nitrogen to afford 350 mg of a colorless solid. The ^{1}H NMR spectrum revealed the presence of two isomers of 1,2,3,4-tetrabromocyclohexane, formed in about a 60:40 ratio. These were identified previously[8] as **5a** and **5b**.

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Table 1. Yields of Bromination Products[a]

starting material	conditions	dibromoalkenes 3a	3b	3c	tetrabromoalkanes 5a	5b	ref
1	−70 °C	77[b]	0[b]	23	88	12	this work
1	kinetic	18	3	79			9
1	25 °C	18[c]	64[c]	18[c]			this work
1	thermodyn	25	59	16			9
3b	25 °C				8[d]	92[d]	this work

starting material	conditions	dibromoalkenes 4a	4b	4c	tetrabromoalkanes 6a	6b	6c	ref
2	−70 °C	82[b]	15[b]	4[b]	56	27	17[e]	this work
2	25 °C	0[f]	20[f]	80[f]	50[d]	30[d]	20[d,e]	this work

[a] Relative NMR yields (±5%) in 1:1 CH_2Cl_2−CCl_4 containing 1 equiv of pyridine for reactions in this work. See Experimental Section for specific conditions. [b] Extrapolated. [c] In addition to 10% benzene in the absence of pyridine. [d] Bromine in large excess. [e] Estimated from ^{13}C spectrum. [f] After 1 day.

The major isomer, **5a** (mp 88−92 °C (lit.[11] mp 90 °C)), was isolated by chromatography on silica gel. The spectral properties of **5a** were consistent with those reported ("broad unresolved peaks of the [^{1}H] NMR" and "four peaks of comparable intensity and one sharp line" for the ^{13}C spectrum[8]). ^{1}H NMR: 4.81 (br s, 1H), 4.78 (s, 2H), 4.40 (br s, 1H), 2.66 (br s, 1H), 2.50 (br m, 2H), 2.00 (br m, 1H). ^{13}C NMR: 59.2 (br), 53.7 (br), 51.1, 33.2 (br), 29.0 (br). X-ray (from ether): space group $P2_1/n$, a = 7.8644(7) Å, b = 10.2295(9) Å, c = 12.2478(12) Å, β = 93.064(8)°.

Stoichiometric Bromination of 1. A three-neck round-bottom flask fitted with an addition funnel, $CaCl_2$ drying tube, and magnetic stirbar was charged with 1.0 mL (10 mmol) of 1,3-cyclohexadiene in 25 mL of carbon tetrachloride. The flask was lowered into a dry ice−ethanol bath, and the temperature was maintained at −70 °C. The flask was protected from room light, the stirrer was started, and a solution of 0.55 mL (10 mmol) of Br_2 in 5 mL of carbon tetrachloride was added dropwise from the addition funnel. When the addition of bromine was complete, the crude material was partitioned into three equal fractions. Two of these fractions were treated as described in the following section. Volatile materials were removed under reduced pressure from the third fraction, which was used for NMR analysis as described next.

NMR analysis of the crude material revealed the presence of three isomers of dibromocyclohexene, **3a**, **3b**, and **3c**, in a ratio 69:8:23, respectively. Similar results were obtained using a 1:1 CH_2Cl_2−CCl_4 solvent system in the presence of 10.5 mmol of pyridine (Table 1). Isomer **3a** rearranged to form **3b** in the NMR sample with a half-life of about 1 h to an equilibrium ratio of **3a**:**3b** of 18:64, whereas the amount of **3c** remained essentially constant at about 20% over a period of 2 days.

3a. ^{1}H NMR: 5.82 (m, 1H), 5.74 (m, 1H), 4.86 (dd, 1H, 4.2, 2.3 Hz), 4.63 (dd, 1H, 4.1, 1.8 Hz), 2.49 (m, 1H), 2.44 (d, 1H, 2.3 Hz), 2.15 (m, 1H), 1.95 (m, 1H). ^{13}C NMR: 130.3, 124.2, 50.7, 48.5, 24.9, 21.3.

3b. ^{1}H NMR: 5.99 (d, 2H, 2.9 Hz), 4.90 (m, 2H), 2.46 (dt, 2H, 11.1, 1.9 Hz), 2.16 (d, 2H, 11.1 Hz). ^{13}C NMR: 129.9, 45.4, 27.2. X-ray (from carbon tetrachloride): $P2_1/n$; a = 7.0065(8) Å, b = 5.6847(5) Å, c = 10.2019(9) Å, β = 109.641(9)°.

3c. ^{1}H NMR: 5.94 (d, 2H, 1.8 Hz), 4.77 (tt, 2H, 3.3, 1.7 Hz), 2.35 (m, 2H), 2.20 (m, 2H). ^{13}C NMR: 131.0, 44.7, 31.1.

Due to overlap of ^{1}H resonances, some of the assignments are tentative. The CHBr resonances at 4.6−4.9 ppm were most resolved, and these were used for integration. The rate constant for the **3a** → **3b** conversion in $CDCl_3$ is estimated to be 1.6×10^{-4} s^{-1} and 4.7×10^{-5} s^{-1} for the reverse. Extrapolation of the concentration of **3a** to zero time indicates that, within the error of the measurement (about 5%), **3b** is not produced in the initial addition of bromine to **1** (Figure 1).

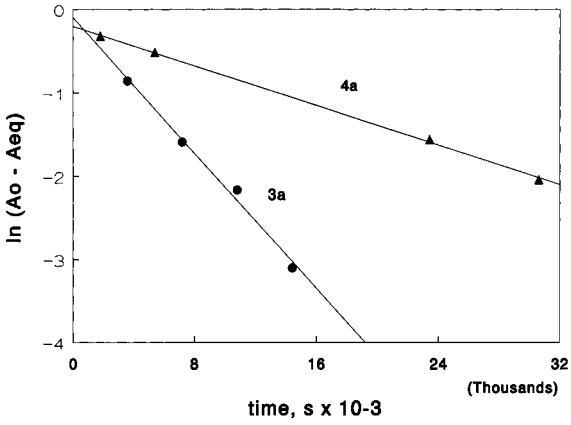

Figure 1. Decay of **3a** and **4a** monitored by NMR in $CDCl_3$.

Bromination of Dibromocyclohexenes (3). A small excess of bromine was added immediately to a second fraction of the reaction described in the preceding section. This reaction was kept cold until the color of bromine had largely been discharged. Afterward, volatile materials were removed by evaporation under reduced pressure, and samples were removed for NMR analysis. A third fraction was set aside in the dark at room temperature and the solvent allowed to mostly evaporate, during which time crystals of **3b** grew spontaneously. The crystals (mp 95.6 °C) were harvested by filtration and then redissolved in CCl_4. A large excess of bromine was added to the CCl_4 solution; the reaction was virtually complete within 30 min. The results for both of these reactions are given in Table 1. The tetrabromides **5** were stable under the reaction conditions.

Low-Temperature Bromination of (*R*,*S*)-Cyclohexa-3,5-diene-1,2-diol (2) Using Excess Bromine. Initial attempts to brominate cyclohexadienediol afforded mostly 2,4-dibromophenol. The following conditions proved optimal. A round-bottom flask equipped with magnetic stirbar and addition funnel with a $CaCl_2$ drying tube was charged with 100 mg (0.89 mmol) of diol **2** and 67 μL (70 mg, 0.89 mmol) of pyridine in 10 mL of carbon tetrachloride and 10 mL of dichloromethane. The flask was lowered into a dry ice−ethanol bath maintained at −70 °C and carefully protected from light. A solution of 0.30 mL (5.3 mmol) of bromine in 5 mL of carbon tetrachloride and 5 mL of dichloromethane was added dropwise from the addition funnel. The addition of bromine was stopped when the color of bromine was no longer discharged. NMR analysis of an aliquot indicated the formation of olefinic products, as well as a small amount of pyridinium salts. Therefore, the remaining bromine solution was added to the reaction at −70 °C, and the reaction mixture was kept overnight in a refrigerator (2 °C). Evaporation of the solvent under reduced pressure afforded 530 mg of brown oil, which was taken up in methylene chloride, filtered to remove 40 mg of insoluble pyridinium hydrobromide, and washed with dilute hydrochloric acid and then water. Analysis of the aqueous layer revealed the presence of only pyridinium salts, which were discarded. The methylene chloride layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure to afford 310 mg (80%) of yellow oil. The ratio **6a**:**6b**:**6c** given in Table 1 was determined by careful integration of the ^{1}H NMR of crude **6**. Identical results were obtained using 14 μL of pyridine.

The crude product was purified by column chromatography on silica gel, eluting fractionally with dichloromethane and methanol. Three isomers were obtained, identified as **6a**, **6b**, and **6c**. Isomer **6b** eluted first (10 mg with 0.5−2% methanol). The following three fractions with higher amounts of methanol were enriched in **6a** (126 mg), and later fractions contained mixtures of **6a** and **6c**. The chromatography was repeated twice more, each time on the fractions increasingly enriched

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in **6a** to obtain **6a** nearly free of the other isomers. Isomer **6a** was obtained nearly pure as a colorless oil. ^{1}H NMR: 4.76 (broad m, 4H), 4.38 (broad d, 2H, 5.1 Hz), 2.98 (broad s, 2H). ^{13}C NMR: 72.7 (broad), 52.0 (very broad). IR (KBr): 3430 (broad, vs), 2931 (s), 1094 (s) cm^{-1}. The 20 eV EI mass spectrum of **6a** (corrected for ^{13}C isotope) exhibited isotopic clusters as follows: $[M]^{2+}$ (RA 4%), $[M - H]^+$ (3%), $[M - Br]^+$ (26%), $[M - HBr]^{2+}$ (24%), $[M - H_2OBr]^+$ (29%), $[M - H_3OBr]^{2+}$ (28%), $[M - HBr_2]^+$ (79%), $[M - H_2Br_2]^{2+}$ (20%), $[M - H_3OBr_2]^+$ (20%), $[M - H_3CO_2Br_2]^+$ (100%), $[M - H_2Br_3]^+$ (52%), $[M - H_2COBr_3]^+$ (18%), $[M - H_3CO_2Br_3]^{2+}$ (29%), $[M - H_4CO_2Br_3]^+$ (25%), $[M - H_2Br_4]^{2+}$ (20%), $[M - H_3Br_4]^+$ (29%), $[M - H_2COBr_4]^{2+}$ (21%), $[M - H_3COBr_4]^+$ (47%), *m*/*z* 53 (23%). Isomer **6b** was obtained as a colorless oil (10 mg)., ^{1}H NMR: 4.44 (m, 3H), 4.14 (m, 2H), 3.79 (m, 1H), 2.77 (dd, 2H, 5.5, 10.2 Hz). ^{13}C NMR: 74.1, 73.0, 57.7, 56.7, 55.6, 55.1. The mass spectrum of **6b** was essentially the same as that of **6a**. Isomer **6c** was not obtained in pure form from this mixture, but contained various amounts of **6a**. The ^{13}C NMR of **6c** could be obtained by subtraction of the peaks assigned to **6a**: 73.9, 71.6, 57.5, 52.3, 49.5, 46.9.

Stoichiometric Bromination of 2. Bromination of **2** at −70 °C was performed as described above except using 1 equiv of bromine. In this case, the reaction was partitioned into two equal fractions. One of the fractions was treated as described in the following section. Volatile materials were removed under reduced pressure from the other fraction, which was used for NMR analysis as described next.

NMR analysis of the crude material revealed the presence of one dibromocyclohexenediol (**4a**) in >80% yield, as determined by ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR ($CDCl_3$−D_2O): 5.90 (1H, br s), 5.89 (1H, br s), 4.75 (1H, d, 7.4 Hz), 4.43 (1H, dd, 10.0, 7.4 Hz), 4.38 (1H, m), 3.85 (1H, dd, 9.9, 4.0 Hz). ^{13}C NMR: 130.4, 128.4. 71.4, 65.1, 57.0, 50.6.

Compound **4a** was unstable and formed two other products (**4b** and **4c**) with a half-life of about 3 h at room temperature. These secondary products were determined to be stereoisomers of **4a** by comparison of their ^{1}H and ^{13}C NMR spectra and isolation of tetrabromocyclohexanediols produced by their bromination (vide infra). Isomer **4b** exhibited the following peaks. ^{1}H NMR ($CDCl_3$-D_2O): 5.83 (1H, ddd, 10.1, 2.9, 1.7 Hz), 5.76 (1H, br dd, 10.1, 2.4 Hz), 4.94 (1H, br sextet, 2 Hz), 4.75 (1H, m), 4.23 (1H, br dd, 4.0, 2.4 Hz), 4.15 (1H, dd, 6.3, 2.2 Hz). ^{13}C NMR: 128.9, 128.1, 74.8, 69.0, 50.0, 49.8. Isomer **4c** exhibited the following peaks. ^{1}H NMR ($CDCl_3$−D_2O): 5.78 (2H, d, 1.5 Hz), 4.73 (2H, dd, 5.2, 1.4 Hz), 4.34 (2H, d, 5.2 Hz). ^{13}C NMR: 128.6, 72.5, 49.1.

The initial ratio of **4b**:**4c** was about 80:20, but after 22 h **4a** was essentially entirely depleted and the ratio **4b**:**4c** was about 20:80. The rate constant for the **4a** → **4b** + **4c** conversion in $CDCl_3$ is estimated to be 5.9×10^{-5} s^{-1}. Extrapolation of the concentration of **4a** to zero time does not exclude **4b** and **4c** from being produced in minor amounts as primary products in the initial addition of bromine to **2** (Figure 1).

Bromination of Dibromocyclohexenediols (5). A small excess of bromine was added immediately to the second fraction of the reaction described in the preceding section. The reaction was kept cold until the color of bromine had largely been discharged. Afterward, volatile materials were removed by evaporation under reduced pressure, and a sample was removed for NMR analysis. The results are given in Table 1. The tetrabromides **6** were stable under the reaction conditions.

Benzoylation of Tetrabromocyclohexadienediol (6). A round-bottom flask equipped with $CaCl_2$ drying tube was charged with 49 mg (0.11 mmol) of a fraction of **6** containing mostly isomer **6a** or isomer **6b** and 0.25 mL of pyridine. The flask was placed in an ice−water bath, and 17.5 μL (0.145 mmol) of benzoyl chloride was added slowly. The reaction mixture was left at 0 °C for about 15 min, after which time the reaction was diluted with 2 mL of dry dichloromethane. The resulting solution was warmed to room temperature and washed successively, twice with 3% hydrochloric acid, twice with saturated aqueous sodium bicarbonate, and finally with water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 53 mg (85%) of a light brown oil. The crude materials were purified by column chromatography on silica gel to afford two products, **7a** or **7b**, identified as monobenzoate esters by their spectroscopic properties. The compound eluting first (**7b**) was obtained as a colorless solid. Yield: 15 mg (15%). Mp: 179−181 °C. ^{1}H NMR: 8.09 (m, 2H), 7.62 (m, 1H), 7.48 (m, 2H), 5.23 (dd, 1H, 2.4, 11.1 Hz), 4.71 (t, 1H, 10.9 Hz), 4.51 (m, 2H), 4.32 (dd, 1H, 2.1, 11.2 Hz), 4.24 (t, 1H, 10.6 Hz), 2.63 (dd, 1H, 0.9, 3.2 Hz). ^{13}C NMR: 165.2, 133.9, 130.0, 128.8, 128.6, 74.3, 71.9, 56.8, 55.3, 51.4. IR (KBr): 3400 (broad, m), 2981 (w), 1717 (s), 1453 (m), 1276 (m), 1116 (s), 708 (s) cm^{-1}. X-ray (from xylene): space group $P2_1nb$, $a = 8.6312(8)$ Å, $b = 14.8105(13)$ Å, $c = 25.650(8)$ Å. The compound eluting second (**7a**) was obtained as a colorless oil that solidified on standing. Yield: 14 mg (14%). Mp: 148−150 °C. ^{1}H NMR: 8.11 (m, 2H), 7.61 (m, 1H), 7.47 (m, 2H), 5.71 (s, 1H), 5.06 (s, 1H), 4.88 (dd, 1H, 3.1, 10.4 Hz), 4.76 (m, 2H), 4.60 (m, 1H), 2.67 (d, 1H, 5.3 Hz). ^{13}C NMR: 165.3, 133.8, 130.2, 128.8, 128.6, 72.8, 70.8, 57.6, 52.5, 51.1, 46.2. IR (KBr): 3500 (s), 3000 (w), 2925 (w), 1708 (s), 1601 (m), 1452 (m), 1274 (s), 1109 (s), 705 (s) cm^{-1}. X-ray (from chloroform): space group $P2_1/a$, $a = 7.1120(9)$ Å, $b = 14.9248(19)$ Å, $c = 15.0591(13)$ Å, $\beta = 90.124(11)°$.

Results and Discussion

Bromination of conjugated dienes proceeds by both direct and conjugate addition. Thus, bromination of 1,3-cyclohexadiene affords three dibromocyclohexenes, *trans*-3,4-dibromocyclohexene **3a**, *trans*-3,6-dibromocyclohexene **3b**, and *cis*-3,6-dibromocyclohexene **3c**. The reported kinetic yields[9] are given in Table 1 and were essentially the same in CCl_4 as in CH_2Cl_2 solvent. The relative thermodynamic yields reported for these isomers in CCl_4 also are given in Table 1 and are virtually the same at 78 °C as at 25 °C.[9]

With additional bromine, the remaining double bond of the dibromocyclohexenes **3** adds bromine to afford the tetrabromocyclohexanes **5**. Two[8] or three[7,12] isomers have been reported to form by addition of 0.4 mol of Br_2 to 0.2 mol of 1,3-cyclohexadiene in $CHCl_3$ at room temperature. The first equivalent of Br_2 is consumed rapidly, although reaction of the second equivalent required 2−3 days. The configuration of one of these isomers with mp 142 °C (**5b**) has been established by an X-ray crystallographic determination to be all-equatorial (i.e., 1,2*t*,3*c*,4*t*).[12] Early disagreement[7,12] concerning the configuration of one of the other isomers, mp 156 °C, has recently been resolved by NMR evidence in favor of the 1,2*c*,3*t*,4*c* isomer, **5c**.[8] The third isomer (mp 90 °C) has been proposed to be 1,2*c*,3*t*,4*t*-tetrabromocyclohexane on the basis of its chemical reactivity.[11] This is consistent with its NMR spectrum, which indicates 2-fold symmetry at higher temperature.[8] The NMR spectra of this isomer exhibit broad peaks for ^{1}H and ^{13}C resonances, indicative of conformational changes that will occur with two bromines equatorial and two bromines axial. However, because of the broadening of the peaks, the NMR spectra do not allow unambiguous structural assignment.

Therefore, we undertook an X-ray crystallographic investigation of the isomer with mp 90 °C. The structure of the molecule, **5a**, is shown in Figure 3. This established the configuration of **5a** to be 1,2*t*,3*t*,4*c*, with two axial and two equatorial substituents. In solution at higher temperature, dynamic conformational equilibration in this molecule would give rise to an "average" structure that possesses an internal plane of symmetry (rather

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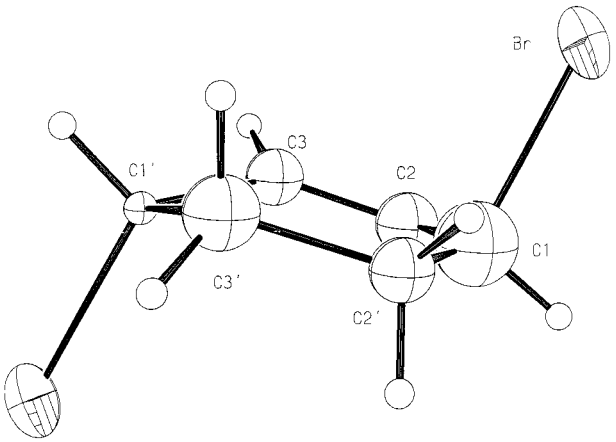


Figure 2. ORTEP of **3b** (30% probability elipsoids).

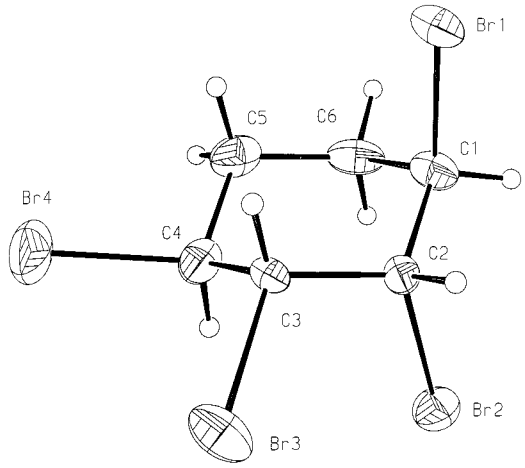


Figure 3. ORTEP of **5a** (30% probability elipsoids).

than a 2-fold axis, as would be exhibited in the 1,2*c*,3*t*,4*t* isomer proposed previously). Two bromines would be equatorial and two axial, consistent with the substantial line broadening observed in the NMR spectrum of this stereoisomer attributed to the conformational exchange at room temperature.

The structure shown in Figure 3 demonstrates that Br2 and Br3 are cis to one another. Assuming that addition to the remaining double bond of **3** must be anti, this indicates that isomer **5a** is formed by two consecutive anti 1,2-additions of bromine (i.e., **1** → **3a** → **5a**, Scheme 1), as an initial conjugate addition would result in a trans relationship between Br2 and Br3.

By the same argument, **5c** (which we did not isolate) should be formed by syn 1,4-addition followed by anti 1,2-addition to the C3−C4 double bond (**1** → **3c** → **5c**), since syn 1,2-addition does not occur.[9] Isomer **5b** could be formed by either two consecutive anti 1,2-additions (**1** → **3a** → **5b**) or alternatively by an anti 1,4-addition followed by an anti 1,2-addition (**1** → **3b** → **5b**).

Although the relative yields of **5** were reported not to depend on whether the solvent was CH_2Cl_2 or CCl_4, the yields do depend on temperature.[9] At −70 °C, the major product is **5a**, whereas at room temperature the product is almost entirely **5b**. Therefore, experiments involving stoichiometric electrophilic bromination of **1**, followed by NMR analysis and further bromination, were performed in order to obtain insight concerning the mechanism of these reactions.

As mentioned above, addition of a single equivalent of Br_2 to **1** has been shown to afford three dibromocyclohexenes: a compound arising from anti 1,2-addition, **3a**, which lacks internal symmetry, and two stereoisomers arising from 1,4-addition, **3b** and **3c**, which exhibit higher symmetry on the NMR time scale.[9] At −70 °C, the dibromocyclohexenes are insoluble in the solvent system used (1:1 CH_2Cl_2−CCl_4), and they precipitate upon formation. Under these conditions, we observed that the reaction afforded mostly the unsymmetrical isomer **3a** (which must be the product of 1,2-addition), together with a lesser amount of a symmetrical isomer, **3c**. Addition of an excess of Br_2 at low temperature resulted in formation of mostly **5a** by a second anti 1,2-addition to the remaining double bond of **3a** (Table 1).[13]

At room temperature, **3a** converted quickly to **3b**, until an equilibrium mixture favoring **3b** was established. The two more symmetrical isomers, **3b** and **3c**, must be the products of formal anti and syn conjugate addition. The assignment of **3b** as the product of anti 1,4-addition (C_2 symmetry) is confirmed by the result of an X-ray crystallographic determination shown in Figure 2. Addition of excess Br_2 to **3b** affords almost entirely **5b**, in which Br1 and Br4 remain trans. In the bromination of **1**, **5b** probably entirely results from rearrangement of the initially formed **3a** to **3b**, which produces **5b** by anti 1,2-addition of bromine (**1** → **3a** → **3b** → **5b**, Scheme 1). At high concentrations of Br_2, the addition of Br_2 to **3b** is complete within about 30 min at 20 °C. However, it is likely that, with a limited amount of bromine, the reactions conform to the Curtin−Hammett principle,[14] since interconversion of **3a** and **3b** occurred relatively fast (half-life about 1 h) compared to the addition of bromine (which reportedly takes about 2 days[9] under these conditions).

Our results would be consistent with the earlier reports of product analyses[9,11] if **5a** is assigned as the 1,2*t*,3*t*,4*c* isomer as shown in Figure 3 and if the original assignment of the structures of **3a** (established by NMR as *trans*-3,4-dibromocyclohexene) and **3c** is reversed (Table 1 and Scheme 1).

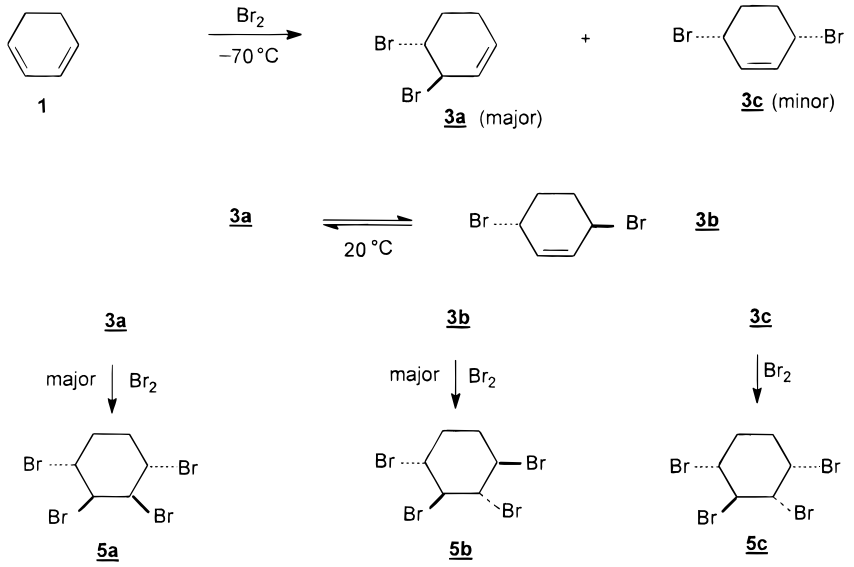
A similar mechanism is proposed for bromination of diol **2** (Schemes 2 and 3). In this case, addition of 1 equiv of Br_2 to **2** afforded a dibromocyclohexenediol **4a**, which lacks internal symmetry, as the major (>80%) product. Compound **4a** in time rearranged to two isomers, **4b** and **4c**, the latter of which exhibits higher symmetry on the NMR time scale (Scheme 2).[15] Although **4b** initially was formed from **4a** in greater amount than **4c**, **4b** also rearranged at longer times to form **4c**. Addition of excess bromine before extensive rearrangement could occur afforded mostly a symmetrical tetrabromide, **6a**, the structure of which is assigned on the basis of an X-ray crystallographic determination of its monobenzoate ester **7a** (Figure 4).[16] A smaller amount of **6b** is formed, the structure of which was assigned likewise from the corresponding monobenzoate **7b** (Figure 5). Isomer **6c**, the bromination product of **4c**, was formed in the smallest

(13) An excess of Br_2 was required to limit isomerization of **3** during trapping with bromine. However, higher concentrations of bromide will affect any equilibrium involving Br^- and Br_3^-.

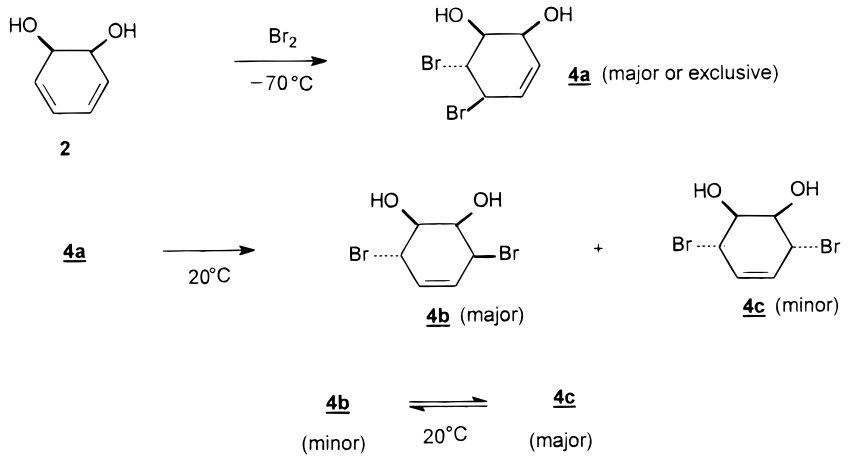
(14) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; p 119.

(15) The presence of the hydroxyl groups slightly inhibits this rearrangement, which has a half-life of about 3 h. This is reflected in the similar product distributions of isomers **6** observed at −70 °C and at 20 °C (Table 1).

Scheme 1



Scheme 2



amount and was not isolated. However, the dibromide of highest symmetry, **4c**, must result from formal syn 1,4-addition, and its bromination would be expected to afford a 3,4*c*,5*t*,6*c*-1,2-diol (Scheme 3). The relative stability of **4c** may be due to a thermodynamic preference for adjacent bromine and hydroxyl groups to be anti, as indicated by the structure of **7a**.[17] The preference of **4a** initially to form **4b** (and of **3a** to form **3b**) may be explained by a least motion 1,3-sigmatropic rearrangement, in which bromide is more likely to reattach to the same face from which it left.

Conclusion

On the basis of X-ray crystallographic determinations and NMR evidence, the configuration of 1,2,3,4-tetrabromocyclohexane (mp 90 °C), **5a**, has been established as 1,2*t*,3*t*,4*c*, and the structures of dibromocyclohexene intermediates **3a** and **3c** have been reassigned.

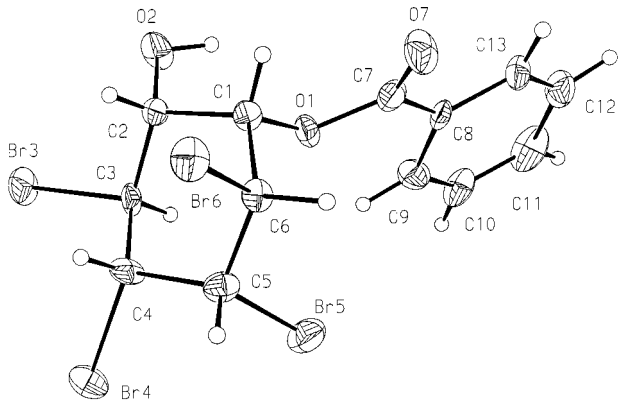


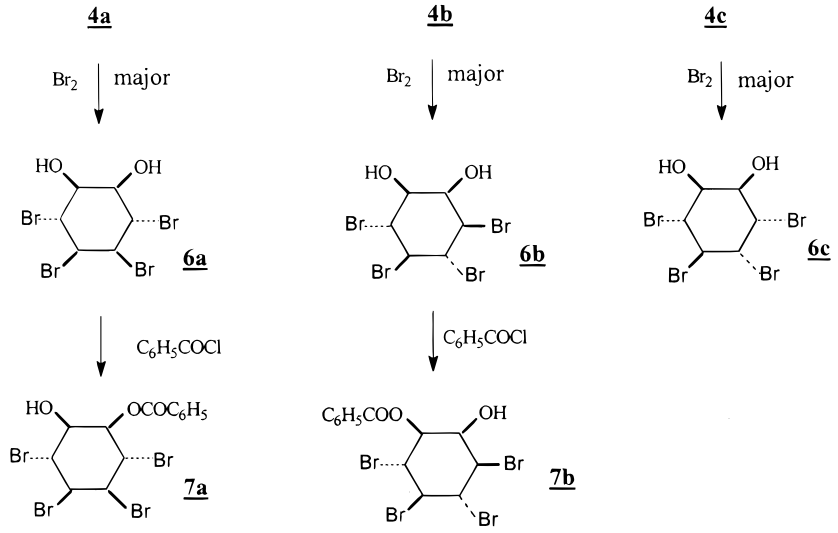
Figure 4. ORTEP of **7a** (30% probability elipsoids).

The mechanistic results are best explained as follows. Bromine adds to 1,3-cyclohexadienes **1** and **2** similarly at −70 °C. The first equivalent of Br_2 affords predominantly or exclusively the anti 1,2-addition products **3a** or **4a**. These kinetic products rearrange at room temperature to form the anti conjugate addition products **3b** or **4b**. In the case of **4**, a subsequent rearrangement of **4b**

(16) The structure of **7a** has two bromines and the hydroxyl group equatorial, and the other two bromines and benzoate group are axial. Benzoate is sterically bulkier than hydroxyl, and the unusual preference is for bulkier groups to be situated equatorial. The axial orientation of benzoate in crystalline **7a** is supported by extensive hydrogen bonding, both inter- and intramolecular, which is evident in this structure. For example, the nonbonded contacts of the hydroxyl hydrogen with O1 of the same molecule is 2.197 Å and with O7 of an adjacent molecule is 1.998 Å.

(17) The structure for **6c** in Scheme 3 was proposed as the 3,4*c*,5*t*,6*c*-tetrabromo-1*t*, 2*t*-diol with this in mind; however, the alternative 3,4*c*,5*t*,6*c*-tetrabromo-1*c*, 2*c*-diol cannot be ruled out.

Scheme 3



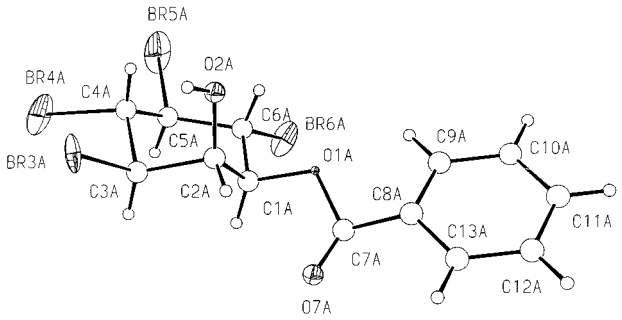


Figure 5. ORTEP of **7b** (molecula A, 30% probability elipsoids).

ultimately affords the syn 1,4-addition product **4c** as the major thermodynamic product. At −70 °C in the presence of excess bromine, the kinetic products **3a** and **4a** afford predominantly or exclusively **5a** and **6a**, the 1,2*t*,3*t*,4*c* isomers. At higher temperatures, the 1,2*t*,3*c*,4*t* isomer **5b**, formed by anti addition to **3b**, becomes the major tetrabromocyclohexane. More specific elucidation of the mechanistic details awaits explicit determination of the kinetics and thermodynamics associated with the various processes in Schemes 1−3 and further structural studies.[13,17,18]

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Supporting Information Available: Tables of crystallographic data, atomic coordinates, and bond distances and angles for **3b**, **5a**, and **7a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The reaction conditions play an important role in the mechanism of addition. For example, additives such as pyridine, necessary to prevent acid-catalyzed dehydration of **2**, may lead to formation of pyridine perbromide[19] or addition compounds[20] in brominations. However, we note that bromination of **1** with or without pyridine proceeds similarly.

(19) McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1951**, *73*, 206.
(20) Han, H.; Baker, R. J.; Masnovi, J. M. *Acta Crystallogr.* **1999**, *C55*, in press.