TOPICS IN
STEREOCHEMISTRY

VOLUME 1

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TOPICS IN STEREOCHEMISTRY

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VOLUME 1

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INTRODUCTION

During the last five 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 As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.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 (and, possibly, biochemists), but involved frequently with fundamental principles of physical chemistry and molecular physics. At a later time perhaps, we hope to devote more space to inorganic stereochemistry.

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

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 assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

N. L. Allinger
E. L. Eliel

January 1967

PREFACE

This volume contains four chapters which the Editors believe will be of general interest. The first chapter, "Stereoisomeric Relationships of Groups in Molecules," by Kurt Mislow and Morton Raban, unfolds and explores many intricate details of the subject which have not previously received widespread attention. While the discussion in this chapter would have been considered quite esoteric by organic chemists only a few years ago, the present great importance of nuclear magnetic resonance spectroscopy makes the detailed consideration of the steric relations of nuclei within a molecule a timely subject. In fact, it may be confidently predicted that the ideas put forth in this chapter will be commonplace within a very short time. The topic has also rather important biochemical implications related to the stereochemical mode of action of enzymes.

The second chapter, "Stereochemistry of Metallocenes," by Karl Schlögl, will be of interest not only to those who work in this area but also to many others, because the unusual symmetry characteristics of the metallocenes lead to stereochemical problems not commonly encountered elsewhere up to now. The way in which some of these problems are attacked should prove generally instructive.

In the third chapter, Pierre Crabbé discusses "Recent Applications of Optical Rotatory Dispersion and Optical Circular Dichroism in Organic Chemistry." The fundamentals of these subjects have been discussed in detail in several textbooks and reviews, and it is the purpose of Crabbé's chapter to bring together for the reader a number of important recent advances in the field. These advances are both in theoretical development and in applications to a wide variety of natural products.

The final chapter in the volume is "Table of Conformational Energies —1967," compiled by Jerry Hirsch. It extends and updates a similar table published a few years ago in *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965) and, with the increased attention which conformational energies are receiving in a wide variety of chemical problems, should prove a useful source of reference for many readers.

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Stereoisomeric Relationships of Groups in Molecules

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I. SPATIAL RELATIONSHIPS BETWEEN MOLECULES AND PORTIONS OF MOLECULES

The terms "enantiomeric" and "diastereomeric" are commonly used to describe relationships between stereoisomeric molecules. Spatial relationships between portions of molecules may be similarly termed (1,2), and such descriptions have provided a convenient guide in the analysis of a variety of stereochemical problems. This paper presents basic definitions and terminology, an elaboration of the original classification (1,2) of groups residing in stereoisomeric environments, and the application of these principles to some problems in NMR spectroscopy and asymmetric synthesis.

In connection with the subsequent descriptions of molecular geometries, a few words concerning symmetry elements, operations, and point groups may be appropriate; see reference 3 for a more complete exposition of the Schoenflies notation used here. The alternative Hermann-Mauguin notation is employed chiefly by crystallographers (cf., e.g., 4).

Two general kinds of symmetry elements and associated operations may be distinguished: axes of rotation (also termed simple axes, or C axes), and rotation–reflection axes (also termed alternate axes, or S axes). Molecules such as difluoromethane (Fig. 1, **1a**) may be superposed upon themselves by rotation by $2\pi/2$ radians; alternatively one may say that rotation of the molecule by $2\pi/2$ radians produces a structure which is indistinguishable from the original. Such a molecule is said to possess a C_2 axis and the rotation is termed a C_2 operation. A molecule is said to possess a C_n axis if rotation by $2\pi/n$ radians produces a structure which is indistinguishable from the original. The trivial C_1 axis is found in all molecules since in every case a rotation by 2π radians (360°) returns the molecule to its original position; the C_1 operation is for this reason also an identity operation.

The simplest rotation–reflection axis, the S_1 axis, is equivalent to a plane of symmetry (σ plane) perpendicular to the axis. A σ plane is a mirror plane which bisects a geometric figure so that the half of the figure on one side of the plane is exactly mirrored by the half on the other side. Chlorofluoromethane (Fig. 2, **2a**) possesses a σ plane which passes through the F, C, and Cl nuclei. Higher order rotation–reflection operations (S_n) may be viewed as rotations by $2\pi/n$, combined with reflection in a plane *perpendicular* to the axis of rotation. The substituted cyclobutane in Figure 3 (**3d**) possesses a S_4 axis perpendicular to the plane of the ring. Neither rotation by $2\pi/4$ about the axis *alone*, nor reflection in the plane of the ring *alone*, is sufficient to produce a structure indistinguishable from the original. However, the combination of these two operations (i.e., an S_4 operation) produces a structure indistinguishable from the original. The tetrahaloethane in Figure 3 (**3a**) possesses a S_2 axis coincident with the C—C bond since rotation by $2\pi/2$ plus reflection in a plane perpendicular to that axis produces a structure indistinguishable from the original. The S_2 symmetry operation is equivalent to inversion of the molecule through a center of symmetry (i), which bisects the C—C bond in this case. Molecules which possess S_n axes are said to be achiral or nondissymmetric and are superposable on their mirror images; contrariwise, molecules devoid of S_n axes are said to be chiral or dissymmetric and are nonsuperposable on their mirror images.

Molecules are conveniently classified into symmetry point groups on the basis of the symmetry elements which they possess. Molecules which possess no symmetry elements aside from the trivial axis (i.e., asymmetric molecules) are said to belong to the point group $\mathbf{C}_1$. Molecules which possess, as their sole symmetry element, a C_n axis belong to the $\mathbf{C}_n$ point groups. Some molecules, for example, the skewed bridged biphenyl ketone (**11c**) (point group $\mathbf{D}_2$), have a C_n axis and in addition have nC_2 axes which are perpendicular to the principal C_n axis. Such a combination of axes gives rise to dihedral symmetry D_n, and molecules possessing only these axes belong to the $\mathbf{D}_n$ point groups. Molecules which belong to the $\mathbf{C}_n$ and $\mathbf{D}_n$ point groups are chiral, and most chiral molecules belong to the $\mathbf{C}_n$ (including $\mathbf{C}_1$) and $\mathbf{D}_n$ point groups, although other point groups (**T**, **O**, **I**) may also accommodate chiral arrays.

Molecules which have only S_n axes (aside from the $C_{n/2}$ axes which are collinear with the S_n axes) belong to the $\mathbf{S}_n$ point groups. The two point groups, which contain molecules having as their sole symmetry elements a σ plane (S_1) and a center of symmetry ($S_2 \equiv i$), are termed $\mathbf{C}_s$ and $\mathbf{C}_i$ ($\equiv \mathbf{S}_2$), respectively. Molecules which contain a C_n together with a collinear S_1 (i.e., a perpendicular σ plane) belong to the $\mathbf{C}_{nh}$ point groups. Those which possess a C_n together with n perpendicular S_1 axes (i.e., $n\sigma$ planes which contain the C_n axis) belong to the $\mathbf{C}_{nv}$ point groups. Those with dihedral symmetry and with an S_1 axis collinear with the principal axis, and those with no collinear S_1 but nS_1 axes perpendicular to the principal axis, belong to the $\mathbf{D}_{nh}$ and $\mathbf{D}_{nd}$ point groups, respectively.

The geometries of the highly symmetrical Aristotelian polyhedra are represented by the $\mathbf{T}_d$ (tetrahedron), $\mathbf{O}_h$ (octahedron and cube), and $\mathbf{I}_h$ (icosahedron and dodecahedron) point groups. The symmetries of the cone and cylinder are represented by the linear point groups $\mathbf{C}_{\infty v}$ and $\mathbf{D}_{\infty h}$, respectively. The $\mathbf{C}_1$, $\mathbf{C}_s$, and C_i point groups are sometimes termed the *non-axial* point groups, since no C_n ($n > 1$) axes are found in such arrays. All other point groups are termed *axial*.

The terminology employed in the subsequent discussion to describe portions of molecules is based on that which is applied to whole molecules, i.e., to conventional stereoisomers. Two molecules are enantiomers (or enantiomorphs) if they are related as an object and its nonsuperposable mirror image. The term "nonsuperposable" in the present context signifies that the object and its mirror image cannot be made to coincide in space by translational or rotational motions; we mean here to exclude any motions which produce a change in the internal coordinates (bond lengths, bond angles, and dihedral angles of the molecule), i.e., we exclude conformational changes. However, an object and its nonsuperposable mirror image can be made to coincide by an operation which includes, beside translational and rotational motions, reflection of the object in a mirror plane. Such objects and their nonsuperposable mirror images are chiral. If an object and its mirror image can be made to coincide in space by translational and rotational motions, they are achiral.

Molecules which are stereoisomers but which are not enantiomers (i.e., molecules which are not superposable by any symmetry operation) are termed diastereomers. This definition (2) of diastereomers (or diastereoisomers) as non-enantiomeric stereoisomers is broader and more inclusive than the more common definition (5) of diastereomers as "stereoisomers, some or all of which are dissymmetric but which are not mirror images of each other," i.e., a set of non-enantiomeric stereoisomers at least one of which is chiral. It has been pointed out by Wheland (6) that, "No general term has been universally adopted for the description of the relationship between two stereoisomers that are not enantiomorphs of each other." Wheland first chose the broader definition of "diastereomer" to designate "any non-enantiomorphous stereoisomer. Thus even fumaric and maleic acids will be described as diastereomers of each other." The description of fumaric and maleic acids as "diastereomers" dramatizes the extent to which the more common definition was broadened by Wheland, who recognized that "this terminology departs somewhat from the most common usage." We have adopted Wheland's definition because we find that a dichotomous subdivision of all pairs of stereoisomers, *regardless of structure*, between those which are related as object and nonsuperposable mirror image (i.e., enantiomers) and those which are not (i.e., diastereomers) provides by far the most consistent, convenient, and generally satisfactory, if not the most common, classification scheme. For example, the *cis* and *trans* forms of 1,2- and 1,3-disubstituted cyclohexanes are diastereomers by all definitions (2,5,6); we advocate that *cis* and *trans* forms of 1,4-disubstituted cyclohexanes also be so designated, even though in this case there can be no possibility of "optical isomerism." Similarly, the stereoisomers (two *meso* forms and four *dl*-pairs) of truxinic (3,4-diphenylcyclobutan-1,2-dicarboxylic) acid are diastereomers by all definitions (2,5,6); it seems most consistent that the stereoisomers (five *meso* forms and no *dl*-pairs) of truxillic (2,4-diphenylcyclobutan-1,3-dicarboxylic) acid also be so designated.

In defining the spatial relationships of portions of molecules, one must distinguish between internal and external comparisons.* In the former, the comparison takes place between portions of the same molecule, whereas in the latter the comparison takes place between corresponding portions which are parts of different molecules. In either case the portion of the molecule may consist of a single atom or a group of atoms and will, for the sake of simplicity, here be referred to simply as a "group." The groups whose spatial relationship is to be defined must be two or more in number and together constitute a set.

II. EQUIVALENT GROUPS AND FACES

Groups are said to be equivalent by internal comparison if they can be interchanged by rotation about an axis of rotation, $C_n(\infty > n > 1)$,

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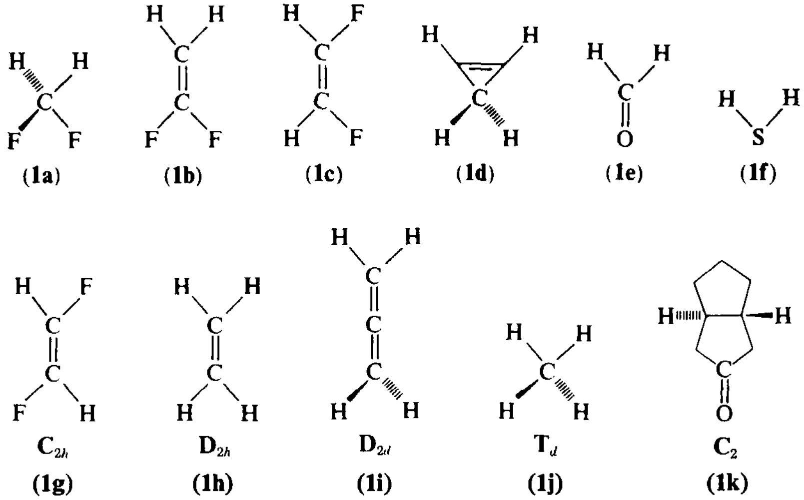
* A single entity cannot be designated as an enantiomer or diastereomer. Such terms refer to relationships within a set of two or more stereoisomers, i.e., one may not describe a molecule simply as an "enantiomer" or as a "diastereomer" but only as the "enantiomer of" or a "diastereomer of" another molecule. Similarly with groups, a "comparison" of some sort is always necessary.

to give a structure indistinguishable from the original. By an "interchange" of groups G and G′ we mean a symmetry operation which places G into the position in space which is vacated by G′ in the same operation. Thus, in ammonia (**C_{3v}**), if we were to label the three hydrogen atoms H_1, H_2, and H_3, rotation about the C_3 axis by $2\pi/3$ radians would place H_1 into the position formerly occupied by H_2, H_2 into the position formerly occupied by H_3, and H_3 into the position formerly occupied by H_1. It should be noted that our use of the term "equivalent" is arbitrarily restricted to those groups which can be interchanged by C_n and excludes those for which an S_n operation is necessary for the interchange (see also page 18).

In molecules containing equivalent groups, the C_n axis must be a symmetry element of the molecule. Figure 1 shows some molecules with sets of equivalent hydrogen atoms which are interchangeable by C_2, the most common operation in this class. The molecules in the top row (**1a**–**1f**) belong to point group **C_{2v}**, and the point groups of the molecules in the bottom row (**1g**–**1k**) are separately indicated.

The structures shown in Figure 1 illustrate several adjunct principles. First, the same molecule may contain more than one set of equivalent groups. For example, the four difluoro compounds (**1a**,**1b**,**1c**,**1g**) each contain a set of two equivalent fluorine atoms, allene (**1i**) and four of the five olefins (**1c**,**1d**,**1g**,**1h**) each contain a set of two equivalent carbon atoms, **1c** and **1g** each contain a set of equivalent HCF groups, and **1k** contains two sets of equivalent methylene groups and one set of equivalent methine groups. Second, molecular dissymmetry is no bar to equivalence in groups, as illustrated by the example of **1k**. Third, a set may contain more than two equivalent groups, as illustrated for ethylene (**1h**), allene (**1i**), and methane (**1j**), each of which contains a set of four equivalent hydrogens. Fourth, as in formaldehyde (**1e**), the two environments of the carbonyl group, above and below the molecular plane, are equivalent (similarly, in hydrogen sulfide (**1f**) the two environments of the sulfur atom, above and below the molecular plane, are equivalent). In these cases one may speak of "equivalent faces." In the event of reaction, the approach of a reagent to either "face" is "seen" to be equivalent in the sense of the term as here defined. The equivalence of "faces" as well as of "groups," ultimately refers to their environments. Equivalent faces are found in chiral as well as achiral molecules, as illustrated by the equivalent faces of the carbonyl group in **1k**.


(1a) (1b) (1c) (1d) (1e) (1f)

C_{2h} (1g) D_{2h} (1h) D_{2d} (1i) T_d (1j) C_2 (1k)

Figure 1

Attack by a reagent at equivalent faces leads to equivalent transition states, as in the lithium aluminum hydride reduction of formaldehyde, the formation of cyclopropanes by reaction of *cis*-2-butene or isobutylene with symmetrically substituted carbenes (CR_2), and in the oxidation of dimethylsulfide to the sulfoxide.* It may be noted that in some cases attack at a particular one of two equivalent faces may result in two non-equivalent transition states. Thus, in the reaction of an unsymmetrically substituted carbene, such as chlorocarbene (CHCl), with *cis*-2-butene, attack at one particular face of the olefin leads to two diastereomeric transition states [and to two product diastereomers, i.e., the *meso*-1-chloro-2,3-dimethylcyclopropanes having the (*r*)- and (*s*)-configurations (7) at C-1]. However, attack at the other equivalent face leads to identical results. The import of our remarks thus is that attack at equivalent faces has identical consequences. It should be noted that this result is obtained whether the equivalent faces are contained in chiral or in achiral molecules.

The operation of equivalent-group interchange is of course not restricted to C_2; for example in chloromethane (C_{3v}) the three equiv-

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*In the last examples, the methyl groups are regarded as equivalent since the methyl hydrogens are equivalent on the time scale of the measurement here considered (see Sect. VI).

alent hydrogen atoms are interchanged by a C_3 operation. Indeed, all molecules which belong to the axial point groups (with the exception of $\mathbf{C}_{\infty v}$) must contain equivalent groups. A plane has equivalent faces when and only when it contains a C_2 axis. It follows that molecules belonging to the three non-axial point groups ($\mathbf{C}_1$, $\mathbf{C}_i$, and $\mathbf{C}_s$) cannot contain equivalent groups or faces because these symmetries exclude the C_n which is essential for the interchange of equivalent groups. Among linear molecules, those with cylindrical symmetry ($\mathbf{D}_{\infty h}$), for example acetylene or carbon suboxide, contain no atoms (except the one at the center) which do not fall into sets of two equivalent groups, whereas those with conical symmetry ($\mathbf{C}_{\infty v}$), for example, chloroacetylene, contain no equivalent groups because the only C_n is a C_∞.

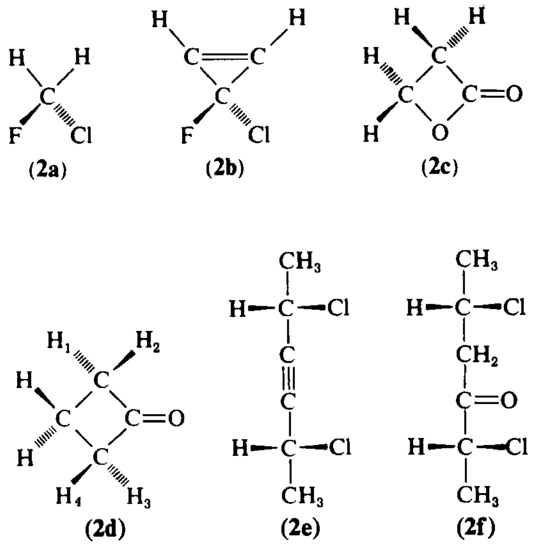
In lieu of the symmetry criterion stated at the beginning of this section, one may employ an alternative test for equivalence or non-equivalence in groups which may be called the "substitution criterion." In an internal comparison between two or more G groups, application of the substitution criterion simply involves replacement of each G (e.g., a hydrogen atom) by a "test group" G′ (e.g., a deuterium atom). If the various structures resulting from the substitution of each G by G′ are indistinguishable (in the sense of being superposable by rotational and translational motions), the G groups are equivalent. This test is readily applied to the molecules in Figure 1 by substitution of hydrogen by deuterium. It is seen that substitution of any one of a set of equivalent hydrogens by a deuterium atom lowers the symmetry but does not generate a set of isomers.

III. ENANTIOTOPIC GROUPS AND FACES

We may distinguish two types of relationships between groups which reside in stereoisomeric environments and which are therefore non-equivalent. If the environments of the groups are enantiomeric we shall refer to the groups as *enantiotopic.** If the environments of the groups are diastereomeric we shall refer to the groups as diastereotopic.* By

---

*The spatial relationship between atoms or groups of atoms, whether reference is made to an internal or an external comparison, is properly the relationship of their environments. In a previous treatment (2) the terminology employed (e.g., "enantiomeric and diastereomeric protons"), though clear in context, did not in itself distinctly convey the intended attribute. After consideration of suitable alternative adjectives, which included the suffixation of "enantio-" and "dia-stereo-" with "scopic" (*scopos* = watcher), suggested to us at the EUCHEM



(2a) (2b) (2c)

(2d) (2e) (2f)

Figure 2

definition, enantiomeric groups, e.g., the CH_3CHCl groups in **2e** (Fig. 2), must be enantiotopic. It follows that the CH_3CHCl groups in compounds such as **2f** (Fig. 2) are not strictly speaking "enantiomeric," since in this case the environments are not enantiomeric and thus the groups are not enantiotopic.

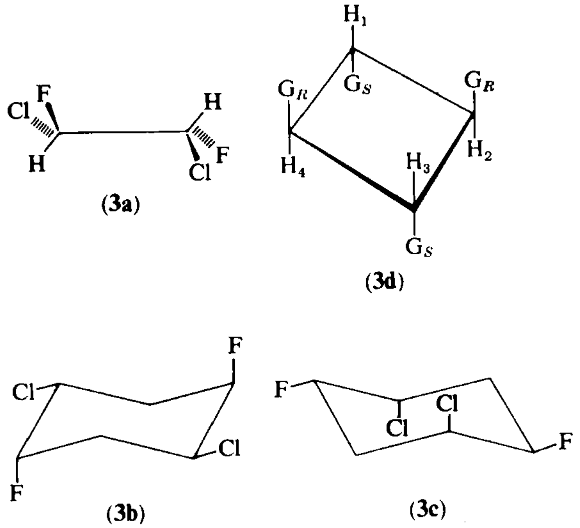
Groups are said to be enantiotopic by internal comparison if they can be interchanged only by a rotation–reflection operation (S_n), and not simply by a rotation [$C_n(n > 1)$], to give a structure indistinguishable from the original. In the sense of our definition of enantiomers, the enantiotopic groups are nonsuperposable. Some examples of molecules containing sets of enantiotopic hydrogen atoms are shown in Figure 2 (**2a**–**2e**). These groups are only interchangeable by a simple reflection in a mirror plane ($\sigma \equiv S_1$) which passes through the molecule.

Conference on Stereochemistry (at Bürgenstock, May, 1966), "peristatic" (*peristasis* = environment), suggested to us by Professor S. D. Atkins (Department of Classics, Princeton University), and "topic" (*topos* = place), suggested to us by Mr. Paul Bickart in our laboratory, we have adopted the last as the most apt and concise term to convey our meaning. The terms "enantiomeric" and "diastereomeric" will be retained to describe groups which are inherently stereoisomeric, i.e., even when removed from their environments.

The structures shown in Figure 2 illustrate several adjunct principles. Enantiotopic groups need not be attached to the same atom, as exemplified by the hydrogen atoms and olefinic carbon atoms of **2b**, and the methine and methyl hydrogen atoms of **2e**. That there may be several sets of enantiotopic groups in the same molecule is also illustrated by propiolactone (**2c**) in the planar (C_s) conformation, which has two constitutionally nonequivalent sets of enantiotopic hydrogen atoms. In contrast to molecules containing only equivalent groups, molecules containing enantiotopic groups may belong to the nonaxial groups C_s (as illustrated for **2a**, **2b**, and **2c**) and C_i (see below), but they may occur in axial groups also. This point is illustrated for cyclobutanone (**2d**)—the conformation in which the four carbon atoms lie in a plane belongs to C_{2v}. The methylene hydrogens on C-3 are equivalent. The pairs of hydrogen atoms H_1/H_4 and H_2/H_3 are equivalent and form two enantiotopic sets which may be referred to as enantiotopic sets of equivalent hydrogen atoms. The pairs of hydrogen atoms H_1/H_2 and H_3/H_4 form two equivalent sets of enantiotopic hydrogens. The pairs of hydrogen atoms H_1/H_3 and H_2/H_4 also form two equivalent sets of enantiotopic hydrogen atoms. Neither linear nor chiral molecules are capable of containing enantiotopic groups, and molecules containing such groups must therefore be nonlinear and achiral. Since asymmetric molecules belong to C_1 which is both non-axial and chiral, it follows that asymmetric molecules may contain neither equivalent nor enantiotopic groups.

Although the enantiotopic hydrogens in the examples of Figure 2 are interchanged by a σ, this symmetry operation is not a necessary condition for the existence of enantiotopic groups and examples may be adduced in which the interconversion requires a rotation-reflection symmetry operation, S_n, of order greater than unity (Fig. 3).

The tetrahaloethane, in the conformation shown in **3a**, belongs to symmetry point group C_i and possesses as its sole symmetry element a center of symmetry. As we have seen, such molecules may not contain equivalent groups because the required C_n is absent. The hydrogen atoms, the chlorine atoms, and the fluorine atoms form three sets of enantiotopic groups which are not interchangeable by rotation or reflection (σ), but which are interchangeable by an inversion operation i ($\equiv S_2$). The same situation is encountered in the isomer of 1,4-dichloro-2,5-difluorocyclohexane which is shown in its two chair conformations (**3b** and **3c**). In either chair conformation there are two sets of enantiotopic



(3a) (3d) (3b) (3c)

Figure 3

halogens and four sets of enantiotopic hydrogens. The cyclobutane derivative **3d**, in which the cyclobutane ring is taken in the planar conformation and in which G_R and G_S represent chiral groupings having the (*R*)- and (*S*)-configurations, respectively, belongs to point group S_4. Since molecules belonging to point group S_n contain a $C_{n/2}$ axis coincident with the S_n axis, this molecule contains a C_2 axis coincident with the S_4 axis, in a direction perpendicular to the plane of the ring. Sets of equivalent groups are therefore formed by G_R/G_R, G_S/G_S, H_1/H_3, and H_2/H_4. One set of enantiotopic groups is formed by $(G_R + G_R)/(G_S + G_S)$ and one by $(H_1 + H_3)/(H_2 + H_4)$. The enantiotopic groups in each of the two sets are interchanged by an S_4 operation.

In molecules such as acetaldehyde, the two environments of the carbonyl group, above and below the C–CO–H plane, are enantiotopic if we select a time scale (see Sect. VI) on which the methyl group has an average conical symmetry. Similarly, the two environments of the sulfur atom in methyl ethyl sulfide, above and below the C–S–C plane, are enantiotopic on the appropriate time scale, as are the two faces in *trans*-2-butene. In these cases one may speak of enantiotopic faces. A necessary and sufficient condition for enantiotopic faces is the presence of an S_n axis perpendicular to the plane and the absence of a C_2 axis in the plane. Approach of an achiral reagent A to one face of acetalde-

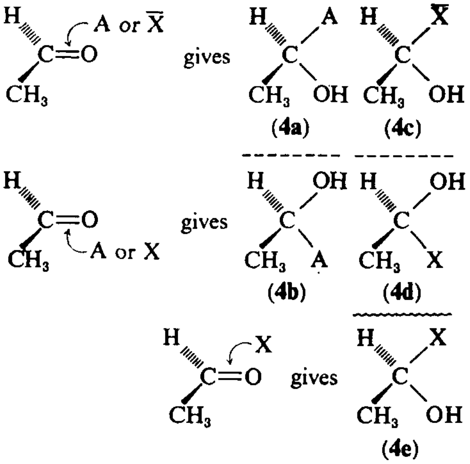


Figure 4*

hyde gives rise to a transition state and product **4a** which is the enantiomer of the transition state and product **4b** arising from approach of A to the other enantiotopic face. Approach of a chiral reagent X to one of the two enantiotopic faces results in a transition state and product **4d** which is the enantiomer of the transition state and product **4c** arising from the approach of the enantiomeric reagent X̄ to the other enantiotopic face. However, approach of the same chiral reagent X to the two enantiotopic faces results in diastereomeric rather than enantiomeric transition states and products (**4d** and **4e**).

Just as in the case of equivalent groups, a substitution criterion may be employed in lieu of the symmetry criterion as a test for enantiotopic groups. If the structures resulting from substitution of the achiral G groups by an achiral G′ group are enantiomers, the groups themselves are enantiotopic.† Thus substitution of enantiotopic hydrogens in the

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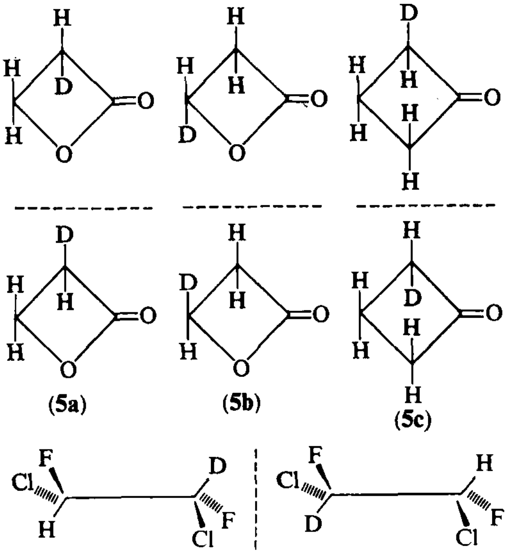
* In Figure 4 and following figures an equal sign (=) represents the identity of two species. A dashed line (---) when placed between two formulas represents an enantiomeric relationship. A wavy line (~) when placed between two formulas represents a diastereomeric relationship.

† According to K. R. Hanson (8a), "If a chiral assembly is obtained when a point ligand in a finite nonchiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral." It follows that any molecule containing enantiotopic groups is "prochiral," and vice versa. Atoms which bear enantiotopic groups (8a) or faces (8b) are also referred to as "prochiral"; atoms which bear diastereotopic groups may or may not be prochiral.



(5a) (5b) (5c)

(5d)

Figure 5

molecules of Figures 2 and 3 by a deuterium atom results in conventional enantiomers. Some examples of this process are shown in Figure 5.

In external comparisons, corresponding portions of enantiomeric molecules, e.g., the methyl groups in D- and L-alanine, constitute sets of enantiotopic groups.

The conclusion that the reaction of a chiral reagent with one or another of two enantiotopic groups leads to diastereomeric transition states has important consequences in asymmetric synthesis and especially in biochemistry (9). If diastereomeric transition states are involved, the activation energies of the various pathways will differ, whether the resultant products are diastereomeric and therefore have different energy contents, or whether the products are enantiomeric or identical and therefore have the same energy content.

The faces (or lone pairs of electrons) in achiral, unsymmetrical sulfides R–S–R′, R $\neq$ R′, are enantiotopic (**6a**). Oxidation with an achiral reagent such as peracetic acid or sodium metaperiodate (O_a, Fig. 6) with face A or face $\bar{A}$ results in enantiomeric transition states **6b** and leads to enantiomeric products **6c**. Since the transition states are

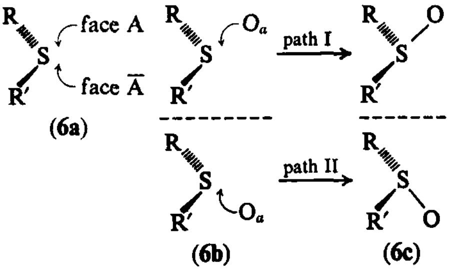
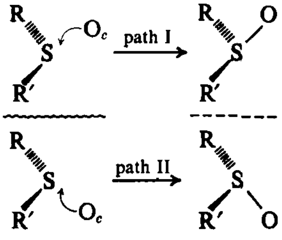


Figure 6

enantiomeric, they will have the same energy content and will be formed with equal probability. Hence rates of reaction via the two transition states in **6b** will be the same. The product will consequently consist of an equimolar mixture of the two enantiomers (**6c**), i.e., of a racemic modification. If, however, oxidation is carried out with an optically active, chiral reagent, e.g., (+)-monopercamphoric acid (O_c, Fig. 7), the transition states (**7a**) are no longer enantiomeric, but are diastereomeric and the two rates of reaction via paths I and II will be different, even though the products are enantiomers (**7b**) and consequently have the same energy content. The product will thus consist of an unequal mixture of the two enantiomers, and will be optically active. In the cited example of oxidation by (+)-monopercamphoric acid the discrimination between the enantiotopic faces by the chiral reagent is not very great, i.e., the stereoselectivity* of the



(**7a**) (**7b**)

Figure 7

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*The term "stereoselectivity" may refer (*a*) to the discrimination between enantiotopic groups or faces by a chiral reagent, or (*b*) to the discrimination between diastereotopic groups or faces by a reagent which may be chiral or achiral; it is useful to remember that there exists a distinction between these two kinds of discrimination.

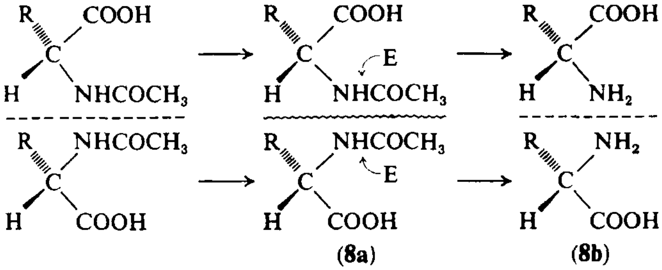
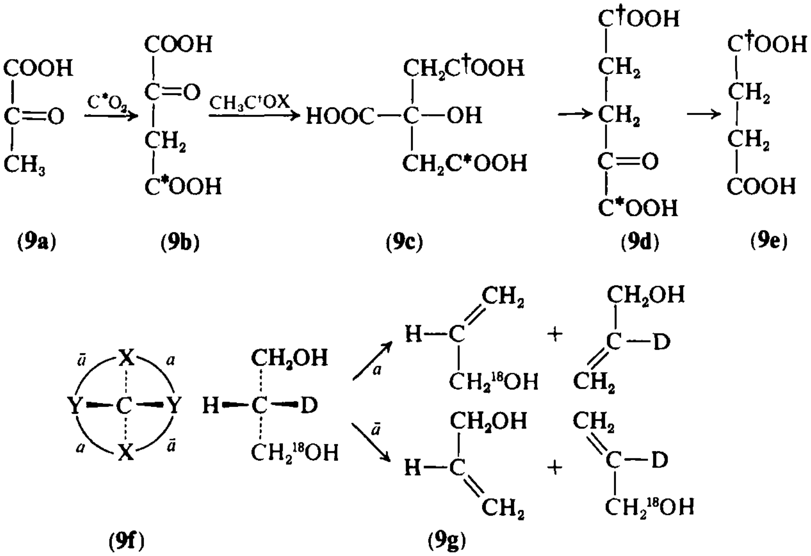


Figure 8

reaction is not very high. Enzymes are usually capable of far greater discrimination between enantiotopic or diastereotopic groups than ordinary chiral reagents, i.e., enzymes are a class of chiral reagents which are generally highly stereoselective. For example, acetyl groups in D- and L-*N*-acetyl amino acids are groups which are enantiotopic by external comparison (Fig. 8). The enzymatic hydrolysis of D- and L-acetyl amino acids proceeds through transition states which are diastereomeric (**8a**) to give products which are enantiomers (**8b**). The important feature here is that the rates of hydrolysis of the enantiotopic acetyl groups are very different; in most cases they are of an order of magnitude of at least 10,000 to 1 (10).

Groups which are enantiotopic by internal comparison likewise should be distinguishable in enzymatic reactions. The different fates of the two enantiotopic carboxyl groups in citric acid (Fig. 9) provide an instructive example (9).

Citric acid (**9c**) was thought to be an intermediate in the conversion of pyruvic acid (**9a**) to succinic acid (**9e**) (in the Krebs or citric acid cycle). When labeled carbon dioxide (C^*O_2) was introduced into the cycle in the initial carboxylation of pyruvic acid, followed by reaction with unlabeled CH_3COX, the α-ketoglutaric acid isolated (**9d**) was found not to contain the label in both carboxyl carbons but only in the carbon alpha to the carbonyl group. On the other hand, when unlabeled CO_2 and labeled acetate ($CH_3C^{\dagger}OX$) were used, it was the other carboxyl group in the α-ketoglutaric acid which was labeled exclusively. These results were widely interpreted to mean that citric acid had to be excluded as an intermediate in the sequence. It was argued that the primary carboxyl groups (CH_2COOH) in citric acid should be indistinguishable and that if a label were introduced it should be equally



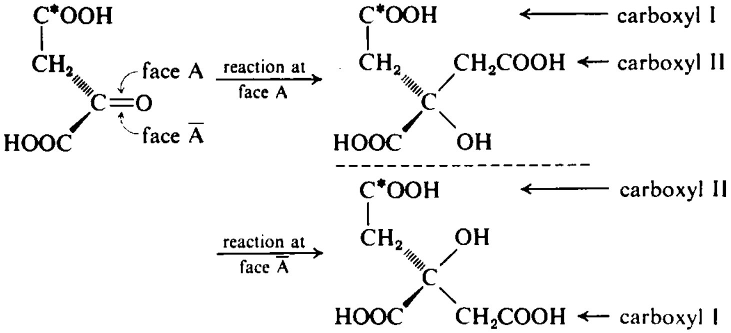
(9a) (9b) (9c) (9d) (9e)

(9f) (9g)

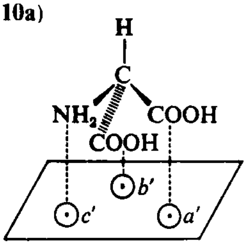
Figure 9

distributed in both primary carboxyl groups of citric acid. Thus if citric acid were an intermediate, the label should be equally distributed in the two carboxyl groups in α-ketoglutaric acid. As subsequent experiments showed, this conclusion had to be invalid. The two carboxyl groups in citric acid, as well as the two faces of the carbonyl group in the precursor oxaloacetic acid (**9b**) are not equivalent: they are enantiotopic and in reactions with a chiral reagent (i.e., the enzyme system) they must react at different rates via diastereomeric transition states of widely differing energy contents. As shown in Figure 10 (**10a**), reaction at face A will give citric acid labeled at the I carboxyl group and at face $\bar{A}$ with the label at the II carboxyl carbon. The reaction apparently takes place exclusively by one of these paths and consequently the citric acid is labeled in only one of the two enantiotopic carboxyl carbon atoms. In subsequent enzymatic (and thus chiral) reactions these enantiotopic groups react at quite different rates, one of them to become the α-ketocarboxyl group and the other to remain as a carboxyl group adjacent to a methylene group.

The carboxyl group lost in the conversion of α-ketoglutaric acid to succinic acid (**9e**) is the one derived from the labeled C^*O_2, and it is



(10a)



(10b)

Figure 10

experimentally observed that the label is lost entirely upon conversion to succinic acid.

Enzymatic stereospecificity in the reactions of molecules of the type CXXYZ (e.g., citric acid) has been discussed (9). Here the two X groups are enantiotopic, i.e., they reside in enantiomeric environments and are distinguishable in chiral circumstances. Less obvious is the stereospecificity which is possible for molecules of the type CXXYY. Here, the two X groups as well as the Y groups are equivalent and cannot be distinguished in chiral or achiral circumstances. However, the relationships between X and Y groups are not all equivalent. The four possible X–Y relationships may be ordered into two enantiotopic sets of two equivalent relationships. This is illustrated in Figure 9 (**9f**) which shows equivalent relationships with the same letters (a,a or $\bar{a},\bar{a}$) and enantiomeric relationships with different letters ($a,\bar{a}$). Alternatively, we may view this molecule as possessing four XCY groups which may be ordered into two enantiotopic sets of two equivalent groups.

A consequence of this non-equivalence is that enzymatic reactions may, in principle, be capable of distinguishing between the enantiotopic

X–Y relationships of XCY groups. If the molecule is stereospecifically labeled, an enzymatic reaction which results in the reaction of an X and Y group may occur in either of two ways which are experimentally distinguishable. As a hypothetical example, consider an enzymatic dehydration of propane-1,3-diol. Here X = H, Y = CH_2OH. If this molecule could be stereospecifically labeled (e.g., X′ = D, Y′ = $CH_2{}^{18}OH$), dehydration could follow two paths (**9g**). In one of these, monolabeled product would result, whereas in the other only doubly labeled and unlabeled product would result. These two consequences could be distinguished by mass spectrometry.

The same considerations lead to the recognition that in molecules such as CH_2F_2 there should, in principle, be two H–F coupling constants in chiral solvents (see Sect. V-B).

We emphasize that in the preceding analyses recourse was taken exclusively to symmetry arguments and that in such arguments the conclusions do not depend on the mechanistic details which govern the energy difference between the diastereomeric transition states; we need know nothing about the details or the character of the reactions and the transition states involved in order to conclude that a difference in rates must in principle occur. The magnitude and direction of the difference in reaction rate constants, which depend on the magnitude and direction of the energy difference between the diastereomeric transition states, depend on the nature and details of the differences between the two transition states. However, the symmetry arguments which assure us that a difference must exist are at the same time incapable of providing information about the magnitude or direction of the difference, or even allowing a decision on whether the difference will be substantial enough to be observable. In other words, although mechanistic hypotheses which rationalize the magnitude and direction of the difference in rates are sometimes available, it is important to recognize that there is a fundamental difference between such mechanistic arguments and the symmetry arguments which we have elaborated upon above. Mechanistic hypotheses are empirical and therefore subject to experimental test. By contrast, conclusions based upon the symmetry properties of enantiotopic groups and faces are not subject to experimental verification or invalidation; they stand only upon the logic of the arguments and they must be valid if the logic of the argument is valid, regardless of the results of experiment. The utility of such conclusions lies in the experimental finding that the differences between enantiotopic groups and faces are frequently large enough to be observed, and are sometimes enormous, as in some enzymatic reactions.

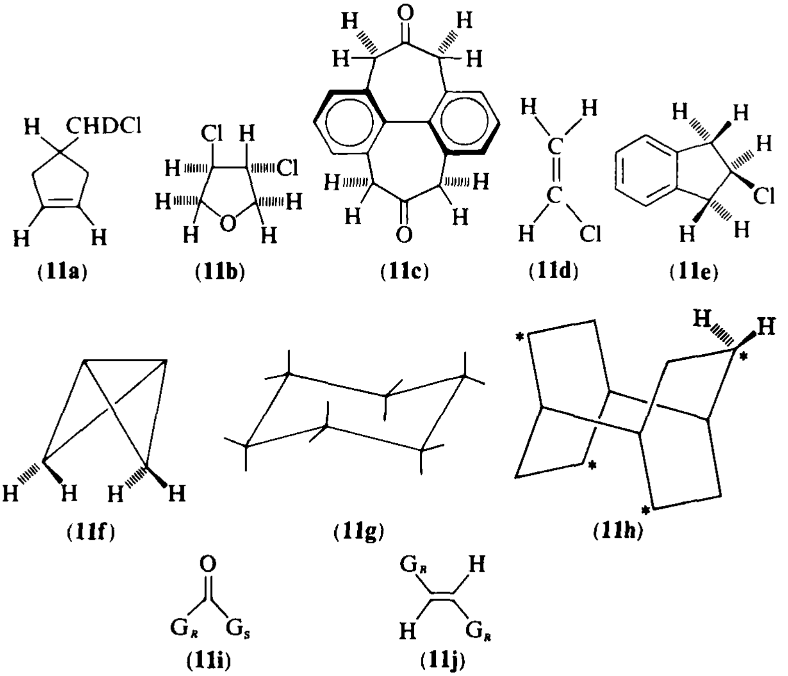
One particular mechanistic rationale, which has been used to explain the differences in reactivity of enantiotopic groups in enzymatic reactions, is the Ogston model of three-point enzyme-substrate attachment (9). Ogston suggested that contrary to the then-accepted notion the two enantiotopic carboxyl groups in citric acid or aminomalonic acid could be distinguished on an enzymic surface. He suggested that aminomalonic acid, for example, could complex with enzyme at three specific sites, *a'*, *b'* (carboxyl sites) and *c'* (amino site) as shown in Figure 10 (**10b**). If the sites *a'* and *b'* are catalytically different the enzyme could distinguish between the two enantiotopic groups in the decarboxylation reaction which leads to glycine. This model may be viewed in two ways. It may be viewed simply as a statement of the symmetry principles which have been expounded above, or it may be considered as a mechanistic description of the way in which enzyme stereospecificity is mediated. As a statement of symmetry principles the model is not subject to experimental test. In this case it should not be viewed as saying anything more than the symmetry arguments based on the properties of enantiotopic groups, i.e., it says nothing about the way that stereochemical control is mediated. On the other hand it may be viewed as a mechanistic picture of enzymatic stereospecificity. In this case Ogston's model is subject to experimental verification or invalidation, i.e., experiments are possible which may provide evidence concerning the way in which enzymes complex with substrates and how stereospecificity is mediated, whether polar interactions or steric interactions are more important, etc. It is essential to note that the validity of Ogston's model as a statement of symmetry principles (which demonstrate that enantiotopic groups may be distinguished in enzymatic reaction) cannot be regarded as evidence for the validity of the model as a mechanistic description of the mediation of enzymatic stereochemical control (9c).

We observe that in some respects enantiotopic and equivalent groups are both "equivalent" in the sense that they are interconvertible by symmetry operations and are indistinguishable in an achiral environment. However, an analogy with enantiomeric molecules may at this point be appropriate. Enantiomers are also "equivalent," meaning "indistinguishable" in most of their ordinary (i.e., scalar) properties (e.g., melting point, boiling point, solubility, etc.) and exhibit their distinctiveness only in chiral circumstances. Similarly, enantiotopic groups exhibit their distinctiveness only in a chiral extramolecular environment (e.g., optically active reagents and solvents, enzymic surfaces, etc.).

IV. DIASTEREOTOPIC GROUPS AND FACES

Groups are said to be diastereotopic in internal comparisons if they have the same constitution, reside in diastereomeric environments, and cannot be interchanged by any symmetry operation. Some examples of molecules containing sets of diastereotopic hydrogen atoms are shown in Figure 11 (**11a–11h**).

Molecules which contain sets of diastereotopic groups, in contrast to molecules which contain sets of equivalent or enantiotopic groups, are not excluded from any except the linear symmetry point groups. Thus asymmetric molecules (C_1), which, as we have seen (p. 9), may contain


(**11a**) (**11b**) (**11c**) (**11d**) (**11e**)

(**11f**) (**11g**) (**11h**)

(**11i**) (**11j**)

Figure 11

neither equivalent nor enantiotopic groups, may yet contain diastereotopic groups as illustrated in Figure 5 for propiolactone-2-*d* (**5a**) (one set of two diastereotopic methylene hydrogens) and cyclobutanone-2-*d* (**5c**) (two constitutionally non-equivalent methylene groups each containing two diastereotopic hydrogens). The two diastereotopic hydrogen atoms need not be situated on the same carbon atom, as exemplified by the olefinic hydrogen atoms in the asymmetric molecule **11a**. Molecules which are chiral but not asymmetric may also contain diastereotopic groupings, as illustrated for *trans*-3,4-dichlorotetrahydrofuran **11b** ($\mathbf{C}_2$) and the twisted doubly bridged biphenyl **11c** ($\mathbf{D}_2$). In **11b** there are two equivalent sets of two diastereotopic methylene hydrogens, whereas in **11c** there are four equivalent methylene groups each containing two diastereotopic hydrogens.

The methylene hydrogens in a group attached to a carbon atom whose three other groups are different (an asymmetric carbon atom is a special case) are sometimes said to be diastereotopic. This alternate definition is not satisfactory and fails, for example, in the case of *trans*-1,2-dichlorocyclopropane (**12a**). This molecule is chiral ($\mathbf{C}_2$), with two asymmetric carbon atoms, yet the methylene hydrogens are equivalent, not diastereotopic (similarly, the methine hydrogens and the chlorine atoms form sets of equivalent groups). Thus it is necessary to append that the methylene group in question be of the type $A\text{–}CH_2\text{–}B$, $A \neq B \neq H$.

Molecular dissymmetry is neither a necessary nor a sufficient condition for the presence of diastereotopic groups. Thus chiral *trans*-1,2-dichlorocyclopropane (**12a**) contains no diastereotopic groups, whereas the five achiral molecules (**11d,11e,11f,11g,** and **11h**) all contain one or more sets of diastereotopic groups. 2-Chloroindane **11e** ($\mathbf{C}_s$) contains two enantiotopic sets of diastereotopic (or two diastereotopic sets of enantiotopic) methylene hydrogens. In the last example, monosubstitution on the benzene ring, for example by chlorine, creates molecular asymmetry ($\mathbf{C}_1$) and converts the two sets into constitutionally non-equivalent sets of diastereotopic hydrogens, as in the case of cyclobutanone-2-*d* (**5c**). In bicyclobutane **11f** ($\mathbf{C}_{2v}$), the two sets of diastereotopic methylene hydrogens are equivalent. In cyclohexane in the chair conformation ($\mathbf{D}_{3d}$), the six sets of diastereotopic (axial and equatorial) hydrogens are interchangeable by C_2 or C_3 and the sets are therefore equivalent. The tricyclic molecule (**11h**) has a very high order of symmetry ($\mathbf{D}_{2h}$) and presents a particularly instructive example of the classification and terminology employed in this paper. The methine hydrogens and the carbon atoms to which they are attached form a set of four equivalent groups. The methylene groups fall into two enantiotopic supersets, one of which is marked in Figure 11 by asterisks. Each of the two enantiotopic supersets contains four equivalent (interchangeable by C_2) sets of diastereotopic methylene hydrogens, one of which is shown.

In asymmetric 3-phenyl-2-butanone and in the achiral (C_s) ketone **11i**, the environments above and below the plane of the carbonyl group bear a diastereotopic relationship, and one speaks of "diastereotopic faces." The faces in the chiral (C_2) olefin **11j** are also diastereotopic.

The substitution criterion may also be applied to test for diastereotopic groups. If substitution of each G by a chiral or achiral group G′ generates a set of diastereomers, the G groups are diastereotopic. This criterion is seen to apply in the sets of diastereotopic hydrogens shown in Figure 11. Substitution of one or another of the diastereotopic hydrogens by a deuterium atom generates diastereomers which may be descriptively distinguished by notation such as *cis–trans*, *exo–endo*, or *axial–equatorial*. The diastereomers may be chiral, as in the derivatives of the three chiral molecules, or they may be achiral, as in the derivatives of chloroethene, bicyclobutane, and chair cyclohexane. In 2-chloroindane (**11e**) and in the tricyclic molecule (**11h**), the sets of diastereotopic hydrogens have enantiotopic counterparts; for this reason, substitution of diastereotopic hydrogens in these molecules by a deuterium atom generates chiral diastereomers, even though the molecules themselves are achiral prior to substitution. Diastereotopic groups differ in their physical (e.g., NMR chemical shifts) and chemical (e.g., rates of reaction) properties, even in an achiral extramolecular environment, given the appropriate time scale of observation (see Sect. VI). Approach of a chiral or an achiral reagent to two diastereotopic faces generates two diastereomeric transition states. Thus lithium aluminum hydride reduction of **11i** generates two *meso*-diastereomers.

In external comparisons, corresponding portions of diastereomeric molecules, e.g., the methyl groups in the diastereomers of

$$C_2H_5CH(CH_3)\text{—}CH(NH_2)COOH$$

(isoleucine and alloisoleucine), constitute sets of diastereotopic groups.

The principal conclusions drawn in this and the two preceding sections are summarized in Table I.

TABLE I

Principal Attributes of the Spatial Relationships among Groups

Type of group	Symmetry criterion	Substitution criterion	Molecular symmetry point groups which are excluded from consideration
Equivalent	Interchangeable by C_n ($\infty > n > 1$)	No isomers are generated with achiral or chiral test groups	Conical ($\mathbf{C}_{\infty v}$) and non-axial ($\mathbf{C}_1$, $\mathbf{C}_s$, $\mathbf{C}_i$)
Enantiotopic	Interchangeable only by S_n	With achiral test groups enantiomers are generated. With chiral test groups diastereomers are generated	Linear ($\mathbf{C}_{\infty v}$, $\mathbf{D}_{\infty h}$) and chiral ($\mathbf{C}_n$, $\mathbf{D}_n$, $\mathbf{T}$, $\mathbf{O}$, $\mathbf{I}$)
Diastereotopic	Not interchangeable by any symmetry operation	With achiral or chiral test groups diastereomers are generated	Linear ($\mathbf{C}_{\infty v}$, $\mathbf{D}_{\infty h}$)

V. SYMMETRY CRITERIA IN NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

A. Chemical Shifts

Nuclei which are equivalent or enantiotopic (i.e., nuclei which can be interchanged by symmetry operations), are equally screened by environments when in achiral solvents and they must as a consequence exhibit the same NMR chemical shift. Such nuclei are said to exhibit chemical shift equivalence or to be isochronous.* In chiral solvents,† however, enantiotopic nuclei will reside in different (diastereomeric) environments and, in principle, will have different chemical shifts. Chemical shift non-equivalence of such nuclei‡ has been observed for enantiotopic fluorine (11a) and hydrogen (11b) nuclei. In 2,2,2-trifluoro-1-phenylethanol, the trifluoromethyl groups are enantiotopic by external comparison. In the achiral solvents carbon tetrachloride and dl-α-phenylethylamine, the fluorine resonance of racemic 2,2,2-trifluoro-1-phenylethanol appears as a doublet (H–F spin coupling), whereas in a chiral solvent (optically active α-phenylethylamine) it appears as two doublets of equal intensity (11a). The chemical shift difference between the enantiotopic fluorine atoms in optically active solvents is independent of the optical purity of the solute but does depend on the optical purity of the solvent. The magnitude of the chemical shift difference is expected to be quite small (in the present instance $\Delta\nu = 0.04$ ppm). Conversely the ratio of integrated intensities of the two doublets equals the ratio of abundances of the two enantiomers of the solute and is independent of the nature or optical purity of the solvent. Similarly the enantiotopic methine protons in the enantiomers of isopropylphenylcarbinol (11b) are isochronous in achiral solvents but are chemically shifted in the chiral solvent (+)-α-(1-naphthyl)-ethylamine ($\Delta\nu = 0.025$ ppm).

Nuclei which are diastereotopic must have different chemical shifts in either chiral or achiral solvents. Such nuclei are said to show chemical shift non-equivalence or to be anisochronous.§ Although we may deduce

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*The term was introduced by A. Abragam in *The Principles of Nuclear Magnetism*, Oxford, 1961, p. 480. Such nuclei have also been referred to as symmetrically equivalent, magnetically equivalent, magnetically equivalent in the chemical shift sense, or chemically equivalent. These terms are less desirable because of their awkwardness, ambiguity, or because they may cause confusion out of context.

†By "chiral solvent" we mean a solvent composed of chiral molecules, and one which is not racemic. In a solvent which is racemic (and hence achiral) enantiotopic nuclei must be isochronous.

‡When molecules containing enantiotopic groups are placed in a chiral medium, these groups will *then* reside in diastereomeric environments. In consequence, they may, in a sense, be regarded as having become diastereotopic.

§This term was suggested by Dr. G. Binsch. Such nuclei have also been described as magnetically non-equivalent, chemically non-equivalent, or magnetically non-equivalent in the chemical shift sense. Again these terms are less desirable; in particular, the term "magnetically non-equivalent" has frequently been used in an entirely different sense, to be discussed below.

from symmetry arguments that diastereotopic nuclei (or enantiotopic nuclei in chiral media) must be anisochronous, such arguments imply nothing about the magnitude of the non-equivalence, that is, about the magnitude of the difference between the chemical shifts. In fact, the non-equivalence in many cases is not large enough to be observed. Such apparent accidental coincidence of NMR signals is also observed for protons which are constitutionally non-equivalent, such as the phenyl hydrogens in many monosubstituted benzenes, for which a singlet is frequently observed, rather than the multiplet which might have been expected. Even when apparent chemical shift equivalence is observed in one solvent, a change to another solvent (or an increase of the magnetic field) may result in observable non-equivalence. Thus, for example, in several bridged biphenyls, such as the diketone **11c**, the diastereotopic protons are measurably shifted in some solvents, such as benzene, but not in others, such as carbon tetrachloride (1). It should be noted that the diastereotopic protons are not isochronous in carbon tetrachloride, but only that the measurement is not sufficiently sensitive to detect the small non-equivalence that must exist. Solvent dependence of the chemical shift non-equivalence in acyclic molecules has been attributed to conformational changes (12). However, it is difficult to see how this can be the case with the conformationally rigid, bridged biphenyls. Solvent-induced changes in the magnitude of the chemical shift non-equivalence have also been observed for the diastereotopic geminal hydrogen atoms in some terminal olefins, and in these instances it has been emphasized that conformational changes cannot be a significant factor (13).

Concentration as well as solvent may affect the magnitude of the chemical shift non-equivalence. For example, in methyl α-naphthylcarbinyl sulfoxide the diastereotopic methylene protons are chemically shifted by 0.33 ppm in 5% solution in chloroform, but upon increasing the concentration to 40%, the non-equivalence decreases to 0.23 ppm (14). It should be remarked that the effects resulting from changes in concentration are necessarily related to those resulting from changes in solvent in the sense that a change in concentration *ipso facto* results in a change in the properties of the medium.

Temperature effects on the chemical shift non-equivalence of diastereotopic atoms will be discussed in Section VI.

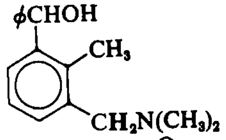
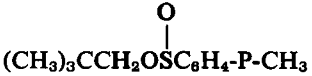
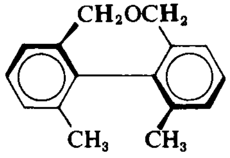
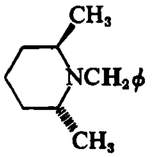
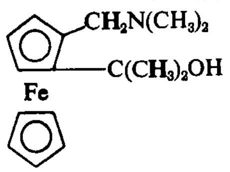
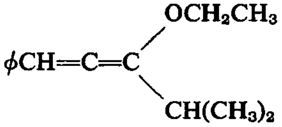
Clearly factors other than the symmetry determine the magnitude of the chemical shift non-equivalence. Although symmetry principles can tell us whether or not the environments of two groups are diastereomeric, the magnitude of the difference in chemical shift of two diastereotopic groups will be influenced by the specific differences in the averaged environments of the two groups including the type and anisotropy of the other portions of the molecule, the distances between the groups and the portion of the molecule responsible for the diastereomerism of the environments, and conformational factors (as discussed in Sect. VI). In particular, although the two CH_2 protons in $C_5H_9OCH_2D$ (C_5H_9 is the chiral grouping cyclopropylmethylcarbinyl) are diastereotopic, the non-equivalence is too small to be measured and an apparent A_2 spin system is observed (15). This result might have been anticipated since the difference between the averaged environments of the two CH_2 protons is certain to be minute (16).

The chemical shift non-equivalence of diastereotopic hydrogen and fluorine nuclei has been observed in a wide variety of structural arrays. An indication of the wide range of compound types in which chemical shift non-equivalence has been observed for diastereotopic nuclei may be gathered from the group of representative examples collected in Table II. The last two compounds entered in this table provide particularly instructive examples of the chemical shift non-equivalence of diastereotopic groups (17r). In the acetylene the two methylene protons in either ethoxy group are diastereotopic and hence anisochronous. The two ethoxy groups, however, are enantiotopic. Consequently, only one ABX_3 spin system is anticipated and only one is observed. By contrast, in the isomeric allene the two ethoxy groups as well as the two methylene protons in each ethoxy group are diastereotopic. Thus, four diastereotopic and hence anisochronous methylene protons are present and two ABX_3 spin systems are expected and observed.

B. Coupling Constants

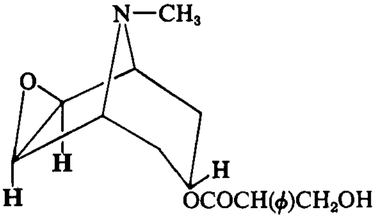
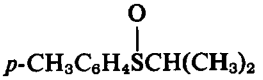
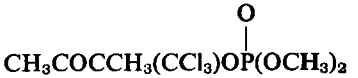
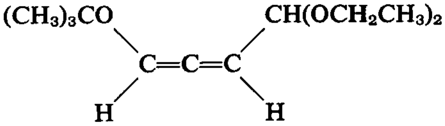
A second kind of NMR non-equivalence results not from differences in environment but from differences in the relationships of two nuclei to other nuclei in the molecule. This is the non-equivalence of spin–spin coupling constants which has been referred to as "magnetic non-equivalence," and "magnetic non-equivalence in the spin coupling sense." We prefer the second, or "spin coupling non-equivalence" since "magnetic non-equivalence" has also been used with reference to chemical shift non-equivalence. It is clear that diastereotopic hydrogens

TABLE II

Compound[a]	Δν[b]	Reference
 $\phi\overset{\mathrm{O}}{\overset{\vert}{\mathrm{S}}}OCH_2CH_3$	0.43	17a
$CH_3CH(OCH_2CH_3)_2$	0.15	17a
$(CH_3CH_2)_2NCH_3{\cdot}HI$	0.54	17b
$CH_2BrCBr(CH_3)COOH$	0.67	13
$CH_2{=}C(CH_3)COOH$	0.85	13
	0.13	17c
 $(CH_3)_3CCH_2O\overset{\mathrm{O}}{\overset{\vert}{\mathrm{S}}}C_6H_4\text{-}P\text{-}CH_3$	0.54	17d
$\phi CHCH_3OCH_2\phi$	0.18	17e
$CH_3CH_2CH(CH_3)CH_2MgBr$	0.17	17f
	0.39	1
	0.13	17g
$(CH_3)_2CHSON(CH_3)_2$	0.18	17h
	1.64 0.27	17i
	0.08 0.01	17j

(continued)

TABLE II (*continued*)

Compound[a]	$\Delta\nu$[b]	Reference
$CH_3CH_2OSSOCH_2CH_3$	0.19	17k
$\phi CH_2N(CH_3)OCH_3$	0.27	17l
	0.58	17m
 $p\text{-}CH_3C_6H_4\overset{\overset{O}{\vert}}{S}CH(CH_3)_2$	0.06	17n
$CF_2BrCHBrCl$	3.34	17o
 $CH_3COCCH_3(CCl_3)O\overset{\overset{O}{\vert}}{P}(OCH_3)_2$	0.07	17p
$\phi CH(OCH_3)CO_2CH(CH_3)_2$	0.09	17q
$\phi CH(OCH_3)CO_2CH_2C(CH_3)_3$	0.10	17q
$(CH_3)_3COCH_2C{\equiv}CCH(OCH_2CH_3)_2$	0.14	17r
	c	17r

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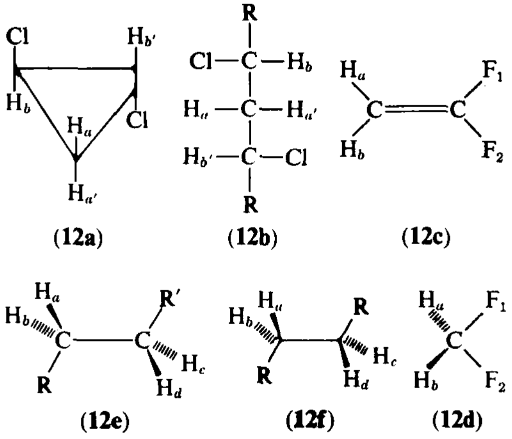
[a] The diastereotopic hydrogens, fluorines, or methyl groups are indicated in boldface type.

[b] The difference in chemical shift in parts per million of the diastereotopic nuclei, $\Delta\nu = |\nu_1 - \nu_2|$, varies for many of the compounds listed with changes in solvent, temperature, or concentration, and the values reported are for a particular set of conditions.

[c] The chemical shifts of the four diastereotopic methylene protons in this compound are (in Hz downfield from tetramethylsilane): A, 216.0; A′, 215.6; B, 208.8; B′, 207.8.

must in principle have different coupling constants with respect to any nucleus in the same molecule, but such non-equivalences are frequently not detectable. Spin coupling non-equivalence can also occur when a set of equivalent or enantiotopic nuclei is spin coupled to another set of



(12a) (12b) (12c)

(12e) (12f) (12d)

Figure 12

equivalent or enantiotopic nuclei, provided that the relationships between one of the nuclei in the first set and those in the second set are diastereomeric. A few illustrative examples will clarify these remarks.

In *trans*-1,2-dichlorocyclopropane (Fig. 12, **12a**) the two methylene hydrogens H_a and $H_{a'}$ are equivalent, as are the methine hydrogens H_b and $H_{b'}$. However, we may discern two types of vicinal methylene–methine coupling, that between H_a and H_b or between $H_{a'}$ and $H_{b'}$, which is a *trans* coupling, and that between H_a and $H_{b'}$ or between $H_{a'}$ and H_b, which is a *cis* coupling. We may refer to two methylene–methine coupling constants as J_{cis} and J_{trans}. In acyclic analogs of *trans*-1,2-dichlorocyclopropane (e.g., the chiral molecule **12b**), the same situation exists. The relationship between H_a and H_b is diastereomeric relative to that between H_a and $H_{b'}$, although in this case also the methylene hydrogen atoms (H_a and $H_{a'}$) and the methine hydrogen atoms (H_b and $H_{b'}$) form two sets of equivalent groups. We note that the relationships $H_a/H_b = H_{a'}/H_{b'}$ and $H_a/H_{b'} = H_{a'}/H_b$ are diastereomeric in any conformation. We may describe the relationships as "intrinsically diastereomeric," since they should be diastereomeric under all conditions of rapid rotation and conformer populations.

Although nuclei in spin systems in which spin-coupling non-equivalence is observed have been termed "spin-coupling non-equivalent," this terminology may be misleading. Nuclei such as H_a and $H_{a'}$ in **12a** or in **12b** are stereochemically equivalent and must show equivalence in all of their properties. It is their *relationships* to other nuclei which are non-equivalent, and from which the non-equivalence of their coupling constants arises. These two nuclei would be non-equivalent only if H_b and $H_{b'}$ were distinguishable, which they are not. This situation may be easily recognized by replacement of H_b or $H_{b'}$ by a test group, as described in previous sections. Such substitution cannot generate a set of isomers since H_b and $H_{b'}$ are equivalent, yet when such substitution is made H_a and $H_{a'}$ become diastereotopic. In this way the "substitution criterion" serves to distinguish spin systems where diastereomeric relationships exist and where spin coupling non-equivalence may occur.

Consider, as another example, 1,1-difluoroethene (**12c**) and difluoromethane (**12d**). Both molecules have C_{2v} symmetry, and it is seen that in both cases the hydrogen atoms as well as the fluorine atoms are equivalent. Hence no chemical shift non-equivalence is expected. The relationships of H_a with F_1 and F_2 in **12d** are enantiomeric. Therefore in **12d** there can be no spin coupling non-equivalence between the hydrogen and fluorine nuclei, and only one HF coupling constant will be observed. In **12c**, on the other hand, one can see that the relationship $H_a/F_1 = H_b/F_2$ is diastereomeric to $H_a/F_2 = H_b/F_1$. Therefore the coupling constant $J_{H_aF_1}$ will not equal $J_{H_aF_2}$, and spin coupling non-equivalence is possible. There will be two different HF coupling constants, $J_{H_aF_1} = J_{H_bF_2} = J_{cis}$ and $J_{H_aF_2} = J_{H_bF_1} = J_{trans}$. The spin system in **12d** is an A_2X_2 spin system and six lines are expected for the hydrogens and the fluorines (neglecting coupling with ^{13}C). The spin system in **12c** is an AA'XX' spin system and a total of twenty lines are expected for the hydrogens and fluorines (neglecting ^{13}C coupling). This difference in the spectra of molecules which on the surface seem to be so similar in their symmetry characteristics dramatizes the importance of recognizing diastereomeric relationships and associated differences in spin couplings when they occur. An important case in which spin-coupling non-equivalence is often observed is **12e**. Here, H_a and H_b are enantiotopic atoms which are constitutionally non-equivalent to another pair of enantiotopic atoms, H_c and H_d. Two non-equivalent vicinal coupling constants are indicated, $J_{ac} = J_{bd}$ and $J_{ad} = J_{bc}$. This system is an AA'BB' system if the difference between chemical shifts of H_a or H_b and H_c or H_d is of the order of the coupling constants. If the magnitude of the chemical shift non-equivalence is a great deal larger, it is an AA'XX' system (as in **12c**). In **12f**, H_a and H_d are equivalent, as are H_b and H_c, since a rotation by π interconverts the nuclei. H_a and H_b (or

H_c and H_d) are enantiotopic and are interconverted by a mirror reflection in the plane of the paper. Although in **12e** there are two geminal coupling constants $J_{ab} \neq J_{cd}$, in **12f** there is only one, $J_{ab} = J_{cd}$. There are in **12e**, as well as in **12f**, two vicinal coupling constants $J_{ac} = J_{bd}$ and $J_{ad} = J_{bc}$. However, since **12f** contains two enantiotopic pairs of equivalent hydrogen atoms all four hydrogen atoms must have the same chemical shift. Since a set of isolated hydrogen atoms which are isochronous gives rise to only one resonance line, neither spin-coupling nor chemical-shift non-equivalence will be observed.* In Table III we have listed the number of lines (allowed transitions) possible for the systems discussed (18).

TABLE III

	Type	A lines	B or X lines	Total
RCH_2CH_2R	A_4	1	—	1
CH_2F_2	A_2X_2	3	3	6
—	A_2B_2	7	7	14
CH_2CF_2	$AA'XX'$	10	10	20
RCH_2CH_2R'	$AA'BB'$	12	12	24

VI. GROUP PROPERTIES AND GROUP INTERCONVERSIONS

When the environments of stereochemically non-equivalent groups are interchanged during the observation of group properties, e.g., by chair–chair interconversion in cyclohexane, an averaged environment is observed as a result and all differences in properties are removed. The time scale of observation relative to the rate of interchange thus becomes a crucial factor in deciding whether stereochemical non-equivalence is maintained; enantiotopic or diastereotopic groups that

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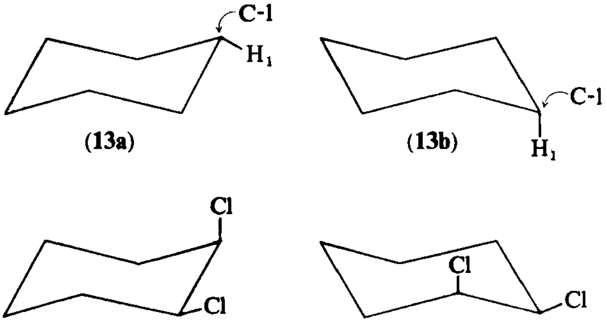
* One must not, however, assert that coupling between enantiotopic or equivalent nuclei is never observed since J_{HH} and J_{FF} do enter into the spectrum of **12c** (AA'XX' spin system). It is precisely in such cases of spin coupling non-equivalence between different (in the sense of neither equivalent nor enantiomeric) sets of enantiotopic or equivalent nuclei that the coupling constants within the sets (between the enantiotopic or equivalent nuclei) are observed.

can be exchanged by conformational changes or by tautomerism may or may not be operationally equivalent depending on the rate of exchange and time scale of observation. If the exchange is rapid on the time scale of observation, the groups will be indistinguishable, whereas if the exchange is slow they will be distinguishable. In absorption spectroscopy, the minimum lifetime necessary to observe distinguishable spectra increases as the transition energy decreases. The minimum half-life necessary for the observation of distinguishable entities decreases in the following order: physical isolation, magnetic resonance spectroscopy (NMR, ESR), vibrational and electronic spectroscopy (IR, Raman, UV, ORD, etc.), and diffraction measurements (electron, neutron, x-ray). Consequently, processes which are fast enough to give the appearance of equivalence as judged by physical isolation may be slow enough for non-equivalence in, for example, the NMR spectra, while processes which are too fast for non-equivalence on the NMR time scale may be slow enough for non-equivalence in, for example, UV or IR spectra. Thus, although it is possible to observe hydrogen-bonded and nonhydrogen-bonded hydroxyl groups in IR spectra, the exchange occurs too rapidly for detection by NMR. As another example, although the inversion of tertiary acyclic amines $R_1R_2R_3N$ occurs too rapidly to permit the isolation of enantiomers, the process is slow enough on the NMR time scale so that non-equivalence of diastereotopic methylene protons in *N*-benzyl-*O*,*N*-dimethylhydroxylamine is observable (17e).

In general, only when barriers to interconversion are above about 18–20 kcal/mole are stereoisomers stable enough for isolation. For detection by NMR, barriers of about 10 kcal are sufficient, and even lower barriers are detectable in some instances. In IR and UV, etc., conformational changes and tautomerism do not result in equivalence. Here even conformers that are interchanged by rotation about a single bond (about 3 kcal/mole or less) are not averaged and the temperature dependence of such spectra is often valuable in the conformational analysis of these systems.

Interconversion between non-equivalent groups in the same molecule may occur even when there is no net change in molecular identity, as in a degenerate interconversion. For example, in the degenerate chair–chair interconversion of cyclohexane (Fig. 13, **13a** $\rightleftharpoons$ **13b**), the environment of C-1 remains the same and this group interconversion is therefore degenerate, but H_1 undergoes an exchange between stereochemically



(13a) **(13b)**

(13c) **(13d)**

Figure 13

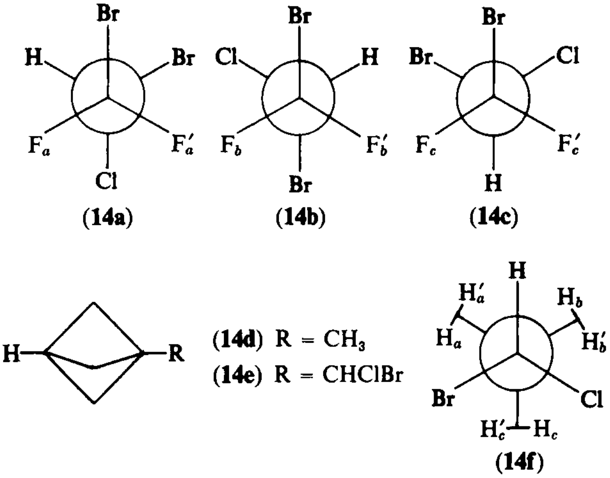
non-equivalent environments (H_1 in **13a** and H_1 in **13b** are diastereotopic by external comparison). Similarly, it has been observed that methyl hydrogens in the same methyl group are isochronous, since rotation about single bonds is rapid on the NMR time scale.

The interconversion of enantiomers is not a degenerate reaction if the individual molecules are considered, but at the bulk level, where a statistical number of molecules are involved, the racemization reaction *dl* $\rightleftharpoons$ *ld* becomes degenerate. Interconversion of enantiomers is illustrated by the chair–chair interconversion of *cis*-1,2-dichlorocyclohexane (**13c** $\rightleftharpoons$ **13d**). In this molecule all atoms undergo interconversions between diastereomeric environments.

The interconversion of diastereotopic or enantiotopic groups by conformational changes as discussed above is to be contrasted with the situation described below (16,19).

The fluorine atoms in CF_2Br—CHBrCl are diastereotopic in all three of the rotational isomers shown in Figure 14.

The chemical shifts of the fluorine atoms F and F′ are consequently different in each of the three rotomers (18). On first glance it might appear that if the CF_2Br group were freely rotating and **14a**, **14b**, and **14c** were thus equally populated, F and F′ would have the same chemical shift since each fluorine atom would spend an equal period of time in each of the three regions, i.e., in an *anti* position relative to Br, Cl, and H. This judgment, however, is incorrect. The two fluorine atoms do not interchange on rotation. In all three conformers and under any conditions of rapid rotation and rotomer populations, fluorine atom F



(14a) (14b) (14c)

(14d) R = CH_3

(14e) R = CHClBr

(14f)

Figure 14

always maintains the same average configurational environment, which is different from that of F′. This can be seen by application of the substitution criterion for diastereotopic groups; replacement of F by a chlorine atom in any of the three conformers (**14a**–**14c**) always leads to the *threo* isomer of BrClHC—CFClBr, whereas similar replacement of F′ always leads to the *erythro* isomer. Although the environment of F in **14a** (i.e., F_a) is similar to that of F′ in **14c** (i.e., F'_c), the reader will note that the environments are neither equivalent nor enantiomeric. Since F and F′ are diastereotopic we would expect that they would have different chemical shifts even under conditions of rapid rotation and equal populations of **14a**, **14b**, and **14c**. Thus, although the difference in chemical shift of F and F′ will change as the conformer populations change, there will be an additive term which will remain invariant and which will be finite even when conformer populations are equal. The total chemical shift difference $\Delta_{FF'}$, will equal the sum of two terms:

$$\Delta_{FF'} = \Delta_{cp} + \Delta_{id}$$

Δ_{cp} which is dependent on *c*onformer *p*opulations, and Δ_{id} which results from the *i*ntrinsic *d*iastereomerism* of the averaged environments of

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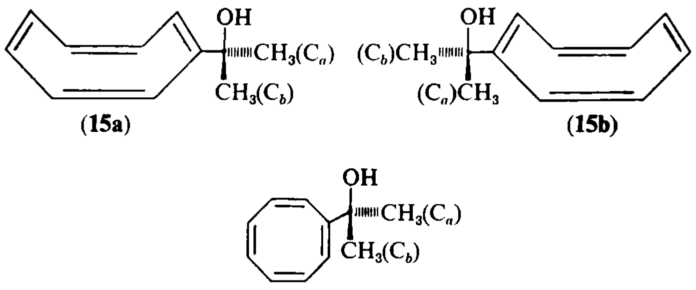
*We prefer the term "intrinsic diastereomerism" (see p. 28) rather than the previously used "intrinsic asymmetry" since the residual chemical shift occurs because F and F′ are diastereotopic and will be present even in compounds which are not asymmetric. The term "asymmetry" is therefore irrelevant to the description of this phenomenon.

F and F′ and which will be as a consequence independent of conformer populations. At room temperature Δ_{cp} for this compound is 2.4 ppm and Δ_{id} for this compound is 1.0 ppm (19).

The Δ_{id} term is identically zero for diastereotopic hydrogens such as those in cyclohexane which at room temperature are interchanged by rapid conformational interconversion and thus become equivalent with respect to the time scale of the measurement (NMR) which is used in the observation.

In contrast to molecules such as CF_2Br—CHBrCl, in which the total non-equivalence is a sum of contributions which depend on conformer populations and intrinsic diastereomerism, hypothetical structures may be adduced in which the only contribution would be that from "intrinsic diastereomerism." Consider as an example the bicyclopentanes in Figure 14. In **14d** the methylene groups are equivalent. In **14e** the methylene groups are equivalent on the NMR time scale since rotation about the C—R bond will exchange all three degenerate rotomers. In **14d** (R = CH_3) the two hydrogen atoms in a particular methylene group are enantiotopic. The six methylene hydrogen atoms in **14d** may thus be ordered into two enantiotopic sets of three equivalent hydrogen atoms. In **14e**, however, where R is a chiral moiety, the two sets of three equivalent hydrogen atoms are no longer enantiotopic but are diastereotopic, since chiral molecules cannot contain enantiotopic groups. Because of the degeneracy of rotation about the C—R bond each of the methylene hydrogens must be in the vicinity of each of the substituents on the asymmetric carbon atom for identical periods of time; this requirement is equivalent to equal rotomer populations in **14a**–**14c**. Further we may note that the H_a' (in the Newman projection, **14f**) is in an environment similar (but diastereomeric) to that of H_b, a similarity of environments not unlike that between F_a and F_c' (in **14a** and **14c**). As in the case of F and F′ in **14a**–**14c**, a chemical shift non-equivalence due to "intrinsic diastereomerism" of the environments of H and H′ will, in principle, result for **14e**.

Cyclooctatetraenyl dimethyl carbinol (Fig. 15) constitutes another interesting case to consider from this point of view (20). The two methyl groups C_a and C_b attached to the carbinol carbon are diastereotopic in the absence of any conformational changes. Rotation about the bond connecting the carbinol carbon to the ring, no matter how rapid, does not interchange the environments of methyl groups and we may expect them to be chemically shifted even under conditions of rapid rotation



(15a) **(15b)**

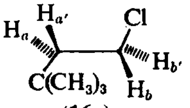
(15c)

Figure 15

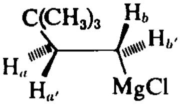
and equal rotomer population. However, a second conformational change, ring inversion (**15a** $\rightleftharpoons$ **15b**), is possible and this will exchange the diastereomeric environments of two methyl groups. This exchange is easily visualized by considering the transition state for the transformation. In the planar ring conformation shown (**15c**) the methyl groups are no longer diastereotopic, but have become enantiotopic. On a time scale where the rate of interconversion is rapid the methyl groups will have averaged environments which are enantiotopic and hence isochronous; under such conditions (elevated temperatures) the methyl group signals coalesce to a single line.

The exchange of enantiotopic groups in a system in which spin-coupling non-equivalence is observed also has implication for the NMR spectrum. By way of illustration, the loss of spin-coupling non-equivalence due to exchange of enantiotopic groups in a AA'XX' spin system (Sect. V-B) has been used to estimate the configurational stability of an aliphatic Grignard reagent (21) as follows.

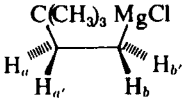
In 1-chloro-3,3-dimethylbutane (Fig. 16, **16a**) the two hydrogens H_a and $H_{a'}$ are enantiotopic and hence isochronous, as are the pair H_b and $H_{b'}$. However, as we have seen (p. 28), two non-identical vicinal hydrogen–hydrogen coupling constants are expected for a molecule of this type, $J_{ab} = J_{a'b'}$ and $J_{a'b} = J_{ab'}$, and spin-coupling non-equivalence (AA'XX' spin system) obtains since twenty of the twenty-four theoretically possible (for AA'BB') transitions have sufficient intensity to be observable. When the halide is reacted with magnesium to form the Grignard reagent (**16b**) the same kind of spectrum (AA'XX') is expected if the Grignard reagent is configurationally stable on the NMR time scale.



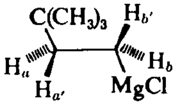
(16a)



(16b)



(16c)



(16d)

Figure 16

On the other hand, if the carbon bearing the MgCl can invert rapidly (**16b** $\rightleftharpoons$ **16c**), and rotation around the C—C bond occurs rapidly (**16c** $\rightleftharpoons$ **16d**), the spin-coupling non-equivalence will be lost and an A_2X_2 spin system will result. The spin-coupling constant J_{ab} in **16b** is the same as $J_{a'b}$ in **16d**; similarly $J_{a'b}$ in **16b** is identical to J_{ab} in **16d**. If the exchange is rapid on the NMR time scale the averaged coupling constants $J_{a'b}$ and J_{ab} will be equal. In this example spin-coupling non-equivalence (AA'XX' spin system) is observed at low temperatures (−60°C) when the exchange is slow, while spin-coupling equivalence is observed at room temperature (A_2X_2 spin system).

In some cases the consequences of exchange are conveniently illustrated by reference to a hypothetical conformation. When considering the exchange of axial and equatorial hydrogens in cyclohexane by chair–chair interconversion it is instructive to visualize the conformationally mobile chair ($\mathbf{D}_{3d}$) as tantamount to a rigid, planar ($\mathbf{D}_{6h}$) conformation, which contains twelve equivalent hydrogens rather than six axial and six equatorial hydrogens. In the cyclotetraenyldimethylcarbinol problem discussed above, reference was made to the planar transition state (Fig. 15, **15c**) in which the two methyl groups are enantiotopic, and which symbolizes the consequence of conformational mobility. On the other hand, the exchange in the Grignard reagent discussed above illustrates that the effects of exchange frequently cannot be represented by an "average" conformation. There is no reasonable conformation in which the two vicinal coupling constants in **16b** are equal.

In concluding our discussion of spatial relationships of groups in molecules, it should be noted that analyses similar to ours, based on symmetry properties, have been previously applied to stereochemical problems, and that such analyses have frequently been of great utility. However, such treatments have tended to divide stereochemically related sets of groups or atoms into only two categories: distinguishable ("non-equivalent") and indistinguishable ("equivalent"). In treatments concerned with asymmetric syntheses and enzymic reactions, enantiotopic as well as diastereotopic groups have been classed as "non-equivalent," whereas in analyses of NMR spectra, only diastereotopic groups have been considered "non-equivalent." We hope that the present scheme, which elaborates concepts presented earlier (1,2), clarifies such symmetry arguments and serves to bring them together into one general treatment which has implications for asymmetric synthesis as well as for NMR spectroscopy.*

Acknowledgments

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*A critical appraisal of the several nomenclatural schemes (8a,22) which have been proposed to provide labels for the designation of enantiotopic and diastereotopic groups and faces is beyond the purview of this chapter.

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Stereochemistry of Metallocenes*

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I. INTRODUCTION

The discovery of biscyclopentadienyl iron, or ferrocene, in 1951 (1) as the first representative of a new class of stable organic transition metal complexes was followed not only by the preparation of numerous other compounds of this type (metal π-complexes with aromatic

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[*] Portions of this article have previously appeared under the title "Stereochemie von Metallocenen," in *Fortschritte der Chemischen Forschung*, Band 6, Heft 3, Springer-Verlag, Heidelberg, 1966.

compounds), but also by the appearance of many questions which occupy theoretical, inorganic, and organic chemists equally (2–4). The organic chemist is particularly interested in two aspects of the chemistry of the metallocenes, as metal π-ring complexes are called owing to their aromatic character (2): (*1*) the nature of this aromatic character, which reveals itself above all in facile electrophilic substitution (and thus in a wide range of organic derivatives, especially of ferrocene), and (*2*) the stereochemistry of these compounds, which brings many new problems to light as a result of their special molecular geometry (sandwich structure).

Ferrocene is still one of the most extensively investigated metallocenes. During the first decade following its discovery (3), the preparative scope of electrophilic substitutions of this and other metallocenes was thoroughly explored (2–7). However, only in the last few years has a more detailed investigation of the stereochemistry peculiar to this class of compounds been in progress (8).

As a consequence of the particular spatial arrangement of the metallocenes, suitable substitution can lead to optical isomerism (9–16) as well as to positional and geometrical isomerism (17). Table I shows

TABLE I

Positional Isomerism in Metallocenes

Substitution		Number of possible positional isomers, Total (racemates, meso)[b]		
Ring 1	Ring 2[a]	Ferrocene	Cymantrene	Benchrotrene
R,R		3 (0,3)	2 (0,2)	3 (0,3)
R,R′		3 (2,1)	2 (2,0)	3 (2,1)
R,R,R		4 (0,4)	2 (0,2)	3 (1,2)
R,R,R′		8 (3,5)	4 (2,2)	6 (4,2)
R,R′,R″		13 (13,0)	6 (6,0)	10 (10,0)
R,R′	R,R′	6 (4,2)	—	—
R,R′,R″	R,R′,R″	13 (8,5)	—	—

[a] Only for ferrocene (ruthenocene, osmocene).

[b] Meso is used here in the sense of "achiral" [i.e. different from that as defined by E. L. Eliel (23)].

the number of possible positional isomers for ferrocene, cyclopentadienyl manganese tricarbonyl ("cymantrene"*), and benzene chromium tricarbonyl ("benchrotrene"*) for some characteristic substitution types; the number of meso forms and racemates is also included. The number of isomers is naturally greatly reduced in the case of metallocenes with only one ring available for substitution, such as cymantrene or benchrotrene. Conversely, the possibilities for isomerism in, e.g., biferrocenyl (Fc—Fc) become rather complicated (19,20).

The following shorthand graphic representations for stereoformulas of substituted metallocenes, as depicted in Figure 1, are used throughout this review.

In a simple case, of the three possible positional-isomeric ferrocenes, **1**–**3**, with two dissimilar substituents (R and R′, cf. Table I), only the heteroannular derivative **3** is symmetrical, while the two homoannular disubstituted α- and β-derivatives† **1** and **2** are asymmetric (cf. Sect. II), are not superimposable on their mirror images, and are therefore chiral‡. When suitable substituents are present such chiral metallocenes can be resolved into optical antipodes, as was demonstrated for the first time in 1959 for a ferrocene derivative (**8**) (9).

Discussion of the stereochemistry of the metallocenes will be restricted in this survey to stereoisomerism, with a more detailed treatment of problems of relative and absolute configuration. Questions raised by positional isomerism have already been the subject of more or less detailed papers (4,17,25–37).

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* Cymantrene has been suggested by Cais et al. (18) as a short name for cyclopentadienyl manganese tricarbonyl; similarly, benchrotrene can be used for benzene chromium tricarbonyl; these abbreviations are used throughout this review.

† Many authors have described racemic disubstituted metallocenes as 1,2- or 1,3-, respectively, for the homoannular derivatives. With the customary method of numbering [e.g., clockwise, cf. Fig. 3 (4)], this description can only be valid for one enantiomer, and moreover presupposes that the absolute configuration is known, which, until recently, was not the case. A racemate is the mixture of the two enantiomers 1,2- and 2,1- (**1**) or of 1,3- and 3,1- (**2**). Thus only the α,β-nomenclature is correct for metallocenes of unknown configuration and for racemic mixtures (14).

‡ It has recently been suggested (21, 22) that the expression chirality (adj. chiral) be reintroduced for the necessary and sufficient condition for the occurrence of enantiomers, replacing the hitherto customary term dissymmetry (23, 24). It will be used in this sense in the present review. The word chirality was coined by Lord Kelvin in 1884, and many current authors wish to see it used exclusively in the sense of "handedness" (24).

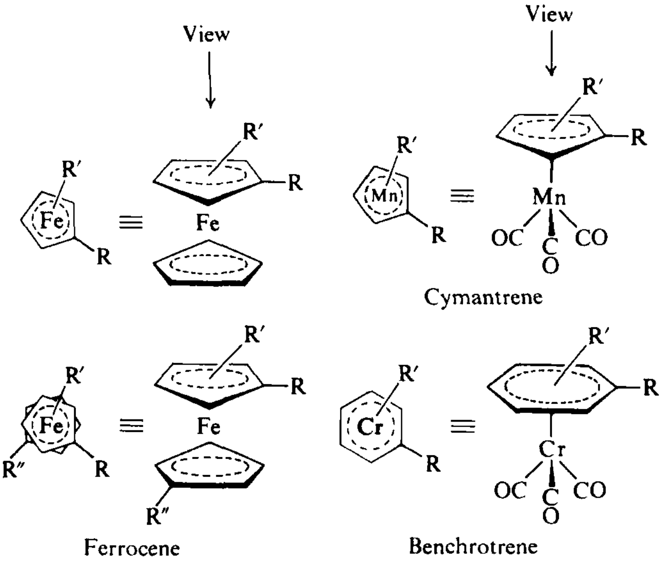

Fig. 1. Stereoformulas of substituted metallocenes.

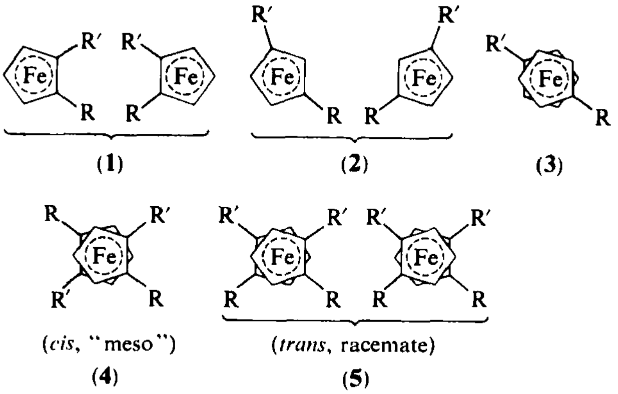

Fig. 2. Isomeric di- and tetrasubstituted ferrocenes.

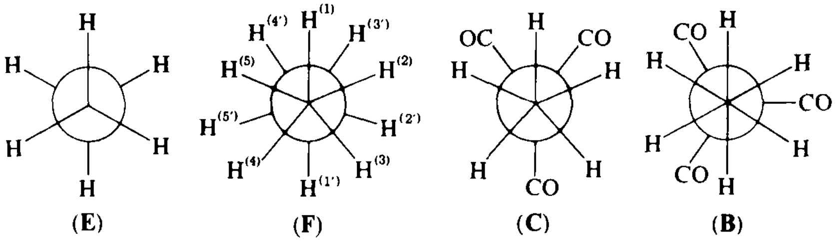

Fig. 3. Newman projection formulas for ethane (**E**), ferrocene (**F**), cymantrene (**C**) and benchrotrene (**B**). The metal atom has been omitted in **F**, **C**, and **B**.

II. SYMMETRY OF METALLOCENES—DEFINITIONS

All considerations of the chirality of metallocene derivatives are of course based on the assumption that rotation about the molecular axis (e.g., C_5-axis of ferrocene) (24,38) is practically unrestricted, an assumption which is in accord with experimental results. For example, no isomeric heteroannular disubstituted ferrocenes (**3**) could be isolated (4,29).*

Rapid establishment of equilibrium between the possible conformers of **3** is only to be expected if we presume that the energy barrier between them is not too high; in fact the experimental value for ferrocene is only 2–5 kcal/mole (4,39,40). Of the five staggered rotational or torsional isomers (24) only one is symmetrical (the 1,1′ isomer in Figs. 2 and 3; cf. Table II). Rapid racemization thus occurs at room temperature and **3** is therefore on the average a "meso form."†

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* It may be noted, that ferrocene itself—apart from two distinct conformers (staggered and eclipsed with the symmetry D_{5d} and D_{5h}, respectively)—may be regarded as an inherently chiral molecule. The same holds true, of course, for simpler compounds such as ethane or biphenyl. Appropriate substitution of these compounds gives rise to "stable" enantiomers.

† The degree of free rotation in heteroannular bridged ferrocenes (28,31–33) depends on the length of the bridge, which makes generalizations difficult. However, models and especially the magnetic equivalence of methylene protons in the NMR spectra (31) show that even in a compound possessing a three-carbon bridge, such as 1,1′-(α-ketotrimethylene)ferrocene (cf. 32), the two (torsional isomeric) enantiomers are easily interconvertible, i.e., here too, continuous racemization takes place.

TABLE II

Point Groups of Metallocenes

	Metallocene			
	Ferrocene			
Substitution[a]	Eclipsed	Staggered	Cymantrene[b]	Benchrotrene[b]
—	D_{5h}	D_{5d}	C_s	C_{3v}
R	C_s	C_s	C_s	C_s
R,R 1,3′	—	C_2	—	—
R,R 1,2′	—	C_2	—	—
R,R 1,1′	—	C_{2h}	—	—

[a] Cf. Figure 3 for positions in ferrocene.

[b] Conformations of highest possible symmetry.

As is clear from a comparison of the Newman projections (Fig. 3), the situation in the case of metallocenes bears a formal resemblance to that of ethane derivatives.

Westman and Rinehart (11) have already drawn attention to this formal similarity. Mislow (24) classifies this type of isomerism together with atropisomerism as torsional isomerism. The difference lies in the symmetry relationships. The point groups (Schoenflies symbols) for some torsional isomers (conformers) of metallocenes are given in Table II.

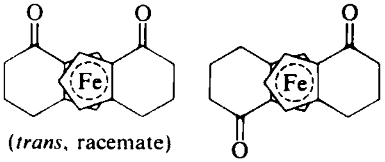
This representation (Fig. 3) shows further that the center of a metallocene ring (point of intersection of the principal axis with the plane of the paper) corresponds to an asymmetric C atom in an ethane derivative as a (imaginary) chiral center (22). However, the advantage of such a simplified representation is coupled with various disadvantages; difficulties arise on assigning the stereochemical symbols (*R* and *S*) in the case of many substitution types (e.g., *β*-disubstituted ferrocenes, **2**, or polysubstituted metallocenes; cf. Sect. III-F-1). For this reason and also for better legibility of the formulas, above all when different types of metallocenes are involved, we shall retain the more detailed (although abbreviated) representation as shown in Figure 1 (cf. also **1**–**5**).

Metallocenes with different ligands at the metal (e.g., cymantrene with symmetry C_s) do in fact become asymmetric on ring substitution with two different groups, which in benchrotrene must occupy *ortho* or *meta* positions. However, even in the case of metallocenes with higher symmetry (ferrocene, ruthenocene, osmocene, D_{5d}), compounds can occur which are chiral despite a twofold axis of symmetry, and which are thus resolvable. These derivatives are such that each ring bears the same pair of non-identical substituents in the same relative positions (α or β); e.g., **5**. An appropriate example is the *trans* form of the bishomoannular bridged ketone **6** (Fig. 4) (and compound **76** derived therefrom) (41).

Aside from this special case, all optically active metallocenes prepared to date are in fact asymmetric compounds, which would seem to justify the term "ferrocene (or metallocene) asymmetry" (14).

This new special type of molecular chirality is distinguished by the optical stability of the enantiomers, since racemization would only be possible if at least one substituent underwent a definite positional change (cf. **1** or **2**). All reactions of optically active metallocenes thus proceed with retention of configuration (100% stereoselective), a circumstance which favors investigations of the stereochemistry of such systems.

From the standpoint of their molecular geometry chiral metallocenes closely resemble chiral *p*-cyclophanes or *ansa* compounds (23,23a), whereas their optical stability is comparable to that of optically active spiranes.*



(*trans*, racemate)
(**6**)

(*cis*, "meso")
(Transoid conformation)
(**7**)

Fig. 4. Bis(α-ketotetramethylene)ferrocenes. Only one enantiomer of **6** is shown.

---

* Attention is drawn to the fact that several transition metal complexes, such as the fumaric acid–$Fe(CO)_4$ complex, are structurally very similar to the metallocenes and can be obtained in optically active form (42). Neither such complexes nor the stereochemistry of primarily inorganic complexes (cf. 43) will be dealt with here.

In view of this special position, the term ferrocene asymmetry (14) (chirality) (44) was proposed for this new type of chiral compound, since the first representative was a ferrocene derivative (9) and the ferrocene series may doubtless be expected to supply the most examples. However, the more general expression *metallocene chirality* is probably preferable.

It was simultaneously suggested (14) that chiral ferrocene (and metallocene) compounds be classified as planar chiral compounds (45), since the chirality follows from asymmetric substitution within one plane, which lies perpendicular to the molecular axis, in contrast to centro- and axial-chiral compounds (23,45).

However, the concept of the chiral center has recently been extended by Cahn, Ingold, and Prelog (22), and it is no longer restricted to compounds with tetrahedral configurations and classical single bonds (asymmetric C atoms). Accordingly, chiral metallocenes contain chiral centers (e.g., all the C atoms of the unsymmetrically substituted ring in a compound such as **1** or **2**) since the "bonds" proceeding from the metal to the C atoms of the ring are also formally regarded as single bonds. This classification problem will be taken up in greater detail in Section III-F-1 (application of configurational notation to chiral metallocenes).

III. METALLOCENE CHIRALITY

From a detailed study of the stereochemistry of metallocenes—above all of ferrocene, the most important special case—interesting contributions to the field of stereochemistry in addition to general information about the chemistry of the metallocenes were hoped for.

Study of these questions necessitates the following stages, many of which are a consequence of the special chemistry of metallocenes:

A. Preparation of chiral (i.e., asymmetrically substituted) metallocenes; *B*. Separation of the possible positional isomers (meso forms, racemates); *C*. Structure elucidation of the individual isomers; *D*. Resolution of racemates; *E*. Determination of relative configuration (configurational correlations); and finally, *F*. Determination of the absolute configuration of metallocenes.

The individual stages and the problems involved will be discussed in some detail.

A. Preparation

The most straightforward and most frequently used method for the preparation of di- or trisubstituted ferrocenes is electrophilic (mono-) substitution (2,4,7) of the easily accessible mono- or dialkylferrocenes (46). As already mentioned (see Table I), three positional isomers (**1–3**) are to be expected in the first case, of which the homoannular (chiral) products (α and β) usually predominate owing to the inductive influence of the alkyl groups (4,26,29,30). Only two trisubstituted ferrocenes can be formed from heteroannular dialkylferrocenes (26). Monosubstituted metallocenes of the cymantrene type (which have only one ring available for substitution) likewise yield at most two isomeric disubstitution products, α and β (47). The steric effect is usually dominant in electrophilic substitution of alkylferrocenes, and therefore the β-isomers (e.g., **2**) are formed in larger amounts (26,30). Recently, however, a method has been reported by which practically pure α-substitution products can be obtained (48), and which proved valuable for the preparation of α-methylferrocenecarboxylic acid (**35**) (16). If the alkyl groups are large (e.g., isopropyl) and the electrophilic substitution reactions employed involve bulky acylating agents, as in the Vilsmeier formylation with the *N*-methylformanilide–$POCl_3$ complex, α-substitution is suppressed to such an extent that practically pure β-isomers result. Thus, formylation of isopropylferrocene by the Vilsmeier method reduces the number of possible isomers to two, while 1,1′-diisopropyl ferrocene yields a single product, β-formyl-1,1′-diisopropylferrocene, which is a racemate (14).

The pronounced steric effect is also apparent from the Vilsmeier formylation of methyl- and 1,1′-dimethylferrocene. As compared with acetylation, here too β-substitution predominates, with the ratio of isomers being α:β:hetero ≈ 15:44:41 (formylation) versus 20:31:49 (acetylation), and α:β ≈ 23:77 versus 42:58 in dimethylferrocene (59).

In contrast to a previous statement of Nesmeyanov et al. (cf. 4), according to which dimethylaminomethylation (Mannich reaction) of methylferrocene or dimethylferrocene should furnish only the β-isomer, this reaction gives the expected mixture of isomeric Mannich bases (in the ratios of 18:42:40 and 27:73, respectively), which can then be converted into many other derivatives (49,59).

Acylation of methyl- and ethylferrocenes also yields the expected mixture of isomers. This was verified by the acetylation of ethyl- (29), methyl- (50), and dimethylferrocene (17,26), and methylcymantrene (47) by the introduction of the carboxamide group into methyl- and isopropylferrocene by the Friedel-Crafts reaction with carbamylchloride–$AlCl_3$ (14), and by many other examples (51) (cf. as well the substitution of heteroannular bridged ferrocene derivatives, where the expected mixtures of positional isomers also resulted) (28,31–33,50).

In view of the problem under consideration (optical isomerism of metallocenes), the groups introduced were primarily polar groups (such as CHO, COMe, or $CONH_2$) which would facilitate the chromatographic separation of the mixtures of isomers (cf. following Sect. III-B). Furthermore, reaction of such groups, or of other functional groups derived from them (e.g., $CONH_2 \rightarrow CH_2NH_2$, $COMe \rightarrow CO_2H$), with optically active auxiliary compounds should make resolution of racemates possible (Sect. III-D).

As the separation of the mixture of isomers is frequently difficult, acylations of alkylferrocenes are not very suitable for preparing pure chiral metallocenes, as they invariably lead to mixtures, with the sole exception of β-formyl-1,1′-diisopropylferrocene (14).

The "total synthesis" of metallocenes from suitably disubstituted primary products offers the possibility of obtaining uniform racemates. This approach was first exploited by Mandelbaum, Neuwirth, and Cais (12), who prepared *m*-methoxybenchrotrenecarboxylic acid from methyl *m*-methoxybenzoate and chromium hexacarbonyl. In a similar way we were recently able to prepare (1-tetralone)chromium tricarbonyl [1,2-(α-ketotetramethylene)benchrotrene, (**59**)] and the isomeric acids α- and β-methylbenchrotrenecarboxylic acid (**41** and **43**, respectively) from the corresponding benzene derivatives and $Cr(CO)_6$ (16). Optically active metallocenes can be obtained directly from such reactions by subjecting an asymmetric starting product to an asymmetric synthesis. For example, the menthyl ester of *o*-methylbenzoic acid ($[\alpha]_D$ −82°) yields dextrorotatory α-methylbenchrotrenecarboxylic acid (**41**, $[\alpha]_D$ +1.9°) on reaction with chromium hexacarbonyl and subsequent hydrolysis of the ester. However, the optical yield amounts to only 1%, probably due to the rather drastic synthesis conditions (16).

By far the most profitable route to uniform (chiral) ferrocene and cymantrene compounds is the intramolecular cyclization of suitable derivatives leading to α-disubstituted products. γ-Metallocenylbutyric acids are especially suited to this purpose, since on ring closure (with trifluoroacetic anhydride, TFAA, or polyphosphoric acid) they yield homoannular bridged ketones [1,2-(α-ketotetramethylene)metallocenes], such as **8**, **56**, or **63** (9,27,35,44,50,52–54). These have proved most valuable for the study of relative and absolute configurations of optically active metallocenes (16,41,44,53,55) (cf. Sects. III-E-1 and III-F-2). Cyclization of ferrocene-1,1′-bisbutyric acid yields the expected mixture of two stereoisomeric ketones (27,41,56), one of which, the *trans* isomer **6**, is a racemate and can be resolved (41), the *cis* compound **7** being the meso form.

By Bischler-Napieralski cyclization of *N*-formyl-β-ferrocenylethylamine, Osgerby and Pauson (57) prepared ferrocenodihydropyridine, which on reduction yielded the saturated homoannular bridged ferrocenotetrahydropyridine (**18**). However, it is more conveniently prepared from β-ferrocenylethylamine by ring closure with formaldehyde (53).

B. Separation of Isomers

Separation of isomeric acylalkylmetallocenes is usually achieved by column chromatography on alumina or by preparative thin-layer chromatography (TLC) (cf. 61 and 70 for vapor-phase chromatography of ferrocene derivatives).

TLC has proved to be very suitable as a general check for synthetic steps and the stages involved in separation and purification in metallocene, and especially ferrocene, chemistry (58).

Separations by fractional crystallization, as in the case of the isomeric methyl cymantrenecarboxylic acids (47), are seldom successful.* Isolation in the pure state of every isomer formed is not always possible, and separation of isomers usually represents the bottleneck in the study of metallocene stereochemistry, which is the reason why the above-mentioned cyclizations are so useful for the preparation of uniform racemic metallocenes.

Of the acylated monoalkylferrocenes mentioned, examples of successful separations are the three isopropylferrocene carboxamides (14), the isomeric acetylmethylferrocenes (50,61), and the acetylethylferrocenes (29). Westman and Rinehart (11) separated the isomeric 1,1′-dimethylferrocenemonocarboxylic acids (**45**,**50**) by chromatography of their

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* It was recently shown, however (10a), that only *one* of the two isomeric carboxylic acids (with the mp 181°) can be obtained pure; the second, mp 134° (47), contains about 30% of the other (β-)isomer. If purified by chromatography of its methyl ester, the mp of the α-acid is 162°.

p-bromobenzyl esters. The monocarboxylic acids were obtained from dimethylferrocene by reaction with butyllithium followed by carboxylation. The lithiation procedure gives, however, only poor yields of the acid mixture (**45** and **50**). A considerable improvement over their method was achieved recently.

This new method involves Friedel-Crafts acylation of dimethylferrocene with diphenylcarbamylchloride, chromatographic separation of the isomeric diphenylamides (which were obtained in a ratio $\alpha:\beta \sim 1:5$) and subsequent hydrolysis (59).

The most satisfactory route for the preparation of isomeric methyl- and 1,1′-dimethylferrocenecarboxylic acids proved to be Vilsmeier formylation of methyl- and dimethylferrocene, respectively, conversion of the mixture of isomeric aldehydes into the carboxylic acids ($CHO \rightarrow CH{=}NOH \rightarrow CN \rightarrow COOH$), and separation of the latter via the methylesters (59).

C. Determination of Structure

The elucidation of the structure of an isomeric metallocene, insofar as the structure is not immediately apparent from the method of preparation (as is the case with homoannular cyclization, with the total synthesis of benchrotrene derivatives, or formylation of diisopropylferrocene), is achieved for the most part by physical methods. Chemical methods are applicable only in a few special cases. Tirouflet et al. determined the structures of the isomeric acids formed on acylation of ethyl- and diethylferrocene with succinic anhydride by cyclization, and made a comparison of the homoannular bridged compounds formed (36,37). The problem of assignment of structure, being of special significance in ferrocene chemistry, has been treated in detail elsewhere (2,4,61) and will only be touched on here.

With the aid of a rule formulated by Rosenblum (9,10 μ-rule) (4,60), homoannular substituted ferrocenes can be distinguished satisfactorily from their heteroannular isomers by infrared spectroscopy, since the bands at 1105 and 1000 cm^{-1} only occur when at least one ring is unsubstituted. Differentiation between α- and β-disubstituted ferrocenes is more problematical and is discussed in detail elsewhere, e.g., 26,29,30,32. In references 31 and 32 the possibility of structural assignments on the basis of ultraviolet spectra is also mentioned.

A more reliable decision can be reached for dialkylferrocenes (26,32). As formyl and acetyl groups can be reduced smoothly with lithium aluminum hydride–aluminum chloride to methyl and ethyl groups, respectively (46), transformation of acylalkylferrocenes to the corresponding dialkyl derivatives presents no problems. Carbamylalkylferrocenes can be hydrolyzed to acids, which in turn can be reduced to methyl derivatives (14). The isomeric dimethylferrocenes were obtained in this way, and structures were assigned to them on the basis of their infrared spectra by comparison with authentic products.

Determination of the positions of substituents in the ferrocene nucleus by proton magnetic resonance spectroscopy is considerably more exact, and to date, by far the most rapid and reliable method. So far most authors have based the structural analysis on the chemical shifts of only the ring protons (4,28,31,61–64a). For substituted methylmetallocenes, which are very important for stereochemical investigations, a rapid and simple determination of the isomer distribution as well as the elucidation of structures is possible on the basis of chemical shifts and relative intensities of the signals of the methyl protons (59b). For some important substitution reactions (such as acetylation, formylation, benzoylation, and the Mannich reaction) the isomer ratios were determined by NMR analysis, and from these ratios the site reactivities were calculated (59b).

X-ray crystal-structure determination is an obvious additional possibility of high reliability; it has been applied to a few cases (e.g., 65,66), but obviously cannot be employed as a routine method.

Serious objections were raised by H. Egger (67) to a suggestion by Cais et al. (18) that structural assignments for isomeric ferrocenes be made with the help of mass spectroscopy (cf. also 68), since in many cases rearrangements can occur, falsifying the results. However, the configuration (*exo* or *endo*) of stereoisomeric metallocenylcarbinols, such as **9**,**10**,**57**,**60**,**65**, or **66**, can be elucidated unambiguously with the mass spectrometer on the basis of fragments which arise by transfer of OH to the metal atom (67,69).

For routine organic work a rule formulated by Rosenblum and Woodward (29) has proved very valuable. According to this rule the acylalkylferrocenes of any type are adsorbed increasingly firmly on alumina in the sequence $\alpha <$ hetero $< \beta$. In all cases investigated to date, this rule also holds for TLC on silica gel, for paper chromatography of alkylferrocenecarboxylic acids (14), i.e., for adsorption and partition chromatography, and for gas chromatography as well (61,70).

The assignment of structure to an isomeric acylalkylferrocene is thus rapidly and conveniently achieved by TLC, whereby the α-derivatives have the highest and the β-isomers the lowest R_F values (14,58).

As such rules for other metallocenes are as yet unknown, one is dependent on physicochemical methods in such cases (e.g., 18,61,68). Riemschneider and Herrmann (10), who were the first to resolve racemates of isomeric methylcymantrenecarboxylic acids, were unable to assign structures (α or β) to the two racemates (mp 180 and 134°).

This assignment was recently made by NMR spectroscopy. According to the chemical shifts of both the ring and the methyl protons, the higher melting acid (mp 181°) has the β-structure, and the other isomer (mp 162° for the pure compound, cf. Sect. III-B, footnote) is α-methylcymantrenecarboxylic acid (10a,59b).

D. Resolution of Racemates

If suitable functional groups are present in a chiral metallocene, the usual optically active auxiliary compounds can be employed for the resolution of racemates (23). As mentioned previously, the groups present must first be transformed by appropriate reactions if necessary; e.g., oxidation of acetyl to carboxyl, reduction of carbamyl to aminomethyl. Racemic acids and amines can then be resolved by formation of salts, with alkaloids (10,11) or optically active α-phenethylamine (16,44) on the one hand, with dibenzoyltartaric acid, malic acid, or optically active dinitrodiphenic acid on the other (14,53). Carbonyl derivatives can be resolved through the hydrazones of (−)-menthydrazide. This reagent was first used for the resolution of camphor (71) and served excellently in the resolution of bridged metallocene ketones (9,13,15, 41,44,53) and of diisopropylferrocenecarboxaldehyde (14). A mild method for the hydrolysis of the menthydrazones was developed (13,53) which proved applicable to cymantrene derivatives as well (15).

The classical resolution procedures can, of course, also be employed for metallocenes in which a chiral center lies outside the metallocene group (Table IV), such as α-ferrocenylethylamine (14), γ-ferrocenyl-(or cymantrenyl-)-α-phenylbutyric acid (15,44) and 2-ferrocenylcyclopropanecarboxylic acid (72).

Chromatographic methods seem very promising for the resolution of less polar metallocene derivatives. For example, the bridged ferrocene mono- or bisketones **8** and **6**, respectively, as well as other metallocenes (Table III) could be at least partially resolved by a single passage in benzene solution through a long column of partially acetylated cellulose (16,73). For the present, however, the optical yields amount to 13% at most (for **8**). For a rapid test of whether or not a given metallocene derivative is chiral, chromatography is probably superior to other methods. Price (74) and Whiting were able to show that phenanthrene chromium tricarbonyl possesses the unsymmetrical structure by chromatographic resolution on lactose. We were recently able to assign structures to the two isomeric bisketones **6** and **7**, of which only the isomer with mp 160° could be obtained in optically active form by chromatography on acetylated cellulose. Consequently, this isomer is the racemate **6** with the *trans* configuration. This had been previously demonstrated by partial resolution through the bismenthydrazone (41).

The first optically active carbodiimide, the axial chiral *N*,*N'*-diferrocenylcarbodiimide (Fc—N=C=N—Fc), was recently obtained by this chromatographic method (75).

Kinetic resolution of racemates has of late proved very useful both for the preparation of optically active metallocenes (16) and, above all, for the assignment of relative and absolute configuration (cf. Sect. III-E-3).

Table III lists the optically active metallocenes (compounds with metallocene chirality) obtained by direct resolution of racemates. The optically active secondary products obtained from them by chemical transformations are contained in Figures 5–9 and 11–14.

Table IV, on the other hand, shows some optically active compounds containing achiral metallocenyl residues.

1. Optical Purity

As with many other classes of compounds, determination of the optical purity of metallocenes is no easy task (23,76).

Optical purity, as is customary, has hitherto been assumed to be 100% (Table III) for those cases where either both enantiomers were obtained with comparable degrees of rotations, or where the specific rotation of an enantiomer remained constant after repeated crystallization of the derivative concerned (e.g., the α-phenethylamine salt).

These values are naturally far more reliable when chemical correlation with compounds of known optical purity is achieved (as with **63b**), or when a product is obtained independently from two different

TABLE III

Optically Active Metallocenes (Metallocene Chirality)

Metallocene	Substituents		Structure number	Resolving agent	Enantiomer				Ref.
	Ring 1	Ring 2			$[\alpha]_D$, deg.	Solvent[a]	Optical purity,[b] %	Absolute configuration	
Ferrocene	Me,CO_2H (α)	—	**35**	(−)-PhCH(NH_2)Me	+53	A	100	(1*S*)	16
					+34	B	100		16
	Me,CO_2H(β)	—	—	(−)-PhCH(NH_2)Me	+33	A	100	?	59a
					+37	B	100		59a
	Me,CO_2H (α)	Me	**45**	(−)-PhCH(NH_2)Me	+31	A	100	(1*S*)	59a
					+23	B	100		59a
	Me,CO_2H (β)	Me	**50**	Cinchonidine,	+36	$CHCl_3$	82		11
				quinidine,	−37	$CHCl_3$	84		11
				(−)-PhCH(NH_2)Me	+44	$CHCl_3$	100	(1*R*)(?)	59a
					+36	A	100		59a
					+35	B	100		59a
	Me,CH_2NH_2 (α)	—	**26**	Bz-tartaric acid,	+26	A	100	(1*S*)	14
				malic acid	−22	A	81	(1*R*)	14
	Me,COMe (α)	—	**37**	Ac-cellulose	+13	B	2.3	(1*R*)	73
	iso-Pr, CHO (β)	iso-Pr	—	(−)-Menthydrazide	+25	A	?		14
	$(CH_2)_3CO$ (α)	—	**8**	(−)-Menthydrazide	+580	A	100	(1*S*)	53
					+550	$CHCl_3$	94(?)		9
				Ac-cellulose	−77	A	13	(1*R*)	49
	$(CH_2)_3CO$ (α)	$(CH_2)_3CO$ (α)	**6**	(−)-Menthydrazide	+110	A	?	(1*S*:1′*S*)	41
				Ac-cellulose	−190	B	?		49

	$\mathrm{CH_2\underset{\underset{Ph}{\vert}}{C}HCH_2CO}$ (α)	—	**74**	(−)-Menthydrazide	−92	B	72	(1*R*)	44
	$(CH_2)_2NHCH_2$ (α)	—	**18**	(+)-Dinitrodiphenic acid	−32	C	100	(1*S*)	53
					0	A	100		53
				(−)-Dinitrodiphenic acid	+30	C	94		53
	$(CH_2)_2CH{=}CH$ (α)	—	**11**	Ac-cellulose	+17	B	0.8	(1*R*)	49
Cyman-trene	Me,CO_2H(α) (mp 162°)	—	—	(−)-PhCH(NH_2)Me	+83	A	100	(1*S*)	10a
					+112	B	100		10a
	Me,CO_2H(β) (mp 181°)	—	—	(−)-Ephedrine	−67	A	100(?)	?	10
					+62	A	93		10
				(−)-PhCH(NH_2)Me	+58	A	87(?)	?	10a
					+76	B			10a
	$(CH_2)_3CO$ (α)	—	**56**	(−)-Menthydrazide	+454	B	100	(1*S*)	15
Benchro-trene	Me,CO_2H (α)	—	**41**	(−)-PhCH(NH_2)Me	+180	B	100	(1*S*)	16
					+103	A	100		
	Me,CO_2H (β)	—	**43**	(−)-PhCH(NH_2)Me	−146	B	100	(1*R*)	16
					−88	A	100		
					−34	NaOH	100		
	OMe,CO_2H (β)	—	—	Brucine	−47	NaOH	100(?)	?	12
					+46	NaOH	100		
	$(CH_2)_3CO$ (α)	—	—	Ac-cellulose	+21	B	?	(1*S*)	16

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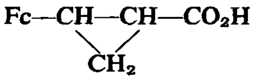
[a] Solvents: A = alcohol (EtOH or MeOH), B = benzene, C = cyclohexane.

[b] See Section III-D-1 for discussion of optical purity of metallocenes.

TABLE IV

Optically Active Compounds Containing Metallocenyl Residues

Compound[a]	Resolving agent	Enantiomer			Ref.
		$[\alpha]_D$, deg.	Solvent	Absolute configuration	
Fc—CH(NH_2)Me	(+)-Dinitrodiphenic acid	+21	A	(*R*)(?)	14
	(−)-Dinitrodiphenic acid	−21	A	(*S*)	14
 (*trans*)	(−)-PhCH(NH_2)Me	+20	A	(1*S*:2*S*)(?)	72
		+27	B		
Fc—$CH_2CH_2CH(Ph)CO_2H$	(−)-PhCH(NH_2)Me	+68	A	(*S*)	44
Cy—$CH_2CH_2CH(Ph)CO_2H$	(−)-PhCH(NH_2)Me	+48	A	(*S*)	15
Fc—N═C═N—Fc	Ac-cellulose	+4.1	B	(*S*)	75
	(+)-Dinitrodiphenic acid	−4.8	B	(*R*)	

[a] Fc = ferrocenyl, Cy = cymantrenyl, C_5H_4—$Mn(CO)_3$.

optically active starting materials (e.g., methylethylferrocene **25** from **18** and **26**, or methylferrocenecarboxaldehyde **28** from **26** and **35**).

Methods available for a more exact determination of optical purity, such as the isotope dilution method, or the procedures recently described by Mislow (76) or Horeau (77) have not yet been applied in the ferrocene series.

In many cases the figures given in Table III are for this reason probably not final; furthermore, the optical rotations were measured with various instruments (some with visual observation, some with photoelectric measurement) and can thus only be compared with reservations.

The sign of rotation is, however, decisive for the elucidation of relative and absolute configuration (Sects. III-E and III-F), and knowledge of the optical purity, however desirable in many cases, is not essential.

E. The Relative Configurations of Metallocenes

The two homoannular bridged compounds, the dextrorotatory ketone (+)-**8** and the enantiomeric amines (+)- and (−)-**18** were especially suitable for the preparation of further optically active ferrocene derivatives owing to their relatively easy accessibility. For correlations with other metallocenes, above all for correlations of the two chiral substitution types α and β (**1** and **2**), the optically active mono- and dimethylferrocenecarboxylic acids **35**, **45**, and **50** were also chosen as starting materials.

Owing to the optical stability of all these compounds, there is no risk of racemization occurring during configurative chemical correlation and all reactions necessarily proceed with 100% stereoselectivity. If the starting material is known to be optically pure (but see Sect. III-D-1), the optical rotations of all subsequent products may with confidence be assumed to be maximal. The rotations given in Figures 5–9 and 11–14 are $[\alpha]_D$ values corrected for optical purity. It follows from the structures of the homoannular bridged compounds **8** and **18** that all the compounds derived from them (also those derived from the acids **35** and **45**) must belong to the α-substitution type, while derivatives of the dimethylferrocenecarboxylic acid **50** are β-substituted ferrocenes.

Individual reactions which were also conducted with the antipodes (of various optical purities) invariably yielded products whose rotations (after correction) agreed excellently with those of the corresponding enantiomers.

The reactions of the key substances **8**, **18** (and **26**), **35**, and **45** (and **50**) are discussed separately in the following and summarized for the sake of clarity in Figures 5–9.

1. (+)-Ferrocenocyclohexenone (**8**) *and Compounds Derived Therefrom*

Figure 5 summarizes some reactions of the ketone **8**. Reduction with lithium aluminum hydride yielded a mixture of the epimeric carbinols **9** and **10**, in agreement with earlier findings (50,78). The isomer ratio (1:10) is interpreted as resulting from preferred hydride ion attack from "outside." Unambiguous assignment of configurations (*exo*- and *endo*-OH for carbinols **9** and **10**, respectively) was possible on the basis of the difference in adsorption (the *exo*-carbinol **9** is adsorbed much more strongly and can therefore be smoothly separated from **10** by chromatography), the infrared spectra (the OH band at 3533 cm^{-1} for **10** is in accord with the assumption of a hydrogen bond to the iron atom) (2,44), the mass spectra (67), and also their different reaction rates. The *exo*-carbinol **9** is oxidized much more rapidly by MnO_2 to the ketone **8** with the original optical rotation than is **10** (53).

Egger and Falk (69) investigated the reduction of the bisketones **6** and **7** in detail. Four of the six possible stereoisomeric carbinols (*endo–endo*, *exo–endo*, and *exo–exo* from each ketone) were obtained pure. They differ distinctly in chemical and physical properties. This represents the first example of a compound where characteristic differences in the mass spectra of the meso and racemic forms appear.

Ferrocenylcarbinols with an OH group in the α-position to the ring can be smoothly dehydrated to vinyl compounds with acid alumina (79); **9** and **10** yield accordingly the levorotatory cyclic vinyl derivative ferrocenocyclohexadiene (**11**), noteworthy for its high specific rotation (cf. also Fig. 15*b*). The significance of this large displacement in the degree of rotation from (+)-**8** to (−)-**11** will be discussed more fully in connection with the absolute configuration of such systems and in the light of Freudenberg's displacement rule (Sect. III-F-3-d; Table V).

The chloroderivative (**15**) of **11** was accessible by treatment of **8** with the Vilsmeier complex from dimethylformamide–phosphorus oxychloride (73). Compound **15** was of interest with regard to the structurally related open chain compound **39** (Fig. 8).

To correlate the ketone **8** and its derivatives with the ring amine **18** (Fig. 6) and related compounds, we chose the Schmidt reaction (80)

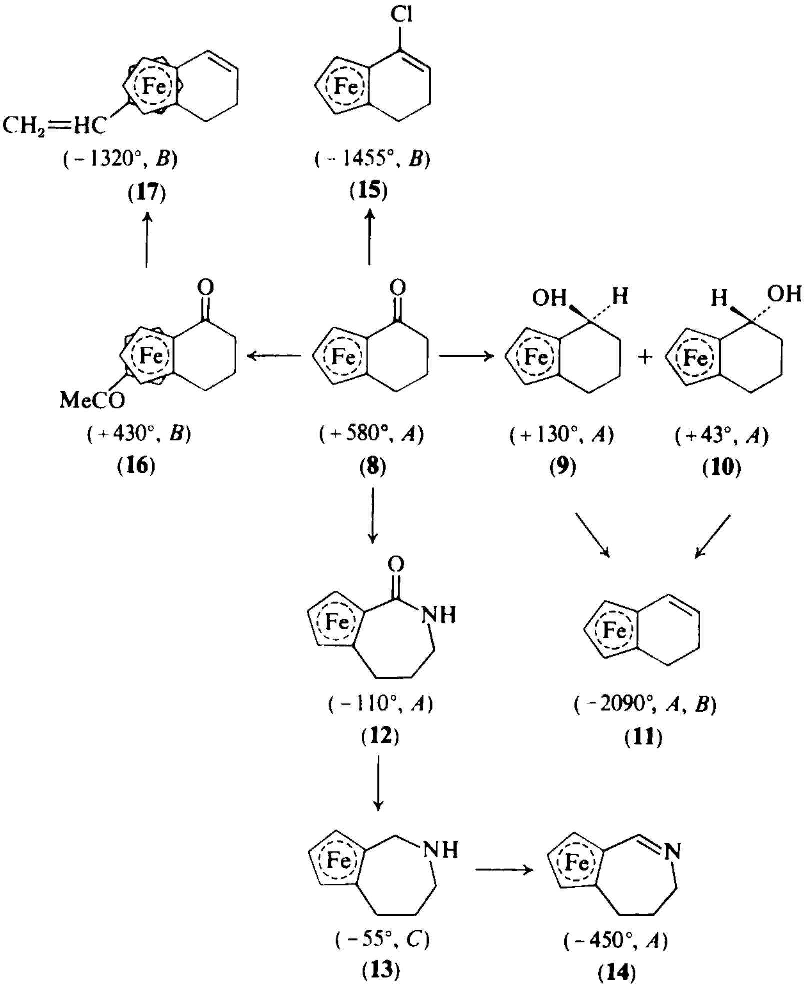


Fig. 5. Reactions of (+)-ferrocenocyclohexenone **8** (13,53). Here, as well as in Figures 6–14, all rotations refer to specific rotations, $[\alpha]_D$, at the sodium D line in alcohol (*A*), benzene (*B*) or cyclohexane (*C*).

which transformed the (+)-ketone to a seven-membered lactam **12**. Assignment of the correct structure (with the CO group in conjugation with the ring) followed from the CO frequency in the infrared spectrum, which, as in other amides of ferrocenecarboxylic acid (81), lies at 1635 cm^{-1}. Analogous benzene derivatives undergo phenyl-group migration to yield aniline derivatives when subjected to the Schmidt reaction (80); 6-methoxy-1-tetralone however, in which the electronic effect of the aromatic group is comparable to that in **8**, yields principally the lactam with CO adjacent to the benzene ring (analogous to **12**) (82). Cais and Narkis (83) observed no migration of the metallocenyl group in acylcymantrenes, while acetyl- and benzoylferrocene yielded in each case a mixture of the two possible isomers, admittedly under reaction conditions different from ours (cf. 84,85).

The seven-membered amine ferrocenotetrahydroazepine (**13**) was obtained by hydride reduction of **12**. Compound **13** has a close structural, and thus very probably configurational, relationship to ferrocenotetrahydropyridine (**18**). A far more reliable conclusion concerning the relative configurations of the two amines can be drawn from the manganese dioxide oxidation to the corresponding dehydrogenated heterocyclics (the cyclic Schiff bases **14** and **19**). In both cases a high negative displacement of rotation resulted on oxidation of the levorotatory amines, so that according to the Freudenberg displacement rule (which also holds true in the metallocene series, cf. Sect. III-F-3-d) the same configuration can be assigned to the antipodes with the same sign of $[\alpha]_D$. By correlating (−)-**14** with the dextrorotatory ketone **8**, the link between this ketone and (−)-ferrocenotetrahydropyridine (**18**) was established via (−)-**19**.

In connection with the comparison of **35** with **45** (cf. Sects. III-E-3 and III-E-4) knowledge of the influence of a substituent in the second ring on the rotational strength was of interest. For this purpose (+)-**8** was acetylated, and the acetyl derivative (+)-**16** was converted into the levorotatory bisvinyl compound **17** by reduction with lithium aluminum hydride and subsequent dehydration (59a).

The values for the rotations (especially the $[M]_D$ values, Table V) of **16** and **17** (Fig. 5), show that additional acetyl or vinyl groups in the second ring exert no marked influence on the rotation of the unsubstituted parent substances **8** and **11**, respectively.

2. *(−)-Ferrocenotetrahydropyridine* (**18**) *and Compounds Derived Therefrom*

Figure 6 summarizes reactions of the levorotatory amine **18**. Some of these transformations were also carried out on the dextrorotatory antipode and yielded analogous results.

Exhaustive methylation and Hofmann elimination caused ring opening of (−)-**18** to give **20** (86). Of the subsequent products, **21** was obtained by hydrogenation, the carbinol **22** by methylation and treatment of the methiodide with alkali, and the aldehyde **23** by oxidation with manganese dioxide (cf. 87). Reaction of **23** with methyl magnesium iodide and dehydration of the secondary alcohol formed yielded the highly dextrototatory α-vinylethylferrocene (**24**). The degree of rotation of **24** decreases rapidly in alcohol owing to ether formation, as does that of the analogous methyl compound **30**. Both **22** and **23** could be reduced with lithium aluminum hydride-aluminum chloride (46) to the simplest optically active dialkylferrocene, the levorotatory α-methylethylferrocene (**25**).

Optically active α-(aminomethyl)-methylferrocene (**26**), obtained by acylation of methylferrocene with carbamylchloride–aluminum chloride followed by separation of the isomeric amides, reduction of the pure α-isomer, and resolution of the racemate (14), could likewise be linked with the ring amine **18** (and hence with the ketone **8**) as follows.

Amine (+)-**26** was transformed into α-(hydroxymethyl)-methylferrocene (**27**) by methylation and treatment of the quaternary salt with alkali. Manganese dioxide oxidation of **27** yielded the aldehyde **28**. From the latter, α-vinylmethylferrocene [(+)-**30**] was accessible via the carbinol **29**, which in turn, on lithium aluminum hydride–aluminum chloride reduction, gave the dextrorotatory α-methylethylferrocene (**25**). Thus both enantiomers of this dialkylferrocene (**25**) have been prepared by independent routes, and in addition the unambiguous correlation of all compounds shown in Figures 6 and 7 has been achieved. Furthermore, the identity of the infrared and nuclear magnetic resonance spectra of the two enantiomers of **25** was a proof of the α-orientation of the two groups in **26**.

The following reactions enabled two trisubstituted ferrocenes to be included in the group of compounds with mutually correlated configurations (53) (Fig. 7).

The amine **26** was converted into the nitrile **31** by exhaustive methylation and reaction of the quaternary salt with cyanide. The nitrile was reduced to **32** and cyclized with formaldehyde to **33**. The positions of the three groups (ring and methyl) relative to each other at the ferrocene nucleus as depicted in structure **33** (Fig. 7) follow unambiguously from the reaction sequence. As with the unmethylated ferrocenotetrahydropyridine (**18**), oxidation of **33** to the dihydrocompound **34** with manganese dioxide resulted in a large negative displacement of the

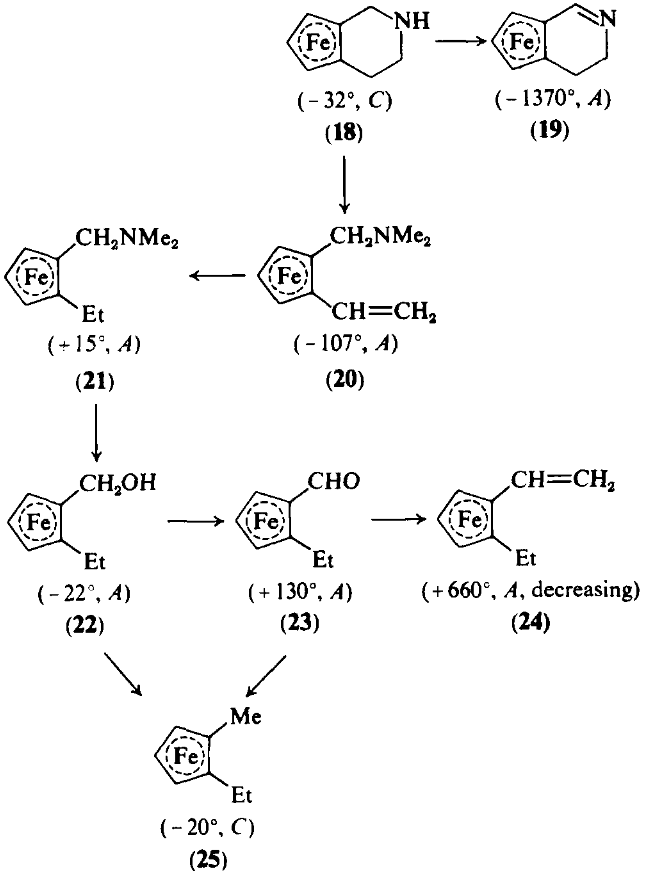


Fig. 6. Reactions of (−)-ferrocenotetrahydropyridine **18** (53).

degree of rotation; as the methyl group is very unlikely to exert any marked influence on the direction of rotation, **26** and **18** were thus linked configurationally by a further independent route. Unequivocal correlation had already been achieved via the enantiomeric methylethylferrocenes (**25**).

From the results it follows that Freudenberg's displacement rule is very probably valid also for compounds possessing ferrocene chirality, which in fact is made especially clear by a comparison of the alteration in degree of rotation accompanying individual synthetic steps, such as:

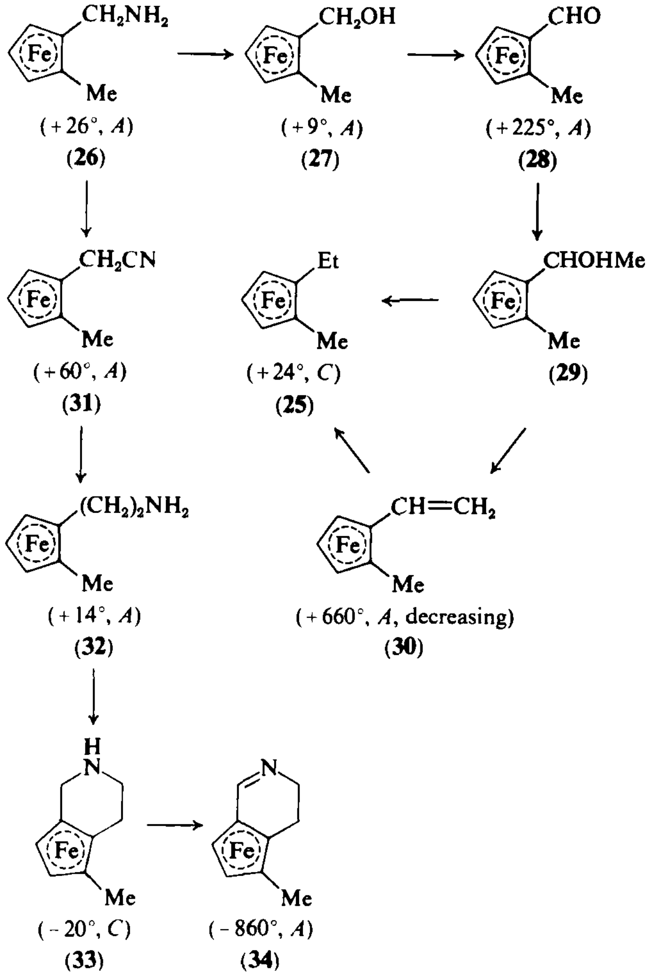


Fig. 7. Reactions of (+)-α-(aminomethyl)methylferrocene **26** (53).

amines (**13**,**18**,**33**) → Schiff bases (**14**,**19**,**34**); alcohols (**22**,**27**) → aldehydes (**23**,**28**) → vinylferrocenes (**24**,**30**). Attention has already been drawn to the pronounced shift of sign of rotation resulting from the reaction: ring ketone (**8**,**16**) → cyclic vinyl compounds (**11**,**17**) (cf. also Sect. III-F-3-d; Table V).

3. (+)-*Methylferrocenecarboxylic Acid* (**35**) *and Compounds Derived Therefrom* (Fig. 8)

As already mentioned, methylferrocenecarboxylic acids (**35**,**45**, and **50**) were investigated primarily because of their importance in the correlation of α- and β-substituted metallocenes (16).

The syntheses and resolutions of the racemic starting products were mentioned earlier (Sects. III-A, III-B, and III-D; Table III).

Esterification of (+)-**35**, reduction of the levorotatory methyl ester **36**, and manganese dioxide oxidation of the carbinol formed yielded the dextrorotatory methylferrocenecarboxaldehyde **28**, thus not only establishing the configurational relationship with the amine **26** (and its derivatives) and therefore with the ketone **8** as well (Figs. 5–8), but also enabling the optical purity of (+)-**28** to be checked. The rotations measured for the aldehydes obtained by different routes were in excellent agreement: +225° from **26** and +220° from **35**.

A further configurative correlation of **35** with **26** (and thus with **18**) was possible via the vinyl derivative **30**: treatment of the chloride of (+)-**35** with dimethylcadmium gave the levorotatory methylacetylferrocene **37**, from which **30** was obtainable by reduction and dehydration. Determination of optical purity was impossible by this route, however, because the optical rotation of **30** was only known in ethanol (+660°) (Fig. 7) and decreases towards 0° in this solvent owing to ether formation (53).

An optically active ketone **37** is also obtainable from the racemate (50) by chromatography on acetylated cellulose (73), but the optical yield amounts to only 2.3% (Table III).

Finally, methylferrocenylacetylene (**40**) was obtained from (−)-**37** by chloroformylation and subsequent fragmentation of **38** with sodium amide, a method which has proved generally useful for the preparation of ethynyl ferrocenes (88). The acetylene **40** was weakly levorotatory (cf. Fig. 15*d* for its ORD curve). Under milder conditions (−)-**37** yields (−)-α-(chlorovinyl)methylferrocene (**39**) as well.

Compound **40** was the first example of an optically active metallocene in which the rotation is due solely to atomic asymmetry (chirality) (23,89), which becomes therefore molecular chirality in this case. As one can see, this contribution (at least at 589 mμ) is very small, especially in consideration of the difference in polarizability between methyl and ethynyl (2.59 and 7.16, respectively). This becomes especially

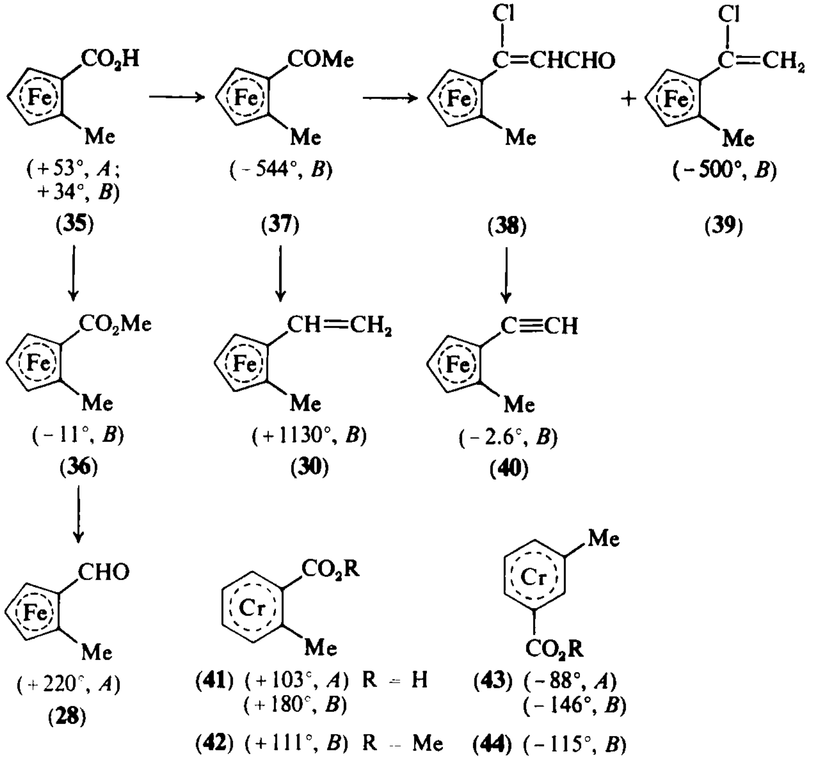


Fig. 8. Reactions of (+)-α-methylferrocenecarboxylic acid **35** and methylbenchrotrenecarboxylic acids **41** and **43** (16,73).

clear upon comparison with those α-disubstituted ferrocenes in which the conformational asymmetry is the principal contributor to rotation (e.g., **11**,**30**,**37**, and **39**).

The great influence of conformational chirality is also revealed by a comparison of **8** with **37** on the one hand, and **15** with **39** on the other, both pairs being structurally very similar, but where the bridged and open-chain compounds stand in contrast. In the case of the ketones (**8** and **37**), even the sign of rotation changes although the configuration is the same (see also Sects. III-F-3-b and III-F-3-e).

The configurational correlation of the α-methylferrocenecarboxylic acid (**35**) with the analogous benchrotrene derivative **41** was achieved by kinetic resolution of the anhydrides of the racemic acids (16). Treatment of these anhydrides with a limited quantity of (−)-α-phenethylamine or (−)-menthol in pyridine resulted in preferential reaction with the (−)-enantiomers of the acids. The liberated acids (**35** and **41**, respectively) were thus dextrorotatory. The optical yields lay between 3 and 20% (cf. the determination of configuration of carbinols by kinetic resolution of α-phenylbutyric anhydride, Sect. III-F-2). These results showed unequivocally that the enantiomers of **35** and **41** with the same sign of $[\alpha]_D$ possess the same configuration.* Application of Freudenberg's displacement rule led to the same conclusion, as esterification of (+)-**35** and (+)-**41** caused negative displacement of rotation in both cases (cf. Fig. 8).

Furthermore, from a comparison of the ORD curves of the two isomeric methylbenchrotrenecarboxylic acids (**41** and **43**), the conclusion can be drawn that (+)-**41** and (−)-**43** very probably possess opposite chiralities (see Sect. III-F-3-b; Fig. 15*c*). So for the first time the configuration of a β-substituted metallocene had been linked with α-substituted reference substances (such as **41** and **35**).

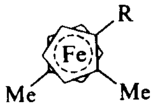
4. *1,1′-Dimethylferrocene-α- and β-carboxylic Acids* (*Fig. 9*) (**45,50**)

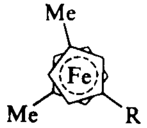
As **50** was the only reasonably easily accessible (optically active) β-substituted ferrocene derivative (cf. Sect. III-D; Table III), this acid was chosen, just as the isomeric α-compound **45**, as starting material for the same reaction sequence as that described for the monomethyl ferrocenecarboxylic acid **35** (59).† In view of the rather limited influence of a substituent in the second ring (cf. **16,17**), an optical comparison between the derivatives of **35** and **45** on the one hand (whereby the correlation of **45** with all other α-disubstituted ferrocenes was established), and between the isomeric α- and β-derivatives (secondary products of **45** and **50**) on the other, seemed justifiable. The corresponding ethynyl derivatives **49** and **54**, obtainable from the acetyl compounds **47** and **52** as already described (cf. **37** → **38** → **40**), and in which the possibly disturbing influence of conformational chirality is eliminated, were considered for this purpose (Fig. 9).

* It has been recently shown that the same also holds true for α-methylcymantrenecarboxylic acid, since kinetic resolution of its anhydride with either (−)-α-phenethylamine or (−)-menthol likewise furnishes the dextrorotatory carboxylic acid (10a).

† In the meantime, pure β-methylferrocenecarboxylic acid was also prepared (59) and resolved via its phenethylamine salt (cf. Table III). For the active carboxylic acid a similar reaction sequence as described for **35**, **45**, and **50** (Figs. 8 and 9) was performed (59a). The results obtained were in good agreement with those obtained from **50**.

From the ORD curves of the acetylenes **40** and **49** (Fig. 15*d*; Sect. III-F-3-b) it follows that the configurations of the two compounds, both derived from the corresponding dextrorotatory acids, (+)-**35** and (+)-**45**, are identical. Hence, (+)-**45** and its derivatives were unambiguously correlated with the series of α-substituted monomethylferrocenes (+)-**35** and its derivatives (Fig. 8), and consequently also with **26**, **18**, and **8**.





	R	
45 (+31°, *A*; +23°, *B*)	CO_2H	**50** (+36°, *A*; +35°, *B*)
46 (−12°, *B*)	CO_2Me	**51** (+23°, *B*)
47 (−290°, *B*)	COMe	**52** (+17°, *B*)
48 (+706°, $[\alpha]_{578}$ + 790°, $[\alpha]_{546}$ + 1180°, $[\alpha]_{436}$ − 915°, $[\alpha]_{364}$ + 440°, *B*)	$CH{=}CH_2$	**53** (−45°, $[\alpha]_{578}$ − 52°, $[\alpha]_{546}$ − 75°, $[\alpha]_{436}$ + 285°, $[\alpha]_{364}$ − 252°, *B*)
49 (+6°, *B*)	$C{\equiv}CH$	**54** (+30°, *B*)
55 (+127°, *A*; +14°, *B*)	CHO	**55a** (−5°, *B*)

Fig. 9. 1,1′-Dimethylferrocenecarboxylic acids and derivatives (59a).

Moreover, the relative configurations of the α-derivatives **35** and **45** were also apparent from an optical comparison of their derivatives; both dextrorotatory acids displayed displacements of rotations of the same sign and magnitude on conversion into the acetyl, vinyl, and formyl derivatives (**37**,**47**; **30**,**48**; and **28**,**55**), respectively (cf. Figs. 8 and 9).

However, in the configurational correlation of the α- with β-methylated ferrocenylacetylenes **49** and **54** by ORD, difficulties were encountered (see Sect. III-F-3-b; Fig. 15*e*). Hence, at present the correlation of the α- and β-series is only possible (although with considerable reservation) on the basis of optical comparison of some derivatives, especially the vinyl compounds **48** and **53**; their specific rotations at various wavelengths and also the signs of the $[\alpha]_D$ values of other derivatives (cf. Fig. 9) could be interpreted as though (+)-**48** and (−)-**53** (and hence (+)-**45** and (+)-**50** as well as all compounds derived therefrom) had opposite configurations (as shown in Fig. 9).

F. The Absolute Configuration of Metallocenes

As Figures 5–9 show, about 50 optically active metallocene derivatives are now known, whose configurations relative to one another have been established. Determination of the absolute configuration of just one of these compounds would of course suffice as proof of the absolute configurations of all of the compounds cited.

As the frequently mentioned ketone ferroceno[1.2]cyclohexen-1-one-3 [1,2-(α-ketotetramethylene)ferrocene, **8**] occupies a key position, this reference substance and its phenyl derivatives **63** and **74** were chosen for the determination of absolute configuration (41,44,55).

Before the methods employed are discussed (Sect. III-F-2), the configurational notation (nomenclature) of metallocenes will be considered.

1. Configurational Notation

With the elucidation of the absolute configuration of an optically active metallocene derivative the problem of the application of the (*R*)(*S*) nomenclature (21,45) to metallocenes became acute.

a. Based on the concept of planar chirality, we had originally suggested the following application of the sequence rule (53) (cf. Fig. 10).

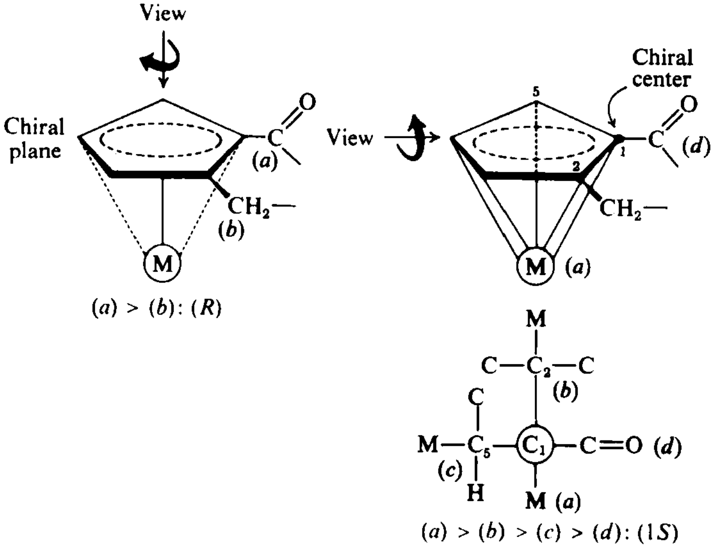


Fig. 10. Application of the sequence rule to chiral metallocenes (8,22).

The observer looks along the principal axis of the molecule (i.e., perpendicular to the plane of paper in the representation chosen here, Fig. 1) so that, in the case of ferrocene derivatives, the more highly substituted ring is directed towards him, whereby the priority of the groups is decisive. The substituents are then, as usual, arranged in decreasing order of priority according to the sequence rule. If more than three groups are present, only the three with highest priority are considered; the choice of symbol (*R*) or (*S*) depends on the resulting direction (clockwise or counterclockwise). If the second ring of a ferrocene derivative is also (asymmetrically) substituted, it is designated with (*R*′) or (*S*′) by the same procedure when it in its turn is directed towards the observer. The dextrorotatory ketone **8** of known absolute configuration (cf. Sect. III-F-2) and all the ferrocenes in Figures 5–9 (with the exception of (−)-**25**) would be designated with the symbol (*R*) according to this nomenclature, while the bisketone (+)-**6** would have the configuration (*R*), (*R*′).

Until recently we used this nomenclature in our publications (41,44,90,91).

b. The Cahn-Ingold-Prelog system has, however, been supplemented and extended recently (22), especially with regard to the terms chiral center and chiral plane (centro and planar chirality).

According to the revised system a chiral center is no longer restricted to compounds with classical tetrahedral configurations, and an asymmetrically substituted carbon atom is only a special case of a chiral center. If the bonds proceeding from the metal atom in a metallocene are arbitrarily regarded as single bonds, then asymmetric substitution of a ring causes all the ring C atoms to become chiral centers and the symbol (*R*) or (*S*) can be assigned to each of them (cf. Fig. 10). Consequently, as a center of chirality has priority before planar chirality, chiral metallocenes are now to be included in the group of centrochiral compounds. In (+)-**8**, four different groups are "bound" to e.g., C atom 1 (which has priority), which is not a classical asymmetric carbon atom. These four groups are arranged as follows (cf. Fig. 10): a = Fe, b = C_2, c = C_5 and d = α-C (C=O), from which the symbol (1*S*), (2*R*), etc., results for the dextrorotatory ketone **8**.

c. If, as mentioned above (Sect. II), the midpoint of the asymmetrically substituted ring is thought of as an imaginary chiral center (cf. the Newman projection, Fig. 3), then the assignment of the stereochemical symbol to α-disubstituted metallocenes in the usual way (21) becomes simple, for (+)-**8** again (*S*). Here, in the case of substituents at 1 and 2, the direction of viewing is unambiguous, namely towards H-4 (H = *d*). On the other hand, β-disubstituted (substituents at 1 and 3 of structure **F**, Fig. 3) and polysubstituted metallocenes cause difficulties, as the observer could look either towards H-2 (between the two groups) or towards H-4 or H-5, and the correct direction would have to be defined by an additional rule.

We shall therefore in the future make use of the nomenclature proposed by Cahn, Ingold, and Prelog (22), which is employed consistently in the present review.

2. *Chemical Methods*

For the chemical determination of the configuration of a ferrocene ("planar") chiral compound (such as **8**), it is necessary to elucidate the absolute configuration of a chiral center which is linked with the configuration of the whole molecule in an unambiguous fashion (23,90).

A suitable compound for this purpose seemed to be the previously mentioned *exo*-carbinol (+)-**9**, which is formed in small quantities along with the epimeric *endo*-carbinol **10** on reduction of (+)-**8** with $LiAlH_4$. *endo*-Carbinols also proved to be perfectly suitable for the elucidation of configuration (15,16). In one such carbinol (**9**) the relative positions of OH and H with respect to the ferrocene nucleus were known, and from a determination of the absolute configuration of the asymmetric carbon atom (carbinol carbon) reliable conclusions concerning the configuration of the metallocene-chiral part of the molecule would necessarily follow.

Of the various methods available for the determination of the configuration of an optically active carbinol (23,90), many were not applicable to the case in hand (41). The ingenious procedure of Horeau (92), based on the kinetic resolution of racemic α-phenylbutyric anhydride (PBA) with an optically active carbinol in pyridine, proved to be very suitable. The direction of rotation of the liberated acid is related to the configuration of the carbinol in question; e.g. dextrorotatory (*S*)-α-phenylbutyric acid indicates the configuration as shown in Figure 11, which usually but not invariably corresponds to the (*R*)-configuration of the carbinol and vice versa (92). As has been shown for numerous examples, this method yields excellent results with high optical yields in the elucidation of configuration of carbinols of the most varied structure. The mechanism of this empirical procedure has been investigated in some detail and the results obtained may also be interpreted theoretically (93).

In order to apply Horeau's method to the present problem, the *exo*-carbinol **9** was required in a pure state. As reduction of **8** affords only moderate yields of **9**, the mixture of epimers (**9** and **10**) obtained from (+)-**8** was converted into (+)-**9** by stereoselective S_N1 hydrolysis of the acetates. Owing to the stability of the intermediate carbonium ion (cf. 50,78,94,95), attack by OH^- takes place almost exclusively from "outside," and pure *exo*-carbinol **9** ($[\alpha]_D$ +130°) is formed.

Reaction of (+)-**9** with racemic PBA in pyridine then afforded (−)-, i.e., (*R*)-α-phenylbutyric acid in 20% optical yield (chemical yield of esterification, 27%). This showed that the asymmetric carbinol carbon atom in (+)-**9** has the (*S*)-configuration, and therefore established the absolute configuration of the dextrorotatory carbinol, of

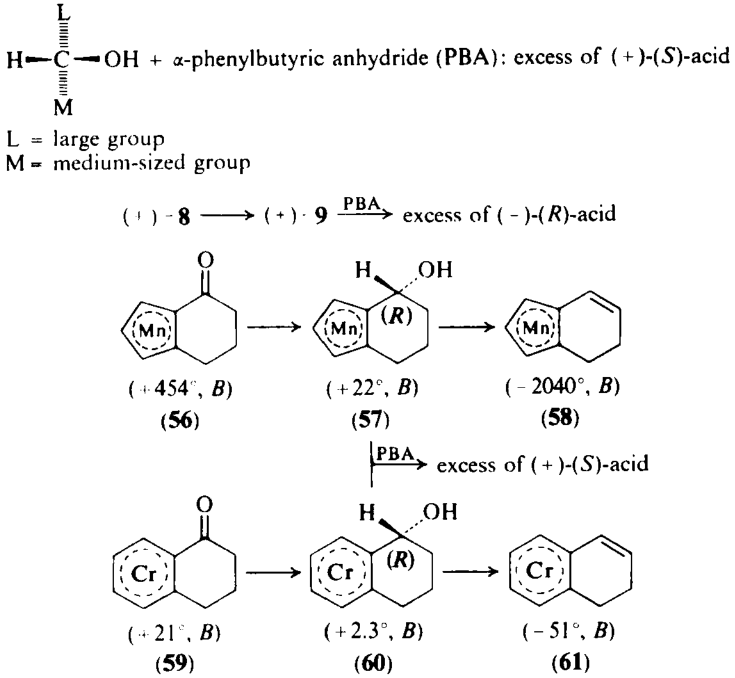


Fig. 11. Application of Horeau's method for determining the absolute configuration of (α-ketotetramethylene)metallocenes (15,16,41).

the (+)-ketone **8**, and of all the compounds derived therefrom. Configurations shown for the compounds in Figures 5–9 are the absolute configurations (cf. Sect. III-F-1 for nomenclature).

Recently, asymmetric reduction of racemic **8** was achieved by partial reaction with the complex from (−)-quinine and lithium aluminum hydride (Červinka's method, 96). After dehydration of the resulting *endo*-carbinol **10**, optically active **11** was obtained ($[\alpha]_D$ −30°) (97). This corresponds to an optical yield of ~1.5%. The sign of the rotation (+) of the carbinol (**10**), however, as follows from (−)-**11**, is in agreement with Červinka's findings, that aryl alkyl ketones with the above-mentioned reducing agent invariably furnish (*R*)-carbinols (96). This result, therefore, is further support for the absolute configuration of (+)-**10**, and consequently for (+)-**8**.

By analogy to the elucidation of the configuration of the bridged ferrocene ketone, (+)-**8**, the absolute configurations of the homoannular bridged cymantrene and benchrotrene derivatives (**56** and **59**, respectively) were also determined (15,16).

The racemic ketone **56** (52) was resolved through its menthydrazone ($[\alpha]_D$ +645°, in benzene) (15). Reduction with sodium borohydride afforded the pure *endo*-carbinol **57**, for which the configuration of the chiral center was shown to be (*R*) by Horeau's procedure: the phenylbutyric acid liberated was dextrorotatory and the optical yield was 52%. The absolute configuration of (+)-**56** is therefore (1*S*), in complete conformity with the ferrocene series. Moreover, the alteration of the direction of rotation on dehydration of the carbinol (+)-**57** to the strongly levorotatory cyclic vinyl compound **58** conformed with that of the corresponding ferrocene derivatives (Fig. 11, Table V).

Analogous results have recently been obtained for the corresponding (1-tetralone)chromiumtricarbonyl [1,2-(α-ketotetramethylene)benchrotrene, **59**] as well (16). The racemic ketone (from 1-tetralone and $Cr(CO)_6$) was partially resolved by chromatography in benzene solution on acetylated cellulose ($[\alpha]_D$ +21°; Table III) since attempts to resolve racemic **59** through the menthydrazone had failed in this case. Reduction of the (+)-ketone with sodium borohydride yielded an *endo*-carbinol **60**, in which the configuration of the asymmetric carbon atom was shown by Horeau's method to be (*R*). Again, the carbinol could be dehydrated to the levorotatory dihydronaphthalenechromiumtricarbonyl (**61**). Thus here as well the dextrorotatory ketone possesses the (1*S*)-configuration.

The absolute chiralities determined for the two ketones **8** and **56** were completely confirmed by further independent chemical methods (15,44). Once again the configuration of the metallocene-(planar) chiral part was traced back to the absolute configuration of a chiral center, which, in this case, was already present in the metallocene derivative subjected to ring closure, whose configuration had previously been determined (cf. Figs. 12 and 13).

Suitable compounds for this purpose were γ-metallocenylphenylbutyric acids, such as **62** and **70** (or **73**), which yield phenyl derivatives of the ring ketones **8** and **56** on ring closure. This had already been established by Tirouflet and co-workers (35,54) in the case of racemic ferrocene derivatives.

Cyclization of e.g. racemic **62** should yield four ketones (**63a** and **b**, **64a** and **b**) consisting of two racemates (mixture of **a** and **b** in each case). In the structures in Figure 12 the stereochemical symbols are given and denoted by *F* or *C* to indicate whether they are assigned to the ferrocene- or centro-chiral part of the molecule, respectively, and to simplify the discussion.

If, instead of the racemate, just one enantiomer is taken as starting material, only two ketones can be formed, e.g., **63b** and **64a** from (*S*)-**62**. These ketones are diastereomeric and should be separable (e.g., by chromatography). If the position of the phenyl group (*exo* or *endo*, cf. **63** and **64**, respectively) in one of these two (optically active) ketones is determined, the absolute configuration of the ferrocene chiral part, $(R)_F$ or $(S)_F$, can be deduced from the previously determined absolute configuration of the chiral center—$(S)_C$ in the example chosen.

Resolution of racemic α-phenyl-γ-ferrocenylbutyric acid (**62**) via the salt with (−)-α-phenethylamine afforded the dextrorotatory acid, whose absolute configuration was determined by oxidation with CrO_3 to (+)-α-phenylglutaric acid (44); the (*S*)-configuration of the latter had previously been proved (98). Resolution of the corresponding cymantrene derivative **70**—likewise via the phenethylamine salts—yielded both antipodes of the acid (cf. Fig. 13), although not in optically pure form (15). On the basis of the ORD curves (at least in the region from 656 to 484 mμ), the (*S*)-configuration is assigned here as well to the (+)-antipode and vice versa (15,99).

In both cases **62** and **70**, cyclization with polyphosphoric acid led to the expected mixture of ketones, which could be separated by

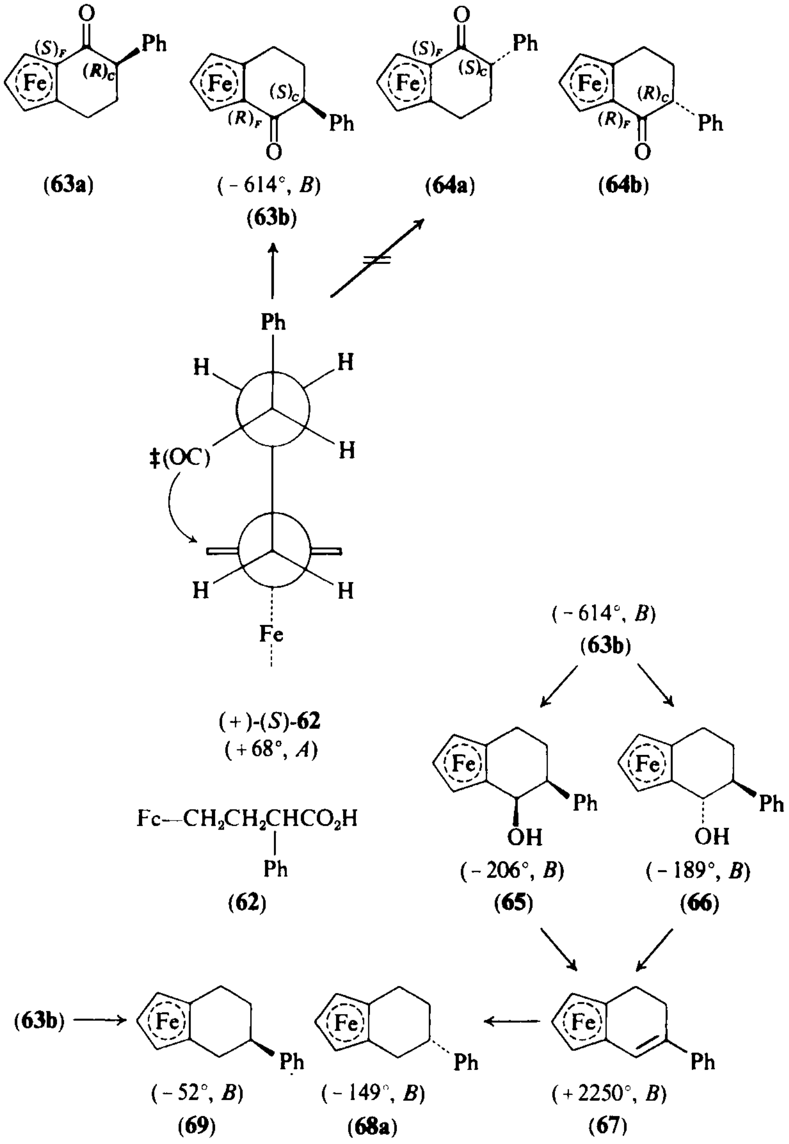


Fig. 12. The absolute configuration of (α-keto-β-phenyltetramethylene)ferrocene (63) and its derivatives (44).

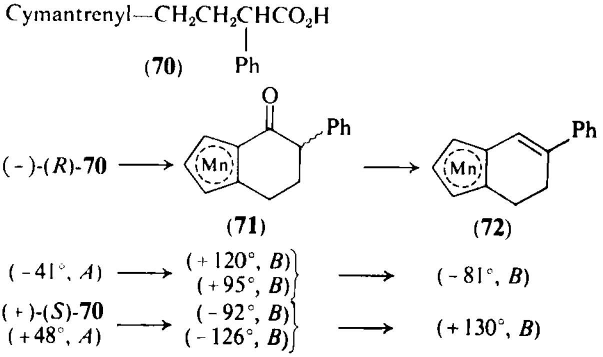


Fig. 13. The absolute configuration of (α-keto-β-phenyltetramethylene)cymantrene (71) and its derivatives (15).

preparative thin-layer chromatography (15,44). From the optically active acids optically active ketones were obtained; in each case, a mixture of the levorotatory ketones from the dextrorotatory enantiomers and vice versa. Under the relatively drastic conditions of cyclization, however, at least partial racemization at the asymmetric center is to be expected; besides, the products formed are likely to depend on their respective thermodynamic stabilities.

In contrast, cyclization of the ferrocene derivative **62** with TFAA proceeded very rapidly, and a homogeneous ketone was formed both from the racemic and from the optically active acid. In the latter case the ketone was strongly levorotatory ($[\alpha]_D$ $-614°$ in benzene). The cymantrene derivative **70** does not cyclize with TFAA owing to the greater inertness of this metallocene towards electrophilic reagents, i.e., owing to its lesser aromaticity (15).

It thus follows that ring closure with TFAA proceeds stereoselectively to a great extent ($>95\%$), which alone suffices for a prediction of the configuration of the levorotatory ketone in question (**63b**), for if it is assumed that the preferred conformation of the transition state (and the transition state is without doubt responsible for the stereochemistry of the final product in such a rapid, i.e., kinetically controlled reaction) is that in which the two large groups (Fc and Ph) are as far apart as possible (cf. Fig. 12), then ring closure in one direction will predominate: (+)-**62** → **63b**. Otherwise (**62** → **64a**), several nonbonded interactions of the groups involved would occur and a considerable energy barrier would have to be surmounted, as is clearly shown with scale models. It follows that the phenyl group in the (−)-ketone **63b** should occupy the *exo* position, and that this compound consequently should have the $(1R)_F$-configuration.

Confirmation of this assumption was obtained as follows. Reduction of **63b** with lithium aluminum hydride yielded a mixture of the two epimeric carbinols (**65**,**66**), in which the epimer ratio (1:18) was even further displaced toward the *endo*-carbinol than in the case of **9** and **10**. Both **65** and **66** could be dehydrated to a strongly dextrorotatory cyclic vinyl compound (ferrocenophenylcyclohexadiene, **67**), thus eliminating the center of chirality. Again we are faced with a significant displacement of rotation accompanying the transition from ketone to vinyl derivative, in line with previous results (cf. **11** and **58**, also Table V).

On catalytic hydrogenation of (+)-**67**, the addition of hydrogen had to occur from "outside" for evident steric reasons, leading to an *endo*-phenyl "hydrocarbon" **68a** ($[\alpha]_D$ −149°). On the other hand, reduction of the levorotatory ketone **63b** both by the Clemmensen method and with lithium aluminum hydride–aluminum chloride resulted in an epimeric "hydrocarbon" **69**, as could be seen from its $[\alpha]_D$ value (−52°). This afforded proof of the configuration of the phenyl group in (−)-**69** (*exo*), and at the same time that (−)-(α-keto-β-phenyltetramethylene)ferrocene (**63b**) has the absolute configuration (1*R*).

The situation with regard to the corresponding cymantrene derivatives (**70**,**71**) was similar (cf. Fig. 13), apart from the much lower selectivity of the ring closure (15), which is due to the reaction conditions employed. Elimination of the chiral center from **71** by reduction with sodium borohydride and dehydration led to the optically active cyclohexadiene derivative **72**. Here as well, the characteristic displacements of the specific rotations occurred. From the mixture of the two epimeric (+)-ketones formed from the (−)-acid **70**, a levorotatory cyclohexadiene derivative **72** was obtained, and vice versa (Fig. 13).

Finally, cyclization of β-phenyl-γ-ferrocenylbutyric acid (**73**), an isomer of **62**, with TFAA (44) again yielded a homogeneous ketone, namely (α-keto-γ-phenyltetramethylene)ferrocene (**74**). In this case, attempts to resolve the racemic acid **73** were unsuccessful, and so the racemic ketone **74** was resolved through its menthydrazone, yielding a levorotatory product. The stereoselective ring closure could be explained by conformational analysis of the transition state, which also made possible a prediction of the configuration of the phenyl group, i.e., *endo* (**74**) (44).

Experimental proof was obtained by conversion into the phenyl "hydrocarbon" **68b** (cf. Fig. 14), which could be correlated with the epimeric products **68a** and **69** on the basis of the sign and magnitude of its specific rotation. The $[\alpha]_D$ value (+150°) characterized **68b** unequivocally as having the configuration given, and therefore the levorotatory ketone **74** possesses the (1*R*)-configuration in analogy to **63b**.

The strongly dextrorotatory phenylcyclohexadiene derivative **75**, intermediate product in the reaction sequence **74** → **68b**, is equally of interest.

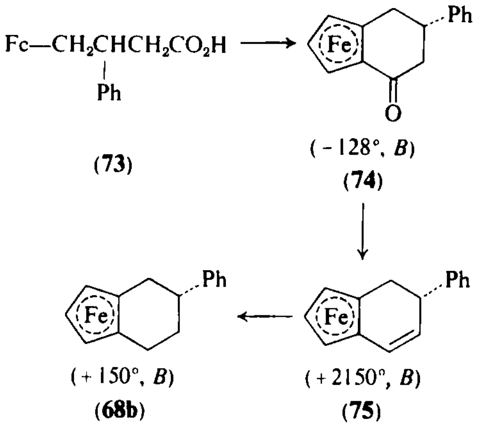


Fig. 14. The absolute configuration of (α-keto-γ-phenyltetramethylene)ferrocene (74) and its derivatives (44).

3. *Physical Methods*

a. X-Ray Method. Since metallocenes contain firmly bound transition metals, they are very suitable for the application of x-ray analysis in the determination of absolute configuration (23,24).

Such investigations are in progress, but no results are at present available.

b. Optical Rotatory Dispersion and Circular Dichroism. *Rotatory Dispersion* (*ORD*). The ORD curves of optically active metallocenes are anomalous, as expected on the grounds of the (active) absorption bands (multiple Cotton effect curves) (23,100). The low intensity, long wavelength absorption maximum in the electronic spectrum of ferrocene (440 mμ) has been ascribed to charge transfer from metal to ring (101, cf. also 102,103). The bands around 320 mμ (325 in ferrocene, 328 in cymantrene, and 318 mμ in benchrotrene) have been assumed to be "characteristic metal–carbon bands" (102). All these bands may be correlated with the corresponding Cotton effects in the ORD and CD curves of metallocenes, although these effects are often much more complex than expected from the electronic absorption spectra (cf. Figs. 15 and 16; especially 15*d* and *e*).

Before the application of ORD as a physical method for the configurational correlation of structurally very similar metallocenes, one should confirm that the group responsible for the chirality of a given compound exerts no noteworthy influence on the "chromophoric moiety" of the achiral parent compound (100,104). Even then difficulties may arise, since compounds with very similar spectra may exhibit quite different ORD curves (e.g., **49** and **54**, Figs. 15*d* and *e*).

The ORD curves of the two isomeric methylbenchrotrenecarboxylic acids (+)-**41** and (−)-**43** (Fig. 15*c*) are very similar but bear a mirror image relationship to each other. The ORD curve of *m*-methoxybenchrotrenecarboxylic acid takes a course very similar to that of **43** (peaks and troughs around 440 and 360 mμ, respectively) (12). Thus the replacement of Me by OMe in **43** has no significant effect on the ORD. Since the electronic spectra of **41** and **43** and of the unmethylated acid (benchrotrenecarboxylic acid) likewise show great similarity, one is justified in assuming opposite chiralities for (+)-**41** and (−)-**43**. Since the absolute configuration of (+)-**41** is (1*S*) (see Sect. III-E-3, Fig. 8), (−)-**43** therefore very probably possesses the chirality (1*R*).

The two isomeric (+)-methylcymantrenecarboxylic acids likewise exhibit very similar electronic spectra and ORD curves (10a). As shown by kinetic resolution (Sect. III-E-3), the dextrorotatory α-isomer has the absolute configuration (1*S*) and hence the same configuration may be attributed to the dextrorotatory β-carboxylic acid.

The correlation of the series of α-substituted mono- and dimethylferrocenes (derivatives of the acids **35** and **45**, respectively, Figs. 8 and 9) was then also possible by ORD (Fig. 15*d*). For this purpose the ferrocenylacetylenes **40** and **49** were employed, since the influence of conformational chirality was here excluded (see Sects. III-E-3 and III-E-4). The electronic spectra of these two acetylenes, as well as of the β-isomer **54** are almost superimposable and are also very similar to the spectrum of ferrocenylacetylene itself. It then follows from the strong resemblance of the ORD curves (Fig. 15*d*) that (+)-**49**, derived from (+)-**45**, has the same configuration as the α-monomethylated ferrocenylacetylene (−)-**40**, derived from (+)-**35**, i.e., (1*S*).

It is noteworthy that the ORD curves of (+)-**35** and of its sodium salt also bear a close resemblance to those of the corresponding acetylene derivatives (**40** and **49**) of the same configuration (1*S*) (59a).

The ORD curve of levorotatory α-methylacetylferrocene, (−)-**37**, on the other hand is very similar in its *shape* to that of the homoannular bridged ketone, (+)-**8** (Fig. 15*a*) (59a). Although both ketones, (+)-**8** and (−)-**37**, have the same configuration (1*S*) the corresponding Cotton effects have opposite signs, which seems to indicate opposite chiralities for the chromophores. This may be explained on the basis of preferred conformations. Whereas the CO group in (+)-**8** is fixed by the fused ring, the (coplanar) acetyl group in (−)-**37** will (because of the steric interference with the adjacent methyl group) obviously point in the "other" direction, i.e., towards the α-methyl group. (Cf. 63 for spectroscopic evidence and Sect. III-F-3-e for further discussion on conformation.)

The molecular amplitudes of the Cotton effects of ketones **8** and **37** on the one hand, and of the carboxylic acid **35** and the acetylene derivative **40** on the other, differ considerably in magnitude (90–120 versus 10) (59a). This may be regarded as strong evidence for the predominance of the conformational asymmetry in the former as compared with the latter (23,89; cf. also Sect. III-E-3).

Relationships analogous to those just discussed for (+)-**8** and (−)-**37** also exist between (−)-**11** and (+)-**30**.

However, no conclusive results were obtained from the ORD curve of the β-isomer, (+)-**54** (Fig. 15*e*) or of the corresponding monomethyl derivative, β-methylferrocenylacetylene, which was obtained recently (59,59a), since in these cases the Cotton effects are too different from those of the α-derivatives **40** and **49**, despite the very similar electronic absorption (Figs. 15*d* and *e*).

Other evidence, however (mainly optical comparison of corresponding derivatives, especially of the vinyl compounds **48** and **53**; cf. Fig. 9 for the specific rotations at various wavelengths) seems to indicate that (+)-**45** (and its derivatives) and (+)-**50** (and its derivatives, including the acetylene **54**) possess opposite configurations; i.e., the configuration (1*R*) could be assigned to the compounds **50**–**55a** (Fig. 9), although with considerable reservation.

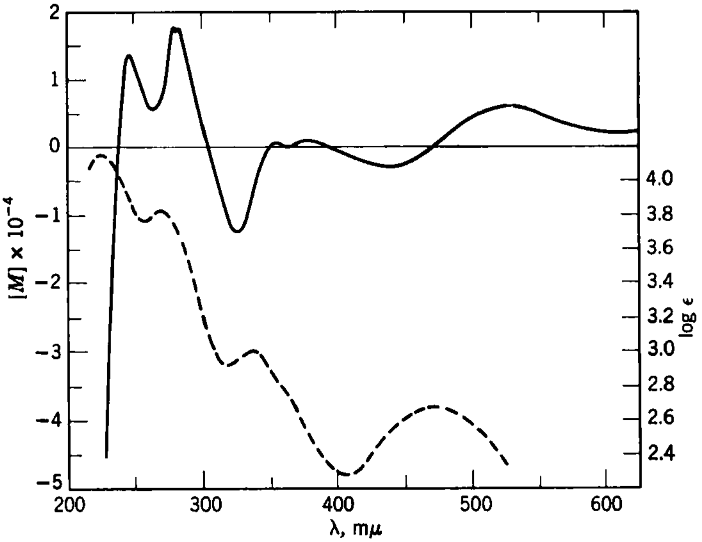


Fig. 15. (*a*) Rotatory dispersion (——) and electronic absorption (---) of (+)-**8** in ethanol (53).

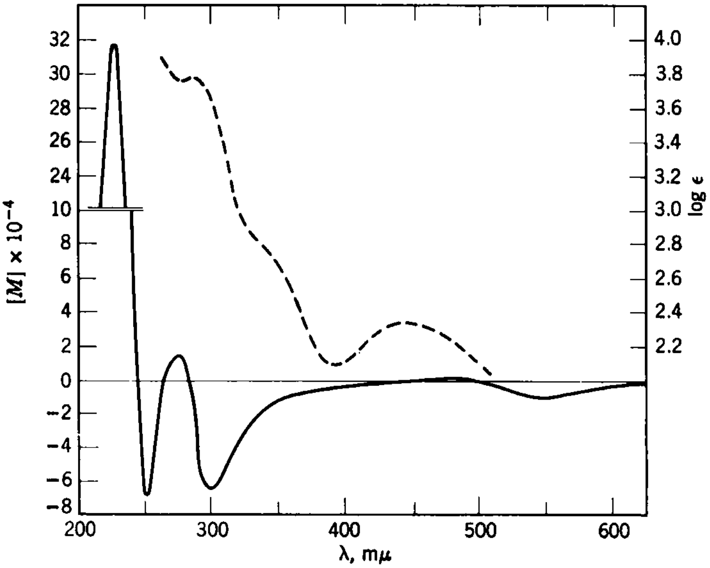


Fig. 15. (*b*) Rotatory dispersion (——) and electronic absorption (---) of (−)-**11** in ethanol (53).

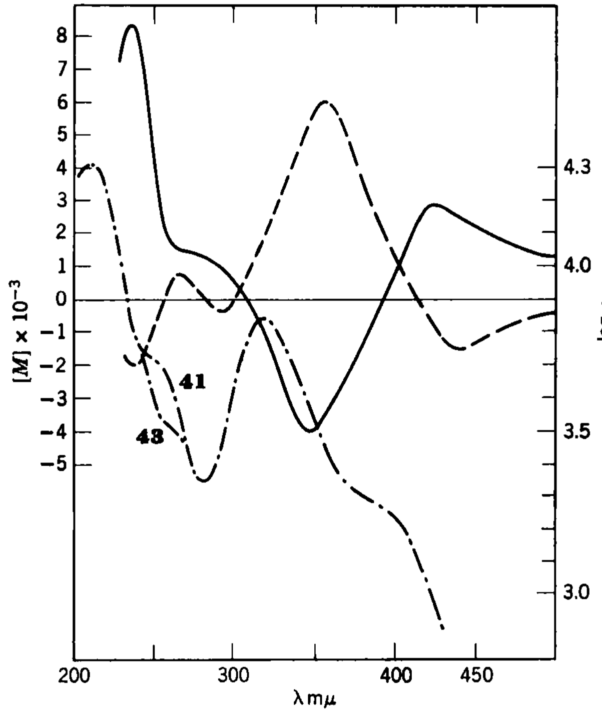


Fig .15. (*c*) Rotatory dispersion and electronic absorption (– • – • – •) of the isomeric methylbenchrotrenecarboxylic acids in methanol. ORD: (+)-**41** (——) and (−)-**43** (– – –) (16).

Hence, the problem of the absolute configuration of β-substituted ferrocenes remains to be solved; unambiguous proof should be gained from any reliable chemical correlation between the α- and the β-series.

Circular Dichroism (*CD*). For the configurative correlation of metallocene ketones of the general type **8**, CD can also be used (Fig. 16). Moreover, the absolute conformation of such homoannular bridged ketones can be deduced from a modified octant rule for cyclohexenones (100,105) on the basis of the sign of the $n \rightarrow \pi^*$ transition (91).

Ferrocene ketones such as **8** or **63** absorb at 470 and 340 mμ (53,91). For the analogous cymantrene compounds (**56**,**71**) the absorption band lies around 335 mμ. Although the $n \rightarrow \pi^*$ band was expected to lie in this region (320–350 mμ) on the basis of comparable derivatives of

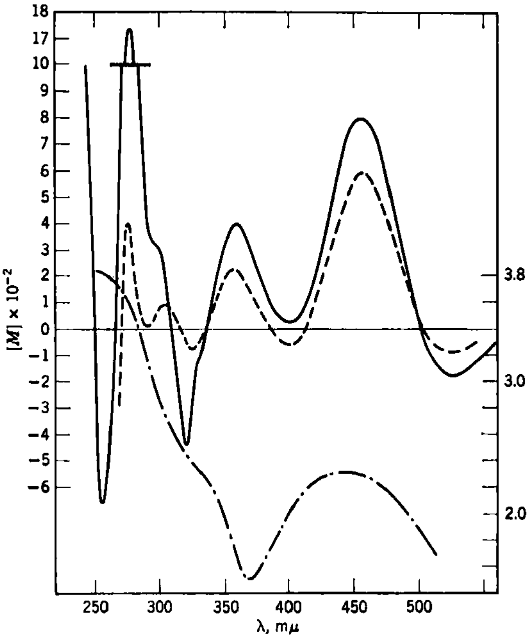


Fig. 15. (*d*) Rotatory dispersion and electronic absorption (–·—·–·) of α-methylferrocenylacetylenes in ethanol. ORD: (−)-**40** (——) and (+)-**49** (– – –) (59a).

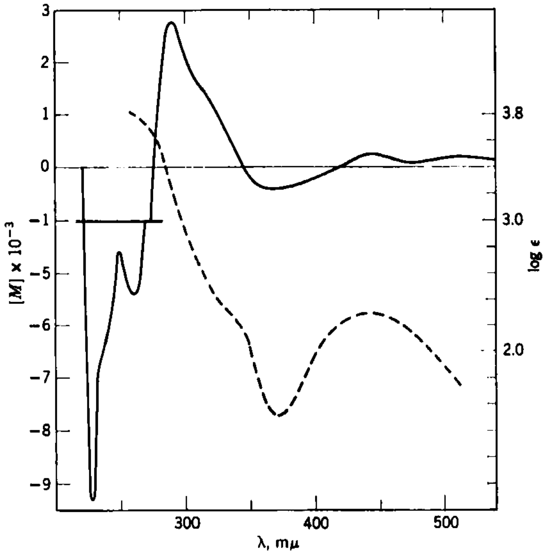


Fig. 15. (*e*) Rotatory dispersion (——) and electronic absorption (– – –) of (+)-β-ethynyldimethylferrocene (**54**) in ethanol (59a).

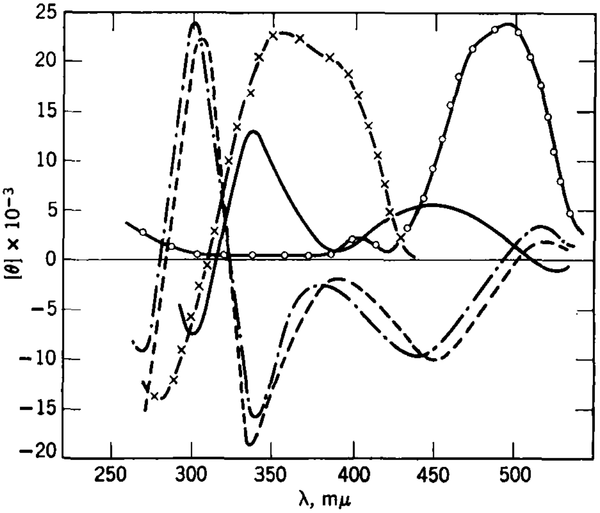


Fig. 16. Circular dichroism of metallocenes. (+)-**8** (——), (−)-**63b** (– – –), (−)-**74** (–·–·–·), (+)-**56** (–×–) and (+)-**67** (–○–) in dioxane (8,44).

similar systems alone (cf. 105), a reliable assignment seemed to be possible by comparison of the CD curves of the ketone **63b** with that of the cyclohexadiene derivative **67** obtained from it (cf. Fig. 12). Only **63b** shows a marked CD at 335 mμ (44,91). Hence the previously mentioned metal–carbon band around 325 mμ, in contrast to the CO-chromophore, is apparently inactive (**63b** vs. **67**, Fig. 16). A further proof of the position of the band in question results from conformational analysis of **74**. In this *endo*-phenyl ketone the phenyl group can occupy the equatorial position only, which locks the carbonyl group in the *exo* position (cf. Fig. 17). Since the absolute configuration is known to be (1*R*) and the conformation is fixed, the sign of the CD of the $n \rightarrow \pi^*$ band follows from the octant projection (105; Fig. 17). The sign agrees with the CD measured for (−)-**74** at 336 mμ: $\Delta\varepsilon \approx -6.0$. The CD curves of other metallocene ketones of known absolute configurations are

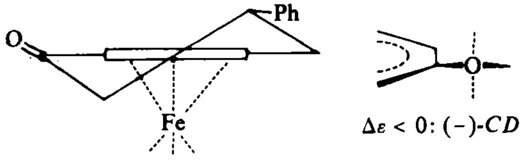


Fig. 17. Conformation and octant projection of (−)-**74** (91,105).

reproduced in Figure 16. A positive CD thus occurs at 340–350 mμ for all dextrorotatory ketones with the configuration (1*S*), and vice versa.

For all these homoannular bridged metallocene ketones (**8**,**56**,**63**,**74**) Snatzke's modified octant rule thus permits assignment, with some probability, of the absolute conformation with the CO group in the *exo* position (cf. Fig. 17) (91).

c. Methods of Calculation. Application of Brewster's semiempirical calculation procedure (89, cf. also 23) provided complete confirmation of the results for the absolute configuration and conformation in the ferrocene series discussed so far. The absolute configurations of the epimeric carbinols (+)-**9** and (+)-**10** were deduced directly from the results of the calculation (i.e., independently of chemical methods; Sect. III-F-2) (91). For the calculation of molecular rotations, such optically active derivatives of 1,2-(α-ketotetramethylene)ferrocene (ferrocenocyclohexene) were chosen in which chiral centers were present in the fused cyclohexene ring in addition to the ferrocene chirality (e.g., **9**,**10**,**65**,**66**,**68**,**69**). The influence of the ferrocene chromophore which absorbs between 440 and 500 mμ (i.e., in the neighborhood of 589 mμ) (102,103), and thus the appearance of a Cotton effect, was cancelled out by restricting the choice to pairs of epimers, since calculations according to Brewster's method would be of doubtful value in the presence of such an effect (89). Agreement between calculated and observed molecular rotations proved to be excellent in all cases, which represents further support for the presumed optical purity of these compounds (cf. Sect. III-D-1). Attention is drawn to the fact that in one case (e.g., **68**,**69**) the calculations were available before the experimental results.

d. Optical Comparison. The fact that Freudenberg's displacement rule is also valid for optically active metallocenes has already been stated repeatedly (cf. Sects. III-E-2 and III-E-3). The reversal of the direction of rotation at 589 mμ which accompanies the conversion of ketones into the corresponding cyclohexadiene derivatives seems highly suitable for the determination of the absolute configuration of such systems, since in all cases strongly negative displacements of the $[\alpha]_D$ values are observed when a (1*S*)-ketone is converted into the cyclohexadiene derivative (and vice versa, cf. Table V).

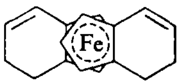
This effect also enabled a statement to be made concerning the absolute configuration of the previously mentioned bis-(α-ketotetra-

TABLE V

Shift in Optical Rotation on Conversion of Metallocenocyclohexenones into Cyclohexadienes

	Cyclohexenone				Cyclohexadiene		
Derivative of	Structure number	Absolute config.	$[\alpha]_D$, deg.	$[M]_D$, deg.	Structure number	$[\alpha]_D$, deg.	$[M]_D$, deg.
Ferrocene	**8**	(1*S*)	+580	+1473	**11**	−2090	−4974
Ferrocene	**6**	(1*S*:1′*S*)	+110	+354	**76**	−320	−928
Ferrocene	**16**	(1*S*)	+430	+1273	**17**	−1320	−3485
Ferrocene	**63b**	(1*R*)	−614	−2026	**67**	+2250	+7065
Ferrocene	**74**	(1*R*)	−128	−422	**75**	+2150	+6751
Cymantrene	**56**	(1*S*)	+454	+1235	**58**	−2040	−5222
Benchrotrene	**59**	(1*S*)	+21	+59	**61**	−51	−135

methylene)ferrocene (**6**), the first tetrasubstituted optically active ferrocene derivative (41). The dextrorotatory enantiomer ($[\alpha]_D$ +110°, optical purity unknown) yielded a levorotatory bisvinyl derivative **76** (Fig. 18) ($[\alpha]_D$ −320°) on reduction (see Sect. III-E-1) and dehydration, indicating that it very probably possesses the configuration (1*S*:1′*S*).



(−320°, *B*)

(**76**)

Figure 18

e. A Rule for the Relationship between Rotation and Configuration. All these results concerning the relative and absolute configurations of metallocenes were summarized in a rule for the relationship between the configuration and the sign of the optical rotation (at 589 mμ) of α-disubstituted metallocenes (73).

This relationship, based on the semiempirical approach of Brewster (89), corresponds to similar relationships in other classes of optically active compounds (89,106), and holds for optically active α-disubstituted metallocenes in all cases known to date.

The rule is applied as follows for metallocenes with conformational chirality (Fig. 19). Of the substituents with conformational chirality,

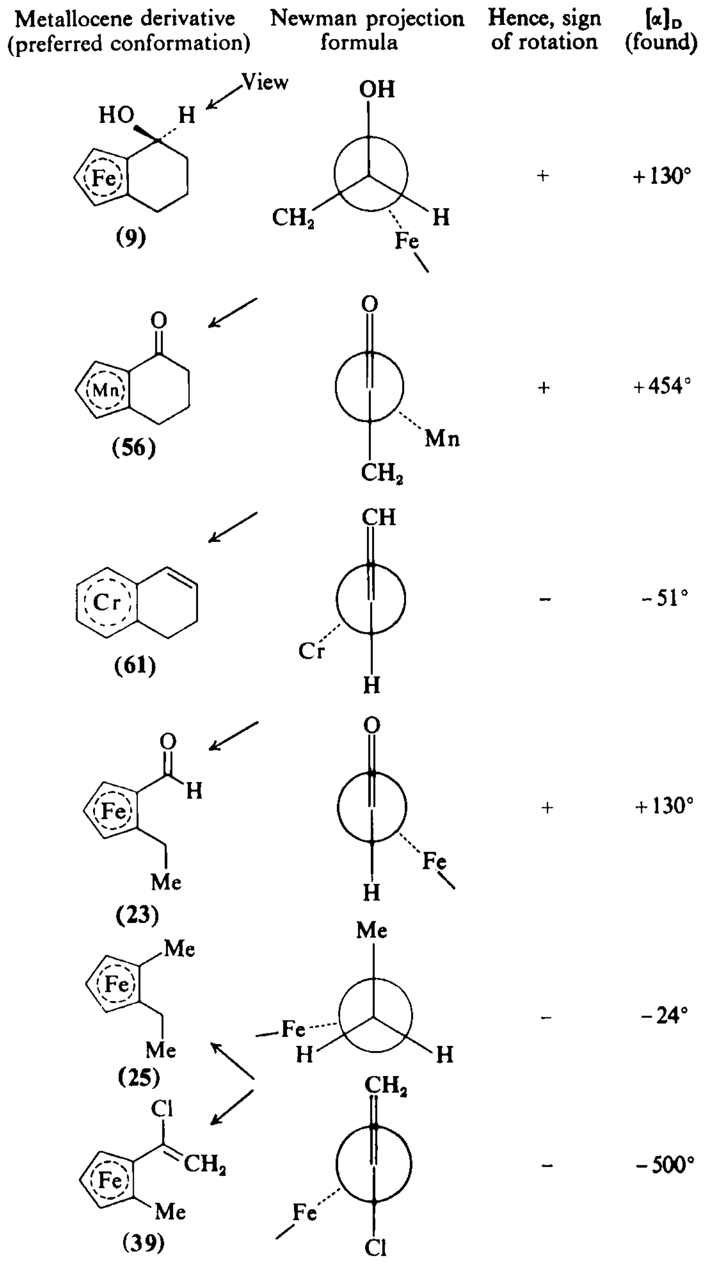


Fig. 19. Application of a rule for correlating the sign of rotation and the configuration of metallocenes (73).

the one with the highest polarizability is selected; the observer then looks along the metallocene–substituent bond from "outside" and rotates the model of the molecule about the axis of this bond until (in the Newman projection) the ligand at the α-atom with the highest polarizability points directly upwards. In this procedure, multiply bound ligands (such as C=O, C=C, C=N) have priority over singly bound ligands. The Newman projection corresponding to the preferred conformation of the compound is chosen for this operation. If the metallocene residue (or its central metal atom) lies to the right of the observer in this arrangement (in the Newman projection formula (+)-syn- or -anticlinal (22) to the reference ligand with the highest polarizability) then the compound is dextrorotatory, and vice versa.

If the sign of $[\alpha]_D$ is known, the absolute configuration (or conformation) can of course be derived.

The preferred conformation of bridged metallocenes (such as **8**,**18**,**34**, etc.) can be deduced unambiguously, and this is usually true for open-chain metallocenes (such as **23**,**25**, or **30**) as well. The position of a conformational equilibrium will depend not only on the relative bulk of the ligands, but also on the solvent, as can be deduced from the often large displacements of rotations in polar and nonpolar solvents. The decisive influence of the conformation on the rotation has already been mentioned in the course of the comparison of bridged and open-chain metallocenes of similar structure (**8** and **37**; **15** and **39**, Figs. 5 and 8).

In cases of doubt it will be advantageous to refer to derivatives of the compound under consideration as well, whereby the displacement rule (Sect. III-F-3-d) can furnish additional information.

The application of the rule for the correlation of direction of rotation and absolute configuration is illustrated in the case of six metallocenes in Figure 19.

IV. CONCLUSIONS AND OUTLOOK

As ample material on the relative and absolute configurations of optically active (primarily α-disubstituted) metallocenes is already available, henceforth the configurational correlation of new active metallocenes, especially with the help of optical methods, will be relatively simple.

This is particularly true for homoannular bridged ketones of the general structure **8**. As the investigations described can be extended to metallocenes other than ferrocene, cymantrene and benchrotrene, a new and broad field stands open to stereochemical as well as metallocene research.

The situation is the same in the case of the β- and polysubstituted metallocenes, which have hitherto been only sketchily investigated (see, however, 59a). In particular, a reliable chemical correlation of the α- and β-substituted compounds is still lacking, as is the independent determination of the absolute configuration of at least one optically active metallocene by x-ray crystallography.

When still more experimental material becomes available, all the experimental results will without doubt be capable of theoretical interpretation; the first steps in this direction have already been taken (73,91).

Numerous aspects of this new and flourishing chapter of stereochemistry are of interest to diverse branches of chemical science—from purely preparative organic chemistry to theoretical studies—and one may await further developments with eagerness.

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Recent Applications of Optical Rotatory Dispersion and Optical Circular Dichroism in Organic Chemistry

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I. INTRODUCTION

Albeit optical activity has been known for a long time (1), the ultraviolet and infrared methods were the first spectroscopic tools to be used extensively in organic chemistry. It is only recently that optical rotatory dispersion and the phenomenologically related optical circular dichroism have drawn the attention of the chemist and biochemist and found major applications in analytical, structural, and stereochemical research problems. Optical rotatory dispersion and circular dichroism are indeed important new physical tools, since they can help us understand broad subjects and aspects upon which several areas of knowledge impinge. The impact of these methods in modern science is very great, covering structural and stereochemical problems in organic chemistry (e.g., in the field of natural products), conformational problems in biochemistry (i.e., helicity of protein chains), and steric aspects of inorganic and organometallic compounds (such as ligands), as well as other fundamental problems like the discovery of optical activity in outer space (e.g., meteorites, etc.). These optical techniques are now at an evolutionary stage, where the examination of the Cotton effect of almost every chromophore, not previously investigated, constitutes an important advance in stereochemistry. However, research in the fields of optical rotatory dispersion and circular dichroism does face impediments, two of which are of particular consequence. The first is a technical one. The wavelength range which can presently be investigated comprises the 700–180 mμ region, but many chromophores absorb below 180 mμ. Second and much more important, even when the optically active chromophore can be examined with the available instruments, structural and stereochemical conclusions are sometimes not easy to draw due to lack of theoretical knowledge (e.g., the Cotton effect associated with $\pi \rightarrow \pi^*$ transition of α,β-unsaturated ketones). Hence, there is an urgent need for closer collaboration between organic chemists, physical chemists, and physicists, which hopefully will lead to conclusions, generalizations, and perhaps new rules establishing safer correlations between the configuration of a center or the conformation of a molecule and the sign and intensity of the Cotton effect(s) (1–4) exhibited by a given chromophore.

Since the application of optical rotatory dispersion and circular dichroism techniques to organic chemical problems has been the subject of several books (1–5) and numerous review articles (6–12), it seems most appropriate in this chapter to focus attention on limited topics and recent achievements in these fields. The first part of this chapter will deal briefly with extensions of the octant rule. The second part is a discussion of the observations and results obtained with aromatic chromophores. The choice of this topic is justified by the fundamental impact of the octant rule (13) from both the theoretical and experimental points of view, and also by the importance of the aromatic chromophore in organic chemistry.

II. THE OCTANT RULE AND ITS EXTENSIONS

A. The Octant Rule

For a given substance the variation of optical activity with wavelength leads to an optical rotatory dispersion curve. For a compound devoid of chromophores, the optical activity progressively decreases as the wavelength increases. A plain positive or negative dispersion curve is obtained (1,2,4). For a compound presenting one or several optically active absorption bands within the spectral range under experimental observation, the rotatory dispersion curve exhibits Cotton effects, i.e., the curve shows one or several peaks and troughs (extrema). The intensity of the Cotton effect of a rotatory dispersion curve, called "molecular amplitude (*a*)" is defined as the difference between the molecular rotation at the extremum (peak or trough) of longer wavelength $[\Phi]_1$ and the molecular rotation at the extremum of shorter wavelength $[\Phi]_2$, divided by one hundred (2,4).

Moreover, when an optically active medium is traversed by plane-polarized light in the spectral range where an optically active chromophore absorbs, not only does the plane of polarization rotate, but the resulting light is also elliptically polarized; this medium is said to exhibit circular dichroism (i.e., ε_L is different from ε_R) (1,3,4). The units currently being used are the differential dichroic absorption ($\Delta\varepsilon = \varepsilon_L - \varepsilon_R$) and the molecular ellipticity ($[\Theta] = 3300\Delta\varepsilon$). The octant rule, which constitutes a major achievement in the field of optical activity (13–16), was the culmination of numerous studies, most of them by Djerassi and co-workers (2,17). It has been considered from both theoretical (13–16) and experimental (18) aspects.

Since we shall deal here with the optical properties of optically active chromophores, it seems appropriate to recall that they can be classified into two extreme types (15): the inherently dissymmetric chromophores and the inherently symmetric, but asymmetrically perturbed, chromophores. The optical activity of compounds belonging to the first group is inherent in the geometry of the chromophore, as in the twisted biphenyls (*vide infra*). The optical activity of compounds belonging to the second class is induced in the chromophore by its environment, e.g., in the carbonyl function situated in an asymmetric vicinity (*vide infra*) (15). The optical rotatory dispersion and circular dichroic properties of a given chromophore are both reflections of the optical properties of an absorption band, and have been discussed thoroughly in recent books (2–5).

The octant rule expresses the relationship between the absolute configuration or conformation of the perturbing environment, and the sign and, semiquantitatively, the intensity of the Cotton effect associated with the carbonyl $n \rightarrow \pi^*$ transition. The rule states (13) that three nodal planes of the n and π^* orbitals of the carbonyl group, in the chair conformation of the cyclohexanone ring, divide the molecular environment of the carbonyl into eight octants: four back octants and four front octants (see Fig. 1). A group or atom, other than fluorine [because

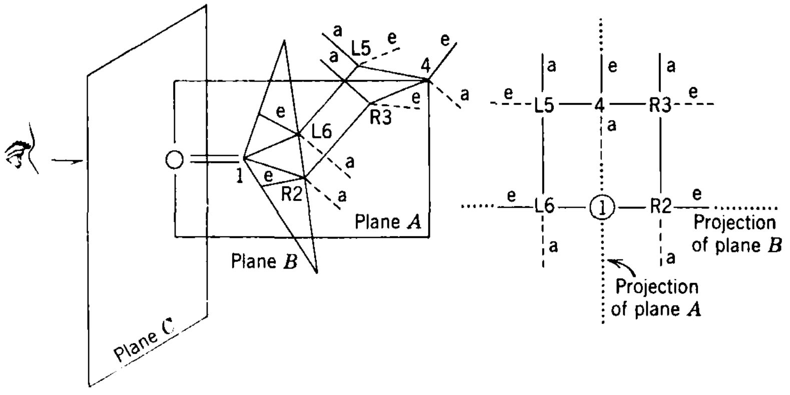
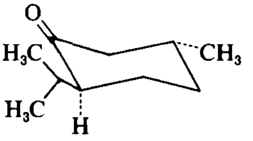


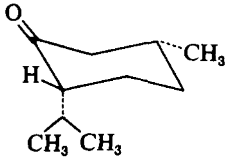
Fig. 1. The octant rule for cyclohexanone in the chair conformation. Three planes, called *A*, *B*, and *C*, create eight octants. The projection, shown on the right, indicates the spatial orientation of the different substituents with respect to the carbonyl function (1). Symbols: a = axial, e = equatorial, L = left, R = right. (Adapted from C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill, 1960.)

of the position of fluorine in the atomic refractivity and specific rotativity scale (19)], placed in the upper-left or lower-right rear octant, relative to an observer looking at the molecule in the O═C direction, induces a positive Cotton effect in the 300-mμ carbonyl absorption. A negative Cotton effect is produced by the corresponding substitution in the upper-right or lower-left back octant (13).

This rule has been successfully applied to aliphatic optically active ketones and aldehydes and to mono- and polycyclic keto derivatives belonging to all classes of natural products, as well as to synthetic optically active substances (2,4,18).



(1)



(2)

An illustration of the application of the octant rule to configurational problems is given in Figure 2. In the case of the monoterpene ketone (−)-menthone (**1**) the equatorially oriented isopropyl grouping, next to the carbonyl, is roughly situated in a nodal plane, and thus has no major action on the Cotton effect (2). The equatorially oriented methyl group falls into a positive octant. Since the size of this group is rather small, but mainly since this alkyl group is far away from the carbonyl chromophore, the perturbation exerted by this substituent on the $n \rightarrow \pi^*$ transition of the ketone is weak. Hence, (−)-menthone (**1**) exhibits a weak positive Cotton effect. Although this monoterpene has a negative rotation at 589 mμ, its Cotton effect is positive. Hence (−)-menthone (**1**) constitutes a clear example for which safer stereochemical conclusions can be drawn from the optical rotatory dispersion curve than from the specific or molecular rotation at the sodium D line. Thermal or base isomerization of (−)-menthone (**1**) affords (+)-isomenthone (**2**). In this compound the isopropyl group, axially oriented, is situated on the right side of the carbonyl. This alkyl substituent falls into a positive octant, thus substantially increasing the positive Cotton effect, as indicated in Figure 2.

Apart from configurational aspects, the octant rule will also give information about the conformation adopted by a carbonyl-containing

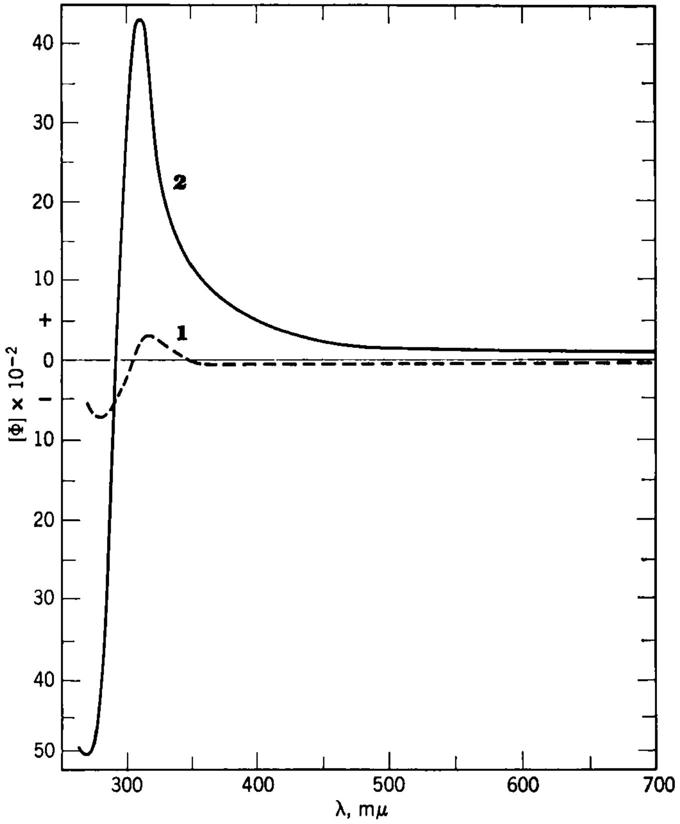


Fig. 2. Positive optical rotatory dispersion curves of (−)-menthone (**1**) and (+)-isomenthone (**2**). [Modified from C. Djerassi, *Proc. Chem. Soc.*, **1964**, 314.]

ring or chain in an optically active environment (2–4,13). Recently, Tai and Allinger (20) derived a theory, based on the one-electron approximation and utilizing the perturbation method, whereby the amplitude of the Cotton effect exhibited by a ketone may be calculated quantitatively. The optical rotatory dispersion properties were theoretically determined for a number of boat conformations which have not been experimentally accessible for study (20). Other recent theoretical considerations (21) support the octant rule for substituents lying in back octants. As far as the front octants are concerned, it has been shown (22) that the one-electron theory predicts for some models an octant rule, others a quadrant rule, depending on the influence of the substituents and on the symmetry of mixing orbitals. In fact in the case of the evaluation of the optical activity of ketones perturbed in front octants it has been suggested (22) that one should consider the superposition of an octant rule and a quadrant rule.

B. The Unsaturated Keto Chromophore

Modifications of the octant rule have been proposed for the $n \rightarrow \pi^*$ band of α,β-unsaturated ketones (23–25). If these propositions seem to account for some experimental data, one should remember that theoretical considerations of the α,β-ethylenic keto chromophore indicate that the electronic pattern of such a system is rather complicated, so that extreme caution should be used before extending the octant rule to α,β-unsaturated chromophores (26).

In the case of β,γ-unsaturated ketones the situation is rather different. It is known that β,γ-unsaturated ketones often exhibit abnormally high ultraviolet extinction coefficients in the 300 mμ region. In order to account for the exaltation of the 295-mμ $n \rightarrow \pi^*$ band in substituted phenylacetones, it was suggested (27) that interaction between carbonyl and phenyl groups takes place directly through space. This interpretation, recognized to be essentially correct, has been further developed by several investigators (28).

According to Labhart and Wagnière (29) in β,γ-unsaturated ketones having the appropriate molecular geometry, the nonbonding n electrons on carbonyl oxygen interact with the π-electrons of the homoconjugated ethylene–carbonyl π-system. It follows that the forbidden $n \rightarrow \pi^*$ transition borrows intensity from the allowed $\pi \rightarrow \pi^*$ transition. Accordingly, the extinction coefficient of the ultraviolet 300 mμ band is enhanced. Furthermore, several authors have remarked that spectroscopic interactions between a carbonyl group and a β,γ-double bond are sometimes accompanied by high optical activity (28,30–33). Recently, Mislow, Moscowitz, and Djerassi (34) formulated the idea that the essential β,γ-unsaturated carbonyl system constitutes an inherently dissymmetric chromophore (15) leading to a modification of the octant rule (13) for this system.

These investigators suggested that the chirality (helicity or sense of skew) of the β,γ-unsaturated keto chromophore may be discussed in

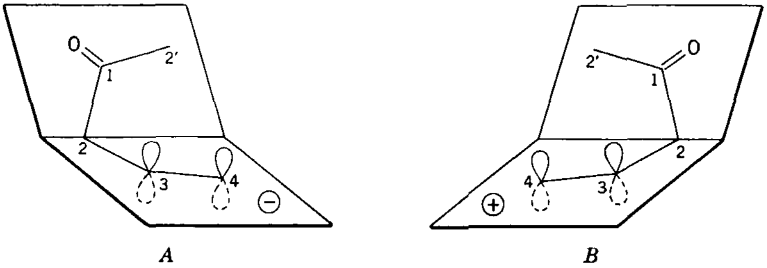


Fig. 3. Schematic representation of the enantiomeric chromophores associated with dissymmetric β,γ-unsaturated ketones. [Adapted from A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).]

terms of the geometric representation shown in Figure 3. Two planes are defined by $C'_2\text{—}\overset{O}{\overset{/\!/}{C_1}}\text{——}C_2$ and $C_2\text{—}C_3\text{—}C_4$ portions of the chromophore which intersect at a dihedral angle greater than 90° (usually about 120° in rigid structures). As indicated in Figure 3, the arrangement $C'_2\text{—}\overset{O}{\overset{/\!/}{C_1}}\text{——}C_2\text{—}C_3\text{—}C_4$ assumes one of two enantiomeric conformations, one giving rise to (*A*) a negative and the other to (*B*) a positive Cotton effect (34).

Several applications of this extension of the octant rule (13) to β,γ-unsaturated systems have already been reported in the chemical literature (4,28–35). Some new examples will be discussed in Section III.

In summary, one can say that the $n \rightarrow \pi^*$ Cotton effects of nonconjugated ketones are low (for example in saturated carbonyls), intermediate (e.g., in axial α-haloketones, cyclopentanones, etc.), or high (as in some β,γ-unsaturated ketones), depending on the extent to which the asymmetrically perturbing orbitals mix with the orbitals of the carbonyl group. The asymmetrically perturbed symmetric chromophore may hence be considered at one end of the scale, while the inherently dissymmetric chromophore is at the other.

C. Cotton Effect of Lactones

Klyne and his collaborators (36) have undertaken an extensive study of the optical rotatory dispersion properties of numerous lactones.

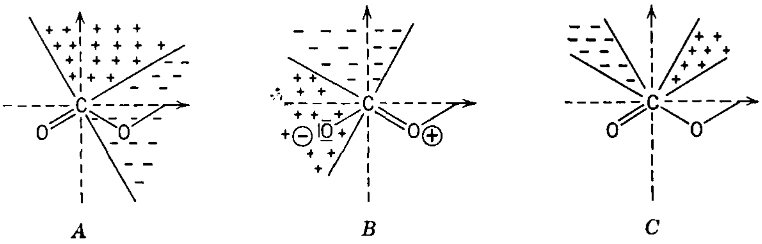
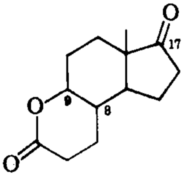


Fig. 4. The lactone sector rule. [Modified from J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, **1965**, 7211.]

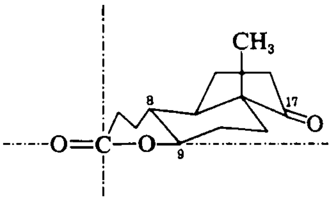
This work has led to a lactone sector rule, and is based on the assumption that the lactone group may be considered to be roughly planar (37). This rule suggests that the space around the lactone group may be divided into sectors by means of planes meeting at the carboxyl carbon atom. From the available data it has been shown (36) that the signs used in the ketone octant rule (13) must be reversed for lactone sectors. Hence, atoms or groups lying in the back upper-right and lower-left sectors make positive contributions to the Cotton effect, whereas atoms situated in the back upper-left and lower-right sectors contribute negatively to the Cotton effect.

According to a semiquantitative treatment, Klyne (36) proposes that both carbon–oxygen bonds of a lactone have some double-bond character. Each carbon–oxygen bond of the lactone group is considered in turn as a double bond, and the signs of the contributions made by the substituents in different octants are allocated according to the octant rule (13). If diagrams *A* and *B* shown in Figure 4 are superimposed as in *C*, the signs of the contributions in some sectors cancel in varying degrees, while in other sectors the contributions reinforce one another leading, on balance, to a positive contribution in the back upper-right sector, and a negative contribution in the back upper-left sector, as shown in Figure 4 (36). Hence, in order to predict the sign of the Cotton effect associated with a lactone group it is necessary to consider two views of each molecule (see Fig. 4) (36).

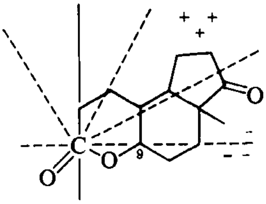
An example of the above proposition is posed by 10-oxa-des-A-androstane-5,17-dione (**3**) (36). This compound contains two optically active chromophores (i.e., the lactone and 17-keto groups) and the corresponding Cotton effects can be observed in its rotatory dispersion curve (36). This substance exhibits a positive Cotton effect for the 17-ketone (ca. 300 mμ), and a negative curve with an inflection at $[\Phi]_{227} = -5250°$, in the region of the carboxyl absorption. This is in accordance with the prediction of the sector rule, as shown in structures **3a** and **3b** (36).



(3)



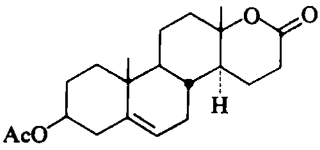
(3a)



(3b)

Different stereochemical types of normal and bridged ring lactones have been examined in terms of the lactone sector rule, and generally the experimental Cotton effect was found to be in agreement with the sector rule (36). Hence this rule seems attractive, since it explains the Cotton effect exhibited by many optically active lactones. However, the important class of carbohydrate lactones does not follow the sector rule. Okuda et al. (39) have interpreted the Cotton effects of some carbohydrate lactones in terms of the ketone octant rule (13), considering mainly the effect of a hydroxyl group adjacent to the lactone carbonyl. Moreover, Wolf (38) has found some exceptions to the sector rule.

Figure 5 shows the optical rotatory dispersion and circular dichroism curves of the unsaturated 17-keto-17*a*-oxa-*D*-homosteroid (**4**) (38). The positive Cotton effect associated with the δ-lactone chromophore is clearly apparent on the circular dichroism curve. The sector rule (36) predicts a negative Cotton effect for the lactone in **4**, because most of the skeleton falls into the upper-left sector. Since the experimental Cotton effect is of opposite sign, another factor had to be taken into consideration (38). Incidentally, Figure 5 clearly shows that the rotatory dispersion curve of **4** is strongly affected by the background rotations (skeleton effect) (4).



(4)

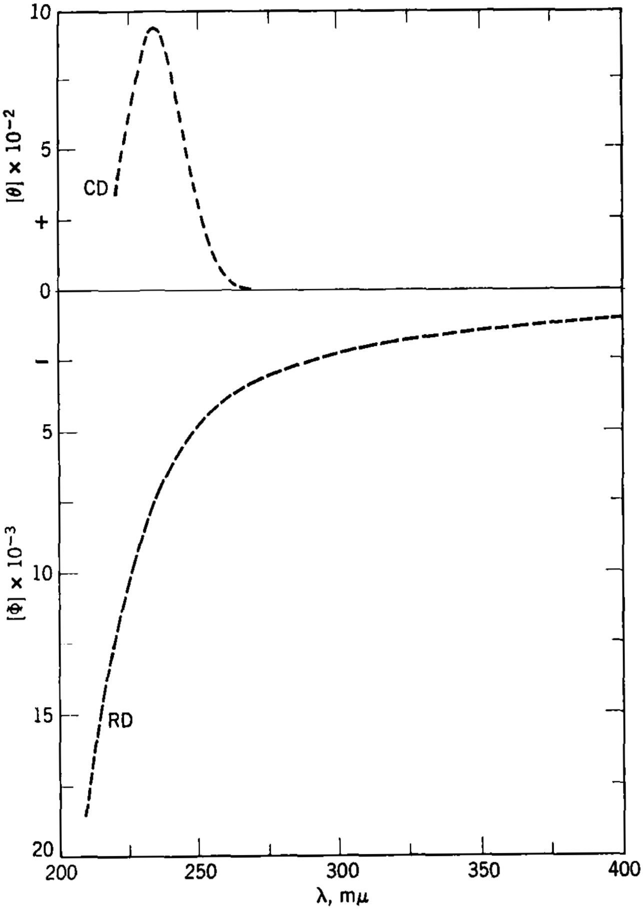


Fig. 5. Rotatory dispersion (RD) and circular dichroism (CD) curves of 3*β*-hydroxy-17-keto-17*a*-oxa-*D*-homo-androst-5-en-acetate (4) (38).

More recently, Wolf (40) investigated the Cotton effect exhibited by several other optically active δ-lactones. The main conclusion drawn from this work is that the optical properties associated with the lactone chromophore seem to depend on the conformation of the δ-lactone ring. Hence, if the chirality of the lactone ring can be established, the sign of its Cotton effect can be deduced. Conversely, from the sign of the

Cotton effect, one can ascertain the conformation of the ring system (40).

X-ray crystallography (37) gives information about the conformation of a rigid molecule (crystalline), while optical rotatory dispersion and circular dichroism data are obtained in solution; i.e. the conformation of a cyclic system is not necessarily the same when examined by these various techniques. This seems particularly true for δ-lactones.

If Wolf's observations can be generalized, one might have a way to interpret the Cotton effect exhibited by the lactones pertaining to the carbohydrate series, and hopefully one will find a sound explanation and interpretation for the Hudson lactone rule (41).

D. Episulfides and Other Sulfur-Containing Chromophores

Another class of extensively studied compounds is the episulfides. Spectroscopic measurements with simple episulfides have shown the existence of a low intensity absorption maximum in the 260-mμ region, which is similar to the $n \rightarrow \pi^*$ absorption of the carbonyl chromophore (42). Djerassi, Kuriyama, Takeda, and their collaborators (43), taking advantage of these favorable spectroscopic properties, have undertaken an extensive optical rotatory dispersion and circular dichroism study of steroidal episulfides. Cookson, McGhie, and co-workers (44) confirmed these findings and extended their observations to other such derivatives. The circular dichroism molecular ellipticity for various episulfides situated in different locations of the steroid and lanostane molecules is listed in Table I (43–45).

From these data it is apparent that in some cases either the sign or the rotational strength, or both parameters, can be utilized for differentiating between the position and/or configuration of the episulfide function in a given molecule. From a theoretical point of view, it should be noted that the isolated episulfide group, like the isolated carbonyl function, represents a type of chromophore classified as "inherently symmetric" (4,15). Hence, the observed Cotton effect results only from the asymmetry induced in the episulfide group by the rest of the molecule. Furthermore, whereas the magnetic dipole moment of an $n \rightarrow \pi^*$ transition is directed along the internuclear axis (e.g., C=S in a thione), it may be at right angles in an $n \rightarrow \sigma^*$ transition, as in a sulfide. Cookson et al. (44) have discussed the shape of episulfide orbitals and the conformational factors responsible for the Cotton effect associated with some such compounds. The dependence of the sign and the

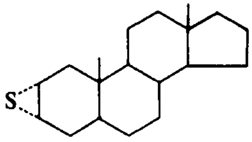
TABLE I

Cotton Effects Exhibited by Episulfides in Some Steroids and Triterpenes

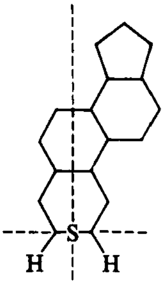
Compound	Name	Circular dichroism molecular ellipticity
a	17β-Hydroxy-androstan-2α,3α-episulfide	$[\Theta]_{269} = -5990$
b	Cholestan-2α,3α-episulfide	$[\Theta]_{268} = -3840$
c	Cholestan-2β,3β-episulfide	$[\Theta]_{264} = +\ 630$
d	Lanostan-2α,3α-episulfide	$[\Theta]_{267} = -6530$
e	Lanostan-2β,3β-episulfide	$[\Theta]_{265} = +1910$
f	Lanost-8-en-2α,3α-episulfide	$[\Theta]_{265} = -5250$
g	Cholestan-3α,4α-episulfide	$[\Theta]_{267} = +4600$
h	17β-Acetoxy-androstan-3β,4β-episulfide	$[\Theta]_{266} = +\ 325$
i	3β-Hydroxy-cholestan-5α,6α-episulfide	$[\Theta]_{272} = +6680$
j	3β-Hydroxy-cholestan-5β,6β-episulfide	$[\Theta]_{268} = -4460$
k	Cholestan-5β,6β-episulfide	$[\Theta]_{267} = -4850$
l	3β,20β-Dihydroxy-5α-pregnan-11α,12α-episulfide	$[\Theta]_{267} = +4060$
m	3β,20β-Dihydroxy-5α-pregnan-11β,12β-episulfide	$[\Theta]_{261} = +3460$
n	3β-Acetoxy-5α-androstan-16α,17α-episulfide	$[\Theta]_{264} = +\ 700$
o	3β-Acetoxy-5α-androstan-16β,17β-episulfide	$[\Theta]_{268} = +5370$

magnitude of the rotatory power associated with the $n \rightarrow \sigma^*$ absorption of episulfides on the stereochemistry of dissymmetric substituents has been tentatively analyzed by these authors, who emphasize that this function has no conformational freedom. However, the episulfide group presents the complications of two possible σ^* orbitals, each with three nodes not quite at right angles to the straight line between the carbon and sulfur atoms (44).

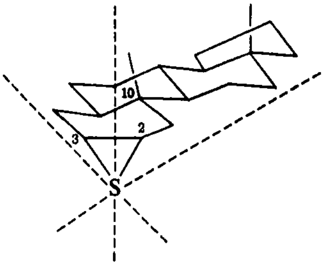
Kuriyama et al. (45) propose a sector rule which explains both the sign and magnitude of the $n \rightarrow \sigma^*$ Cotton effect of episulfides. The sector rule for episulfides is illustrated in Figure 6. This proposition, which results from theoretical calculations, shows the sign of contribution made by atoms or groupings located in different sectors. One has to



(5)



(5a)



(5b)

consider two views of each molecule in order to predict the sign of its Cotton effect, *in extenso* (*1*) the view along the bisectrix of the C–S–C angle, and (*2*) the view of the molecule from above, projected on the plane of the episulfide ring, as shown in structures **5a** and **5b**. On the one hand, when the molecule is viewed along the bisectrix of the C–S–C angle, it lies almost entirely in the back upper sector (**5a**) and on the other hand, the projection (**5b**) shows that all atoms, except carbon atoms 4, 5, 6, and 7, lie in the region of negative contribution. This is in agreement with the experimental observation, since androstan-2α,3α-episulfide (compound a of Table I) exhibits a negative Cotton effect ($a = -70$; $[\Theta]_{269} = -5990$). The same sector rule was proposed for oxathiolanes (45).

In cyclic dithio- and trithiocarbonates, if the plane formed by the two-ring heteroatoms and the carbon atom of the thiocarbonyl group is looked at from the thiocarbonyl sulfur atom through its carbon atom,

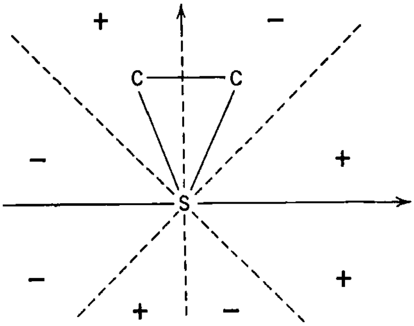
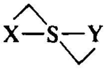
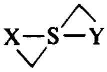


Fig. 6. The sector rule for the $n \rightarrow \sigma^*$ Cotton effect of episulfides (45).

the signs of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects will result from the chirality of the chromophoric system (45,46). This is summarized in Table II.

TABLE II

Cotton Effect of Dithio- and Trithiocarbonates

Chirality	Cotton effect	
	$n \rightarrow \pi^*$ Transition	$\pi \rightarrow \pi^*$ Transition
	Negative	Positive
	Positive	Negative

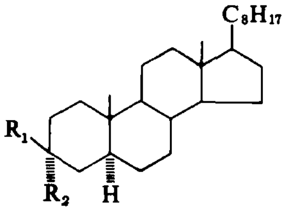
E. Azides

Djerassi, Moscowitz, Ponsold, and Steiner (47a) have undertaken an analysis of the relevant orbitals involved in 280–290 mμ transition of azides. From this study an octant rule for the azide chromophore has been proposed which accounts for the Cotton effects experimentally observed.

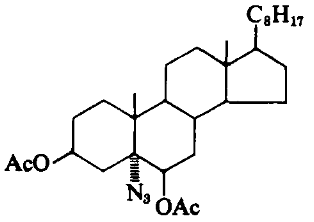
Alkyl azides exhibit a weak transition in the vicinity of 280–290 mμ (47). This transition is roughly attributed (47b) to the promotion of an electron from a nonbonding $2p_y$ orbital situated mainly on the nitrogen atom N_1 concerned with bonding to the alkyl group, to an antibonding π_x^* orbital associated principally with $2p_x$ atomic orbitals from the remaining two nitrogen atoms (N_2, N_3).

As in the case of the saturated ketones (13) only two of the surfaces specifying the "octants" are well-defined in terms of symmetry (47a). In order to determine the sign associated with a particular octant, it is convenient to look at the chromophore along the N_3–N_2–N_1 axis from N_3 towards N_1, with the bond specifying the lone pair of electrons on N_1 lying in a vertical plane, as shown in Figure 7 (47a). As a result, the signs of the azide octants are the same as those of the carbonyl octants (see Fig. 1). This results from the fact that the analogous viewpoint for C=O would be along the C—O bond from the carbon atom towards the oxygen atom, with the carbonyl group rotated through 90° about the C—O axis from its normal orientation for application of the octant rule (13). This corresponds to a double change of signs, which is equivalent to no change at all (47a).

The rotational strength ($R_k = \mu_e^k \mu_m^k$) (2,4,15) of the azide chromophore is considerably weaker than that of the carbonyl group (47a). For example, the molecular ellipticity exhibited by 3α-azido-5α-cholestane [**6a**; $[\Theta]_{290} = +200\,(25°)$; $[\Theta]_{292} = +360\,(-192°)$] is rather weak. Nevertheless the sign of the Cotton effect is opposite in the 3α-isomer (**6a**) when compared to its 3β-isomer (**6b**; $[\Theta]_{282} = -233$) (47a), in agreement with the extension of the octant rule for azides. Among the various azides examined so far, 5α-azido-3β,6β-diacetoxycholestane (**7**; $[\Theta]_{287} = -2484$) exhibited the most intense Cotton effect (47a).



(**6a**) $R_1 = H$; $R_2 = N_3$
(**6b**) $R_1 = N_3$; $R_2 = H$



(**7**)

Sensu stricto the helicity rule of skewed dienes is not an extension of the octant rule. Hence it will only be mentioned briefly in Section III-B-3-b-(6) in connection with other chromophores. Recently, sector rules have been proposed, mainly by Snatzke's group, for various nitrogen-containing chromophores (see refs. 18 and 182).

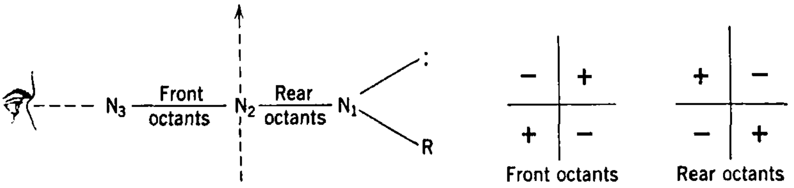


Fig. 7. The azide octant rule. [Adapted from C. Djerassi, A. Moscowitz, K. Ponsold, and G. Steiner, *J. Am. Chem. Soc.*, **89**, 347 (1967).]

III. AROMATIC CHROMOPHORES

A. Definitions

Kekulé's elucidation of the structure of benzene (48) a little over one century ago (49), has had for a long time and still has an unusual impact on theoretical and experimental studies related to aromaticity and aromatic substances.

So far the Cotton effects exhibited by optically active aromatic substances have not been adequately studied, apart from a recent review (50). It is only in restricted fields that attempts have been made to relate the sign of the Cotton effects to the configuration of an asymmetric center (or centers) near an aromatic chromophore, or to the chirality of the molecule as a whole.

The development of optical rotatory dispersion and circular dichroism equipment which permits the penetration of the absorption bands of aromatic compounds in the region of the α band (260–280 mμ) (see Table III) and sometimes below 240 mμ, has led to a good deal of exploration of the aromatic field during recent years. Although at present this work is of a piecemeal character, a pattern begins to appear, and it now seems to be the appropriate time to make a general survey of the field.

Although theoretical studies are as yet limited to a few groups of compounds which have been intensively studied, empirical approaches show that from the sign and magnitude of the Cotton effect(s), the stereochemistry, including the absolute configuration of asymmetric centers, and the conformation of rings or conjugated systems may often be deduced.

There are three criteria of aromaticity (51): (*a*) the presence of $(4n + 2)$ out-of-plane π-electrons, as stated by Hückel (52); (*b*) a reasonably planar configuration; and (*c*) a ring size below certain limits. Hence, "a compound is considered to be aromatic if there is a measureable degree of cyclic delocalization of a π-electron system in the ground state of the molecule" (51).

Simple aromatic compounds usually show three major transitions between 180 and 300 mμ; two strong absorption bands appear near 180 and 200 mμ, and a weak transition, usually showing considerably fine structure, occurs at about 260 mμ (53–59). Several different nomenclature systems are used for the first three ultraviolet (UV) absorption

TABLE III

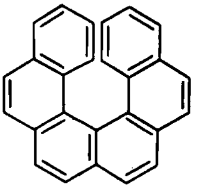
Nomenclature for the Three Ultraviolet Absorption Bands Appearing in the 180–280 mμ Region

Wavelength, mμ	Denomination of the band
260–280	α $'L_b$ $'A_{1g} \rightarrow 'B_{2u}$ $^1A \rightarrow {}^1L_b$ B
200–220	p $'L_a$ $'A_{1g} \rightarrow 'B_{1u}$ $^1A \rightarrow {}^1L_a$ E_2
180–190	β $'B_a$ $'A_{1g} \rightarrow E_{1u}$ $^1A \rightarrow {}^1B$ E_1

bands of aromatic structures; going (usually) from longer to shorter wavelengths (*in extenso* from lower to higher frequencies), they are as mentioned in Table III. In the present chapter we shall refer mainly to the weak band around 260 mμ.

If an aromatic compound is symmetrical (e.g., benzene) the weak transition at 260 mμ is a formally "forbidden" band. However, in any dissymmetric aromatic system, this $\pi \rightarrow \pi^*$ transition at ca. 260 mμ will become optically active.

The group of different types of aromatic compounds which are dissymmetric is very wide. These compounds range from polycyclic structures of dissymmetric character such as hexahelicene (**8**) (60) and the various benzophenanthrene derivatives (**9**) on the one hand, to the compounds containing a simple benzene ring attached to a classical "asymmetric carbon atom" as, e.g., in mandelic acid (**10**) (61) on the other.



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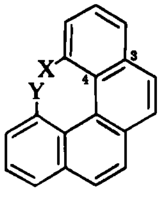

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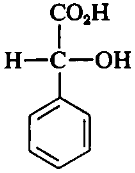
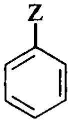


(10)

The two extremes of this range correspond to the two classes of dissymmetric structures viz., those with inherently dissymmetric chromophores, and those with symmetrical but asymmetrically perturbed chromophores (2,15). It will be seen that within the aromatic field there are many intermediate stages between these two extremes.

It is easier to treat compounds of a fixed conformation or shape than those in which the conformation is flexible. While proceeding from the inherently dissymmetric chromophores to the essentially symmetric but perturbed types, one will at each stage deal logically with the more rigid before the more flexible structures.

As defined above, "aromatic" generally means a benzene ring with or without substituents; it can also mean naphthalene, tropone, or a heterostructure like furan, pyrazole, indole, pyrimidine or purine in nucleosides, etc.



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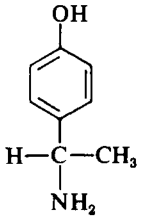

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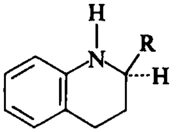
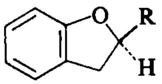


(13)

Heteroatoms (O, N, S, halogen) directly attached to an aromatic ring are called "arylic" (**11**). This term is used both for "ordinary" heterosubstituents not associated with the alicyclic part of structure (e.g., —OH, —OCH_3, —NH_2, —NHAc, —Br, etc.) (**12**), and also for heteroatoms in a reduced ring and adjacent to an aromatic nucleus, as a nitrogen atom in 1,2,3,4-tetrahydroquinoline (**13**) or oxygen in 2,3-dihydrobenzofuran (**14**). Centers of asymmetry which are adjacent to an aromatic ring, or heteroatoms carried by them, are called "benzylic"



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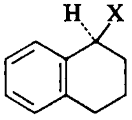

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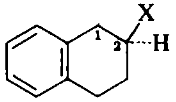


(16)

(15). Centers of asymmetry which are separated from an aromatic ring by one methylene or another saturated group, are called "phenethylic" **(16)**.

B. The Inherently Dissymmetric Aromatic Chromophores

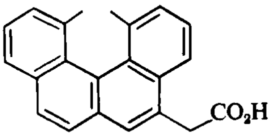
As emphasized earlier (15) in inherently dissymmetric chromophores the optical activity results from the intrinsic geometry of the chromophore. The optical isomerism—also called "atropisomerism" for skewed biaryls—existing in these compounds is due to restricted rotation about single bonds (62–65). Thus atropisomerism will be observed when the energy barrier separating conformational isomers is high enough to permit their isolation and identification (66–68). Such isomerism has been found in biphenyls, binaphthyls, bianthryls, and the like (15,28,60,62–69).

Optical activity is associated with the inherently dissymmetric chromophore of these aromatic compounds, thus leading to Cotton effects which can be investigated either by optical rotatory dispersion or by circular dichroism. It will be recalled that these substances are characterized by very high optical activity, as a result of the nature of their chromophore; i.e., the high degree of dissymmetry of such a chromophore is to be contrasted with the second-order dissymmetry of a carbonyl for which the optical activity is merely induced by its surroundings.

1. Hexahelicene and Similar Compounds

The optical properties of several substances belonging to this class have already been examined (60,62–83). Hexahelicene (**8**) constitutes a classical example of an inherently dissymmetric chromophore. This compound (**8**) consists of six benzenoid rings fused into a roughly helical form. There is no symmetry element in the molecule to prohibit optical activity, but neither is there any asymmetric carbon atom. The entire molecule acts as a single chromophore, and the asymmetry necessary for optical activity is built into the chromophore itself (15,60). All the transitions of the chromophore, which in this case is identical with the molecule, are both electric-dipole and magnetic-dipole allowed, Hence all the transitions have relatively large R_k (rotational strength) values, and the optical activity exhibited is very high (60).

During a recent study of the optical rotatory dispersion properties of derivatives of triptycene, the authors (70) emphasized that the direction of electronic polarization constitutes the determining factor for the sign of the Cotton effect.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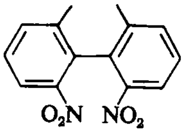

(18)

The 3,4-benzophenanthrene type of compounds (**9**) belong to this group. These have been examined in detail by Moscowitz, Mislow, Djerassi, and their collaborators (15,28,60,77–80), as well as by Mason and Kemp (83). These studies show that the chiralities—*M* or *P* in the newest terminology of Cahn, Ingold, and Prelog (84)—of certain 3,4-benzophenanthrene derivatives (**9**) may be determined from the signs of the Cotton effects associated with their *p*- and β-bands (see Table III), as exemplified in Figure 8 for the acid (**17**) (83).

2. *Conjugated Structures*

a. Biphenyls and Binaphthyls. The transitions in the ultraviolet spectra of dissymmetric biphenyls, binaphthyls, and similar substances are optically active and lead to Cotton effects, whose signs reflect absolute configuration and conformation (28).

Figure 9 shows the circular dichroism curve and the ultraviolet spectrum of the unbridged (*S*)-6,6′-dinitro-2,2′-dimethylbiphenyl (**18**) (79). The short-wavelength positive circular dichroism maximum at 251 mμ corresponds to the $\pi \rightarrow \pi^*$ ultraviolet transition at 260 mμ, and the negative circular dichroism maximum at 298 mμ is related to the ultraviolet inflection at about 310 mμ. The long-wavelength negative dichroism maximum around 350 mμ is associated with a transition which is not apparent in the ultraviolet spectrum. These features are

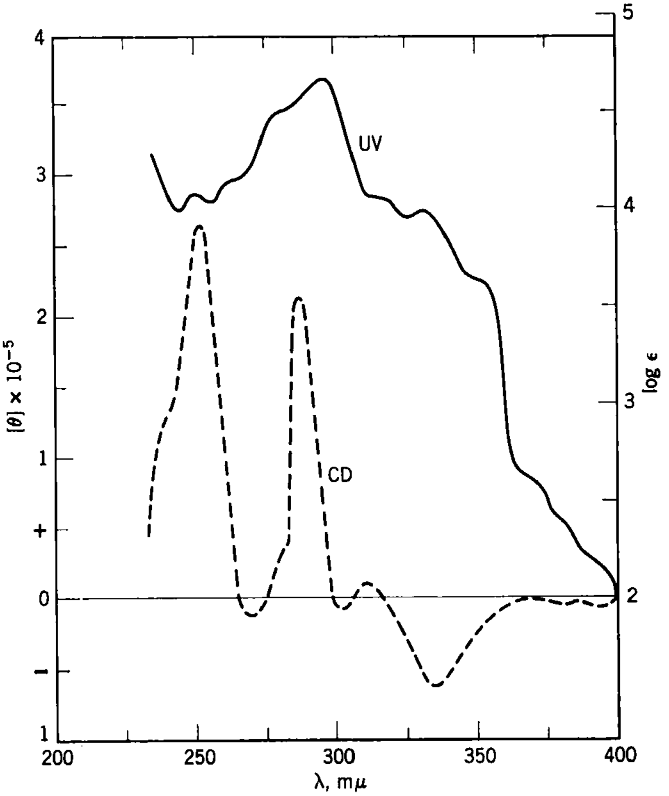


Fig. 8. Ultraviolet (UV) and circular dichroism curves of the substituted benzophenanthrene (**17**). [Adapted from C. M. Kemp and S. F. Mason, *Tetrahedron*, **22**, 629 (1966).]

characteristic of the (*S*) configuration (84). The rotatory dispersion curve of the (*R*) optical isomer of (**18**) (see Fig. 9) (78) exhibits a positive Cotton effect near 330 mμ and confirms the above observation. In the rotatory dispersion curve of (*R*)-6,6′-dinitro-2,2′-dimethylbiphenyl (**18**) a second Cotton effect, which is negative and centered near 260 mμ, is also apparent. The opposite configurations characterizing these (*R*) and (*S*) isomers are then expressed by the reversed signs associated with their Cotton effects.

It is particularly noteworthy that the nitrobenzene transition near

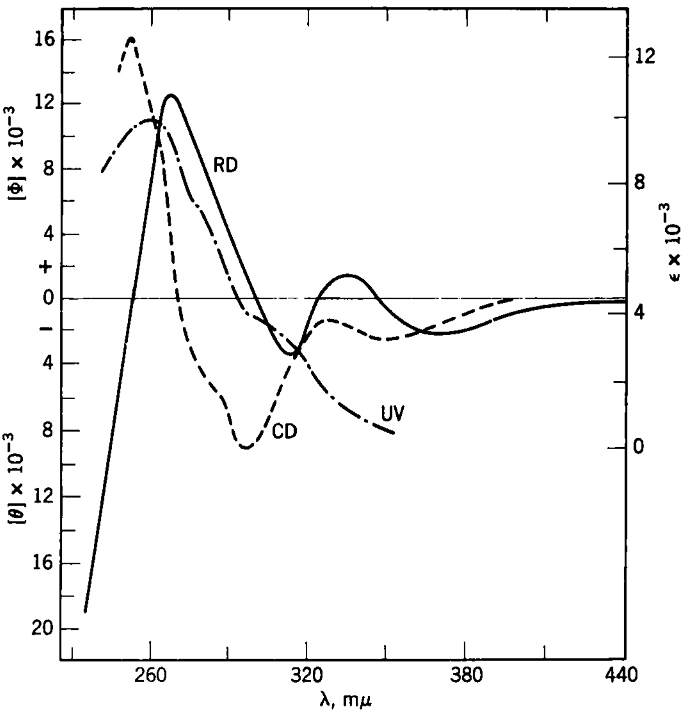


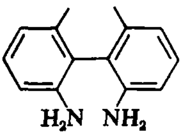
Fig. 9. Circular dichroism (CD) and ultraviolet (UV) curves of (*S*)-6, 6′-dinitro 2,2′-dimethylbiphenyl (**18**) and rotatory dispersion curve (RD) of its (*R*)-isomer. [Modified from K. Mislow, E. Bunnenberg, R. Records, K. Wellman, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1342 (1963).]

340 mμ, which is hardly detected by ultraviolet absorption, is clearly revealed by both circular dichroism and optical rotatory dispersion. Moreover, the transition near 300 mμ is shown by circular dichroism to be optically active, a fact which is not observed by rotatory dispersion, since tails of neighboring Cotton effects obscure the small Cotton effect associated with this transition (79).

The high extinctions in the absorption spectra of such compounds sometimes parallel the intensity of the circular dichroism curves as well as the high amplitude in the dispersion curves. All three phenomena are characteristic of molecules which contain inherently dissymmetric chromophores. They may be used simultaneously for structural and configurational assignments, since circular dichroism and rotatory dispersion phenomena are complementary manifestations of the Cotton effect associated with a particular electronic transition. In some cases (see Fig. 9), circular dichroism measurements have distinct advantages over rotatory dispersion, whose background rotations may hide weak Cotton effects. Conversely, the presence of high-intensity Cotton effects lying in wavelength regions which at present are not reached by the available instrumentation can often be detected by the dispersion curve at shorter wavelengths (79). Hence a judicious use of both circular dichroism and rotatory dispersion is indicated, since these techniques complement each other (85). On the one hand, with the instrumentation presently available high-intensity Cotton effects lying in low-wavelength regions ("invisible giants") are best detected by rotatory dispersion measurements, since their Cotton effects are felt as background curves and frequently even as the dominant effect of optical rotatory power in the region under investigation. On the other hand, circular dichroism is most useful in identifying relatively weak optically active transitions, especially in the longer-wavelength region, where their presence may be obliterated in both ultraviolet absorption and rotatory dispersion spectra by broad, overlapping neighboring bands.

Musso and Steckelberg (73) have also examined the optical properties of some skewed biphenyls, such as the (*S*)-diamine (**19**) (73).

The optical rotatory dispersion (80), ultraviolet, and circular dichroism data (79) have been obtained for (*R*)-9,10-dihydro-4,5-dimethylphenanthrene (**20**). The conjugated-band Cotton effect of this compound has its circular dichroism maximum at 262 mμ. This corresponds well with the ultraviolet absorption maximum at 261 mμ. The molecular ellipticity of bridged compounds such as **20** is considerably higher than in "open" biphenyls such as **19**. The rotatory dispersion curve of **20** allowed detection of only the long-wavelength low-intensity features. However, this curve clearly shows that the positive long-wavelength extremum of low intensity is superimposed on a strong negative background rotation, due to the "invisible giant" located at a much lower wavelength.



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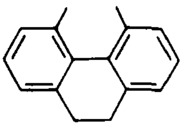
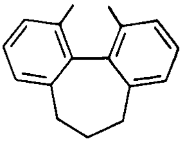


(20)

The circular dichroism and ultraviolet spectra of two other twisted bridged biphenyls **21** and **22** have also been obtained (34c). The relative displacement of the biphenyl conjugation band in **21** and **22** is mirrored in the shift observed in the position of the circular dichroism maximum. In many seven-membered ring bridged biphenyls a long-wavelength Cotton effect of low amplitude accompanies the conjugation-band Cotton effect, and both effects are of the same sign. However, it has been pointed out that oxepin (**22**) does not exhibit the long-wavelength Cotton effect (78). This observation is unusual, since most optically active biaryls present multiple Cotton effect curves. The binaphthyl (**23**), exhibits this multiple Cotton effect pattern. The negative long-wavelength and positive short-wavelength circular dichroism maxima are in agreement with the rotatory dispersion results (78). The extremely high intensity of the optical rotatory dispersion peak and circular dichroism molecular ellipticity characterizing this compound (**23**) are in fairly good agreement, making both methods appropriate for such Cotton effect studies.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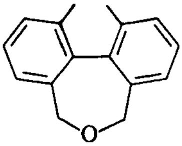

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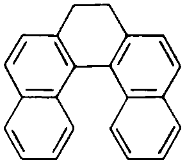
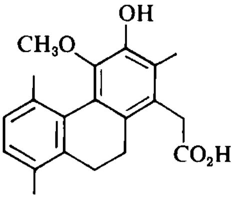

(23)

The dihydrophenanthrene (**24**), a degradation product of the triterpene chaparrin (**25**) (86) is optically active. The shape of the rotatory dispersion curve is very similar to, and of the same sign as, that of 2,2′-dimethyldihydrophenanthrene (**26**) from 600 to about 300 mμ, to which Mislow and Hopps (80) attribute the (*R*) configuration (84). The change of a methoxyl for a methyl in an unchanged



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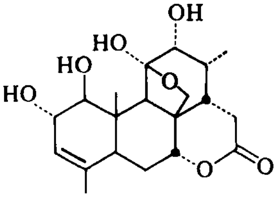

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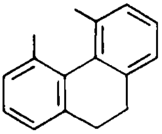
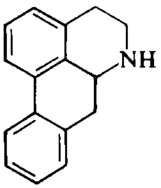

(26)

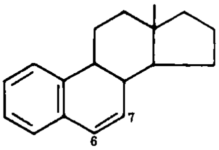
stereochemical situation gives the (*S*) configuration for the absolute stereochemistry of the dihydrophenanthrene (**24**).

Other compounds of the biaryl-type include natural products, such as the aporphines (**27**), which provide excellent rigidified analogs, extensively investigated (87–91), as well as some colchicine derivatives (92), and alkaloids from the *Lythraceae* group which have also been examined (93).

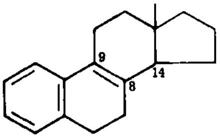


(**27**)

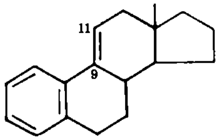
b. Other Conjugated Chromophores. *1. Styrenes.* The next class which has not hitherto been fully considered elsewhere, is that of the skewed styrenes. These may be considered as formally analogous to a biaryl, except that one aromatic nucleus is replaced by an olefinic double bond. Examples of optical rotatory dispersion curves of hexahydronaphthalenes, which are "rigidified styrenes," are shown in Figure 10. In addition, Table IV gives the rotatory dispersion data for skewed styrenes belonging to the steroid series (**28**–**30**) (94–96), and for the hexahydrobenzo-(*f*)-quinolines (**31**) obtained during a stereochemical study of lysergic acid (97).



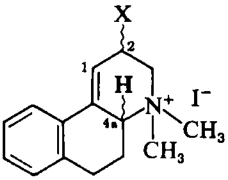
(**28**)



(**29**)



(**30**)



(**31**)

An examination of the geometry of the chromophore with molecular models (98) shows that the chirality of the conjugated system in Δ^6-estrogens (**28**) (left-handed helix; negative Cotton effect) is opposite to that in the Δ^8- and $\Delta^{9(11)}$-compounds (**29,30**) (right-handed helix; positive Cotton effect). Moreover, the nature of the substituent at C-3 (H, OH, OAc, OCH_3, OBz) sometimes has an important influence on the amplitude of the Cotton effect of such styrenes, although not on its sign, in agreement with the helicity rule for cisoid dienes (*vide infra*).

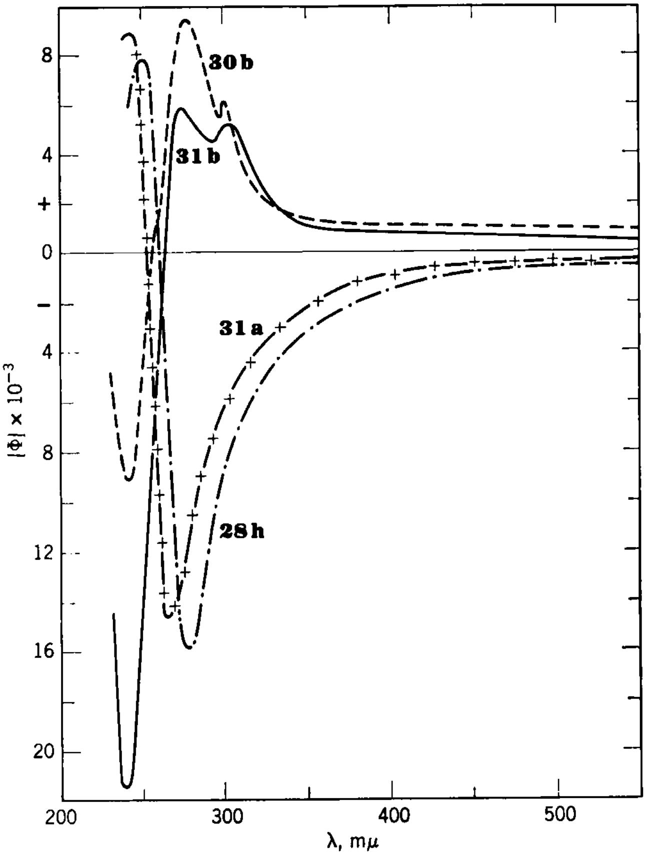


Fig. 10. Optical rotatory dispersion curves of the styrenes **28h**, **30b**, **31a**, and **31b**. [Modified from P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco, 1965.]

TABLE IV

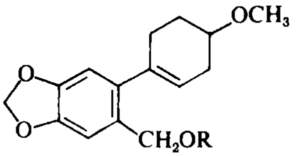
Optical Rotatory Dispersion Data for Rigid Styrene-Type Structures

Compound number	Compound	Other substituents	Molecular amplitude of the styrene chromophore (a)	Wavelengths at extrema, mμ
	Δ^6-Estrogens (**28**)-substituents in aromatic ring A			
28a	3-OH	17-Cycloethylene-ketal	−293	274/256
28b	1-Me,3-OH	Spirostan	−150	279/260
28c	1,2-Dimethyl,3-OH	17β-OH	−118	285/256
28d	3-OAc	17β-OAc	−236	276/247
28e	3-OAc	17-Cycloethylene-ketal	−337	273/238
28f	3-OAc	Spirostan	−129	276/244
28g	3-OAc,7-OAC (enol-acetate)	17-Ketone	− 40	276/256
28h	1-Me,3-OAC	17β-OAc	−268	279/249
28i	3-OBz	17β-OH	−316	270/244
28j	1-Me,3-OMe	17β-OH	−118	279/255
	Δ^8-Estrogens (**29**)			
29a	3-OMe	17-Ketone (14βH)	+601	276/248
29b	3-OMe	17α-OH,17β-C≡CH(14βH)	+288	278/224
	$\Delta^{9,11}$-Estrogens (**30**)			
30a	3-OH	17β-OH	+203	264/240
30b	3-OAc	17β-OAc	+194	268/238
30c	3-OMe	17β-OH	+210	260/235
30d	3-OAc	17β-Bismethylene-dioxy	+169	268/243
	Hexahydrobenzo (*f*)quinolines (**31**)			
31a	4aα-H,2ξ-OH		−236	263/238
31b	4aβ-H,2ξ-OH		+268	267/239
31c	4aβ-H,2ξ-OH,2ξ-Me		+422	276/236

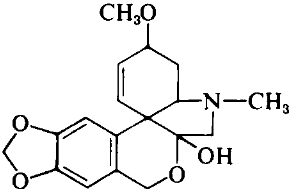
Since the Δ^8-14β-steroid (**29b**) exhibits a positive Cotton effect in the 260-mμ region, its conformation can be deduced; the 7-methylene group is very probably below the plane of ring A and the 8(9) double bond. In this conformation the nonbonded interactions between hydrogen atoms are minimal.

The absolute configurations at C-4a of the *N*-methylhexahydrobenzo-(*f*)-quinolines (**31**) (97) are assigned in accordance with the same principles, by correlation with the model steroids (see Fig. 10) of known absolute stereochemistry (99).

The optical rotatory dispersion properties of derivatives **32a** and **32b**, belonging to the tazettine (**33**) series, have been reported (100). Whereas the rotatory dispersion curve of the alcohol (**32a**) exhibits a multiple Cotton effect between 350 and 220 mμ, the ester (**32b**), devoid of hydrogen bonding, presents in this region a single Cotton effect centered ca. 250 mμ (100).



(**32a**) R = H
(**32b**) R = CO—CH$_2$—N(CH$_3$)$_2$



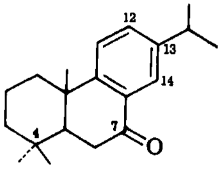
(**33**)

It may be that the patterns of substitution in the aromatic nuclei themselves are not of primary importance in determining the optical rotatory dispersion and circular dichroism behavior of such twisted chromophores. The empirical studies of alkaloids and lignans (*vide infra*) lead one to think that the general structure and stereochemistry are generally the major factors responsible for the optical properties (with substitution in many cases a secondary one).

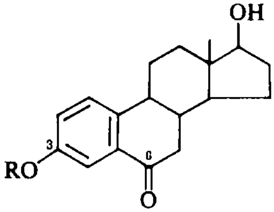
Several of the styrene-type estrogens listed in Table IV illustrate this also. Substitution on an olefinic double bond by a polar group, such as an acetoxyl (in an enol-acetate), makes a major difference in the amplitude (cf. compound **28g**); probably as a result of the inductive effect of the substituent. Methyl would affect the amplitude in a much less pronounced fashion.

It is interesting to note that the nature of the substituent at C-17 seems to play an important role on the chirality of the styrene chromophore in Δ^8-steroids, as is revealed by the difference in intensity associated with the styrene chromophore in **29a** and **29b** (see Table IV). Another possible explanation could be a conformational mobility of the cyclic system, which could be investigated by temperature- and/or solvent-dependent rotatory dispersion or circular dichroism studies.

2. Aryl Ketones. In this section we will consider the conjugated aryl ketones, e.g., structures of types **34** (Table V) (101–104) and **35** (Table VI). The Cotton effects of many other α-aryl ketones and α-naphthyl ketones are reported in references 101–105.



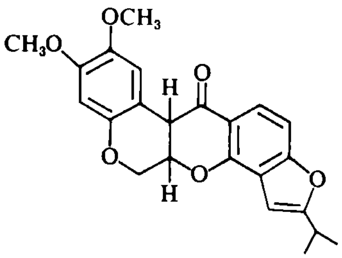
(34)



(35)

As shown in Tables V and VI, a strong Cotton effect is associated with the acetophenone-type chromophore when it is situated in an asymmetric surrounding. Moreover the sign of the Cotton effect reflects the chirality of the group.

Some studies have been devoted to the application of optical methods for the determination of configurational relationships characteristic of flavonoids, isoflavonoids, rotenoids, and related natural occurring aromatic substances (106–120). For example, it has been shown (109) that (−)-isorotenone (**36**) exhibits a positive Cotton effect in the 360-mμ region. Recently, Mabry and Markham (119) have investigated the optical properties of several dihydroflavonols of general formula **37**. These investigators noted that at least three Cotton effects are observed in the near ultraviolet, corresponding to each of the absorption maxima. Hence, taxifolin (**38**), in which the absolute configuration is (2*R*:3*R*),



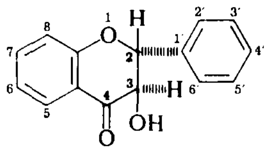
(36)

TABLE V

Cotton Effects of Some Diterpenes with an Aromatic C Ring and a Carbonyl Group at C-7 (34)

Substituents	Ultraviolet absorption		Cotton effect (RD and CD)	Reference
	λ, mμ	log ε	*a* or $[\Theta]$	
4α-CH$_2$Me,4β-Me				
13-Isopropyl	303	3.23	$a = +75$	101
	248	4.04		
4α-Me,4β-CO$_2$Me, 12-OMe	276	4.15	$a = +54$	102
			$[\Theta] = +1{,}301$	101
4α-Me,4β-CO$_2$H, 12-OMe			$[\Theta] = +641$	101
12-OMe	345	1.92	$a = +11!$	102
13-Isopropyl	297	3.90	$[\Theta] = +3{,}330$	
	274	3.96		
	237	4.17		
12-OH	288	4.15	$a = +204$	101
13-Isopropyl			$[\Theta] = +12{,}900$	103
13-OH	326	3.42	$a = +128$	102
14-Isopropyl	258	3.74	$[\Theta] = +5{,}780$	
12-OAc	297	3.47	$a = +38!$	103
13-Isopropyl	256	4.14	$[\Theta] = +8{,}610$	103
			$[\Theta] = +10{,}590$	
12-OBz			$a = +41$	101
13-Isopropyl			$[\Theta] = +7{,}030$	102
			$[\Theta] = -6{,}090$	

exhibits a weak positive Cotton effect ca. 340 mμ, a strong negative Cotton effect around 296 mμ and a fairly intense Cotton effect at ca. 222 mμ, corresponding to the ultraviolet absorption bands [λ_{max} 335 (sh.), 290 and 222 mμ] (119).



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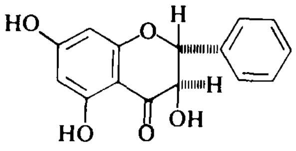


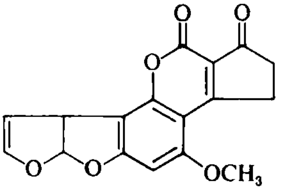
(38)

TABLE VI

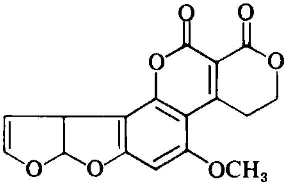
Cotton Effects of 6-Keto Aromatic Steroids (35)

Substituents	Cotton effect *a* or [Θ]	Reference
3-OH; 17βOH	$[\Theta]_{345} = +25{,}000$ $[\Theta]_{310} = -206$	102
3-OMe; 17βOH	$a = +251$	96

The situation is obviously quite complicated in such compounds, since one deals with a molecule having two asymmetric centers. The first is situated next to the acetophenone-type chromophore, whereas the second center is β to this chromophore, but adjacent to an aromatic ring. Furthermore, there is very probably an orbital overlap between both chromophores which form a bis-homoconjugated π-system (i.e., the benzene ring at C-2 and the acetophenone system), so that one is dealing here with quite a complicated electronic pattern.



(39)



(40)

Still more complicated is the situation encountered in the highly conjugated aflatoxins studied by Büchi and his co-workers (120). Aflatoxin B (39) exhibits a very intense circular dichroism negative maximum ca. 355 mμ ($[\Theta] = -19{,}800$), followed by a less intense Cotton effect at lower wavelength ($[\Theta]_{271} = -10{,}500$). Aflatoxin G_1 (40) also presents a negative Cotton effect around 355 mμ ($[\Theta] = -16{,}500$)*.

Some other extended conjugated chromophores will be discussed in sequence. Brief mention shall now be made of a more flexible acetophenone-type system.

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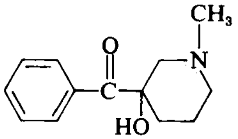
*We want to express our gratitude to Professor G. Büchi for samples of these compounds and to Professor G. Ourisson for the measurements.



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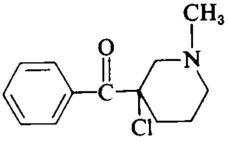

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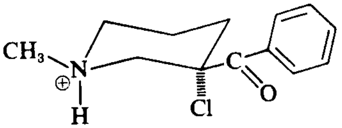


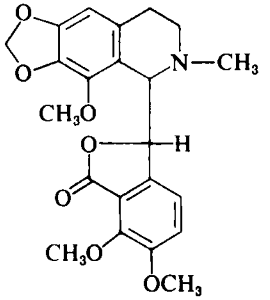
(42a)

During a stereochemical study of the mechanism of the quasi-Favorskii rearrangement (121), the optical rotatory dispersion properties of (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (**41**) and (−)-1-methyl-3-benzoyl-3-chloropiperidine (**42**) were obtained in different solvents. Application of the octant rule (13) allowed an explanation of the Cotton effect when considering that in the α-haloacylcycloalkanes, the halogen is attached to the ring carbon and the quasi-axial orientation with respect to the carbonyl group is achieved by rotation about the acyl-to-ring bond. This conformation is stabilized by electrostatic constraints in the 3-halo-3-acylpiperidines under consideration (121). Examination of molecular models reveals that the more stable conformations of the two enantiomeric forms of **42** are those in which the chlorine is axial with respect to the ring. In acidic medium, the preferred antipodal rotational conformers are those in which the carbonyl oxygen electrons are closer to the cationoid nitrogen (**42a**). An inversion of the Cotton effect exhibited by **42** was noted in octane solution. This inversion in sign caused by a change of solvent is rationalized by the electrostatic repulsion between the free electron pair on nitrogen and the carbonyl oxygen electrons. Therefore the molecule chooses the antipodal rotational conformation (121). Other similar observations have been described (122); the main conclusion which can be reached is that such molecules are conformationally flexible. Dilling (123) has made a careful study of the ultraviolet spectra of several benzophenones in solvents of varying polarity. Substantial changes were observed in both $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ absorption maxima, which were correlated by

Kosower' solvent polarity Z parameter (123). In view of these observations, the optical rotatory dispersion and circular dichroism properties of such chromophores should of course also be affected.

There is also little doubt that in the near future the rotatory dispersion and circular dichroism techniques will play an important role in the assignment of relative and absolute configurations to other similar compounds, such as skewed thiobenzophenones (124).

3. Lactonic Aromatic Compounds. Numerous lactonic alkaloids are aromatic substances in which the lactone is conjugated with an aromatic ring (125). When optically active, such natural products are worth investigation by optical rotatory dispersion and/or circular dichroism.



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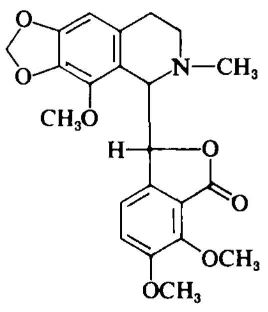
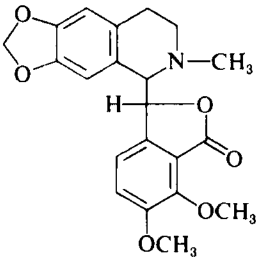
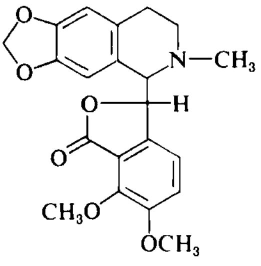


(44)

This assumption will be illustrated in the case of natural α-narcotine (**43**) and the isomeric β-narcotine (**44**) and related lactonic aromatic alkaloids.



(45)



(46)

During the study of the absolute configuration of α- and β-narcotine, various optical rotatory dispersion curves were obtained (126). Figure 11 gives the dispersion curves of 1-α-narcotine (1*R*, 9*S*) (**43**), 1-β-

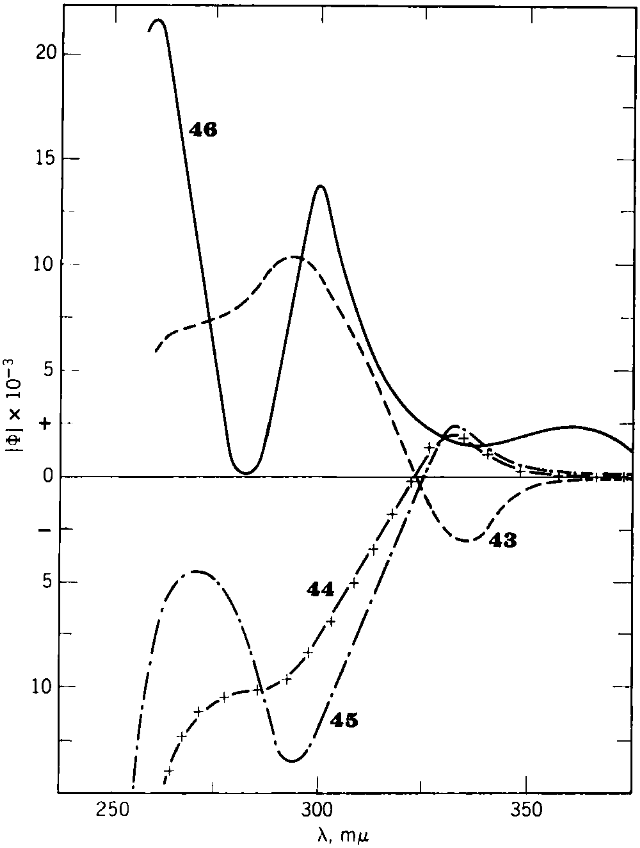
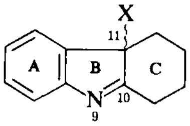


Fig. 11. Optical rotatory dispersion curves of 1-α-narcotine (**43**), 1-β-narcotine (**44**), 1-α-hydrastine (**45**) and 1-β-hydrastine (**46**) in 2*N* hydrochloric acid solution. [Modified from M. Ohta, H. Tani, S. Morozumi, and S. Kodaira, *Chem. Pharm. Bull.* (*Japan*), **12**, 1080 (1964).]

narcotine (1*R*, 9*R*) (**44**), 1-α-hydrastine (1*R*, 9*R*) (**45**), and 1-β-hydrastine (1*R*, 9*S*) (**46**) (127). The opposite absolute stereochemistry which differentiates **43** and **44**, and **45** from **46** is reflected in their rotatory dispersion curves. Moreover, the "partial" Cotton effect which can be observed at about 260 mμ, as well as the weaker Cotton effect occurring at higher wavelength, expresses the different configurations characterizing these α-aryl-γ-lactones.

Similarly, the partial rotatory dispersion curves of some aromatic lactones derived from cnidilide and neocnidilide have allowed the authors (127) to establish the absolute configuration at the asymmetric center.

4. Indolenines. Klyne, Schmid, and their co-workers (128a) have examined the optical rotatory dispersion curves of a range of alkaloids of the aspidospermine and strychnine types, of general formula **47**. Here the sign of the first Cotton effect at 290–240 mμ depends on the configuration at the center C-11 adjacent to the chromophore (11α-X: positive; 11β-X: negative). The skeletons in which the chromophore is bound are represented by **48** and **49**. Amplitudes are given in Table VII. Figure 12 is a reproduction of the rotatory dispersion curves of (+)-tubotaiwine (**50**) and (−)-tabersonine (**51**) (128), which possess a homoconjugated chromophore (see below). It is quite clear, however, that here also the sign of the Cotton effect is related to the stereochemistry at C-11.



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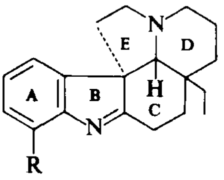

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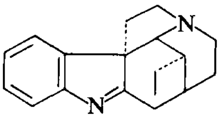

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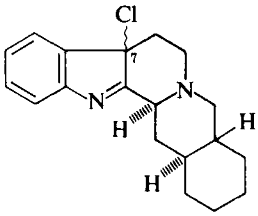
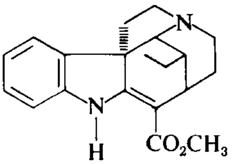


(49a)



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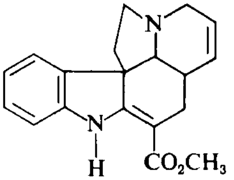


(51)

Finch et al. (128b) have made similar observations. These authors have compared the rotatory dispersion curves for the pair of epimeric 7-chloro-7*H*-yohimbans (**49a**) and observed that they bore a virtual mirror image relationship to each other (128b).

5. Other Conjugated Chromophores. Numerous other aromatic systems with extended conjugated chromophores have been described.

TABLE VII

Optical Rotatory Dispersion Curves of Indolenines

Compound	First Cotton effect (290–240 mμ)
Strychnine-like system (**48**)	
(+)-Condyfoline	$a = +911$
(−)-Tubifoline	$a = -1414$
Aspidospermine-like system (**49**)	
(+)-1,2-Dehydroaspidospermidine	$a = +579$
(+)-1,2-Dehydro-*N*-deacetyl-aspidospermine	$a = +550$

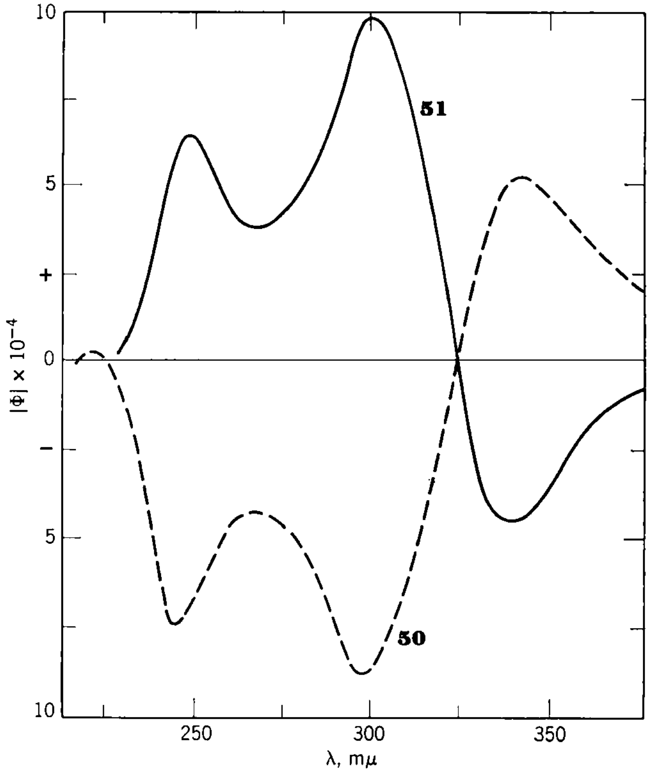
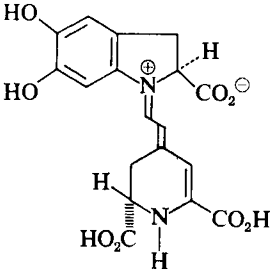


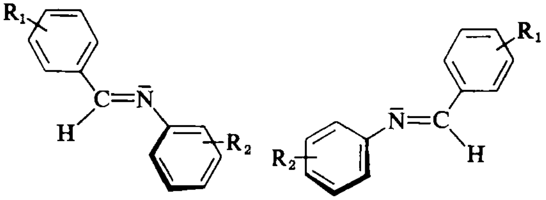
Fig. 12. Optical rotatory dispersion curves of (+)-tubotaiwine (**50**) and (−)-tabersonine (**51**) (128).

Only a few compounds will be mentioned here in order to illustrate the wide variety of chromophores this group involves.

Dreiding and his collaborators (129) used the optical rotatory dispersion technique during their work on betanin. More specifically, these investigators report the rotatory dispersion curves of natural (*S*-*S*)-betanidin (**52**) and its synthetic (*R*-*R*)-enantiomer. In such substances, the conjugation between the aromatic ring and the ethylenic bonds implies a quaternary ammonium salt (*vide infra*).



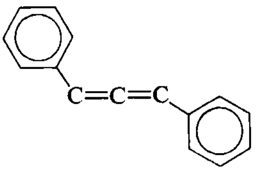
(**52**)



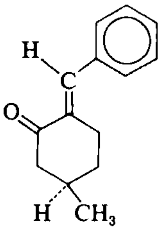
(**53**)

Minkin et al. (130) describe a new form of optical isomerism observed with compounds of type **53**.

Several publications have dealt with the optical activity associated with aryl allenes (69,131–134). Although van't Hoff (131) predicted as early as 1875 that unsymmetrically substituted allenes would exist in two enantiomeric forms, it was sixty years later that Maitland and Mills (132) synthesized the enantiomeric 1,3-diphenyl-1,3-di-α-naphthylallenes. Lately, Mason et al. (134) have deduced the absolute configuration of (+)-1,3-diphenylallene (**54**) from the electronic absorption and circular dichroism spectra of this compound.



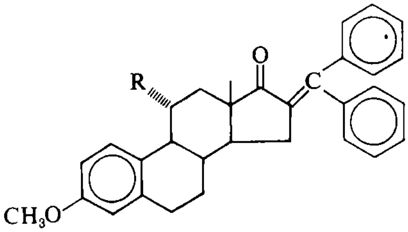
(**54**)



(**55**)

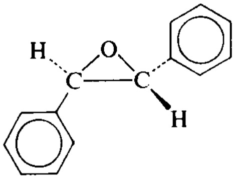
The optical properties of other conjugated systems, such as (*R*)-(−)-

2-benzylidene-5-methylcyclohexanone (**55**) and related compounds have been discussed by Brewster and Privett (135). Somewhat related to **55** are both substituted steroids **56a** and **56b** (136). In ring D, these substances possess a highly conjugated chromophore. This is reflected in their complex optical rotatory dispersion curves, which exhibit very intense Cotton effects (136).



(**56a**) R = H
(**56b**) R = OH

The optical properties of stilbene oxides and related compounds (137) seem to be worth investigating. Indeed, the specific rotation reported for (+)-(*R*:*R*)-stilbene oxide (**57**) is $[\alpha]_D$ +357° (137a), probably indicative of an intense positive Cotton effect.



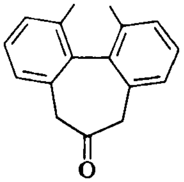
(**57**)

3. *Homoconjugated Systems*

By the term "homoconjugated," one implies compounds in which two unsaturated moieties are separated by one (or possibly two) saturated carbon atoms. These compounds can perhaps best be treated by the coupled oscillator model.

a. Homoconjugation between a Biphenyl and a Ketone. Bridged ketones, such as the (*R*)- and (*S*)-dimethylbiphenyl derivatives (**58**), have been investigated (77). These compounds (**58**) are characterized by the extraordinarily high amplitudes of their rotatory dispersion curves

($a \cong 1400$) and by a fine structure, reflected in the ultraviolet spectra. To account for the fine structure, heretofore encountered only with conjugated systems, Mislow, Djerassi, and their co-workers (77)



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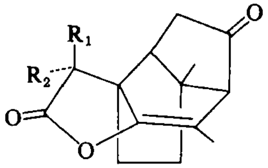


(**59a**) $R_1 = CH_3$; $R_2 = H$
(**59b**) $R_1 = H$; $R_2 = CH_3$

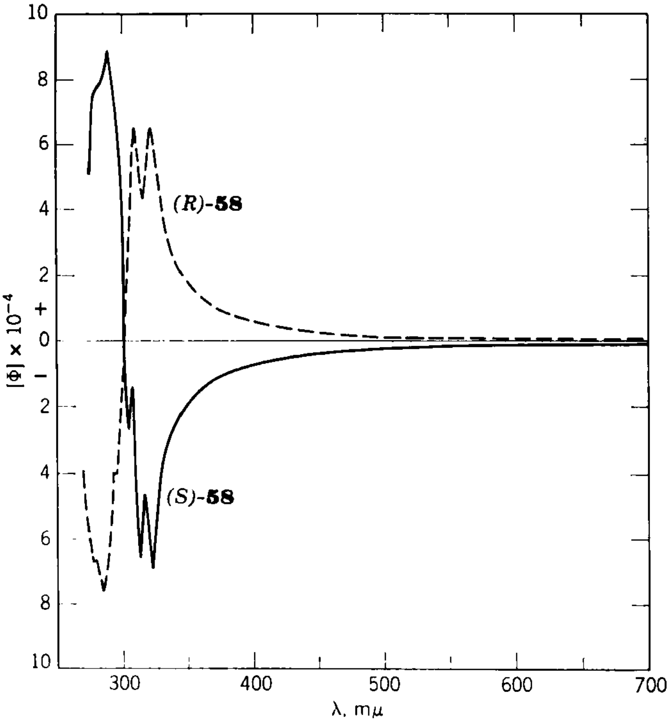
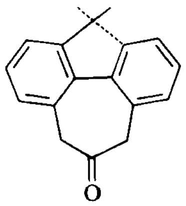


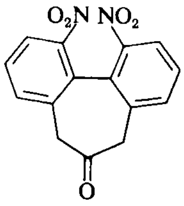
Fig. 13. Optical rotatory dispersion curves of the (*R*)- and (*S*)-dimethylbiphenyl bridged compounds (**58**). [Modified from K. Mislow, M. A. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 4740 (1960).]

postulated homoconjugation between the carbonyl and benzene π-electrons. The rotatory dispersion curves of (*R*)-(**58**) and (*S*)-(**58**), reproduced in Figure 13, illustrate the advantage this technique offers in the detection of nonconjugated π-orbital overlaps (77).

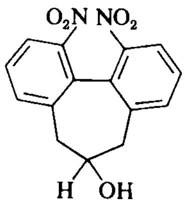
A direct correlation of configuration has recently been established between the biaryls and a class of sesquiterpenes by optical rotatory dispersion (138). As indicated in Figure 14, there is a close similarity between the rotatory dispersion curve of parasantonide (**59a**) and that of dimethyldibenzsuberone (**60**). These observations led to the assignment of the (*R*)-configuration to (+)-dimethyldibenzsuberone (**60**) (34b), since the absolute configuration of parasantonide (**59a**) [and also of santonide (**59b**), exhibiting almost superimposable dispersion curves (138)] is known (31a,139).



(**60**)



(**61**)



(**62**)

Inspection of the circular dichroism and rotatory dispersion curves of bridged ketones, such as the dinitroketone (**61**), indicates that there is a marked deviation from the pattern exhibited by other bridged 2,2′-dinitrobiphenyls. The various chromophores appear to contribute individually to the resultant Cotton effect curves (78,79). This is shown in Figure 15, in which the algebraic summation of the circular dichroism curves of bridged (*S*)-2,2′-dinitrobiphenyl (**62**) and the (*S*)-dimethyl bridged biphenyl ketone (**58**) bears a fair similarity to the experimental curve of the *S*-dinitro bridged biphenyl ketone (**61**) (79).

Another important conclusion from the above observations is the extension of the octant rule (13) proposed by Moscowitz, Mislow, Glass, and Djerassi (34) for dissymmetric nonconjugated chromophores. The long-wavelength carbonyl transition of an aromatic or ethylenic moiety, such as occurs in β,γ-unsaturated ketones (see above), justifies treating the composite carbonyl-carbon-π-system as an inherently dissymmetric chromophore (31). The Cotton effect associated with such systems is a

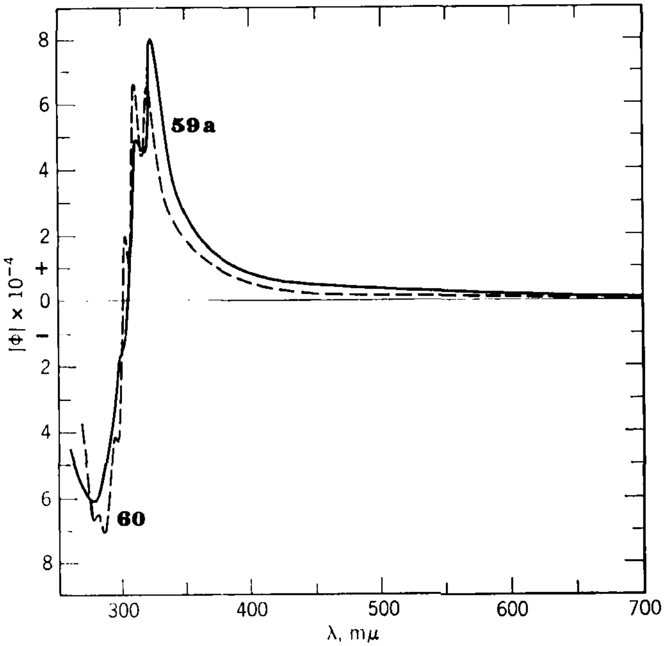


Fig. 14. Optical rotatory dispersion curves of parasantonide (**59a**) and (*R*)-(+)-dimethyldibenzsuberone (**60**) (34b).

reflection of the absolute conformation (i.e., chirality) characterizing this combined grouping (34).

b. Homoconjugated Biphenyls and Related Substances. In the previous sections we have already discussed the optical properties of some aromatic alkaloids. This class of natural products offers a broad variety of spectral properties, so that the use of ultraviolet spectroscopy in structural elucidation of natural alkaloids is a time-honored method (140). If the ultraviolet transitions of aromatic alkaloids are optically active, important stereochemical conclusions may sometimes be deduced, as shown in the case of indolenines mentioned above. Many similar applications will be discussed in sequence, emphasizing the fundamental impact optical rotatory dispersion and circular dichroism have, and will continue to have, in natural products chemistry, e.g., in the alkaloid field, because they often offer information generally unavailable by other techniques.

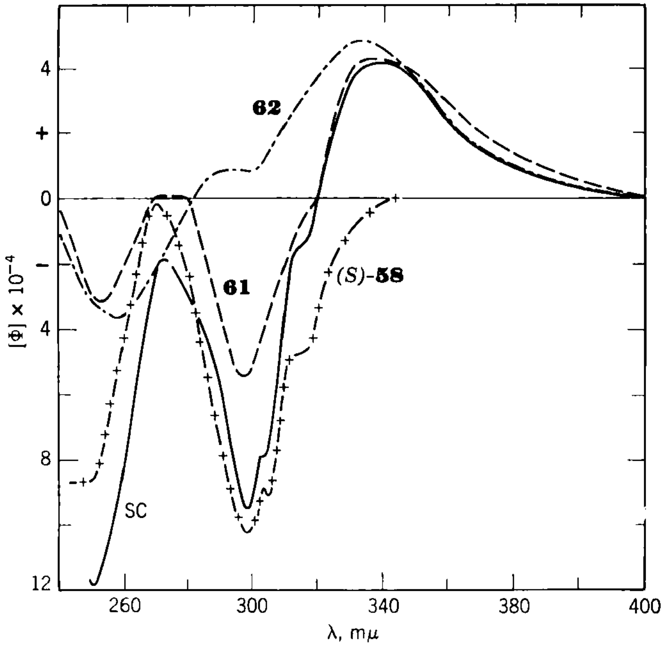
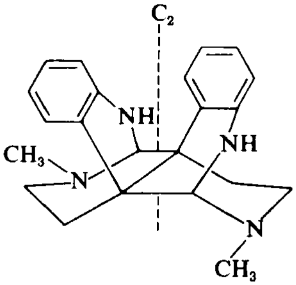


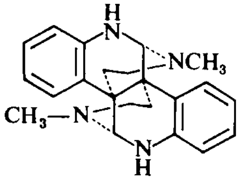
Fig. 15. Circular dichroism curves of the (*S*)-dimethyl bridged biphenyl ketone (**58**), the (*S*)-dinitro bridged biphenyl ketone (**61**), the bridged (*S*)-2,2′-dinitrobiphenyl (**62**) and the summation curve (SC) of **58** and **62**. [Adapted from K. Mislow, E. Bunnenberg, R. Records, K. Wellman, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1342 (1964).]

(*l*) *Calycanthine.* A perfect example of a rigid system, which represents an elegant choice for the application of theory, is the alkaloid calycanthine (**63**) studied by Mason (141). From the purely steric viewpoint this molecule may be considered as a dibenzo-*cis*-hexalin (**63a**) modified by substitution (two NH groups for two CH_2) and rigidified by crosslinking (dashed lines in **63a**).

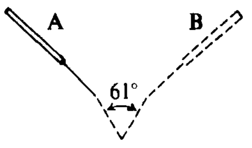
Mason (141) considers the compound on the basis of the coupled oscillator theory as consisting optically of two aniline chromophores; the planes of the two aromatic rings make an angle of 61° with one another (**63b**), and the twofold axis of each aniline residue makes an angle of 28° with this intersection (**63c**). He then calculates the dipole strengths of the transitions in calycanthine, and relates them to the two circular dichroism bands associated with the 310-mμ absorption band. This analysis permits the assignment of the absolute configuration shown in structure **63**.



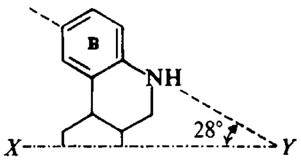
(63)



(63a)

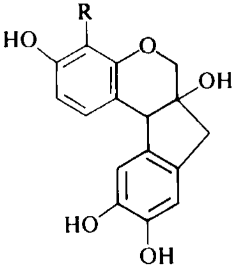


(63b)

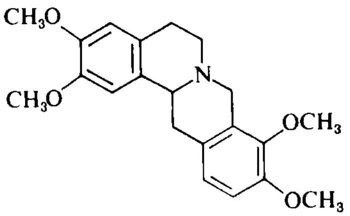


(63c)

(*2*) *Brazilin-Haematoxylin.* Another rigid type is represented by the heterocyclic compounds brazilin (**64a**) and haematoxylin (**64b**), studied as their tetraacetate and pentaacetate by J. C. Craig et al. (142). These compounds give strong, fairly simple negative Cotton effects between ca. 285 and 273 mμ (**64a**: $a = -234$; and **64b**: $a = -130$). The absolute configuration of this group of compounds is as yet unknown.

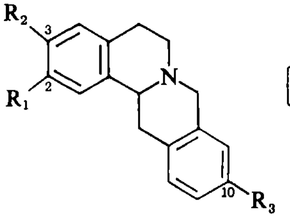


(64a) R = H
(64b) R = OH

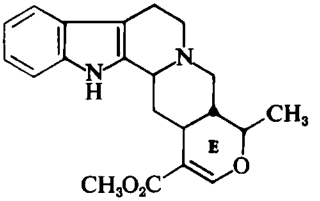


(65)

(*3*) *Tetrahydropalmatine—Berbine and Related Alkaloids.* Tetrahydropalmatine is a simple example of a dibenzoquinolizidine structure (**65**); its rotatory dispersion curve has been studied by Lyle (143) and also by Craig and Roy (144), and its circular dichroism has been reported by Legrand and Viennet (91). Ohta et al. (146) have given evidence for the absolute configuration which depends on monochromatic rotations (145). Berbine (**66a**), from the levo series, has also been examined by circular dichroism (91) and has been shown to give five bands between 190 and 350 mμ.



(**66a**) $R_1 = R_2 = R_3 = H$
(**66b**) $R_1 = R_2 = OCH_3$; $R_3 = OH$
(**66c**) $R_1 = R_2 = OCH_3$; $R_3 = NH_2$



(**67**)

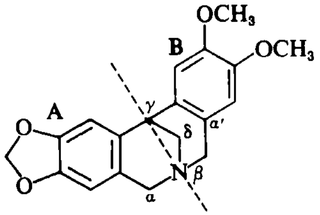
In 2,3-dimethoxy-10-hydroxy berbine (**66b**) and 2,3-dimethoxy-10-aminoberbine (**66c**) (91), when going from the visible to the far ultraviolet, the first circular dichroism band which is observed is negative, and its intensity varies with the substituents in ring D. In tetrahydropalmatine (**65**) there is even a change in sign (91). The behavior of the second band is similar, although its intensity is stronger and negative for the compounds belonging to the levo series (91). The third band, at ca. 216 mμ, is weak and sometimes hidden, as in the case of tetrahydropalmatine (**65**). This band seems to be due to a transition involving the nitrogen atom at the ring junction, since the Cotton effect disappears in acid medium, whereas the other bands are only slightly affected. This is in keeping with similar observations made with cyclic amines in this spectral region (144). The fourth band is the main one of the spectrum. This transition is highly optically active and slightly sensitive to substitution. The very strong intensity of the 203-mμ band, corresponding presumably to a $^1A \rightarrow {}^1B$ transition of the benzene ring (see Table III), seems to indicate that the chromophore belongs to the inherently dissymmetric type (15,60).

The absolute configurations of the related tetrahydroprotoberberine alkaloids have also been determined by Corrodi and Hardegger (145).

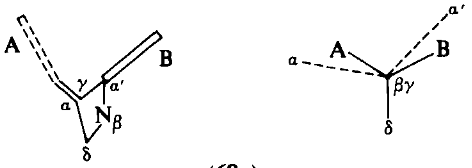
Since a negative rotation or a negative Cotton effect in this group of alkaloids has been shown to correspond to an angular α-hydrogen configuration (143,147), the optical properties have permitted the determination of the stereochemistry of corydaline and some related compounds (148).

(*4*) *Heteroyohimbine Alkaloids.* The rotatory dispersion curves of the heteroyohimbine alkaloids, such as (**67**), discussed by Finch et al., (149) have as their most striking feature a large Cotton effect in the region of 250–230 mμ. This appears to be due to an interaction between the methoxycarbonyl-enol ether grouping ($MeO_2C \cdot C{:}C{-}OR$) in ring E and the indole nucleus. The sign of the Cotton effect is related to the chirality of this coupled oscillator.

(*5*) *A Nearly-Rigid System: Quasi-Enantiomeric Conformers.* Another example, where the optical properties highlight the skewing of an apparently almost symmetrical molecule, is the following. The azocine derivative (**68**) (2,3-dimethoxy-6,12-methano-9,10-dimethylenedioxy-5,6,12,13-tetrahydro(7*H*)dibenz-[*c*,*f*]-azocine) (150) appears to be almost symmetrical, because the difference between the two "halves" of the molecule is only that of two methoxyl groups versus a methylenedioxy group. Nevertheless this compound has a Cotton effect around 300 mμ ($a = -88$) and a strong positive Cotton effect ($a = +565$) around 245 mμ. This must be due to the essentially twisted character of the molecule, leading to interaction between the two π-electron systems.



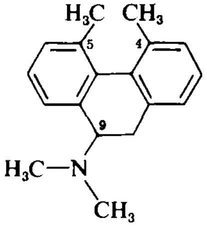
(**68**)



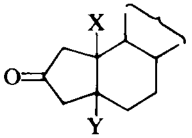
(**68a**)

Disregarding the arylic substituents for the moment, the constitutional formula **68** has an apparent plane of symmetry (dashed line). Study of molecular models shows however that **68** would probably exist as a mixture of two conformations of enantiomeric type (as **68a** and its mirror image). The actual existence of a pronounced Cotton effect in **68** must be due to a preponderance of one conformer, arising from subtle electronic effects of the arylic substituents in the two terminal rings.

This provides a third example of a stereochemical phenomenon which has come to the surface only in the last two years, viz., that of structures which appear constitutionally to be of point group C_{2v} (151) and therefore nonchiral; but which conformationally belong to the chiral point group C_2, and therefore exist as one or the other (or a mixture) of a pair of nearly enantiomeric interconvertible conformers. Related examples are the 9-dimethylamino-9,10-dihydro-3,4-dimethylphenanthrene (**69**) of Mislow and Joshua (152), and the *cis*-hexahydroindan-2-ones (**70**) discussed by Klyne (153).

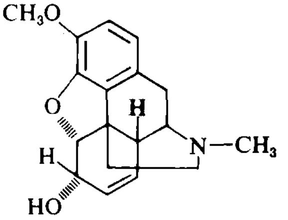


(69)

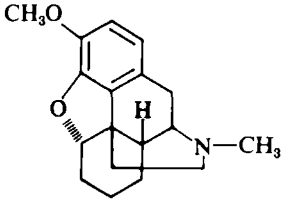


(70)

(*6*) *Morphine Alkaloids.* The optical properties of natural substances belonging to the morphine, thebaine, codeine, and similar classes of alkaloids have been extensively examined (4,154–158). According to Albrecht and Simpson (159), in some aromatic compounds the 260–280 mμ transition ($'A_{1g} \rightarrow {}'B_{2u}$ of Table III) would be polarized



(71)



(72)

in the y direction and the 200–220 mμ transition ($'A_{1g} \rightarrow 'B_{1u}$ band in Table III) in the x direction. In the case of calycanthine (**63**) discussed above, both polarized transitions were observed (141).

An analogous phenomenon has been noted in the morphine alkaloid series. Weiss and Rüll (156) report that the circular dichroism curves of

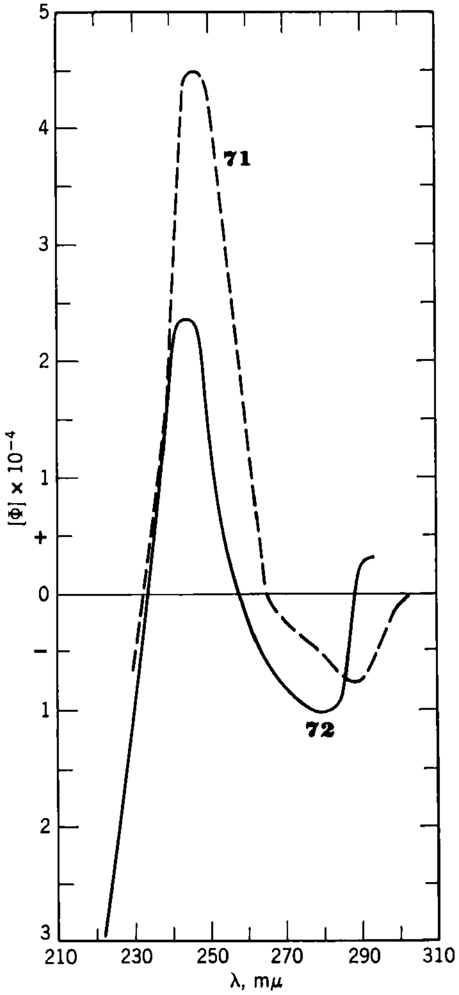
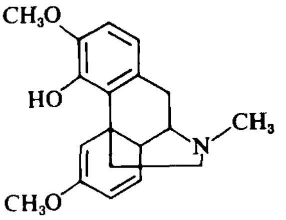
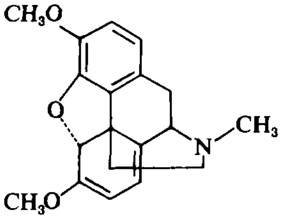


Fig. 16. Circular dichroism curves of codeine (**71**) and dihydrodeoxycodeine D (**72**). [Modified from U. Weiss and T. Rüll, *Bull. Soc. Chim. France*, **1965**, 3707.]

these compounds exhibit two extrema, due to the aromatic ring, if the molecule does not possess any other chromophore like a ketone or a diene. In compounds with an oxygen bridge, the first maximum ca. 280 mμ is negative, the second extremum in the 240-mμ region is positive. These extrema seem to correspond to the above-mentioned transitions of the aromatic chromophore (156) (*vide infra*). If homoconjugation can exist in the molecule, the Cotton effects are sometimes extremely intense. This is illustrated in Figure 16, which shows the circular dichroism curves of codeine (**71**) and dihydrodeoxycodeine D (**72**) (156). The circular dichroism of proaporphin-type alkaloids has been discussed recently by Snatzke (210).

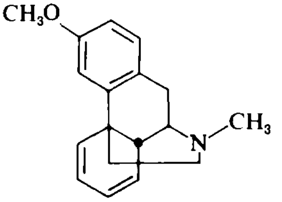


(73)

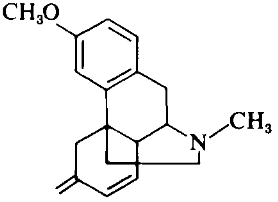


(74)

In thebainone methyl enol ether (**73**) and in thebaine (**74**), it has been shown (158) that the sign of the Cotton effect reflects the chirality of the diene chromophore. The rule of cisoid dienes states that a strong positive Cotton effect associated with the lowest frequency diene $\pi \rightarrow \pi^*$ absorption band (at ca. 270 mμ in polycyclic compounds) indicates that the diene chromophore is twisted in the form of a right-handed helix. A negative Cotton effect is indicative of a left-handed twist (158). Since compound **73** presents a positive, and the diene **74** a strong negative amplitude, the Cotton effects are in agreement with the chiralities of the diene systems (158). The intense Cotton effect is probably also due in part to the homoconjugated chromophore, i.e.,

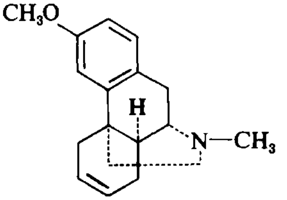


(75)

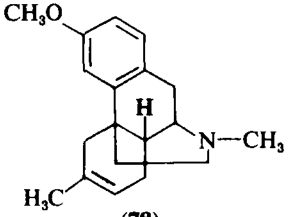


(76)

partial orbital overlap between the aromatic ring and the diene system. While the cisoid diene **75** exhibits an intense positive Cotton effect, its isomer (**76**) shows a negative curve (4). The very strong Cotton effect shown by the diene (**75**) could also be due to homoconjugation between both chromophores present in the molecule.

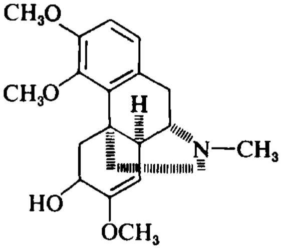


(**77**)

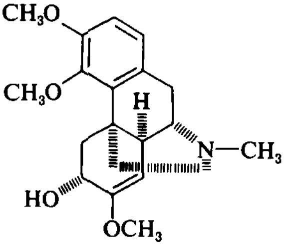


(**78**)

Somewhat related to the above-mentioned compounds are the tetracyclic alkaloids **77–80** (4). Compounds **77** and **78**, having an opposite stereochemistry at the asymmetric centers, exhibit mirror-image dispersion curves. Moreover, the intensity of the Cotton effect is not only due to overlap of the π-electrons of the double bond with the aromatic nucleus, but is also affected by the substitution of the nucleus, as indicated by the noticeable difference between the rotatory dispersion curves of compounds **79** and **80** (4).



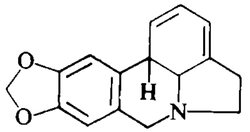
(**79**)



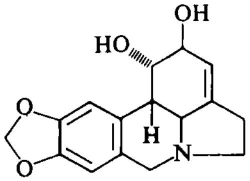
(**80**)

(7) *Miscellaneous Examples.* A similar homoconjugation phenomenon has been observed recently with alkaloids, or their derivatives, belonging to other classes (e.g., see ref. 160–162). For instance, the circular dichroism curve of the diene **81**, obtained during the stereochemical study of lycorine (**82**) and related alkaloids, presents two negative maxima ($[\Theta]_{295} = -13900$ and $[\Theta]_{264} = -17400$) (162). The helicity rule for cisoid dienes (158) predicts a positive Cotton effect for

81. The opposite and intense Cotton effect which is observed indicates that homoconjugation exists in this molecule (162).

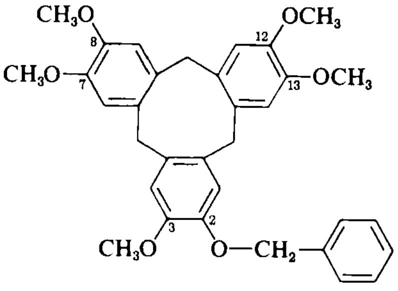


(81)

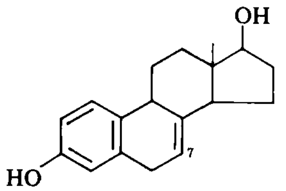


(82)

Recently, Lüttringhaus and Peters (163) discussed the conformational enantiomerism of a derivative of cyclotriveratrylene, namely a nine-membered cyclic compound called 2-benzyl-3,7,8,12,13-pentamethoxy-tribenzo-[*a*,*d*,*g*]-cyclo-1,4,7-nonatriene (**83**).



(83)



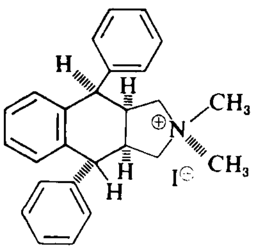
(83a)

The Δ^7-aromatic steroid (**83a**)* has a homoconjugated chromophore, and thus exhibits a Cotton effect between 290 and 265 mμ (a = +22) (164).

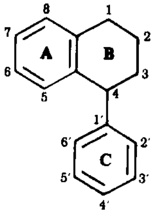
Finally, Quinkert and his co-workers (74) have reported the synthesis and optical properties of several homoconjugated derivatives. The enantiomers of compound **84** exhibit mirror-image rotatory dispersion curves whose Cotton-effect intensities account for the homoconjugated chromophore present in these molecules.

The homoconjugated chromophore is less rigid in **84** than in the other compounds discussed above. It is the purpose of the next section to discuss other similar chromophoric systems.

*This sample was obtained from Ayest McKenna and Co., Montreal, and was examined at Westfield College by Professor Klyne.



(84)



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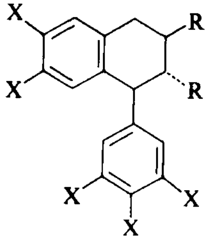
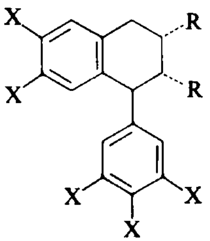


(86)

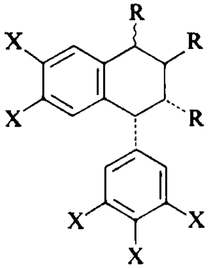
(*8*) *Lignans: 4-Aryltetralins.* Many good examples of a partially rigidified system are found in the 4-aryltetralins of the lignan series (general structure **85**).

Swan and Klyne (165) have studied the rotatory dispersion curves of more than one hundred members of this group, which includes many important natural products—e.g., podophyllotoxin, the peltatins, the conidendrins—and their derivatives.

These compounds all give two Cotton effects, the first between 290 and 280 mμ and the second between 245 and 230 mμ. The second Cotton effect is not easy to study, because it lies near the lower wavelength limit which can be reached by the presently available instruments; it appears to be opposite in sign to the first Cotton effect in nearly all cases. We will consider here the regularities found in the first Cotton effect (ca. 280 mμ). The compounds which have been examined may be considered as falling into three general diastereoisomeric classes (each, of course, in two enantiomeric forms). These may be represented by structures **86**–**88** (with their enantiomers), where R_2 and R_3 (and R_1 in **88**) are either CH_3, CH_2OH, CH_2OTs, CO_2H, CO_2Me etc.—or —$CH_2 \cdot O \cdot CO$—, —$CH_2 \cdot O \cdot CH_2$— linking C-2 and C-3. The substit-



(87)



(88)

uents X at positions 6,7,3′,4′, and 5′ are usually OH, OMe, or —O·CH_2·O— linking C-6 and C-7.

The overriding generalization is that all 4β-aryl compounds give negative Cotton effects and all 4α-aryl compounds give positive Cotton effects. Table VIII summarizes the ranges of amplitudes which were found (165).

Table VIII

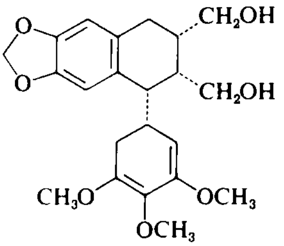
Optical Rotatory Dispersion of 4-Aryltetralins: Signs and Amplitudes of First Cotton Effects in the 285-mμ region

Type	Configuration	No. of compounds	Sign and amplitude of first Cotton effect (*a*)
86	2β,3α,4β	20	−290 to 410
E86[a]	2α,3β,4α	3	+180 to 260
87	2α,3α,4β	8	−100 to 200
E87[a]	2β,3β,4α[b]	15	+ 80 to 130
88	2β,3α,4α[b]	30	+ 25 to 90

[a] E indicates "enantiomer of."

[b] Many of the compounds in these two classes have substituents at C-1 (either 1α or 1β).

Figure 17 shows the rotatory dispersion curves of structures **89–92** (165). One will notice the influence of the substituents on the saturated ring on the intensity of the Cotton effects. A circular dichroism study of some of these compounds has been made (166). As expected (85), circular dichroism allows a better quantitative estimation of the Cotton effects.



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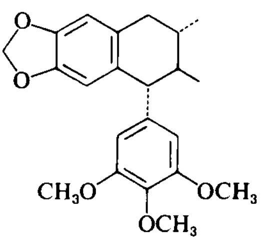


(90)

Some tentative comments on the effect of substituents at C-1, C-2, and C-3 in the alicyclic ring have been made elsewhere (165). Here one may draw attention to a point concerning substitution in the mobile aromatic ring C, which can pivot about the bond joining it to C-4. All compounds of classes **E86** and **E87** have three methoxyl groups at positions C-3′,

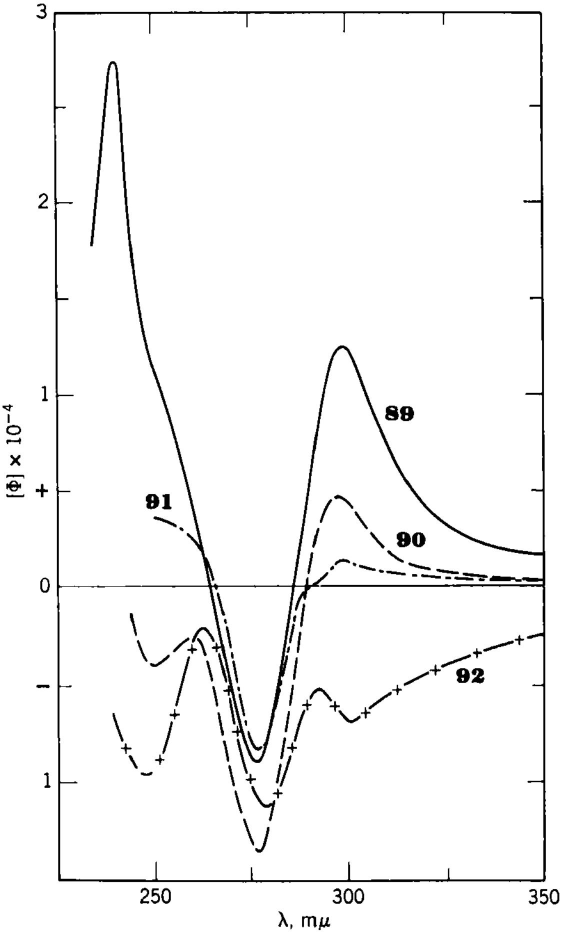
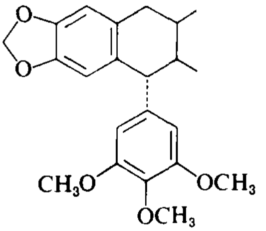


Fig. 17. Optical rotatory dispersion curves of the substituted 4-aryltetralins **89**–**92**. [Modified from P. Crabbé and W. Klyne, *Tetrahedron*, in press.]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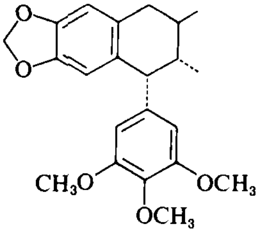
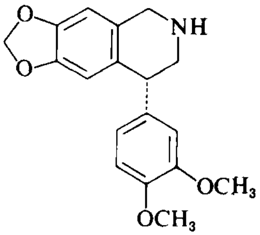
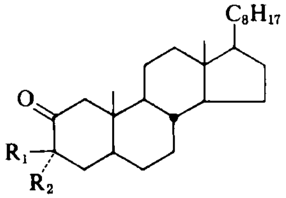

(92)

C-4′, and C-5′ in ring C, while the comparable compounds in classes **86** and **87** have two such methoxyl groups (at C-3′ and C-4′). The amplitudes for classes **E86** and **E87** are about two-thirds of those for classes **86** and **87**.

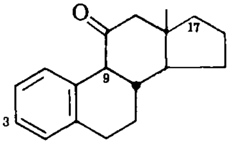
The optical properties of a few 2-aza-analogs of lignans—dehydrococcinine derivatives (**93**) have also been examined. The circular dichroism curves are generally similar in shape to those of the carbocyclic analogs (167).


(93)

c. **Homoconjugated Aryl Ketones.** The very intense Cotton effect sometimes exhibited by these chromophores can be interpreted in terms of homoconjugation of carbonyl and benzene π-electrons (see Sect. II-B). Cookson and co-workers (31) have indicated that in 3-phenyl-5α-cholestan-2-one the very intense positive Cotton effect ($a = +374$) of the axial 3α-isomer **94a**, which is accompanied by the typically intense ultraviolet absorption in the carbonyl region, (ϵ_{max} 220, at 299 mμ) suggests the prevalence of conformations in which the orientation of π-electrons of the benzene ring relative to electrons of the carbonyl group is geometrically favorable to enhancement of absorption. Furthermore, the sign of the Cotton effect of the steroid **94a** is in harmony with the geometry *B* of Figure 3 (Sect. II-B) (34) for the absolute configuration indicated. Conversely, the equatorial 3β-isomer **94b** in which such orientations are not possible, has a normal absorption spectrum and molecular amplitude (*a* = +45). The recent paper by McKenzie et al. (168) suggests that the conformational situation may be still more complicated.



(**94a**) $R_1 = H; R_2 = C_6H_5$
(**94b**) $R_1 = C_6H_5; R_2 = H$



(**95**)

Moscowitz et al. (34) treated a wider range of compounds in terms of the coupling between the π-orbitals of two unconjugated π-systems (*vide supra*). Other similar examples of homoconjugated aryl ketones have been reported recently (169).

The circular dichroism technique has permitted a detailed study of the conformation of the 11-oxo-A-ring aromatic steroids (**95a–95h**) listed in Table IX. The isomeric compounds **95a** and **95b** (170) for example, differ in the configuration of the hydrogen atom at C-9. The

TABLE IX

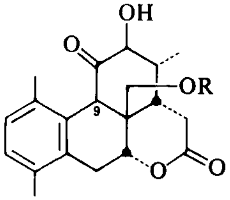
Circular Dichroism of "Homoconjugated" Arylketones—A-Aromatic 11-ketosteroids

Compound	Substituents in aromatic ring A	Other substituents	Molecular ellipticity, [Θ]	
			9αH	9βH
95a,b	3-OMe	17β-acetyl	+ 8,900	+50,200
95c,d	3-OH	17β-acetyl	+ 8,700	+50,200
95e,f	3-OBz	17β-acetyl	+ 9,800	+34,200
95g,h	1-Me,3-OAc	17α-OH,20-keto, 21-OAc	+16,200	+26,700

very strong positive Cotton effect of **95b** can be interpreted in terms of homoconjugation of the carbonyl and benzene π-electrons, since the geometry is favorable for such interactions (4).

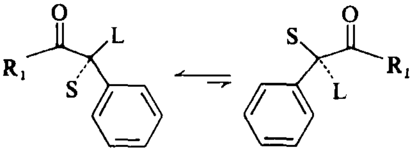
Table IX lists a number of such isomeric steroids, and shows that the compounds with the 9β-stereochemistry always exhibit a much more positive Cotton effect than the 9α isomers. Moreover, since a 20-keto steroid (in a 17β-side chain) presents a strong positive Cotton effect ($a = +190$; $[\Theta] = +11{,}200$) (4), and provided there is no vicinal effect between the 11 and 20-carbonyl groups, a negative Cotton effect seems to be associated with the homoconjugated 11-keto chromophore in **95a**, **95c**, and **95e**. Conversely, a positive Cotton effect is associated with the same chromophore in **95g**, thus indicating that ring C in 1-methyl-11-keto-aromatic-steroids probably has a different conformation. Finally, as indicated in Table IX, the nature of the substituent at C-3 does not modify the sign, but has only a mild influence on the intensity of the Cotton effect associated with these homoconjugated chromophores (170,171).

Similar reasoning has been used to assign the stereochemistry at C-9 in chaparrol monoacetate (**96a**) and neochaparrol (**96b**) obtained from the triterpene chaparrin (**25**) (86). Chaparrol monoacetate (**96a**) exhibits a negative Cotton effect ($a = -56$), in agreement with the octant rule (13), whereas neochaparrol (**96b**) presents a very strong positive Cotton effect ($a = +250$), in agreement with the stereochemistry proposed for this homoconjugated π-system (86,172).



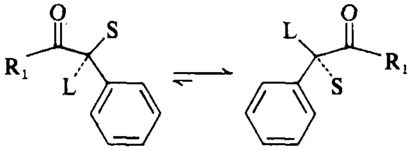
(**96a**) 9αH; R = Ac
(**96b**) 9βH; R = H

In cases in which free rotation may occur, the Cotton effect sometimes permits the assignment of conformations to β,γ-unsaturated ketones. Such a concept, which is supported by theoretical considerations, has allowed Moscowitz, Mislow, Glass, and Djerassi (34) to extend their conclusions to conformational analysis of open-chain α-phenyl ketones. They considered only the conformations in which the phenyl and carbonyl groups have the appropriate orientation for high optical activity, thus including the conformers approximating the geometry shown in Figure 3. For each enantiomer (*R*) and (*S*), two relevant diastereomeric conformations exist, one (**97a**) corresponding to a positive, the other (**97b**) to a negative Cotton effect. In the (*S*)-(**97a**)



(*S*)-**97a** (*S*)-**97b**

conformation, the smaller S group on the α-asymmetric carbon is in a less favorable steric position than the larger L group, because of steric compression against R_1 and against the phenyl *ortho*-hydrogen. Instead, in conformation (*S*)-(**97b**) it is the larger group which occupies

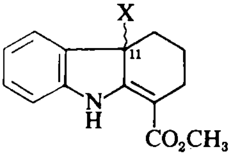


(*R*)-**98a** (*R*)-**98b**

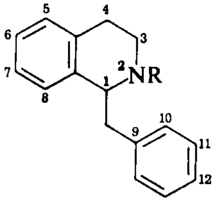
the unfavorable position; hence conformation **97a** predominates in the equilibrium. For similar reasons, the conformer (*R*)-(**98b**) predominates in the enantiomeric equilibrium. It follows that the (*S*)-isomer exhibits a net positive and the (*R*)-isomer a net negative Cotton effect. The intensity of the Cotton effect is a function of the relative difference in size of the L and S groups: the larger the relative difference, the greater the deviation of the **97a**/**97b** or **98a**/**98b** ratio from unity, and the more pronounced the net Cotton effect (34b).

These important concepts have permitted clarification of a number of previously unexplained observations which had been reported in the chemical literature.

d. Homoconjugated Systems with a Heteroatom. (*1*) *β-Anilino-acrylic Esters.* The homoconjugated systems in which a heteroatom (*N*) lies between the two unsaturated units include certain alkaloids of the aspidospermine and strychnine groups, most of which may be considered as β-anilinoacrylic esters (**99**). These compounds present two Cotton effects, generally one (*a*) between 340 and 270 mμ, and the other (*b*) below 250 mμ (128a). The signs of these Cotton effects are related to the neighboring center of asymmetry (C-11) as follows. If the configuration is 11α, *a* is positive, and *b* is negative; in case of 11β-stereochemistry *a* is negative and *b* positive.



(99)



(100)

(*2*) *Benzyltetrahydroisoquinolines.* Several groups of investigators have studied the rotatory dispersion curves of a number of 1-benzyltetrahydroisoquinolines of the general formula **100** (its enantiomer and related alkaloids) (144,173–181,237).

These compounds, which might be considered as dihomoconjugated, show an aromatic Cotton effect at about 290–270 mμ, and also the first extremum of a second Cotton effect at ca. 240 mμ. All members of the (*S*)-series have two positive Cotton effects, while the enantiomeric (*R*)-compounds have double negative curves. A summary of some of the results obtained in these series is given in Table X.

Recent evidence (175,176) suggests that quaternization of nitrogen in a benzyltetrahydroisoquinoline makes no change in the sign of the rotatory dispersion curve, although there may be changes in the wavelength and amplitude of the Cotton effect. In quaternary ammonium compounds the transition giving a significant in-plane magnetic moment might be of $s \rightarrow \pi^*$ character, or it may involve *d* orbitals (176).

A recent publication (176) deals with tetrahydro-*N*-methyl-1-(2-phenylethyl)-isoquinolines, i.e., compounds in which there is an additional saturated carbon atom between both aromatic nuclei. Moreover, Battersby et al. (177) utilize the rotatory dispersion technique in order to assign the absolute configuration to melanthoidin, a bis-phenylethylisoquinoline alkaloid.

e. Flexible Homoconjugated Compounds—The Proximity Rule. Some diphenylpropylamines have recently been submitted to an optical rotatory dispersion examination (183). Figure 18 shows the rotatory

TABLE X

Optical Rotatory Dispersion of Some 1-Benzyltetrahydroisoquinolines (**100**) and Quaternary Derivatives (50)

Compounds	Substituents				First Cotton effect (ca. 280 mμ) (*a*)		Second Cotton effect (ca. 230 mμ) (*a*)	
	N R_1	C-7 R_2	C-11 R_3	C-12 R_4	*S*(+)	*R*(−)	*S*(+)	*R*(−)
Armepavine	Me	MeO	H	HO	+113	−173	+297	−151
Armepavine methiodide	$Me_2^+I^-$	MeO	H	HO	+52		+1064	
O-Methyl-armepavine methiodide	$Me_2^+I^-$	MeO	H	MeO		−66		−776
Norarmepavine	H	MeO	H	HO	+110		+242	
(−)-Petaline iodide	$Me_2^+I^-$	MeO	H	MeO		−50		−121
Laudinidine	Me	MeO	HO	MeO		−602		−478
Laudanosine	Me	MeO	MeO	MeO	+185		+322	
Laudanosine hydrochloride	MeH^+Cl^-	MeO	MeO	MeO	+211		+436	
Laudanosine methiodide	$Me_2^+I^-$	MeO	MeO	MeO	+70 +105		+516 +296	
N-Acetyltretrahydropapaverine	MeCO	MeO	MeO	MeO	+78	−104	+92![a]	−110[a]
N-Benzoyltetrahydropapaverine	PhCO	MeO	MeO	MeO	+142	−135		
Reticuline hydrochloride	MeH^+Cl^-	HO	HO	MeO	+83	−94	+168[a]	−148[a]
Orientaline hydrochloride	MeH^+Cl^-	HO	MeO	HO	+48	−85	+156[a]	−136[a]
OO'-Dibenzyl-reticuline	Me	$PhCH_2O$	$PhCH_2O$	MeO	+84	−141	+195[a]	−260[a]
OO'-Dibenzyl-orientaline	Me	$PhCH_2O$	MeO	$PhCH_2O$	+93	−129	+203![a]	−266

[a] These figures correspond to [Φ] × 10^{-2} values for the first extremum at ca. 240 mμ.

dispersion and ultraviolet curves of the isomeric 1-cyano-2-methyl-1,1-diphenylpropan-3-*N*,*N*-dimethylamine (**101**). The D-isomer exhibits a positive rotatory dispersion curve, on which the multiple Cotton effect associated with the aromatic band at ca. 265 mμ is clearly apparent. The strong activity around 300 mμ is attributed to homoconjugation

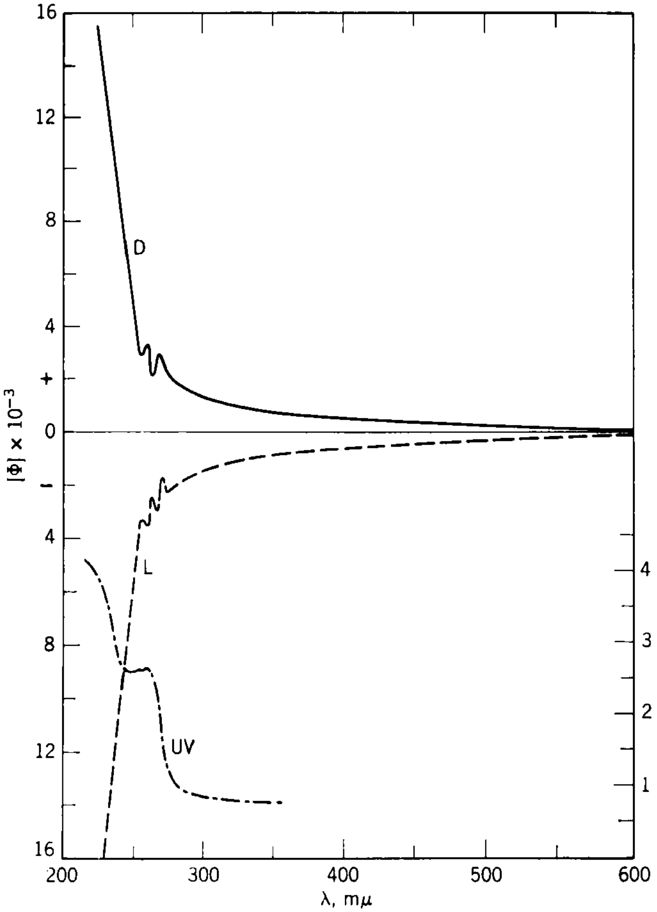
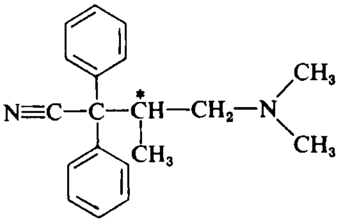


Fig. 18. Ultraviolet (UV) and rotatory dispersion curves of the isomeric 1-cyano-2-methyl-1,1-diphenylpropan-3-*N*,*N*-dimethylamine (**101**). [From P. Crabbé, P. Demoen, and P. Janssen, *Bull. Soc. Chim. France*, **1965**, 2855, by permission of the Editor.]

between the triple bond of the nitrile grouping and the two phenyl groups. The L enantiomer, of course, shows a dispersion curve which is the mirror image of its D isomer (183).



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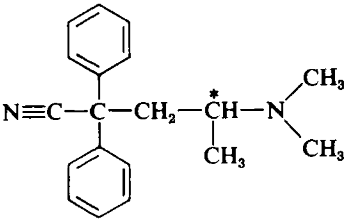
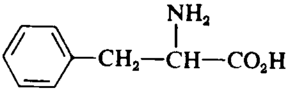


(102)

Figure 19 shows the rotatory dispersion and ultraviolet curves of a pair of isomeric diphenylpropylamines (**102**) (1-cyano-1,1-diphenylbutan-3-*N*,*N*-dimethylamine), in which the asymmetric center is separated from the CPh_2 group by one methylene. The D isomer exhibits a negative multiple Cotton effect at ca. 270 mμ, and its enantiomer a positive Cotton effect in the same region (183). This phenomenon of inversion of the Cotton effect by introduction of a methylene grouping between an asymmetric center and a chromophore, first noted for saturated ketones (184), seems to be rather general. Indeed, the proximity rule (172,183), i.e., the inversion of the Cotton effect by introduction of a methylene between a chromophore and an asymmetric center, can be extended to at least some other chromophores besides the keto group.

In this respect, Legrand and Viennet (91) mention that the sign of the circular dichroism Cotton effect associated with phenylalanine (**103**) in



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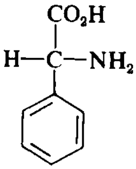
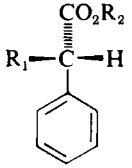


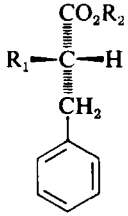
(104)

the 260-mμ region is different from that of L-mandelic acid (**10**) and L-phenylglycine (**104**), although these three compounds possess the same configuration (see Sect. C). Moreover, Verbit and Heffron (185) have recently reported the circular dichroism results in the 300–200 mμ region for several substituted phenylacetic (**105**) and 3-phenylpropionic

(**106**) acids and derivatives of known absolute configuration. A positive Cotton effect was observed in the carboxyl absorption region at ca. 210 mμ for compounds of the L configuration, thus substantiating the rotatory dispersion results of other workers (see below). Nevertheless,



(**105**)



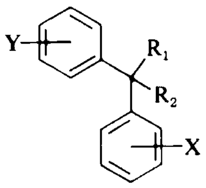
(**106**)

a negative Cotton effect was found in the aromatic absorption region at ca. 260 mμ for those molecules having the aromatic ring directly attached to the asymmetric center, whereas a positive Cotton effect was observed for molecules in which the ring is one carbon removed from the asymmetric center (185). However, one should keep in mind that the nature of the groupings involved in the chromophoric system and/or located on the asymmetric center might have a direct bearing on the Cotton effect in these compounds.

Comparison of Figures 18 and 19 indicates that the Cotton effect occurring at low wavelength is much weaker for compound **102** than when the asymmetric carbon atom is situated closer to the homoconjugated chromophore as in **101** (183).

It is also significant that, as might be expected, the ultraviolet absorption curves of the position-isomers **101** and **102** are almost identical, while the rotatory dispersion curves which reflect the chirality of the structure and, in particular, of the chromophore vis-à-vis the asymmetric center, are very different.

To this class of flexible, homoconjugated compounds belong diaryl methanes and some quinones, such as dalbergione (187), latifolin and related substances (**107**), and dihomoconjugated representatives, such as



(**107**)

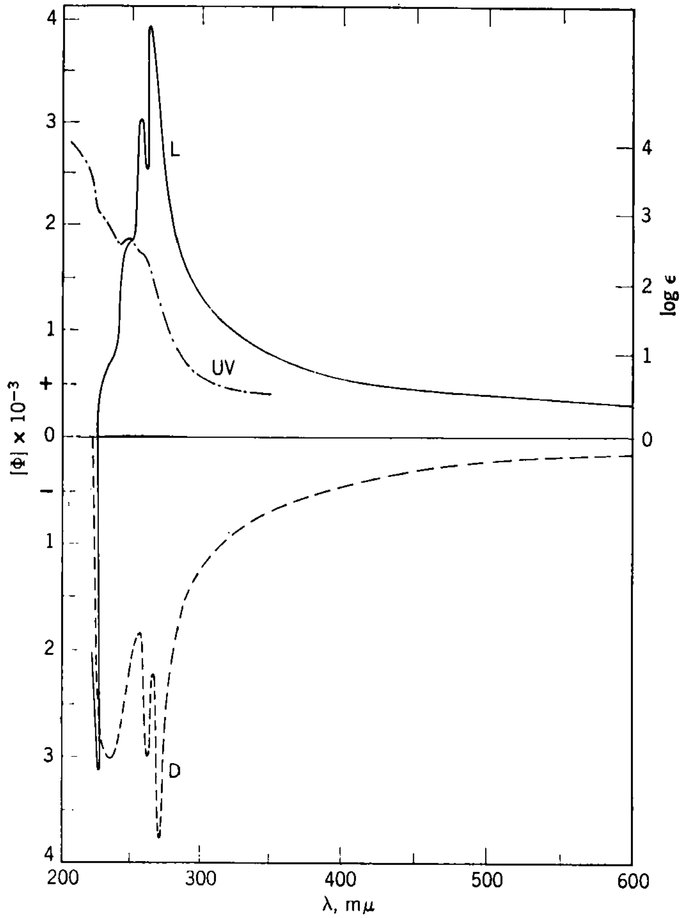
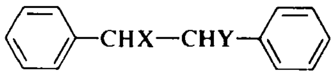
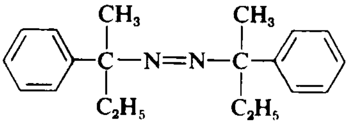


Fig. 19. Rotatory dispersion and ultraviolet (UV) curves of the isomeric D- and L-1-cyano-1,1-diphenylbutan-3-*N*,*N*-dimethylamines (**102**). [Reproduced from P. Crabbé, P. Demoen and P. Janssen, *Bull. Soc. Chim. France*, **1965**, 2855 by permission of the Editor.]

diaryl ethanes (**108**) and the like (188–194). Of particular interest are



(108)



(109)

the optical properties recently reported for azo-bis-2-phenyl-2-butane (**109**) (195), and other azoalkanes. Figure 20 reproduces the ultraviolet absorption and optical properties of compound (**109**) (195). It would probably be worthwhile to investigate the rotatory dispersion and

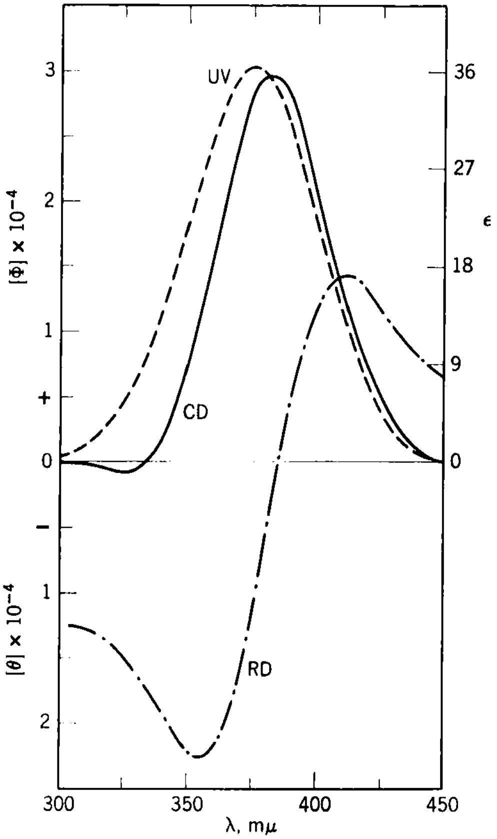


Fig. 20. Ultraviolet (UV), rotatory dispersion (RD), and circular dichroism (CD) curves of azo-bis-2-phenyl-2-butane (**109**). [Modified from E. M. Kosower and D. J. Severn, *Tetrahedron Letters*, **1966**, 3125.]

circular dichroism properties of optically active 1,2-diphenylcyclopropanes also (196).

C. Symmetrical Chromophores Which Are Dissymmetrically Perturbed

The second major class is that in which there is only one chromophore (a single aromatic system) which has many elements of symmetry but is dissymmetrically perturbed by "a center or centers of asymmetry." Some evidence suggests that a heterosubstituent on the aromatic ring itself (arylic substituent) is necessary to provide an optically active transition of high intensity (9,91,197–200). There are, however, several exceptions which will be discussed below.

The logical subdivision of this general class is difficult, and the following suggestions are put forward tentatively. First we will consider structures which are bicyclic or polycyclic, with one aromatic ring and at least one alicyclic ring (for a summary, see Table XI).

The subclassification must take account of (*1*) the relationship between the center or centers of asymmetry and the aryl nucleus, (*2*) the presence or absence of heteroatoms with lone pairs adjacent to these centers of asymmetry, and (*3*) the pattern of substitution on the aryl nucleus itself (character and local symmetry).

The center(s) of asymmetry in the side chain (or second ring) may be associated with (*a*) alkyl groups; (*b*) heteroatoms with lone pairs of electrons (either in or out of the second ring); and/or (*c*) heteroatoms without lone pairs (e.g., quaternary ammonium groups).

1. Geometrical Basis for Optical Activity of Aromatic Transitions

The rotational strength (R_k) of a transition k of a chromophore is related to its electric (μ_e^k) and magnetic (μ_m^k) dipole transition moments as defined previously (15). If one considers the angle (θ) between the two transition moments, the rotational strength is equal to:

$$R_k = \mu_e^k \mu_m^k \cos\theta$$

According to Moscowitz (197), the weakness of the 260 mμ Cotton effect of many aromatic compounds is due to the C_{2v} effective local symmetry of the aromatic ring. If one constructs the π-molecular orbitals of the system solely from linear combinations of $2p_z$ orbitals

TABLE XI

Classification of Compounds with Perturbed Aromatic Chromophores

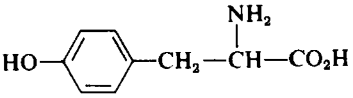
No arylic substituents	With arylic substituents
Class 1. *No benzylic heteroatoms*	
1-Alkyltetralin ($R = \mathrm{Alk}$; $A = H$)	Steroid estrogens: A ring aromatic, with OH (without alcoholic OH near A ring); also D-homo-ring aromatic (enantiomeric-type)
Class 2. *With benzylic heteroatoms*	
a. Not in ring B	
1-Tetralol ($R = \mathrm{OH}$; $A = H$)	6-OH, estrogen with OH at 6α or 6β; tetralin-1,5-diol $R = A = \mathrm{OH}$; also thebaine derivatives, chaparrol derivatives
b. In ring B	
Benzquinolizidine	Tetrahydroisoquinolines
In classes 3 and 4 the heteroatom serves to make the aromatic unit unsymmetrical; therefore all compounds may be considered as carrying arylic substituents.	
Class 3. *Arylic heteroatoms in ring B*	
Tetrahydroquinoline	
Dihydrobenzofuran	
Dihydroindoles	
Aspidospermine-type	
Neblinine-type	
Class 4. *Heteroaromatic structures*	
Tetrahydroharman	
Steroid-indole	
Yohimbine type (N_b is benzylic on indole; N_a is heteroaromatic) (results for effects of OMe and OAc)	
Quebrachamine (N_b is phenethylic on indole; N_a is heteroaromatic)	
Indolenines (see above)	
Other chromophores	
Tropones Pyrazoles Furans	

of carbon, then all $\pi \rightarrow \pi^*$ transitions from the ground state have their nonvanishing electric dipole transition moments μ_e^k directed in the plane of the ring, and their nonvanishing magnetic dipole transition moments μ_m^k directed perpendicular to that plane; thus $\cos \theta$ is zero. Hence, no amount of mixing of the $\pi \rightarrow \pi^*$ transitions among themselves can lead to a nonvanishing scalar product, $R_k = \mu_e^k \mu_m^k$, and thus to optically active $\pi \rightarrow \pi^*$ transitions.

To produce an optically active $\pi \rightarrow \pi^*$ transition by mixing in of other transitions, the essential factor is the generation of an in-plane magnetic moment in the right direction. This is most readily brought about by lone pairs of electrons in the vicinity of the aromatic nucleus, but it could come from other sources. This question will be discussed later in connection with compounds of fixed conformation.

The substitution in the aryl nucleus itself is usually of prime importance in determining the magnitude of the Cotton effect. Hence, the weak 260-mμ band is a "forbidden" band in benzene and "allowed" in toluene. Moreover, in any optically active system the 260-mμ band is formally "allowed" and is then called a $\pi \rightarrow \pi^*$ transition (197). It appears that in most cases an arylic hetero-substituent is necessary to make apparent a $\pi \rightarrow \pi^*$ transition and to give a significant Cotton effect at ca. 260 mμ (91,197,200).

A pair of compounds illustrating the importance of arylic heteroatoms is provided by the aromatic amino acids L-phenylalanine (**103**) and L-tyrosine (its *p*-hydroxy analog) (**110**). As pointed out by Moscowitz (197) the unsubstituted compound **103** gives an almost negligible Cotton effect at 260 mμ; while in **110** the hydroxyl group gives rise to a much larger Cotton effect ($a = +12$), as shown in Figure 21 (197–206).



(**110**)

The extreme weakness of the Cotton effect associated with phenylalanine (**103**) is due to the unfavorable geometry of the electric and magnetic dipole transition moments in this structure, since the $\pi \rightarrow \pi^*$ transition is only weakly allowed. If one accepts the above argument regarding local symmetry in the benzene nucleus, one sees that the dissymmetric molecular environment provided for the aromatic chromophore by the amino acid moeity in **103** is ineffective for the

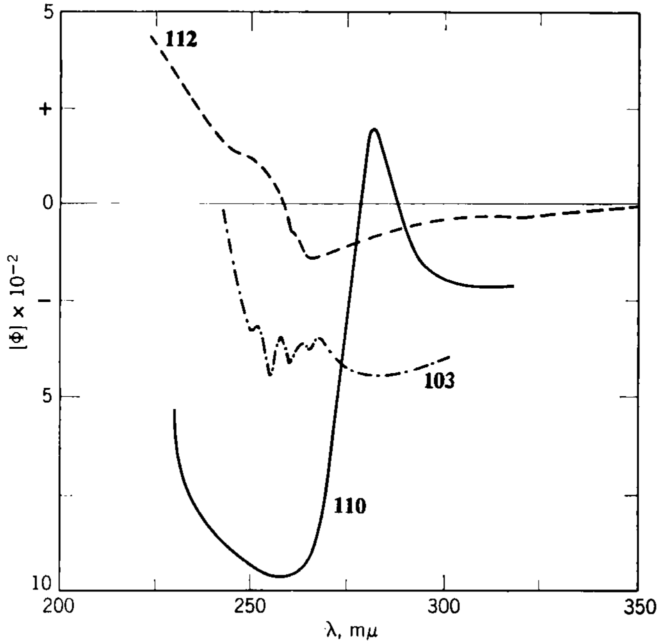


Fig. 21. Optical rotatory dispersion curves of phenylalanine (**103**), tyrosine (**110**), and α-phenylethylamine hydrochloride (**112**). [Adapted from P. Crabbé and W. Klyne, *Tetrahedron*, in press.]

generation of a $\pi \rightarrow \pi^*$ Cotton effect, so long as π-states of the sort described are the only states involved. Moreover, if one can ignore the possibility of charge transfer or the mixing of transitions between the aromatic and amino acid groups, then the only way the requisite in-plane magnetic moment can be achieved is by mixing the $\pi \rightarrow \pi^*$ transitions with some perpendicular transitions of the aromatic chromophore, e.g., a $\sigma \rightarrow \pi^*$ or $n \rightarrow \pi^*$ transition, or by expanding the basis set and invoking, e.g., 3*d* orbitals.

In tyrosine (**110**), the oxygen atom of the aromatic chromophore is a ready source of nonbonding orbitals for $n \rightarrow \pi^*$ transitions. Hence, the long-wavelength aromatic Cotton effect can be detected without difficulty (199,202–207). Conversely, in phenylalanine (**103**), where the 260-mμ electric moment is itself only very weakly allowed, this important mechanism for producing a properly directed magnetic moment

TABLE XII

The Cotton Effects of Some Aromatic Steroids and Similar Substances

Compound	Substituents[a]		Cotton effects		Ref.
	A ring	D ring and side chain	λ, mμ	[Θ] (or *a*), deg.	
		Normal 9α-configuration			
118a	None	17β-OH	ca. 270	Very weak	96
118b	4-Me	17β-OH	ca. 270	Very weak	96
118c	3-OH	17β-OH	$[\Theta]_{280}$	−1,980	91
			$[\Theta]_{230}$	+10,560	
			$[\Theta]_{208}$	−1,980	
			$[\Theta]_{198}$	+41,600	
118d	1-OH,4-Me	17β-OH	$[\Theta]_{282}$	+8,050	91
			$[\Theta]_{232}$	+6,600	
			$[\Theta]_{209}$	−18,500	
			$[\Theta]_{198}$	+53,800	
			290/270	$a \cong +100$	50
118e	3-OH,2-Me	17β-OH	$[\Theta]_{280}$	+660	91
			$[\Theta]_{233}$	+12,540	
			$[\Theta]_{211}$	−11,600	
			$[\Theta]_{202}$	+19,500	
118f	3-OH,4-Me	17β-OH	$[\Theta]_{282}$	−2,300	91
			$[\Theta]_{230}$	+8,250	
			$[\Theta]_{208}$	−14,850	
			$[\Theta]_{193}$	+28,000	
118g	3-OMe,4-Me	17β-OH	$[\Phi]_{313}$	+860	50
			$[\Phi]_{284}$	−400	
			$[\Phi]_{256}$	+3,670	
			$[\Phi]_{232}$	+8,550	
118h	3-OMe,2-Me	17β-OH	$[\Phi]_{290}$	+1,760	50
			$[\Phi]_{263}$	+2,770	
			$[\Phi]_{238}$	+7,600	
118i	3-OMe,2-CH_2OH	17β-OH	$[\Phi]_{297}$	+1,060	214
			$[\Phi]_{259}$	+2,660	
			$[\Phi]_{236}$	+5,400	
118j	3-OMe,4-CH_2OH	17β-OH	$[\Phi]_{287}$	+860	214
			$[\Phi]_{263}$	+2,850	
			$[\Phi]_{234}$	+7,100	

(continued)

TABLE XII (*continued*)

	Substituents[a]		Cotton effects		
Compound	A ring	D ring and side chain	λ, mμ	[Θ] (or *a*), deg.	Ref.
118k	3-OMe,2-CHO	17-ketone	$[\Theta]_{297}$	+10,700	214
			$[\Theta]_{283}$	+5,800	
			310/272	*a* = +140	
118l	2,3,4-Me	C_8H_{17}	$[\Phi]_{300}$	+3,430	50
			$[\Phi]_{282}$	+4,100	
			$[\Phi]_{270}$	+4,380	
			$[\Phi]_{232}$	+8,370	
			$[\Phi]_{229}$	+7,600	
118m	3-OMe	17α,20β-Dihydroxy	286/263	*a* = −16	170
			$[\Phi]_{236}$	+5,300	
118n	3-OMe	17,20,21 BMD	$[\Phi]_{286}$	−3,350	171
			$[\Phi]_{275}$	−3,030	
			$[\Phi]_{266}$	−2,220	
			$[\Phi]_{253}$	−2,400	
			$[\Phi]_{234}$	−630	
			$[\Phi]_{218}$	−8,900	
118o	3-OH,1-Me	17β-OH	ca. 270	Very weak	50
118p	3-OAc,1-Me	Spiro	278/249	*a* = −164	50
118q	3-OAc	6α-OAc	$[\Phi]_{224}$	−10,500	211
		17β-OAc	$[\Phi]_{221}$	−5,800	
118r	3-OH	6β-OH	283/261	*a* = −18	211
		17β-OH	229/213!	*a* = +232!	
118s	3-OAc	6β-OAc	ca. 270	Faint negative	211
		17β-OAc	224/208	*a* = +394	
118t	3-OH	9α-OH	284/263	*a* = −19	212
		17β-OH			
120	Chaparrol		283/270	*a* = +24	86
		Abnormal 9β-configuration			
118u	3-OH	17β-OH	287/256	*a* = +22	96
			232/212	*a* = −110	
			$[\Theta]_{280}$	+1,490	91
			$[\Theta]_{230}$	−12,540	
			$[\Theta]_{205}$	+16,830	
			$[\Theta]_{190}$	+17,500	

(*continued*)

TABLE XII (*continued*)

Compound	Substituents[a] A ring	 D ring and side chain	Cotton effects λ, mμ	 [Θ] (or *a*), deg.	Ref.
118v	3-MeO	17β-OH	285/255	*a* = +23	96
			$[\Theta]_{233}$	−6,000	
118w	3-OMe	17α,20β-Dihydroxy	286/260	*a* = +16	170
			$[\Phi]_{236}$	−5,850	
118x	3-OH	17,20,21 BMD	290/275	*a* = +37	171
118y	3-OAc	17,20,21 BMD	$[\Phi]_{298}$	−1,250	171
			$[\Phi]_{276}$	−1,040	
			$[\Phi]_{250}$	−3,480	
			$[\Phi]_{225}$	−4,860	
118z	3-OH	9β-OH 17β-OH	286/272	*a* = +14	212
119	3β,17-OAc,17αCH$_3$ Aromatic D-homo-androstane		$[\Phi]_{288}$	−13,410	96
			$[\Phi]_{250}$	−4,590	
			$[\Phi]_{226}$	−5,920	
121	Isochaparrol		288/278	*a* = −4	86

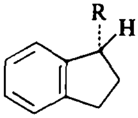
[a] Abbreviations: BMD = bismethylenedioxy derivative of corticoid side chain; spiro = spirostan side chain.

is absent, and only the less effective mechanisms of mixing with π → π* transitions or transitions involving 3*d* or higher orbitals are available. This explains the faintness of the 260-mμ Cotton effect in phenylalanine (91,197), (see Fig. 21).

The same concept applies to the substantial differences observed in the Cotton effects associated with the aromatic compounds carrying different substituents listed in Table XII (*vide infra*).

2. *Comparison of Rigid and Flexible Systems*

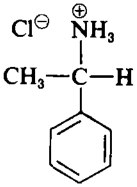
The rotatory dispersion curves of indane-1-amine (**111k**) (208) and α-phenylethylamine (**112**) (209), both as hydrochlorides are reproduced on Figures 21 and 22. Comparison of these curves shows that the Cotton effect at about 280 mμ is negligible in the flexible compound **112**, but of significant size in the rigid indane derivative **111k**.



(111a) R = H
(111b) R = CO_2H
(111c) R = $CO_2^-Na^+$
(111d) R = CH_2OH

(111e) R = $COCH_3$
(111f) R = $OCOCH_3$
(111g) R = OH
(111h) R = NH_2

(111i) R = $NH_3^+Cl^-$
(111j) R = CH_3
(111k) R = $^+NH_2CH_3Cl^-$

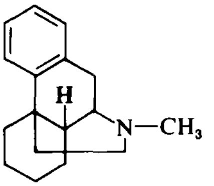


(112)

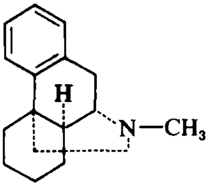
3. *Anomalies*

There are, however, some anomalies. The enantiomeric morphinans **(113)** and **(114)** have no arylic substituent, but they exhibit substantial multiple Cotton effects, as illustrated in Figure 23 (4).

On the other hand, possession of an arylic hydroxyl group is not sufficient in itself to guarantee a strong Cotton effect. See, e.g., compounds **115** and **116** (200), where the local surroundings of the hydroxyl group are symmetrical. In contrast, compound **117**, which is not symmetrical about the hydroxyl group, shows a strong Cotton effect at 280–260 mμ. The greatly increased rotational strength of the structure of type **117** may be due, on the one hand, to the relative geometry of the electric and magnetic moments (i.e., a more favorable cos θ factor in the formula mentioned above). On the other hand, it may also be due to hindered rotation of the hydroxyl group at C-1 by the adjacent alkyl group (methylene at C-11 in a steroid molecule).



(113)



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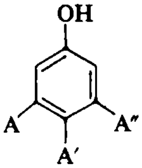
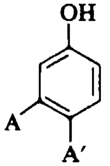


(115)



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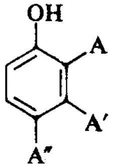

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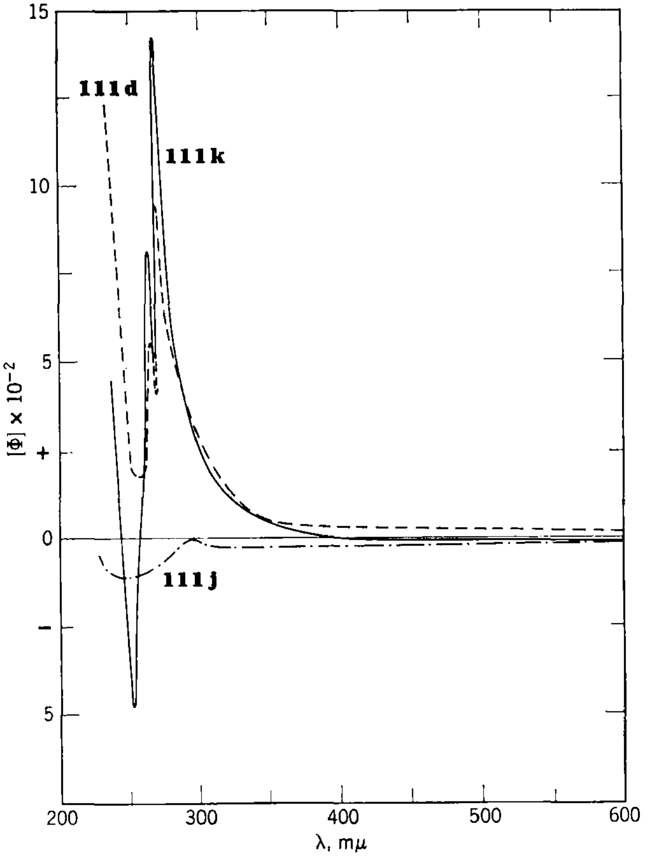


Fig. 22. Optical rotatory dispersion curves of the indane derivatives (**111d**), (**111j**), and (**111k**). [Adapted from J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966).]

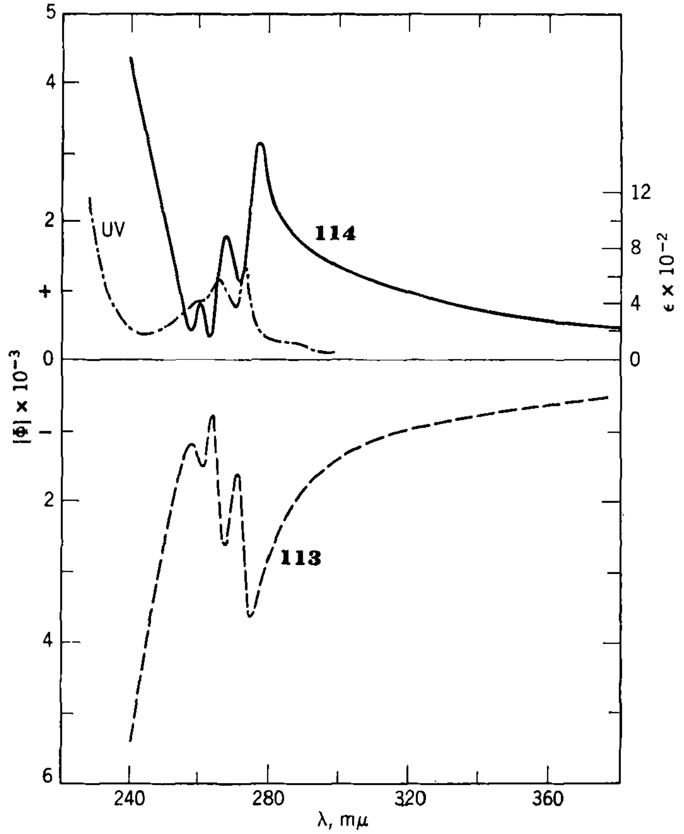
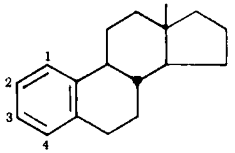


Fig. 23. Rotatory dispersion and ultraviolet (UV) curves of the enantiomeric morphinans **113** and **114**. [Reproduced from P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco, 1965, by permission of the Editor.]

4. Tetracyclic Aromatic Compounds

The estrogenic steroids (**118**) and related compounds **119–121** provide a good range of substances with differing stereochemistry, and arylic and benzylic substituents. The aromatic Cotton effects of some such compounds are summarized in Table XII (50,211–214).



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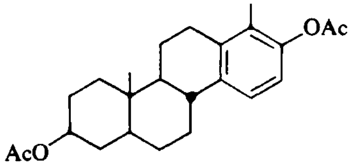
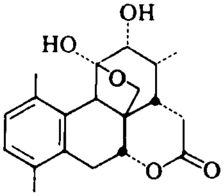


(119)



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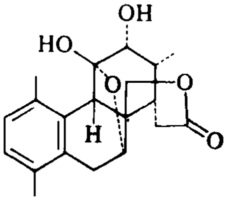


(121)

5. *Tetralols*

(+) and (−)-β-Tetralols (215) give almost plain curves ([Φ] ±3800° at 227 mμ) with only a slight inflection in the region of 270 mμ.

6. *Indanes*

Brewster and Buta (208) have prepared a series of optically active 1-indanes and have measured their optical rotatory dispersion curves. Weak phenyl Cotton effects could be detected in the 260–270 mμ region of the acid (**111b**), carbinol (**111d**), methyl ketone (**111e**), alcohol (**111g**), acetate (**111f**), amine (**111h**), and amine salt (**111k**). However, no Cotton effect was observed in the curves of the methyl derivative (**111j**) and of the carboxylate salt (**111c**). Some related compounds have been prepared recently by Gagnaire et al. (216). An application of the Eyring-Jones method (217) for the prediction of optical activity gave results that were in general agreement with the experimental findings.

Brewster and Buta's work was undertaken to determine whether the rotatory properties of an optically active molecule having a "fixed" phenyl group adjacent to the asymmetric center would differ significantly from those of a similar molecule in which the phenyl group could rotate freely (see below). It had been anticipated that phenyl compounds, having weak absorption bands in the near ultraviolet, might well exhibit rotatory properties different from those expected by application of the conformational dissymmetry rule (218), that rule applying to effects related to strong absorption bands. According to Kuhn (219), interference with free rotation of the phenyl group would be significant for the consideration of optical activity; the vicinal effect of the nonfreely rotating phenyl group would be different from that effect due to the freely rotating phenyl group, the latter being cylindrically symmetrical.

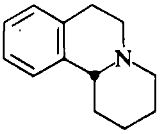
One of the simplest molecules containing an asymmetric carbon and a rigid phenyl group is the 1-methyl-indane **111j**. This system is comparable to the α-phenylethyl system **(112)** which has a phenyl group capable of essentially free rotation.

Fredga (220) has resolved indane-1-carboxylic acid and found the absolute configuration of the (+)-isomer to be (*R*). Brewster and Buta transformed this acid into a whole range of 1-substituted indanes with retention of configuration at the asymmetric center (208).

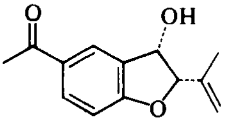
In all of these compounds the multiple Cotton effect at ca. 260 mμ is easily observed, except for the methyl analog **111j** and carboxylate salt **111c** (208); the intensity of the Cotton effect varies substantially with the nature of the substituent on the asymmetric center (see the three representative curves in Fig. 22). Although all the compounds examined by Brewster and Buta (208) have the same (*R*)-absolute configuration, they do not all exhibit a positive multiple Cotton effect ca. 260 mμ. For example, in the methyl ketone **111e** the β,γ-aryl-carbonyl chromophore must probably be considered as a coupled oscillator; this compound shows a negative Cotton effect (contrast **111b,d,f,g**).

7. *Heterocyclic Systems*

a. Benzoquinolizidines. The benzoquinolizidine **(122)** studied by Horii et al. (221) represents a very simple rigid type of heteroaromatic structure with no arylic substituent. Similar results have been obtained with compounds recently described (222).



(122)



(123)

b. Benzodihydrofuran. The benzodihydrofuran type is represented by toxol (**123**) (223), which gives a strong negative Cotton effect between 290 and 250 mμ (*a* = −200). The situation is complicated here by the carbonyl group conjugated with the aromatic chromophore. Although the acetyl group is conformationally free and remote from the asymmetric centers its effect cannot be neglected, since one deals here with an acetophenone chromophore and not a simple aromatic ring.

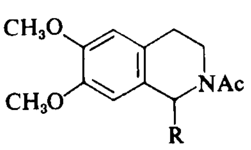
c. Tetrahydroisoquinolines. Simple 1-substituted tetrahydroisoquinolines (**124**) show a small aromatic Cotton effect in the region of 290–270 mμ. 1β-Substituted compounds (*S*-series) give positive effects; 1α-(*R*)-compounds give negative Cotton effects. The molecular amplitudes are summarized in Table XIII (173).

TABLE XIII

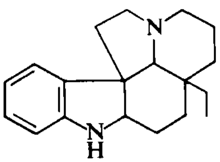
Optical Rotatory Dispersion Data for Simple Tetrahydroisoquinolines (**124**)

Series	Substituents: Position C-1 R_1	Substituents: At N R_2	Molecular amplitude, *a*
1β (*S*)	CH_2OH	Ac	+22
1α (*R*)	CH_2OH	Ac	−36
1β (*S*)	Me	$SO_2C_7H_7$	+52
1α (*R*)	CH_2OSO_2Me	SO_2Me	−13

Benzyltetrahydroisoquinolines which contain two aromatic nuclei per molecule have been considered in an earlier section (see Table X).



(**124**)



(**125**)

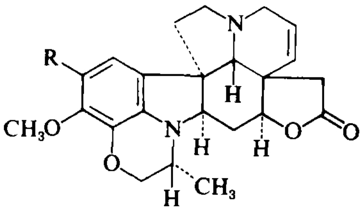
d. Dihydroindoles. The dihydroindole series is represented by members of the aspidospermine group (**125**) (128a,224); see Table XIV.

TABLE XIV

Optical Rotatory Dispersion of Dihydroindoles

Compound	Molecular amplitude, *a* (310–250 mμ)
(+)-Aspidospermidine (**125**)	−51
(+)-*N*-Deacetylaspidospermine	−66
Obscurinervine (**126a**)	−50
Obscurinervidine (**126b**)	−50
Neblinine (**126c**)	−25

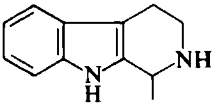
Still more complex polycyclic structures which have the dihydroindole chromophore are the alkaloids of the neblinine-obscurinervine group studied by Brown and Djerassi (**126**) (224). Their first Cotton effect is around or above 300 mμ and is negative; their second Cotton effect (first extremum at 270 mμ) is also negative. The midpoint of the first Cotton effect agrees well with the first ultraviolet absorption maximum; ~315 mμ for R = MeO at C-15; but 300 mμ for R = H at C-15. The amplitudes for both series are moderate (*a* = −20 to −60).



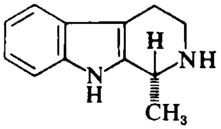
(**126a**) R = H (**126b**) R = OCH$_3$
(**126c**) R = H

e. Indoles. Several widely differing classes of compounds studied so far include the indole nucleus as their principal chromophores (**127**). Tetrahydroharman (**128**) (225) gave a negligible Cotton effect in the 280–260 mμ region; however some tetracyclic compounds of this series exhibit a considerable positive Cotton effect between 300 and 250 mμ. The steroid 2,3-indole (**129**) has a positive Cotton effect in the 260-mμ region (*a* = +75) (226).*

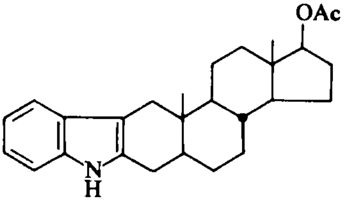
*This compound was prepared at Syntex S.A. by Dr. J. C. Orr.



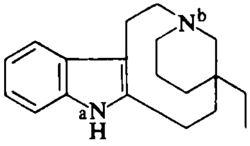
(127)



(128)



(129)



(130)

(−)-Quebrachamine **(130)** has a nine-membered ring fused to the indole nucleus; it has only one center of asymmetry and one heteroatom (N_b), each separated from the chromophore by two methylene groups. It gives a weak negative Cotton effect in the 300–250 mμ region, followed by an intense positive Cotton effect between 240 and 220 mμ.

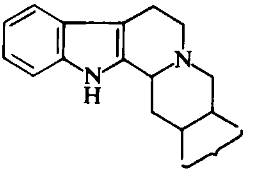
Finally, a wide variety of yohimbine derivatives and related compounds **(131,132)** have been investigated (128b,227,228). One important group with another chromophore in ring E should be considered utilizing the coupled-oscillator model; some comments on this group are included in Section III-B-3-b-(4). In the simpler compounds the sign of the Cotton effect in the 270-mμ region depends on the stereochemistry at C-3; see Table XV.

Table XV

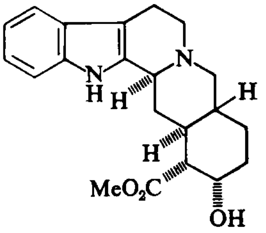
Optical Rotatory Dispersion of Yohimbine Derivatives

Compound	Configuration	*a*	Wavelengths of peaks and troughs, mμ
Yohimbine	3α-H	+ 82	296/250
Ψ-Yohimbine	3β-H	−146	288/248
Dihydrocorynantheol	3α-H	+125	282/251
Isodihydrocorynantheol	3β-H	− 51	298/253

Numerous other alkaloids and related substances have been investigated by optical rotatory dispersion and circular dichroism (229,230), but the above-mentioned examples give a fairly objective picture of the variety and complexity of the aromatic chromophores encountered in this important class of natural products.



(131)

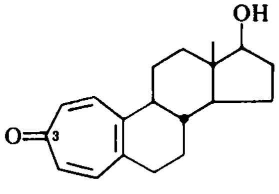


(132)

8. Other Chromophores

Optical techniques have been used for structural and stereochemical studies of numerous other aromatic-type chromophores.

a. Tropones. The rotatory dispersion and ultraviolet absorption curves for a pair of isomeric tropone-steroids (**133**,**134**) (231) are given in Figure 24. The ultraviolet spectra of these isomers are very similar, but their dispersion curves exhibit Cotton effects of opposite sign below 250 mμ; the 3-tropone (**133**) has a positive Cotton effect, whereas its 4-tropone analog (**134**) shows a negative Cotton effect. The rotatory dispersion technique is therefore ideally suited for the location of the carbonyl group in such systems.



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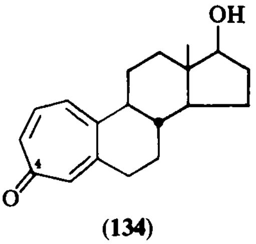
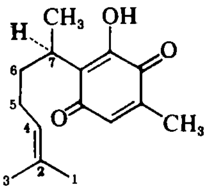


(134)

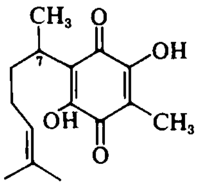
b. Quinones. The optical properties of several sesquiterpenes possessing the quinone chromophore have recently been examined (232). *Sensu stricto* a quinone is not an aromatic chromophore (*vide supra*);

however, because of the close relationship existing between quinones and phenols, some rotatory dispersion properties will briefly be mentioned in sequence (232,233).

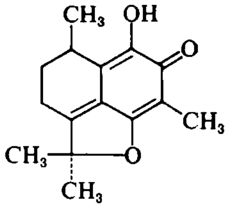
(−)-Perezone (**135**) is characterized by three ultraviolet absorption bands, in the 206-, 266-, and 412-mμ regions. Since the chromophore is situated next to an asymmetric center, the optical properties were expected to depend on its configuration. The 206-mμ transition is indeed optically active and its Cotton effect is negative (232). Similarly, hydroxyperezone (**136**) and (−)-perezinone (**137**) both present negative Cotton effects in the same spectral region. The (*R*)-configuration has been assigned to the asymmetric center at C-7 in these molecules (232).



(**135**)

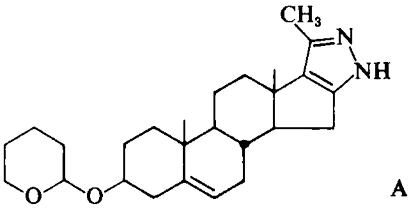


(**136**)

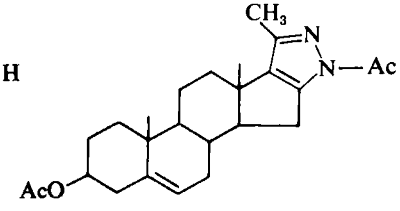


(**137**)

c. Pyrazoles. The rotatory dispersion curves of the steroid pyrazoles, **138–143**, have been obtained. The simple 16,20-pyrazole (**138**),* which contains no other chromophore, shows that the pyrazole chromophore is indeed optically active when in asymmetric surroundings (234). In the case of pyrazole **138**, a negative Cotton effect is observed in the 230-mμ region. The *N*-acetyl derivative (**139**) also exhibits a Cotton effect in the 260-mμ region.



(**138**)



(**139**)

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*These compounds were prepared by Mr. J. Iriarte in the Syntex Research Laboratories, Mexico.

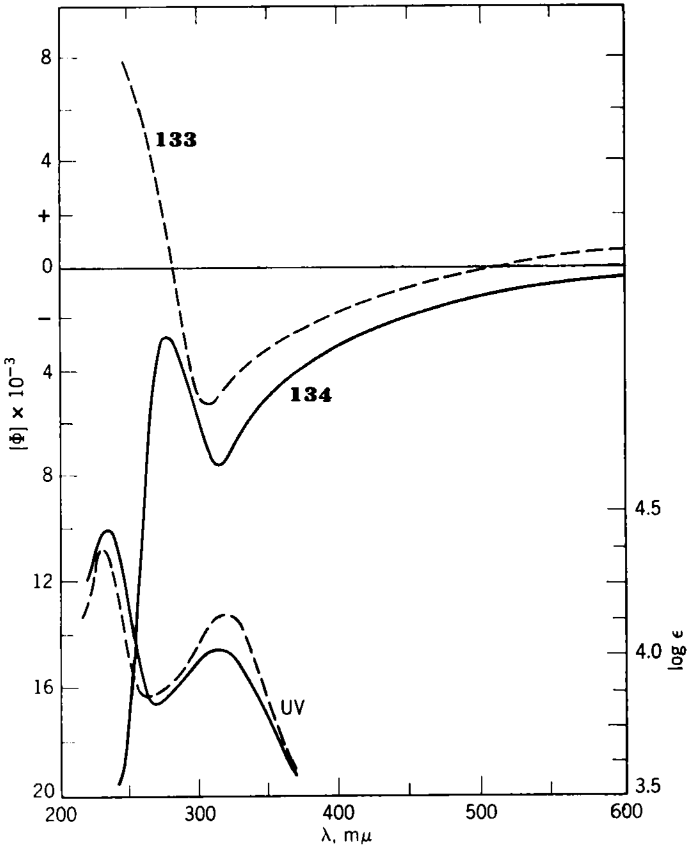


Fig. 24. Ultraviolet (UV) and rotatory dispersion curves of 17β-hydroxy-*A*-homo-estra-1,4(4a),5(10)-trien-3-one (**133**) and 17β-hydroxy-*A*-homo-estra-1(10), 2,4a(5)-trien-4-one (**134**). [Adapted from P. Crabbé, *Vietnamica Chimica Acta*, **1966**, 1.]

The phenylpyrazoles, **140** (235) to **143** (236), are all optically active. Figure 25 clearly indicates that the rotatory dispersion curves of these compounds reflect both the structural and stereochemical features of these molecules. The Cotton effect associated with the 250-mμ transition is negative in **140**. A very strong negative Cotton effect characterizes the 260-mμ band in the conjugated phenylpyrazole (**141**; $a = -622$).

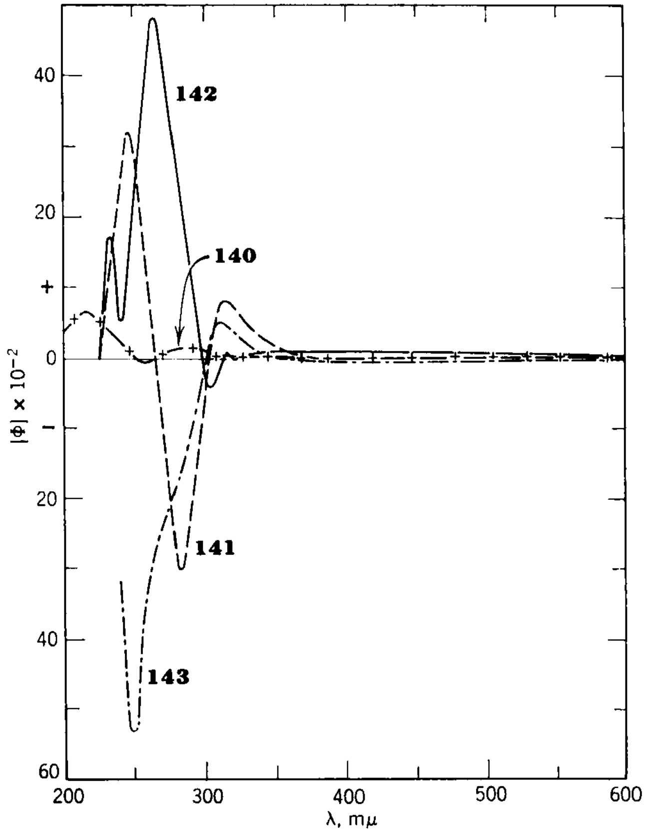


Fig. 25. Rotatory dispersion curves of the steroid phenylpyrazoles **140–143**.

Moreover the rotatory dispersion curve of the steroid **142** exhibits an intense peak at ca. 260 mμ. Conversely pyrazole **143** presents a strong negative molecular rotation in the 246-mμ region. Besides the phenylpyrazole chromophore, the last two compounds (**142** and **143**) possess a carbonyl grouping at C-20. However, one notices that it is the Cotton effect of the phenylpyrazole which predominates in these curves (Fig. 25). Worth mentioning is the fact that the aromatic systems present in **140–143** are conjugated aromatic chromophores.

d. Furans. Figure 26 reproduces the rotatory dispersion curves of optically active molecules containing a furan ring. While the monoterpene menthofuran (**144**) (237) exhibits a strong positive Cotton

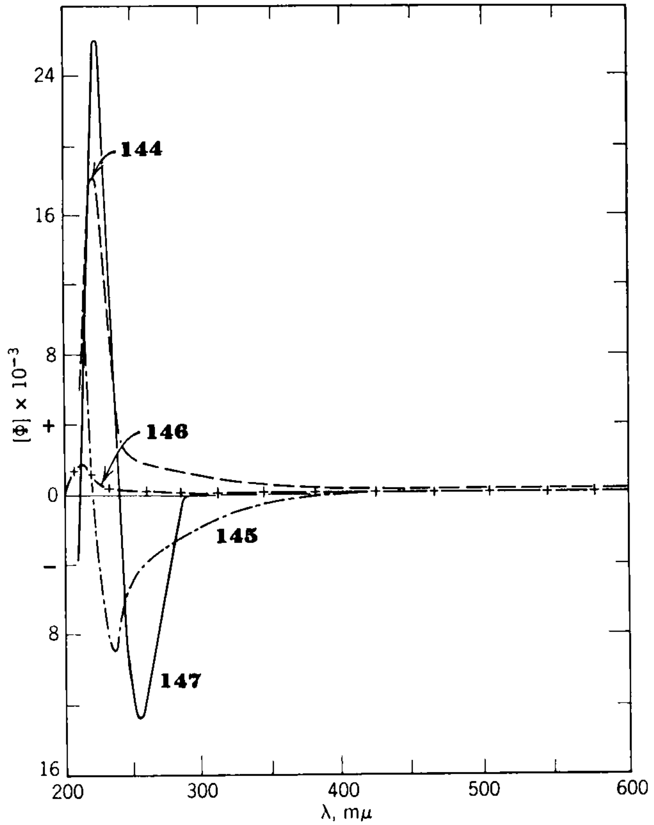
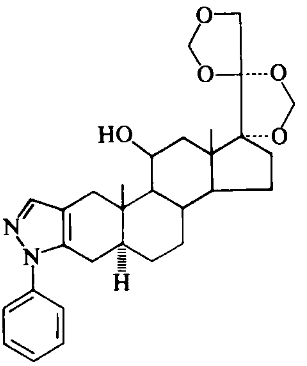
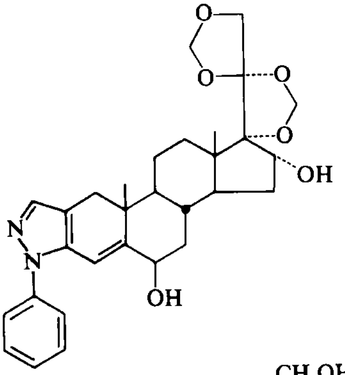


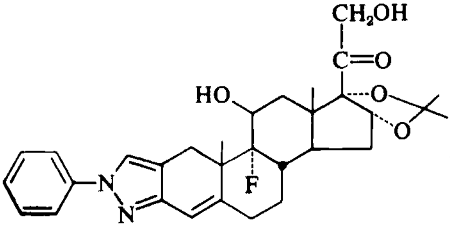
Fig. 26. Rotatory dispersion curves of menthofuran (**144**), cafestol (**145**), and the steroidal furan derivatives **146** and **147**.

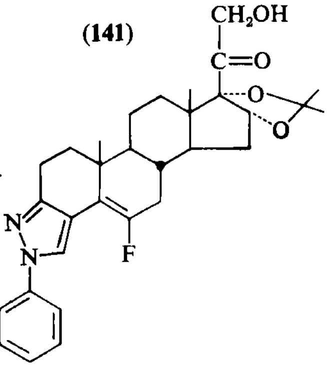
effect, the diterpene cafestol (**145**) (238) shows an intense negative Cotton effect in the 220-mμ region. It is apparent that the different stereochemical surroundings of the furan chromophore lead to opposite Cotton effect curves in these terpenes. The steroid, **146** (239), shows a weak positive Cotton effect in the 200-mμ region, while the conjugated furano-steroid (**147**) (240) exhibits a negative Cotton effect, centered at 239 mμ. The weak Cotton effect shown by **146** is probably due to free rotation around the C-17 to C-20 bond.

Optical rotatory dispersion has also been applied for the assignment of absolute configuration to α-methyl-α′-(β-furyl)tetrahydrofuran (**148**) from sweet potato fusel oil (241).


(140)


(141)


(142)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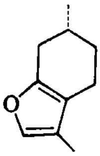
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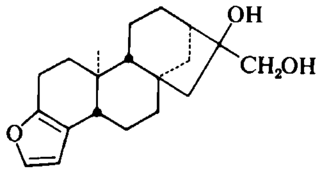
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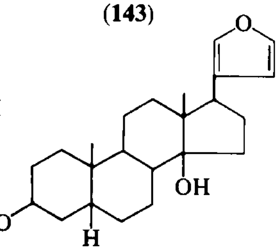
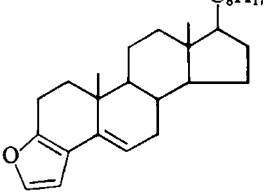

(146)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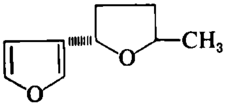
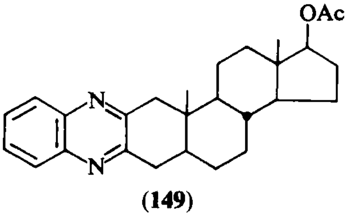
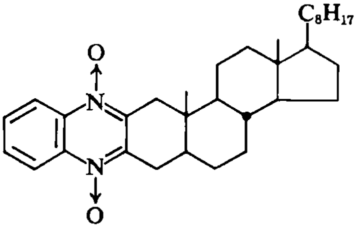

(148)

e. Quinoxaline and Related Compounds. The steroid quinoxaline (**149**) (242) shows two Cotton effects, ($[\Phi]_{333}$ +1200°; $[\Phi]_{319}$ −600°; $[\Phi]_{255}$ +7500°) both positive, corresponding to the two ultraviolet maxima. It is possible that the unusual shape of the second Cotton effect may be the resultant of two Cotton effects of opposite sign. The *N*-oxide derivative (**150**) (243) exhibits a positive Cotton effect ca. 395 mμ ($a = +86$). The last compounds belong to the group with a conjugated aromatic chromophore.



(**149**)



(**150**)

D. Flexible Compounds

Many scattered optical rotatory dispersion measurements have been made on simple compounds, the aryl groups of which should be conformationally free to rotate. The results are summarized in outline in Table XVI.

Several references dealing with different types of aromatic hydrocarbons, alcohols, arylamines, etc. show that these compounds present plain or very weak Cotton effect curves (50,91,190,197–207,244–252, 261). For many compounds the curves could profitably be measured again with modern equipment (especially by circular dichroism) that will penetrate farther into the ultraviolet, and also permit more sensitive measurements in the 280–260 mμ region.

Most of these flexible compounds have very weak aromatic Cotton effects for reasons already considered. This may in itself be of structural significance; however, the signs of these weak Cotton effects should be used with caution for the assignment of absolute configuration. Sometimes, some other similar compounds which carry arylic substituents [adrenaline and noradrenaline (**151**)] give significant Cotton

TABLE XVI

Cotton Effects of Flexible Compounds Containing an Aromatic Nucleus and One or More Asymmetric Centers in a Side Chain

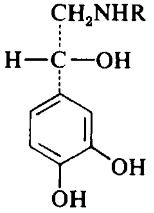
Compounds	Rotatory dispersion		Reference
	Wave-length, mμ	Amplitude *a*	
Hydrocarbons, alcohols, and amines,			
2-Phenylbutane Me-CHPh-Et	260; very small		244
2-Phenylbutane (derivatives from *ar*-turmerone)	(Only plain section of curve above 300 mμ measured)		245
2-Phenylbutan-1-ol $HO—CH_2·CHPh·Et$	—	Nil	246
2-Phenylbutane-1,4-diol $HO·CH_2CHPh·CH_2CH_2OH$	—	Nil	247
2-Phenylpentane-1,5-diol		+4!	244
(−)-Methylphenylcarbinol	265	+2	244
(1-phenylethanol)		+7	
$Ph—CHOH—CH_3$			
$Ph·CHR^1·CH(OH)R^2$ (several examples)	Some diastereoisomers show apparent Cotton effect with first extremum at 310 mμ		190
Other aryl carbinols			248
Dibenzylcarbinol or 1,3-diaryl-propan-2-ol types	Essentially plain curve		249
Phenylethane-1,2-diol	260	+7	246
1-Phenylethylamine $Ph·CHNH_2·Me$			250
Adrenaline (**151a**)	270 238	−33 [Φ] −2400°	207
Noradrenaline (**151b**)	270 238	−19 [Φ] −5000°	207, 251
Ephedrine (**152**)			252

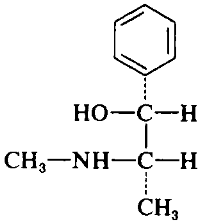
(continued)

Table XVI (*continued*)

Compounds	Rotatory dispersion Wave-length, mμ	 Amplitude *a*	Reference
Carboxylic acids and derivatives			
Phenylbutyric acid			
$PH \cdot CHMe \cdot CH_2CO_2H$	Very weak positive		91
Mandelic acid (**10**)			
$PH \cdot CHOH \cdot CO_2H$	Very weak negative		91, 207, 256
3,4-OCH_2O-mandelic acid		Nil	246
Hydratropic acid	270	Small	257
Phenylsuccinic acid			
$HO_2C \cdot CHPh \cdot CH_2 \cdot CO_2H$			247
Phenylalanine (**103**)			
$Ph \cdot CH_2CHNH_2 \cdot CO_2H$	260	Very faint	197
p-HO-Phenylalanine (tyrosine) (**110**)	270	+12	91, 199, 204, 205
Glycosides			
1*β*-*C*-Phenyl-1-deoxy D-glucopyranose			
(2,3,4,6-tetra-*O*-acetate)	265	+14	253
Phenyl-α-D-glucopyranoside			
(2,3,4,6-tetra-*O*-acetate)	265	+4!	254
Phenyl-α-D-glucopyranoside (not acetylated)	265	−15	254
Pyridine derivatives			
2(3-Pyridyl) derivatives of *N*-methylpyrrolidine			
(*S*-nicotine)		−80	142
Piperidine (*S*-anabasine)		−48	142
N-Methyl-5-pyrrolidone			
(*S*-cotinine)		−59	142

effects in this region (207,251). Mateos and Cram (190) found that some of the aryl-substituted alcohols showed notable changes in their rotatory dispersion curves when these were measured in solvents of different polarity, probably indicating variations in the degree of hydrogen bonding with the solvents.


(151a) R = CH_3
(151b) R = H


(152)

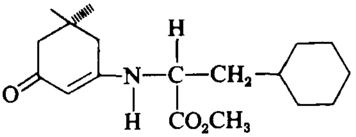
For compounds with two centers of asymmetry, the first extrema of the Cotton effects of ephedrine (**152**), halostachine and phenylephrine have been reported by Lyle (252).

The optical properties of *C*-aryl and *O*-aryl derivatives of some carbohydrates have also been examined (see refs. 4,253,254,262), as well as those of *N*-thioacyl derivatives of α-amino acids (4,255). This leads us to mention that numerous compounds presenting both aromatic and carboxyl groups have been submitted to rotatory dispersion and/or circular dichroism examination (1–7,61,91,197–207,246, 247,256–261). Here again, those examples where no arylic substituents are present generally give rise to weak Cotton effects (*vide supra*), unless there is a possibility of homoconjugation between two functions (e.g., an aromatic ring and a carboxyl group); related compounds with arylic substituents give moderate Cotton effects (256,261).

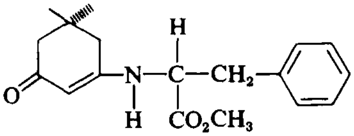
Few simple dissymmetric derivatives of pyridine have as yet been studied, but some alkaloids measured by Craig (144) all give strong Cotton effects.

Space does not permit extended references to compounds containing aryl groups with other double bonds conjugated between the aryl nucleus and the asymmetric center; however, many of these give strong Cotton effects and references are given in Table XVI. Moreover, several aromatic derivatives of optically active amines have been examined by optical rotatory dispersion and circular dichroism (1–4,263,264). Some of these substances, such as Schiff bases, exhibit strong Cotton effects reflecting the absolute configuration of the asymmetric center(s).

Among the derivatives of optically active amines and amino acids, the dimedonyl condensation compounds (265) deserve special mention. Indeed, it has been shown that the dimedonyl chromophores of the D-amino acids, such as of the ester **153**, exhibit positive Cotton effects, and their L-enantiomers, negative Cotton effects. However, substitution of the cyclohexane ring **153** for an aromatic ring, as in the phenylalanine methyl ester derivative **154**, reverses the sign of the Cotton effects associated with this chromophore. This inversion of the sign by mere substitution of a cycloalkyl chain for an aryl group, which incidently has some precedent (e.g., see refs. 256a,261b), indicates that the chromophore involved is the entire π-system and not just the vinylogous amide grouping (265).



(153)

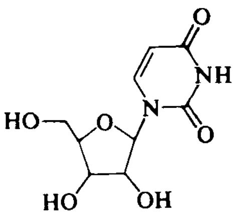


(154)

Recently considerable attention has been paid to asymmetric sulfoxides, many of which bear one or two aryl groups (266–273).

E. Nucleosides and Nucleotides

A special group of aromatic compounds, in which the nucleus itself (pyrimidine or purine) has little or no symmetry apart from the plane of the ring, consists of the nucleosides and nucleotides. Representative formulas of a pyrimidine-riboside and of a purine-2-deoxyriboside are **155** and **156**.



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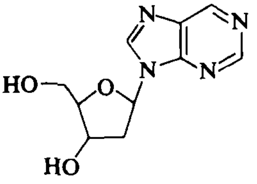

(156)

Much work has already been done on the rotatory dispersion and circular dichroism properties of polynucleotides, partly to study their helical character in connection with biochemical problems (see, e.g., refs. 274–289). Studies on the monomers and oligomers (274,275) indicate that there are many interesting problems in this field quite apart from its great biochemical importance. The ring systems involved (pyrimidine and purine), which contain several heteroring atoms, are very easily perturbed and give strong Cotton effects generally between 250 and 300 mμ. Some rotatory dispersion data are summarized in Table XVII (274–277).

Some speculations regarding preferred conformations of the asymmetric (carbohydrate) unit relative to the heteroaromatic chromophore have been presented by Ulbricht et al. (274). While it would have been expected that α- and β-anomers give curves of roughly enantiomeric types, it is of special interest to note that a pyrimidine and a purine derivative of the same anomeric type give Cotton effects of opposite sign.

IV. CONCLUSIONS

The optical rotatory dispersion and circular dichroism properties of numerous other aromatic compounds have been reported in the chemical literature (e.g., refs. 1–9,290–300). Lack of space does not permit an exhaustive discussion of all the compounds which have been investigated, however, with the above-mentioned examples, we have tried to show that the optical properties of the aromatic chromophore are sensitive to the molecular dissymmetry. The Cotton effects associated with a given compound are a function of the nature of the π-system involved, the nature of the substituent(s) on the aromatic nucleus, and sometimes also of the distance separating the asymmetric center(s) from the chromophore under investigation.

The fundamental importance of the octant rule has been mentioned, as well as extensions of this rule and several new applications. This is justified by the basic impact these rules have for the understanding of the optical phenomena associated with some specific molecular dissymmetric patterns.

It is hoped that new generalizations of the octant rule or similar propositions, resulting from a better understanding of the optical

TABLE XVII

Optical Rotatory Dispersion of Some Nucleosides and Nucleotides

Compounds	Molecular amplitude *a* α-Anomer	 β-Anomer
Pyrimidine Nucleosides and Nucleotides		
(Extrema 280–290/245–265 mμ)		
Thymidine	−104	+95
Thymidine, 5′-PO$_3$H		+71
D-Arabinofuranosylthymine	−103	+293
D-Ribofuranosylthymine,2′-deoxy	−138	+85
Uridine		+117
Uridine, 5′-fluoro-5′-deoxy	−159	+120
Cytidine		+152
Cytidine, 2′-deoxy (HCl)	−175	+111
Cytidine, 2′-deoxy 5′-PO$_3$H		+124
Purine Nucleosides and Nucleotides		
(Extrema 290–270/250–230 mμ)		
Adenosine	+123	−58
Adenosine, 2′-deoxy	+80	Negative
Adenosine, 2′-deoxy 5′-PO$_3$H		−27
Guanosine		Negative
Guanosine, 2′-deoxy		Negative
Guanosine, 2′-deoxy 5′-PO$_3$H		−29
Inosine		−59

properties associated with other chromophores (such as these present in aromatic molecules, proteins, peptides, and polymers, for example) will be deduced in the near future from the large array of data being obtained today.

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Table of Conformational Energies—1967

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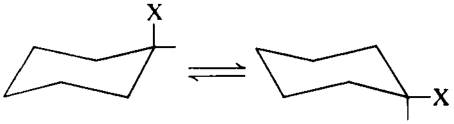
INTRODUCTION

Conformational energy is defined as the excess energy of a given conformation over that conformation of minimum energy of the same molecule. For the equilibrium shown below, the conformational energy of the system is the negative of the standard free energy change ($-\Delta G_x^\circ$) for the equilibrium as written:



This table contains all of the values for free energy changes of this type which have been located in the literature. Values obtained utilizing erroneous theoretical foundations have been omitted. Unfortunately, several good values have also probably been missed. Those tables given in references 114 and 116 have been extensively utilized to minimize omissions. Where only standard enthalpy changes ($-\Delta H_x^\circ$) are available, these have been included.

An attempt has been made to evaluate the data and arrive at best values for those substituents where there is sufficient information to do so. These "best values" are contained in the table in boldface type directly below the functional atom or group under discussion, and should be treated as ±0.1 kcal/mole values (see refs. 114 and 115 for other assignments of best values). Where two "best values" are given herein, the first value refers to aprotic solvents and the second to hydrogen-donor solvents.

Table of Conformational Energies—1967

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
F	0.09	NMR-1[a]	RT[b]	NO_2B	1
0.15	0.10	NMR-1[a]	RT	CF_3COOH	1
	0.13	NMR-1[a]	RT	CCl_4, CS_2	1
	0.14	NMR-1[a]	RT	Cyclohexane	1
	0.15	NMR-1[a]	RT	[c]	1
	0.15	NMR-F	29	CCl_3F	2
	0.17	ED	RT	Gas phase	3
	0.18	NMR-1[a]	RT	Neat,[f] $CDCl_3$	1
	0.19	NMR-1[a]	RT	*t*-BuOH, *N*-methylacetamide	1
	0.19	NMR-F[a]	RT	[c]	1
	0.20	NMR-1[a]	RT	AcOH	1
	0.24	NMR-2	RT	CS_2	4
	0.24	NMR-F	−55	CCl_3F	2
	0.25	NMR-3	−93	CS_2	4
	0.27	NMR-3	−91	CS_2	2
	0.40 ± 0.30	MW	Dry Ice	Gas phase	4a
	0.46–0.71	NMR-1[d]	RT	Neat, NO_2B, cyclohexane, $CDCl_3$, CCl_4, *t*-BuOH, CS_2, AcOH, *N*-methylacetamide	1
	0.49	NMR-F[d]	RT	[c]	1

Cl	<0.26	ED	?	Gas phase	5
0.43	0.3–0.4[f]	IR-1	?	Neat	6
	0.3	Ind. Eqb.[g]	230	Neat	7
	0.3	Ind. Eqb.[g]	80	$EtOH/H_2O$	7
	0.33	IR-1	25	CS_2	8
	0.34	IR-1	117–200	Gas phase	8
	0.34	NMR-1[a]	RT	Neat, MeOH–20% $(n\text{-}C_4H_9)_4\overset{+}{N}\overset{-}{I}$	1
	0.38–0.40	IR-2	RT	Cyclohexane	1
	0.39	NMR-1[a,e]	35	CCl_4	10
	0.4	IR-1[a]	RT	CS_2	46
	0.40	NMR-1[a]	RT	NO_2B, CH_3CN	1
	0.41	NMR-3	−93 to −80	CS_2	9
	0.42[i]	NMR-1[a,e]	36	*cis*-Decalin	9
	0.42	NMR-1[a]	RT	MeOH–22% *p*-TsOH[h], CS_2	1
	0.43	NMR-1[a]	RT	Cyclohexane, DMA	1
	0.43	NMR-1[a]	RT	[c]	1
	0.44–0.45[i]	NMR-1[a,e]	36	DiClB, 3,5-dimethyl-3-hexanol	10
	0.44	NMR-1[a]	RT	*N*-Methylacetamide	1
	0.44	IR-1	25	MeOAc	8
	0.45	NMR-1[a]	RT	DMF, MeOH	1
	0.46	NMR-1[a]	RT	$CDCl_3$, CCl_4	1

(*continued*)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
Cl	0.47	Kerr[j]	RT	CCl_4	11
0.43	0.48	NMR-2	RT	CS_2	4
	0.49	NMR-1[a]	RT	HOAc–17% *p*-TsOH	1
	0.51	NMR-1[a]	RT	CF_3COOH, HOAc	1
	0.51	NMR-3	−81	CS_2	4
	0.52[f]	IR-2	?	Vapor phase	10
	0.52	NMR-2[j]	−73	CS_2	12
	0.61–0.94	NMR-1[d]	RT	Neat, NO_2B, cyclohexane, CF_3COOH, $CDCl_3$, CCl_4, CS_2, HOAc, *N*-methylacetamide	1
	0.60[w]	D. Eqb.[a]	46	HCl	45,46
	0.65[w]	IR-1[a], IR-2	25	Ether, CS_2	46
Br	0.2[f]	IR-1	?	Neat	6
0.38	0.24	NMR-1[a]	25	Neat	13
	0.26	Kerr[j]	RT	CCl_4	11
	0.27	NMR-1[a]	RT	Neat	1
	0.31	NMR-1[a]	RT	CCl_4	1
	0.33	NMR-1[a]	RT	NO_2B	1
	0.35	NMR-1[a]	RT	Cyclohexane, DMA	1

0.36	NMR-1[a]	RT	CS_2	1
0.37	NMR-1[a]	RT	[c]	1
0.37	NMR-1[a,e]	35	CCl_4	10
0.38[f]	IR-2	7	Vapor phase	10
0.38	NMR-1[a]	RT	CH_3CN	1
0.39[i]	NMR-1[a,e]	36	*cis*-Decalin	10
0.39	NMR-1[a]	RT	$CDCl_3$, *N*-methylacetamide	1
0.41[i]	NMR-1[a,e]	36	3,5-Dimethyl-3-hexanol	10
0.42[i]	NMR-1[a,e]	36	DiClB	10
0.43	NMR-1[a]	RT	CF_3COOH	1
0.44	NMR-2	RT	CS_2	4
0.45	NMR-1[a]	RT	HOAc, HOAc–17% *p*-TsOH	1
0.46[k]	IR-2	25 (?)	Various solvents	14
0.48	NMR-3	−81	CS_2	4
0.48	NMR-3[j]	−73	CS_2	12
0.51	NMR-3	−104 to −86	CS_2	9
0.6	Kin.	25	87% EtOH	15
0.61	IR-2	30	CS_2	14
0.63[l]	IR-2	25 (?)	Various solvents	14
0.7	[m]	?	Gas phase (?)	16
0.70 ± 0.20	NMR-4[a]	20	CCl_4	17
0.73	Kin.	25.1, 0.1	87% EtOH	18
0.94[n]	NMR-1[a]	25	$CHCl_3$	13

(continued)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
I	0.30	Kerr[j]	RT	CCl_4	11
0.43	0.41	NMR-2	RT	CS_2	4
	0.43	NMR-3	−81	CS_2	4
	0.46	NMR-2[j]	−73	CS_2	12
CN	0.15	D. Eqb.[a]	25	*t*-BuOH	19
0.17	0.15	D. Eqb.[o]	76	*t*-BuOH	20
	0.17	D. Eqb.[p]	76	*t*-BuOH	20
	0.19	D. Eqb.[a]	76	*t*-BuOH	20
	0.19	D. Eqb.[a]	80	*t*-BuOH	19
	0.25	D. Eqb.[a]	66	THF	21
CH_3	1.18	NMR-1	27	?	22
1.70	1.25[r]	US	20	Neat	23
	1.3[s]	NMR-1[a], NMR-5	40	DMSO	25
	1.5 ± 0.1[s]	Ind. Eqb.	35	Ether	26
	1.56[s]	Ind. Eqb.	35	Ether	27
	1.54–1.72[f]	Thermo.	25	Neat	28
	1.54–2.47[s]	L-HA	100	H_2O	29
	1.60 ± 0.06	NMR-1[a,e]	30	2-D-2-PrOH	30
	1.67[s,i]	Ind. Eqb.	25	*i*-PrOH	31
	1.68 ± 0.06[t]	NMR-1[a]	30	CCl_4	30

	1.69–2.18^s	L-HA	140	H_2O	29
	1.70^s	NMR-1^e	32	CCl_4	32
	1.71 ± 0.02^{s,l}	NMR-2	36	*cis*-Decalin	33
	1.73 ± 0.03^{s,l}	NMR-2	36	CCl_4	33
	1.75^s	Ind. Eqb.	35	Ether	27
	1.75 ± 0.10	D. Eqb.	200–300	Neat	34
	1.78 ± 0.06^l	NMR-1^u	30	$CDCl_3$,^{u}	74
	1.83 ± 0.25^l	US	25 (?)	Neat	24
	1.87^s	Ind. Eqb.	25	EtOH	36
	1.87–1.96^f	Thermo.	25	Gas phase	28,37
	1.9–2.1	D. Eqb.	25	99.8% H_2SO_4	38
	1.91–1.96^f	Thermo.	25	Gas phase	39
	1.97 ± 0.30^f	D. Eqb.	257–327	Neat	40
	1.97	IR-2	30	CS_2	14
	1.98^s	Ind. Eqb.	93	EtOH	41
	2.0 ± 0.35	Ind. Eqb.	20	EtOH	42
	2.0–2.1^f	D. Eqb.	25–300	Gas phase	43
	2.1 ± 0.3^r	US	25 (?)	Xyl, NO_2B	44
CF_3	2.1^s	IR-2	25	Cyclohexane	47
C_2H_5	1.67^s	Ind. Eqb.	35	Ether	27
1.75	1.68 ± 0.06^t	NMR-1^{a,e}	30	CCl_4	30
	1.77 ± 0.07	NMR-1^{a,e}	30	2-D-2-PrOH	30
	1.80^s	Ind. Eqb.	25	EtOH	36

(*continued*)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G^\circ_x$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
C_2H_5	1.8 ± 0.3^f	D. Eqb.	258–320	Neat	40
1.75	1.86^s	Ind. Eqb.	35	Ether	27
	$1.86^{s,l}$	Ind. Eqb.	25	*i*-PrOH	31
	1.97^s	Ind. Eqb.	93	EtOH	41
	2.0^s	p*K*	25	50% EtOH–H_2O	48
	2.09^s	L-HA	143	H_2O	29
	2.27^s	L-HA	100	H_2O	29
—CH_2—C—$(CH_3)_3$	2.0^s	p*K*	25	50% EtOH–H_2O	48
—CH_2OTs	$1.7–1.8^s$	Kin.	100–110	AcOH	49
—$CH(CH_3)_2$	1.87	^{m}	?	?	31
2.15	1.90^s	Ind. Eqb.	35	Ether	27
	1.91 ± 0.01	D. Eqb.	287	Neat	40
	1.91	D. Eqb.	287	?	36
	2.1 ± 0.1^s	Kin.	100–110	AcOH	50
	2.11^s	Ind. Eqb.	25	EtOH	36
	$2.22 \pm 0.08^{s,t}$	NMR-1^a	30	CCl_4	30
	2.25 ± 0.08^s	NMR-1^a	30	2-D-2-PrOH	30
	2.30^s	Ind. Eqb.	35	Ether	27

	2.38[s]	Ind. Eqb.	93	EtOH	41
	2.43–2.62[s,i]	Ind. Eqb.	25	MeOH, *i*-PrOH	31
	2.5[s]	p*K*	25	50% EtOH–H_2O	48
	2.63[s]	L-HA	139	H_2O	29
	3.55[s]	L-HA	100	H_2O	29
C_6H_{11}	2.15[s]	NMR-1[e]	32	CCl_4	32
$C(CH_3)_3$	> 3.6[s]	L-HA	140	H_2O	29
	> 4.2	D. Eqb.	220	Neat	51
	> 4.43[s]	L-HA	100	H_2O	29
	ca. 12.0	[m]	25	Gas phase	113
C_6H_5 **3.0**	2.0	D.M.	25	ΦH	52
	2.6[s]	Ind. Eqb.	35	Ether	26
	3.1[i,s]	D. Eqb.[a]	25	DMSO	53
	3.0[s]	NMR-7	25	$CDCl_3$ (?)	53
—CH═CH_2	1.35[s,w]	NMR-1[a,j]	RT (?)	CCl_4	54
—C≡CH	0.18[s,w]	NMR-1[a,j]	41	CCl_4	55
COOH **1.35**	0.7	Kin.	30	Absolute EtOH	57
	1.15[s]	p*K*[a]	25	80% MeOE	58
	1.2	Ind. Eqb.	78	MeOH–H_2O	31

(*continued*)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
COOH **1.35**	1.359 ± 0.15[i]	D. Eqb.[a]	25	4 Diglyme–1 H_2O (mole fractions)	59
	1.387 ± 0.10[i]	D. Eqb.[a]	25	*n*-Dodecane	59
	1.456 ± 0.12[i]	D. Eqb.[a]	25	1 Diglyme–1 H_2O (mole fractions)	59
	1.5–1.6	p*K*	25	50% EtOH–H_2O	48
	1.58–1.86	p*K*	25 (?)	66% DMF–34% H_2O	60
	1.6 ± 0.3	p*K*	25 ± 0.05	80% MeOE	61
COO^- **1.92**	1.8[s]	p*K*[a]	25	80% MeOE	58
	1.86	D. Eqb.[p]	180	Ethylene glycol	20
	1.89	D. Eqb.[a]	180	Ethylene glycol	20
	1.9[s]	p*K*[s]	25	50% and 78.5% MeOE	31
	1.95	D. Eqb.[o]	180	Ethylene glycol	20
	1.96 ± 0.20[i]	D. Eqb.[a]	25	Ethylene glycol	59
	2.0–2.8	p*K*	25 (?)	66% DMF–34% H_2O	60
	2.1–2.3	p*K*	25	50% EtOH–H_2O	48
	2.2 ± 0.3	p*K*	25 ± 0.05	80% MeOE	61
	2.21	D. Eqb.[d]	180	Ethylene glycol	20
$COOCH_3$ **1.27**	1.05	D. Eqb.	66	Absolute MeOH	62
	1.15[s,i]	D. Eqb.	25	MeOH	31

	1.27	D. Eqb.[a]	25	MeOH	59
	1.27	D. Eqb.[o,p]	90	MeOH	20
	1.28	D. Eqb.[a]	90	MeOH	20
	1.38	D. Eqb.[d]	90	MeOH	20
	1.7[x]	D. Eqb.	67	MeOH	63
$COOCH_2CH_3$	1.0–1.2	Kin.	25.2	70% EtOH	64
1.20	1.07 ± 0.05	NMR-1[a]	38	CCl_4	56
	1.1	NMR-1[a]	25	CCl_4	65
	1.12 ± 0.14	D. Eqb.	80	Absolute EtOH	62
	1.2	D. Eqb.	80	EtOH	64
	1.21[l]	D. Eqb.	25 (?)	EtOH	66
	1.24 ± 0.10[l]	D. Eqb.	25 (?)	EtOH	41
	1.11 ± 0.06[s]	NMR-1[a]	38	CCl_4	56
$COOCH(CH_3)_2$	0.96[l,s]	D. Eqb.	25	*i*-PrOH	31
COCl	1.2	D. Eqb.[a]	130–140	Neat	67
1.25	1.294 ± 0.15[l]	D. Eqb.[a]	25	*n*-Dodecane	59
$COCH_3$	1.173 ± 0.010[l]	D. Eqb.[a]	25	MeOH	59
OH	0.29–0.37	IR-2	RT(?)	CH_2Cl_2, $CHCl_3$, CCl_4, CS_2, $Br(CH_2)_2Br$, Acet, Xyl, Tol, ΦH, Hex	68
0.52, 0.87					

(*continued*)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G^\circ_x$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
OH	0.31–0.41[f]	IR-1	?	Neat	6
0.52, 0.87	0.33	Thermo.	25	H_2O (pH = 5.5)	69,70
	0.33–0.35	IR-2	RT	$CHCl_3$, CH_2Cl_2, CS_2, CCl_4, Acet	71
	0.33–0.37	IR-2	RT (?)	Xyl, Tol, ΦH, Hex	68
	0.36–0.41	IR-2	RT (?)	Neat, CH_2Cl_2, $CHCl_3$, CCl_4, CS_2, Acet, $Br(CH_2)_2Br$	68
	0.38	IR-1	−30 to 50 (?)	Neat	72
	0.4	IR-2	20	CS_2	73
	0.43 ± 0.17	NMR-4[a]	20	CCl_4	17
	0.47 ± 0.04	D. Eqb.	110–170	Cyclohexane	74
	0.5	Ind. Eqb.[g]	230	Neat	7
	0.52 ± 0.04	D. Eqb.	90	Absolute EtOH	74
	0.52–0.55	Kin.	25	Pyr	75
	0.54[s]	NMR-5[a]	RT (?)	DMSO, DMSO-d_6	76
	0.56	Kin.	25	Pyr	77
	0.59	D. Eqb.	80	ΦH	78
	0.6	NMR-1[a]	RT	CCl_4	65
	0.6	NMR-C[a]	RT (?)	Neat, CS_2	79
	0.6–0.7	D. Eqb.[a]	Boiling solvent	Cyclohexane, ΦH, Tol, THF, DME	80

0.61[s,x]	D. Eqb.	150	Cyclohexane	78
0.61 ± 0.11[s]	NMR-5[y]	RT (?)	DMSO, DMSO-d_6	76
0.64–0.66	Raman	30–68	Neat	81
0.65	NMR-2[j]	26	CS_2	12
0.66	NMR-6[e]	28	CS_2	88
0.66[s]	NMR-8[y]	RT (?)	DMSO, DMSO-d_6	76
0.68[s]	D. Eqb.	80 (?)	ΦH	78
0.72[s]	NMR-1[y]	RT (?)	*i*-PrOH	76
0.73 ± 0.02[t]	NMR-1[a]	30	CCl_4	30
0.73[s,x]	D. Eqb.	80 (?)	ΦH	78
0.73[s]	D. Eqb.	83 (?)	*t*-BuOH	78
0.75[s]	D. Eqb.	82 (?)	*i*-PrOH	78
0.75	NMR-8[a,j]	40	CCl_4	82
0.77[s]	D. Eqb.	82 (?)	*i*-PrOH	78
0.77	NMR-1[y]	RT (?)	DMSO, DMSO-d_6	76
0.79[s]	D. Eqb.	83 (?)	*t*-BuOH	78
0.8[c]	Kin.	40	75% AcOH	83
0.80	NMR-8[a,j]	40	DMSO, Pyr	82
0.81	D. Eqb.[d]	80 (?)	OH	78
0.82	NMR-1[a]	36	CCl_4	32
0.83	NMR-1[a]	36	Pyr	32
0.84	NMR-1[a]	36	Oct	32
0.84[s,x]	D. Eqb.	82 (?)	*i*-PrOH	78
0.85	D. Eqb.[o]	90	*i*-PrOH	20
0.85[s,x]	D. Eqb.	82 (?)	*i*-PrOH	78

(continued)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
OH	0.85	NMR-8^y	RT (?)	DMSO, DMSO-d_6	76
0.52, 0.87	0.85^{s,x}	D. Eqb.	Boiling solvent	*i*-PrOH	84
	0.86	NMR-5^a	40	DMSO	25
	0.88 ± 0.02	NMR-1^a	30	2-D-2-PrOH	30
	0.88^{s,x}	D. Eqb.	150	*t*-BuOH	78
	0.88	D. Eqb.^{a}	83 (?)	*t*-BuOH	80
	0.89^{s,x}	D. Eqb.	82 (?)	*i*-PrOH	78,80
	0.89	D. Eqb.^{o}	90	*i*-PrOH	20
	0.9^m	Ind. Eqb.	22	H_2O	85
	0.90	D. Eqb.	90	*i*-PrOH	20
	0.9	Ind. Eqb.^{g}	80	Aqueous EtOH	7
	0.91^{s,x}	D. Eqb.	83 (?)	*t*-BuOH	78
	0.92	NMR-1^a	40	DMSO	25
	0.93	D. Eqb.^{o}	115	*i*-PrOH	86
	0.94	D. Eqb.^{a}	82 (?)	*i*-PrOH	80
	0.96	D. Eqb.^{a}	89	*i*-PrOH	87
	0.97	NMR-1^a	36	BrB	32
	0.97^{s,x}	D. Eqb.	82 (?)	*i*-PrOH	80
	0.98–1.12	D. Eqb.	Reflux temperature	ΦH, Tol, Xyl	74
	0.98 ± 0.15	NMR-5^y	RT (?)	DMSO, DMSO-d_6	76
	0.99^s	D. Eqb.	82 (?)	*i*-PrOH	78
	1.0	D. Eqb.	89	*i*-PrOH	74

	1.0	NMR-4^{a,e}	28	CCl_4	88
	1.02^{s,x}	D. Eqb.	83 (?)	*t*-BuOH	78
	1.02^{s}	D. Eqb.	82 (?)	*i*-PrOH	78
	1.04	D. Eqb.^{d}	82 (?)	*i*-PrOH	78
	1.05	NMR-1^{a}	36	*t*-BuOH	32
	1.06^{s,x}	D. Eqb.	82 (?)	*i*-PrOH	78
	1.07	NMR-1^{a}	RT	CCl_4	89
	1.11–1.22^{s,x}	D. Eqb.	Boiling solvent	*i*-PrOH	84,90
	1.12^{s}	D. Eqb.	82 (?)	*i*-PrOH	78
	1.13	D. Eqb.^{d}	90	*i*-PrOH	20
	1.14	D. Eqb.	83 (?)	*t*-BuOH	78
	1.15^{s}	D. Eqb.^{d}	82 (?)	*i*-PrOH	78
	1.16	D. Eqb.^{d}	82 (?)	*i*-PrOH	78
	1.20	D. Eqb.^{d}	82 (?)	*i*-PrOH	78
	1.25	NMR-4^{e}	28	D_2O	88
	1.35	NMR-5^{a}	RT (?)	DMSO, DMSO-d_6	76
	1.5^{s,w}	D. Eqb.^{a}	83	EtOH	46
OCH_3	0.4	Ind. Eqb.^{g}	230	Neat	7
0.60	0.6	NMR-C^{a}	RT (?)	Neat, CS_2	79
	0.6	NMR-1^{a}	RT	CCl_4	65
	0.73^{s}	L-HA	140	H_2O	29
	0.74^{s}	L-HA	100	H_2O	29
OCD_3	0.56 ± 0.02	NMR-2	−96	CD_2CDCl	91

(*continued*)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
OC_2H_5	0.89[s]	L-HA	140	H_2O	29
	0.98[s]	L-HA	100	H_2O	29
$OCOCH_3$	0.36	D. Eqb.	25	$AcOH–Ac_2O$ (1:1)	92
0.60	0.41	NMR-2[e]	37	CCl_4	33
	0.43[i]	NMR-2[e]	36	Trichloroethanol	33
	0.44[i]	NMR-2[e]	36	Oct	33
	0.46[i]	NMR-2[e]	36	3,5-Dimethyl-3-hexanol, propionic acid, DiClB	33
	0.52[i]	NMR-2[e]	36	BrB	33
	0.6–0.7	Ind. Eqb.[g]	230	Neat	7
	0.65	NMR-C[a]	RT (?)	Neat, CS_2	79
	0.66	NMR-5[e]	28	CS_2	88
	0.68	NMR-2	25	CS_2	93
	0.7	NMR-1[a]	RT	CCl_4	65
	ca. 0.76	NMR-3	−110	CS_2	88
	1.5	Kin.	40	H_2O–Diox (1:1)	94
	1.6	Kin.	15–63	H_2O–Diox (1:1, 1:3)	95
$OCOCF_3$	0.68	NMR-2	25	CS_2	93
OCHO	0.27	NMR-2	25	CS_2	93

OTs[z]	0.21	NMR-2[a,e]	36	CCl_4	33
0.50	0.26[i]	NMR-2[a,e]	36	Oct, 3,5-dimethyl-3-hexanol	33
	0.32[i]	NMR-2[a,e]	36	DiClB	33
	0.38[i]	NMR-2[a,e]	36	BrB	33
	0.41	NMR-2[a,e]	36	Pyr	33
	0.6	NMR-1[a]	RT	CCl_4	65
	0.7	Kin.	25	87% EtOH	96
	0.7	Kin.	25.1	90% EtOH	97
	1.7[c]	Kin.	25, 50, 75	EtOH, AcOH, formic acid	83
ONB[z]	0.98	Kin.	25	80% aqueous acet	98
ONO_2	0.59	NMR-2	25	CS_2	93
NH_2	1.0 ± 0.5	NMR-4[a,d]	20	ΦH	17
1.20, 1.60	1.1–1.2	NMR-1[a]	RT	Cyclohexane, CCl_4, CH_3CN, Pyr	99
	1.22–1.30[s]	NMR-1[a,d,e]	RT (?)	$CHCl_3$	100
	1.23[s]	NMR-7[a,d,e]	RT (?)	$CHCl_3$	100
	1.4–1.5	NMR-1[a]	RT	$CDCl_3$, 95% EtOH, 90% *t*-BuOH, *t*-BuOH	99
	1.7	p*K*	20	80% MeOE	101
	1.8	Kin.	25.1 or 56.6	98% EtOH	99

(continued)

Table of Conformational Energies—1967 (*continued*)

Atom or group	$-\Delta G_x^\circ$, kcal/mole	Method	Temp., °C	Solvent or state	Reference
$NH(CH_3)$	0.9[s]	NMR-7[a,d,e]	RT (?)	$CHCl_3$	100
1.0	1.0–1.1[s]	NMR-1[a,d,e]	RT (?)	$CHCl_3$	100
$N(CH_3)_2$	2.1	p*K*	20	80% MeOE	101
NH_3^+	1.55–1.86	NMR-1[a]	RT	CF_3COOH, AcOH, CF_3COOH–AcOH (1:8), CF_3COOH–*t*-BuOH (1:8)	99
1.9					
	2.0	p*K*	20	80% MeOE	101
$NH(CH_3)_2^+$	2.4	p*K*	20	80% MeOE	101
NO_2	0.78 ± 0.10	NMR-7[a,e]	37	Neat, $CDCl_3$	102
1.10	0.8	NMR-7[a]	25	$CDCl_3$	103
	1.02 ± 0.15	NMR-7[a]	26	$CDCl_3$	104
	1.1	NMR-4[a,•]	25	$CDCl_3$	103
	1.16[i]	D. Eqb.[a]	25	*t*-BuOH	66
	1.2	NMR-7[a,*]	25	$CDCl_3$	103
	1.3[s]	NMR-7[*]	25	$CDCl_3$	103
—SH	−0.41 ± 0.04[f]	IR-1	−50 to 25	?	105
0.9	0.6	p*K*	25	DMF	106
	0.9	NMR-1[a]	RT	CCl_4	107

—SCH_3	0.7	NMR-1[a]	RT	CCl_4	107
—SC_6H_5	0.8	NMR-1[a]	RT	CCl_4	65
—SCH_2—R	0.4[s]	Ind. Eqb.[a,d]	35	Ether	108
	0.7[s]	Ind. Eqb.[a,d]	35	Ether	109
	−0.4[s]	Ind. Eqb.[a,d]	80	ΦH	109,110
—S^-	1.3	p*K*	25	DMF	106
SOC_6H_5	1.9	Kin.	0	90% *i*-PrOH	109
$SO_2C_6H_5$	2.5	NMR-1[a]	RT	CCl_4	109
HgBr	0	D. Eqb.	95	Pyr	111
HgCl	0.3[m]	Opt. Rot.	25 (?)	EtOH	112

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[a] 4-*t*-Butylcyclohexane-type reference substances or substrates. [b] Room temperature. [c] Mean value of these authors. [d] 3-*t*-Butylcyclohexane-type reference substances or substrates. [e] Deuterated substrates. [f] Δ*H* value. [g] 3β-Substituted-5α- and 5β-cholestan-6-one substrates. [h] *p*-Toluenesulfonic acid. [i] Calculated from Δ*H* and Δ*S*. [j] Infinite dilution. [k] Recalculated from ref. 6 using the ratio of extinction coefficients. [l] Recalulated from ref. 11 using the ratio of extinction coefficients. [m] Calculated by indirect argument. [n] Considered to be a bad result and redone in ref. 1. [o] *trans*-2-Decalin-type substrates. [p] *trans*-5-Hexahydroindanyl-type substrates. [q] From 4-methylcyclohexanone dimethyl ketal with 3-methylcyclohexanone dimethyl ketal as model. [r] For criticism, see ref. 24. [s] Indirect determination based on assumed value of another group and additivity of conformational energies. [t] Recalculated value. [u] 4,4-Diazirine unit type substrates; also run in CCl_4, DMF, CS_2, ΦH, and $(CD_3)_2CO$ with only minor changes in results. [v] 3α-Substituted-5α- and 5β-6-ketosteroid substrates. [w] Tertiary system. [x] Vicinal group probably affecting value. [y] *cis*-4-*t*-Butyl- and *trans*-3-methylcyclohexyl compounds as reference substances. [z] Ts = *p*-toluenesulfonate; NB = *p*-nitrobenzoate. [*] 100 Mc NMR determination.

METHODS

ED	Electron diffraction
Kerr	Molar Kerr constant
Kin.	Kinetic method
Thermo.	Thermochemical method
D. Eqb.	Equilibrium method
Ind. Eqb.	Indirect equilibrium method
L-HA	Lactone–hydroxy acid equilibrium method
DM	Dipole measurement
pK	pK measurement–dissociation constant
IR-1	Infrared method, ΔH value obtained by application of van't Hoff equation (intensity ratio vs. temperature)
IR-2	K (equilibrium constant) from molar extinction coefficient
NMR	Nuclear magnetic resonance method
NMR-1	Proton chemical shift method using reference substances
NMR-2	Proton chemical shift method using cyclohexyl-X spectrum at low temperature as reference
NMR-3	Proton measurement utilizing areas under peaks measured at low temperatures
NMR-4	Average proton coupling constants method based on α-proton using reference substances
NMR-6	Average proton coupling constants method using low temperature methods
NMR-7	Band width technique based on proton measurements
NMR-8	Chemical shift method using hydroxyl proton signal with reference substances
NMR-F	Fluorine^{19} magnetic resonance method
NMR-C	Carbon^{13} magnetic resonance method
US	Ultrasonic method
Opt. Rot.	Optical rotation technique
MW	Microwave transition intensity method

SOLVENTS

THF	Tetrahydrofuran
Ether	Diethyl ether
DMF	Dimethylformamide
CCl_4	Carbon tetrachloride
ΦH	Benzene
AcOH	Acetic acid
MeOAc	Methyl acetate
$CHCl_3$	Chloroform
Diox	Dioxane

DMSO	Dimethylsulfoxide
Hex	*n*-Hexane
Pyr	Pyridine
DMA	Dimethylacetamide
Oct	Isooctane
Tol	Toluene
Xyl	Xylene
Acet	Acetone
DiClB	*o*-Dichlorobenzene
BrB	Bromobenzene
MeOE	2-Methoxyethanol
Neat	Pure liquid
MeOH	Methanol
i-PrOH	Isopropyl alcohol
EtOH	Ethanol
CS_2	Carbon disulfide
CH_2Cl_2	Methylene chloride
DME	Dimethoxyethane
t-BuOH	*tert*-Butyl alcohol
Ac_2O	Acetic anhydride
NO_2B	Nitrobenzene

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