Radical Bromination of Cyclohexene in CCl_4 by Bromine: Addition versus Substitution

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The radical reaction of bromine (10^{-2}–10^{-5} M) with cyclohexene in CCl_4 in the light has been investigated. The reactions have been found to be highly reversible and controlled by both thermodynamics and the availability of Br_2 and HBr as equilibrating agents. The selectivity of substitution over addition is controlled by [Br_2]. Bromine addition to the double bond and allylic substitution occur at comparable rates at room temperature. The limiting substitution/addition ratio was found to be 4.0 ± 0.2 for [Br_2] less than 10^{-3} M. While the β-bromocyclohexyl radical is generated very rapidly, its steady-state concentration is kept low by its rapid reversion to cyclohexene. Substitution via the allyl radical, while relatively slow, is irreversible and fast enough to maintain the concentration of bromine at sufficiently low level to prevent significant addition. The equilibrium constant for the reaction **1** + Br ⇌ **2a** is estimated to be 500 M^{-1}, and the rate constant for substitution k_{2s} as 2000 M^{-1} s^{-1}. The ratio of removal of hydrogen from cyclohexene, 3-bromocyclohexene, and 3,6-dibromocyclohexene by bromine radical was found to be 2.2:1.0:0.1. The ratio for addition of bromine to the double bond was 5.5:1.0:<0.1. A series of polybromo derivatives have been obtained and characterized by NMR spectroscopy as stable intermediates in the exhaustive bromination of cyclohexene. *m*-Dibromobenzene is the major aromatic product.

We have used the addition/substitution ratio for the bromination of cyclohexene to monitor the dilution efficacy of the continuously rotated cellular reactor[1,2] (CRCR). In the course of that work, a wide range of products were obtained under a variety of conditions. In order to interpret the results, it was necessary to establish the relative reactivity of cyclohexene and a number of its brominated derivatives to bromine. The results can be rationalized by a series of reversible radical reactions occurring at essentially diffusion-controlled rates. The activation barriers are determined by radical stabilities and the availability of HBr and Br_2 to participate in equilibrating processes. This paper provides evidence for these conclusions and the characterization of several polybromocyclohexenes.

Background. The reaction of bromine and *N*-bromosuccinimide, NBS, with hydrocarbons and their bromo derivatives has been a continuing source of subtlety and complexity throughout the history of organic chemistry.[3–8] The diversity of reactions and difficulty of interpretation arise from the easy reversibility of many radical reaction steps involving bromo compounds (Scheme 1). The following pertinent facts have been established previously.

1. The reaction of cyclohexene with bromine in the light in CCl_4 solution occurs by a radical process.[9–12] Electrophilic bromine addition occurs through a charge-transfer complex[6,12–14] and is too slow to compete with radical processes in CCl_4, especially at low concentration.[6,13–15]

2. Bromine atoms react with alkenes by both addition to the double bond and also abstraction of an allylic hydrogen. The evidence is summarized in the critical

Scheme 1. Basic Processes for the Addition/Substitution of Cyclohexene by Bromine

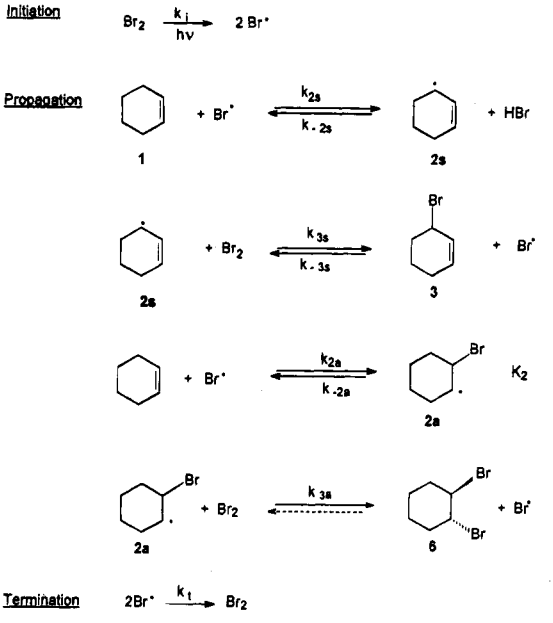

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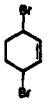
Table 1. Distribution of Product Yields as a Function of Time for the Consecutive Bromination of Cyclohexene

time		yields (mmol)				
addition (min)	relative[a]					total
0	0	0.996	0	0	0	0.996
6	0.207	0.810	0.085	0	0.0245	0.920
9	0.229	0.792	0.115	0	0.0363	0.943
12	0.419	0.655	0.198	0.00896	0.0569	0.910
18	0.638	0.526	0.242	0.0301	0.0869	0.885
24	0.953	0.384	0.327	0.0416	0.109	0.862
25	0.984	0.372	0.282	0.0618	0.135	0.851
32	1.32	0.265	0.339	0.0860	0.150	0.840
30	1.47	0.229	0.356	0.0780	0.159	0.822
36	1.59	0.204	0.353	0.105	0.156	0.818
36	1.95	0.141	0.358	0.126	0.190	0.815
36	2.14	0.117	0.335	0.158	0.192	0.802
40	2.19	0.111	0.355	0.138	0.191	0.795
39	2.25	0.105	0.369	0.109	0.202	0.785
41	2.37	0.0928	0.375	0.139	0.213	0.820
44	2.65	0.0702	0.351	0.186	0.192	0.799

[a] $\ln([\text{cyclohexene}]_0/[\text{cyclohexene}])$.

work which established the Goldfinger mechanism for the NBS reaction of alkenes.[16-18] NBS serves two essential functions: to generate low steady-state bromine concentrations and to remove HBr.

3. β-Bromoalkyl radicals reversibly generate bromine atoms and alkenes.[3,11,15,18-22]

4. HBr is an effective chain propagator and hydrogen abstraction by bromine atoms is a reversible process.[15,17,23,24]

5. Alkyl radicals react with Br_2 and HBr at almost diffusion controlled rates.[24,25]

6. Addition to form the saturated dibromide is thermodynamically preferred over allylic substitution. For propene for example,[25-28]

$$\Delta H_{addn} = -29.7 \text{ kcal/mol} \quad \text{and}$$

$$\Delta H_{subs} = -11.5 \text{ kcal/mol}$$

7. Radical addition of bromine to cyclohexene gives *trans*-1,2-dibromocyclohexane with almost no cis adduct.[15,20,21]

There is nothing to prohibit the first-formed reaction products undergoing further reaction by the same processes. The reaction to form **6** is the only one which is sufficiently exergonic to limit reversibility. Thus the actual outcome of the reaction will be subtly controlled by the concentrations of Br_2, HBr, and intermediates.

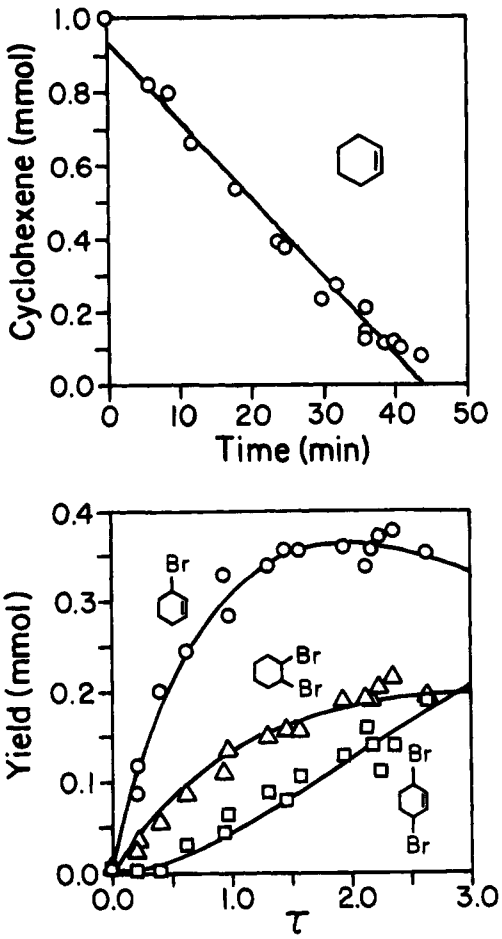


Figure 1. (a) Plot of cyclohexene concentration versus time for the addition of bromine (7.1×10^{-7} mol/s) to 0.10 M cyclohexene in carbon tetrachloride (10 mL) in the apparatus of Figure 2. (b) Plot of yield of 3-bromocyclohexene (O), 3,6-dibromocyclohexene (□), and *trans*-1,2-dibromocyclohexane (Δ) versus relative time (τ) for reaction. The lines represent the best fit to the data with eqs 1, 2, and 3, respectively.

Results

Competitive Allylic Bromination of Cyclohexene (1), 3-Bromocyclohexene (3), and 3,6-Dibromocyclohexene (5). In order to form substantial yields of allylic products from the direct reaction of bromine with cyclohexene, bromine concentrations below 10^{-4} M are needed. This was achieved by entraining dilute gaseous bromine (7.1×10^{-7} mol/s) into a stream of dry nitrogen (1.8 mL/s) bubbling into 0.996 mmol of cyclohexene in CCl_4 (10 mL) in a round-bottom flask exposed to a sunlamp. Under photolytic conditions, the concentration of bromine in the reaction solution never exceeded 10^{-4} M as the solution remained colorless for the duration of the reaction.[8] However, the addition product, *trans*-1,2-dibromocyclohexane, was still formed, even at this high degree of dilution. The absence of the other addition

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product, cyclohexyl bromide, indicates that the rapid stirring and the flowing nitrogen gas efficiently removed hydrogen bromide from the solution. The kinetics for the competitive allylic bromination of **1**, **3**, and **5** were determined by repeating the reaction for a selected series of times taken in random order. The combined requirements for high dilution and NMR analysis necessitated this nontraditional approach. The data are shown in Table 1 and Figure 1.

The cyclohexene concentration was found to decay linearly in time rather than exponentially, Figure 1a. This shows that the rate of bromine introduction into the solution was rate limiting. Some bromine was also lost by evaporation. In order to interpret the kinetics, it was then assumed that the loss of cyclohexene was occurring by three competing processes each first order in cyclohexene—substitution, addition, and evaporation.

An effective time, τ, for the reaction was then defined by the relationship $k_T\tau = \ln([\mathbf{1}]_0/[\mathbf{1}]_t)$, where k_T has a value of unity and is a scaling factor representing the sum of the normalized rate constants for substitution, k_s, addition, k_a, and evaporation, k_e. The data were then analyzed to obtain the relative reactivities using Scheme 2 and eqs 1–3. The rate expressions are

$$\frac{d[\mathbf{1}]}{dt} = -(k_s + k_a + k_e)[\mathbf{1}]$$

$$\frac{d[\mathbf{3}]}{dt} = k_s[\mathbf{1}] - k'_s[\mathbf{3}]$$

$$\frac{d[\mathbf{5}]}{dt} = k'_s[\mathbf{3}]$$

$$\frac{d[\mathbf{6}]}{dt} = k_a[\mathbf{1}]$$

giving

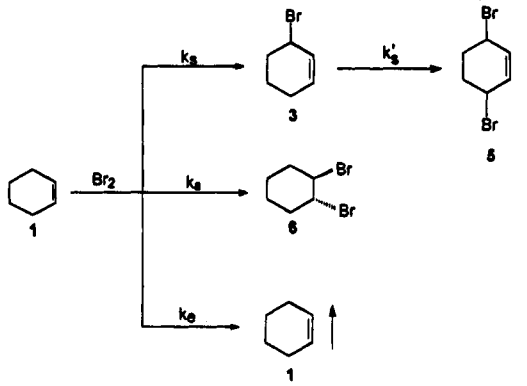
$$[\mathbf{3}] = \frac{k_s}{1 - k'_s}[\mathbf{1}]_0\{\exp(-k'_s\tau) - \exp(-\tau)\} \quad (1)$$

$$[\mathbf{5}] = k_s k'_s[\mathbf{1}]_0 \left\{\frac{1}{k'_s} - \frac{1}{k'_s(1 - k'_s)}\exp(-k'_s\tau) + \frac{1}{1 - k'_s}\exp(-\tau)\right\} \quad (2)$$

$$[\mathbf{6}] = k_a[\mathbf{1}]_0(1 - \exp(-\tau)) \quad (3)$$

Plots of concentration versus τ are shown in Figure 1b together with the best fit curves. Least-squares analysis gave $k_s = 0.556$, $k'_s = 0.217$, and $k_a = 0.136$. An unconstrained best fit for 3,6-dibromocyclohexene alone gave $k_s = 0.267$ and $k'_s = 0.662$. When these data were refittedwith k'_s fixed at 0.217, k_s was fitted to be 0.596. The difference arises from the poor fit in the region with $\tau < 0.5$. Both parameter sets fit the data within experimental error. As a further check on the ratio of k_s/k'_s a second set of experiments was run with the same procedure starting with equal concentrations of cyclohexene and 3-bromocyclohexene. The data are reported in Table 2. The initial increase in 3-bromocyclohexene proves directly that k_s is greater than 1. A quantitative determination of k_s/k'_s was made from the average of the ratio of k values obtained from Table 1 and the average yield ratio shown in the last column of Table 2. The ratio

Scheme 2. Pathways Contributing to the Loss of Cyclohexene

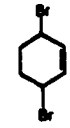
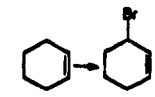


was found to be 2.2 ± 0.2. In these and subsequent experiments (data not shown), less that 5% of the 3,6-dibromocyclohexene was further brominated and so the relative rates of hydrogen atom abstraction by bromine are cyclohexene:3-bromocyclohexene:3,6-dibromocyclohexene 2.2:1.0:≤0.1. Thus allylic hydrogen removal is inhibited significantly by a bromine atom attached to the same carbon but is almost unaffected by a homoallylically located bromine substituent. The selectivity k_s/k_a was estimated to be 4.0 ± 0.2 from the initial slope ratio in Figure 1.

Addition. Competitive bromine radical addition reactions were done in the same manner as the competitive allylic substitution reactions. To favor the addition reaction, the rate at which the gaseous bromine was delivered was increased. A bromine addition rate of 5.5 × 10^{-6} mol/s to cyclohexene gave *trans*-1,2-dibromocyclohexane (70%) and 3-bromocyclohexene (30%). Higher delivery rates were avoided to prevent complications from the electrophilic addition reaction. The solution became colored with bromine during the reaction. The radical mechanism for the process was established by the competitive formation of allylic products and the much slower reaction in the absence of light. Without photolysis, the solution immediately became colored with bromine (>10^{-3} M). The coloration persisted for 5 min after the addition of bromine was finished. The ratio of the yield of *trans*-1,2-dibromocyclohexane to 3-bromocyclohexene more than doubled to 5.6. The competitive bromine addition to an equimolar mixture of cyclohexene and 3-bromocyclohexene gave *trans*-1,2-dibromocyclohexane and 1,2,3-tribromocyclohexane in a ratio of 5.5 ± 1.3. *trans*-1,2-Dibromocyclohexane was the sole product of the competitive reaction of cyclohexene and *trans*-3,6-dibromocyclohexene. Increasing the ratio of the *trans*-3,6-dibromide versus cyclohexene to 5.0 did not change the results. The tetrabromide **7** was not detected under these conditions.

Exhaustive Allylic Bromination of 3-Bromocyclohexene (3). The methodology employed for the reaction was identical to that for the bromination of cyclohexene described above. Gaseous bromine was slowly added to a solution of **3** under photolytic conditions. **3** was employed instead of cyclohexene to avoid the addition reaction. The reaction was sampled every 60 min and the composition of the mixture determined by NMR (Table 3). Products were identified by comparison with authentic samples. After 3 h, **3** had nearly been exhausted, and the dibromocyclohexenes (**4**, **5**) accounted for more than 90% of the product mixture. The lack of the higher brominated olefins is attributed to the lower

Table 2. Yields from the Competitive Reaction of Cyclohexene and 3-Bromocyclohexene for Bromine[a]

 initial	 initial	 final	 final	 final	 final		k_s/k'_s
2.00	2.00	1.17	2.18	0.274	0.140	0.454	1.66
2.04	2.01	1.24	2.20	0.348	0.176	0.538	1.54
2.00	2.00	1.15	2.21	0.312	0.121	0.522	1.67
2.47	2.02	1.66	2.37	0.256	0.0728	0.606	2.36

[a] All quantities in mmol.

Table 3. Product Composition at Various Times (h) for the Bromination of 3-Bromocyclohexene (3) with Gaseous Bromine in CCl_4

		relative solution composition at various times					
	products	1 h	2 h	3 h	4 h	5 h	6 h
3	(3)	22	12	3	0	0	0
5 + 4	di (3,6+3,4)	8	35	92	46	20	0
8	tri (1,3,4)	0	~1	2	13	23	23
9	tri (3,4,6)	0	0	0	37	42	46
10	tetra (1,3,4,6)	0	0	0	0	6	13
11	tetra (1,3,4,6)	0	0	0	2	3	5
12	tetra (1,3,4,5)	0	0	0	0	~1	5
14	(1−)	0	0	0	0	0	1
16	(*m*-)	0	0	0	0	0	1
17	(*p*-)	0	0	0	0	0	~1
7		0	~1	3	2	6	6

Table 4. Product Composition of the Aromatic Region. Data from the ^1H NMR Spectra

	relative solution composition at various times					
products	6 h	7 h	8 h	9 h	11 h	13 h
14 (1−)	50	44	35	28	12	10
15 (*o*-)	0	14	10	8	4	3
16 (*m*-)	50	41	34	41	50	58
17 (*p*-)	?	?	?	?	?	?
18 (1,2,4−)	0	1	11	20	27	25
19 (1,3,5−)	0	0	4	3	6	4

reactivity of the dibromocyclohexenes toward allylic bromination relative to **3**. Hydrogen abstraction at the allylic position is deactivated if a bromine also resides at that position.

Once **3** is consumed, formation of the tribromocyclohexenes is realized. The tetrabromocyclohexenes are formed before the dibromocyclohexenes are consumed (Table 3, 5 h). For the first 5 h, the solution remained colorless and then the reaction turned red with bromine after 6 h. Analysis demonstrated that the dibromocyclohexenes had been consumed. The product mixture had become complex as demonstrated by the NMR spectra. In addition to the products listed in Table 3, singlets at 6.73 and 6.87, likely due to pentabromocyclohexenes, were observed.

At 7 h, the mixture had become too complex to fully assess its composition. The major products are the tetrabromocyclohexenes. The strongest signal belongs to (3*R**,4*R**,6*S**)-1,3,4,6-tetrabromocyclohexene (**10**). The 1,3,4-tribromocyclohexene (**8**) has been consumed. The aromatic region of the ^1H NMR could be analyzed to give the composition of the aromatic products (Table 4). Bromobenzene (**14**) and *m*-dibromobenzene (**16**) are the major components formed in roughly equal amounts together with significant amounts of *p*-dibromobenzene (**17**).

The bromine addition was stopped after 8 h as the solution was dark red but photolysis was continued. The olefinic resonances have largely disappeared from the NMR. A broad signal attributed to 3,4,5,6-tetrabromocyclohexene (**13**) is present together with signals attributed to pentabromocyclohexenes. Tribromobenzenes (**18**−**19**) are now present, in addition to bromobenzene (**14**) and the dibromobenzenes (**15**−**17**). The contribution of the aromatic signals to the total spectral intensity increased correspondingly.

The solution remained colored with bromine for the remainder of the reaction. Although there was no observable change in the bromine concentration, the conversion of the polybrominated olefins to aromatics continued. Absolute quantitation was not done, but it was estimated that at least 50% of the starting material was present as brominated aromatics at the end of the reaction (13 h). *m*-Dibromobenzene (**16**) accounted for more than 50% of the aromatics. *p*-Dibromobenzene (**17**) was not quantified because of signal overlap. From the signal intensity it is present in significant concentration. Barnes reported that **16** and **17** were isolated from the reaction of cyclohexene with 6 equiv of NBS in yields of 38 and 19%, respectively.[29] This is in agreement with the above data.

The formation of the polybrominated aromatics does not proceed via the bromination of **14**. There was no reaction of bromine (19.7 mmol, 0.50 M) with bromobenzene (0.10 mL, 9.7 mmol) under photolytic reaction conditions.

Structure of 1,2,3,4-Tetrabromocyclohexanes (7, 21, 22). Two isomers were formed when the literature preparation was repeated.[30,31] The all-equatorial isomer (**7**) (mp 142 °C) has been well characterized.[31,32] Hassel and Lunde reported that the crystal structure of the tetrabromo compound of mp 156 °C is isomorphous with (+)-2*c*,3*t*-dibromo-1*r*,4*c*-dichlorocyclohexane.[30,33] This is in disagreement with Cornubert et al., who reported that the compound was the 1*r*,2*c*,3*t*,4*t*-tetrabromo isomer, based on chemical reactivity.[31] Hassel's original assignment is supported by our NMR data. On the basis of proton NMR splitting patterns (Table 5), the isomer with the melting point of 156 °C is assigned as (+)-1,2*c*,3*t*,4*c*-tetrabromocyclohexane (**21**). The coupling constants were obtained from simulated spectra.[34] The experimental spectrum could only be reproduced by assuming the assignment of the geminal pairs shown in Table 5. The remaining couplings were directly traced around the ring.

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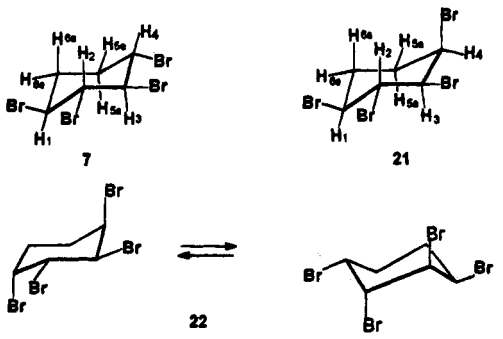
(34) Simulations done using the software RACCOON written by Paul F. Schatz of the University of Wisconsin/Madison. The simulations were performed by trial and error.

Table 5. Proton NMR Data for Bromo-Substituted Alkanes[a]

compd	shift (ppm)		couplings (Hz)
20	H6a	2.55	−15.00, 12.01, 2.83
	H6e	2.99	−15.00, 4.44, 3.62
	H2	4.27	10.62, 10.48
	H4	4.31	10.71, 3.17
	H3	4.56	10.71, 10.48
	H5	4.64	3.17, 3.62, 2.83
	H1	4.70	12.01, 10.62, 4.44
21	H6a	2.02	−14.6, 9.75, 3.09
	H5a	2.34	−14.6, 3.09, 3.09, 3.09
	H6e	2.39	−14.6, 3.09, 3.09
	H5e	2.62	−14.6, 9.75, 9.75, 3.09
	H4	4.19	9.75, 9.75, 3.09
	H2	4.15	9.75, 3.09
	H3	4.51	9.75, 9.75
	HI	4.69	3.09, 3.09

[a] Obtained from simulated spectra.

The second isomer has been assigned, also based on chemical reactivity, as the 1*r*,2*c*,3*t*,4*c*-tetrabromo isomer (mp 90 °C).[31] The broad unresolved peaks of the NMR data suggest that there is a rapid exchange between two almost equally populated conformers. This is consistent with the ^{13}C spectrum which shows four peaks of comparable intensity and one sharp line. This indicates a symmetrical structure with two bromines axial and two equatorial. Such a conformational equilibration would be satisfied by the 1*r*,2*c*,3*t*,4*t*-tetrabromo isomer (**22**).



Photolytic Bromine Addition to 3,6-Dibromocyclohexene (5). The literature preparations of the 1,2,3,4-tetrabromocyclohexanes were conducted under electrophilic bromination conditions.[30,31] The reaction of *trans*-3,6-dibromocyclohexene with less than 1 equiv of bromine in the dark at 10 °C was still colored red with bromine after 2 days. The solid that formed during the reaction was **7** (yield, 37%). TLC indicated the presence of the other two isomers.

The same reaction under photolytic conditions became colorless within 3 min. A solid immediately formed and was identified as pure **7** (yield, 52%). Proton NMR analysis of the entire product mixture revealed that **7** composed 80% of the products. The remaining products were **21** (18%) and **8** (2%).

The reaction was repeated except that *cis*-3,6-dibromocyclohexene (**5**) was brominated. The reaction was colorless within 1 min of the addition of bromine to the solution. No solid was formed. The product mixture was composed of **7** (46%), **21** (49%), and **8** (5%).

Discussion

The reaction of bromine with alkenes is subtle. The level of complexity[6-8] is rarely considered in introductory treatments. Critical issues such as reversibility,[24,25] stereochemistry in radical processes,[21] solvent effects, and the essential intermediacy of charge-transfer complexes in slightly polar media[6] are often ignored. Our key experimental observations are as follows: 1. Addition is competitive with substitution even at bromine concentrations of $\sim 10^{-5}$ M. This is discussed in detail below. 2. Several tri- and tetrabrominated cyclohexenes have been identified and their stereochemistry determined. 3. *m*-Dibromobenzene was prepared in over 50% yield by the exhaustive bromination of cyclohexene under radical conditions. 4. The relative rates for allylic bromination of **1:3:5** are 2.2:1.0:0.1. Relative rates for Br_2 addition are 5.5:1.0:<0.1.

Addition and Substitution. In his pioneering work on gas-phase kinetics, Kistiakowsky[35] showed that addition of bromine atoms to alkenes occurred at approximately diffusion-controlled rates. The recent thorough study by Gutmann[25] gives a value of 5.5×10^9 M^{-1} s^{-1} for addition of bromine atoms to propene in the gas phase. Yet for over 30 years, it has been widely known that substitution was the almost exclusive result of radical bromination of alkenes with low concentrations of bromine, either directly or via NBS.[3,8-12] In our current work, the lowest ratio of addition to substitution we have found for cyclohexene is 1:4 with bromine concentrations as low as 10^{-5} M. This was confirmed in our CRCR study[2] where the same 1:4 ratio was obtained from the intercept of the plot of addition/substitution versus bromine concentration from reactions in the 10^{-3} M range. These apparently disparate observations can be reconciled with the recognition that the reaction

$$\text{alkene} + Br^{\bullet} \rightleftharpoons \beta\text{-bromoalkyl radical}$$

is both rapid *and rapidly reversible* even at room temperature. The observed addition/substitution ratio then reflects the competitive diffusion-limited trapping by bromine of both the allyl radical and the β-bromoalkyl radical. The allyl radical is generated slowly by hydrogen atom abstraction in a step which is irreversible provided HBr is removed. The β-bromoalkyl radical is formed very rapidly but is present only in low steady-state concentrations because of the ease of the reverse reaction. At higher temperatures, this steady-state concentration is reduced further as the equilibrium shifts to the left. This explains why NBS reactions which give high selectivity for substitution products are commonly run in refluxing CCl_4. The high temperature increases the rate of substitution and simultaneously reduces the concentration of addition product precursor. Reflux conditions are required for high selectivity not for rapid reaction under photolytic conditions. The facile removal of HBr as insoluble succinimide is also essential. Other amine bases facilitate addition through the competing charge-transfer complex.

Kinetic Analysis. The results shown in Figure 1 can generate a quantitative estimate of the rate and equilibrium constants, based on the initial reaction rates. Assuming steady-state concentrations for Br and **2a**, and rapid removal of HBr, the rate expressions from Scheme 1 become

(35) Kistiakowsky, G. B.; Sternberg, J. C. *J. Chem. Phys.* **1953**, *21*, 2218.

$$\frac{d[\mathbf{3}]}{dt} = k_{2s}[\mathbf{1}][Br^{\bullet}]k_{3s}[Br_2] \quad (4)$$

$$\frac{d[\mathbf{6}]}{dt} = K_2[\mathbf{1}][Br^{\bullet}]k_{3a}[Br_2] \quad (5)$$

$$\frac{d[Br^{\bullet}]}{dt} = 0$$

and so

$$2k_i[Br_2] + k_{-2a}[\mathbf{2a}] + [Br_2](k_{3s}[\mathbf{2s}] + k_{3a}[\mathbf{2a}]) = 2k_t[Br^{\bullet}]^2 + [\mathbf{1}][Br^{\bullet}](k_{2s} + k_{2a}) \quad (6)$$

$$\frac{d[\mathbf{2a}]}{dt} = 0 = k_{2a}[\mathbf{1}][Br^{\bullet}] - k_{-2a}[\mathbf{2a}] - k_{3a}[\mathbf{2a}][Br_2] \quad (7)$$

The initial slopes in Figure 1b show that the rate of substitution is greater than the rate of addition. The ratio of these slopes is obtained from eqs 4 and 5, giving $k_{2s}/K_2 = 4.0(k_{3a}/k_{3s})$. Equation 5 is valid provided $[Br_2] \ll k_{-2s}/k_{3a} \sim 10^{-3}$ M based on eq 7. In the following discussion, it is assumed that k_{3s} and k_{3a} are equal and are at the diffusion limit of $\sim 10^9$ M^{-1} $s^{-1} = k_3$. The other consequence is that the addition/substitution ratio ([**6**]/[**3**]) = K_2/k_{2s} is independent of both bromine and cyclohexene concentrations and has its minimum value of 0.25.

Furthermore, since the input flow of bromine was rate determining, the molecular bromine concentration also rapidly reaches steady state at least for the early stages of reaction where cyclohexene is in excess. The steady-state bromine concentration is given by

$$\frac{d[Br_2]}{dt} = 0 = k_f + k_t[Br^{\bullet}]^2 - k_i[Br_2] - k_{3a}[\mathbf{2a}][Br_2] - k_{2s}[\mathbf{1}][Br^{\bullet}]k_{3s}[Br_2] \quad (8)$$

where k_f (M/s) is the effective input flow rate given by the rate of loss of cyclohexene = 3.4×10^{-5} M/s. Note that the effective flow rate is comparable to but lower than the actual input flow rate (7.1×10^{-5} M/s) because of the evaporative loss of bromine from the solution. Thus, we have

$$[Br_2]_{ss} = k_f/k_3([\mathbf{2a}] + [\mathbf{2s}])$$

Now from (7),

$$[\mathbf{2a}] = K_2[\mathbf{1}][Br^{\bullet}] = 0.25k_{2s}[\mathbf{1}][Br^{\bullet}]$$

because the β-bromoalkyl radical reaches its equilibrium concentration much more rapidly than it is trapped by bromine. Thus,

$$k_{2s} = k_f/1.25k_3[\mathbf{1}][Br^{\bullet}][Br_2]_{ss}$$

Now k_{2s} can be estimated either as $4K_2$ or if the concentrations of molecular and atomic bromine are known from eq 8. The lack of color in the reaction mixture showed that the bromine concentration was 10^{-4} M or lower. Then $k_{2s}[Br]$ is at least 2.7×10^{-9} s^{-1}. Since k_{2a} is diffusion controlled, K_2 can be determined from knowledge of k_{-2a}. In turn k_{-2a} can be estimated from the minimum bromine concentration necessary to make the addition/substitution ratio proportional to bromine concentration which occurs when $k_{-2a} = k_{3a}[Br_2]$. The critical bromine concentration was found[2] to be 2×10^{-3} M. This gives $k_{-2a} = 2 \times 10^6$ s^{-1} and $K_2 = 500$ M^{-1}, and so $k_{2s} = 2000$ M^{-1} s^{-1}. This leads to realistic estimates of the steady-state bromine atom concentration of 1.3×10^{-12} M, and the 2-bromocyclohexyl radical as 6.5×10^{-11} M. The exact values of these quantities will be modified by any differences in the assumption that

$$k_{2a} = k_{3a} = k_{3s} = 10^9 \text{ } M^{-1} \text{ } s^{-1}$$

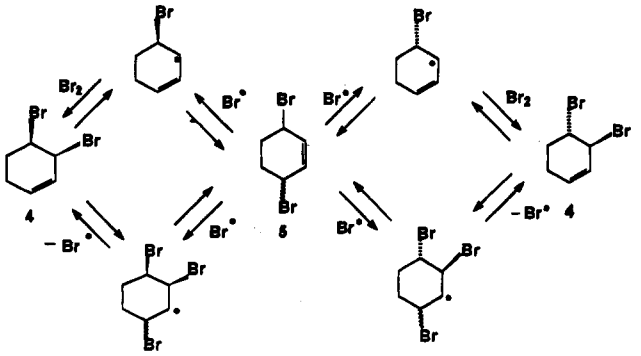
Tanner's study[19] of the gas-phase bromination of 2-butene can be analyzed similarly. The critical bromine concentration for minimizing addition was 1×10^{-5} M and the limiting addition/substitution ratio was found to be 0.07. This gives for 2-butene, $k_{-2a} = 10^4$ s^{-1} and $K_2 = 10^5$ M^{-1} and so $k_{2s} = 7000$ M^{-1} s^{-1}. These values are in satisfactory agreement with our values for cyclohexene. It is interesting that provided the cyclohexene concentration is greater than 2×10^{-3} M, the steady-state concentration of β-bromoalkyl radicals, **2a**, is greater than that of bromine atoms. Thus, chain termination will occur by formation of the addition product rather than regenerating bromine. (This conclusion does not affect the above kinetic analysis.) The steady-state bromine atom concentration is maintained by the decomposition of **2a**. The overall picture then is of bromine atoms repetitively adding to the alkene and decomposing again. Approximately one in a million times an "error" is made and a hydrogen is removed. The newly generated allyl radical then reacts rapidly with molecular bromine to hold the bromine steady-state concentration below $k_{-2s}/k_{3a} \sim 10^{-3}$ M.

Sequential Allylic Bromination and Dehydrobromination. The study of the bromination of 3-bromocyclohexene (**3**) demonstrates that the isolated polybrominated alkenes arise from a series of sequential allylic brominations. These alkenes then undergo dehydrobromination to give brominated aromatics. The bromination of cyclohexene and **3** was shown above to be a statistical process kinetically. Allylic bromination at the free allylic site of **3** is not hindered by the remote bromine substituent. However, the subsequent bromination of the 3,6-dibromocyclohexenes (**5**) is relatively slow. Bromocyclohexene (**3**) is totally consumed before significant yields of the tribromocyclohexenes (**8**, **9**) are obtained. (Table 3). We have been unable to isolate dibromide **4** in pure form as it is extremely labile and cannot be separated from the 3,6-dibromocyclohexenes. Its ^1H NMR signals are obscured by those of its isomers. It has been assigned as the *trans* isomer by other authors on the basis of its rapid isomerization to **5**. The formation of minor quantities of *cis* **4** cannot be rigorously excluded.

The interconversion of *cis* and *trans* **4** and **5** proceeds rapidly by repeated additions and eliminations. Two potential pathways are shown as part of Scheme 3. The addition of bromine atoms to alkenes occurs at essentially diffusive rates. The allyl radical pathway is also kinetically and thermodynamically viable. In a repeated cycle of such steps, each C—Br in **4** and **5** can be broken and formed to give the thermodynamic mixture of dibromides including all possible stereoisomers. Similar rearrangements are assumed to occur with the higher bromides.

The second basic process is allylic substitution. This is slower than the addition/elimination/allylic radical

Scheme 3



equilibration sequence. The formation of **4** and **5** prior to the formation of tribromides **8** and **9** shows that allylic hydrogen abstraction α to bromine is significantly slower than when hydrogen alone is present. This was also observed in the kinetic studies above. The conversion of tribromides to tetrabromides is slower still because hydrogen abstraction α to bromine is again required.

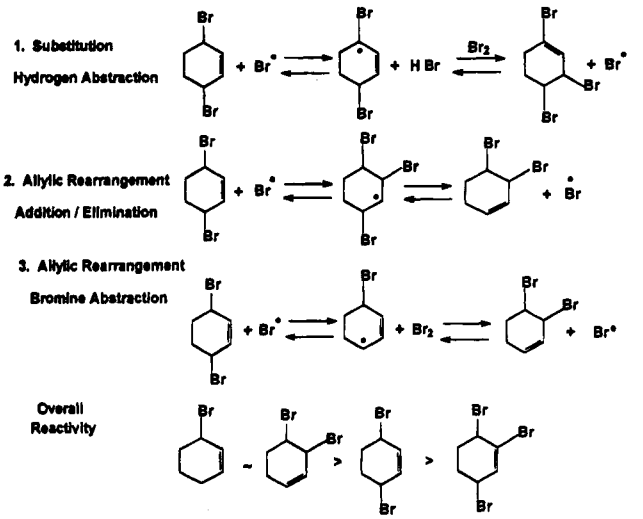
The stereochemical preferences evident in the preferential formation of tribromoalkenes **8** and **9** and tetrabromoalkenes **10**, **11**, and **12** is intriguing. We think that this selectivity is of thermodynamic rather than kinetic origin.[36] Firstly the ratios of **8** to **9**, and **10** to **11**, to **12** are approximately independent of the extent of conversion. Secondly the equilibration of **4** and **5** is much more rapid than substitution. The avoidance of α,α dibromo and vicinal tetrabromo derivatives is readily rationalized on steric grounds. The more subtle differences involving the geometrical preference of vicinal dibromides for *trans* in **8** yet *cis* in **9** for example are more difficult to understand. The *cis* 3,6-diallylic substitution pattern and compounds with three or more bromines on the same face of the ring are disfavored. While it is possible that kinetic selectivity is involved, especially in such a multifaceted reaction sequence, we will adopt the thermodynamic approach. The following schemes show a general ambivalence to stereochemistry because it is assumed that stereoisomers are rapidly equilibrated under reaction conditions. The basic mechanistic steps and the presumed order of reactivity is shown in Scheme 4.

From these basic processes, a tentative reaction flowchart has been developed to suggest routes to each isomer (Schemes 5–7). It should again be emphasized that equilibration of stereoisomers is presumed to be rapid especially in the presence of bromine. Furthermore other intermediates are almost certainly formed under these conditions, but they are present in small amounts at most. Substitution is the slow step at each stage and is even slower when a hydrogen α to bromine is being removed. Addition of bromine atoms α to bromine is also relatively unfavorable. Reversible addition/elimination may be used for allylic rearrangement and conversion of stereochemistries such as **4** ⇌ **5**. However irreversible hydrogen abstraction is required for each increment in bromine substitution level.

Tribromide **24** has not been isolated (Scheme 5). However, in the isolation of **9**, additional ^{1}H NMR signals were detected. In the olefinic region one-half of an AB pair with coupling constants of 1.2, 4.6, and 9.5 Hz was resolved. This is consistent with a vicinal coupling between an olefinic hydrogen and a vinylic neighbor and

(36) Jensen, F. R.; Bushweller, H. C. *J. Am. Chem. Soc.* **1969**, *91*, 5774.

Scheme 4. Basic Processes



an allylic methylene group. Unfortunately, the rest of the signals were obscured. Thus **24** is at best a minor product.

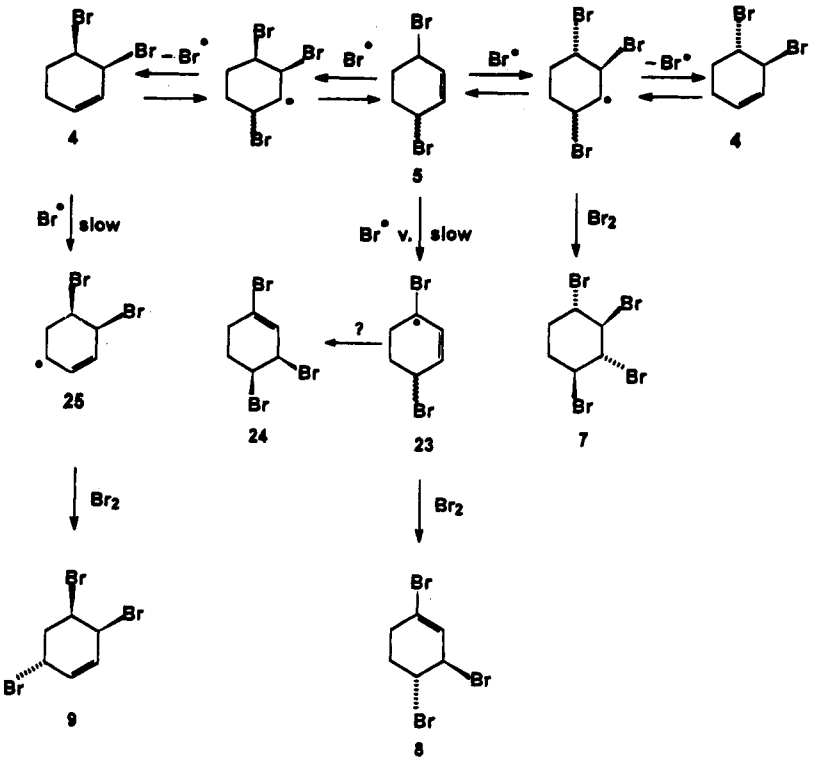
The formation of the tetrabromocyclohexenes from the tribromides (Scheme 6) is not as rapid as the previous sequence of reactions. After the dibromocyclohexenes **4** and **5** were consumed the solution became colored with bromine. Hydrogen abstraction from **8** forms an unsymmetrical allyl radical with two active sites. Of the four possible tetrabromocyclohexenes, only isomer **10** has been identified in the product mixtures. The preference for formation of intermediate **26** relative to **27** accounts for the formation of **10**. Evidence for the presence of tetrabromide **28** was not found despite a thorough search.

The bromination of tribromide **9** is slowed because allylic hydrogen abstraction geminal to bromine is required. Four stereoisomers of the tetrabromide are possible. The expected isomers, **11** and **12**, have indeed been identified and isolated from the reactions. As shown in Scheme 6, several other tri- and tetrabromides such as **28** and **29** would be expected as intermediates in the reaction. Small amounts of these compounds may be present, but detection is limited by spectral overlap and low yields. For example, **13** has been identified in related reactions, but its broad peaks make it particularly difficult to detect in these complex mixtures.

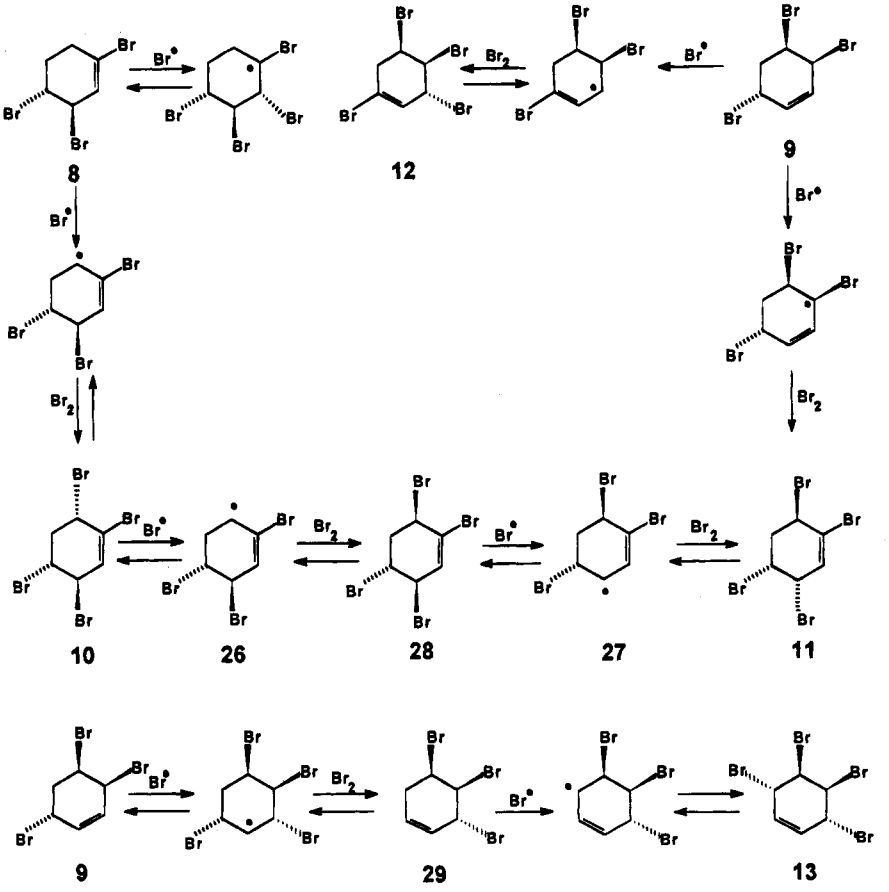
The aromatic compounds are presumably formed via dienes as shown in Scheme 7. The proposed pathway is based on the observations that benzene is not formed and that *m*-dibromobenzene is the first formed and predominant aromatic dibromide. Higher brominated olefins are present. The large number of products and lack of significant yields precluded their isolation. Once the tetrabromides start forming, the reaction mixture becomes complex as the proliferation of products increases. The reaction mixture has become colored with bromine as a consequence of the decreased reactivity of the polybrominated olefins.

One of the major pathways in the later stages of the reaction is the elimination of HBr to give brominated aromatics. Allylic bromides are known to eliminate HBr. This elimination is particularly favorable if it results in conjugation of double bonds or aromaticity. A direct path to the dibromobenzenes is by elimination of 2 equiv of HBr from the tetrabromocyclohexenes. It is only after significant amounts of the tetrabromides are formed that

Scheme 5. Proposed Allylic Bromination Pathway for the Formation of Tribromocyclohexenes



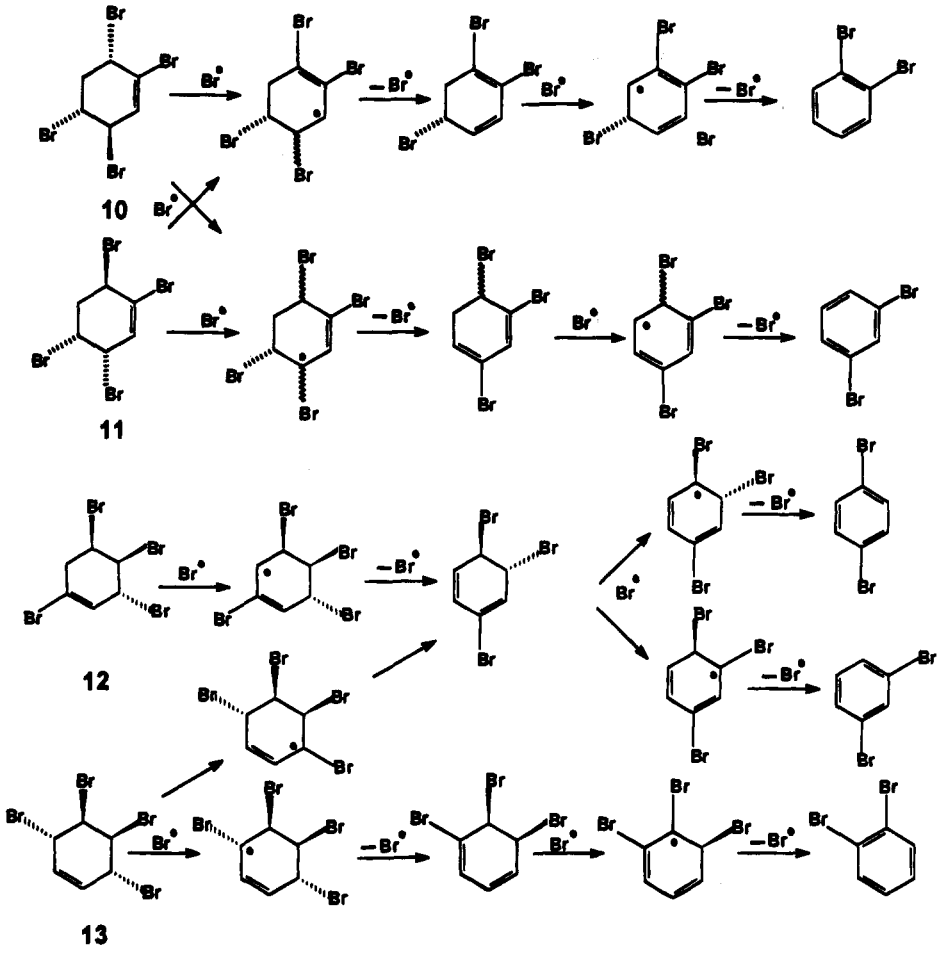
Scheme 6. Proposed Pathway for the Formation of Polybrominated Cyclohexenes



the aromatics are detected. Furthermore, the growth of the aromatics is associated with the disappearance of the signals in the olefinic region. The determining factors for the selectivity toward **16** and **17** have not been rigorously established.

Although not examined in detail, all of the observed polybrominated cyclohexanes can be explained by addition of bromine across the double bond of the appropriate alkene. It was demonstrated that the 1,2,3,4-tetrabromocyclohexanes (**7**, **21**, and **22**) can be derived from

Scheme 7. Proposed Pathway for the Formation of Bromo Aromatics



bromine addition to the 3,6-dibromocyclohexenes. Tetrabromide **7** was also observed in the bromination study of **3**. The tribromocyclohexanes, however, were noticeably absent despite the higher reactivity of **3** relative to **5** toward radical bromine addition.

The difficulty is understandable from comparison of the relative rates of addition versus substitution. Under the conditions employed for the bromination of **3** via gaseous bromine, cyclohexene brominates to give a 70:30 mixture of **3** and *trans*-1,2-dibromocyclohexane. Although the presence of the bromine substituent does not hinder allylic bromination at the other allylic position, the addition of bromine is slowed, and the reaction of **5** is decreased by a factor of 5 relative to **3**. Therefore, allylic bromination dominates the reaction. Once both allylic positions are occupied, the substitution reaction diminishes enough to permit the addition reaction. In the presence of concentrated bromine solutions (0.10 M), the addition reaction dominates.

The stereospecific anti addition of bromine to give *trans*-1,2-dibromocyclohexane is observed from the bromination of cyclohexene under conditions conducive to radical-chain reactions. This is in accord with the radical-chain reactions of 1-bromocyclohexene and 1-methylcyclohexene with hydrogen bromide, respectively, to give stereospecific anti additions.[21a] More significantly, Thaler reported that the photobromination of cyclohexyl bromide gave *trans*-1,2-dibromocyclohexane but that none of the cis isomer was detected.[15] The intermediate β-bromocyclohexyl radical, **2a**, formed by hydrogen abstraction from cyclohexyl bromide, is the same intermediate as from bromine atom addition to cyclohexene.

Conclusions

The radical bromination of cyclohexene in CCl_4 occurs via initial bromine atom addition to the double bond at a diffusion-controlled rate. The formation of the β-bromoalkyl radical is rapidly reversible. At low bromine concentration ($<10^{-3}$ M), the competition between addition and substitution products is governed by this equilibrium ratio K_2 (i.e. the thermodynamics) and the rate constant for allylic hydrogen abstraction. At room temperature for cyclohexene the ratio of substitution to addition is 4.0. In refluxing CCl_4 where NBS reactions are performed, substitution is dominant. Addition–elimination reactions allow rapid equilibration of stereoisomers. The formation of geminal dibromides is thermodynamically unfavorable.

Experimental Section[2b]

Reagents. Reagent grade CCl_4 (3 L) was refluxed over basic $KMnO_4$ (40 g in 2 M KOH, 0.5 L), washed with deionized water (0.1 L), dried (Na_2SO_4), distilled, and stored in brown bottles. Immediately prior to reaction, CCl_4 was fractionally distilled from P_2O_5 under N_2. Cyclohexene (Baker AR) was deoxygenated by bubbling with N_2 prior to use. Bromine (Baker AR, >99% purity) was used directly. In initial work, bromine was purified by drying over $CaBr_2$ and distilling from P_2O_5. No discernable difference was seen between reactions run with the different bromine samples so the AR reagent was used routinely.

The following products were prepared directly using literature procedures: 1-bromocyclohexene,[37] 3-bromocyclohexene

(37) Goering, H. L.; Sims, L. L. *J. Am. Chem. Soc.* **1957**, *79*, 6270.
(38) Greenwood, F. L.; Kellert, M. D.; Sedlak, J. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. 4, p 108.

Table 6. Proton NMR Data for Bromo-Substituted Olefins

compd		shift (ppm)	couplings (Hz)[a]
8	H5	2.05	complex; (H5′) and/or (H6′), (H6), (H4)[b]
	H5′	2.60 2.68	complex; (H6), (H6′), (H5), (H4)[b]
	H6′	2.60 2.68	(H6), (H5′), (H5), (H4)
	H6	2.88	(H5), (H5′) and/or (H6′), (H2)[c]
	H4	4.65	3.7(H5), 2.4(H3), 2.4, 1.1, 1.1
	H3	4.93	5.4(H2), 2.4(H4), 2.4, 0.7
	H2	6.19	5.4(H3), 2.3, 1.1, 1.1
9	H5e	2.64	14.5, 5.7, 5.7, <1.0, <1.0
	H5a	2.92	14.6, 8.4, 2.9
	H6	4.60	5.7, 2.9, 2.9
	H3	4.85	4.0, 4.0
	H4	4.97	complex
	H2	5.87	4.3, 10.0, <1.0, <1.0
	HI	6.05	10.0, 2.8, <1.0, <1.0
10	H5e	2.76	14.7, 8.39, 5.21, 0.9
	H5a	3.00	14.7, 5.98, 3.21
	H4	4.56	8.51, 5.82, 3.22
	H3	4.77	5.1, 5.1, 1.26, 1.26
	H6	4.83	5.9, 5.9
	H2	6.32	4.51
11	H5e	2.61	14.8, 2.81, 1.79, 1.79
	H5a	2.97	14.8, 12.37, 4.44
	H4	4.58	12.38, 3.31, 3.31
	H6	4.77	4.48, 1.99
	H3	4.86	5.49, 3.70, 1.46
	H2	6.38	5.82
12	H6e	3.10	14.4, 6.2, 1.0
	H6a	3.27	14.4, 10.2, 2.5, 1.4
	H3	4.65	2.4, 2.4, 2.4
	H5	4.74	10.18, 6.07, 2.40
	H4	5.02	5.21, 2.12, 1.0
	H2	6.20	5.35, 2.40, 1.2, 1.2

[a] The characters within the parentheses represent crosspeaks detected in the COSY. [b] A weak crosspeak was detected for H5 to the 2.55−2.73 region. [c] A weak crosspeak was detected.

(**3**),[38] 4-bromocyclohexene, *trans*-l,2-dibromocyclohexane,[39] *cis*-1,2-dibromocyclohexane,[40] *trans*-2-bromocyclohexanol,[41] cyclohexyl bromide,[42] *trans*-3,6-dibromocyclohexene,[43−45] *cis*-3,6-dibromocyclohexene,[43−45] *trans*-3,4-dibromocyclohexene,[43−45] 1*r*,2*t*,3*c*-tribromocyclohexane,[46] and 1*r*,2*c*,3*t*-tribromocyclohexane.[46] Dibromobenzenes and l,2,4-tribromobenzene (Aldrich) were commercial samples. Baker analyzed cyclohexene (**1**), reagent grade bromine, and reagent grade CCl_4 were used for the sample preparations.

Proton NMR data for new compounds are listed in Tables 5 and 6 and actual spectra are included in the Supplementary Material.

Low-Concentration Bromine Reaction Procedure. The reaction was performed using the apparatus of Figure 2. Nitrogen flow rates were optimized to favor allylic bromination in the minimum delivery time possible: 0.041−0.042 mL/s for the carrier nitrogen through inlet A and 1.6−1.8 mL/s for the combined flows. The 25-mL round-bottom flask was charged with CCl_4 (10 mL) and purged with nitrogen for 5 to 10 min. Cyclohexene (0.996 ± 0.006 mmol) was injected directly into the solvent via a calibrated syringe. The sunlamp (150 W) was turned on and the reservoir (B) filled with 0.10 mL of bromine. The reaction was started by closing the reservoir. The bromine gas colored the addition line until its dilution by the diluent nitrogen gas. The solution never became colored with bromine for the duration of the reaction (10^{-4} M bromine solutions give visually detectable coloration). Addition of bromine was completed in 45 min (rate 7.1×10^{-4} mmol/s). The reactions were run in random order for the times given in Table 1. The reaction was terminated by abruptly ending the bromine addition by opening the top of the reservoir. The entire solution was removed via syringe and added to a 25-mL vial, sealed with parafilm, and stored in the dark. Naphthalene (0.129 M) in carbon tetrachloride (1.00) was added as internal standard, and an aliquot was removed and analyzed by ^{1}H NMR.

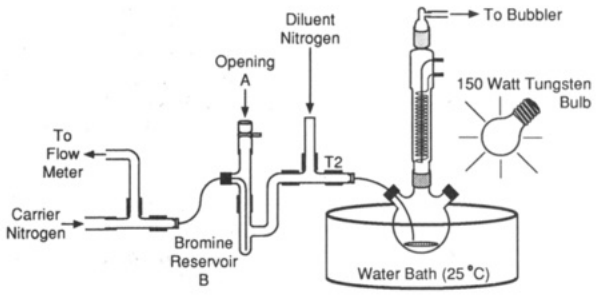


Figure 2. Apparatus for the gaseous bromination of alkenes by entrainment in carrier nitrogen flow. To initiate reaction, the required volume of liquid bromine is injected into the bromine reservoir and opening A closed. Reaction is stopped by opening A.

Product Analysis. Quantitation of products was done by 200-MHz ^{1}H NMR using a 45° pulse and a delay of 23 s. **3** and **5** gave overlapping signals in the regions of δ = 3.90−4.30 ppm (2H from each) and δ = 5.92−6.03 ppm (1 and 2H, respectively). The areas of the two olefins are given by $2A1 + 2A2 = A_{5.92-6.03}$ and $A1 + 2A2 = A_{4.90-5.00}$, where A1 and A2 are the contributions to the total area from **3** and **5**, respectively. The remaining compounds gave clean integrable signals: cyclohexene (δ 5.50−4.60 ppm), *trans*-l,2-dibromocyclohexane (δ 4.45−4.51 ppm), 1*r*,2*t*,3*c*-tribromocyclohexane (δ 3.90−4.30 ppm), and 1*r*,2*t*,3*c*,4*t*-tetrabromocyclohexane (δ 4.00−4.29 ppm). Competitive reactions giving both 1*r*,2*t*,3*c*-tribromocyclohexane and 1*r*,2*t*,3*c*,4*t*-tetrabromocyclohexane as products were avoided. It was shown by comparison with standard solutions that careful shimming of the NMR magnet and proper phasing of the signal allowed reproducibility in product yields within ±5.0%.

Competitive Allylic Bromination of Cyclohexene and 3-Bromocyclohexene. Cyclohexene was distilled from sodium wire prior to use. The KI acetic acid test was negative for peroxide. Bromine was added by passing nitrogen carrier gas over bromine contained in a 250-mL gas washing flask. Optimized flow rates of 0.1 mL/s and 1.5 mL/s for the carrier nitrogen and combined flows, respectively, gave **3** and **6** in a ratio of 5.0:1.0 when a large excess of cyclohexene was brominated. Bromination of excess **3** gave a mixture of 3,6-dibromocyclohexenes as the only products.

In the competitive experiment cyclohexene (0.164 g, 2.00 mmol) and **3** (0.322 g, 2.00 mmol) were dissolved in carbon tetrachloride (50 mL) in a 100-mL round-bottom flask fitted with a West condenser. The lamp was turned on, bromine (0.20 mL, 1.2 mmol) was added to the trap, and the reaction was started by closing the reservoir. The bromine gas colored the addition line until its dilution by the diluent nitrogen gas. The solution never became colored with bromine for the duration of the reaction. Total addition of bromine to the round-bottom flask was completed in 60 min, giving a delivery rate of 5.5×10^{-4} mmol/s. The entire solution was removed via syringe and added to a 100-mL flask, sealed with parafilm, and stored in the dark. Naphthalene (0.298 M) and nonane (0.242 M) in carbon tetrachloride (1.00 mL) were added, and an aliquot was analyzed by ^{1}H NMR. The yields of products, cyclohexene, 3-bromocyclohexene, 3,6-dibromocyclohexenes, *trans*-l,2-dibromocyclohexane, are reported in Table 2.

Competitive Bromine Addition to Cyclohexene and 3-Bromocyclohexene. The apparatus diagrammed in Figure

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2 was used. The flow rate of the carrier nitrogen was 2.0–2.1 mL/s. The diluent nitrogen was not used. Under these conditions the bromination of cyclohexene gave **6** and **3** in a ratio of 2.2:1.0. The 25-mL round-bottom flask was charged with carbon tetrachloride (10 mL), **3** (1.558 g, 9.67 mmol), and **1** (0.804 g, 9.79 mmol). The lamp was turned on, bromine (0.10 mL, 1.9 mmol) was added to the reservoir, and the reaction was started. The bromine gas colored the addition line until entry into the solution. The solution never became colored with bromine for the duration of the reaction. Total addition of bromine to the round-bottom flask was completed in 2.8 min, giving a delivery rate of 1.1×10^{-5} mol/s.

The entire solution was removed via syringe and added to a 25-mL vial, sealed with parafilm, and stored in the dark. Naphthalene (0.488 M) and nonane (0.393 M) in carbon tetrachloride (1.00 mL) were added, and an aliquot was removed and analyzed by ^{1}H NMR: **6** (1.05 mmol) and *1r,2t,3c*-tribromocyclohexane (0.175 mmol) were present.

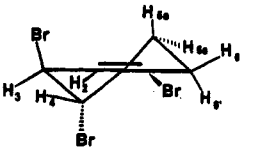
Competitive Bromine Addition to Cyclohexene and *trans*-3,6-Dibromocyclohexene. The reaction was performed as above. The 25-mL round bottom flask was charged with carbon tetrachloride (10 mL), **5** (2.33 g, 9.71 mmol), and **1** (0.799 g, 9.73 mmol). The lamp was turned on, bromine (0.10 mL, 1.9 mmol) was added to the reservoir, and the reaction was started. The bromine gas colored the addition line until entry into the solution. The solution never became colored with bromine for the duration of the reaction. Total addition of bromine to the round-bottom flask was completed in 3.3 min, giving a delivery rate of 0.96×10^{-5} mol/s. Product analysis by ^{1}H NMR showed *trans*-1,2-dibromocyclohexane as the only product. Less than 1% tetrabromocyclohexane was detected.

Bromination of Cyclohexene in the Dark. The 25-mL round-bottom flask was charged with carbon tetrachloride (10 mL) and cyclohexene (0.200 mL, 19.7 mmol). Bromine (0.10 mL, 1.9 mmol) was added to the reservoir. The reservoir opening was closed and the time recorded. The bromine gas immediately colored the solution red ($\geq 10^{-3}$ M). Upon completion of bromine addition (3.8 min), the color faded to a pale yellow over the next 5 min ($\sim 10^{-4}$ M). The solution finally became colorless after 1 h. NMR analysis gave **6** (1.56 mmol) and **3** (0.278 mmol).

Product Identification. The molecular formulae were established from consistent proton and ^{13}C NMR spectroscopy and mass spectrometry. The bromine isotope composition in the mass spectrum confirms the number of bromine substituents. The stereochemistry of the products were based on proton coupling constants. The rings are conformationally fixed for all the following polybrominated olefins with the possible exception of **10** on the basis of the magnitude of the couplings.

(3*R,4*R**)-1,3,4-Tribromocyclohexene (8).** The connectivity of **8** was established by homonuclear COSY experiments and coupling constants (Table 6). The COSY experiments establish that the four protons in the aliphatic region are tightly coupled, consistent with vicinally related geminal pairs. The aliphatic resonance H5 and one of the resonances in the 2.60–2.68 region form one geminal pair, both showing crosspeaks with H4. Only the 2.4 Hz coupling of H4 to H3 can definitely be assigned. The assignment of the 3.7 Hz coupling of H4 to H5 explains the intense crosspeak in the COSY spectrum. H3 is coupled to the olefinic proton, H2, with 5.4 Hz coupling. The remaining two couplings of H3 are not readily assigned. But two of the three remaining small couplings of H2 can be assigned as long range allylic coupling to H6 and its geminal partner in the 2.55–2.73 region. The remaining 1 Hz coupling of H2 is probably to the equatorial resonance H4, as they are in a W-type orientation. This leaves H4 with one more coupling of 1.1 Hz which is assigned as a long range coupling to H6e. However, the W-orientation is not as well established in this case.

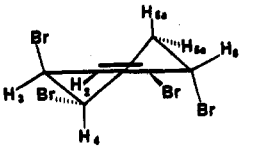
The stereochemistry of this tribromide is tentatively assigned on the basis of the couplings. H4 has already been assigned as equatorial on the basis of the small couplings to the adjacent methylene group. The other clearly resolved resonance H3 is also equatorial, on the basis of the large coupling to H2. This is in agreement with the small value of J_{34}. The relative stereochemistry of the two stereocenters is (R)-C3 and (R)-C4:



8

(3*R,4*S**,6*S**)-1,3,4,6-Tetrabromocyclohexene (11).** The olefinic proton H2 is coupled to H3 by 5.6 Hz (Table 6). One of the two remaining couplings of H3 (3.70 Hz) is to H4. The axial H4 is coupled to the geminal pair H5a and H5e by 12.37 and 2.81 Hz, respectively. The AB pair is further coupled to H6. The resonance's H3 and H6 also share a 1.8 Hz homoallylic coupling. The well-defined coupling constants allow for unambiguous assignment of stereochemistry. H3 is clearly pseudoequatorial on the basis of the large coupling to the olefin proton H2. If H3 was in the axial position, it would be nearly perpendicular to H2 and the coupling constant would be near zero. This assignment is also consistent with the observed 3.5 Hz coupling of H3 to H4. H4 is axial on the basis of the coupling to the geminal pair H5a and H5e with J_{45a} taking the axial–axial value of 12.4 Hz. Assignment of H6 as pseudoequatorial explains the observed coupling to the geminal pair. In the pseudoequatorial position, H6 does not bisect the dihedral angle of the geminal pair. Instead, the angle between H6 and H5a is decreased and that between H6 and H5e is increased. The deviations from the expected 3 Hz coupling are in accordance with the Karplus relationship.

The relative stereochemistry is assigned as (*R*)-C3, (*S*)-C4, (*S*)-C6:



11

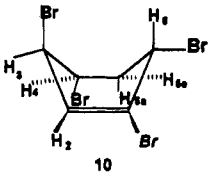
(3*R,4*R**,6*S**)-1,3,4,6-Tetrabromocyclohexene (10).** The olefinic proton H2 is coupled to H3 by 4.51 Hz. The resonance H3 is further coupled to H4 by 5.82 Hz. The 5.1 Hz couplings at H3 are the average of the 4.51 and 5.82 Hz couplings. The remaining two couplings of H4 are to the geminal pair H5a and H5e by 3.21 and 8.39 Hz, respectively. This AB pair is further coupled to H6. The connectivity is thus identical to **11**.

The assignment of the relative stereochemistry is not as straightforward. The ambiguity arises from the difficulty in the determination of the relative position of the geminal pair H5a and H5e. Assignment of H5e as equatorial satisfies the W-plane conformation necessary for the long range coupling to H3 and the upfield shift of H5e relative to H5a. However, H5e has a much larger coupling to H4 than does H5a. But, from the assignment of the stereochemistry of **11**, a 12 Hz coupling constant is expected if H5e and H4 are axially oriented. The apparent discrepancy can be resolved if it is assumed that H4 and H5e are equatorial and nearly eclipsed. The deviation from the expected half-chair conformation to the twisted half-boat can be explained if each of the bromine substituents at C-3, C-4, and C-6 is axially located in the half-chair conformation. At C-6 and C-3 the bromines would adopt pseudoaxial positions by virtue of their allylic location. A pseudoaxial conformation for the bromine at C-4 in the twist boat orients it perpendicular to the C3–Br bond. This reduces the unfavorable dipole–dipole interaction between the vicinal halogens.

Strong support for the twist half-boat conformation comes from the identical coupling of H5a and H5e to H6. This not only requires H6 to be pseudoequatorial but also implies that the C6–H bond bisects the dihedral angle between H5a and H5e. This is only possible if H5e and H5a deviate from their

respective equatorial and axial positions in the half-chair. The assignment of H3 as pseudoequatorial is consistent with the large coupling to the vinyl H2 hydrogen. The 5.4 Hz coupling to H4 suggests the pseudoequatorial arrangement of H3 and H4. The 8.5 Hz coupling between H4 and H5e conforms to an eclipsing geometry in the twist boat. The above analysis assumes that **10** is predominantly in a single conformer. We cannot unequivocally exclude the possibility that **10** is conformationally equilibrating. If it is equilibrating, the stereochemistry at C6 may be reversed.

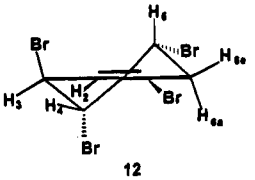
The relative stereochemistry is assigned as (*R*)-C3, (*R*)-C4, and (*S*)-C6:



10

(3*R,4*R**,5*R**)-1,3,4,5-Tetrabromocyclohexene (12).** The geminal protons H6e and H6a are an AB pair and are coupled to H5 by 6.1 and 10.2 Hz, respectively. H5 has a 2.4 Hz coupling constant that is common to H2 and H4. But the olefinic H2 is coupled to the adjacent H3 by 5.3 Hz. Therefore, H4 is next to H5. Furthermore, H4 is coupled to H3 by 2.4 Hz. Long range coupling is straightforward: H2 is coupled to the allylic protons H6e and H6a by 2.4 Hz and 1.2 Hz, respectively. Resonance H6e is further homoallylically coupled to H3.

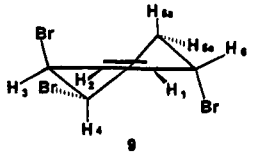
H5 is axially oriented, with respect to H6a. H4 has only small couplings, typical of an equatorial arrangement. The 5.2 Hz coupling of H2 to H3 requires H3 to also be equatorial. The relative stereochemistry is thus (*R*)-C3, (*R*)-C4, and (*R*)-C5:



12

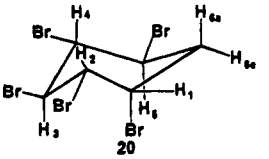
(3*R,4*S**,6*S**)-3,4,6-Tribromocyclohexene (9).** H5e and H5a are a geminal pair and share a 14.5 Hz coupling. H6 shares coupling constants of 5.7 and 2.9 Hz with H5e and H5a, respectively. The remaining coupling constant of 2.9 Hz can be traced to the olefinic proton H1. As is evident from the AB pattern, H1 is strongly coupled to H2. Assignment of the 10.0 Hz coupling leaves an unassigned coupling of 4.3 Hz for H2. H2 must be coupled to either H3 or H4. Although the coupling of 4.0 Hz for H3 is slightly lower than the 4.3 Hz for H2, the two must be coupled. If H2 were coupled to H4, H3 would be adjacent to the geminal pair. H2 does not share couplings with either hydrogen of the geminal pair. H4 then must be coupled to the geminal pair by 5.7 and 8.4 Hz and to H3 by about 4.0 Hz. These couplings can be found in the multiplet. There also exist at least two couplings of ~1 Hz.

H6 is assigned as pseudoequatorial on the basis of the 5.7 Hz coupling to the equatorial H5e and the small coupling to H1. In the pseudoaxial position, the C—H6 bond is nearly perpendicular to the C—H1 bond. The 4.3 Hz coupling constant shared between H2 and H3 then places H3 in the pseudoequatorial position. The remaining resonance H4 is axial by virtue of the large axial coupling to H5a. The relative stereochemistry of the three stereocenters is (*R*)-C3, (*S*)-C4, and (*S*)-C6:



9

1*r*,2*t*,3*c*,4*t*,5*t*-Pentabromocyclohexane (20). The ^1H spectrum had overlapping second-order signals. Therefore, chemical shifts and coupling constants were obtained from simulated spectra[34] (Table 5). The geminal pair H6a and H6e are coupled to H1 by 10.62 and 4.44 Hz, respectively. The connectivity around the ring can be traced back to the geminal pair through H2, H3, H4, and H5. As judged from the coupling constants, H5 is the only methine resonance which is equatorial. The relative stereochemistry is thus (*S*)-C1, (*R*)-C2, (*S*)-C4, and (*S*)-C5:



20

3,4,5,6-Tetrabromocyclohexene (13). The tetrabromide was not purified well enough to allow characterization. The only evidence for its presence is ^1H NMR spectra of crude mixtures. The broad peak at 5.93 ppm, the broad doublet at 4.95 ppm, and the broad peak at 4.73 ppm were assigned to the same compound. All three peaks yield the same integral area. The presence of two olefinic hydrogens suggests that this is **13**. This is in agreement with the low relative intensity in the aliphatic region (1.0–2.5 ppm). Since the ring flip is comparable to the NMR time scale, the orientation of the bromines about the ring must be 3-*r*, 4-*t*, 5-*t*, 6-*c* or 3-*r*, 4-*c*, 5-*t*, 6-*t*.

Sequential Bromination of 3. A 100-mL three-necked round-bottom flask was charged with CCl_4 (30 mL) and **3** (5.0 g, 0.031 mol). Bromination was done according to the procedure described for the consecutive allylic bromination of cyclohexene. The bromine reservoir was charged with 0.3 mL of bromine. The rate of bromine addition was approximately 7.0×10^{-7} mol/s. The reservoir was charged every 2 h with additional bromine. This required that the addition of bromine be interrupted momentarily. The solution in the round-bottom flask was also charged every 2 h with enough CCl_4 to maintain the volume at 30 mL. After 5 h, the reaction started to turn a pale yellow. Over the next 2 h, the solution gradually became red with bromine. At 8 h, the addition of bromine was halted but the reaction was continued. The intensity of the color persisted for the duration of the reaction. Samples (1.0 mL) were removed from the flask at the times listed below. Selected proton NMR spectra are shown in the supplementary material. ^{13}C NMR data were also utilized to identify the compounds present (shift in ppm, intensity). 1 h: (19.0, 150), (25.1, 141), (28.2, 63), (33.2, 145), (46.3, 44), (49.5, 95), (129.4, 114), (130.8, 49) and (131.6, 116). 2 h: (19.0, 107), (22.0, 36), (25.1, 114), (25.6, 33), (28.2, 21), (28.2, 174), (31.8, 28), (33.2, 110), (45.3, 23), (46.3, 136), (49.1, 24), (49.5, 77), (51.4, 30), (125.0, 34), (129.4, 89), (130.8, 144), (131.1, 35), (131.6, 92), and (131.8, 24). 3 h: (19.0, 28), (22.0, 70), (25.1, 30), (25.6, 69), (28.2, 377), (31.8, 58), (33.2, 25), (37.6, 26), (45.3, 49), (46.3, 300), (46.5, 19), (48.6, 17), (49.2, 67), (51.5, 53), (54.2, 17), (111.4, 18), (112.8, 16), (125.0, 46), (129.4, 25), (130.8, 338), (131.1, 67), (131.6, 30) and (131.8, 58). 4 h: (22.0, 34), (25.6, 31), (27.4, 31), (28.2, 205), (31.8, 37), (31.9, 31), (38.0, 28), (42.4, 30), (45.3, 28), (46.3, 175), (47.2, 24), (48.6, 25), (49.1, 28), (49.2, 34), (49.7, 30), (51.5, 34), (125.0, 31), (126.3, 28), (127.5, 29), (130.8, 158), (131.1, 29), (131.7, 26) and (131.8, 39). 5 h: (27.4, 54), (28.2, 65), (31.9, 53), (33.7, 18), (37.5, 22), (38.0, 46), (42.4, 58), (46.3, 47), (47.2, 50), (48.6, 45), (49.1, 51), (49.7, 52), (124.9, 17), (126.3, 38), (127.5, 51), (127.7, 20), (129.6, 18), (130.8, 48), and (131.7, 54). 6 h: (27.4, 54), (31.9, 63), (37.5, 25), (38.0, 78), (38.8, 18), (41.5, 37), (41.8, 21), (42.4, 56), (46.2, 20), (47.2, 74), (48.0, 39), (48.6, 15), (49.0, 60), (49.0,26), (49.1, 58), (49.6, 34), (49.7, 68), (52.4, 22),(54.2, 19), (126.3, 52), (127.4, 19), (127.5, 65), (127.7, 27), (129.6, 23), (129.6, 19), (129.7, 28), (131.6, 39) and (131.7, 65). 7 h: (32.0, 24), (37.5, 32), (38.0, 30), (39.8, 19), (41.5, 67), (42.1, 30), (42.4, 30), (42.4, 30), (47.3, 51), (48.0, 55), (48.1, 29), (48.7, 20), (49.0, 58), (49.1, 21), (49.6, 54), (49.7, 54), (50.5, 21), (52.4, 27), (54.2, 23), (55.4, 65), (55.4, 19), (123.0, 19), (124.2, 20), (126.1, 22), (126.3, 26), (126.7, 23),

(127.5, 27), (131.6, 50) (131.7, 29) and (136.8, 37). 8 h: (37.5, 25), (42.2, 44), (42.9, 22), (48.1, 18), (50.3, 18), (50.4, 22), (50.4, 22), (50.4, 37), (54.2, 26), (55.3, 69), (57.4, 16), (126.1, 17), (130.7, 30), (136.5, 18) and (136.8, 41).

Photolytic Bromination of *trans* 5. In a 25-mL round-bottom flask *trans*-**5** (0.50 g, 2.1 mmol) was dissolved in CCl_4 (4 mL). Bromine (0.10 mL, 2.0 mmol) was added via syringe. The addition of bromine to the solution was complete within a couple of seconds. The solution was irradiated with a 250-W tungsten filament bulb placed approximately 1 in. from the side of the flask. The solution became colorless within 3 min. A solid, identified as **7** by NMR, precipitated from the solution (0.41 g). The solid was redissolved in the product solution and NMR analysis performed. Three products were found: **7**, **21**, and **8**, integrated ratio 40:9.0:1.0, respectively. The proton resonance of 7 had to be corrected for overlap of one of the resonances of **21**.

Photolytic Bromination of *cis*-5. In a 25-mL round-bottom flask *cis*-**5** (0.50 g, 2.1 mmol) was dissolved in CCl_4. Bromine (0.10 mL, 2.0 mmol) was added via syringe. The addition of bromine to the solution was complete within a couple of seconds. The solution was irradiated with a 250-W tungsten filament bulb placed approximately 1 in. from the side of the flask. The solution became colorless within 45 s. NMR analysis was performed on the solution (no workup). Three products were found: **7**, **21**, and **8**, integrated ratio 9.2: 9.8:1.0, respectively.

(3*R,4R*)-1,3,4-Tribromocyclohexene (8).** NBS (0.19 g, 1.1 mmol) was added to a mixture of **5** (0.26 g, 1.1 mmol) in CCl_4 (4 mL). The mixture was kept at reflux for 1 h, at which time the NBS that had been converted to NHS quantitatively was removed via filtration. TLC (pentane) revealed the presence of a least five compounds. Rotary evaporation gave a dark oil. Flash chromatography (hexane) gave a tan oil (0.052g) as the second component. The major constituent (>90%) of the oil was identified as **8**. Tribromide **8** was further purified by repeating the chromatography procedure.

(3*R,4S*,6S*)-3,4,6-Tribromocyclohexene (9).** **9** was prepared by reacting **3** (0.35 mL) in CCl_4 (10 mL) with gaseous bromine. The methodology employed was identical to the consecutive bromination of cyclohexene described above. Addition of bromine to the solution of **3** was stopped as soon as the solution became yellow with bromine. TLC (40:1 pentane: ethyl ether) revealed that at least six compounds were present including **8** (R_f 0.44) and **5** (R_f 0.40). Rotary evaporation gave a dark oil (0.45 g) which was dissolved in hexane (5 mL). The dibromide **5** was removed by repeated cooling of the solution in an ice bath and removal of the solvent from the precipitate until a spot was no longer observed for **5**.

The remaining oil was separated by flash chromatography on a 4.5 cm diameter column (28 cm, 60–120 mesh silica gel) with eluent 45:1 hexane:ethyl ether. A second flash chromatography on a 3.0 cm diameter column (36 cm, 60–120 mesh silica gel) and elution with 45:1 hexane:ethyl ether (~30 mL/min) gave **9**.

Tetrabromocyclohexenes (10–13). A 250 mL flask was charged with CCl_4 (100 mL), 5 (5.00 g, 20.8 mmol), and NBS (7.81 g, 43.9 mmol). The mixture was kept at reflux for 1 h, at which time the NBS had been converted quantitatively to NHS which was removed via filtration. TLC (30:1 pentane: ethyl ether) revealed nine spots (R_f values of 0.69, 0.62, 0.56, 0.50, 0.45, 0.39, 0.33, 0.16, and 0.06). Rotary evaporation at room temperature resulted in a tan oil. The oil was subjected to repeated flash chromatography on a 4.5 cm diameter column (29 cm, 60–120 mesh silica gel) with eluant hexane (~60 mL/min). **(3*R**,4*R**,6*R**)-1,3,4,5-Tetrabromocyclohexene (12)** (R_f 0.62) was isolated as an oil. The geometric isomers **10** and **11** were isolated together (R_f 0.39). Upon addition of deuterated chloroform, **11** precipitated from solution. The isomers were cleanly separated by fractional crystallization from deuterated chloroform. Anal. Calcd: C, 18.12; H, 1.52; Br, 80.36. Found: C, 18.35; H, 1.51.

After the fractional crystallization of **11**, **10** was isolated as an oil by via rotary evaporation.

At least one other tetrabromide was present (R_f 0.45, 0.50, and 0.56). Due to the closeness of the R_f values and the small amount of material, the tetrabromide was not isolated pure enough to characterize. Pentabromocyclohexenes are likely responsible for the remaining spots with R_f values of 0.45, 0.50, and 0.56. Again isolation of the compounds was not feasible. The only identification is from ^1H NMR of crude samples. But the spectra were too ill defined to establish the molecular formula of the compounds much less the stereochemistry.

1*r*,2*t*,3*c*,4*t*,5*t*-Pentabromocyclohexane (20) (R_f 0.33) was also isolated from the product mixture. The compound crystallized from the combined fractions of the original separation. The solid was further purified by repeated crystallization from chloroform. Anal. Calcd: C, 15.05; H, 1.48; Br, 83.41. Found: C, 15.17; H, 1.52; Br, 83.40.

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Supplementary Material Available: The proton NMR spectra of **7–12** and **20–22** are shown. The spectra from which the data in Tables 3 and 4 were obtained are shown. CI mass spectra of **8–12** are included (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.