Influence of Solvent and Brominating Agent on the Steric Course of the Bromine Addition to 1-Phenylcyclohexene and 2-Phenyl-3-bromocyclohexene

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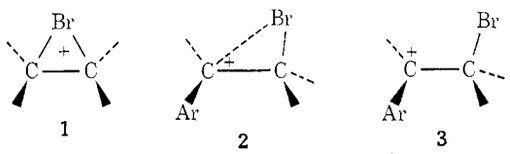
The addition of bromine to 1-phenylcyclohexene yields complex mixtures of up to five products, identified as the unsaturated bromide **8**, the *trans*- and *cis*-dibromides **5** and **6**, and the *meso*- and *dl*-tribromides **9** and **10**, in ratios which depend largely on the reaction conditions. While the addition of free bromine in $CHCl_3$ or benzene affords larger amounts of **6**, **9**, and **10**, the use of pyridine perbromide as the brominating agent remarkably reduces their formation in favor of the *anti*-dibromo adduct **5**. It is shown that **9** and **10** arise from bromine addition to **8**, formed in part from **4** through cationic intermediate **15** and in part through bromine-catalyzed elimination of HBr from the primary product **5**. The marked decrease in the formation of *syn*-dibromo adduct **6** and of unsaturated bromide **8** with pyridine perbromide is ascribed to the intervention of a more concerted addition mechanism and to nucleophilic solvation by base in the transition state for the addition. The bromination of **8** with free bromine in $CHCl_3$ leads to an excess of the *dl*-tribromide **10**, whereas the use of ethyl ether as the solvent or pyridine perbromide or pyridinium hydrobromide perbromide as the brominating agent strongly favors the formation of the meso isomer **9**, arising through anti addition.

The mechanism of the electrophilic addition of bromine to alkenes has been widely investigated both from the kinetic and the stereochemical point of view.[1,2] Apart from the relative importance of the various kinetically significant processes involved, it is now known[8-9] that the nature of the intermediates of the addition depends on the structure of the substrate and on the reaction medium, ranging from strongly bridged bromonium ions of the type originally postulated by Roberts and Kimball[10] (**1**) to weakly bridged species of the type **2**, or open ions like **3**.



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While intermediates of type **1** are involved in the bromination of nonconjugated olefins, which give only anti adducts irrespective of the reaction medium,[4] in the case of aryl-substituted compounds the unsymmetrically bridged **2** or open species **3** must be involved to rationalize the nonstereospecific course of the addition, which leads to syn as well as to anti adducts and depends on the reaction medium.[4,6-8]

The solvent polarity has been considered as the main factor affecting the extent of bridging in the intermediate, and consequently the stereochemical results of the bromination of a conjugated substrate.[7,8] However, also the ability of the solvent to coordinate with the attacking electrophile and to solvate cationic intermediates must be taken into account.[4] Our previous work[11] on the addition of bromine to nonconjugated substituted cyclohexenes revealed a marked influence of the coordination of bromine by a basic solvent or by added tertiary amines on the ratio between diaxial and diequatorial adducts. As an extension of our research, we therefore chose 1-phenylcyclohexene as a substrate suitable for a study of the influence of the solvent and the brominating agent on the ratio of syn to anti addition. Only very inadequate reports are found in the literature[12-15] concerning bromine addition to this olefin, the complexity of the reaction having prevented the isolation of the products. Previous systematic studies on the steric course of the bromination of aryl-substituted olefins were confined to acyclic derivatives, in which the possibility of rotation about the carbon–carbon single bond in the intermediates **2** or **3** makes the understanding of the mechanism of the syn addition ambiguous. Such uncertainty is obviously eliminated by using a cyclic compound like **4**; this is a further reason for our interest in this substrate.

Results

The addition of bromine to 1-phenylcyclohexene was accompanied by the evolution of hydrogen bromide and yielded complex mixtures of up to five products, containing from one to three bromine atoms, in ratios which depended largely on the reaction conditions. Although it was usually not possible to separate the single components of these mixtures, we succeeded in identifying all of them as compounds **5**, **6**, **8**, **9**, and **10**, and in analyzing the mixtures through pmr methods.

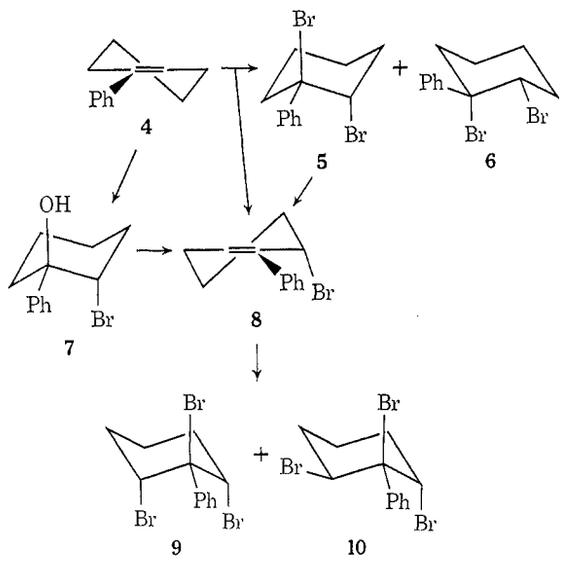
The *trans*-dibromide **5** was isolated by low-temperature crystallization of the bromination mixture obtained by treatment of **4** with pyridine perbromide in carbon tetrachloride; its configuration was assigned on the

(1) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, N. Y., 1966.
(2) R. C. Fahey in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, p 280.
(3) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469 (1969).
(4) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1477 (1969).
(5) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1483 (1969).
(6) R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).
(7) R. E. Buckles, J. M. Bader, and R. J. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962).
(8) J. Heublein, *J. Prakt. Chem.*, **31**, 84 (1966).
(9) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, **32**, 888 (1967).
(10) I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.*, **59**, 947 (1937).
(11) P. L. Barili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **37**, 4353 (1972).
(12) C. D. Nenitzescu and D. V. Curcăneanu, *Bull. Chim. Soc. Chim. România*, [2], **1**, 125 (1939).
(13) M. Mousseron and F. Winternitz, *Bull. Soc. Chim. Fr.*, **12**, 70 (1945).
(14) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1246 (1954).
(15) J. Heublein and I. Koch, *Z. Chem.*, **9**, 28 (1969).

basis of the half band width (6 Hz)[16] of the pmr signal at δ 5.10 ppm, due to the proton α to Br.[17]

The tribromides **9** and **10** were prepared as shown in Scheme I. Treatment of **4** with NBS in DMSO–water

SCHEME I



gave the bromohydrin **7**, whose structure was defined by its resistance to oxidation with Jones reagent and its transformation in 1-phenyl-1,2-epoxycyclohexane by treatment with alkali. Dehydration of **7** with sulfuric acid in acetic acid afforded 2-phenyl-3-bromocyclohexene (**8**), which, by treatment with bromine in chloroform, gave a mixture of the tribromides **9** and **10**. The main component **10** was separated by crystallization. The diastereoisomer **9** was similarly isolated from the bromination mixture obtained from the reaction of **8** with pyridine perbromide in carbon tetrachloride. Its meso configuration and its conformation with axial bromine atoms were deduced from the pmr spectrum, which showed a narrow signal at δ 5.34 ppm (half band width 6 Hz) due to the two magnetically equivalent equatorial hydrogens α to bromine.[18] On the other hand, the spectrum of the less symmetric isomer **10** displayed a more complicated pattern of signals, owing to overlap of the resonances of the two protons α to bromine; their nonequivalence was, however, deduced by the comparison of spectra obtained in different solvents, like carbon tetrachloride and benzene-d_6, which affect in a different way their chemical shifts (Figure 1). Unfortunately, no bromination procedure of **4** led to formation of the *cis*-dibromo derivative **6** in sufficient amount to permit its isolation, which was also made difficult by an extensive decomposition during attempts at chromatographic separation. However, its formation in small amount under all examined conditions was inferred from the presence of the typical doublet of doublets[16] (X part of an ABX system, $J_{AX} + J_{BX} = 15$ Hz) in the pmr spectra of all the bromination mixtures from **4**. Furthermore, the same signal was observed, though with very low intensity, besides that of **5** in the spectrum of the reaction product obtained by treatment of **7** with hydrogen bromide in chloroform. Although this substitution reaction prevalently gives the *trans*-dibromide **5**, as expected on the basis of an SNi type mechanism,[19] favored by anchimeric assistance by the vicinal bromine atom, the formation of a small amount of the inverted substitution product **6** is also conceivable owing to the tendency of the phenyl substituent to stabilize an open ion intermediate of type **3**, which may lead to **6** in addition to **5**.

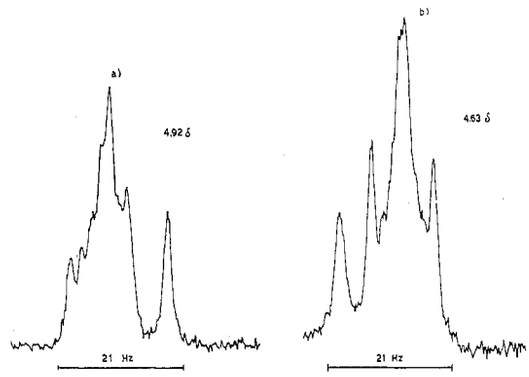


Figure 1.—The medium field part of the pmr spectrum of dibromide **10** in CCl_4 (a) and in C_6D_6 (b).

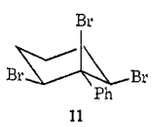
Preliminary experiments of bromination of 1-phenylcyclohexene were carried out by slowly adding a 1 *M* solution of bromine in chloroform to solutions of the olefin. Development of hydrogen bromide was observed and the pmr analysis of the crude reaction mixtures showed that the product composition considerably changed according to the amount of added bromine and to reaction time. In order to reduce the amount of unreacted olefin in the reaction products, and to obtain comparable results in the quantitative experiments in different solvents, the additions were carried out with an excess of the brominating agents for fixed times. The product distributions were determined by pmr analysis, the signals of the protons α to bromine being sufficiently separated to allow for an acceptable integration (Figure 2). The results are summarized in Table I.

The fact that the tribromides **9** and **10** were obtained also when the addition of bromine in chloroform was performed in the dark and, although in slightly smaller amounts, at −70°, speaks against their formation through a free-radical process. The use as the brominating agent of pyridine perbromide, either preformed or produced *in situ*, remarkably reduced

(16) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 286.

(17) Since *trans*-1,2-dibromocyclohexane has a preferred conformation with axial bromine atoms [P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 3, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1967, p 231, and H. Booth, in Vol. 5, 1969, p 149; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967)] and a phenyl group prefers the equatorial position, conformations other than those shown for **5** and **6** in Scheme I can practically be excluded.

(18) The more stable conformation of the alternative meso form would have two axial equivalent hydrogens α to bromine (**11**), which should give a



11

broad multiplet. Furthermore, structure **11** would hardly account for the easy isomerization of the *meso*- into the *dl*-tribromide (see Discussion).

(19) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **22**, 189 (1966).

TABLE I

PRODUCT COMPOSITION IN THE BROMINATION OF 1-PHENYLCYCLOHEXENE

Solvent	Brominating agent (% excess)	Reaction time, min	Products, mol % 5	6	8	9	10
$CHCl_3$	Br_2 (50)	15	52	11		12	25
$CHCl_3$	Br_2 (100)	195	22	11		16	51
$CHCl_3$ + Py	Br_2 (50)	30	76	6	12	6	
$CHCl_3$ + Py	Br_2 (100)	120	62	6		26	6
CCl_4	$C_5H_5NBr_2$ (50)	30	86	4	10		
CCl_4	$C_5H_5NBr_2$ (100)	120	82	4		14	
C_6H_6	Br_2 (50)	15	50	13		22	15
C_6H_6	Br_2 (100)	120	43	13		21	23
Et_2O	Br_2 (50)	30	62	8	10	16	4
Et_2O	Br_2 (100)	120	52	8		32	8

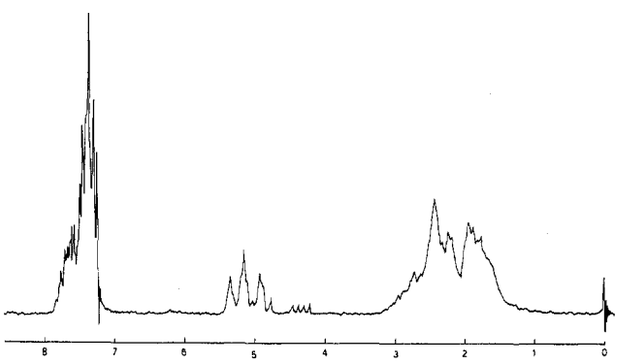


Figure 2.—Pmr spectrum in CCl_4 of a typical mixture obtained by bromination of **4** with an excess of Br_2 in $CHCl_3$.

the formation of the *cis*-dibromide and of the tribromides. A similar, although less marked effect, was found when the addition of bromine was carried out in a basic solvent like ethyl ether. In these cases, however, the reaction mixtures contained appreciable amounts of the unsaturated bromo derivative **8**, in spite of the excess of brominating agent employed. On the other hand, the addition of free bromine in chloroform or benzene led to formation of larger amounts of **6**, **9**, and **10**, while only traces of unsaturated compounds were found. Larger excesses of bromine and longer reaction times resulted in a decrease of the *trans*-dibromide and an increase of the tribromo derivatives, this effect being more pronounced in the addition performed with free bromine. In contrast, the amount of *cis*-dibromide was completely unaffected. Furthermore, the ratio between the relative amounts of tribromides changed according to the reaction conditions. All these observations suggested that concomitant transformation of **5** into **9** and **10** and of **9** into **10** could occur in the reaction medium, **6** being stable. Consistent with this was the fact that when solutions of the *trans*-dibromide **5** in various solvents were exposed to bromine, hydrogen bromide was evolved and the tribromides **9** and **10**, but not the *cis*-dibromide **6**, were slowly formed. On the other hand, **5** was completely stable when exposed to hydrogen bromide. The extent of transformation of **5** into **9** and **10**, as a function of the amount of added bromine, of reaction time, and of solvent is reported in Table II.

Several points of interest emerge from these results. Firstly, the rate of conversion of **5** into **9** and **10** appears to depend on the bromine concentration and on the solvent employed, the rate order being chloroform > benzene > ethyl ether. However, in all solvents the transformations were too slow to account for the whole amounts of tribromides formed in the bromine addition to **4**. Therefore it can be concluded that most of **9** and **10**, formed from **4** after short reaction times, arises through a pathway which does not involve the formation of **5** as the primary product. Moreover, while in ethyl ether the *meso*-tribromide **9** was the main product irrespective of the extent of conversion, in chloroform and in benzene the product composition markedly changed in favor of the *dl* isomer **10** with increasing degree of conversion, showing that in the presence of bromine **9**, which is formed under kinetic control, isomerizes to the more stable isomer **10**. This point was confirmed by experiments carried out with pure **9** and **10**: whereas **10** was unaffected by prolonged exposition to bromine in chloroform, **9** under the same conditions was slowly transformed into **10**. On the other hand, the bromine-catalyzed isomerization was slower in ethyl ether as the solvent, and hydrogen bromide alone had no effect.

TABLE II

CONVERSION OF DIBROMIDE **5** INTO TRIBROMIDES **9** AND **10** IN THE PRESENCE OF BROMINE

Solvent	Molar ratio of **5**:Br_2	Reaction time, min	Products, mol % 5	9	10
$CHCl_3$	2:1	15	85	5	10
$CHCl_3$	1:0.75	15	81	6	13
$CHCl_3$	1:1	15	78	7	15
$CHCl_3$	1:1	1440	10	14	76
C_6H_6	2:1	15	95	3	2
C_6H_6	1:1	1440	16	12	72
Et_2O	2:1	30	97	3	
Et_2O	1:1	160	78	18	4
Et_2O	1:1	1440	44	40	16

The formation of tribromides in the bromination of **4** can be visualized (Scheme I) as arising from bromine addition to the unsaturated bromo derivative **8**, formed in part directly from **4** and in part through bromine-catalyzed elimination of hydrogen bromide from the primary product **5**. In order to verify this scheme, the product composition from the bromination of **8** under several conditions was examined. Since the rate of addition to **8** appeared to be slower than that to **4**, longer reaction times (2 hr) and smaller excesses of brominating agents (20%) were employed. Under these conditions the isomerization of the adduct **9** to **10** was minimized. The results, obtained by pmr analysis, are reported in Table III.

As observed for **4**, the product distribution was strongly influenced by the reaction conditions: while

TABLE III

PRODUCT COMPOSITION IN THE BROMINATION OF 2-PHENYL-3-BROMOCYCLOHEXENE

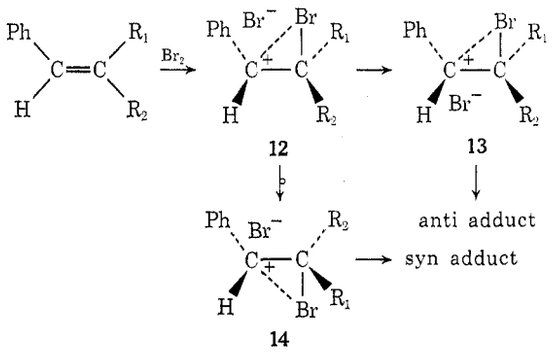
Solvent	Brominating agent	Reaction time, min	Products, mol % 9	10
$CHCl_3$	Br_2	120	25	75
CCl_4	$C_5H_5NBr_2$	120	90	10
Et_2O	Br_2	120	80	20
CH_3COOH	$C_5H_5NHBr_3$	120	90	10

pyridine perbromide as the brominating agent and ethyl ether as the solvent strongly favored the formation of the unstable isomer **9**, bromine in chloroform afforded an excess of **10**. It is emphasized that the **9** to **10** ratios are in fairly good agreement with those obtained in the brominations of **4** under similar conditions (see Table I), thus confirming the formation of the tribromides **9** and **10** from **4–8**.

Discussion

According to recent views, the electrophilic step in the bromine addition to styrene derivatives in nonpolar solvents leads to the initial formation of an intimate ion pair, whose positive moiety should be an unsymmetrically bridged ion of type **2**, resembling a benzylic cation more than a bromonium ion.[4,6,9,20,21] Nucleophilic attack by bromide counterion can occur through two different pathways, affording either *anti*- or *syn*-dibromo adducts (Scheme II). Owing to steric

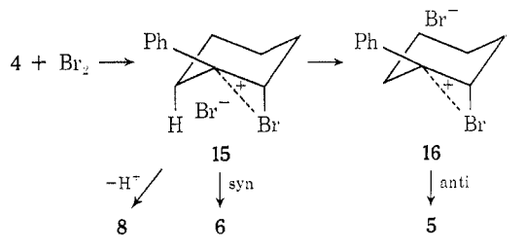
SCHEME II



and ion–dipole repulsion between the first bonded bromine and the attacking bromide ion in the ion pair **12**, a reorientation of **12** to **13** can occur before the attack, leading to anti adducts. However, since the neighboring bromine bridging in the intermediate should be very weak, internal rotation around the C_α–C_β bond has been postulated to give **14**, whose collapse would result in net syn addition. It should be pointed out that a direct collapse of **12** to syn adducts has been considered less probable owing to the bulk of the first bonded bromine atom.[4,6]

According to this picture, the first formed intermediate in the bromine addition to 1-phenylcyclohexene in chloroform or benzene could be represented as **15** (Scheme III); reorientation and rear-side attack by bromide ion can lead to the *anti*-dibromo adduct **5**, which is actually the main product of the primary reaction. On the other hand **15**, owing to the restric-

SCHEME III



tions imposed by the six-membered ring, cannot undergo internal rotation around the C_α–C_β bond and according to Scheme II should not give the syn adduct. In contrast, appreciable amounts of **6** are found in the bromination mixtures of **4**, showing that internal rotation followed by rear-side attack is not a necessary path for syn addition, which can also occur through direct collapse of an intimate ion pair intermediate. Our results also show that in a cyclohexene system syn additions to give products such as **6** are quite possible sterically; therefore the fact that cyclohexene itself gives exclusively trans product demonstrates clearly that in the parent system (without phenyl stabilization) anti addition is almost certainly due to strong cyclic bromonium ion formation, and not due to the steric effect of the first attached bromine atom in an open ion.

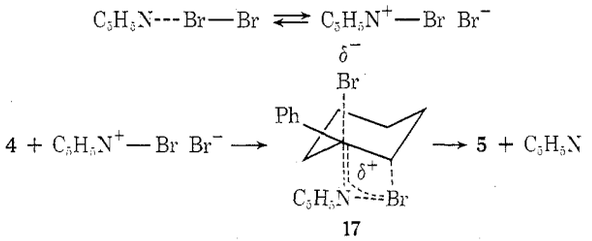
The benzylic cation character of the positive moiety of **15** is confirmed by the extensive occurrence of proton loss from C-6 to give the unsaturated bromo derivative **8**, which undergoes further bromine addition affording the tribromides **9** and **10**. Owing to the necessity for the bromide counterion of **15** to reorient to the less hindered side, presumably through a solvent-separated ion pair, the lifetime of the cation should be long enough to cause proton elimination. The extent of proton loss from **15** can be roughly estimated by subtracting from the total amounts of **8**, **9**, and **10**, reported in Table I, those of **9** and **10** arising from the bromine-catalyzed transformation of the firstly formed **5** under the reaction conditions (see Table II). Although accurate values cannot be obtained, since the reaction conditions and particularly the bromine concentrations cannot be exactly reproduced, these data permit the inference that about 20–30% of intermediate **15** loses a proton to yield **8**, the larger amount being formed in benzene. Values ranging from 30 to 40% of proton elimination have been reported[15] for the bromination of **4** in acetic acid and in its mixtures with carbon tetrachloride, nitromethane, and water. Such a marked tendency to elimination seems to be peculiar to the aryl-substituted cyclohexene system, since no formation of allylic bromides was reported in the bromination of side-chain methyl-substituted styrenes,[3,4,6] with the exception of α,o,o,p-tetramethylstyrene, which yields only substitution products owing to steric inhibition of the development of an sp^3 character at the benzylic carbon atom owing to the presence of the two *o*-methyl groups.[22]

The marked decrease in the formation of the *syn*-dibromo adduct **6** when using pyridine perbromide as the brominating agent parallels a considerable reduc-

(20) P. B. D. de la Mare, *Quart. Rev., Chem. Soc.*, **3**, 126 (1949).
(21) J. E. Dubois and W. V. Wright, *Tetrahedron Lett.*, 3101 (1967).
(22) E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 1243 (1968).

tion in the proton loss to give **8**. This suggests that a more concerted anti attack should be involved under these conditions. In a previous paper[11] we suggested that an ionization of the pyridine–bromine complex could simultaneously provide both the electrophile and the nucleophile. If this is true, a rapid rear-side attack by an external bromide ion on the α carbon could occur without the necessity of any reorientation of the intermediate; furthermore, the base, which conveys the electrophilic bromine to the reaction site, could solvate from the cis side the incipient benzylic cation, hindering a syn attack by bromide ion. The transition state for the addition could therefore be represented as **17** (Scheme IV), which is similar

SCHEME IV



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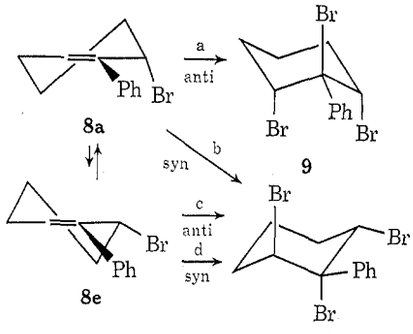
to that proposed[23] for the E2Hal elimination of bromine from *trans*-1,2-dibromocyclohexane with thiophenoxide as base.

The fact that the use of ethyl ether instead of chloroform or benzene as the solvent for the addition of bromine to **4** tends to decrease, although less markedly, the amount of syn adduct may conceivably be attributed to coordination of the halogen, since it is known that ethers form addition compounds with bromine.[24] However in this case, the ether being present in a large excess, solvation can be provided for the incipient benzylic carbocation both from the cis side by the molecule of ether carrying the electrophile and from the trans side by external molecules of solvent. The lack of a specific syn solvation could account for the smaller degree of suppression of the syn addition than expected on the basis of the coordination of the halogen. Solvation of the β-bromo-α-phenylcarbonium ion by an ether solvent such as dioxane to give an unstable oxonium ion intermediate has been postulated[4] to rationalize the stereochemical results of the bromination of *cis*- and *trans*-β-methylstyrenes.

The effect of the coordination of bromine by bases on the steric course of the addition to 2-phenyl-3-bromocyclohexene is also striking. However, in this case the interpretation is complicated by the presence of the bromine atom in **8**, which prevents establishing the mode of formation of the *dl*-tribromo derivative **10**. Indeed, whereas the *meso*-tribromide **9** can only be formed through anti addition, the isomer **10**, having one bromine in a trans and one in a cis relationship to the central halogen atom, could be formed either through anti diaxial addition or through syn addition from the side opposite to the allylic bromine of **8**. It is therefore impossible to infer with certainty, from the present data, the occurrence of syn addition of bromine to **8**, since the stereochemical results could also be explained on the basis of an exclusive anti diaxial addition on the two possible conformers with pseudoaxial (**8a**) or pseudoequatorial bromine (**8e**) (Scheme V, paths a and c; anti diequatorial additions,

SCHEME V



which could also give **9** from **8e** and **10** from **8a**, are not considered in the scheme since they would involve less favorable preboat transition states).

Although the half band width of the proton α to bromine (6 Hz) in the pmr spectrum of **8** indicates that conformation **8a** is strongly preferred over **8e**, in agreement with reports on similarly substituted cyclohexene derivatives,[25] it cannot be excluded that part of the addition may occur through the less stable conformer **8e**. However, since pyridine perbromide has been shown to suppress the syn addition to **4**, this suggests that a decrease of importance of paths b and d, rather than a diversion from path c to path a, could be responsible for the strong increase in the **9** to **10** ratio in the bromination of **8** with this reagent. Consistent with this is the fact that identical results are obtained by performing the bromination in acetic acid with pyridinium hydrobromide perbromide, a reagent which is known[26] to suppress the syn addition to phenyl-substituted olefins. A similar trend is found in the addition of bromine in ethyl ether, which, like pyridine, can coordinate bromine.

The *meso*-tribromide **9** is slowly transformed into **10** on treatment with bromine at room temperature. Since a single inversion of configuration on C-2 seems to be very unlikely, this isomerization can be visualized as the result of a 1,2 interchange on two vicinal centers bearing trans-oriented bromine atoms, resembling the thermal interconversions between diaxial and diequatorial dibromocyclohexanes and steroid derivatives.[27-29] In this case the driving force for the easy isomerization clearly is due to strong syn-diaxial interaction between the 1,3 bromine atoms. Thus, the role of molecular bromine should be that of increasing the extent to which bond breaking occurs in the transition state (**18**) by causing a lowering of electron density in the benzylic carbon–bromine bond (Scheme VI). Similar catalytic effects by carboxylic acids and phenols[30] and by mercuric bromide[31] have

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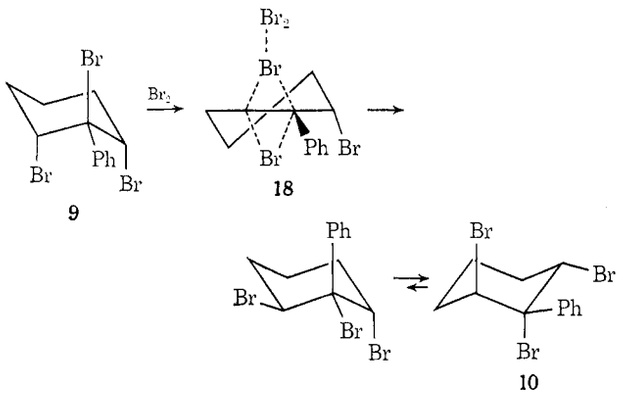
SCHEME VI



been reported for the thermal rearrangement of steroidal dibromides. In an analogous way, molecular bromine can cause the elimination of hydrogen bromide from dibromide **5** to give **8**.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Pmr spectra were registered with a Jeol C-60 HL spectrometer from CCl_4 solutions with TMS as internal standard. $MgSO_4$ 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.—1-Phenylcyclohexene was prepared according to Garbisch.[32] Bromine was purified by refluxing with $CaBr_2$ and distillation.[33] Preformed pyridine perbromide was prepared immediately before use from bromine and pyridine in CCl_4.[34] Pyridine hydrobromide perbromide was prepared by the Fieser method.[35] CCl_4 was Rudi Pont spectranalyzed reagent grade. $CHCl_3$ 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. Et_2O was freed from peroxides by washing with a solution of $FeSO_4$. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled.

***r*-1,*t*-2-Dibromo-1-phenylcyclohexane (5).**—Preformed pyridine perbromide (1.8 g, 7.5 mmol) was added to a solution of **4** (1.0 g, 6.3 mmol) in CCl_4 (25 ml) at 0°. The reaction mixture was stirred for 15 min, then poured into saturated aqueous Na_2SO_3; the organic layer was washed with water, 2 *N* HCl, and water, dried, and evaporated. Crystallization of the residue from pentane at −20° gave **5** (0.8 g): needles; mp 66–67.5°; pmr δ 5.10 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{14}Br_2$: C, 45.31; H, 4.44; Br, 50.25. Found: C, 45.50; H, 4.47; Br, 49.98.

***t*-2-Bromo-1-phenyl-*r*-1-cyclohexanol (7).**—NBS (13.4 g, 75.3 mmol) was added portionwise to a solution of **4** (6.0 g, 37.9 mmol) in a mixture of DMSO (80 ml) and water (4 ml) at 0° under an atmosphere of nitrogen. After standing for 1 hr at room temperature, the reaction mixture was poured into water and extracted with Et_2O. Evaporation of the organic layer after washing with water and drying gave an oily residue (9.6 g) which crystallized as prisms from petroleum ether at −20° (6.0 g). After recrystallization the solid had mp 48–49°; pmr δ 4.24 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.48; H, 5.92; Br, 31.32. Found: C, 56.58; H, 5.87; Br, 31.60.

A sample of this product was recovered unchanged after treatment with Jones reagent.[36] A solution of **7** (91.1 mg, 0.36 mmol) in MeOH (5 ml) was titrated with 0.1 *N* aqueous NaOH with phenolphthalein as the indicator. The consumption of base amounted to 3.6 ml. Dilution with water, extraction with $CHCl_3$, and evaporation of the dried organic layer gave pure 1-phenyl-1,2-epoxycyclohexane (52 mg).

2-Phenyl-3-bromocyclohexene (8).—The bromohydrin **7** (1.5 g) was treated with freshly prepared 20% (v/v) H_2SO_4–AcOH (4 ml) and the resulting mixture was swirled for 2.5 min and poured into petroleum ether–water. Evaporation of the organic layer, after washing with water, saturated aqueous $NaHCO_3$, and water and drying, afforded **8** (1.3 g), which crystallized as needles from petroleum ether: mp 50–52°; pmr δ 6.07 (–CH=, m, $W_{1/2}$ = 8 Hz, 1 H), 5.18 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{13}Br$: C, 60.77; H, 5.52; Br, 33.70. Found: C, 60.65; H, 5.44; Br, 33.55.

***r*-1,*t*-2,*c*-3-Tribromo-2-phenylcyclohexane (9).**—Preformed pyridine perbromide (0.77 g, 3.2 mmol) was added to a solution of **8** (0.60 g, 2.53 mmol) in CCl_4 (10 ml); after stirring at room temperature for 2 hr the reaction mixture was poured into saturated aqueous Na_2SO_3, and the organic layer was separated, washed with 2 *N* aqueous HCl, water, and saturated aqueous $NaHCO_3$, dried, and evaporated. The solid residue (0.89 g), dissolved in petroleum ether at room temperature, crystallized on cooling at −20° to give pure **9** (0.50 g): prisms; mp 95.5–97.5°; pmr δ 5.34 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 2 H).

Anal. Calcd for $C_{12}H_{13}Br_3$: C, 36.30; H, 3.30; Br, 60.39. Found: C, 36.35; H, 3.18; Br, 60.70.

***r*-1,*c*-2,*t*-3-Tribromo-2-phenylcyclohexane (10).**—A 1 *M* solution of Br_2 in $CHCl_3$ (2.5 ml) was added dropwise at 0° to a solution of **8** (0.50 g, 2.1 mmol) in the same solvent (10 ml). The consumption of Br_2 was slow. After standing overnight, the solution was poured into saturated aqueous Na_2SO_3, washed with water, dried, and evaporated. Crystallization of the solid residue (0.77 g) from petroleum ether, carried out as described for **9**, gave pure **10** (0.35 g): needles; mp 134–135.5°; pmr δ 4.92 (–CHBr–, 2 overlapping m, 2 not equivalent H).

Anal. Calcd for $C_{12}H_{13}Br_3$: C, 36.30; H, 3.30; Br, 60.39. Found: C, 36.44; H, 3.35; Br, 60.70.

Brominations of 4 and 8 under Different Conditions. A. With Br_2.—A 1 *M* solution of Br_2 in $CHCl_3$ was added dropwise within 2 min to a stirred solution of 1.5 mmol of the unsaturated compound in 5 ml of the appropriate solvent. The additions were carried out at 0°, by using a 50 or 100% excess of Br_2 in the case of **4** and a 20% excess in the case of **8**. After the additions were complete, the reaction mixtures were stirred at room temperature for the times reported in Tables I and III, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The residues were directly analyzed by pmr.

B. With Br_2 in the Presence of Pyridine.—A 50 or 100% excess of a 1 *M* solution of Br_2 in $CHCl_3$ was added at 0° to a stirred $CHCl_3$ solution (5 ml) containing an equimolar amount of pyridine and 1.5 mmol of **4**. After stirring at room temperature for the times reported in Table I, the solution was washed with saturated aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated.

C. With $C_5H_5NBr_2$.—The solid brominating agent (50 or 100% excess in the case of **4**, 20% excess in that of **8**) was added to a solution of 1.5 mmol of the olefin in 5 ml of CCl_4. The mixture was stirred at room temperature for the times reported in Tables I and III, then treated as described in B.

D. With $C_5H_5NHBr_3$.—A 20% excess of the brominating agent was added to a solution of **8** (1.5 mmol) in dry AcOH (7 ml). After stirring for 2 hr at room temperature, the mixture was diluted with water and extracted with Et_2O; the organic layer was washed with water, saturated aqueous $NaHCO_3$, and water, dried, and evaporated.

The bromination mixtures arising from **4** were analyzed through their pmr spectra by integration of the signals at δ 4.32 (**6**, 1 H), 4.92 (**10**, 2 H), 5.10 (**5**, 1 H), 5.34 (**9**, 2 H), and 6.07 (**8**, 1 H); when appreciable amounts of **8** were present, the area of the signal of **5** was corrected for the presence of the overlapping signal of **8** at δ 5.18, by assuming that its area was equal to that of the vinylic proton signal at δ 6.07. The mixtures arising from the brominations of **8** were similarly analyzed on the basis of the signals at δ 4.92 and 5.34. The results are reported in Tables I and III.

Treatment of 5 with Br_2.—The required amount of a 1 *M* solution of Br_2 in $CHCl_3$ was added to solutions of 0.38 mmol of **5** in 1.5 ml of the appropriate solvent. The solutions were stored at room temperature in the dark for the times reported in Table II, then poured into saturated aqueous $NaHSO_3$. The organic layers were washed with water, dried, and evaporated.

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The residues were analyzed by pmr. The results are reported in Table II.

Isomerization of 9 and 10. A.—A solution of **9** (0.40 g, 1.0 mmol) in $CHCl_3$ (3 ml) was treated with a 1 *M* solution of Br_2 in $CHCl_3$ (1 ml). After standing at room temperature in the dark for 100 hr, the solution was poured into saturated aqueous $NaHSO_3$; the organic layer was washed with water, dried, and evaporated. The pmr spectrum of the crude product showed the signals of **9** and **10** in the ratio 55:45; a third signal at δ 4.3 (doublet of doublets, W = 18 Hz) was also present (<5%). In contrast **10** was recovered unchanged after identical treatment with Br_2.

B.—A solution of **9** (0.40 g, 1.0 mmol) in Et_2O (3 ml) was treated with a 1 *M* solution of Br_2 in $CHCl_3$ (1 ml), left at room temperature in the dark for 100 hr, and worked up as described under A. The pmr spectrum of the crude reaction mixture indicated the presence of **9** and **10** in the ratio 73:27.

C.—A solution of **9** (0.40 g) in $CHCl_3$ (4 ml) was saturated with dry HBr and left at room temperature for 100 hr. After washing with water and saturated aqueous $NaHCO_3$, drying, and evaporation, unchanged **9** (ir and pmr) was recovered.

Treatment of 7 with HBr.—A solution of **7** (0.13 g) in $CHCl_3$ (5 ml) was saturated with dry HBr and left at room temperature for 3 hr. After washing with water, saturated aqueous $NaHCO_3$, and water, drying, and evaporation, a solid residue (0.14 g) was obtained, consisting of **5** accompanied by a small amount (~3%) of the isomer **6** (pmr). The dibromide **5** was recovered unchanged after standing for 15 hr in a $CHCl_3$ solution saturated with dry HBr.

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Registry No.—**4**, 771-98-2; **5**, 40940-62-3; **7**, 40940-63-4; **8**, 40940-64-5; **9**, 40940-65-6; **10**, 40940-66-7.

Stereochemistry of the Acid-Catalyzed Cyclization of 2-(3-Butenyl)-1-phenylcyclohexanols

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Acid-catalyzed cyclization of the phenyl-substituted alcohols **4** and **5** was shown to give cis-fused bicyclic formates with no detectable amount of trans-fused products. Since cyclization in deuterioformic acid led to no incorporation of deuterium into the cyclic product, intervention of cyclohexenyl intermediates cannot be involved in the reaction. This divergence from results obtained with other substituted cyclohexanols is considered to be a direct consequence of steric interactions involving the bulky and geometrically anisotropic phenyl group. The results show that the substituent at the cationic carbon in acid-catalyzed olefin cyclizations may significantly alter the mechanism and stereochemistry of acid-catalyzed olefin cyclizations.

Olefinic cyclizations have recently become established as a key method for the construction of complex polycyclic compounds. In the course of a model study[1] on the stereochemistry and mechanisms of biogenetic-like olefin cyclizations, we have prepared and studied the acid-catalyzed cyclization of several 2-alkenylcyclohexane systems such as **1**, **2**, and **3**. We have now examined the cyclization of the related benzylic alcohols **4** and **5**. Although not directly relevant to biogenetic systems,[2] these cyclizations are of particular interest since the results are directly divergent from those obtained with previously studied systems.

The synthesis of the cyclization substrates is outlined in Chart I. Spectral and chromatographic data gave evidence for the presence of only one isomer in the product obtained from reaction of phenylmagnesium bromide with ketone **6**. By analogy with the reaction of 2-alkylcyclohexanones with Grignard reagents,[3] this

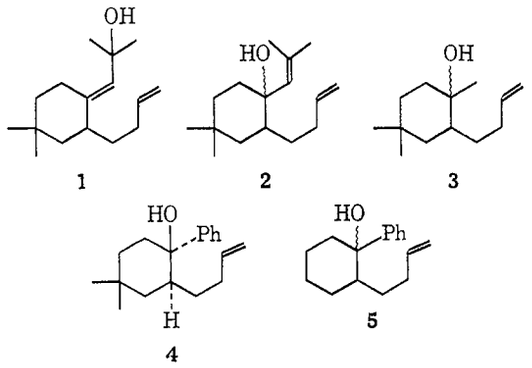
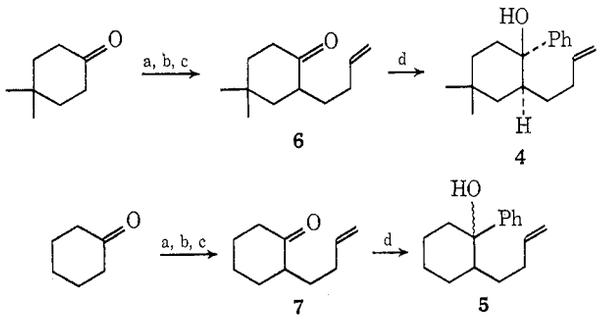


CHART I

SYNTHESIS OF CYCLIZATION ALCOHOLS[a]



[a] a, cyclohexylamine, $-H_2O$; b, EtMgBr; c, $CH_2{=}CH{-}CH_2CH_2X$; d, C_6H_5MgBr.

(1) Other papers in this series follow: (a) K. E. Harding, R. C. Ligon, T.-C. Wu, and L. Rode, *J. Amer. Chem. Soc.*, **94**, 6245 (1972); (b) K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973).

(2) Cyclization of alcohol **4** was considered of interest in relation to other biogenetic-like olefin cyclizations because the phenyl group might be expected to stabilize the intermediate cyclohexyl cation and thus reduce elimination–reprotonation reactions known to complicate many early attempts to examine cyclizations of cyclohexyl cations.[1b] However, it was recognized from the beginning that this alcohol was less satisfactory than alcohol **1** as a model compound because of the increased steric factors present with a phenyl substituent.

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