Mihály Nógrádi

# Stereoselective Synthesis

## A Practical Approach

Foreword by A. I. Meyers

Second, Thoroughly Revised and Updated Edition


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# Foreword

The quest for selectivity in synthesis still continues as the most important focal area for chemists, and the drive for stereoselectivity is among the most coveted goals. For the past fifty years, organic chemists have pursued the understanding and control of stereochemical behavior, and in 1956 an outstanding monograph appeared entitled "Steric Effects in Organic Chemistry", edited by M. S. Newman. This work placed stereochemistry, both qualitatively and quantitatively, in its proper position of importance in organic chemistry. Following this, in 1969, Hassel and Barton shared a Nobel Prize for the concepts of molecular conformation, further propelling stereochemistry into the limelight. Again, in 1975, the Nobel Prize was awarded to Cornforth and Prelog for stereochemical reactions, and further intensified efforts to enhance both relative and absolute stereoselectivity. Thus, a large number of papers appeared between 1975 and 1980 dealing with asymmetric syntheses of diastereomers and enantiomers. Many, if not most of these, are based on stereoelectronic effects (e.g., chelation) as the major component to control selectivity in molecular construction. In 1984, the now famous five-volume series, "Asymmetric Synthesis", was published. This series chronicled the effort in what was then the most intense research area in organic chemistry. What was a mechanistic curiosity in the 1960s, has today become one of the most valuable techniques of organic chemistry – the ability to perform enantioselective syntheses in the laboratory. This long sought-after goal of organic chemists has now reached the level where organic compounds of virtually every type can be obtained in complete enantioselective or diastereoselective form. How did this come about in the short period of 20–25 years? The contributions of many brilliant investigators from all parts of the world were key to these successes. The clearer understanding of reaction mechanism, kinetics, and solution and solvent effects all contributed to the phenomenal leaps forward in the rational planning of stereoselective syntheses. Thus, it would be unjust to celebrate the advances in stereochemical synthesis without paying due homage to those investigators who helped build a sound foundation in reaction theory. For without this knowledge, many rational routes to absolute and relative stereochemistry would not have been possible. Furthermore, one must not ignore the multitude of analytical tools (e.g., HPLC, NMR) which were also invaluable in allowing researchers to assess the level of their stereochemical control.

The many synthetic reactions that Professor Nógrádi has laid out, in this and the previous edition of this book, are truly a tribute to the excellent work of the modern organic chemist. The road has now been cleared for future generations to address more complex problems in biology and materials science by using the tools developed in these recent synthetic studies.

Fort Collins, Colorado, July 1994

A. I. Meyers
Professor of Chemistry
Colorado State University

# Preface to the Second Edition

The favorable acceptance of the first edition of this book and the unabated flow of important publications on stereoselective synthesis prompted us to publish a thoroughly revised second edition. Over the past years, developments in stereoselective synthesis have been impressive. Just in the past ten years, the number of publications devoted to this topic has much surpassed the total number of all papers written from Emil Fischer's time until 1984. In addition, two new journals devoted in part to our topic, *Tetrahedron Asymmetry* (Pergamon Press) and *Asymmetry* (Plenum Press), have been launched. Also some important qualitative changes can be perceived: (i) catalytic variants have been developed for almost all types of stereoselective reactions and (ii) the number of serious attempts to clarify the mechanistic aspects of stereoselectivity increased, although the share of such studies is still negligible, compared with the total number of publications.

The dramatic development of stereoselective methods is well illustrated by the following statistics about this book: Abstracts were prepared from 1400 papers; from these 831 were selected for citation in the new edition. In turn, 350 references were omitted from the first edition, giving a total of 1874 references for the second one. Literature in this edition is covered up to December 1992.

Rewriting the book was not easy, due not only to the formidable amount of information to be covered, but also due to our firm resolution to keep the price of the new edition within the reach of individual buyers. This required a rigorous adherence to the standards of selection explained in the *Preface to the First Edition*, and, in addition, sizeable parts of the first edition had to be deleted. This was a very painful exercise, and I felt guilty each time I had to cut out a method, which was pioneering in its own time, but has since been superseded by more selective ones.

Now some technicalities should be mentioned: (i) In order to avoid repetition of chiral moieties within the same equation, they are separated from the part of the molecule undergoing transformation by a wavy line and symbolized later by R*. (ii) To save space, usually only the major product is depicted, even when more than one minor product is also formed. (iii) In order to be able to compare competitive methods, when enantiomerically impure substrates or chiral auxiliaries were used, ee values were recalculated for 100% enantiomeric purity. (iv) For methods that have been optimized, the best conditions are quoted. (v) When the optical purity of a product was upgraded by crystallization or chromatography, selectivity values for the crude product are quoted. (vii) When both a preliminary and a full paper cover the same subject, only the latter is quoted.

Finally we call attention to the section *General References*, a rather arbitrary list of important reviews, which does not fit into any single chapter.

The author is indebted to Dr. Thomas Mager, Dr. Ute Anton, Eva Schweikart and Dipl.-Ing. Hans-Jörg Maier for bearing all the nuisance of welding together old and new, to Dr. Gy. M. Keserü for drawing the new formulas, and to Mrs. I. Berényi for assistance in editing.

Budapest, September 1994 M. Nógrádi

# Preface to the First Edition

The present work is an attempt to review practical methods of stereoselective synthesis with emphasis on recent advances. It embraces a wide variety of subjects, such as hydrogenations over chiral catalysts, reductions with chiral hydride donors, stereoselective epoxidations, pericyclic reactions and the rapidly expanding field of "acyclic stereoselection".

This is a very broad topic and therefore several restrictions had to be imposed on the subjects to be covered.

First of all, enzymatic transformations were omitted because these have been extensively reviewed [1]. Neither are we going to discuss stereochemical aspects of reaction mechanisms in general. There is an almost endless number of examples in the literature for syntheses starting from an optically active compound, which are carried through a number of more or less selective transformations, to end up with a product in which the original stereogenic element is retained. No coverage will be given to such syntheses since this would have required the inclusion of such immense fields as transformations of steroids, terpenoids, carbohydrates and the like.

Although there is no specific date from which the literature has been processed, earlier methods giving poor stereochemical yields will not be discussed, unless they served as a starting point for more efficient processes. Most of these methods have been amply described in earlier works [2, 3].

The hectic activity in the field of stereoselective synthesis precludes a comprehensive treatment of even the literature of the last 15 years. Therefore, methods with low stereochemical yields and the application of efficient methods to molecules of high complexity will generally be omitted.

Again for reasons of space, this book is somewhat biased in favor of methods falling under the rather ill-defined term "asymmetric synthesis". Just by their sheer number diastereoselective methods could not have been covered with any claim to comprehensiveness. On the other hand, it would have been rather controversial not to deal at all with diastereoselectivity, since, as will be apparent from the introductory chapter, the underlying phenomenon of enantioselectivity is in fact diastereoselectivity.

In summary, we wish to serve the practically minded, synthetic organic chemist rather than the theoretician.

The author was induced to write this book, not only by the extremely rapid advancement and fascination of this field, but also by his conviction that the development of stereoselective synthetic methods has reached a turning point from which

applications to practical problems have become a realistic proposition. Synthesis of natural amino acids, of non-racemic pharmaceuticals with fewer side-effects, of prostanoids and steroids, of insect hormones and pheromones are only the most rewarding fields in which such methods are of key importance.

The literature has been reviewed up to December 1984.

The author is indebted to Dr. C. Dyllick-Brenzinger for carefully revising the manuscript and to Mr. T. Goschi for his help in preparing the figures.

Budapest, August 1986 M. Nógrádi

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[1] J. Rétey and J. A. Robinson, *Stereospecificity in Organic Chemistry and Enzymology.* Verlag Chemie, Weinheim, 1982 and refs. 16 through 20 in Chapter 1.

[2] J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions.* Prentice-Hall, Englewood Cliffs, N. J., 1971.

[3] Y. Izumi and A. Tai, *Stereodifferentiating Reactions.* Academic Press, New York, 1977.

# Contents

# List of Symbols and Abbreviations

## Groups

| | |
|---|---|
| Ac | acetyl |
| acac | 2,4-pentanedione |
| BBN | 9-borabicyclo[3.3.1]nonyl |
| Bn | benzyl |
| Bu | 1-butyl |
| Bz | benzoyl |
| cHex | cyclohexyl |
| cP | cyclopentadienyl |
| cPent | cyclopentyl |
| Et | ethyl |
| Hept | 1-heptyl |
| Hex | 1-hexyl |
| iBu | 2-methylpropyl |
| iPr | 2-propyl |
| M | metal |
| Me | methyl |
| MEM | (2-methoxyethoxy)methyl |
| (−)Ment | (−)menthyl |
| Oct | 1-octyl |
| Pent | 1-pentyl |
| Ph | phenyl |
| Pr | 1-propyl |
| sBu | 2-butyl |
| tBu | 1,1-dimethyl-1-ethyl |
| Tf | trifluoromethylsulfonyl |
| Tol | *p*-tolyl |
| Tos | *p*-toluenesulfonyl |

# Reagents and solvents

| | |
|---|---|
| COD | 1,5-cyclooctadiene |
| DBU | 1,5-diazabicyclo[5.4.0]undec-5-ene |
| DME | 1,2-dimethoxyethane |
| DMPU | 1,3-dimethyl-2-oxohexahydropyrimidine |
| HMDS | hexamethyldisilazane |
| HMPA | hexamethylphosphoric amide |
| LDA | lithium diisopropylamide |
| LAH | lithium aluminum hydride |
| MCPBA | metachloroperbenzoic acid |
| MEM | (2-methoxyethoxy)-methyl |
| MS | molecular sieve |
| NBD | norbornadiene |
| NMO | *N*-methylmorpholine oxide |
| PCC | pyridinium chlorochromate |
| PhMe | toluene |
| THF | tetrahydrofuran |
| TMEDA | *N,N'*-Tetramethylethylenediamine |

# Introduction

Ever since the stereoisomerism of organic molecules was discovered and the amazing stereoselectivity of living systems in synthesizing their products was recognized, chemists have been challenged to try their hands at preparing stereoisomers in a planned manner.

First their role was rather passive and confined mainly to the observation that in some reactions diastereomers were produced in unequal amounts. The reasons for such a selectivity remained obscure for a long time, and therefore it was left to chance which of the possible stereoisomers was obtained in excess. In fact, there was also not much practical demand for achieving stereoselectivity.

The birth of stereoselective synthesis probably dates back to 1890, when Emil Fischer recognized that the reaction of L-arabinose with hydrogen cyanide provided about 66% of one of the two possible diastereomers, namely, L-mannononitrile [1]. In this way asymmetric induction was discovered, and thus one of the cornerstones of diastereoselective synthesis laid down. This was followed at the turn of the century by the discovery of the partial kinetic resolution of racemic mandelic acid by esterification with (−)-menthol by Marckwald and McKenzie [2], the first example of a non-enzymatic enantioselective method.

During the next four decades stereoselective synthesis remained a marginal field of organic chemistry. After World War II, however, steroid hormones, manufactured industrially mostly by semi-synthesis, acquired enormous economic importance. This stimulated the interest of many of the leading organic chemists to search for practical methods for the preparation of a predetermined diastereomer of a compound. It was a logical development of this endeavor that in 1950 Barton was able to propose a rationalization for a large number of hitherto unexplained examples of diastereoselection in the steroid and terpene field [3]. Barton's concepts were based on work by Hassel and Pitzer, who recognized that the stable conformation of cyclohexane derivatives was the chair form, and the substituents preferred equatorial positions. Barton's ideas then became known as "conformational analysis", although nowadays this term is used in a somewhat different context. It was the adoption of Barton's concepts that first enabled, at least with compounds containing six-membered saturated rings, the planning of syntheses directed towards a given diastereomer.

However, methods for producing a required diastereomer of an acyclic compound remained in their infancy for a long time, although the rules of Cram [4] and Prelog [5] concerning nucleophilic addition to prochiral carbonyl groups were important

milestones on the way towards efficient acyclic stereoselection. Furthermore, attempts at enantioselective synthesis using a wide variety of chiral aids (removable chiral groups, chiral catalysts, *etc.*) were almost invariably frustrated by low enantiomeric purity of the products. Characteristic of this situation is the book "Asymmetric Organic Reactions" by Morrison and Mosher [6], which reviewed the literature up to 1968. Here less than ten examples could be quoted in which products with more than 90% enantiomeric purity were obtained. The usual values were less than 20%.

Progress remained slow as long as steric hindrance alone was invoked to direct transformations towards a preselected stereoisomer. Perhaps influenced by the knowledge of how enzymes work, it slowly became clear that for high stereoselectivity it was necessary to immobilize the substrate in a suitable conformation. This fixation usually also involves the shielding of one of the molecular faces and thereby sets the stage for a stereoselective attack of the reagent. Two metals proved to be prominent aids to chemists in the realization of this concept, namely rhodium and lithium. Enantioselectivities which can be achieved in homogeneous hydrogenation using rhodium complexes of chiral biphosphines are really spectacular: by this method certain amino acids can now be prepared in almost total optical purity [7]. The process has also been realized on an industrial scale [8]. No less impressive are the results of methods in which lithium plays a key role. With selected combinations of substrates and reagents, electrophilic attack on lithium enolates may give rise to acyclic products with total diastereoselectivity, while that on chiral lithium enamides may provide almost total enantioselectivity [9]. Today one may venture to say that non-enzymatic stereoselective processes devised by organic chemists are almost as efficient as enzymatic systems. Both are characterized by achieving total stereoselectivity for a limited number of substrate-reagent pairs under strictly specified conditions, and both break down rapidly when either the optimal substrate-reagent combination or optimum conditions are abandoned.

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# 1 General Concepts of Stereoselective Synthesis

Although the present book is primarily oriented towards the practical aspects of stereoselective synthesis, it is necessary to describe briefly the basic principles of stereoisomerism, chemical selectivity in general and stereoselectivity in particular. Also, it is important to define the nomenclature and the system of notation to be used. The following introductory sections, however, should not be regarded as stereochemistry in a nutshell since only aspects important for our topic will be discussed.

## 1.1 Principles of Differentiating Molecules

The two main objectives of chemistry are the analysis and synthesis of molecules. The analysis of molecules is a rather abstract task, since there is no obvious, easily recognizable correlation between the outer appearance of a chemical substance and its internal properties which we generally call chemical structure. Differences in the structures of molecules are manifold, and it is possible to define a hierarchy of characteristics by which molecules can be distinguished. As we go down this ladder of hierarchic characteristics, molecules become more and more similar until we reach complete identity. Molecules which are identical in terms of higher ranking features may be distinguished by lower ranking ones.

(i) Molecules can differ in their *qualitative composition, i.e.* by the nature of elements they contain. Potassium carbonate and sodium carbonate, though both colorless crystalline solids, are of different qualitative composition.

(ii) Molecules of identical qualitative composition may differ in their *quantitative composition i.e.* by the ratio of the different elements they contain. Carbon monoxide and carbon dioxide, *e.g.,* differ in this respect.

(iii) Compounds of identical qualitative and quantitative composition may differ in their *molecular weight.* Acetylene, benzene, and cyclooctatetraene are examples for such a relationship.

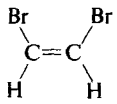
(iv) Molecules which are found to be identical by criteria (i)–(iii), may be different due to the different *connectedness* of their atoms. Here we enter the domain of *isomerism*, and molecules which only differ by the sequence of their atoms are called *constitutional isomers*. Constitutional isomers, and of course the constitution of a single molecular species, can be fully characterized by enumerating each of their atoms and stating the nature and number of all the atoms connected to each particular atom by chemical bonds.

It should be noted that the constitution of a molecule can always be adequately characterized without using words denoting directions such as "under" or "over", "left" or "right".

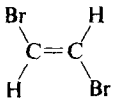
Molecules which are found to be identical by criteria (i)–(iv), but are nevertheless distinguishable are *stereoisomers*. Stereoisomers occupy two steps on our scale of differentiation.

(v) *Diastereomers* are molecules of identical constitution but which can be differentiated by some scalar property, the most important being internuclear distances of a selected pair of groups (atoms) or in complex cases by the distances of several such pairs.

The following examples serve to illustrate how we can characterize diastereomers by internuclear distances. Thus diastereomers of 1,2-dibromoethene differ by the internuclear distance of the two bromo atoms. Conventional prefixes attached to names describing constitution enables one to identify diastereomers without taking recourse to formulas.




(*Z*)-1,2-dibromoethene




(*E*)-1,2-dibromoethene

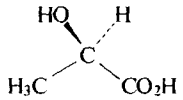
The prefix *Z* in the above formula means that the distance between the selected pair of groups in this diastereomer is smaller than that in the *E* isomer. Rules for assigning the above and other conventional prefixes have been agreed upon by international conventions called the IUPAC Rules of Nomenclature. Most important from our point of view are the "Rules of Stereochemical Nomenclature" [1]. Any pair of diastereomers, however complex their constitution should be, can be adequately characterized by a set of statements referring to internuclear distances.

Differences in internuclear distances serve not only for the identification of diastereomers, more importantly they form the basis of differences in their physical and chemical characters.

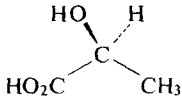
(vi) *Enantiomers* are pairs of stereoisomers with the highest level of similarity. If their formulas are written down according to the same convention, internuclear distances for any given pair of atoms are identical. Enantiomers can, however, be distinguished by stating the *sequence* of selected groups following a certain convention. The conventional character of distinguishing enantiomers must be emphasized, because words such as clockwise – anticlockwise or right-handed – left-handed are

meaningless in themselves and come to life only by a world-wide agreement about their significance.

A typical statement describing the difference between dextrorotatory and levorotatory lactic acid is the following: when their formulas are depicted according to the same convention (hydrogen remote from the viewer) the sequence of the groups hydroxy, carboxy and methyl is anticlockwise for the dextrorotatory and clockwise for the levorotatory enantiomer.




(−)-(*R*)-lactic acid




(+)-(*S*)-lactic acid

A system of nomenclature for the unambiguous characterization and distinction of enantiomers by pairs of simple prefixes (*R* and *S*, *P* and *M*) has been worked out by R.S. Cahn, C.K. Ingold, and V. Prelog (the s.c. C.I.P. convention) [2].

When represented following the same conventions, formulas of diastereomers are *not* mirror-images, while those of enantiomers are mirror-images. An object (*e.g.* a molecule) which is not identical with its mirror image is called *chiral*, otherwise it is achiral. Molecules forming enantiomers are chiral by definition, while chirality is not a condition for a diastereomeric relationship. Thus the diastereomeric 1,2-dibromoethenes are both achiral. (−)-Tartaric acid and *meso*-tartaric acid are diastereomers, the former is chiral, the latter is achiral.

The last stage in our molecular identity-non-identity hierarchy is complete identity, which we are not interested in. Note that identity is a concept dependent on the depth of our insight. Thus molecules which we regard in our discussions as being identical may differ in their isotopic composition, electronic or nuclear quantum levels *etc.*

# 1.2 Characterization of Stereoisomers. Conformation and Configuration

Molecules can be characterized by a set of geometrical parameters. These are the van der Waals radii of the individual atoms (relevant to the concept of steric hindrance), equilibrium bond lengths between directly bonded atoms, equilibrium bond angles formed by the bonds of two atoms bonded to a common third atom and, finally, torsional angles describing the spatial relationship of the terminal atoms in a linear chain of four atoms.

The complete set of all possible torsional angles of a molecule defines its *conformation*. Certain well characterized conformations are called *conformers*. For practical purposes we usually disregard the torsional angle of bonds attached to a double bond (which we take as fixed at 0° and 180°, respectively) and those associated with groups rotating very fast, such as the methyl group. Molecular species having different conformations are, by definition, stereoisomers, since they are different entities with the same constitution, although such stereoisomers are usually inseparable due to their rapid interconversion. Examples for stereoisomers which differ in their conformation are the (*P*)-synclinal and antiperiplanar conformers of n-butane (inseparable) and (*R*)- and (*S*)-2,2′-diiodobiphenyl-6,6′-dicarboxylic acid [(*R*)- and (*S*)-(*1*)] (Fig. 1-1) (separable). The relationship of any two conformers may be either diastereomeric (as that of the two *n*-butanes) or enantiomeric (as that of the two biphenyls).

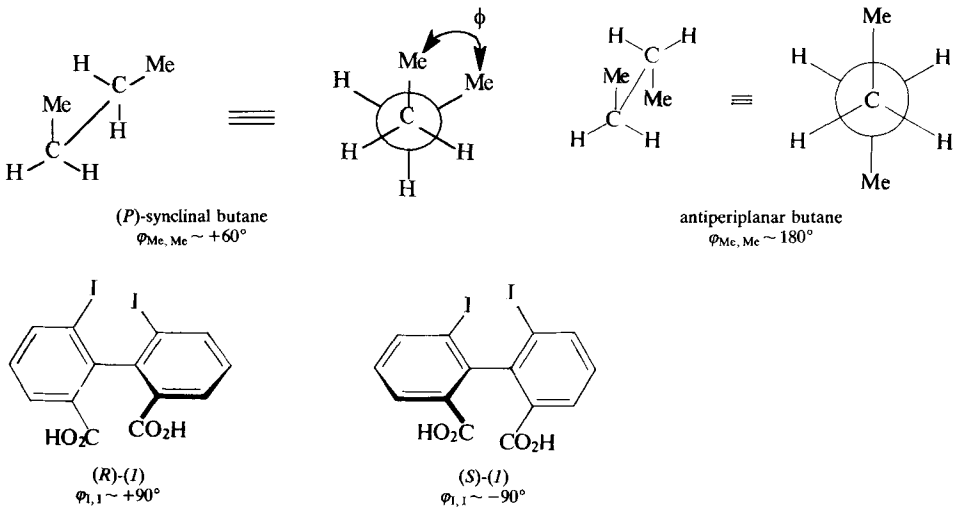



*Fig. 1-1.* Characterization of conformations.

While (apart from signs) conformation, *i.e.* describing stereoisomers by a set of torsional angles, is essentially a quantitative approach, *configuration* characterizes a molecule in a qualitative way. Configuration has a different role when describing diastereomers and enantiomers, but in both cases it essentially covers a system of conventions.

Diastereomers may be compared by their *relative configuration, i.e.* by differences in the intramolecular relationship of selected groups within each diastereomer. An example for such an internal comparison was given in the preceding section, in which the distinguishing features were epitomized as conventional prefixes such as *E* and *Z*.

Diastereomers which are interconvertible by rotation around a single bond can be described by the pertinent torsional angles or, more conveniently, by conventional names associated with specific ranges of torsional angles, such as synperiplanar (or syn) for $0\pm30°$, synclinal (or gauche) for $\pm60\pm30°$, anticlinal for $\pm120\pm30°$ and antiperiplanar for $180°\pm30°$ *etc.*

Diastereomers which arise by different combinations of two or more chiral centers can be conveniently labelled by listing the configurational symbols *R* and *S* for each center, e.g. 2*R*,3*R* for dextrorotatory and 2*R*,3*S* for *meso*-tartaric acid.

In this book, in conformity with the IUPAC rules, the following nomenclature will be used to describe the relative configuration of diastereomers.

For geometrical isomers the *Z*–*E* notation will be used with some unavoidable exceptions, when, in order to embrace wider groups of compounds, we will be forced to fall back on the *cis-trans* notation. The prefixes *cis* and *trans* are useful to define the relative arrangement of groups attached to rings, for which purpose *Z* and *E* should not be used.

The names recommended by IUPAC (occasionally in their abbreviated form) will be applied to conformers generated by rotation around a single bond. Note that *syn* and *anti* are also used to describe the stereochemistry of addition and elimination [3].

Considerable confusion was created some years ago in describing the relative configuration of two chiral centers in a linear molecule. Originally, the relative configuration of two groups which are on the same side in a Fischer projection (as in erythrose) was called *erythro*, while that of those on opposite sides (as in threose) *threo*. Apart from occasional difficulties in selecting the main chain, this system served well with two chiral centers. The Fischer projection is undoubtedly an unnatural representation, and when the chain is drawn in the more realistic zig-zag form, *erythro* substituents end up on opposite sides whereas *threo* ones are on the same side. In Fig. 1-2 the (2*R*,3*R*) and the (2*R*,3*S*) diastereomers of 3-hydroxy-2-methylbutanoic acid are shown in Fischer projection, in the zig-zag conformation and in a simplified representation of the latter. In order to put substituents back into their "customary" relationship, Heathcock suggested in 1981 [4] an inversion of the nomenclature, thereby causing bewildering confusion in the literature. Thus the (2*R*,3*R*)-compound (a) previously called *erythro* now became *threo*, while its diastereomer was renamed *erythro*. Also, Heathcock's suggestion gained rapid and widespread acceptance. The new problem was soon recognized and several sugges-

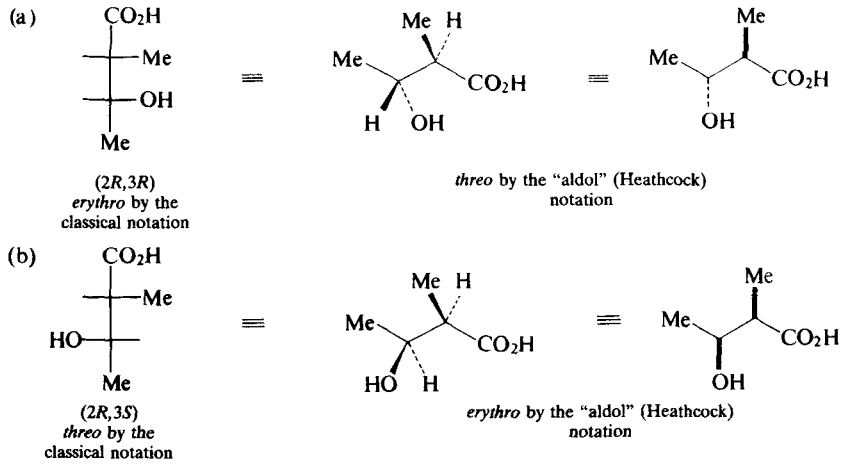
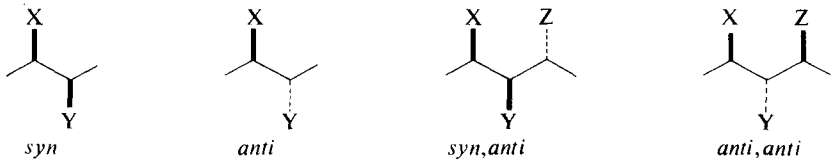



*Fig. 1-2.* Characterization of relative configuration in aldol-type compounds.

tions for alternative ways to identify relative configuration in acyclic molecules have been devised [5–7]. The most comprehensive and consistent among them is the one by Prelog and Seebach [8] (*cf.* p. 21). To dissociate ourselves from both the old and new usage of *erythro* and *threo*, the prefixes *syn* and *anti* will be used in the sense shown in the following examples:*




The steric disposition of groups with a geminal hydrogen atom will be indicated by heavy and broken lines, respectively. In the case of quaternary centers or when it is deemed necessary for a better presentation of the situation, traditional wedges will be used as well.

Enantiomers can be identified by quoting the sign of their optical rotation, by constructing or drawing a model representing the molecule or by reference to a certain convention. Fortunately nowadays only one system of convention, that of Cahn, Ingold and Prelog, also called the sequence rules, is in use. Its basic principles and application, at least for simple cases, is well known and need not be discussed here [2].

Well known optically active compounds containing more than one center of chirality, such as menthol, α-pinene, ephedrine *etc.* can be conveniently identified by their sign of rotation. Even this can be omitted for some compounds, such as the *Strychnos* alkaloids and steroids, which in nature only occur in one enantiomeric form.

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* This is not a perfect solution either, since IUPAC recommended these words for the characterization of the mode of approach in addition reactions. Later Heathcock turned to the *syn-anti* notation too [3].

# 1.3 Intramolecular Symmetry. Topicity and Prochirality

## Topicity

Analysis of molecular symmetry is of fundamental importance for stereochemistry and therefore also for the thorough understanding of stereoselective reactions.

While for the discussion of stereoisomerism it is the global symmetry of a molecule which is relevant, from the point of view of stereoselectivity we also have to consider the symmetry relationships of certain subunits of the molecule, namely, those of groups and faces.

As a *group* we define in our context any subunit of a molecule; this can be as simple as a hydrogen atom or as complicated as a monosaccharide unit. Groups may be classified according to a hierarchical scheme similar to that used for molecules.

Thus groups, when regarded in isolation, may differ (i) in qualitative composition (*e.g.* Br and I), (ii) in quantitative composition (*e.g.* CHO and $CO_2H$), in constitution (*e.g.* propyl and isopropyl) and (iii) in stereostructure (*e.g.* bornyl and isobornyl which are diastereomeric or (*R*)- and (*S*)-2-phenylethyl which are enantiomeric*).

Two or more groups in a molecule which are identical by the above criteria may have different relationships to each other.

(i) Groups can have the same or different connectedness with the rest of the molecule, in other words their *constitutional position* may be the same or different. Thus in 2,4,6-trinitrotoluene nitro groups in the 2- and 6-position have the same connectedness, while those in 2- and 4-position are constitutionally different.

In discussing stereoselectivity we are only interested in identical groups of the same connectedness. Their relationship can be diastereotopic, enantiotopic or homotopic [10].

(ii) *Diastereotopic* are groups which cannot be exchanged by any symmetry operation. Since in asymmetric molecules such as *2* in Fig. 1-3 symmetry elements cannot be present by definition, geminal groups in such molecules (set boldface) are always diastereotopic. Similarly to diastereomers, diastereotopic groups can be readily distinguished by their relationships (near-remote) to a reference group, *i.e.* in scalar terms. Chiral molecules with rotational symmetry (*e.g. 3*) and achiral molecules (*e.g. 4*) may also contain diastereotopic pairs of groups, but the symmetry element(s) must be unrelated to these groups. Thus geminal hydrogens within each $CH_2$ group (but not those at different carbons) of the cyclopentanone *3* ($C_2$ symmetry) are diastereotopic, one being near to, the other remote from the adjacent methyl group.

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* Note that although often done for convenience, the assignment of *R* and *S* descriptors to groups is ambiguous since these are dependent on the nature of the fourth ligand.

Note that although *4* has a plane of symmetry, methyl and carboxyl groups resp. which lie in this plane cannot be exchanged by it. Although for conformationally mobile molecules such as *2* a given near-remote relationship between diastereotopic groups is only valid for a certain conformation, the molecular environment surrounding each member of the group is inherently different for each conformation. Although the magnitude of the difference (expressed as some physical parameter, *e.g.* magnetization) is dependent on conformational equilibria, the mere fact of this difference cannot be eliminated by fast rotation or ring inversion [11].

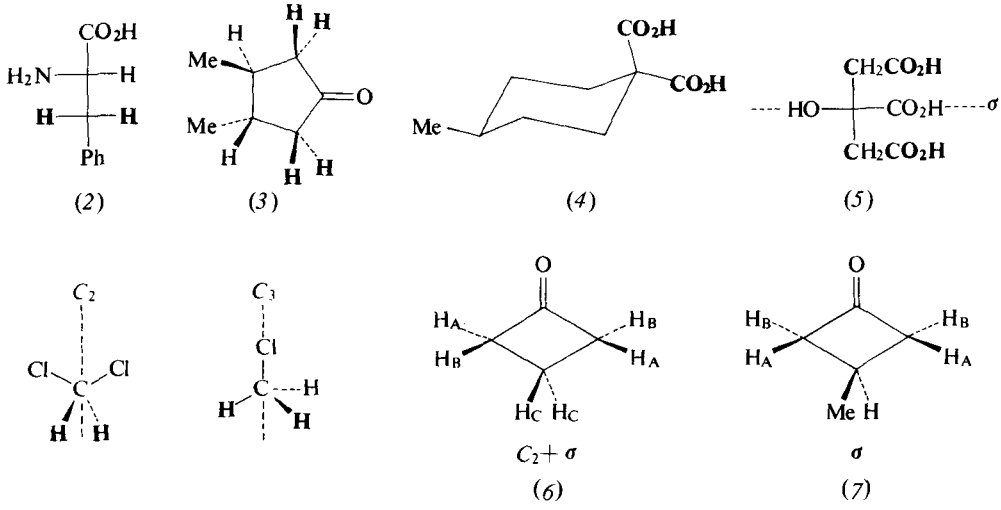


*Fig. 1-3.* Molecules with diastereotopic, enantiotopic and homotopic groups.

(iii) *Enantiotopic* are groups which can be exchanged by a rotation-reflection axis, which is most often a plane ($\sigma = S_1$) or a center ($C_i = S_2$) of symmetry. Thus enantiotopic groups can only occur in achiral molecules.

Enantiotopic are $CH_2CO_2H$ groups in citric acid (*5*) and subunits thereof ($CH_2$, $CO_2H$).

(iv) *Homotopic* are groups which can be exchanged by a symmetry axis. It follows that any achiral or chiral molecule which has an axis of symmetry contains at least one set (usually a pair) of homotopic groups.

Compounds which contain a set of two and three homotopic hydrogens, respectively, are dichloromethane and chloromethane (Fig. 1-3).

Diastereo- and enantiotopic groups are called *heterotopic*.

The terms dia-, enantio- and homotopic express the relationship of one group to another and may therefore change with the partner. Thus, in *6* atoms $H_A$ are homotopic and each has two kinds of enantiotopic relationships to atoms $H_B$, which also form a homotopic set. Neither is connected by any symmetry operation to the homotopic pair of atoms $H_C$ which have a different connectedness. In *7* the $H_A$ and $H_B$ atoms form two enantiotopic sets, while any $H_A$ is diastereotopic to any $H_B$.

One of the most frequent synthetic operations is the addition of a group to a tricoordinate center to form a tetracoordinate center. The tricoordinate center is usually a double bonded atom, the three valencies of which constitute a plane with two faces. The topicity notation explained above for groups can be conveniently extended to the symmetry relationships of such faces (Fig. 1-4).

(i) *Diastereotopic* are two faces of any molecular plane which is no plane of symmetry and does not contain a coplanar axis of symmetry. Thus faces in asymmetric molecules (*e.g.* that of both C=O and C=C in *8*) are always diastereotopic, no matter how fast bond rotation may be.

A plane of symmetry perpendicular to the plane to be qualified is not incompatible with diastereotopicity, as can be seen with compound *7* which contains a carbonyl group with diastereotopic faces.

(ii) *Enantiotopic* are two faces of a molecular plane which is at the same time a molecular plane of symmetry but which does not contain a coplanar axis of symmetry. Enantiotopic are the faces of acetaldehyde and of phenyl-methyl-sulfide.

(iii) *Homotopic* are two faces of a molecular plane which contains a coplanar axis of symmetry. Such faces can be found both in achiral molecules, such as acetone, isobutene, and in chiral ones as, *e.g.*, in *3*.

For conformationally mobile molecules symmetry relationships usually change with conformation. Here a practical standpoint can be adopted and conformational changes much faster than the process investigated should be disregarded. Thus for a low temperature NMR study the methyl groups and the faces of the carbonyl group of 2,2-dimethylcyclohexanone should be regarded as diastereotopic (*9*), while for a hydride transfer reaction at room temperature the s.c. *statistical symmetry* of the molecule, *i.e.* that of its most symmetrical (possibly non-populated) conformer (*10*, enantiotopic in the present case), should be invoked.

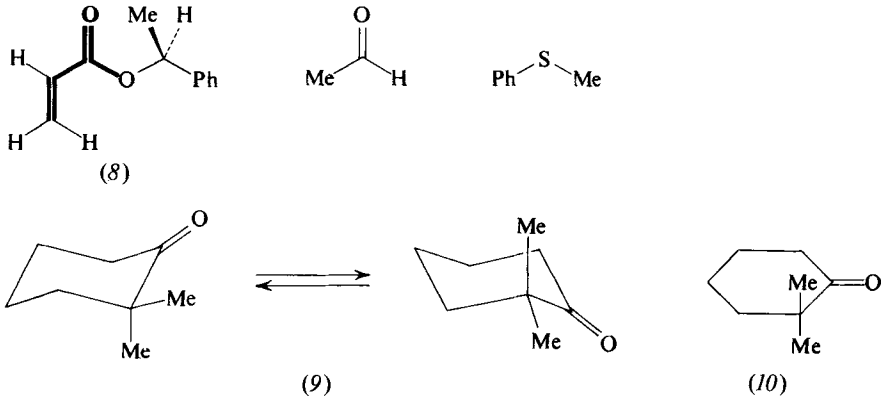


*Fig. 1-4.* Molecules with diastereotopic and enantiotopic faces.

**Prochirality**

Since, as will be discussed later, transformation of any one group of an enantiotopic pair of groups into another group or addition of a new group to a center with enantiotopic faces gives rise to a chiral compound, enantiotopic groups and faces are called *prochiral* [12]. The same is true for diastereotopic groups which do not coincide with a plane of symmetry and for diastereotopic faces which have no perpendicular plane of symmetry.

By application of the sequence rules, the labels pro-*R* and pro-*S* are given to geminal prochiral groups and prochiral faces. This is very convenient because it avoids referring to a drawing. According to Prelog and Helmchen [13], a prochiral group is called pro-*R* (or briefly *Re*) when the sequence of ligands in decreasing order of priority (the other group is remote from the observer) is clockwise, and pro-*S* (*Si*), when it is anticlockwise (Fig. 1-5). The procedure for faces is even simpler: regarding the center to be qualified from the pro-*R* (*Re*) face the sequence of ligands in decreasing order of priority is clockwise, while anticlockwise from the pro-*S* (*Si*) face.

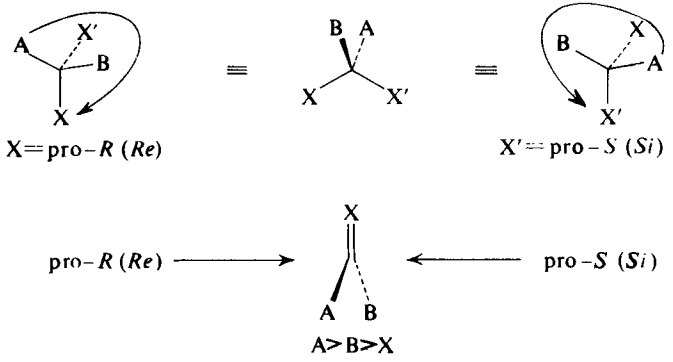


*Fig. 1-5.* Prochirality.

Note that there is no correlation between the prochirality descriptor and the configuration of the product arising from transformation of the group or face concerned, e.g.: