TOPICS IN
STEREOCHEMISTRY

VOLUME 4

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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 As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.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

PREFACE

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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Topics in Stereochemistry, Volume 4
Edited by Norman L. Allinger, Ernest L. Eliel

The Stereochemistry of Cyclohexyl and Vinylic Radicals

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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 $R_1R_2R_3C:^-$, 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

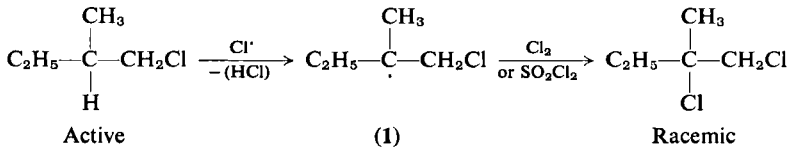


Fig. 1. Racemization in homolytic chlorination of active 1-chloro-2-methylbutane.

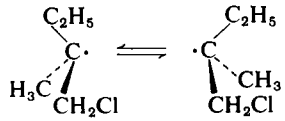


Fig. 2. Interconversion of enantiomeric alkyl radicals.

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 (**1**) 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 $Br_3\cdot$ rather than $Br\cdot$, 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).

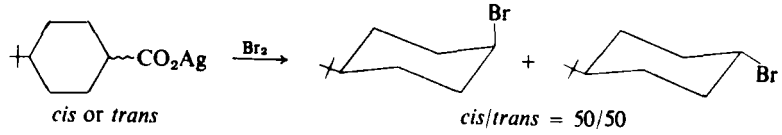


Fig. 3. The Hunsdiecker reaction of silver 4-*t*-butylcyclohexanecarboxylates.

(17) (*cis*/*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 *cis* and *trans* bromide.

The reaction of *cis*- and *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% *trans*- and 47% *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 *cis*- and *trans*-4-*t*-butylcyclohexanecarbonyl peroxide in 1,1,2,2-tetrabromoethane at 51°. The intermediate *t*-butylcyclohexyl radical generated from the peroxides abstracts a bromine atom, giving rise to mixtures of *cis*- and *trans*-4-*t*-butylcyclohexyl bromide containing 52–55% of the *trans* isomer irrespective of the configuration of the starting materials (20).

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

Solvent	X	*cis*, %	*trans*, %
CCl_4	Cl	73	27
$CBrCl_3$	Br	69	31

Fig. 4. Decomposition of 4-*t*-butylcyclohexanecarbonyl peroxides.

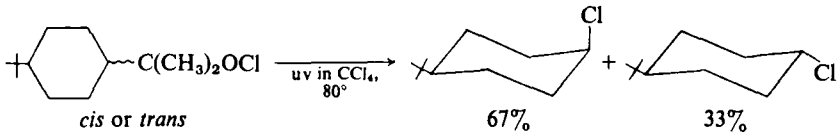


Fig. 5. Decomposition of dimethyl-(4-*t*-butylcyclohexyl)-carbinyl hypochlorites.

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*-butylcyclohexanecarbonyl peroxide is that its photochemical decomposition with benzophenone 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-hydroxycyclohexyl 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-hydroxycyclohexyl 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.

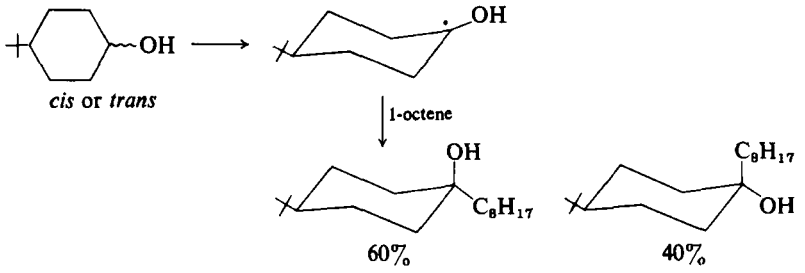


Fig. 6. Homolytic addition of 4-*t*-butylcyclohexanols to 1-octene.

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

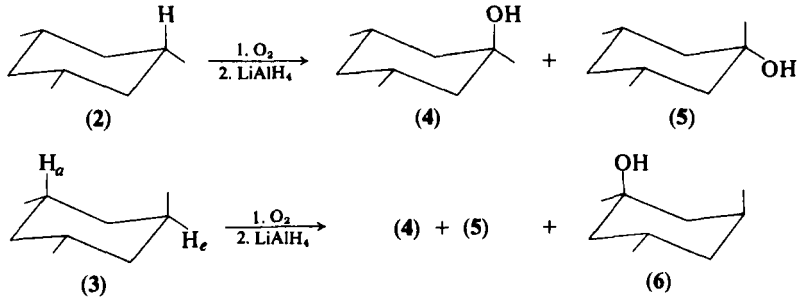


Fig. 7. Autoxidation of 1,3,5-trimethylcyclohexanes.

*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 H_e and 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. 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, 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-cholestanylmagnesium bromide, whether it is prepared from 3α- or 3β-bromocholestane, 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.

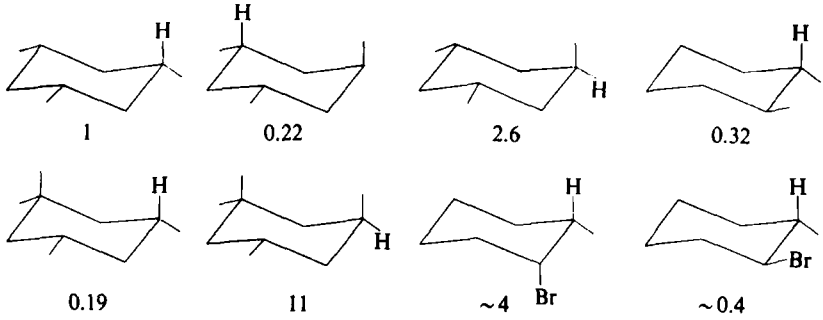


Fig. 8. Relative rates of hydrogen abstraction from methylcyclohexanes.

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**).*

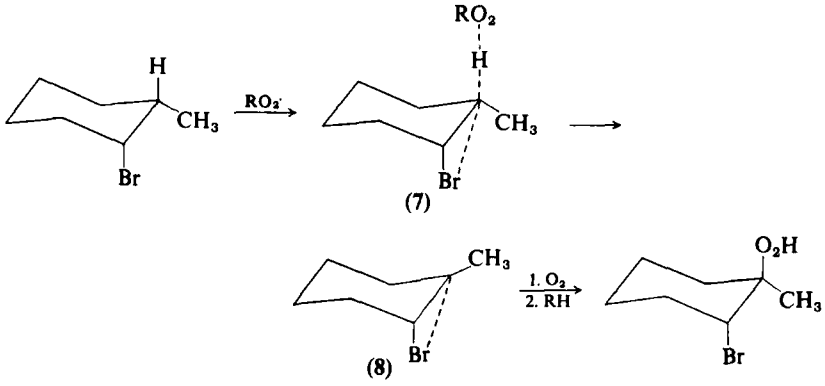
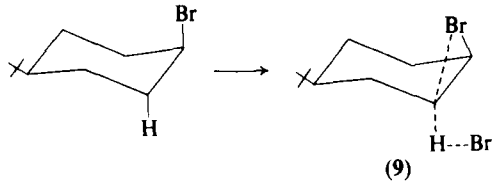


Fig. 9. Autoxidation of *cis*-2-bromo-1-methylcyclohexane.

* For the concept of bridged radicals advocated by P. S. Skell and his school see ref. 32.



(9)

Fig. 10. Bromination of *cis*-4-bromo-1-*t*-butylcyclohexane.

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

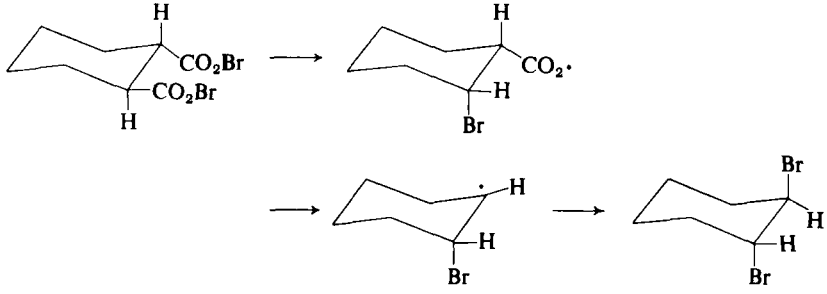


Fig. 11. The Hunsdiecker reaction of silver *trans*-1,2-cyclohexanedicarboxylate.

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-*t*-butylperoxycarbonyldecalin at 50° (Fig. 12). These isomeric peresters decompose with about the same first-order rate ($\sim 1.4 \times 10^{-4}$ 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 *trans* products (i.e., 10% *cis* and 90% *trans* hydroperoxide). The initial radical (**10**) from the *trans* perester may be readily converted into the planar radical **12**, with little activation energy, whereas the *cis* radical **11** requires inversion of a chair-shaped ring. The latter process is, accordingly, slow enough for the *cis* radical to react as such with oxygen at high concentrations; but at low concentrations of oxygen the *cis* radical is converted into the planar form prior to reaction with oxygen. The *trans* radical changes to the planar radical so quickly that it cannot be trapped even with oxygen at high pressures. The lifetime of the *cis* radical is estimated at 10^{-8} to 10^{-9} sec.

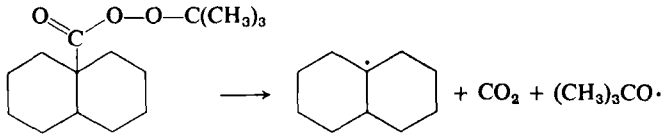


Fig. 12. Decomposition of 9-*t*-butylperoxycarbonyldecalin.

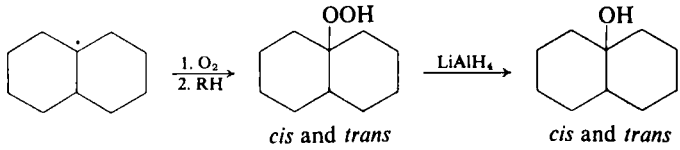


Fig. 13. Reaction of the 9-decalyl radical with oxygen.

Greene and Lowry (39) have examined the nature of the 9-decalyl radical generated by ultraviolet irradiation of *cis*- and *trans*-9-decalylcarbinyl 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 ($R_c\cdot$) from the *cis* and one ($R_t\cdot$) 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 $R_c\cdot$ and $R_t\cdot$ might possibly be planar at carbon 9, conformational differences still existing elsewhere.

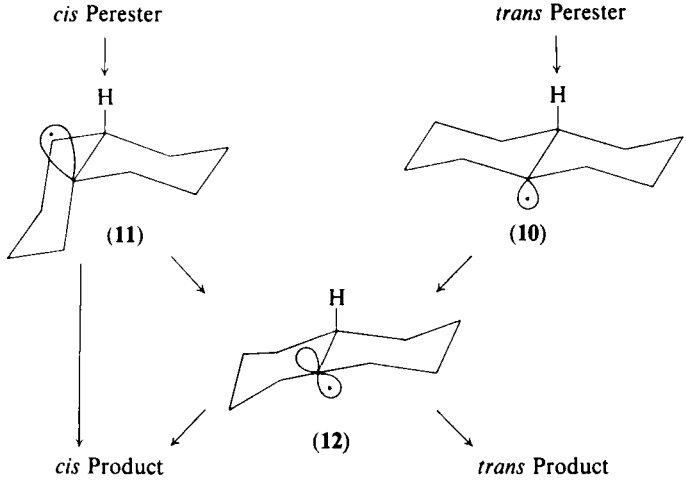


Fig. 14. Conformational change of 9-decalyl radicals.

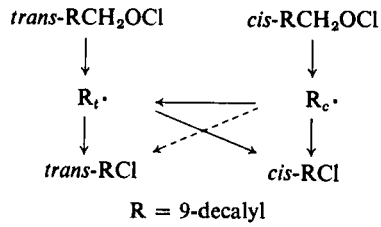


Fig. 15. Decomposition of 9-decalylcarbinyl hypochlorite.

Alkyl halides (RX) are reduced with organotin hydrides through a free radical chain mechanism to give RH (40):

$$RX + \cdot SnR'_3 \longrightarrow R\cdot + XSnR'_3$$

$$R\cdot + HSnR'_3 \longrightarrow RH + \cdot SnR'_3$$

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

Substrate	Temp., °C	Product ratio *trans*/*cis*	*cis*-Trapping[a]	Ref.
Oxygen	50	7	Yes	38
Decalylcarbinyl	50	11	No	39
hypochlorite	0	15	Yes	39
Tri-*n*-butyltin	50	7	No	41
hydride	0	11	No	41
Cumene	50	2	No	38
Toluene	50	5.5	No	38
Cyclohexane	50	5	No	38

[a] This column indicates whether the *cis*-9-decalyl radical has been successfully trapped or not.

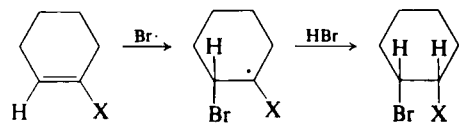
D. Free Radical Additions to Cyclohexenes

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



X = CH_3, 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.

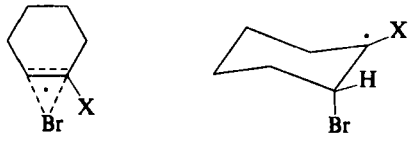
cis- or *trans*-2-butene (45) at $-80°$, at which low temperature rotation is slow compared to chain transfer.

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.

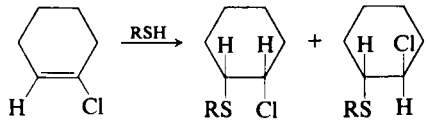
2. Additions of Thiols to Cyclohexenes

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



(**13**) (**14**)

Fig. 17. Intermediate radicals in homolytic addition of hydrogen bromide.



R	*cis*, %	*trans*, %
C_6H_5	95	5
H	90	10
CH_3CO	70	30

Fig. 18. Addition of thiols to 1-chlorocyclohexene.

sulfide > thiolacetic acid. The observed steric preference has been explained by assuming an intermediate radical (**15**) (Fig. 19) in which an incoming thiyl 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

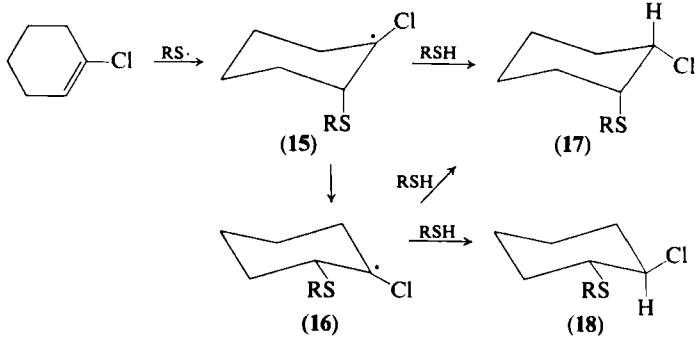


Fig. 19. Intermediate radicals in the addition of thiols to 1-chlorocyclohexene.

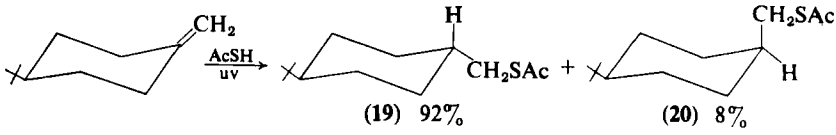


Fig. 20. Addition of thiolacetic acid to 1-methylene-4-*t*-butylcyclohexane.

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-methylenecyclohexane, 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

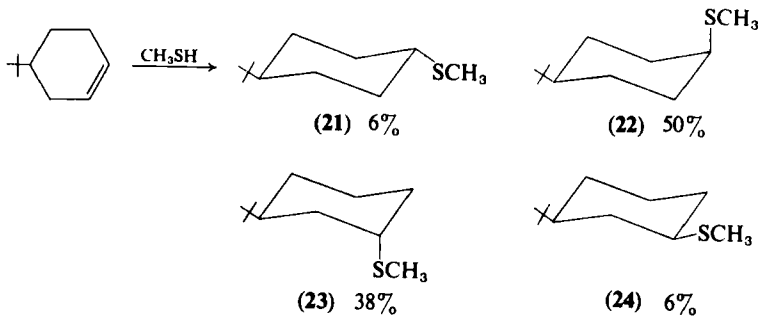


Fig. 21. Addition of methanethiol to 4-*t*-butylcyclohexene.

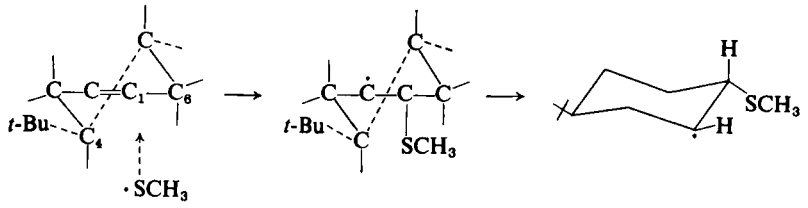


Fig. 22. Initial attack of a radical on a double bond in 4-*t*-butylcyclohexene.

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*-Δ^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 thiyl radicals takes place in each case mainly from the side away from the

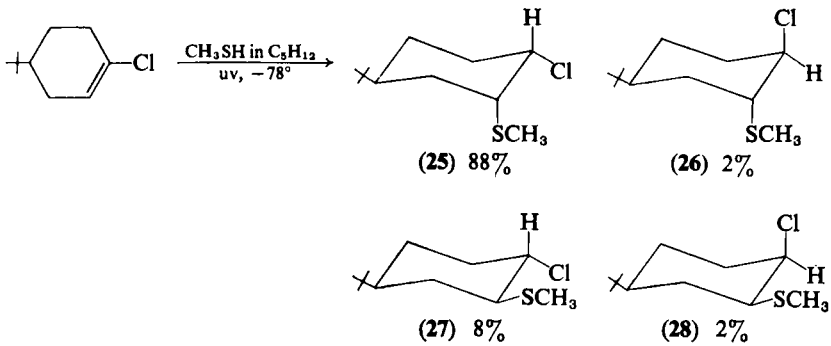


Fig. 23. Addition of methanethiol to 1-chloro-4-*t*-butylcyclohexene.

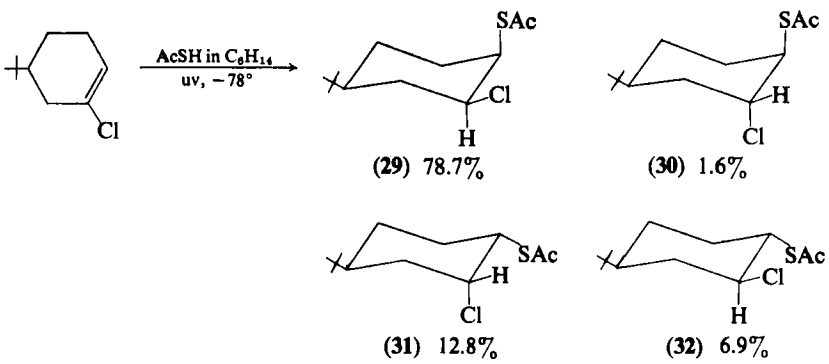


Fig. 24. Addition of thiolacetic acid to 2-chloro-4-*t*-butylcyclohexene.

pseudoaxial hydrogen adjacent to the double bond, and most of the intermediate radicals thus formed abstract a hydrogen atom in an axial position to give **25** or **29**.

Readio and Skell (54), assuming unsymmetrical sulfur-bridged intermediate radicals, have formulated these steps as shown in Figure 25 ($\cdot SR = \cdot SCH_3$).

LeBel and DeBoer (55), on the other hand, propose structure **34** as the intermediate radical instead of a sulfur-bridged structure (**33**); the axial SR ($=CH_3COS$) group in the radical (**34**) should direct abstraction of a hydrogen nearly exclusively to the opposite side of this group.

Products **27** and **28** (Fig. 23) are formed through attack of the thiyl radical on the double bond from the less favored side producing a twist-boat radical which subsequently undergoes conformational change to place the methylthiyl group in an equatorial position (**35**) (Fig. 25). This radical then abstracts a hydrogen atom preferentially in an axial position. Prefer-

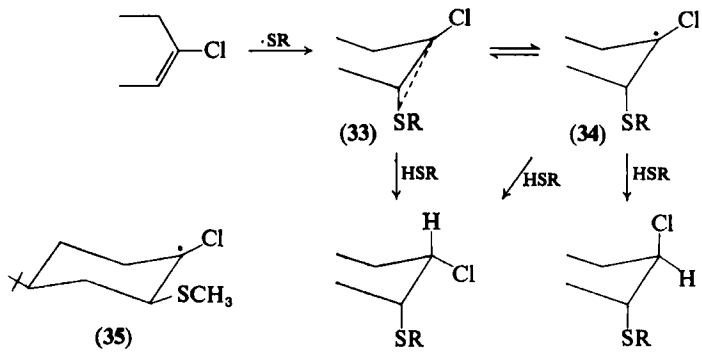
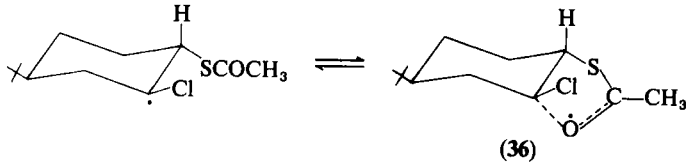


Fig. 25. Intermediates in addition of thiyl radicals.



(36)

Fig. 26. Intermediates in addition of acetylthiyl radicals.

ence for axial abstraction is generally observed in the other cases already discussed.

Products **31** and **32** (Fig. 24) are certainly formed by way of an intermediate radical with an acetylthiyl group in an equatorial position, but the isomer ratio is the reverse of that of the pair **27** and **28**. A possible explanation is through a bridged intermediate radical involving an acetylthiyl group (**36**) in equilibrium with the classical radical (55) (Fig. 26).

A further example of a radical system containing sulfur which shows stereospecificity in its reactions is the 2-arylthioindanyl radical. In the reaction of indene with oxygen to give a polymeric peroxide containing alternating indene and oxygen units (Fig. 27), the addition of oxygenated indanyl radicals to oxygen takes place nonstereospecifically (56). In the cooxidation of benzenethiol and indene, however, the addition of oxygen to the 2-phenylthioindanyl radical is reported to be very stereoselective, giving exclusively *trans*-2-phenylthioindanyl hydroperoxide (Fig. 28), which then rearranges to *trans*-2-phenylsulfinyl-1-indanol (57).

Szmant and Rigau (58) have shown, however, that the stereospecificity of this reaction is not so high as had previously been thought, the *cis* adduct also being formed in a 14% yield in hexane. Further, with *p*-toluenethiol and *p*-chlorobenzenethiol in hexane, the *cis* addition of oxygen takes place to the extent of 9 and 19%, respectively. These findings are explained by assuming that an equilibrium is established between the sulfur-bridged radical, which adds oxygen in *anti* fashion, and the classical intermediate radical, which reacts nonstereospecifically, and that an electron-donating group substituted in the benzene nucleus of the attacking thiyl radical favors the bridged form because of an enhanced electron density at the sulfur atom, leading to the formation of the *trans* compound in increased amount.

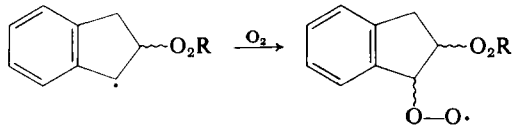


Fig. 27. Copolymerization of indene and oxygen.

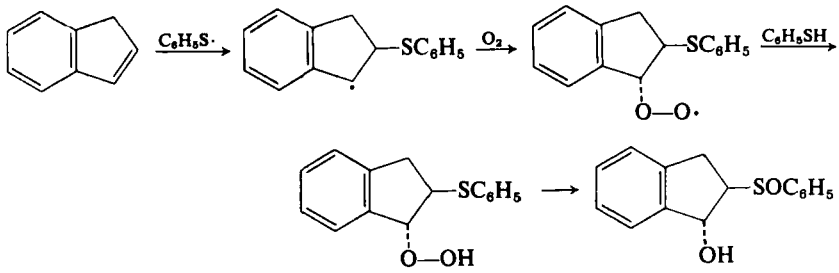


Fig. 28. Cooxidation of benzenethiol and indene with oxygen.

In connection with the addition of thiyl radicals to olefinic bonds, it is interesting to note that thiobenzophenone adds to cyclohexene under irradiation to give a 2:1 adduct, 3,3,4,4-tetraphenyl-2,5-dithiabicyclo-[4.4.0]decane, in high yield; the addition seems to be strictly stereospecific, the product appearing to have *trans*-fused rings on the basis of NMR measurements (59).

3. Additions of Other Reagents to Cyclohexenes

Free radical addition of bromotrichloromethane to cyclohexene gives a 1:1 adduct (60), which seems to be a *trans* compound (61).

Nitrogen dioxide undergoes homolytic addition to 1-methylcyclohexene in ether at 0° yielding 1-methyl-*trans*-2-nitrocyclohexyl nitrite stereospecifically, while addition to cyclohexene gives 58% of *trans*-2-nitrocyclohexyl nitrite (62).

Addition of nitrogen dioxide to $\Delta^{9,10}$-octalin gives *trans*-9,10-dinitrodecalin exclusively, but when oxygen is passed through the reaction mixture for the entire reaction period, 10-nitro-9-decalyl nitrate of unknown stereochemistry is a major product (63). The 10-nitro-9-decalyl radical is an intermediate which adds nitrogen dioxide on the sterically less hindered side, i.e., away from the 10-nitro group, or is trapped by oxygen to give an oxygenated radical which, on reaction with nitrogen dioxide, is ultimately converted into the nitrate.

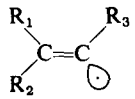
The addition of silicochloroform to 1-methylcyclohexene initiated with acetyl peroxide at 45° yields a mixture of 85% *cis*- and 15% *trans*-1-methyl-2-trichlorosilylcyclohexane (64).

Bromodicyanomethane adds to cyclohexene at 35° under illumination to give a 1.1/1 mixture of *trans*- and *cis*-1-bromo-2-dicyanomethylcyclohexane, while addition to 1-methylcyclohexene yields a 2.2/1 mixture of the corresponding *trans* and *cis* adducts. The products are not the thermodynamically controlled ones, and the observed stereoselectivity is explained on steric grounds, on the assumption that the radical carbon atom has a planar or a flat pyramidal form (65).

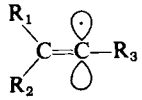
III. VINYLIC RADICALS

Although some reactions which are thought to involve vinylic radicals were investigated quite some time ago, it is only recently that particular emphasis has been placed on the stereochemical aspects of the structure and reactions of vinylic radicals.* These aspects were dealt with at first in connection with the homolytic addition to acetylenic compounds and subsequently by studying the vinylic radicals generated by the homolytic decomposition of appropriate ethylenic compounds.

There are two *a priori* possibilities for the structure of a vinylic radical, a bent form (**37**) and a linear form (**38**). In **37**, the unpaired electron



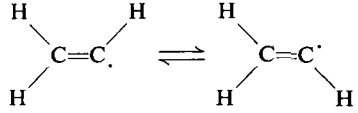
(**37**)



(**38**)

occupies an sp^2 hybrid orbital in the plane of the double bond, whereas in **38**, it occupies a *p* orbital (also in the plane of the double bond), the carbon atom carrying this electron being in *sp* hybridization.

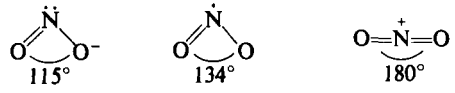
Electron spin resonance measurements (11) on the vinyl radical in liquid ethylene plus ethane (at $-180°$) (10) and in an argon matrix at 4°K (67) and on the 1-methylvinyl radical in allene plus ethane (at $-172°$) (10) have shown that these radicals have a bent form (**37**). The vinyl radical inverts its configuration quickly in solution at $-180°$; its lifetime is



estimated at 3×10^{-8} to 3×10^{-10} sec and the barrier to inversion at about 2 kcal/mole. The 1-methylvinyl radical is configurationally stable at $-172°$, and the barrier to inversion is estimated to be larger than about 2.7 kcal/mole (68). Another ESR investigation suggests that the possibility of the vinyl radical trapped in a neon matrix near 4°K having a linear structure (**38**) could not be excluded (69).

In this connection it is of interest to note that the formyl radical H—Ċ=O has a bent structure with an angle ∠HCO of 120° (70). Pryor (2) has discussed the following series of nitrogen compounds, drawing attention to the influence of an odd electron and an unshared electron pair in determining the shape of triatomic molecules (2).

*For a review see ref. 66.



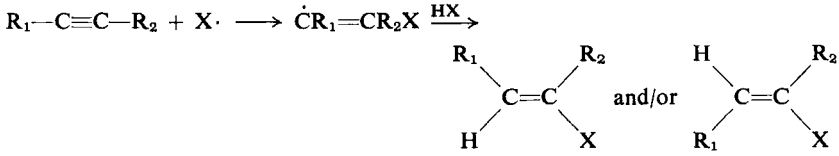
Nitrite ion Nitrogen dioxide Nitronium ion

A. Vinylic Radicals Generated by Radical Additions

A variety of compounds including hydrogen bromide, thiols, and organometallic hydrides add to acetylenic compounds through a free radical mechanism to yield substituted olefins (71,72).

$$R_1{-}C{\equiv}C{-}R_2 + HX \longrightarrow CHR_1{=}CR_2X$$

The propagation reaction involves the addition of radicals to an acetylenic bond to yield a vinylic radical, which subsequently abstracts a hydrogen atom from HX to yield the final product. Discussion of the stereochemical aspects of such an addition reaction is pertinent to the theme of this review.

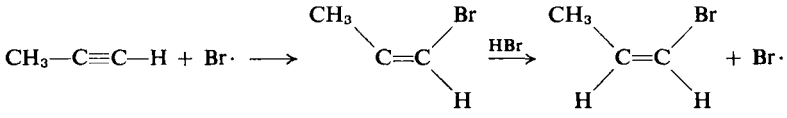


1. Addition of Hydrogen Bromide to Acetylenes

Although hydrogen bromide is a very common reagent to undergo homolytic additions, comparatively little is known of the stereochemistry of its addition to acetylenic bonds.

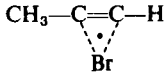
It has been observed (73) that 2-butyne reacts with an excess of hydrogen bromide under homolytic conditions to give solely *dl*-2,3-dibromobutane, a product which can result from two successive *anti* or *syn* additions. Since both *cis*- and *trans*-2-bromo-2-butenes have subsequently been shown to add hydrogen bromide homolytically in *anti* fashion (44), the addition of an initial mole of hydrogen bromide to 2-butyne is concluded to be *anti* also.

Skell and Allen (74,75) have shown that propyne and hydrogen bromide react in the liquid phase (-78 to $-60°$) under illumination to give *cis*-1-bromo-1-propene, the addition taking place in a stereospecific *anti* fashion. Assuming the initial production of configurationally stable 2-bromo-1-methylvinyl radicals, they have explained the results by the following reaction scheme:



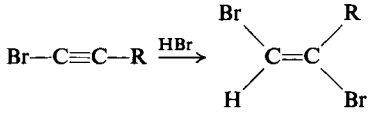
In both gas- and liquid-phase reactions *at room temperature cis-* and *trans*-1-bromo-1-propene are produced in equilibrium or near-equilibrium mixtures. In explaining the production of such *cis–trans* mixtures, Skell and Allen exclude the possibility of quick equilibration between *cis* and *trans* vinylic radicals before abstraction of a hydrogen atom from hydrogen bromide takes place on grounds of the observed high *cis/trans* isomeric ratio of the product at lowest conversion. They prefer a mechanism in which the *cis*-1-bromo-1-propene initially formed is converted into the *trans* isomer by the agency of bromine atoms. They have estimated the rate constant for the *cis* to *trans* conversion of the bromopropenyl radical at $k_{cis \to trans} \leqslant 2 \times 10^6$ sec^{-1} and the activation energy at $E_a \geqslant 17$ kcal/mole.*

Skell and Allen (75) have also suggested that the postulate of a bridged radical instead of a stable *cis* vinylic radical could explain the



observed results. The ESR measurements, which were carried out on a mixture of hydrogen bromide and 2-butyne or 3-hexyne under irradiation with ultraviolet light at 77°K, support the concept of bridged radical intermediates (76).

1-Bromo-1-alkynes are reported to add hydrogen bromide homolytically to yield *trans*-dibromoethylenes by *syn* addition (77):



where R = CH_3, $(CH_3)_3C$.

In this connection Bergel'son's work on the homolytic addition of bromine to a variety of substituted acetylenes is of interest; the results are tabulated in a review (4). Both *anti* and *syn* additions take place, and, roughly speaking, the steric nature of the substituent appears to influence the course of addition, larger substituents favoring *syn* addition in the case of monosubstituted acetylenes and *anti* addition in the case of disubstituted acetylenes.

2. Additions of Thiols to Acetylenes

Early studies have revealed that homolytic additions of thiols to acetylenes give mainly the products resulting from *anti* addition, sometimes accompanied by geometrically isomeric adducts. Examples are additions

*J. Kampmeier and G. Chen (86, footnote 22) adduce a value of about 10 kcal/mole.

of cyclohexanethiol to acetylenedicarboxylic acid (78); of α-toluenethiol to propiolic acid (79); of ethanethiol to propyne and 1-butyne (80), to ethoxyacetylene (81), and to ethyl ethynyl sulfide (82); of *p*-toluenethiol to phenylacetylene (83); of mesitylenethiol to mesitylacetylene (83); and of hydrogen sulfide to propyne (84).

Oswald and his co-workers (85) have made a detailed study of the addition of thiol compounds to phenylacetylene, paying special attention to the stereoselectivity of the reaction. They have found that when benzenethiol, methanethiol, thiolacetic acid, etc., are allowed to react with an equimolecular amount of phenylacetylene under the conditions of homolytic addition, mainly *anti* addition occurs yielding *cis*-1-substituted mercapto-2-phenylethenes. The apparent stereoselectivity of the reaction increases when an excess of phenylacetylene is used (Table II). The *cis* adducts produced are readily isomerized by thiyl radicals to equilibrium mixtures consisting mainly of the corresponding *trans* isomers.

Kampmeier and Chen (86) have obtained similar results in the homolytic addition of thiolacetic acid to 1-hexyne. When the hexyne/thiolacetic acid ratio is greater than about 6, the isomeric composition of adduct mixtures is independent of the extent of reaction and the *cis*/*trans* ratio is constant at 82/18, indicating that the isomerization of the adduct produced is unimportant during the reaction. Since the composition of the equilibrium mixture is approximately 50/50, the ratio of 82/18 is a kinetically controlled ratio; the addition of thiolacetic acid to 1-hexyne is, therefore, preferentially *anti*. When the hexyne/thiolacetic acid ratio is small, the isomer ratio changes towards that of the equilibrium mixture.

Possible steps involved in the homolytic addition to an acetylenic bond are shown in a generalized scheme in Figure 29. The ratio in which the *cis* and the *trans* adducts are formed depends on the relative rates of these steps.

TABLE II

Addition of Benzenethiol to Phenylacetylene at 0° with UV Irradiation for 2 hr

M in C_7H_{16}		
C_6H_5SH	$C_6H_5C{\equiv}CH$	*cis* adduct, %
0.05	1.1	>95
1.0	1.1	56
1.0	0.05	16

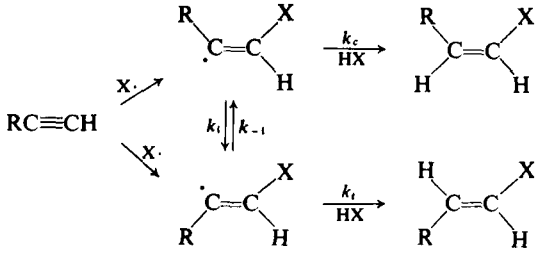


Fig. 29. Homolytic addition to an acetylenic bond.

By reference to this scheme, Skell's conclusion from the results of the addition of hydrogen bromide (75) is that the initial addition of X·(=Br·) to propyne (R = CH_3) is stereospecific, producing only the *cis* radical, and that k_c[HBr] $\gg k_t$.

In the 1-hexyne/thiolacetic acid system, however, it is unlikely that k_c[HSAc] $\gg k_i$ and k_t[HSAc] $\gg k_{-i}$ hold, for if it were so, one would have to assume that the initial addition of X· (=AcS·) to a triple bond takes place in a nonstereospecific fashion to give the *cis/trans* product ratio of 82/18. It seems highly unlikely that there should be so great a stereochemical difference between a thiyl radical and a bromine atom in the addition process. It is therefore concluded (86) that in the 1-hexyne/thiolacetic acid system the interconversion between the *cis* and *trans* radicals takes place much faster than the hydrogen abstraction from thiolacetic acid, in which case the *cis/trans* product ratio is expressed by the formula: *cis/trans* = $(k_c/k_t)(k_{-i}/k_i)$.*

3. *Additions of Other Reagents to Acetylenes*

Addition of silicochloroform to monosubstituted acetylenes (RC≡CH; where R = *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}) at 60–70° in the presence of benzoyl peroxide gives RCH=CHSiCl_3 in a *cis/trans* ratio of about 3/1 (87). With 3,3-dimethyl-1-butyne, addition products much richer in the *trans* isomer are obtained (ranging from 76 to 100% *trans* according to the amount of

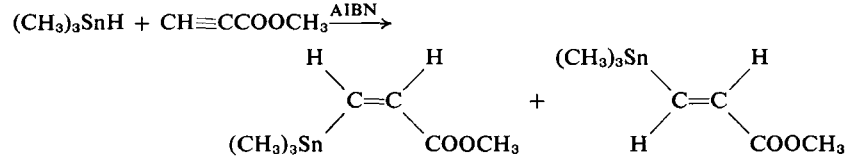


Fig. 30. Addition of trimethyltin hydride to methyl propiolate.

*For an estimate of k_c/k_t in terms of free energy difference see Table III.

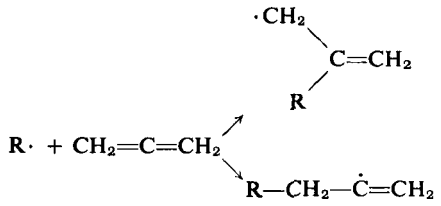


Fig. 31. Intermediates of radical addition to allene.

silicochloroform used); this result, however, was shown (87b) to be due to *cis–trans* isomerization of the initially formed product.

Addition of organotin hydrides to an acetylenic bond can take place through a radical mechanism and the stereochemistry seems to be preponderantly that of *anti* addition (e.g., Fig. 30) (88).

Trimethyllead hydride adds similarly to acetylenes through a free radical *anti* mechanism (89).

4. Additions to Allenes

Another system which can give a vinylic radical intermediate in homolytic addition is allene (Fig. 31). Although some information (90) has been obtained concerning the positional orientation of the initial attack on allene and substituted allenes, the stereochemistry of the vinylic radicals produced by the terminal addition to substituted allenes is not known.

Trimethyltin hydride has been shown to add, in the presence of azobisisobutyronitrile at 100°, to 1,2-butadiene giving *trans*- and *cis*-trimethylcrotyltin in yields of 10 and 3.5%, respectively (Fig. 32) (91).

B. Vinylic Radicals Generated by Homolytic Decomposition

Homolytic decomposition of the *cis* or *trans* isomers of suitable ethenoid compounds will generate vinylic radicals unequivocally in the *cis* or *trans* form without the ambiguity inherent in the production of these radicals by homolytic addition to acetylenic bonds. Such an approach has been made in the study of the products from the decomposition of *t*-butyl esters of *cis*- and *trans*-substituted percinnamates (92,93,95) and of *cis*- and

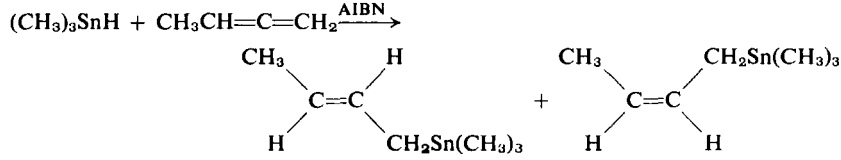


Fig. 32. Addition of trimethyltin hydride to 1,2-butadiene.

trans-cinnamoyl peroxide (94) in a variety of solvents. It has been found that vinylic radicals produced in the *cis* or *trans* form generally undergo rapid interconversion before they abstract an atom of hydrogen or chlorine from solvents, thus giving a mixture of *cis* and *trans* olefins.

Decomposition of *t*-butyl *cis*- or *trans*-α,β-dimethylpercinnamate in cumene at 110° gives mixtures of *cis*- and *trans*-2-phenyl-2-butene in a *cis*/*trans* ratio of about 1.1 regardless of the geometrical configuration of the starting materials (93). This finding is readily explained by Figure 33 assuming that *cis*- and *trans*-1-methyl-2-phenylpropenyl radicals equilibrate much more quickly than they react with cumene by abstracting an atom of hydrogen (in Fig. 33, R_1, $R_2 = CH_3$ and $k_1 \gg k_t$[cumene], $k_{-1} \gg k_c$[cumene]). The ready equilibration of isomeric vinylic radicals relative to hydrogen abstraction is also observed at 110° in the decomposition of *t*-butyl *cis*- and *trans*-α-methyl- or α-phenyl-percinnamate in cumene at 110° (in Fig. 33, $R_1 = H$, $R_2 = CH_3$ or C_6H_5) (92). The α-methylpercinnamates give 1-phenylpropenes in the same *cis*/*trans* ratio of 1.55/1, and the diastereomeric α-phenylpercinnamates yield identical mixtures of *cis*- and *trans*-stilbene in ratios which vary from 5/1 to 10/1 increasing with the initial concentration of the perester.

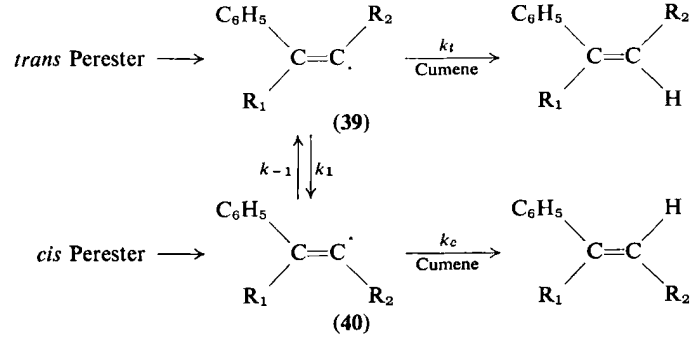


Fig. 33. Decomposition of *t*-butyl esters of substituted percinnamates.

trans- or *cis*-Cinnamoyl peroxide, when decomposed in carbon tetrachloride at 77°, gives a mixture of *cis*- and *trans*-β-chlorostyrene in the same *cis*/*trans* isomer ratio of 19/81, irrespective of the geometrical configuration of the peroxide used. It is concluded that the styryl radical initially generated equilibrates quickly between the *cis* and the *trans* form before it abstracts a chlorine atom from carbon tetrachloride to give β-chlorostyrene (94) (Fig. 34).*

*In connection with the discussion of the styryl radical, it is of interest to note that the Hunsdiecker reaction of the silver salt of *cis*- or *trans*-cinnamic acid gives β-bromostyrene exclusively in the *trans* form (J. D. Berman and C. C. Price, *J. Org. Chem.*, **23**, 102 (1958)).

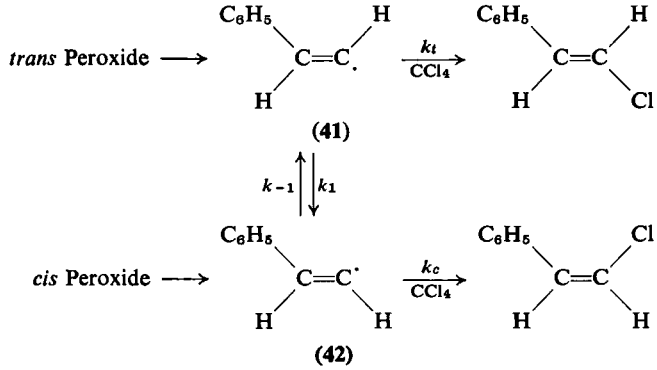


Fig. 34. Decomposition of cinnamoyl peroxide in carbon tetrachloride.

In the foregoing explanations a quick equilibration between *cis* and *trans* vinylic radicals has been assumed, but an obvious alternative involves one and the same linear type of vinylic radical as a common intermediate from both *cis* and *trans* radical generators. This possibility may be ruled out by evidence from ESR measurements (10,67); in addition, the results of the decomposition of cinnamoyl peroxides in bromotrichloromethane at 77° definitely exclude such a possibility for the styryl radical (94). The *trans* peroxide gives a mixture of β-bromostyrene in a *cis*/*trans* ratio of 14/86, whereas the ratio from the *cis* peroxide is 27/73. If the *cis* and the *trans* peroxides generated the same linear styryl radical, this, in turn, would necessarily give the same mixture of *cis*- and *trans*-bromostyrene.

The possibility of a linear radical (**38**, p. 21) is still of interest especially with a species carrying a conjugating group such as a phenyl at the radical center, since the odd electron can be delocalized into the benzene nucleus if the latter lies perpendicular to the plane of the double bond as shown in Figure 35. This may lead to the stabilization of the radical, since the energy gained by this delocalization exceeds, although only by a little, the energy lost by the severance of the conjugation between the phenyl group and the double bond, as is shown by π-electron energy calculation according to the simple Hückel molecular orbital method. However, this attractive possibility of the α-phenylstyryl radical existing in a linear form has been ruled out by experiments with *t*-butyl *cis*- and

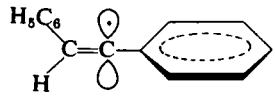


Fig. 35. Linear α-phenylstyryl radical.

trans-α-phenylpercinnamate (96). Here, although decomposition in carbon tetrachloride at 110° leads to the same mixture of *cis*- and *trans*-chlorostilbene (*cis*/*trans* = 76/24), at a lower temperature (80°) the *trans*-α-phenylpercinnamate gives a mixture of *cis*/*trans* = 84/16 and the *cis* isomeride a mixture of *cis*/*trans* = 77/23.

The finding presented above, *viz.*, that different *cis*/*trans* ratios of β-bromostyrenes are obtained from the isomeric cinnamoyl peroxides in bromotrichloromethane (94), indicates that with an efficient transfer agent the abstraction reaction competes with the equilibration between *cis* and *trans* vinylic radicals. Variation of the concentration of bromotrichloromethane (from neat to 0.2*M* in benzene at a concentration of the peroxides of 0.02*M*) does not change the *cis*/*trans* ratios of β-bromostyrenes beyond experimental error (97). On the other hand, the earlier-cited results of the experiments with α-phenylpercinnamates in carbon tetrachloride (96) indicate that with the α-phenylstyryl radical the abstraction of even a chlorine atom from carbon tetrachloride is able to compete with the *cis*–*trans* interconversion at 80° and show that the α-phenylstyryl isomerizes much more slowly than the styryl radical, probably because the inverting group is heavier in the former radical.

Singer and Kong (95) have observed that decomposition of *cis*- and *trans*-*t*-butyl α-bromopercinnamate in cumene or cyclohexene or in benzene containing dihydroanthracene at 110° does not give the same proportion of *cis*- and *trans*-β-bromostyrene, thus indicating that α-bromostyryl radicals do not equilibrate before hydrogen abstraction. They estimate the rate constant for inversion of the α-bromostyryl radical to be $\lesssim 10\ \text{sec}^{-1}$ as compared with the value of $> 10^3\ \text{sec}^{-1}$ for the α-methylstyryl radical. The lower inversion rate for the former radical is probably due to the difference in mass between methyl and bromine. An alternative mechanism is also suggested which involves complexing of the intermediate acyloxy radical with a hydrogen donor followed by decarboxylation with an enhanced rate of hydrogen atom transfer.

By reference to the reaction scheme shown in Figure 34, when the equilibration between the isomeric styryl radicals takes place much faster than their chlorine abstraction reaction, the *cis*/*trans* ratio of β-chlorostyrenes produced is expressed by the formula

$$\frac{(\textit{cis}\text{-}\beta\text{-chlorostyrene})}{(\textit{trans}\text{-}\beta\text{-chlorostyrene})} = \frac{k_c}{k_t}\frac{1}{K}$$

where K stands for the equilibrium ratio of the *trans* (**41**) and *cis* (**42**) radicals, $K = k_{-1}/k_1$. In the absence of any specific evidence available for assessment of the value for K, it may be assumed to be about unity, since the steric effect caused by the odd electron in this radical does not seem to

be significantly different from that of a hydrogen atom. Then, since the isomer ratio is 19/81, k_c/k_t will be about 0.23, i.e., the *trans* radical (**41**) abstracts a chlorine atom about 4 times as fast as the *cis* radical (**42**); evidently this result suggests that in the *cis* radical the phenyl group imposes steric hindrance on the abstraction reaction. Since the rate constant k_r of a chemical reaction is expressed by

$$k_r = (\kappa kT/h) \exp(-\Delta G^{\ddagger}/RT)$$

according to the transition-state theory, the ratio of $k_c/k_t = 0.23$ is, neglecting the possible difference in transmission coefficients κ, equivalent to a difference in free energy of activation of $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger} = 1.0$ kcal/mole (Table III).

Similarly, for hydrogen abstraction from cumene by α,β-dimethylstyryl radicals at 110° (Fig. 33, R_1, $R_2 = CH_3$)

$$\frac{(cis\text{-2-phenyl-2-butene})}{(trans\text{-2-phenyl-2-butene})} = \frac{k_c}{k_t}\frac{1}{K}$$

Since the equilibrium ratio of *cis*- and *trans*-2-phenyl-2-butene is reported to be about 4 at 100° in glacial acetic acid (98), it is not an unreasonable assumption to estimate the equilibrium ratio K at about 0.25. This value leads to $k_c/k_t = 0.3$, which corresponds to $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger} = 0.93$ kcal/mole, since the isomer ratio has been found to be 1.1:1. This result is obviously due to steric hindrance by the phenyl group which is located on the same side as the odd electron.

In the decomposition of isomeric *t*-butyl α-methylpercinnamates at 110° in toluene, cyclohexene, and cumene, the *cis*/*trans* isomer ratios of β-methylstyrene are found to be 0.758, 0.844, and 1.55, respectively, regardless of the geometrical configuration of the starting peresters (92b). If we assume that the equilibrium ratio between the *cis*- (**40**) and the *trans*- (**39**) α-methylstyryl radicals (Fig. 33, $R_1 = H$, $R_2 = CH_3$) is 3* independent of the solvents used, the ratios k_t/k_c of the rate constants of hydrogen abstraction by the *trans* or the *cis* radical are calculated to be 2.27, 2.53, and 4.65 or expressed as the difference in free energy of activation $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger} = 0.63$, 0.71, and 1.18 kcal/mole for toluene, cyclohexene, and cumene, respectively, as hydrogen transfer agents.

In Table III are summarized $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger}$ values for various vinylic radical pairs including some besides those discussed above. On the whole the table seems to present a consistent picture regarding the steric effect of substituents in radicals in spite of the diversity of the sources of

*According to footnote 6 in ref. 92b, the equilibrium constant at 110° for the *cis–trans* isomerization of propenylbenzene may be taken to be 3 in favor of the *trans* isomer.

the experimental data used and of the approximate nature of the theoretical assumptions. Comparison of the data for hydrogen abstraction from cumene by the α-methylstyryl and the α,β-dimethylstyryl radicals indicates the order $C_6H_5 > CH_3 > H$, which is quite reasonable. The value for the 1-methylpropenyl radicals also shows $CH_3 > H$. The values of about 4 kcal/mole for the α-phenylstyryl radicals are only approximate, but it is certain that they are larger than what one would expect just on grounds of the presence of a phenyl group at the β-position. This fact is explained by noting that the disposition of the α-phenyl group is different between the two radicals. In $(Radical)_c$ the α-phenyl lies in the plane of the double bond, so that its *ortho*-hydrogen exerts steric hindrance toward an approaching reagent in addition to that exerted by the β-phenyl group, whereas in $(Radical)_t$ the α-phenyl is twisted away from the plane of the radical because of the β-phenyl group on the same side of the double bond, so that the hindrance due to the *ortho*-hydrogen is absent.

The *cis*/*trans* isomer ratio in which β-methylstyrenes are formed diminishes in each of the three solvents used when measurements are extended to lower temperatures using *trans*-α-methylcinnamoyl peroxide (thermolysis and photolysis). From these variations Singer and Kong (92b) have estimated the difference in activation enthalpy for hydrogen abstraction from solvent between the *trans*- and the *cis*-α-methylstyryl radicals and compared the values for the three solvents. The differences in activation enthalpy in cumene and cyclohexene are 0.53 and 0.10 kcal/mole, respectively, relative to the value in toluene; thus, the increase in stereoselectivity is in the order: toluene < cyclohexene < cumene as expected on steric grounds.

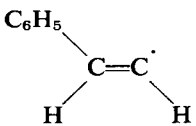
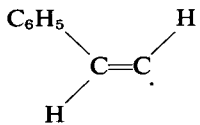
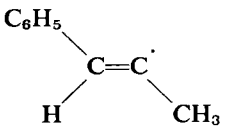
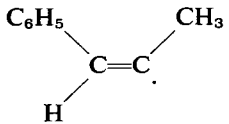
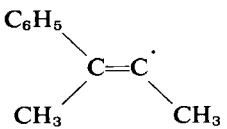
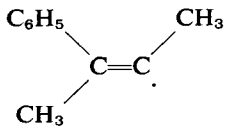
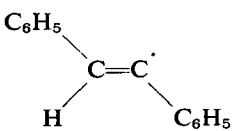
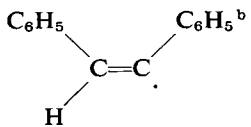
C. Vinylic Radicals Generated from Halogeno-Olefins

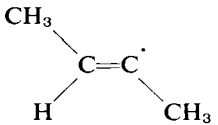
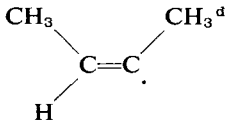
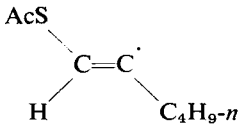
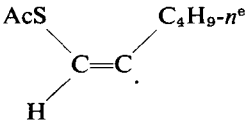
Reduction of *cis*- or *trans*-2-bromobutene with tri-*n*-butyltin hydride yields the same mixture of 65% *trans*- and 35% *cis*-2-butene at ambient temperature (101). The reduction of halides with organotin hydrides is known to proceed through a free radical chain mechanism (40). That equilibration between intermediate *cis*- and *trans*-1-methylpropenyl radicals occurs is evident, and the isomeric ratio of the products suggests that a methyl does not exert as much steric hindrance to hydrogen abstraction as a phenyl group (see Table III).

Alkyl radicals are generated from alkyl halides by electron transfer from the naphthalene radical anion (102,103). Sargent and Browne (104) have observed that reaction of sodium naphthalenide with *cis*- or *trans*-3-chloro-3-hexene in tetrahydrofuran at 0° gives a mixture of isomeric 3-hexenes in a ratio of *trans*/*cis* = 69/31 and 85/15, respectively. A similar

TABLE III

Difference in Free Energy of Activation for Abstraction Reaction between Isomeric Vinylic Radicals[a]

(Radical)$_c$	(Radical)$_t$	Abstraction reaction	$\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger}$, kcal/mole	Temp., °C	Ref.
		Cl from CCl_4	1.0	77	94
		H from			
		cumene	1.2	110	92b
		cyclohexene	0.7	110	92b
		toluene	0.6	110	92b
		H from cumene	0.9	110	93
		H from cumene[c]	~4	110	92b
		Cl from CCl_4	~3.9	110	96

		H from $(n\text{-}C_4H_9)_3SnH$	0.3	Ambient temp. 101
		H from AcSH	0.8[e]	0 86

[a] The values for $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger}$ were calculated from product isomer ratios and the hypothetical equilibrium ratios (K) of the isomeric radicals shown in the first two columns; the latter ratios (K) were approximated by the equilibrium ratios of the corresponding isomeric olefins. For details see text (p. 30).

[b] The equilibrium ratio K of these radicals is tentatively taken to be 50. For the equilibrium between *cis*- and *trans*-stilbene see refs. 99 and 100.

[c] The *cis*/*trans* ratio of the stilbenes formed, 84/16.

[d] The equilibrium ratio K of these radicals is taken to be 3.2, the same value as the equilibrium constant of *trans*- and *cis*-2-butene.

[e] The equilibrium ratio K of these radicals is taken to be 1, since the *cis*/*trans*-1-hexenyl thiolacetate equilibrium mixture is reported to be approximately 50/50 at 90° (86). The value of 1 for K seems to be too low; if K is larger, say 3, $\Delta G_c^{\ddagger} - \Delta G_t^{\ddagger}$ will be 1.3 kcal/mole.

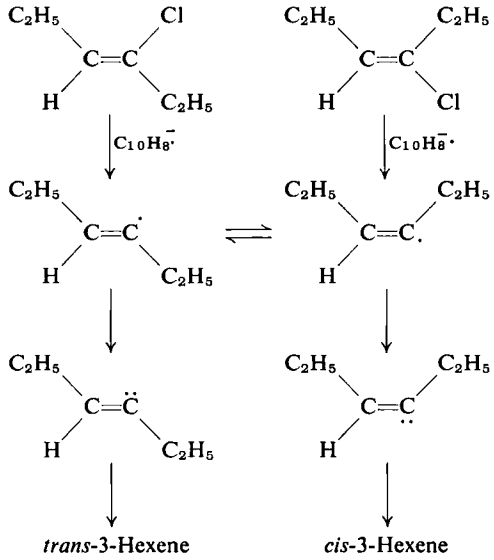


Fig. 36. Reduction of 3-chloro-3-hexenes with sodium naphthalenide.

trend in the isomeric ratio is observed at 27° and also in 1,2-dimethoxyethane at 0 and 27°. These results eliminate the possibility of a linear 1-ethylbutenyl radical as an intermediate; and, in fact, the authors hypothesize that the reaction involves carbanions (Fig. 36) and that the conversion of the 1-ethylbutenyl radical initially formed into the isomeric radical competes with the electron transfer from naphthalenide radical anions to give configurationally stable vinylic carbanions. The electron transfer should take place with equal ease to the *cis*- and the *trans*-vinylic radical.

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Geometry and Conformational Properties of Some Five- and Six-Membered Heterocyclic Compounds Containing Oxygen or Sulfur

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I. INTRODUCTION

In the historical development of the conformational analysis of heterocyclic compounds the pioneering investigations of Böeseken (1–3) (dipole moments, chemical methods), Kohlrausch (4) (Raman spectra), Haworth (5) (shape of carbohydrate molecules), and Hassel (6) (X-ray and electron diffraction) have been of far-reaching importance. However, it was not until a detailed knowledge of the behavior of carbocyclic compounds had been acquired that the quantitative conformational analysis of heterocyclic systems could be tackled. At present, prospects for understanding the properties of (substituted) six- and five-membered carbon-ring compounds seem promising. The application of various refined chemical and physical methods of investigation has, in a number of cases, led to a satisfactory description of carbocyclic compounds. Moreover, progress in computing methods (7–9) has permitted the *a priori* calculation of potential barriers between rotational isomers, of conformational energies of substituents, of flattening effects, etc. Also, medium-sized rings have been treated in this way with considerable success (9).

When hetero atoms are included in the ring, the situation with respect to a detailed approach is more difficult. It is true that there are many overall similarities in the preferred conformations assumed by homocyclic and heterocyclic ring structures. This is especially the case with the six-membered rings, where, as a rule, the chair form appears to be preferred (cf. refs. 10 and 11). On the other hand, significant differences exist between the forces that determine the exact geometry and the conformational equilibrium of heterocyclic and homocyclic compounds.

It seems timely to offer an account of at least part of the data and of the understanding achieved in the heterocyclic field as well as of the many provocative problems that may be amenable to fruitful study by present experimental and theoretical tools. It has been deemed advisable in this article to concentrate on a few classes of compounds with respect to which the authors have experimental experiences, viz., oxygen- and sulfur-containing five- and six-membered ring systems, mostly with halogens as substituents. Even in this limited area complete coverage has not been

attempted. While, of course, related results obtained by other investigators have been included, the discussion is centered mainly around the authors' own research interests. Furthermore, attention has been directed preferably to those compounds where the discussion could, at least partly, be based on X-ray data. The only justification of the authors for the ensuing deficiencies in balance and completeness lies in their hope that the article may yet serve the purpose of stimulating and aiding future research.

One of the aims of stereochemistry is to give an accurate description of molecular geometry, i.e., of the exact relative positions of the atoms. Because, more often than not, it is cumbersome to work with sets of atomic coordinates, the chemist is accustomed to describing molecular geometry in terms such as bond length, bond angle, torsional angle, nonbonded distance, and geometric factors in general. Corresponding dynamic and energy parameters are, e.g., bond stretching, angle deformation, torsional barrier, nonbonded interactions, hydrogen bonding, and stereoelectronic (orbital) interaction.

The energy terms, in particular, remain a matter of conjecture for many heterocyclic systems. The common practice of taking these factors from data of simple aliphatic compounds and assuming that they do not change with environment would appear hazardous.

In closed rings there exist certain mathematical relations between the geometrical parameters (see Sect. II). Any substituent that changes an internal bond angle, a torsional angle, or a bond distance changes the geometry of the ring in its entirety. It seems to be the rule that geometrical changes are distributed evenly over the ring skeleton. In some cases the deformations are rather drastic and one hesitates to call, say, the resulting shape of a six-membered ring still a chair or boat form. It is clear that in such cases "indirect physical methods" (dipole moments, spectroscopy) will hardly be able to give definite information without recourse to the basic geometric data obtainable through X-ray (neutron or electron) diffraction.

This point prompts a general remark on methodology that will be elaborated in Section III; in order to collect sufficient data to draw reliable conclusions regarding geometry and conformational equilibrium, particularly in the case of flexible molecules but also quite generally in the case of heterocyclic compounds, one should combine as many methods of investigation as is feasible.

Diffraction methods will probably soon become routine methods of primary importance in conformational studies. Even if one deals with notoriously flexible molecules such as cyclopentane derivatives, X-ray analysis often yields data which are indispensable in a quantitative treatment of the pseudorotation phenomena in the liquid and gaseous phases.

From a considerable amount of accumulated experience it is now clear that the geometry in a molecular lattice often corresponds closely to the geometry of one of the major conformers occurring in the liquid state or in solution.

The mutually complementary tools of infrared and Raman spectroscopy—apart from yielding characteristic information in their own right—form a bridge in that such spectra for a given compound may be taken in both the liquid (solution) and crystalline states; comparison will often permit identification of one of the conformers present in a conformational equilibrium mixture in the liquid state with the form present in the crystal and recognizable by X-ray data.

NMR spectroscopy at various temperatures—sometimes complemented by ESR, ORD, and CD techniques—affords information that, in the study of heterocyclic compounds, has proved to be of value, particularly in the quantitative description of group interactions and conformational equilibria. The measurement of dipole moments in different solvents has been found profitable in this field as in the field of cyclohexane derivatives (12–14). The magnitude of the dipole moment for a conformationally fixed species gives direct information regarding the charge distribution. The recently developed (15) relation of dipole moment and NMR coupling constants (μ^2/J) has been of great help, especially in cases where no conformationally fixed model compounds can be obtained to estimate the properties of each of two conformers in dynamic equilibrium.

As explained above, the results obtained by X-ray diffraction will be emphasized in this article. Such data often fail to come to the attention of scientists not familiar with the methodology and language of diffraction analysis. A presentation of structural data in terms of valency angles and especially torsional angles seems best suited to facilitate the understanding and handling of the results by stereochemists. Such treatment may give convenient access to information in this field, which is growing rapidly thanks to the availability of modern diffractometers and large-size computers. Attention will be given to torsional angles in particular in Section II. In Section III a comparison of the various physical methods will be made for specific molecules.

Six-membered rings, with few exceptions (see Sect. VII), possess the unique simplifying feature that their chair conformations correspond to deep and narrow energy minima. It is therefore logical that they were the first ones to be studied in the heterocyclic series as they were earlier in the homocyclic series. Section IV, mainly as an introduction to Section V, deals with the parent (nonsubstituted) six-membered 1,4-heterocyclic compounds. Section V comprises halogeno-substituted 1,4-dioxanes,

1,4-dithianes, and 1,4-thioxanes. In the case of the 1,4-thioxane derivatives it is interesting to see how the various inherently different valency angles and bond lengths combine to form a highly irregular chair.

The investigations of the halogeno-substituted compounds have brought to light a distinct preference of the halogen atoms α to the oxygen or sulfur atoms for the axial position. This "anomeric" effect, first observed with the pyranose forms of carbohydrates, is still but little understood and will be discussed in detail in Section VIII. Strong preference for an axial orientation seems to be inherent to the S=O grouping, as is evident from the conformation of 1,4-dithiane-1,4-dioxide (Sect. V) and of cyclic sulfites (Sect. VII).

Section VI reviews the results obtained with six-membered rings containing oxygen or sulfur atoms at locations 1 and 3, and Section VII reviews those with the hetero atoms at the 1,2; 1,2,3; 1,3,5; and 1,2,4,5 positions. Section IX deals with five-membered ring systems. A few concluding remarks are formulated in Section X.

II. TORSIONAL ANGLES

The concept of torsional, or dihedral, angle is fully discussed in the standard text of Eliel, Allinger, Angyal, and Morrison (10). The use of such angles in cyclic compounds is extremely valuable for an adequate description of the conformational aspects of these molecules. The numerical values of the torsional angles can be calculated in a straightforward manner for compounds whose molecular geometries have been analyzed by X-ray or electron diffraction methods (Sect. III). The practice of stating dihedral angle values is beginning to find acceptance in the crystallographic world. Torsional angles of molecules in solution can in principle be obtained from NMR spectra and dielectric measurements (cf. Sect. III).

For cyclohexane with molecular symmetry D_{3d} ($=\bar{3}\,2/m$) the following relation* holds between the torsional angle φ and the endocyclic valency angle ϑ:

$$\cos\varphi = -\cos\vartheta/(1 + \cos\vartheta) \tag{1}$$

*A more general equation, relating torsional angles and bond angles in an n-membered ring (n even, point group symmetry D_{nh}) was first given by Pauling (16). Early in 1964 eq. (1) was rediscovered independently and almost simultaneously by several investigators (7,17,18), who realized its significance for the conformational analysis of six-membered rings. Accepting the fact that the "normal" C—CH_2—C angle in hydrocarbons is about 3° greater than the tetrahedral value, they proposed the concept of the flattened chair ($\varphi = 54.5°$) for cyclohexane and its derivatives. Axial substituents, including hydrogens, are thus splayed outward by several degrees.

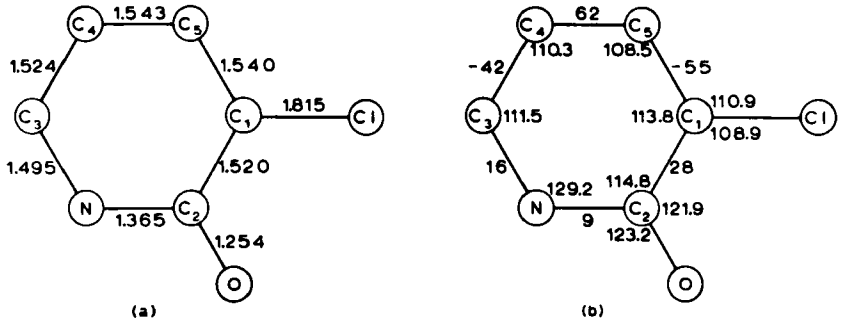


Fig. 1. (*a*), Bond lengths (Å) and (*b*), valency and torsional angles of α-chloro-δ-valerolactam (**1**).

It has been shown (17,22,23) that this relation is equally valid for substituted cyclohexane derivatives and for heterocyclic compounds, giving:

$$\cos \varphi_{av} = -\cos \vartheta_{av}/(1 + \cos \vartheta_{av}) \qquad (2)$$

where φ_{av} and ϑ_{av} are average values for the torsional and valency angles. The numerical value of φ_{av} is a measure of the puckering of the ring, this value being zero for planar molecules.

The most discussed conformations of six-membered rings are chair, half-chair, ideal boat, skew-boat, sofa or 1,2-diplanar, and 1,3-diplanar forms.* Tables of appropriate dihedral angles for all these forms have been published by several authors (8,9). Inspection of such tables gives better insight into the molecular shape than does the calculation of least squares planes through the atoms of the molecule traditionally performed by crystallographers. The analysis of α-chloro-δ-valerolactam (**1**) by Romers et al. (24) may be quoted as a characteristic example. Figure 1*a* presents the interatomic distances and Figure 1*b* the valency and torsional angles†

X-ray studies of substituted dioxanes (17), cyclohexanes (19–21), steroids (29), and of numerous other saturated six-membered rings, as well as chemical evidence and NMR spectroscopy, amply supported this view which soon gained general recognition. A scrutiny (21) of available X-ray structural data of simple (equatorially substituted) cyclohexane derivatives now seems to indicate that the *mean* torsional angle in these cyclohexanes is slightly greater than currently accepted, values of $\varphi = 55.3$–$56.7°$ being observed.

* The first four conformations are generally familiar and are discussed in standard texts (e.g., ref. 10). The sofa (or 1,2-diplanar) and 1,3-diplanar forms have been described by E. Toromanoff in Volume 2 of this series (p. 162).

† The torsional angle φ is called *positive* (7) if the planes 1–2–3 and 2–3–4 (see Fig. 2*a*) enclose this angle and the bond in front 1–2 has to be rotated *clockwise* in order to cover the bond in back 3–4. The angle φ is *negative* if the front bond 1–2 has to be rotated *counterclockwise* in order to cover 3–4. The indication $+\varphi$ or $-\varphi$ specifies the absolute configuration.

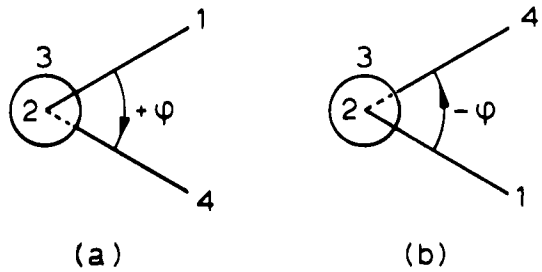


Fig. 2. Newman projection of the system 1–2–3–4 projected along the bond 2–3. The torsional angle is positive in *a* and negative in *b*.

TABLE I

Dihedral Angles in Six-Membered Rings for Half-Chair and Sofa Forms, Compared with Actual Values for Compound **1**

Half-chair	15	0	15	−45	62	−45
Sofa	0	0	27	−54	56	−28
Compound **1**	16	9	28	−55	62	−42

of this molecule. Inspection of Table I and Figure 2 immediately shows that the molecule has a half-chair conformation with the Cl atom in the (pseudo-) equatorial position. This form is, however, not ideal, but somewhat distorted towards the sofa form.

The geometrical picture is far more complicated for five-membered systems. In cyclopentane itself the puckering is not fixed, but rotates around the ring without intervention of any substantial potential energy barriers (9,10,25) (pseudorotation). On introducing a substituent or a hetero atom into the ring, a potential barrier restricting pseudorotation may occur. Of the possible puckered conformations, the two that contain elements of symmetry are usually selected for discussion of conformational properties of cyclopentanes: the C_2 or half-chair (26) form and the C_s or envelope

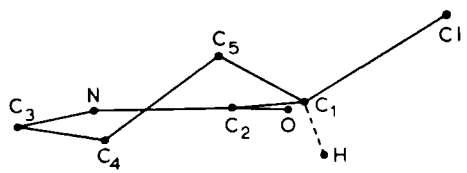


Fig. 3. Orthogonal projection of α-chloro-δ-valerolactam viewed on a plane perpendicular to the plane of atoms C_1, C_2, N, and C_3 and parallel to the bond C_2—N.

(26) form. However, there is no *a priori* reason to assume that either of these "basic" forms actually represents an energy minimum in any given substituted cyclopentane.

The torsional angles of the basic forms as well as the intermediate ones may be characterized by the following relation (27,28):

$$\varphi_j = \varphi_{max} \cos [\tfrac{1}{2}\Delta - j\delta], \qquad j = 0, 1, 2, 3, 4 \tag{3}$$

where φ_0 is the torsional angle of bond 5–1, φ_j is the torsional angle of bond (j)—$(j + 1)$ and Δ is the phase angle of pseudorotation (Fig. 4).* The maximum attainable value of φ is φ_{max}; $j\delta$ is a phase lag allowing for the fact that the torsional angles successively obtain the maximum value. The numerical value of δ is 144°.

The advantage of this approach, using eq. (3), is that it provides a description of the conformational aspects of five-membered rings in relation to the parent compound cyclopentane. We will show in Section IX how these concepts can be worked out for some dioxolanes and a few other systems with respect to their physical and conformational properties in solution.

The angle φ also has a physical corollary: the torsional energy of a molecule is considered to be the sum of the torsional strains about the individual bonds. The torsional strain present in a single C—C bond (threefold barrier) may be calculated by the equation of Pitzer (25):

$$E = \tfrac{1}{2}E_0(1 + \cos 3\varphi) \tag{4}$$

where the torsional strain E is equal to the energy E_0 for the eclipsed molecular fragment ($\varphi = 0°$) and $E = 0$ for the *gauche* ($\varphi = 60°$) and *anti*-periplanar ($\varphi = 180°$) conformations.

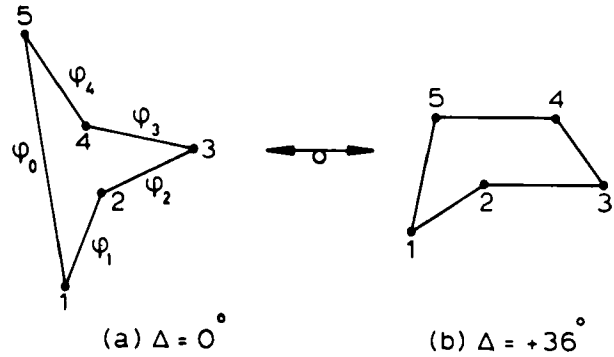


Fig. 4. (*a*) Half-chair form of a five-membered ring with $\Delta = 0°$ and (*b*) envelope form with $\Delta = 36°$.

*A similar description has been presented (181) for the boat/twist-boat pseudorotation in flexible six-membered rings.

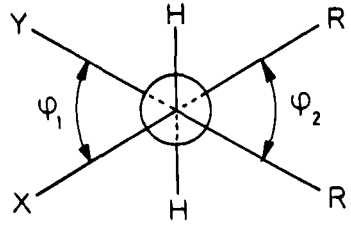


Fig. 5. Torsional angles depend on the values of the valency angles.

It should be recognized that torsional angles are not independent of bond angles; e.g., in a system such as the one shown in Figure 5 the sum $\varphi_1 + \varphi_2$ amounts to 120° only if all bond angles are tetrahedral. Large deviations have been observed in several cases (29); some examples are shown in Figure 11 in Section V.

III. PHYSICAL METHODS

A. General

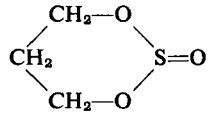
A review of the physical methods usually applied to conformational problems, such as diffraction methods, spectroscopic methods, and dipole moments, has recently been given by Eliel, Allinger, Angyal, and Morrison (10). Therefore, in this section, we shall touch on only those aspects of the above methods which have proved particularly useful in the analysis of the compounds under discussion in this article, viz., X-ray and other diffraction methods, nuclear magnetic resonance spectroscopy, electric dipole moments (relation between the spin coupling constants and dihedral angles, correlation of spin coupling constants with dipole moments), and infrared and Raman spectroscopy (carbon–halogen stretching frequencies). As has been stressed in Section I, it appears essential to use diverse methods in a cooperative way in order to arrive at a reliable, detailed conformational analysis, with heterocyclic compounds no less than with carbocyclic systems.

B. Diffraction Methods

The diffraction methods, notably X-ray structure analysis, are less popular than other physical methods because rather specialized and extensive training is required to use them. An organic chemist is inclined to resort to X-ray analysis only when other procedures fail to produce significant and consistent answers to his problems. As a result the application of diffraction methods has been incidental and less systematic than,

say, the employment of NMR spectra. To underline the advantages of including diffraction techniques in conformational study we will discuss a few examples.

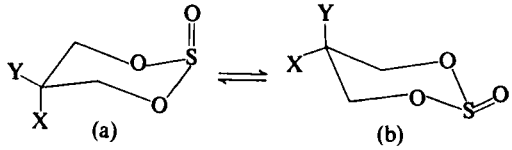
1. Trimethylene Sulfite (2)



(2)

Conflicting conformational assignments of cyclic sulfites, notably trimethylene sulfite, have been made in the course of the last decade, but the major problems now seem to have been solved, though not without the aid of X-ray diffraction.

By infrared techniques, de la Mare and his co-workers (30) in 1956 came to the conclusion that **2** and its derivatives are chair shaped with an equatorially oriented S=O group. From NMR spectra Pritchard et al. (31,32), in 1963, concluded that a flexible boat form is more probable. On the basis of NMR and IR spectra and dipole moments Hellier et al. (33) in 1963 agreed with de la Mare on the rigid chair form of **2**, but assigned the axial orientation to the sulfite group. The same conclusion was reached by Edmundson (34) in 1965 by interpretation of NMR spectra and by van Woerden (35) in 1966 by measurements of the rates of alkaline hydrolysis. Arbuzov (36) suggested in 1960 that trimethylene sulfites exist in solution as mixtures of the two possible chair forms *a* and *b*:



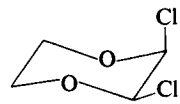
Overberger et al. (37) in 1965 proposed the same equilibrium mixture of **2** carrying axial as well as equatorial sulfite groups. In 1966, Wood and Miskow (38) interpreted the NMR spectra in a different way and again favored the flexible boat conformation.

These conflicting statements, depending on different interpretations of physical data, may seem disturbing. The reasons for the disagreements must be sought in the complex nature of the infrared spectra and in the difficulties in the derivation of the correct orientation of the S=O group with respect to the ring and in the assignment of a proper partial electric moment to the sulfite group.

Van Woerden and Havinga (39–41) measured dipole moments of a number of substituted cyclic sulfites in solution and succeeded in deriving a consistent and constant value for the partial electric moment of the sulfite group (2.5 D), if and only if chair conformations with axial orientation of the S=O group were assumed to predominate strongly. The following set of partial moments gave a quantitatively consistent picture for all compounds studied: S=O, 2.7 D; S—O, 0 D; lone pair on the S atom, 1.0 D. The preference of the S=O for the axial orientation in these trimethylene sulfites was estimated to correspond to a $\Delta G^\circ = 3.5 \pm 1$ kcal/mol.

Still it was considered a decisive contribution to this picture when Altona, Geise, and Romers (22) succeeded by X-ray investigation at -100° of trimethylene sulfite—and later also of 2,2′-dichlorotrimethylene sulfite (23)—in determining beyond a doubt the chair conformation and the exact molecular geometry in the crystalline phase. The similarity of this form with the form predominating in solution had been established by infrared spectroscopy (39,40).

2. *cis-2,3-Dichloro-1,4-dioxane* (3)

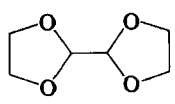


(3)

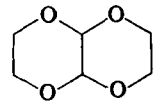
Caspi and co-workers (42) deduced from NMR measurements that **3** in solution probably exists in a rigid boat conformation. The analysis was not complete leaving the interpretation open to doubt. A similar difficulty appeared in the work of Chen and Le Fèvre (43). Altona and Romers (44) —on the basis of the NMR spectrum—preferred a chair form and established that the IR spectra in the solid state and in solution are practically identical. X-ray analysis (44) of crystalline **3** then proved that the molecule is, indeed, the *cis*-2,3-dichloro isomer with a chair conformation, one chlorine atom being in the axial and the other in the equatorial position.

The molecule lacks a center of symmetry. Single crystals of **3** are hemihedric (see also Table V) and composed of either *ea* or *ae* chair forms. However, a solution of a selected single crystal is optically inactive, indicating that rapid racemization takes place. The NMR spectrum of **3** in solutions at room temperature and down to -118° (the coalescence temperature) shows that the molecule rapidly interconverts between *ea* and *ae* chair forms (44–46,50).

3. 2,2'-Bis-1,3-dioxolane (**4**) *and 1,4,5,8-Naphthodioxane* (**5**)



(**4**) mp 111°, μ = 1.9 D



(**5**) mp 136°, μ = 0.7 D

These two isomers can be isolated from a reaction mixture of *trans-* or *cis*-2,3-dichloro-1,4-dioxane and ethylene glycol. The original investigations (47) led to the conclusion that the two isomers were *trans-* and *cis*-1,4,5,8-naphthodioxane on the basis of analogy with *trans-* and *cis*-decalin. The main arguments in favor of this assignment were the observed melting points (111 and 136°, respectively), the dipole moments (1.9 and 0.7 D, respectively), and the presumed mechanisms of formation.

Hassel and co-workers have determined the crystal structures of these isomers. The X-ray analysis (48) of the low-melting form **4** leaves no doubt about its molecular structure: 2,2'-bis-1,3-dioxolane. The molecule has a center of symmetry in the solid state. The five-membered rings are puckered in a peculiar way, neither as an envelope, nor as a half-chair form, but rather "in-between." The conformation of the compound and the reason why its dipole moment (1.9 D) in solution is so high are discussed in Section IX.

The crystal structure analysis of the high-melting form (49) was, however, rather inconclusive. The electron density projection shown is interpretable in terms of space groups $P2/c$, $P2_1/c$, C_2, and $C2/m$. Inspection of this projection reveals that it is also possible to locate a *cis*-naphthodioxane molecule with the dioxane moieties in the chair conformation on the proposed atomic sites, assuming the space group to be C_2. Here the quantitative interpretation of the NMR spectrum of **5** in solution by Altona and Havinga (50) and recently by Fraser and Reyes-Zamora (51) gave a clear-cut answer: the spectrum is in accord with a molecular structure consisting of two *cis*-fused chairs; the two antipodal conformers are in dynamic equilibrium. The observed dipole moment (0.7D) is slightly too high for a purely centrosymmetric molecule, but quite reasonable for a mobile molecule of the *cis*-decalin type with symmetry C_2.

The example **4** clearly shows the success of X-ray analysis when properly applied. Although this particular structure determination was performed in two projections only, the excellent agreement between calculated and observed structural factors leaves no doubt that the proposed structure is correct. The conditions were, however, unfavorable for a proper X-ray analysis of compound **5**, and the definitive conclusions in this case were based primarily on NMR and dipole moment studies.

All remarks concerning the use of X-ray analysis are true, *mutatis mutandis*, for neutron diffraction. Although the experimental equipment is entirely different and its applicability (52) restricted to the immediate neighborhood of an atomic reactor, the output, in terms of a crystal structure refinement, is essentially the same and has about the same accuracy. It offers one clear advantage over X-ray diffraction, namely, that hydrogen positions can be determined with far greater accuracy. An illustrative example is the very accurate three-dimensional neutron diffraction analysis of α-D-glucose by Brown and Levy (53).

Electron diffraction of gases of simple and highly symmetric molecules can be performed with an even higher accuracy than is possible in X-ray analysis. Standard deviations of bond lengths of only 0.002–0.003 Å have been reported by several authors (54,55). The method is less adequate for molecules of more intricate and lower symmetry because of the unavoidable overlap in the molecular radial distribution function. Nevertheless, volatile derivatives of cyclohexane, dioxane, pyran, cyclobutane, norcamphane, etc., may be tackled successfully by this method which often yields the correct conformation and may even be used to assign the correct positions of side groups in the molecule. By feeding in some chemical information on shape, bond angles, and atomic distances (56) and by the application of constraints (56–59) in the least squares refinement much progress has been made. Of special merit in the electron diffraction method is the fact that it directly yields information about the molecular shape of molecules in the gaseous state where no complications from neighboring molecules arise. Moreover, it is the preferred diffraction method for those compounds which fail to produce single crystals on cooling.

C. Nuclear Magnetic Resonance

1. Introduction

The general applications of NMR spectroscopy to conformational analysis have been thoroughly reviewed elsewhere (60). Hence, we will deal here only with some aspects of the angular dependence of the proton spin coupling constants.

In principle, torsional angles of molecules in solution can be obtained from NMR data. Much information is now available on the relation between the torsional angle and the coupling constant $^3J_{HH}$ between vicinal hydrogen nuclei [Karplus equation (61)]. Developments in the near future may include the use of other nuclei, long-range coupling constants ^4J and ^5J (62,63), and possibly also the use of ESR data of free radicals (64).

Valence bond calculations (61) show that the coupling constant $^3J_{HH}$ describes an asymmetrical U-shaped curve on increasing the torsional angle between vicinal protons from 0 to 180° according to the equation:

$$J = A\cos^2\varphi - B\cos\varphi + C \qquad (0° \leqslant \varphi \leqslant 180°) \tag{5}$$

The theoretical Karplus constants, based on ethane, are $A = 9.0$, $B = 0.5$, $C = -0.3$ cps. Recent MO calculations (65) of vicinal couplings in ethane yielded coupling constants for various φ values that can be approximated by eq. (5) with $A = 9.4$–9.6, $B = 1.9$–2.0, $C = 0.2$ cps. Chandra and Narasimhan (66) found $A = 8.5$, $B = 0.6$, $C = -0.2$ cps from a perturbation approach to the proton spin coupling in ethane. However, these "constants" are now known to be dependent on the system under investigation and would best seem to be treated as empirically adjustable parameters with special emphasis on the largest constant A (15,67,68). It is here that the combination of NMR data with the geometrical results of diffraction studies, in particular those comprising conformationally homogeneous six-membered rings, is rewarding (cf. Sect. III-C-3).

Electronegativity of atoms directly bound to the C—H fragments seems to play a role in the dependence of the Karplus constants on the particular system under study. It has been found (69) that the vicinal coupling constants of a proton are decreased by an electronegative substituent in the *anti* position.

Torsional angles φ_{HH} and corresponding HH couplings are now known for many 2,3- and 2,5-disubstituted 1,4-diheterocyclic compounds. The conclusion is that φ_{HH} and J_{HH} do not appear to be related by the simple Karplus equation [eq. (5).] Two electronegativity corrections (of still unknown form), one of them rotation dependent, seem to be necessary (70).

It is evident that the application of eq. (5) for the determination of torsional angles is a dangerous procedure, because the constants A, B, and C are not well known. This statement is illustrated by Table II. It has been pointed out (68) that for the X—CH_2—CHR—Y or X—CH_2—CH_2—Y fragment of a molecule which exists as an equilibrium mixture of two identical conformers (Figs. 6 and 7), the sum

$$J_{trans} + \tfrac{1}{2}J_{cis} = \tfrac{3}{4}A + \tfrac{3}{2}C \tag{6}$$

should be independent of the dihedral angles between the protons. The variation of $J_{trans} + \frac{1}{2}J_{cis}$ with the system, viz., the variation of the Karplus parameters with the system, is, however, clearly demonstrated by the examples in Table II.

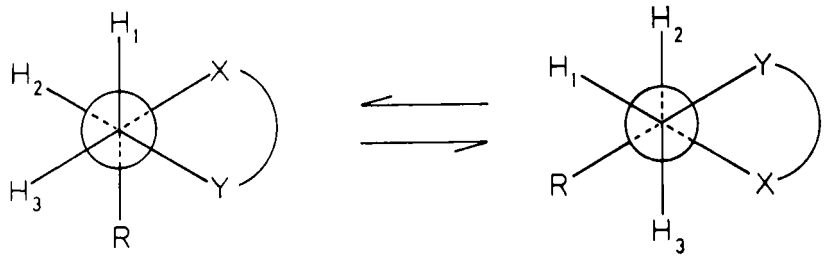


Fig. 6. Conformations of X—CH_2—CHR—Y fragment. $J_{trans} = J_{23}$, $J_{cis} = J_{12}$.

TABLE II

$J_{trans} + \frac{1}{2}J_{cis}$ (cps) for Various X—CH_2—CHR—Y Fragments (50,68)

Fragment	Compound	$J_{trans} + \frac{1}{2}J_{cis}$
H—CH_2—CH_2—H	Theoretical constants	6.3
—O—CH_2—CHR—O—	Carbon substituted 1,4-dioxanes	7.4
—O—CH_2—CH_2—O—	1,4-Dioxane	7.9
—N—CH_2—CH_2—O—	Morpholine	8.1
—S—CH_2—CH_2—O—	1,4-Thioxane	8.7
—S—CH_2—CH_2—S—	1,4-Dithiane	9.4
—C—CH_2—CH—O—	Cyclohexanols	9.3
—O—CH_2—CH_2—O—	1,3-Dioxolane	9.7
—C—CH_2—CH_2—C—	Cyclohexane	9.9[a]

[a] Calculated from data in ref. 180

2. *The R-Value Method*

For six-membered ring compounds of the type shown in Figures 6 and 7, the ratio $R = J_{trans}/J_{cis}$ has been found to be a direct measure of conformational effect by Lambert et al. (71–73). For molecules in the perfect chair conformation, R is close to 2.0; for molecules in the flexible form, $R = 1.2 \pm 0.2$ and a "puckered-chair" form corresponds to $R > 2.75$. This "R-value method" was extended (74) by calculating R as a function of the ring dihedral angle φ in the —CH_2—CH_2— or —CH_2—CHR—

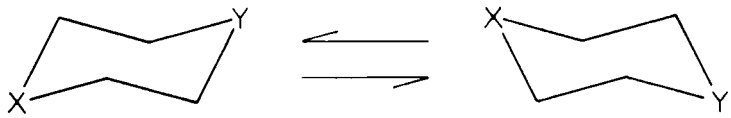


Fig. 7. Example of an equilibrium of two identical conformers.

fragment with the aid of the simplified Karplus equation: $J_{HH} = A \cos^2 \varphi_{HH}$ (the small parameters B and C are set equal to zero). This yields

$$\cos^2 \varphi = 3/(2 + 4R) \tag{7}$$

which can be applied to all systems which exist as equilibrium mixtures of two identical conformers and which contain a —CH_2—CH_2— or —CH_2—CHR— fragment. A reasonable value for φ can be calculated from the experimental R value when φ is not too large (74), but, of course, the reliability and accuracy of the result are less than in the case of diffraction methods.

3. Correlation between Vicinal Coupling Constants and Dipole Moments

For a series of compounds that have similar geometry and similar vicinal polar substituents and that exist as equilibrium mixtures of two conformers, Altona, Buys, Hageman, and Havinga (15,63,75–78) found a linear relation between the squares of the electric dipole moments and the vicinal coupling constants as the conformational equilibrium constant varied. As an example we may consider the equilibrium in *trans*-1,2-dihalogeno(1-alkyl)cyclohexanes (Fig. 8). The square of the electric dipole moment (μ^2) is equated with the properties of the individual conformers by

$$\mu^2 = x_{ee}\mu_{ee}^2 + (1 - x_{ee})\mu_{aa}^2 \tag{8}$$

and the sum of the vicinal proton coupling constants $J = J_{AX} + J_{BX}$, which can readily be determined from the NMR spectrum, by

$$J = x_{ee}J_{ee} + (1 - x_{ee})J_{aa} \tag{9}$$

From eqs. (8) and (9) it is seen that a linear relation between μ^2 and J holds for a series of these compounds (provided μ_{aa}^2, J_{aa}, μ_{ee}^2, and J_{ee} are the same for each compound and independent of the external factors used to vary the equilibrium constant) with a slope:

$$H = \frac{d\mu^2}{dJ} = \frac{(\mu_{ee}^2 - \mu_{aa}^2)}{(J_{ee} - J_{aa})} \tag{10}$$

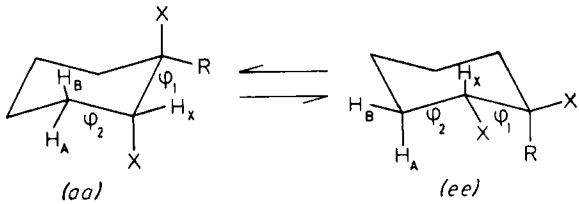


Fig. 8. Conformational equilibrium in *trans*-1,2-dihalogeno(1-alkyl)cyclohexanes. R = H or alkyl, X = Cl or Br.

The slope H can be calculated in terms of molecular geometry with the aid of the usual vector calculation of dipole moments and the Karplus equation [eq. (5)]. For the *trans*-1,2-dihalogenocyclohexanes (Fig. 8, $\varphi_1 = \varphi_2$):

$$H = 2\mu_p^2 \sin^2 \alpha/(A \cos \varphi + B) \tag{11}$$

where μ_p is the partial C—X moment, α is the valency angle C—C—X, and φ is the ring dihedral angle. As the geometry of the cyclohexane ring is well known (21,79), eq. (11) relates the experimental slope to the Karplus parameters A and B. Taking $B = \frac{1}{2}$, A was found to be equal to 12.9 cps for the CH_2—CHX moiety in *trans*-1,2-dihalocyclohexanes (77). For the corresponding cyclopentanes, where $\varphi_1 \neq \varphi_2$, eq. (11) becomes more complicated (77); the value of A was found to be equal to 10.0 cps. Here, again, we find a strong dependence of A on the system under consideration.

The relation between μ^2 and J may serve several other useful purposes: (*a*) It provides a ready check on the reliability of the observed data and is a test of "isogeometry" (i.e., constancy of geometry of the ring framework) of a series of compounds. (*b*) When only one physical constant (either μ^2 or J) for the pure conformers can be obtained (from calculation or from experiment), the other may be determined from the straight line experimentally found. (*c*) The occurrence of a single straight line suggests (77) that only two conformers predominate in the equilibrium mixture. An application of this method to heterocyclic compounds is presented in Section IX.

4. Benzene Effect

A remark on solvent effects may be in order here. With increasing solvent polarity, the position of equilibrium will usually be shifted to the more polar conformer. While NMR spectra may be obtained from solutions in a wide variety of solvents, dipole moments in dilute solutions are measured only in nonpolar solvents such as alkanes, carbon tetrachloride, and benzene. Curiously, it has been found that benzene favors the more polar conformer in vicinal dihalogenides (13,80–82) and in 1,1,2-trihalogenides (63,76) to the extent of 0.2–0.4 kcal/mol with respect to carbon tetrachloride, although the dielectric constant for the two solvents is about the same. This "benzene effect" is ascribed to the solvent dependence of the halogen–halogen *gauche* interaction (81) and has been the object of a special study in this laboratory (83–85). Comparison of the dipole moments or vicinal spin coupling constants of a vicinal dihalogenide in benzene and carbon tetrachloride usually furnishes unequivocal indication that two or more different conformers are present at equilibrium, each in substantial percentage.

D. Infrared and Raman Spectra: Carbon–Halogen Stretching Frequencies

The study of group vibrations is, of course, useful for conformational analysis if the group in question absorbs at different frequencies when in different conformations (e.g., axial or equatorial in the case of substituted cyclohexanes). This is true for many atoms or groups (86); the carbon–halogen (C—X) stretching frequencies in halogeno-substituted aliphatic or saturated ring compounds especially are highly dependent on the geometrical arrangement about the neighboring carbon atoms. As halogeno-substituted compounds constitute the main class discussed in this article and as the C—X stretching vibrations have been thoroughly studied in this laboratory, a short description of their characteristics is given here. Other aspects of the applications of vibration spectra to conformational problems may be found in ref. 87.

1. Monohalogenides

The carbon–halogen stretching frequency in a monohalogenide is determined by the chemical and geometrical environment. The single most important factor seems to be the nature (carbon, hydrogen, oxygen, etc.) of the atom or atoms *anti* to the halogen. The chemical type of halogenide is specified by *P* (primary), *S* (secondary), and *T* (tertiary), the atom or atoms in the *anti* position are indicated by a subscript (H,C,O, etc.). This convenient notation was introduced by Mizushima et al. (88) and recently extended by Altona (89), who derived an empirical set of parameters for the assignment of the C—Cl, C—Br, and C—I stretching frequencies for a variety of chemical–geometrical combinations. Some examples, taken from ref. 89, are shown in Figure 9 and in Table III.

TABLE III

C—Cl and C—Br Stretching Frequencies (cm^{-1}) for Various Chemical–Geometrical Combinations

Type	C—Cl	C—Br	Type	C—Cl	C—Br
S_{HH}	611	535	S_{HO}	700	660
S''_{HH}[a]	685	660	S_{CO}	767	728
S_{CH} (S_{XH})	650	596	T_{HHH}	560	505
S_{CC}	742	686	T_{CHH} (T_{XHH})	612	588

[a] Cf. ref. 89.

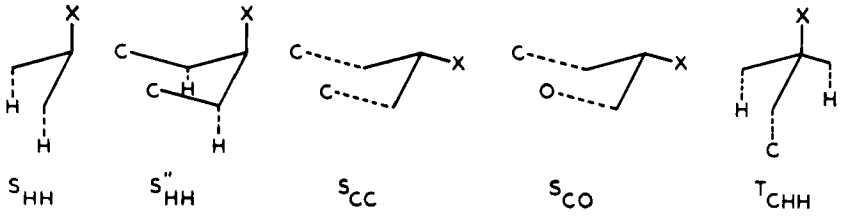


Fig. 9. Examples of some chemical-geometrical combinations (X = halogen).

2. *Vicinal Dihalogenides*

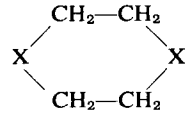
A study of *vic*-dihalogeno compounds in the cyclic (90) and open-chain (91) series reveals that the two C—X stretching frequencies of the *anti* configuration usually occur as a strongly coupled pair: an intense Raman band is observed at the higher frequency (ν_{sym}), whereas ν_{asym} is found as a strong IR active mode of vibration at lower wave number. Consequently, it is only from the *combination* of infrared and Raman data that the two C—X stretching modes can be assigned. In the notation of Table III, the subscripts C and X are interchangeable. $\nu_{av} = \frac{1}{2}(\nu_{sym} + \nu_{asym})$ can easily be predicted from Table III by taking the average of the appropriate stretching parameters. The frequency difference $\Delta\nu = \nu_{sym} - \nu_{asym}$ increases in the series: *TT* (both halogens tertiary) → *PP* → *SS,ST*.

The vibrations of vicinal dihalogenides in the *gauche* configuration are treated similarly. The coupling ($\Delta\nu$) is much weaker than in *anti* systems. Two medium-intensity bands are found in the IR as well as in the Raman spectra.

IV. GEOMETRY OF NONSUBSTITUTED SIX-MEMBERED 1,4-HETEROCYCLIC COMPOUNDS

A. Diffraction Data

In this section the geometrical features of systems



where X = CH_2, NH, O, S, and Se are discussed. Davis and Hassel (79) investigated cyclohexane (**6**), piperazine (**7**), and 1,4-dioxane (**8**) in the vapor state by means of electron diffraction. The corresponding sulfur and selenium compounds, 1,4-dithiane (**9**) and 1,4-diselenane (**10**), were examined by Marsh and McCullough (92,93) by means of crystal structure

determinations. No diffraction data are available for 1,4-thioxane (**11**), tetrahydropyran, thiane, and piperidine. Some relevant bond distances, valency angles ϑ as well as ϑ_{av} and φ_{av} (average torsional angles) are listed in Table IV. This table also includes the geometrical data for piperidine hydrochloride (**12**) derived from the X-ray analysis by Rérat (94).

All these compounds are in the chair conformation. The observed bond lengths are quite regular and require no comment. Using eq. (1) we calculate for cyclohexane $\varphi = 54.5°$, a value significantly smaller than the perfect-chair value of 60°, indicating that the ring system is flatter than the model system with tetrahedral valency angles (109.5°). On the assumption of trigonal-symmetrical geometry $\bar{3}\,2/m$ for the other compounds of Table IV, one similarly calculates the values for φ_{av} listed in the last column [eq. (2)]. Evidently, the dihedral angle φ_{av} increases with increasing atomic weight of the hetero atoms, i.e., the molecules with heavy atoms are more puckered. In the case of 1,4-dithiane and 1,4-diselenane the obvious reason for this generalization lies in the well-known small values for the valency angles C—S—C and C—Se—C (99° and 98.6°, respectively).

B. Conformational Properties in Solution

The shape of the six-membered 1,4-diheterocyclic compounds has also been studied in solution by spectroscopic methods, dipole moments, etc. Of course, these methods do not yield as much detailed quantitative

TABLE IV

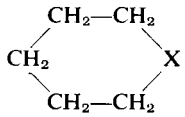
Bond Lengths (Å) and Valency and Torsional Angles (in Degrees) of Some 1,4-Heterocyclic Compounds

X	Compound[a]	C—C	C—X	C—H	∠CCX	∠CXC	ϑ_{av}	φ_{av}
CH_2	**6**	1.528		1.104	111.6		111.6	54.5
NH	**7**	1.527	1.471	1.112	109.8	112.6	110.7	56.8
O	**8**	1.523	1.423	1.112	109.2	112.5	110.3	57.9
S	**9**	1.49	1.81[b]		112.7[b]	99	108	63.5
Se	**10**	1.50	2.01[b]		111.1[b]	98.6	106.9	67.7
NH_2^+, CH_2	**12**	1.505	1.497		110.4	112.3	111.0	56.0

[a] **(6)** Cyclohexane
(7) Piperazine
(8) 1,4-Dioxane
(9) 1,4-Dithiane
(10) 1,4-Diselenane
(12) Piperidine hydrochloride
[b] Average value

information as diffraction methods, but, in general, the results support the chair shape for all these molecules. References may be found in the review by Riddell (11).

One application of NMR spectroscopy to these compounds is worth mentioning here—the *R*-value method which was discussed in Section III-C-2. The values of $R = J_{trans}/J_{cis}$ for a number of 1,4-diheterocyclic six-membered compounds have been given by Lambert (71). For compounds **7** and **8**, *R* is equal to 2.15 and 2.20, respectively, which should correspond to a chair-shaped molecule (see Sect. III-C-2). For compounds **9** and **10**, the *R* values are appreciably greater, 3.38 and 3.49, respectively, in accordance with the "puckered-chair" conformation. 1,4-Thioxane (**11**) has an *R* value of 2.77, suggesting it is a little less puckered than compounds **9** and **10**. Recently, *R* values for some heterocyclic systems of the type:

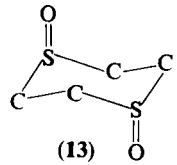


were also presented (73) which were calculated from the NMR spectra of the corresponding 4,4-dideutero-substituted compounds. They suggest a chair form for tetrahydropyran ($R = 1.9$) and a puckered-chair form for thiane ($R = 2.61$), selenane ($R = 2.74$), and tellurane ($R = 2.76$).

V. MOLECULAR STRUCTURE OF HALOGENO DERIVATIVES OF 1,4-DIOXANE, 1,4-THIOXANE, 1,4-DITHIANE, AND 1,4-DITHIANE-1,4-DIOXIDE

A. X-Ray Investigations

The geometry and conformations of most of the molecules under discussion in this section were determined accurately by X-ray diffraction methods with frequent application of low-temperature techniques (95). All molecules are chair shaped, and, with one exception, the halogen atoms of all known disubstituted compounds are exclusively found in axial positions. The exception is *cis*-2,3-dichloro-1,4-dioxane (**3**) which, of course, has one chlorine in the equatorial and one chlorine in the axial position. It is interesting that the S=O groups of 1,4-dithiane-1,4-dioxide (**13**) also occur in axial positions. Even *trans-syn-trans*-2,3,5,6-tetrachloro-1,4-dioxane (**19**) has all chlorine atoms in axial positions. This remarkably



(13)

large preference for halogens to assume the axial orientation does not exist in cyclohexane chemistry. The enhanced stability of halogeno substituents in axial positions in 1,4-heterocyclic compounds even persists in solutions (Sect. V-B) and is closely related to the *anomeric effect* which will be dealt with in Section VIII.

In Table V are listed the crystallographic data for those 1,4-heterocyclic compounds which have been subjected to complete structure determinations. Since the space groups of **15** and **17** and of **23** and **24** are the same and the respective unit cell dimensions nearly equal, it may be concluded that the crystal structures of **17** (17) and of **24** (96) are isomorphous with those of **15** and **23**, respectively. This supposition is confirmed by preliminary structure factor calculations, and it may be concluded that **17** and **24** have molecular structures and conformations similar to those of **15** and **23**, respectively. The structures of the tetrachloro compounds **18**, **19**, **20**, and **21** have been established by a combination of X-ray diffraction (17,97), NMR spectral data, and dipole moments and will be discussed elsewhere (98).

In order to compare interatomic distances and bond and torsional angles in the various molecules we have adopted the numbering of the atoms depicted in Figure 10. The endocyclic and exocyclic bond lengths are given in Tables VI and VII, respectively. The most prominent features apparent from these tables are:

a. The endocyclic atomic distances from an O or S atom to a carbon atom carrying a halogen atom are significantly smaller than the corresponding distances to carbon atoms without halogen atoms.

b. The C—Cl and C—Br distances in axial positions are longer than the corresponding paraffinic C—Cl and C—Br bond lengths (1.79 and

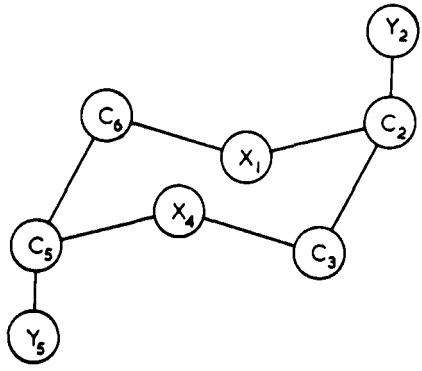


Fig. 10. The numbering of atoms in various 1,4-dioxane, 1,4-thioxane, and 1,4-dithiane compounds. X = O,S. Y = H,Cl,Br.

TABLE V

Unit Cell Dimensions (Å), Space Groups, and Number of Molecules per Unit Cell (Z) for Compounds 3 and 13–26

Compound[a]	a	b	c	α	β	γ	Z	Space group	t, °C[b]
13	6.34	6.46	8.22	90	104	90	2	$P2_1/n$	20
14	5.685	7.59	15.82	90	90	90	4	$P2_12_12_1$	−100
15	7.203	5.704	15.79	90	107.3	90	4	$P2_1/c$	−145
3	4.463	10.72	13.13	90	90	90	4	$P2_12_12_1$	−140
16	4.573	5.491	6.665	86.3	104.1	106.2	1	$P\bar{1}$	−125
17	7.39	5.80	16.45	90	108	90	4	$P2_1/c$	20
18	13.45	13.45	4.60	90	90	90	4	$P4_2/n$	20
19	6.724	7.552	7.626	90	93.1	90	2	$P2_1/n$	20
20	9.77	9.61	8.64	90	90	90	4	$Pna2_1$	20
21	8.46	8.46	11.35	90	90	90	4	$P4_12_12$	20
22	14.808	7.120	6.318	90	90	90	4	$P2_12_12_1$	−185
23	7.174	7.511	6.726	90	93.9	90	2	Pn	−180
24	7.40	7.60	6.96	90	93.5	90	2	Pn	20
25	14.54	7.52	7.60	90	90	90	4	$Pna2_1$	20
26	6.53	7.14	9.01	90	111.5	90	2	$P2_1/c$	20

[a] **(13)** 1,4-Dithiane-1,4-dioxide (99)
(14) *trans*-2,3-Dibromo-1,4-dioxane (100)
(15) *trans*-2,3-Dichloro-1,4-dioxane (101)
(3) *cis*-2,3-Dichloro-1,4-dioxane (44)
(16) *trans*-2,5-Dichloro-1,4-dioxane (102)
(17) *trans*-2-Bromo-3-chloro-1,4-dioxane (17)
(18) *cis-anti-cis*-2,3,5,6-Tetrachloro-1,4-dioxane
(19) *trans-syn-trans*-2,3,5,6-Tetrachloro-1,4-dioxane (97)
(20) *trans-cis*-2,3,5,6-Tetrachloro-1,4-dioxane
(21) *trans-anti-trans*-2,3,5,6-Tetrachloro-1,4-dioxane
(22) *trans*-2,3-Dichloro-1,4-thioxane (103)
(23) *trans*-2,3-Dichloro-1,4-dithiane (96)
(24) *trans*-2-Bromo-3-chloro-1,4-dithiane (96)
(25) *trans*-2,3-Dibromo-1,4-dithiane (96)
(26) *trans*-2,5-Dibromo-1,4-dithiane (104)

[b] Temp. of investigation

TABLE VI

Endocyclic Bond Lengths (Å) for Selected Compounds

Compound[a]	Bond					
	2–3	5–6	1–2	1–6	3–4	4–5
13	1.51	1.51	1.82	1.80	1.80	1.82
14	1.48	1.44	1.37[b]	1.47[b]	1.37[b]	1.47[b]
15	1.48	1.50	1.38[b]	1.43[b]	1.38[b]	1.43[b]
3	1.528	1.513	1.394	1.466	1.425	1.473
16	1.513	1.513	1.388	1.428	1.428	1.388
19	1.502	1.502	1.398	1.398	1.398	1.398
22	1.522	1.521	1.378	1.447	1.795	1.820
23	1.54	1.47	1.78	1.84	1.80	1.84
26	1.53	1.53	1.81	1.81	1.81	1.81

[a] See footnote a to Table V.
[b] Average value.

1.93 Å). It will be shown in Section VIII that these features may be connected with the observed preference of the halogen substituents for the axial orientation.

Table VIII shows that most endocyclic bond angles are significantly larger than 109.5° with the exception of bond angles involving sulfur as the central atom. The conclusion is that these halogeno-substituted rings are flatter than the corresponding unsubstituted rings whose ϑ_{av} values are

TABLE VII

Exocyclic Carbon–Halogen Bond Lengths (Å) for Selected Compounds

Compound[a]	Bond				Y
	C_2—Y_2	C_3—Y_3	C_5—Y_5	C_6—Y_6	
14	2.03[b]	2.03[b]	—	—	Br
15	1.844	1.833	—	—	Cl
3	1.819	1.781	—	—	Cl
16	1.845	—	1.845	—	Cl
19	1.823	1.823	1.823	1.823	Cl
22	1.842	1.810	—	—	Cl
23	1.81	1.80	—	—	Cl
26	1.99	—	1.99	—	Br

[a] See footnote a to Table V.
[b] Average value.

TABLE VIII

Endocyclic Valency Angles for Selected Compounds (in degrees)

Compound[a]	Angle						ϑ_{av}
	6–1–2	1–2–3	2–3–4	3–4–5	4–5–6	5–6–1	
13	97.9	113.3	111.2	97.9	113.3	111.2	107.4
14	112.6[b]	114.1[b]	114.1[b]	112.6[b]	111.0	111.0	112.6
15	113.4	113.2	115.2	111.6	111.7	110.8	112.6
3	111.6	110.8	112.3	108.5	109.1	110.8	110.5
16	113.1	112.4	111.7	113.1	112.4	111.7	112.4
19	119.4	113.9	113.9	119.4	113.9	113.9	115.7
22	117.4	116.3	113.9	96.8	111.5	112.7	111.4
23	101.3	116.6	115.1	99.9	113.9	110.8	109.6
26	102	115	115	102	115	115	111.0

[a] See footnote a to Table V.
[b] Average value.

listed in Table IV. A close inspection of Table IX and Figure 11 reveals that the introduction of halogen atoms flattens the ring and indicates that the distortion is largest near those bonds carrying the exocyclic atoms. The distortion is greatest for *trans-syn-trans*-2,3,5,6-tetrachloro-1,4-dioxane. Evidently, the molecules make up for the severe *syn*-diaxial crowding largely by flattening of the ring system. This effect is smaller in the dithianes on account of the large C—S bond length, combined with the relatively small C—S—C valency angle.

TABLE IX

Torsional Angles about Endocyclic Bonds for Selected Compounds (in degrees)

Compound[a]	Bonds						φ_{av}
	1–2	2–3	3–4	4–5	5–6	6–1	
13	62.7	70.8	61.1	62.7	70.8	61.1	64.9
14	48.7	47.5	48.7	54.1	55.1	54.1	51.4
15	49.5	48.4	49.5	52.8	54.1	52.8	51.2
3	54.0	56.9	58.6	59.2	58.1	56.6	57.2
16	52.3	51.4	52.0	52.3	51.4	52.0	51.9
19	40.5	38.3	40.5	40.5	38.3	40.5	39.8
22	54.7	53.5	48.9	53.1	60.5	58.7	54.9
23	54.0	58.7	52.9	61.8	70.9	59.6	59.6
26	55	62	55	55	62	55	57

[a] See footnote a to Table V.

The *anti*-group Y—C—C—Y present in *trans*-2,3-disubstituted compounds is not planar. The C—Y vectors on atoms C_2 and C_3 are not antiparallel, but enclose angles in the range of 151–167° (Fig. 11). Another feature is the value of the valency angle C—C—Y (~106.5°) which is significantly smaller than the tetrahedral angle. Consequently, cyclic compounds with 2,3-disubstituted axial halogen atoms (Table X) should have an appreciable electric dipole moment. The dipole moments listed in Table X have been measured in dilute solutions (benzene and carbon tetrachloride as solvents), in which the compounds exist exclusively in the

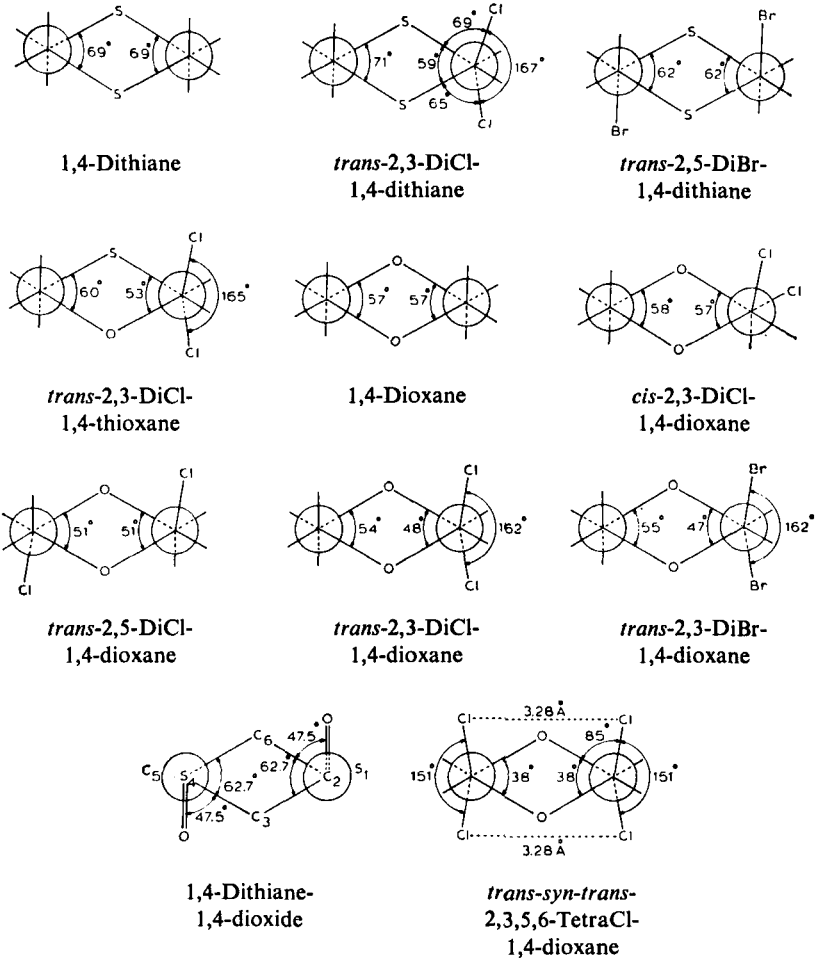


Fig. 11. Newman projections along the bonds 3–2 and 5–6 of several 1,4-dioxanes, thioxanes, and dithianes.

TABLE X

Valency Angle C—C—Y (Average Values), Torsional Angle φ, Vector Angle α, and Electric Dipole Moment μ (Debye units) in the *anti* System Y—C—C—Y

Compound	∠C—C—Y	φ	α	μ
trans-2,3-Dibromo-1,4-dioxane (**14**)	106	161.6	162.2	1.88
trans-2,3-Dichloro-1,4-dioxane (**15**)	106	162.3	163.0	1.62
trans-2,3-Dichloro-1,4-thioxane (**22**)	106.9	165.3	165.0	1.64
trans-2,3-Dichloro-1,4-dithiane (**23**)	107.4	166.7	167.3	1.63

diaxial conformation (cf. Sect. V-B). Havinga and co-workers (17,105,106) have shown that the observed geometrical distortions account for a portion of about 0.7 D of the total observed moments of 1.6–1.9 D. The remaining part of the moments is explained by the assumption of inductive moments in the ring, which are thought to occur also, though to a smaller extent, in *trans*-1,2-dihalogenocyclohexanes (15,107–110).

B. Conformational Properties in Solution

In the previous section, it was shown that *trans*-2,3-dihalogeno-1,4-dioxanes, -thioxanes, and -dithianes occur in the diaxial form in the solid state. In order to investigate the possible existence of a conformational equilibrium in the liquid state or in solution, these compounds (**14**, **15**, **17**, **22–25**) have been studied by means of dipole moments and spectroscopic methods. It appears that:

(*a*) The dipole moments of the compounds (105,106,111), some of which are listed in Table X, are solvent independent, suggesting that only one form is present. The values of μ suggest the diaxial form.

(*b*) The vibrational spectra in the liquid and in the solid state are identical both for the dioxanes (17,105) and for the dithianes (106), indicating that the same conformer is present in both states.

(*c*) The characteristic C—Hal stretching vibrations (cf. Sect. III-D) for the *anti* group Hal—C—C—Hal can easily be detected in the vibrational spectra for the dioxanes (90). Those for the equatorial C—X bond cannot be found.

(*d*) The spin coupling constant between the protons on C_2 and C_3 is small (0–4 cps) for the dioxanes (17,45,46,70,112), thioxanes (111,113), and dithianes (114), in agreement with what is generally found for two equatorially situated hydrogen nuclei (115).

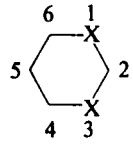
It appears, therefore, that halogen atoms α to the ring oxygen or sulfur have a strong preference for the axial position in solution (cf. Sect. VIII) as they have in the crystalline phase. This same regularity has also

been deduced from the dipole moments, vibrational spectra, and NMR data (116–118) in the case of 2-halogeno- and *trans*-2,3-dihalogenotetrahydropyrans. On the other hand, the 3-halogeno-, 4-halogeno-, and *trans*-3,4-dihalogenotetrahydropyrans, in which no "anomeric" halogen atom is present, prefer the equatorial conformation (116).

The S=O groups in 1,4-dithiane-1,4-dioxide (**13**) are also exclusively axially oriented in solution, as is seen from infrared spectral data (119).

VI. SIX-MEMBERED 1,3-HETEROCYCLIC COMPOUNDS

In this section some heterocyclic systems of the type



in which X = O (1,3-dioxane) and X = S (1,3-dithiane), are discussed. Diffraction studies on the unsubstituted rings have not been carried out; spectroscopic and dipole moment data are in agreement with chair conformations (10,11).

No data on the conformational properties of halogeno derivatives of these systems are available, so that a discussion analogous to that given in Section V cannot be presented. However, some conclusions relating to the structure of the ring have been drawn from the properties of the alkyl and aryl derivatives; these will be summarized briefly.

In the last few years a number of NMR and equilibration studies on 1,3-dioxanes have appeared. References are to be found in the recent paper of Eliel and Knoeber (120). On the basis of models it was concluded (120) that the ring is a "puckered chair" in the O_1—C_2—O_3 region and a flattened-chair in the C_4—C_5—C_6 region. The flattening has also been deduced from NMR data of alkyl derivatives (121) and is indicated as well by the vicinal coupling constants for unsubstituted 1,3-dioxane* (122). The skew-boat form in this system was found to be at least 4 kcal/mol less stable than the chair (120).†

*From the NMR data given in ref. 122 for 1,3-dioxane we calculate $R = J_{trans}/J_{cis} = 1.8$ (in the C_4—C_5 as well as in the C_5—C_6 moiety). This rather low value (see Sect. III-C-2) is in agreement with the "flattened-chair" conformation in the C_4—C_5—C_6 region.

†K. Pihlaja, *Acta Chem. Scand.*, **22**, 716 (1968) has determined a $\Delta H°$ value for the chair–boat interconversion in 1,3-dioxane of 6.8 kcal/mole by heat-of-combustion measurements. See also K. Pihlaja and S. Luoma, *ibid.*, **22**, 2401 (1968).

As a consequence of the puckering, as well as of the shortness of the C—O bond distance, the $-\Delta G^\circ$ values for 2-alkyl substituents are large compared to those for cyclohexane (120) (for the 2-methyl group $\geqslant 3.6$ kcal/mole in 1,3-dioxane, 1.7 kcal/mole in cyclohexane). On the other hand, the $-\Delta G^\circ$ values for 5-alkyl substituents are rather low (120) as a consequence of the smaller degree of puckering in that region and of the absence of *syn*-axial hydrogens (the steric requirement of an electron pair on oxygen seems to be smaller than that of a *syn*-axial hydrogen). The $-\Delta G^\circ$ value for the 5-*t*-butyl group amounts to no more than 1.4 kcal/mol (120), indicating that 5-*t*-butyl-1,3-dioxane should exist in the conformation with the *axial* *t*-butyl group to the extent of about 10% at room temperature.

Alkyl- and aryl-substituted 1,3-dithianes have been studied by Havinga, Kalff, and Romers (123–125) and by Eliel and Hutchins (126). Kalff and Romers (125) carried out an X-ray study of 2-phenyl-1,3-dithiane (**27**) at 20°. The crystallographic data and the structural parameters of compound **27** are collected in Table XI.

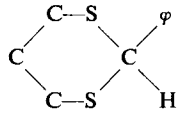


Fig. 12. 2-Phenyl-1,3-dithiane (**27**).

TABLE XI

Crystallographic Data and Structural Parameters (cf. Tables V–IX) for 2-Phenyl-1,3-Dithiane (**27**)

Crystallographic Data

a	*b*	*c*	*α*	*β*	*γ*	*Z*	Space group
22.87	7.774	5.802	90°	90°	90°	4	$Pna2_1$

Endocyclic Bond Lengths, Å

1–2	2–3	3–4	4–5	5–6	6–1
1.80	1.79	1.81	1.51	1.46	1.83

Endocyclic Valency Angles, degrees

1–2–3	2–3–4	3–4–5	4–5–6	5–6–1	6–1–2	ϑ_{av}
115.2	100.9	114.9	116.5	116.1	99.2	110.5

Dihedral Angles about Endocyclic Bonds, degrees

1–2	2–3	3–4	4–5	5–6	6–1	φ_{av}
57.0	56.9	56.1	62.5	60.7	53.6	57.8

The conformation of the 1,3-dithiane ring in **27** is a chair, and the phenyl group is in the equatorial position with its plane approximately perpendicular to the "plane" of the dithiane ring. It is clear that the small C—S—C valency angle and especially the long C—S bond length will impart some special steric features to the 1,3-dithiane chair.

The dipole moments, in solution, of 1,3-dithiane, 2-phenyl-1,3-dithiane, and of some 2-alkyl- and 2,2-dialkyl(aryl)-substituted 1,3-dithianes were found to be equal to 2.0 ± 0.1 D (124), indicating that in all these compounds the ring geometry is similar to that found in **27** by the X-ray analysis. In the NMR spectra, the *ortho* protons of an axial phenyl group in 2-phenyl-1,3-dithianes are found at significantly lower field than the *meta* and *para* protons, an effect absent in the corresponding dioxanes and probably attributable to the electronic structure about the sulfur atoms (124).

Recently, Eliel and Hutchins (126) reported equilibration and NMR studies for a series of alkylated 1,3-dithianes. The $-\Delta G^\circ$ values for 2- and 4-alkyl groups appear to be of the same order of magnitude as those for the corresponding cyclohexanes; for 5-alkyl groups the $-\Delta G^\circ$ values are rather low on account of the absence of *syn*-axial hydrogen atoms. The flexible boat conformation of 1,3-dithiane seems to be of relatively low energy, the difference from the chair being about 3.4 kcal/mol (126). Therefore, in cases where a *t*-butyl group would be forced to occupy an axial position in the chair form (e.g., in *cis*-2,5-di-*t*-butyl-1,3-dithiane) a flexible conformation seems to be preferred (126).

VII. SIX-MEMBERED RINGS WITH HETERO ATOMS AT POSITIONS 1,2; 1,2,3; 1,3,5; AND 1,2,4,5

A. X-Ray Investigations

In this section some six-membered rings with hetero atoms at positions 1,2 (3,6-dicarboxylic acids of 1,2-dithiane and 1,2-diselenane), 1,2,3 (sulfites and phosphoric acid esters), 1,3,5 (trioxane, trithiane, and triselenane), and 1,2,4,5 (3,6-diphenyl-1,2,4,5-tetraoxacyclohexane) are discussed.

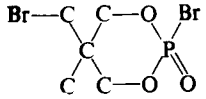
The chair conformations of symmetrical trioxane (**28**) and trithiane (**29**) were established as early as 1937 by X-ray analysis (127,128). Recent refinements of the crystal structure of these compounds (129,130) have fully confirmed the earlier results. The crystal structure of 1,3,5-triselenane (**30**) (131) was found to be isomorphous with that of 1,3,5-trithiane, leading to the conclusion that **30** also occurs in the chair conformation.

TABLE XII

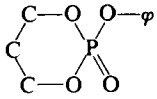
Unit-Cell Dimensions (Å), Space Groups, Number of Molecules per Unit Cell (Z), and Temperature of Diffraction

Compound[a]	a	b	c	α	β	γ	Z	Space group	t, °C
28	6.096	6.096	6.096	99	99	99	2	$R3c$	20
29	7.668	7.003	5.285	90	90	90	2	$Pmn2_1$	20
30	7.985	7.265	5.442	90	90	90	2	$Pmn2_1$	20
31	13.470	11.453	6.240	90	90	90	4	$P2_12_12_1$	20
32	15.55	11.06	5.97	90	90	90	4	$Pna2_1$	20
2	7.451	7.703	8.98	90	90	90	4	$P2_12_12_1$	−100
33	6.173	6.500	8.986	90	104.7	90	2	$P2_1$	20
34	9.62	9.26	9.70	90	102.5	90	4	$I2/c$	20
35	9.97	9.43	9.78	90	105	90	4	$C2/c$	20
36	6.09	7.85	12.37	90	93.9	90	2	$P2_1/c$	20

[a] **(28)** 1,3,5-Trioxane (130)
(29) 1,3,5-Trithiane (129)
(30) 1,3,5-Triselenane (131)

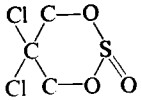
(31) 

2α-Bromo-5β-bromomethyl-5α-methyl-2β-oxo-1,3,2-dioxaphosphorinane (134)

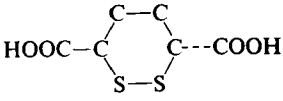
(32) 

2-Oxo-2-phenoxy-1,3,2-dioxaphosphorinane (135)

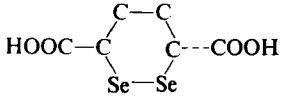
(2) Trimethylene sulfite (22)

(33) 

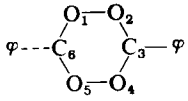
2,2′-Dichloro-trimethylene sulfite (23)

(34) 

1,2-Dithiane-*trans*-3,6-dicarboxylic acid (136)

(35) 

1,2-Diselenane-*trans*-3,6-dicarboxylic acid (136)

(36) 

trans-3,6-Diphenyl-1,2,4,5-tetraoxacyclohexane (137)

TABLE XIII

Endocyclic Bond Lengths (Å)

Compound[a]	Hetero group	1–2	2–3	3–4	4–5	5–6	6–1	l_{av}
28	O—C—O	1.429	1.430	1.429	1.430	1.429	1.430	1.429
29	S—C—S	1.812	1.812	1.808	1.817	1.817	1.808	1.812
31	O—P—O	1.58	1.54	1.47	1.64	1.47	1.46	1.53
32	O—P—O	1.56	1.57	1.43	1.49	1.49	1.45	1.50
2	O—S—O	1.59	1.60	1.42	1.52	1.51	1.49	1.52
33	O—S—O	1.615	1.631	1.471	1.522	1.523	1.453	1.536
34	S—S	2.07	1.85	1.53	1.53	1.53	1.85	—
35	Se—Se	2.32	1.97	1.51	1.48	1.51	1.97	—
36	O—O	1.48	1.41	1.43	1.48	1.41	1.43	1.44

[a] See footnote a to Table XII.

The crystallographic properties, bond lengths, and valency and torsional angles for the heterocycles shown below are listed in Tables XII, XIII, XIV, and XV, respectively. The bond lengths and valency angles were, as usual, taken from the original literature; the dihedral angles were calculated with the aid of a computer program written by Geise, Rutten, and de Graaff (132,133). The numbering of the atoms is in agreement with chemical convention for the trioxane, trithiane, dithiane, diselenane, and tetraoxacyclohexane compounds; for the sulfites and the phosphoric acid esters the numbering shown in Figure 13 is used.

TABLE XIV

Endocyclic Valency Angles (degrees)

Compound[a]	1–2–3	2–3–4	3–4–5	4–5–6	5–6–1	6–1–2	ϑ_{av}
28	107.8	108.0	107.8	108.0	107.8	108.0	107.9
29	115.3	101.7	116.2	99.6	116.2	101.7	108.4
31	105.5	118	?	?	?	120	?
32	107	118	112	110	110	118	112.5
2	100	116	111	110	106	116	109.8
33	97.8	116.6	108.5	110.6	109.0	115.8	109.7
34	99	110	117	117	110	99	108.7
35	96	113	125	125	113	96	111.3
36	105.5	106.9	105.5	105.5	106.9	105.5	106.0

[a] See footnote a to Table XII.

TABLE XV

Dihedral Angles about Endocyclic Bonds (degrees)

Compound[a]	1–2	2–3	3–4	4–5	5–6	6–1	φ_{av}
28	63.7	63.7	63.7	63.7	63.7	63.7	63.7
29	61.6	61.6	64.1	65.1	65.1	64.1	63.6
32	43	42	52	59	59	54	51.5
2	57	54	59	60.3	60.6	64.0	59.1
33	58.4	57.2	61.2	57.3	59.2	64.3	59.6
34	60.3	62.9	63.0	61.5	63.0	62.9	62.3
35	56.6	60.7	61.5	58.7	61.5	60.7	60.0
36	67.1	68.0	68.0	67.1	68.0	68.0	67.7

[a] See footnote a to Table XII.

From Tables XII–XV it may be seen that trioxane (**28**, $\varphi_{av} = 63.7°$) and trithiane (**29**, $\varphi_{av} = 63.6°$) are more puckered than 1,4-dioxane ($\varphi_{av} = 57.9°$); they have about the same puckering as 1,4-dithiane ($\varphi_{av} = 63.5°$). As in 1,4-dithiane, the valency angles C—S—C ($\vartheta_{av} = 101.0°$) are small, bringing about an enlargement of the bond angles S—C—S ($\vartheta_{av} = 115.9°$); this results in an average bond angle in trithiane of 108.4° which is slightly smaller than the tetrahedral value (109.5°). The situation is less clear for trioxane. The C—O—C angles (107.8°) are larger than the corresponding C—S—C angles in trithiane, a feature discussed for the corresponding 1,4-heterocyclic compounds in Section IV. Nevertheless, these C—O—C angles are still significantly smaller than the tetrahedral value. On the other hand, a compensating effect of enlargement of O—C—O angles (108°) is lacking. The corresponding C—O—C angles are 112.5° in 1,4-dioxane and the C—C—O angles are 109.2°, indicating that 1,4-dioxane is less puckered than 1,3,5-trioxane.

Surprisingly, the overall geometrical aspects of the six-ring esters **2**, **31**, **32**, and **33** closely resemble those of cyclohexane; the average bond length ($l_{av} = 1.52$ Å, average taken over the four compounds) is about the same as for cyclohexane (1.528 Å). The sulfites **2** and **33** are slightly more puckered ($\varphi_{av} = 59.1°$ and 59.6°, respectively), whereas the dioxaphosphorinane compound **32** ($\varphi_{av} = 51.5°$) is somewhat flatter than cyclohexane ($\varphi = 54.5°$).

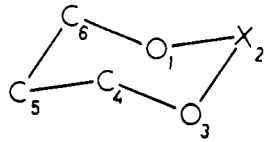


Fig. 13. The numbering of ring atoms for sulfites and phosphoric esters.

Close inspection of Table XV reveals that the trimethylene moieties are the most puckered parts in compounds **2** and **32**. The relevant data are lacking for compound **31**; it is stated, however, that the ring is somewhat flattened at the phosphate end (134). The situation is different with 2,2'-dichlorotrimethylene sulfite (**33**). The two chlorine atoms have a closing effect on the torsional angles about the 4–5 and 5–6 bonds, counterbalancing the trend towards larger torsional angles φ observed in the corresponding moieties of **2** and **32**.

Even the 1,2-heterocyclic compounds **34** and **35** with two adjacent sulfur and selenium atoms exhibit the features of well-behaved molecules in the chair conformation. Judged from their endocyclic bond lengths (Table XIII) they would represent cases of serious misfit. However, their dihedral angles (Table XV) are "normal" and their puckering is about the same as that in 1,3,5-trithiane. A much larger puckering ($\varphi_{av} = 67.7°$) is found in the 1,2,4,5-heterocyclic compound **36**.

The carboxylic groups of **34** and **35** are in equatorial positions. The S=O groups of **2** and **33** are axial and the P=O groups in **31** and **32** are equatorially oriented. The phenyl groups in **36** occupy the equatorial position; the benzene ring plane is approximately normal to the plane defined by the four O atoms of the tetraoxacyclohexane ring (137).

B. Conformational Properties in Solution

Spectroscopic and dipole moment data (10,11) suggest the chair form for 1,2-dioxane, 1,2-dithiane, 1,3,5-trioxane, and 1,3,5-trithiane in solution. Some conformational investigations of trimethylene sulfite and its derivatives were dealt with in Section III. These molecules are exclusively in the chair conformation, and the axial position is preferred by the S=O group to the extent of 3.5 ± 1 kcal/mol. In the case of compounds with bulky groups (e.g., *t*-butyl groups) as *trans*-2-substituents, both chair forms are present (40) at equilibrium in substantial percentage (Fig. 14).

It may be concluded that the saturated six-membered heterocyclic systems discussed in this review occur exclusively in chair forms. As in the case of the cyclohexane derivatives, exceptions to this rule may be expected when carbon atoms are in states deviating from sp^3 hybridization or when

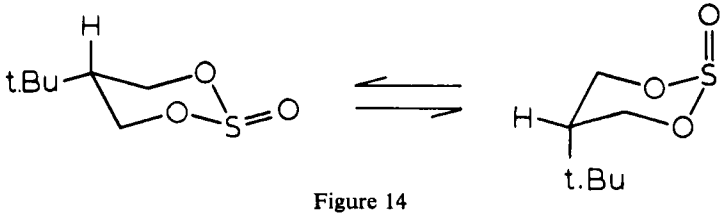


Figure 14

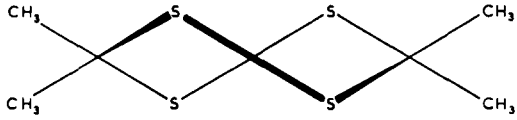


Fig. 15. Duplodithioacetone.

bulky substituents (e.g., *t*-butyl) are to be forced into unfavorable orientations in the chair form.

In multisulfur heterocycles flexible forms may be favored. On the basis of NMR studies of duplodithioacetone (tetramethyl-*s*-tetrathiane) the skew-boat form of this compound has recently been found (138,139) to be more stable than the chair form by 0.8 kcal/mol at 0° in CS_2 (Fig. 15). A boat form has also been found for this compound in the solid state through preliminary X-ray investigation (140). In the corresponding oxygen heterocyclic compound (acetone diperoxide) only the chair form exists in solution, as indicated by NMR spectroscopy (141) (compare also compound **36** in the solid state).

VIII. THE ANOMERIC EFFECT

In halogeno-1,4-dioxanes, -thioxanes, and -dithianes the halogen atoms were found to be preferentially in axial orientations (see Sect. V), in contradistinction to the well-known situation in monohalogenocyclohexanes (14,142). An illustrative case is presented by the monochloro- and bromotetrahydropyrans. When the halogen substituent is at the 2- (or 6-) position it takes up the axial orientation, whereas in the C_3—C_4—C_5 moiety the equatorial conformer is predominant (cf. Sect. V and refs. 116–118).

A comparable effect has been known for a long time in carbohydrate chemistry, where alkoxy, acyloxy, and halogeno substituents at the anomeric carbon atom of pyranosides show a tendency to occupy the axial position ("anomeric effect") (143–145).

A simple acyclic model compound, monochloromethoxymethane, was studied by electron diffraction (146,147). It occurs in the *gauche* conformation, which corresponds to the axial conformation in the six-membered ring systems. This seems to indicate that the anomeric effect or the preference of systems such as C—O—C—Hal for the *gauche* conformation is a general phenomenon. Most intriguing is the finding that, at least for Cl or Br as substituents, the anomeric effect amounts to several kilocalories per mole; in the *trans*-2,3- and 2,5-dihalogeno-1,4-dioxanes and -dithianes the diaxial conformer is strongly predominant in solution (Sect. V). Even the

trans-syn-trans-2,3,5,6-tetrachloro-1,4-dioxane molecule exists in the tetraaxial form in the solid state and persists in that conformation to a considerable extent in solution, notwithstanding severe *syn*-diaxial crowding (Sect. V, refs. 97 and 98).

The magnitude of the anomeric effect has been defined as being equal to the free energy difference between the (favored) axial and the equatorial anomer plus the ordinary conformational preference (*A* value) of the anomeric substituent.* According to this definition, the anomeric effect for chlorine, bromine, and iodine was found to be equal to 2.7, >3.2 and >3.1 kcal/mol (neat liquid values), respectively, in 2-halotetrahydropyrans on the basis of an NMR study on the 4-methyl substituted compounds (118). In polar solvents such as acetonitrile the value for chlorine seems to be smaller than in the neat liquid (118). These values are much higher than those for the anomeric effect of hydroxy, alkoxy, or acyloxy groups in the appropriately 2-substituted tetrahydropyrans (0.9–1.4 kcal/mol), which were found to be significantly solvent dependent (148–151,179).

As an explanation for the anomeric effect, simple dipole–dipole interactions have been invoked (143,152). Although such a description may account for part of the effect, in most cases it cannot represent the whole story. As an example we may consider *trans*-2,5-dichloro-1,4-dioxane (**16**), the molecular geometry of which is known from X-ray analysis (Sect. V). If one calculates the electrostatic interaction energy using the formula

$$E = \frac{e_{Cl}}{\varepsilon} \sum \left(\frac{e_i}{r_i}\right) 1.44 \times 10^{13} \text{ kcal/mol}$$

with values of $\mu = 2.2$ and 1.4 D for the dipole moments of the C—Cl and C—O bonds, respectively, and $\varepsilon = 2.3$ for the dielectric constant, one arrives at an energy difference of about 1 kcal/mol in favor of the diaxial form (153). This difference is too small to account for the strong preponderance of the diaxial conformation (105). Of course, one may obtain larger differences if one chooses a significantly lower value for the dielectric constant in the case of the diaxial conformer (118,149), but this seems hardly warranted with the type of molecule under consideration, dissolved in various solvents. Anderson and Sepp (118,149) have carried out approximate calculations for the anomeric effect in the above-mentioned 2-halotetrahydropyrans, arriving at 2.8 and 2.6 kcal/mol for chlorine and

*Thus the anomeric effect measures the stability of an axial over an equatorial substituent in an appropriately substituted heterocycle over the expected value in cyclohexane (where the equatorial substituent is favored). It has been pointed out (148) that this is *not* equal to the extra stabilization of the axial substituent in the hetero compound, since one is not justified in assuming that in the absence of such stabilization ΔG° would be the same for the heterocyclic system as for cyclohexane (see, for example, the ΔG° value for a 2-substituted 1,3-dioxane on p. 67).

bromine, respectively. Comparison of these values with the experimental data (see above) shows that for bromine the agreement is poor here also. All such calculations are, in any case, subject to much uncertainty, mainly because the results are highly dependent on the rather arbitrarily chosen value for the dielectric constant ε.

In the authors' opinion there is a better prospect for calculations using a more detailed electrostatic approach. In these calculations it is essential to take into account that a substantial fraction of the negative charge at the ether oxygen is attributable to the lone pairs,* the "center of gravity" of which does not coincide with the position of the atomic nucleus. If, somewhat incorrectly,† but suggestively, the nonbonding electrons are pictured as being localized in sp^3 "lobes" which, for the major part, extend axially and equatorially, the interaction with the halogen substituent may be visualized, e.g., in a Newman projection (Fig. 16). This leads to describing a substantial part of the preference for the axial conformer as being due to the fact that this conformer shows only one *gauche* halogen–lone pair interaction, whereas the equatorial form has two. In a first approximation this difference in (mainly Coulombic) interaction energy is estimated to amount to about 1–2 kcal/mol (cf. the values of halogen–halogen *gauche* interactions (81,82,154).

There is still another aspect that emerges from considerations of the detailed geometry of the halogenodioxanes, -thioxanes, and -dithianes (as revealed by X-ray analysis) and of chloromethoxymethane (studied by electron diffraction). Table XVI summarizes the experimental information (taken from Tables VI and VII).

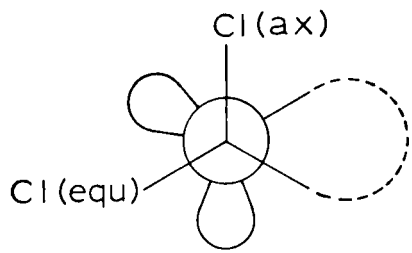


Figure 16

*A suggestive remark in this respect may be found in the paper of Edward (152).

†Probably the distribution of the nonbonded electrons is much more diffuse, a considerable density existing in the area between the lobes indicated. Of course, a description that considers such a more realistic electron density distribution also shows the stronger repulsion of the negative halogen in the equatorial as compared to the axial position. A quantitative treatment on this basis would be of great value to future discussion.

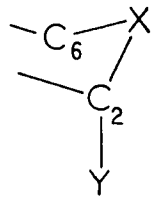


Fig. 17. C—X—C—Y fragment in halo-1,4-dioxanes, -thioxanes, and -dithianes and in chloromethoxymethane having the *gauche* conformation. X = O or S, Y = Cl or Br.

The most suggestive feature is that in all cases (except for *trans*-2,5-dibromo-1,4-dithiane, where the accuracy of the measurements was too small) the C_2—X distances are significantly shorter than the C_6—X distances. When compared to the lengths of C—O bonds in aliphatic ethers, the C_6—O distances appear to be normal, whereas the C_2—O distances are shorter than normal. A second suggestive, though less certain, regularity is shown by the axial C_2—Y bond lengths, which seem to be somewhat larger than the corresponding equatorial bond lengths (in *cis*-2,3-dichloro-1,4-dioxane the axial C—Cl bond length is 1.819 Å, the equatorial bond length is 1.781 Å, cf. Table VII) and than the values accepted for aliphatic C—Cl and C—Br bonds (1.79 and 1.93 Å, respectively). These abnormalities in bond lengths in the system C—X—C—Y suggest a description (17, 44, 102, 103) in which nonbonding electrons on oxygen (or sulfur) are delocalized by mixing of the oxygen (or sulfur) *p* orbital*

TABLE XVI

Bond Distances (taken from Tables VI and VII) and Torsional Angles φ about the X—C_2 Bond in the Group C_6—X—C_2—Y (Fig. 17)

Compound	X	Y	C_6—X	C_2—X	C_2—Y	φ, deg.
trans-2,3-Dibromodioxane (**14**)	O	Br	1.47[a]	1.37[a]	2.03[a]	71
trans-2,3-Dichlorodioxane (**15**)	O	Cl	1.43[a]	1.38[a]	1.84[a]	70
cis-2,3-Dichlorodioxane (**3**)	O	Cl	1.466	1.394	1.819	71
trans-2,5-Dichlorodioxane (**16**)	O	Cl	1.428	1.388	1.845	70
Chloromethoxymethane	O	Cl	1.414	1.368	1.813	74
trans-2,3-Dichlorothioxane (**22**)	O	Cl	1.447	1.378	1.842	68
trans-2,3-Dichlorothioxane (**22**)	S	Cl	1.820	1.795	1.810	72
trans-2,3-Dichlorodithiane (**23**)	S	Cl	1.84	1.79[a]	1.805[a]	70
trans-2,5-Dibromodithiane (**26**)	S	Br	1.81	1.81	1.99	67

[a] Average value.

*Since excited states are being mixed the ether oxygen (or sulfur) electron escort should be pictured as sp^2 hybridized.

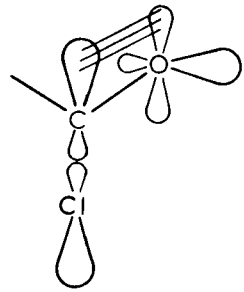


Figure 18

with the suitably oriented *anti*-bonding σ orbital of the C—Hal grouping. This type of delocalization will strengthen the C—O (or C—S) bond and will slightly weaken the C—Hal bond (Fig. 18).

Further detailed experimental investigations, as well as theoretical calculations, are needed in order to evaluate the contribution to the anomeric effect of each of the following three contributing factors: (*a*) Coulomb interactions between partially charged atoms, (*b*) *gauche* interactions between halogen and nonbonding electrons of ring oxygen (or sulfur), and (*c*) delocalization of nonbonding electrons as a result of the mixing in excited levels. It would seem promising to perform numerical calculations of these various interaction energies on the basis of available data relating to molecular structure and shape as furnished by X-ray analysis and other physical methods.

Perhaps for the anomeric effect of "oxygen (or sulfur) substituents," such as hydroxy, alkoxy, and acyloxy groups, the situation may prove to be somewhat different from that in the case of halogen substituents.* For the regularities found in pyranosides and their ethers and esters, the reader is referred to the articles of Sundaralingam (157), and Chu and Jeffrey (155) and of Angyal (145). The C—O bond lengths in these compounds do not show the same simple regularities found with the halogeno-1,4-dioxanes, -thioxanes, and -dithianes. A more detailed insight may be expected especially from exact measurements of the magnitude of the anomeric effect of the halogeno derivatives of heterocyclic rings as well as of their solvent dependence, a feature found to be significant in the case of "oxygen (sulfur) substituents" [cf. the paper of Eliel and Giza (148) where references are to be found as well as an explanatory discussion which, in many respects, parallels the one presented in this section].

*The first observations that the bond distances, and hence the bond energies in some C—X—C—Y systems varied with the C—X—C—Y torsional angle are due to Altona and Romers (44), Altona (17), and, independently, to Sundaralingam (157).

IX. FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

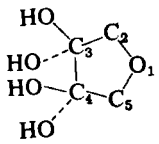
A. Introduction

The conformational analysis of nonplanar five-membered ring compounds is considerably more complex than that of chair-shaped six-membered ring derivatives which are easily characterized by the orientation of substituents (axial or equatorial), the degree of puckering (φ_{av}), and the appearance of deformation (individual φ values). The five-membered rings are pseudorotational systems in the liquid and gas phases and assume a continuous set of conformations, each of which can be characterized by a phase angle Δ and the maximum value of the ring dihedral angle φ_{max} (see Sect. II-C). Along the pseudorotation circuit, as Δ varies from 0 to 720°, ten envelope (C_s) and ten half-chair (C_2) forms are met. If Δ is taken as zero for an arbitrary C_2 form, C_2 forms arise at $\Delta = 0°$, 72°, 144°, etc.,

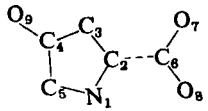
TABLE XVII

Unit Cell Dimensions (Å), Number of Molecules per Unit Cell (Z) and Space Groups of Some Five-Membered Heterocyclic Systems

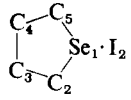
Compound[a]	a	b	c	α	β	γ	Z	Space group
37	10.66	10.66	10.01	90	90	90	8	$P\bar{4}2_1c$
38	5.00	8.31	14.20	90	90	90	4	$P2_12_12_1$
39	12.804	7.625	9.256	90	90	90	4	$Pn2_1a$
4	4.46	7.76	11.64	90	121.5	90	2	$P2_1/c$
40	4.92	13.23	6.94	90	96	90	2	$P2_1/n$
41	5.34	5.85	10.75	93.5	89.5	109.5	2	$P\bar{1}$
42	6.746	10.67	10.98	90	90	90	4	$P2_12_12_1$
43	19.512	9.296	7.272	90	90	90	8	$Pbca$
44	11.29	5.96	9.09	90	113	90	4	Cc
45	6.963	11.71	5.402	90	90	90	4	$P2_12_12_1$
46	5.774	14.540	5.801	90	101.3	90	4	$P2_1/a$

[a] (37) 

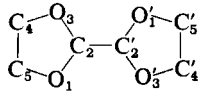
3,3,4,4-Tetrahydrofurantetrol (158)

(38) 

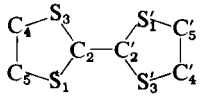
trans-4-Hydroxyproline (159)

(39) 

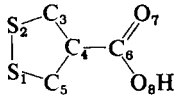
Complex of iodine with tetrahydroselenophene (160)

(4) 

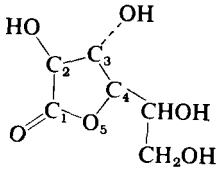
2,2′-Bis-1,3-dioxolane (48)

(40) 

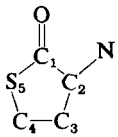
2,2′-Bis-1,3-dithiolane (161)

(41) 

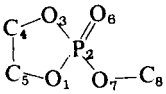
1,2-Dithiolane-4-carboxylic acid (162)

(42) 

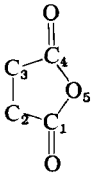
Galactono-γ-lactone (163)

(43) 

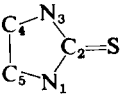
Homocysteine thiolactone hydrochloride (164)

(44) 

Methyl ethylene phosphate (165)

(45) 

Succinic anhydride (166)

(46) 

Ethylene thiourea (167)

and C_s forms at $\Delta = 36°$, 108°, 180°, etc. A barrier restricting pseudorotation separates energy minima which may have different conformational characteristics (e.g., with axial and equatorial substituents); in each minimum Δ may oscillate considerably ["pseudolibration" (156)]. On account of this lack of rigidity of the individual conformers, the interpretation of dipole moments and spectroscopic data is often difficult for five-membered ring compounds. Figure 19 shows the half-chair form and the envelope form for cyclopentane with axial, equatorial, and bisectional (26) valencies. An energy minimum in a five-membered ring system is, however, not necessarily represented by one of these "basic" forms. The conformational analysis of ring D in fourteen steroids by Altona, Geise, and Romers (28), using dihedral angles as the main analytical tool (cf. Sect. II), has shown that in only two molecules ring D occurs as $C_s(14)$ envelope ($\Delta = -36°$) and as $C_s(13)$ envelope ($\Delta = +36°$), respectively.

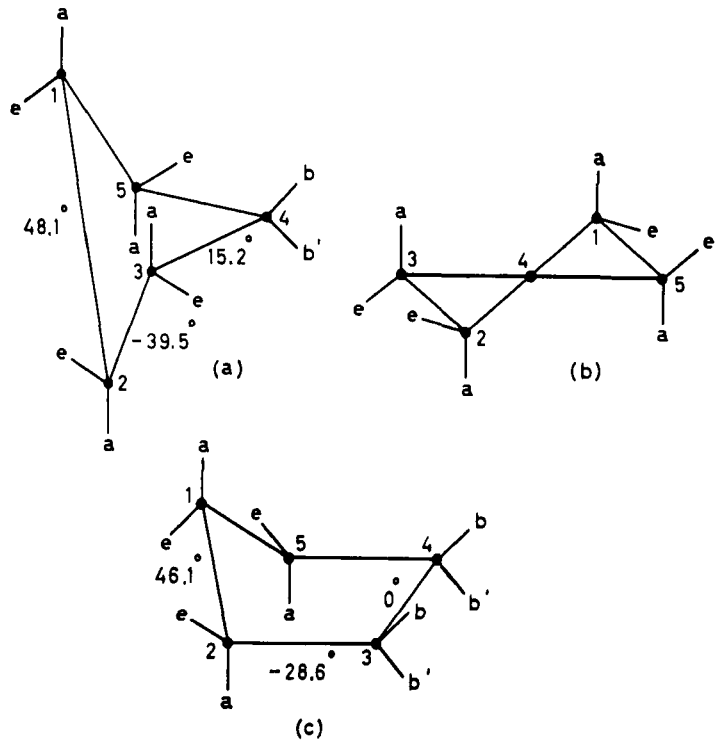


Fig. 19. Half-chair form (*a*), in perspective, (*b*), in projection, and (*c*), envelope form with axial, equatorial, and bisectional valencies. The torsional angles were taken from Pitzer and Donath (25).

TABLE XVIII

Bond Lengths (Å) in Five-Membered Rings

Compound[a]	1–2	2–3	3–4	4–5	5–1
37	1.41	1.52	1.56	1.50	1.43
38	1.50	1.53	1.50	1.52	1.48
39	1.96	1.52	1.59	1.55	1.96
4	1.39	1.41	1.41	1.51	1.42
40	1.86	1.82	1.84	1.52	1.89
41	2.10	1.85	1.48	1.55	1.83
42	1.52	1.52	1.55	1.46	1.36
43	1.53	1.52	1.52	1.81	1.76
44	1.57	1.57	1.45	1.52	1.41
45	1.48	1.51	1.47	1.38	1.37
46	1.32	1.34	1.48	1.53	1.46

[a] See footnote a to Table XVII.

The remaining steroids analyzed have rings D occurring in forms intermediate between half-chair and envelope and are characterized by phase angles Δ in the range between -8 and $+21°$.

It is tempting to apply the same analytical method to heterocyclic five-membered ring systems notwithstanding the difficulty that eq. (3) is valid only in cases where the endocyclic bond lengths and the force constants governing the bending of the valency angles are equal. However, as will be shown below, the required geometry is not seriously disturbed in systems containing C—N, C—O, or P—O bonds, the lengths of which

TABLE XIX

Endocyclic Valency Angles in Five-Membered Rings (degrees)

Compound[a]	1–2–3	2–3–4	3–4–5	4–5–1	5–1–2
37	106.2	100.2	100.4	106.5	110.1
38	104.5	107.6	103.9	105.5	109.4
39	105	106	108	102	93
4	105	109	102	104	111
40	104	109	100	109	102
41	97	111	114	104	93
42	102.2	100.3	103.0	109.3	109.5
43	107.4	105.5	105.8	94.3	109.0
44	99.1	112.0	106.0	107.8	112.0
45	105.2	104.1	110.4	110.1	110.2
46	110	112	102	103	113

[a] See footnote a to Table XVII.

TABLE XX

Dihedral Angles (as Defined in Sect. II-C) of Five-Membered Rings and Their Conformational Designations (degrees)

Compound[a]	φ_{12}	φ_{23}	φ_{34}	φ_{45}	φ_{51}	φ_{max}	Designation[b]	Orient. subst.
37	+13.9	−33.4	+39.6	−33.0	+13.0	40	$C_2(1)$	See text
38	+5.2	+14.0	−27.2	+29.9	−22.1	31	$C_2(2)$–$C_s(4)$	See text
39[c]	−18	+45	−62	+45	−16	62	$C_2(1)$	—
4	−28	+14	+5	−21	+30	31	$C_s(1)$–$C_2(3)$	Equatorial
40	+11	+15	−37	+45	−37	45	$C_2(2)$	Bisectional
41	−27	−4	+28	−51	+44	54	$C_s(5)$	Axial
42	−20.4	+35.1	−38.5	+27.7	−4.8	40	$C_s(3)$	Equatorial
43	−27.1	+43.6	−40.8	+22.3	+2.6	45	$C_s(3)$	Equatorial
44	−2	−11	+20	−20	+13	21	$C_s(4)$	Bisectional
45	0.9	1.5	1.6	1.1	0.1	—	Planar	—
46	−3	+1	−1	+1	0	—	Planar	—

[a] See footnote a to Table XVII.

[b] $C_s(1)$: envelope with atom no. 1 as flap; $C_2(1)$: half-chair with twofold rotation axis passing through no. 1; $C_s(1)$–$C_2(3)$: roughly halfway between $C_s(1)$ and $C_2(3)$.

[c] Dihedral angles averaged over the two geometries calculated in ref. 160.

are in the range of 1.4–1.6 Å (Table XVIII). A further justification of the method is the narrow range of the endocyclic bond angles, which cluster about the value of 105° (Table XIX). The deviations are larger for C—S and C—Se bonds (1.8–2 Å), but the results still seem to justify the procedure used (see Table XX).

B. X-Ray Investigations

In the solid state, a well-defined conformation for a five-membered heterocyclic system is generally found. Therefore, the crystal structure offers a good starting point for conformational study, provided care is taken not to extrapolate the findings injudiciously to the liquid state. Unfortunately, the available crystal data are limited and the accuracy obtained in some cases is poor. Tables XVII–XX give crystallographic and structural parameters for all the saturated hetero rings investigated, other than those of furanoid sugars.

Generally the molecules investigated are nonplanar, with the exception, of course, of those systems where planarity is imposed by π-bonding. The data, combined with the available information on rings D in steroids (28) and of furanoid rings (157) in carbohydrates, establish beyond doubt that five-membered rings are puckered.

The maximum torsional angle for the five-membered carbocyclic ring D in steroids is 47° (28). Table XX indicates that φ_{max} is smaller for five-membered rings containing oxygen atoms, the value being 40° for the tetrahydrofuran derivative **37** and 31° for 2,2'-bis-1,3-dioxolane.* According to a survey of Sundaralingam (157) the maximum torsional angle in furanoid sugars is about 39°. In agreement with the results found for six-membered rings the puckering is larger in sulfur and selenium compounds, φ_{max} being 54° in **41** and 62° in **39**. As observed for the steroid rings D the conformations of the hetero five-membered rings are not necessarily pure C_s or C_2 forms; "in-between" forms also occur. In Table XX the approximate designation is given for each compound.

In 3,3,4,4-tetrahydrofurantetrol (**37**) the value of φ_{max} is in good agreement with that found in the furanoid sugars (157, 157a) and with recent far infrared (184) and electron diffraction studies (168) on the unsubstituted tetrahydrofuran molecule. The conformation of **37** is that of an almost symmetrical half-chair form, the substituents occupying the axial and equatorial positions in the most puckered part of the ring (Fig. 20).

*Note added in proof: From a far infrared investigation on unsubstituted 1,3-dioxolane φ_{max} was found to be about 40° (185).

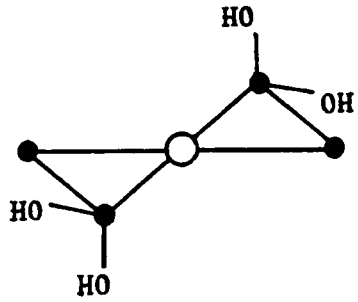


Fig. 20. The conformation of 3,3,4,4-tetrahydrofurantetrol (**37**).

An in-between form is found for the pyrrolidine ring in *trans*-4-hydroxyproline (**38**). The OH group is axially oriented in the puckered part of the ring, the carboxyl group is bisectional in the planar part. The zwitterion structure of **38** in the solid state is indicated by the equal lengths of the two C—O bonds (1.26 Å) in the carboxyl group. The description is completed by a Newman projection along the exocyclic bond C_2—C_6 (Fig. 21).

For 2,2′-bis-1,3-dioxolane (**4**) the orientation of the two rings with respect to the exocyclic bond C_2—$C_{2'}$ is *anti* (see Fig. 24). The space group $P\,2_1/c$ (see Table XVII) combined with the number of molecules per unit cell ($Z = 2$) requires a center of symmetry to be present in the molecule, indicating that the two rings are enantiomeric in conformation. The exocyclic C_2—$C_{2'}$ bond is equatorially oriented in the puckered part of the molecule.

The conformation of 2,2′-bis-1,3-dithiolane (**40**) differs considerably from that of **4**, the exocyclic bond C_2—$C_{2'}$ being bisectionally oriented in the planar part of the rings. The five-membered rings are considerably more puckered than those of **4**, φ_{max} being 45°.

In 1,2-dithiolane-4-carboxylic acid (**41**) C_5 (located at the flap of an envelope) is above the plane of S_1, S_2, C_3, and C_4, whereas the carboxylic

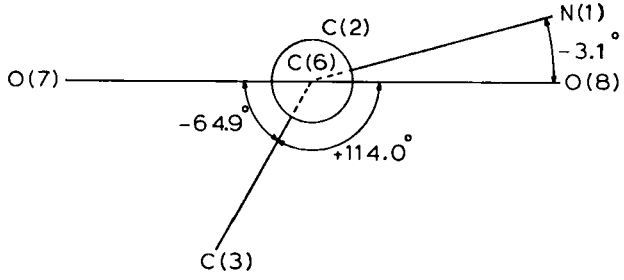


Fig. 21. Newman projection along the exocyclic bond C_2—C_6 for *trans*-4-hydroxyproline (**38**).

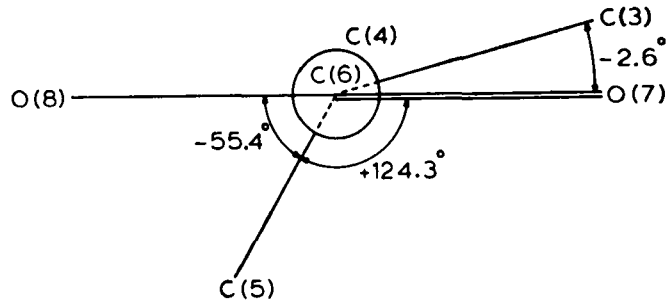


Fig. 22. Newman projection along the exocyclic bond C_4—C_6 for 1,2-dithiolane-4-carboxylic acid (**41**).

acid group is found below this plane. The COOH group has the axial orientation. Figure 22 shows a Newman projection along the exocyclic bond C_4—C_6. The lactone group C—C(=O)—O—C in galactono-γ-lactone (**42**) appears to be planar. It is postulated (169) that this group is planar in general because of the valence bond resonance form C—C(O⁻)=O⁺—C, but deviations from planarity appear to occur in ring systems which are more highly strained, such as glucurono-γ-lactone (170) and ascorbic acid (171). The remaining ring atom, C_3, is the flap of an envelope, lying 0.64 Å out of the plane of the other four ring atoms (163). The substituents on C_2, C_3, and C_4 are equatorially oriented. The conformation in the —CHOH—CH_2OH chain is described in ref. 163.

The thiolactone group in **43** is also planar. C_3 deviates 0.7 Å from this plane, thus constituting the flap of the envelope (164). The substituent on C_2 is in the equatorial conformation. The puckering of this sulfur-containing ring is, as usual, greater than that of the corresponding oxygen-containing ring system (**42**).

The construction of a model of methyl ethylene phosphate (**44**), as well as the inspection of its dihedral angles, clearly shows that the two bonds P_2—O_6 and P_2—O_7 are bisected by the planar part of the molecule containing ring atoms O_1, P_2, O_3, and C_5. C_4 is the flap of the envelope and is located at the same side of the molecule as the bond P_2—O_6. Consequently, the double bond P_2—O_6 (1.44 Å) and the single bond P_2—O_7 (1.57 Å) are assigned to be bisectional. The Newman projection along the bond P_2—O_7 clearly shows (Fig. 23) that the methyl group C_8 occupies the *anti* orientation with respect to the ring.

The computed values of the endocyclic torsional angles of compounds

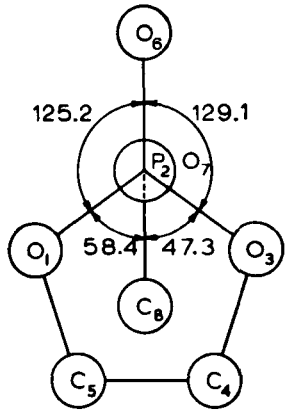
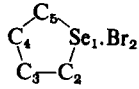


Fig. 23. Newman projection along the exocyclic bond P_2—O_7 indicating the *anti* orientation of C_8 with respect to the ring in methyl ethylene phosphate (**44**).

45 and **46** are so small that it is impossible to decide whether the puckering is real or whether these structures are planar. Wheatly (167) has put forward statistical criteria to argue that ethylene thiourea (**46**) is not planar. By the same sort of argument one might say that succinic anhydride (**45**) is likewise not planar. However, the deviations from planarity, if real, are very small.

Note added in proof: Very recently diffraction data of two further five-membered heterorings have become available:

47 1,2,4-trioxacyclopentane (182)



48 1,1-dibromotetrahydroselenophene (183)

	φ_{12}	φ_{23}	φ_{34}	φ_{45}	φ_{51}	φ_{max}
47	+50	−41	+17	+17	−41	50
48	+14	−41	+61	−47	+16	61

Compound **47** was investigated by means of electron diffraction; the dihedral angles presented are based on the assumption of $C_2(4)$ symmetry (assuming $C_s(4)$ symmetry yields $\varphi_{max} = 54°$). The ring is considerably puckered, which was also found for the six-membered peroxide *trans*-3,6-diphenyl-1,2,4,5-tetraoxacyclohexane (**36**, cf. Section VII.A).

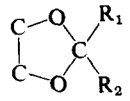
The puckering and the conformation of compound **48** are in excellent agreement with the results of the corresponding iodine compound **39** (see Table XX). The conformational designation in both cases is $C_2(1)$.

C. Conformational Properties in Solution

1. 1,3-Dioxolanes

A series of 2-substituted 1,3-dioxolanes has been investigated in solution by Altona and van der Veek (68). As described in the previous section, in the solid state 2,2′-bis-1,3-dioxolane exists in the *anti* form (see Fig. 24) with respect to the exocyclic C_2—$C_{2'}$ bond, which is equatorially attached to the rings (*ee*). In solution a considerable dipole moment (μ = 2.06 D) was found and the infrared spectra in the solid state (KBr pellet) and in solution (CS_2) show striking differences. The data were interpreted in terms of an *anti–gauche* equilibrium (Fig. 24) in solution, the polar *gauche* form predominating by a large factor.

Three 2-substituted 1,3-dioxolanes of the type



(2-methoxy-, 2-methyl-2-methoxy-, and 2-*t*-butoxy-1,3-dioxolane) have been investigated by dipole moments and NMR spectra (68). The geometry of the ring at the energy minimum along the pseudorotation circuit was considered to correspond more or less closely to the conformation of **4** in the solid state, the torsional angle in the CH_2—CH_2 moiety being about 20–25°. Four conformers may occur in the equilibrium mixture: axial and equatorial with respect to the position on the ring and *anti* and *gauche* with respect to the rotation about the *exo* C_2—OR bond.

The dipole moments of the three compounds may be interpreted on the basis of a *gauche–anti* equilibrium (Fig. 25). Assuming localized lone pairs of electrons on the oxygen atoms, the moment of the *anti* form was estimated to be about 2.1 D, that of the *gauche* form about 1.5 D. The

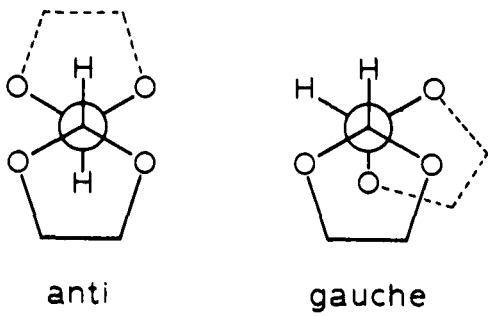


Fig. 24. Newman projection along the bond C_2—$C_{2'}$ for *anti* and *gauche* forms of 2,2′-bis-1,3-dioxolane.

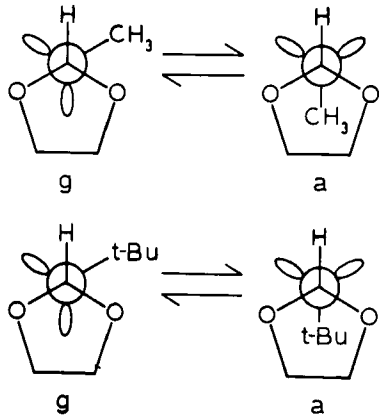


Fig. 25. *gauche* (*g*) and *anti* (*a*) Conformers in equilibrium mixtures of 2-alkoxy-1,3-dioxolanes.

anti form possesses two clinal C—O—C—O arrangements, thought (50, 172) to be more stable than antiperiplanar C—O—C—O, whereas the *gauche* form contains only one. Hence, notwithstanding greater steric repulsions, the *anti* conformer in 2-methoxy-1,3-dioxolane seems to be preferred over the *gauche* form. However, the 2-*t*-butoxy derivative exists almost exclusively in the *gauche* form on account of large steric strain in the *anti* conformer.

From the NMR spectra of the compounds under consideration the vicinal spin coupling constants in the AA'BB' part were determined (68). These coupling constants and the dipole moments may be related to the properties of the individual conformers by the equations

$$J = x_g J_g + (1 - x_g) J_a$$

$$\mu^2 = x_g \mu_g^2 + (1 - x_g) \mu_a^2$$

where x_g is the molar fraction of the *gauche* form. As was discussed in Section III-C-3 a linear relationship should exist between μ^2 and J provided J_g, J_a, μ_g^2, and μ_a^2 are equal for the three compounds and independent of the solvents used (benzene and carbon tetrachloride). A plot of J_{cis} (the coupling constant most sensitive to changes in molecular geometry) versus μ^2 gives a straight line within the error of the measurement (68), suggesting (77) that two out of the four possible conformers predominate in the equilibrium mixture. However, an unambiguous choice between axial and equatorial conformers cannot be made.

The shift of J_{cis} with the *anti–gauche* equilibrium was interpreted on the basis of a different mean phase angle of pseudorotation Δ for both

forms, the dihedral angle in the CH_2—CH_2 moiety being a little smaller in the *gauche* form than in the *anti* conformer.

2. *Halogeno-Substituted Tetrahydrofurans and γ-Lactones*

According to the data in Section IX-B, the tetrahydrofuran (THF) ring is appreciably puckered ($\varphi_{max} \sim 40°$), indicating that its derivatives in solution may exist as equilibrium mixtures of axial and equatorial conformers.

The infrared and Raman spectra of 3-chloro- and 3-bromotetrahydrofuran show one strong band, the position of which (at 605 and 535 cm^{-1}, respectively) corresponds to expectation for the S_{HH} type (cf. Sect. III-D) and which may safely be assigned to the axial C—Hal stretching mode. Bands attributable to equatorial C—Hal bonds are hardly, if at all, detectable. These data together with the values of the dipole moments ($\sim$2.1 D) prove that, in solutions of 3-halogenotetrahydrofurans, the conformation with the halogen in the axial orientation in the most puckered part of the ring predominates strongly (173). The energy minimum probably does not correspond to a C_s or C_2 form of the ring but rather lies in-between (173).

NMR spectra, dipole moments, and vibrational spectra also suggest axial positions for the chloro substituents in *trans*-2,3-dichlorotetrahydrofuran (174).

The infrared and Raman spectra of *trans*-3,4-dihalogenotetrahydrofurans (173) show the characteristic pattern of carbon–halogen stretching frequencies for the *anti* conformation of the Hal—C—C—Hal group, whereas bands due to the *gauche* conformation seem to be absent. These data, combined with theoretical considerations, suggest (173) that the energy minimum along the pseudorotation circuit corresponds to a symmetrical half-chair form with the halogen atoms axially oriented in the most puckered part of the ring (with a dihedral angle between the halogen atoms of about 160°), the oxygen atom lying in the planar part (Fig. 26).

The frequency differences $\Delta\nu = \nu_{sym} - \nu_{asym}$ for the dichloro (25 cm^{-1}) and dibromo (74 cm^{-1}) compounds are considerably smaller than those for the corresponding six-membered ring compounds [*trans*-3,4-dichlorotetrahydropyran: $\Delta\nu = 68\ cm^{-1}$, *trans*-3,4-dibromotetrahydropyran: $\Delta\nu = 110\ cm^{-1}$ (116)]. This feature seems to be characteristic for the vicinal dihalogenides in five-membered rings, in particular, the dichloro compounds (78,173,178).

It seems significant that, in contrast to the very broad C—X stretching bands of the chlorocyclopentanes (83,178), the bands of the chlorotetrahydrofurans appear sharp. This is interpreted to indicate that the conformational energy well of the tetrahydrofuran derivatives is deeper than

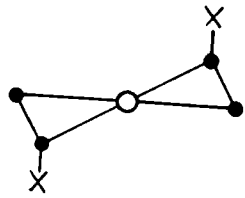


Figure 26

that of the cyclopentanes and that, consequently, pseudolibration is more restricted.

NMR data for substituted γ-lactones (175–177), in which the ring is expected to exist in the envelope conformation on account of the planarity of the lactone group (see previous section), suggest axial orientations of the halogen atoms in 2- and 3-halo-γ-butyrolactones and in *trans*-3,4-dibromo-γ-valerolactone.

It may be concluded that halogen atoms in the tetrahydrofuran and in the γ-lactone rings occupy the axial position exclusively. A similar preference was also found, though to a smaller extent, in halogeno-substituted cyclopentanes (75,83,178).

X. CONCLUDING REMARKS

In the preceding paragraphs we have reviewed conformational features of five- and six-membered ring systems containing, as hetero atoms, oxygen and sulfur (and in a few cases other atoms as well). The discussion has been centered mainly on halogeno-substituted derivatives—chlorides and bromides in particular—since such compounds offer a number of advantages with regard to synthesis, X-ray analysis, measurement and interpretation of dipole moments, and analysis of vibrational and NMR spectra. Although this subject constitutes but a very small part of the total domain of the conformational aspects of organic compounds, the authors feel that the approach and the results described are representative of the stage which conformational analysis has reached today. In many respects research in this area is still in an exploratory phase, but exact quantitative data begin to become available.

One of the main overall impressions emerging from the experimental results is that of a great variation of conformational aspects in the various classes of compounds investigated. The preference of the cyclohexane derivatives for the chair form persists in six-membered heterocyclic

systems; flexible forms seem to be able to exist in appreciable concentrations only in the cases of ring constituents with sp^2 hybridization or of serious steric crowding by substituents and, perhaps, in polythianes. However, the introduction into the ring of an oxygen, sulfur, or other hetero atom brings about many changes in geometry and electric properties. It is not only the resulting difference in overall symmetry and molecular shape and in the electric polarizability that leads to differences in physical and chemical behavior. More subtle, but no less conspicuous, effects are caused, e.g., by the relative shortness of the C—O bond and the large value of the C—S bond length. Another feature showing up in the six-membered, as well as in the five-membered, ring systems is the small internal valency angle about sulfur or selenium which enhances the puckering in the pertinent part of the ring systems. Whereas such geometric factors may, to a certain extent, be inferred directly from diffraction data, the electrostatic interactions due to hetero atoms with their nonbonded electron pairs are much more difficult to tackle by experimental methods. Here the anomeric effect may serve as an illustrative example. There can thus be little doubt that, although certain general principles do become discernible, one has to be careful about extrapolation of "rules," even within the family of six-membered rings.

Substantial changes are encountered when the ring size is varied. This is exemplified by the discussion (Sect. IX) of the highly flexible five-membered rings, in contrast to the more rigid six-membered rings. Although in five-membered rings a mathematical treatment involving integration and averaging over a continuous range of conformations is indicated, it was shown to be possible to give a reasonable description of some properties (NMR spectra, dipole moments, vibrational spectra) by adhering to the simplified picture of an equilibrium in which one or two well-defined conformers predominate. The larger rings—not dealt with in this article—will no doubt show a wealth of new characteristic properties and phenomena which, for the greater part, still await discovery and quantitative study.

On the one hand, therefore, the results presented in this review support the traditional experience of the chemist, viz., that each class of compounds—and even each compound itself—forms an individual entity. On the other hand, there is unmistakable progress in the knowledge and understanding of molecular geometry and in the rational interpretation of data from the diverse physical measurements. Moreover, the increased computational facilities have begun to lend fruitful support to the experimental studies and even permit valuable prediction of conformational properties and equilibria in a number of instances. As has been stressed in

the introduction, the intricate problems that present themselves in the conformational analysis of heterocyclic systems demand the cooperative effort of different methods of investigation, including systematic chemical variation of molecular structure. What at the moment seems to be a major gap is a fundamental and, at the same time, workable theoretical treatment providing insight into the nature of rotational barriers and allowing for *a priori* calculation of nonbonded interactions. The discussion of the anomeric effect presented in Section VIII may have made clear what is lacking in this respect no less than what now seems to be within reach.

Returning finally to the selection of material dealt with in this article, it is felt that the stress laid on molecular geometry and the restriction of the discussions to the results of physical measurements will in the minds of many chemists—the authors included—call for a counterpart in which the reactions and specific chemical behavior of the pertinent compounds receive attention. Although at the moment this part of the study of the heterocyclic nonaromatic compounds is still fragmentary and mostly qualitative, there can be little doubt that growth will be rapid in the next decade. The understanding of mechanisms and rates of reaction requires as a basis the detailed knowledge of molecular shape and electronic structure. From this point of view it is perhaps not unrealistic to express the hope that the present article may contribute a little to the chemical as well as to the physical aspects of future conformational studies in the field of nonaromatic heterocyclic compounds.

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Topics in Stereochemistry, Volume 4
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The Stereochemical Analogy Model*— A Mathematical Theory of Dynamic Stereochemistry

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I. SOME DEFINITIONS

Stereoisomers are chemical compounds of identical constitution differing in the spatial arrangement of their atoms.† They cannot be transformed into each other without breaking and reforming bonds.‡ On the other hand, energetically preferred geometrical arrangements of molecules which can be interconverted by movements of some parts of the molecules without breaking bonds are termed conformers of the same stereoisomeric species. Constitution, by definition, determines bonds and bonded neighbors and thus implies a convention as to which rearrangements of parts within the molecule may occur without breaking bonds.

* We use this expression as equivalent to the original German "Stereochemisches Strukturmodell" used in the original publications (1).

† Using this definition we understand by stereoisomers what are sometimes called nonconformational stereoisomers.

‡ Since constitution may be defined according to any appropriate convention, "partial bonds" originating from delocalized π-electron systems may be considered as bonds for the purpose of this definition. The rotation operations by which π-electron systems are affected (e.g., *cis–trans* isomerization) are thus considered as "bond breaking."

Molecules which cannot be brought into coincidence with their mirror images by rigid motions (translations and rotations) are termed chiral (2). Chiral molecules exist as two species of equal chemical constitution, differing only by having the opposite configuration as an object and its mirror image. Species of this kind are called optical antipodes or enantiomers (3). Stereoisomers which are not mirror images are called diastereoisomers. Whereas the measurement of scalar properties, e.g., energy, will in general yield different results for diastereoisomers, such properties are identical for enantiomers. Chemical reactions by which stereoisomers are formed or used up at different rates are called stereoselective reactions (4).

Stereoselective reactions can be controlled either thermodynamically or kinetically, depending on whether the stereoisomeric reaction products are observed in thermodynamic equilibrium or at a considerable time prior to the establishment of thermodynamic equilibrium.

In order to understand the phenomenon of stereoselectivity it is advisable, even in the most general case of a kinetically controlled stereoselective reaction, to reduce the stereoselectivity to the competing occurrence of "subreactions," the stereoselectivity of which is given by the relative amounts of stereoisomers assumed in thermodynamic equilibrium. A systematic treatment in this sense is possible and requires the analysis of a given reaction in terms of what we define as *corresponding reactions.*

II. CORRESPONDING REACTIONS

We may call stereoselective reactions corresponding reactions if the reaction products are stereoisomers in thermodynamic equilibrium or are formed by kinetically controlled reactions via a set of corresponding transition complexes (5) which are stereoisomers in thermodynamic equilibrium. In both cases the relative amounts of reaction products are independent of the initial concentrations of the starting materials and, by this very property, corresponding reactions stand out from other stereoselective reactions.

According to the above definition, the following reaction patterns represent corresponding reactions.

A. Thermodynamically Controlled Reactions

Obviously, all thermodynamically controlled reactions are corresponding reactions. The simplest example is that of a pair of stereoisomers in thermodynamic equilibrium [eq. (1)].

$$P_1 \rightleftharpoons P_2 \tag{1}$$

The coupled equilibrium system [eq. (2)] of n stereoisomers P_1, P_2, ..., P_n, which may also be in equilibrium with further compounds A_1, $A_2, \ldots, A_m$ (starting materials, intermediates, by-products), is an example of a more complex thermodynamically controlled reaction.

$$\{A\mu\}_1^m \rightleftharpoons \{P_\nu\}_1^n \qquad (2)^*$$

B. Kinetically Controlled Reactions

The amounts of products formed by kinetically controlled corresponding reactions are proportional to the concentrations of the respective stereoisomeric transition complexes in thermodynamic equilibrium. Therefore, the relative concentrations of products represent, at the same time, the stereoselectivity of kinetically controlled reactions and the equilibria of the corresponding stereoisomeric transition complexes.

Reaction (3) is a particularly simple example of a pair of corresponding reactions. Here the transition complexes $S_1^\ddagger$, $S_2^\ddagger$, leading to the products P_1, P_2, are stereoisomeric.

$$P_1 \longleftarrow [S_1^\ddagger] \xleftarrow{k_1} A \xrightarrow{k_2} [S_2^\ddagger] \longrightarrow P_2 \qquad (3)$$

The stereoselectivity is given by eq. (i)

$$c_1/c_2 = c_{[1]}/c_{[2]} = k_1/k_2 \qquad (i)$$

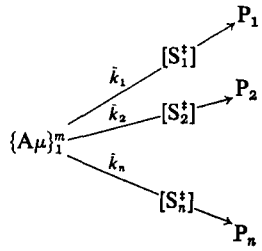
with c_1 and c_2 denoting the concentrations of the products, $c_{[1]}$ and $c_{[2]}$ the concentrations of the corresponding transition complexes, and k_1 and k_2 the rate constants.

Reactions (4a) and (4b) are examples of an n-fold set of corresponding reactions leading to the products $P_1, P_2, \ldots, P_n$ via the stereoisomeric transition complexes $S_1^\ddagger, S_2^\ddagger, \ldots, S_n^\ddagger$ from the starting materials $A_1, A_2, \ldots, A_m$. The prerequisite for reactions (4) to be sets of corresponding reactions is that the equilibrium $\{A\mu\}_1^m$ be attained sufficiently fast so that the formation of the products P_i does not upset the equilibrium of the reactants and intermediates. The product concentration ratios of reactions (4a) and (4b) are described by eqs. (ii-a) and (ii-b), respectively,

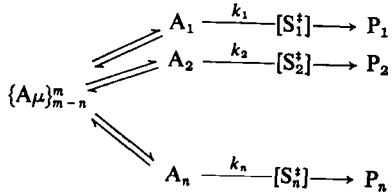
$$c_i/c_j = \bar{k}_i/\bar{k}_j \qquad (ii\text{-}a)$$

$$c_i/c_j = (a_i k_i)/(a_j k_j) \qquad (ii\text{-}b)$$

*In this paper thermodynamic equilibrium systems are denoted by braces. Thus, $\{A\mu\}_1^m$ means that the compounds $A_1, A_2, \ldots, A_m$ are in thermodynamic equilibrium.



(4a)



(4b)

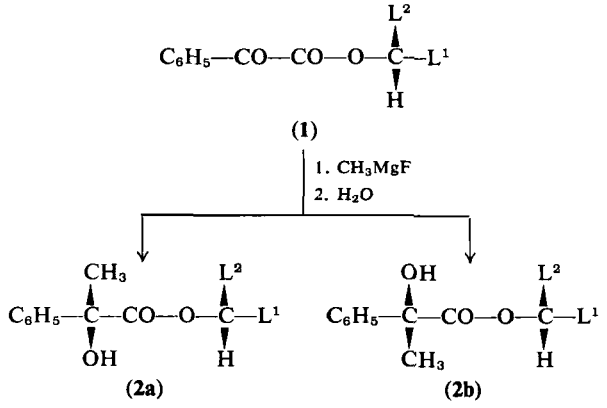
with $i, j = 1, 2, \ldots, n$. The equilibrium concentrations of the intermediates A_ν are denoted by a_ν if intermediates A_ν are involved in the formation of the products P_ν via the transition complexes $S_\nu^\ddagger$.

Corresponding reactions, in general, are characterized by eq. (iii).

$$c_i/c_j = e^{-(\Delta G)ij/RT} \tag{iii}$$

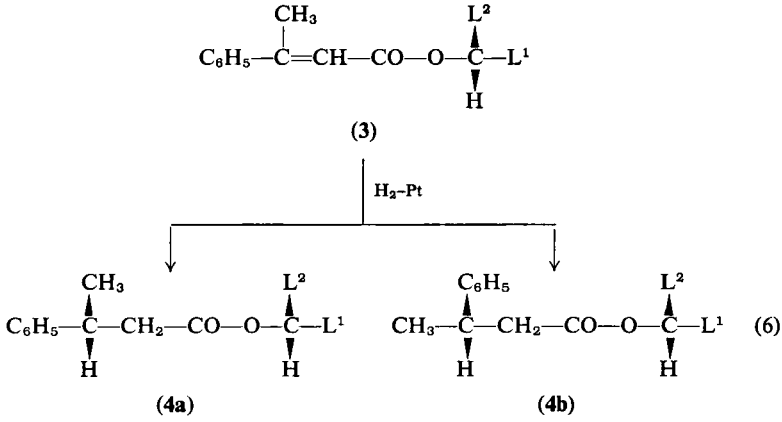
The (Gibbs) free energy difference $(\Delta G)ij$ refers to the reaction products P_i, P_j in thermodynamically controlled cases and to corresponding transition complexes $S_i^\ddagger$, $S_j^\ddagger$ if the reactions are kinetically controlled.*

Referring to eq. (iii) it is possible to decide, on the basis of the temperature dependence of the stereoselectivity and its independence of the concentrations of the starting materials, whether kinetically controlled



(5)

*Cf. the "Curtin-Hammett principle" (4).



stereoselective reactions are sets of corresponding reactions or not. Some examples of stereoselective reactions which have been analyzed according to these criteria are given below.

Asymmetrically induced syntheses (4) are stereoselective reactions by which *new elements of chirality* are created in the *presence of chiral reference systems* (e.g., in starting materials, catalysts, solvents). Prelog (6) has investigated the phenomenon of asymmetrical induction on the basis of reactions (5) and (6). These reactions are examples of pairs of corresponding reactions.

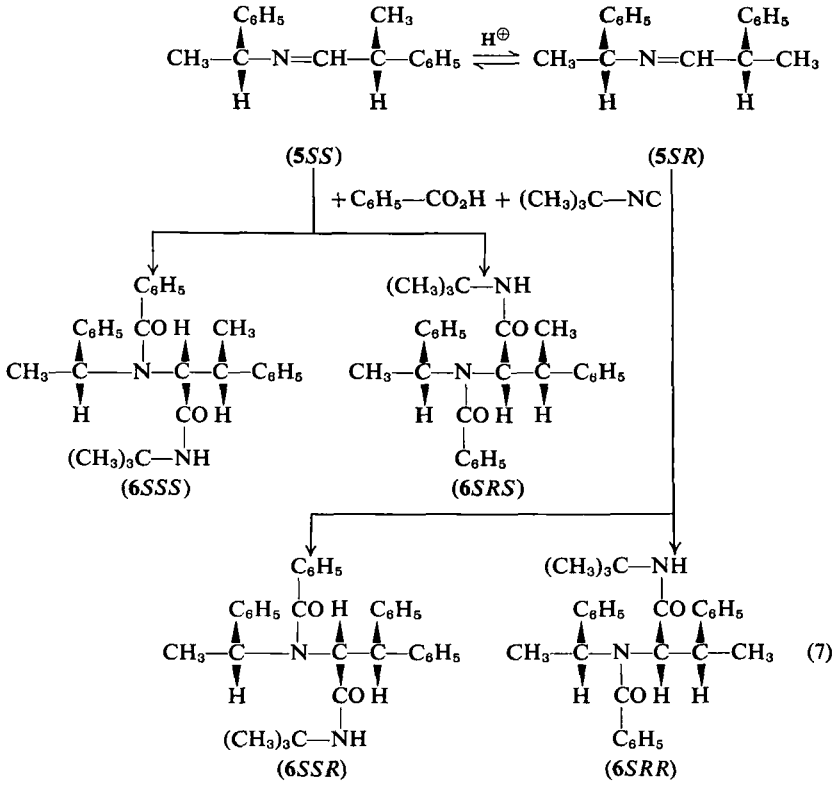
Reaction (7) is an illustration of stereoselective reactions which do not occur via simple pairs, but via higher sets of corresponding reactions (7). The four stereoisomeric products (**6**) are formed from the rapidly established equilibrium of the diastereoisomeric starting materials (**5**) by quadruplets of corresponding reactions, the stereoselectivities of which are determined by the (Gibbs) free energies of the corresponding quadruplets of transition complexes.

The general case of a kinetically controlled stereoselective reaction comprises systems of parallel and consecutive reactions each of which may contain many competing sets of corresponding reactions. By making use of eqs. (iv) the stereoselectivity of such reactions may be reduced to the internal stereoselectivities of the sets of corresponding reactions involved.

$$\gamma_t = \sum_{\mu=1}^{m} \bar{\gamma}_\mu \gamma_t^\mu \qquad \text{(iv)}$$

with

$$\gamma_t^\mu = \bar{k}_t^\mu / \sum_{\nu=1}^{n} \bar{k}_\nu^\mu \qquad \text{or} \qquad \gamma_t^\mu = a_t^\mu k_t^\mu / \sum_{\nu=1}^{n} a_\nu^\mu k_\nu^\mu$$



(7)

The meaning of the symbols is as follows:

γ_i is the mole fraction of the product P_i

$\bar{\gamma}_\mu$ is the mole fraction of all products which are formed by the set μ of corresponding reactions

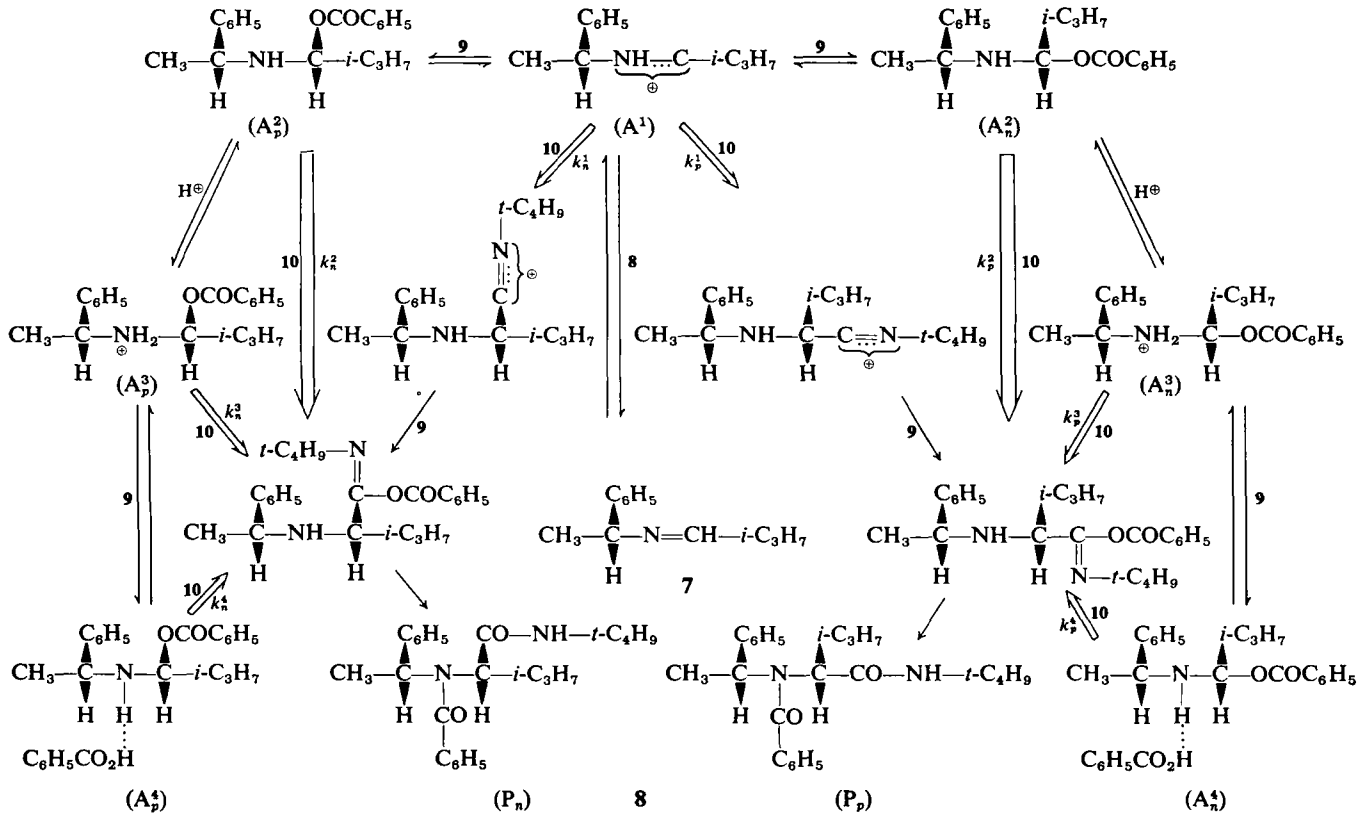
γ_i^μ is the mole fraction of P_i with reference to all products formed by the set μ of corresponding reactions

$\bar{k}_i^\mu$, k_i^μ are the rate constants for the product P_i formed by the set of corresponding reactions according to reaction schemes (4a) and (4b), respectively

a_i^μ is the concentration of the intermediate A_i^μ from which the product P_i is formed according to reaction (4a).

Thus, the overall stereoselectivity of the reaction is given by the ratio of the numbers $\gamma_1, \gamma_2 \cdots \gamma_n$, and the internal stereoselectivity of the set μ of corresponding reactions is represented by the numbers $\gamma_1^\mu, \gamma_2^\mu \cdots \gamma_m^\mu$.

The internal stereoselectivities of sets of corresponding reactions may be determined by kinetic analysis of the total system of reactions.



Reaction (8). The boldface arrows represent stereoselectivity-determining steps and belong to pairs of corresponding reactions. Structure **9** is $C_6H_5COO^-$ and **10** is $(CH_3)_3NC$.

Reaction (8), the synthesis of the *N*-benzoyl-*N*-α-phenylethylvaline *N'*-*t*-butyl amides P_p and P_n* from (*S*)-isobutyraldehyde-1-phenylethyl imine (**7**), benzoic acid (**8**), and *t*-butyl isocyanide (**10**), is an example of a completely analyzed (8–10) system of competing sets of corresponding reactions (see p. 103). The reaction pattern follows from an experimental investigation of the product ratio $Q = c_p/c_n$ as a function of the initial concentrations of the reactants in methanol at 0° (10). An analysis of the experimental data yielded the following internal stereoselectivities.

$$Q_1 = k_p^1/k_n^1 = \gamma_p^1/\gamma_n^1 = 11.4$$

$$Q_2 = a_p^2 \cdot k_p^2/a_n^2 \cdot k_n^2 = \overline{k_p^2}/\overline{k_n^2} = 0.655$$

$$Q_3 = a_p^3 \cdot k_p^3/a_n^3 \cdot k_n^3 = \overline{k_p^3}/\overline{k_n^3} = 3.45$$

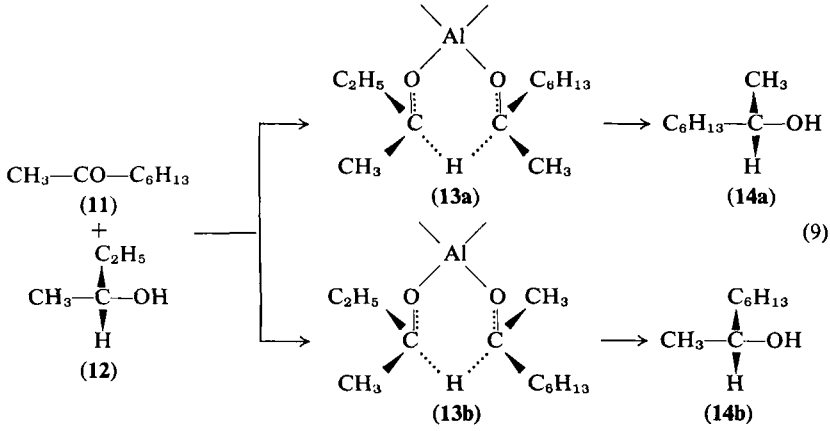
$$Q_4 = a_p^4 \cdot k_p^4/a_n^4 \cdot k_n^4 = \overline{k_p^4}/\overline{k_n^4} = 0.204$$

III. THE NECESSITY FOR A MATHEMATICAL MODEL

An estimate, by simple geometric considerations, of the relative Gibbs free energy of stereoisomeric transition complexes which lead to the various products observed is possible only in a few exceptional cases. Such estimates are particularly questionable if the transition complexes occur in different conformations for each of which a given method of estimating the Gibbs free energy would lead to different results with regard to the expected product ratio. For relatively rigid *cis–trans* isomeric systems, however, such an estimate may be possible using the argument of maximum separation of bulky groups. Reaction (9), the Meerwein-Ponndorf-Verley reduction of 6-methyl-2-heptanone (**11**) by (*S*)-(2)-butanol (**12**) catalyzed by (*S*)-(2)-butoxide (11), is an illustration for the occasional success of this type of argument.

The stereoisomer appearing preferentially (**14b**) is formed via transition complex (**13b**), the bulkiest groups of which are in the *trans*-relationship. Reaction (10), on the other hand, illustrates how questionable the method, outlined above, of estimating the (Gibbs) free energy may be in other instances. Here all three conformations (**15a–15c**) of the starting material are assumed to be significant, each being associated with one preferred conformation of the two transition complexes. As seen in reaction scheme (10), different preferred conformations of the transition complexes will lead to different products (**16a** and **16b**). It is not possible in such a

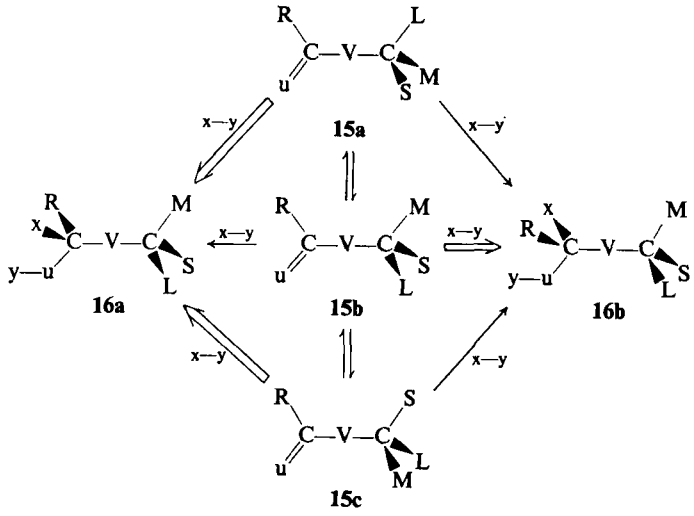
*The indices *p* (for positive) and *n* (for negative) refer to the *p,n*-nomenclature for diastereoisomers (8), where *p* stands for (*R*)(*R*) or (*S*)(*S*) and *n* for (*R*)(*S*) or (*S*)(*R*).



(9)

case to decide which of the conformations determines the selectivity of the reaction and thus a prediction is not possible. Furthermore, the question arises whether the assumed conformations of the reactants really determine the course of the reaction and if the criteria used for reaction (9) are really, *mutatis mutandis*, applicable to reaction (10).

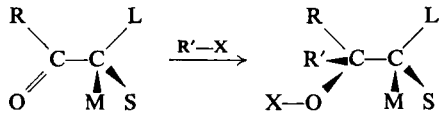
An empirical justification for this kind of reasoning limited to special conformations may be found, in particular cases, in the rules of Cram



(10)*

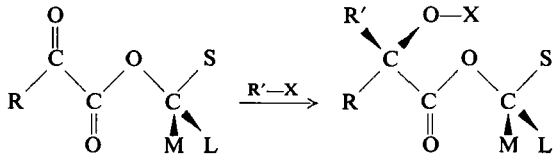
*The large arrows represent that reaction of a certain conformation which is assumed to be preferred because the addend attacks on the side of the reactant which carries less steric bulk (S < M < L), thus allowing for a favorable conformation of the transition complex.

and Prelog which state that products **17** and **18** are the stereoisomers formed predominantly in reactions (11) and (12).



17 (11)

Cram's rule (12)



18 (12)

Prelog's rule (6)

We may thus conclude from the foregoing considerations that a model should be set up which does not depend on the uncertainties of determining the relevant conformations, i.e., a model drawing from the "black box" (13) of a stereochemical reaction just those features which are directly relevant to its stereoselectivity. Quantitative statements concerning stereoselectivity will be among the mathematical consequences of this model.

IV. THE STEREOCHEMICAL ANALOGY MODEL

Our general aim is to make predictions concerning the product ratios in stereoselective reactions. Accordingly, we shall attempt to abstract the typical and representative characteristics of such reactions and provide the means for the theoretical treatment of the idealized general case. This idealization will be represented mathematically by the so-called "stereochemical analogy model." At this point we will not discuss specific reactions which justify this idealization and for which a description by the equations of our model is possible with adequate accuracy. If we do find a sufficient number of reactions which can be interpreted on the basis of this model and also find so good a correlation between theory and experiment as to allow the establishment of a rule, then a discussion of possible discrepancies between the theory and specific experimental observations may yield additional chemically interesting information.

In developing such a theory we employ sets of corresponding reactions. As we have seen in the previous sections, complex systems of stereoselective reactions are reducible to sets of corresponding reactions.

We start out with a discussion of stereoisomeric reactants being in thermodynamic equilibrium on the basis of the system of eqs. (v). The

$$c_\sigma = K \sum_{r}^{(S_\sigma)} exp\,(-\epsilon_{\sigma,r}/kT) \qquad \sigma = 1, 2, \ldots, n \tag{v}$$

index σ distinguishes the various stereoisomeric reactants, the c_σ's denote their equilibrium concentrations, and each summation is done over all molecular states with the characteristics of the respective stereoisomeric species S_σ. K is a constant which has the same value for all equations of system (v).

The system of eqs. (v) describes kinetically controlled stereoselective reactions as well, provided they are corresponding reactions in the above sense. To be more precise, if we denote by c_σ the concentrations of reaction products, formed via activated complexes uniquely related to them, then the partition functions on the right-hand side of eqs. (v) refer to the states of the corresponding transition complexes.* Hence, eqs. (v) hold for both cases, provided they are interpreted in appropriately different ways, namely,

a. In the thermodynamically controlled case the c_σ's denote the concentrations of the reactants and the partition functions are sums over the states of the reactants.

b. In the kinetically controlled case the c_σ's denote the concentrations of the reaction products and the partition functions are sums over the states of the corresponding transition complexes.

The discussion of the system of eqs. (v) will prove to be feasible on the basis of a general mathematical model if the reactants and the transition complexes are in a stereoisomeric relationship to each other in the thermodynamically and kinetically controlled cases, respectively.

The question whether, in the kinetically controlled case, the reaction products have the stereochemical characteristics of the transition complexes or even whether they are stereoisomers at all is irrelevant for the further treatment. In any case the partition functions refer to stereoisomeric molecules or transition complexes and we shall analyze the phenomenon of stereoisomerism with a view to how it applies to these partition functions.

The energy values $\epsilon_{\sigma,r}$ of each partition function $\sum^{(S_\sigma)} \cdots$ refer to states which have the steric characteristics of the stereoisomeric species S_σ. It is feasible to identify these states with the eigenstates of model

*According to transition state theory (5).

energy operators which already possess the steric characteristics of the stereoisomeric species. But we can also use energy operators which are determined by the gross formulas of the molecules only and therefore contain the nuclei as quantum-mechanical particles. Then it turns out that only linear combinations of eigenfunctions of similar energies yield functions with the proper steric characteristics of a species and the $\epsilon_{\sigma,r}$ must be interpreted as expectation values of the energy for states with stereoisomeric criteria. Thus, regardless of the procedure chosen, the $\epsilon_{\sigma,r}$'s are always energy values of wave functions with steric features. The wave functions can be classified according to steric criteria only below some energy threshold which is as difficult to determine precisely as it is to answer the question as to which stationary arrays may still be considered as stereoisomeric molecules. As states of high energy do not contribute appreciably to partition functions, owing to the exponential form of the terms, this uncertainty is not of critical importance and parallels a corresponding uncertainty in the interpretation of measurements of the concentration ratios.

The common feature of isomeric molecules is their gross chemical formula, while for the class of stereoisomeric molecules it is the constitution—a concept which embodies bonds and bonded neighbors in addition to the molecular formula. Constitution relates to the concept of the "chemical bond," itself not always unequivocally defined, and is therefore determined either within an agreed upon frame of reference for ordinary classes of molecules or by appropriate definition for special cases. For many classes of stereoisomeric molecules, however, the following state of affairs seems to be characteristic.

It is possible to differentiate between a molecular framework and an assortment of ligands. Either all ligands, or all those in a given subassortment, are bound to the same atomic neighbors in an "equivalent" manner. We shall call such ligands *constitutionally equivalent*. The relative positions of constitutionally equivalent ligands are largely defined by the constitution—except for permutations of these ligands. However, some of these permutations may be performed without breaking and reforming bonds, e.g., rotations around σ-bonds of the molecular framework, whereas others may not. Certain geometrical stituations of stereoisomers which are favored energetically represent conformers. Such additional restrictions in mobility are caused by forces which do not originate directly from the bonds within a given constitution. Assuming that all essential contributions to the energy are accounted for by the bonds within a given constitution, the conformers of a stereoisomeric species are then primarily characterized by states of low energy. States of higher energy may represent motions which do not permit a distinction between conformers.

A stereoisomer which occurs in several conformations is, therefore, in general a representative of states with and without the characteristics of conformers.

A permutation of constitutionally equivalent ligands leads from one stereoisomer to another unless the result of this rearrangement may be achieved as well by some "constitution-allowed" motion within the molecular framework or corresponds to a rotation of the whole molecule. This is also true for transition complexes if proper definitions of the constitution of the reaction partners can be given. We call permutations of constitutionally equivalent ligands *constitution-preserving permutations* and conventionally refer these permutations to numbered ligands rather than to numbered positions on the molecular framework. We consider a situation in which all arrangements of ligands which can be obtained from all conformations by constitution-preserving permutations are feasible as the *stereochemical standard situation*. That is, no arrangements of ligands which are possible in principle shall be excluded, or strongly disfavored, on grounds of the specific nature of the ligands for reasons of steric hindrance. Thus, in a rigid model any constitution-preserving permutation which refers to the numbered ligands effects either a permutation of the conformations within the stereoisomeric species or a transition of all conformations of a species into conformations of another species.

The above considerations of plausibility comprise the assumption of an analogy with regard to the states of stereoisomeric molecules. This analogy implies a similarity of states which becomes evident if one excludes differences due to permutations of constitutionally equivalent ligands. Analogous states, for instance, represent nuclear motions which are similar except for a permutated ligand arrangement. They differ, in essence, only by their particle density distributions which can, within certain limits, be brought to coincidence by constitution-preserving permutations of the particle density distributions of the ligands.

In general, the analogy relation can certainly not be defined for all states with stereoisomeric characteristics, i.e., there are wave functions which, after a constitution-preserving permutation, neither stay almost unaltered nor are transformed, within an appropriate approximation, into other wave functions of stereoisomeric characteristics. Yet, we can use the analogy to deal with a stereochemical problem even if we have several states with stereoisomeric characteristics for which analogous states do not exist provided those states have only little influence on the measured quantities to be discussed. In particular, states of high energy which cannot be classified in this sense are not relevant for the discussion of eq. (v) because of the exponential nature of the terms of the partition functions.

We regard the *analogy phenomenon* as the *typical phenomenon of stereochemistry* and we therefore consider influences which destroy this analogy, such as steric hindrance, as exceptions to be discussed on the basis of additional arguments in individual cases.

The analogy hypothesis outlined above will now be formulated in terms of a mathematical model, which we call the "stereochemical analogy model." In this context concepts of group theory need to be used.

Let M be the set of all wavefunctions representing stable states with stereoisomeric characteristics belonging to a given constitution. Let P be a group of operators which can be applied to all wavefunctions belonging to a subset $\overline{M} \subset M$ and which give rise to a mapping within $\overline{M}$. This mapping may be used to define the analogy of states in the following way. Any operator of P relates those states of M to each other which, in essence, differ only by a certain constitution-preserving permutation of the ligand particle densities. We may call those wavefunctions, or states, analogous and may similarly call the operators of P constitution-preserving permutations. We do so since each operator of the group P effects a permutation of wavefunctions which can be understood approximately as arising from a certain permutation of equivalent ligands. The restriction to the subset $\overline{M}$ allowing the application of all operators belonging to P may be done without physically relevant limitations.*

For cases in which the analogy criterion does not suffice for an unambiguous assignment of wavefunctions the assignment will be made by appropriate definition. The original interpretation of the elements of P as operators permuting conformations must, on the basis of the latter definitions, be considered as a simplified description of the analogy having in mind a special geometrical picture. Referring to the preliminary plausibility arguments outlined above, the following are valid for the group P and the set $\overline{M}$:

1. There is a classification of the set $\overline{M}$ of functions in subsets $\overline{M}_1, \overline{M}_2, \ldots, \overline{M}_n$ which contain the wavefunctions of the different stereoisomers $S_1, S_2, \ldots, S_n$. The classification of the states by such "species sets" is to be permitted with regard to the group P, i.e., the operations from P rather than to destroy this classification effect permutations of these subsets. A classification by such subsets shall also be given if some of the stereoisomers become indistinguishable because of the equality of some of the ligands.†

*The relevance of such limitations depends upon the nature of the physical problem.

†The original classification by species subsets can be maintained by an appropriate choice of linear combinations of wavefunctions.

2. Those permutations from P which do not eject the states of a subset $\overline{M}_\sigma$ from this subset are elements of a subgroup U_σ, the elements of which correspond to permitted motions within the stereoisomeric species S_σ. In accordance with differing descriptions of motions by permutations of ligands in permuted arrangements the allowed subgroups U_σ of the subsets M_σ are mutually conjugated,

$$U_\tau = \pi U_\sigma \pi^{-1}$$

π being a permutation which transforms functions from $\overline{M}_\sigma$ into functions from $\overline{M}_\tau$.

3. A second classification of $\overline{M}$ by subsets $\overline{M}^\nu$ of analogous states ($\nu = 1, 2, \ldots$) corresponds to a resolution of $\overline{M}$ into regions of transitivity with regard to the operations from the group P.

It should be emphasized that the analogy of states pinpointed in this form is no longer tied to the geometrical picture of preferred conformations.

Figure 1, in which the wavefunctions from $\overline{M}$ are represented by dots, illustrates the above twofold classification into subsets $\overline{M}^\nu_\sigma$. The dots in each column represent states of a species, whereas the dots in each row represent analogous states. It is to be noted that the number of functions is the same for all boxes of a row, but this is not necessarily so for all boxes of a column. This corresponds to the fact that nonanalogous wavefunctions of the same stereoisomeric species S_σ may behave differently toward constitution-preserving permutations, depending on whether said functions have the characteristics of a conformation or not. In the first case a constitution-preserving permutation must always be considered as a mapping onto an analogous function representing a different conformation. In the latter case it may be that the density distribution derived from the function remains nearly unchanged so that the effect of this permutation must be seen as a reproduction. Functions of the latter type represent motions of the nuclei involving interconversion conformers of a given stereoisomeric species.

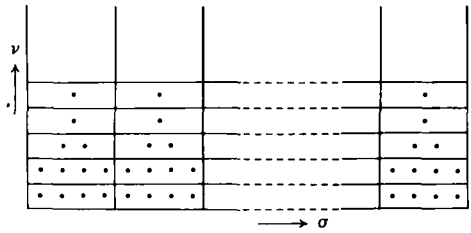


Figure 1.

According to the above twofold classification by the criteria of stereoisomerism and analogy, the states may be characterized by quantum numbers σ and ν. These quantum numbers, in combination with a third one, κ, which differentiates between analogous states within a species, uniquely classify the state functions of stereoisomeric molecules. The range of values of κ is not necessarily the same for all values of ν (see Fig. 1).

The structure of the set $\overline{M}$ of wavefunctions, defined by the *analogy operations* of the group P, provides an aspect, formal as well as methodical, for the discussion of eqs. (v).

The partition functions $\sum^{(S_\sigma)} \cdots$ of eqs. (v) are not the same for two different species S_σ unless said species are enantiomers. Nonetheless, we shall also differentiate formally between the partition functions of enantiomeric species. The partition functions may be regarded as functions which depend on the kind of ligands belonging to the ligand assortment of the molecule and on their relative arrangement. These functions are not altered in their values if the ligands are subjected to the permutations of the respective species subgroup, since this changes only the order of the terms within a sum. A permutation which does not belong to the group U_σ transforms the partition function of the species S_σ into the partition function of some other species since a corresponding change occurs in the states and thereby in the energies. Two permutations, $\boldsymbol{\pi}$ and $\boldsymbol{\pi}'$, for which the product $\boldsymbol{\pi}^{-1}\boldsymbol{\pi}'$ lies within U_σ, transform $\sum^{(S_\sigma)} \cdots$ into the same sum $\sum^{(S_\tau)} \cdots$. Different partition functions may possibly become equal as the result of the equality of several ligands. Therefore, we may consider such a sum $\sum^{(S_\sigma)} \cdots$ as a function of numbers $L_1, L_2, \ldots, L_n$, representing the nature of the ligands and this function is reproduced by permutations or transformed into another function depending on whether the permutation stems from the species subgroup U_σ or one of its left cosets. If we use the notation

$$\sum^{(S_\sigma)} \cdots = \sum_\sigma (L_1, L_2, \ldots, L_n)$$

with $\sum_\sigma$ as a symbol for a function, we have:

$$\sum_\sigma = \boldsymbol{\pi}_\sigma \sum_1$$

Here $\boldsymbol{\pi}_\sigma$ is an operator which, on being applied to the function $\sum_1$, produces the above permutation of the $L_1, L_2, \ldots, L_n$, corresponding to a ligand permutation from the left coset σ of U_1. In this way the set of functions $\sum_1, \sum_2, \ldots, \sum_n$ is generated from one function, e.g., from $\sum_1$, by applying the operators $\pi_2, \ldots, \pi_n$. This set of functions has the transformational properties of a basis belonging to a representation which has been induced *regularly* (14) by the unit representation of U_1. The matrices

of the representation contain a one in each row and column and zeros elsewhere. It is evident that we meet the same conditions if we replace the partition functions by their logarithms, which we may regard as a basis also.

The advantage of using logarithms for the treatment of the stereoselectivity problem will become apparent in the following paragraphs.

As in most applications of group theory, the irreducible components of the representations we have just discussed for the stereoselectivity problem are of physical significance. We need especially the real one-dimensional representations, with the exception of the identity representation, i.e., irreducible representations with the characters $+1$ and -1. As may be concluded from theorems of Frobenius (15), irreducible components of the desired type do exist if and only if there are normal subgroups N, with index 2, containing the species groups U_σ ($\sigma = 1, 2, \ldots, n$). Using the logarithmic basis we obtain the moduli for the representations of the above-mentioned type in the form*:

$$\ln \textstyle\sum_{\sigma_1} + \cdots + \ln \sum_{\sigma_{n/2}} - \ln \sum_{\tau_1} - \cdots - \ln \sum_{\tau_{n/2}}$$

$$= \ln \frac{\sum_{\sigma_1} \cdot \sum_{\sigma_2} \cdot \cdots \sum_{\sigma_{n/2}}}{\sum_{\tau_1} \cdot \sum_{\tau_2} \cdot \cdots \sum_{\tau_{n/2}}} = \ln \frac{c_{\sigma_1} \cdot c_{\sigma_2} \cdot \cdots c_{\sigma_{n/2}}}{c_{\tau_1} \cdot c_{\tau_2} \cdot \cdots c_{\tau_{n/2}}} = Q(L_1, \ldots, L_n) \quad \text{(vi)}$$

The indices σ and τ refer to stereoisomeric species differing in ligand permutations from N. The numerator and the denominator are reproduced or interchanged when permutations belonging to the normal subgroup N or to its coset respectively, are applied. Therefore $Q(L_1, L_2, \ldots, L_n)$ is a function which is invariant with respect to all permutations of the L_i's, belonging to the invariant subgroup N, whereas a change in sign is produced by operations from the coset. The examples discussed below indicate that for most of the cases eq. (vi) has the form of eq. (vi-a).

$$\ln (\textstyle\sum_\sigma / \sum_\tau) = \ln c_\sigma / c_\tau = Q(L_1, \ldots, L_n) \quad \text{(vi-a)}$$

In eq. (vi-a) the subgroup U_σ is a normal subgroup of index 2 of the group P or of a subgroup $\bar{P} \subset P$ to which the problem may be reduced. With this condition we drop the index, as $U_\sigma = U_\tau$, and just speak of the species group U. We also do not need to distinguish between left and right cosets. Q is invariant with respect to permutations from U and changes sign upon permutations from the coset of U.

If ligands of the same kind are involved and if there exists a permutation from the coset of U which affects only ligands of the same kind,

* It may be mentioned that the procedure outlined above which leads to eq. (vi) sometimes becomes possible if we confine ourselves to a subgroup $\bar{P} \subset P$.

then the function Q must, on one hand, be invariant under the corresponding permutation of equal numbers L_i, but, on the other hand, must change its sign; it is therefore zero. At the same time, numerator and denominator species are no longer different, and the equation

$$\ln c_\sigma/c_\tau = 0$$

expresses the obvious fact that the concentration of a species is identical with itself.

For many stereoselectivity problems the permutations from U may be interpreted geometrically as rotations and the elements of the coset as reflections of parts of the molecules. Here the difference between numerator and denominator species is due to the chirality of parts of the molecules and the two species become identical if these parts lose their chirality for reasons of some special ligand assortment.

The knowledge of $Q(L_1, \ldots, L_n)$ for all sets of stereoisomeric products or transition complexes differing only in the type of ligand for a given reaction type would be equivalent to a complete solution of the stereoselectivity problem for that class of reactions. In order to achieve this solution at least in an approximation we now turn to the quantitative aspect of the analogy phenomenon.

A. The Quantitative Aspect of the Model

As a rule, molecules with different ligand assortments differ appreciably in number and energy of states. In accordance with our model, on the other hand, the number of terms in the partition functions varies but is always the same for the numerator and denominator of eqs. (vi) or (vi-a). As a further consequence of the model, the energies of analogous states occurring correspondingly in numerator and denominator are similar because their differences are due only to interactions which do not depend on the nature of the bonds (i.e., the constitution).

Therefore, we may expect that the values of Q which vary with the ligand assortment may be represented by a relatively smooth function of some suitably chosen ligand quality. In other words, we may find some one-parameter measure of a physically relevant ligand quality such that the function $Q(L_1, \ldots, L_n)$ can be replaced by a function $q(\lambda_1, \ldots, \lambda_n)$ of variables λ_i which represent the ligand parameters λ of the ligands L_i. Since neither the nature of the ligand quality nor the scale by which it is measured have been set *a priori*, one may assume that on the basis of an appropriate choice a sufficiently smooth function of the λ_i's with the required transformational properties will characterize the problem in adequate terms.

The approximation we have in mind takes advantage of the fact that the scale by which the ligand quality is measured is not fixed *a priori*. Thus, we shall try to approximate the function $q(\lambda_1, \ldots, \lambda_n)$ by a certain mathematically simple function χ of new parameters μ_i. Thereby, we choose ligand parameters μ_i such that the relevant ligand quality is measured on a proper scale related to which the two functions q and χ differ as little as possible with regard to some defined deviation.

The choice of a suitable scale for the parameters is equivalent to the choice of a suitable function $\mu(\lambda)$, with $\partial\mu/\partial\lambda \neq 0$ over some domain

$$\lambda_0 - \lambda \leq \lambda_i \leq \lambda_0 + \lambda$$

such that

$$q(\lambda_1, \ldots, \lambda_n) = q(\lambda(\mu_1), \ldots, \lambda(\mu_n)) = \bar{q}(\mu_1, \ldots, \mu_n) \approx \chi(\mu_1, \ldots, \mu_n)$$

yields an optimum approximation, where $\chi(\mu_1, \ldots, \mu_n)$ is a given, mathematically simple function with the transformational properties of q. This approximation should at least be reasonable provided the ligands in question are not too different with regard to their relevant quality.

As has been outlined in a more general investigation (16) without direct reference to the present problem, there are two approximation procedures for finding functions with the transformational properties of the function $q(\lambda_1, \ldots, \lambda_n)$ and functions for 16 different examples have been formulated explicitly. One of these procedures, the method of polynomials, will be applied here.

The function $q(\lambda_1, \ldots \lambda_n)$ is replaced by the polynomial $\chi(\mu_1, \ldots, \mu_n)$ of the lowest possible degree possessing the desired transformational properties. This polynomial can be found by standard methods and one can show that it is homogeneous, depending only on the differences $\mu_i - \mu_k$ $(i, k = 1, 2, \ldots, n)$. It has the general form

$$\chi(\mu_1, \ldots, \mu_n) = \sum_{\nu=1}^{s} a_\nu p_\nu(\mu_1, \ldots, \mu_n)$$

Here the p_ν's are homogeneous polynomials of equal order in the μ_i's which are also functions of μ-differences. They are completely defined by the required transformational properties. The coefficients q_ν may depend on the reaction type and conditions, such as temperature, solvent, etc.

One may think of $\chi(\mu_1, \ldots, \mu_n)$ as the first term of a Taylor expansion of the function $\bar{q}(\mu_1, \ldots, \mu_n)$ around μ_0. There the a_ν's depend upon the origin of the expansion, μ_0, and the region of validity of this approximation is confined to the vicinity of this point. Thus the approximation is acceptable for molecules with similar ligands, i.e., for ligands the μ-values of which do not differ appreciably.

However, it is also possible to consider the polynomials $\chi(\mu_1, \ldots, \mu_n)$ as the first term of an expansion in a series of orthonormalized polynomials by which the function $\bar{q}(\mu_1, \ldots, \mu_n)$ is approximated over a finite region in the sense of minimization of the mean square deviation. Here the coefficients a_v follow from the solution of the corresponding variational problem.

The polynomials of the lowest degree, according to both approximation procedures, are of the same form. Because of its homogeneity and its exclusive dependence on μ-differences, a transformation of the parameter

$$\mu_i \rightarrow \bar{\mu}_i = k\mu_i + c$$

may be compensated for by a common factor in the coefficients of the polynomial. We may thus represent two particular kinds of ligands in an arbitrary manner by real numbers, e.g., by 0 and 1. For the computation of the μ-values of M ligands and the S coefficients of the polynomial one has to carry out about $M + S$ measurements on systems with different combinations of ligands. The number of different combinations of ligands, however, is $\binom{M}{n}$, a number rising considerably faster with M than $M+S$. Thus, even if one does not attempt a theoretical calculation of the ligand-specific μ-values, one obtains new information from the above equations.

Before entering upon the discussion of individual examples of stereoselective reactions it is appropriate to point out a fundamental property of the function $q(\lambda_1, \ldots, \lambda_n)$, which also holds for the approximation function $\chi(\mu_1, \ldots, \mu_n)$. This property has been expressed and was proved with regard to the interpretation of the function q as a chirality function in a study relating to the systematics of the phenomenon of chirality (18) without specific reference to the problem of stereoselectivity. As related to the meaning of q in eq. (vi-a) and to the interpretation of numerator and denominator species as being different by reflections of parts of the molecule (transition complex), it may be expressed in the following way.

We differentiate between stereoselectivity problems of a category *a* and a category *b* depending on whether vanishing stereoselectivity in eq. (vi-a) follows generally from the coincidence of the quality of just two suitably placed ligands (i.e., ligands having the same parameter value) or whether there are cases in which only further reduction of the number of ligands with differing qualities leads to the concentration ratio of unity. It can be shown (18) that for stereoselectivity problems of category *a* there are functions which are zero if and only if the quality of two ligands, measured by the parameters μ or λ is equal. For examples of category *b*, on the other hand, any function q has zero values which

describe only the equality of the concentrations of two species but do not simultaneously indicate the coincidence of ligand qualities. It has been shown as well (18) that for cases of category *a* polynomials of the lowest order in μ are of the special form

$$\chi(\mu_1, \ldots, \mu_n) = \rho \prod_{i<k}^{(1\ldots\nu_1)} (\mu_i - \mu_k) \cdot \prod_{i<k}^{(\nu_1+1\ldots\nu_2)} (\mu_i - \mu_k) \cdot \cdots \prod_{i<k}^{(\nu_{r-1}+1\ldots\nu_r)} (\mu_i - \mu_k) \qquad \text{(vii)}$$

where the indices i, k in each factor $\prod_{i<k}^{(\nu_{\rho-1}+1\ldots\nu_\rho)} (\mu_i - \mu_k)$ run over all values

$$\nu_{\rho-1} + 1 \leq i < k \leq \nu_\rho \qquad \text{with} \qquad \nu_0 = 1 \quad \text{and} \quad \nu_r = h$$

Polynomials χ of the above type may be called chirality products for reasons which become apparent on the basis of a special geometrical interpretation (cf. refs. 17 and 18). Chirality products have zero values which necessarily imply identity or enantiomerism of the numerator and denominator species, provided coincidence of the ligand quality may be interpreted as equality of ligands. Most stereoselectivity problems belong to category *a*, and in this case we have to deal with special polynomials of the form of eq. (vii).

The stereochemical analogy model does not contain any assumptions other than that of the analogy of states and its applicability is therefore not confined to special types of reactions. Furthermore, beyond the specific problem of stereoselectivity, the model comprises an algebraic formalization of the phenomenon of stereoisomerism. The characterization of stereoselectivity by polynomials of the lowest order in μ_i, according to the second method as outlined in ref. 16, is a possible way to put the analogy hypothesis into a form providing means for approximate comparison of theoretical and experimental data.

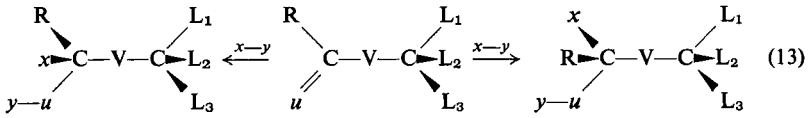
The closeness of the approximation by either method depends mainly on how well the condition of analogy is fulfilled. Factors interfering with the analogy, such as partial steric hindrance, certain solvent effects, and hydrogen bonding, could possibly be included in the description through mathematically more involved functions such as polynomials of higher order.

We turn now to the treatment of special cases. In the polynomials for the examples discussed in the following pages we write λ instead of μ, again with the understanding that this λ is the best possible parameter in the above sense.

Examples

The application of the theory in the form based upon the approximation outlined above will be illustrated first by the cases of the stereoselective syntheses [reactions (5) and (6)] which have been investigated by Prelog et al.

Reactions (5) and (6) follow the general pattern of reaction (13):



(13)

Henceforth we shall assume that all ligands denoted by L_1, L_2, L_3, R, u, are achiral or that their chirality may be neglected in the prediction of the stereoselectivity of reaction (13).

Reaction (13) is controlled kinetically and therefore the concentration ratio of the products **20a** and **20b** is given by the concentration ratio of the corresponding transition states. Replacing the starting material by its enantiomer, we obtain a pair of transition states which differ only with regard to the configuration of the chiral center determining the stereoselectivity. Said replacement changes neither the values of the partition functions nor the concentration ratio. The analogy of these transition complexes is described by the permutation group $P = S_3$ of the ligands L_1, L_2, and L_3, with the alternating group A_3 representing allowed rotations around the V—C bond, thus corresponding to the species subgroup U. U is a normal subgroup of index two, and the operations from the coset can be interpreted as reflections of the center of chirality which determines the stereoselectivity.

Since the stereoselectivity must disappear if and only if at least two of the ligands L_1, L_2, L_3 become equal, the polynomial of the lowest order is a chirality product of the ligand parameters λ_1, λ_2, λ_3. It describes the stereoselectivity of the reaction as depending on the chirality of the chirality center which determines stereoselectivity, namely,

$$\ln c_{1'2'3'}/c_{1'3'2'} = \rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1) \qquad \text{(viii)}$$

Here the concentrations of the stereoisomeric reaction products, which differ by interchange of two of the ligands x, R, and u—y, are denoted by $c_{1'2'3'}$ and $c_{1'3'2'}$, with 1′2′3′ being the place numbers of the ligands x, R, u—y of the newly formed center of chirality according to some defined rules of numbering. 1′3′2′ symbolizes the reverse order.

In terms of the *R,S*-nomenclature of Cahn, Ingold, and Prelog (19) the concentrations of the diastereoisomeric products are denoted by

c_{RR}, c_{RS}, c_{SR}, and c_{SS}, the subscripts referring to the configurations of the stereoselectivity-determining and the induced chirality center.

Therefore, we define the sign of ρ such that for given values of λ-parameters eq. (viii-a) is true (valid for a certain ligand assortment with

$$\ln c_{RR}/c_{SR} = \rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1) \qquad \text{(viii-a)}$$

given parameter values λ_1, λ_2, λ_3).

Equation (viii-a) is not valid for an arbitrary set of ligands since, in contrast to that of eq. (viii), the left side of eq. (viii-a) is dependent on the chosen nomenclature.

We have

$$\ln c_{RR}/c_{SR} = -\ln c_{RS}/c_{SS} = -\ln c_{SR}/c_{RR} = \ln c_{SS}/c_{RS} = \ln c_p/c_n$$

and the notations R and S, as well as p and n (see p. 106 and ref. 8), depend upon the Cahn-Ingold-Prelog sequence (19) of L_1, L_2, and L_3 or, respectively, x, R, and u—y.

We must now introduce a nomenclature factor on the left-hand side of eq. (viii-a) in order to make sure that the equation is valid for any ligand assortment [eq. (ix), valid for any λ_1, λ_2, λ_3],

$$\delta\delta' \ln c_{RR}/c_{SR} = \delta'' \ln c_p/c_n = \rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda') \qquad \text{(ix)}$$

with δ or δ' being equal to $+1$ if 1′2′3′, or, respectively, 1, 2, 3, correspond to an R-sequence and to -1 if they are in an S-sequence. In addition $\delta'' = \delta\delta'$ holds.

The experimental stereoselectivity data of Table I were used for the determination of the λ-values of nine ligands and of the ρ-values of reactions (v) and (vi) (8). Since the number of experimental data exceeds the number of parameters we may consider the fact that the experimentally observed stereoselectivities are described by eq. (ix) within the accuracy of the experiments as experimental confirmation of the theory outlined above. It is noteworthy that eq. (ix) represents a *linear free energy relationship* in which the chirality product characterizes the influence of the substituents. This linear relationship is supported by the data of Table I.

On the other hand, disregarding the linear free energy relationship we cannot consider the experimental material of Table I as being a sufficient confirmation of eq. (ix). But this shortcoming is at least partly remedied if we draw attention to the following.

The relevant quality of the ligands may vary for different types of reactions described by different polynomials such that the same ligands must be characterized by different parameters. However, we may expect (with good reason) that it is at least a similar one-parameter quality of the ligands which is measured on different scales for different types of reactions

TABLE I

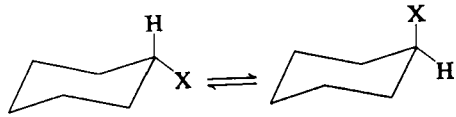
The Dependence of the Stereoselectivities of eq. (5) ($\rho = 0.313$) and eq. (6) ($\rho = 0.129$) upon the Ligands

			2a [mole %]		**4a** [mole %]	
L_1	L_2	L_3	Calcd.	Obsd.	Calcd.	Obsd.
$(CH_3)_3C$	CH_3	H	62	62	45	46
CH_3	$(C_6H_5)_3C$	H	21	25	—	—
endo-$C_{10}H_{17}$	CH_3	H	75	77	—	—
C_6H_5	CH_3	H	56	52	48	48
CH_3	2,4,6-$(CH_3)_3\cdot C_6H_2$	H	35	35	57	57
CH_3	2,4,6-(cyclo-$C_6H_{11})_3\cdot C_6H_2$	H	16	17	62	64
α-$C_{10}H_7$	CH_3	H	56	56	47	46
C_6H_5	$(C_6H_5)_3C$	H	67	64	—	—
endo-$C_{10}H_{17}$	C_6H_5	H	27	29	—	—

as we have different λ-polynomials. In this case the parameters $\bar{\lambda}$ and λ of two different reaction types should be monotonous functions of each other. This hypothesis can be checked by reaction (14) which represents the equilibrium concentration ratios of the stereoisomers of the monosubstituted cyclohexanes [eq. (14)]. According to our approximation the concentration ratio is described by eq. (x), which can be derived easily

$$\ln c_1/c_2 = \rho(\bar{\lambda}_X - \bar{\lambda}_H)(= -\Delta G/RT) \qquad (x)$$

taking into account that the group P in this case is the symmetric permutation group S_2 while the species group consists only of the unit element.

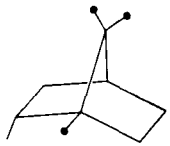
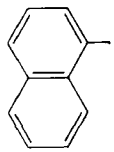


(14)

The $\bar{\lambda}_X$-values and the factor ρ are easily obtained from experimental ΔG-values with $\bar{\lambda}_H = 0$ and $\bar{\lambda}_{CH_3} = 1$ (20). The trial equation $\bar{\lambda} = k\cdot\lambda^3$ for these $\bar{\lambda}$-values and a proper choice of the factor k, in accordance with the hypothesis of a monotonous dependence, lead to the λ-values of Table II within the limits of experimental accuracy. In this sense we may regard the λ-values of Table II as given by experiments not related to reaction (5) and (6). Disregarding the fact that the special relation $\bar{\lambda} = k\lambda^3$ cannot yet

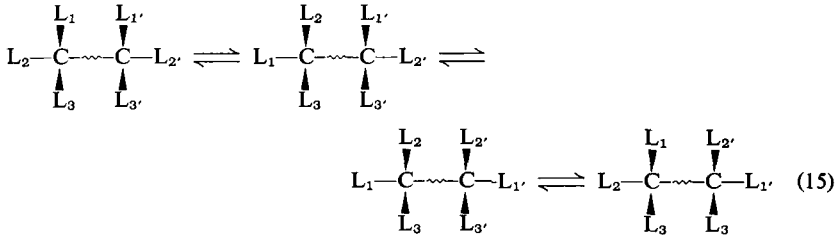
TABLE II

Ligand Constants

L	λ
H	0
CH_3	1
$(CH_3)_3C$	1.45
$(C_6H_5)_3C$	1.70
	1.83
C_6H_5	1.24
2,4,6-$(CH_3)_3 \cdot C_6H_2$	1.55
2,4,6-(cyclo-$C_6H_{11})_3 \cdot C_6H_2$	2.03
	1.28

be derived theoretically, the experimental correlation which becomes obvious in a comparison of the calculated and observed data in Table I is amazing and may be regarded as confirmation of eq. (ix).

A problem which may be treated similarly according to our model is the equilibrium of diastereoisomers [reaction (15)]. In this case the



(15)

analogy group is the direct product of the permutation groups of the unprimed and primed ligands, $S = S_3 \times S_3'$. The species subgroup $A_3 \times A_3'$ is a normal subgroup of index 4 and is contained in the group

$$N = \{A_3 \times A_3'; (A_3 \times A_3') \cdot (12)(1'2')\}$$

which is a normal subgroup of index 2 in S. It is worth mentioning that in the species group some of the elements represent rotations of the whole molecule, but this does not affect the validity of our general considerations. According to the general relation (vii) we obtain:

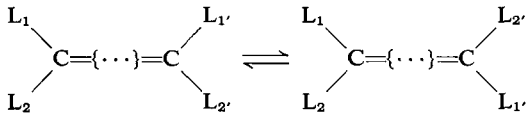
$$\delta'' \ln c_{RR}c_{SS}/c_{SR}c_{RS} = 2\rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)(\lambda_{1'} - \lambda_{2'})(\lambda_{2'} - \lambda_{3'})(\lambda_{3'} - \lambda_{1'})$$

(The factor 2 is introduced for formal reasons.) Since the species S_{RR} and S_{SS}, or S_{SR} and S_{RS}, respectively, are enantiomers, the stereoselectivity problem is completely described and we have:

$$\ln c_{RR}/c_{SS} = \ln c_{SR}/c_{RS} = 0$$

$$\delta'' \ln c_p/c_n = \rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)(\lambda_{1'} - \lambda_{2'})(\lambda_{2'} - \lambda_{3'})(\lambda_{3'} - \lambda_{1'}) \quad \text{(xi)}$$

The last example we want to discuss, reaction (16), is the thermodynamic equilibrium of *cis–trans* isomers.



(16)

Here we obtain eq. (xii)

$$\ln c_{cis}/c_{trans} = \rho(\lambda_1 - \lambda_2)(\lambda_{1'} - \lambda_{2'}) \quad \text{(xii)}$$

with "*cis*" referring to the *cis*-relationship of the ligands L_1 and $L_{1'}$.

All these examples of stereoselectivity problems belong to category *a*, i.e., the respective λ-polynomials are chirality products. Accordingly, the zeroes of the polynomial in eq. (ix) characterize vanishing chirality of the chirality center determining the stereoselectivity and indicate enantiomerism of the reaction products, as well as of the corresponding transition complexes due to the identity of two ligands. The zeroes of eq. (x) result exclusively from both species being equal in the equilibrium reaction (15). The polynomial of eq. (xi) shows that equal concentrations of a pair of species results only when the species are enantiomers or become identical due to the achirality of one or both "chirality centers." Finally, according to eq. (xii) the concentration ratio of the equilibrium reaction (16) becomes 1 if and only if the *cis* and *trans* species are identical.

Since we only find reaction classes of category *b* which are of minor chemical interest, there is no need for discussing examples.

Acknowledgment

We should like to thank Prof. G. L. Hofacker for assistance in translating the German manuscript.

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Chirality Due to the Presence of Hydrogen Isotopes at Noncyclic Positions

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I. INTRODUCTION

Soon after the discovery of deuterium by Urey in 1932 (1), organic chemists became interested in the problem of whether compounds whose dissymmetry or "chirality" (see Sect. II) is due to the replacement of one or more hydrogen atoms by deuterium can be obtained in optically active form. Compounds of this type may be divided into two categories, those in which the deuterium atom is directly attached to the "chiral center" (type **1**), and those in which chirality is caused by a more remote substitution of hydrogen by deuterium (type **2**). Although all the attempts at obtaining compounds of type **1** or **2** in optically active form made prior

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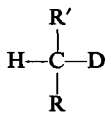
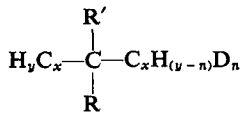
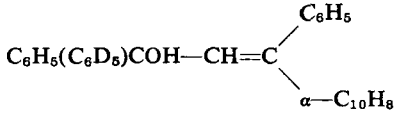


(1)

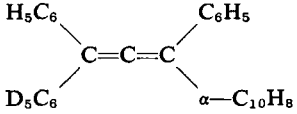


(2)

to 1948 failed or remained inconclusive (2–16), it is now known (see below) that both types do, in fact, exist in enantiomeric forms which usually rotate polarized light. It may therefore be of interest to speculate why so many attempts by some of the leading chemists of the day were unsuccessful. Many of the early attempts involved resolution of racemic deuterium compounds by the classical method of crystallization of diastereoisomeric derivatives (3,4,6,8,13,16), and while this method has more recently (in one single instance) been reported to be successful (17), it cannot in general be expected that diastereoisomers which differ only in the relative placement of one or several hydrogen and deuterium atoms would be separable by crystallization. In fact, in one of the classic studies (6) it was reported that the presumably diastereoisomeric catalytic deuteration products of diethyl maleate and diethyl fumarate (diethyl *meso-* and *dl-*α,α'-dideuteriosuccinate and the acids obtained therefrom by saponification) were not palpably physically distinct.* Other studies foundered because they relied on reactions which are now known to involve racemization prior to incorporation of deuterium [such as the reaction of RR'CHMgBr with D_2O (2) and presumably also the reaction of $C_6H_5CHBrCOOH$ with C_6D_6 in the presence of zinc (8)]. Of various attempts to obtain active deuterium compounds by asymmetric synthesis (5,12,14,15), one, the dehydration (15) of the racemic carbinol



to the potentially active allene



by means of active camphorsulfonic acid, was condemned to failure *a priori*, since it is not to be expected that two transition states which differ

*Physical examination, in 1936, did not include examination of the infrared spectrum, since instruments for such examination were not then commercially available. In fact, the infrared spectra of the diastereoisomeric α,α'-dideuteriosuccinates are distinct: C. R. Childs and K. Bloch, *J. Org. Chem.*, **26**, 1630 (1961).

only in the relative position of a C_6H_5 and a C_6D_5 group would be traversed at appreciably different rates.* The cause for failure in two of the other cases (5,14) is less obvious; these cases involve catalytic deuteration of optically active (resolved) carbinols $C_6H_5CHOHCH{=}CH_2$ and $C_6H_5CH{=}CHCHOHCH_3$ to the corresponding saturated carbinols $C_6H_5CHOHCHDCH_2D$ and $C_6H_5CHDCHDCHOHCH_3$ in which the "classical" chiral center (carbinol) was then destroyed by oxidation to the ketones $C_6H_5COCHDCH_2D$ and $C_6H_5CHDCHDCOCH_3$ which were purified through crystalline derivatives. Neither of these ketones was significantly optically active. It should be noted that in these instances the supposed asymmetric deuteration of the double bond has nothing to do with the deuterium as such, but relies on the fact that the two faces of the double bonds in each active carbinol are diastereotopic (cf. p. 136) (20) and therefore catalytic reduction from the two faces is not expected to be equally fast; the deuterium merely serves to "document" the difference in approach from the two sides. The two diastereoisomers of RCHOHCHDR′ should therefore have been obtained in unequal amounts and, upon oxidation to RCOCHDR′, one enantiomer should have predominated to the same extent that one of the diastereoisomers predominated in the precursor. That the scheme nevertheless failed may be explained by one of four reasons: (*1*) The catalytic reduction itself is not stereoselective or the selectivity is very low.† (*2*) Two diastereoisomers are formed but are equilibrated over the hydrogenation catalyst by a process of hydrogenation—dehydrogenation.‡ The equilibrium ratio would obviously be close to unity, since the two diastereoisomers differ only by interchange of an H and a D. In addition, exchange would give rise to scrambling of H and D and probably to overdeuteration. This could be readily checked by modern mass spectrometric or NMR methods but was not easy to establish in the late 1930's. (*3*) Racemization (and deuterium exchange) took place during or after oxidation. This is plausible with $C_6H_5COCHDCH_2D$, but with $C_6H_5CHDCHDCOCH_3$ one of the two chiral centers of the RCHDR′ type should be preserved even after exchange.

*Recently the reaction of an optically active RCHDOH with the anhydride of racemic $C_6H_5CH(C_2H_5)COOH$ has been studied (18); the stereoselectivity of this process is such that the recovered acid has of the order of 0.5% of its maximum rotation. If the optical yield (19) in an asymmetric synthesis of an active deuterium compound (specific rotation not likely to excede 5°) were comparable, the rotation could not be observed.

†The point could be checked by hydrogenating a molecule of the type $RCHOHC(C_2H_5){=}CH_2$ and analyzing the ratio of diastereoisomers formed.

‡The fact that the phenyldideuterioethylcarbinol itself had only about 20% of the maximum rotation suggests that considerable equilibration through dehydrogenation–hydrogenation took place during the catalytic reduction.

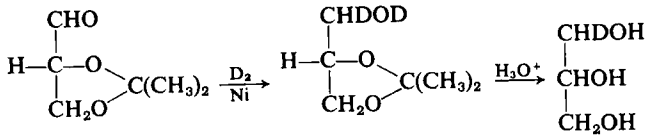


Figure 1

(*4*) The compounds were, in fact, optically active, but the rotation was too low to be observed. This explanation is a likely one in the case of $C_6H_5CHDCHDCOCH_3$ where the reported (14) rotation was 0.01° in a 0.25-dm tube, and while this value was not considered significant (14), it may correspond to a specific rotation of the order of 0.2° if the stereoselectivity in the deuteration of the active carbinol was of the order of 20%; the value would be even higher if the carbinol was not completely resolved.

Even more surprising is the failure to obtain an optically active compound in the synthesis shown in Figure 1 (12). Asymmetric synthesis at C-1 might have been expected to be successful in this case and the resulting glycerol-1-*d* should have been optically active; in fact, however, it was not. [$\alpha_D = 0.00 \pm 0.01°$ ($l = 0.5$ dm) at four different wavelengths.] Here, again, H–D (or racemizing D–D) exchange at C-1 may be to blame; the rotation due to chirality at C-2 may have been too small to be observed.

Another surprising failure is the synthesis from optically active precursors shown in Figure 2 (11). Once again the long duration of hydrogenation (80 hr) may have led to H–D exchange and resulting concomitant racemization.

Figure 3 shows another attempt at obtaining an optically active deuterated compound (this time of type **2**) from a resolved precursor (10a). The observed rotation of the product (0.019° for the neat liquid in a 1-dm tube) may well have been real, but, in view of its smallness, no definitive conclusions were drawn from the experiment. A similar situation pertains to the corresponding ethyl compound, $C_2H_5CH(CH_3)CH_2D$ (10b).

A few other attempts at preparing optically active deuterium compounds were inconclusive because one could not be sure that the activity in the compound obtained was not due to a contaminant. In this category falls the synthesis of camphane-*2*-*d* from the Grignard reagent prepared from bornyl chloride and D_2O (Fig. 4, left). The product was slightly active, but so was the camphane (achiral!) obtained in a control experiment with H_2O (9). In contrast, the camphane-*2,3*-d_2 obtained by catalytic

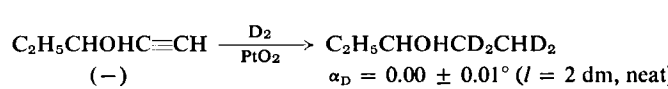


Figure 2

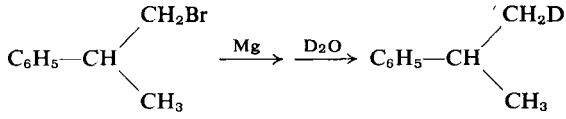


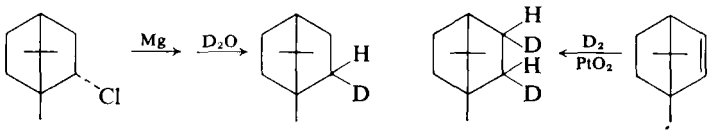
Figure 3

deuteration of optically active camphane (Fig. 4, right) was stated to be inactive (7). However, the observed rotation of 0.02° corresponds to a specific rotation of 0.13° and, in the light of the later work by Alexander (21) (see below), may have been quite real.

The deuteration of active (+)-*trans*-2-menthene, carried out in 1948 (21), did, in contrast, give a dideuteriomenthane (Fig. 5) of the clearly measurable activity of −0.14° (pure liquid, 2-dm tube), corresponding to a specific activity of 0.09°. Since hydrogenation of (+)-*trans*-2-menthene gave inactive *trans*-menthane and since the activity of the deuterated product survived treatment with hydrogen and nickel, oxidation with permanganate, washing with sulfuric acid–nitric acid, and boiling over sodium, it may be assumed that the activity was intrinsic to the deuterated menthane and that the synthesis shown in Figure 5 does, in fact, constitute the first definitive instance where an optically active compound of type **1** was obtained. (It should be noted, however, that menthane-*2,3-d*$_2$ at the same time corresponds to type **2**.)

In the following year, the ability of a compound of type **1** to rotate the plane of polarized light was proved beyond all reasonable doubt when the reduction of optically active α-chloroethylbenzene with lithium aluminum deuteride (22) gave rise to α-deuterioethylbenzene of an observed activity of 0.51° in a 2-dm tube. The chemical transformations shown in Figure 6 leave little question about the purity, if not of the ethylbenzene-α-*d* itself, at least of that of the derived *p*-acetyl compound which was also optically active (22).

In the same year, active menthane-*2-d*, $[\alpha]_D^{25}$ −0.09°, was obtained by the $LiAlD_4$ reduction of (−)-2-menthyl tosylate (Fig. 5) (23). Shortly thereafter, a compound of type **2** was obtained in an optically active form



Active but impure

$\alpha = 0.02 \pm 0.01°$
(l = 1 dm, c ≈ 15% in ethyl acetate)

Figure 4

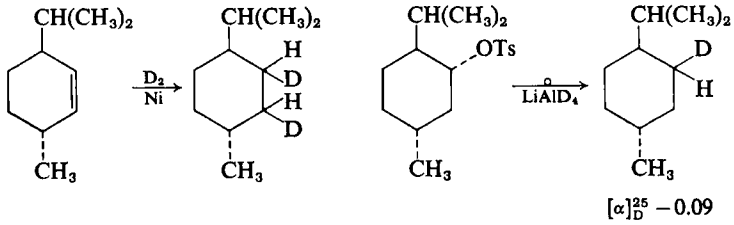


Figure 5

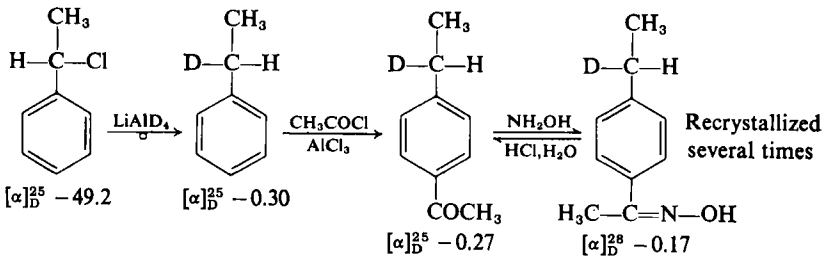
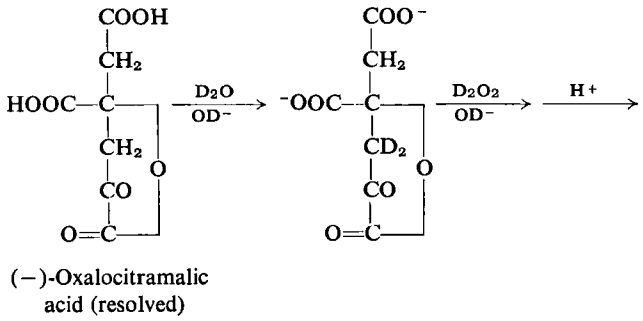
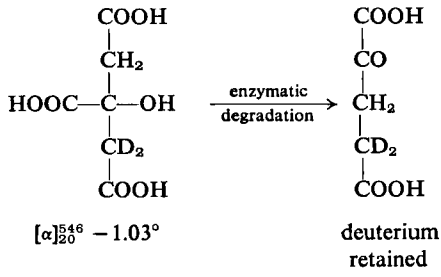


Figure 6





(3)

Figure 7

(24a) by the process shown in Figure 7.* The α,α-dideuteriocitric acid (**3**) had a specific activity of 1.03° and its ammonium molybdate complex had the remarkably high specific activity of 33.6°. The suggestion has been made (25) that the high activity is due to the fact that the citric acid forms a molybdate complex with a light absorption maximum near the wavelength of the measurement of the optical rotation so that the measurement of rotation was taken near the extremum of a Cotton effect where rotations are known to be high (26), but this remains to be proved. An additional interesting and important outcome of the study of **3** was the finding (24b) that its enzymatic degradation to oxaloacetic acid would lead to either complete retention (Fig. 7) or complete loss of deuterium, depending on which enantiomer served as the substrate. The two acetic acid substituents (CH_2COOH and CD_2COOH) in **3** are "enantiotopic" (20) and therefore distinct *vis-à-vis* a (chiral) enzyme. The enzymatic study (24b) thus constituted the first of a large number of important papers in which compounds of type **1** or **2** were used to investigate biochemical reaction mechanisms; we shall return to it later in this chapter.

A rather simple compound of type **2** obtained in optically active form (27a) is 2-propanol-*1*, *1*, *1*-d_3, synthesized in several steps from optically active methyl lactate:

$$(-)\text{-}CH_3CHOHCOOMe \longrightarrow CH_3CH(OCH_2Ph)COOMe$$
$$\longrightarrow CH_3CH(OCH_2Ph)CD_2OH \longrightarrow CH_3CH(OCH_2Ph)CD_2OBs$$
$$\longrightarrow CH_3CH(OCH_2Ph)CD_3 \longrightarrow (+)\text{-}CH_3CHOHCD_3,$$
$$[\alpha]_D^{27} + 0.2°,\ [\alpha]_{365}^{25} + 1.2°$$

Other known chiral compounds of type **2** are $C_6H_5CH(CH_3)CD_3$ (27b) and CH_3SOCD_3 (27c).

In 1953, two important studies appeared, one (28) concerned with the asymmetric reduction of butanal-*1*-*d*, $CH_3CH_2CH_2CDO$ with the optically active 2-octanol derivative $CH_3CHO(MgBr)C_6H_{13}$ to give optically active butanol-*1*-*d*, $CH_3CH_2CH_2CHDOH$, and the other (29) involving the enzymatic reduction of ethanal-*1*-*d*, CH_3CDO, with NADH (the reduced form of NAD^+, nicotinamide adenine dinucleotide) to optically active ethanol-*1*-*d* and the corresponding asymmetric enzymatic reduction (29) of acetaldehyde with NAD^2H. The former study set the stage for a number of subsequent investigations of reaction mechanisms at primary carbon, whereas the latter gave rise to an extensive field of research dealing with the stereochemistry of enzyme reactions and biosynthetic processes. It is these two topics, especially the latter, which will form the major subject matter of this chapter.

*The compounds in Figure 7 are shown in the absolute configuration now known to be the correct one (cf. p. 192 ff).

Before concluding this introduction, it should be mentioned that some theoretical work on the optical activity of compounds of type RCHDR′ has also been undertaken. The original calculation (30) made prior to any experiments implied negligible activity but did not have a very sound theoretical basis. Later calculation (31) based on the Kirkwood theory of optical activity (32) did correctly assess the configuration and approximate specific rotation of $C_6H_5CHDCH_3$ and $CH_3CHDCH_2CH_3$.

II. NOMENCLATURE

It will be assumed, in the sequel, that the reader is familiar with the nomenclature of stereochemistry (20,25,33,34); however, a brief survey and review, especially of the more recent terminology, may be in order.

We will use the term "chiral" (= "handed") for molecules capable of existing in enantiomeric (i.e., mirror image) forms. This term is thus synonymous with "dissymmetric," but not with "asymmetric." Chiral compounds may have axes of symmetry and may belong to the symmetry classes $\mathbf{C}_n$ or even $\mathbf{D}_n$ as well as $\mathbf{C}_1$ (33). The term "chirality" will be used to denote not only the property of a molecule of being chiral, but also the two opposite kinds of handedness found in enantiomers; thus enantiomers have opposite chirality. Specification of chirality (or configuration) is made by means of the symbols *R* and *S* (35); it is important to recall that these symbols are unrelated to rotation and are defined without regard to any genetic relationship of configurationally related series. In the present chapter the order of precedence (35) T > D > H will frequently be used.

Whereas "enantiomers" are stereoisomers which are mirror images, we use the term "diastereoisomers" for *any* stereoisomers which are not related as object and image. Most of the diastereoisomers to be discussed will have two (in a few cases more than two) chiral centers, and when we deal with *dl*-pairs (racemic modifications) of such species, we will use the terminology shown in Figure 8. When we deal with individual enantiomers

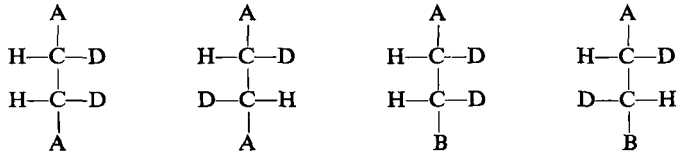


Figure 8

of the compounds shown in Figure 8, we shall usually specify the chirality at each chiral atom; thus the particular enantiomer of the racemic form shown in the second formula in Figure 8 would be *R,R*, assuming that A has a higher atomic number than carbon. In cases where the *erythro-threo* nomenclature is not readily usable (for example, in the case of molecules of the type CabcCdef) we shall use the systematic nomenclature for racemates (35). Systematic names may also be used as alternatives to *erythro* and *threo*; thus, assuming that A and B are atoms of higher atomic number than carbon, the *dl-erythro* form corresponding to Figure 8 would alternatively be called 1*RS*,2*SR*, whereas the *dl-threo* isomer would be called 1*RS*,2*RS*.

The term "enantiotopic"* (20) is used for two chemically equal atoms or groups which, stereochemically speaking, bear a mirror image relationship in a molecule, such as the two methylene hydrogens in ethanol (Fig. 9). There are two ways of deciding whether two such groups are stereochemically equivalent ("homotopic") or whether they are enantiotopic. One is to search for axes of symmetry in the molecule and, if there are such axes, to check whether rotation about a symmetry axis will bring the two groups in question into superposition. If it does, the groups are homotopic (equivalent); if it does not (or if there is no axis of symmetry), the groups are enantiotopic (or diastereotopic, see below). A simpler criterion (Fig. 9) is to replace first one and then the other of the two atoms or groups by a different atom or group and see whether the two resulting new species are identical or enantiomeric. If they are identical, the groups in question are equivalent; if they are enantiomeric, the groups in question are enantiotopic. In this chapter we will often be concerned with the replacement of hydrogen by deuterium, and thus the easiest check for enantiotopic hydrogens in RCH_2R' is the demonstration that their (separate) replacement by deuterium gives rise to enantiomeric RCHDR′ compounds (cf. Fig. 9).

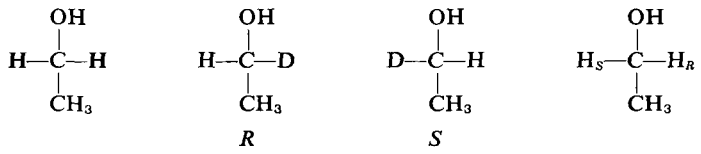
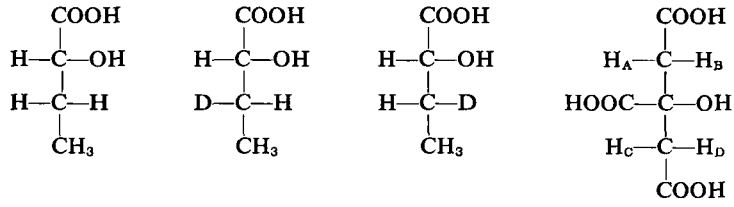


Figure 9

*The terms "enantiotopic" and "diastereotopic" supersede "enantioscopic" and "diastereoscopic" which were also used for a brief time.



(*R*)-Malic acid (diastereotopic hydrogens)

Diastereoisomeric β-deuterated (*R*)-malic acids

Citric acid

Figure 10

"Diastereotopic groups" (20) are constitutionally equal atoms or groups whose respective replacement will give rise to diastereoisomers. The methylene hydrogens of (*R*)-malic acid (Fig. 10) are of this type; their separate replacement by deuterium gives rise to two diastereomeric deuteriomalic acids (Fig. 10). Citric acid is an interesting example in which H_A and H_C (or H_B and H_D) are enantiotopic and H_A and H_B (or H_C and H_D or H_A and H_D or H_B and H_C) are diastereotopic. The two CH_2COOH groups as a whole are also enantiotopic; this is the reason why they are not equivalent in enzymatic degradation (Fig. 7).

Just as a center of the type Cabcd—which gives rise to enantiomers or diastereoisomers—is called a "chiral center," so a center of the type Caabc—which bears enantiotopic or diastereotopic groups—is called a "prochiral" (or "pro-chiral") center (36). It will be noted that replacement of one of the hydrogen atoms at a prochiral center CH_2ab by a hydrogen isotope gives rise to a chiral center CHDab or CHTab.

Sometimes we wish to state that two atoms or groups are not homotopic (equivalent) without, however, committing ourselves as to whether the groups are enantiotopic or diastereotopic. In such a case we shall designate the atoms or groups in question "heterotopic."*

*The term is particularly useful in certain enzymatically controlled reactions in which the enzyme distinguishes between given substituents at a prochiral center without caring about whether there is or is not another truly chiral center in the molecule. If there is not, then the groups at the prochiral center are enantiotopic, but if there is, they are diastereotopic. In any case, they are heterotopic. H. Hirschmann and K. R. Hanson, in consultation with K. Mislow, have also adopted a common term for these two categories, viz., "stereoheterotopic," (personal communication). They wish to use "heterotopic" as a more general term comprising both the above class and the class of constitutionally different environments ("constitutionally heterotopic groups"), for example, the methylene protons at C-2 and C-3 in butanol-1, $CH_3CH_2CH_2CH_2OH$.

It will often be convenient to have symbols to distinguish heterotopic hydrogen atoms (or other ligands) that are attached to the same atom. We shall call that hydrogen which, when replaced by deuterium, gives rise to a chiral center RCHDR′ of *R*-configuration the *pro-R* hydrogen and denote it by H_R, and, correspondingly, we shall call the hydrogen which, when replaced by deuterium, gives rise to a center of *S*-chirality *pro-S* (symbol H_S). These replacements and symbols are illustrated in Figure 9 for an achiral molecule with a single prochiral center. A more general naming procedure (which is clearly equivalent to the previous one for the case of heterotopic hydrogens) is the following (36): Arbitrarily give one of the heterotopic ligands at the prochiral center Sequence Rule preference over the other in the Cahn-Ingold-Prelog system (35) and then determine the configurational symbol of the hypothetical chiral center so produced by that system. (It is immaterial which ligand is chosen.) If the appropriate configurational symbol is now *R*, then the designated ligand L is the *pro-R* ligand (denoted as L_R) but if the symbol is *S*, then the designated ligand is named *pro-S* (denoted as L_S). (The use of the names *pro-R* and *pro-S* serves to emphasize that it is the ligand which is being specified by reference to a chiral center and not the chirality, if any, of the ligand itself which is under consideration. Thus we shall avoid such terms as "*R*-hydrogen" or "*S*-hydrogen.")

In discussing enzymatic reactions, we shall be particularly interested in the use of stereospecifically labeled compounds to determine the steric course of a reaction when unlabeled substrates are employed. It follows from the above definition that if deuterium is quantitatively removed from a center which has *R*-chirality because of the presence of this isotope, we can infer that it is the *pro-R* hydrogen (H_R) of the corresponding prochiral center in the unlabeled compound which is removed. For example, with reference to Figure 9, if a stereospecific oxidation reaction removes the deuterium from (*R*)-ethanol-*1-d*, it follows that H_R is the hydrogen removed in the corresponding oxidation of ordinary (unlabeled) ethanol.

We shall use this type of argument repeatedly without any further explanation of the symbols involved. It might be emphasized that, because the Sequence Rule procedure treats isotope-generated chirality (Fig. 9, middle) with the same status as chirality due to any other source, we *cannot* speak, for example, of C-1 in (*R*)-ethanol-*1-t* as being prochiral (it is chiral) and we *cannot* call the deuterium atom in (*R*)-ethanol-*1-d* (Fig. 9) D_R even though it corresponds to H_R in the unlabeled analog.

Prochirality exists not only in the cases of atoms of the type Caabc (sometimes called "*meso*-atoms"), but also in the case of double bonds. For example, it is easily seen (Fig. 11) that the addition of a phenyl Grignard reagent to acetaldehyde will give rise to opposite enantiomers

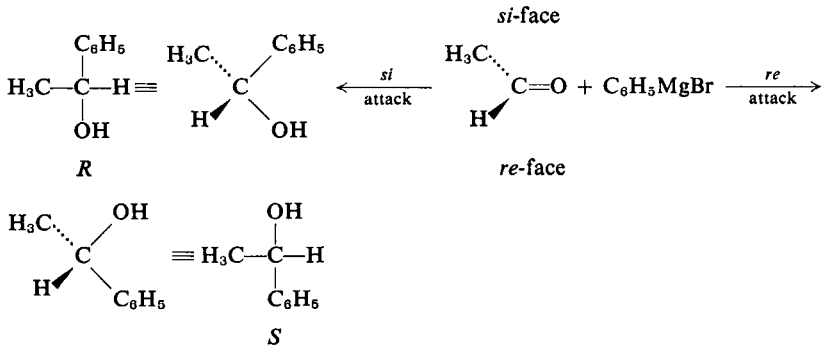


Figure 11

of phenylmethylcarbinol, depending on whether the top or bottom face of the acetaldehyde is approached. This type of prochirality exists in any grouping of the type RR'C=X. Here the faces are named by looking at the prochiral group from the side of the face in question and by applying the Cahn-Ingold-Prelog Sequence Rule to the substituents R, R', and X: If the arrangement is clockwise, the symbol is *re* (for *rectus*), if counterclockwise, it is *si* (for *sinister*) (36). Thus the top face of the acetaldehyde molecule as arranged in Figure 11 is *si* and the bottom face *re*; *si*-attack of phenyl Grignard gives (*R*)-phenylmethylcarbinol, *re*-attack gives the (*S*)-carbinol.

In the case of a C—C double bond, both ends may be subject to the *re–si* specification and one may have *re–re* and *si–si* faces or (in other cases) *re–si* and *si–re* faces. Maleic and fumaric acid (Fig. 12) illustrate this kind of nomenclature. (In contrast to Fig. 11, in Fig. 12 the plane of the double bond is the plane of the paper and is being viewed from the front side.) It

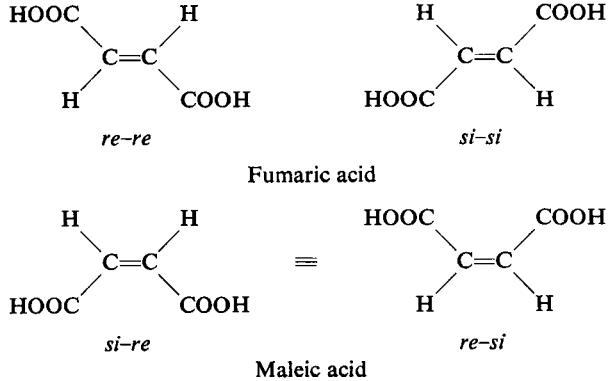


Figure 12

might be noted that in maleic acid, because of the presence of a C_2 axis in the plane of the molecule, the two faces are, in fact, equivalent; this is not true in the *trans* isomer (fumaric acid) nor in the methyl homolog (citraconic acid, *cis*).

To name olefins, we shall usually employ the common *cis–trans* nomenclature. However, occasionally this nomenclature is ambiguous (for example, in olefins of the type abC=Ccd); in such cases we shall use systematic nomenclature (37), arranging the substituents, a,b (and also c,d) by the Cahn-Ingold-Prelog sequence. Then when the ligands of higher precedence (a,c) are on the same side, we use the symbol "*Z*" (*zusammen*), but if they are on opposite sides, we use "*E*" (*entgegen*) (37). Thus maleic acid would be (*Z*)-butenedioic acid and fumaric acid would be (*E*)-butenedioic acid.

III. GENERAL CONSIDERATIONS. SCOPE

Chemical resolution is, in general, not applicable to compounds which owe their chirality to the presence of deuterium or tritium (see, however, ref. 17).* This is because chemical resolution of enantiomers depends on the conversion to diastereoisomers followed by separation of the latter, and the interchange of two hydrogen isotopes at one chiral center in such diastereoisomers, while usually producing spectral differences, rarely leads to separability. Therefore, essentially only two methods are available for producing the desired compounds in chiral form—stereospecific synthesis from chiral precursors and asymmetric synthesis or destruction. While synthesis of a chiral compound of the R_HCHXR_D type, such as $CH_3CHOHCD_3$, from a chiral precursor or synthesis of one chiral RCHDR′ compound from another in principle poses no problem, stereospecific synthesis of RCHDR′ or RCHTR′ from a chiral precursor of the type RR′CHX (or RR′CDX or RR′CTX) must, of necessity, involve a reaction *at* the chiral center. Such reactions frequently involve partial racemization; moreover, it is not always clear whether they involve retention or inversion of configuration, such information often having to be deduced from precedent or from mechanistic considerations. Asymmetric synthesis and destruction usually leave even greater doubt as to the configuration of the product; and while optical purity is usually as close to 100% as one can detect in enzymatic synthesis or destruction, ordinary chemical asymmetric synthesis tends to give material of relatively modest

*For the purpose of this statement we exclude kinetic resolution and the closely related methods of asymmetric synthesis and destruction from the term "chemical resolution"; in other words, we exclude methods depending on diastereoisomeric transition states rather than diastereoisomeric ground states.

optical purity, usually 50% or less. Thus it becomes clear that the determination of configuration plays a very important part in the study of compounds owing their chirality to hydrogen isotopes, be these compounds of ordinary synthetic or biosynthetic origin. In addition, determination of optical purity is relevant in the case of chemically synthesized RCHDR′ and RCHTR′ compounds.

Available methods for determining optical purity have been summarized elsewhere in this series (19). Those which have been applied to RCHDR′ compounds are the NMR method of Raban and Mislow (38),* the asymmetric esterification method of Horeau and Nouaille (18), and, most important of all, enzymatic methods. In the NMR method (38), the given enantiomer of RCHDR′ is chemically transformed, by reaction with an optically active (and optically pure) auxiliary reagent ACHXB, into a new compound R—CHD—R′... A—CHX—B, the nature of the chemical connection depending on the nature of RCHDR′ and ACHXB. If the starting material RCHDR′ is a pure enantiomer, only a single diastereoisomer of R—CHD—R′... A—CHX—B will be formed (assuming that there is no epimerization in the reaction leading to it). However, the presence of the second enantiomer in the starting material will lead to the formation of a mixture of two diastereoisomers in a ratio which reflects the extent of enantiomeric contamination (assuming absence of epimerization or kinetic resolution). In principle, the two diastereoisomers should have distinct NMR spectra in which the ratio of pertinent signals is a direct measure of the ratio of the two stereoisomers; in practice, calibration experiments with deliberately prepared mixtures of the two diastereoisomers are needed to determine whether the two sets of signals are, in fact, palpably distinct.

The method of Horeau and Nouaille (18) is applicable to chiral alcohols of the type RCHDOH and involves esterification of such alcohols with racemic α-phenylbutyric anhydride. The sign of rotation and optical yield of the α-phenylbutyric acid produced in the reaction $[C_6H_5CH(C_2H_5)CO]_2O$ + RCHDOH → $C_6H_5CH(C_2H_5)COOCHDR$ + $C_6H_5CH(C_2H_5)COOH$ are an indication of the configuration and optical purity, respectively, of the RCHDOH alcohol. The success of the method has been remarkable, considering that it depends on kinetic resolution caused by a compound which owes its chirality only to the difference between H and D and that the assumption is made that not only the sign of rotation of the α-phenylbutyric acid, but also the extent of resolution are independent of the nature of the R group of the alcohol. In the four cases where the method has been used (*n*-butanol-*1*-*d*, neopentyl-*1*-*d*

* The same method has been independently developed by H. Gerlach (181); cf. p. 226.

alcohol, hexanol-*1-d*, and benzyl-α-*d* alcohol) it has given results consistent with those obtained in other ways.

In contrast to the above methods,* the enzymatic method is applicable to both RCHDR′ and RCHTR′ compounds; in fact, it is the only method now applicable to the determination of optical purity of the latter. In principle, any chiral reagent when reacting with the enantiotopic hydrogens in RCH_2R' will show a preference for one over the other (20), but only in the case of enzyme reactions is the preference frequently so extreme that only one hydrogen is attacked and the other, in essence, is not. This means, of course, that in a labeled substrate, RCHDR′ or RCHTR′, the light isotope will react in one stereoisomer and the heavy one in the other. "Reaction" here may be removal by exchange with H_2O, transfer to the enzyme, intramolecular rearrangement to some other part of the same molecule, or transfer to some other part of a new molecule formed by reaction at the RCH_2R' site. In any case, it can usually be readily decided whether H or D (or T) has reacted by determining the amount of D (or T) in the recovered substrate and/or the enzyme or coenzyme, or by determining the location of the D or T in the transformed substrate through degradation or (in the case of D) through mass spectrometry or NMR spectroscopy. For example, in the oxidation of CH_3CHDOH to acetaldehyde by yeast alcohol dehydrogenase in the presence of the coenzyme nicotinamide adenine dinucleotide (NAD^+) one enantiomer yields CH_3CDO by transfer of hydrogen to the NAD^+, whereas the other yields CH_3CHO by transfer of deuterium; *mutatis mutandis* the same argument, of course, applies to CH_3CHTOH. If the substrate is enantiomerically impure CH_3CHDOH, some hydrogen and some deuterium is transferred to the coenzyme and measurement of the relative amounts of the two isotopes transferred permits assessment of enantiomeric purity. (See p. 144 regarding possible complications by isotope effects.) Numerous examples of the applications of these methods will be found in the text.

Only a limited number of the classical methods of determining configuration (39) are applicable to RCHDR′ and RCHTR′ compounds. The most generally useful one is the method of chemical correlation through transformations not involving the chiral center, for example, correlation of CH_3CHDOH with HOOCCHDOH through transformation of the COOH group to CH_3 (p. 159). This method clearly requires the availability of some reference compounds. Such standards have been obtained by application of the following additional methods.

*In principle, a modification of Horeau's method involving detection of increase or decrease of T level of RCHTOH (necessarily admixed with RCH_2OH) following partial esterification with optically active α-phenylbutyric anhydride might be used to determine optical purity of tritiated alcohols.

(*1*) A neutron diffraction analog of the Bijvoet method of determining absolute configuration by anomalous X-ray scattering. This method has been applied to glycolic-*d* acid.

(*2*) Correlations through diastereoisomers containing a chiral center of the RCHDR′ type and a conventional chiral center of the ACHXB type of known configuration and in which the configuration of the two centers can be connected by NMR (or possibly by some other *physical* method).* This method has been applied to ethanol-*1-d* (p. 157).

(*3*) Correlation involving reactions of known stereochemistry at the chiral center. The most common of these reactions are epoxide ring openings with deuteride and reactions of tosylates and bromides with deuteride. Inversion is assumed to occur in these particular cases.

It might be noted that only method *3* is available for tritium compounds, inasmuch as tritium is always used at the tracer level. However, in addition to the earlier-mentioned correlation method for determining configuration, the configuration of chiral RCHTR′ compounds may sometimes be determined through comparison with analogous RCHDR′ compounds. We shall return to this point below.

Since configurational arguments based on assumed reaction mechanisms and stereochemical analogies are rarely airtight, it is fortunate that many of the configurational correlations to be discussed which are based on this method have been effected in more than one way. In this fashion, a "self-consistent network" of configurational assignments and correlations is established and the assignment for a given compound no longer depends on the stereochemistry of just one reaction. In other words, to change the configurational assignments of all the chiral RCHDR′ compounds involved in such a network one would have to assert that the stereochemical course of a large number of reactions involved in the network is the opposite of that commonly assumed.

A rather important problem in the determination of configuration of RCHDR′ and RCHTR′ compounds is the matter of characterization. Ordinary optically active compounds are routinely characterized by their rotation or rotatory dispersion long before the task of determining their configuration is undertaken. In contrast, chiral RCHDR′ and RCHTR′ compounds are frequently synthesized in the first instance in such a way that their configuration is known (by correlation with that of other compounds, *vide supra*), and the question then arises as to how to characterize and recognize the enantiomer of a given configuration. In principle, optical

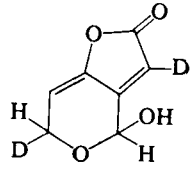
*A little reflection will convince the reader that the method of *chemically* correlating two different chiral centers in a molecule (ref. 25, p. 97–106) cannot be applied to RCHDR′, since RCHDR′ cannot be conformationally anchored in a ring and still have a functional group left for chemical correlation.

rotation can be used for chiral RCHDR′ compounds, since such species generally do rotate the plane of polarized light (21–23), although there are exceptions, such as neopentyl-*1-d* alcohol which has no measurable rotation at any wavelength investigated (see p. 164). In practice, however, the rotations of RCHDR′ compounds at the sodium D line are small, usually of the order of 1–2° (observed rotation for the neat liquid in a 1-dm tube), and if the amount of material is limited (as often happens in enzymatic studies), so that only a dilute solution can be investigated, it may not be possible to record the specific rotation reliably. In particular, there is the danger that a spurious rotation may be caused by small amounts of a highly rotating chiral impurity.* In some cases, such as in the case of carboxylic acids or aromatic compounds (40) where a chromophore absorbing above 200 nm is close to the chiral center, substantial optical rotatory dispersion may be observed, and high and significant rotations in the 250-nm region may then be measured. In two cases—succinic-*d* acid (41) and butyl-*1-d* acetate (42)—Cotton effects have actually been reported with extrema in the 220-nm region. In all such cases ORD is a convenient tool for characterization.†

In reporting specific rotations for optically active deuterated compounds whose chirality is due solely to deuterium, it is necessary, of course, to correct for isotopic purity (which is rarely in excess of 95%) by multiplying the observed rotation by 100/isotopic purity, inasmuch as the RCH_2R' impurity in RCHDR′ will be optically inactive.‡

*It is clear that 1% of an impurity of [α] 100° will cause a spurious rotation of an apparent [α] of 1° in the deuterated material.

†The remarkably high molecular rotation $[M]_{300} = +3800°$ recently reported for the dideuterated patulin (i) in the vicinity of the extremum of a Cotton effect (A. I. Scott and M. Yalpani, *Chem. Commun.*, **1967**, 945) is in error (personal communication); the actual rotation is +16°.



(i)

‡Although rotations and optical purities of RCHDR′ compounds will be frequently mentioned in this chapter (along with statements of isotopic purity), the confidence limit of such data is probably no better than ±10%. Rotations at a given wavelength depend not only on optical purity (often not reliably known) and the precision of the measurement of isotopic purity, but also on chemical purity and the conditions of the measurement (solvent, concentration, temperature).

In RCHDR′ compounds whose optical rotation is small, even at wavelengths as low as 210–220 nm, one must either prepare a derivative of high ORD (this technique does not seem to have been much used yet in this field) or resort to different methods. Rotation methods are, in any case, not useful for RCHTR′ compounds, since, for reasons of radiological safety of the observer and in order to avoid autoradiolysis of the compound, such species are always used at the tracer level so that the rotation is reduced below the observable limit by dilution with the achiral carrier material. Fortunately, the same enzymatic methods which are used to determine the optical purity of RCHDR′ and RCHTR′ (*vide supra*) can also be used to characterize such compounds. Thus, clearly, the two enantiomers of CH_3CHDOH may always be recognized (even if their rotation is not measured) by the fact that one gives up its deuterium to NAD^+ in the presence of yeast alcohol dehydrogenase and the other does not. Moreover, enzymes may be used not only to characterize RCHTR′ compounds, but also to correlate their configurations with those of the corresponding RCHDR′ compound. Thus, if (*R*)-RCHDR′ gives up its deuterium in an enzymatic reaction and (*S*)-RCHDR′ retains it, it may be safely concluded that the configuration of a specimen of RCHTR′ which gives up its tritium to the same enzyme is *R* and that of a specimen which retains its tritium under the same conditions is *S*. By way of an example, the enantiomers of ethanol-*1-t* can be readily recognized as being *R* or *S* in this way (p. 167).

Application of Brewster's rules to the rotation of compounds of the RCHDR′ type has also been valuable in reaching conclusions as to configuration (43). In this way, Brewster predicted correctly (43) that ethanol-*1-d* and butanol-*1-d* of the same sign of rotation have opposite configurations.

A few general remarks on isotope effects may be in order here, although a detailed treatment is beyond the scope of this chapter. Three cases are of particular practical importance.

Case 1. The substrate is optically and isotopically pure (this is possible only for deuterated, not for tritiated compounds) and the reaction studied is completely stereospecific. In this case possible isotope effects do not affect the composition of the product or recovered substrate, although they will affect the rate at which the two enantiomers react.

If the substrate is contaminated with unlabeled RCH_2R' (as it always will be in the case of tritiated material) but is still enantiomerically pure, the unreacted starting material may become enriched in the labeled component as the result of a primary isotope effect in those cases where the attack is on the labeled site. As far as the *product* is concerned, however, it is important to realize that the presence of RCH_2R' is irrelevant. For if RCHDR′ reacts stereospecifically at the nondeuterated site, no primary

isotope effect is to be expected* in the competition with RCH_2R'; if it reacts stereospecifically at the deuterated site, even though a primary isotope effect is to be expected, the product will, in any case, be devoid of deuterium and it is not important whether that result follows because the deuterium has been removed or because the reaction occurred preferentially with the undeuterated RCH_2R' contaminant. An analogous argument applies to tritiated substrate.

Case 2. The reaction is stereospecific but the substrate is enantiomerically impure. In this case false conclusions may be reached unless conversion of the substrate is complete.† This is easy to demonstrate by means of the example of the enzymatic dehydrogenation of RCHDOH to RCDO and RCHO. If both enantiomers of RCHDOH are present in the substrate, the operation of a primary isotope effect is likely to cause faster dehydrogenation of the enantiomer which gives up H as compared with the one which gives up D. As a consequence, in the early stages of the reaction mostly RCDO will be obtained. If the product is analyzed for deuterium at this point, the conclusion might be falsely reached that mostly one enantiomer of the substrate (the one giving up hydrogen) is present or, if it is known that both enantiomers were present but it is not known whether the enzyme is stereospecific, it might be erroneously inferred that it is not. Both types of misinterpretation can be avoided by letting the reaction go to completion, for eventually abstraction of D will catch up with abstraction of H due to depletion of one of the enantiomers in the substrate, so that, in the end, product composition will reflect substrate composition and stereospecificity of the enzyme.

Case 3. The reaction is not stereospecific. In this case, regardless of whether the substrate is optically pure or not, if there is a primary isotope effect (and this commonly happens), attack at the nonlabeled site will be preferred over attack at the labeled site. Thus RCHDR′ will be attacked mainly at the undeuterated site to give deuterated product, and RCHTR′ in a high-conversion reaction‡ will be attacked mainly at the untritiated

*A secondary isotope effect could affect the product composition slightly; fortunately, such an effect, if present, is likely to be small.

†In many enzymatic reactions equilibrium is reached considerably short of complete conversion to substrate. In such cases, additional complications may occur due to equilibrium isotope effects. These effects are likely to be negligible only when transfer of the isotopic species to and from similar atoms (e.g., from C to C) is involved.

‡When the conversion is low, intermolecular competition between RCHTR′ and RCH_2R' will almost exactly counterbalance the intramolecular competition between the H and T sites, and no enrichment of tritium in the product is to be expected. This is because for tritiated substrates the ratio of RCH_2R' (carrier) to RCHTR′ is very high.

site to give tritiated product. The result may thus give the spurious impression of a stereochemical preference for the unlabeled site. Therefore, in cases where preferential attack at the unlabeled site occurs, it is always necessary to perform a control experiment either by carrying out the same reaction with the other enantiomer (as explained above, no ambiguity attaches to a result in which the labeled site is preferentially attacked) or by carrying out the reaction with the racemate at high conversion (*vide supra*). If discrimination between the two sites is due to stereospecificity, it will, of course, not occur in the racemate (at high conversion), but if it is due to an isotope effect, it will occur in the racemate just as much as in the pure enantiomers. Comparison between racemic and enantiomeric substrates is particularly useful in those cases where lack of optical purity of a substrate or partial racemization during a degradation step leads to a stereochemically unclean result (for example, 70% of the label may be retained in one enantiomer and 10% in the other). In such cases an experiment with racemic substrate may serve as a convenient blank.

In the organization of this chapter we have attempted to present the subject matter in the most logical manner apparent to us. While we have tried to keep together chemically related compounds (such as hydrocarbons and alcohols) as far as possible, we have deviated from this practice where the subject matter appeared to demand it. Thus glycolic acid has been treated prior to alcohols because it serves as a configurational standard for ethanol; succinic acid and a number of related compounds have been treated prior to a number of terpene alcohols for the same reason. Biochemically related studies have been kept together; thus all the reactions related to squalene biosynthesis are treated in one block and all those reactions related to aldolase and isomerases in another. Although we have tried to be fair in assigning priorities, we have deviated from the historical–chronological presentation in cases where a different order seemed to make the material easier to understand. Finally, and with some regret, we have refrained from discussing details of biochemical mechanisms, not only because such discussions would have made this chapter too extensive, but also because they would have required the inclusion of much material extraneous to the question of chirality due to hydrogen isotopes.

For a similar reason, i.e., to keep this chapter within reasonable limits of length, we have omitted systematic consideration of achiral diastereoisomers of the type RCHDCHXR′ except insofar as such compounds are essential relays in the determination of configuration of chiral RCHDR′ species. In extending our decision to omit achiral diastereoisomers, we have also omitted virtually all cyclic compounds bearing CHD or CHT sites (hence the title of this chapter). This was done because such cyclic compounds are either achiral (e.g., 4-*t*-butylcyclohexane-*1-d*) or

their chirality is incidental (e.g., cholestane-3-*d*). While a number of such compounds have been synthesized, the physical, chemical, and biochemical differences between axial and equatorial deuterium are only very tenuously related to the corresponding differences between enantiomers which form the main topic of this chapter. The discussion of cyclic CHD and CHT diastereoisomers could profitably form the subject of a separate review.

We feel that the main purpose of this chapter will be to give a convenient literature survey (with some background as to nomenclature and the fundamental stereochemical concepts involved) to those specifically interested in the field while, at the same time, pointing out to organic chemists at large an important and fruitful application of the field of stereochemistry.

The literature has, as far as possible, been covered through 1967; however, since there is no systematic way of searching for chiral deuterium and tritium compounds, a number of cases have undoubtedly been missed. Several papers appearing in 1968 have been included as they have come to the attention of the authors.

General references and prior reviews of the topic are listed at the end of the chapter (p. 237).

IV. INDIVIDUAL COMPOUNDS

A. Hydrocarbons

Known optically active hydrocarbons with chirality due to the presence of deuterium are *trans*-menthane-*2,3*-d_2 (21), ethylbenzene-α-*d* (22), *trans*-menthane-*2*-*d* (23), butane-*2*-*d* (44), pentane-*2*-*d* (45), *n*-butylbenzene-α-*d* (46), 2-methylbutane-*3*-*d* (47), 2-methyl-1-butene-*3*-*d* (47), and various deuterated squalenes and other terpenoid hydrocarbons (Sect. IV-G).

The configuration at C-2 and C-3 and optical purity of *trans*-menthane-*2,3*-d_2 obtained by catalytic deuteration of *trans*-2-menthene (21) (Fig. 5) are hard to assess; the compound has no less than four chiral centers, two of them introduced during the deuteration, and is probably a mixture of several diastereoisomers. In contrast the *trans*-menthane-*2*-*d* obtained by $LiAlD_4$ reduction of menthyl tosylate (23) (Fig. 5) is probably predominantly the diastereoisomer with the *S*-configuration at C-2, since deuteride reduction of (2*R*)-menthyl tosylate should involve substantial inversion of configuration (see below). (−)-Ethylbenzene-α-*d* has been assigned (22) the *R*-configuration (Fig. 6) on the basis of an analogous assumption;

and while the configuration of the compound has not been established unequivocally, the underlying hypothesis (inversion in RX–deuteride reduction) has found independent support, as will be shown below; moreover, the assigned configuration is in agreement with the prediction based on polarizability considerations (43). Since the optical purity of the α-phenethyl chloride from which PhCHDMe was originally prepared (Fig. 6) did not exceed 47% (maximum $[\alpha]_D^{25}$ observed 103.5–104.2°) (48,49), the specific rotation of optically pure ethylbenzene-α-*d* must be in excess of ±0.63°; later estimates (46,50–52) have placed this value between 0.7 and 0.8°. This range, however, may still be a low estimate, since it does not take into account that the specific rotation of PhCHClMe may be as high as 125° (53) and makes no allowance for possible racemization in the $LiAlD_4$ reduction (*vide infra* and p. 153).

The most thorough study of configuration and optical purity has been made in the case of butane-*2-d* (44,54), stimulated by the fact that the rotation and configuration of this molecule had been calculated on a theoretical basis (31); the correlation is shown in Figure 13. The starting material, *trans*-2-epoxybutane, was estimated to be 97% optically pure and gave nearly optically pure 2-butanol-*3-d* (based on maximum rotation values in the literature) upon deuteride reduction. Since, on the basis of evidence in the literature (55), hydride reduction of epoxides proceeds with inversion, it is assumed that the deuteriobutanol **4** is the *erythro*-isomer. There is corroborating evidence for this assumption, e.g., based on the

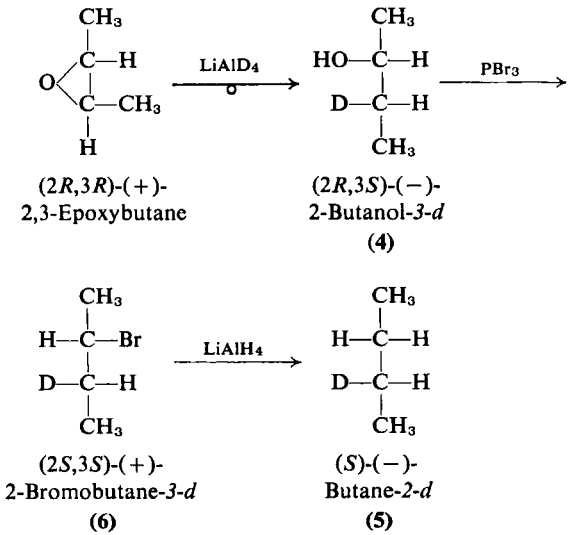


Figure 13

deuterium content of the 2-butenes obtained in base-catalyzed dehydrotosylation of the *p*-toluenesulfonate of **4** and of its *threo* diastereoisomer, as well as in the pyrolysis of the acetates of the two diastereoisomers (56). Moreover, the same *erythro*-isomer was obtained (57) by borodeuteration–oxidation of *cis*-2-butene, a reaction known in the case of trisubstituted olefins to involve *cis*-addition (58). Regarding the configurational homogeneity of the deuterated carbon (C-3) in **4**, it has been shown (56) that **4** is at least 95% pure *erythro*, and since its configurational homogeneity at C-2 is ca. 98%, that at C-3 must be in excess of 93%. Removal in two steps (not likely to involve racemization at C-3) of the alcohol group in **4** (Fig. 13) leads to butane-*2-d* (**5**) of $[\alpha]_D^{25} - 0.56°$, corrected to $-0.61°$ by taking into account the presence of 8.4% undeuterated butane. The specific rotation of **5** is thus between 0.61 and 0.655° and the configuration of the levorotatory material is *S*. This is the same configuration predicted by *a priori* calculation (31). The measured rotation (54) is somewhat smaller than the predicted one ($[\alpha]_D^{25}$ 1.1°) (31) but this may reflect an imprecision in the calculation rather than a defect in the experiment.

Availability of $[\alpha]_D$ for **5** within narrow limits permitted an assessment of the steric course and stereospecificity of the reduction of 2-butyl methanesulfonate, $CH_3CHOMesC_2H_5$, and 2-butyl bromide, $CH_3CHBrC_2H_5$, with lithium aluminum deuteride (54). The methanesulfonate of (*R*)-2-butanol (**4**, H instead of D) prepared from the ca. 98% optically pure alcohol upon lithium aluminum deuteride reduction gave (*S*)-butane-*2-d* (**5**) of $[\alpha]_D^{25} - 0.47°$, equivalent to $-0.50°$ after correction for the presence of 5% undeuterated butane. Surprisingly, then, it appears that the deuteride reduction of the methanesulfonate entails about 20% racemization, even though the reaction proceeds with the expected inversion of configuration (which may thus be assumed to occur generally in the reduction of secondary alkyl sulfonates with $LiAlD_4$). An even more puzzling finding concerns (*S*)-2-bromobutane (**6**, H instead of D); material of $[\alpha]_D^{25} + 28.45°$ prepared by the reaction of (*R*)-2-butanol with PBr_3 upon lithium aluminum deuteride reduction gave (*R*)-butane-*2-d* (enantiomer of **5**) with $[\alpha]_D^{25} + 0.50°$. The occurrence of two inversions in this sequence —one in the PBr_3 reaction of the alcohol and one in the deuteride reduction—is unexceptional, but the rotation of the product is surprising when it is taken into account that later work (59) indicated the specific rotation of optically pure (*S*)-2-bromobutane to be ca. 39.4°. One is forced to conclude that the bromide used for the deuteride reduction was only 73% optically pure and even if no racemization at all occurred in the reduction itself (see, however, the situation with respect to the methanesulfonate discussed above), the butane-2-*d* obtained could not have been purer than 73%, which leads to a calculation of its minimum rotation of 0.685°,

appreciably in excess of the earlier mentioned maximum value of 0.61–0.655°.*

The diastereoisomers of butane-*2,3-d*$_2$ have also been synthesized (54)—the *meso* isomer, $[\alpha]_D^{25} - 0.03°$, by reduction of **6** (Fig. 13) by lithium aluminum deuteride† and the 2*S*,3*S*, isomer, $[\alpha]_D^{25} - 1.01°$, by similar reduction of the methanesulfonate of the alcohol **4** (Fig. 13). If the rule of optical superposition holds, i.e., if one may assume that (2*S*,3*S*)-butane-*2,3-d*$_2$ has twice the rotation of (*S*)-butane-*2-d*,‡ then the predicted rotation for the pure active dideuterated isomer is $2 \times 0.61 = 1.22°$, and the material actually obtained was about 20% racemized. The extent of racemization in the deuteride reduction of the methanesulfonate is therefore about the same as in the analogous reduction of the methanesulfonate of undeuterated 2-butanol (*vide supra*).

Pentane-*2-d* has been synthesized in various ways (45,76), as summarized in Figure 14.

Starting material **7** was 13% optically pure (60); allowing for that and assuming that no racemization occurred in the mesylate–deuteride reduction (but see above), the specific rotation of **8** was calculated to be $-0.515°$. Starting material **9** was 44% optically pure and the specific rotation of the pentane-*2-d* prepared from it was 0.19°; thus that of optically pure pentane-*2-d* is at least $0.19 \times 100/44$ or 0.43°, assuming no racemization. An argument will be made later (p. 162) that the optical purity of the pentane-*2-d* of $[\alpha]_D - 0.25$ (recalculated for optically pure pinene) prepared by the third path was no more than 37.5% and this would lead to a calculated rotation of $-0.51°$ for optically pure material. The three values are in fair agreement, and it seems likely that the specific rotation of pentane-*2-d*

*The argument concerning the maximum rotation of 2-bromobutane-*3-d* is based on the assumption, corroborated by the work of P. S. Skell and R. G. Allen [*J. Amer. Chem. Soc.*, **81**, 5383 (1959)], that E_2 elimination of HBr or DBr by base is stereochemically cleanly *anti* in this case. *See, however, the following footnote.*

†The pure *meso* isomer should, of course, be optically inactive. The small rotation is presumably due to contamination with the active 2*S*,3*S* isomer. It might be noted that if bromide **6** is only 73% optically pure at C-2 as claimed above, it should contain 13.5% of the 2*R*,3*S* isomer which should, upon deuteride reduction, give at least 10% (allowing for some racemization) of (2*S*,3*S*)-butane-*2-*,*3-d*$_2$, so that the rotation should be about $-0.12°$, appreciably in excess of that observed. ADDED IN PROOF: This discrepancy, as well as the one regarding the maximum rotation of butane-*2-d* mentioned in the text, now seems to stem from the fact that the maximum rotation of 2-bromobutane was overestimated by about 10% in ref. 59: cf. D. G. Goodwin and E. R. Hudson, *J. Chem. Soc., B*, **1968** 1333. See also P. Salvadori, L. Lardicci, and M. Stagi, *Ric. Sci.*, **37**, 990 (1967).

‡Since the chiral centers in the mono- and dideuterated species are different only to the extent that the substituent in the latter is CH_3CHD, where that in the former is CH_3CH_2, this should be a case where the rule holds, if it ever does.

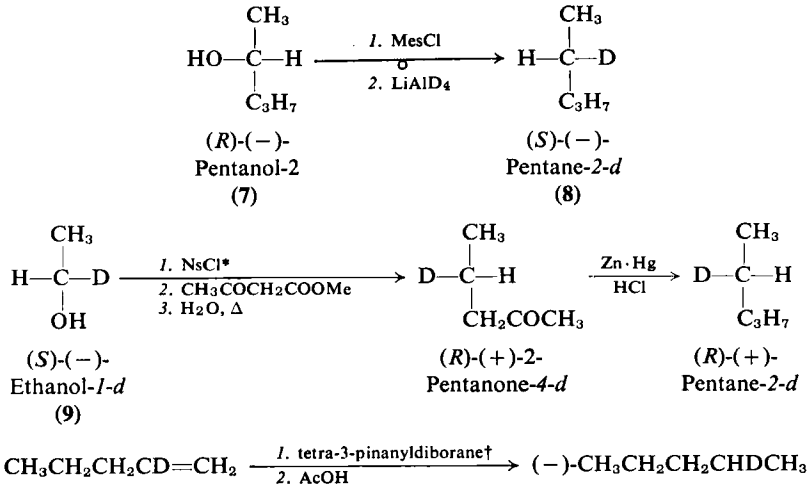


Figure 14

is not much in excess of the calculated minimum value of $\pm 0.52°$ which would give the hydrocarbon nearly the same molecular rotation, $[M]_D = \pm 0.38°$ as that of butane-*2-d*, $[M]_D = \pm 0.36°$. The two levorotatory hydrocarbons also have the same configuration, *S*, *n*-propyl in one case taking the place of ethyl in the other.

(+)-Butylbenzene-α-*d* (**10**), α_D^{25} 0.57° (*l* = 1 dm, neat), has been obtained (61) by the sequence shown in Figure 15. The starting (−)-phenyl-*n*-propylcarbinol (**11**) was 85% optically pure (62,63), and while its configuration has never been determined by direct chemical correlation, there are several lines of evidence (64–67) suggesting that it is *S*. Since, as has already been discussed in connection with ethylbenzene-α-*d*, both the phosphorus

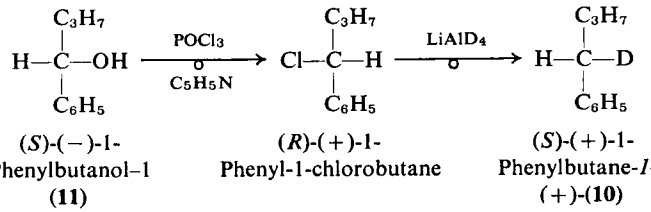


Figure 15

*p-Nitrobenzenesulfonyl chloride.

†The more common name for tetra-3-pinanyldiborane (prepared from (+)-α-pinene and diborane in a 4:1 ratio) is diisopinocampheylborane. Apart from our preference for *Chemical Abstracts* nomenclature, the name used here points out the fact that the reagent is, in fact, dimeric; cf. ref. (87).

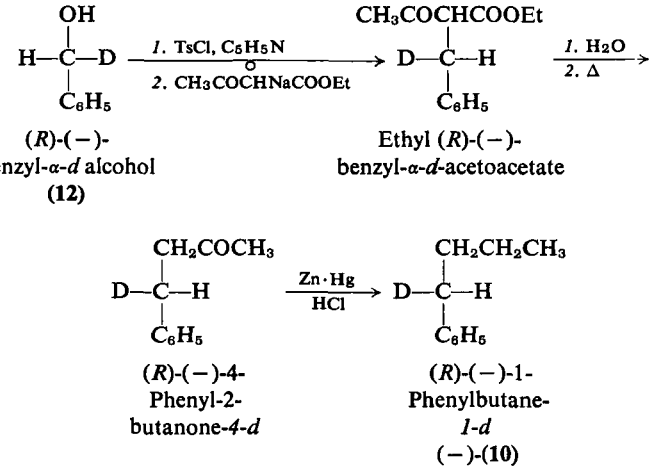


Figure 16

oxychloride and lithium aluminum deuteride reactions are likely to involve inversion of configuration, it would appear (Fig. 15) that (+)-**10** has the *S*-configuration. Its minimum rotation may be computed to be $\alpha_D^{25} = 0.57 \times 100/85 = 0.67°$ (l = 1 dm), corresponding to $[\alpha]_D^{25} = 0.85°$ on the basis of a density of 0.827 (61) and the presence of 4% of undeuterated hydrocarbon. The specific rotation is much below the maximum value observed (see below), suggesting that a large amount of racemization (over 50%) occurred in the two steps shown in Figure 15.

n-Butylbenzene-α-*d* has also been synthesized (46) from (−)-benzyl-α-*d* alcohol (**12**) by the sequence shown in Figure 16. The only step presumably involving inversion is the acetoacetic ester alkylation and the configurational assignments are thus as shown, assuming that (−)-**12** has the *R*-configuration (*vide infra*). It may be seen that on this basis (−)-**10** is *R*, consistent with the conclusion reached above (Fig. 15) and that to be reached below (Fig. 17). The argument here is clearly of the "network" type (p. 142) and might alternatively be construed to support the *R*-configuration for

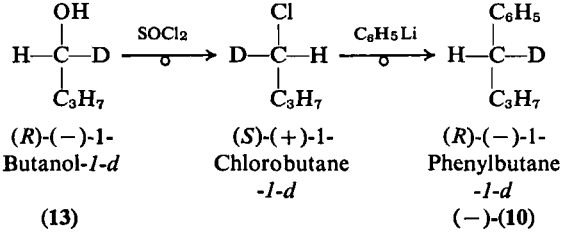


Figure 17

(−)-**12**. From the specific rotation of pure **12** (61), $[\alpha]_D^{24}$ 1.58° (*vide infra*), and the rotations of the starting material, intermediates, and products shown in Figure 16 (46) it may be concluded that for pure (−)-**10** $[\alpha]_D^{26}$ = 1.76°, assuming that no racemization occurs in the inversion step. A third optical correlation (46) involving **10** is shown in Figure 17 where **13** of $[\alpha]_D^{25}$ − 0.0441 gives **10** of $[\alpha]_D^{25}$ − 0.179. The starting material when optically pure has a specific rotation of 0.47° (61), and the minimum rotation for **10** calculated from the correlation is thus 1.91°; a more likely minimum value is actually 2.1°, since the first step of the sequence very probably involves about 10% racemization (68). Since this step is known (68) to involve inversion of configuration and on the assumption (46) that the phenyllithium reaction also involves inversion, the scheme shown in Figure 17 constitutes a correlation of the configuration of (−)-butanol-*1-d* (13) and (−)-**10**; it may be taken to support the *R*-configuration for (−)-**13**, but since there is independent evidence for this configuration (see below) it may also be taken to support the *R*-configuration for (−)-**10** or it may be cited in support of the inversion course of the PhLi reaction (network argument).

When one compares the specific rotations of the products **10** in Figures 15–17, it comes as somewhat of a surprise that the reaction which perhaps *a priori* might have been least believed to be stereospecific (phenyllithium on halide) in fact produces the most active product. Even more surprising is the indication that the sequence of Figure 15 produces very substantial (> 50%) racemization. If true, this finding throws considerable doubt on the analogous synthesis of ethylbenzene-*α-d* (Fig. 6) being even approximately stereospecific. From the available data, the minimum molecular rotation of PhCHDMe is 0.8° and that for **10** is 2.6°; on grounds of additional "conformational asymmetry" (66), however, the difference should (43) be only 0.33° rather than 1.8°. Thus the presently highest observed specific rotation for PhCHDMe may be substantially too low.

2-Methyl-1-butene-*3-d* was obtained (47) by the sequence shown in Figure 18 (top), which presumably involves a neopentyl cation generated in basic medium. The configuration of the major product, (*S*)-(+)-2-methyl-1-butene-*3-d*, was proved by diimide reduction to the saturated hydrocarbon which was independently synthesized from the known (*S*)-(+)-3-methyl-2-butanol as shown in Figure 18 (bottom). The two syntheses produced materials of opposite configuration and it therefore follows (Fig. 18) that the $CHBr_3$–KOH reaction involves inversion of configuration. It is likely that this inversion is nearly complete, for the saturated hydrocarbon produced from neopentyl-*1-d* alcohol (Fig. 18, top) had $[\alpha]_D^{17}$ − 0.85°, whereas the comparison material (Fig. 18, bottom), prepared

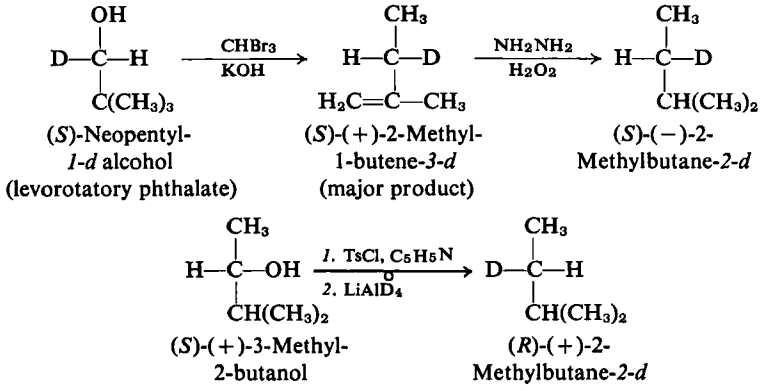


Figure 18

from pure carbinol, had $[\alpha]_{20}^{D}$ + 0.76°, i.e., was less optically pure. On the assumption (cf. earlier discussions) that the $LiAlD_4$ reduction of tosylates involves 15 ± 5% racemization, the hydrocarbon from the neopentyl-*1-d* alcohol would be nearly stereochemically pure.

Solvolysis of the tosylate of (*S*)-neopentyl-*1-d* alcohol* (47a) similarly proceeds with 91% inversion, on the assumption that the olefin shown in Figure 18 ($[\alpha]_{D}^{20}$ 1.01°) is, in fact, optically pure.

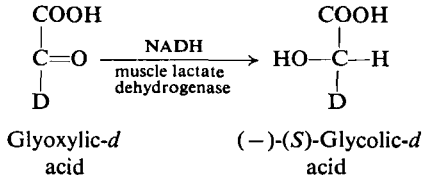
B. Glycolic-*d* Acid

Glycolic-*d* acid has been synthesized by enzymatic reduction of glyoxylic-*d* acid by the reduced form (NADH) of nicotinamide adenine dinucleotide (NAD^+) about which more will be said later. The reduction, shown in Figure 19,† is catalyzed by muscle lactate dehydrogenase (which normally catalyzes the dehydrogenation of (*S*)-lactic acid to pyruvic acid and the reverse process)‡; in order not to use a stoichiometric amount of

*As will be seen later (p. 164), there is no absolute proof for the configuration of the neopentyl alcohol which yields the (−)-phthalate. The two reactions here described ($CHBr_3$–KOH and tosylate solvolysis) could thus involve nearly complete *retention*, but this appears highly unlikely on mechanistic grounds, and the steric course of the reaction (high preservation of optical purity, therefore presumably inversion) may be taken in support of the *S*-configuration of the neopentyl-*1-d* alcohol produced by fermentation (network argument).

†Here and elsewhere we shall represent the substrates as free carboxylic acids although in this and many other cases they are in effect present in the ionized form at the pH at which the enzyme functions.

‡A preliminary (and, as it now turns out, correct) assignment of the *S*-configuration to the glycolic-*d* acid produced as shown in Fig. 19 was made on the basis of this analogy and a corresponding analogy in the glycolate oxidase-catalyzed dehydrogenation of the same glycolic-*d* acid to glyoxylic-*d* acid and of (*S*)-lactic [but not (*R*)-lactic] acid to pyruvic acid (97).



Glyoxylic-*d* acid

(−)-(*S*)-Glycolic-*d* acid

Figure 19

the very expensive NADH, this material was used in catalytic amount and the NAD^+ formed in the reduction was reduced back to NADH by a combination of ethanol and liver alcohol dehydrogenase. (This use of a so-called "coupled system" constitutes a common biochemical trick.) The optically active glycolic-*d* acid was converted to its ^6Li salt which was then subjected to X-ray and neutron diffraction analysis (69). The X-ray pattern not unexpectedly failed to distinguish the hydrogen and deuterium, but the neutron diffraction pattern showed this distinction and, by applying an analog of the Bijvoet method for X-rays (70), it was possible to establish the absolute configuration of (−)-glycolic-*d* acid as *S*. Glycolic-*d* acid thus serves as a primary configurational standard for the correlation of other RCHDR′ compounds (cf. p. 141).* Stereospecifically tritiated glycolic-*t* acid has been correlated, configurationally, with the deuterated acid through correspondence in enzymatic degradation (p. 167); details of this correlation and of the utilization of the tritiated acid as a configurational standard will be presented later.

C. Alcohols

Among the most important optically active deuterated compounds are the alcohols of type RCHDOH. On the one hand, these compounds have been of great importance in the elucidation of the stereochemistry of displacement reactions at primary carbon (especially in the hands of Streitwieser and co-workers) and, on the other, the reversible oxidation of the first member, ethanol-*1-d*, to acetaldehyde, which occurs stereospecifically, is a prototype reaction for many biochemically significant transformations. The configuration of ethanol-*1-d* has therefore been studied particularly intensively and arguments pertaining to it will be presented first, followed by similar arguments for some of the higher alcohols.

Optically active ethanol-1-*d* may be prepared by the enzymatic reduction of acetaldehyde with deuterated NADH (*vide supra*), i.e., NAD^2H

*The ORD curves for (+)- and (−)- glycolic-*d* acids have been measured by J. W. Cornforth and D. Ryback (unpublished results), $[\alpha]_{250}$ 27°, $[\alpha]_{227}$ 115°.

(for convenience henceforth denoted as NAD-D) or, more conveniently, by the enzymatic reduction of acetaldehyde-*d* with NADH. The enzymes commonly used are yeast alcohol dehydrogenase (YADH) or liver alcohol dehydrogenase (LADH), though there are other enzymes which also catalyze the reaction. It has already been mentioned (cf. Fig. 11) that the two faces of acetaldehyde are not identical but bear a two-dimensional object–image relationship to each other.

Toward a chiral enzyme, the *si*-face and the *re*-face of acetaldehyde are distinct, as one may readily visualize if one thinks of the active site of the enzyme as an ordered surface*; the place occupied by CH_3, when the enzyme is placed on one face, would have to be occupied by H if it is placed on the other face, and *vice versa*. Since, however, specific sites of enzymes have a differential (often highly differential) affinity for different groups, it is not surprising that transfer of hydrogen takes place essentially only to one of the two faces of acetaldehyde; conversely, only one of the two enantiotopic hydrogens is removed in the enzymatic dehydrogenation of ethanol. In the case of the enzymes YADH and LADH the acetaldehyde is reduced from the *re*-face and the hydrogen removed from ethanol is the H_R†; the situation is depicted in Figure 20 where one of the two hydrogens in question is replaced by deuterium; it is important to recognize, however, that the stereospecificity of the enzyme reaction, *vis-à-vis* the prochiral face

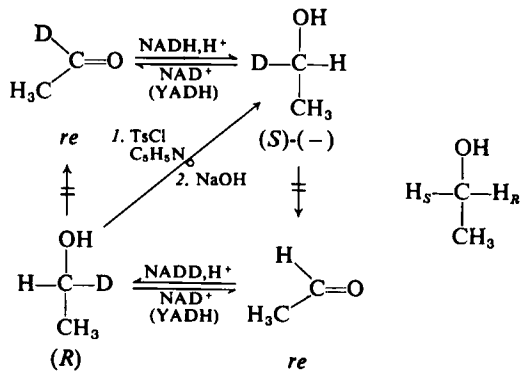


Figure 20

*This is no doubt an oversimplification, but the argument is the same—if somewhat more difficult to grasp—for a three-dimensional active site as long as the site is chiral. Cf. the classical paper of A. G. Ogston, *Nature*, **162**, 963 (1948).

†The situation might be otherwise with different enzymes. Since the topography of enzymes differs, their stereospecificity may be expected to differ also. In the particular case of the reduction of acetaldehyde with YADH and LADH it has been shown, however, that the hydrogen transferred is the same (H_R) (A. Umani-Ronchi, H. Weber, and D. Arigoni, unpublished results.)

in acetaldehyde or the prochiral center in ethanol, is entirely independent of the labeling.

Experimentally, stereospecificity in acetaldehyde reduction and ethanol oxidation was first established by Loewus, Westheimer, and Vennesland who discovered (29) that reduction of ethanal-*d* with NADH gave ethanol-*1-d* which, upon enzymatic reoxidation, returned only ethanal-*1-d* without loss of deuterium. Conversely, reduction of ordinary acetaldehyde with NAD-D gave ethanol-*1-d* which, upon reoxidation, lost all of its deuterium to give back ordinary acetaldehyde. The two series of experiments are shown in Figure 20. The fact that in the oxidation of the alcohol obtained by the NAD-D reduction of CH_3CHO [now known to be (*R*)-ethanol-*1-d*] all the deuterium was transferred back to the NAD^+ was corroborated by allowing the NAD-D obtained to reduce pyruvic acid ($CH_3COCOOH$) to lactic acid ($CH_3CDOHCOOH$); the lactic acid proved to be completely α-deuterated. Figure 20 also shows that the ethanol-*1-d* isomer which loses deuterium was converted to the enantiomer which loses hydrogen by a Walden inversion of the tosylate with NaOH. Clearly all the processes shown in Figure 20 are highly stereospecific and isotope effects are in no way involved in the findings.

Subsequent experiments on a larger scale (71) using a coupled system (*vide supra*) established that the alcohol shown on the upper right in Figure 20 (from CH_3CDO and NADH) was levorotatory, $[\alpha]_D^{28} - 0.28 \pm 0.03°$.

In order to learn something about the stereospecificity at the active site, it became important to establish the configuration of one of the ethanol-*1-d* isomers, say, the levorotatory one, alternatively characterized by the fact that on enzymatic oxidation with NAD^+ it gives ethanal-1-*d* without loss of deuterium. This has, by now, been accomplished in four different ways: by correlation with a pyranose sugar whose configuration at the CHD center was established by NMR (72), by correlation with glycolic-*d* acid of known absolute configuration (cf. Fig. 19) (73), by correlation with 2-butanol-*3-d* of known configuration (57), and by correlation with pentane-*2-d* of known configuration (45). Additional evidence for the *S*-configuration of the (−)-alcohol thus established comes from mechanistic considerations in asymmetric synthesis (45) and from Brewster's rules (43) based on rotation.

The first definitive assignment of configuration of (+)-ethanol-*1-d* (72) departs from β-D-xylose-5β-*d* (**14**, Fig. 21) obtained, in turn, from a glucofuranose derivative (**15**) by selective hydrolysis, oxidation to a C-5 aldehyde, asymmetric $LiAlD_4$ reduction to a C-5 alcohol with a CHDOH grouping, and conversion to the pyranose in which the β-*d* isomer could be shown to predominate over the α-*d* epimer in an approximately 1.85:1 ratio. The conformation of the C-5 deuterium in 14 was shown by NMR to be

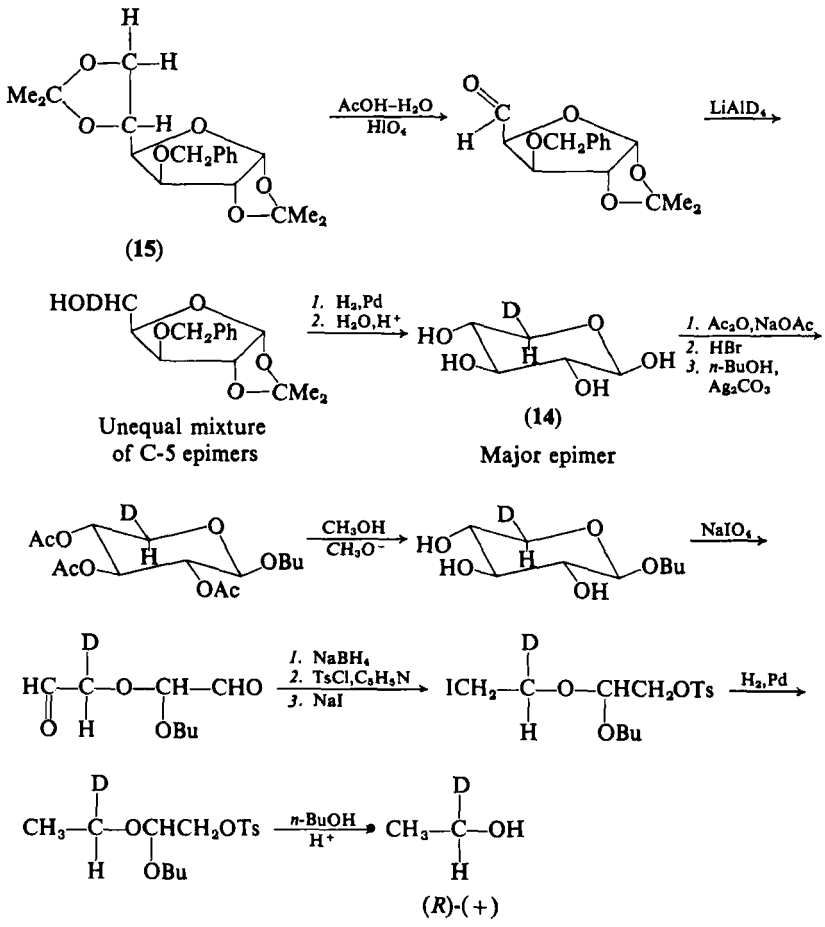


Figure 21

predominantly equatorial (more precisely, the corresponding C-5 hydrogen was shown to be axial in the predominant isomer). Since the absolute configuration of D-xylose is known and the conformation of the molecule is completely biased on the side of equatorial OH's, it follows that the configuration at C-5 of the predominant deuterated epimer was *R*, as shown. This chiral center was then separated from the rest of the molecule as indicated in Figure 21. The resulting ethanol-*1-d* must be *R*; its rotation was found to be 0.065° (neat, 1 dm) versus an expected 0.066 based on the maximum rotation $[\alpha]_D^{25} \pm 0.28°$, the known density, and the fact that the starting material had only a 30% excess of one of the diastereoisomers. It is concluded that (+)-ethanol-*1-d* has the *R* configuration.

As an aside here it might be mentioned that D-xylose-*5-t* formed from externally administered myoinositol-*2-t* in strawberries (Fig. 22) has been subjected (74) to the same degradation as the deuterated material of Lemieux and Howard, but this time with the aim of ascertaining the unknown configuration at C-5 in the xylose. Formation of (*R*)-ethanol-*1-t* in the degradation was established by the fact that treatment with NAD^+–YADH (cf. Fig. 20) led to unlabeled acetaldehyde and tritiated NAD-T (whose tritium was then transferred back to pyruvic acid for purposes of counting).

In view of the establishment of the absolute configuration of glycolic-*d* acid (Fig. 19), a chemical correlation of ethanol-*1-d* with that acid, though originally carried out to determine the configuration of the acid (73), serves as additional proof of the *S*-configuration of (−)-ethanol-*1-d*. As shown in Figure 23, the (*S*)-(−)-acid, prepared as shown in Figure 19, was reduced in two stages to ethanol-*1-d*, which, by its method of preparation, must be *S* and which was characterized by YADH-catalyzed dehydrogenation to ethanal-*1-d* retaining all the deuterium (cf. Fig. 20). As indicated earlier, this behavior toward the enzyme corresponds to the levorotatory isomer of ethanol-*1-d*.

A third correlation (57), giving the same result, is shown in Figure 24. (2*R*,3*S*)-(−)-2-butanol-*3-d* was synthesized by asymmetric hydroboration of *cis*-2-butene with optically active tetra-3-pinanyldiborane-*d*, followed by hydrogen peroxide oxidation. Addition was cleanly *cis*, as was shown by spectroscopic comparison of the product 2-butanol-*3-d* with authentic

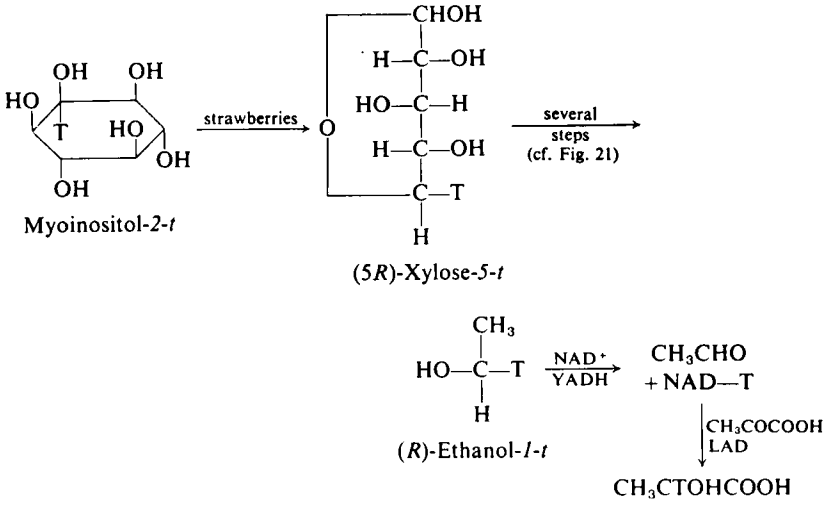
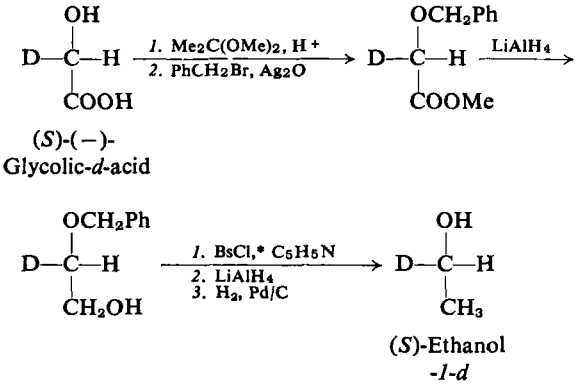


Figure 22



*p-Bromobenzenesulfonyl chloride

Figure 23

samples of *dl-threo* and *dl-erythro* isomers obtained by reduction of *cis*- and *trans*-2-epoxybutane with lithium aluminum deuteride, respectively (cf. Fig. 13). The hydroboration product was cleanly *erythro*; however, its optical purity at C-2 (and therefore also at C-3) was only 56% as deduced from comparison of its rotation with that of optically pure 2-butanol (cf. Fig. 13).* The remainder of the transformation proceeded essentially stereospecifically; in particular, the 2-butanone-*3-d* lost almost none of its deuterium by exchange and therefore could not have been appreciably racemized. The (*S*)-ethanol-*1-d* obtained in accordance with Figure 24 was characterized by NAD^+–YADH dehydrogenation which gave 67%

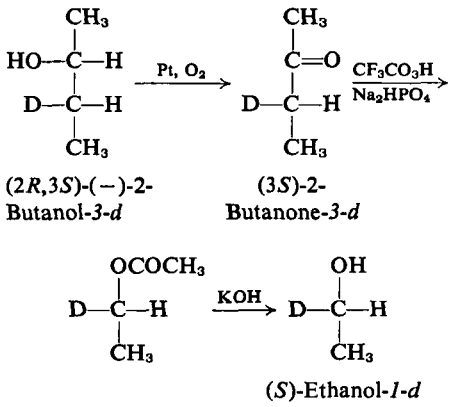


Figure 24

*The starting pinene was 87.5% pure; thus asymmetric synthesis proceeds to the extent of 56/87.5 × 100 or 64%.

ethanal-*1-d* (and 33% ethanal), as compared to 67.5% expected on the basis of the deuterium content of the ethanol-*d* (86.5%) and the optical purity of the butanol starting material.* Of the 19% deuterium lost in the dehydrogenation, 16% could be transferred back enzymatically from the reduced coenzyme to pyruvic acid.

A fourth correlation of configuration of (−)-ethanol-*1-d* with (+)-pentane-*2-d* (45) is shown in Figure 14.

Considerations of "atomic asymmetry" (43) also indicate that (*S*)-ethanol-*1-d* should be levorotatory, and the postulated course of its asymmetric synthesis from deuterated isobornyloxymagnesium bromide and acetaldehyde (45) (Fig. 25) is in agreement, as are mechanistic considerations of the course of the enzymatic reaction shown in Figure 20 when compared to similar reactions of known stereochemistry involving ketones (75).

(+)-Butanol-*1-d*, $[\alpha]_D^{27}$ + 0.47° is obtained by the reduction of butanal-*1-d* with fermenting yeast (61). This method probably produces optically pure material. Subsequent studies on the extent of asymmetric reaction of the alcohol with α-phenylbutyric anhydride (18, see also 19) indicate a range of 0.47–0.61° for the specific rotation of the optically pure material. The asymmetric esterification (18) also leads to prediction of the *R*-configuration for the levorotatory alcohol. Reduction of butanal-*1-d* by yeast thus produces the *S*-alcohol; its steric course is therefore analogous to that of the enzymatic reduction of ethanol-*1-d* (Fig. 20), suggesting that the effective reducing system in fermenting yeast either *is* NADH–YAD

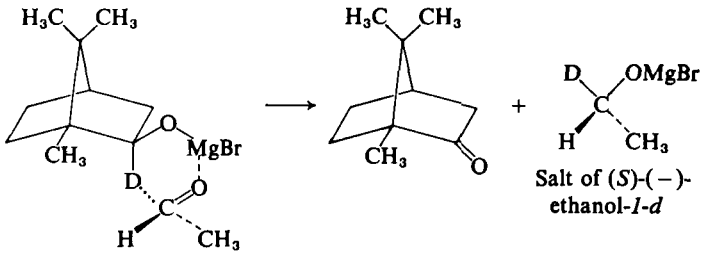
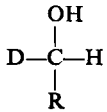


Figure 25

*Evidently the sequence in Figure 24 is highly stereospecific; i.e., the Baeyer-Villiger rearrangement proceeds without loss of optical purity. Of the two *a priori* possibilities—that it proceeds with complete retention or that it proceeds with complete inversion—only the former is compatible with the other two configurational assignments of ethanol-*1-d* and with the accepted stereochemistry of the rearrangement as deduced in other cases (ref. 25, p. 120).

or at least attacks the same enantiotopic face of the aldehydes as NADH–YAD. The difference in sign of rotation between the configurationally related (*S*)-ethanol-*1-d* (**16**, R = CH_3) ahd (*S*)-butanol-*1-d* (**16**, R = n-C_3H_7) is worthy of note; it has been explained theoretically (43) as being due to the conformational dissymmetry contribution of the extra two carbon atoms in butanol-*1-d*.



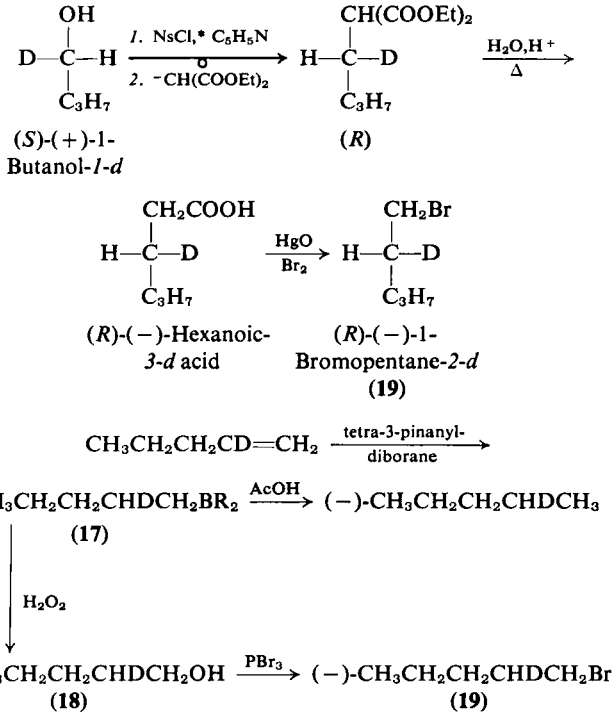
(16)

Further support for the *S*-configuration for (+)-butanol-*1-d* comes from the results of its asymmetric synthesis from butanal with deuterated isobornyloxymagnesium bromide, a reaction similar to that shown in Figure 25. On mechanistic grounds this reduction is expected to produce an excess of the *S*-isomer and in fact it gives (46) dextrorotatory material.

The configurational assignments of the butanol-*1-d* enantiomers are supported by two additional lines of evidence. One is shown in Figure 17: The (−)-alcohol is *R* if (−)-1-phenylbutane-*1-d* is *R* and both steps of the transformation involve inversion. Independent evidence for the *R*-configuration of the hydrocarbon (given earlier) and for inversion in the thionyl chloride step (to be given later) is strong, and the weakest link in this particular correlation is the assumption that the phenyllithium reaction involves inversion. However, an independent and perhaps stronger argument exists (76); it is shown in Figure 26.

Since (−)-pentane-*2-d* has the *S*-configuration (Fig. 14), its precursor, borane **17**, the (−)-carbinol **18**, and the levorotatory bromide **19** must all have the same configuration (CH_2BR_2, CH_3, CH_2OH, and CH_2Br being corresponding groups); the proper configurational symbol for (−)-**19** is therefore *R* (Fig. 26) and that of the (+)-butanol-*1-d* which gives rise to the same bromide is *S* on the assumption, well founded in the literature (77), that the malonic ester alkylation proceeds with inversion of configuration. It might be noted here that the bromide **19** obtained via the asymmetric hydroboration had only 37.5% of the rotation of that obtained from butanol-*1-d* (based on the rotation of the pure deuteroalcohol) and that therefore the pentane-*2-d* also could not have been more than 37.5% optically pure, as mentioned earlier (p. 150).

Optically active butanol-*1-d*, $[\alpha]_D^{21}$ 0.21°, was also obtained (78) by treatment of *cis*-1-butene-*1-d*, $CH_3CH_2CH{=}CHD$ (obtained from butyne-*1-d* by hydroboration followed by acid cleavage), with tetra-3-pinanyldiborane followed by hydrogen peroxide oxidation. The optical purity of the



*p-Nitrobenzenesulfonyl chloride.

Figure 26

alcohol obtained in this synthesis starting with 80% optically pure α-pinene was 44.5%; thus the optical yield is 56%. Another asymmetric synthesis of levorotatory butanol-*1-d*, albeit of low optical purity, involves reduction of butyraldehyde with 2-octyloxy-2-*d*-magnesium bromide from (+)-2-octanol-*2-d* (28) or reduction of butanal-*1-d* with 2-octyloxy-magnesium bromide from (−)-2-octanol (79).

(+)-Benzyl-α-*d* alcohol, C_6H_5CHDOH, is obtained by the reduction of benzaldehyde-α-*d* with fermenting yeast (61); the material is presumably optically pure, and its rotation, after correction for 14% undeuterated material, is $[\alpha]_D^{24}$ 1.58° (neat); its configuration might be inferred to be *S* from the method of preparation.* Both the optical purity and the configuration are supported by the Horeau method (18). The configuration is

*The argument that the same enzyme will lead to reaction of similar substrates in stereochemically related fashion (for example, that YADH-NADH will reduce aldehydes from the *re*-side) is tenuous at best because of the uncertainty of what is meant by "similar substrates" and by "stereochemically related fashion." The argument becomes even more uncertain when applied to a complex biochemical system,

further confirmed by an asymmetric synthesis (Fig. 25, benzaldehyde-α-*d* instead of acetaldehyde, undeuterated isoborneol derivative) which gives levorotatory material (46); on mechanistic grounds (Fig. 25) its configuration should be *R*. The strongest support for the configuration of the levorotatory alcohol as being *R* comes through correlation with (R)-(−)-1-phenylbutane-*1-d* (Figs. 15 and 16) through reactions of rather well defined stereochemistry.

(+)-Benzyl-α-*d* alcohol has also been obtained by asymmetric reduction of benzaldehyde-α-*d* with the Grignard reagent derived from (+)-2-methyl-1-chlorobutane (61). A supposedly convenient synthesis of the (*S*)-(+)-alcohol by reduction of benzaldehyde with tetra-3-pinanyldiborane-d_2 (79a) has recently become the subject of a controversy (79b).

Neopentyl *1-d*-alcohol, $(CH_3)_3$ CCHDOH, may similarly be obtained by reduction of deuterated pivalaldehyde, $(CH_3)_3CCDO$, with fermenting yeast (80) the configuration of the material so obtained being presumed to be *S* by the previously indicated analogy argument. The material fortuitously does not measurably rotate the plane of polarized light at wavelengths down to 300 nm (80a), but is characterized by forming a levorotatory acid phthalate, $[\alpha]_D^{28}$ −1.14° (after correction for undeuterated impurity). The optical purity of this material is confirmed by the method of Mislow (38; cf. 19) which involves esterification of the alcohol with optically pure (*R*)-*O*-methylmandelic acid, $C_6H_5CH(OCH_3)COOH$ and search for a diastereoisomeric impurity (*R*, *R*) in the ester so formed (*R*, *S*) by means of NMR spectroscopy. No chemical proof of configuration is available for neopenyl-*1-d* alcohol; it is of interest, however, that reduction of the deuterated aldehyde with (+)-2-methyl-1-butylmagnesium chloride gives (81) preferentially the same enantiomer of the alcohol (albeit of rather low optical purity) as fermentation, the situation here being completely analogous to that with benzaldehyde-α-*d*. Freudenberg's rule of shift (82) as applied to the phthalates of deuterated alcohols also supports the *S*-configuration for (−)-neopentyl-*1-d* acid phthalate, since, in general, an increase in levorotation is produced when (*S*)-RCHDOH is converted to its phthalate (80).

Hexanol-*1-d* has been synthesized in both enantiomeric forms (83) by the asymmetric hydroboration (84) of *cis*-1-hexene-*1-d* and *trans*-1-hexene-*1-d*, respectively, with tetra-3-pinanyldiborane (Fig. 27). In view of previous results of hydroboration of olefins of type $RR'C{=}CH_2$ (85) and

such as fermenting yeast, which contains more than one enzyme and where different enzymes may be involved in the reduction of different substrates; for a detailed criticism of this particular case, see (72). Fortunately, in the case of benzyl-α-*d* alcohol, as in the earlier cited case of butanol-*1-d*, the argument is supported by independent evidence.

the proposed mechanism of asymmetric hydroboration (86,87) the configurations of the hexanol-*1-d* isomers were tentatively assigned as shown in Figure 27. The configurations are supported by the results of dehydrogenation of the deuterated alcohols to aldehydes with NAD^+ in the presence of yeast alcohol dehydrogenase; it has already been shown (Fig. 20, p. 156) that the action of this enzyme leads to removal of H_R in the case of ethanol, and it was considered highly likely that it would also remove H_R from hexanol-1. In fact, the hexanol-*1-d* obtained from *trans*-hexene-*1-d* (Fig. 27) retained the major portion of its deuterium in the corresponding hexanal and that obtained from the *cis* olefin lost most of it by transfer to NAD^+*; therefore it was concluded, in agreement with the mechanistic considerations, that the former material was *S* and the latter *R*. The result was confirmed by the method of Horeau and Nouaille (18). The optical yield in the synthesis of the *S*-isomer was calculated to be 86% on the basis of the results of the enzymatic degradation as well as Horeau's method, but that of the *R*-alcohol, surprisingly, was only 42%, even though both starting olefins were shown by NMR spectroscopy to be diastereomerically pure. The most likely explanation for this result is a steric isotope effect: Since H is larger than D, the bulky groups in *trans*-1-hexene-*1-d* (Fig. 27), H and C_4H_9, are on the same side and their steric influence in the

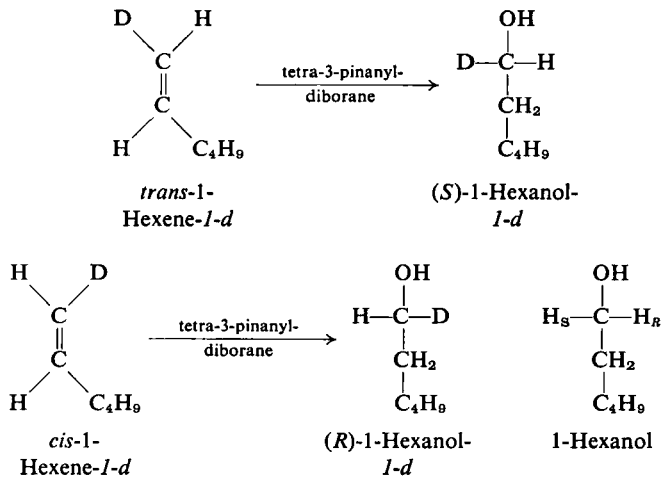


Figure 27

*The hexanal obtained was analyzed for deuterium by mass spectrometry of its 2,4-dinitrophenylhydrazone; the NADH (or NAD-D) was allowed to transfer its hydrogen or deuterium back to pyruvic acid in the presence of lactate dehydrogenase, and the resulting lactic acid was analyzed mass spectrometrically as the phenacyl derivative.

hydroboration reaction should be cumulative, whereas in the *cis*-olefin they are on opposite sides and their steric effects are in conflict.*

In connection with an investigation of the enzymatic decarboxylation of α-amino-acids (see Sect. IV-8), it became necessary to synthesize 2-(*p*-methoxyphenyl)ethanol-*1-d* of known configuration. This was done (88) by reducing *p*-methoxyphenylacetaldehyde with isobornyloxy-*1-d*-magnesium bromide in a manner analogous to that shown in Figure 25. On the basis of the mechanism shown in Figure 25, the configuration of the resulting $p\text{-}CH_3OC_6H_4CH_2CHDOH$ is *S*; the observed specific rotation was $[\alpha]_D^{24} - 1.44°$, but, in view of its method of preparation and the results of subsequent biochemical transformations (see Sect. IV-8), the material was undoubtedly not optically pure.

Geraniol-*1-t* has been synthesized in chiral form by the reduction of geranial-*1-t* with isobornyloxymagnesium bromide (89) (Fig. 28). In view of the earlier postulated mechanism of this reduction (cf. Fig. 25) and in analogy to the steric course of reduction of acetaldehyde and deuterated

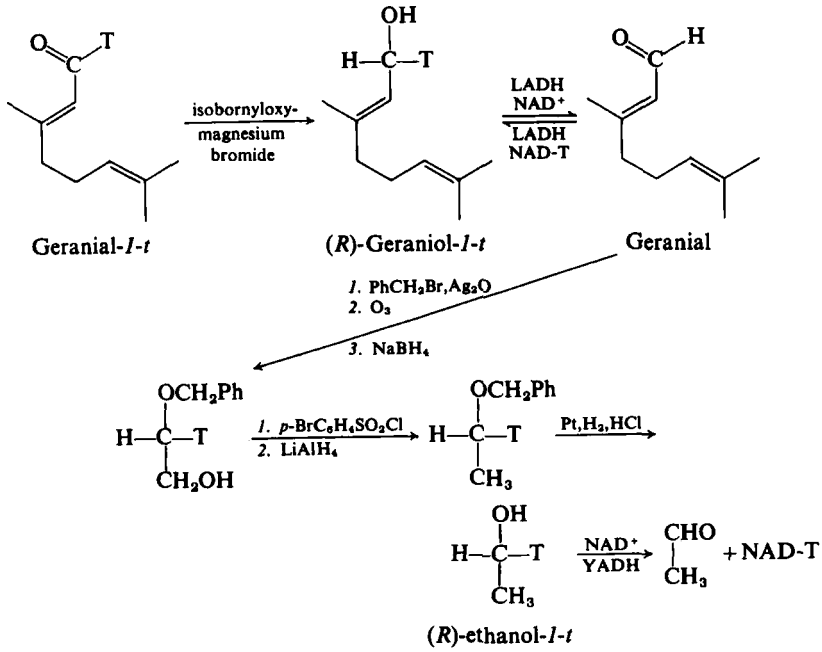


Figure 28

*A more detailed explanation would require a detailed mechanistic picture of hydroboration. Regarding such a picture and an alternative explanation of the isotope effect see ref. 87.

isobornyloxymagnesium bromide, it was assumed that the product had the *R*-configuration. Enzymatic oxidation of this geraniol-*1-t* in the presence of LADH led to geranial which had lost 70–80% of the tritium present in its precursor. If the *R*-configuration is accepted on the basis of the mechanism of formation (Figs. 25 and 28), then this result means that liver alcohol dehydrogenase, like yeast alcohol dehydrogenase, removes H_R (see also the earlier discussion on p. 156). Complete confirmation of the stereochemical assignment of (*R*)-geraniol-*1-t* was subsequently obtained (90) by degrading the tritiated alcohol (obtained, this time, by reduction of geranial with NAD-T in the presence of LADH) to (*R*)-ethanol-*1-t* by the sequence of reactions shown in Figure 28; the *R*-configuration of the final product was demonstrated in the usual way by showing that complete loss of tritium occurred on oxidation with NAD^+–YADH.

The synthesis of chiral farnesol-*1-t* will be discussed in connection with squalene (p. 217), and the synthesis of the chiral α-deuterated *cis*- and *trans*-4-methylcyclohexylcarbinols, $CH_3C_6H_{10}CHDOH$, will be described in conjunction with the synthesis of the corresponding amines (p. 230).

The synthesis of (*S*)-(+)-2-methylpropanol-*1-d*, $[\alpha]_D$ 0.61°, has also been reported (79b).

Figure 29 shows a correlation of the stereochemistry at C-3 of (2*R*)-glyceric-*3-t* acid, obtained by enzymatic reduction of tartronic semialdehyde (91). Degradative oxidation led to glycolic-*t* acid whose configuration was shown to be *R* since, upon dehydrogenation with glycolate oxidase, it lost all its tritium to the water (cf. p. 154). The C-3 hydrogen transferred to give glyceric acid (Fig. 29) is therefore H_R.

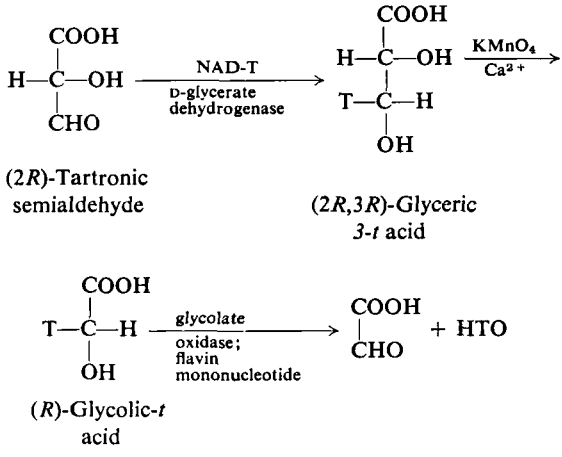


Figure 29

(2*S*)-Serine-*3-t*, $HOCHTCH(NH_2)COOH$ has been biosynthesized from glycine and tritiated formate, $TCOO^-$, by incubation with rat liver slices (91a). Its configuration at C-3 was determined to be *S* by degradation, in several steps, to ethanol-*1-t*, $HOCHTCH_3$, which, in turn, was found to be predominantly the *S*-isomer by enzymatic dehydrogenation (NAD^+–YADH) to largely tritiated acetaldehyde; the NADH obtained was shown to be largely untritiated by transfer of the hydrogen to pyruvic acid and analysis of the resulting lactic acid (cf. Fig. 22). It follows that the formate hydrogen becomes predominantly H_S in serine. The significance of this finding in terms of the intervention of methylenetetrahydrofolate in the transfer of formate to glycine to form serine has been discussed (91a).

D. Carbohydrates: Aldolase and Isomerase

Among important intermediates in sugar biosynthesis and metabolism are ketol phosphates of the type $CH_2OHCO(CHOH)_nCH_2OPO_3^{2-}$, such as dihydroxyacetone phosphate ($n = 0$), ribulose-5-phosphate ($n = 2$), and fructose-6-phosphate ($n = 3$). In the investigation of the isomerases which convert these ketose phosphates into aldose phosphates of the type $OHCCHOH(CHOH)_nCH_2OPO_3^{2-}$ and of the enzyme aldolase which condenses aldose phosphates with ketose phosphates to give larger sugars, the stereochemistry of a number of 1-deuteroketose phosphates, $CHDOHCO(CHOH)_nCH_2OPO_3^{2-}$, has been elucidated and will be treated in the sequel.

The enzyme aldolase catalyzes the condensation of dihydroxyacetone phosphate (DHAP) with (*R*)-glyceraldehyde-3-phosphate (G3P) to give fructose-1,6-diphosphate, as shown in Figure 30. The process is an interesting one from the stereochemical point of view, since two new chiral centers are created in a highly stereoselective aldol condensation in which only one of the four possible diastereoisomers is formed. It has been reported that even in a nonenzymatic reaction only two of the four possible diastereoisomers, namely, the ones in which the newly created chiral centers

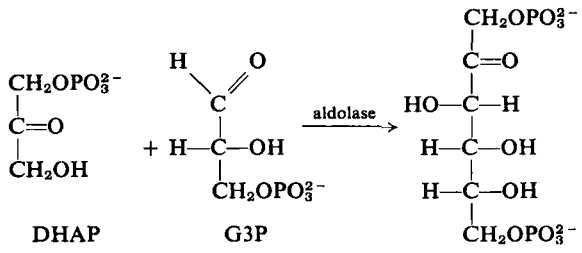


Figure 30

at C-3 and C-4 are *threo* (fructose and sorbose), are formed in more than trace amounts (92).* The enzyme-induced stereospecificity thus relates largely to C-3, and most of the biochemical studies have been concerned with this center. The first question which arose was whether the removal of the C-3 hydrogen in DHAP was or was not stereoselective. It was found (93-95) that DHAP in tritiated water (THO) in the presence of aldolase exchanges one and only one hydrogen; this exchange is independent of the condensation reaction shown in Figure 30, for it occurs even in the absence of G3P. Moreover, the fructose 1,6-diphosphate synthesized in the presence of G3P and THO contains no tritium and acquires no tritium by exchange,† showing that the same hydrogen of DHAP which is exchanged is the one which is lost (stereoselectively!) in the condensation.‡

Triosephosphate isomerase, the enzyme which converts DHAP into G3P (see below), is stereoselective for the mobilization of the hydrogen at C-3 enantiotopic with that mobilized by aldolase as can be seen by the experiment shown in Figure 31; the hydrogen which is incorporated with aldolase is not removed by triose phosphate isomerase (and *vice versa*), even though the latter enzyme does cause exchange of a hydrogen at C-3 (94,96).

The absolute configuration of the dihydroxyacetone-*3-t* 1-phosphate obtained in the aldolase-catalyzed exchange§ was proved to be *S* (97) by correlation with (*S*)-glycolic-*2-t* acid as shown in Figure 32. The glyoxylate formed from the glycolic acid by oxidation with riboflavin phosphate catalyzed by glycolate oxidase from tobacco leaves‖ retained all the tritium; inspection of Figure 19 suggests that H_R is mobilized in the enzymatic reaction, provided glycolate oxidase and muscle lactate dehydro-

* However, an enzyme (L-fuculose 1-phosphate aldolase) has been found in *Escherichia coli* which catalyzes the condensation of L-lactaldehyde and dihydroxyacetone phosphate to L-fuculose 1-phosphate, a sugar with C-3/C-4 in the *erythro* configuration: M. A. Ghalambor and E. C. Heath, *J. Biol. Chem.*, **237**, 2427 (1962).

†As will be seen later, this result is critically dependent on the absence of the enzyme triosephosphate isomerase. Because of the difficulty of completely eliminating this contaminant from aldolase preparations, some of the results in the literature are not quite as clear-cut experimentally as represented here.

‡The same hydrogen is exchanged by muscle aldolase and by aldolase from yeast (95).

§That the exchange in fact occurs in the free (and not in the phosphate-esterified) CH_2OH group in both the aldolase- and isomerase-catalyzed exchanges was proved by oxidation of the labeled phosphate with periodic acid: essentially the entire radioactivity was found in the formaldehyde produced (96).

‖ Glycolate oxidase from spinach mobilizes the same hydrogen (H_R) (cf. ref. 91), Interestingly, leaf glyoxylate reductase, an NADH-dependent enzyme which catalyzes the inverse reaction is known to display the opposite stereochemistry: G. Krakow and B. Vennesland, *Biochem. Z.*, **338**, 31 (1963).

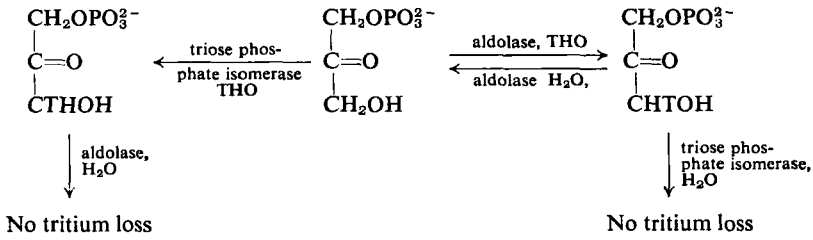
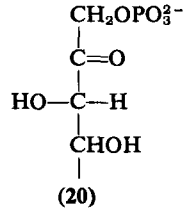


Figure 31

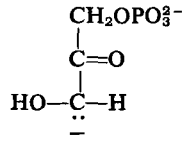
genase have the same stereospecificity.* This last point was proved (97) by reducing glyoxylic acid with NAD-T in the presence of LADH and then reoxidizing the resulting (*R*)-glycolic-*t* acid so formed with glycolate oxidase; the tritium is integrally removed, again demonstrating that both enzymes mobilize the same hydrogen (H_R).

Comparison of Figure 32 with Figure 30 indicates that the hydrogen in DHAP exchanged by aldolase (H_S) occupies a position at C-3 which is stereochemically analogous to that occupied by the C-4—C-5—C-6 chain of the sugar in the aldolase-catalyzed condensation with G3P. Also, it is found that C-3 of *all* sugars synthesized from DHAP (D-fructose, D-xylulose, L-sorbose, D-seduheptulose) is of the same (*S*) configuration (**20**).



(20)

This strongly suggests (although it does not prove) that aldolase functions via an enzyme-bound anion of the type



which may either exchange tritium or condense with an aldehyde.

When the sequence shown in Figure 32 was carried out with DHAP which was T-labeled in the first step by triose phosphate isomerase, the final oxidation with glycolate oxidase led only to unlabeled glyoxylic acid

*It should never be taken for granted that two different enzymes acting on the same substrate to produce the same reaction do so in stereochemically analogous fashion.

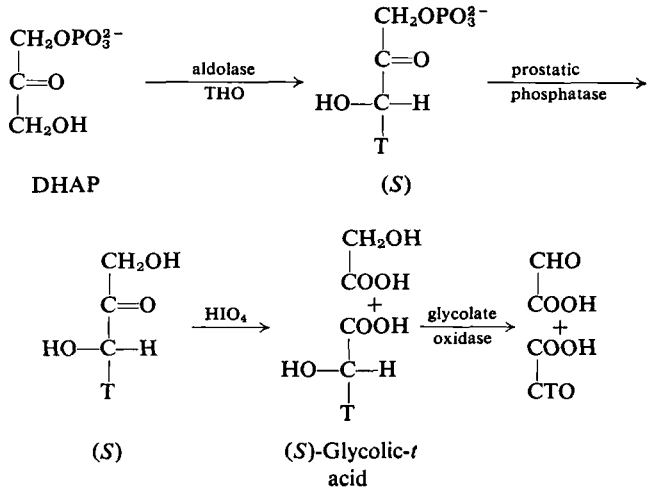


Figure 32

(97), showing that in this case all the tritiated intermediates have the *R*-configuration at C-3 and proving once again that the C-3 hydrogen exchanged by triose phosphate isomerase (H_R) is enantiotopic with that labilized by aldolase (H_S).

Investigation as to whether the transfer of hydrogen from C-3 to C-2 in the isomerization of DHAP to G3P by triose phosphate isomerase is or is not intramolecular is made difficult by the reversibility of the reaction and the rapid concomitant exchange of DHAP; thus some special ruses had to be resorted to in the very elegant investigation of this process (96). C-3 tritiated DHAP of the *R*-configuration obtained from DHAP and THO in the presence of triose phosphate isomerase was freed of any concomitant (and possibly labeled) G3P by treatment with aldolase which removes G3P by condensation with DHAP (Fig. 30). The tritiated DHAP was then incubated with isomerase in H_2O in the presence of glyceraldehyde 3-phosphate dehydrogenase, arsenate, and NAD^+, the dehydrogenating enzyme–coenzyme–arsenate combination serving to oxidize any G3P formed to 3-phosphoglyceric acid before it has a chance to go back to DHAP. The result of the experiment is shown in Figure 33. The tritium removed from the DHAP showed up integrally in the water; none was left in the glyceric acid phosphate (i.e., none was transferred to C-2) and none was left on the carbonyl group of the aldehyde (whence it would have been transferred to NAD-T, which was not, however, formed). This experiment rules out a hydride shift from C-3 to C-2 of DHAP; rather, the hydrogen which is stereoselectively removed from the C-3 position of DHAP (H_R) is exchanged with the medium before being delivered stereoselectively at

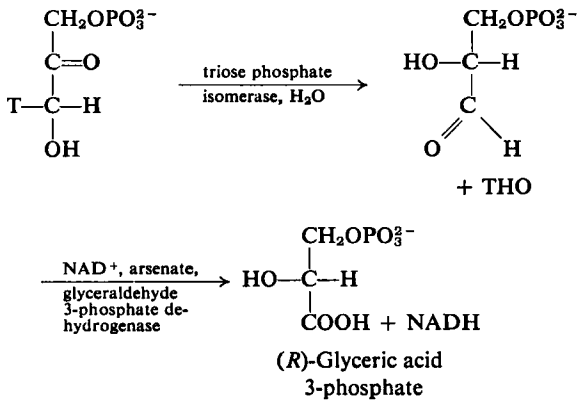
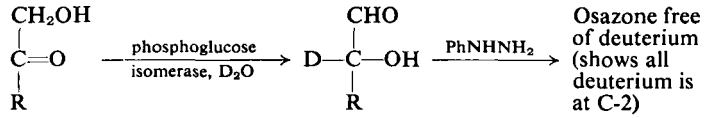


Figure 33

C-2 to give (*R*)-glyceraldehyde 3-phosphate. (If the DHAP starting material is the *S*-isomer, obtained from DHAP, THO, and aldolase, the hydrogen removed in the first step is, of course, the unlabeled one and the tritium stays in the —CTO group of the glyceraldehyde; it is therefore not released into the water but eventually ends up, in the oxidation step, as NAD-T.)

The isomerization reaction between higher aldoses and the corresponding ketoses has also been studied (98–100): glucose or mannose 6-phosphate to fructose 6-phosphate (or *vice versa*) and ribose 5-phosphate to ribulose 5-phosphate. Here, as in the later-investigated DHAP-G3P interconversion (*vide supra*), there is no hydride transfer but the hydrogen delivered in the isomerization originated at least partially from the water (98) (Fig. 34).* Hydrogen is removed and delivered stereospecifically not only at C-2 (only glucose is formed in the isomerization, not mannose), but also at C-1 as shown by the fact that glucose-*1-d* phosphate loses no deuterium when it is equilibrated with fructose-*1-d* phosphate (98) (Fig. 35). However,

* Careful reinvestigation [I. A. Rose and E. L. O'Connell, *J. Biol. Chem.*, **236**, 3086 (1961); cf. I. A. Rose, *Brookhaven Symposia in Biology*, **15**, 293 (1962)] has indicated that the process shown in Figure 34 represents an oversimplification. When fructose-*1-(R)-t* 6-phosphate was isomerized by phosphoglucose isomerase and the glucose 6-phosphate formed was immediately trapped as the insoluble barium salt (to prevent back-reaction), about half the tritium was transferred from C-1 of fructose to C-2 of glucose and the other half of the hydrogen at C-2 of glucose was ordinary hydrogen derived from the water. (When the isomerization experiment is carried out in D_2O, about half the initially incorporated hydrogen is the deuterium isotope.) The result has been interpreted in terms of an enzyme–substrate complex in which a proton is first transferred from C-1 in fructose 6-phosphate to the enzyme; in part that same proton is transferred back to C-2 of glucose 6-phosphate, but in part exchange with the medium (water) occurs on the enzyme before the proton is delivered back to the substrate. [See also H. Simon, R. Medina, and G. Müllhofer, *Z. Naturforsch*, **23b** 59 (1968).]



R = CHOH—CHOH—CHOH—$CH_2OPO_3^{2-}$

Figure 34

when phosphomannose isomerase is used as the isomerizing enzyme for fructose-*1-d* phosphate, not only is the hydrogen delivered at C-2 from the opposite side (to give mannose in this case), but the hydrogen mobilized at C-1 is diastereotopic with that mobilized by phosphoglucose isomerase (Fig. 35). The absolute configuration of the hydrogens in question was elucidated (100), both for the phosphoglucose and the corresponding phosphoribose isomerization, by degrading the rearranged ketose to glycolic-*t* acid whose configuration was established enzymatically as indicated earlier (cf. Fig. 32). The total reaction sequence, shown in Figure 36, shows that in both instances the proton delivered by the enzyme becomes H_R and that the steric relation of the hydrogen abstracted from the aldose at C-2 to the hydrogen delivered to the ketose at C-1 is the same in the D-glucose and D-ribose isomerization as in the (R)-glyceraldehyde isomerization (Fig. 33). From the transformations shown in Figure 34, and, keeping in mind that the fructose 6-phosphate–mannose 6-phosphate interconversion is also reversible, it then follows that the hydrogen delivered to D-fructose 6-phosphate in the isomerization of D-mannose 6-phosphate has the opposite stereochemistry (H_S), but since the configuration of D-mannose at C-2 is also opposite to that of D-glucose, D-ribose, and (*R*)-glyceraldehyde, the *steric relation* of the hydrogen abstracted and the hydrogen delivered is still the same as in the other cases (100).

A reaction slightly more complex than those previously discussed, in that it involves a decarboxylation as well as an oxidation step, is the conversion of 6-phosphogluconic acid to ribulose 5-phosphate by the enzyme 6-phosphogluconate dehydrogenase in the presence of $NADP^+$ (Fig. 37). When the reaction was carried out in tritiated water (101), the ribulose 5-phosphate became tritiated at C-1. C-1 tritiated ribulose 5-phosphate

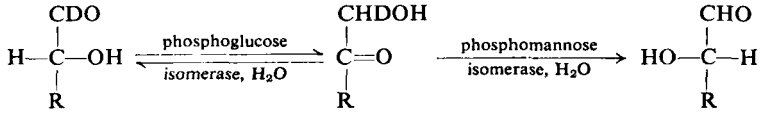
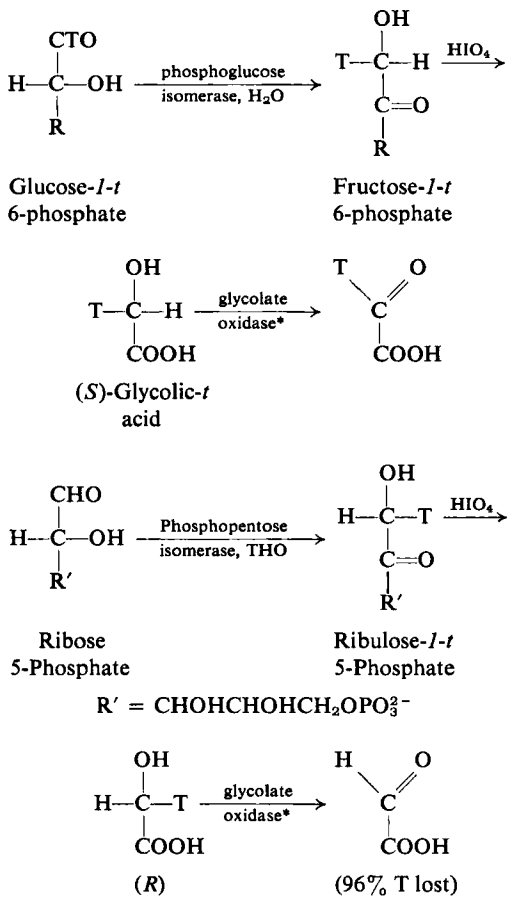


Figure 35



*From tobacco leaves.

Figure 36

could also be obtained from 6-phosphogluconic-2-*t* acid, but the two tritiated samples obtained by the two different paths were diastereoisomeric at C-1 (both having become specifically labeled), as shown by the finding (101) that the former sample rapidly lost its tritium when treated with 6-phosphogluconate dehydrogenase, H_2O, and NADPH, whereas the latter sample lost its tritium only very slowly. The configuration of the two ribulose-*1-t* 5-phosphates was established (101) by degradation to glycolic-*t* acid whose configuration was then shown, by enzymatic oxidation with tobacco leaf glycolic oxidase (*vide supra*), to be *R* in the first case and *S* in the second (cf. Fig. 37). It follows (Fig. 37) that the decarboxylation step proceeded with inversion of configuration.

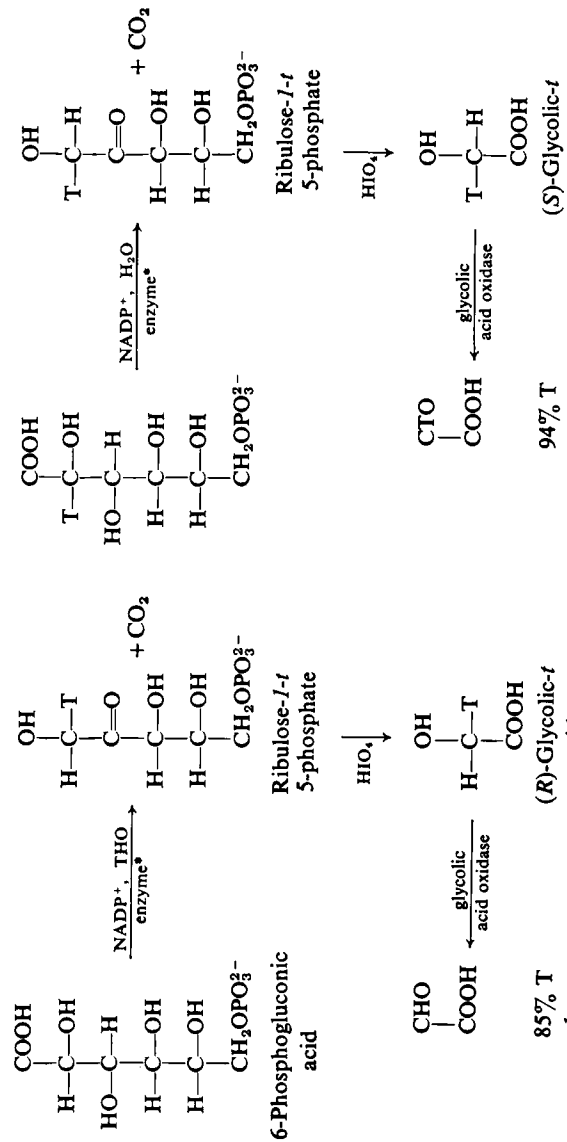

6-Phosphogluconic acid
NADP+, THO enzyme*
+ CO2
Ribulose-1-t 5-phosphate
HIO4
(R)-Glycolic-t acid
glycolic acid oxidase
85% T lost
Ribulose-1-t 5-phosphate
NADP+, H2O enzyme*
+ CO2
HIO4
(S)-Glycolic-t acid
glycolic acid oxidase
94% T retained

Figure 37

TABLE I

Stereochemical Course of Alcohol Oxidations or Disproportionations

Substrate	Enzyme	Hydrogen removed	Refs.
Ethanol	Yeast alcohol dehydrogenase	H_R	29, 72
	Liver alcohol dehydrogenase	H_R	*
Glycolic acid	Glycolate oxidase from tobacco leaves or spinach leaves	H_R	97
	Muscle lactate dehydrogenase	H_R	69
(*R*)-Glyceric acid	(*R*)-Glycerate dehydrogenase	H_R	91
Dihydroxyacetone phosphate	Aldolase	H_S	97
	Triose phosphate isomerase	H_R	97
Ribulose 5-phosphate	Phosphopentose isomerase	H_R	100
Fructose 6-phosphate	Phosphoglucose isomerase	H_R	100
	Phosphomannose isomerase	H_S	98

* See second footnote on p. 156

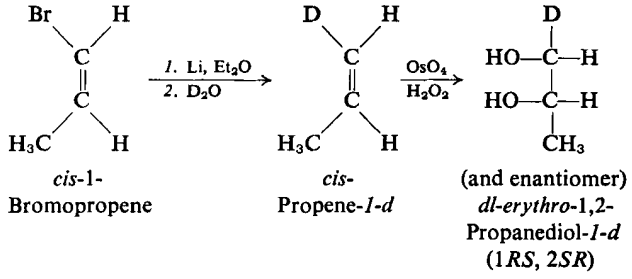
In Table I we have summarized the stereochemical course of a number of oxidations or disproportionations of alcohols RCH_2OH (usually studied as RCHDOH or RCHTOH) to the corresponding aldehydes RCHO.

E. 1,2-Propanediol

The configuration of the 1,2-propanediols has been of interest in connection with the propanediol dehydrase reaction (see Sect. IV-F). Elucidation of this problem involves an elegant combination of chemical (including NMR) and biochemical arguments.

Authentic specimen of *dl-erythro-* and *dl-threo*-1,2-propanediol-*1-d* were prepared (102) as shown in Figure 38. The configurations follow from the method of preparation if it is assumed, in accordance with precedent (103), that the reaction of a vinyl halide with lithium followed by water involves retention of configuration and the osmium tetroxide–hydrogen peroxide reaction involves *cis-* (or *syn-*) addition. The two diastereoisomers of 1,2-propanediol-*1-d* were characterized through the NMR spectra of their *p*-nitrobenzaldehyde acetals; as expected, the two spectra are distinct.

To elucidate the configuration of the optically active 1,2-propanediol-*1-d* isomers, two of the four possible stereoisomers were synthesized by reduction of (*R*)- and (*S*)-lactaldehyde, respectively, with NAD-D (actually



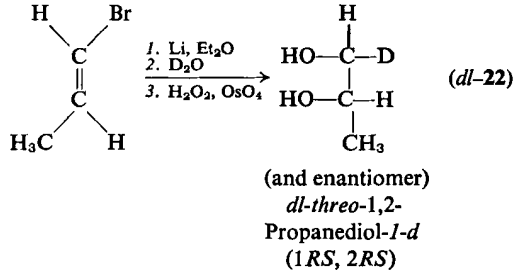


Figure 38

a coupled system: NAD^+ and CH_3CD_2OH) in the presence of LADH (104). Since the configuration at C-2 is not changed in the reduction, the (*R*)-lactaldehyde gives the levorotatory (2*R*)-1,2-propanediol-*1-d*, whereas the (*S*)-lactaldehyde gives the dextrorotatory (2*S*)-diol (Fig. 39). The NMR spectra of the *p*-nitrobenzaldehyde acetals of the two products showed that

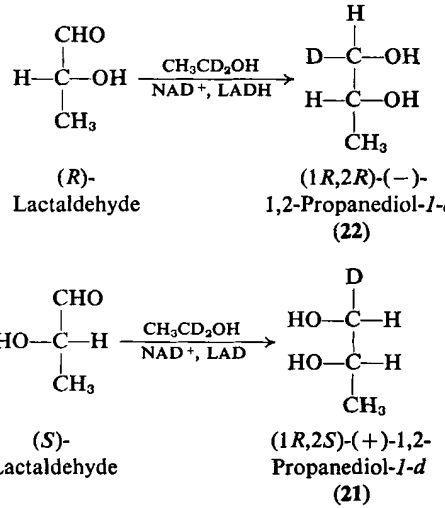


Figure 39

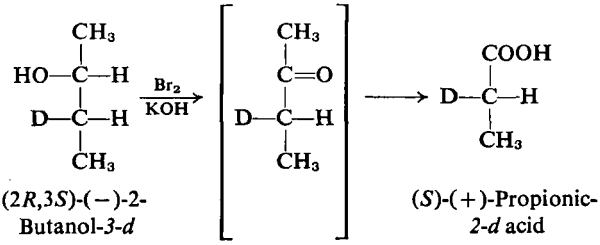
they were diastereoisomeric, and comparison with the corresponding derivatives of the authentic *erythro* and *threo* racemates (Fig. 38) disclosed that **22** was the *threo*-isomer and **21** the *erythro*. Therefore the configuration of both **21** and **22** at C-1 is *R* and the course of the NAD-D–LADH reduction of either enantiomer of lactaldehyde takes the same steric course as that of acetaldehyde (Fig. 20), i.e., the newly introduced hydrogen is *pro-R*; this result is independent of the configuration at C-2.

F. Carboxylic Acids

(*S*)-(+)-Propionic-*2-d* acid, $[\alpha]_{230}$ + 82 ± 3° (H_2O), $[\alpha]_{400}$ + 2°, has been synthesized (105) from (*R*)-(+)-2,3-epoxybutane by lithium aluminum deuteride reduction (Fig. 13) followed by hyprobromite oxidation of the (2*R*,3*S*)-(−)-2-butanol-*3-d* so obtained (Fig. 40).*

Since the starting epoxide and alcohol were optically pure, the method should give optically pure acid, provided no racemization occurs at C-3 in the intermediate ketone (Fig. 40). Such racemization is very unlikely since no H–D exchange at C-3 was observed and since, in any case, any anion formed at C-3 should have been intercepted by bromine and thus should not have given rise to propionic acid.

(*R*)-(−)-Propionic-*2-d* acid has been prepared from (*S*)-(−)-alanine in three steps as shown in Figure 41 (106). Since the rotation of the bromopropionic acid intermediate (Fig. 41) corresponds to only about 50% of the maximum value in the literature, the observed specific rotation, $[\alpha]_{400}$ − 1.54° (solvent not specified) of the propionic-*2-d* acid (Fig. 41) must represent a value for the optically pure material of at least 3° (quite possibly more, since there may have been further racemization in the reduction of the bromoacid). It is surprising that this value should be greater than the observed value for the (*S*)-(+)-acid (*vide supra*) which, by



(2*R*,3*S*)-(−)-2-Butanol-*3-d*

(*S*)-(+)-Propionic-*2-d* acid

Figure 40

* The CD curve of the compound has been measured by G. Snatzke and shows a maximum at 203 nm (unpublished observation).

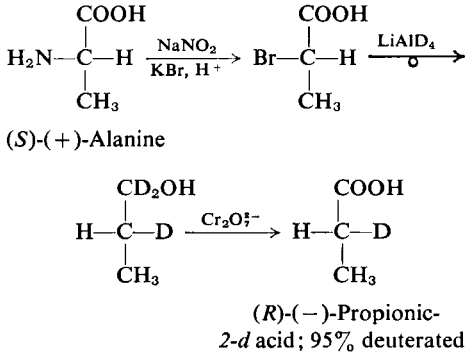


Figure 41

its method of preparation (Fig. 40), might be expected to be optically pure. Both samples had an isotopic purity of 95%.

(*S*)-(+)-Propionic-*2-d* acid has been prepared from (*R*)-(−)-alanine by the same method as its enantiomer (106). A somewhat similar method has also been used (107) to prepare (*R*)-(−)-propionic-*2-d* acid from methyl (*S*)-(−)-lactate by lithium aluminum deuteride reduction of the corresponding tosylate followed by reoxidation of the primary alcohol so obtained (Fig. 42). The material had $[\alpha]_{230} - 74 \pm 3°$ and was therefore somewhat less optically pure than the sample obtained from the epoxide (Fig. 40), perhaps because of slight racemization during the tosylate reduction, in analogy with the cases mentioned earlier. Isotopic purity was again 95%. (*R*)-Propionic-*2-d* acid has also been prepared by homologation of (*S*)-(−)-ethanol-*1-d* (Fig. 43) (104b).

Knowledge of the configuration of propionic-*2-d* acid has been utilized to establish the steric course of the conversion of 1,2-propanediol to propionaldehyde in the presence of propanediol dehydrase and a B_{12}-coenzyme. It is known that both enantiomers of 1,2-propanediol undergo the reaction. By employing diols specifically deuterated at C-1 (Fig. 39) and of known configuration, it was possible to show (102,104) that H_R-1 migrates in the (2*R*) enantiomer whereas H_S-1 migrates in the (2*S*) enantiomer (Fig. 44).

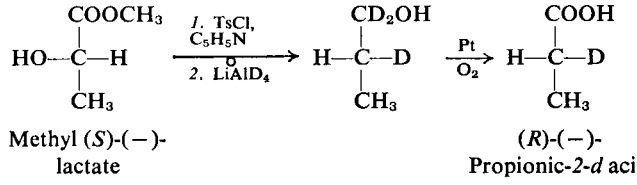
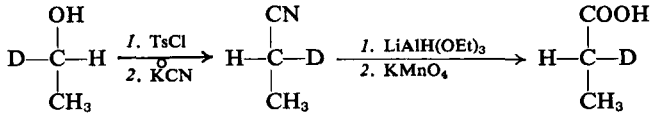


Figure 42

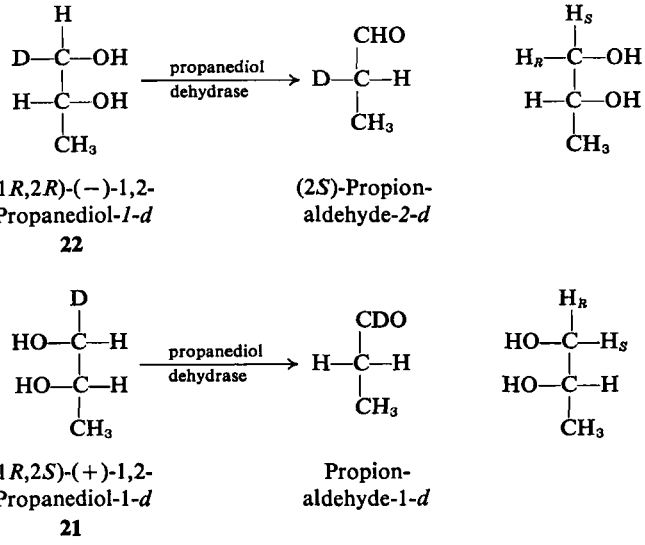


(*S*)-(−)-Ethanol-*1-d* | (*R*)-Propionitrile-*2-d* | (*R*)-Propionic-*2-d* acid (ORD of Na salt negative)

Figure 43

The stereochemistry at the reaction terminus was established (105) by allowing the reaction to proceed with (*S*)-propanediol-*2-d* and (*R*)-propanediol-*1,1-d*$_2$ prepared as shown in Figure 45. Rearrangement of both species in the presence of propanediol dehydrase from *Aerobacter aerogenes* and B_{12}-coenzyme gave propionaldehyde-*2-d* which, to avoid exchange, was reduced *in situ* to propanol-*2-d* by means of added NADH–YAD. The alcohol was finally oxidized to propionic-*2-d* acid which, in both cases, proved to be dextrorotatory, i.e., *S* (*vide supra*). It follows (cf. Fig. 45) that the propanediol rearrangement involves inversion at the migration terminus.

In an independent investigation (104b) the same conclusion was reached by oxidizing the propionaldehyde-*2-d*, obtained as shown in Figure 44, with potassium permanganate to propionic-*2-d* acid whose configuration was established to be *S* through comparison of its ORD



(1*R*,2*R*)-(−)-1,2-Propanediol-*1-d* **22** | (2*S*)-Propionaldehyde-*2-d*

(1*R*,2*S*)-(+)-1,2-Propanediol-1-*d* **21** | Propionaldehyde-1-*d*

Figure 44

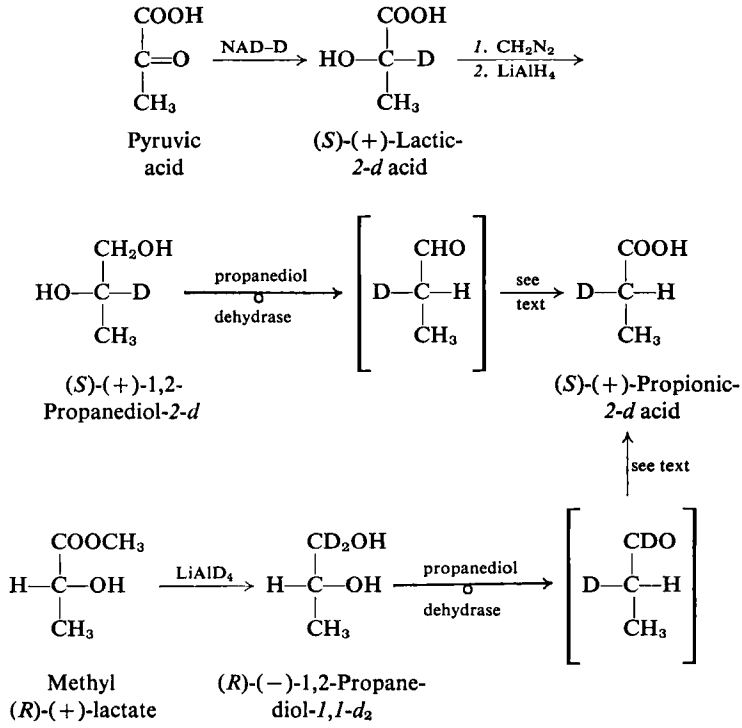
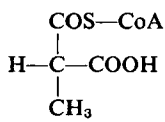


Figure 45

curve with that of an authentic specimen of the salt of the *R*-acid (Fig. 43); the two curves were opposite in sign.

Both (*S*)-propionic-2-*t* acid (108) and its *R*-isomer (109) have been synthesized by routes analogous to those shown for the deuterated homologs in Figures 40 and 43, respectively. The acids were distinguished by the fact that on treatment of the corresponding acyl-SCoA compounds with bicarbonate in the presence of propionyl-CoA carboxylase, the *S*-isomer gave a methylmalonyl-SCoA which retained 80% of its tritium (108), whereas the *R*-isomer lost over 95% of its tritium (109). [For comparison, racemic propionic-2-*t* acid retains 30% of its tritium (108)]. It might be mentioned here (see also p. 201) that the methylmalonyl-SCoA thus obtained has been shown by two groups of investigators (108, 110, 111) to have the *S*-configuration (**23**) and it follows, therefore, that the



23

enzymatic carboxylation of propionic acid proceeds with retention of configuration (108). This result has been confirmed by carboxylation of stereospecifically 2-deuteriolabeled propionic acids (106).

Of the higher monofunctional carboxylic acids, only stearic acid stereospecifically labeled in the 9- and 10-positions has been subjected to determination of configuration, in conjunction with the elucidation of the steric course of its dehydrogenation to oleic acid using *Corynebacterium diphtheriae* (112).

Starting with methyl (−)-9-hydroxystearate of natural origin [whose configuration had been previously (113) established and was confirmed in the present work], the *R*- and *S*-isomers of stearic-*9-t* acid were synthesized as shown in Figure 46. The *R*- and *S*-isomers of stearic-*10-t* acid were similarly synthesized from the two enantiomeric 10-hydroxystearic acids; the hydroxy acid giving a levorotatory methyl ester* is obtained by enzymatic hydration of oleic acid in the presence of a *Pseudomonas* species. The configurational correlations are summarized in Figure 47 which shows

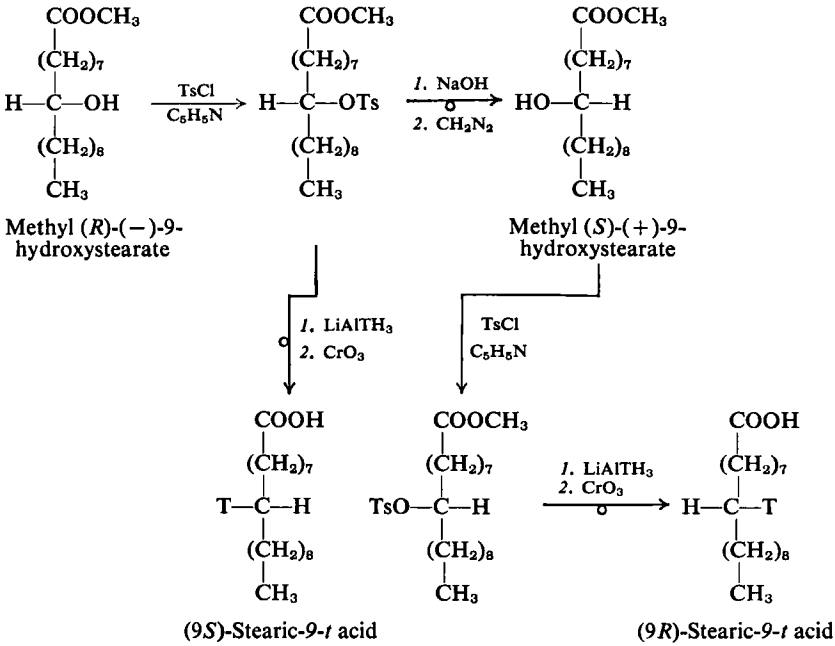


Figure 46

*9- and 10-Hydroxystearic acids themselves have negligible optical rotation, presumably because of the small difference in their hydrocarbon chains, $(CH_2)_nCOOH$ and $(CH_2)_nCH_3$ where $n = 7$ or 8. The rotations of the methyl esters are small but measurable.

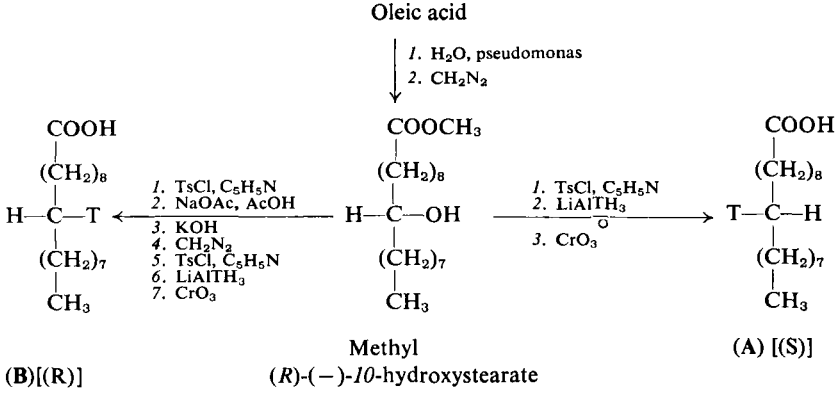


Figure 47

the correct absolute configurations of all the compounds involved; these configurations were actually not known at the outset of the investigation (112), but may be deduced from an argument to be presented below. With the four stereospecifically labeled stearic-acids (9*R*-*t*, 9*S*-*t*, 10*R*-*t*, and 10*S*-*t*) available, the dehydrogenation of each one to oleic acid in the presence of *Corynebacterium diphtheriae* was investigated (112). It was found that the 9*R* and the 10**B** (cf. Fig. 47) compounds lost most of their tritium (65–69% in the former case, 89–91% in the latter*), whereas the enantiomeric 9*S* and 10**A** acids retained most of their tritium (89–93% in one case, 87% in the other). Moreover, it was found that the unreacted (9*R*)-stearic-9-*t* acid was enriched in tritium, pointing to an isotope effect in its dehydrogenation; none of the other three tritiated stearic acids was significantly changed in tritium content after partial dehydrogenation.

It follows from these results that the dehydrogenation is largely or completely stereospecific and that it involves removal of H_R at C-9 in the rate-determining step.

To prove the configuration of the H-10 removed, the series of reactions shown in Figure 48 was carried out (112). Hydrogenation of the *cis*-double bond of oleic acid with diimide-d_2 would be expected (114, 115) to proceed with *cis*-addition to give *dl-erythro*-stearic-9,10-d_2 acid as shown. Enzymatic dehydrogenation of the *erythro* acid led to oleic acid containing mostly d_2 and d_0 and relatively little d_1 material, and what there was of the

* The fact that tritium loss was not complete in one series and that some tritium was lost in the other is probably not due to incomplete stereospecificity of the enzymatic reaction, but rather to lack of stereochemical purity of the substrates. The apparently greater enantiomeric purity of 10**B** over 9*R* may reflect cleaner inversion in the tosylate–acetate reaction (Fig. 47) than in the tosylate–hydroxide reaction (Fig. 46).

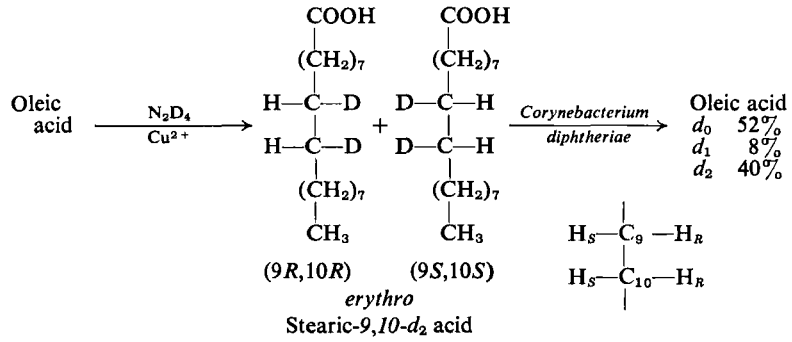


Figure 48

latter is in part accounted for by d_1 impurity of the stearic acid (90% d_2-labeled) and in part, probably, by incomplete stereospecificity of the diimide reaction. In view of the fact that the hydrogen affected at C-9 in stearic acid has already been shown to be H_R, it is clear from Figure 48 that the hydrogen atom mobilized at C-10 is H_R as well, resulting in elimination of D-9, D-10 from the (9*R*, 10*R*) isomer and in elimination of H-9, H-10 from the (9*S*, 10*S*) isomer. The result is incompatible with an elimination of H_S-10 since such elimination would produce an HD loss from either enantiomeric *erythro*-d_2 compound, rather than H_2 or D_2 loss as experimentally observed.

On the basis of the result shown in Figure 48 it follows that H_2 elimination from stearic acid by *Corynebacterium diphtheriae* is formally* *syn*. It also follows that the A-isomer of stearic-*10-t* acid (Fig. 47) has the *S*-configuration and the **B**-isomer has the *R*-configuration; and since **A** is obtained from methyl (−)-10-hydroxystearate by a single inversion ($LiAlTH_3$ step) and **B** by a double inversion (NaOAc and $LiAlTH_3$ steps), it follows that the levorotatory hydroxy ester has the configuration shown in Figure 47, i.e., *R*. This is a case, then, where the absolute configuration of a "classical" chiral center was established through a series of labeling experiments.

The hydration reaction of oleic acid using *Pseudomonas* (Fig. 47) was subsequently subjected to a more detailed stereochemical investigation (116) involving addition of D_2O. As shown in Figure 49, the hydroxyl group was eliminated in conventional fashion and the resulting stearic-*9-d* acid was dehydrogenated enzymatically with *Corynebacterium diphtheriae* giving oleic acid which retained 94% of its deuterium. Since the enzymatic

*The formalism involves the tacit assumption that the conformation of the transition state resembles that of the product, i.e. that the alkyl chains of the stearic acid are nearly eclipsed in the transition state.

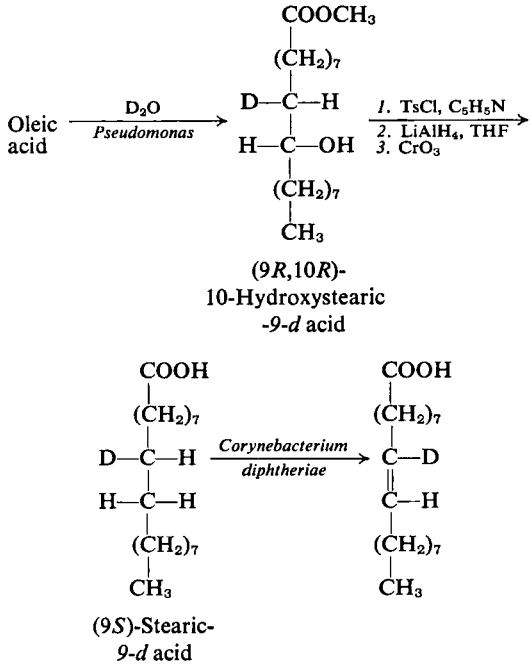


Figure 49

dehydrogenation removes H_R-9, it follows that the stearic acid was 9*S* and its precursor therefore 9*R* as shown.* Since the configuration at C-10 had already been proved to be *R* (*vide supra*), the addition of D_2O to oleic acid in the presence of the *Pseudomonas* species is *anti*, the deuterium at C-9 approaching the double bond from the *re–si* face and the hydroxyl at C-10 approaching from the *si–re* face.

Enzymatic dehydrogenation of octadecanoic-*11*-(*R*)-*t* acid in the presence of *Tetrahymena pyriformis* gives all-*cis*-6,9,12-octadecatrienoic-*11*-(*R*)-*t* acid which, in turn, has been converted, by malonic ester homologation, into all-*cis*-8,11,14-eicosatrienoic-*11*-(*R*)-*t*-acid (116a). The latter acid has served as a substrate in various enzymatic oxidations: the lipase-catalyzed oxygenation to 15-(*S*)-hydroperoxy-8,11,13-eicosanoic acid and the conversion, in the vesicular glands of sheep, to 12-hydroxy-*trans*, *trans*-8,10-heptadecadienoic acid and to prostaglandin E_1 and prostaglandin $F_{1\alpha}$. The stereochemical course of these transformations has been elucidated (116a).

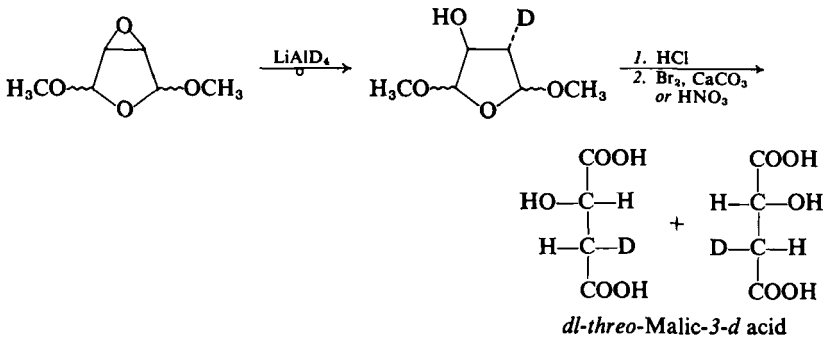
*This is one of the many cases where the configurational *symbol* changes (simply because of the way it is defined), although "the configuration" (i.e., the arrangement of identical or corresponding groups around the chiral center at C-9) does not.

A stereospecific hydrogen removal has also been demonstrated in the biosynthesis of oleic acid from (9*R*)- and (9*S*)-stearic-*9-t* acids and of linoleic acid from (12*R*)- and (12*S*)-stearic-*12-t* acids by *Chlorella vulgaris* (116b) and in the hydroxylation of (12*R*)- and (12*S*)-oleic-*12-t* acids to ricinoleic acid [(12*R*)-hydroxyoleic acid] in the castor bean (116c). In all these cases H_R is removed, the former two cases involving *cis*-elimination, the latter replacement with retention (116d).

The synthesis of (*R*)-(−)-hexanoic-*3-d* acid has already been mentioned (Fig. 26, p. 163). Attempted synthesis of various optically active α-deuterated acids, RCHDCOOH (where R = C_2H_5, *n*-C_4H_9 and $C_6H_5CH_2$) by decarboxylation of malonic acids $RCH(COOD)_2$ in various optically active bases (117) did not give material of significant optical activity.

The stereochemistry of hydration of fumaric acid to malic acid is of considerable interest, not only because of the intervention of this step in the citric acid cycle, but also because malic-*3-d* acid, containing both a conventional chiral center and one of the CHD type, serves as a convenient relay for the configurational correlation of other CHD compounds, particularly succinic-*d* acid. Malic-*3-d* acid, HOOCCHOHCHDCOOH, can, of course, exist in four stereoisomeric forms, the (*R*)- and (*S*)-*erythro*- and the (*R*)- and (*S*)-*threo*.* Whether the acid is *R* or *S* can easily be determined from optical rotation, since it is known that the *S*-configuration corresponds to the levorotatory acid. *Erythro*- and *threo*-configurations can be distinguished by either IR or NMR spectroscopy (*vide infra*) and thus all four isomers are readily characterized.

After some initial uncertainty (118,119) the configuration of malic-*3-d* acid was determined by two groups of investigators (120,121) by the method



dl-threo-Malic-*3-d* acid

Figure 50

*Here *R* and *S* refer to the configuration of the conventional (carbinol) chiral center at C-2. Alternatively, the *erythro*-configurations may be designed (2*R*,3*S*) and (2*S*,3*R*), whereas the *threo* isomers are (2*R*,3*R*) and (2*S*,3*S*).

shown in Figure 50. The reaction of 3,4-epoxy-2,5-dimethoxytetrahydrofuran with lithium aluminum deuteride may be assumed, in accordance with other epoxide openings, to proceed with inversion of configuration. Subsequent opening of the tetrahydrofuran ring then leads to the *threo*-isomer of malic-*3-d* acid, obtained, of course, as a *dl*-pair. The material was characterized (as disodium salt) by its relatively small H-2/H-3 coupling constant (ca. 4 Hz), which is as expected, since the hydrogens are *gauche* in the preferred conformation shown in Figure 51 (carboxyl groups *anti*). In contrast, the salt of (*S*)-(−)-malic acid obtained by the stereospecific* (122,123) addition of D_2O to fumaric acid in the presence of the enzyme pig heart fumarase shows a different NMR spectrum and a coupling constant of 6–7 Hz (cf. Fig. 51; in this isomer the H-2 and H-3 protons are predominantly *anti* to each other); this acid has thus the *erythro*-configuration and is therefore (2*S*,3*R*)-malic-*3-d* acid (Fig. 51).

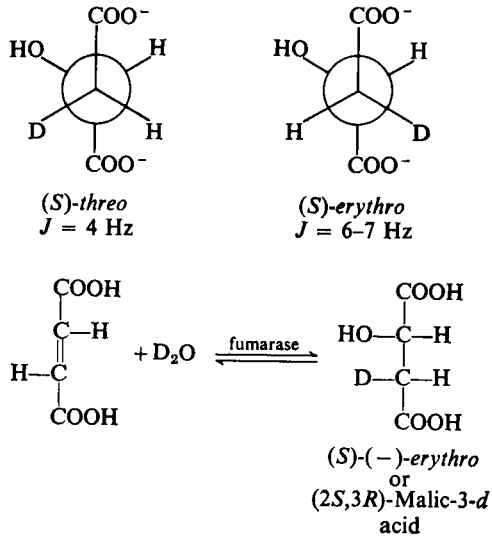


Figure 51

*The stereospecificity of the addition is inferred from the finding (122) that even after the reversible, fumarase-catalyzed addition of D_2O to fumaric acid (Fig. 51) has gone on for some time, the recovered fumaric acid does not become labeled and not more than one deuterium is incorporated in the malic acid. If the deuterium labeling were not confined to *one* of the two heterotopic C-3 hydrogens, the recovered fumaric acid would necessarily become doubly labeled and some molecules of malic acid would eventually acquire as many as three deuterium atoms. The stereospecificity of the D_2O addition catalyzed by bacterial fumarase (123) is similarly shown to be the same as that catalyzed by pig heart fumarase: malic-*3-d* acid obtained with bacterial fumarase returns unlabeled fumaric acid when dehydrated with pig heart fumarase.

Maleic acid, the *cis*-isomer of fumaric acid, also undergoes stereospecific addition of D_2O in the presence of an enzyme isolated from rabbit kidney (maleate hydratase) (124). The product is (*R*)-(+)-malic-*3-d* acid, identified as the cinchonidine salt and was, moreover, shown to be *threo* through measurement of J_{23} which was found to be 4.2 ± 0.1 Hz. The absolute configuration of this material is thus represented by the last formula in Figure 50; comparison with Figure 51 shows that configuration at C-3 is the same as in the fumarase-catalyzed addition of D_2O to fumaric acid, but configuration at C-2 is opposite. As may be seen in Figure 52, addition of D_2O to both fumaric and maleic acid involves a *re*-attack of D^+ and an attack at the opposite face (i.e., *anti*) of OH^-.*

Closely related to the addition of water to fumaric acid to give malic acid is the addition of ammonia in the presence of the enzyme aspartase to give (*S*)-(−)-aspartic acid. When the reaction is carried out in D_2O (which is equivalent to adding ND_3, since the protons of water and ammonia are in rapid exchange) (*S*)-(−)-aspartic-*3-d* acid is formed stereospecifically (125). The steric course of the ammonia addition was shown by Krasna (125) to be analogous to that of the water addition in the manner indicated in Figure 53. Chemical conversion of the (*S*)-(−)-aspartic-3-*d* acid obtained in the ND_3 addition to malic acid by means of nitrous acid gave the (−)-*erythro*-isomer, the sign of rotation following from direct polarimetric observation and the *erythro*-configuration from the NMR coupling constant (6 Hz) which was the same as that of a sample obtained by direct enzymatic

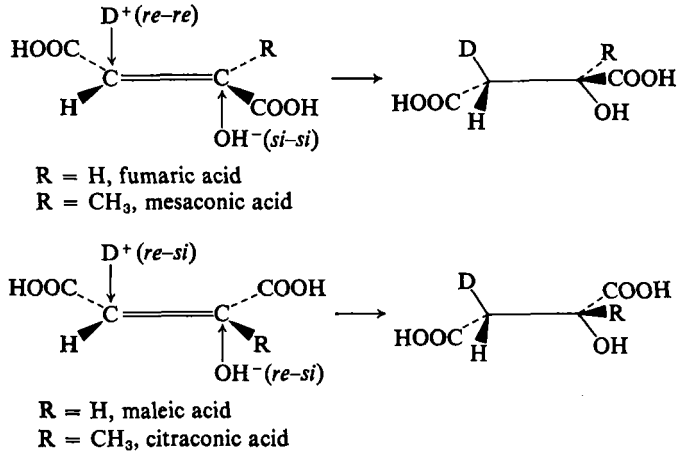


Figure 52

*Further confirmation of the (*R*)-configuration at C-3 comes from reduction, via 2-chlorosuccinic-*3-d* acid, to (−)-succinic-*d* acid, *vide infra*.

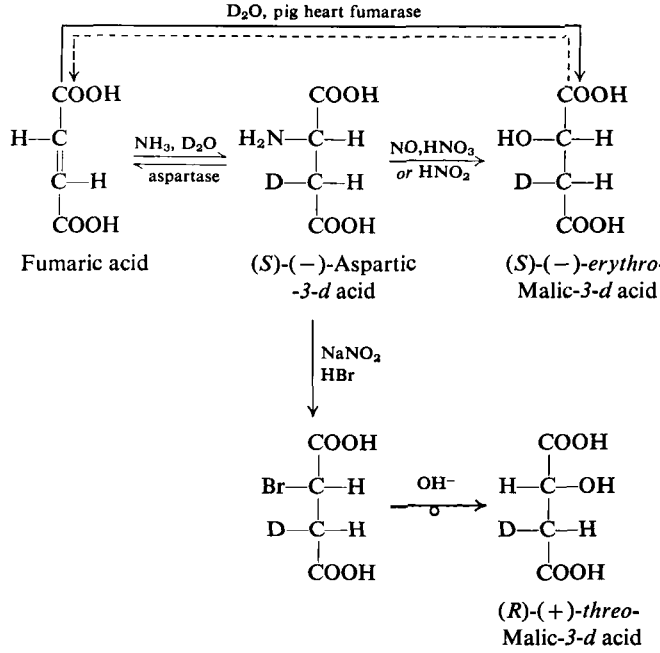


Figure 53

hydration of fumaric acid (as was the sign of optical rotation). Since the absolute configurations of (−)-malic and (−)-aspartic acids are known to be *S*, and since no change of configuration is expected at C-3 in the nitrous acid reaction (no deuterium was lost), it follows that the configuration of both acids at C-3 is *R* and that the aspartic-*3-d* acid also is the *erythro*-isomer. Confirmation of this result was obtained by transforming the (−)-aspartic to (+)-malic acid in two steps of which the first (conversion to 2-bromosuccinic-*3-d* acid by NOBr) involves retention at C-2, and the second (replacement of Br by OH using hydroxide) involves inversion. Here again, no change of configuration at C-3 is expected (although this time 20% of the deuterium was lost, presumably by a base-catalyzed exchange) and therefore the *threo*-isomer of (*R*)-(+)-malic-*3-d* acid should be obtained; in fact, the NMR spectrum of the material was different from that of the *erythro*-isomer and showed the typical 4-Hz coupling constant.*

*It should be noted that the correct assignment of configuration at C-3 of aspartic and malic acid is dependent on the correct assignment of the C-2/C-3 relative configuration (*erythro* or *threo*). At the time Krasna's and Englard's papers appeared, the relative configurational assignments were still inverted in the literature, and although the findings in refs. 123 and 125 are internally consistent as well as experimentally correct, the conclusions as to the C-3 configuration are the reverse of those now known to be the right ones.

An independent confirmation (123) of the correspondence of configuration at C-3 in enzymatically synthesized malic-*3-d* and aspartic-*3-d* acids is indicated by the dashed line in Figure 53: when the aspartic-*3-d* acid was converted to malic-*3-d* acid by nitrous acid and the latter then dehydrated enzymatically, all but 3% of the deuterium was lost in the recovered fumaric acid.

(*S*)-(−)-Aspartic acid serves as a biosynthetic source of ammonia in certain amination reactions, such as citrulline → arginine or 1-hydroxypurine → 1-aminopurine (in nucleotides), as well as in certain amidation reactions ($RCOOH \rightarrow RCONH_2$); in the process, it is converted to fumaric acid. It has been shown (126,127) in three such cases that the stereochemistry of the reaction is the same as in the aspartase-catalyzed direct conversion to fumaric acid.

The stereochemistry of the enzymatic addition of water to both mesaconic acid and citraconic acid to give citramalic acid (Fig. 54) has been studied in detail (128) and was found to be entirely analogous to that of the addition of water to fumaric and maleic acid (Fig. 52). The absolute configuration of (+)-citramalic acid was proved (129) to be *S* by classical correlation with (+)-mevalolactone of known (130) *S*-configuration (Fig. 55), and the relative configuration of C-2 and C-3 in enzymatically synthesized citramalic-*3-d* acid was elucidated by synthesizing the (2*RS*,3*RS*)-acid* by a method analogous to that shown in Figure 50 for the lower

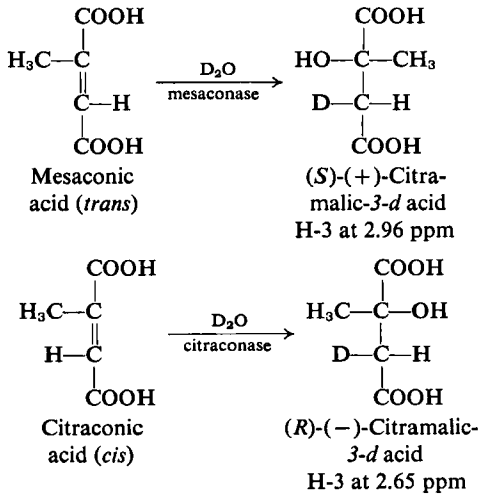


Figure 54

* The *threo–erythro* nomenclature is not conveniently applied to this acid; therefore, the systematic configurational symbolism for a racemic diastereoisomer (35) is used.

homolog (Fig. 55). The (2*RS*,3*RS*)-citramalic-*3-d* acid is characterized by the H-3 proton NMR signal at 2.68 ppm; since ordinary (unlabeled) citramalic acid shows an AB signal for the two H-3 protons with centers at 2.68 and 2.91 ppm, the 2.91 ppm signal must correspond to the second (diastereotopic) proton at C-3. As is seen in Figure 54, addition of D_2O to mesaconic acid in the presence of the enzyme mesaconase from *Clostridium tetanomorphum* gives dextrorotatory (i.e., *S*) citramalic acid whose relative configuration at C-3 follows from the nonidentity of the H-3 NMR signal with that in the synthetic (2*RS*,3*RS*)-acid (Fig. 55); the material is therefore (2*S*,3*R*), and the D_2O addition is *anti*.

The addition of D_2O to citraconic acid in the presence of citraconase from *Pseudomonas fluorescens* proceeds in *anti* fashion also; the citramalic acid obtained has the opposite rotation (−) from that derived from mesaconic acid and its NMR spectrum is different also (131) (Fig. 54). It may be inferred that the citraconate-derived citramalic acid has the opposite configuration at C-2 and the same configuration at C-3 as the mesaconate-derived acid, and since the latter acid is (2*S*,3*R*) (*vide supra*), the former must be (2*R*,3*R*). Accordingly, the citraconate-derived (2*R*,3*R*) acid has the same NMR spectrum as the synthetic acid shown in Figure 55 (128a).

The complete stereochemistry of the water addition to mesaconic and citraconic acids is shown in Figure 52.

By the above-mentioned procedures, the (2*S*,3*R*) and (2*R*,3*R*) isomers of citramalic-*3-d* acid are available. The remaining two diastereoisomers, (2*S*,3*S*) and (2*R*,3*S*), have been synthesized stereospecifically (128a) by the

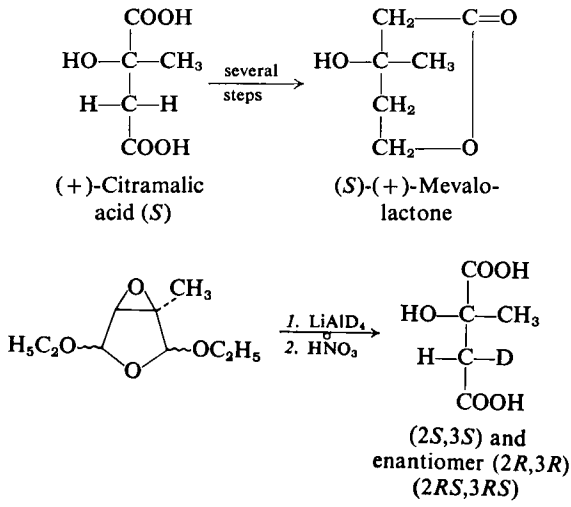


Figure 55

enzymatic addition of ordinary water (H_2O) to mesaconic-*3-d* and citraconic-*3-d* acid, respectively. Methods, to be discussed later, were developed to convert two of these isomers into the natural (3*R*)-mevalolactone stereospecifically deuterium labeled at either of the C-2 or either of the C-4 positions (p. 224).

One of the key reactions in the citric acid cycle is the reversible hydration–dehydration of aconitic acid to either citric acid or isocitric acid catalyzed by the enzyme aconitase. The reactions, together with the formation of citric acid from oxaloacetic acid and acetyl-CoA and the oxidation and decarboxylation of isocitric acid to α-ketoglutaric acid are shown in Figure 56. The steric course of the addition of water to *cis*-aconitic acid to give (+)-isocitric acid is relatively readily elucidated* since the dissymmetry of isocitric acid at C-2 and C-3 is of the conventional type, and once it was established, both by X-ray methods (relative C-2/C-3 configuration: 132; absolute configuration: 133) and by classical stereochemical correlation (relative C-2/C-3 configuration: 134; absolute configurational correlation: 135, 136) that (+)-isocitric acid is (2*R*,3*S*), both the relative (*anti*) and absolute stereochemistry of the addition process followed.

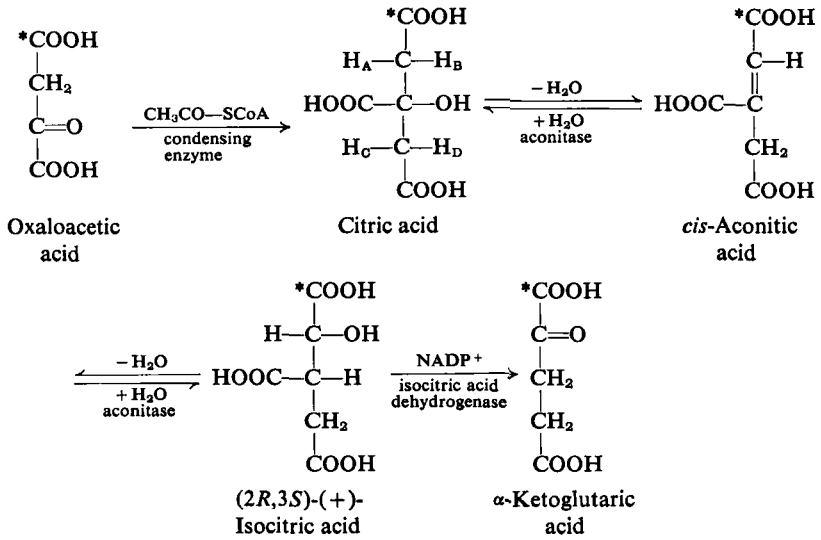


Figure 56

*It must, however, be pointed out, that for about five crucial years the absolute configuration of isocitric acid was incorrectly assigned on the basis of empirical rules based on rotation [J. P. Greenstein, N. Izumiya, M. Winitz, and S. M. Birnbaum, *J. Amer. Chem. Soc.*, **77**, 707 (1955); M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **77**, 716 (1955)].

The stereochemistry of the formation of citric acid from aconitic acid on one hand* and from oxaloacetic on the other is, in principle, more complex. As explained earlier (Fig. 10), citric acid has four stereotopically different methylene hydrogens—two enantiotopic sets, H_A/H_C and H_B/H_D (Fig. 10) which, with respect to each other, are diastereotopic (i.e., H_A and H_B are diastereotopic as are H_C and H_D). Toward an enzyme, all four hydrogens are, in principle, distinct. In fact, it was shown several years ago by Englard and Colowick (137) that, when aconitic acid is incubated with aconitase in the presence of D_2O and thus brought into equilibrium with citric and isocitric acids, the citric acid acquires only *one* deuterium, the aconitic acid acquires none, and the isocitric acid also acquires one, located at C-3. This shows not only that the addition of D_2O to *cis*-aconitic acid to give citric acid is stereospecific, but also that, in the reverse reaction, only one of the four methylene hydrogens is activated, namely, the same one which originated from the D_2O in the addition.

In order to deduce which hydrogen is the labile one, it is best to factorize the problem into two parts: one, to find out which of the two enantiotopic CH_2COOH groups contains the mobile hydrogen, and the second, to elucidate which of the two diastereotopic hydrogens in the aconitase-active CH_2COOH group is implicated in the water elimination. Priority in solving the first problem belongs to Hanson and Rose (138); however, in order to present the solution in what we consider the simplest fashion, we shall, to some extent, deviate from the historical order.

Early research (139–142) had already indicated, through carbon-labeling experiments, that the oxaloacetic acid-derived CH_2COOH group of citric acid is also the aconitase active one; this information has been indicated in Figure 56 by placing an asterisk on the pertinent labeled COOH group. There was even some tentative evidence, based on deuterium labeling, albeit derived from rotation rules, as to which end of citric acid was which (143; see, however, the contrary but incorrect inference in 144).

A conclusive identification of the aconitase-active CH_2COOH group was achieved in two ways (129, 138); as already explained, we shall present the later solution of the problem first. (*S*)-Citric 1-1-^{14}C acid of determined configuration was synthesized from a derivative of optically active chlorocitramalic acid whose configuration in turn was correlated with that of citramalic acid. Since the configuration of citramalic acid is known (Fig. 55), that of the citric-1-^{14}C acid follows, as shown in Figure 57. Dimethyl chlorocitramalate, obtained by a cyanohydrin synthesis from

*Although we shall always write the interconversion of isocitric and citric acids as if it proceeded via free aconitic acid, there is some evidence that free aconitic acid is not necessarily involved as an intermediate. The stereochemical arguments are not affected by this finding, however.

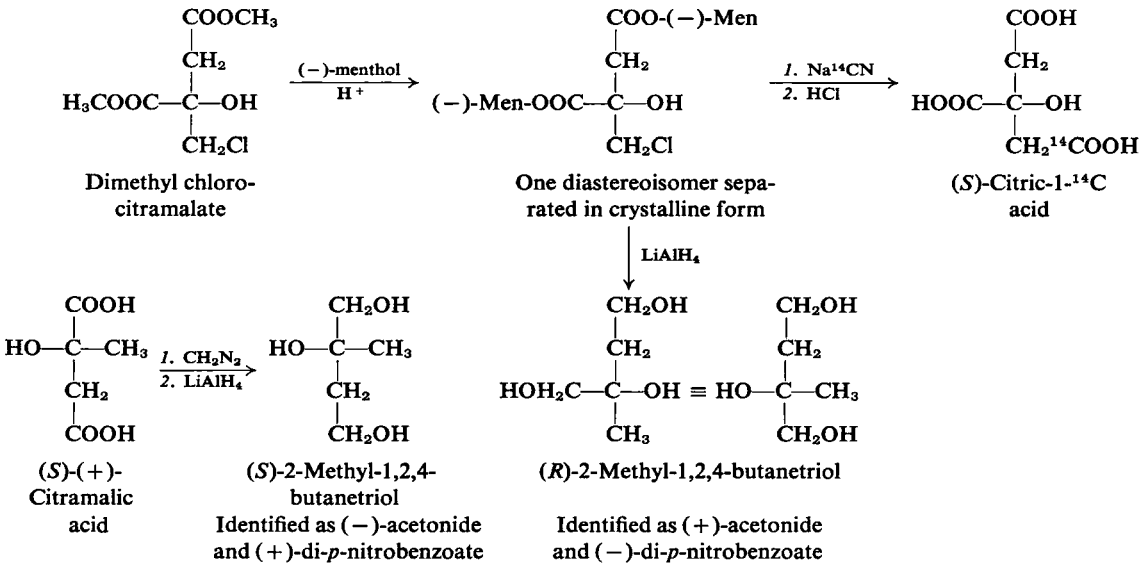

COOCH3
CH2
H3COOC—C—OH
CH2Cl
Dimethyl chloro-citramalate
(−)-menthol
H+
COO-(−)-Men
CH2
(−)-Men-OOC—C—OH
CH2Cl
One diastereoisomer separated in crystalline form
1. Na14CN
2. HCl
COOH
CH2
HOOC—C—OH
CH2 14COOH
(S)-Citric-1-14C acid
LiAlH4
COOH
HO—C—CH3
CH2
COOH
(S)-(+)-Citramalic acid
1. CH2N2
2. LiAlH4
CH2OH
HO—C—CH3
CH2
CH2OH
(S)-2-Methyl-1,2,4-butanetriol
Identified as (−)-acetonide and (+)-di-p-nitrobenzoate
CH2OH
CH2
HOH2C—C—OH ≡ HO—C—CH3
CH3
CH2OH
(R)-2-Methyl-1,2,4-butanetriol
Identified as (+)-acetonide and (−)-di-p-nitrobenzoate

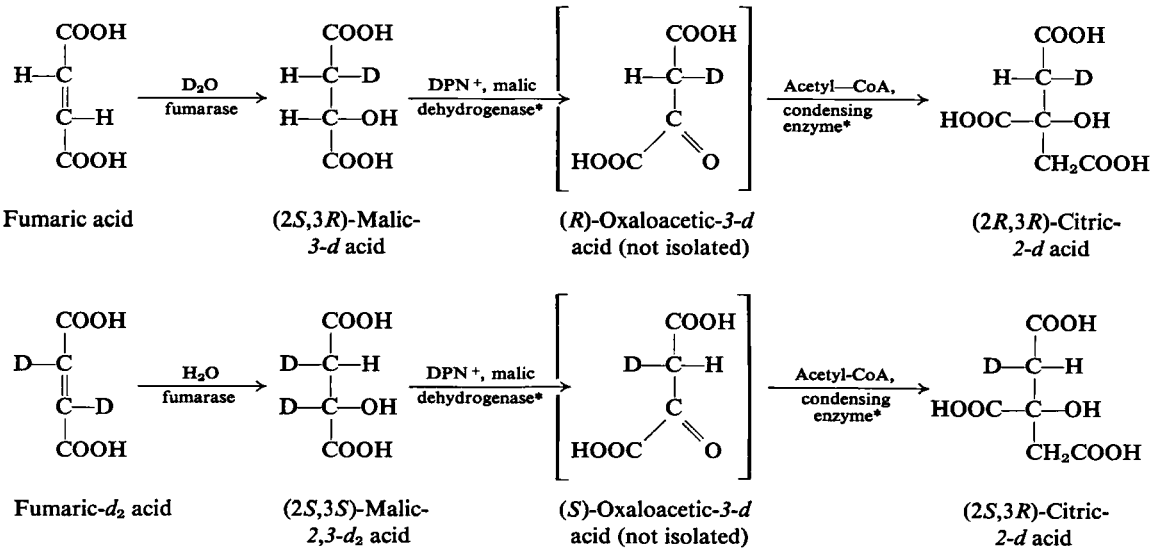
Figure 57

methyl chloroacetoacetate, was resolved by conversion to the diastereoisomeric dimenthyl esters, one of which was crystalline. The crystalline ester was reduced to 2-methyl-1,2,4-butanetriol, identified by the rotation of its crystalline derivatives to be *R*, since the same derivatives of the *S*-triol, obtained in turn by reduction of authentic (*S*)-(+)-citramalic acid, had the opposite rotation. The configuration of the chlorocitramalic acid moiety of the crystalline dimenthyl ester is thus *R* (Fig. 57), and chain extension with labeled cyanide finally gives (*S*)-citric-1-^{14}C acid. This acid, though chiral, is, of course, nonrotating, since the chirality depends only on the difference between ^{12}C and ^{14}C. The acid was completely characterized, however, by degradation through the citric acid cycle as shown in Figure 56 (using pig heart aconitase, isocitric acid dehydrogenase, and $NADP^+$) which gave 2-ketoglutaric-5-^{14}C acid*; the position of the label was readily† proved by further chemical oxidative degradation to succinic acid (which contained the radioactivity) and CO_2 (which was essentially inactive). It follows that the CH_2COOH branch shown at the top in Figures 56 and 57 is the aconitase active one; this branch (which is also the one derived from oxaloacetic acid) may properly be called $(CH_2COOH)_R$ by extension of the nomenclature introduced earlier from a single atom (such as H) to a ligand or group of atoms. It follows, furthermore, that the condensation of acetyl-CoA with oxaloacetic acid in the citric acid cycle in the presence of the common condensing enzyme (from pig heart) involves attack on the keto-carbonyl group from the *si*-side.†

Assignment of configuration to the enantiotopic CH_2COOH groups is equivalent to deciding that, in the notation of Figure 56, it is the pair of hydrogens H_A/H_B rather than H_C/H_D which is involved in the aconitase reaction, but it remains to be decided which of the two diastereotopic hydrogen atoms, H_A or H_B, is, in fact, eliminated. The answer to this question was provided (145) through a synthesis of citric acid from oxaloacetic acid specifically deuterium labeled at C-3 followed by a determination of which of the two hydrogens derived from C-3 in oxaloacetic acid was removed by aconitase. The complete sequence is shown in Figure 58; the required oxaloacetic-*3-d* acids (*R* and *S*) were biosynthesized from fumaric acid and fumaric-d_2 acid, respectively, via (*S*)-malic-*3-d* acid (3*R* and 3*S*) and were not actually isolated but were directly converted into citric-*2-d* acid, whose configuration at C-2 is either *R* or *S*, depending on its source, but whose configuration at C-3 is always *R*, since, as discussed earlier, it is the $(CH_2COOH)_R$ ligand which is derived from

*Condensing enzymes from other sources may give the opposite result [cf. G. Gottschalk and H. A. Barker, *Biochemistry*, **5**, 1125 (1966); **6**, 1027 (1967)].

†The reader should note that the citric acid shown in Figure 57 is labelled at the opposite end from that in Figure 56.



* These two reactions were carried out simultaneously.

Figure 58

oxaloacetic acid and which therefore becomes deuterium labeled in the above sequence.

In order to identify the hydrogen involved in the aconitase reaction, both citric-*2-d* acids shown in Figure 58 were treated with aconitase, isocitric dehydrogenase, and $NADP^+$ (cf. Fig. 56). The aconitase leads to dehydration of the citric acid to aconitic acid and then rehydration to isocitric acid. We have already seen that it is the labeled (i.e., *R*-) branch of the citric acid (the oxaloacetate-derived one) which is aconitase active. One substrate shown in Figure 58 will eliminate H, the other D, which substrate (citric acid) loses which isotope depending on the steric course of the reaction. In the case where hydrogen is eliminated, the isocitric acid eventually formed will have a CDOH group, but where deuterium is eliminated, the isocitric acid will have a CHOH group. The two cases are easily distinguished in the subsequent $NADP^+$-induced dehydrogenation (Fig. 56): The CDOH acid transfers deuterium and reduces the $NADP^+$ to NADP-D, whereas the CHOH-acid has no deuterium to transfer and the $NADP^+$ is converted to NADP-H. Experimentally it was found (145) that the (2*R*)-*d* acid transferred only hydrogen to $NADP^+$, but the (2*S*)-*d* acid transferred 80% of the expected amount of deuterium. Therefore the (2*R*)-acid (Fig. 58) lost its deuterium already in the conversion to aconitic acid and it follows that H_R is the hydrogen which is lost from the $(CH_2COOH)_R$ branch in citric acid. This information now completely specifies the steric course of the *cis*-aconitic acid—citric acid interconversion which is summarized (138) in Figure 59. It is seen that both processes are *anti* and that addition of the proton (and consequently of OH as well)

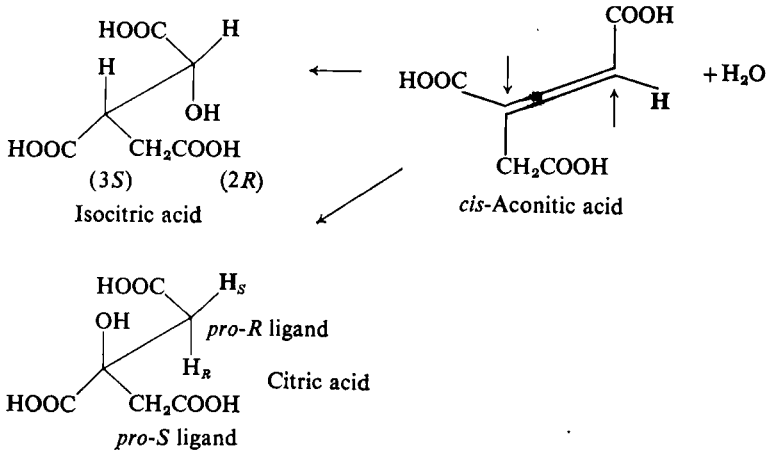


Figure 59

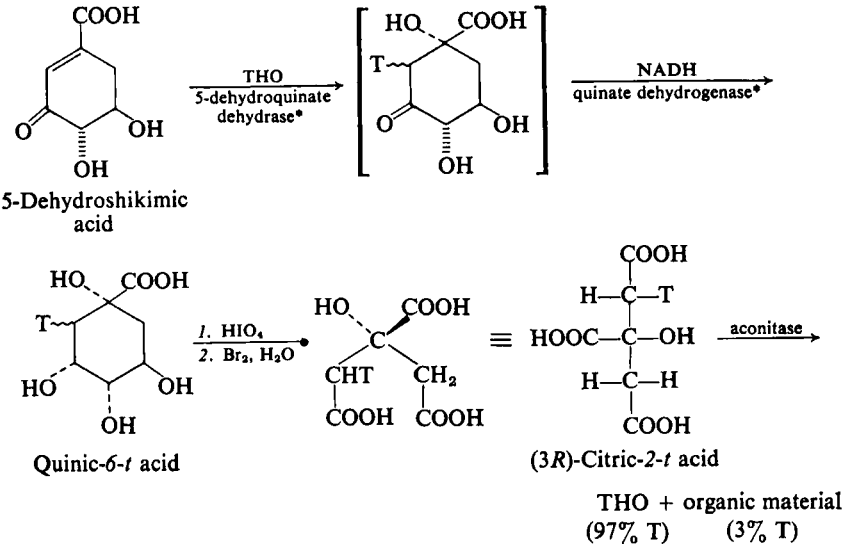


Figure 60

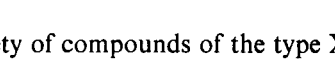
occurs from *different* sides with respect to the plane of the double bond, depending on whether citric or isocitric acid is being produced.

We shall now return to what was actually the first unequivocal determination as to which CH_2COOH group is the aconitase-active one (138): we have postponed description of this determination only because, unlike the one discussed earlier (p. 193), it can be understood only in conjunction with the stereochemistry embodied in Figure 58. The determination now to be presented involves a correlation of citric-*2-t* acid with quinic acid. The pertinent information is summarized in Figure 60. Enzymatic hydration of (−)-5-dehydroshikimic acid with THO and enzymatic reduction of the resulting keto acid gives quinic-*6-t* acid. The configuration at C-1 in this acid is known to be *R*; this follows from the known absolute configuration of (−)-5-dehydroshikimic acid and the known relative configuration of the COOH group in quinic acid. Oxidative degradation of (1*R*)-quinic-*6-t* acid necessarily gives (3*R*)-citric-*2-t* acid. When this acid (Fig. 60) was dehydrated with aconitase, 97% of the tritium was found in the water and only 3% in the aconitic acid and its transformation products (e.g., isocitric acid). It may be concluded directly that it is the *pro-R* CH_2COOH branch which is aconitase-active.†

* Steps performed jointly.

† If the water eliminated in the aconitase reaction had not contained the tritium it might have been because the tritium was in the aconitase-inactive CH_2COOH branch or because it was in the aconitase-active one, but in the wrong diastereotopic

The fact that the tritium was liberated in the water not only discloses that it was in the aconitase-active branch, but also, in conjunction with Englard's earlier-discussed work (145), indicates that the citric-*2-t* acid obtained in the degradation of quinic-*6-t* acid (Fig. 60) has the 2*R* configuration, as shown in the figure. It follows that in the quinic-*6-t* acid, the 1-hydroxyl group and the tritium are *cis*; the enzymatic addition of water to 5-dehydroshikimic acid therefore follows the rather unusual stereochemical course of *syn*-addition.

Succinic-*d* acid is a key reference compound in the determination of configuration of deuterated organic compounds. It has the advantage of being readily purified by crystallization,* of being readily obtainable from a variety of compounds of the type  (X and Y hetero atoms) by oxidative degradation, and of having a rather high specific rotation (ca. 20° at 250 nm) (146,147). In fact, a Cotton effect has been reported (124) for succinic acid with an extremum at 220 nm† and a specific rotation of 75°. The configurational correlation (146) of (−)-succinic-*d* acid with (2*S*,3*R*)-malic-*3-d* acid (*vide supra*) is shown in Figure 61 as is the independent correlation (147) with (2*S*,3*R*)-aspartic acid (*vide supra*). Both correlations agree in revealing the *R*-configuration for (−)-succinic-*2-d* acid. The correlation with malic acid was repeated later (124) by direct preparation of (2*S*,3*S*)-(−)-chlorosuccinic-*3-d* acid from (2*R*,3*R*)-malic-*3-d* acid (using $SOCl_2$-pyridine) followed by catalytic reduction of the chloro acid to (−)-succinic-*d* acid over palladium–charcoal.

(*S*)-(+)-Succinic-*d* acid was synthesized in a manner similar to that used for the (*R*)-(−)-enantiomer (Fig. 61, right half), but starting with (2*S*,3*S*)-(−)-aspartic-*3-d* acid (148). The starting material is less readily available than the (3*R*)-epimer; it must be prepared from fumaric-*2,3-*d_2 acid (cf. Fig. 58) by aspartase-catalyzed addition of ordinary ammonia. This, of

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position. In the former case, the isocitric acid obtained would have been of the CHOH type, in the latter, of the CTOH type; $NADP^+$ oxidation would have disclosed the difference. Several controls were carried out by Hanson and Rose (138) to eliminate the possibility of difficulties due to isotope effects.

*One would like to be able to say also that no change in isotopic composition occurs during crystallization. However, such changes do, in fact, occur, although fortunately they are usually small (< 5% deuterium in either direction). In the mass spectrometry of labeled succinic acid it is important to grind and homogenize the crystals, since appreciable fluctuations of deuterium content may occur in a single crystal (J. Rétey, J. Seibl, and D. Arigoni, personal communication).

†The CD curve measured by G. Snatzke (unpublished observations) shows the minimum for the (*R*)-d_1-acid near 208 nm, however.

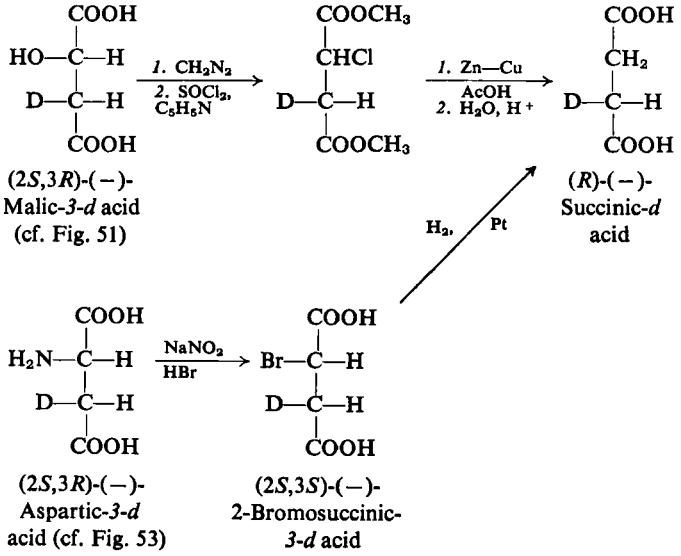


Figure 61

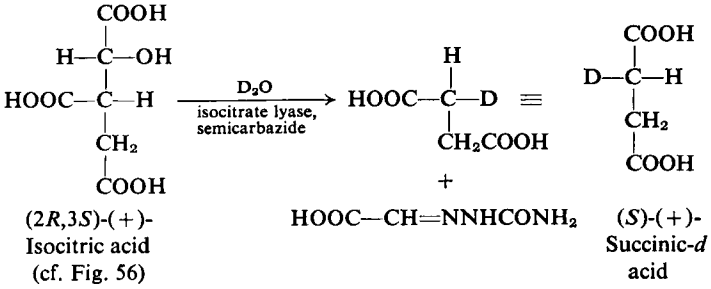
course, produces a 2,3-dideuterated aspartic acid; the deuterium at C-2 is removed, prior to chemical conversion to (*S*)-(−)-succinic-*d* acid (Fig. 61), by treating the aspartic acid with transaminase and H_2O, the offending deuterium being eliminated by reversible interconversion of the amino acid (in the form of a pyridoxal-linked Schiff base) to an imino acid, with the hydrogen reintroduced at C-2 coming from the water. The synthesis of (*S*)-(+)-succinic-*d* acid by catalytic deuterolysis of (*S*)-(−)-chlorosuccinic acid (deuterium gas over palladium) (149) leads to material of only 31% optical purity and the corresponding deuterolysis of (*S*)-(−)-bromosuccinic acid gives racemic succinic-*d* acid (148).

A rather simple synthesis of the relatively inaccessible (*S*)-(+)-succinic-*d* acid (150) starts with dimethyl (*R*)-(+)-chlorosuccinate, $MeOOCCHClCH_2COOMe$, available from the corresponding acid which, in turn, is readily prepared from (*R*)-(+)-aspartic acid, $NaNO_2$, HCl, and NaCl. Reduction of the chloro-diester with lithium aluminum deuteride proceeds with inversion to give $HOD_2CCHDCH_2CD_2OH$ which is then oxidized with Jones' reagent to (*S*)-(+)-succinic-*d* acid. The optical rotation, $[\alpha]_{250}$ + 19.5°, at 93.5% d_1-content shows that the acid is nearly optically pure. Other specifically deuterated and tritiated succinic acids, such as the (*R,R*)- and (*S,S*)-2,3-d_2 acids and the (*R*)- and (*S*)-2,2,3-d_3 acids, have been obtained, in most cases by enzymatic synthesis. A number of these compounds will be encountered in the sequel; a summary of the synthesis of all of them has been published (151).

An enzymatic reaction (151, 152) leading to (*S*)-(+)-succinic-*d* acid, albeit not in pure form, is shown in Figure 62. The reaction is of interest in disclosing inversion of configuration in what amounts to an enzyme-catalyzed reverse aldol condensation. No H–D exchange of the succinic acid occurs in the absence of glyoxylic acid, although such an exchange proceeding through an enzyme-bound enolate anion would be quite conceivable (cf. the case of aldolase, p. 170). Although reversal of the reaction shown in Figure 62 was largely prevented by the addition of semicarbazide (which intercepts the glyoxylic acid as semicarbazone), some back-reaction did occur as indicated by the incorporation of 1.4 D atoms (instead of 1) in the succinic acid. It is easy to see that back-reaction of the succinic-*d* acid may occur at either the deuterated or undeuterated methylene group; if it occurs at the undeuterated CH_2, the isocitric acid formed will be deuterated at C-4 (*S*-configuration) and will eventually give rise to (*S,S*)-(+)-succinic-*2,3*-d_2 acid. On the principle of optical superposition, this acid might be expected to have twice the specific rotation of the monodeuterated homolog, and, in fact, it was found that the acid containing 1.4 D had 1.4 times the rotation of authentic monodeuterated acid. Carrying out the isocitrate lyase reaction with D_2O in the absence of semicarbazide may, in fact, be a convenient way for synthesizing (2*S*,3*S*)-succinic-d_2 acid.

A rather interesting reaction, because it has no conventional chemical analogy, is the conversion of methylmalonyl-CoA to succinyl-CoA induced by beef liver mitochondria in the presence of a B_{12} coenzyme. The reaction involves migration of a CO—SCoA group from methine to methyl and replacement of the departed group by hydrogen (Fig. 63). Although the stereochemistry at the migration terminus (the methyl group) cannot be determined with presently available techniques, that at the migration origin has been shown (110b) to involve retention of configuration, as shown in Figure 63.

(*S*)-Methylmalonyl-CoA was synthesized enzymatically by carboxylation of propionyl-CoA (p. 181). Its configuration was determined (153)



(2*R*,3*S*)-(+)-Isocitric acid (cf. Fig. 56)

(*S*)-(+)-Succinic-*d* acid

Figure 62

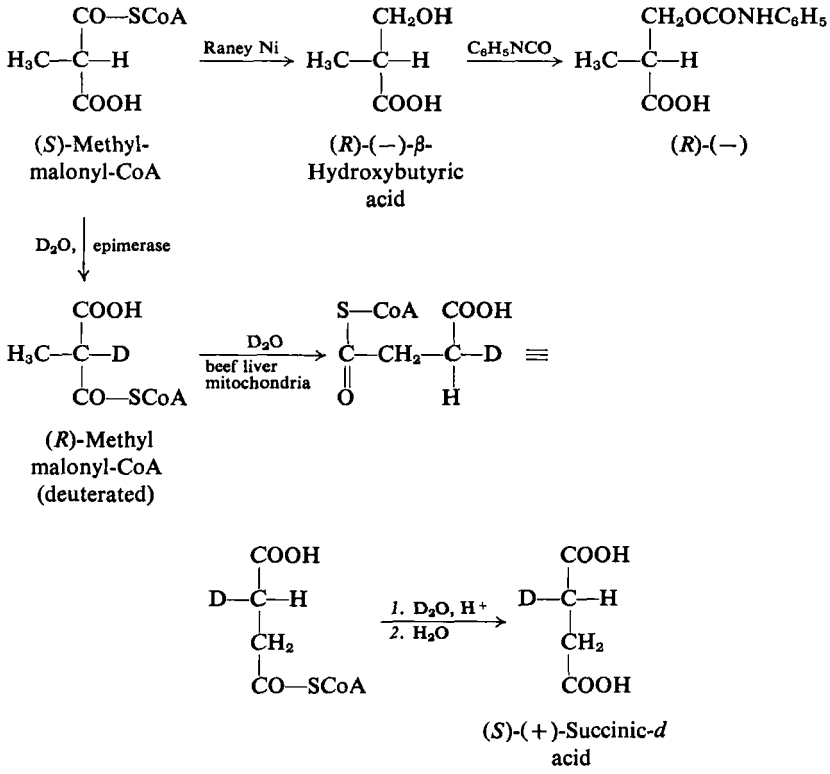


Figure 63

by rapid conversion to (*R*)-(−)-β-hydroxyisobutyric acid (some racemization unavoidably occurs in this process), identified by its levorotatory carbamate whose configuration, in turn, was established to be *R* by classical correlations. (*S*)-Methylmalonyl-CoA is not attacked by the beef liver mitochondria unless an epimerase enzyme is present which converts it to the *R*-isomer. By carrying out this epimerization in D_2O, 2-deuterated (*R*)-methylmalonyl-2-*d*-CoA was obtained and was then transformed enzymatically to 3-deuteriosuccinoyl-CoA which was hydrolyzed to succinic-*d* acid. The dextrorotation of this acid (which was not cleanly d_1, but through intervention of unknown processes also contained about 15% each of d_0 and d_2 material) shows that it is the *S*-isomer and that the migration shown in Figure 63 involves retention of configuration at the migration origin. (It should be noted that the hydrogen which takes the place of the CH_2CO—SCoA group is supplied intramolecularly by the methyl group.)

An entirely analogous stereochemical result has been obtained in the rearrangement of 2-deuteriomethylmalonyl-CoA with methylmalonyl-CoA

mutase from *Propionibacterium Shermanii*. In this case the contamination with d_0- and d_2-succinic acid was about 20% each and the rotation of the d_1 acid was the expected one on the assumption that the d_2 material was inactive (154).

A reaction which bears some resemblance to the previous one is the rearrangement of methylaspartate to glutamate (Fig. 64). The established configuration of succinic-*d* acid plays a part in this rearrangement, because it serves as a reference point in the determination of the configuration of glutamic-*4-d* acid (147). (2*S*,3*S*)-*threo*-Methylaspartic-*3-d* acid* was synthesized by the methylaspartase-catalyzed addition of deuterioammonia (as ND_4^+) to mesaconic acid (*anti*). Rearrangement, catalyzed by glutamate mutase (a reaction requiring a B_{12} coenzyme), gave (2*RS*,4*R*)-glutamic-*4-d* acid whose configuration at C-4 was shown to be *R* by oxidation to levorotatory succinic-*2-d* acid (Fig. 64) (147). In this case the (intramolecular) transfer of hydrogen to replace the departed $CH(NH_2)COOH$ group at C-3 of the methylaspartic acid proceeds with inversion of configuration.

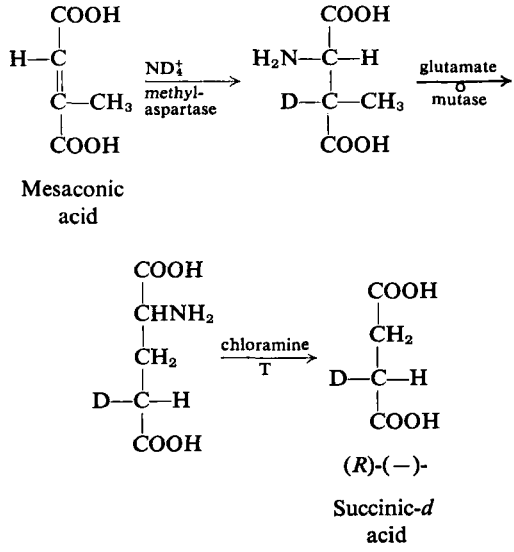
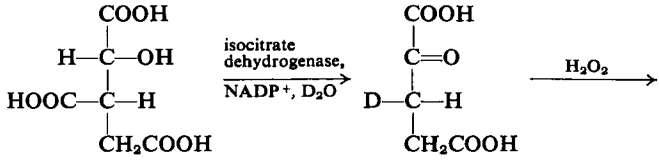


Figure 64

*The configuration at C-3 of the enzymatically produced acid is secure on the basis of a classical correlation with (*S*)-methylsuccinic acid (153). The configuration at C-2 is inferred to be *S* from the enzymatic behavior of the acid which is that of a natural amino acid. Since, during the rearrangement, racemization occurs at C-2 (because of the presence of a contaminating enzyme, glutamic acid racemase), the configuration at that center is of no further concern here.

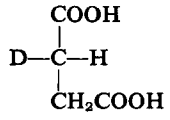
Reference to Figure 56 might suggest that in the last step there indicated, the conversion of isocitric acid to α-ketoglutaric acid, the isocitric acid dehydrogenase would catalyze the dehydrogenation at C-2 and that the decarboxylation of the resulting β-ketoacid would occur spontaneously. Evidence has, however, accumulated to indicate that the decarboxylation step is also enzyme controlled. Thus when the product, α-ketoglutaric-*3,3-t*$_2$ acid (really a nonstereospecifically labeled sample of α-ketoglutaric-*3-t* acid) is incubated with isocitrate dehydrogenase and NADPH in H_2O, one-half of the tritium is exchanged out, i.e., the hydrogen in one of the two enantiotopic sites of the C-3 methylene groups is mobilized by the enzyme (155). Furthermore, specifically labeled α-ketoglutaric-*3-t* acid will lose either none or all of its tritium, depending on its configuration (156); the residual α-ketoglutaric-*3-t* acid obtained by T–H exchange of randomly labeled material will, of course, lose no further tritium on prolonged treatment with the enzyme, whereas tritiated α-ketoglutaric acid obtained from isocitrate and THO in the presence of NADPH and isocitrate dehydrogenase will have its tritium built into the exchangeable position, so that all of it will be lost on treatment with the same enzyme-coenzyme combination and H_2O.

The configuration of the α-ketoglutaric-*3-t* (or *-3-d*) acid obtained in the isocitrase dehydrogenase reaction was established by two groups of investigators (156, 157). The more direct correlation starts with the deuterated material obtained from isocitric acid and involves succinic-*d* acid as a reference material (157) as shown in Figure 65. In the correlation involving the tritiated material (156), nonstereospecifically labeled α-ketoglutaric-*3-t* acid was allowed to undergo exchange with H_2O in the



Isocitric acid

(*S*)-α-Ketoglutaric-*3-d* acid



(*S*)-(+)-Succinic-*d* acid

Figure 65

presence of $NADP^+$ and isocitrate dehydrogenase; this treatment leaves the tritium in the enzymatically nonactive 3-position. The then stereospecifically labeled α-ketoglutaric-*3-t* acid was enzymatically aminated to glutamic acid which was then degraded (by loss of COOH-5) to aspartic acid which, in turn, was converted to fumaric acid either by direct treatment with aspartase or by chemical conversion to malic acid followed by treatment with fumarase (Fig. 53). In both cases, the fumaric acid retained 90% of the tritium; reference to Figure 53 shows that the configuration at C-3 in the malic acid, aspartic acid, and thus also the original α-ketoglutaric acid must have been *R*. The two investigations thus agree in that the hydrogen introduced into the α-ketoglutarate acid by isocitrate dehydrogenase and also labilized by the same enzyme is H_S and the nonactive hydrogen is H_R. It follows that the decarboxylation step in the conversion of isocitric to α-ketoglutaric acid proceeds with retention of configuration,* in contradistinction to the formally similar conversion of 6-phosphogluconic acid to ribulose-5-phosphate (Fig. 37).†

A reaction related to the earlier discussed ketose–aldose transformations is the transformation of (4*R*)-4,5-dihydroxy-2-ketovaleric acid to 2-ketoglutaraldehydic acid (Fig. 66) by *Pseudomonas saccharophila.* When the reaction is carried out in D_2O, deuterium is introduced at both C-3 and C-4 (158). Degradation (Fig. 66) leads to levorotatory succinic-d_2 acid containing nearly two D atoms and having nearly twice the optical rotation of the (*R*)-d_1-acid. Further degradation (Fig. 66) shows that both chiral centers do, in fact, have the *R*-configuration.

Perhaps the most important compound to have been correlated with succinic-*d* acid and the one for the sake of whose correlation the configuration of (*R*)-(−)-succinic-*d* acid was first established by Cornforth, Ryback, Popják, Donninger, and Schroepfer (146, 175), is nicotinamide adenine dinucleotide in the reduced form (NADH, or rather its deuterated analog NAD-D). The oxidized form, NAD^+, (Fig. 67, **A**) and the corresponding phosphate, nicotinamide adenine nucleotide phosphate ($NADP^+$ or, in reduced form, NADPH) (Fig. 67, **B**), are common hydride-transfer agents

*It might be noted that the introduction of the C-3 label in the enzymatic reaction and its removal by the enzyme from randomly labeled substrate lead to 3-labeled α-ketoglutaric acids of opposite configuration. This is an example of the general proposition that enzymatic synthesis of an enantiomer and enzymatic destruction of one enantiomer in a racemate always lead to products of opposite (i.e., enantiomeric) configuration, provided the same enzyme is used (which presumes reversibility of the enzymatic synthesis). This follows because the same enantiomer which is synthesized by the enzyme is also the one which is destroyed in the reverse reaction.

†The difference between the two reactions has been interpreted in terms of *consecutive* (rather than concerted) decarboxylation and protonation steps [see I. A. Rose, *Ann. Rev. Biochem.*, **35**, 26 (1966)].

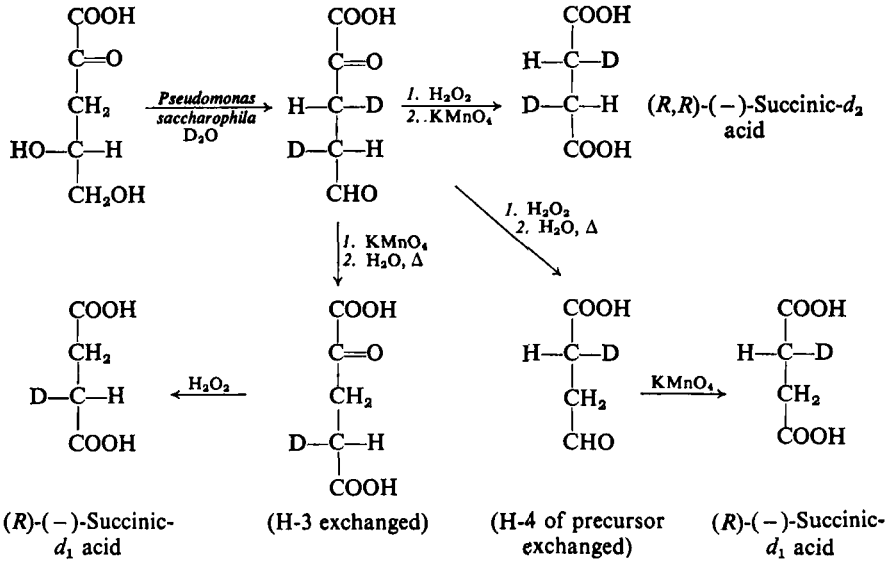


Figure 66

in biochemical oxidation–reduction reactions and have been mentioned a number of times previously in this review. In the reduced form (see Fig. 68), the hydrogens at the 4-position of the dihydropyridine ring are heterotopic and it has been shown in a number of investigations that, depending on enzyme and substrate, sometimes one and sometimes the other hydrogen

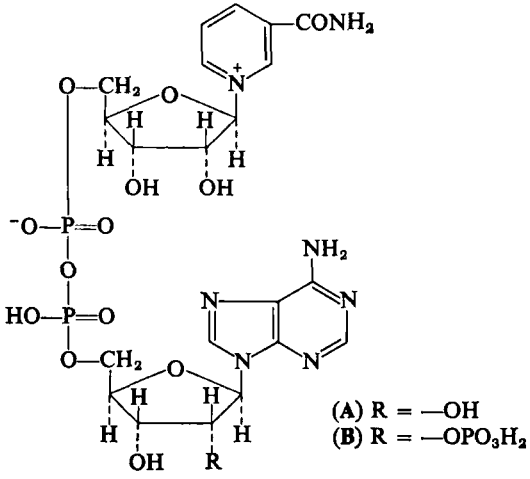


Figure 67

is transferred (159). The two hydrogens were arbitrarily called H_A and H_B, and corresponding positions in NADH and NADPH had been correlated (160). The question to be solved, then, concerned the absolute configuration of H_A and H_B, where H_A is taken to be the hydrogen transferred to acetaldehyde (or acquired from ethanol) when the enzyme is yeast alcohol dehydrogenase or liver alcohol dehydrogenase. The solution of the problem (146) is summarized in Figure 68.

An H_A-labeled NAD-D was produced by LAD-catalyzed transfer of deuterium from $(CH_3)_2C{=}CHCD_2OH$ to NAD^+, whereas H_B-labeled NAD-D was obtained by transfer of hydrogen from ethanol to deuterated NAD^+ in the presence of the same enzyme. Addition of methanol to NAD-D occurred in the presence of acetic acid; this reaction entails addition of an alcohol to an enamine to give an aldehyde ammonia ether; spectral evidence suggests that it occurs away from the side of the conjugating amide group, leaving this group in what is a vinylogous urea function. Ozonolysis followed by mild oxidation then cleaves the dihydropyridine

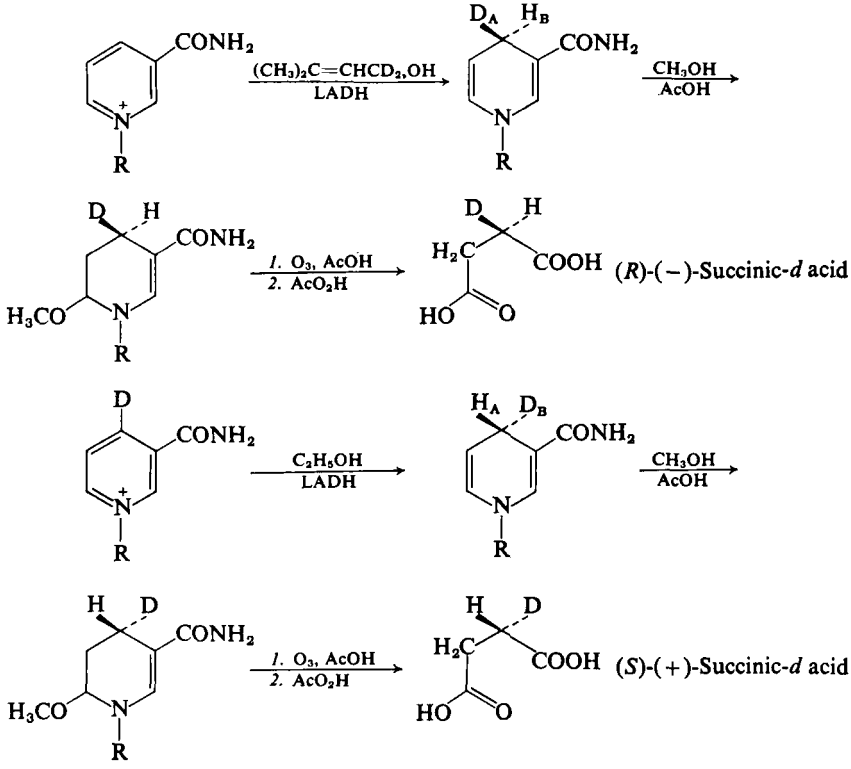


Figure 68

moiety yielding succinic-*d* acid. The acid produced from NAD-D containing deuterium in the A-position (Fig. 68, top row) is levorotatory and hence *R* (*vide supra*), whereas the acid obtained from NAD-D with deuterium in the B-position (Fig. 68, bottom row) has a positive ORD curve and is therefore *S*. It follows that $H_A = H_R$ and $H_B = H_S$, i.e., the prochirality of the two hydrogens, the pyridine-derived one and the alcohol-derived one (using LADH or YADH as enzymes), is completely specified.

meso-Succinic-*2,3*-d_2 acid and its *dl*-isomer have been prepared (161) as shown in Figure 69 with a view to determining the stereochemistry of the succinic dehydrogenase-catalyzed hydrogen elimination from succinic acid to give fumaric acid (122). The finding (161) that the racemic acid gives almost exclusively fumaric-d_1 acid (with less than 4% d_2 material), whereas the *meso*-acid gave an almost 50:50 mixture of d_2 and d_0 fumaric acids indicates that the hydrogen elimination is *anti*, i.e., that one H_R and one H_S hydrogen of the succinic acid are involved.

Under anaerobic conditions, succinic dehydrogenase catalyzes exchange of hydrogen atoms between water and the methylene groups of succinate. It has been shown (162) that in the presence of D_2O, deuterium is preferentially introduced in the H_R position, for the succinic acid becomes levorotatory—so much so that after some time there is evidently formed a substantial amount of the (*R,R*)-d_2-acid. Conversely, when succinic-d_4 acid is similarly made to undergo exchange with H_2O, the acid becomes dextrorotatory, indicating the formation of (*R,S,S*)-d_3- and (*S,S*)-d_2-species

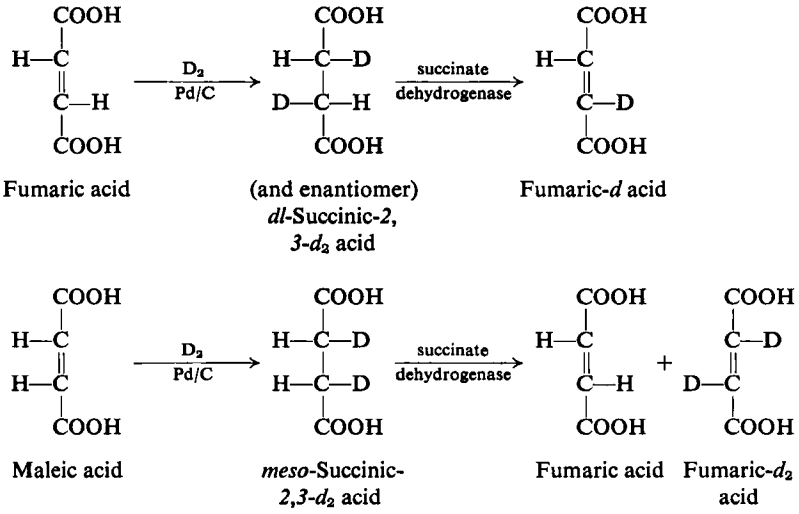
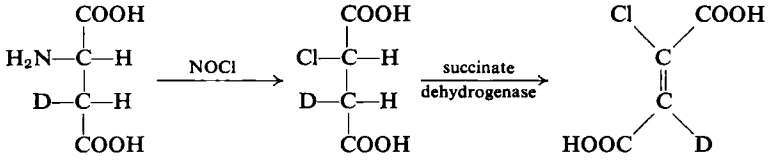


Figure 69



(2*S*,3*R*)-(−)-Aspartic-*3-d* acid (cf. Fig.53) | (2*S*,3*R*)-Chlorosuccinic-*3-d* acid | Chlorofumaric-*d* acid

Figure 70

(162), again through preferential exchange of H_R (or rather, in this case, D_R).

(2*S*,3*R*)-2-Chlorosuccinic-*3-d* acid has been prepared from (2*S*,3*R*) aspartic-*3-d* acid (Fig. 53) by treatment with NOCl (cf. Fig. 61) (163, 164) (Fig. 70). Upon treatment with succinate dehydrogenase it gives rise to chlorofumaric-*d* acid, indicating that elimination is formally *anti* (Fig. 70) (163). (2*S*,3*S*)-Chlorosuccinic-*3-d* acid and (2*S*,3*S*)-chlorosuccinic-*2,3-d*$_2$ acid have been similarly prepared from appropriately labeled (*R*)-(+)-aspartic acids (164), and the hydrogen–deuterium exchange of these species has also been reported (164–166).

G. The Biosynthesis of Squalene

The acyclic triterpene squalene (Fig. 71) is a key intermediate in the biosynthesis of the cyclic triterpene lanosterol which, in turn, gives rise, biogenetically, to other steroids such as cholesterol (167). Squalene itself is biosynthesized from (*R*)-mevalonic acid (Fig. 72) *via* isopentenyl pyrophosphate, geranyl pyrophosphate, and farnesyl pyrophosphate (Fig. 72) (168). Although squalene is an achiral molecule, it contains two (equivalent) sets of five pairs of enantiotopic hydrogens, and additional heterotopic hydrogens are found in its precursors. Stereospecific labeling experiments have therefore played an extensive part in the elucidation of the details of the biosynthesis of squalene. Virtually all of this very elegant work has been carried out in the laboratories of J. W. Cornforth and G. Popják.

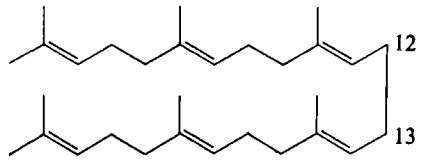


Figure 71

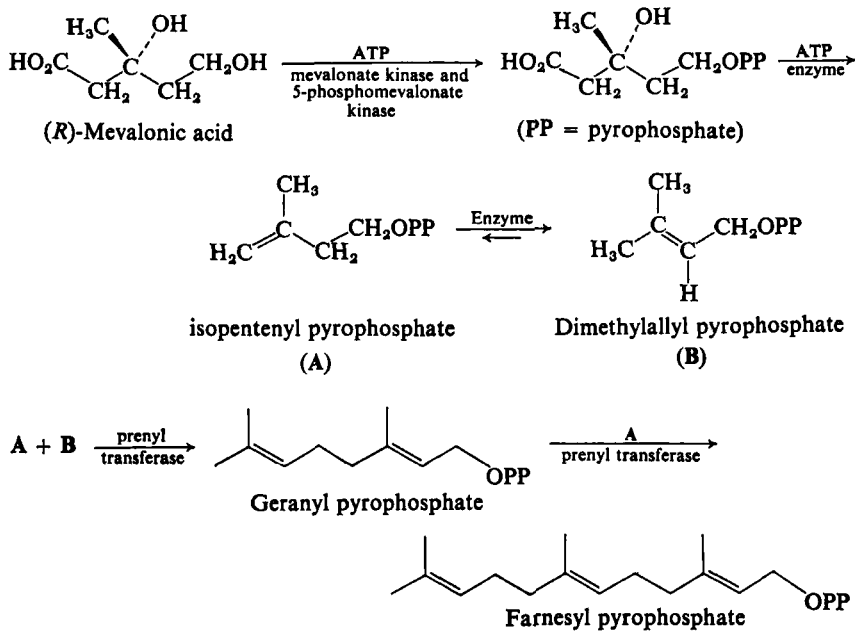


Figure 72

The first step—conversion of (*R*)-mevalonic acid via the pyrophosphate to isopentenyl pyrophosphate—is a concerted decarboxylative dehydration. (The absence of incorporation of hydrogen from the water solvent at the CH_2 group rules out a separate decarboxylation step preceding or following dehydration.) The stereochemical question arises as to whether the elimination is *syn* or *anti*; the question has been answered by stereospecifically labeling the C-2 methylene group with deuterium obtaining a —CHD—COOH compound of known configuration and by establishing the stereochemistry of the $CHD{=}C(CH_3)CH_2CH_2OPP$ product resulting from the decarboxylative dehydration (169).

The first step—stereospecific labeling of mevalonic acid at C-2—was accomplished (170, 169) as shown in Figure 73. This process actually produces the diastereoisomers of mevalonic-*4-d* acid and of mevalonic-*2-d* acid as racemic modifications, but this is of no consequence, as in the subsequent step (phosphorylation with mevalonate kinase) only the "natural" 3-(*R*)-mevalonic acid is phosphorylated (171) and therefore only the natural enantiomer of each diastereoisomeric pair is available for the subsequent decarboxylative dehydration.*

* In one of the studies reported (ref. 169) the (labeled) 3-(*R*)-phosphomevalonate was actually separated from the unphosphorylated 3-(*S*)-mevalonic acid before being subjected to further enzymatic reaction (Fig. 74).

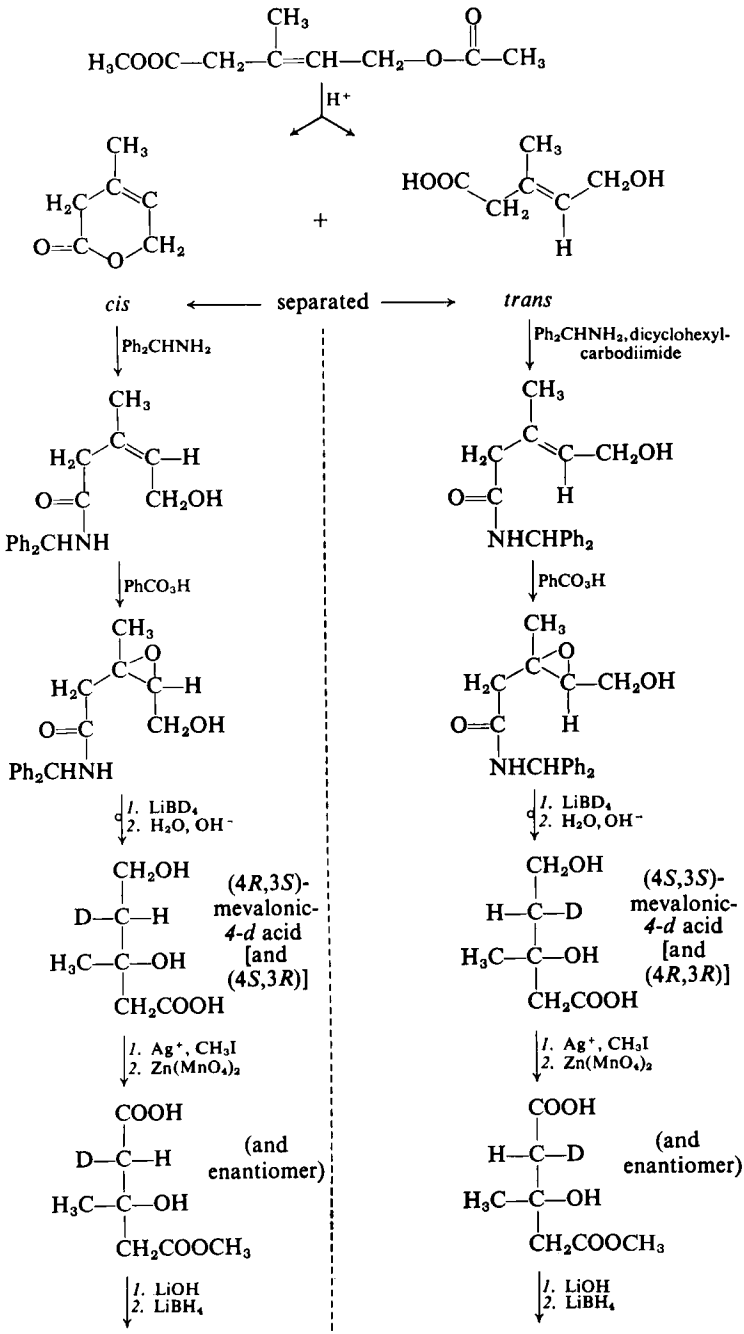
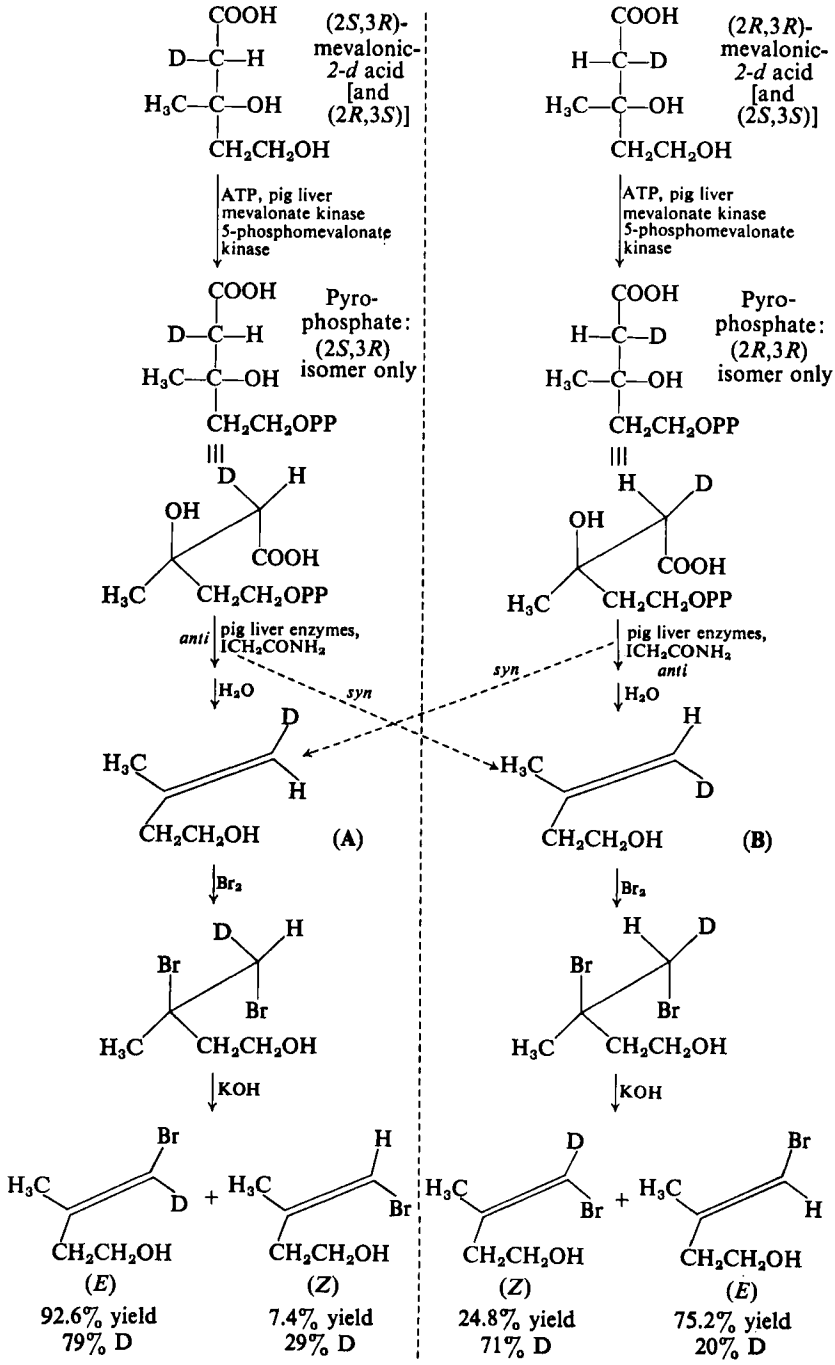

H+
+
cis
separated
trans
Ph2CHNH2
Ph2CHNH2, dicyclohexyl-carbodiimide
PhCO3H
PhCO3H
1. LiBD4
2. H2O, OH−
1. LiBD4
2. H2O, OH−
(4R,3S)-mevalonic-4-d acid [and (4S,3R)]
(4S,3S)-mevalonic-4-d acid [and (4R,3R)]
1. Ag+, CH3I
2. Zn(MnO4)2
1. Ag+, CH3I
2. Zn(MnO4)2
(and enantiomer)
(and enantiomer)
1. LiOH
2. LiBH4
1. LiOH
2. LiBH4

Figure 73

Figure 73 (*contd.*)

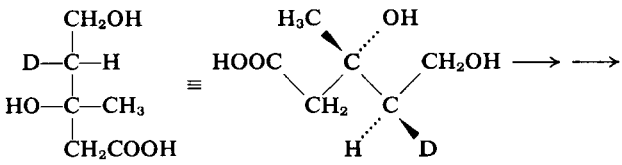


It may be seen from Figure 73 (solid arrows) that *anti*-stereochemistry in the decarboxylative dehydration of mevalonate-(*S*)-*2-d* would give that diastereoisomer of 3-methyl-3-buten-1-ol-*4-d* in which the methyl and the deuterium are *cis* (**A**) whereas mevalonate-(*R*)-*2-d* will give the corresponding *trans* isomer (**B**). If the stereochemistry in the decarboxylative dehydration were *syn*, however, (dashed arrows) the correlation of the olefins with the deuteriomevalonates would be reversed. The stereochemistry of the olefins was established by bromination (assumed to proceed with *anti* addition) followed by base-catalyzed dehydrobromination (also assumed to involve *anti* stereochemistry). It may be seen that, with the assumption of *anti* addition and *anti* elimination, **A** should either produce deuterated (*E*)-4-bromo-3-methyl-3-buten-1-ol or the undeuterated *Z*-isomer (cf. 37), whereas **B** will form the deuterated *Z*- and undeuterated *E*-isomer. In fact, it was found that **A** formed mainly the deuterated *E*- and undeuterated *Z*-isomer, whereas **B** formed mainly the deuterated *Z*- and undeuterated *E*-isomer. Unfortunately, the reaction course was not entirely clean,* but the stereochemistry of **A** and **B** is further supported by the finding that, although **A** and **B** both gave rise predominantly to the (more stable) *E*-isomer of 4-bromo-3-methyl-3-buten-1-ol (**C**), the proportion of *E*-isomer was substantially higher in the transformation of **A** than in that of **B**. This, of course, is to be expected on the basis of an isotope effect, for the, transformation of **A** into the *E* isomer of **C** involves loss of hydrogen, whereas the corresponding transformation of **B** into (*E*)-**C** involves the less favored elimination of deuterium.

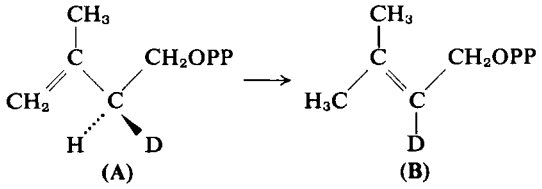
The next stereochemical question that arises in the sequence shown in Figure 72 is which of the two enantiotopic hydrogens at C-2 in isopentenyl pyrophosphate is eliminated in the double bond rearrangement to dimethylallyl pyrophosphate; the answer to this question should help elucidate the mechanism of bond migration.† The question was answered (170) by investigating the biosynthesis of farnesol separately from (4*S*,3*R*)-mevalonic-*4-d* acid and its (4*R*,3*R*)-diastereoisomer: the two diastereoisomers, specifically labeled, were prepared in racemic form as shown in Figure 73 (first four transformations); here, again, biochemical phosphorylation

*The reason for this is probably not lack of stereospecificity in the biochemical decarboxylative dehydration, but more likely lack of stereospecificity in the bromine addition (cf. R. C. Fahey, *Topics in Stereochemistry* Vol. 3, N. L. Allinger and E. L. Eliel, Eds., Interscience, New York, 1968) or possibly lack of stereospecificity in the base-induced elimination.

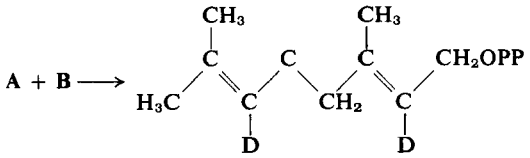
†The question as to the stereochemistry of the proton addition at C-4, i.e., the CH_2 group, is also meaningful, but cannot be solved with presently available techniques since the hydrogens of a methyl group are stereochemically equivalent. The problem could, however, in principle be tackled by double labeling: the protons in CH_2D are enantiotopic and could be distinguished by tritium labeling; cf. Sec. IV-J.



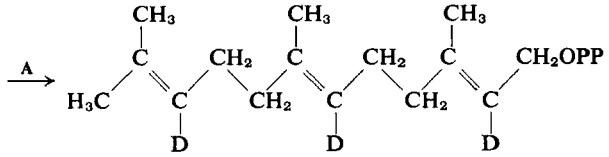
(3*R*,4*R*)-Mevalonate-*4-d* (hydrogen at C-4 is H_S in unlabeled compound)



(hydrogen at C-2 is H_R in unlabeled compound)



Geranyl pyrophosphate



Farnesyl pyrophosphate

Figure 74

allows only the (3*R*)-enantiomers to enter into the biosynthetic scheme. Since isolation of the intermediate 3,3-dimethylallyl alcohol in quantity was not feasible, the biosynthesis was allowed to proceed as far as farnesyl pyrophosphate which was then hydrolyzed to farnesol and assayed for deuterium; as may be seen in Figure 74, the deuterium present (if any) in the dimethylallyl pyrophosphate will also be present in the final farnesol. It was found that the (4*S*)-deuterated mevalonate lost virtually all its deuterium in enzymatic conversion to farnesol, whereas the (4*R*)-isomer gave rise to farnesol containing three atoms of deuterium; the same result was obtained using tritium labeling. It follows that the hydrogen eliminated

at C-4 in mevalonate is H_S; this hydrogen corresponds to H_R in isopentenyl pyrophosphate* (Fig. 74).

It follows also (since either all three deuterium atoms were lost or else all three were retained in the farnesol) that the stereochemistry of the hydrogen loss in the addition of 3,3-dimethylallyl pyrophosphate (**B**) to isopentenyl pyrophosphate (**A**) to give geranyl pyrophosphate and the subsequent addition of the latter to a second molecule of **A** to give farnesyl pyrophosphate is entirely analogous to the stereochemistry of hydrogen loss (presumably following the addition of a proton) in the conversion of **A** to **B**.

The next stereochemical problem of interest still concerns the stereochemistry of addition of **A** to **B**, but now with respect to the side of the double bond (*re*-face or *si*-face, cf. p. 138) of **A** to which **B** adds. As may be seen from Figure 75, if the isopentenyl pyrophosphate involved in the addition step is deuterated at C-4 (as it will be if it is biosynthesized from (2*R*,3*R*)-mevalonic-*2-d* acid—cf. Fig. 73), the configuration at C-4 of the

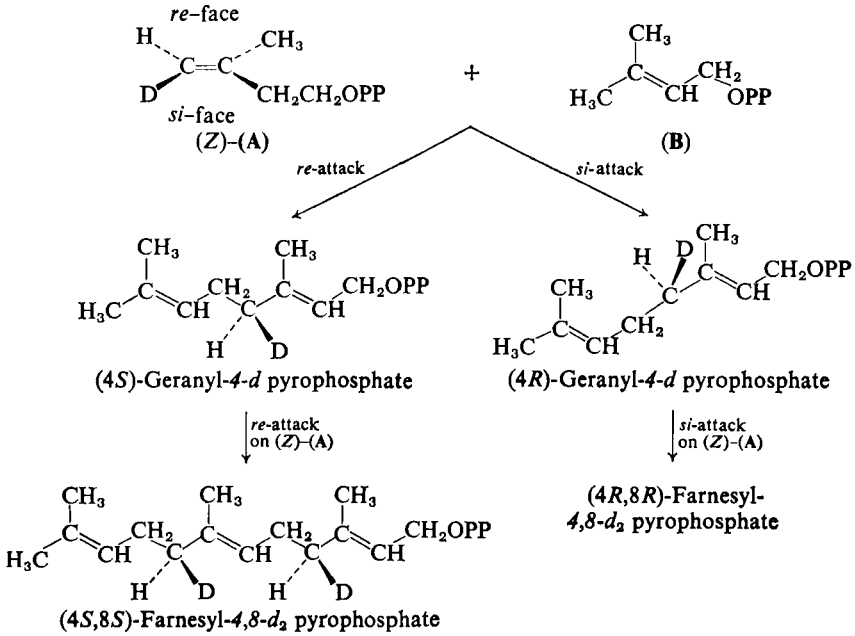


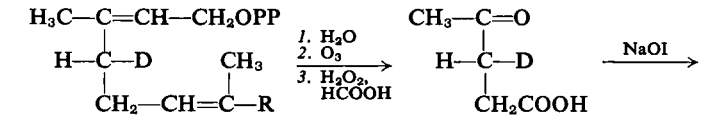
Figure 75

*That H_S at C-4 in mevalonate becomes H_R at C-2 in isopentenyl pyrophosphate is a consequence of the Sequence Rule in the Cahn-Ingold-Prelog (*R*–*S*) system of nomenclature (CRR′OH precedes CH_2OH, but CH_2OH precedes $C(CH_3)=CH_2$); the configurations of the two hydrogen atoms are, in fact, corresponding ones.

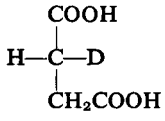
geranyl pyrophosphate biosynthesized from it and the configuration at C-4 and C-8 of the subsequently formed farnesyl pyrophosphate will depend on the stereochemistry of addition to the double bond. Specifically, if the deuterium in **A** is on the side of the CH_2CH_2OPP group (*Z*-configuration) and the addition occurs from the *re*-face, the configuration at C-4 in geraniol and at C-4 and C-8 in farnesol will be *S*, but if in the same stereoisomer of **A** addition is from the *si*-face, the configuration at the newly created CHD groups will be *R*.

Experimentally, the configuration at C-4 and C-8 of the biosynthetically prepared farnesol was determined (170) by oxidative ozonization to levulinic-*3-d* acid followed by hypoiodite degradation to succinic-*2-d* acid (Fig. 76). Control experiments showed that under proper conditions this sequence of reactions could be carried out with little H–D exchange. The succinic acid which was obtained from the biosynthetic farnesol had a negative ORD curve, and its configuration is thus known, from other work (cf. Sect. IV-6), to be *R*. It follows that its farnesol precursor also has the *R*-configuration at both C-4 and C-8 (cf. Fig. 76) and that the attack on the double bond of **A** (Fig. 75) is therefore *si*. The mechanistic implications of this finding will be discussed later.

The next problem to be solved was that of the stereochemistry at the CH_2OPP groups of dimethylallyl pyrophosphate (**B**, Fig. 74) and geranyl



Farnesyl-(4*R*,8*R*)-d_2 pyrophosphate (R— = $Me_2C{=}CH{-}CH_2{-}CHD{-}$)*



(2*R*)-(−)-Succinic-*d*-acid

Figure 76

*In actual fact the biosynthesis was carried out starting from specifically 2-deuterated mevalonic acid (Fig. 73) rather than from the intermediate 5-deuterated isopentenyl pyrophosphate (**A**, Fig. 75). It follows that the dimethylallyl pyrophosphate (**B**, Fig. 75) formed from **A** bears a deuterium in one of the terminal methyl groups and the farnesol finally obtained will bear the same deuterium at C-12 and will actually be trideuterated (at C-4, C-8, and C-12) rather than dideuterated as implied in Figure 76. This experimental detail is irrelevant to the stereochemical argument.

pyrophosphate in the attack on the double bond of Δ^3-isopentenyl pyrophosphate (**A**). To this end (170) mevalonic acid was stereospecifically labeled with either deuterium or tritium at C-5 (CH_2OH group) (172) and then used in the biosynthesis of both farnesol (Fig. 77) and squalene (Fig. 78). The configuration of the farnesol at C-1 must be the same as that of the mevalonic acid precursor; enzymatic oxidation with LADH–NAD$^+$ of the farnesol-*1-t* gave farnesal unlabeled at C-1 and NAD-T whence it was inferred* that the configuration of the farnesol-*1-t* and its mevalonic-*5-t* acid precursor was *R*.

Mevalonic-(*5R*)-*d* acid was then synthesized using NAD-D on mevaldate and was transformed biosynthetically into squalene (Fig. 78). At the moment we are only interested in the stereochemistry at C-5 and C-9 of the farnesol intermediate, and from this point of view the biosynthesis might have been arrested at the farnesol stage, as shown in Figure 77. In fact, the experiment shown in Figure 78 served two purposes (the second of which will be discussed later) and for this reason was allowed to proceed

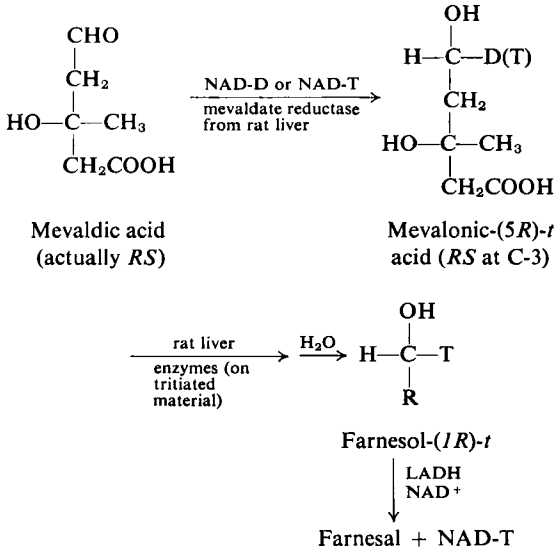
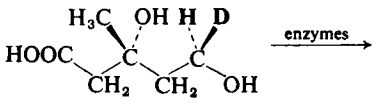
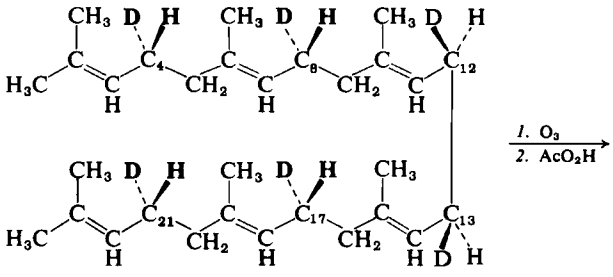


Figure 77

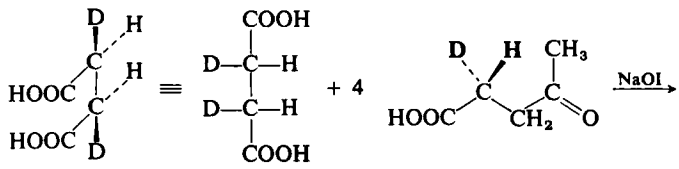
*The inference originally rested on an assumed analogy between the oxidation of farnesol by LADH–NAD$^+$ and that of ethanol by YADH–NAD$^+$ (Fig. 20). Meanwhile, however, it has been *proved* (cf. Figs. 27 and 28) that the LADH–NAD$^+$ oxidation of geraniol-*t* follows the same steric course as the YADH–NAD$^+$ oxidation of ethanol (i.e., H_R is removed); the remaining assumption, namely, that farnesol-*1-t* and geraniol-*1-t* correspond in their stereochemistry of oxidation, is a very safe one in view of the close chemical similarity of the two substrates.



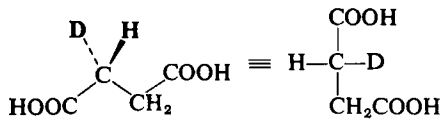
(5*R*)-Mevalonic-*5-d* acid



Squalene-*4,8,12,13,17,21-d*$_6$



(2*S*,3*R*)-Succinic-*d*$_2$ acid (*meso*) Levulinic-*2-d* acid (separated)



(2*R*)-(-)-Succinic-*d* acid

Figure 78

all the way to squalene; we have, however, indicated the enantiotopic hydrogens in the farnesol backbone in bold face letters in Figure 78 to focus attention on them. The pertinent methylene groups were carved out of the biosynthesized squalene as shown in Figure 78: The first step was oxidative ozonization to a mixture of succinic acid and levulinic acid which was carefully separated. The levulinic acid was then degraded by hypoiodite to succinic-*d* acid which proved to have a negative ORD curve and is therefore *R*. Contemplation of Figure 78 with respect to the configuration at C-4, C-8, C-17, and C-21 of the squalene (bold face hydrogen isotopes)—which corresponds to that of the succinic acid obtained via levulinic acid—leads to the conclusion that it is, in a sense, opposite to that

at C-5 in the mevalonic acid precursor.* It follows that the displacement of the pyrophosphate leaving group by the double bond (**A** + **B** in Fig. 34) proceeds with inversion, the double bond acting as an entering group in a bimolecular nucleophilic displacement.

We have now reviewed all the evidence with respect to the stereochemistry of the farnesol biosynthesis from mevalonate. The first step following phosphorylation is an *anti* decarboxylative dehydration (Fig. 73). The stereochemistry of the second step (rearrangement of isopentenyl pyrophosphate to 3,3-dimethylallyl pyrophosphate: Fig. 74, **A**→**B**) is not yet completely elucidated although it is known which hydrogen at C-2 is lost. The third step—condensation of **B** with **A** to give geranyl pyrophosphate (and the completely analogous condensation of the latter with a second molecule of **A** to give farnesyl pyrophosphate) is recapitulated in Figure 79. The reaction proceeds with inversion at C-1 of **B**, and attack is at the underside (*si*-face) of the double bond of **A**. It is clear now that the electrons forming the bond linking C-2 to H_R in **A** are on the same face of the double bond (given the fact that in the final product the CH_3 and CH_2OPP groups are *cis*) and it is therefore difficult to see how the reaction of **A** and **B** can be concerted. It has been suggested (170) that the reaction actually occurs in two stages, the first stage involving the attack of a nucleophile X^- from the enzyme surface, which is then displaced again in the second step (Fig. 79, bottom). An alternative cyclic mechanism is also possible.

We must now turn our attention to the biosynthesis of squalene from farnesyl pyrophosphate. This reaction is formally a dimerization (2 R—CH_2—OPP → R—CH_2—CH_2—R), but it was early recognized that, mechanistically speaking, the two farnesol pieces which come together are not equivalent. This follows from the observation (173) that in the biosynthesis of squalene from mevalonic-2-^{14}C-5-d_2 acid (as the lactone†), the ratio of deuterium to ^{14}C (as determined by radioactivity measurements and total combustion) indicates that only 11 (rather than 12) deuterium atoms have entered the squalene product.‡ This finding

*The meaning of "opposite configuration" requires definition here: The double bonds in squalene are taken to correspond to C-3—C-4 in mevalonic acid (whence they are derived by dehydration) and the continuing chain (—CH_2—) in the hydrocarbon is taken to correspond to the 5-OH group in the acid.

†When mevalonic acid is liberated from its salt, it slowly comes to an equilibrium with its lactone, mevalolactone. We have not generally tried to make a distinction between mevalonic acid, its salts, and its lactone in this review, assuming that they can generally be used interchangeably.

‡Here, as in many other earlier instances (not specifically mentioned) ^{14}C labeling of biogenetic precursors is resorted to, so that the squalene (or other product) synthesized *de novo* from the added precursor may be distinguished from squalene

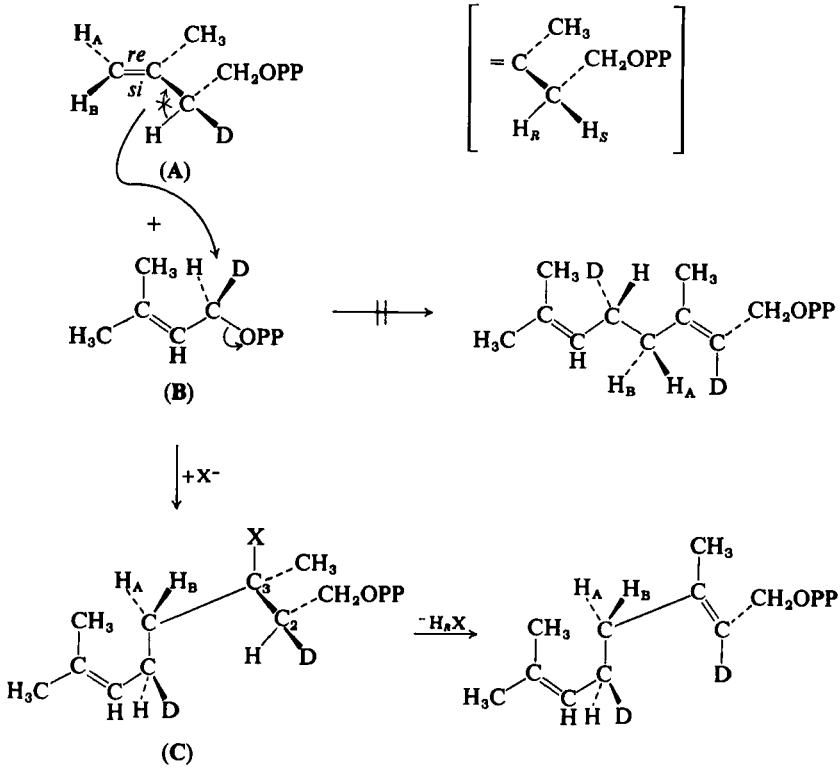


Figure 79

suggests that the "dimerization" of farnesol may actually correspond to 2 R—CD_2—OPP → R—CD_2—CHD—R. That it is in fact the central part (C-12—C-13, cf. Fig. 71) which acquires the extraneous hydrogen was shown (173) by degrading the squalene to succinic acid by oxidative ozonization (cf. Fig. 78) and demonstrating, mass spectrometrically, that

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already in the tissues. In the present experiment, it would not be sufficient to determine the absolute deuterium content of the squalene formed from the mevalonate-*5*-d_2, since that squalene is diluted by unlabeled squalene biosynthesized prior to (or independent of) the addition of the labeled precursor. The problem might be obviated by analyzing the squalene by mass spectrometry (which distinguishes d_0, d_1, d_2 . . . d_{11}, d_{12} species) and by assuming that the squalene must be either completely labeled or not at all, so that looking at the amount of d_{11} and d_{12} species would give the answer to the present problem. The difficulty with this approach is that it requires isotopically pure mevalonate-*5*-d_2. The alternative used here is to employ double labeling and to determine the deuterium/^{14}C ratio in the product; since only the *de novo* synthesized squalene contains ^{14}C, dilution with extraneous squalene will affect the numerator and denominator of this ratio by the same factor.

part of the acid was succinic-d_3 and none of it succinic-d_4 acid. Finally it was shown (173) that one of the hydrogens at C-12 and C-13 actually is derived from NADPH; for when squalene was biosynthesized from farnesyl pyrophosphate in the presence of NADP-T (173), one atom of tritium is incorporated at C-12, as shown from the radioactivity of the squalene and the fact that it may be degraded (Fig. 78) to succinic acid* of the same specific activity.

The stereochemical fate of the hydrogen which is lost and the stereochemistry at the CH_2 group which does not lose hydrogen were investigated in detail. In regard to the first point, mevalonate-4-^{14}C-(*5R*)-*t*, synthesized essentially as shown in Figure 77, was converted to squalene by a rat liver homogenate (172). From the ^{14}C /tritium ratio it was concluded that all six tritium atoms from the six mevalonate units making up the squalene were incorporated. Hence the hydrogen lost in the "dimerization" step is H_S. To confirm this point, the squalene was ozonized and reduced to give 1,4-butanediol (cf. Fig. 78—instead of oxidation to succinic acid, reduction to the corresponding diol was resorted to); the ^{14}C/T ratio in the butanediol was 1:1 showing that *both* methylene groups (C-12 *and* C-13) were equally labeled with one T. The result was confirmed with deuterium labeling (173), the butanediol obtained from *de novo* synthesized squalene containing two deuterium atoms (Fig. 78).

Of equal interest with the question, answered above, of which enantiotopic hydrogen from farnesyl pyrophosphate is *lost* in the "dimerization" is the question of the stereochemical position in the squalene product of the hydrogen which is transferred from NADPH. To answer this question, the configuration of the succinic-d_3 acid, earlier isolated from the ozonization of squalene biosynthesized from mevalolactone-*5*-d_2 (*vide supra*), was reinvestigated (174, 175). The acid gave a positive ORD curve and must therefore have the *S*-configuration on the basis of the earlier-mentioned configurational assignment of (+)-succinic-2-d_1 acid and the reasonable assumption that dideuteration at C-3 does not affect the sign of the ORD curve. The configuration of the newly introduced hydrogen (from NADPH) in squalene is therefore H_R as can be inferred from Figure 80.

A completely independent investigation (175a) of the configuration of the NADPH-derived hydrogen of biosynthetic squalene involves biosynthetic transformation of the squalene obtained from ^{14}C-farnesyl pyrophosphate and NADP-T to cholesterol. In this transformation, C-12

*In the absence of NADPH, no squalene is formed and an intermediate accumulates, which, on subsequent treatment with NADPH, gives squalene [H. Rilling, *J. Biol. Chem.*, **241**, 3233 (1966)]. See also G. Krishna, H. W. Whitlock, D. H. Feldbruegge, and J. W. Porter, *Arch. Biochem. Biophys.*, **114**, 200 (1966); G. Popják, J. Edmond, K. Clifford, and V. Williams, *J. Biol. Chem.*, **244**, 1897 (1969).

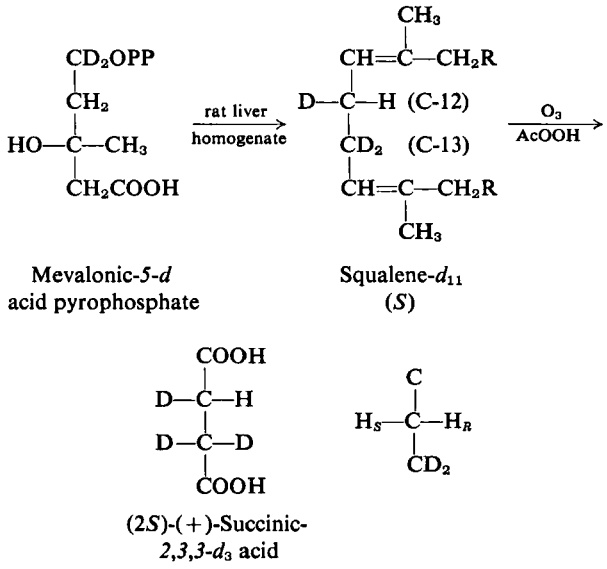
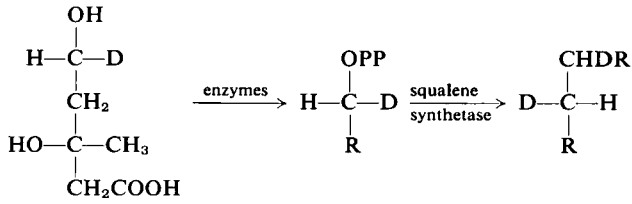


Figure 80

and C-13 of squalene become C-11 and C-12 of cholesterol. Biological oxidation converted the cholesterol-*t* to cholic acid (3α,7α,12α-trihydroxycholanic acid) which still contained 98% of the tritium in the cholesterol precursor. Since the oxidation at C-12 is known to proceed with retention of configuration (for references, see 175a), the tritium cannot be present at C-12α. When the cholic acid was oxidized to the corresponding 12-keto acid, the tritium content dropped to 45%, indicating that half the tritium was present in the 12β position. Finally, enolization of the keto acid (exchange) reduced the tritium content to 3% of that of the cholesterol, indicating that the remaining tritium was at C-11. The fact that the tritium is evenly distributed between C-11 and C-12 in cholic acid is a consequence of the symmetry of the squalene molecule, which renders C-12 and C-13 of the latter superimposable,* and the fact that the labeled hydrogen becomes 12β in cholesterol indicates that it is H_R in squalene, in agreement with the earlier-summarized result.

It remained to investigate the stereochemistry of the transformation of C-5 in mevalonic acid via C-1 in farnesyl pyrophosphate to that one of the central carbon atoms in squalene which retains both hydrogens from its biogenetic precursors (C-13 in Fig. 80). The experiments to solve this problem have already been discussed and were summarized in Figure 78;

*On the assumption that *free* squalene is actually an intermediate. As long as the squalene is attached to an enzyme surface, C-12 and C-13 need not be equivalent.

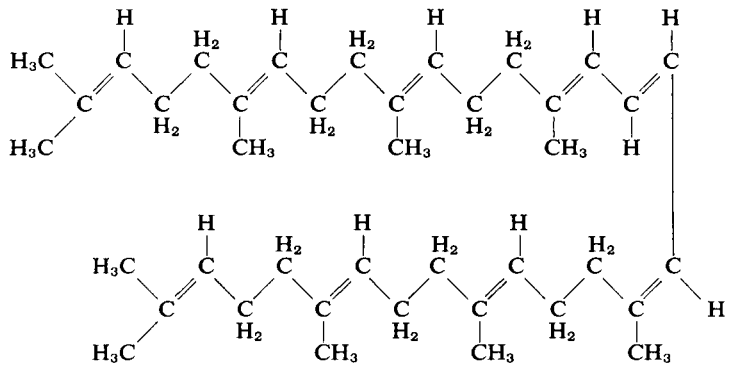


Mevalonic-(5*R*)-*d* acid | Farnesyl pyrophosphate, (*R*) at C-1 | Squalene, (*R*) at C-13

Figure 81

C-13 in squalene obtained from mevalonic (5*R*)-*d* acid becomes one of the methylene carbons of the succinic-d_2 acid which is isolated immediately after oxidative ozonization, prior to hypoiodite treatment. When the rotatory dispersion of this succinic acid was determined (170) it was found to be inactive. Clearly the acid cannot be racemic, for in the corresponding sequence starting with mevalonic-5-d_2 acid (Fig. 80) active succinic acid was obtained. The only possible conclusion, then, is that the acid obtained was the *meso* form, and since the configuration at C-2 has already been shown to be *S* (Fig. 80) that at C-3 must be *R*. Consideration of Figure 78 indicates that C-13 in squalene thus also has the *R*-configuration. The transformation of mevalonic-(5*R*)-*d* acid via farnesyl-(1*R*)-*d* pyrophosphate to squalene is shown once again in Figure 81, in which only the methylene group of the intact farnesol progenitor is shown. It is clear that in the attachment of C-12 to C-13 with displacement of the pyrophosphate group, inversion of configuration occurs.

This, in the main, completes the fascinating story of the biosynthesis of squalene—a molecule which contains not a single chiral center, yet in



Phytoene

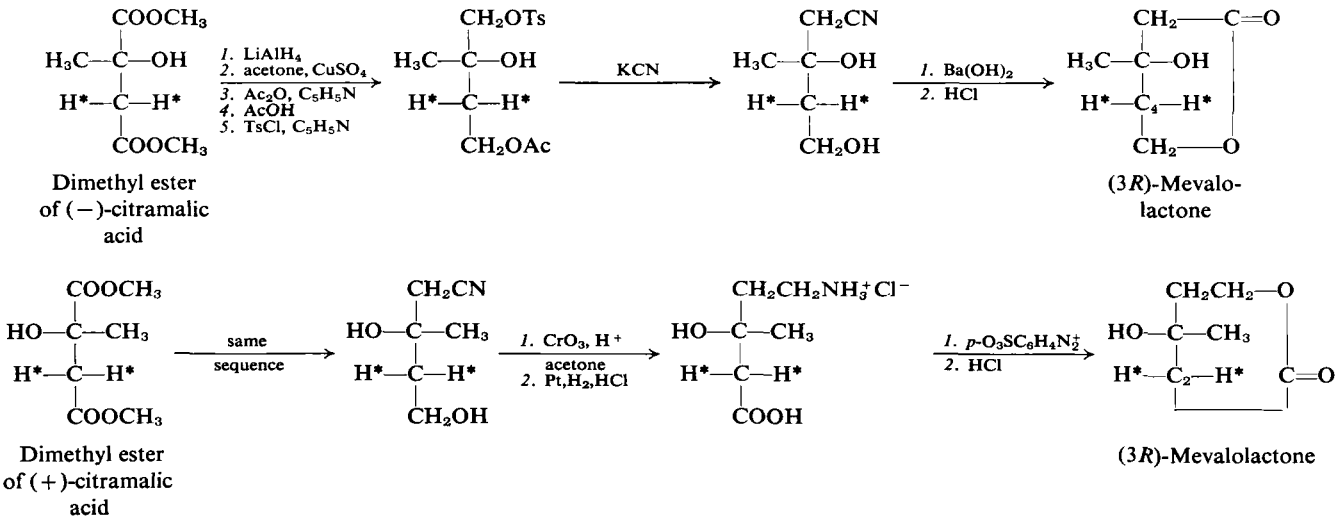
(24)

the course of whose biosynthetic study in essence every methylene group has at one time or another been made chiral by labeling, using as precursors mevalonic acids stereospecifically labeled in each of the methylene groups at C-2, C-4, and C-5.

We will complete this section with a brief account of the biosynthesis of two other isoprenoid compounds, phytoene (**24**), a C-40 hydrocarbon related to the carotenes, and rubber. In the synthesis of phytoene from mevalonic *4-t* acid it was shown (176) that tritium is incorporated into the product when the configuration of the precursor is 4*R*, whereas a tritium-free product is obtained when the precursor is 4*S*.* The situation is similar to the biosynthesis of farnesol (Fig. 74) and suggests that at least the early stages of the biosynthesis of phytoene (up to the C-20 halves) is similar to the biosynthesis of squalene. When the biosynthesis of rubber in latex starting from labeled mevalonate-4-*t* was studied (177), it was found that the farnesol which is produced as a by-product is labeled when the precursor is 4*R* and unlabeled when it is 4*S*, in analogy with the synthesis (using different enzymes) shown in Figure 74. In contrast, the rubber formed is *un*labeled when the precursor is 4*R* and labeled when it is 4*S*. A study of Figure 79 will show that this result is perhaps not unexpected. The elimination of H_R and retention of H_S in the farnesol synthesis is predicated on the formation of a *trans*-substituted (or perhaps better *E*-substituted) double bond in which CH_3 and CH_2OPP are *cis*. In rubber, which is a *cis*-olefin, the double bond is *Z*-substituted and CH_3 and CH_2OPP are *trans*; this requires a rotation about the C-2—C-3 bond in intermediate **C** such that X will be *anti* to D rather than to H, so that H is retained and the isotope is eliminated.

Since the completion of the above-described work, syntheses of *optically active* mevalolactones stereospecifically deuterium labeled at C-2 or C-4 have been effected (128a) starting with appropriate stereoisomers of citramalic-*3-d* acid (p. 191). The general scheme chosen for the synthesis of mevalolactone from citramalic acid is shown in Figure 82 (128a, 129). (3*R*)-Mevalolactone stereospecifically deuterium-labeled at C-4 can evidently be obtained from (3*R*)-*d*- and (3*S*)-*d*-labeled (*R*)-(−)-citramalic acid (Fig. 82, top line) by conversion of COOH-1 into —CH_2COOH and COOH-4 into CH_2OH. On the other hand, through conversion of

*Actually the precursors were (3*R*,4*R*)- and (3*R*,4*S*)-mevalonic-4-*t*-acids, respectively, admixed in each case with their enantiomers [(3*S*,4*S*) in one case, (3*S*,4*R*) in the other] (see p. 210). The inference as to which H-4 is incorporated (*vide infra*) thus rests on the assumption that phytoene and latex syntheses proceed from the (3*R*)-isomer of mevalonic acid, in analogy with squalene biosynthesis in rat liver. If this analogy does not hold, the absolute stereochemistry of the hydrogen incorporated would be the reverse of that indicated here, though the relative stereochemistry (cf. Fig. 74) would still be as discussed.



• One or the other of the asterisked hydrogen atoms may be replaced by deuterium.

Figure 82

COOH-1 into CH_2CH_2OH (Fig. 82, bottom line), a method is at hand to transform (3*R*)-*d*- and (3*S*)-*d*-labeled (*S*)-(+)-citramalic acid into (3*R*)-mevalolactone specifically labeled at C-2.

H. Amines

n-Butylamine-1-*d*, $[\alpha]_D$ − 0.009° has been prepared (178) from (−)-1-butanol-*l*-*d*, $[\alpha]_D^{25}$ − 0.034° by conversion to the *p*-bromobenzenesulfonate, treatment with sodium azide in methanol, and reduction of the azide so formed with lithium aluminum hydride. The corresponding reaction with 2-octyl *p*-toluenesulfonate involves over 97% inversion (178). Since (−)-*l*-butanol-*l*-*d* has the *R*-configuration and its specific rotation is at least 0.47° (p. 161), it may be concluded that the levorotatory amine has the *S*-configuration and that its specific rotation is not less than 0.12°. An independent check of the maximum rotation of the material does not appear to be available, although it has been used in mechanistic studies (179).

Benzylamine-α-*d* has been synthesized (180) by an analogous method: treatment of (−)-benzyl-α-*d* alcohol, $[\alpha]_D$ − 0.215°, with *p*-toluenesulfonyl chloride and sodium hydroxide to give the *p*-toluenesulfonate which was then treated as described above to give amine of $[\alpha]_D$ + 0.24°. A check on possible racemization in the conversion was performed by converting the amine to the quaternary ammonium salt, $PhCHDNMe_3^+$ OAc^-, which was then pyrolyzed to PhCHDOAc and finally cleaved to PhCHDOH; the specific rotation of the recovered alcohol was −0.180° and the overall conversion therefore involved an even number of inversions and 17% racemization. Inversion is likely to occur in the azide reaction and in the acetate pyrolysis (both nucleophilic displacements); thus since the (−)-alcohol is *R* (p. 163), the (+)-benzylamine-α-*d* is *S*. If the specific rotation of optically pure benzyl-α-*d* alcohol is taken to be 1.58° (p. 163), that of benzylamine-α-*d* is between 1.76 and 2.12°, depending on whether the 17% racemization mentioned above occurs in the conversion of the alcohol to the amine or in the reconversion of the amine to the alcohol. The rotation of optically pure (+)-benzylamine-α-*d* has been determined unequivocally by Gerlach (181) by conversion to 3-benzyl-α-*d*-4-phenyloxazolidine-2-thione involving complete resolution of the classical chiral center (Fig. 83), the diastereoisomeric purity of the resolved material then being determined by an NMR method which, though independently conceived, is quite similar to that discussed earlier (p. 140). Material of $[\alpha]_D^{25}$ 1.07° (assuming a density of 0.99) was 62.5 ± 2% optically pure; thus, taking into account the presence of 3.8% undeuterated impurity, the specific rotation of benzylamine-α-*d* is 1.78°, close to the lower value estimated above.

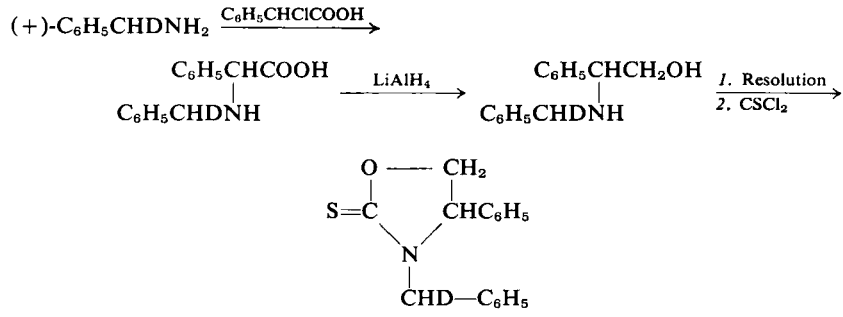


Figure 83

2-(*p*-Hydroxyphenyl)ethylamine-*1-d* (tyramine-*1-d*) has been synthesized from the corresponding methoxy-alcohol (p. 166) in both enantiomeric forms, as shown in Figure 84 (88). The two enantiomers were characterized (88, 182) by the rate of their reaction with rat liver monoamine oxidase: Through the operation of an isotope effect, the *S* isomer is oxidized faster than the *R*. (Apparently, H_R is removed by the oxidase in the rate-determining step.) Knowledge of the configuration of the two amines permitted establishment of the fact that the enzymatic decarboxylation of amino acids proceeds with retention of configuration (Fig. 85) (182). Decarboxylation of L-tyrosine in D_2O gave the *R*-enantiomer of tyramine-*1-d* (initial oxidation rate 0.43), whereas decarboxylation of *dl*-tyrosine-*α-d* (the racemate was used for convenience; the enzyme system does not attack the unnatural D-isomer) gave the *S*-enantiomer of tyramine-*1-d*, characterized by an initial oxidation rate of 1.0. (For comparison, the oxidation rate of tyramine-*1,1-d*$_2$ was 0.43, that of the *R*-isomer shown in Figure 84 0.50, and that of the *S*-isomer shown there 0.80.) Evidently, the two amines prepared as shown in Figure 84 were not enantiomerically pure;

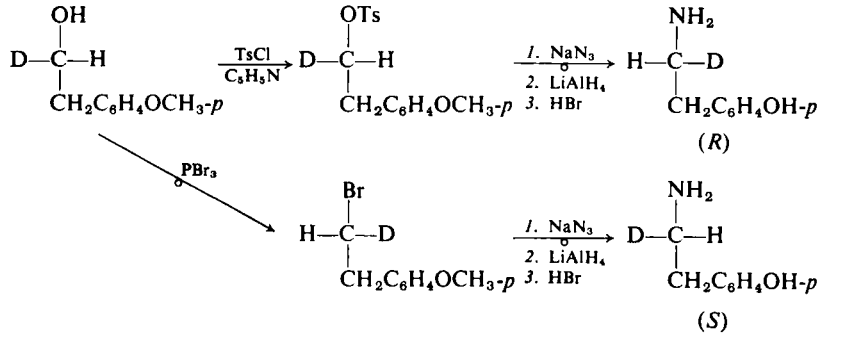


Figure 84

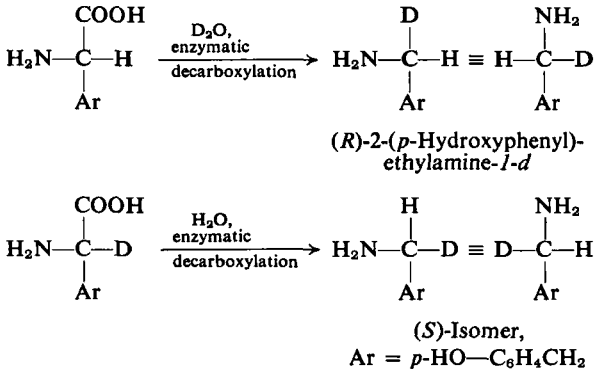


Figure 85

this is to be expected in view of the method of preparation of their precursor alcohols (p. 166).

A very interesting material, both because of its method of synthesis and because of its high optical rotation, is α-methylbenzylideneneopentylamine-α-*d* (Fig. 86) (183). It has the remarkable rotation of α_D + 5.24° (neat, l = 1), and the hydride shift must be very nearly completely stereospecific, for it was shown, by reduction to α-phenethylneopentylamine-α-*d*, classical resolution of the latter substance, and NMR examination (cf. the experiment of Gerlach described earlier) that practically only one diastereoisomer was present. (If both configurations at the N—CHD—CMe_3 chiral center had been present, two diastereoisomers should have been obtained in the resolution process.) It is also of interest that the two resolved amines—in this case not enantiomers but diastereoisomers—differed substantially in rotation, $[\alpha]_D^{25}$ being +23.0 for one and −20.6 for the other (although both were nearly equally stereochemically pure—one 93%, the other 98%) and both differed in rotation from the corresponding hydrogen compound, $[\alpha]_D^{25}$ − 22.8°. The neopentyl-α-*d* chiral center evidently makes an unusually large contribution to the rotation in all these cases.

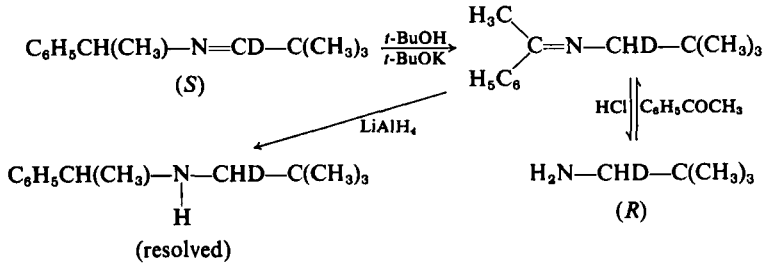


Figure 86

Hydrolysis of the Schiff base (Fig. 86) gave rise to neopentylamine-α-*d* of α_D^{25} + 0.20° (neat, l = 1). Although no loss of optical purity occurred in the hydrolysis (treatment with acetophenone returned the Schiff base with undiminished rotation), the amine was not quite pure chemically and the rotation of pure material was estimated to be ca. 0.30° (183). The configuration of the amine was assigned as *R* on the basis of Brewster's rules (43).

(*R*)-Neopentylamine-α-*d*, α_D^{26} + 0.23 ± 0.02 (l = 1, neat) has also been synthesized from (*S*)-neopentyl-α-*d* alcohol (p. 164) by conversion to the tosylate, reaction with sodium azide in hexamethylphosphoramide, and reduction of the azide with lithium aluminum hydride (Fig. 87) (184). The optical purity of the material was shown to be in excess of 98% by the use of Mislow's method [NMR analysis of the amide obtained with $C_6H_5C(OCH_3)COCl$]. Assuming inversion in the tosylate–azide reaction

CF_3

(remarkable in that it involves a bimolecular displacement at a neopentyl carbon), the dextrorotatory neopentylamine-α-*d* is *R*, in agreement with Brewster's rules (*vide supra*).

A stereospecific hydride shift similar to that shown in Figure 86 appears to be involved in the conversion of a methylene-deuterated pyridoxamine Schiff base of an α-ketoacid to the pyridoxal Schiff base of the corresponding α-amino acid (184a). In the reverse transformation it has been shown unequivocally (184b) that the hydrogen is transferred to

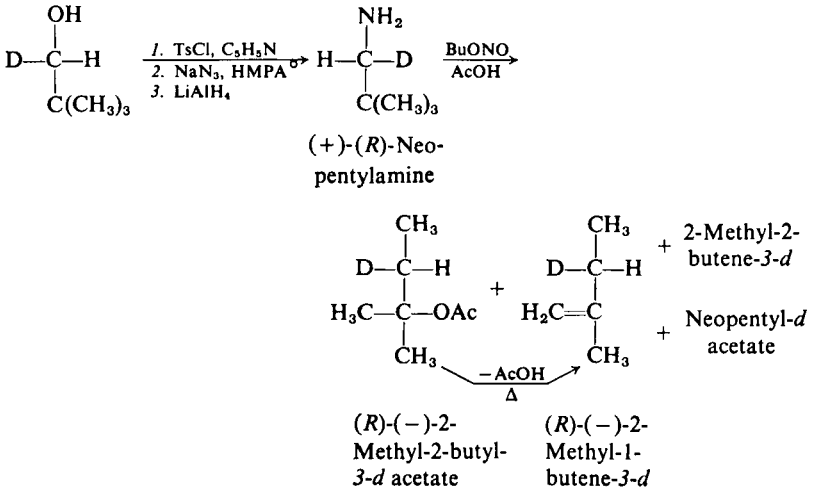


Figure 87

the pyridoxal Schiff base from the *si*-side so as to occupy the *pro-S* position (see also, 184c); for when the source of the hydrogen is THO, the tritiated pyridoxamine may be ozonolytically degraded (184b) to (2*S*)-glycine-*2-t* (*vide infra* and Fig. 89). The stereospecificity is the same for the enzymes apoglutamate aspartate transaminase (184b, 184c) and pyridoxamine pyruvate transaminase (184a).

Availability of optically active neopentylamine-α-*d* permitted the study of the steric course of the deamination of neopentylamine (185) (Fig. 87). The starting material had an estimated 93.5% optical purity and its configuration is presumably *R* (see above). The configuration (p. 153) and optical rotation, $[\alpha]_D^{20}$ 1.01 (47), of the olefin product were known from earlier work and it could thus be established, on the basis of the deuterium content and rotation of the products, that both acetate and olefin formation (Fig. 87) proceeded with inversion and with a high degree (over 85%) of preservation of optical purity.

The α-deuterated *cis*- and *trans*-4-methylcyclohexylmethylamines have been synthesized in optically active form as relays in the elegant determination of the absolute configuration of (+)-4-methylcyclohexylideneacetic acid by Gerlach (186). Catalytic hydrogenation of the deuterated acid gave a mixture of *trans*-4-methylcyclohexylacetic-α-(*S*)-*d* acid and *cis*-4-methylcyclohexylacetic-α-(*R*)-*d* acid (Fig. 88). The acids were separated and their geometric configurations (*cis* or *trans*) were established by correlation with the known 4-methylcyclohexanecarboxylic acids. Each acid was then converted to the corresponding amine (isolated as the benzylurethane) by a Curtius degradation (Fig. 88). Amines of known absolute configuration at the $RCHDNH_2$ center were then prepared for comparison by the route shown in Figure 88: reduction of 4-methylcyclohexanecarboxaldehydes by isobornyloxymagnesium chloride (which gives the *S*-alcohol, cf. Fig. 25) and conversion of the carbinols (RCHDOH) so obtained to the amines via the tosylates and azides in a pathway involving inversion of configuration (Fig. 88). The *trans*-amines were compared as the benzylurethanes; in the *cis*-series the benzylurethanes were nonrotating and comparison was made through the corresponding phthalimides. The sign of rotation and configuration of all the intermediates are shown in Figure 88; exact information on optical purity is not available in this series.

In concluding the section on amines, we shall take up the configuration of glycine-*t*, $H_2NCHTCOOH$ (187). The compound has been synthesized in two ways: from serine in the presence of the enzyme hydroxymethyl transferase (formally loss of formaldehyde) and from glycine by a stereoselective hydrogen exchange with tritiated water brought about by the enzyme L-alanine aminotransferase; the former reaction produces the

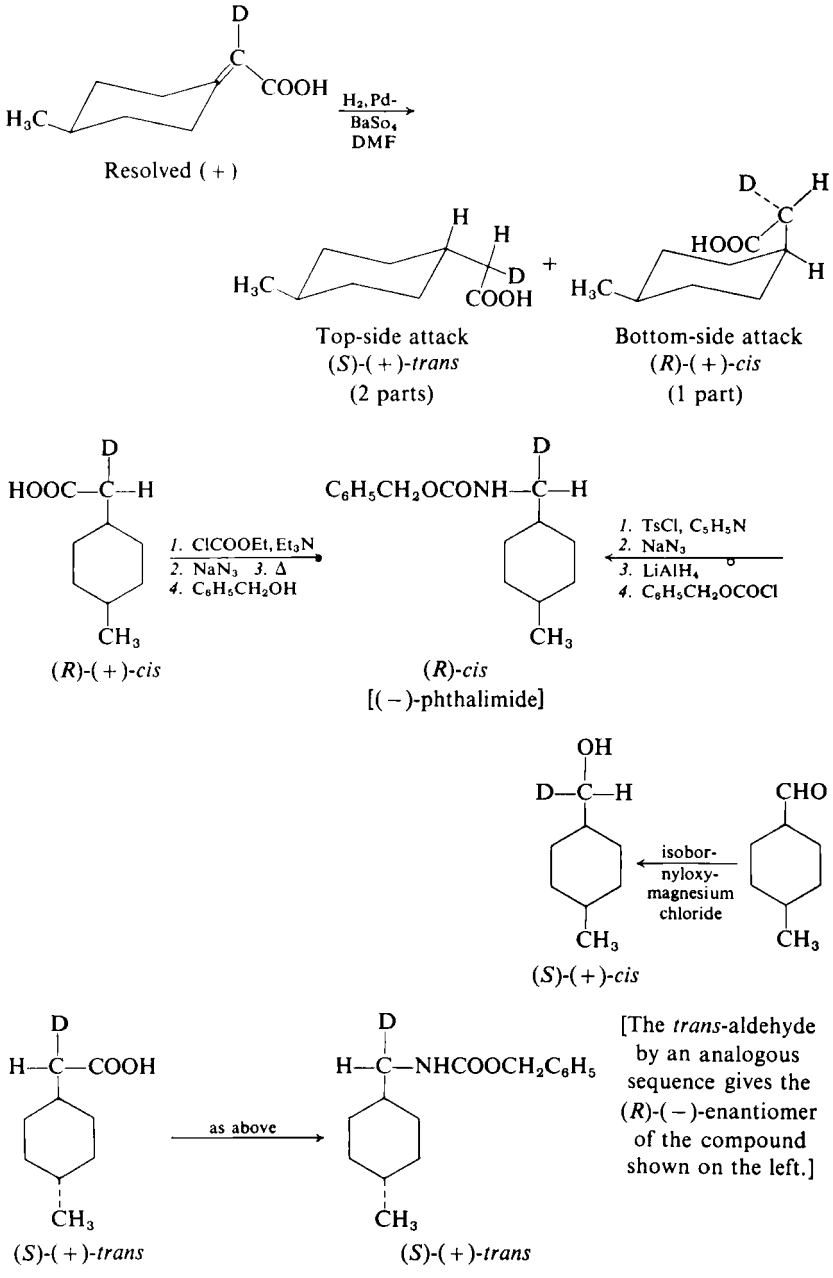

D
C
COOH
H3C
H2, Pd-BaSO4 DMF
Resolved (+)
H
H
D
COOH
H3C
+
D
H
HOOC
H3C
H
Top-side attack
(S)-(+)-trans
(2 parts)
Bottom-side attack
(R)-(+)-cis
(1 part)
HOOC—C—H
CH3
1. ClCOOEt, Et3N
2. NaN3 3. Δ
4. C6H5CH2OH
(R)-(+)-cis
C6H5CH2OCONH—C—H
CH3
1. TsCl, C5H5N
2. NaN3
3. LiAlH4
4. C6H5CH2OCOCl
(R)-cis
[(−)-phthalimide]
OH
D—C—H
CH3
isobor-nyloxy-magnesium chloride
CHO
CH3
(S)-(+)-cis
H—C—COOH
CH3
as above
H—C—NHCOOCH2C6H5
CH3
(S)-(+)-trans
(S)-(+)-trans
[The trans-aldehyde by an analogous sequence gives the (R)-(−)-enantiomer of the compound shown on the left.]

Figure 88

CH2OH
H—C—NH2
COOH
(S)-(−)-Serine
serine-hydroxymethyl-transferase, THO/THF
T
H—C—NH2
COOH
(S)-Glycine-t
HNO2
T
H—C—OH
COOH
(S)-Glycolic-t acid
glycolate oxidase
O
C
T
COOH
NH2
H—C—D
COOH
(R)-Glycine-d
L-alanine-aminotrans-ferase, D2O
NH2
H3C—C—H2
COOH
Glycine
L-alanine-amino-transferase, THO
NH2
H—C—T
COOH
(R)-Glycine-t
HNO2
OH
H—C—T
COOH
glycolate oxidase
O
C
H
COOH
(R)-Glycolic-t acid

Figure 89

S-enantiomer, the latter the *R* (Fig. 89). Assignment of the configuration was effected by deamination to glycolic-*t* acid by means of nitrous acid, a reaction which, by analogy with other cases (e.g., p. 189), may safely be assumed to involve retention of configuration. The configurations of the glycolic acids so obtained were ascertained by enzymatic oxidation to glyoxylic acid in which H_R is known to be lost (cf. Figs. 19, 29). The L-alanine–aminotransferase reaction was also carried out in D_2O, and the glycine-*d* so obtained was deaminated to glycolic-*d* acid whose configuration was directly established as being *R* from its ORD curve (cf. p. 155). These correlations are summarized in Figure 89. The reaction involving formal loss of CH_2O clearly proceeds with retention of configuration and the isotopic exchange in the glycine catalyzed by the transferase enzyme affects H_R. The ORD curve of glycine has been measured (187), $[\alpha]_{227} + 68°$.

I. Miscellaneous Compounds

Cyclopentanone-3-*d* has been synthesized in chiral form, but appears to show no measurable rotation (188). A number of chiral alkyl halides of the type RCHDX and derivatives of alcohols, RCHDOX, have been prepared, mainly by Streitwieser and co-workers, in connection with mechanistic studies. A table of correlations of rotations of some of these derivates has been published (46, 189) and since a comprehensive review of the work is about to appear (189), it is not covered in the present chapter.

A recent study (190) of the conversion of the unsaturated side-chain of lanosterol-*24-t* (also tritiated in other positions) to the saturated side-chain of cholesterol shows that the hydrogen newly introduced at C-24 is *pro-S*.

J. Compounds of the Type CHDTX

In principle, substitution of hydrogen in a methyl compound $CH_3X + Y \rightarrow YCH_2X + H$ has a stereochemical aspect: Y may engage the same lobe of the sigma orbital which held the departing hydrogen (retention of configuration) or it may engage the rear of that lobe with resulting inversion. As this chapter passed through galley proof two successful demonstrations of the stereochemistry of events of this type were reported (191) involving compounds of the type CHDTX. These experiments seem of sufficient general importance to warrant consideration here.

In one investigation (191b) (*S*)-glycolic-*2-t* acid was synthesized similarly as shown in Figure 19 and was chemically converted into (*R*)-ethanol-*2-d-2-t* as shown in Figure 90. Because the intermediate tritiated

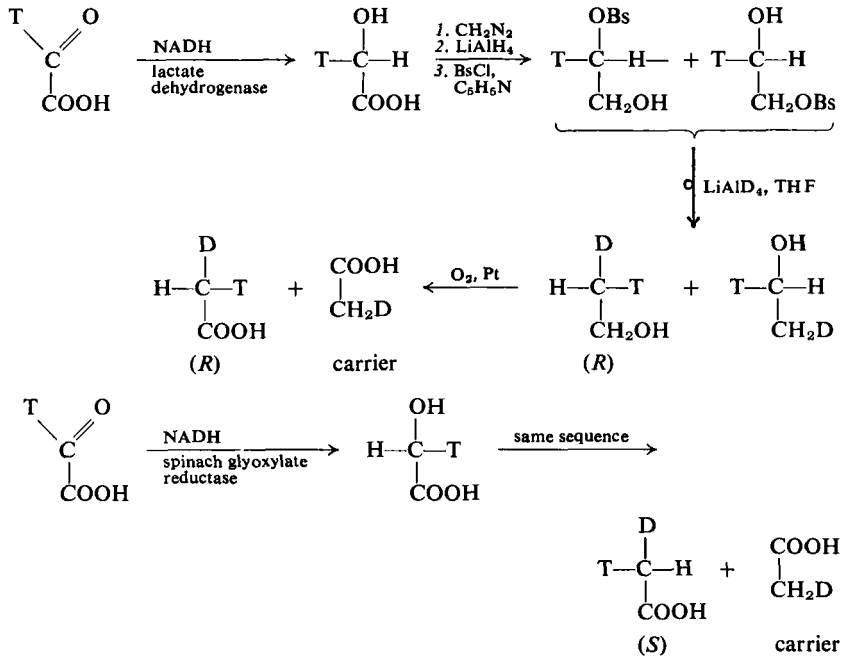
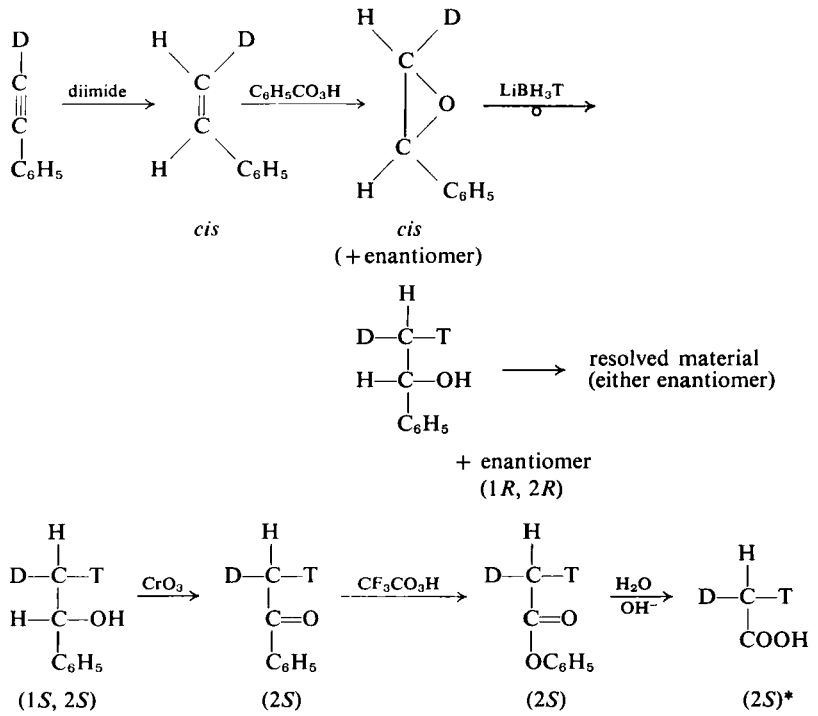


Figure 90

ethylene glycol is brosylated almost indiscriminately at the two hydroxyl groups, $CH_2DCHTOH$ will be formed concomitantly; however, it may be noted (Fig. 90) that in the final oxidation to (*R*)-acetic-α-*d*-α-*t* acid, the by-product yields CH_2DCOOH, indistinguishable from the carrier material. (Tritium is, of course, used at the usual tracer level.) (*S*)-Acetic-α-*d*-α-*t* acid was synthesized analogously but using in the initial reduction glyoxylate reductase from spinach leaves which produces stereochemical results opposite to that of lactate dehydrogenase (Fig. 90) (cf. p. 169). An alternate synthesis (190a) of the enantiomeric acetic-α-*d*-α-*t* acids involves synthesis of the pure *dl-cis* isomer of styrene-β-*d* oxide, reduction with lithium borotritide, resolution, by classical methods, of the phenylmethylcarbinol so formed and finally degradation to chiral acetic-α-*d*-α-*t* acid (Fig. 91). This synthesis entails the interesting principle of bringing about resolution of a chiral center by building it into a pure *dl*-diastereoisomer, resolving at the second chiral center in that diastereoisomer and finally destroying the second chiral center.

The two enantiomers of CHDTCOOH cannot, of course, be distinguished by the usual measurements of chirality (optical rotation, rotatory dispersion, or circular dichroism) since they are labeled only at the tracer level; an enzymatic distinction was therefore called into play.



* The 2*R* enantiomer is obtained analogously from the enantiomeric (1*R*, 2*R*) carbinol.

Figure 91

Both isomers were condensed, in the form of their CoA-derivatives, with glyoxylic acid in the presence of malate synthetase (191). The condensation may be assumed, *a priori*, to involve an isotope effect with respect to the hydrogen of the methyl group which is lost, and in fact it could be shown, by counting the malic acid formed and comparing it with the acetic acid precursor, that H is lost in preference to T with an isotope effect of 8–10; it may be inferred that the H/D isotope effect is about 4–5 (192).

If H is removed in preference to D* then, because of the chirality of the acetic acid precursor, the malic acid will be chiral about the CDT-group, as shown in Figure 92. The sense of chirality will depend on

* It must be understood that this preferential removal is due to an isotope effect, not to sterically different placement (as it might be in the case of a CHDRR'-group). For reasons of symmetry, the three hydrogens of a freely rotating methyl group are intrinsically equivalent, even in a chiral environment. However, the two hydrogens in RCH_2D are heterotopic and this fact may be demonstrated if, for reasons of isotopic discrimination, the D-ligand may be considered chemically distinct from the H-ligands.

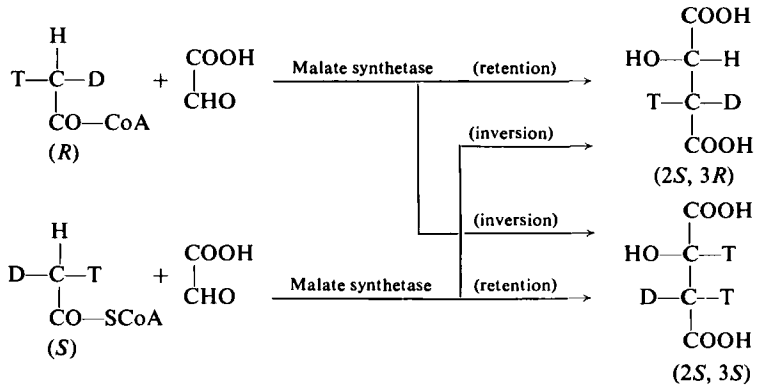


Figure 92

whether the condensation involves retention or inversion of configuration.*

The configuration at C-3 of the resulting malic acid (Fig. 92) was determined by conventional means by determining whether or not tritium was labilized (exchanged) in reversible dehydration to fumaric acid in the presence of fumarase. As shown in Figure 51 (p. 187) this process leads to exchange of H_R. When the malic acid obtained from the (*R*)-acetate was subjected to this exchange, a minimum of 10% (191b) and a maximum of 33% (191a) of the tritium was lost, whereas the malic acid from (*S*)-acetate exchanged between 69% (191a) and 90% (191b) of its tritium. It follows (compare Figs. 51 and 92) that the (*R*)-acetate gave mainly (3*S*)-tritium labeled malate whereas the (*S*)-acetate yielded mostly (3*R*)-tritiated malate; in other words, the malate synthetase condensation involves inversion of configuration at the methyl group.

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* For the sake of simplicity in the argument, we shall assume that the H/D isotope effect is infinite, i.e., that only hydrogen, not deuterium is removed in the condensation shown in Figure 92. (The removal of tritium is of no concern here, since it leads to untritiated malic acid which is indistinguishable from the carrier.) To the extent that some D is, in fact, removed there is leakage between the two chiral series shown in Figure 92, since the H and D are enantiotopically placed as seen by the tritium. Such leakage is actually observed (see below) to the extent of about 10–30%.

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