TOPICS IN
STEREOCHEMISTRY

VOLUME 4

A WILEY-INTERSCIENCE SERIES
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The paper used in this book has a pH of 6.5 or higher. It has been used because the best information now available indicates that this will contribute to its longevity.
INTRODUCTION TO THE SERIES

During the last seven years several texts in the areas of stereochemistry and conformational analysis have been published, including *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965). While the writing of these books was stimulated by the high level of research activity in the area of stereochemistry, it has, in turn, spurred further activity. As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.

For both human and economic reasons, standard textbooks can be revised only at infrequent intervals. Yet the spate of periodical publications in the field of stereochemistry is such that it is an almost hopeless task for anyone to update himself by reading all the original literature. The present series is designed to bridge the resulting gap.

If that were its only purpose, this series would have been called “Advances (or “Recent Advances”)” in Stereochemistry.” It must be remembered, however, that the above-mentioned texts were themselves not treatises and did not aim at an exhaustive treatment of the field. Thus the present series has a second purpose, namely to deal in greater detail with some of the topics summarized in the standard texts. It is for this reason that we have selected the title *Topics in Stereochemistry.*

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental import, aimed primarily at an audience of organic chemists but involved frequently with fundamental principles of physical chemistry and molecular physics, and dealing also with certain stereochemical aspects of inorganic chemistry and biochemistry.

It is our intention to bring out future volumes at approximately annual intervals. The Editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of Editorial Advisors who have been of great assistance by suggesting topics and authors for several articles and by helping us
avoid duplication of topics appearing in other, related monograph series. We are grateful to the Editorial Advisors for this assistance, but the Editors and Authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

_N. L. Allinger_

_E. L. Eliel_

January 1967
The appearance of Volume 4 of our series less than a year after Volume 3 is an indication of the continued high activity in the field as well as of the continued willingness of the active workers in many of the pertinent areas to make timely contributions. Volume 4 contains our first chapter relating to stereochemical aspects of biochemistry. The fact—which we are pleased to acknowledge—that Professor John C. Bailar, Jr. has joined our advisory board hopefully indicates that future volumes will also contain contributions in the area of inorganic stereochemistry.

The first chapter in this volume, by O. S. Simamura, deals with the stereochemistry of free radicals. Although the author, in order to keep his chapter within bounds, has confined himself to cyclohexyl and vinylic radicals, it is believed that the stereochemistry of these particular classes is representative of that of radical stereochemistry as a whole. We hope to present additional chapters on the stereochemistry of radical reactions in future volumes.

Chapter 2, by C. Romers, C. Altona, H. R. Buys, and E. Havinga relates to the conformation of saturated heterocycles. A very extensive body of knowledge has been built up in this area just in the last five or six years and the authors faced the choice of giving a superficial survey of the entire field or of presenting a treatment in depth of some facets of it. We are happy that they have chosen the latter course and concentrated on five- and six-membered sulfur- and oxygen-containing rings. By so doing, they were able to present detailed structural data obtained by a wide variety of techniques including X-ray diffraction, NMR spectroscopy, and measurement of dipole moments. We expect to publish chapters on other heterocyclic systems in future volumes.

Chapter 3, by E. Ruch and I. Ugi, deals with group-theoretical predictions of the course of asymmetric syntheses. The original publications in this field have been largely in the German language. We consider presentation of the authors' model in its present form to the English-speaking world of chemistry as an experiment which will hopefully encourage applications to more extensive experimental material. Only such applications will tell whether the model has strong predictive powers.

The final chapter, by D. Arigoni and one of the editors, is an attempt to bring together the fairly extensive classical stereochemical studies
involving optically active RCHDR' compounds with the more recent applications of these compounds and the corresponding stereospecifically tritiated analogs in the elucidation of biosynthetic mechanisms. We hope that this chapter will serve as a bridge between organic chemists and biochemists. To the former it should give an easily understandable insight into how relatively simple basic stereochemical concepts can be used in the elucidation of complex enzyme mechanisms. To the latter it should provide a convenient survey which includes basic stereochemical definitions and a discussion of nomenclature.

While Chapter 4 was being written, we learned of a similar chapter being prepared by Dr. Lawrence Verbit for Volume 7 of the Streitwieser-Taft Series Progress in Physical Organic Chemistry. Fortunately, Dr. Verbit's chapter is concentrated on the organic-mechanistic uses of stereospecifically deuterated compounds whereas the chapter in this volume deals much more extensively with the biochemical aspects.

Norman L. Allinger
Ernest L. Eliel

April, 1969
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The Stereochemistry of Cyclohexyl and Vinylic Radicals

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Tokyo University, Tokyo, Japan

I. Introduction

Much interest has recently been centered on the stereochemistry of free radical reactions,* and several reviews dealing with this subject have appeared.† This review is concerned with the stereochemical behavior of cyclohexyl radicals and vinylic radicals, generated from diverse sources, in their reactions with various reagents. Cyclohexyl radicals are analogous to alkyl radicals in that the radical center seems to be in a planar or flat

*For chapters in textbooks see refs. 1 and 2.
†For an early review see ref. 3, for free radical additions to unsaturated systems see ref. 4, and for reactions of bridged cyclic compounds see refs. 5 and 6.
pyramidal form which inverts its configuration quickly, while vinylic radicals are in a bent form corresponding to $sp^2$ hybridization, and although they also invert their configuration readily, the rate of inversion is sometimes comparable to rates of competing reactions.

Alkyl radicals $R_1R_2R_3C\cdot$ are, along with carbonium ions $R_1R_2R_3C^+$ and carbanions $R_1R_2R_3C^-\cdot$, very reactive chemical species which contain a carbon atom in a tricovalent state. On the basis of a wide range of investigations it is concluded that carbonium ions are planar and carbanions are pyramidal (1). They are analogous to certain stable molecules, such as boron trifluoride, which is planar, and ammonia, which exists in two interconverting pyramidal forms. Boron compounds resemble carbonium ions in that they have six valence electrons around the central atom, and ammonia and amines may serve as models for carbanions in that they have a lone pair of electrons. It is intuitively suggested that alkyl radicals may take a pyramidal form which is intermediate between a planar and a tetrahedral structure, because they have a single (unpaired) electron (or an odd electron as it is often called) in an orbital which is not used for bonding.

A theoretical treatment based on molecular orbital energy levels (7) suggests that a molecule of any hydride $AH_3$ is planar or pyramidal depending on whether the number of its valence electrons is six or more; the methyl radical $CH_3\cdot$ is, therefore, in a pyramidal form. However, evidence from physical measurements including ultraviolet (8), infrared (9), and electron spin resonance (10,11) spectra points to the planar or near-planar structure of alkyl radicals. The trifluoromethyl radical $CF_3\cdot$ seems to be nonplanar according to infrared (12) and ESR (13) evidence. It is interesting to note that $SiH_3\cdot$, $GeH_3\cdot$, and $SnH_3\cdot$ also appear to be nonplanar (14).

When an alkyl radical is produced by breaking a bond to an asymmetric carbon atom in an optically active compound, this radical usually loses the configurational identity of the original molecule in the course of subsequent reactions. Reference to the work of Brown, Kharasch, and Chao (15), among other cases (1), is sufficient to illustrate this point: optically active 1-chloro-2-methylbutane, when subjected to photochlorination with chlorine at 0° or to chlorination by means of sulfuryl chloride

![Image of chemical reactions](image_url)

Fig. 1. Racemization in homolytic chlorination of active 1-chloro-2-methylbutane.
in the presence of benzoyl peroxide at 80°, gives 1,2-dichloro-2-methylbutane in the racemic form (Fig. 1). This result indicates that the intermediate 1-chloromethyl-1-methylpropyl radical (I) generated by abstraction of a hydrogen by a chain-carrying chlorine atom is in a planar form or in enantiomeric pyramidal forms which interconvert their configurations rapidly before the chlorine transfer reaction gives the final product (Fig. 2).*

II. CYCLOHEXYL RADICALS

With cyclohexyl radicals the stereochemical situation is similar to that for alkyl radicals. It is inferred on the basis of ESR measurements (10,16) that the cyclohexyl radical is planar at the radical center. Cyclohexyl radicals react on both sides of the radical center, but owing to the difference in steric environment between the two sides of the radical center an appreciable difference in reactivity is usually observed as will be shown in this section.

A. Cyclohexyl Radicals Generated by Homolytic Bond Breaking

Silver cis- or trans-4-t-butylcyclohexanecarboxylate, subjected to the Hunsdiecker reaction by boiling with bromine in carbon tetrachloride, gives rise to the same mixture of cis- and trans-4-t-butylcyclohexyl bromide

* Under certain circumstances asymmetry at a radical center can be maintained long enough to give an asymmetric product. Thus, photobromination of (+)-1-bromo-2-methylbutane with bromine gives (−)-1,2-dibromo-2-methylbutane; this observation is explained by postulating a bromine-bridged intermediate radical [P. S. Skell, D. L. Tuleen, and P. D. Readio, J. Amer. Chem. Soc., 85, 2849 (1963)]. Another example is the photobromination of (+)-3-methylpentanenitrile with bromine yielding (+)-3-bromo-3-methylpentanenitrile. In this case a bridged radical is not conceivable, and the reaction of the intermediate radical with bromine must be fast enough to compete with the loss of asymmetry. It is proposed by way of explanation that the species which abstracts a hydrogen from the nitrile is Br⁻, rather than Br₂⁻, and that the bromine molecule thus regenerated in the immediate neighborhood of the intermediate radical as it is formed at once reacts with this radical (W. O. Haag and E. I. Heiba, Tetrahedron Letters, 1965, 3679).
Fig. 3. The Hunsdiecker reaction of silver 4-t-butylcyclohexanecarboxylates.

(17) \((\text{cis}/\text{trans} = 50/50)\) (Fig. 3) (17b). This fact requires the formation of a common intermediate from both starting substances, and this is likely to be the 4-t-butylcyclohexyl radical according to the prevalent view which regards the Hunsdiecker reaction as a radical reaction (18). The intermediate 4-t-butylcyclohexyl radical evidently reacts with bromine or a bromine donor at equal rates from the two sides, giving rise to equal amounts of \textit{cis} and \textit{trans} bromide.

The reaction of \textit{cis}- and \textit{trans}-4-methylcyclohexylmercuric bromide with bromine in carbon tetrachloride or carbon disulfide to give 4-methylcyclohexyl bromide takes place through a radical mechanism as is evidenced by the fact that the reaction is inhibited by oxygen, and both mercuric bromides yield the same product mixture consisting of 53\% \textit{trans}- and 47\% \textit{cis}-4-methylcyclohexyl bromide, the 4-methylcyclohexyl radical evidently being involved as a common intermediate (19).

Analogous results have been obtained in the decomposition of \textit{cis}- and \textit{trans}-4-t-butylcyclohexanecarboxyl peroxide in 1,1,2,2-tetrabromoethane at 51\(^\circ\). The intermediate \textit{t}-butylcyclohexyl radical generated from the peroxides abstracts a bromine atom, giving rise to mixtures of \textit{cis}- and \textit{trans}-4-t-butylcyclohexyl bromide containing 52–55\% of the \textit{trans} isomer irrespective of the configuration of the starting materials (20).

It is of interest to note that, in similar experiments with \textit{cis}- and \textit{trans}-4-t-butylcyclohexanecarboxyl peroxide in carbon tetrachloride or bromotrichloromethane at 80\(^\circ\), products have been obtained in which \textit{cis} halides are favored over \textit{trans} halides (Fig. 4) (21). \textit{cis}-4-t-Butylcyclohexyl chloride has also been preferentially formed over the \textit{trans} chloride in the

<table>
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<th>trans, %</th>
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<td>Cl</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>CBrCl(_3)</td>
<td>Br</td>
<td>69</td>
<td>31</td>
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</tbody>
</table>

Fig. 4. Decomposition of 4-\textit{t}-butylcyclohexanecarboxyl peroxides.
decomposition of dimethyl-(cis- or trans-4-t-butylcyclohexyl)-carbinyl hypochlorite (22) (Fig. 5).

In these two cases reported by Greene the intermediate 4-t-butylcyclohexyl radical reacts with a chlorine donor to give preponderantly that isomer which is evidently the thermodynamically less favored one. Greene suggests by way of an explanation that the 4-t-butylcyclohexyl radical may assume a twist-boat conformation in the transition state, in which the attack on the radical center from the trans side to the 4-t-butyl group may be sterically hindered by the quasi-axial hydrogen atom at position 4.*

Another interesting observation with trans-4-t-butylcyclohexane-carbonyl peroxide is that its photochemical decomposition with benzo-phenone as a sensitizer in carbon tetrachloride at 0° gives rise to 4-t-butylcyclohexyl chlorides in a cis/trans isomer ratio of 23/77. Since hexachloroethane was formed in 66% yield, the homolytic nature of the reaction is certain, and the intermediate t-butylcyclohexyl radical reacts under these conditions to give preferentially the thermodynamically more stable product (24).

B. Cyclohexyl Radicals Formed by Abstraction of a Hydrogen Atom

Homolytic addition of cis- or trans-4-t-butylcyclohexanol to 1-octene initiated by di-t-butyl peroxide either heated at 150° or irradiated with ultraviolet light at room temperature gives the same mixture of 4-t-butyl-1-octylcyclohexanols in an isomer ratio of 60% axial and 40% equatorial alcohol (25) (Fig. 6). Thus, in the addition step of the 4-t-butyl-1-hydroxy-cyclohexyl radical (a common intermediate) to 1-octene, equatorial attack is preferred. Since 3-t-butylcyclohexanols afford mixtures of 3-t-butyl-1-octylcyclohexanols containing 65-66% of the axial alcohol, stereoselectivity is somewhat more pronounced with the 3-t-butyl-1-hydroxy-cyclohexyl radical than with the 4-t-butyl radical. Similar preference of an equatorial attack

*For an alternative explanation see ref. 23 in which it is proposed that hyperconjugation involving the axial C-H bonds at positions 2 and 6 (evidenced by the large ESR hyperfine coupling of the two axial β-protons in the cyclohexyl radical) results in an asymmetric distribution of charge such that the electron-rich chlorine attacks preferentially cis to the t-butyl group.
is also observed with the isomeric pair of cholestanols or coprostanols (25). Gritter and Albers ascribe the observed preponderance of axial-hydroxyl products to steric restriction to an axial attack by 1-octene.

Methylcyclohexanes are autoxidized with oxygen in the presence of azobisisobutyronitrile at 60° to the corresponding tertiary hydroperoxides, which, on reduction with lithium aluminum hydride, are converted into the corresponding alcohols. Thus, cis- or trans-1,3,5-trimethylcyclohexane (2 and 3 in Fig. 7) gives isomeric 1,3,5-trimethyl-1-cyclohexanols in the same ratio of 54% axial (4) to 46% equatorial (5) alcohol (26,27). Apparently, each of the isomeric trimethylcyclohexanes, on abstraction of the 1-hydrogen atom, gives the 1,3,5-trimethylcyclohexyl radical as a common intermediate, and a molecule of oxygen attacks this intermediate radical from the axial side a little more readily than from the equatorial side. From the point of view of conformational energy, the intermediate peroxy radical corresponding to alcohol 4 should be favored, at equilibrium, over that corresponding to alcohol 5 by a factor of about 4*; consequently, the

*Assuming that the conformational energy difference between 4 and 5 is the difference between axial Me (1.7 kcal/mole) and an axial oxygen function (ca. 0.7 kcal/mole), i.e., ca. 1.0 kcal/mole.
observed ratio of 54/46 indicating an almost random attack of oxygen on both sides of the intermediate trimethylcyclohexyl radical is best explained by the current view that the reaction between the alkyl radical and oxygen is an extremely rapid process requiring little activation energy. The slight preference for axial attack by oxygen may be accounted for by the difference in stability between the products or by the steric hindrance placed by the axial hydrogen atoms at positions 2 and 6 to oxygen approaching from the equatorial side or by both causes. Such steric hindrance has also been suggested to explain the stereochemistry of several reactions including reduction with metal hydrides undergone by various cyclohexanones (28).

trans-1,3,5-Trimethylcyclohexane (3) gives, besides 1,3,5-trimethylcyclohexanols (4 and 5), a third isomeric alcohol (6) in an amount of 32% of alcohol (4). The relative amounts in which cyclohexanols 4–6 are formed approximately reflect the relative reactivities of hydrogen atoms at different positions towards the abstraction by cyclohexylperoxy radicals. Thus, the relative rate constants of abstraction of \( \text{H}_e \) and \( \text{H}_a \) hydrogen in trans-1,3,5-trimethylcyclohexane shown in Figure 7 have been calculated to be 2.6 and 0.22, respectively, relative to the 1-hydrogen atom in cis-1,3,5-trimethylcyclohexane (2), for which the value is taken to be unity. \( \text{H}_e \) is more reactive, since it is a less hindered equatorial hydrogen; moreover, the steric strain between the axial methyl group and the hydrogens at positions 3 and 5 will be relieved by the tilting of the methyl group in the transition state of hydrogen abstractions. In contrast, \( \text{H}_a \) is less reactive because of the steric effect due to the axial methyl group at position 3.

Relative rates of hydrogen abstraction from methylcyclohexanes, as determined by competitive oxidation with cis-1,3,5-trimethylcyclohexane, are shown in Figure 8. It is noteworthy that the equatorial tertiary hydrogen in 1,1,3,5-tetramethylcyclohexane shows a relative rate of 11; this large value is certainly due to steric acceleration caused by relief of the 1,3-diaxial strain between the two methyl groups at positions 1 and 3 in the transition state for hydrogen abstraction.

Autoxidation of trans- or cis-4-t-butyl-1-methylcyclohexane at 100° followed by reduction gives the same cis/trans (55/45) mixture of 4-t-butyl-1-methyl-1-cyclohexanols (29).

The observation that reaction of 3-cholestanymagnesium bromide, whether it is prepared from 3α- or 3β-bromocholestan, with oxygen gives a nearly 50/50 mixture of 3α- and 3β-cholestanol (30) is best explained by postulating the 3-cholestanyl radical as a common intermediate, produced through one-electron transfer from the Grignard reagent to oxygen (31), which is subsequently attacked by oxygen from either side of the ring at nearly equal rates.
cis-2-Bromo-1-methylcyclohexane, on autoxidation under conditions similar to those used with the trimethylcyclohexanes and subsequent reduction, gives only trans-2-bromo-1-methylcyclohexanol, and the relative rate of abstraction of the hydrogen at position 1 is estimated to be about 4 by a competitive oxidation experiment with cis-1,3,5-trimethylcyclohexane (Fig. 8) (27). A special effect due to the bromine at position 2 is apparent with this isomer, since autoxidation of a sample of 2-bromo-1-methylcyclohexane, containing about 90% of the trans isomer, took place very slowly as compared with the cis isomer, thus indicating a retarding inductive effect of a bromine substituent. A possible explanation of both the acceleration of hydrogen abstraction and the stereospecific oxygen attack in cis-2-bromo-1-methylcyclohexane (Fig. 9) may be that the axial bromine substituent anchimerically delocalizes an incipient odd electron in the transition state of hydrogen abstraction (7) and then forms a bridged intermediate radical (8).*

\[ \text{cis-2-Bromo-1-methylcyclohexane} \]

\[ \text{Autoxidation of cis-2-bromo-1-methylcyclohexane.} \]

* For the concept of bridged radicals advocated by P. S. Skell and his school see ref. 32.
Photobromination of cyclohexyl bromide with bromine at 60° gives preferentially *trans*-1,2-dibromocyclohexane (94%), but with cyclohexyl chloride only 9.4% of *trans*-1-bromo-2-chlorocyclohexane is produced, and the positional preference in hydrogen abstraction is much less pronounced than with the bromide. This finding suggests participation of bromine-bridged radicals in the case of the bromide (33). In photochlorination of chloro- or bromo-cyclohexane with chlorine the formation of *trans*-1,2-dihalides is similarly favored over that of the *cis* isomers (e.g., to an extent of *trans*/*cis* = 92/8); the chlorination, in contrast to the bromination (33), produces the 1,3- and 1,4-dihalides as well, in amounts comparable to the 1,2-dihalides, but with the *trans* isomer slightly predominating in both cases (34). *cis*-4-Bromo-1-t-butylcyclohexane is halogenated with bromine in carbon tetrachloride at 30–40° under illumination to give *trans*-3-*cis*-4-dibromo-t-butylcyclohexane in a highly selective reaction, whereas *trans*-4-bromo-t-butylcyclohexane is considerably less reactive and less selective in attack by bromine atoms (35); anchimeric assistance from an axial bromine is invoked in the transition state for hydrogen abstraction (9 in Fig. 10).

Silver *cis*- or *trans*-1,2-cyclohexanedicarboxylate, when subjected to the Hunsdiecker reaction, give the same product, *trans*-1,2-dibromocyclohexane (36), and an optically active form of the *trans* salt has been shown to yield optically active *trans*-1,2-dibromocyclohexane with net inversion of configuration (37). For the explanation of this stereospecificity, conformational control has been invoked as shown in Figure 11 (see also...
Fig. 17 and text), and an argument has been advanced against symmetrically bridged bromo radicals which would give racemic trans-1,2-dibromide (37).

C. The 9-Decalyl Radical

Bartlett and his co-workers (38) have investigated the stereochemistry of 9-decalyl radicals generated from cis- or trans-9-\textit{t}-butylperoxycarbonyl-decalin at 50° (Fig. 12). These isomeric peresters decompose with about the same first-order rate (\(~1.4 \times 10^{-4} \text{ sec}^{-1}\) in cumene at 55°). The 9-decalyl radicals thus generated abstract a hydrogen from the solvent to give trans- and cis-decalin in the same ratio irrespective of the nature of the starting perester, trans-decalin predominating over cis-decalin. Thus, it is obvious that a common 9-decalyl radical intermediate is involved. However, in the presence of oxygen at high pressures it has been demonstrated that stereoisomeric 9-decalyl radicals can be trapped as the isomeric 9-decalyl hydroperoxides (Fig. 13). In the presence of oxygen at 1 atm in cyclohexane or 1,2-dimethoxyethane, 10\% cis- and 90\% trans-9-decalyl hydroperoxide are formed from either perester. The same ratio of hydroperoxides is also obtained from the trans perester at 600 atm of oxygen in 1,2-dimethoxyethane, but at high pressures the cis perester gives a greatly increased fraction of cis hydroperoxide (e.g., 70\% cis and 30\% trans at 545 atm of oxygen).

These results are explained in terms of two different chair-shaped radicals (Fig. 14), each of which retains the configurational feature of the original cis or trans perester but quickly changes to the same planar radical, which reacts to form both cis and \textit{trans} products (i.e., 10\% cis and 90\% \textit{trans} hydroperoxide). The initial radical \((10)\) from the \textit{trans} perester may be readily converted into the planar radical \((12)\), with little activation energy, whereas the \textit{cis} radical \((11)\) requires inversion of a chair-shaped ring. The latter process is, accordingly, slow enough for the \textit{cis} radical to react as such with oxygen at high concentrations; but at low concentrations of oxygen the \textit{cis} radical is converted into the planar form prior to reaction with oxygen. The \textit{trans} radical changes to the planar radical so quickly that it cannot be trapped even with oxygen at high pressures. The lifetime of the \textit{cis} radical is estimated at \(10^{-8}\) to \(10^{-9}\) sec.

\[
\begin{align*}
\text{O} & \text{C} \text{-} \text{O} - \text{O} - \text{C} \text{(CH}_3\text{)}_3 \\
\text{cis-decalin} & \rightarrow \text{trans-decalin} + \text{CO}_2 + \text{(CH}_3\text{)}_3\text{CO}^{-}
\end{align*}
\]

Fig. 12. Decomposition of 9-\textit{t}-butylperoxycarbonyldecalin.
Fig. 13. Reaction of the 9-decalyl radical with oxygen.

Greene and Lowry (39) have examined the nature of the 9-decalyl radical generated by ultraviolet irradiation of cis- and trans-9-decalyl-carbinyl hypochlorite, which yields formaldehyde and cis- and trans-9-decalyl chloride through a radical chain mechanism. The cis/trans ratio of 9-decalyl chloride from the trans hypochlorite is independent of the initial concentration of the hypochlorite and favors the trans chloride (1/30 at -40°, 1/15 at 0°). The isomer ratio of products from the cis hypochlorite is dependent on the concentration of the hypochlorite; at low concentrations this ratio is the same as that from the trans hypochlorite, but high hypochlorite concentrations favor the cis chloride (1.3/1 at 3M, -80°). These results are explained as in the case of the 9-t-butylperoxycarbonyldecalins by assuming two different 9-decalyl radicals, one (R_c^·) from the cis and one (R_t^·) from the trans hypochlorite as intermediates (Fig. 15). Although a pyramidal structure is a serious possibility for these intermediates, it has been pointed out that R_c^· and R_t^· might possibly be planar at carbon 9, conformational differences still existing elsewhere.

Fig. 14. Conformational change of 9-decalyl radicals.
Alkyl halides (RX) are reduced with organotin hydrides through a free radical chain mechanism to give RH (40):

\[
RX + \cdot \text{SnR}'_3 \rightarrow R\cdot + X\text{SnR}'_3
\]

\[
R\cdot + H\text{SnR}'_3 \rightarrow RH + \cdot \text{SnR}'_3
\]

Reduction of trans- and cis-9-decalyl chloride with tri-n-butyltin hydride gives the same mixture of trans- and cis- decalin (trans/cis = 3.5/1 at 130°, 6/1 at 60°, 11/1 at 0°) (41). This result indicates that the abstraction of a hydrogen atom from the organotin hydride is a much slower process than the conversion of the cis-decalyl radical into the common intermediate radical, in contrast to the reaction with oxygen or hypochlorite.

Greene and Lowry (41) summarize the stereoselectivities observed with the 9-decalyl radical as a common intermediate as shown in Table I.

**Table I**

Stereoselectivity in Reactions of the 9-Decalyl Radical with Various Substrates

<table>
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<td>No</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>50</td>
<td>5.5</td>
<td>No</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>50</td>
<td>5</td>
<td>No</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

*This column indicates whether the cis-9-decalyl radical has been successfully trapped or not.
D. Free Radical Additions to Cyclohexenes

Free radical additions to cyclohexenes will produce cyclohexyl radicals as intermediates. The cyclohexyl radicals generated in such a way may show stereochemical differences in their reactions as compared with the cyclohexyl radicals generated from the cyclohexane system through homolytic scission, for, although their equilibrium structures will be the same, at the moment they are generated they may retain the conformations of their respective precursors. This section deals with stereochemical aspects of free radical additions to the cyclohexene system.*

1. Additions of Hydrogen Bromide to Cyclohexenes

The free radical addition of hydrogen bromide has been investigated in great detail, and it is for this reaction that it was first established that a radical addition takes place preferentially in anti fashion.† Thus, Goering, Abell, and Aycock (42) have shown that 1-bromo- and 1-methyl-cyclohexene add hydrogen bromide in pentane in the presence of benzoyl peroxide or ultraviolet light to give exclusively cis-1,2-dibromo- and cis-1-bromo-2-methyl-cyclohexane, respectively, both thermodynamically less stable than the trans isomers (Fig. 16). Further work by Goering and Sims (43) has made it clear that radical addition of hydrogen bromide to 1-bromo- and 1-chloro-cyclohexene in pentane gives the corresponding cis-1,2-dihalides accompanied by less than 0.5% of the trans isomers, the reaction being almost wholly stereospecific.

With acyclic olefins the results of addition of hydrogen bromide are complicated by the ready rotation about the new single bond created in the intermediate radical, but it has been established that the addition is stereospecific, occurring in anti fashion, in the reaction of hydrogen bromide with cis- or trans-2-bromo-2-butene (44) and of deuterium bromide with

\[
\text{H} \quad \text{X} \quad \text{Br} \quad \text{H} \quad \text{Br} \quad \text{X}
\]

\[
X = \text{CH}_3, \text{ Br}
\]

Fig. 16. Homolytic addition of hydrogen bromide to cyclohexenes.

*For a review on the stereochemistry of free radical additions to olefins in general see ref. 4.

†For the reasons explained in Vol. 3 of this series (p. 238) the terms “syn” and “anti” will generally be used in preference to cis and trans to denote the stereochemical course of addition.
cis- or trans-2-butene (45) at \(-80^\circ\), at which low temperature rotation is slow compared to chain transfer.

To explain the observed stereospecificity of homolytic addition of hydrogen bromide to cyclohexenes, a bromine-bridged radical (13) (Fig. 17), analogous to the bromonium ion involved in ionic additions (46), was proposed for the structure of the intermediate (42,43). Attack of hydrogen bromide on this structure is possible only from the side away from the bromine atom, thus resulting in anti addition. Another possible structure for the intermediate radical is structure 14, in which the bromine atom occupies an axial position, causing steric hindrance to hydrogen bromide approaching from the same side (43) (Fig. 17).

It is known that the action of hydrogen bromide on olefins in the presence of oxygen gives rise to bromine-containing hydroperoxides (47) or oxygenated bromine compounds, probably through intermediate hydroperoxides (48). The action of a mixture of hydrogen bromide and oxygen on cyclohexene or 1-methylcyclohexene followed by reduction with lithium aluminum hydride gives trans-2-bromocyclohexanol or trans-2-bromo-1-methylcyclohexanol to the exclusion of the respective cis isomers; these findings indicate that both the intermediate bromocyclohexyl radicals add oxygen only on the side opposite the bromine substituent (49). Thus, the 2-bromocyclohexyl radicals behave differently from the cyclohexyl radicals generated in the autoxidation of methylcyclohexanes (26), but similarly to those generated in autoxidation of 2-bromo-1-methylcyclohexane (27). The intermediacy of bromine-bridged radicals like structure 8 (Fig. 9) is, therefore, suspected.

2. Additions of Thiols to Cyclohexenes

The radical addition of thiols has been shown not to be as stereospecific as the addition of hydrogen bromide. In the reaction of hydrogen sulfide, thiophenol, and thiolacetic acid with 1-chlorocyclohexene anti addition predominates, resulting in preferential formation of cis-1,2-disubstituted cyclohexanes which are thermodynamically less stable than the trans isomers (50). Typical results are shown in Figure 18. The stereospecificity of the addition decreases in the order: thiophenol > hydrogen

\[
\begin{align*}
\text{Fig. 17. Intermediate radicals in homolytic addition of hydrogen bromide.}
\end{align*}
\]
sulfide > thiolacetic acid. The observed steric preference has been explained by assuming an intermediate radical (15) (Fig. 19) in which an incoming thyl radical has occupied an axial bond. In this conformation hydrogen abstraction from the addend will take place on the side away from the 2-substituent on steric grounds. If intermediate 15 undergoes conformational change to structure 16, the latter will then be able to give the trans compound (18), since hydrogen abstraction is possible on both sides of the radical center. According to this interpretation the lifetime of the intermediate radical determines the stereospecificity. This is supported by the observation that the cis/trans product ratio increases with an increase in the ratio of addend to 1-chlorocyclohexene. Obviously, at high thiol concentration, extensive hydrogen abstraction takes place before intermediate 15 has the opportunity to undergo conformational change into 16. On the basis of this view, the high stereospecificity in the radical addition of hydrogen bromide may be taken to mean that the rate of hydrogen abstraction from hydrogen bromide is greater than that of the conformational inversion of substituted cyclohexyl radicals.

The homolytic addition of thiolacetic acid to 1-methylene-4-t-butylcyclohexane gives a product mixture in which the trans isomer predominates; obviously the more stable isomer is favored (Fig. 20) (51). The cause
for this stereoselectivity in hydrogen abstraction by intermediate 4-t-butyl-1-acetylthiomethylcyclohexyl radicals is not certain. It may be due to the difference in stability between products 19 and 20, this difference being reflected in the difference in ease of formation of the corresponding transition states, if the hydrogen abstraction requires much energy. Another possibility is that a sulfur-bridged intermediate may be formed in such a way that the sulfur atom is situated on the side trans to the 4-t-butyl group, since this side seems to be sterically less restricted than the other side.

In similar additions of thiolacetic acid to 2- and 3-methyl-1-methylene-cyclohexane, hydrogen is abstracted preferentially also into an axial position, but stereoselectivity is less pronounced than in the 4-t-butyl case.

The results of homolytic addition of methanethiol to 4-t-butylcyclohexene afford an insight into the steric course of the initial attack of radicals on an olefinic bond. The reaction carried out at 0° under illumination gives 4-t-butyl-1- and 2-methylthiocyclohexanes in the percentages shown in Figure 21 (52). Attack of a methylthiyl radical on carbon 1 in 4-t-butylcyclohexene will be more difficult on the side trans to the 4-t-butyl group than on the cis side, because the pseudoaxial hydrogen on carbon 6 offers steric hindrance to such an attack, and the radical to be formed will be in a twist-boat form having a higher energy (Fig. 22). This twist-boat intermediate may ultimately change conformation into a chair form. Attack on carbon 1 on the side cis to the 4-t-butyl group, on the other hand, encounters no hindrance from the pseudoaxial hydrogen, and the
intermediate radical is produced in the chair conformation. Thus it is understandable that the formation of the 1-axial isomer (22) is preferred over that of the 1-equatorial isomer (21) by a ratio of 50 to 6. With attack on carbon atom 2, approach from the side trans to the 4-t-butyl group is preferred on the same grounds, leading to the isomer ratio of $23/24 = 38/6$.

Similarly, in addition of thiolacetic acid to 1-methyl-4-t-butylcyclohexene the steric effect due to a pseudoaxial hydrogen adjacent to the double bond is apparent, since 80% of trans-3-t-butyl-cis-6-methylcyclohexyl thiolacetate (corresponding to 23) and 20% of cis-3-t-butyl-trans-6-methylcyclohexyl thiolacetate (corresponding to 24) are formed (51), the 6-methyl group being equatorial in both cases.

The same steric effect is also observed in the light-induced addition of methane- or ethane-thiol to trans-$\Delta^2$-octalin to give a mixture of axial and equatorial 2-alkylthio-trans-decalins: the axial isomers predominate over the equatorial ones by a factor of about 10 to 1 (53).

The stereochemistry of the hydrogen abstraction step is shown by the results of the additions of methanethiol to 4-t-butyl-1-chlorocyclohexene (Fig. 23) (54) and of thiolacetic acid to 4-t-butyl-2-chlorocyclohexene (typical results are shown in Fig. 24) (55). Evidently, the initial attack by thiy radicals takes place in each case mainly from the side away from the