[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA]

A Stereochemical Study of the Cleavage of Organomercurials by Various Brominating Agents[1-3]

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The cleavage by brominating agents of *cis-* and *trans-*4-methylcyclohexylmercuric bromides to yield 4-methylcyclohexylbromide has been studied under a variety of conditions. The reaction with bromine in non-polar solvents occurs by a free radical mechanism with both mercury compounds to give the identical mixture of *cis*(47.4%)- and *trans*(52.6%)-4-methylcyclohexyl bromides. Under other conditions, the reaction also occurs by a polar mechanism. The polar reaction occurs completely stereospecifically with retention of configuration. This is the first example using simple stereoisomers indicating that the steric course of electrophilic substitution of organometallic compounds is retention of configuration.

Considerable speculation has been made concerning the stereochemical path of electrophilic aliphatic substitution. Hughes and Ingold[5] early postulated that SE2 reactions proceed with inversion while SE1 reactions proceed with retention of configuration. Similarly, Dewar[6] predicted that the steric course of electrophilic and nucleophilic aliphatic substitution are identical. In 1955, Winstein, Traylor and Garner[7] considered that retention of configuration might be an entirely plausible and possibly general stereochemical outcome of concerted electrophilic substitution. These authors reported that mercuric chloride cleavage of *cis*-2-methoxycyclohexylneophylmercury proceeded with predominant retention of configuration but cautioned that the presence of a β-alkoxyl group prevented these results from being generalized to other reagents and systems. More recently Wright,[8] while discussing the interchangeability of the anionomercury group by bromine or iodine, stated that it is expected that configuration is lost whenever replacement occurs at carbon–metal linkages.

These views, which represent the entire spectrum of possible stereochemical results of electrophilic aliphatic substitution, point out the need for definitive experimental evidence on this type of substitution. The lack of experimental data has arisen primarily because there have been few suitable stereoisomers available for electrophilic studies.[9]

A preliminary account has been reported of the results of a study of electrophilic substitution at saturated carbon for carbanion-type reactions.[10] These results indicate that carbanions may react with partial inversion or partial retention of configuration or complete racemization. No examples have been reported for the concerted or bimolecular type of substitution using simple stereoisomers, although studies have been reported using compounds which have stereochemical features which might alter the course of the reactions.[11] The availability of *cis-* and *trans-*4-methylcyclohexylmercuric bromides[9] has now made possible a broad and definitive study of various types of electrophilic aliphatic substitution. In this paper the stereochemical results of the bromine cleavage of *cis-* and *trans-*4-methylcyclohexylmercuric bromides are reported.

Some evidence indicating the stereochemical course of the halogen cleavage of organomercury compounds has been reported. Van Loon and Carter,[12] in repeating the earlier work of Schrauth and Geller,[13] reported that the brominolysis of a pure diastereomeric 3-acetoxy-2-bromomercuri-3-phenylpropanoic acid gives a mixture of the two diastereomeric 2-bromo-3-phenylpropanoic acids. They found that the relative amounts of the two diastereomers obtained depends upon the temperature, solvent and other experimental conditions. Whitmore, Whittle and Harriman[14] found that neopentylmercuric chloride is converted by halogen to the corresponding bromide or iodide without rearrangement. More recently, Winstein and Traylor[15] have studied the iodine cleavage of 4-camphylmercuric iodide. They postulated from kinetic evidence that, depending upon reaction conditions, the reaction proceeds by either a free radical or polar mechanism. Furthermore, they found that the polar reaction does not have a large preference, if any, for a mechanism which proceeds by rearward attack; 4-camphylmercuric iodide and *n*-butylmercuric iodide are cleaved at about the same rate by triiodide ion.

Results and Discussion

The results of preliminary experiments indicated that no detectable rearrangement occurs in the cleavage of *cis-* and *trans-*4-methylcyclohexylmercuric bromides with various brominating agents. However, it was found that the relative amounts of the *cis-* and *trans-*4-methylcyclohexyl bromides obtained varies markedly with reaction conditions. In order to determine the various factors influencing the isomer distribution, small samples (0.0053 mole) of the *cis-* and *trans-*mercury compounds

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(3) For a preliminary account of some of these results see F. R. Jensen and L. H. Gale, THIS JOURNAL, **81**, 1261 (1959).

(4) Allied Chemical and Dye Corp. Fellow, 1958–1959.

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TABLE I

CLEAVAGE OF *cis*- AND *trans*-4-METHYLCYCLOHEXYLMERCURIC BROMIDES BY BROMINE IN A VARIETY OF SOLVENTS

Expt.	Solvent	Isomer	Temp., °C.	Atm.	4-Methylcyclohexyl bromide % *cis*-	% *trans*-	Retention, %
1	CCl_4	*trans*	0	N_2	47.6	52.4	0
2	Carbon disulfide	*trans*	0	N_2	47.2	52.8	0
3	CCl_4	*cis*	0	N_2	47.4	52.6	0
4	Carbon disulfide (1% EtOH)	*trans*	0	N_2	44	56	8
5	Acetic acid	*trans*	25	N_2	39	61	18
6	Acetic acid	*cis*[a]	25	N_2	52	48	11[b]
7	Chloroform (0.75% EtOH)	*trans*	0	N_2	32	68	3
8	Carbon disulfide	*trans*	0	Air	47	53	0
9	Acetic acid	*trans*	25	Air	9	91	8
10	Methyl alcohol	*trans*	25	Air	7	93	85
11	Chloroform (0.75% EtOH)	*trans*	0	Air	4	96	92

[a] Impure *cis*-4-methylcyclohexylmercuric bromide containing 10% *trans* isomer. [b] Corrected for *trans* isomer present in starting mercury compound.

TABLE II

CLEAVAGE OF *cis*- AND *trans*-4-METHYLCYCLOHEXYLMERCURIC BROMIDES BY VARIOUS BROMINATING AGENTS AT 25°

Expt.	Brominating agent	Solvent	Isomer	Atm.	4-Methylcyclohexyl bromide % *cis*-	% *trans*-	Retention, %
12	N,N-Dibromobenzenesulfonamide	Acetic acid	*trans*	Air	35	65	24
13	Hypobromous acid	50% dioxane 50% water	*trans*	Air	5	95	90
14	Br_2 with $ZnBr_2$	Acetic acid	*trans*	Air	4	96	92
15	Pyridinium bromide perbromide	Acetic acid	*trans*	Air	<1	>99	>98
16	Pyridinium bromide perbromide	Acetic acid	*trans*	N_2	13	87	73
17	Bromine–pyridine complex	Pyridine	*trans*	Air	0	100	100
18	Bromine–pyridine complex	Pyridine	*trans*	N_2	0	100	100
19	Hypobromous acid, 0.1 N H_2SO_4	50% dioxane 50% water	*cis*	N_2	46	54	0
20	Br_2 with $ZnBr_2$	Acetic acid	*cis*[a]	N_2	54	46	18[b]
21	Pyridinium bromide perbromide	Acetic acid	*cis*[a]	Air	80	20	79[b]
22	Pyridinium bromide perbromide	Acetic acid	*cis*[a]	N_2	72	28	60[b]
23	Bromine–pyridine complex	Pyridine	*cis*	Air	100	0	100
24	Bromine–pyridine complex	Pyridine	*cis*[a]	N_2	91	9	100[b]

[a] Impure *cis*-4-methylcyclohexylmercuric bromide containing 10% *trans* isomer. [b] Corrected for *trans* isomer present in starting mercury compound.

were cleaved with different brominating agents under a variety of conditions. The relative amounts

of the *cis*- and *trans*-4-methylcyclohexyl bromides produced were determined by infrared analysis.

The results obtained by cleaving the mercury compounds with bromine in a variety of solvents under an atmosphere of air or nitrogen are given in Table I. In non-polar solvents such as carbon tetrachloride and carbon disulfide, both isomers yield the identical mixture of *cis*- and *trans*-4-methylcyclohexyl bromides (expts. 1,2,3,8). Under these conditions the reactions likely proceed through a common intermediate which allows complete loss of configuration. Since the product distribution is 47.4 ± 0.2% *cis*- and 52.6 ± 0.2% *trans*-alkyl bromide, or nearly the statistical distribution, the common intermediate must be very reactive and have low selectivity.

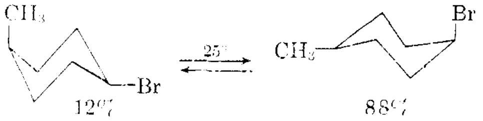
In more polar solvents, or solvents containing a trace of alcohol, the reactions occur with partial retention of configuration (expts. 4,5,6,7). Under these conditions, the addition of air to the reaction vessel results in a marked increase in the amount of retention (expts. 9,10,11). However, in pure carbon disulfide as solvent in the presence of air, complete loss of retention occurs (expt. 8).

These results suggest that the reaction occurs by two pathways. One process occurs through a very reactive intermediate with loss of configuration and is inhibited or not favored by oxygen and traces of alcohol. It is likely that this process proceeds by a free radical mechanism involving the 4-methylcyclohexyl radical as the reactive intermediate. The other pathway, which is referred to here as the polar reaction, occurs at least partially stereospecifically with retention of configuration. These results do not indicate whether the preponderance of the polar reaction in the polar solvents is due to assistance of the polar reaction or inhibition of the radical reaction.

In an attempt to cleanly separate the polar reaction, the cleavage was investigated using various brominating agents (Table II). More than 90% retention is obtained with four sources of positive or partially positive bromine (expts. 13,14,15,17) under an atmosphere of nitrogen. With pyridinium bromide perbromide as the cleavage agent, the reaction is more stereospecific in air than in nitrogen (expts. 15,16). The bromine–pyridine complex cleaves the mercury compound completely stereospecifically both in the presence and absence of air (expts. 17,18).

Similarly, samples of *cis*-4-methylcyclohexylmercuric bromide were cleaved with various brominating agents (expts. 19–24). The *cis* isomer is more sensitive to the free radical reaction as indicated by the lesser amount of retention obtained. As with the *trans* compound, the *cis* isomer yields less retention in nitrogen than in an air atmosphere (expts. 21,22). The *cis* isomer is cleaved completely stereospecifically both in air and nitrogen atmospheres by the bromine–pyridine complex (expts. 23,24).

Larger samples of the *cis*- and *trans*-mercury compounds were cleaved by the bromine–pyridine complex to yield pure samples of *cis*- and *trans*-4-methylcyclohexyl bromides for use as infrared standards for the product distribution analyses. The *trans*-mercury compound yielded a product which solidified in the condenser of the distillation apparatus and was identified as *trans*-4-methylcyclohexyl bromide by its infrared spectrum. The spectrum contained a strong equatorial C–Br absorption at 704 cm.$^{-1}$ [16] and contained no axial C–Br absorption. Similarly, when the *cis* isomer was cleaved, *cis*-4-methylcyclohexyl bromide was obtained which showed strong axial C–Br absorption at 685 cm.$^{-1}$ and weak equatorial C–Br absorption shifted to 707 cm.$^{-1}$. The presence of weak equatorial C–Br absorption is not surprising. From the known $\Delta F(a\text{-}e)$ values for the bromine (0.6 kcal. mole)[17] and methyl (1.8 kcal. mole)[18] groups, it is calculated that *cis*-4-methylcyclohexyl bromide exists as approximately 12% of the conformation where the C–Br bond is equatorial at 25°.



The index of refraction for the *cis*-4-methylcyclohexyl bromide is higher than that of the *trans* isomer, $n^{29.9}_{D}$ 1.4843 and 1.4800, respectively, as was found in the case of the *cis*- and *trans*-4-*t*-butylcyclohexyl bromides.[17]

Aside from the theoretical aspects of the reactions, the cleavage of organomercury compounds by bromine appears to hold promise as a synthetic method for preparing very pure alkyl halides. Our results indicate that the reaction occurs with no rearrangement and with suitable choice of reaction conditions completely stereospecifically. Because of the difficulty of preparing pure secondary bromides,[19] this method should be especially important for their preparation.

The results in Table II appear to indicate that N,N-dibromobenzenesulfonamide, hypobromous acid, bromine with zinc bromide and pyridinium bromide perbromide all cleave the alkylmercury bromides by both free radical and polar pathways. Surprisingly, the addition of zinc bromide has almost no effect upon the amount of retention obtained (expts. 9 and 6, Table I, and expts. 14 and 20, Table II). Under identical reaction conditions, zinc chloride is an excellent catalyst for the electrophilic bromination of aromatic compounds.[20] This result might indicate that bromine adds to the mercury compound as a unit. The possible catalytic activity of zinc chloride and other metal halides is under investigation.

The high stereospecificity of the bromine-pyridine complex as a cleaving agent may be due to one or a combination of factors: (a) the bromine molecule is so highly polarized by complexing with pyridine that it has little tendency to dissociate or react homolytically, (b) the pyridine solvent complexes the organomercury compound polarizing the carbon–mercury bond, (c) the pyridine acts as a free radical inhibitor, and (d) the polar character of pyridine greatly favors the polar reaction.

Possible mechanisms for the polar reaction with bromine include: (a) a S$_E$2 reaction which occurs by direct attack on the carbon–mercury bond by positive bromine, (b) a S$_E$2 reaction which occurs by direct frontal attack on carbon, (c) a four center reaction involving attack by Br–Br simultaneously on carbon and mercury, and (d) a S$_E$i mechanism which occurs by attack of bromine on mercury followed by rearrangement to give the products. The results do not allow a decision as to the mechanism and therefore a discussion of the mechanism will be deferred until more results have been obtained.

Experimental

A typical experiment is described for each type of solvent or brominating agent.

Cleavage of 4-Methylcyclohexylmercuric Bromide by Bromine in Carbon Tetrachloride.—In a flask, which had been flamed out under a nitrogen atmosphere, was placed 20 g. (0.053 mole) of *trans*-4-methylcyclohexylmercuric bromide and 200 ml. of anhydrous carbon tetrachloride (distilled from calcium hydride). The reaction flask was cooled in an ice-bath and a nitrogen atmosphere was maintained. A solution of bromine (8.5 g., 0.05 mole, the bromine was purified by washing with concd. sulfuric acid) in carbon tetrachloride (40 ml.) was added over a period of 4 hr. to the stirred, cooled suspension. After stirring the reaction mixture at 0° for 8 hr., the carbon tetrachloride solution was filtered, washed with 10% sodium thiosulfate and water, and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the product was distilled through a 20-cm. Vigreux column yielding 5.8 g. of 4-methylcyclohexyl bromide (62%), b.p. 55–56° (10 mm.), reported[21] b.p. 83° (30 mm.). The product contained 47.6% *cis*- and 52.4% *trans*-4-methylcyclohexyl bromides as determined by infrared analysis.

Similarly, 2 g. (0.0053 mole) of *cis*-4-methylcyclohexylmercuric bromide was cleaved in carbon tetrachloride at 0° under a nitrogen atmosphere to yield 0.63 g. of 4-methylcyclohexyl bromide (67%). Infrared analysis of the product indicated that it contained 47.4% *cis*- and 52.6% *trans*-4-methylcyclohexyl bromides. The average reproducibility for a number of runs was ±0.2%.

Cleavage by Bromine in Acetic Acid.—To a solution of 2 g. (0.0053 mole) of *trans*-4-methylcyclohexylmercuric bromide in 20 ml. of glacial acetic acid at 25° was added slowly a solution of 0.85 g. (0.0053 mole) of bromine dissolved in 5 ml. of glacial acetic acid. After the reaction was complete, the solution was filtered and 50 ml. of pentane was added. The resulting solution was washed successively with two portions

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of water, 10% sodium thiosulfate, water, concd. sulfuric acid, water, 10% sodium bicarbonate, water and dried over anhydrous magnesium sulfate. The pentane was removed at reduced pressure through a 20-cm. Vigreux column and the remaining product was distilled at 10 mm. in a micro distillation apparatus yielding 0.75 g. of 4-methylcyclohexyl bromide (80%). Infrared analysis of the product indicated that it contained 9% *cis*- and 91% *trans*-4-methylcyclohexyl bromides.

Cleavage by Pyridinium Bromide Perbromide in Acetic Acid.—A mixture of 1.9 g. (0.0060 mole) of pyridinium bromide perbromide and 2 g. (0.0053 mole) of *trans*-4-methylcyclohexylmercuric bromide was dissolved in 25 ml. of glacial acetic acid. The solution was stirred for 2.5 hr. at 25° and the product was worked up as described for the bromine cleavage in acetic acid to yield 0.70 g. of 4-methylcyclohexyl bromide (74%). Infrared analysis of the product indicated that it contained greater than 99% *trans*-4-methylcyclohexyl bromide.

Cleavage by N,N-Dibromobenzenesulfonamide in Acetic Acid.—The experimental procedure was the same as described for the pyridinium bromide perbromide cleavage in acetic acid.

Cleavage by Bromine and Zinc Bromide in Acetic Acid.—The experimental procedure was the same as described for the bromine cleavage in acetic acid with the exception that a molar amount of zinc bromide was added to the reaction flask.

Cleavage by Hypobromous Acid in 50% Dioxane–50% Water.—To a solution of 2 g. (0.0053 mole) of *cis*-4-methylcyclohexylmercuric bromide in 70 ml. of dioxane was added a solution of 0.078 *M* hypobromous acid (the hypobromous acid was prepared by stirring a mixture of mercuric oxide, bromine and water together, distilling at reduced pressure and washing the distillate with carbon tetrachloride) and 0.40 ml. of concd. sulfuric acid, over a period of one hour at 25°. The entire reaction was carried out under a nitrogen atmosphere in the dark. After stirring for 2 hr., a sample was titrated with standard sodium thiosulfate solution and the reaction was found to be 90% complete. The solution was filtered and 50 ml. of pentane was added. The pentane layer was separated and washed successively with water, concd. sulfuric acid, water, 5% sodium bicarbonate, water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the product was distilled at 10 mm. in a micro distillation apparatus to yield 0.26 g. of 4-methylcyclohexyl bromide (28%). Infrared analysis of the product indicated that it contained 46% *cis*- and 54% *trans*-4-methylcyclohexyl bromides.

Cleavage by Bromine in Pyridine.—In a 300-ml., 3-necked round-bottom flask fitted with a Teflon mechanical stirrer and a 60-ml. dropping funnel was placed 30 g. (0.079 mole) of *trans*-4-methylcyclohexylmercuric bromide and 150 ml. of pyridine. (The pyridine was purified by distilling from toluenesulfonyl chloride through a 30-plate column.) In the dropping funnel was placed 13.0 g. (0.081 mole) of anhydrous bromine in 25 ml. of pyridine. The bromine solution was added slowly over a period of 0.5 hr. at 25°. The reactants were stirred at 25° for 1 hr. and poured into a 1-l. beaker containing 150 ml. of hexane. Approximately 300 ml. of water was added and the resulting mercuric bromide precipitate was removed by filtration with suction. The hexane layer was removed and the remaining pyridine–water layer was reëxtracted with hexane. The combined hexane layers were washed successively with water, concd. sulfuric acid, water, 5% sodium bicarbonate, water and dried over anhydrous magnesium sulfate. The hexane was removed by distilling at reduced pressure through a 15″ tantalum spiral wire column. The remaining product was distilled to yield 9.3 g. of *trans*-4-methylcyclohexyl bromide (66%), b.p. 57.0° (9.5 mm.), m.p. 25.0–26.0°, $n^{29.9}_{\mathrm{D}}$ 1.4800; characteristic infrared maxima (carbon disulfide): 7.50(m), 8.89(m), 9.30(w), 9.95(m), 10.35(s), 11.33(w), 11.63(s), 12.75(m) and 14.20(s) μ.

Similarly, 12 g. (0.0318 mole) of *cis*-4-methylcyclohexylmercuric bromide was cleaved by bromine in pyridine at 0° yielding 3.1 g. of *cis*-4-methylcyclohexyl bromide (55%), b.p. 57.0–57.8° (9.5 mm.), $n^{29.9}_{\mathrm{D}}$ 1.4843; characteristic infrared maxima (carbon disulfide): 7.41(m), 7.67(m), 9.06(m), 9.75(m), 10.32(w), 10.40(m), 10.57(m), 11.46(w), 11.80(m), 14.13(w) and 14.60(s) μ.

Anal. Calcd. for $C_7H_{13}Br$: C, 47.47; H, 7.40; Br, 45.13. Found for *trans*-$C_7H_{13}Br$: C, 47.53; H, 7.58; Br, 44.88. Found for *cis*-$C_7H_{13}Br$: C, 47.30; H, 7.52; Br, 45.09.

Within the sensitivity of our methods for detecting each isomer (infrared, less than 1%), the *cis*- and *trans*-4-methylcyclohexyl bromides are homogeneous.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Conformation of 3α-Phenyl-3β-tropanyl Phenyl Ketone; a Novel Nitrogen–Carbonyl Interaction

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The abnormal spectral behavior of 3α-phenyl-3β-tropanyl phenyl ketone (IIa) is interpreted as evidence that the piperidine ring exists in the boat conformation with resultant nitrogen–carbonyl interaction. The normal spectral behavior of appropriate model compounds indicated that IIa adopts this conformation to relieve the non-bonded interaction between the 3α-phenyl group and the ethylene bridge.

During synthetic studies directed toward the preparation of 3α-phenyl-3β-tropanecarboxylic acid we prepared 3α-phenyl-3β-tropanyl phenyl ketone (IIa) by a route analogous to that used for the corresponding piperidine derivative (IV).[1] The starting material, α-ecgonine methyl ester (Ia), has long been known[2] but only recently been assigned the correct stereochemical structure on the basis of chemical and spectral evidence.[3] Before Heusner's observations were available we had relied on the observation of intramolecular hydrogen bonding in the infrared spectrum to arrive at the same formulation.

Reaction of the α-ecgonine ester with phenyllithium afforded 3α-diphenylhydroxymethyl-3β-tropanol (Ib) which was transformed by zinc chloride in acetic anhydride to a crystalline base whose analysis and those of its derivatives were in accord with the values expected for the ketone IIa. Reduction either catalytically or with lithium aluminum hydride furnished the alcohol IIIa which could be oxidized to the parent ketone with chromic acid in acetic acid; IIa formed an oxime but only under forcing conditions indicating the relatively unreactive condition of the carbonyl group. Other trans-

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