Studies on the Mechanism of the Oxymercuration of Substituted Cyclohexenes[1]

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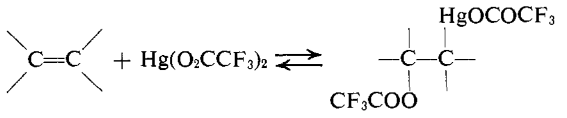
Abstract: The stereochemistry of the oxymercuration of 4-*tert*-butylcyclohexene (**5**) and 1-methyl-4-*tert*-butylcyclohexene (**6**) has been determined, and has been shown to give exclusively trans-diaxial products. The stereochemistry of the bromination and methoxybromination, both of which proceed *via* cyclic bromonium ion intermediates, of **5** and **6** similarly produces only trans-diaxial products. In contrast, the hydrobromination, known to occur by an open Ad_E3 addition mechanism, of **5** and **6** produces mixtures of axial and equatorial bromides, the former predominating. It is concluded that the oxymercuration of substituted cyclohexenes proceeds *via* mercurinium ion intermediates which are formed in fast, reversible pre-rate-determining step equilibria. This is in contrast to the mechanism of oxymercuration of norbornene derivatives which does not proceed *via* mercurinium ion intermediates.

Since the discovery of the oxymercuration of olefins by Hofmann and Sand[2] in 1900, the solvomercuration of olefinic compounds has been developed into a synthetically very useful reaction. For example, the hydroxy-,[3] acetoxy-, alkoxy-,[4] hydroperoxy-,[5] alkylperoxy-,[6] amino-,[7] amido-,[8] and azidomercuration[9] of olefins, followed by reductive demercuration with sodium borohydride,[3,0] has been developed into synthetically important methods for the synthesis of alcohols,[3] ethers,[4] dialkyl peroxides,[6] amines,[7,11] and amides.[8]

Although numerous kinetic and stereochemical investigations have been devoted to the study of the intimate details of the solvomercuration reaction, the nature of reaction intermediates and/or transition states involved in the addition reactions in many systems is still unresolved. In 1939 Lucas, *et al.*,[12] proposed that the oxymercuration of alkenes occurred by an anti addition (by analogy with the bromination of alkenes), and that the anti addition proceeded *via* a cyclic cationic intermediate, or mercurinium ion,[13] which underwent ring opening by nucleophilic attack at carbon with inversion. It was later established that the oxymercuration of cyclopentene and cyclohexene had in fact occurred in an anti manner,[14,15] although it has also been established that norbornene derivatives undergo exclusive cis-exo oxymercuration.[15]

In an effort to derive support for the proposed formation of an intermediate mercurinium ion, Winstein and coworkers measured the distribution equilibria of cyclohexene between carbon tetrachloride and aqueous solutions of mercuric nitrate. Winstein interpreted the distribution equilibrium constants in terms of equilibrium constants for the formation of mercurinium ions, analogous to the formation of silver ion–olefin complexes studied previously by similar techniques. However, in a recent kinetic investigation of the oxymercuration of olefins, Halpern and Tinker[16] could not derive substantive evidence for or against the intermediacy of mercurinium ions as reaction intermediates. Brown, *et al.*,[17] recently reported the measurement of equilibrium constants for the rapid and reversible formation of oxymercurials from olefins and mercuric trifluoroacetate in aprotic solvents (eq 1), but, similarly, could derive no evidence concerning the possible formation of mercurinium ions in these reactions.[18]



$$\rangle C{=}C\langle + Hg(O_2CCF_3)_2 \rightleftarrows -\underset{CF_3COO}{\overset{|}{\underset{|}{C}}}-\overset{HgOCOCF_3}{\overset{|}{\underset{|}{C}}}- \qquad (1)$$

Whitham and coworkers[19] studied the acid-catalyzed methanolysis of *trans*-2-hydroxycyclohexyl mercuric acetate in the presence of 1-methylcyclohexene and concluded that a mercurinium ion was not an intermediate in the deoxymercuration reaction, and, by the principle

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[1] (a) Submitted by J. A. G. in partial fulfillment of the requirements for the Ph.D. degree, University of Notre Dame, Notre Dame, Ind., 1970. (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work (PRF-1225-Al, 3), and to the Alfred P. Sloan Foundation for partial support of this work.

[2] K. A. Hofmann and J. Sand, *Chem. Ber.*, 1340 (1900).

[3] H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

[4] H. C. Brown and M.-H. Rei, *ibid.*, **91**, 5646 (1969).

[5] V. I. Sokolov and O. A. Reutov, *Zh. Org. Khim.*, **5**, 174 (1969).

[6] D. H. Ballard, A. J. Bloodworth, and R. J. Bunce, *Chem. Commun.*, 815 (1969).

[7] A. Latter and J. J. Perié, *Tetrahedron Lett.*, 5165 (1967); J. J. Perié and A. Latter, *ibid.*, 2289 (1969).

[8] H. C. Brown and J. T. Kurek, *J. Amer. Chem. Soc.*, **91**, 5647 (1969).

[9] C. H. Heathcock, *Angew. Chem.*, **81**, 148 (1969).

[10] (a) G. M. Whitesides and J. San Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 6611 (1970); (b) G. A. Gray and W. R. Jackson, *ibid.*, **91**, 6205 (1969); (c) D. J. Pasto and J. Gontarz, *ibid.*, **91**, 719 (1969); (d) F. G. Bordwell and M. L. Douglass, *ibid.*, **88**, 993 (1966); (e) J. Sand and F. Singer, *Chem. Ber.*, **35**, 3170 (1902).

[11] *Via* hydrolysis of alkyl amides formed in amidomercuration.[8]

[12] H. J. Lucas, F. R. Hepner, and S. Winstein, *J. Amer. Chem. Soc.*, **61**, 3102 (1939).

[13] It has been pointed out by a referee that the term "mercurinium ion" is not consistent with the nomenclature of other cyclic cationic species of the same nature; *i.e.*, onium ion intermediates. The term mercurinium ion is well established, and to change the designation of the cyclic intermediate in the oxymercuration reaction from mercurinium ion to mercuronium ion at this time would result in confusion and thus seems unwarranted.

[14] A. Brook and G. Wright, *Acta Crystallogr.*, **4**, 50 (1951); M. Anderson and P. Henry, *Chem. Ind.* (*London*), 2053 (1961).

[15] T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).

[16] J. Halpern and H. B. Tinker, *ibid.*, **89**, 6427 (1967).

[17] H. C. Brown, M.-H. Rei, and K.-T. Liu, *ibid.*, **92**, 1760 (1970).

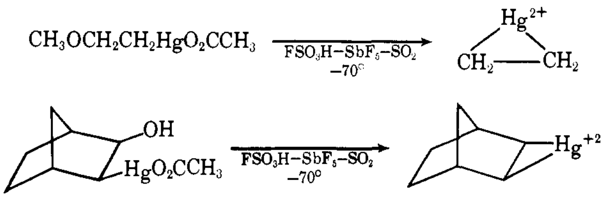
[18] In view of these foregoing results it would appear that Winstein and coworkers[12] did not measure equilibrium constants for mercurinium ion formation, but probably measured adduct formation or phase solubility equilibrium constants.

[19] S. Bentham, P. Chamberlain, and G. H. Whitham, *Chem. Commun.*, 1528 (1970).

of microscopic reversibility, a mercurinium ion is not an intermediate in the oxymercuration of a cyclohexene. We will return to these observations and discuss them later in this article.

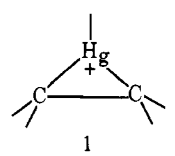
Nuclear magnetic resonance spectral data taken of the reaction solutions of the oxymercuration of ethylene[20] and cyclohexene[21] have been interpreted as indicating the presence of mercurinium ions in solution; however, Kitching, *et al.*,[22] have reported that the resonances observed by Saito and Matsuo and attributed to mercurinium ions are actually due to impurities formed in oxymercuration side reactions. Parker and Roberts[23] report that the ^{13}C nmr spectra of methanol solutions of alkene and mercuric acetate show only the presence of the expected methoxymercuration products.

After the appearance of a preliminary communication from our laboratories presenting evidence in favor of mercurinium ions as intermediates in the kinetically controlled oxymercuration of substituted cyclohexenes,[24] Olah and Clifford[25] reported the direct observation by nmr of mercurinium ions derived from 2-methoxyethylmercuric acetate and *exo*-3-hydroxy-*exo*-2-norbornyl mercuric acetate.



Stereochemical evidence concerning the possible intermediacy of mercurinium ions has been derived with two distinctly different types of unsaturated systems. Waters and coworkers[26] have studied the stereochemistry of the oxymercuration of optically active 1,3-dimethylallene, and have compared the stereochemical course of the oxymercuration reaction with that of bromination, methoxybromination, and iodination,[26b] reactions known to proceed *via* onium ion-type intermediates. Waters and coworkers concluded that the oxymercuration of 1,3-dimethylallene involved a preequilibrium formation of a σ-bonded mercurinium ion. In a recent review on electrophilic addition reactions Fahey[27] has pointed out that there was no compelling evidence which demands the intermediacy of mercurinium ions in the solvomercuration of unstrained olefins, and suggested that the data of Waters and coworkers could be equally rationalized as proceeding *via* an AdE3-type mechanism involving a transition state illustrated as **2**.

Bach[28] has studied the ethoxymercuration of 1,2-cyclononadiene and proposed the formation of a mercurinium ion as a reaction intermediate. Bach[28] also observed that the stereoselectivity of the ethoxymercuration was dependent on the mercuric salt used.



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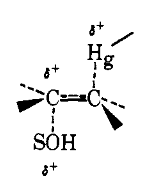

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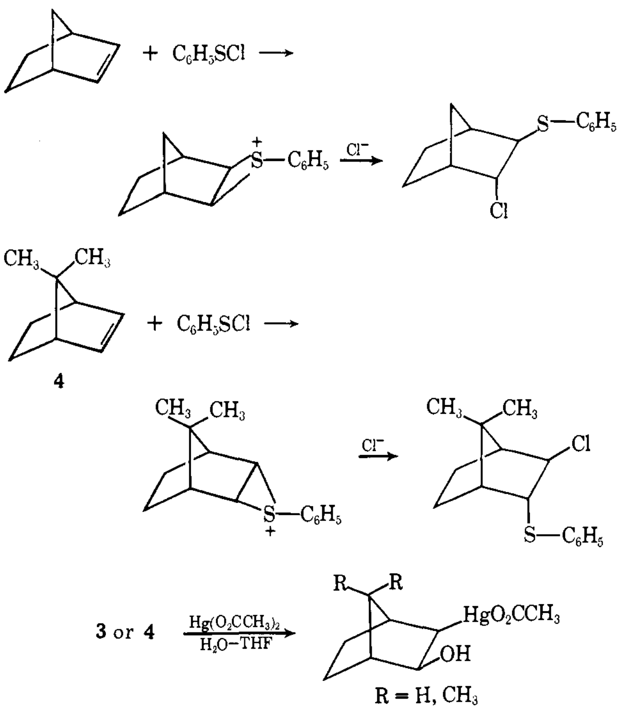
Brown and Liu[29] have compared the stereochemical course of the oxymercuration with that of the addition of benzenesulfenyl chloride to norbornene (**3**) and 7,7-dimethylnorbornene (**4**). These authors observed that in the benzenesulfenyl chloride additions to **3** and **4**, which proceed *via* episulfonium ion intermediates, the reagent undergoes exclusive anti addition, and the 7,7-dimethyl bridge of **4** imparts a distinct steric effect on the course of episulfonium ion formation. In contrast, the oxymercuration of **3** and **4** gave only cis-exo products leading Brown to conclude that "a cyclic transition state or intermediate, *e.g.*, a mercurinium ion, is probably not involved in this addition reaction."[29,30]



Our interest in steric effects in electrophilic addition[31] and other reactions[32] led us to investigate the stereochemical aspects of the oxymercuration of a series of substituted cyclohexenes, and to compare the stereochemical course of the oxymercuration reaction with other electrophilic addition reactions known to proceed *via* onium ion-type intermediates and noncyclic AdE3 transition states. A preliminary account of these results has appeared;[24] the present publication reports the details of the structural assignments and a more detailed discussion of the results.

[20] Y. Saito and M. Matsuo, *Chem. Commun.*, 961 (1967).

[21] V. Sokolov, U. Yustynyuk, and O. Reutov, *Dokl. Akad. Nauk SSSR*, 173, 1103 (1967).

[22] W. Kitching, A. J. Smith, and P. R. Wells, *Aust. J. Chem.*, **21**, 2395 (1968).

[23] R. G. Parker and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 743 (1970).

[24] D. J. Pasto and J. Gontarz, *ibid.*, **92**, 7480 (1970).

[25] G. A. Olah and P. R. Clifford, *ibid.*, **93**, 1262 (1971).

[26] (a) W. L. Waters and E. F. Kiefer, *ibid.*, **89**, 6261 (1967); (b) W. L. Waters, W. S. Linn, and M. C. Caserio, *ibid.*, **90**, 6741 (1968).

[27] R. C. Fahey, *Top. Stereochem.*, **3**, 318 (1968).

[28] R. D. Bach, *J. Amer. Chem. Soc.*, **91**, 1771 (1969).

[29] H. C. Brown and K.-T. Liu, *ibid.*, **92**, 3502 (1970).

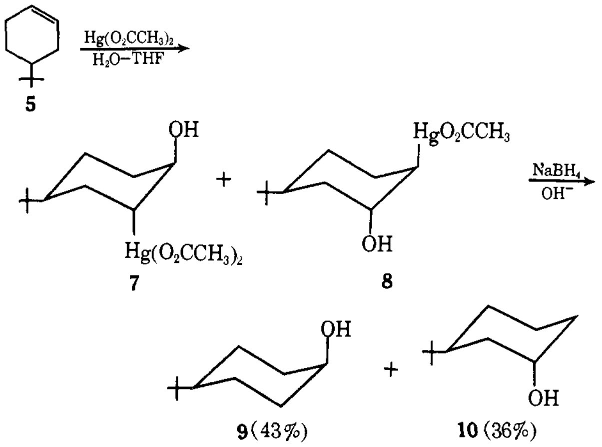
[30] The results of Brown and Liu[29] would appear to be in conflict with the results of Olah and Clifford.[25] However, the experimental conditions are extremely different and the two observations are not comparable. Olah and Clifford do note that at −30° the nmr spectrum of the norbornene mercurinium ion coalesces to a single broad line indicating the reversible formation of equilibrating, open cationic structures.

[31] D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

[32] D. J. Pasto and D. R. Rao, *J. Amer. Chem. Soc.*, **92**, 5151 (1970).

Results

Oxymercuration of 4-*tert*-Butylcyclohexene (5) and 1-Methyl-4-*tert*-butylcyclohexene (6). The oxymercuration of 4-*tert*-butylcyclohexene in 50% aqueous tetrahydrofuran at 25° for short periods of time followed by reductive demercuration with sodium borohydride produces a 54:46 mixture of *cis*-4- (**9**) and *trans*-3-*tert*-butylcyclohexanol (**10**). None of the equatorial *trans*-4- (**11**) or *cis*-3-*tert*-butylcyclohexanols (**12**) could be detected by glpc analysis.[33] Although the orientation of the hydroxyl group in the reduced products specifies the orientation of the hydroxyl group in the oxymercuration adducts,[34] the stereochemical relationship of the acetoxymercuri functional group to the hydroxyl group remained to be determined. This stereochemical relationship was determined by analysis of the nmr spectrum obtained directly on the adduct mixture formed by oxymercuration of **5** in 50% deuterium oxide–hexadeuterioacetone. The resonances of the hydrogens bonded to the carbon atoms bearing the acetoxymercuri functional group appeared as overlapping multiplets at δ 3.12 and 3.18 with half-height bandwidths of approximately 9 Hz. Integration of this resonance signal, with correction for the ^{199}Hg satellite intensities, indicated 1.03 ± 0.03 hydrogens relative to the well-resolved resonance of the *tert*-butyl hydrogens. The carbinol hydrogens appeared as overlapping multiplets at δ 4.27 and 4.42 with half-height bandwidths of ~7 and 9 Hz, respectively. The observed half-height bandwidths correlate well with those expected of equatorial hydrogens in substituted cyclohexanes reported by Lemieux and coworkers.[35] The nmr data, along with the observed reduction of the intermediate oxymercurials to only the axial alcohols **9** and **10**, allow the assignment of the stereochemical relationship between the deuteroxyl and acetoxymercuri functional groups in the intermediate organomercurials as trans-diaxial.

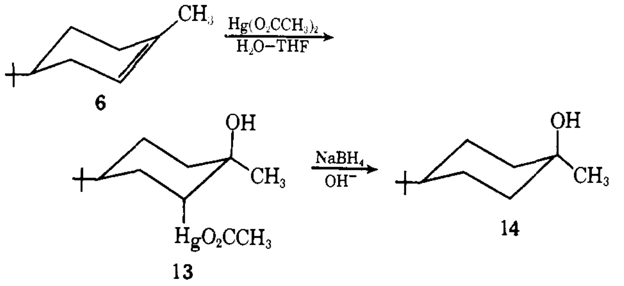


Reaction of **5** with an excess of mercuric acetate for periods of time longer than 45 min leads to the formation of equatorial alcohols on reduction. The total amount of equatorial alcohol approached 79% after 10 days at 25° (see Table I). During this period of time a precipitate slowly formed. Due to the presence of the insoluble material it was not possible to determine the stereochemical relationship between the hydroxyl and acetoxymercuri functional groups by nmr. It would appear that the initial trans-diaxial products are formed in kinetically controlled reactions whereas the equatorial products are formed in thermodynamically controlled reactions.[33,36] All of the results reported in the present articles are for the kinetically controlled reactions only.

Table I. Product Distribution Derived from the Oxymercuration of **5** in the Presence of Excess Mercuric Acetate for Prolonged Reaction Times Followed by Sodium Borohydride Reduction

Reaction time, hr	% *tert*-butylcyclohexanol			
	cis-4 (**9**)	*trans*-3 (**10**)	*trans*-4 (**11**)	*cis*-3 (**12**)
0.33	53.4	46.6	0.0	0.0
4.0	46.7	48.0	2.7	2.6
7.0	43.2	44.3	9.8	2.7
26.0	41.2	43.2	7.2	8.4
78.0	31.8	25.8	14.2	18.2
171.0	20.4	21.1	26.2	32.3
244	10.8	10.1	41.1	37.0

The oxymercuration of 1-methyl-4-*tert*-butylcyclohexene (**6**) produces a single addition product, assigned structure **13** on the basis of the nmr spectral data. The methyl group appears as a sharp singlet at δ 1.37 indicating the presence of a single addition product. The C-2 hydrogen of **13** appears as a narrow multiplet at δ 3.15 with a half-height bandwidth of 6.7 Hz which integrates to 1.03 ± 0.03 hydrogen (including the ^{199}Hg satellites, $J_{^{199}\mathrm{Hg}\mathrm{H}} = 242$ Hz) relative to the *tert*-butyl group. Again, the nmr spectral data indicate that the acetoxymercuri functional group is axial. Reduction of the addition product with sodium borohydride produced only 1-methyl-*cis*-4-*tert*-butylcyclohexanol (**14**) in 93.7% absolute yield.[38] The formation of the axial alcohol rigorously defines the stereochemistry in the oxymercuration product as that shown in **13**.



Bromination of 5 and 6. The bromination of **5** with pyridinium hydrobromide perbromide in pyridine at 0° produced only the trans-diaxial bromide **15**.[39] The

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[33] Whitham and coworkers[19] have also studied the oxymercuration of **5** and **6** in 50% aqueous tetrahydrofuran for 1 hr in the presence of 3% perchloric acid and note the formation of small quantities of equatorial alcohol which increases on further standing.

[34] The reductive demercuration with sodium borohydride produces β-hydroxyalkyl free radicals[10c] in which the stereochemistry about the carbon originally bearing the acetoxymercuri functional group is lost; however, the stereochemistry about the carbinol carbon atom is retained.

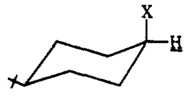
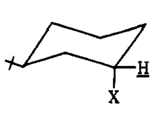
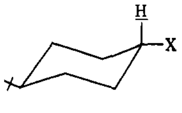
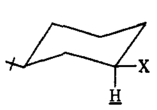
[35] R. U. Lemieux, R. H. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, 80, 6098 (1959).

[36] The formation of equatorial products (4–7%) in the oxymercuration of *cis*-5-*tert*-butyl- and 5-phenylcyclohex-2-enol has been reported;[3] however, the experimental conditions were not described and it is not possible to judge whether the equatorial products are formed in a kinetically controlled reaction.

[37] J. Klein and R. Levene, *Tetrahedron Lett.*, 4833 (1969).

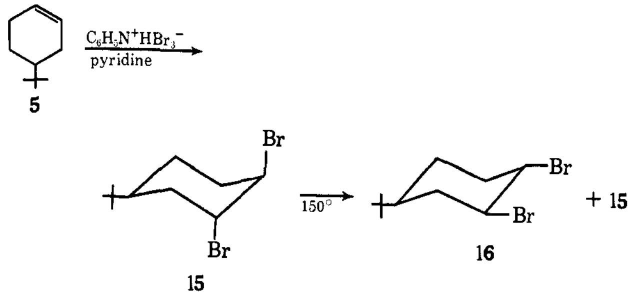
[38] The formation of only the axial alcohol **14** from **6** represents an excellent procedure for the preparation of 1-alkyl-*cis*-4-*tert*-butylcyclohexanols. Other procedures involving the addition of an alkyllithium or magnesium compound to 4-*tert*-butylcyclohexanone produce mixtures of difficultly separable and identifiable products.

Table II. Chemical Shifts (δ) of Equatorial and Axial Hydrogens in 3- and 4-Substituted *tert*-Butylcyclohexanes[a]

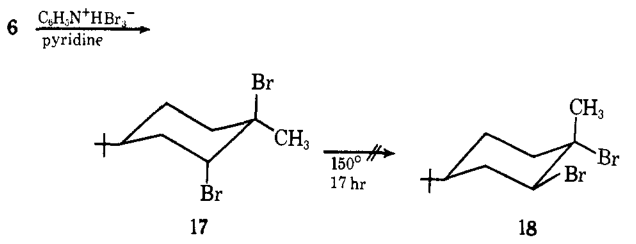
X				
OH[b]	4.05	4.17	3.39	3.43
Br[b]	4.57	4.69	3.94	3.98
Cl[c]	4.45	4.57	3.78	3.84
F[c]	5.18	5.29	4.80	4.81

[a] Recorded 20% in deuteriochloroform. [b] Recorded in this study. [c] Taken from E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 689 (1968).

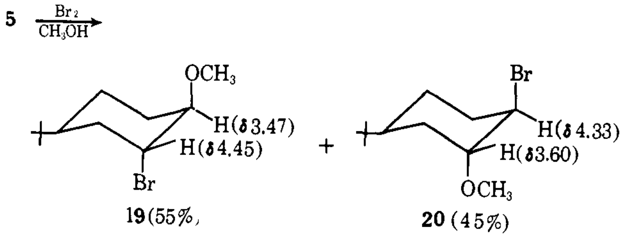
nmr spectrum of **15** was identical with that reported by Skell and Readio[40] with the hydrogens on carbon bonded to bromine appearing as a narrow multiplet at δ 4.70. None of the trans-diequatorial isomer **16**, formed by the thermal isomerization of **15** (nmr, broad multiplet at δ 4.00), was detected by nmr techniques.



The bromination of **6** similarly gave only a single product (by nmr analysis), assigned structure **17**. The hydrogen on the carbon bearing bromine appears as a very narrow multiplet at δ 4.73 (4.0 Hz half-height bandwidth), consistent with the chemical shift of an equatorial hydrogen bonded to carbon bearing bromine (see Table II). The diaxial dibromide **17** could not be thermally isomerized to the diequatorial bromide **18** even on heating at 150° for 17 hr.



Methoxybromination of 5 and 6. The methoxybromination of **5** with a dilute solution of bromine in methanol[26b] produced a mixture of the two methoxy bromides **19** and **20** in a 55:45 ratio as determined by nmr analysis. The structures of the two methoxybromination products were assigned by comparison of the chemical shifts of the methine hydrogens with those of the corresponding methine hydrogens of 3- and 4-*tert*-butylcyclohexyl derivatives (see Table II). The nmr spectrum of the product mixture displayed a series of multiplets at δ 3.47, 3.60, 4.33, and 4.45. The multiplets at δ 4.33 and 4.45 were assigned to the equatorial hydrogens bonded to carbon bearing bromine by analogy with the chemical shifts of the similar hydrogens in the 3- and 4-*tert*-butylcyclohexyl bromides. The multiplets at δ 4.45 and 4.33 were assigned to **19** and **20**, respectively, as follows. Inspection of the data in Table II reveals that the equatorial hydrogen of the trans-3-substituted *tert*-butylcyclohexanes appears approximately 0.12 ppm downfield relative to the similar equatorial hydrogen of the 4-*tert*-butyl isomers. Thus the resonance at δ 4.45 is assigned to isomer **19**. Unfortunately the chemical shifts of the 3- and 4-methoxy-*tert*-butylcyclohexanes have not been reported. However, use of the above indicated correlation allows assignment of the δ 3.60 resonance to equatorial hydrogen on carbon bearing the methoxyl in compound **20**. Saturation of the ring hydrogens of **19** and **20** resulted in collapse of the δ 3.60, 4.33, and 4.45 multiplets to doublets with J of 2.4 Hz resulting from coupling of the hydrogens on carbon bearing bromine and methoxyl. The magnitude of these coupling constants is consistent with the average 2.7-Hz coupling constants reported for trans-diaxially substituted cyclohexanes.[41] All of the nmr data are consistent with the formation of **19** and **20** in the methoxybromination of **5**.



The methoxybromination of **6** gave **21** as the only methoxybromination product in ~80% yield. The structure of the product was assigned from nmr data. The hydrogen on carbon bearing bromine appeared at δ 4.31 with a half-height bandwidth of 4.0 Hz. Both the chemical shift and bandwidth are consistent with an equatorial orientation for the hydrogen. In addition to the formation of **21**, 5% of **17** and approximately 15% of another compound assigned structure **22** were formed. The nmr spectrum showed equal intensity methoxyl singlets at δ 3.26 and 3.32 with the equatorial hydrogen on the carbon bearing the methoxyl appearing as a narrow multiplet at δ 3.46. The formation of **22**

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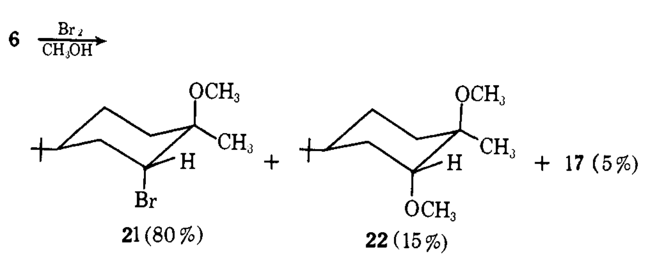
(39) E. L. Eliel and R. G. Haber (*J. Org. Chem.*, **24**, 143 (1959)) have reported that the bromination in carbon tetrachloride at 0° followed by distillation at 12 mm (no temperature specified) yields a mixture of **15** and **16**. Under the present reaction conditions **16** was not detected as a product in the bromination of **5**.

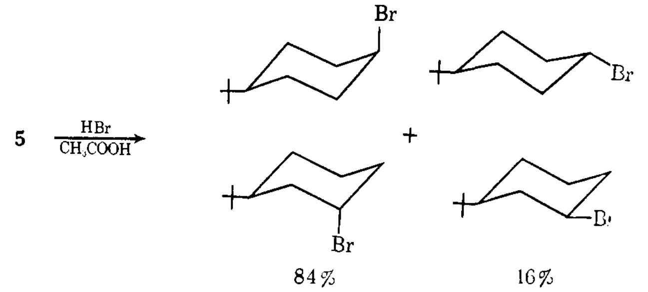
(40) P. S. Skell and P. D. Readio, *J. Amer. Chem. Soc.*, **86**, 3334 (1964).

(41) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, New York, N. Y., 1967.

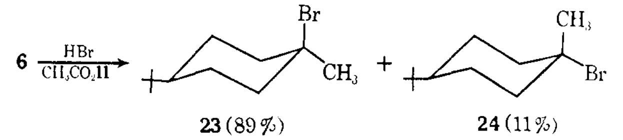


is believed to occur by the methanolysis of **21** with neighboring group participation.

Hydrobromination of 5 and 6. The reaction of **5** with hydrogen bromide in acetic acid produced a mixture of 3- and 4-*tert*-butylbromocyclohexanes. The nmr spectrum of the reaction product mixture showed overlapping multiplets for axial and equatorial bromides in a ratio of 84:16. All attempts at further analysis of the reaction mixture failed.

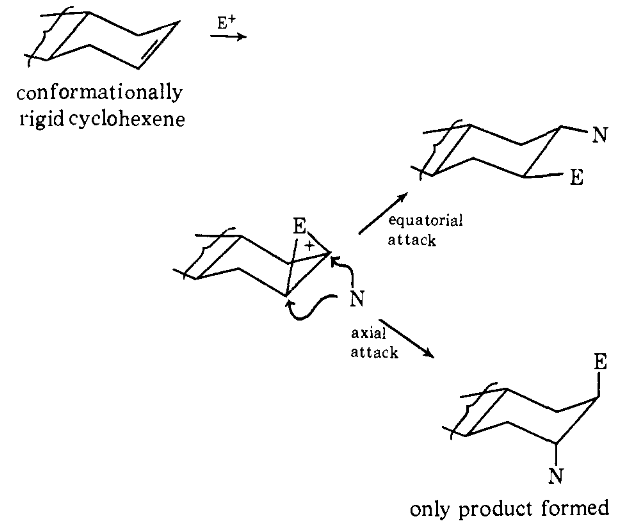


Hydrobromination of **6** in acetic acid produced a mixture of **23** and **24** in an 89:11 ratio. Although **23** and **24** could not be separated by glpc, the nmr spectrum of the mixture showed two *tert*-butyl singlets at δ 0.83 and 0.87 and two methyl singlets at δ 1.71 and 1.73, both sets of peaks appearing in an 11:89 ratio. The assignment of the major isomer as **33** is based on analogy with the hydrobromination of **5** in which the axial products are formed in largest quantity.

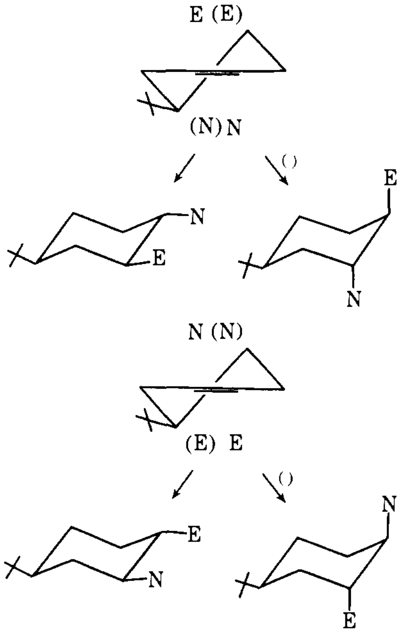


Discussion

The distinction between AdE2 onium ion intermediate and AdE3 anti-addition processes involving a conformationally biased cyclohexene can be made by consideration of the stereochemistry of the addition processes. The intermediacy of a cyclic cationic species, or onium ion, in an electrophilic addition to a cyclohexene is predicted to give rise to the formation of trans-diaxial addition products. The intermediate onium ion is expected to open only by axial attack as has been demonstrated in the nucleophilic ring-opening reactions of cyclohexene oxides.[42] Examples of electrophilic additions to substituted cyclohexenes proceeding *via* onium ion-type intermediates are provided by the bromination[43,44] and methoxybromination[26b] of **5** and **6** which produce only trans-diaxial products.



In contrast, an anti AdE3-type of reaction is expected to produce both trans-diaxial and trans-diequatorial addition products as illustrated below. As an example of an AdE3-type addition reaction we have used hydrobromination in acetic acid.[45] Unfortunately, this reaction is complicated by the fact that with cyclohexenes a low percentage of syn hydrobromination also occurs (not shown in the scheme below). In the case of cyclohexene approximately 8% of syn addition occurs which places an upper limit of 8% on the formation of equatorial product that can be derived *via* a syn addition. In reality, the amount of equatorial product that is formed *via* a syn addition is probably much less than the full 8%. In the case of the hydrobromination of **5**, therefore, a major portion of the 16% of equatorial bromide must be formed *via* anti-diequatorial addition reactions. It is doubtful that changing the electro-



E = electrophilic portion of the addition reagent
N = nucleophilic portion of the addition reagent
( ) indicates individual addition pathways

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(42) C. Djerassi and T. Nakano, *Chem. Ind.* (*London*), 1385 (1960); K. Takeda, T. Okanishi, H. Osaka, A. Shinoaka, and N. Aezone, *Chem. Pharm. Bull.*, **9**, 388 (1961).

(43) See P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, N. Y., 1966.

(44) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1477 (1969).

(45) G. R. Meyer, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1970.

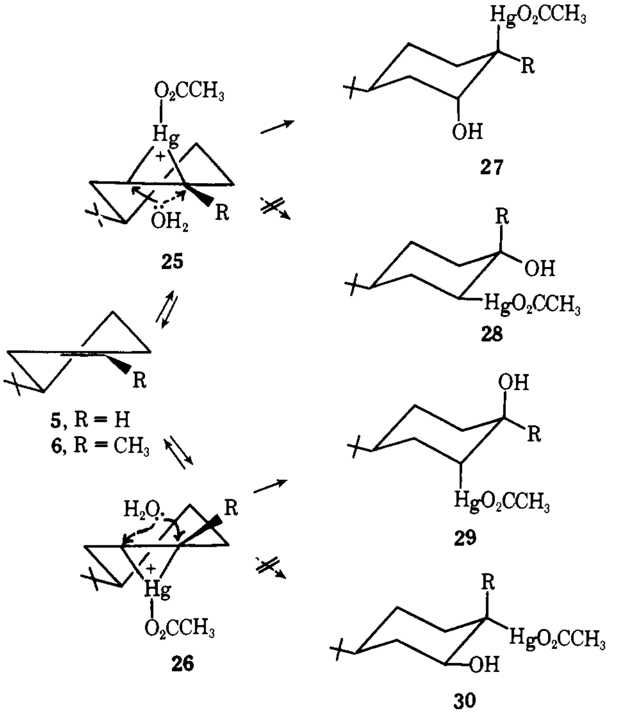
(46) R. C. Fahey and R. A. Smith, *J. Amer. Chem. Soc.*, **86**, 5035 (1964).

philic addition reagent from hydrogen bromide to mercuric acetate will substantially alter the nature of the proposed AdE3 anti addition reaction. As the stereochemistry of the addition of hydrogen bromide to **6** has not been determined, the amount of equatorial bromide formed *via* an anti-diequatorial addition process cannot be reasonably estimated. However, one would not expect the full 11% of the equatorial bromide to be formed by a syn-diequatorial addition process, and thus a considerable amount of **24** must be formed by an anti-diequatorial addition process.

The identical stereochemical results obtained in the oxymercuration, bromination, and methoxybromination of **5** and **6**, as compared to the hydrobromination of **5** and **6**, strongly implies the formation of a mercurinium ion in the oxymercuration of **5** and **6**.[47]

In the oxymercuration of **5** mercurinium ion formation occurs with essentially equal facility at both faces of the cyclohexene double bond as evidenced by the nearly equivalent amounts of the two adducts **7** and **8** which are formed. From prior studies on the steric effects of alkyl groups at various positions of the cyclohexene ring on the ease of attack on the two faces of the cyclohexene double bond, it has been shown that the introduction of a methyl group at the 1 position does not affect the ratio of attack cis and trans (relative to the 4-*tert*-butyl group) relative to the unsubstituted system.[31] However, in the oxymercuration of **6** product is formed only from one of the two possible mercurinium ions that can be derived from **6**. As both mercurinium ions are capable of being formed with nearly equal facility, the intermediate mercurinium ions must be formed in a pre-rate-determining step equilibrium as illustrated in the following scheme.[48] Attack by a mercuric ion cis to the *tert*-butyl group in **5** or **6** leads to the formation of **25**. Attack by water at C-2 occurs with inversion of configuration at C-2 producing the trans-diaxial product **27**. In the case of **25** with R = CH_3, this mode of attack is electronically disfavored leading to anti-Markovnikov addition (not observed). Attack by water at C-1 with inversion with either R = H or CH_3 leads to the formation of trans-diequatorial product **28**. This is not a favorable process because of poor orbital overlap in the transition state for mercurinium ion opening. Attack by mercuric ion trans to the 4-*tert*-butyl group in **5** or **6** leads to the formation of mercurinium ion **26**. Nucleophilic attack by water at C-1 with inversion leads to the formation of the trans-diaxial product **29**. This mode of mercurinium ion opening is possible with both R = H and CH_3. Attack by water at C-2 produces trans-diequatorial product **30**, a process which again is disfavored because of poor orbital overlap in the transition state. The formation of product from **6** *via* **26** (R = CH_3) in >90% yield, and the essentially equal formation of **25** and **26** from **5**, implies that the formation of **25** and **26** must be reversible and pre-rate-determining.[49]

The present conclusions are not incompatible with the results of Whitham and coworkers.[19] Whitham and coworkers attempted to trap the mercurinium ion by reaction with a nucleophile (solvent). If the forma-



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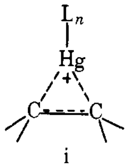
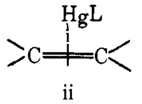
[47] J. E. Herz and E. Gonzalez (*Ciencia*, **26**, 29 (1968)) have reported that the hydroxymercuration of 5-cholest-2-ene gives only trans-diaxial products and suggest that a mercurinium ion is involved as a reaction intermediate.

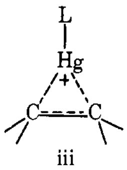
[48] Since the introduction of the mercurinium ion concept by Winstein[12] several other descriptions of this species, and other supposedly closely related species, have appeared. Traylor and Baker[15] have described the mercurinium ion as a π complex of structure i (L represents ligand(s) bonded to mercury). Waters and Kiefer[26a] have used the term π-bonded mercurinium ion formulated as ii and the term σ-bonded mercurinium ion formulated as iii. Waters, *et al.*,[26b] later represented the σ-bonded mercurinium ion as iv. Bach[28] has written the structure v for the proposed mercurinium ion formed in the ethoxymercuration of 1,2-cyclononadiene. Olah and Clifford[25] have represented the mercurinium ion as illustrated in vi. Except for possible differences in stoichiometry between i, ii, iiii, and vi, there is no difference in the orbital descriptions in i, ii, iii, and vi (except that implied by the various authors). The mercuric ion, or solvated mercuric ion approaches the π electron system until a stable bonding configuration is attained, and thus there is no real distinction between the σ- and π-bonded mercurinium ions. We will represent the mercurinium ion as iv, keeping in mind that resonance structures such as vii and ix must contribute to the structure of the mercurinium ion, and that the mercurinium may not be a symmetrical species in unsymmetrical systems.



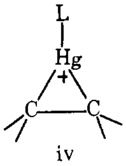
i



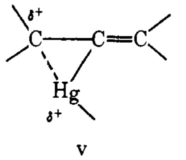
ii



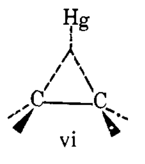
iii



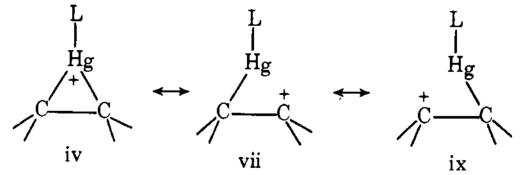
iv



v



vi



[49] The formation of essentially equal quantities of **19** and **20** in the methoxybromination of **5** and the formation of only **21** in ~85% yield in the methoxybromination of **6** implies that bromonium ion formation is also reversible. This is contrary to the generally accepted belief that bromonium ions are formed irreversibly (see ref 23, p 287).

tion of mercurinium ions occurs in a fast and reversible process, the unimolecular decomposition of the mercurinium ion to alkene and mercuric ion is expected to occur more rapidly than reaction with solvent in a bimolecular reaction to give the "trapped" mercurinium ion product.

The results derived with the kinetically controlled oxymercuration of **5** and **6**, which proceed *via* mercurinium ion intermediates, differ from the results reported by Brown and Liu[27] for the oxymercuration of **3** and **4** which do not proceed *via* a cyclic intermediate. It would appear that the oxymercuration reaction can proceed by at least two different mechanistic pathways differing only slightly in energetics, and that the relative energetics of the two reaction pathways are a sensitive function of the structure of the olefin and ligands attached to the mercury atom. Evidence for two different types of addition mechanisms was derived in this study with the observation that thermodynamically controlled products could be formed on prolonged exposure of the reaction product to excess mercuric acetate.

Experimental Section

4-*tert*-Butylcyclohexene (5). A mixture of 250 g (1.16 mol) of *cis*- and *trans*-4-*tert*-butylcyclohexanol and 250 g of potassium pyrosulfate was heated at 210° producing a distillate composed of **5** and water. The distillate was washed with water, dried over $MgSO_4$, and fractionally distilled on a Nester/Faust Annular Teflon spinning band column, bp 71° (19 mm) [lit.[50] 65–66° (20 mm)].

1-Methyl-4-*tert*-butylcyclohexene (6). 1-Methyl-4-*tert*-butylcyclohexene (**6**) was prepared by dehydration of a mixture of *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanols following the procedure of DePuy and King,[51] bp 80° (17 mm) [lit.[51] 74.5° (11 mm)]. Analysis by glpc on a 30-ft 20% QF-1 on Chromosorb P column at 120° indicated a purity of >99%.

Hydroxymercuration of 5 and 6. A procedure similar to that reported by Brown and Geoghegan[3] was used. In a 20-ml flask equipped with a magnetic stirrer was placed 638 mg (2.0 mmol) of mercuric acetate, 2.0 ml of water, and 2.0 ml of tetrahydrofuran. The olefin (2.0 mmol) was added to this mixture and the reaction mixture was stirred for 30 min at 25 ± 1°. (The data appearing in Table I were obtained by periodically removing aliquots from a larger scale reaction mixture and treating as described in the remainder of this section.) The reaction mixture was reduced by the addition of 2.0 ml of 3 *M* sodium hydroxide and 0.5 *M* sodium borohydride dissolved in 3.0 *M* sodium hydroxide. The mercury was allowed to settle and sodium chloride was added to saturate the aqueous solution. The aqueous solution was extracted with three 2-ml portions of ether.

To the extract derived from **5** was added 0.5 ml of pyridine and 0.5 ml of acetic anhydride, and the solution was allowed to stand at 25° for 2 days. The reaction mixture was analyzed directly by glpc[31] on a 30-ft 20% THEED on Chromosorb W column at 130°. Peak areas were corrected using previously determined response ratios.

The extract derived from **6** was analyzed directly by glpc on a 46-ft 5% Carbowax 20M on Chromosorb G (AW-DCMS) column.

Deuteroxymercuration of 5 and 6. In a 1-ml ampoule was placed 1 mmol of **5** or **6**, 0.25 ml of hexadeuterioacetone, 0.25 ml of deuterium oxide, and 380 mg (1 mmol) of mercuric acetate. The reaction mixture was shaken vigorously at 25° for 10 min and then filtered through a cotton plug into an nmr tube. The nmr spectrum was recorded immediately (see Results for the pertinent nmr data).

Bromination of 5 and 6. Pyridinium hydrobromide perbromide was prepared according to the procedure of Fieser,[52] mp 130–133° (lit.[52] 132–134°).

To a solution of 6 mmol of pyridinium hydrobromide perbromide in 10 ml of pyridine contained in a black-painted flask was added 7 mmol of olefin. The reaction mixture was stirred for 1 hr at 0°, after which time 10 ml of water was added. The mixture was made slightly acid by the addition of 10% hydrochloric acid and was extracted with several small portions of pentane. The combined pentane extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was quickly distilled at low pressure giving 70–80% yield of distillate. The pertinent nmr spectral data ($CDCl_3$ solution) are given in the Results section.

Isomerization of *trans*-3-*cis*-4-Dibromo-*tert*-butylcyclohexane. A neat sample of **15** was heated in a sealed ampoule at 150° for 17 hr and the product was distilled at 0.1 mm (microstill). The nmr spectrum of the distillate showed in addition to the narrow multiplet at δ 4.71 for **15**, broad multiplets at δ 4.00 for **16**.

Attempted Isomerization of 17. A neat sample of **17** was heated in a sealed ampoule at 150° for 17 hr. Nmr analysis of the distilled recovered material showed the presence of only **17**.

Methoxybromination of 5 and 6. A procedure similar to that reported by Waters, *et al.*,[26b] was used. To a solution of 2.7–3.0 mmol of olefin in 300 ml of redistilled methanol was slowly added a solution of 3.0 mmol of bromine in 50 ml of methanol. The reaction mixture was stirred under a nitrogen atmosphere at 25° for 2 hr. Sodium carbonate (∼1.5 mmol) was added and the solvent was removed under reduced pressure. The residual oil was dissolved in ether and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was totally distilled in a molecular still at 0.1 mm (80–83% yield). The nmr spectra of the samples were recorded; the pertinent nmr data are given in the Results section.

Hydrobromination of 5 and 6. To 10 ml of 2.12 *M* hydrogen bromide in glacial acetic acid was added 6 mmol of olefin. The reaction mixtures were stirred at 10° for 2 hr whereupon 30 ml of water was added and the resulting mixtures were extracted with three 20-ml portions of pentane. The combined pentane extracts were washed with saturated sodium bicarbonate and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residues were distilled under reduced pressure (1.5 mm) giving 80–85% yield of bromide mixtures. The nmr spectra were recorded; the pertinent nmr data are given in the Results section.

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(50) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

(51) C. H. DePuy and R. W. King, *ibid.*, **83**, 2743 (1961).

(52) L. F. Fieser, "Organic Experiments," Raytheon Education Co., Lexington, Mass., 1968, p 68.