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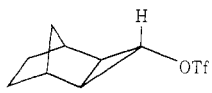

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Substituent, Reagent, and Solvent Effects on the Steric Course of Additions Initiated by Electrophilic Bromine to 3-Bromocyclohexene. A Comparison with the Stereoselectivity of Epoxidation and the Regioselectivity of Ring Opening of Epoxides

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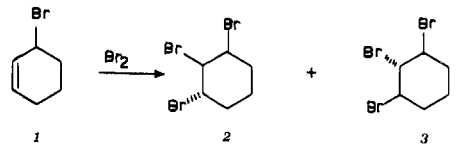
The steric course of the addition of bromine, pyridine perbromide, and acetyl hypobromite to 3-bromocyclohexene in several low polarity nonprotic solvents has been investigated. The bromination always produces nonequilibrium mixtures of two 1,2,3-tribromocyclohexanes resulting from anti addition, in ratios which are markedly affected by the solvent. The addition of pyridine perbromide gives, besides the same tribromo derivatives, a bromo–pyridinium adduct arising from electrophilic attack by bromine anti to the allylic substituent followed by nucleophilic attack by pyridine at C_1. The addition of acetyl hypobromite affords three isomeric anti bromo–acetate adducts, whose distribution is almost solvent independent. The comparison of the stereo- and regioselectivity of the last addition reaction with those of the epoxidation of 3-bromocyclohexene and of the hydrogen bromide opening of its cis and trans epoxides shows a stringent analogy. In both cases the electrophilic attack occurs preferentially (80–90%) anti to the allylic bromine atom; moreover, both the nucleophilic attack by bromide on the protonated epoxides and that by acetate on the epibromonium ions, which are assumed as intermediates for the addition reaction, occur exclusively or with very high preference at the ring carbon which is farther from the substituent. The steric course of the addition of bromine in the presence of bases (like pyridine or ethyl ether) is rationalized on the basis of a ionic two-stage mechanism involving product control by steric, electronic, and conformational factors during the nucleophilic rather than the electrophilic step.

The steric course of halogen additions to 3-substituted cyclohexenes has been shown to markedly depend both on the reagent and solvent employed and on the nature of the allylic substituent.[1-3] Whereas alkyl groups exert mainly a steric effect in both the electrophilic and nucleophilic step of the additions, a polar substituent may also affect the stereo- and regioselectivity in several additional ways. For instance, the product distribution found in the bromination of some 2-cyclohexen-1-ol derivatives has been interpreted[3] on the basis of a syn directive effect of a hydroxy (or methoxy) group, operating in the electrophilic step, in conjunction with an inductive effect, operating in the nucleophilic one. As a part of a research program concerning the stereochemistry and the mechanism of electrophilic additions to alkenes, we extended our investigation to 3-halogenocyclohexenes, starting with the bromo derivative **1**.

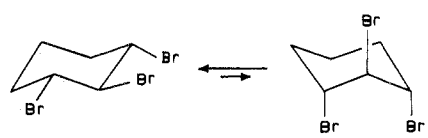
Results

Addition of Bromine. The addition of bromine to 3-bromocyclohexene (1) in chloroform at 0° gave a mixture of two diastereoisomeric tribromocyclohexanes (2 and 3), which was separated by column chromatography into a liquid and a solid component.



1 2 3

The relative configurations of tribromides 2 and 3 had already been attributed by chemical methods[4] and that of 3 also by electron diffraction.[5] They were confirmed in this work on the basis of NMR spectra and equilibration experiments. Although the two diastereoisomeric adducts could not be identified through their 60-MHz NMR spectra run in CCl_4, $CDCl_3$, CD_3COCD_3 and Me_2SO-d_6 owing to overlap of the signals relative to the α protons, which appeared in every case as unresolved and rather narrow multiplets, their identification was easily made in C_6D_6. In the latter solvent the signals of the protons α to halogens were still overlapping and narrow for the liquid compound, but became much broader and showed considerable fine structure for the solid one, which was therefore regarded as diastereoisomer 3 in its triequatorial conformation. This conclusion was confirmed by the 100-MHz spectrum of 3 in C_6D_6, which showed for H(2) a distorted triplet with J = 10 Hz and for the two chemically equivalent protons H(1) and H(3) a rough doublet of triplets (W = 25.4 Hz). Since a value of 10.4 Hz has been given[6] for the coupling constant between two vicinal protons α to equatorial bromine atoms in rigid *trans*-1,2-dibromocyclohexanes, the value of $J_{1,2}$ is consistent with a strong preference for conformation **3e** over **3a.** This shows that, at least in benzene as the solvent,



3e 3a

a bromine–bromine 1,3-diaxial repulsive interaction, present in the triaxial conformation **3a,** is much stronger than the gauche dipole–dipole repulsions between vicinal equatorial halogens present in conformation **3e.** An interaction of the latter type is responsible for the preferential diaxial conformation in *trans*-1,2-dihalogenocyclohexanes.[7] The conformational preference of 3 could not be evaluated in other solvents, such as $CDCl_3$, CCl_4, or Me_2SO-d_6, owing to extensive overlap of the signals of the α protons; however, the rather narrow shape of the multiplets would suggest a contribution by triaxial or twist conformations. It can be observed that the conformational population of 3 in the gas phase has been estimated by electron diffraction[5] to involve 19 ± 5% of triaxial conformer. However, benzene as the solvent has been found to stabilize the diequatorial (or gauche) conformers in a number of *trans*-1,2-dihalogenocyclohexanes[7d] and -cyclopentanes[8] and in open-chain dihalides.[9]

The trans relationship between two vicinal bromine atoms in each component of the diastereoisomeric couple 2–3 was also confirmed by their thermal interconversion through the well-known 1,2-interchange mechanism,[10–12] requiring anti-oriented halogen atoms. The equilibrium ratio at 150° between tribromides 2 and 3 was 87:13, in agreement with the expectedly lower stability of diastereoisomer 3 due to repulsive interactions between three equatorial bromine atoms. On the basis of the different reaction rates of 2 and 3 with sodium hydroxide Cornubert had reported[4] an equilibrium ratio of 95:5 after refluxing at 135° (12 mm).

The ratios between the dibromo adducts 2 and 3 obtained by addition of bromine to 3-bromocyclohexene in several solvents at 0° are reported in Table I.

Table I
Ratios between the Two Trans Diastereoisomeric Adducts Obtained by Addition of Bromine to 1

Solvent	Ratio 2:3	Solvent	Ratio 2:3
CH_2Cl_2	20:80	CCl_4	42:58
CH_2Cl_2[a]	23:77	CCl_4[a]	43:57
C_6H_6	28:72	Et_2O	67:33
$CHCl_3$	28:72	Et_2O[a]	69:31
$CHCl_3$[a]	28:72		

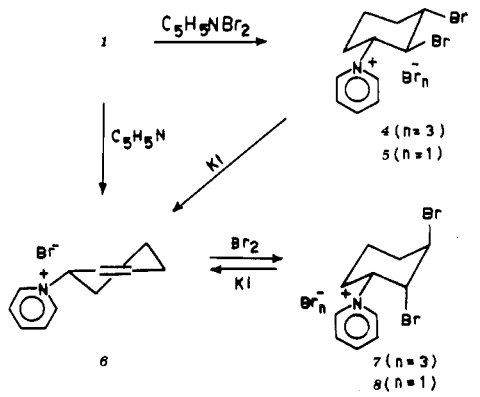
[a] Additions carried out in the presence of di-*tert*-butylcresol.

To avoid the formation of mixed adducts arising from nucleophilic attack by solvent, only low-polarity nonprotic solvents were employed. The product distributions were determined by GLC: only the peaks corresponding to the trans dibromo adducts 2 and 3 were detected in every case. Runs performed either in the absence or in the presence of di-*tert*-butylcresol, a typical free-radical inhibitor, gave very similar results, providing strong evidence against a free-radical addition mechanism. The data of Table I show that the product distribution was considerably affected by the solvent. A similar, although less marked, solvent effect had previously been observed[1] also in the bromination of 3-alkyl-substituted cyclohexenes.

Addition of Pyridine Perbromide. When a chloroform solution of 3-bromocyclohexene was stirred with a 100% molar excess of pyridine perbromide at 0°, a crystalline, red precipitate was slowly formed, besides a mixture of the dibromo adducts 2 and 3 in a 67:33 ratio (GLC). The yield of the red product increased and that of the dibromo adducts decreased when the reaction was carried out in pyridine as the solvent. However, the 2:3 ratio remained practically unchanged. Elemental analysis showed that the red crystals arose from the combination of one bromocyclohexene, one pyridine, and two bromine molecules. Stirring a suspension of the red adduct in chloroform with cyclohexene converted it into a white, crystalline product, *trans*-1,2-dibromocyclohexane being concurrently formed. Elemental analysis of the white adduct showed it to consist of one bromocyclohexene, one pyridine, and one bromine molecule. The presence of a pyridinium cation was inferred from the typical downfield NMR signals[13] in both the red and the white products. On the other hand, a bromide salt structure was suggested by the immediate precipitation of silver bromide on treatment of the latter adduct with silver nitrate solution. All these data indicated that the crystalline adduct was formed by addition of a bromine atom and a pyridine molecule to the double bond to give a pyridinium cation, whose counterion was a tribromide ion in the red compound and a bromide ion in the white one. Structures 4 and 5 were proposed for these adducts on the basis of the evidence outlined in Scheme I.

The pyridinium salt 6, obtained from 3-bromocyclohexene and pyridine, gave on bromination a different red adduct, which was regarded as isomer 7 and was transformed into the white salt 8 on treatment with cyclohexene. This demonstrated that the reaction of 1 with pyridine perbromide does not proceed through the formation of 6 as an

Scheme I



intermediate, but rather involves an electrophilic attack by bromine on the double bond of **1**, followed by a nucleophilic one by pyridine. The vicinal position as well as the trans relationship of the two bromine atoms in both **5** and **8** was shown by their conversion into **6** by heating with potassium iodide.

Configurations and conformations given in Scheme I were confirmed by the examination of the medium-field part of the 100-MHz NMR spectra of the bromo–pyridinium adducts, in which the signals of the cyclohexane protons α to the halogen atoms and to the pyridinium substituent could be sufficiently separated by a proper choice of the solvent (see Experimental Section). While the shapes and widths of these signals in **8** indicated one axial and two equatorial α protons, in **4** and **5** they were clearly consistent with three axial α protons. No evidence was found for the formation of any diastereoisomer of **4** in the reaction of **1** with pyridine perbromide both in chloroform and in pyridine: the ir and NMR spectra of the crude precipitates were identical with those of pure **4**. It is also to underline that the **2:3** ratio found in both reactions, which was the same in spite of the very different total yields of dibromo adducts, was quite different from that obtained with free bromine in chloroform but similar to that found in ethyl ether (Table I).

Addition of Acetyl Hypobromite. The treatment of a carbon tetrachloride solution of 3-bromocyclohexene with a ca. 0.1 *M* solution of acetyl hypobromite in the same solvent gave a complex mixture containing three isomeric acetate esters of dibromocyclohexanols besides very small amounts of the tribromo derivatives **2** and **3**. On heating with methanolic sulfuric acid the esters were cleanly converted into the corresponding dibromo alcohols, which were more easily analyzed by GLC. Three isomeric dibromocyclohexanols were detected. The major isomer was identified as **14** by comparison of its *p*-nitrobenzoate (**18**) with that of the minor product obtained from the bromination of cyclohex-2-en-1-ol.[3] The treatment of the same crude mixture of dibromocyclohexanols with sodium hydroxide in 2-propanol led to two isomeric 3-bromo-1,2-epoxycyclohexanes (**20** and **21**) in a 80:20 ratio. The cis con-

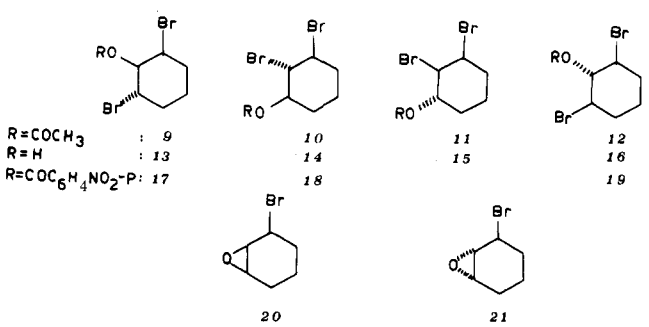


Table II
Product Distribution in the Addition of Acetyl Hypobromite to 3-Bromocyclohexene

Solvent	Products, % 9	10	11
CCl_4	4	77	19
CH_2Cl_2	8	75	17
Et_2O	6	75	19

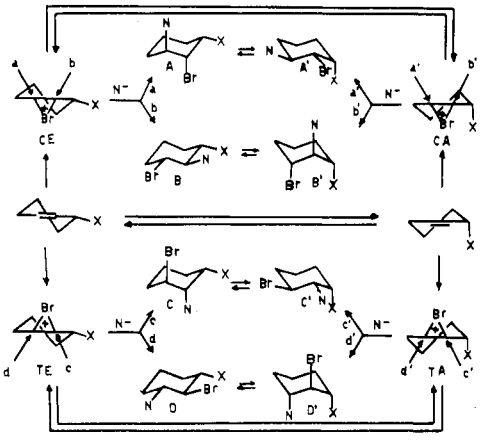
figuration **20** was assigned to the main product, which was separated by fractional distillation, since it should arise from the main dibromo alcohol **14**. On the other hand, epoxidation of 3-bromocyclohexene with *p*-nitroperoxybenzoic acid afforded a 10:90 mixture of the same epoxides **20** and **21**. Pure **21** was obtained by preparative GLC.

The opening of **20** with hydrogen bromide in chloroform afforded practically only one dibromocyclohexanol which was different from **14** and was therefore regarded as the alternative product of trans opening **13**. This was confirmed by the NMR spectrum of the *p*-nitrobenzoyl derivative **17**, which showed three medium-field signals, the one at lowest field, attributable to the hydrogen α to the *p*-nitrobenzoate group, appearing as a doublet of doublets due to coupling with two nonequivalent protons α to the bromine atoms. On the other hand, the opening of the trans epoxide **21** gave two products in a 97:3 ratio (GLC). The main product was easily identified as **16** since the NMR spectrum of its *p*-nitrobenzoyl derivative **19** showed for the hydrogen α to the *p*-nitrobenzoate group a triplet (J = 10 Hz) due to coupling of one axial proton with two chemically equivalent axial protons α to the bromine atoms. The minor product of opening of **21**, which was formed in too small amount to permit its isolation, was therefore regarded as the alternative product of trans ring opening, **15**. The comparison of the GLC retention times of all four dibromo alcohols **13–16** with those of the mixtures obtained by addition of acetyl hypobromite to 3-bromocyclohexene in different solvents followed by deacetylation permitted us to deduce that the above addition reactions gave compounds **9**, **10**, and **11** in the ratios reported in Table II, the fourth possible adduct, **12**, being not formed in appreciable amount.

Discussion

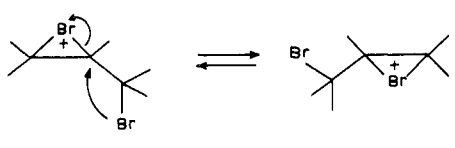
On the basis of the evidence reported above for the brominations and of literature reports about the addition of acetyl hypobromite[14] the usual two-step ionic mechanism[15] will be assumed for all additions under discussion. For the sake of simplicity the intermediates formed in the electrophilic step will be represented as epibromonium ions, as generally assumed for the bromination of nonconjugated alkenes, but it must be kept in mind that probably the distribution of positive charge on the three-membered ring is not symmetrical, owing to the presence of the adjacent electron-withdrawing halogen atom. Furthermore, ion pairing of the cationic intermediates (which in Scheme II are simply represented as free ions) with the anionic nucleophile is almost certainly involved in the nonpolar solvents employed. The alternative pathways leading from the two half-chair conformers of a 3-halogenocyclohexene to two pairs of conformationally isomeric bromonium ions (CE–CA and TE–TA) and to four pairs of adducts (A–A′, B–B′, C–C′, and D–D′) are represented in Scheme II (where X = Br). Paths a, b′, c, and d′ correspond to antiparallel attacks[16] by the nucleophile N^- and involve chair-like transition states, whereas paths a′, b, c′, and d consist in parallel attacks,[16] passing through boat-like transition states.

Scheme II



Owing to the symmetry of the reagent and to the conformational mobility of the alkene as well as of the resulting cis and trans epibromonium ions, the bromine addition (where N^- is Br^- or Br_3^-) is difficult to interpret, since four routes to each of the two diastereoisomeric trans dibromo adducts are available (a, a′, c, and c′ on one hand, b, b′, d, and d′ on the other). The situation is less complicated when N^- is an acetate anion. In this case only two routes are available for the formation of each of the four possible diastereoisomeric trans adducts, and, even if the conformational aspects of the reaction pathways cannot be unambiguously distinguished, the stereoselectivity of the electrophilic attack as well as the regioselectivity of the nucleophilic one can be directly inferred from the product distribution.

A further complication could be in the fact that halonium ions with a halogen in the 3 position (**22**) could rearrange to isomeric ions (**23**) through intramolecular electrophilic attack, as found, for instance, in some electrophilic additions to allyl halides.[17-20]



22 **23**

However, although it is not possible to verify the occurrence of such a rearrangement in the ionic intermediates formed in the additions initiated by electrophilic bromine to 3-bromocyclohexene, it is irrelevant for the present discussion, since in the trans ion it would just result in the conformational inversion TA ⇄ TE, whereas in the cis ion, in the very unlikely case that it were possible, it would simply cause the conversion to its enantiomer.

The data of Table III show a striking similarity between the electrophilic step of the addition of acetyl hypobromite in different solvents and the epoxidation of 3-bromocyclohexene, the allylic bromine atom exerting a remarkably strong anti directing effect in both reactions, which could be due to a number of electronic and steric effects which have been discussed in a previous paper.[3] This preference for anti attack is remarkably high, particularly in the epoxidation reaction, if compared for instance to the epoxidation of 3-methoxycyclohexene, where the syn/anti ratio is 37:63.[21] The known preference for pseudo-axial bromine in 3-bromocyclohexene[22] may be the cause for this anti stereoselectivity of the electrophilic attack.

Also the regioselectivity of the nucleophilic attack by the acetate anion on the intermediates TE–TA and CE–CA and that of the attack by bromide on the protonated forms

Table III
Stereoselectivity and Regioselectivity of the Addition of Acetyl Hypobromite Compared with Epoxidation and HBr Opening of the Epoxides from 3-Bromocyclohexene

Reagent (solvent)	Stereoselectivity of the electrophilic attack	Regioselectivity of the nucleophilic attack	
	syn/anti ratio	a(a′)/b(b′)	c(c′)/d(d′)
AcOBr (CCl_4)[a]	19:81	100:0	5:95
AcOBr (CH_2Cl_2)[a]	17:83	100:0	10:90
AcOBr (Et_2O)[a]	19:81	100:0	7:93
PNPBA ($CHCl_3$)[b]	10:90	100:0	3:97

[a] With reference to Scheme II, N^- being AcO^-. [b] With reference to Scheme II, Br being replaced by OH, N by Br.

of epoxides **21** and **20** are very similar (Table III), the ring opening occurring with high preference at C_1 through path d or d′ in the trans epibromonium ion and trans epoxide, and exclusively at C_1, presumably through the antiparallel path a, in the cis ion and cis epoxide. The observed regioselectivity, which is similar but even more marked than that found for the analogous reactions of 3-methoxy substituted compounds,[23,24] is consistent with a strong inductive effect of the electron-withdrawing substituent, which should decrease the rate of nucleophilic attack on the nearer epoxide or bromonium ring carbon, provided that bond breaking is more important than bond making. Moreover, also stereoelectronic and conformational factors favor the opening of the cis epibromonium ion and cis epoxide through path a, while steric and electrostatic repulsions between the attacking anion and the polarized halogen substituent can hinder the opening of the trans ion and trans epoxide via c in favor of paths d′ or d, especially if the attack is collinear with the direction of the breaking C–Br or C–O bond.[21] Such a geometric requirement has been assumed recently for the nucleophilic opening of epoxides.[25]

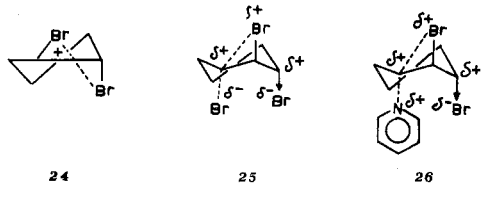
When compared with the strong solvent dependence of the addition of bromine to **1**, the absence of appreciable solvent effect in the addition of acetyl hypobromite is quite surprising. Perhaps it could be related to the different polarizability and capability of interaction with the solvent of the two electrophilic reagents. Anyway, previous work on additions to 3-substituted cyclohexenes initiated by electrophilic bromine[21,26] has shown that the changes in product distribution with changing reagent and solvent are mainly determined by a different stereoselectivity of the electrophilic step, the regioselectivity of the nucleophilic attack on the intermediate epibromonium ions being fairly constant in all conditions and similar to that of the hydrogen bromide opening of the corresponding epoxides. On this basis, if also the partition of the reaction intermediates CE–CA and TE–TA derived from 3-bromocyclohexene between the possible nucleophilic paths is assumed to be roughly constant and reagent and solvent independent, the changes in the ratios between tribromides **2** and **3** obtained in the various solvents (Table I) must be attributed to a different contribution of the two epibromonium ions. If one assumes for the cis ion an exclusive opening at C_1 and a mean value of 93:7 for the ratio of the opening at C_1 to that at C_2 in the trans ion (Table III), one can elaborate the data in Table I to give the following values for the ratio of syn to anti attack in the electrophilic step of the bromine addition in the various solvents: CH_2Cl_2, 14:86; $CHCl_3$ and C_6H_6, 23:77; CCl_4, 38:62; Et_2O, 65:35. Although these data must be taken as a rather crude approximation, they indicate a predominant contribution of TE–TA in all solvents,

except ethyl ether, in which the situation is practically reversed.

Since no reason can be seen for the preference for irreversible syn electrophilic attack in the latter solvent, the already proposed hypothesis[1] that in the presence of a basic solvent this step can be reversible seems therefore to be valid also in the present case. Under these conditions the product distribution would be determined mostly by steric, electronic, and conformational factors during the nucleophilic step. The inductive effect of the 3 substituent disfavors paths b, b′, c, and c′. On the other hand, path a involves a stereoelectronically favorable antiparallel attack leading to the product in its stable conformation A (Scheme II), while path d involves a stereoelectronically adverse parallel attack leading to the product in a twist conformation (which only subsequently passes to the stable form D) and path d′ an antiparallel attack leading to the product in its less stable triaxial conformation D′. Provided that the transition state of the nucleophilic attack is more similar to the products than to the epibromonium ions, as proposed for the attack on protonated epoxides,[27] path a should therefore be expected to be favored and **2** should be the main product. This is actually found in the bromination of 3-bromocyclohexene in ethyl ether.

The incorporation of pyridine in additions to alkenes initiated by electrophilic halogens has been previously observed with dipyridine bromine(I) perchlorate in dichloromethane[28] and with iodonium nitrate in chloroform–pyridine as the solvent.[29] In all cases the formation of halogeno–pyridinium salts has been related to the stability of the halonium or β-halogeno-α-carbenium ions formed in the electrophilic stage, those alkenes leading to more stable ionic intermediates favoring the attack by pyridine. It was also shown[29c] that an allylic hydroxy group causes an increase in the yield of pyridinium adducts with respect to the parent alkene in the reaction with iodonium nitrate in chloroform–pyridine. This was attributed to an increased stabilization of the intermediate iodonium ion by hydroxy group participation.

No pyridinium adducts are formed in the bromination of cyclohexene itself or its 3-alkyl derivatives with pyridine perbromide in chloroform,[1] and only when pyridine is used as the solvent[30] it successfully competes with the more nucleophilic[31] bromide ions for the nucleophilic attack. In contrast, appreciable amounts of pyridinium adducts are formed in the reaction of 3-bromocyclohexene with pyridine perbromide even in chloroform, when equal amounts of pyridine and bromine are present in the reaction medium. However, only the trans ion TE–TA appears to be susceptible to attack by the weaker nucleophile, since compound **4** is the only bromo–pyridinium adduct obtained. This would be consistent with the requirement of stabilization through neighboring group participation by the halogen, as shown in **24**, but would not explain the regiospecificity of the reaction, since nucleophilic attack occurs exclusively at C_1 whereas the positive charge would be stabilized on C_2. An alternative explanation of the ability of pyridine to compete with bromide ions in attacking the intermediate TA through path d′ when X is bromine could be found in the different interactions which develop in transition states **25** and **26**. Whereas the attack by a negatively charged nucleophile may be slowed down by electrostatic repulsions with the C–Br bond dipole in transition state **25**, the attack by a neutral nucleophile like pyridine in **26** could be facilitated, in spite of its lower nucleophilicity, by a favorable interaction between the partial negative charge on halogen and the incipient positive charge on nitrogen. An attractive interaction between vicinal iodo and pyridinium groups has been previously shown[29d] in iodoalkyl pyridinium salts.



24 25 26

As far as the tribromide distribution is concerned, the stringent similarity between the **2:3** ratio obtained with pyridine perbromide and with bromine in ethyl ether suggests that also with the former reagent the electrophilic step be reversible. In fact, since the dibromo adduct **3** as well as the bromo–pyridinium adduct **4** arise from the trans and the dibromo adduct **2** should arise mostly from the cis bromonium ion, an about 4:3 preference for CE–CA over TE–TA can be deduced (see Experimental Section) for the addition of pyridine perbromide to 3-bromocyclohexene in chloroform. Moreover, the **2:3** ratio does not change also when the addition is carried out in pyridine as the solvent, although in these conditions about 65% of the trans bromonium ion is substracted by reaction with the solvent to give **4**. The constancy in the **2:3** ratio obtained in the brominations performed in the above conditions rules out an irreversible formation of the bromonium ions and brings a further stringent evidence for the equilibration between intermediates CE–CA and TE–TA and for product control during the nucleophilic step.

In conclusion, the results reported in this paper confirm the great importance of the effect of an electronegative 3 substituent on the steric course of electrophilic additions to cyclohexenes as well as of the opening of the corresponding epoxides. Furthermore they are also consistent with the interpretation previously proposed[1,2] to explain the preferential formation of diaxial adducts in additions to 3-substituted cyclohexenes when bromine is coordinated by a basic atom, like nitrogen or oxygen.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were registered with a Jeol C-60 HL and a Jeol PS-100 spectrometer using Me_4Si as internal standard. GLC analyses of tribromides **2** and **3** and of dibromo alcohols **13–16** were performed on a Perkin-Elmer Model F11 instrument fitted with a 2-m glass column, 2.5 mm i.d., packed with 3% neopentyl glycol succinate on sylanized Chromosorb W 80–100 mesh (column 140°, evaporator 160°, detectors 160°, nitrogen flow 30 ml/min). The mixtures of epoxides **20** and **21** were analyzed with a C. Erba Fractovap Model G.V. gas chromatograph, equipped with a 1.5-m glass column, 2 mm i.d., packed with 15% Carbowax 20M on sylanized Chromosorb W 80–100 mesh (column 80°, evaporator 130°, detectors 150°, nitrogen flow 30 ml/min). The preparative separation of **20** and **21** was achieved with a Perkin-Elmer F21 instrument fitted with a 2-m column, 8 mm i.d., packed with 5% OV 17 on sylanized Chromosorb G 60–80 mesh (column 110°, evaporator 150°, nitrogen flow 250 ml/min). $MgSO_4$ was always used as the drying agent. Evaporations were made in vacuo (rotating evaporator) at 30°. Petroleum ether refers to the fraction of boiling range 40–60°.

Starting Materials. 3-Bromocyclohexene was obtained from cyclohexene and *N*-bromosuccinimide.[32] Bromine was purified by refluxing with $CaBr_2$ and distillation. Pyridine perbromide was prepared immediately before use from bromine and dry pyridine in carbon tetrachloride.[33] Dichloromethane was refluxed over P_2O_5 and rectified. Chloroform was purified by washing with 2 *N* NaOH, concentrated H_2SO_4, and water, drying with K_2CO_3, and distillation and was immediately used. Carbon tetrachloride was Rudi Pont spectroanalyzed reagent grade. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled. Ethyl ether was freed from peroxides by washing with a solution of ferrous sulfate.

1,*c*-2,*t*-3-Tribromocyclohexane (2) and 1,*t*-2,*c*-3-Tribromocyclohexane (3). A solution of bromine (1.9 g, 0.012 mol) in $CHCl_3$ (5 ml) was added dropwise with stirring to a solution of 1

(1.6 g, 0.01 mol) in the same solvent (5 ml) at 0°. After 10 min the reaction mixture was diluted with $CHCl_3$ (10 ml), washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated to give a viscous oil (3.0 g). Chromatography of this oil on a neutral silica gel column with petroleum ether as the eluent gave pure **2**, oil: $n^{17}D$ 1.5990; NMR (60 MHz) in $CDCl_3$ δ 4.47–4.90 (–CHBr–, 3 overlapping m, 3 H), in C_6D_6 δ 4.25–4.65 ppm (–CHBr–, 3 overlapping m, 3 H).

Anal. Calcd for $C_6H_9Br_3$: C, 22.46; H, 2.83; Br, 74.71. Found: C, 22.34; H, 2.81; Br, 74.80.

Further elution with petroleum ether gave mixtures of **2** and **3** and then pure **3**: mp 50–51° (from petroleum ether) (lit.[4] mp 51°); NMR (60 MHz) in $CDCl_3$ δ 4.21 (–CHBr–, 2 overlapping m, $W_{1/4}$ = 13 Hz, 3 H), in CCl_4 δ 4.17 ($W_{1/4}$ = 12.7 Hz), in Me_2SO-d_6 δ 4.42 ($W_{1/4}$ = 12.7 Hz), in acetone-d_6 δ 4.34 ppm ($W_{1/4}$ = 13.5 Hz).

Thermal Equilibrations of 2 and 3. Samples of each pure diastereoisomer (0.01 g) were sealed in Pyrex tubes and heated into a thermostatted bath at 150 ± 2°. Samples were withdrawn at intervals, cooled, and analyzed by GLC. The results are summarized in Table IV.

Table IV
Equilibration of 2–3

Time, min	Ratio 2:3	Time, min	Ratio 2:3
0	0:100	960	87:13
10	9:91	0	100:0
20	18.5:81.5	360	87.5:12.5
31	25:75	900	87:13
360	82.5:17.5		

Bromination of 1 in Different Solvents. Stirred solutions of 1 mmol of 1 in 3 ml of the appropriate solvent at 0° were treated dropwise with a 20% excess of 1 *M* solutions of Br_2 in the same solvent. For the bromination in ethyl ether a solution of Br_2 in a different solvent (CCl_4) was employed. After the additions were complete, the reaction mixtures were left at room temperature for 15 min, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. For each solvent a reaction in the presence of di-*tert*-butylcresol (10 mg) was also carried out with the same procedure. The reaction mixtures were directly analyzed by GLC. The relative retention times of the tribromo derivatives **2** and **3** were 1:2. The average values listed in Table I were obtained from at least four reactions and were reproducible within ±2%.

Additions of $C_5H_5NBr_2$ to 1. A. In $CHCl_3$. A solution of 1 (3.2 g, 0.02 mol) in $CHCl_3$ (60 ml) was cooled at 0° and treated with freshly prepared $C_5H_5NBr_2$ (9.6 g, 0.04 mol). The mixture was stirred at 0° for 30 min, in which time a red precipitate of **4** was formed, and left overnight at −20°. The red salt **4** was collected (1.5 g, 13% yield): NMR (100 MHz) in C_5D_5N δ 4.66 (–CHBr–, m, W = 26.7 Hz, 1 H), 5.41 (–CHBr–, t, $J \simeq$ 10.5 Hz, 1 H), 5.70 (–$CHN^+C_5H_5$, m, W = 26.5 Hz, 1 H), 8.44, 8.80, 9.79 ppm (–$N^+C_5H_5$, 3 m, 5 H). The mother liquors were diluted with petroleum ether and cooled at −20°. After several hours a second crop consisting of unreacted $C_5H_5NBr_2$ (1.5 g) was collected. The mother liquors were then washed with 10% aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated to give a mixture of **2** and **3** (4.7 g, 73% yield) in a ratio of 67:33 (GLC). A sample of **4** crystallized twice from acetic acid had mp 170–172°, and ir and NMR spectra identical with those of the crude product.

Anal. Calcd for $C_{11}H_{14}Br_5N$: C, 23.60; H, 2.52; Br, 71.37. Found: C, 23.98; H, 2.35; Br, 69.90.

Another sample of **4** (1.0 g) was suspended in $CHCl_3$ (5 ml), cyclohexene (2 ml) was added, and the mixture was stirred for 30 min. During this time the red color disappeared and a white, crystalline solid consisting of **5** remained (0.7 g): NMR (100 MHz) in CF_3CO_2H δ 4.35 (–CHBr–, m, W = 24 Hz, 1 H), 4.68 (–CHBr–, t, J = 10 Hz, 1 H), 4.98 (–$CHN^+C_5H_5$, m, W = 26 Hz, 1 H), 8.10, 8.57, 8.95 ppm (–$N^+C_5H_5$, 3 m, 5 H). After crystallization from methanol–benzene **5** had mp 209–210° and ir and NMR spectra identical with those of the crude product.

Anal. Calcd for $C_{11}H_{14}Br_3N$: C, 33.03; H, 3.53; Br, 59.93. Found: C, 32.98; H, 3.51; Br, 59.67.

GLC analysis of the chloroformic solution from which crude **5** was collected showed the presence of *trans*-1,2-dibromocyclohexane.

B. In C_5H_5N. 3-Bromocyclohexene (1.0 g, 6.2 mmol) was dissolved with cooling in dry pyridine (3 ml) and immediately added to a solution of $C_5H_5NBr_2$ (3.0 g, 12.4 mmol) in pyridine (3 ml) cooled at 0°. The mixture was stirred at 0° for 30 min, left overnight at −20°, and then diluted with $CHCl_3$ (50 ml). After storing at −20° for several hours a red precipitate of **4** (2.25 g, 65% yield) was collected, having ir and NMR spectra identical with those of the red product obtained in A. Further dilution did not cause any precipitation. The light yellow mother liquors were washed with 10% aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated to give a mixture of **2** and **3** (0.24 g, 12% yield) in a 66:34 ratio (GLC). Stirring of **4** with cyclohexene in $CHCl_3$ quantitatively converted it into **5**, having ir and NMR spectra identical with those of the white product obtained with procedure A.

Bromination of 6. Equimolar amounts of **1** and dry pyridine were mixed and left at 0° overnight, during which time a low melting, hygroscopic product (**6**) was formed. A sample of this product was dissolved in ethanol and treated with an equimolar amount of sodium tetraphenylboron. The white precipitate was collected and crystallized from ethanol to give pure *N*-cyclohex-2-enyl pyridinium tetraphenylboron, mp 159–160°.

Anal. Calcd for $C_{35}H_{34}BN$: C, 87.67; H, 7.15; N, 2.92. Found: C, 87.54; H, 6.96; N, 2.75.

Another sample of **6** (0.24 g, 1 mmol) was suspended in $CHCl_3$ (5 ml) and treated at 0° with a 1 *M* chloroform solution of bromine (2 ml). The mixture was stirred for 30 min, during which time a red, crystalline solid consisting of **7** (0.5 g) was formed. After two crystallizations from acetic acid **7** had mp 138–140°.

Anal. Calcd for $C_{11}H_{14}Br_5N$: C, 23.60; H, 2.52; Br, 71.37. Found: C, 23.48; H, 2.50; Br, 71.83.

A suspension of **7** (0.5 g) in $CHCl_3$ (5 ml) containing cyclohexene (1 ml) was stirred for 2 hr and then filtered off. The white product **8** so obtained (0.3 g) crystallized from methanol–benzene had mp 169–170°, NMR (100 MHz) in CF_3CO_2H δ 4.96 (–CHBr–, 2 overlapping m, $W_{1/4}$ = 7.7 Hz, 2 H), 5.74 (–$CHN^+C_5H_5$, d of m, J = 11.5 Hz, 1 H), 8.14, 8.74, 8.97 ppm (–$N^+C_5H_5$, 3 m, 5 H).

Anal. Calcd for $C_{11}H_{14}Br_3N$: C, 33.03; H, 3.53; Br, 59.93. Found: C, 32.97; H, 3.51; Br, 60.12.

Debromination of 5 and 8. A. A mixture of **5** (0.2 g) and potassium iodide (0.2 g) in ethanol (2 ml) was sealed in a Pyrex tube, heated at 100° for 48 hr, and then evaporated. The residue, dissolved in water and treated with an excess of aqueous solution of sodium tetraphenylboron, gave a white precipitate which was collected, washed with water, and crystallized from methanol to yield *N*-cyclohex-2-enyl pyridinium tetraphenylboron, with ir and NMR spectra identical with those of the product previously obtained from 3-bromocyclohexene, pyridine, and sodium tetraphenylboron.

B. A mixture of **8** (0.2 g) and potassium iodide (0.2 g) in ethanol (2 ml) was heated at 100° in a sealed tube for 30 hr. After the treatment described under A, *N*-cyclohex-2-enyl pyridinium tetraphenylboron was obtained.

***trans*-3-Bromo-1,2-epoxycyclohexane (21).** *p*-Nitroperoxybenzoic acid (2.2 g, 0.012 mol) was added to a solution of **1** (1.6 g, 0.01 mol) in $CHCl_3$ (30 ml) and the mixture was left at 0–5° for 3 days. *p*-Nitrobenzoic acid was then filtered off and the solution was washed with 3% aqueous Na_2CO_3 and water, dried, and evaporated to give a liquid residue (1.0 g) consisting of epoxides **20** and **21** in a ratio of 10:90 (GLC, relative retention times 2.55:1). The main component **21** was separated by preparative GLC: NMR (60 MHz) in CCl_4 δ 3.24 and 3.33 (epoxy H, 2 overlapping m, 2 H), 4.50 ppm (–CHBr–, m, $W_{1/2}$ = 10.5 Hz, 1 H).

Anal. Calcd for C_6H_9BrO: C, 40.70; H, 5.12; Br, 45.13. Found: C, 40.53; H, 5.15; Br, 45.03.

***cis*-3-Bromo-1,2-epoxycyclohexane (20).** A 0.1 *M* carbon tetrachloride solution of acetyl hypobromite[34] (300 ml) was added dropwise at 0° to a solution of **1** (4.0 g, 0.025 mol) in the same solvent (40 ml). After the addition was complete, the solution was stirred at 0° for 1 hr and left for another 1 hr at room temperature, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The residue (6.3 g), whose ir spectrum showed a strong carbonyl band at 5.75 μ, was dissolved in 2.5% methanolic sulfuric acid, refluxed for 2.5 hr, and then poured into water and extracted with petroleum ether. The extracts, washed with water, dried, and evaporated, gave an oily residue (4.6 g) the ir spectrum of which did not show the carbonyl band but showed a strong hydroxyl band near 3 μ. This oil was dissolved in 2-propanol (50 ml) and titrated with 1 *N* aqueous NaOH at room temperature, with phenolphthalein as indicator. The consumption of base was slow and amounted to 17 ml (theoretical 18 ml). The mixture was then diluted with water and extracted with petroleum ether. The ex-

tracts, washed with water, dried, and evaporated, yielded a mixture of epoxides **20** and **21** (2.8 g) in a ratio of 80:20 (GLC), which was distilled to give the following fractions: I (0.4 g), bp 102–104° (20 mm), **20:21** ratio 56:44; II (0.6 g), bp 104–108° (20 mm), **20:21** ratio 72:28; III (1.1 g), bp 108–120° (20 mm), **20:21** ratio 91:9; IV (0.4 g), bp 120° (20 mm), pure **20**, NMR (60 MHz) in CCl_4 δ 3.3 (epoxy H, 2 overlapping m, $W_{1/2}$ = 4 Hz, 2 H), 4.37 ppm (–CHBr–, m, $W_{1/2}$ = 17 Hz, 1 H).

Anal. Calcd for C_6H_9BrO: C, 40.70; H, 5.12; Br, 45.13. Found: C, 40.56; H, 5.18; Br, 45.06.

Opening of 21 with HBr. Dry HBr was bubbled for 5 min into a solution of **21** (0.5 g) in $CHCl_3$ (15 ml) at room temperature. The reaction mixture was then washed with water and 3% aqueous $NaHCO_3$, dried, and evaporated to give a solid residue (0.65 g) consisting of **16** and **15** in a ratio of 97:3 (GLC, relative retention times 1:1.3). Crystallization from petroleum ether gave pure **16**, mp 95.5–96.5°, NMR (60 MHz) in $CDCl_3$ δ 3.8 ppm (–CHBr– and –CHOH–, 2 overlapping m, $W_{1/4}$ = 19.5 Hz, 3 H).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.93; H, 3.91. Found: C, 28.13; H, 4.13.

A sample of **16** (0.1 g) was dissolved in dry pyridine (2 ml) and treated with *p*-nitrobenzoyl chloride (0.1 g). After several hours the reaction mixture was diluted with $CHCl_3$, washed with 10% aqueous H_2SO_4 and water, dried, and evaporated to give the *p*-nitrobenzoate **19** which, after crystallization from methanol, had mp 202–204°, NMR (60 MHz) in $CDCl_3$ δ 4.05 (–CHBr–, m, W = 26.5 Hz, 2 equivalent H), 5.55 (–CHO–, t, J = 10.1 Hz, 1 H), 8.37 ppm ($-C_6H_4NO_2$, s, 4 H).

Anal. Calcd for $C_{13}H_{13}Br_2NO_4$: C, 38.35; H, 3.22; N, 3.44. Found: C, 38.58; H, 3.21; N, 3.51.

Opening of 20 with HBr. The opening of **20** under the same conditions described for the isomer **21** gave pure **13** (GLC) as an oil. Treatment with *p*-nitrobenzoyl chloride as reported above afforded the *p*-nitrobenzoate **17**, mp 103–105° (from ethanol), NMR (100 MHz) in $CDCl_3$ δ 4.60 (–CHBr–, m, $W_{1/4}$ = 24 Hz, 1 H), 4.90 (–CHBr–, m, $W_{1/4}$ = 16 Hz, 1 H), 5.25 (–CHO–, d of d, J = 3.15 and 8.60 Hz, 1 H), 8.37 ppm ($-C_6H_4-NO_2$, s, 4 H).

Anal. Calcd for $C_{13}H_{13}Br_2NO_4$: C, 38.35; H, 3.22; N, 3.44. Found: C, 38.53; H, 3.14; N, 3.36.

Additions of Acetyl Hypobromite to 1. A 10% excess of a 0.1 *M* solution of acetyl hypobromite in carbon tetrachloride[34] was added dropwise to a stirred solution of **1** (2.5 mmol) in the appropriate solvent (10 ml) at 0°. After the addition was complete the reaction mixture was left for 15 min at 0° and then poured into saturated aqueous $NaHSO_3$. The organic layer was washed with water, dried, and evaporated and the residue was dissolved into 1.5% methanolic sulfuric acid (20 ml), refluxed for 2.5 hr, and then diluted with water and repeatedly extracted with petroleum ether. The extracts, washed with water, dried, and evaporated, gave mixtures of **13**, **14**, and **15** accompanied by traces of tribromides **2** and **3**, which were analyzed by GLC. The dibromo alcohols **13**, **14**, and **15** were identified by comparison of their retention times with those of authentic samples. Furthermore, the treatment of one of these mixtures (0.5 g) with *p*-nitrobenzoyl chloride (0.5 g) in dry pyridine (10 ml) gave, after crystallization of the crude product from ethanol, pure **18** (0.3 g), mp 108–110° (lit.[3] mp 103–105°).

The percentages of the addition products **9**, **10**, and **11**, assumed to be equal to those of **13**, **14**, and **15**, are reported in Table II and were reproducible within ±2%. Equal product distributions were found in the addition performed in ethyl ether by increasing the volume of solvent to 25 ml. Control experiments with mixtures of **13**, **14**, and **15** showed that their composition remained unchanged after treatment with methanolic sulfuric acid under the above conditions.

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Registry No.—**1**, 1521-51-3; **2**, 56391-30-1; **3**, 56391-31-2; **4**, 56391-33-4; **5**, 56421-01-3; **6**, 56391-34-5; **7**, 56452-60-9; **8**, 56421-02-4; **13**, 56391-35-6; **14**, 56421-03-5; **15**, 56421-04-6; **16**, 56391-36-7; **17**, 56391-37-8; **19**, 56391-38-9; **20**, 56421-05-7; **21**, 56421-06-8; bromine, 7726-95-6; $C_5H_5NBr_2$, 17691-27-9; *p*-nitroperoxybenzoic acid, 943-39-5; acetyl hypobromite, 4254-22-2; *p*-nitrobenzoyl chloride, 122-04-3.

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