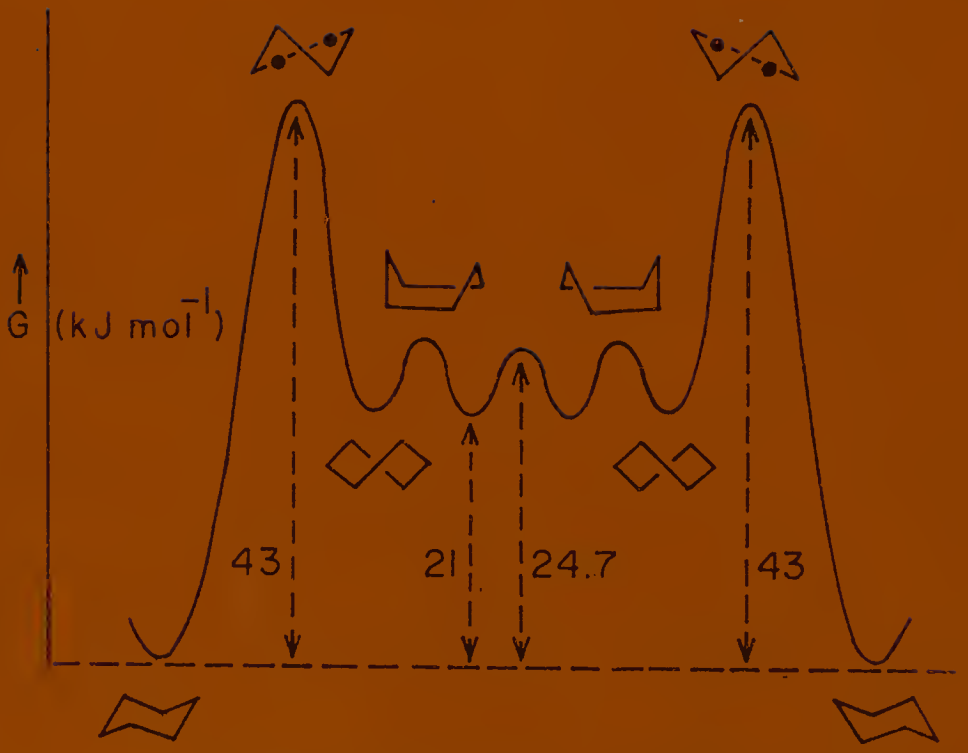
Stereochemistry of Organic Compounds

Principles and Applications

D. NASIPURI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D. NASIPURI
Formerly Professor of Chemistry
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To the Memory of

MARIAN KOCOR

Foreword

Since the publication of my own book "Stereochemistry of Carbon Compounds" nearly thirty years ago, there has been a remarkable, almost explosive growth of the subject. There are several reasons for that, among them the surging interest in reaction mechanism in the 1960's culminating in the Woodward-Hoffmann rules at the end of that decade, the mounting interest in total synthesis including diastereoselective and (since the mid-nineteen seventies) enantioselective synthesis, and the development and expansion of new techniques, such as ^{13}C nuclear magnetic resonance and, more recently, 2-D and solid-state nmr. The subject has been recognized by two Nobel prizes in the area—to Barton and Hassel in 1969 and to Cornforth and Prelog in 1975. Yet there have been few comprehensive stereochemistry books in that period, despite the growth of the subject and despite the increasing interest of not only organic chemists, but also biochemists and, more recently, medicinal chemists and pharmacologists. Most of the books that did appear have been short ones, either specialized or aimed at the advanced undergraduate. My own second edition, originally planned for the late seventies, has been delayed; instead there will, in the near future, be an entirely new book, coauthored with S.H. Wilen and L. Mander. In the meanwhile, a book suitable for beginning graduate students and incorporating up-to-date nomenclature as well as modern concepts and new facts has been in abeyance.

Professor Nasipuri is filling this gap in the present book. The book is comprehensive and includes leading references. Nasipuri is well qualified for the task; his own research has been in the area of stereochemistry and I have had the pleasure of collaborating with him in this area at the University of Notre Dame in the mid-nineteen sixties. Subsequently he paid visits to the W.R. Kenan, Jr. Laboratories of the University of North Carolina in 1977 and again in 1987. His understanding of the subject is thorough and extensive and this reflects itself in his writing. The book covers the entire area of stereochemistry, including both static and dynamic aspects and physical, especially spectroscopic properties as well as chemical behavior. In addition, the author has made a serious effort to clear a path through the jungle of overgrown stereochemical nomenclature.

I believe graduate students and others interested in learning stereochemistry beyond what they find in elementary textbooks will greet this book with applause.

June 1989

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Preface

Organic stereochemistry started with Louis Pasteur in 1848, was placed on a firm three-dimensional basis by Le Bel and van't Hoff in 1874, and subsequently passed through several phases of intensive development. Introduction of the principles of conformational analysis by Barton and Hassel in 1950 set another landmark in its progress helping to understand the temporal aspect of molecular geometry and its significance in physicochemical properties and reaction mechanisms. Modern instrumentation methods such as X-ray diffraction, nuclear magnetic resonance spectroscopy, circular dichroism and optical rotatory dispersion measurements have helped to solve many intricate stereochemical problems. Considerable progress has been made in the recent past in some selected areas such as asymmetric synthesis, stereodynamics, topicity and prostereoisomerism, cyclostereoisomerism, and chemical topology. There have been important developments on the terminological front so that many stereochemical concepts can now be defined in more precise terms. Changes have also been made at the basic level such as in the definition and classification of stereoisomers and even in the understanding of molecular chirality. Stereochemistry is no longer an isolated field of study for organic chemists; it is inseparably linked with virtually all branches of chemistry notably synthetic and mechanistic chemistry, biological chemistry (including molecular biology), medicinal chemistry, and polymer chemistry. It has important bearing even on such diversified subjects as spectroscopy, engineering, and exobiology.

Inspite of the importance of the subject, however, there are not many comprehensive textbooks on stereochemistry excepting the one by Professor E.L. Eliel published in 1962 which has catered to the need of the students and research workers the world over for nearly twenty five years. A few textbooks have since then appeared incorporating some of the latest developments but not in a comprehensive manner. Some advanced series of monographs, e.g., 'Topics in Stereochemistry', edited by Eliel, Allinger, and Wilen are available but their approach is highly specialised and clearly meant for the initiated.

The present text is an effort to fill up this void in the stereochemical literature. It would be inappropriate to claim that a complete coverage of organic stereochemistry has been made - this is almost impossible to do under a single cover with limited space. Attempts have, nevertheless, been made not to leave out any of the major areas which might be significant in later study. The subject has been treated from the fundamental level and slowly developed so that the book may be adopted at any stage of university teaching and at the same time be useful to the practising organic chemists. Special emphasis has been given to conformational analysis and dynamic stereochemistry which include correlation of conformation and reactivity, stereoselective methodologies, and a brief account of pericyclic reactions. A large cross section of reaction mechanisms has been incorporated with

stereochemical implications. For reasons of space, no problem solving exercises could be included - they are intended to be taken up in a supplementary volume. Each chapter is provided with a summary which highlights the main points discussed in the text. Selected references, mostly of textbooks, monographs, review articles, and significant original papers, are given at the end of each chapter extending through early 1990.

The author is extremely grateful to Professor E.L. Eliel who not only inspired him to write this book but meticulously went through the entire first draft of the manuscript and enriched it with valuable comments and suggestions. He also very kindly wrote a foreword to the book. Any error in facts and figures is, however, the sole responsibility of the author. The author takes this opportunity to express his gratitude to his numerous friends and colleagues who assisted him in one way or the other in completing the book. He is specially thankful to Dr. Satyesh C. Pakrashi, Director, Indian Institute of Chemical Biology, Calcutta for providing hospitality in his laboratories and other facilities and to Professor Sunil K. Talapatra, University of Calcutta for his helpful comments and improvement on certain diagrams. Drs. Anup Bhattacharya, Pranab K. Bhattacharya, and Ranjan Mukherjee (all of IICB, Calcutta) went through the final manuscript; the last-named also assisted with the reading of the galley proof.

Thanks are also due to Professor Dibyendu N. Roy, University of Toronto, Canada, Dr. Abhik Ghosh, University of Minnesota, USA, Professor Mihir Chowdhuri, Professor Usha R. Ghatak, Dr. Brindaban Ranu, Dr. Ashis De (all of Indian Association for the Cultivation of Science, Calcutta), Professor Amareswar Chatterjee, Jadavpur University, Calcutta, Professor S.P. Singh, Kurukshetra University, Kurukshetra, Dr. Ranjit K. Roy (Calcutta), Arabinda Saha, and Dr. Basudev Achari (both of IICB, Calcutta). Tapan, author's eldest son helped with the compilation of the subject index. The author records his appreciation to Namita, his wife for her understanding and endurance and to Asis, his youngest son and Sunil, his son-in-law for their cooperative enthusiasm during the period of writing. The credit for artwork and cover design goes to S.K. Sahoo and H.N. Datta. The manuscript was typed by S.K. Chhatui.

Finally, the author expresses his sincere thanks to the University Grants Commission, New Delhi for financial support.

March 1991

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Chapter 1

Molecular Geometry and Chemical Bonding

1.1 Introduction

Literally, stereochemistry means *chemistry in space* and describes chemistry as a function of molecular geometry. Historically, it happened the other way round—certain molecular phenomena were observed and in order to explain them, the stereochemical principles had to be developed. One such observation which marked the beginning of organic stereochemistry was made by the French physicist Biot (1815) who found that certain organic molecules rotate the plane of a polarised light in solution or in the gaseous phase—a property known as optical activity. Later, Louis Pasteur (1848), who may be regarded as the *father* of organic stereochemistry, ascribed this property to the presence of some *dissymmetric grouping* of atoms in a molecule. It was, however, van't Hoff and Le Bel* (1874), working independently of each other, who laid the foundation of organic stereochemistry by postulating the *tetrahedral* geometry of carbon compounds and thus added a third dimension to the two-dimensional chemistry of earlier days. With the help of the new structural hypothesis, they not only explained optical activity in terms of asymmetric atoms but also made certain predictions which have since then been experimentally verified, e.g., the existence of optical activity in substituted allenes and spiranes. The tetrahedral disposition of the four carbon bonds has now received firm support from physical measurements of a more direct nature, e.g., electron diffraction and X-ray diffraction experiments and also from theoretical calculations.

The next important event which brought a revolutionary change in the field of stereochemistry was the introduction of the concept of conformational analysis during the early nineteen-fifties by Barton and Hassel. This concept not only helped chemists to appreciate certain detailed aspects of molecular structure in relation to physical and chemical properties but added another dimension, a time-dependent (temporal) one to the three-dimensional stereochemistry and extended its scope to reaction processes marking the advent of dynamic stereochemistry.

1.2 Molecular structure and chemical bonding

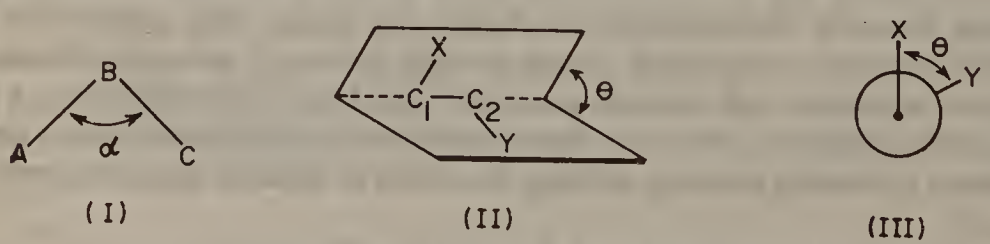
To gain an insight into the molecular structure, one must know the nature of

*Actually, Le Bel never advocated the tetrahedral theory although it was indirectly implied in his treatment (see Ramsay 1981).

chemical bondings which hold the atoms in a molecule together. For organic compounds, chemical bonding is relatively simple since it usually involves stable covalent linkages of carbon atoms with other carbon atoms, with atoms of a few other common elements like hydrogen, halogens, oxygen, and nitrogen, with other heteroatoms, and occasionally with some metals. What makes the chemistry of carbon compounds so fascinating is the unique *catenating* property of carbon atoms which combine among themselves by single and multiple covalent bonds to give almost infinite varieties of structural patterns. The non-planar geometry of a tetrahedral carbon having four ligands (connected atoms or groups) and the planar geometry of a trigonal carbon having three ligands permit the existence of structural isomerism and stereoisomerism by multiplying the possible arrangements of the ligands. Chemical bonding in carbon compounds has been adequately dealt with in numerous textbooks in organic chemistry and books on reaction mechanism and theoretical chemistry. Only a few salient features of the chemical bonding of carbon are included here which are pertinent to stereochemical discussion.

1.2.1 **Bond length, bond angle, and dihedral angle**

Three basic parameters are of primary importance in defining the bonding geometry of a molecule. They are bond length (l), bond angle (α), and dihedral angle (θ)*. The bond length is measured by the distance between two atomic nuclei joined together by single or multiple covalent bonds, the bond angle (α) by the angle subtended by two atoms covalently linked to a third atom as in A—B—C (I), and the dihedral angle (θ) by the angle between the two planes containing X—C_1—C_2 and C_1—C_2—Y respectively in a molecule, X—C_1—C_2—Y as shown in (II) (Figure 1.1). The dihedral angle is best seen in a Newman projection formula (III) in which the molecule is viewed along C_1—C_2 bond, the dot in the front indicating C-1 and the circle behind it indicating C-2 (the remaining four bonds are not shown). The bond length, bond angle, and dihedral angle are one-dimensional, two-dimensional, and three-dimensional parameters of a molecule involving two atoms, three atoms, and four (or more) atoms respectively. Because of vibration along a bond axis (stretching and compression) and of scissoring motion (bending in and out) across the plane of an angle, mean or equilibrium values of bond lengths and bond angles are used. The deformation of a bond is a high energy process and seldom needs to be taken into consideration. On the other



(I) (II) (III)

Figure 1.1 Bond angle and dihedral angle

*Different symbols are used by different authors for these parameters.

hand, deformation of bond angles is relatively easy requiring approximately 0.04 kJ mol^{-1} for a change of 1° and may be sizeable thus causing substantial deviation in the molecular geometry from the *idealised* model based on the equilibrium values of bond lengths and bond angles. These deviations are, however, not sufficiently high to invalidate the usefulness of describing molecules in their idealised forms (see Chapter 9).

1.2.2 Covalent radii and van der Waals atomic radii

A useful concept has been introduced to express the bond length between two atoms, as in A—B, in terms of the hypothetical radii r_A and r_B, known as covalent radii of atoms A and B respectively, so that $r_A + r_B$ is equal to the equilibrium bond length. The covalent radius of an atom is independent of the nature of the other atom to which it is bonded. The bond lengths and the covalent radii of a few common elements are given in Table 1.1.

Bond energy is another very important parameter of a bond but we are not concerned with it at the moment.

Table 1.1 Bond lengths and covalent radii

Bond	Bond lengths (nm)	Element	Coordination number	Covalent radii (nm)
C—C	0.154	C	4	0.077
C=C	0.133	C	3	0.0665
C≡C	0.121	C	2	0.0605
C—H	0.110	H	1	0.033
C—O	0.143	O	2	0.074
C=O	0.121	O	1	0.062
C—N	0.147	N	3	0.074
C=N	0.127	N	2	0.062
C≡N	0.115	N	1	0.055
C—Cl	0.177	Cl	1	0.100
C—Br	0.191	Br	1	0.114
C—I	0.210	I	1	0.133

To each atom or neutral grouping corresponds a definite distance within which it resists penetration by other atoms. Pauling has estimated this distance, known as van der Waals atomic or group radius for a number of atoms and groups (Table 1.2). When two non-bonded atoms approach each other, weak attractive forces, known as van der Waals attraction (or London forces) operate until at a certain distance (r), an energy minimum is reached. Beyond this, the attractive forces are replaced by a very strong repulsive force (van der Waals repulsion or Born force). The sum of the attractive and repulsive forces is known as non-bonded interaction and the distance r is the sum of the van der Waals radii of the two atoms. It corresponds to the optimal approach between two non-bonding atoms or groups and plays an important role in determining steric strain in a molecule. The values given in Table 1.2 are from crystallographers' data which are slightly lower (by approximately 0.03 nm) than the more realistic values applied to isolated atoms (Allinger 1976) in which, unlike in crystals, intermolecular packing forces are absent.

Table 1.2 van der Waals atomic and group radii (nm)

H	0.120	O	0.140	N	0.150	Cl	0.180
C	0.150	S	0.185	P	0.190	Br	0.195
CH_3	0.200	Se	0.200	F	0.135	I	0.215

1.3 Hybridisation and chemical bonding

The electronic configuration of carbon in the ground state is $1s^2 2s^2 2p^2$ which suggests bivalency (2 empty p orbitals) for carbon. In order to provide a simple rationalisation of the bonding in carbon compounds, Pauling suggested that the four P-shell orbitals (2s, $2p_x$, $2p_y$, $2p_z$) be mixed together and then split into a set of four equivalent hybrid orbitals, designated sp^3—a process known as hybridisation. These hybrid orbitals, under idealised condition are directed towards the four corners of a regular tetrahedron. The two important consequences of hybridisation are: four bonds instead of two may be formed to carbon; and secondly, the highly directional sp^3 orbitals provide more effective overlap during bond formation which more than compensates for the extra energy required in placing the valence electrons in the hybrid orbitals. Methane and carbon tetrachloride with four identical ligands form a perfect tetrahedron with valency angles of 109.5° as shown in structure (IV) (Figure 1.2). H's joined to carbon by full lines are in the plane of the paper, H joined by a dotted line is below the plane, and H joined by a thick line is above the plane. During bonding between two sp^3 hybridised carbons as in ethane (V), two sp^3 orbitals overlap forming a C—C σ bond while the remaining six sp^3 orbitals form bonds with hydrogens by overlapping with their s orbitals. Because of the cylindrical symmetry of electron distribution in a σ bond, free rotation about a single bond might be expected.

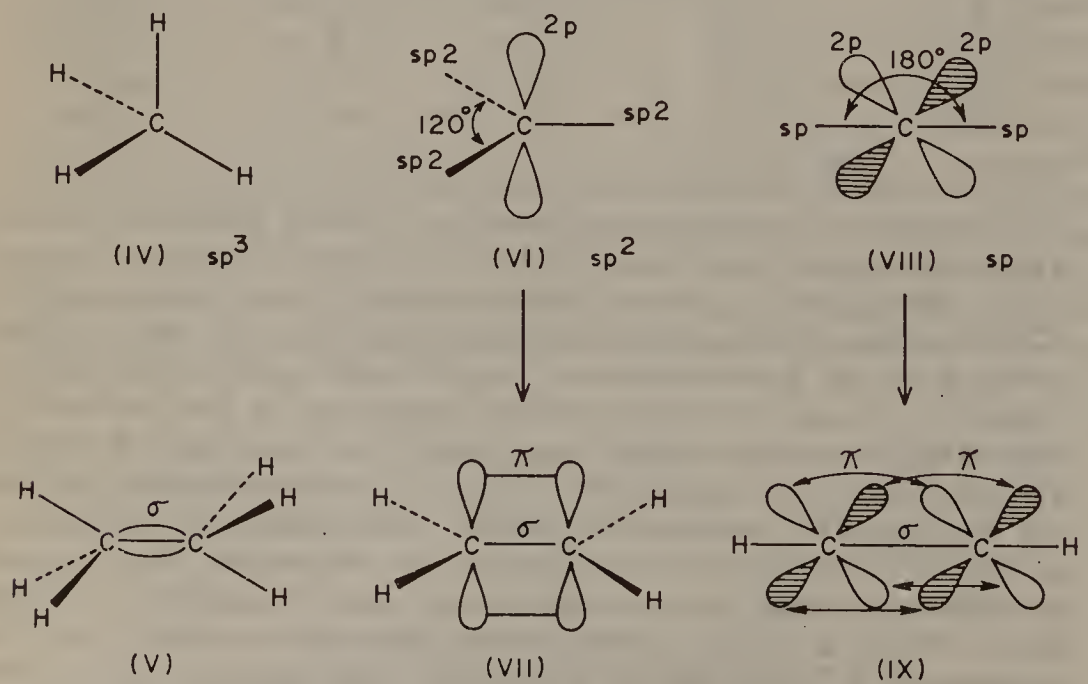


Figure 1.2 Hybridisation and bonding (only axes of hybrid orbitals are shown).

In a similar manner, one 2s and two 2p orbitals may be hybridised to give three equivalent sp^2 hybrid orbitals. They lie in a plane and are equidistant from one another making an interorbital angle of 120° (VI). Two of the sp^2 hybrid orbitals can undergo axial overlap forming a C—C σ bond as in ethylene (VII) with the remaining four hybrid orbitals forming σ bonds with four hydrogens. Each carbon is left with one 2p orbital (containing an electron) perpendicular to the $—CH_2$ plane; these orbitals can undergo lateral overlap with each other forming a π bond. The two carbons are thus doubly linked which shortens the bond length and confers extra stability to the bond. In order to provide most effective overlap between the two p orbitals, the molecule should necessarily be planar and any deviation from planarity would weaken the π bond. As a result, rotation around a double bond is highly restricted.

Hybridisation of one 2s and one 2p orbital similarly gives two equivalent sp hybrid orbitals which are linearly oriented (maximum separation) and the interorbital angle is 180° (VIII). In acetylene (IX), a σ bond is formed between the two carbons by axial overlap of an sp orbital of each and two more σ bonds to hydrogen are formed by overlap of carbon sp and hydrogen s orbitals. In addition, two π bonds are formed due to lateral overlap of two sets of mutually perpendicular 2p orbitals. The two carbon atoms are triply bonded which causes a further shortening of the bond length and an increase in the bond energy. Because of the radial distribution of electron density, rotation about the triple bond is expected to be free; in any case, it does not alter the shape of the molecule. The geometries of sp^3, sp^2, and sp hybridised carbon are tetrahedral, trigonal, and linear with four, three, and two ligands respectively.

Nitrogen with an electronic configuration, $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$ and oxygen with an electronic configuration, $1s^2 2s^2 2p_x^2 2p_y^1 2p_z^1$ are also assumed to form bonds through similarly hybrid orbitals with the difference that one (in nitrogen) and two (in oxygen) of the hybrid orbitals are occupied by a lone pair or pairs of electrons. In Table 1.3, the characteristic properties of a few common bonds are summarised.

Table 1.3 Characteristic properties of some C—C, C—N, and C—O bonds

Type of bond	State of hybridisation	Molecular geometry	Bond length[1] (nm)	Bond angle (idealised)	Bond energy (kJ mol^{-1})	Rotation
C—C	sp^3	tetrahedral	0.154	109.5°	350	"free"[2]
C=C	sp^2	trigonal	0.134	120°	670	restricted
C≡C	sp	linear	0.120	180°	960	free
C—N	sp^3	tetrahedral	0.147	109.5°	305	"free"[2]
C=N	sp^2	trigonal	0.127	120°	616	restricted
C≡N	sp	linear	0.115	180°	893	free
C=O	sp^2	trigonal	0.121	120°	750	restricted[3]

[1] The bond lengths are already included in Table 1.1 but reproduced here for the sake of comparison.

[2] Not really free; see later.

[3] As seen in complexes.

1.3.1 Hybridisation and bond angles

In Table 1.3, the idealised values of bond angles are given. However, deviation of bond angles is rather a rule than an exception. Thus in propane (X) (Figure 1.3), the C—C—C angle is 112° and the H—C—H bond angle is 107°. Similarly, in compounds containing trigonal carbons, the bond angle is seldom 120°. Two factors are generally responsible for the deformation of bond angles: steric and electronic. Thus in propane, the bulky methyl groups interact with each other sterically and the angle between them increases with a simultaneous decrease in H—C—H angle (Thorpe-Ingold effect). In contrast, in dichloromethane (XI) the Cl—C—Cl angle is smaller (108°) and H—C—H angle is larger (112°). Here the electronic factor predominates. The C—H bond being shorter than C—Cl, the bonding electrons in the former are nearer than in C—Cl bond and exert greater electrostatic repulsion. In general, there is a balance between the two factors and it is not often easy to predict which will dominate. An alternative explanation is based on the change of hybridisation of the bonding orbitals to accomodate steric and electronic effects. In a p orbital, the electron distribution is away from the centre of a bond while in an s orbital, it is directed towards the centre. So any factor which moves the bonding electrons away from the centre (e.g., electronegativity of Cl) would increase the p character of the orbital and decrease the bond angle. This is more strikingly exhibited in H_2O and H_2S molecules where the

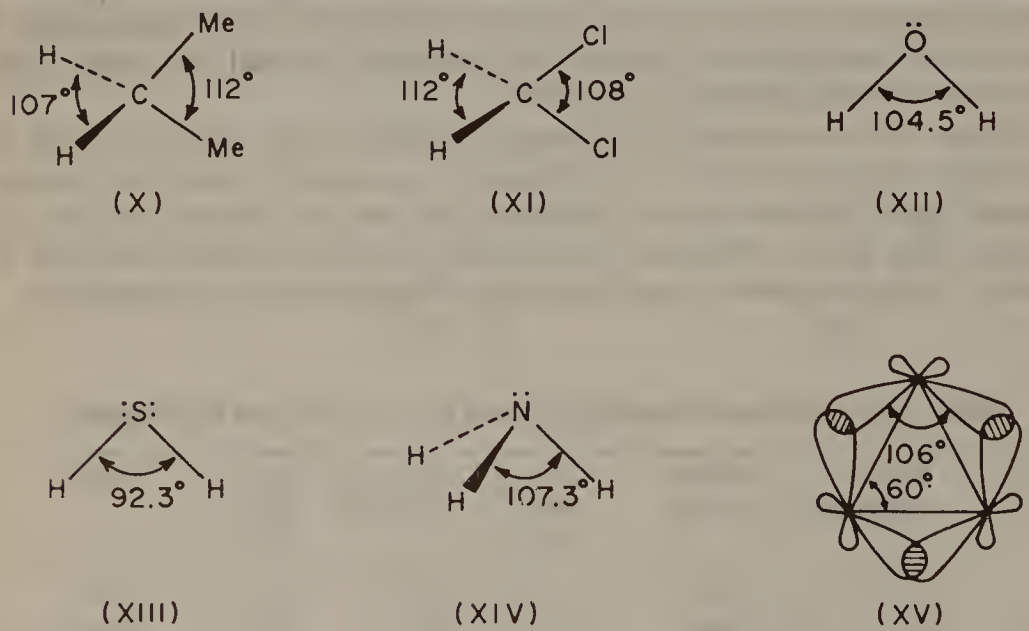


Figure 1.3 Deviation of bond angles

bond angles are respectively 104.5° and 92.3° shown in (XII) and (XIII). The bonding electrons are closer to oxygen in H_2O than to sulphur in H_2S because of higher electron affinity of oxygen which explains the difference in bond angles. Alternatively, the repulsive interactions of the lone pairs of electrons occupying the non-bonding hybrid orbitals increase the interorbital angle on their side and decrease the angle between the two hydrogens, the effect being stronger in H_2O

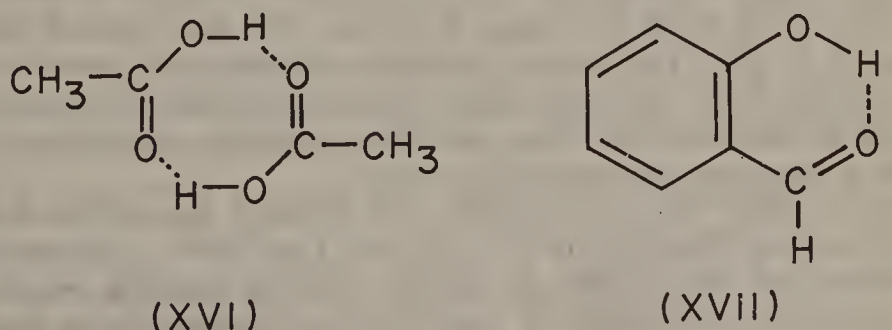
because of higher electronegativity of oxygen. The order of the repulsive interaction between pairs of electrons is: lone pair-lone pair > lone pair-bond pair > bond pair-bond pair. The H—N—H angle in ammonia (XIV) is 107.3° and may be ascribed to the interaction between lone pair and bond pair electrons.

1.3.2 Bond angle deformation in small ring compounds

Bond angle deformation plays a more important part in cyclic compounds. Thus in cyclopropane, the internuclear angle is, by necessity, 60° much smaller than the ideal interorbital angle, 109.5°. This gives rise to serious angle strain (Baeyer strain) in the molecule which can be partially relieved by rehybridising the endo ring orbitals (increasing the p component) so that the *ideal interorbital angle* is reduced to 106° or even less. The orbitals forming C—C bonds overlap partly along the axial and partly in the lateral direction. This type of bond is known as a *banana* or *bent* or τ bond and is intermediate between a pure σ and a pure π bond. The region of maximum overlap (see XV in Figure 1.3) does not correspond to the internuclear axis and cyclopropane behaves like an unsaturated compound in certain respects (e.g., addition of bromine). In cyclobutane, the internuclear and interorbital angles are 90° and 109.5° respectively and the angle strain is considerably less. The different strains in other ring systems will be discussed in a later chapter.

1.4 Hydrogen bonding

No discussion of chemical bonding can be complete without the consideration of hydrogen bonding. When a proton donor group (A—H, A being an electronegative element) interacts with an electron donor (:B) having a lone pair of electrons or a π bond, a weak bond is formed represented by A-H · · · B known as hydrogen-bond (H-bond). If the two groups belong to two different molecules, the H-bond is called intermolecular and association between the two molecules occurs. If they form part of the same molecule, the H-bond is called intramolecular and, by default, opposes association. Examples are shown in acetic acid dimer (XVI) and salicylaldehyde (XVII) respectively (Figure 1.4). The molecules of



(XVI) (XVII)

Figure 1.4 Hydrogen bonding

water and alcohols are highly associated due to intermolecular H-bonds. The bond angle in A-H · · · B is preferably 180° (linear) but may vary (especially in crystals or when the bond is intramolecular) depending on the requirements of the

molecular geometry. The bond length is typically 0.3 nm and the bond energy lies within 8-40 kJ mol^{-1} but can be as high as 170 kJ mol^{-1}, e.g., in F-H $\cdots$ F . The bond energy depends on the electronegativity of the acceptor centre (B), the bond angle, and the acidity of the donor group. Because of its directional property and its ability to connect groups which are many bonds apart, H-bonds play a very important part in shaping molecular geometry; they are particularly significant in molecules of biological importance. Thus the secondary structure of protein molecules, for example, arises out of H-bonds formed between N—H (donor) and C=O (acceptor) groups of non-adjacent peptide moieties. H-bonding affects the physical, chemical, and spectroscopic properties of the molecules in which it occurs. Being next to covalent bonds in energy, its occurrence profoundly influences the relative stability of molecular shapes (conformations) and is thus an important factor in conformational analysis to be discussed later. For other aspects of H-bonding, the readers are advised to consult the literature cited at the end of this chapter.

1.5 Rotation around bonds and change in dihedral angle

It has previously been noted that rotation about a single bond (e.g., C—C) is relatively free while rotation around a double bond (e.g., C=C) is highly restricted. Between these two extremes, there exist also intermediate bonds with fractional bond order arising out of internuclear delocalisation of electrons. Rotation around these bonds are also more or less restricted. These three types of bonds are discussed in the context of restricted rotation and change of dihedral angle.

1.5.1 Rotation around a single bond

According to the *principle of free rotation* of classical stereochemistry, rotation around a single bond was considered to be free. Strictly speaking, this would mean that the potential energy of the molecule is independent of the dihedral angle. However, calculation of enthalpy and entropy of ethane based on statistical mechanics showed that in order to bring agreement between the calculated and experimental values, an energy barrier of 12.5 kJ mol^{-1} has to be assumed. The diagram (Figure 1.5) shows the change of enthalpy with the change of dihedral angle from 0° to 360°. Three energy minimum conformations*, known as conformers and three energy maximum conformations representing the energy barrier arise during the operation. For ethane, the three conformers are equivalent as are also the three energy maxima (barriers to rotation).

In order to specify the conformations, it is necessary to represent them in perspective formulae following certain conventions. Three modes of representations are commonly used, namely, sawhorse formula, Newman projection formula, and flying wedge formula (see Chapter 3). The first two are illustrated by the structures (XVIII) and (XIX) (for ethane) respectively. In sawhorse formula, the C—C bond is viewed sideways while in Newman projection formula, the C—C bond lies

*Spatial orientations of a molecule which differ only in the dihedral angle and are easily interconvertible are called conformations. More detailed definition is given in Chapter 10.

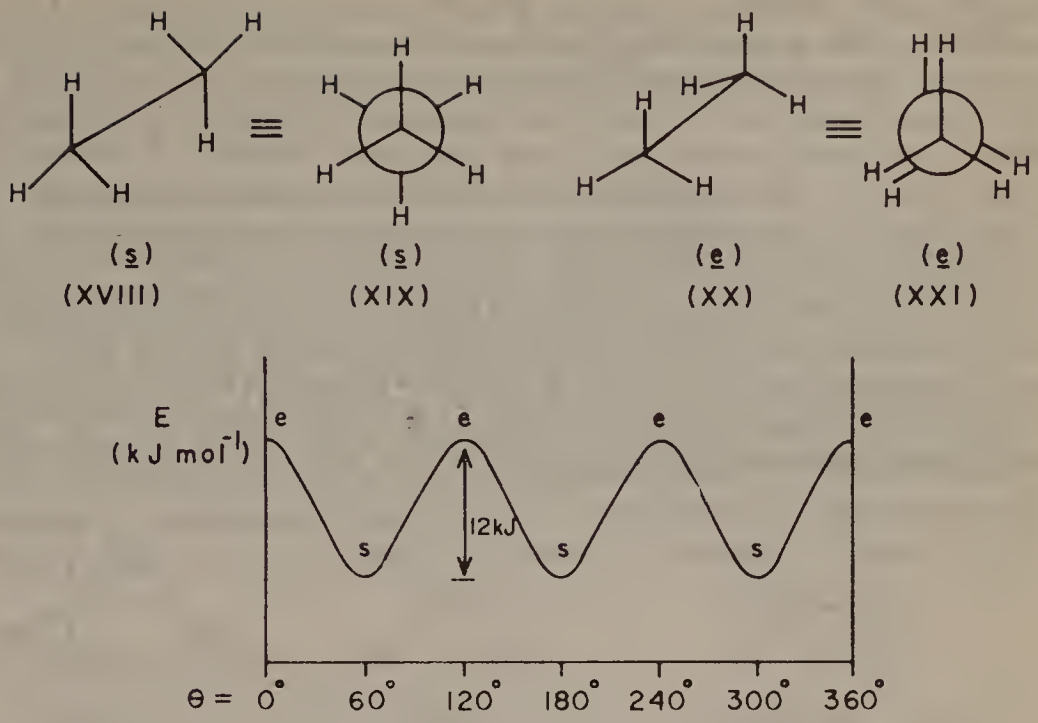


Figure 1.5 Restricted rotation in ethane

along the line of vision and cannot be seen. The other bonds are oriented radially making 120° angle with one another. The 109.5° angle of a tetrahedral carbon and 120° angle of a trigonal carbon would appear as 120° and 180° respectively when projected on a plane. The conformation (XVIII) or (XIX) with the six hydrogen atoms positioned as far apart as possible is called staggered (*s*). The conformation (XX) or (XXI) with the hydrogen atoms in pairwise conjunction is called eclipsed (*e*). The dihedral angles are respectiely 60° and 0° in these two conformations. A detailed nomenclature will be given elsewhere.

According to the spectral evidence, the staggered conformations are energetically preferred and contribute to the ground state population of ethane. The eclipsed conformations correspond to the energy maxima in the diagram and serve as barriers between the conformers. Since the energy barrier is low (12.5 kJ mol^{-1}), the interconversion of conformers in ethane is fast even at a comparatively low temperature, i.e., their kinetic stability is very low.

The torsional strain in the eclipsed ethane is believed to originate from the interaction of the eclipsed C—H bonds. Steric contribution due to non-bonded interaction between the vicinal hydrogens is negligible since the internuclear distance (0.23 nm) is almost equal to twice the value of van der Waals atomic radius of hydrogen (0.12 nm) (see Chapter 9).

1.5.2 **Rotation around a double bond**

Rotation around a double bond is highly restricted because it disrupts a π bond. 2-Butene can be represented by two isomeric structures (XXII) and (XXIII) (Figure 1.6), both being planar and having dihedral angles of 0° and 180°

respectively (see Newman projection formulae, *a* and *b* viewed along C = C bond). They differ in the relative disposition of the methyl groups and are called cis and trans isomers respectively. This type of stereoisomerism will be discussed in more general terms later. Starting from the structure (XXII, *a*), an increase of dihedral angle to 90° breaks the π bond completely resulting in a high-energy species (XXIV, *c*) in which the two p orbitals are mutually perpendicular. A further rotation of 90° regenerates the π bond giving the trans isomer (XXIII, *b*) (which is more stable than the cis isomer by approximately 4.2 kJ mol^{-1} due to the absence of non-bonded interaction between the two methyls) with a large drop of energy (see the diagram). Another energy maximum occurs at dihedral angle 270° corresponding to a species (*c'*) which is the mirror image of XXIV (*c*) and finally, the molecule returns to the original structure (XXII) after a rotation of 360°. The energy barrier separating the two isomers is very high and as a result, inter-

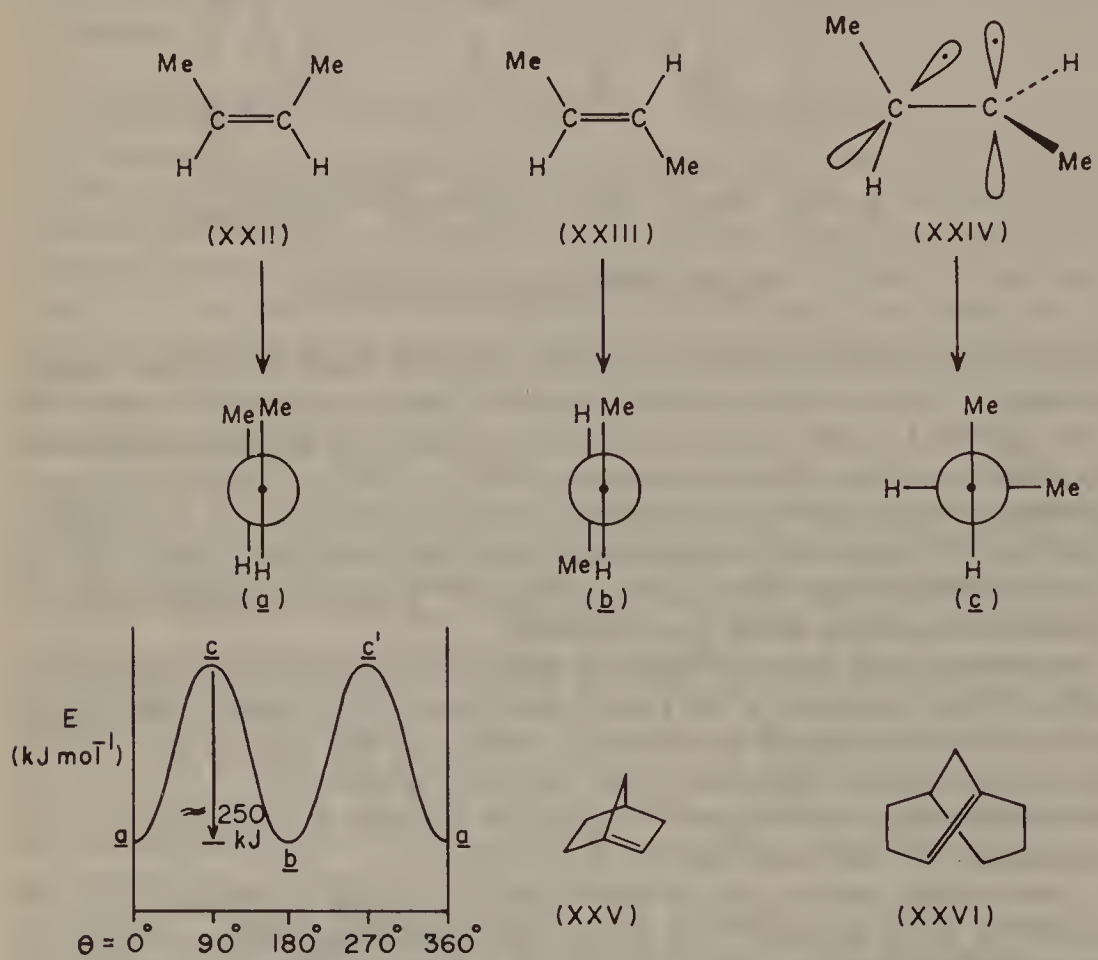


Figure 1.6 Restricted rotation around double bond. Examples of Bredt's rule

conversion between them is not possible under ordinary conditions. Other double bonds, e.g., C = N, N = N behave similarly and may lead to cis-trans isomerism.

Bredt's classical rule which states that double bond cannot exist at a bridgehead position finds its justification in the special geometrical requirement of a double bond. Thus the bicycloheptene (XXV) is not formed because the planarity required

by the π bond cannot be maintained in the rigid ring system. On the other hand, the bicyclononene (XXVI) with a bridgehead double bond is stable. Here the planarity of the π bond is accommodated by the puckering of the large ring. Many exceptions to Bredt's rule are now known*.

1.5.3 Restricted rotation around intermediate (hybrid) bonds

There are molecules in which a particular bond is neither a purely single nor a purely double bond but a hybrid between the two. A common example is 1,3-butadiene (XXVII) (Figure 1.7) in which the bond connecting the second and the third carbon develops some double bond character due to resonance between the two canonical forms (XXVIIa) and (XXVIIb). An alternative explanation based on delocalisation of the four π electrons over the σ framework of the molecule (π-orbital overlap) may be given. Two conformations, cisoid (XXVIII) and transoid† (XXVII) are possible and are separated by an energy barrier of approximately 25 kJ mol^{-1} which is much higher than in ethane but not high enough to permit

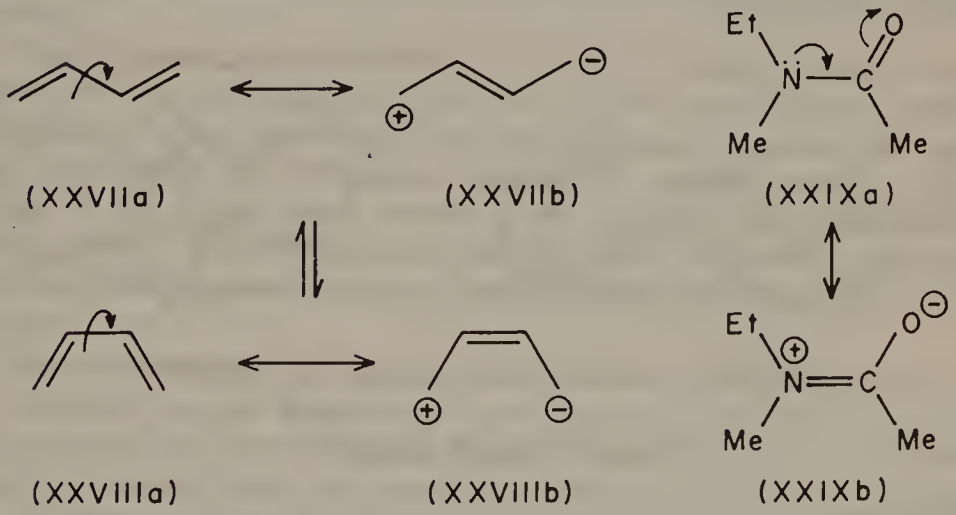


Figure 1.7 Restricted rotation around partial double bond

isolation under ordinary conditions‡. A still higher energy barrier (about 75 kJ mol^{-1}) is encountered in the rotation around C—N bond in N-methyl,N-ethylacetamide (XXIX), the double bond character of the amide bond arising out of delocalisation of the nitrogen lone pair of electrons. Here also, restricted rotation leads to two distinct isomers; however, the rotation is too fast to permit their isolation although they can be distinguished by low temperature NMR. It may be noted that any two species in equilibrium cannot ordinarily be separated at room temperature unless they are separated by a minimum energy barrier of 100

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* See Buchanan (1974) for a review of Bredt's rule and Keese (1975) for a review on bridgehead olefins.

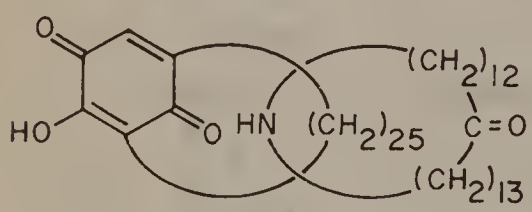
† Also called *s*-cis and *s*-trans respectively (*s* stands for single bond).

‡ The *s*-cis form has been trapped on CsI plate and characterised by UV and IR (Anet et al 1979) by suddenly cooling a hot vapour (400-900°C) of butadiene to 30 K (matrix separation); λ_{max} of *s*-cis and *s*-trans is 226 and 220 nm respectively.

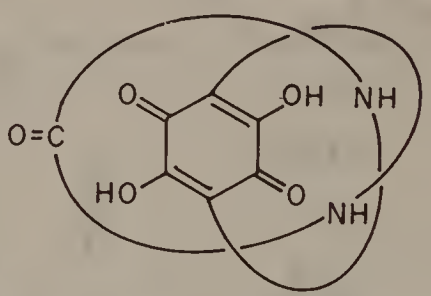
kJ mol^{-1}. Below that, they can be detected by various physical measurements (IR, NMR etc.) depending on the time-scale of observation, instrument frequency, and the average lifetime of the species in equilibrium.

1.6 Catenanes

An interesting class of compounds in which two or more rings are held together not by any chemical bond but through interlock between rings (Figure 1.8) is known as *catenanes*. One of the earliest catenane synthesised is represented by structure (XXX). Some DNA's provide examples of naturally occurring catenanes, the two closed strands being interlocked with each other. A catenane may be called a *topological isomer* of the two isolated composite rings. The catenanes pose certain intriguing problems regarding their physicochemical properties (Dmitriev 1981). The trefoils are another interesting type of molecules in which a single chain is knotted, e.g., XXXI. They are topological isomers of the corresponding unknotted molecules (Schill 1971). Topological stereochemistry has been recently reviewed (Walba 1985).



(XXX)



(XXXI)

Figure 1.8 Catenane and trefoil

1.7 Summary

1. Three basic parameters, namely, bond length, bond angle, and dihedral angle which affect the molecular geometry have been defined. Deformation of a bond length is a high energy process but change of bond angle is relatively easy and of general occurrence. Fairly drastic change in bond angles is seen in small ring compounds like cyclopropane and cyclobutane in which the internuclear and interorbital bond angles are widely different. This leads to angle strain also known as Baeyer strain.

2. Bond length can be expressed as the sum of the covalent radii (a hypothetical parameter) of the two atoms forming the bond. Each atom and group has a definite radius within which it resists penetration by other atoms and groups. These radii are known as van der Waals atomic or group radii and define the optimal approach that two non-bonding atoms or groups can make. They determine the intra- and intermolecular non-bonded interactions which are responsible for steric effects in stereochemistry.

3. The formation of covalent bonds (single, double and triple) in carbon compounds has been rationalised using the concept of hybridisation of bonding

orbitals. The geometry and other characteristic properties of bonds formed by overlap of sp^3, sp^2, and sp hybrid orbitals have been discussed with particular reference to stereochemistry. Deviations of bond angles from the mean or equilibrium values expected from bond hybridisation (*idealised* values) have been explained on the basis of steric (Thorpe-Ingold effect) and electronic factors. Alternative explanation based on the change of hybridisation of bonding orbitals to accommodate steric and electronic factors is also thought to be important. The sp^3, sp^2 and sp hybridised carbons are called tetrahedral, trigonal, and linear with bond angles of 109.5°, 120°, and 180° respectively.

4. When a proton donor group (A—H) and electron donor group (:B) interact, a weak bond known as H-bond, A-H· · · B is formed with an everage energy of 8-40 kJ mol^{-1} and a typical bond length of 0.3 nm. In view of its directional property and its ability to join two groups many bonds apart, this bond plays an important part in stereochemistry. Depending on whether the two groups, A—H and :B belong to the same molecule or to different molecules, the H-bond is called intramolecular or intermolecular. The two types affect molecular properties differently.

5. When two atoms in a molecule are joined by a single bond, the molecule behaves as a dynamic system in which a few species with different geometries (conformers) exist in equilibrium. They are usually separated by low energy barrier. Nevertheless, this affects the physical and chemical behaviour of the molecule. If the energy barrier separating the conformers is sufficiently high (>100 kJ mol^{-1}), stable stereoisomers may be expected. Rotations around single, double, and intermediate bonds have been discussed with the help of energy diagrams.

6. The different strains and interactions encountered during the discussion are weak attractive van der Waals forces (London forces), non-bonded interaction (van der Waals repulsion), angle or Baeyer strain, coulombic or electrostatic interactions, torsional strain, and interaction due to H-bond. Other interactions such as dipole-dipole and dipole-induced dipole are not separately discussed but may be collectively considered along with the H-bond, under the general term, electrostatic interactions.

7. A class of compounds in which two or more rings are interlocked without any chemical bonds between them is called catenanes.

References

1. J.B. Biot (1815), *Bull. Soc. Philomath. Paris*, 190.
2. J.H. van't Hoff (1875), *Bull. Soc. Chim. France*, **23**, 295; original paper published in 1874 in Dutch.
3. J.A. Le Bel (1874), *Bull. Soc. Chim. France*, **22**, 337.
4. O. Bertrand Ramsay (1981), in *'Nobel Prize Topics in Chemistry : Stereochemistry'*, Heyden, London.
5. N.L. Allinger (1976), in *'Methods in Advances in Physical Organic Chemistry : Calculation of Molecular Structures and Energy by Force-field'*, vol. 13. Eds. V. Gold and D. Bethel, Academic Press, London.
6. G.L. Buchanan (1974), *Chem. Soc. Rev.*, **3**, 41.

7. R. Keese (1975), *Angew. Chem. Int. Edn. Engl.*, **14**, 528.
8. G. Schill (1971), in '*Catenanes, Rotaxanes, and Knots*' Academic Press, New York.
9. D.M. Walba (1985), *Tetrahedron*, **41**, 3136.

General Readings

1. E.L. Eliel (1962) in '*Stereochemistry of Carbon Compounds*' McGraw-Hill, New York.
2. K. Mislow (1965) in '*Introduction to Stereochemistry*', Benjamin, New York.
3. A. Bassindale (1984) in '*Third Dimension in Organic Chemistry*', Wiley, New York.
4. B. Testa (1979) in '*Principles of Organic Stereochemistry*', Marcel Dekker, New York.
5. S.F. Mason (1976) in '*Topics in Stereochemistry*', vol. 9, Eds. N.L. Allinger and E.L. Eliel, Wiley, New York.
6. C.A. Coulson (1961) in '*Valence*', 2nd Edn., Oxford University Press.
7. L. Pauling (1960) in '*Nature of Chemical Bond.* 3rd. Edn. Cornell University Press, Ithaca, New York.
8. N.G. Clark (1977) in '*The Shapes of Organic Molecules*', Murray, London.
9. F.A. Carey and R.J. Sundberg (1986) in '*Advanced Organic Chemistry : Structure and Mechanisms*', Part A, 2nd Edn., Plenum/Roseta, New York.
10. M. Nogradi (1981) in '*Stereochemistry : Concepts and Applications*', Pergamon Press, New York.

Chapter 2

Molecular Symmetry and Chirality

2.1 Introduction

Stereochemistry is primarily concerned with molecular geometry and molecular geometry is best described in terms of symmetry. Molecules consist of atoms held together by more or less well defined bonds and may usually be treated as rigid bodies (see Chapter 1). The multitude of molecular structures can be brought into some sort of order by classifying them into several categories based on the symmetry operations that can be performed on them. The classification not only helps to understand the stereochemical behaviour of the molecules but finds significant applications in other branches of chemistry as well. For non-rigid molecules, the symmetry is considered either for a particular conformation or for a time-average one. An elementary treatment of symmetry classification is presented here as being useful in several aspects of organic stereochemistry.

2.2 Symmetry operations and symmetry elements

In order to study the symmetry of a molecule, certain operations such as rotation and reflection are performed and if by so doing, an arrangement is obtained which is indistinguishable from (superposable on) the original one, the operation is called a symmetry operation and the molecule is said to possess an element of symmetry defined by the operation performed. The symmetry operation and symmetry element are thus inseparably linked and often represented by the same symbols. There are basically only two symmetry operations, namely, rotation and reflection (and a combination thereof). Symmetry based solely on simple rotation is often called symmetry of the first kind whereas symmetry based on reflection or rotation-reflection is known as symmetry of the second kind. It is customary to describe the symmetry of a molecule in terms of four symmetry operations and four corresponding elements of symmetry.

2.2.1 Simple or proper axis of symmetry

If a molecule is rotated around an appropriate imaginary axis by an angle of $360°/n$ and arrives at an arrangement indistinguishable from the original, the axis is called an n-fold simple or proper axis of symmetry or a simple axis of order n. The axis is designated C_n and the operation is called a C_n operation. The operation

if repeated n times leads to an orientation identical* with the original. The molecule of water has one two-fold simple axis of symmetry (C_2) bisecting the H—O—H angle, chloroform (I) (as also NH_3 and NR_3) has one C_3 axis along the C—H bond, benzene (II) has one perpendicular C_6 axis and in addition, six C_2 axes lying in the molecular plane (three passing through opposite atoms and three bisecting the opposite C—C bonds), *cis*- and *trans*-1,3-dimethylcyclobutanes (III) and (IV) have one C_2 axis (vertical in III, horizontal in IV), *trans*-dichloroethylene (V) has one C_2 axis perpendicular to the molecular plane, and cyclopropane (VI) has one vertical C_3 and three horizontal C_2 axes (Figure 2.1). A C_1 axis is trivial since rotation of any molecule around any axis by 360° leads to the original arrangement (an identity operation). On the other extreme, linear molecules like H—C≡C—H and H—C≡N possess a C_∞ axis coincident with the internuclear axis since rotation around it by any angle gives an equivalent structure. Acetylene (VII) in addition possesses in infinite number of C_2 axes perpendicular to the centre of the C_∞ axis.

It is customary to write a molecule so that the axis of the highest order known as the principal axis is placed vertically, i.e., along the z-axis shown in the diagram (Figure 2.1) and thus provides a good reference for describing other axes and planes. In the case where a molecule has several symmetry axes of the same order, the one passing through the greatest number of atoms is taken as the principal axis, see, for example, naphthalene (VIII), ethylene (IX) and allene (X). All of them contain several C_2 axes but those shown vertically pass through more than one atom. It is also to be noted that during the operations, one point in the molecule (the centre of gravity) remains unchanged in space. Symmetry of this kind is called point symmetry to distinguish it from translational symmetry which involves displacement in space.

2.2.2 Plane of symmetry

A plane of symmetry is a plane which divides the molecule (or an object) into two halves which are mirror images of each other. In other words, reflection of the two halves of the molecule across the plane (a reflection plane) gives a structure indistinguishable from the original. The plane is called a σ plane and the operation a σ operation. Two σ operations are equivalent to an identity operation since they turn the molecule into the original. It is important to note that the two halves themselves may not be superposable. The molecule of water has two mutually perpendicular σ planes, chloroform (I) has three, each containing a H—C—Cl grouping, benzene (II) has one horizontal (the molecular plane) and six vertical (a set of three passing through opposite atoms and another set of three passing through the opposite bonds), *cis*-1,3-dimethylcyclobutane (III) has two vertical (one passing through the methyl-bearing carbons and the other passing through the two methylene carbons), the trans isomer (IV) has one vertical (passing through

*The terms *indistinguishable* and *identical* have different connotations in the present context. The former refers to any equivalent arrangement arrived at by exchanging similar atoms or groups while the latter refers strictly to the original. The operation which leaves the molecule unchanged, i.e., as if nothing had been done to it, is called an identity operation, denoted by E or I, equivalent to C_1, C_2^2, C_n^n, σ^2 etc. (the superscripts represent the number of times the operation is performed.).

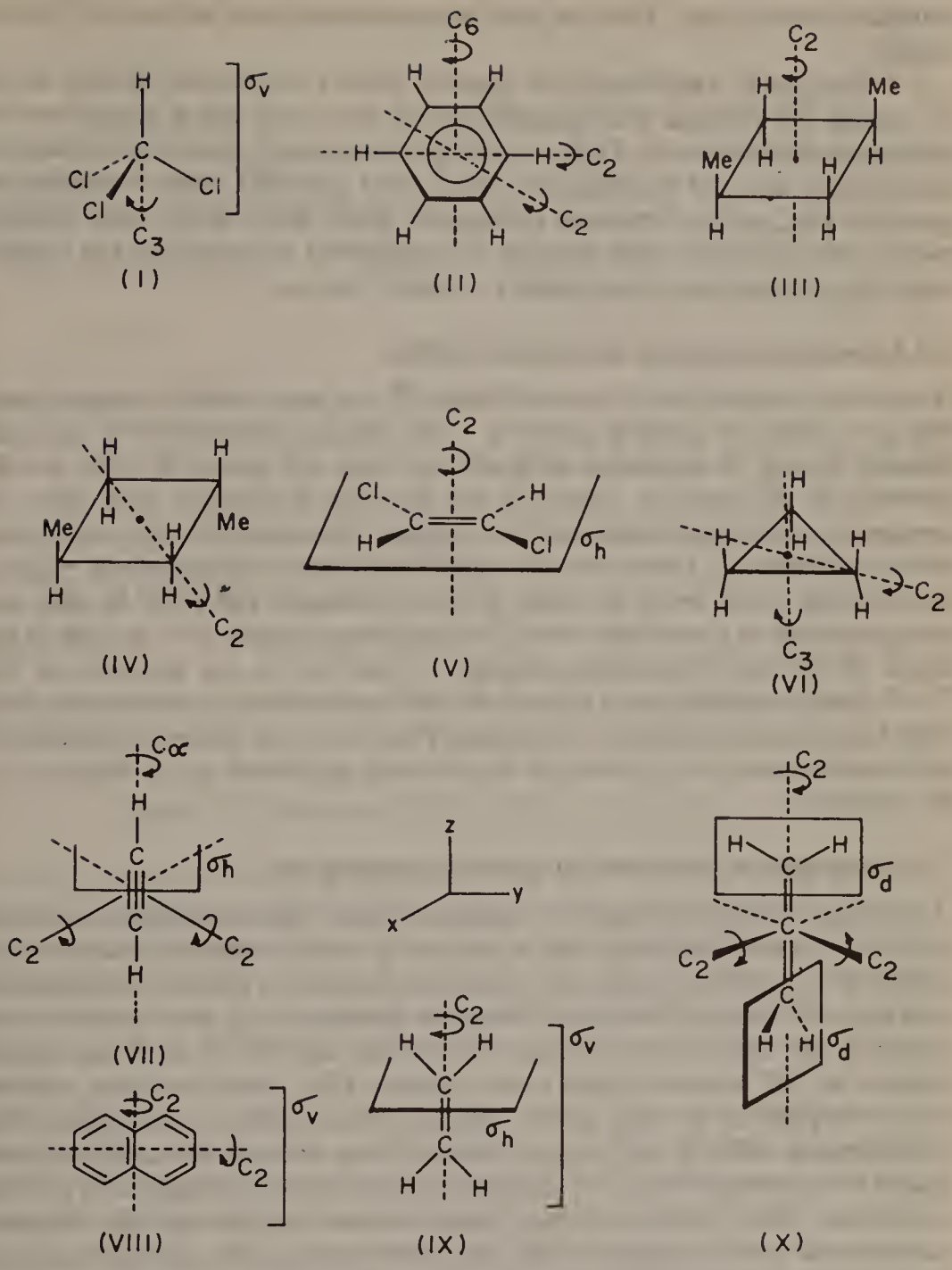


Figure 2.1 Examples of C_n, σ_h, σ_v, and σ_d (dotted lines represent axes)

the methyl-bearing carbons), *trans*-dichloroethylene (V) has one coincident with the molecular plane, cyclopropane (VI) has one horizontal and three vertical (each passing through an apex of the ring and bisecting the opposite side), acetylene (VII) has one horizontal at the centre and an infinite number passing through the internuclear axis (C_∞), naphthalene (VIII) has one horizontal and two vertical, ethylene (IX) has two vertical and one horizontal, and allene (X) has two vertical

mutually perpendicular. They are easy to comprehend even without the help of models.

σ Planes and C_n axes often occur together. Since a convention has been set up by placing the principal axis vertically (along the z-axis), the σ planes may be designated in relation to it. Thus σ_h refers to a (horizontal) plane perpendicular to the principal axis and is unique; σ_v, stands for a (vertical) plane containing the principal axis, and σ_d, represents a (diagonal) plane bisecting the angle between two C_2 axes. The three types of planes are exemplified in Figure 2.1. The number of σ_v and σ_d planes may be and usually is greater than one.

2.2.3 Centre of symmetry or inversion centre

A centre of symmetry or an inversion centre (i) is a point within a molecule such that if an atom (or point) is joined to it and the line extrapolated to an equal distance beyond, it encounters an equivalent atom (or point). In other words, inversion of all atoms (or points) in the molecule through the point gives an arrangement indistinguishable from the original. Mathematically, for every atom with coordinates x, y, z there must be a similar atom with coordinates $-x$, $-y$, $-z$, the inversion centre being the origin of the coordinates. There can be only one inversion centre in a molecule. *trans*-1,3-Dimethylcyclobutane (IV) has one at the centre of the ring, *trans*-dichloroethylene (V) has one at the mid-point of the C = C bond; α-truxillic acid (XI) and the anti conformation of *meso*-tartaric acid (XII) have one each marked by a heavy dot (Figure 2.2). The presence or absence of an inversion centre in any molecule can be easily ascertained by an inspection of the molecule.

2.2.4 Improper or alternating or rotation-reflection axis

An improper or an alternating or a rotation-reflection axis of symmetry of order n (S_n) is an (n-fold) axis such that a rotation of $360°/n$ around it followed by reflection in a plane perpendicular to the axis generates a structure indistinguishable from the original. The order of the two operations may be reversed without change in the result. The vertical axis in α-truxillic acid (XI) is an S_2 axis since a rotation of 180° around it leads to the structure (XIa) which on being reflected across the plane of the ring, gives a structure superposable on the original (XI). Conformation (XII) of *meso*-tartaric acid on being similarly reflected in a plane placed at the centre of the C—C axis and at right angles to it (Figure 2.2) gives an orientation (XIIa) which on being rotated around the axis by 180° becomes superposable with the original (XII). The conformation (XII), therefore, contains an S_2 axis. Sometimes, it is more convenient to imagine a mirror (a mirror plane) placed perpendicular to the axis but outside the molecule followed or preceded by rotation. In this case, a translational operation is necessary in order to superpose the image on the original and the centre of gravity of the molecule is displaced during the operation which contravenes the definition of point symmetry. The same conclusion, however, is reached and this procedure is recommended for molecules in which a reflection plane is not easily visualised. The S_n axis is called an alternating axis of symmetry because the equivalent atoms or groups exchanged by the operation lie alternately above and below the reflection plane.

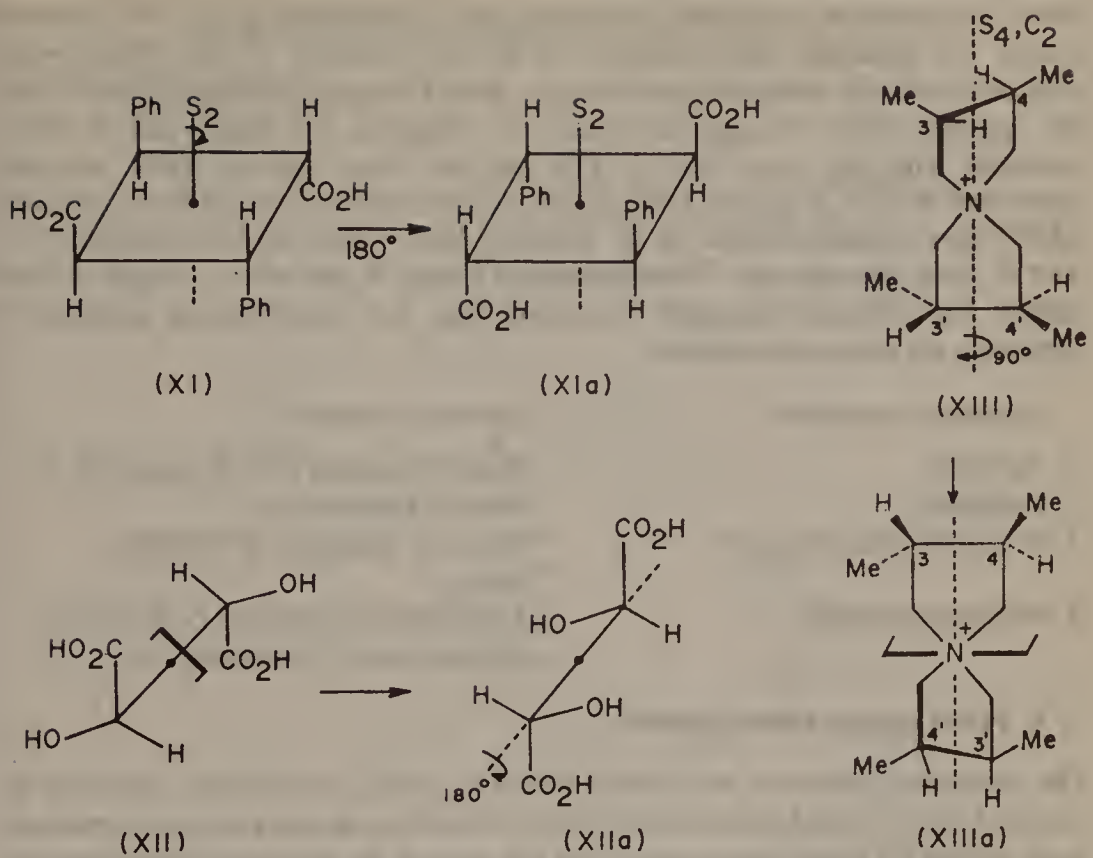


Figure 2.2 Examples of inversion centre, S_2, and S_4 axes

It may be observed that an S_2 operation brings about the exchange of like pairs of atoms or groups which are equidistant but in opposite directions from a centre. i.e., their coordinates change from x, y, z to $-x$, $-y$, $-z$ with respect to the centre. This is precisely what an inversion operation (*i*) does. Thus an S_2 axis is equivalent to an inversion centre (*i*). In fact, *any axis* passing through a molecule having an inversion centre is an S_2 axis. The readers may confirm this with the help of models.

An S_1 operation consists of two operations, namely, a C_1 and a σ. Since the C_1 operation leaves the molecule unchanged (i.e., an identity operation), the S_1 operation can be equated to a σ operation (the axis and the plane are not the same though the operations are). Therefore, instead of looking for S_1 and S_2 axes in a molecule, one may look for a σ plane and an inversion centre respectively.

There are few known molecules which do not have a σ plane (S_1) or an inversion centre (S_2) but have an S_n ($n > 2$) axis as the only element of reflection symmetry*. An example is found in 3,4,3′,4′-tetramethyl-spiro-(1,1′)-dipyrrolidinium ion (XIII) (Figure 2.2) which has been specially prepared (as salt) to study this type of symmetry. The structure does not have a σ plane nor an inversion

*An S_n axis without a σ plane must have n even and always encompasses a $C_{n/2}$ axis ($S_n = C_{n/2}$ but not necessarily the reverse).

centre but possesses a four-fold alternating axis of symmetry (S_4). A 90° rotation around the molecular axis transforms it into the structure (XIIIa) which when reflected across the horizontal plane shown, gives a structure indistinguishable from the original (XIII). During the process of reflection, the upper half of XIIIa coincides with the lower half of XIII and the lower half of XIIIa with the upper half of XIII. It may be noticed that carbons marked 3 and 4 in the structure (XIII) have *R*-configuration (to be discussed later) while the carbons marked 3′ and 4′ have the opposite *S*-configuration (*R* and *S* are mirror images of each other). The different symmetry operations and the corresponding elements of symmetry are summarised below:

Symmetry operations	*Symmetry elements*
1. Rotation	Simple or proper axis of symmetry, C_n
2. Reflection	Plane of symmetry, σ
3. Inversion through a point	Centre of symmetry or inversion centre, *i*
4. Rotation-reflection	Alternating or improper or rotation-reflection axis of symmetry, S_n

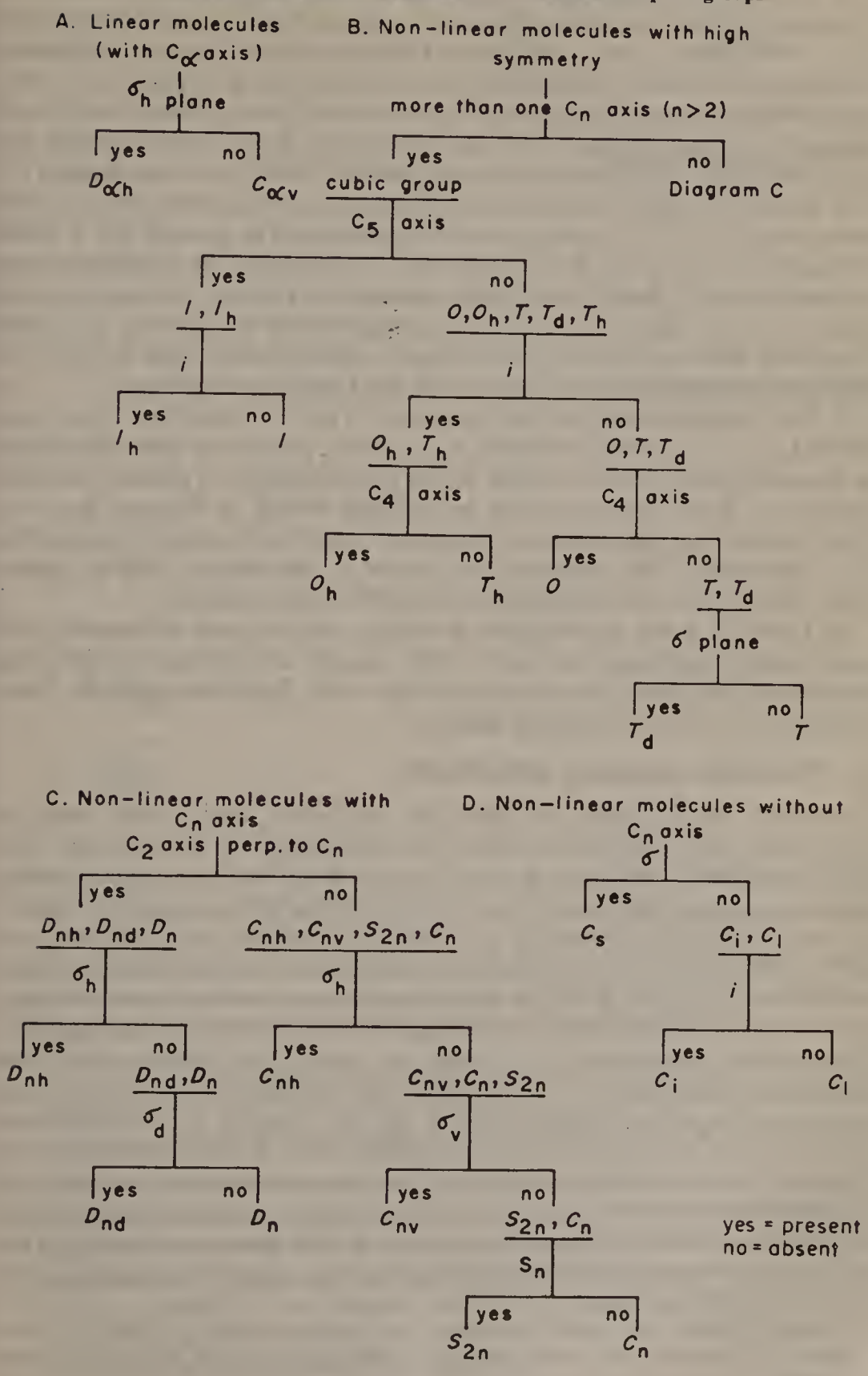
2.3 Point group classification

The molecular structures are almost infinitely varied; nevertheless they can be classified into a limited number of symmetry-related categories known as symmetry point groups (or simply point groups) on the basis of the symmetry operations that can be performed on them. These symmetry operations (or symmetry elements) combinedly form a group and since each of the operations leaves the centre of gravity of the molecule unchanged, the group is called a *point group*. There are some mathematical requirements for a set of symmetry operations to constitute a group, the most important one being the existence of certain binary relationship among them. Thus when two operations in the group are multiplied, i.e., carried out one after the other, the result should correspond to a third operation in the same group. For further details, the readers are referred to the textbooks cited at the end of the chapter. The scheme for classification into point groups is summarised below:

1. Linear molecules with a C_∞ axis and a σ_h plane, e.g., $HC \equiv CH$, $O = C = O$, belong to the point group $D_{\infty h}$. Those with a C_∞ axis but no σ_h plane, e.g., $H—C \equiv N$, belong to the point group $C_{\infty v}$ (see diagram A).

2. Non-linear molecules of high symmetry are classified under point groups T_d (tetrahedral symmetry), O_h (octahedral symmetry), and I_h (icosahedral symmetry). Methane and carbon tetrachloride having four C_3 axes, three C_2 axes (which are also S_4 axes), and six σ planes belong to the T_d point group and octahedral species like SiF_6 having a still higher number of symmetry elements belong to the O_h point group. Molecules containing a C_5 axis (actually several) belong to I_h point group and are the most highly symmetrical molecules (see dodecahedrane in Chapter 11). The classification is shown in diagram B. The K_h point group contains infinite number of C's and σ's and does not apply to molecules.

Flow-sheet diagrams for classification of molecules into point groups



3. Non-linear molecules with lesser symmetry may have a principal simple axis of symmetry (C_n, $n > 1$). If in addition to C_n, they possess n C_2 axes perpendicular to C_n, they belong to the point groups D_{nh}, D_{nd} or D_n (D stands for dihedral symmetry). In order to differentiate them, one looks for a σ_h plane. If it exists (along with n σ_v planes), point group D_{nh} is indicated. If there is no σ_h but only σ_d planes, the molecule belongs to the point group D_{nd}. In the absence of both, the point group is D_n. This is shown on the left hand side of the flow-sheet diagram C.

4. In the case where C_n is the only axis with no C_2 axis perpendicular to it, four point groups, C_{nh}, C_{nv}, C_n, and S_{2n} are to be considered. The presence of a σ_h plane indicates point group C_{nh}; if it is absent but σ_v's are present, the molecule belongs to point group C_{nv}. Both of them being simultaneously absent, the point group is either S_{2n} or C_n which can be readily distinguished by the presence (S_{2n} point group) and absence (C_n point group) of an S_{2n} axis (the order must be even and hence $2n$ is used). This is shown on the right hand side of the diagram C.

5. For molecules which do not have any C_n ($n > 1$) axis, only three point groups C_s, C_i, C_1 are to be considered. If a σ plane is present, the molecule belongs to the point group C_s; if it is absent but an inversion centre is present, the point group is C_i. In the absence of both, the molecule belongs to the point group C_1 which does not have any element of symmetry except for the trivial C_1 axis and is truly asymmetric. The assignments are shown in the diagram D. For organic molecules, point groups under diagrams C and D are more pertinent.

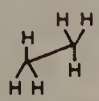
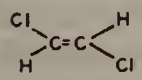
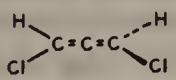
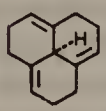
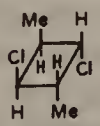
In Table 2.1, a few representative molecules, their elements of symmetry and point group classification are given. The readers are advised to verify the assignment of the point groups with the help of the flow-sheet diagrams. More examples will follow in subsequent chapters.

2.4 Molecular symmetry and chirality

A molecule (or an object) can have only one mirror image. If the image is superposable on the original, the molecule is called achiral. On the other hand, if it is not superposable, the molecule and its mirror image form two distinct species called enantiomers (see Chapter 3) giving rise to a type of stereoisomerism known as enantiomerism. Such molecules are called chiral and the two enantiomers are said to differ in their sense of chirality or handedness in the same way as a right hand differs from a left. A case in hand is the two forms of lactic acid (XIV) and (XIV') (Figure 2.3) which are mirror images of each other but non-superposable. The former is dextrorotatory, i.e., it turns the plane of the polarised light to the right when the light beam is viewed end on and the other is levorotatory, i.e., it turns the plane of the polarised light to the left. Chirality is a necessary and sufficient condition for the occurrence of enantiomerism and is determined by the absence of rotation-reflection symmetry (S_n axis of any order) in the molecule. All molecules belonging to the point groups C_1, C_n and D_n (shown in the flow-sheet diagrams) lack reflection symmetry and are chiral while molecules belonging to the rest of the point groups shown in the diagrams* are achiral. For example, lactic

*In principle, molecules with tetrahedral, octahedral, and icosahedral symmetry but lacking plane of symmetry or inversion centre (point groups *T*, *O*, and *I*) are also chiral. But they are almost non-existent.

Table 2.1 Some molecules with their symmetry elements and point group classification

Molecules[a]	Symmetry elements[b]	Point group	Instruction
1. $CHCl_3$ (I)	C_3 (C_n), $3 \times \sigma_v$ no C_2 and σ_h	C_{3v}	Follow right hand side of Chart C
2. 	C_6 (C_n), $6 \times C_2$, σ_h	D_{6h}	Follow left hand side of Chart C
3. 	C_3 (C_n), C_2,σ_d	D_{3d}	"
4.  (Twist boat)	C_2 (C_n), $2 \times C_2$ no σ_n and σ_d	D_2	"
5. 	C_2 (C_n), C_2,σ_h	C_{2h}	Follow right hand side of Chart C
6. 	C_2 (C_n) no C_2, σ_v, σ_h and S_n	C_2	"
7. 	C_3 (C_n) no C_2, σ_v, σ_h and S_n	C_3	"
8. 	σ no C_n	C_s	Follow Chart D
9. 	i no C_n and σ	C_i	"
10. XIII	C_2 (C_n), S_4 no C_2, σ_n, and σ_v	S_4	Follow right hand side of Chart C
11. Allene (X)	C_2 (C_n), $2 \times C_2$, $2 \times \sigma_d$	D_{2d}	Follow left hand side of Chart C
12. Lactic acid (XIV)	No C_n, C_i and σ	C_1	Follow Chart D

[a] Some of the molecular structures will be better understood after going through later chapters.
[b] C_n in parenthesis indicates the principal axis, other C_2 axes are perpendicular to it.

acid (Figure 2.3) belonging to point group C_1 and 1,3-dichloroallene belonging to point group C_2 (see Table 2.1) are chiral. Since chiral molecules may contain C_2 axis, it is not proper to equate chiral with 'asymmetric' or achiral* with 'symmetric'.

There are two practical ways to determine the chirality of a molecule without first classifying it into a point group. One is to construct the mirror image of the molecule and see whether it is superposable on the original. With complex molecules, this is often not an easy task, particularly because the molecules are usually represented in two dimensions following some conventions which impose

* It is better to call achiral molecule as non-dissymmetric.

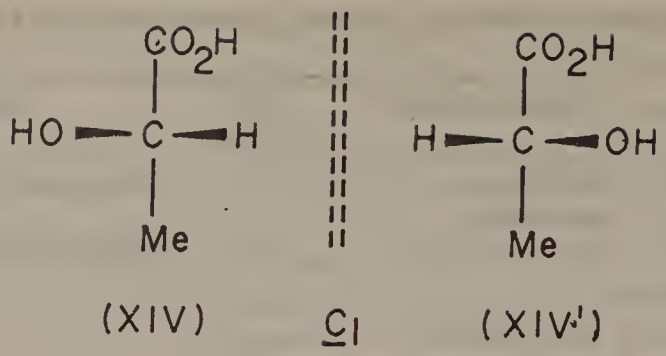
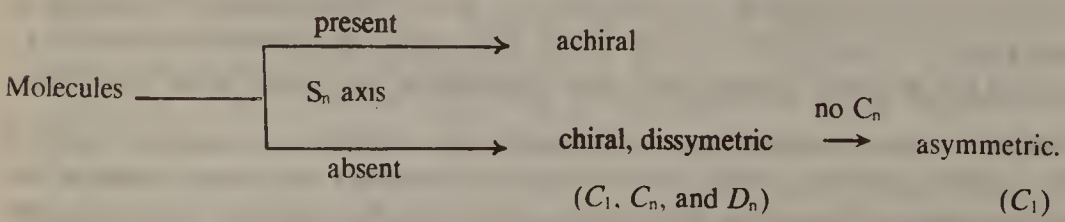


Figure 2.3 Enantiomers of lactic acid

certain restrictions on their movement in the plane of the paper. Thus it is preferable to take recourse to molecular models*. The second way is to look for the absence of reflection symmetry in a molecule. The presence of a σ plane (S_1) is *sufficient* to make a molecule achiral. However, it is not a *necessary* condition since even in its absence, a molecule may be achiral due to the presence of an S_n axis of higher order, see, for example, molecules (XI) and (XIII). One should, therefore, ascertain the absence of an S axis of any order before proclaiming a molecule chiral. In practice, it is advisable to look for a σ plane (S_1) and an inversion centre (S_2) in the first place and then for an S_n axis of higher order if the situation warrants. The σ plane and inversion centre are easy to locate and except for a few molecules specially prepared to prove a point (as XIII), a molecule is achiral due to the presence of either of these two elements of symmetry.

The presence of one or more C_n axes does not interfere with a molecule being chiral and existing as two enantiomers; thus molecules belonging to point groups D_n and C_n are chiral. Three terms have almost been interchangeably used to describe molecules which show enantiomerism : asymmetric, dissymmetric, and chiral. The term *chiral* (whence *chirality*) is synonymous with *dissymmetric* (Eliel and Wheland 1962) although the former is now getting wider currency. The term *asymmetric* (or asymmetry) has a slightly different connotation in the sense that while an asymmetric molecule is a chiral molecule, it lacks C_n axis also; i.e., all symmetry elements are absent except for the trivial C_1 axis. The following diagram clarifies the situation.



*The readers are advised to make use of molecular models throughout the reading of the book.

2.5 Point groups and symmetry number

Another symmetry parameter, namely, symmetry number (σ) is defined as the number of equivalent positions a molecule can be turned into through simple rotation around an axis or axes. The symmetry number is important since it is related to the entropy of a molecule, the entropy contribution due to symmetry being $-R\ln\sigma$. The benzene molecule has a symmetry number twelve calculated as follows. The six carbons are numbered as in the structure (XV) (Figure 2.4). During the rotation of the molecule around the C_6 axis through 360°, six equivalent arrangements result counting the original to which it returns. This operation thus contributes six to the symmetry number. Next, the molecule is rotated around a C_2 axis passing through carbons marked 1 and 4 by an angle of 180°. A new arrangement (XVI) is reached as evident from the positions of the numerals. A second rotation of 180° around the axis, however, leads to an arrangement identical with the original (XV) which has been counted already. Thus each of the six horizontal C_2 axes contributes one to the symmetry number making the total twelve.

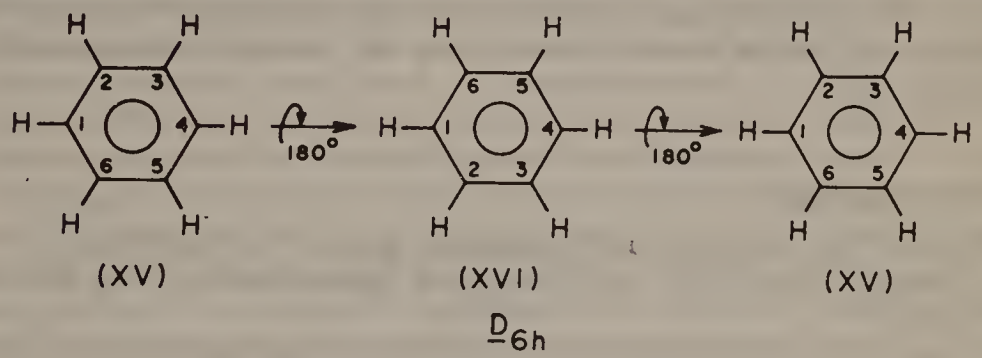


Figure 2.4 Symmetry number of benzene

The symmetry number is related to the point groups to which the molecule belongs in the manner shown below:

Point groups	*Symmetry No.*	*Point groups*	*Symmetry No.*
$C_{\infty v}$, C_1, C_s, and C_i	1	$D_{\infty h}$	2
C_n, C_{nh}, and C_{nv} ($n \neq \infty$)	n	T_d	12
D_n, D_{nd}, and D_{nh} ($n \neq \infty$)	$2n$	O_h	24
		I_h	48

2.6 Summary

(*i*) Four symmetry operations, namely, rotation, reflection, inversion, and rotation-reflection are described through which similar atoms and groups in a molecule can be interchanged to give arrangements indistinguishable from the original.

(*ii*) Four symmetry elements have been defined in terms of the above symmetry

operations which are: a simple (proper) axis of symmetry (C_n), a plane of symmetry (σ), an inversion centre (i), and an alternating (improper) axis of symmetry (S_n). The same symbols are used for the symmetry operations and the symmetry elements.

(*iii*) The molecules have been classified into a number of symmetry point groups based on the symmetry operations that can be performed on them. Schemes for classification as well as flow-sheet diagrams are given.

(*iv*) Molecules which are not superposable with their mirror images are called chiral and those which are superposable are called achiral. Chiral molecules exhibit a type of stereoisomerism known as enantiomerism and belong to point groups C_1, C_n or D_n; they can be recognised by the absence of an S_n axis of any order. The common method of ascertaining the chirality of a molecule is to look for a plane of symmetry (S_1) and an inversion centre ($i = S_2$) and if the situation warrants, for an S_n axis of order higher than two. In general, the absence of a σ plane and an inversion centre (i) is sufficient to ensure chirality in a molecule.

(*v*) The symmetry number (σ)* of a molecule is defined by the number of equivalent orientations that a molecule can assume through rotations around axis or axes. The symmetry number is relevant for the calculation of the entropy of a molecule and can be inferred directly from the symmetry point group by a character table.

Selective Readings

1. K.Mislow (1965) in *Introduction to Stereochemistry*, Benjamin, New York, Chapter 1.
2. A. Bassindale (1984) in *The Third Dimension in Organic Chemistry*, Wiley, New York, Chapter 3.
3. M. Orchin and H. H. Jaffe (1970) in *Symmetry Point Groups and Character Tables, J. Chem. Educ.*, 47, 246, 372.
4. J.D. Donaldson and S.D. Ross (1972) in *Symmetry and Stereochemistry*, Wiley, New York.
5. S.F.A. Kettle (1985) in *Symmetry and Structure*, Wiley, New York.
6. L. Tarasov (1986) in *'This Amazingly Symmetrical World'*, Mir Publishers, Moscow.

*It is unfortunate that the plane of symmetry and symmetry number are both designated σ.

Chapter 3

Stereoisomerism : Definitions and Classification

3.1 Introduction

In the light of the bonding geometry (Chapter 1) and symmetry properties (Chapter 2) of molecules, it may be appropriate to examine the nature of the different molecular species that a given set of atoms specified by a molecular formula can furnish. Except for a few simple molecules, e.g., H_2O, CH_4, CH_3X, CH_2X_2, CHX_3 etc., the molecular formula alone cannot describe uniquely the structure of a molecule. Two additional pieces of information, namely, the nature of linkages among atoms regardless of direction in space (bonding connectivity) and the relative orientation of atoms and groups in space (configuration) are necessary. Depending on these two parameters, a certain combination of atoms can give rise to a number of molecular species, known as *isomers* which are separated by energy barrier and differ in their chemical and physical properties. Molecules with the same molecular formula but differing in bonding connectivities are called *constitutional isomers**. They may differ in the nature of the functional group, e.g., CH_3CH_2OH and CH_3OCH_3, or in the position of an atom or a group. e.g., 1-propanol and 2-propanol, or in the nature of the skeletal structure, e.g., *n*-butane and *i*-butane and are further subdivided into functional group isomers, tautomers, positional isomers, ring chain isomers etc. which are discussed in all texts on organic chemistry. When molecules differ only in the relative orientation of atoms and groups in space, *stereoisomerism* results. Stereoisomers thus have the same bonding connectivity but differ in their configurations and are often called *configurational isomers*. Stereoisomers resemble one another only in the general properties of the functional group(s) common to them but may otherwise differ substantially in chemical, physical, physicochemical, and biochemical properties including chemical reactivities. These differences which form the basis of stereochemistry are manifest in the various stereodifferentiating reactions so useful in organic syntheses and in biochemical reactions so vital for life processes. Most of the natural products and biologically important molecules occur in specific stereoisomeric forms and their chemical and biochemical behaviours are regulated by their molecular architecture.

*They are also called structural isomers in many textbooks. However, the term *structure* is now used in a broader sense comprising constitution, configuration, and conformation.

3.2 Molecular representation

Since stereochemistry refers to molecules in three dimensions, appropriate modes of representations of three-dimensional molecules on two-dimensional paper is essential. Two systems of representation commonly used, namely, sawhorse and Newman projection have already been introduced in Chapter 1. A tetrahedral carbon containing four different groups, e.g., Cabcd (see lactic acid in Chapter 1) known as asymmetric (chiral) carbon is represented by the structures (I) and (II) (Figure 3.1a) which are non-superposable mirror images of each other. When

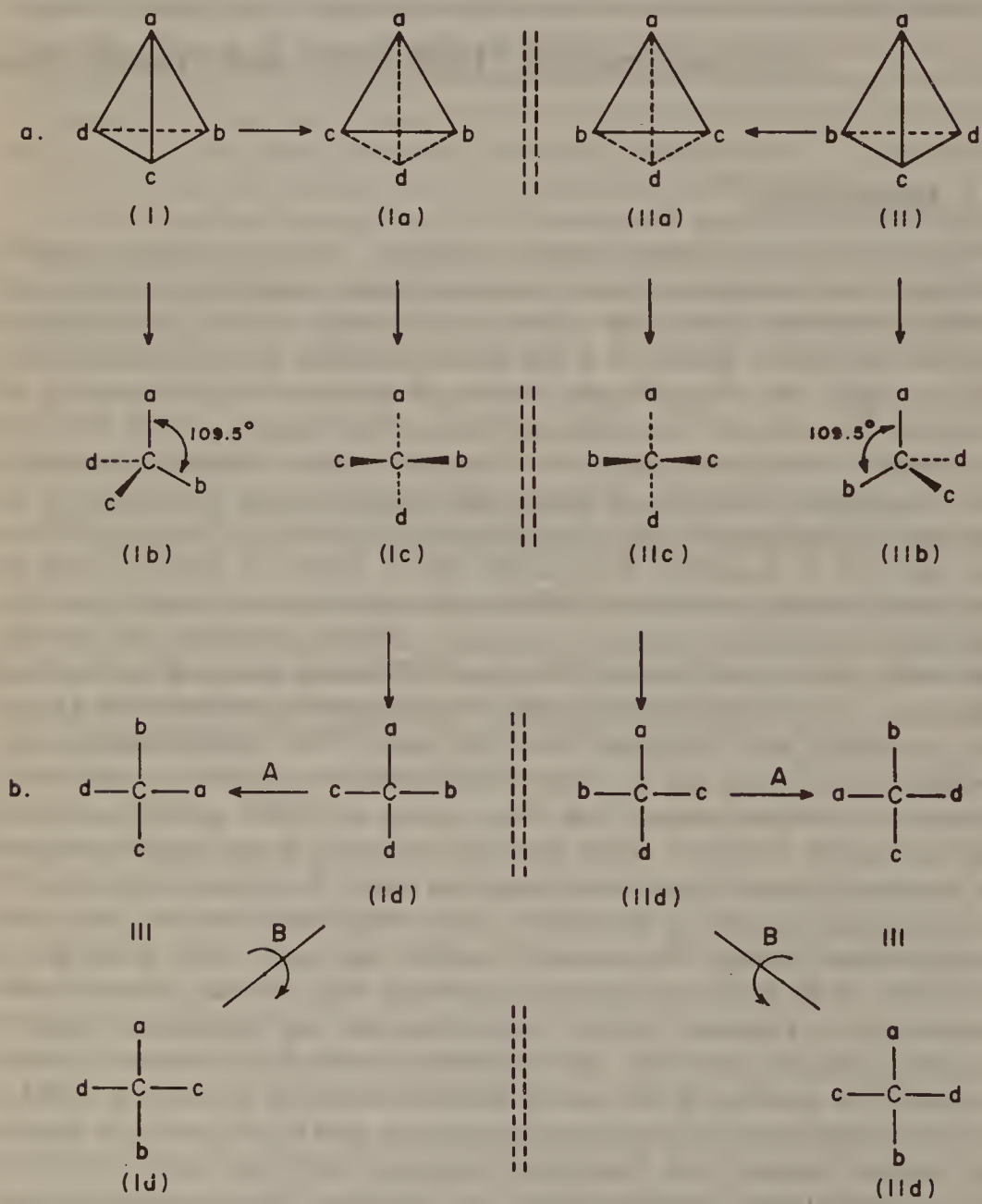


Figure 3.1 Molecular representation : I_b and II_b are flying wedges and I_c (= I_d) and II_c (= II_d) are Fischer projection (dotted double lines represent mirrors)

complemented with chemical bonds, they appear as Ib and IIb respectively, with the implication that the uniform lines lie in the plane of the paper, the thick wedge is in front of the plane (projecting towards the observer), and the dotted line is behind the plane (projecting away from the observer). These are called *flying wedge* notations and are very often used to depict molecules with a single asymmetric (chiral) centre.

The tetrahedral structures (I) and (II) with slight change of positions lead to another set (Ia) and (IIa) in which b and c are horizontally placed. When complemented with chemical bonds, they appear as Ic and IIc in which b and c (horizontal groups) are in front of and a and d (vertical groups) are behind the plane. They still give three-dimensional perspectives of the molecules but when projected on the plane of the paper are reduced to two-dimensional figures (Id) and (IId) which are known as Fischer projection formulae. They are frequently used in the literature for their simplicity and it is desirable to know their characteristics and limitations which are as follows :

(*i*) By convention, the horizontal substituents are in front of (up) and the vertical substituents are behind (down) the plane of Fischer projection formula.

(*ii*) The structures are not to be lifted out of the plane; they can, however, be rotated in the plane through 180° and 360° which keeps the horizontal substituents horizontal and vertical substituents vertical without mixing them up.

(*iii*) Rotations of 90° and 270° are not permitted since such operations exchange horizontal substituents (up) with the vertical ones (down) contravening the convention (*i*).

(*iv*) Conversion of one Fischer projection formula into an equivalent one with the substituents differently ordered may be done in two ways, by exchanging two pairs of substituents as shown in process 'A' (Figure 3.1b) or by rotating the substituents in a group of three keeping the fourth one (e.g., 'a') fixed as shown in process 'B'.

(*v*) Exchange of a pair of substituents leads to the enantiomeric structure (both in Fischer projection and in any three dimensional structure).

The Fischer projection formula may be extended to compounds containing more than one chiral centre. Thus the molecule, Cabc-Cxyz exists in four stereoisomeric forms, two of which are represented by the formulae (III) and (IV), (Figure 3.2) the other two being their mirror images. As before, the horizontal groups (b, c, x, z) are in front of and the vertical groups (a, y) are behind the plane of the paper. In order to convert them into the sawhorse formulae, the bottom chiral centre is written at the front and the top one at the rear while the substituents are placed in front (up) and behind (below) as implied in the Fischer projection. The structures (IIIa) and (IVa) result which are direct translation of the structures (III) and (IV) respectively. The front carbon is next rotated through 180° in each case to give the conventional staggered sawhorse formulae (IIIb) and (IVb). Conversion of the sawhorse formulae into the Newman projection formulae (IIIc) and (IVc) is easy. Direct translation of the Fischer projection into a Newman projection can likewise be done through the intermediate eclipsed conformations (IIId) and (IVd) which are subsequently transformed into the usual staggered Newman projection formulae (IIIc) and (IVc) by rotating the front carbon. Two points may be noted

in this connection: The Fischer projection formula actually represents a molecule in eclipsed conformation (III = IIIa = IIId; IV = IVa = IVd) which is energetically unfavourable and thus gives an improper perspective of the molecule. Secondly, for each of the stereoisomers (III) and (IV), three staggered Newman and sawhorse formulae can be drawn (by successive 120° rotations of the front carbon) each corresponding to a distinct conformer. Care should be taken so that during the above interconversions, the order (clockwise or anticlockwise) of the groups in space around a chiral centre is not disturbed. Sawhorse and Newman projection formulae can likewise be converted into Fischer projection formulae by reversing the procedure.

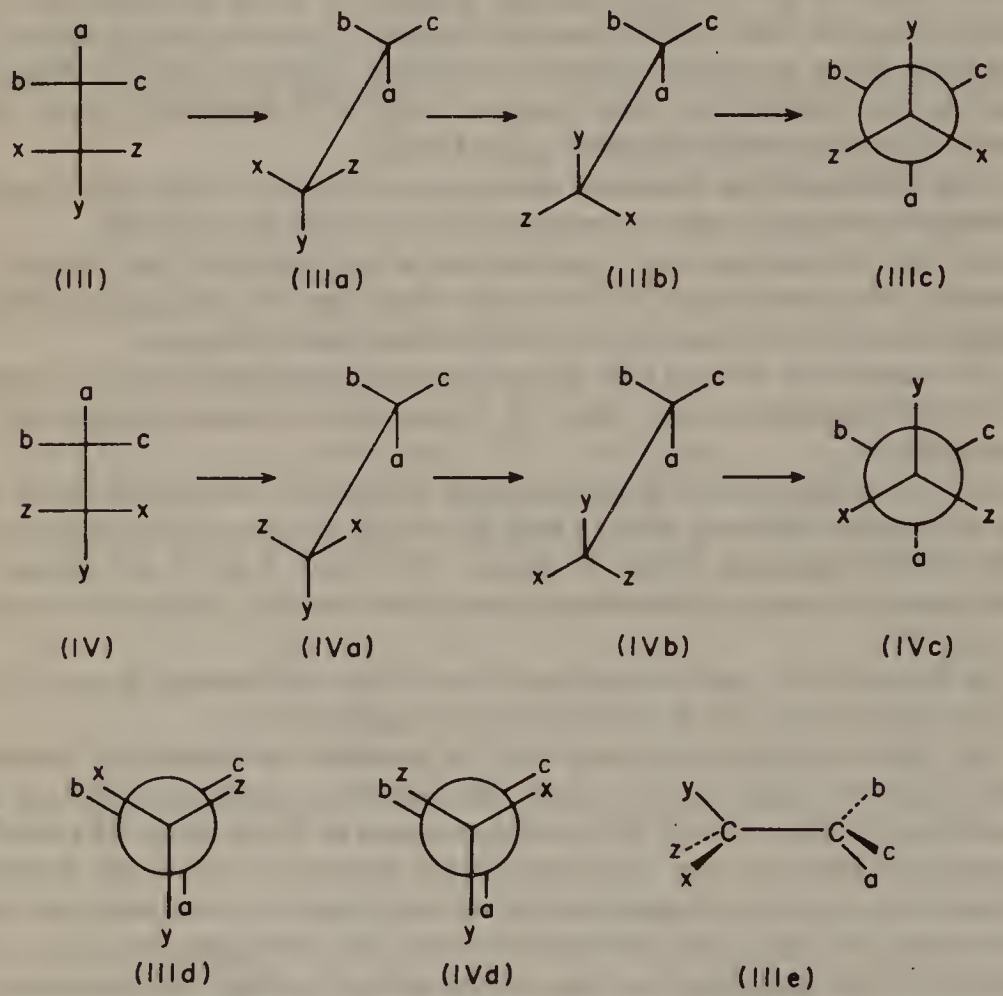


Figure 3.2 Interconversion of Fischer projection, saw-horse, and Newman projection formula. Structures (III) and (IV) refer to the same molecules irrespective of subscripts.

The structures can also be represented by flying-wedge notation in which the molecule is viewed *side on*. Thus the sawhorse formula (IIIb) in flying wedge notation would appear as IIIe. The only advantage of this system is that it shows the valency angles in their proper magnitude. In the present text, this notation will not be used except to denote a single chiral centre.

3.3 Classification of stereoisomers

In classical stereochemistry (see Eliel 1962), stereoisomers were divided into three classes: optical isomers, diastereomers, and geometrical (or cis-trans) isomers. Mislow (1965) has suggested a new system of classification based on symmetry and energy criteria which is now generally adopted and is discussed below.

3.3.1 Classification based on symmetry criterion

The classification of stereoisomers based on symmetry criterion is simple and straightforward. Only two types are recognised: enantiomers and diastereomers.

If two stereoisomers are related to each other as object and mirror image which are not superposable, (like a left hand and a right hand) they are called *enantiomers* and said to exhibit an *enantiomeric relationship*. As discussed in Chapter 2, such molecules are necessarily chiral and belong to point groups C_1, C_n, and D_n only. Since enantiomers are usually optically active, i.e., they turn the plane of a polarised light to an equal degree but in opposite directions, they are also called *optical isomers* or *optical antipodes*. These terms, however, are losing popularity and better be abandoned since some enantiomers, e.g., *R*- and *S*-*n*-butyl ethyl-*n*-hexyl-*n*-propylmethane do not show any detectable optical rotation. On the other hand, many optically active compounds display diastereomerism (see below).

Stereoisomers which are not related to each other as object and mirror image, i.e., which are not enantiomers, are called *diastereomers* and said to exhibit a *diastereomeric relationship*. A broad range of molecules falls under this category. Some typical examples of enantiomers and diastereomers are shown in Figure 3.3. The classification is summarised in the flow sheet chart 3.1. which also includes constitutional isomers. The following points serve to highlight some of the distinctive features of enantiomers and diastereomers.

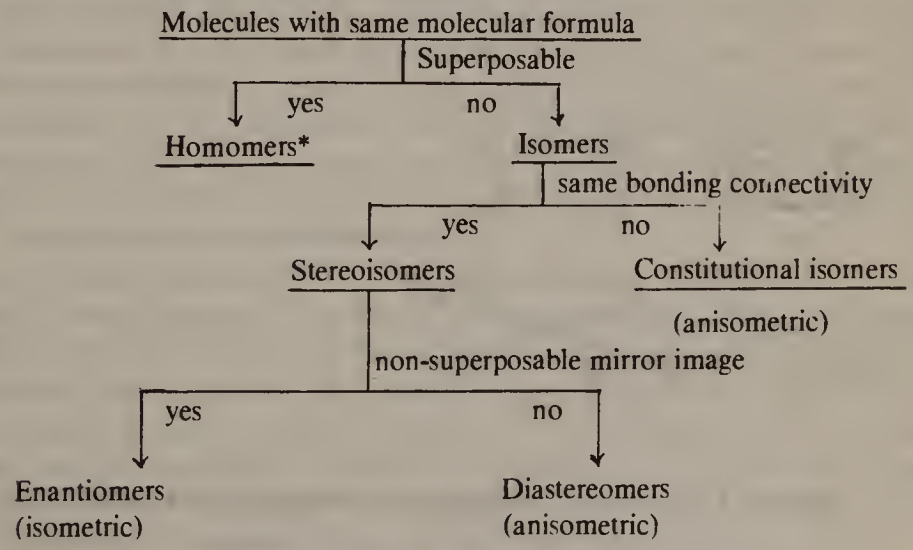


Chart 3.1 Symmetry-based classification of stereoisomers

*At first sight, it appears superfluous to represent homomers as a class, since they are in essence identical. However, the concept of homomers as opposed to isomers is useful as will be seen later.

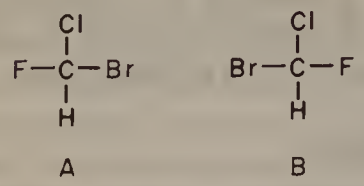
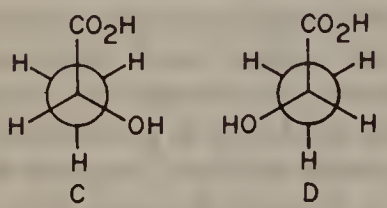
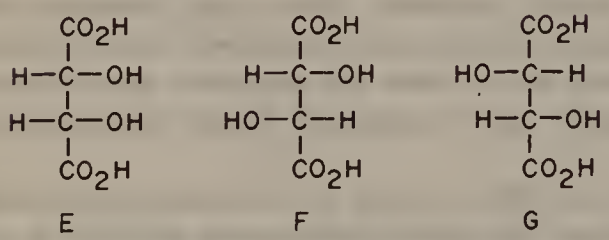
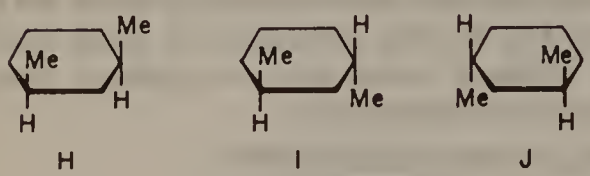
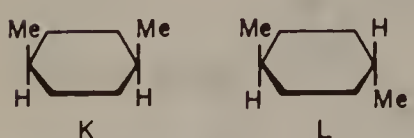
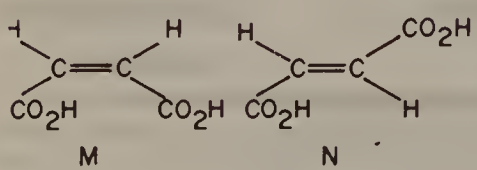
Entry	Compounds	Enantiomers	Diastereomers
1.	 A, B	A,B	—
2.	 C, D	C,D	—
3.	 E, F, G	F,G	E,F E,G
4.	 H, I, J	I,J	H,I H,J
5.	 K, L	—	K,L
6.	 M, N	—	M,N

Figure 3.3 Examples of configurational enantiomers and diastereomers

(*i*) Enantiomers being mirror images of each other are related by symmetry elements of the second kind, i.e., σ plane, i, and S_n axis but diastereomers are not related by any such symmetry element.

(*ii*) Since a molecule (or an object) can have only one mirror image, enantiomers can exist only in pairs. On the other hand, structural conditions permitting, a molecule can have any number of diastereomers.

(*iii*) No two stereoisomers can be enantiomers and diastereomers at the same time, i.e., enantiomeric and diastereomeric relationships are mutually exclusive.

(*iv*) Diastereomers may be (but do not have to be) chiral in which case each of them in turn would exhibit enantiomerism. Thus cholesterol is one stereoisomer of a set of one hundred twenty eight diastereomers each of which has an enantiomer. It is, therefore, diastereomeric with two hundred fifty four molecules and enantiomeric with one.

(*v*) Diastereomers in the new definition include all stereoisomers (except enantiomers) such as optically active diastereomers, geometrical isomers, and cis-trans isomers of classical stereochemistry. Thus 1,3-dimethylcyclohexane containing two chiral centres in previous nomenclature was said to exist in two diastereomers (cis and trans) one of which (trans) is resolvable into enantiomers (I and J in Figure 3.3) while similarly constituted but achiral 1,4-dimethylcyclohexane was said to exist in two geometrical or cis-trans isomers (K and L) none of which is resolvable. In the present system, this dichotomy is removed and both of them are said to exhibit diastereomerism. Like optical isomerism, the term geometrical isomerism has thus become redundant although the analogous term cis-trans isomerism still finds application as a subclass of diastereomerism.

(*vi*) In a chiral molecule, the atoms have exactly the same relative positions with respect to interatomic distances and interactions as they have in its enantiomer. The two enantiomers are thus *isometric* to each other and in achiral media, behave in identical fashion, as if they were homomers (any two structures which are superposable are called *homomers*). Thus the enantiomers have same melting points, boiling points, densities, solubilities, refractive indices, dipole moments, etc., and same thermodynamical and spectroscopic properties. They also show the same reactivity towards achiral reagents. In contrast, the diastereomers differ in the spatial relationship of atoms and groups and are, therefore, *anisometric* relative to one another (Coxeter 1969). They differ, in principle, in all the above mentioned properties, however small the difference may be.

(*vii*) Two enantiomers have all their geometrical parameters identical as mentioned above. They differ only in terms of absolute direction in space (algebraic sign of the coordinates of atoms)—a vector rather than a scalar quantity described by the science of topography which individualises each point and deals with the properties of each separately (Klein 1968). It is thus appropriate to say that enantiomers are geometrically equivalent (molecules or structures are called geometrically equivalent if they can be made superposable by any of the symmetry operations mentioned in Chapter 2) but differ in their topography (in the sense of chirality). In contrast, diastereomers differ both in geometry and in topography.

(*viii*) Chirality or enantiomeric relationship cannot be specified without comparison with an external reference which itself must be chiral. Thus when one says

right-handed chirality (or *R* and *S* configuration), one refers it to a right hand (which, too, is a right hand only by convention). Chirality can be recognised only through the diastereomeric relationship a chiral object establishes either with its own kind or with another chiral object. Two enantiomers behave differently toward a plane-polarised light because a plane-polarised light is composed of two dissymmetric components, a right-handed and a left-handed circularly polarised light beam (see Chapter 15) and thus constitutes a chiral environment. The well known enzyme stereospecificity is another example of chiral recognition of a chiral substrate by a dissymmetric system or reagent (here the enzyme).

Diastereomers and diastereomeric relationship, on the other hand, can be specified and recognised without any external reference.

(*ix*) As a corrolary of the above, a single stereoisomer cannot be designated an enantiomer or a diastereomer since such terms refer to relationship within a set of two or more stereoisomers. A molecule is either an enantiomer of (or a diastereomer of) or enantiomeric with (or diastereomeric with) another molecule.

(*x*) Both constitutional isomers and diastereomers containing the same functional group(s) usually differ in scalar properties, e.g., boiling points, melting points, density, refractive index, thermodynamical and spectroscopic properties, and even in their reactivities. In fact, two diastereomers may differ in their properties as much as (in some cases, even more than) two constitutional isomers. From an operational point of view, therefore, distinction between these two classes appear to lose their significance (Mislow 1965).

3.3.2 **Classification based on energy criterion**

It has already been stated that isomers are separated by energy barrier and their kinetic stabilities depend on the barrier height. Stereoisomers separated by *high energy barrier* ($>$ 100 kJ mol^{-1}) are quite stable and at room temperature are isolable. They are called configurational isomers. Stereoisomers separated by relatively *low energy barrier* ($<$ 60 kJ mol^{-1}) are easily interconvertible at ambient temperature and are known as conformational isomers or conformers. The difficulty arises when one goes to define *high* and *low* (the use of 100 and 60 kJ mol^{-1} as above is quite arbitrary) since it is almost impossible to set a standard acceptable to all. For a synthetic chemist who is interested in isolating stable stereoisomers, the desired barrier is high ($>$ 100 kJ mol^{-1}). For a spectroscopist who is interested in identifying the different stereoisomers in equilibrium, a low energy barrier is sufficient as long as the physical technique (e.g., infrared, nuclear magnetic resonance, microwave spectroscopy etc.) used has a time scale of measurement which is short in comparison to the rate of interconversion of the isomers. If the rate of interconversion is fast compared to the time scale of measurement, only an average picture of the species in equilibrium is obtained. According to Eliel (1976), it is appropriate that we accept an energy barrier of RT (2.58 kJ mol^{-1} at room temperature) as the standard below which two species may be considered as homomers. From energy criterion, the stereoisomers are thus classified into three categories. Stereoisomers which are separated by high energy barrier are known as configurational isomers. Stereoisomers which are separated by low energy barrier are known as conformational isomers. Finally, stereoisomers which are separated by energy barrier of intermediate magnitude (falling within

gray area) may be called configurational isomers at low temperature and conformational isomers at ambient temperature.

The two classifications (based on symmetry and on energetics) are not mutually exclusive. Enantiomers or diastereomers may be configurational enantiomers or configurational diastereomers if the energy barriers are high. Similarly, one can have conformational enantiomers and conformational diastereomers when the energy barriers are relatively low. Examples are given in Figure 3.4*. The combined classification is shown in the flow sheet Chart 3.2.

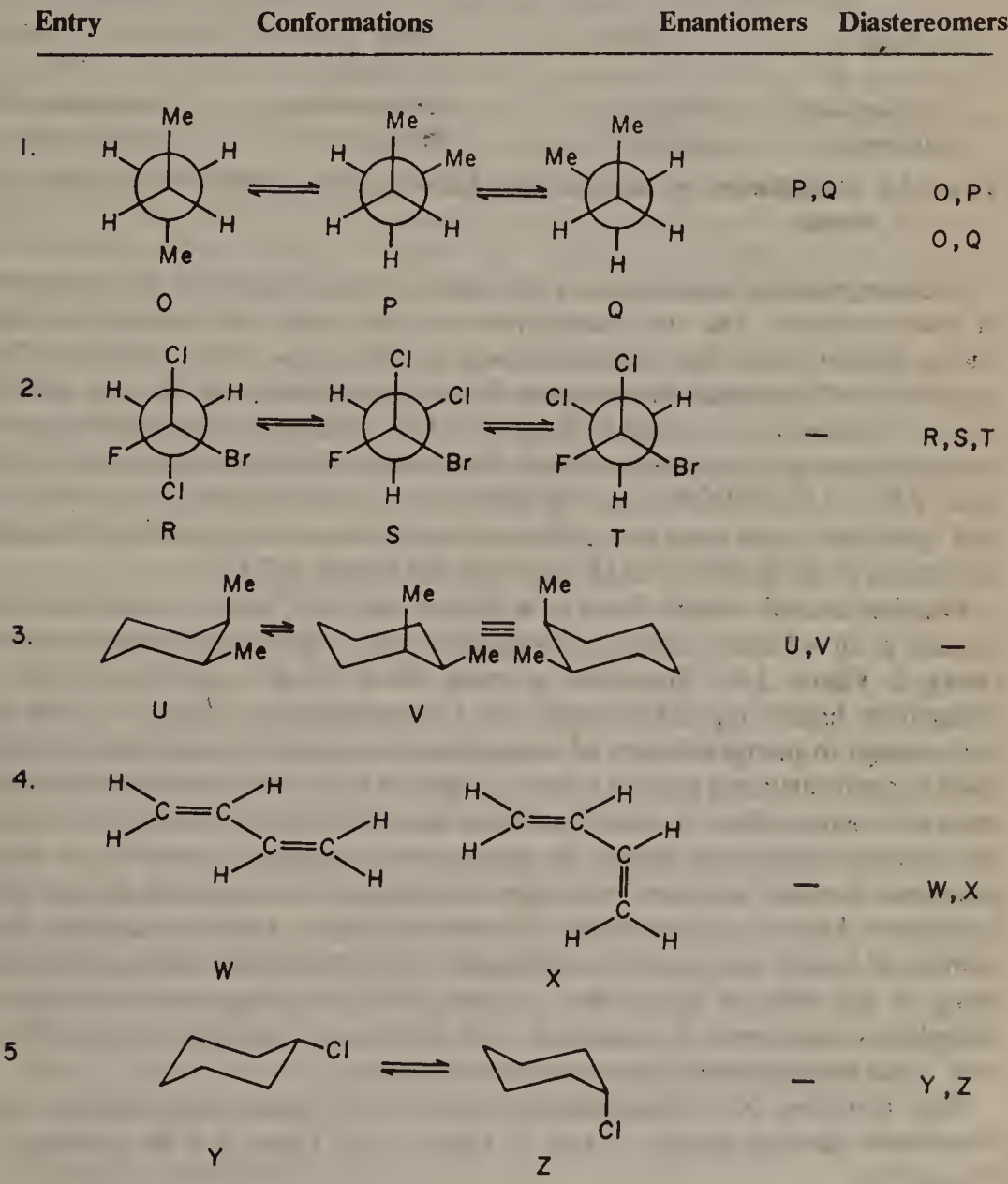


Figure 3.4 Examples of conformational enantiomers and diastereomers

*Some of the examples will be better understood later.

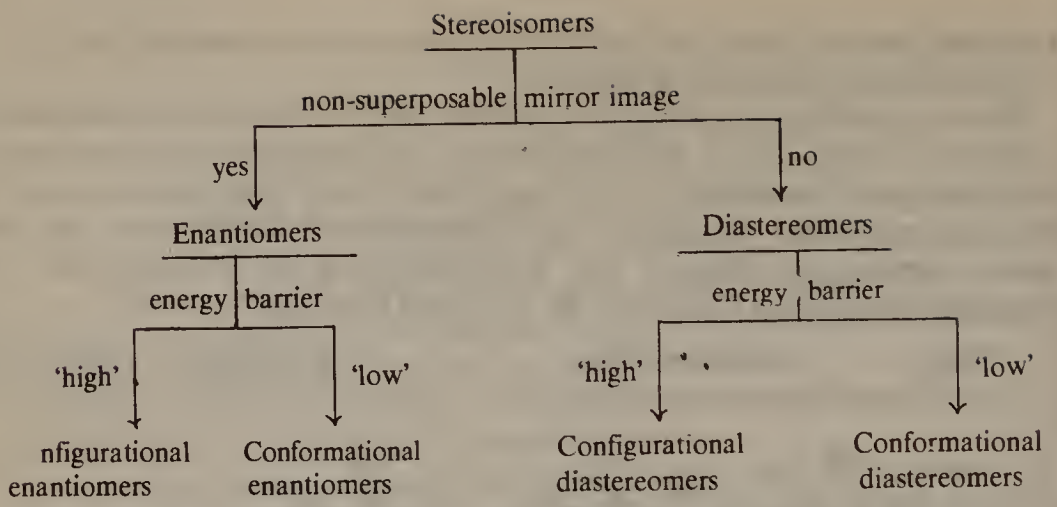


Chart 3.2 Classification of stereoisomers based on joint criteria of symmetry and energy.

The energy barrier separating any two stereoisomers depends on the mechanism of interconversion. The two enantiomers of lactic acids are separated by high energy barrier since their interconversion involves a σ bond breaking. They represent configurational enantiomers. In the isomerisation of *cis*- and *trans*-2-butene (Chapter 1), a π bond is disrupted which requires an appreciable amount of energy; they are also configurational diastereomers. Ethylenic compounds of the type, RR′C = C(OR)(OR′), on the other hand. have relatively low (60-70 kJ mol^{-1}) torsional energy and give conformational diastereomers at ambient temperature inspite of the double bond (Kalinowski and Kessler 1973).

Rotation around a single bond is in general easy and leads to conformational isomers as in *n*-butane (entry 1, Figure 3.4) and in dichlorobromofluoroethane (entry 2, Figure 3.4). Rotational energies about sp^2-sp^2 single bonds are in comparison higher, e.g., 25 kJ mol^{-1} for 1,3-butadiene (see Chapter 1) but not high enough to permit isolation of stereoisomers at ambient temperature and thus leads to conformational isomers (entry 4, Figure 3.4). In some crowded molecules, however, rotation about a single bond may be sufficiently restricted to give stable and isolable conformers known as atropisomers (Chapter 5) which are configurational isomers. Inversion in nitrogen compounds is normally facile and give conformers known as invertomers. The barrier height, however, depends on a number of factors and can vary enormously (see Chapter 10), the average value being of the order of 25 kJ mol^{-1} (Lehn 1970). In comparison, inversion in phosphorus compounds is associated with high energy (of the order of 150 kJ mol^{-1}) and configurational isomers are encountered.

Ring inversion (also pseudorotation) is a facile process and leads to conformational isomers (entries 3 and 5, Figure 3.4). These will be discussed in Chapter 10.

3.4 Stereoisomerism, conformation, and chirality

The concept of conformation has widened the definition of stereoisomerism and introduced a time-dependent element in the molecular structures. The molecule in

most cases cannot be treated as a static system of fixed geometry but as a dynamic system consisting of a number of species in equilibrium continuously changing their geometries. Molecules containing a single bond between two sp^3 hybridised carbons reside in three conformers which can be homomeric, enantiomeric, or diastereomeric with one another. Compounds containing two such bonds can have as many as nine conformers of which only a few are preferred on energy ground. Thus the number of conformers increases in geometric progression with chain length*. Ethane (Chapter 1) exists in three conformers all of which are homomeric. *n*-Butane, an achiral molecule has three distinct conformers based on rotation around C_2—C_3 bond, two of which are enantiomeric and the third is diastereomeric with both (entry 1 in Figure 3.4). The other conformers arising out of rotations around C_1—C_2 and C_3—C_4 bonds are homomeric with one or other of the above three. In the case of a chiral molecule, the three conformers of a particular enantiomer can either be all homomeric or all diastereomeric (see 1,2-dichlo rofluorobromoethane, entry 2, Figure 3.4). No two conformers of a given enantiomer can have enantiomeric relationship although all the conformers must be necessarily chiral.

From the above discussion, it is quite clear that if a particular conformer of a molecule is chiral, the molecule is not necessarily chiral. There are two simple rules to determine the chirality or achirality of a molecule from its conformers:

(*i*) If during a 360° rotation about one or more single bonds, a conformer passes through a conformation (may be with an energy maximum) which is achiral, the molecule is achiral. If there is no achiral conformation or conformer, then the molecule is chiral. This rule is specially useful in deciding the chirality of an acyclic molecule. The optically inactive meso form of tartaric acid (E in Figure 3.3.) possesses a plane of symmetry in the eclipsed conformation (C_s point group), as in the Fischer projection formula and a centre of symmetry in one of the staggered conformers (C_i point group) and so the meso form is achiral. On the other hand, all the conformers of optically active tartaric acid (F and G, Figure 3.3) are chiral.

(*ii*) The second rule is to see whether any two conformers of a molecule are mirror images of each other, i.e., enantiomeric. If they are, the molecule is achiral (see two conformational enantiomers in *n*-butane). This rule is specially useful for cyclic compounds in which conformers originate through ring inversion or pseudorotation and in the case of invertomers which originate through inversion at a centre. The two rules should be used simultaneously. An achiral species with two chiral conformers does not show any chiral manifestation because the two are equally populated by virtue of their identical free energy content. Thus the species is a racemic mixture of too rapidly interconverting enantiomeric conformers. An example is *cis*-1,2-dimethylcyclohexane (entry 3, Figure 3.4).

3.5 Racemic modifications

When equimolecular quantities of two enantiomers of a chiral molecule are mixed

*This is true in principle but actually because of homomerism (degeneracy), improbability of high energy conformations, and excluded volume problems there are not all that many. Homomers are not usually counted more than once.

together or formed in a reaction, the resultant mixture is called a racemic modification, or a racemic mixture, or a racemate, or simply a (±)-pair. Since the differentiation of stereoisomers is made at the molecular level, racemic modifications do not really represent a separate class of stereoisomers although they differ from the corresponding pure enantiomers in certain physical properties, especially in the solid state. In addition, they do not show any optical rotation, the rotation due to one enantiomer being exactly cancelled by an equal and opposite rotation of the other enantiomer (external compensation). The difference in properties between a racemic modification and the corresponding pure enantiomer arises from the difference in the intermolecular interactions which govern the molecular packing in the crystal lattice and the intermolecular association in the liquid state or in concentrated solution. The situation may be compared to two boxes one holding only right-handed or left-handed gloves and the other holding an equal mixture of both. The stacking of the gloves in the two boxes would be different which at the molecular level is equivalent to packing enantiomers of the same chirality, e.g., (++) or (−−) and of opposite chirality, e.g., (+−) in two crystal lattices. The two crystals are thus diastereomerically related and behave so as long as the intermolecular interactions are appreciable. Under this condition, they will have different physical and spectroscopic properties. In dilute solutions or in the gaseous form, the molecular species are usually well segregated i.e., the intermolecular interactions become negligible and as a result, the differences in physical and spectroscopic properties between a racemate and the corresponding pure enantiomers are minimised (except for optical activity) (Mislow 1965). What happens is that the diastereomeric relationship between them disappears.

3.5.1 **Racemic modifications and thermodynamic properties**

A racemic modification being a mixture of two molecular species possesses an entropy of mixing (ΔS) which can be calculated (assuming the mixture to be an ideal one) as follows:

$$\Delta S = -Rx_1 \ln x_1 - Rx_2 \ln x_2; (x_1 \text{ and } x_2 \text{ are the mole fractions}).$$
$$= -R \ln \tfrac{1}{2} = R \ln 2 \approx 6 \text{ J mol}^{-1} \text{ degree}^{-1}, \quad (x_1 = x_2 = \tfrac{1}{2})$$

The entropy of mixing is thus a positive quantity. Conceptually, a racemic modification consisting of two molecular species corresponds to a more random or less orderly system than the enantiomeric form which consists of a single molecular species. Entropy which is a measure of randomness is, therefore, expected to be higher in racemic modification.

The changes of free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) are related by the equation :

$$\Delta G = \Delta H - T\Delta S$$

At room temperature (300 K), the change of free energy due to mixing is 300×6 J or 1.8 kJ mol^{-1} assuming that the enthalpy remains constant. This means that the conversion of pure enantiomers into the racemic modification—a process known as racemisation—is thermodynamically favourable and a spontaneous process.

3.5.2 Classification of racemic modifications

On the basis of the difference in the nature of packing in the crystal lattice, racemic modifications are divided into three classes (Jaques et al 1981).

(*i*) **Racemic conglomerate** (A). If the crystal lattices are formed entirely from enantiomers of like chirality (see diagram A in Figure 3.5), the racemic modification is called a conglomerate (A) (previously also called a racemic mixture). Two crystals containing enantiomers of opposite chirality are enantiomorphous* and under favourable conditions may be separated mechanically.

(*ii*) **Racemic compound** (B). If, on the other hand, each unit crystal contains an equal number of (+) and (−) enantiomers, the racemic form is called a racemic compound (B) (see diagram B) (previously called a racemate) which in the solid state behaves as a separate entity distinct from either of the enantiomeric form.

(*iii*) **Pseudoracemate** (C). Finally, in some rare cases, the lattice energy becomes almost independent of the configuration of the constituent enantiomers and the unit crystals are formed indiscriminately from both the enantiomers (see diagram C). Such form is known as a pseudoracemate, a racemic solid solution, or mixed crystals (C).

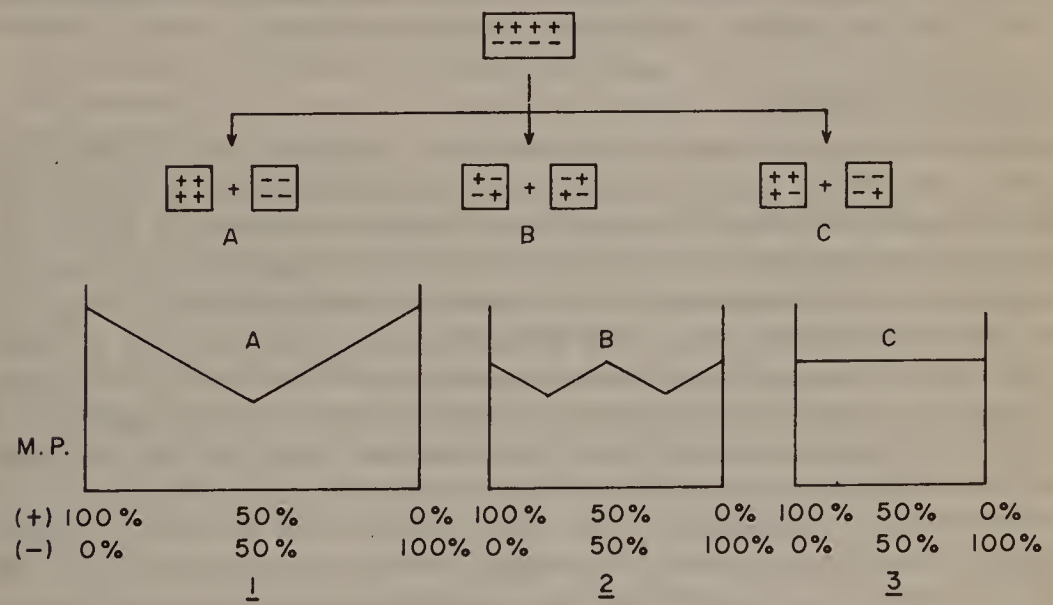


Figure 3.5 Racemic modifications and their melting point diagrams (Diagrams 1, 2 and 3 are idealised).

The above-mentioned three types of racemic modifications can be distinguished by their solid phase behaviour and in the case of the racemic compounds also by infrared spectra in the solid state and by X-ray diffraction pattern. The conglomerate (A) is a true eutectic mixture and corresponds to the lowest temperature in the melting point diagrams drawn for different mixtures of enantiomers

*The terms 'enantiomer' and 'diastereomer' (and the corresponding adjectives) generally refer to molecules and compounds while the terms 'enantiomorph' and 'diastereomorph' refer to macroscopic objects and models.

(diagram 1, Figure 3.5). It is exemplified by (±) sodium ammonium tartrate crystallised from an aqueous solution at a temperature below 27° (first observed by Pasteur and used for the resolution of tartaric acid). The solid solutions or pseudoracemates (C) do not change melting points appreciably with changes in composition of the mixture (diagram 3). An example is found in (±)- camphor oxime crystallised above 103°. The racemic conglomerate (A) and the racemic solid solution (C) both give infrared spectra and X-ray power diagram identical with those of their enantiomers.

In contrast, a racemic compound (B) retains the diastereomeric relation with respect to the enantiomeric form even in the unit crystals and gives an infrared spectrum (in the solid state) and an X-ray diffraction pattern quite different from those of the enantiomers. It has a lower enthalpy than the enantiomers and its melting point is usually higher (although it can also be lower) than that of the pure enantiomers (diagram 2). As expected of a new compound, the melting point diagram shows two depressions. Racemic compounds are more commonly encountered than the other two racemic modifications (conglomerates and pseudoracemates).

The solubility behaviour of the three racemic modifications is also different but is less reliable as a guide in distinguishing them (see Eliel 1962).

3.5.3 **Quasi-racemates**

Sometimes, analogous compounds of the same constitution and relative configuration and having similar geometry and charge distribution can replace each other in the crystal lattice. In that case, they are called isomorphous. If two such compounds with opposite configurations* are mixed in equimolecular proportion, quasi-racemic modifications may result. Like true racemic modifications, they may also form quasi-racemic compounds or quasi-racemic solid solutions. Of these, quasi-racemic compounds (or more properly, quasi-racemates) are important because they are used for configurational correlation. Thus (+)-chlorosuccinic acid and (−)-bromosuccinic acid form a quasi-racemic compound as recognised by their mixed melting point diagram similar to the diagram 2 (Figure 3.5) but dissymmetrical in appearance—a fact which indicates that they are of opposite configurations. They may be called heterochiral or said to be heterochirally related like two almost equal and similar right and left hands which are of opposite-chirality but are never *perfect* mirror images of each other. Conversely, (+)-chloro- and (+)-bromosuccinic acids are homochiral (like two almost equal and similar right hands) having the same gross chirality† (Mislow and Bickart 1967-77).

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*Such pairs of opposite chirality may be called quasi-enantiomers (also heterochiral, see below).

†The terms 'homochiral' and 'heterochiral' have been used here in the sense first used by Lord Kelvin, *Baltimore Lectures* (1904), referred to by Mislow and Bickart (1976-77). The two terms have been later elaborated by Ruch (1977) by analogy with shoes and screws. Thus an assorted number of shoes may be sorted out in two sets : right-footed and left-footed. Members of each set may be called homochiral while members of different sets are heterochiral. The terms have also found application in segmentation of an achiral object such as an apple (or a sphere of K_h symmetry) into two homochiral halves, a French parlour trick known as '*la coupe du roi*' (the royal cut). Two vertical half-cuts perpendicular to each other, one from the top to the equator and the

3.6 Summary

1. A particular molecular formula may correspond to several molecular species, known as isomers, differing in bonding connectivity (nature of linkage among the constituent atoms) and in configuration (relative orientation of atoms and groups). Isomers differing in bonding connectivity are called constitutional isomers and isomers of the same constitution but with different configurations are called stereoisomers.

2. The different modes of representation of three dimensional molecular structures on two dimensional paper, namely, Fischer projection, sawhorse, and Newman projection formulae are discussed. Mention has also been made of the flying wedge notation which is important in denoting a single chiral centre. The interconversion of the various projection formulae is illustrated.

3. Stereoisomers have been classified into enantiomers and diastereomers based on symmetry criteria. Two stereoisomers which are related as an object and a mirror image but are non-superposable are called enantiomers. If not so related, they are called diastereomers which include compounds containing more than one chiral centre, cyclic compounds, and compounds containing double bonds. The distinctive features of enantiomers and diastereomers have been highlighted.

4. Enantiomers are isometric with each other, i.e., all the intramolecular interactions are similar in the two enantiomers. On the other hand, diastereomers as also constitutional isomers are anisometric with one another, i.e., intramolecular interactions in them are different.

5. Stereoisomers are also classified on the basis of the energy barrier separating them. Stereoisomers separated by a high energy barrier are called configurational isomers and those separated by comparatively low energy barrier so that interconversion is easy under ordinary conditions are called conformational isomers. The two methods of classification, one based on symmetry criterion and the other on energy criterion are not mutually exclusive. One can have, for example, configurational enantiomers, configurational diastereomers, conformational enantiomers, and conformational diastereomers. All of them have been illustrated with examples.

6. The inter-relationship between conformers and the molecules representing the conformers has been discussed and certain rules have been formulated which permit one to deduce the chirality (or otherwise) of a compound from one or more of its conformers.

7. The racemic modifications arising out of mixing equimolecular quantities of enantiomers have been subdivided into three classes, namely, a conglomerate, a racemic compound, and a solid solution (pseudoracemate). A racemic form in the

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other from the bottom to the equator, followed by two non-adjacent horizontal quarter-cuts along the equator give two homochiral halves of an apple. Homochiral halves of opposite chirality are obtained by reversing the direction of the horizontal quarter-cuts (see Anet et al 1983 and also Cinquini et al 1988 for such bisection of an achiral molecule). The interesting thing is that only the combination of two homochiral segments gives the original achiral apple.

Recently, Masamune et al (1985) have used the term homochiral to mean enantiomerically pure substance, i.e., either all (+)- or all (−)-forms of chiral molecules. This terminology has gained wide currency.

solid state or in concentrated solution exhibits a diastereomeric relationship with enantiomeric form which is reflected in the difference in certain physical properties between the two. Methods for distinguishing the three kinds of racemic modifications are discussed.

References

1. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
2. K. Mislow (1965) in *Introduction to Stereochemistry*, W.A. Benjamin, New York.
3. J.N. Lehn (1970) in *Dynamic Stereochemistry : Topics in Current Chemistry*, Springer Verlag, Berlin.
4. P. Klein (1968) in *Elementarmathematik von höheres Standpunktaus,* 2nd Edn., Springer Verlag, Berlin, p. 141; see also v. Prelog and G. Helmchen (1982), *Angew. Chem. Int. Edn. Engl.,* **21**, 567 (footnote).
5. E.L. Eliel (1976-77), *Israel J. Chem.*, **15**, 7.
6. J. Jaques, A. Collet, and S.H. Wilen (1981) in *Enantiomers, Racemates, and Resolution*, Wiley, New York.
7. K. Mislow and P. Bickart (1976-77), *Israel J. Chem.*, **15.**, 1.
8. E. Ruch (1977), *Angew. Chem. Int. Edn. Engl.*, **16**, 65; also (1972), *Acc. Chem. Res.*, **5**, 49.
9. F.A.L. Anet, S.S. Miura, J. Siegel, and K. Mislow (1983), *J. Amer. Chem. Soc.*, **105**, 1419.
10. M. Cinquini, F. Cozzi, F. Sannicolo, and A. Sironi (1988), *J. Amer. Chem. Soc.,* **110**, 4363.
11. S. Masamune, W. Choy, J.S. Petersen, and L.R. Sita (1985), *Angew. Chem. Int. Edn. Engl.,* **24**, 1.

General Readings

1. K. Mislow (1977), *Bull. Soc. Chim. Belg,* **86**, 595.
2. IUPAC Commission on Nomenclature of Organic Chemistry (1974), Section E: Fundamental Stereochemistry, *Pure Appl. Chem.,* **45**, 11.
3. H.S.M. Coxeter (1969) in *Introduction to Geometry*, 2nd Edn., Wiley, New York.
4. H.O. Kalinowski and H. Kessler (1973), Fast Isomerisation about Double Bonds in *Topics in Stereochemistry*, vol. 7. Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.

Chapter 4

Stereoisomerism and Centre of Chirality

4.1 Introduction

Organic stereochemistry is based mainly on the tetrahedral geometry of carbon and a few other atoms such as N, P, Si, and S and to a lesser extent on the trigonal geometry of sp^2 hybrid carbon and nitrogen (and of course on the unique catenating property of carbon). The regular tetrahedron provides an achiral three-dimensional framework of T_d symmetry having four topologically equivalent vertices. If they are occupied with four different achiral atoms (or groups) so that the four vertices become distinguishable, all elements of symmetry disappear, and the tetrahedron turns into a three-dimensional four-point chiral simplex of C_1 symmetry which is non-superposable with its mirror image (see Figure 3.1a in Chapter 3). Actually a fifth point, a tetracovalent atom (e.g., C) is also necessary at the centre of the tetrahedron to which the four ligands are bonded giving what is known as an asymmetric or a chiral centre (e.g. Cabcd). The presence of a chiral centre usually leads to molecular chirality*. One unique feature of this chiral tetrahedral model is that transposition (exchange or permutation) of any two ligands reverses the chirality of the centre giving a new stereoisomer. If all the ligands are achiral, the transposition leads to an enantiomer; on the other hand, if one or more of the ligands are chiral, a diastereomer results (e.g., *meso*-tartaric acid to optically active tartaric acid and vice versa). The chiral centre is, therefore, a stereogenic centre, or in short a stereocentre.† The number of stereoisomers (enantiomers and diastereomers) goes on increasing with the number of chiral centres. For tricoordinate atoms such as N, P, and S, (in sulphoxides), the three ligands form the base of a trigonal pyramid with the ligating atom placed at an

*The centre of chirality is only one source of molecular chirality. According to Cahn, Ingold, and Prelog (1966), 'three-dimensional space can, in principle, be occupied asymmetrically about the zero-, one-, or two-dimensional elements of symmetry, that is, the point (centre), the line (axis), and the plane'. Molecular chirality is thus factorised into central, axial, and planar chirality, collectively known as elements of chirality (see Chapter 5). Recently, Mislow and Siegel (1984) have pointed out some apparent arbitrariness in the process of factorisation and opined that these elements of chirality are related more properly to stereogenicity than to molecular chirality. Prelog and Helmchen (1982) have also designated these elements as stereogenic units following a suggestion of McCasland (1953).

†A special name, *chirogen* (whence *chirogenic* and *chirogenicity*) has been suggested (Brewster 1986, Mezey 1986) for a tetrahedral chiral centre which is reflection variant, i.e., on reflection gives a stereoisomer (e.g., an enantiomer).

apex (a tripodal arrangement). The molecule becomes chiral provided all the ligands are different. In such cases, the ligating atom usually carries a lone pair of electrons which serves as the fourth substitutent (as in :Nabc) completing the tetrahedral arrangement (see Prelog and Helmchen 1982 for alternative approaches). The chiral centre is the most common of chiral elements.

4.2 Molecules with a single chiral (stereogenic) centre

Molecules containing a single tetracoordinate or tricoordinate chiral centre exist only as a pair of enantiomers and may be represented by the type formulae, Xabcd and :Xabc respectively in which a, b, c, and d are all achiral. Before discussing the stereoisomerism of these molecules, it is important to know how and to what extent two enantiomers can be distinguished, most of their physical and chemical properties being identical.

4.2.1 Chiral manifestations

The terms *chiral* and *achiral* when applied to geometrical models are sharply defined but when applied to real molecules, they must be related to the presence or absence of some observable properties. It has already been mentioned (Chapter 3) that two enantiomers can be distinguished only by establishing diastereomeric relationship either with a chiral environment or with other chiral molecules. There are three principal methods for detection of chirality in molecules based on the above principle. (*i*) Measurement of optical rotation and other chiroptical properties (polarimetric method); (*ii*) reactions with other chiral molecules including enzymes (chemical and biochemical method); and (*iii*) nuclear magnetic resonance spectroscopy using chiral solvents or additives (spectroscopic method). These methods are also used for the determination of the sense of chirality (chiral recognition) which is, however, more complex and is discussed elsewhere. Here only the method based on optical rotation is discussed. A plane-polarised light being constituted of two oppositely (right and left) circularly polarised components (see Chapter 15) provides a chiral medium and the two enantiomers interact differently rotating the plane of the polarised light either in a clockwise direction or in an anticlockwise direction. The former is known as dextrorotatory enantiomer denoted by (+) or by the prefix, dextro and the latter is known as the levorotatory enantiomer denoted by (−) or by the prefix, levo. In the older literature, the terms, dextro and levo are abbreviated as *d* and *l* respectively, but the practice is now discouraged. The chiral sample under consideration is usually taken in a tube of definite length (*l* in dm) either as a neat liquid or more often as solution in an achiral solvent of definite concentration (*c* in g/ml). According to Biot's law :

$\alpha = [\alpha]. l.c.$ where $[\alpha]$ is proportionality constant called 'specific rotation'.

It is customary to denote the rotation of an optically active compound in terms of its specific rotation and since it depends on temperature (T) and the wavelength (λ) of monochromatic light used, the specific rotation is expressed as follows:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l.c.} \qquad (1)$$

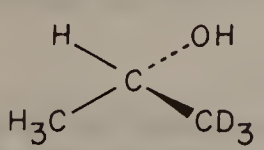
For neat liquids, the concentration term in the equation is replaced by the density (d) of the liquid.

For compounds which undergo association in solution, the solvent and concentration (as well as the temperature) affect the specific rotation and must be mentioned. In such cases, the rotation may not be directly proportional to concentration due to different degrees of association at different concentrations. It becomes sometimes necessary to compare the rotatory powers of analogous compounds of different molecular weights (M) and in such cases, the comparison is more meaningful if the molecular rotations $[M]$ or $[\phi]$ are used instead of specific rotations as defined below:

$$[M] = [\phi] = \frac{[\alpha].M}{100} = \frac{\alpha}{l(\text{dm}).\, c\ (\text{moles}/100\ \text{ml})} \qquad (2)$$

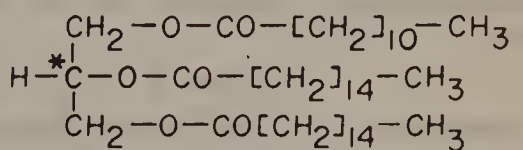
With the improvement of the polarimetric instruments, it is now possible to measure as small a rotation as 0.001°. Generally, sodium light ($\lambda = 589$ nm) commonly known as D line is used for polarimetric measurements and the specific rotation is expressed as $[\alpha]_D^T$. However, in many instances, the rotation at this particular wave length may be small in which case shorter wavelengths (e.g., 546 nm, provided by a mercury lamp) may be used.

A very small structural difference which arises out of replacement of one isotope by another (e.g., H by D) imparts chirality to a molecule which can be measured by polarimetric method. Thus the deuterated isopropanol (I) (Figure 4.1) in which one CH_3. has been replaced by CD_3 shows a specific rotation of 0.27°. However, if one considers compounds of the type, CH_3-$(CH_2)_n$-CHOH-$(CH_2)_n$-CD_3 the higher the value of n, the smaller is the specific rotation or any other measurable chiral property. This type of situation is similar to that encountered in triglyceride of the type (II) in which the two terminal hydroxyl groups of glycerol are esterified with fatty acids of similar character. As a result, even though such a triglyceride may be enantiomerically pure, it shows very little or no rotation. Another interesting example is a long chain fatty acid with a methyl group at a carbon atom to make the molecule chiral. As the Me group shifts away from the carboxyl group along the chain, the rotation falls (distance rule) and when it is situated near the centre of the chain, the rotation is barely detectable. Other methods of chiral recognition may be equally ineffective in such cases and the phenomenon has been called 'cryptochirality' (Mislow and Bickart 1976-77).



(I)

$\alpha_D = 0.27°$



(II)

Figure 4.1 Molecules with low 'degree' of chirality

4.2.2 Molecules with a tetracoordinate chiral centre

By far the most common tetracoordinate chiral centre in organic compounds is provided by sp^3 hybrid carbon, examples of which are given in Chapter 3. To these may be added appropriately substituted quaternary ammonium compounds (III), N-oxides (IV), silane derivatives (V), phosphonium compounds (VI), phosphine oxides (VII), hexavalent sulphur compounds (VIII) (Figure 4.2.), and also tetracovalent compounds of arsenic, antimony, germanium, and tin. These molecules are more or less stable configurationally and enantiomers in most cases can

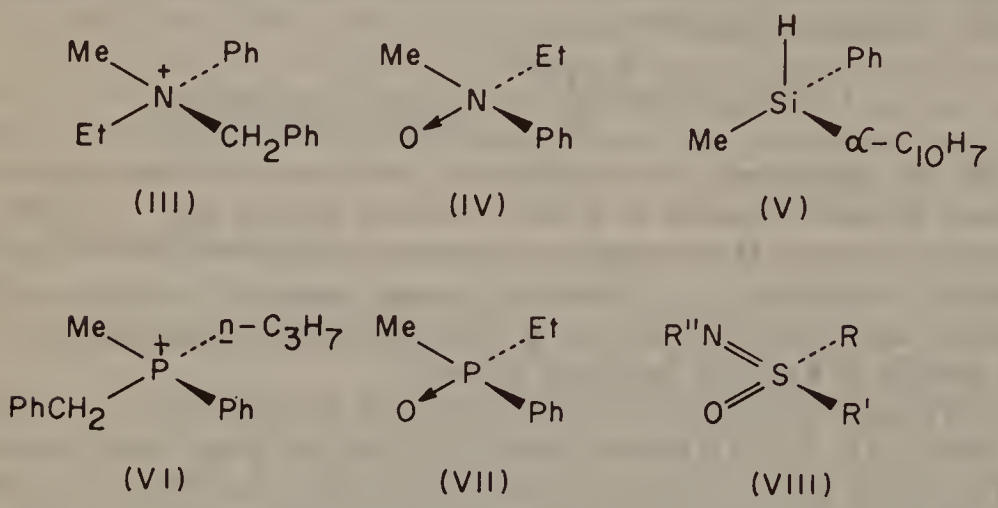


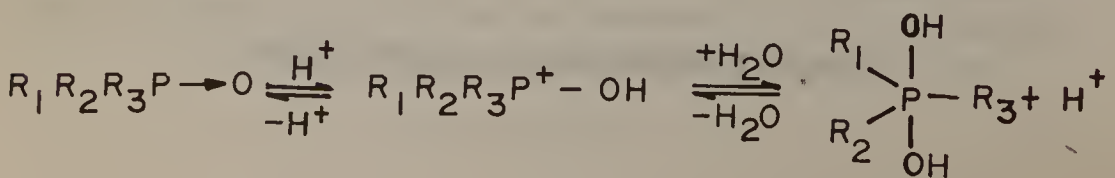
Figure 4.2 Molecules with tetracoordinate chiral centres (only one enantiomer shown)

be isolated in pure forms. Among these, chiral carbon compounds are ordinarily most stable since racemisation involves a bond cleavage or similar high energy processes. However, compounds which can easily tautomerise or can form carbanions, carbonium ions, or radicals involving the asymmetric carbon racemise with relative ease. Silicon being the nearest analogue of carbon in the periodic table is very similar to carbon with respect to stereoisomerism. Sommer (1965) has prepared a large number of optically active silicon compounds (e.g., V) in enantiomerically pure forms. They are configurationally very stable (see also Corriu et al 1984).

Enantiomerism in ammonium and phosphonium compounds with chiral N and P atoms has been widely studied. They are less stable configurationally than their carbon counterparts. Racemisation can take place through the following equilibrium process:

$$M^+abcd\ X^- \rightleftharpoons :Mabc + X{-}d$$

The feasibility of the forward reaction depends on the nucleophilicity of the anion X^-. With X^- as $SO_4^{=}$, NO_3^- etc., racemisation does not ordinarily take place. N-oxides and P-oxides are configurationally quite stable but can be racemised in acid medium through a symmetrical bipyramidal intermediate as shown :



4.2.3 Molecules with a tricoordinate chiral centre

Molecules with a tricoordinate chiral atom (e.g., :Xabc)* may be treated in the same way as the tetracoordinate compounds with the lone pair acting as the fourth substituent. They can, however, often undergo racemisation through inversion at the centre. Examples are tertiary amines (IX), phosphines (X), sulphonium salts (XI), sulphoxides (XII), carbanions (XIII), C-radicals (XIIIa) (Figure 4.3.), arsines, stilbines etc. The stability of the pyramidal configuration increases with increasing

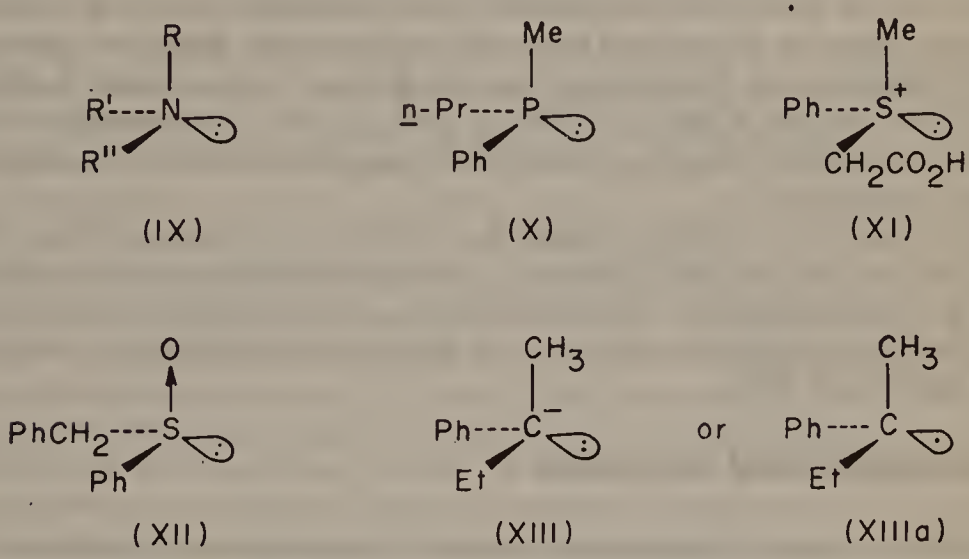


Figure 4.3 Molecules with tricoordinate chiral centres

atomic number. Thus tricoordinate derivatives of carbon, nitrogen, and oxygen (first row atoms of the periodic table) undergo fast inversion and give only conformational enantiomers or diastereomers (if there is a second chiral centre). When a nitrogen atom forms part of a ring, the barrier to inversion increases substantially. It is more so in aziridine derivatives (see Chapter 10). Thus 2-methyl-3,3-diphenyloxaziridine (XIV) has been obtained in stable optically active form (levo) by asymmetric epoxidation of diphenylmethylenemethylamine with (+)–peroxycamphoric acid (Figure 4.4a)

In Tröger's base (XV) (Figure 4.4b), nitrogen is placed on a bridgehead and

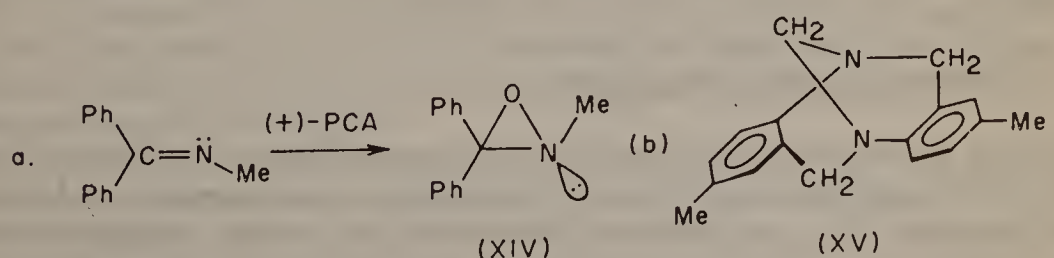


Figure 4.4 (a) Chiral oxaziridine and (b) Tröger's base : 2,8-dimethyl-6 *H*, 12 *H*-5, 11-methanodibenzo[b,f][1,5]diazocine

*In the absence of a lone pair, the molecule tends to be planar such as trialkylboranes (Babc).

cannot undergo inversion without breaking a bond and stable enantiomers are, therefore, formed which are separated by column chromatography using naturally occurring lactose.

There are three tricoordinate species derived from carbon compounds, namely, carbanions, carbon radicals, and carbonium ions which are of interest because they are reaction intermediates and often determine the stereochemical course of reactions. The carbanions $:^{-}$**Cabc** (as XIII) are isoelectronic with amines and like tertiary amines are pyramidal and undergo inversion very easily. The carbonium ions, C^{+}abc are isoelectronic with trivalent boron compounds and by all available evidences appear to be planar. Theoretical calculation also shows that the most stable hybridised state of carbonium ions should be sp^2 with a vacant p orbital. The carbon radicals, •**Cabc** (as XIIIa) (Figure 4.3) have been examined in the gaseous state and in solutions and the physical measurements indicate that they are planar or near planar.

In contrast, the tricovalent compounds of sulphur, phosphorus, arsenic, antimony etc. (see Shriner 1945) belonging to second and third rows of the periodic table give configurationally stable enantiomers*. Inversion barriers of molecules involving first and second row tricoordinate elements are available in the literature (see Ohkuba et al 1976).

4.3 Configurational nomenclature

The different modes of representation of three-dimensional chiral molecules on two-dimensional paper, have already been discussed which include Fischer projection, sawhorse, and Newman projection formulae. These formulae show the spatial structures of the molecules in their relative and absolute configuration which might be or might not be known but no nomenclature was given to the formulae. For example, lactic acid has been represented by two Fischer projection formulae, one for dextrorotatory and the other for the levorotatory enantiomer. The problem now resolves itself into two: (i) Appropriate configurational 'descriptors' have to be given to the structures in the way one says 'right' and 'left' to distinguish one's two hands. (ii) Next, one must know which structure belongs to which enantiomer (assignment of configuration). It is necessary first to settle on some system of configurational nomenclature so that each structure may be identified by a specific name.

4.3.1 Fischer's D and L nomenclature

As early as 1890, Fischer while working in the sugar and amino acid chemistry felt the need for establishing configurational relationship among members of a family of compounds (e.g., carbohydrates). He established the relative configuration of (+)-glucose and arbitrarily represented it by the structure (XVI, Figure 4.5) (he

*The s character in lone pair and the p character in bonds increase as one goes down the periodic table; hence planar transition state with sp^2 ligands and p lone pair is disfavoured.

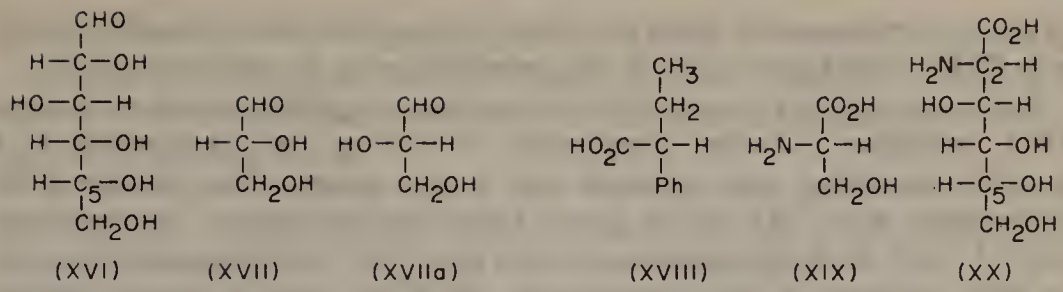


Figure 4.5 D and L Nomenclature

could have very well chosen its mirror image)*. He called it D-(+)-glucose, the descriptor 'D' referring to the configuration implied in the formula (XVI). Any sugar which could be genetically related to (+)-glucose through chemical transformations such as (+)-mannose and (−)-fructose was placed in the D family irrespective of their sign of rotation (Fischer originally used lower case *d* and *l*). The enantiomers were put in the L family. Since D-glucose (XVI) can be degraded into or synthesised from (+)-glyceraldehyde, the latter was arbitrarily given the D-configuration represented by XVII and (−)-glyceraldehyde the L-configuration represented by XVIIa (they retain the C-5 chiral centre of D and L-glucose respectively). Most of the sugars (and analogous compounds) may, in principle, be genetically related either to D- or to L-glyceraldehyde and their configurations were accordingly defined by D or L. This genetic nomenclature, however, did not work since in many cases, both the enantiomers of a compound may be chemically correlated to the same glyceraldehyde, e.g., (+)- and (−)-lactic acid to D-glyceraldehyde; the former is obtained by reduction of CHO to Me and oxidation of CH_2OH to CO_2H and the latter by oxidation of CHO to CO_2H and reduction of CH_2OH to CH_3.

To circumvent the difficulty, Rosanoff (1906) modified the system and suggested a *projection* nomenclature according to the following conventions :

(*i*) As in Fischer's system, the molecule is written with the longest carbon chain placed vertically.

(*ii*) The most highly oxidised end of the chain is placed at the top (as CHO in glucose), again following Fischer's convention.

(*iii*) If in the projected structure, the OH group (or any negative group, X) at the bottom-most (highest-numbered) chiral centre (C-5 in glucose) is on the right hand side, the molecule is given D configuration and if it is on the left, the molecule is given L configuration (as in D- and L-glyceraldehyde respectively). The Fischer-Rosanoff system does not refer to the origin of the compound (non-generic) and is commonly used in all textbooks.

However, only molecules which can be projected in a manner similar to sugars, can fit into this scheme of nomenclature. For example, 1-phenylbutyric acid (XVIII) cannot be written in Fischer projection following both the specifications

*The configuration of D-(+)-glucose given by Fischer turned out to be correct when, in 1951, the absolute configuration of molecules was determined for the first time by X-ray diffraction experiments (Chapter 8).

(i) and (ii) simultaneously: either the longest carbon chain can be placed vertically as in XVIII or the highest oxidised end, carboxylic group be placed at the top.

For amino acids, L-(−)-serine with the configuration (XIX) is used as reference which introduces a further complication in defining the configuration of a molecule containing both hydroxyl and amino groups. Thus 2-amino-2-deoxymannonic acid (XX) may be given D label with reference to glyceraldehyde (see C-5) but L label with reference to serine (see C-2). The problem can be solved by using subscripts 'g' for glyceraldehyde and 's' for serine so that the aminomannonic acid may be designated either as D_g or as L_s (Slocum, Sugarman, and Tucker 1971).

4.3.2 R and S Nomenclature

A self-consistent and unambiguous system of configurational nomenclature based on the three-dimensional structures of molecules was first introduced by Cahn and Ingold (1951) and subsequently elaborated by Cahn, Ingold, and Prelog (1955, 1966). The system is known as CIP nomenclature after the names of the authors. According to this system, the configuration of a molecule is specified uniquely either as *R* (from *rectus*, Latin for right) or as *S* (from *sinister*, Latin for left) which is independent of nomenclature and numbering. Like D and L, *R* and *S* are also topographical descriptors, used as prefixes* and have nothing to do with the signs of rotation.

Assignment of configuration is done by the application of two rules: the sequence rule (consisting of several standard subrules) and the chirality rule. The sequence rule arranges the four ligands of a chiral centre (Cabcd) in a priority sequence, e.g., a > b > c > d ('a' having the highest priority and 'd' the lowest), or the ligands may be numbered: 1 > 2 > 3 > 4. The chiral centre is then viewed from the side remote from the lowest ranking group ('d' or 4) (Figure 4.6). If from

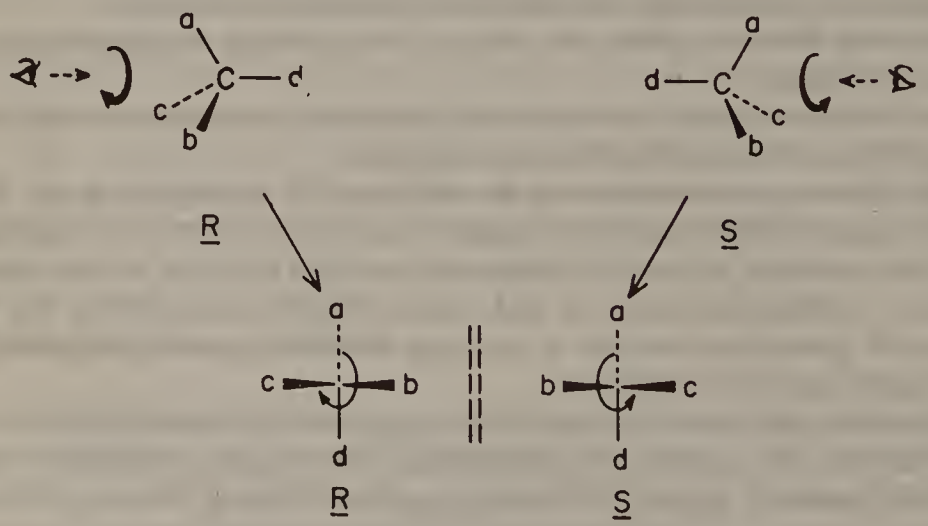


Figure 4.6 Chirality rule: *R* and *S* nomenclature

*R and S are usually put within parenthesis but not necessarily, as in this text.

this point of view, the arrangement a → b → c (or 1 → 2 → 3) appears in the clockwise (right-handed) direction, the configuration is *R* and if the arrangement appears in the anticlockwise (left-handed) direction, the configuration is *S*. This is known as the chirality rule.

The standard subrules which determine the priority order are six in number (actually, they themselves may be called the sequence rules) and have been stated under the headings (0)-(5) (Cahn, Ingold, and Prelog 1966)*. They must be applied in succession, i.e., one after the other in the order stated.

Sequence rules or standard subrules

(0) Nearer end of an axis or a plane precedes the farther end (proximity rule).
(1) Higher atomic number precedes lower, e.g., S > F > O > N > C > H.
(2) Higher atomic mass number precedes lower, e.g., T > D > H.
(3) Cis precedes trans; and *Z* precedes *E*.†
(4) Like pair *R,R* or *S,S* precedes unlike pair *R,S* or *S,R*; *M,M* or *P,P* precedes *M,P* or *P,M*; *R,M* or *S,P* precedes *R,P* or *S,M*; *M,R* or *P,S* precedes *M,S* or *P,R*; and *r* precedes *s*.
(5) *R* precedes *S*; and *M* precedes *P*.

For the majority of compounds, only subrules (1) and (2) are important; the other subrules apply only to special cases. Subrule (0) is applicable to axial and planar chirality to be discussed in Chapter 5. Subrule (1) needs further elaboration which is done in the following paragraphs:

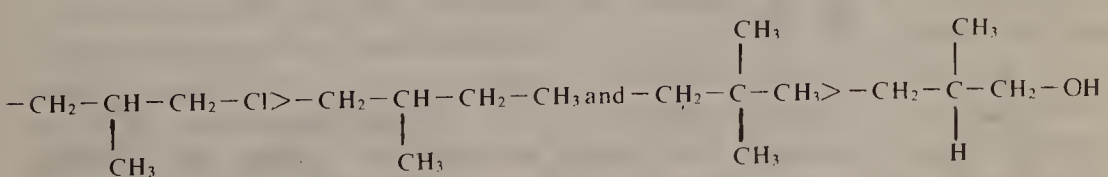
1. Atoms directly attached to the central chiral atom must be sequenced first according to subrule (1). If the priority still remains undecided for some of the ligands, one passes over to the next atom in the ligands and the exploration continues until a decision is reached on the basis of the subrules. The following examples illustrate the point :

$$\text{-}CH_3\mathit{C}H_3 > \text{-}CH_2\mathit{H};\ \text{-}CH_2\ \mathit{O}H > \text{-}CH_2\mathit{N}H_2;\ \text{-}CH_2CHF\ \mathit{Br} > \text{-}CH_2CHF\mathit{Cl}$$

(Decision is reached at the italicised atoms)

It may be noted that subrule (2) must not be used until subrule (1) is completely exhausted; thus $-CH_2CH_2CH_3 > -CD_2CH_3$ because propyl > ethyl (subrule 1); but $-CH_2CD_2CH_3 > -CH_2CH_2CH_3$ (subrule 2).

2. In case a ligand bifurcates, one must proceed along the branch providing the highest precedence until a difference is encountered. The decision must be made at the *earliest* opportunity and once made, cannot be changed from consideration of substituents farther along the chain. These points are illustrated below:



*Prelog and Helmchen (1982) have proposed a few revisions and modifications of the subrules which are mostly minor in nature. For some recent suggestions, see Dodziuk and Mirowicz (1990).

†Some of the terminologies such as *Z, E, M, P, r,* and *s* are discussed later.

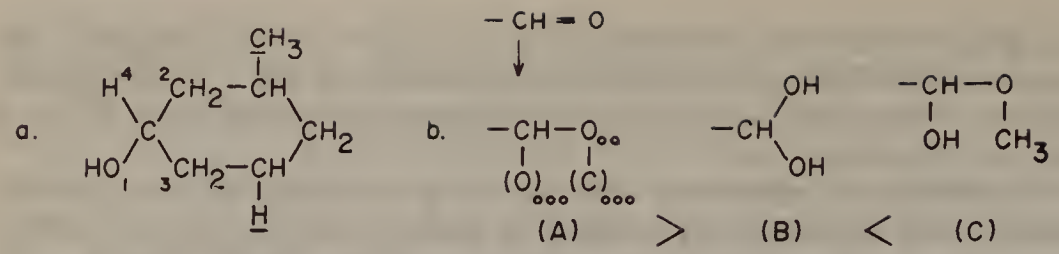


Figure 4.7 (a) Priority sequence in ring system; (b) aldehyde versus hydrated aldehyde versus hemiacetal

3. When the central atom is a part of a ring system, each branch is followed until a decision is reached as shown in Figure 4.7a above (see Prelog and Helmchen 1982 for complicated cases):

4. In the case of atoms with multiple linkages, the atom to which they are multiply bonded must be duplicated or triplicated as the case may be at both ends of the multiple bond. The duplicate atoms are put into parenthesis and except for hydrogen are made up (complemented) to ligancy four with phantom atoms of atomic number zero. Thus the representation of the aldehyde group, —CHO is shown (Figure 4.7b) along with its hydrated form and hemiacetal for comparison. From the structures (A), (B), and (C), it is clear that —CHO has preference over the hydrated form (B) but the hemiacetal (C) has preference over the aldehyde (A). The last point illustrates the utility of the phantom atom which has lower priority than hydrogen. In the following illustrations, (Figure 4.8) the phantom atoms are omitted.

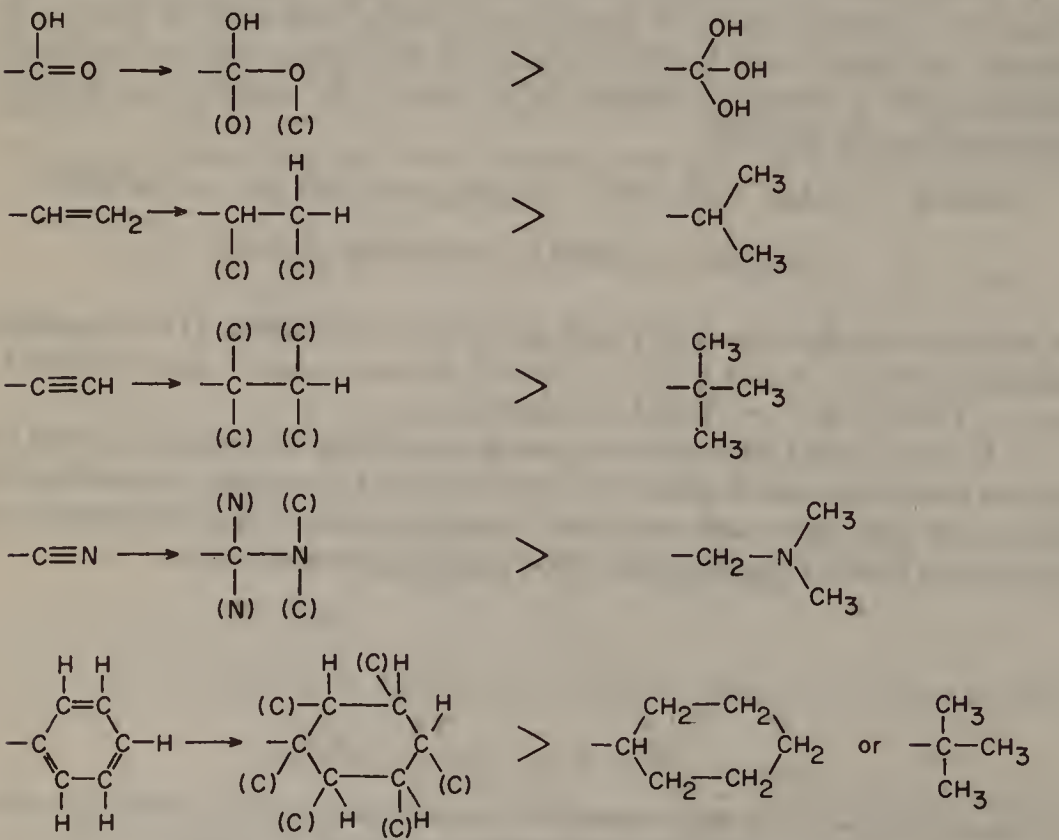


Figure 4.8 Priority sequence of some common groups

In Table 4.1, a few atoms and groups are listed in order of increasing priority. In the absence of a lone pair of electrons (in the case of tricoordinate atoms), H has the lowest priority. Actually, a lone pair (as on N) is equated to a phantom atom of atomic number zero.

Table 4.1 Atoms and groups with increasing priority

1. H	10. $CH=CH_2$	19. CO_2R	28. OCOR
2. D	11. $C(CH_3)_3$	20. NH_2	29. F
3. CH_3	12. $C\equiv CH$	21. $NHCH_3$	30. SH
4. CH_2CH_3	13. C_6H_5	22. $N(CH_3)_2$	31. SR
5. $CH_2(CH_2)_nCH_3$	14. CH_2OH	23. NO	32. SOR
6. $CH_2-CH=CH_2$	15. $CH=O$	24. NO_2	33. SO_2R
7. $CH_2-C\equiv CH$	16. COR	25. OH	34. Cl
8. $CH_2C_6H_5$	17. $CONH_2$	26. OCH_3	35. Br
9. $CH(CH_3)_2$	18. CO_2H	27. OC_6H_5	36. I

Once the priority order of the ligands is settled, the configurational assignment is made by applying the chirality rule. If one deals with a three-dimensional model, the task is very simple; one only has to look at the molecule from the side opposite to 'd' and determine the order of a → b → c. Difficulty arises since most of the molecules are represented by Fischer projection. The method recommended earlier by Eliel (1962) was to draw the projection always with 'd' at the bottom as shown in Figure 4.6 (bottom row) and then describe a semicircle joining a → b → c the direction of which indicates the configuration. Any Fischer projection can be manipulated either by exchanging two pairs of ligands or rotating a group of three either clockwise or anticlockwise to conform to this requirement. This is demonstrated in assigning the configurational descriptors to D-(+)-glyceraldehyde and L-(−)-serine respectively (Figure 4.9). In both the instances, *R* and *S* correspond to D and L respectively but this does not mean that the two pairs of descriptors are necessarily synonymous (e.g., L-cysteine ≡ *R*-cysteine)*.

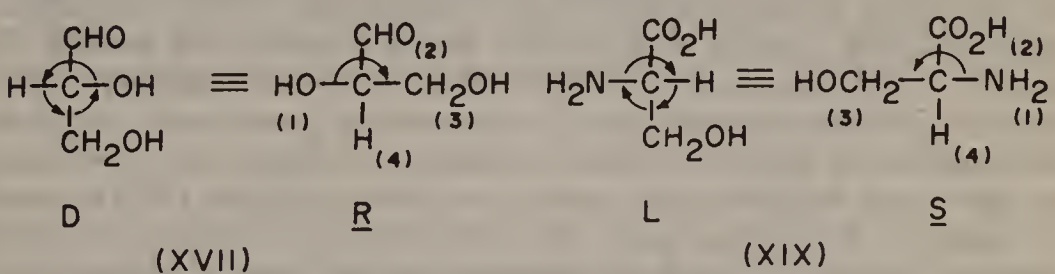


Figure 4.9 Assignment of *R* and *S* descriptors

A number of alternative procedures for assigning *R* and *S* on the basis of Fischer projection have been suggested from time to time. The simplest and most widely accepted one is due to Epling (1982). The procedure, named as "very good" (a mnemonic device for "vertical = good") consists of two operations : fixing up the priority order of the ligands and tracing a semicircle joining a → b → c ignoring 'd', the lowest priority group. If 'd' is on the vertical line in

*In cysteine, CH_2OH of serine is replaced by CH_2SH having higher priority over CO_2H which accounts for the change of CIP nomenclature.

Fischer projection (it does not matter whether it is at the top or at the bottom), the sequence gives the correct descriptor*; if on the other hand, 'd' is on the horizontal line, the sequence gives the wrong answer and the descriptor assigned on this basis should be reversed. The procedure is illustrated with (+)-tartaric acid (XXI), D-(−)-arabinose (XXII), and 3-bromobutan-2-ol (XXIII) (Figure 4.10). In the first two cases, H is on the horizontal line in all the chiral centres and so the descriptors arrived at from the sequence a → b → c have to be reversed. In the third case, H is on the vertical line in both the chiral centres and the sequence a → b → c gives the correct descriptor.

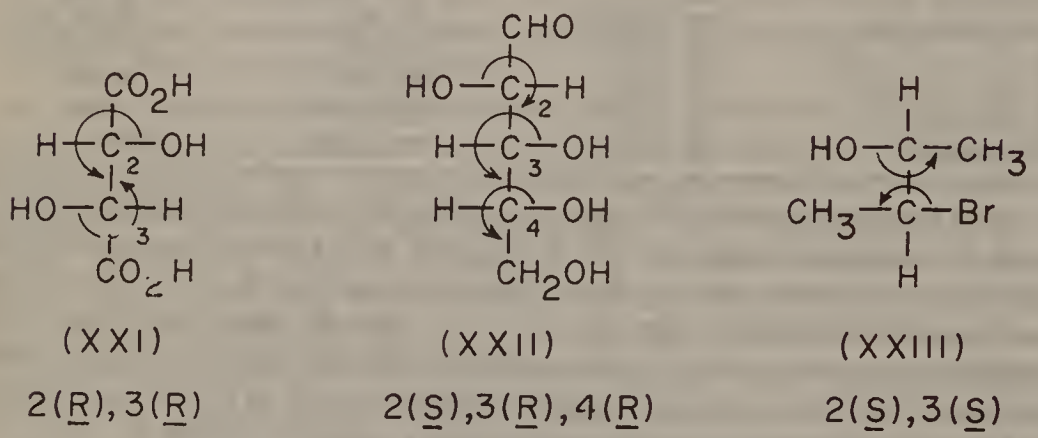


Figure 4.10 Examples of the 'very good' mnemonic

Cyclic molecules such as steroids and terpenes are usually projected on the plane of the paper and hydrogens (or substituents) located below and above the plane are assigned α and β descriptors respectively (α represented by dotted and β by thick lines as shown in 3-cholestanol XXIV in Figure 4.11)—a system recommended by the Chemical Abstract Service (*Pure and Applied Chem.*, 1972, **31**, 283). These descriptors relate to relative configuration and are meaningful if the cyclic system is drawn in an accepted way as in steroids and terpenes. For absolute configuration, each of the chiral centre in the cyclic molecule must be defined by *RS* descriptors following CIP nomenclature. A convenient method has been suggested by Eliel (1985) which is as follows. At any particular chiral centre, one ligand must be clearly in the front (F) or clearly in the back (B). This would be regarded as the reference ligand. The order (clockwise or anticlockwise) of the remaining three can be very easily determined, all three being in the plane of the paper. If this reference ligand is 4/B (lowest locant and in the back), the sequence of the remaining three ligands would give the correct descriptor. So 4/B(+) may be used as a mnemonic [(+) stands for correct]. For other combinations, the numbers will alternate with signs, e.g., 4/B (+), 3/B(−), 2/B(+), 1/B(−) and 4/F(−), 3/F(+), 2/F(−), 1/F(+). For example, the C-10 chiral centre of cholestanol (XXIV) corresponds to 4/F and so although the order 1 → 2 → 3 is

*The method is simply an extension of Eliel's since a Fischer projection is permitted 180° rotation and it is immaterial whether d is put at the bottom or at the top of the projection.

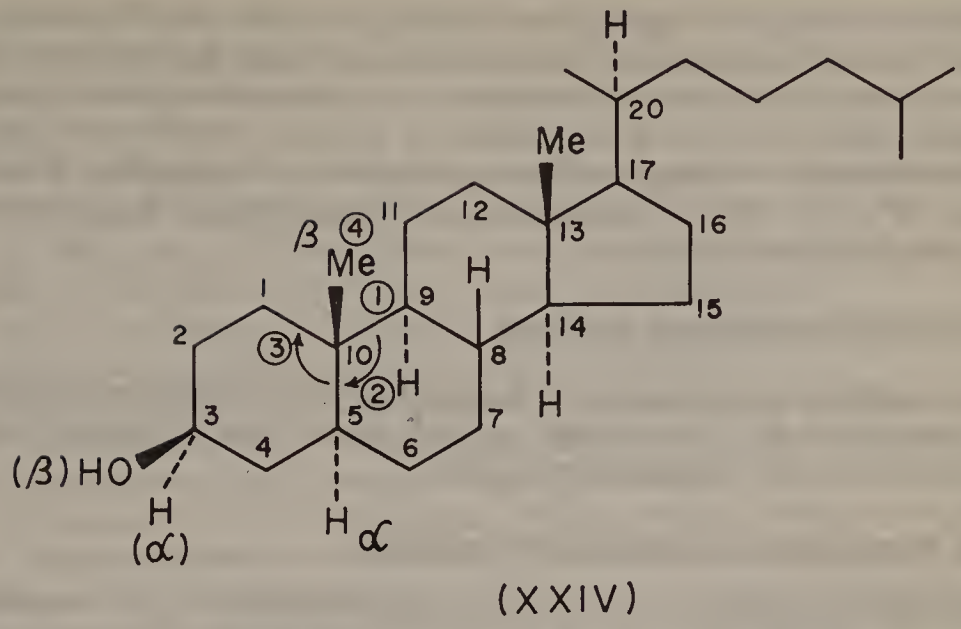


Figure 4.11 2(*S*), 5(*S*), 8(*R*), 9(*S*), 10(*S*), 13(*R*), 14(*S*), 17(*R*), 20(*S*),-Cholestan-3-ol (Numerals in circle represent priority order of substituents at C-10)

clockwise, the configuration is *S*. The configurational labels at the other chiral centres may be worked out likewise.

An algorithmic rule for assigning *R* and *S* descriptors to a chiral centre in cyclic molecules has recently been worked out (Kotera 1986). However, the procedure is difficult to remember and it may be of academic interest only.

4.3.3 R* and S* Nomenclature

The *R,S* nomenclature when applied to a molecule with multiple chiral centres, fixes both the relative and the absolute configuration. Thus 1*R*-bromo-3*S*-chloro-5*R*-fluorocyclohexane refers only to the enantiomer (XXV) (Figure 4.12). It often

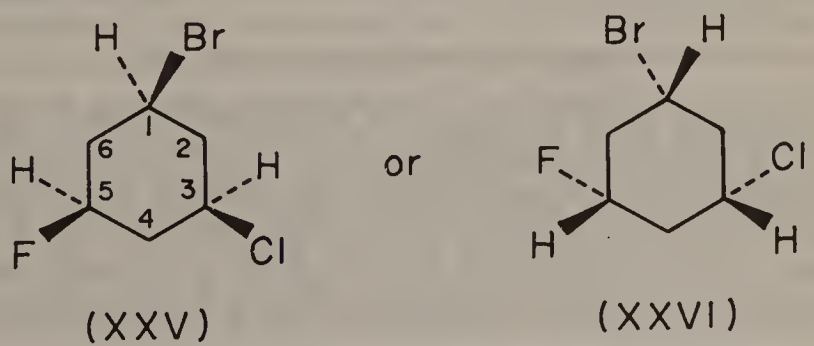


Figure 4.12 *R** and *S** Nomenclature: 1(*R**)-bromo-3(*S**)-chloro-5(*R**)-fluorocyclohexane

happens that pure enantiomer is available with known relative but unknown absolute configuration. In such cases, the *R, S* system of nomenclature is modified as follows (IUPAC Commission 1976). The atoms are numbered such that the

chiral centre having the highest priority ligand, e.g., C-Br in XXV is given the lowest number (lowest locant). The molecule is so written that the lowest chiral locant gets the *R* configuration. Assignment to the other chiral centres is made by the usual method and each of the decriptors is put under asterisk (pronounced as R-star and S-star) to indicate that they represent relative configuration. Thus 1*R**-bromo-3*S**-chloro-5*R**-fluorocyclohexane represents either of the enantiomeric structures (XXV) and (XXVI).

4.3.4 CIP Nomenclature of racemates

For the configurational assignment to racemates, IUPAC Commission recommends the joint use of *R, S* for labeling, a chiral centre, Thus (±)-tartaric acid is designated 2*RS*, 3*RS*-dihydroxysuccinic acid.

4.3.5 Nomenclature of polysubstituted cyclanes

Polysubstituted cyclanes, e.g., cyclopentanes, cyclohexanes etc. exist in a number of stereoisomers (diastereomers and enantiomers) depending on the number and nature of the substituents. The disubstituted cyclanes give two diastereomers which can be conveniently and unambiguously described as cis and trans isomers, e.g., *cis*- and *trans*-2-methylcyclohexanols (XXVII) and (XXVIII) (Figure 4.13). Each of the diastereomers in turn gives two enantiomers which can be named, following the *R,S* nomenclature, as *R,S* and *S,R* for the cis and *S,S* and *R,R* for the trans isomer (use 4/B rule) as shown in the Figure.

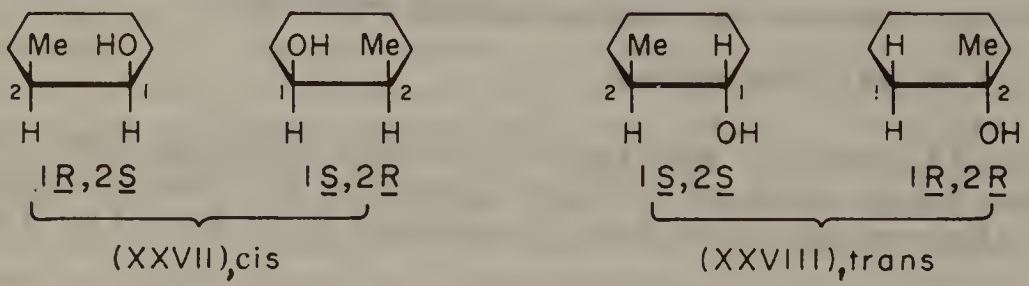


Figure 4.13 Disubstituted cyclohexanes

Difficulty arises when the number of substituents increases, e.g., dimethyl-cyclohexanols (XXIX)-(XXXII) (Figure 4.14). The prefixes, cis and trans are no longer unambiguous and, if applied without any reference, lead to confusion; thus compound (XXIX) may be called cis with respect to the two methyl groups but trans with respect to the 4-methyl and 1-hydroxyl group. Since many of these compounds are achiral (meso) (XXIX-XXXI), the *R, S* nomenclature also become

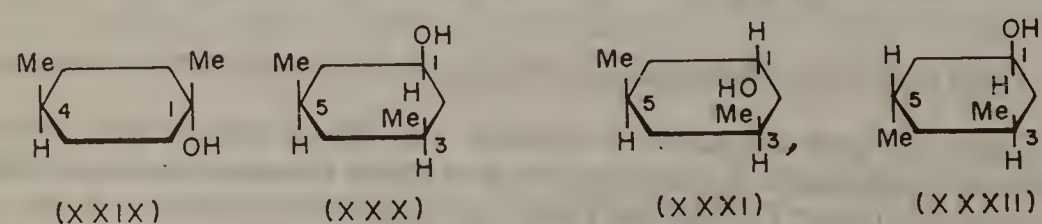


Figure 4.14 Polysubstituted cyclohexanes

inapplicable. Moreover, the steric relationship does not become immediately apparent from such nomenclature. To obviate this difficulty, a method of nomenclature known as Beilstein system (see Eliel 1971) has been adopted which is as follows:

(*i*) A reference group denoted by symbol '*r*' is specified with respect to which the other substituents are described as cis or trans.

(*ii*) The *r*-group is so chosen that it is attached to the lowest locant (the lowest numbered ring member) according to IUPAC rules (vide supra).

(*iii*) If two ligands are attached to the lowest locant, that one is selected as *r*-group which has preference in the IUPAC nomenclature.

(*iv*) When there are two constitutionally equivalent pathways of going around the ring starting from the lowest locant, that giving the cis attachment to the second substituent (the first being the *r*-group) is chosen.

Following the rules, the compounds (XXIX), (XXX), (XXXI), and (XXXII) are named respectively as 1,*trans*-4-dimethylcyclohexan-*r*-1-ol, (4-Me is trans tc OH), *cis*-3,*cis*-5-dimethylcyclohexan-*r*-1-ol, *trans*-3,*trans*-5-dimethylcyclohexan-*r*-1-ol, and *cis*-3-*trans*-5-dimethylcyclohexan-*r*-1-ol [according to rule (iv), the carbon bearing cis methyl is counted as 3]. The common practice is to abbreviate the names, by replacing *cis* and *trans* by *c* and *t* respectively.

The structure (XXXII), although chiral, has *S*-configuration both at C-3 and at C-5 which makes it impossible to give a configurational descriptor to C-1. In fact, C-1 is chirotopic (as judged by local symmetry) but non-stereogenic (exchange of H and OH does not give any new stereoisomer). On the other hand, C-1 in XXIX-XXXI is achirotopic but stereogenic (see discussion under trihydroxyglutaric acid).

4.4 E and Z Nomenclature

It has been shown that olefinic compounds like 2-butene can exist in two diastereomeric forms which are called cis and trans isomers. The necessary and sufficient condition for this type of isomerism is that 'a' and 'b' in Cab=Cab must be non-equivalent. In the case of Cab=Nx, (or Nx = Nx), the missing substituent is the lone pair of electrons on nitrogen. Since this isomerism owes its existence to the presence of a π-bond, it has been called π-diastereomerism (Pierre 1971) to distinguish it from σ-diastereomerism exhibited by cyclic compounds*. The π-diastereomers are two-dimensional molecules (if one ignores the geometry of the 'a' and 'b' groups), possess a plane of symmetry, and therefore are achiral.† On the other hand, the σ-diastereomers are three dimensional and may be chiral. For molecules of the type, Cab=Cab or Cab=Cac, the terms 'cis' and 'trans' are adequate and unambiguous. But if three or four of the substituents are different, this nomenclature leads to ambiguity and sometimes to total confusion.

An easy solution to the problem is provided by arranging the pair of ligands at each trigonal carbon in CIP sequence. Then if the groups of higher priority are on the same side, the configuration is seq-cis; if they are on the opposite sides, the

*This terminology, however, is used very rarely (Testa 1979).

†Provided 'a' and 'b' are achiral.

configuration is seq-trans (CIP 1966). Thus if a precedes b and a′ precedes b′, the configuration of the compounds (XXXIII) and (XXXIV) (Figure 4.15) are seq-cis and seq-trans respectively. Later, the system has been modified (Blackwood et al 1968), the two terms being replaced by two shorter symbols, *Z* (from the German *zusammen* meaning 'together') and *E* (from the German *entgegen* meaning 'across') which are used as prefixes to the olefins. According to this system, β-methylcinnamic acid (XXXV) is called *E*-3-phenylbut-2-enoic acid (here Ph and CO_2H groups are fiducial*). The previously called *cis*-1,2-dichlorobromoethene (XXXVI) is now known as *E*-1-bromo-1,2-dichloroethene ,which goes to prove that *E* and *Z* do not always correspond to trans and cis.

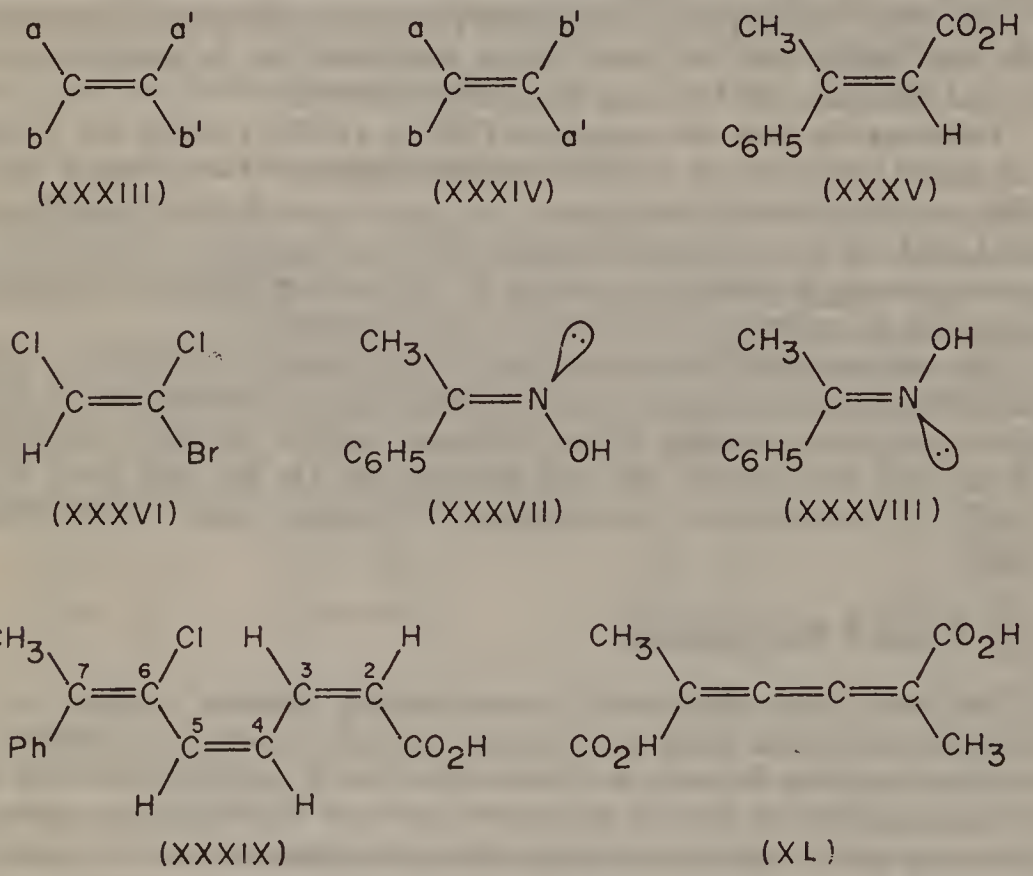


Figure 4.15 Examples of *E* and *Z* nomenclature

This system leads to a great simplification in the nomenclature of the diastereomeric oximes for which the (often ambiguous) terms 'syn' and 'anti' were previously coined. Thus the syn (XXXVII) and the anti (XXXVIII) oximes of acetophenone are now called *Z*- and *E*-isomers respectively.

In the case of compounds, containing more than one non-cumulated (belonging to different carbon atoms) double bonds, the number of π-diastereomers (2^n where n is the number of non-equivalent double bonds) increases. The descriptors *Z* and *E* can be applied to each diastereogenic unit. Thus the triene (XXXIX) is named as 7-phenylocta-2*Z*,4*Z*,6*E*-trienoic acid. Cumulenes with an odd number of cumulated (consecutive) double bonds with two = Cab as terminal groups display

*The word 'fiducial' means 'fixed basis of reference'.

π-diastereomerism and *E*, *Z* nomenclature is applicable to them also. Thus the cumulene (XL) is an *E*-isomer.

4.5 Molecules with a centre of chirality and simple axes of symmetry (C_n)

Centrally chiral molecules of the type, Cabcd (a, b, c, and d are achiral) are completely asymmetric (point group C_1). The symmetry increases as two or more of the ligands become equivalent as in the series: Caabc, Caabb, Caaab, and Caaaa (see Table 4.2). These molecules are achiral since they possess one or more σ planes. If the planes could be eliminated—a process called desymmetrisation—the resultant molecules would be chiral containing one or more C_n axes (except for Caabc) and would belong to point groups other than C_1 (which means that an sp^3 stereogenic atom need not always be asymmetric).

Table 4.2 Symmetry of tetracoordinate centre

Type	Symmetry elements	Point groups
Cabcd	none	C_1
Caabc	σ	C_s
Caabb	$C_2 + 2\sigma$	C_{2v}
Caaab	$C_3 + 3\sigma$	C_{3v}
Caaaa	$4C_3 + 3C_2 + 6\sigma$	T_d

The hypothetical molecule (XLI) belongs to the type caabb and can be desymmetrised by pairwise bridging the unlike ligands to give the spiro-hydantoin (XLII) (Figure 4.16). The process destroys the two σ planes but retains the C_2 axis which passes through the chiral centre and bisects the angle between the two rings. The molecule now belongs to point group C_2. In order to assign configurational nomenclature to the molecule, one starts with either of the rings (both are

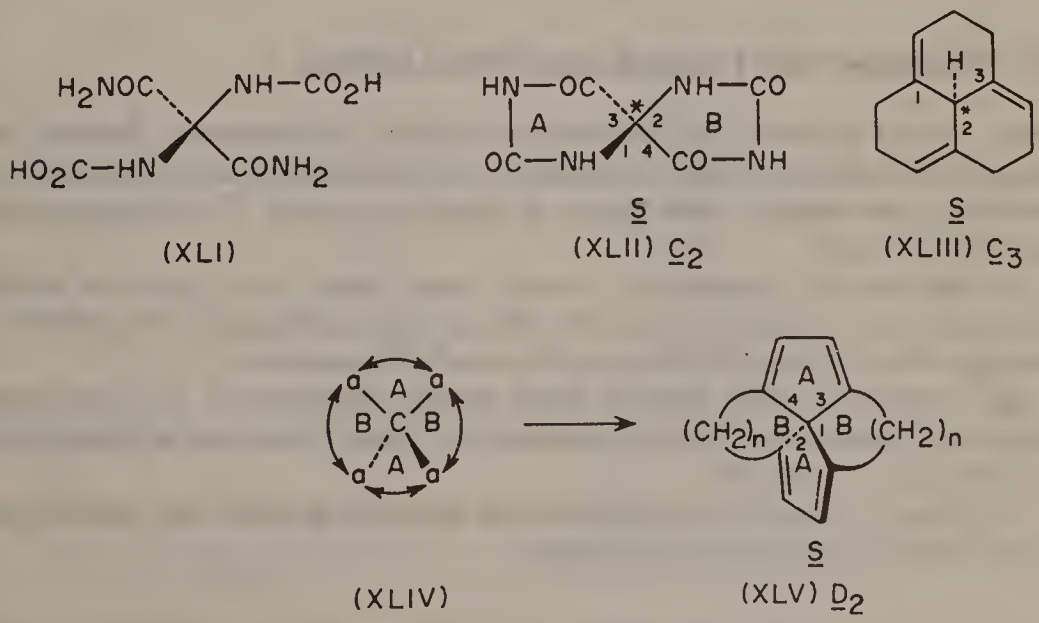


Figure 4.16 Desymmetrisation scheme

equivalent), say ring A, and assign priority 1 to NH (the sequence rules). Priority 2 is then assigned to NH of the ring B. Priority 3 is given to CO in ring A which also contains 1-NH, since exploration from it outwards and round the ring leads to the more preferred 1-NH while similar exploration from CO in ring B leads to the less preferred 2-NH. The configuration of the particular enantiomer of the spiro-hydantoin (XLII) is thus *S*.

An achiral molecule of the type, Caaab can be desymmetrised by connecting the identical ligands by directed bridges, i.e., bridges with different ends pointing either clockwise or anticlockwise. This eliminates the σ planes but retains the C_3 axis. The hexahydrophenalene (XLIII) (as yet a hypothetical molecule) serves as an example. The molecule possesses a chiral centre and belongs to point group C_3. In order to fix its configuration, any of the equivalent ligand is given priority 1. Priority 2 goes to that ligand from which outward exploration along the route of highest precedence (i.e., along the double bond) leads to number 1. The third ligand constituting the ring system has priority 3 and hydrogen is numbered 4 which settles the configuration as *S*. If H is replaced by an atom of higher atomic number than that of carbon, the symbol will be reversed.

Finally, the molecule of the type, Caaaa (T_d symmetry) can be desymmetrised by connecting the ligands with two pairs of different and symmetrical bridges (A and B) as shown in the scheme (XLIV). The molecules known as vespirenes (XLV, n = 6-8) illustrate the point. They are actually double spirans, C* being common to two pairs of equivalent rings. The original 6σ planes in XLIV are destroyed and so also the four C_3 axes. Only the three C_2 axes directed along x, y, and z coordinates remain. The molecules contain a centre of chirality and belong to point group D_2*. To determine the chirality, any of the ligand, say the lower right hand one is numbered 1, then the one which shares the unsaturated ring A with it is numbered 2, and that which shares the second ring B with it is numbered 3. The configuration is thus *S*.

4.6 Molecules with two and more chiral centres

Many natural products such as steroids, terpenes, carbohydrates, proteins, and alkaloids contain two or more chiral centres. An understanding of stereochemistry of molecules with multiple chiral centres is, therefore, essential. The following points are worthy of note:

(*i*) Addition (or creation) of a new chiral centre to a molecule already containing one or more always gives rise to new diastereomers the number of which doubles for each addition except in cases of degeneracy.

(*ii*) In molecules with multiple chiral centres, diastereomers and enantiomers occur side by side. Depending on symmetry, any diastereomer can be either achiral or chiral (and so resolvable).

(*iii*) Special systems of nomenclature are needed to designate two diastereomers which differ in the relative configuration.

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*It may be noted that if ring A = ring B, the molecule would have been an achiral one with D_{2d} symmetry.

These points are discussed here with reference to molecules containing chiral centres (stereocentres) only. The same principle, however, applies to compounds containing other elements of chirality, e.g., axial, planar, and helical chirality and any combination thereof.

4.6.1 Constitutionally unsymmetrical chiral molecules

A molecule containing two or more chiral centres is constitutionally unsymmetrical if the two end groups (in the case of acyclic molecules) are non-equivalent as in D-erythrose (XLVI) and in D-threose (XLVII) (Figure 4.17) or if each of the chiral centres is substituted differently as in 3-bromo-2-butanols (XLVIII) and

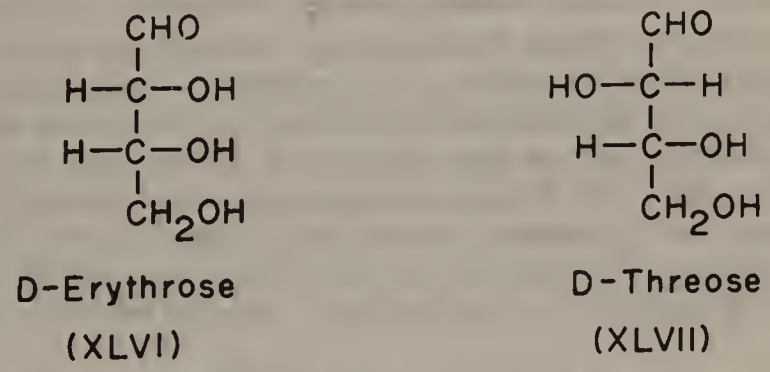


Figure 4.17 D-Erythrose and D-threose

(XLIX) (Figure 4.18) and in 1-bromo-2-hydroxycyclobutane (LV) (Figure 4.23). Each chiral centre is capable of existing in two configurations, *R* and *S* and the total number of stereoisomers is thus 2^n where n is the number of chiral centres. Alternatively, one may express the number of stereoisomers as $2^{(n-1)}$ (±)-pairs (or

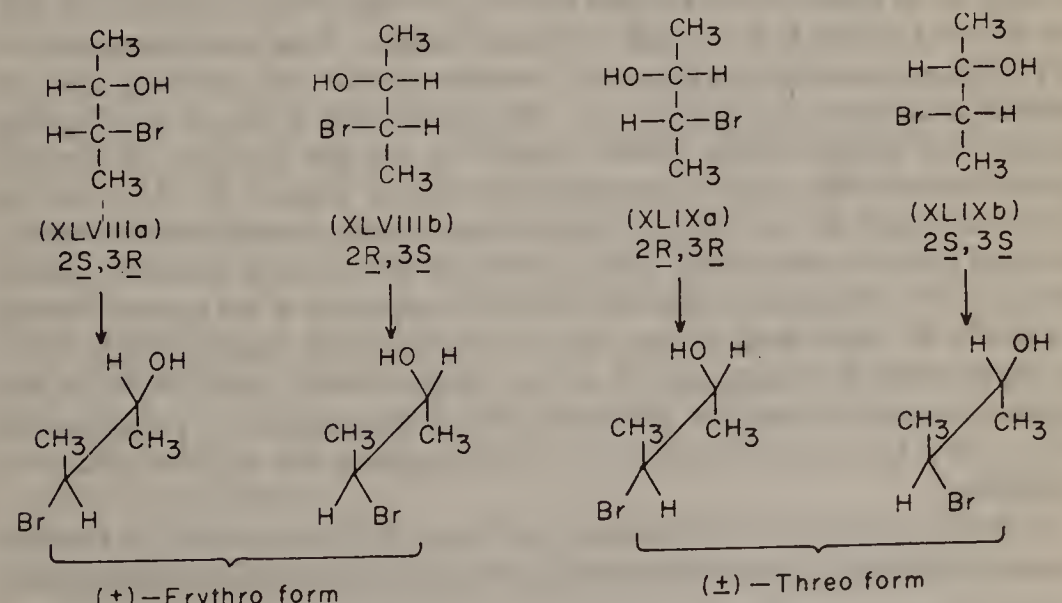


Figure 4.18 Stereoisomers of 3-bromo-2-butanol

racemates) since they are enantiomeric in pairs. Any stereoisomer in the series will have one enantiomer and 2^n-2 diastereomers. Two diastereomers can differ in the configuration of a single chiral centre when they are called *epimers* or in the configuration of as many as n-1 chiral centres but not in *all* in which case they are enantiomers. D-erythrose and D-threose are epimers and so are 3α-hydroxy- and 3β-hydroxycholestanes (Figure 4.11). Compounds with two adjacent chiral centres are used extensively in the study of reaction mechanisms and conformational analysis and discussion here is mainly confined to them.

A compound containing two non-equivalent chiral centres gives rise to four stereoisomers as two diastereomeric (±)-pairs, e.g., (±)-erythrose and (±)-threose (Figure 4.17, only one enantiomer of each is shown). The diastereomers differ in their relative stereochemistry (geometry) whereas the enantiomers have identical geometry but differ in their topography. Although the four stereoisomers can be uniquely defined by assigning *R, S* descriptors to each chiral centre, it is desirable to give some stereochemical notation to the diastereomers which makes their relative stereochemistry at once obvious as in erythrose (the two OH groups are on the same side in the Fischer projection) and threose (the two OH groups are on different sides), similar to cis and trans isomers in cyclic compounds. Several such systems of notation (not less than ten) are now available including a recent one by Brewster (1986). They are briefly discussed below (see also Brook 1987).

1. Erythro and **threo.** In the oldest system, the diastereomers are represented as erythro and threo in analogy with erythrose and threose. The diastereomer in which two like (or similar) groups are on the same side of the Fischer projection (as the two OH groups in erythrose) is called the erythro form whereas the diastereomer in which two like (or similar) groups are on opposite sides of the Fischer Projection (as the two OH groups in threose) is called the threo form. The two diastereomeric 3-bromo-2-butanols (XLVIII) and (XLIX), each shown as (±)-pair (a, b) (Figure 4.18) are thus erythro and threo isomers respectively (the two H's on C-2 and C-3 are used as fiducial groups). Since such molecules are very often represented by sawhorse or Newman formula, the definition may be modified to conform to such structures. The erythro form is the one in which the two terminal groups (in the Fischer projection) and the two like (or similar) groups have the same relative stereochemistry (anti or gauche); the threo form is the one in which the two pairs of groups have different relative stereochemistry (anti and gauche or vice versa). This is evident in the sawhorse formulae* shown in Figure 4.18. The system works very well for compounds of the general formula R-Cab-Cac-R′ which have at least one pair of substituents matched (Eliel 1962) but falters badly for compounds of the type R-Cab-Ccd-R′ which have no two substituents properly matched. One has to decide the similarity of groups on the basis of steric bulk, state of oxidation, or electronegativity and the system becomes ambiguous.

2. Pref and **parf.** The diastereomers with two chiral centres may be formally regarded to form by the combination of two trigonal faces (two-dimensionally

*Each of the four stereoisomers exists in three distinct conformations (Chapter 3); only the ones with the terminal methyl groups anti are shown.

chiral) represented by the two planes in Figure 4.19. The faces are designated *Re* if the three ligands a, b, and c or x, y, and z arranged in their priority order (CIP)

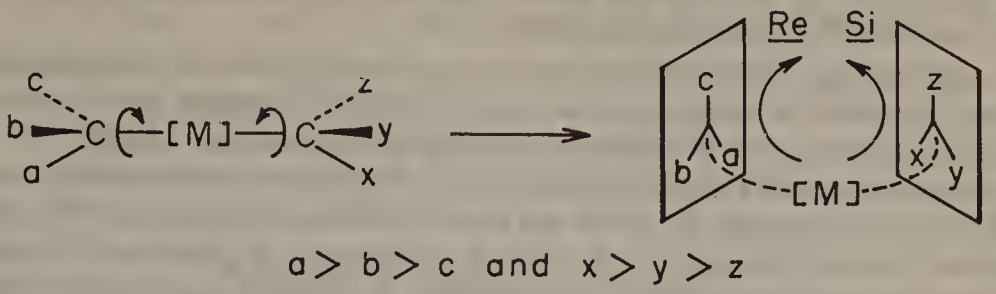
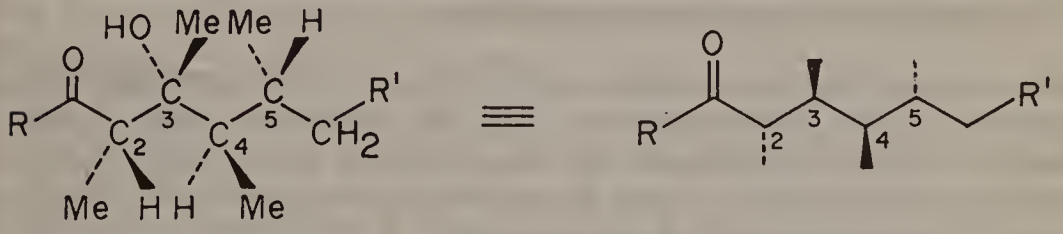


Figure 4.19 Pref (and Parf) notation

trace a clockwise path and *Si* if they trace an anticlockwise path as shown (see Chapter 6 for *Re* and *Si*). Carey and Kuehne (1982) have used the prefix pref (priority reflective) for the diastereomer formed by the combination of two unlike faces (*Re-Si* or *Si-Re; Re* and *Si* are reflective like *R* and *S*) and the prefix parf (priority antireflective) for the diastereomer formed by the combination of two like faces (*Re-Re* or *Si-Si*). The diastereomer shown in Figure 4.19 is pref (*Re-Si*) by this definition. Earlier, Noyori et al (1981) used threo in place of parf and erythro in place of pref. The system is general, conformation independent, and may be used even when the two chiral centres are separated by achiral atom or atoms embodied in [M].

3. Like (*l*) and **unlike** (*u*). Prelog et al (1982) have proposed a very similar system for configurational designation of molecules with multiple chiral centres by using *l* (like) and *u* (unlike) for diastereomers formed by the combination of radicals of like chirality (*R*R**) and of unlike chirality (*R*S**)* respectively for each adjacent pair of chiral centres as illustrated in Figure 4.20. The structure in the Figure is represented by the prefix *ull* meaning unlike, like, and like. The



2*S*, 3*R*, 4*R*, 5*R* (CIP)

2,3-*anti*-3,4-*syn*, 4,5-*anti*- (Masamune)

u l l (Prelog)

S(2*l*, 3*u*, 4*u*, 5*u*) (Brewster)

Figure 4.20 Stereochemical notations for compounds with multiple chiral centres

R*R and *R*S** refer to relative stereochemistry (see Section 4.3.3).

nomenclature has been extended to define the steric course of diastereoselective reaction using *lk* and *ul* (instead of *l* and *u*) for approaches of reactants with like faces (or groups) as *Re*Re** and *Re*R** and with unlike faces (or groups) as *Re*Si** and *Re*S** respectively (see Chapter 13).

4. Anti and syn. Aldol chemists have used a simple system of nomenclature specially adaptable to aldol-type compounds containing multiple chiral centres. The longest carbon chain is written in a zigzag fashion (also see Chapter 13). If two substituents (usually alkyl and hydroxyl) on the adjacent chiral centres are on the same side of the plane, the prefix syn is used; if they are on opposite sides, the prefix anti is used (Masamune et al 1980) as illustrated in the right hand formula (Figure 4.20). Heathcock (1984) has used erythro for syn and threo for anti using the same system but the practice is better to be avoided (too many erythro's and threo's with different meanings are confusing).

5. Brewster's system. Recently Brewster (1986) has suggested a system of nomenclature 'that balances and distinguishes geometry and topography' by blending Prelog's *l, u* notation with *R, S* specification of CIP which is best explained with the help of the example in Figure 4.20. The configurational descriptor of the lowest locant (here *S* of C-2) is placed outside the bracket while inside the bracket, are placed *l* and *u* notations for each of the chiral centres. The descriptor *S* is taken as an external reference to which the chirality of each centre is matched. C-2 is like itself and so is designated *l* and the others are labeled accordingly. Thus the molecule in the Figure is defined by *S*(2*l*, 3*u*, 4*u*, 5*u*) and its enantiomer by *R*(2*l*, 3*u*, 4*u*, 5*u*)* which means that the nomenclature depicts the chirality as a property of the whole molecule. Advantages of this system are: Topography at each centre is readily recoverable, a racemic mixture may be represented as *RS*(2*l*, 3*u*, 4*u*, 5*u*); a partially resolved mixture, say consisting of 90*R* and 10*S*, is represented as [90*R*, 10*S*] (2*l*, 3*u*, 4*u*, 5*u*); any centre of unknown chirality (say C-4) may be indicated by putting an *x* as in *S*(2*l*, 3*u*, 4*x*, 5*u*).

4.6.2 Constitutionally symmetrical chiral molecules

Acyclic molecules containing multiple chiral centres are called constitutionally symmetrical if chiral atoms equidistant from the geometrical centre of the molecules are identically substituted. The two end groups of such molecules are necessarily equivalent. When n is even, the geometrical centre is not located at any atom but at the centre of a bond and the number of stereoisomers is given by $2^{(n-1)} + 2^{(n-2)/2}$. When n is odd, the geometrical centre rests on an atom and the number of stereoisomers is given by $2^{(n-1)}$. The reason for lesser number of stereoisomers ($< 2^n$) is due to the fact that some of the diastereomers are achiral (meso) and do not give enantiomers and some are degenerate. In the acyclic system, only two such molecules, namely, 2,3-dihydroxysuccinic acid (tartaric acid) (n = 2) and 2,3,4-trihydroxyglutaric acid (n = 3) are discussed.

(*a*) **2,3-Dihydroxysuccinic acid**. 2,3-Dihydroxysuccinic acid exists in two enantiomeric forms (La) and (Lb) and one meso form (LI) (Figure 4.21), the total

*Since the external reference has changed from *S* to *R*, the *l, u* notations of the chiral centres remain unchanged in the enantiomer.

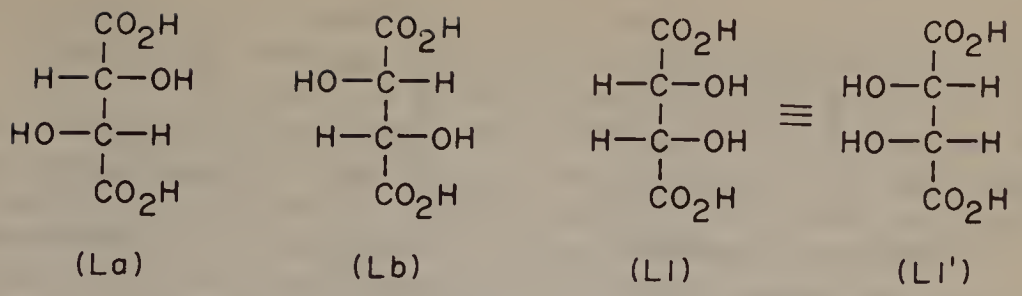


Figure 4.21 2,3-Dihydroxysuccinic acid

number of stereoisomers being three [$2^{(2-1)} + 2^{(2-2)/2}$]. The dextro form has the *R,R*, the levo form the *S,S*, and the meso form the *R,S* or *S,R* configuration. The dextro and the levo forms are diastereomeric with the meso form and differ substantially from it in physical and chemical properties. The meso form (LI) is superposable with its mirror image (LI'). A rotation of 180° makes the two structures indistinguishable. The meso form may be desymmetrised by preferentially esterifying one of the carboxylic groups. All the conformations of the two enantiomers are chiral. On the other hand, the meso form (LI) has an achiral conformer with a centre of inversion and two chiral conformers with *P* and *M* helicity respectively (see Chapter 5). Because the last two are equally populated, the molecule possesses statistical symmetry, and hence is optically inactive.

It is worth noting that the dextro and the levo isomers in the Fischer projection have their horizontal groups so disposed that equivalent groups are on opposite sides and in that respect, may be regarded as the counterparts of threo isomers encountered in constitutionally unsymmetrical molecules. The meso form has all the equivalent groups eclipsed (i.e., on the same side) and thus bears analogy with the erythro isomers.

(*b*) 2,3,4-**Trihydroxyglutaric acid.** 2,3,4-Trihydroxyglutaric acid, a constitutionally symmetrical molecule has three chiral centres and exists as four [$2^{(3-1)}$] stereoisomers. Two of them (LIIa) and (LIIb) (Figure 4.22) are enantiomers and the remaining two (LIII) and (LIV) are meso forms being diastereomeric with each other and also with the two enantiomers. The meso forms can be desymmetrised by esterifying any of the two equivalent carboxyl groups thus giving two pairs of enantiomers. The two carboxylic groups in the two active compounds (LIIa) and (LIIb) are non-equivalent and so monoesterification of each gives two (±)-pairs of diastereomers. Thus the total number of half esters of trihydroxyglutaric acid is eight (2^3) corresponding to a constitutionally unsymmetrical structure with three chiral centres. There are some long-standing ambiguties regarding the status of the C-3 centre in these molecules which are discussed below in the context of a recent observation of Mislow and Siegel (1984).

The two enantiomeric structures (LIIa) and (LIIb) are considered first. The chiral grouping, $-CH(OH)CO_2H$ can be designated by either *R* or *S* and accordingly, the enantiomers (LIIa) and (LIIb) are abbreviated as A and B shown at the bottom of Figure 4.22. The C-3 centre is thus achiral, two of the ligands, *R,R* in LIIa and *S,S,* in LIIb being identical, and no configurational assignment (*R* and *S*) can be given to C-3. Moreover, C-3 is also non-stereogenic; the interchange

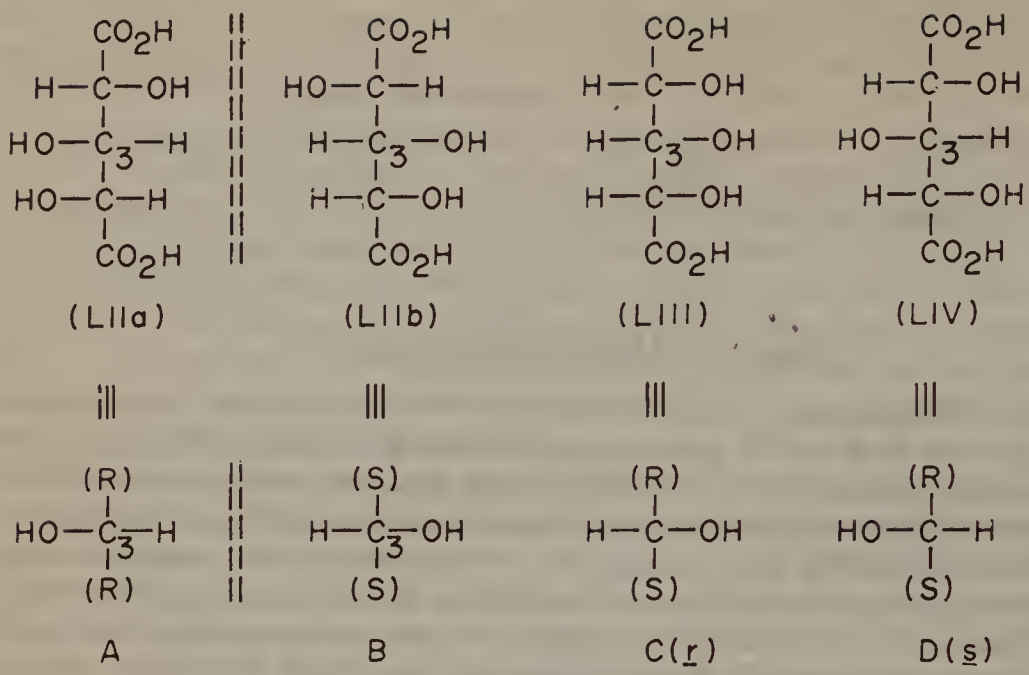


Figure 4.22 2,3,4-Trihydroxyglutaric acid

of H and OH at this centre followed by 180° rotation keeps the two structures (LIIa,b) unchanged.* i.e., (+)-form remains (+) and (−)-form remains (−). So far there is no conflict with the concepts of classical stereochemistry. The molecules (LIIa,b) contain two more chiral centres (C-2 and C-4) which make them chiral as a whole (no reflection symmetry) and are similar to the two enantiomers of tartaric acid if one ignores the achiral C-3 grouping. As pointed out by Brewster (1986), this shows 'that chirality does not reside in stereogens and that it is the chiral sense of the whole molecule that matters'.

Recently, Mislow and Siegel (1984) have suggested that stereogenicity and chirotopicity are two distinct characters of an asymmetric atom which happen to overlap and are most closely associated in organic stereochemistry. Stereogenicity is dependent on bonding connectivity but chirotopicity is quite independent of it and is determined only by local symmetry (Anet and Mislow 1983). A chirotopic atom is one which resides in a chiral environment. Thus all the five atoms in bromochlorofluorobutane (CHFClBr) are chirotopic although only the C atom is a stereogen. Judged from local symmetry, C-3 in LIIa,b is chirotopic but it is non-stereogenic, i.e., in this case, the two properties of a regular asymmetric tetrahedral centre are delinked. Since *R* and *S* relate to stereogenicity and not to chirotopicity, these descriptors are not applicable here.

The case of the two meso forms (LIII) and (LIV) is more complex. According to common definition, C-3 in both is chiral (see the abbreviated structures C and D). The centre is also stereogenic: interchange of ligands generates diastereomers (actually converts one into the other). Judged from local symmetry, however, C-3 is achirotopic (presence of a σ plane). The situation here is just the opposite to that

*This may also be seen in the abbreviated structures : exchange of a pair of ligands at C_3 either in A or in B restores the original structure (a topomerisation process).

encountered with the active isomers. In the active isomers (LIIa,b), C-3 is chirotopic but non-stereogenic while in the meso isomers (LIII) and (LIV), C-3 is achirotopic but stereogenic—a fact which once again proves that stereogenicity and chirotopicity are two distinct properties and can be delinked. Consistent with its stereogenic property, C-3 in both the compounds can be given configurational descriptors: *r* to LIII and *s* to LIV (CIP system). The use of lower case symbols indicates that the two molecules are invariant to reflection. Even though the C-3 centre is made truly chiral by esterifying 3-OH with an optically active acid, e.g., *S*-lactic acid, the configurational descriptors *r* and *s* remain invariant to reflection.

Such an achirotopic but stereogenic centre is called pseudoasymmetric (in classical stereochemistry) and is designated as $Ca^{+}a^{-}bc$ (Hirschmann and Hanson 1974), a^{+} and a^{-} representing two enantiomorphous ligands. Cyclic molecules such as 1,3-disubstituted cyclobutanes and the three dimethylcyclohexanols (XXIX)—(XXXI) (Figure 4.14) also illustrate this category, i.e., they have achirotopic but stereogenic centre or centres.

A constitutionally symmetrical molecule with four chiral centres exists as ten stereoisomers consisting of two meso forms and four (±)-forms; see, for example, 2,3,4,5-tetrahydroxyadipic acids (Eliel 1962). The question of pseudoasymmetric centre arises only when n is odd, there being one pseudoasymmetric centre and (n−1) asymmetric centres in such molecules.

4.6.3 Stereoisomerism in cyclic compounds

Stereochemistry of cyclic compounds with two or more chiral centres is basically the same as that of the acyclic. For constitutionally unsymmetrical molecules such as cholestanol (XXIV, p 55) (with nine chiral centres) and 1-bromo-2-hydroxycyclobutane (with two chiral centres), the number of stereoisomers is usually given by 2^n. Thus the latter exists as two diastereomers, cis (LV) and trans (LVI) (Figure 4.23), both being resolvable. However, cyclic compounds, in general, possess

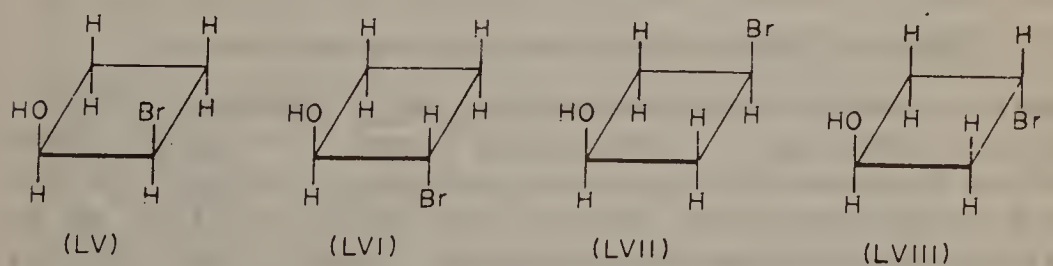


Figure 4.23 Stereoisomerism in cyclic systems

increased symmetry and exhibit lesser number of stereoisomers than their acyclic counterparts. For an example, 1-bromo-3-hydroxycyclobutane with two non-equivalent chiral centres exists only in two (diastereomeric) meso forms (LVII) and (LVIII). Here the C-1 and C-3 centres are achirotopic but stereogenic. Since their stereogenicity is interlinked, together they form a stereogenic dyad (see Brewster 1986).

An interesting example is provided by the naturally occurring inositol (hexahydroxycyclohexane) which contains six equivalent chiral centres. It exists in eight

diastereomeric forms only one of which is resolvable into an enantiomeric pair (LIX and LIX′) (Figure 4.24). The remaining seven isomers are meso having one or more σ planes. One (LXI) shown in the Figure has an inversion centre and three σ planes. Other cyclohexane derivatives of the general formula $C_6X_6Y_6$ show similar stereochemistry e.g., hexachlorocyclohexane, the well known insecticide. Their conformations will be discussed in Chapter 10.

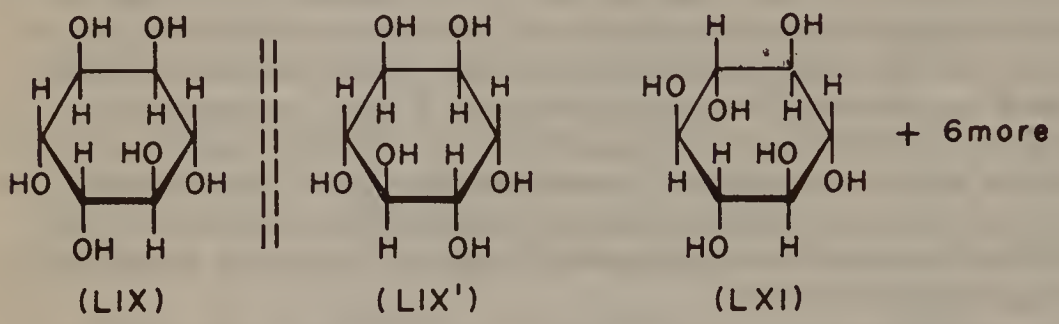


Figure 4.24 Stereoisomers of inositol

In the bridged ring compounds (Chapter 11), there is yet another factor which sometimes restricts the number of stereoisomers: certain diastereomers cannot form due to steric reason. Thus camphor (LXII) (Figure 4.25) in which C-1 and C-4 are

Figure 4.25 Stereoisomerism in some bridged ring compounds

joined by a methylene bridge exists only as a pair of enantiomers although it contains two chiral centres. A more complex example is provided by twistane (LXIII) of D_2 symmetry which contains four equivalent chiral centres (*) but exists only in two enantiomeric forms. The hydrocarbon, adamantane (as LXIV, Me, Br, and CO_2H replaced by H) has a highly symmetrical structure (having T_d symmetry like CH_4). When, however, all the four bridgehead substituents are different as in LXIV, it becomes completely asymmetric (C_1 point group). But inspite of the fact that it contains four non-equivalent chiral centres, it exists only as a (±)-pair. The four substituents form a regular tetrahedral arrangement and the chirality of the molecule may be referred to a centre (represented by a dot) in the unoccupied space of the adamantane frame*. This shows that the centre of chirality in a molecule may not necessarily lie on an atom. This is also true for twistane (LXIII) although not so obvious.

*The stereogenicity of the compound depends on the four atoms, C-1, C-3, C-5, and C-7 simultaneously which together form a stereogenic (or chirogenic) tetrad.

Finally, a completely different type of stereoisomerism is exhibited by bridged ring compounds in which the two bridgehead atoms are joined through three large rings as shown for bicyclo[8.8.8]hexacosan (for nomenclature, see Chapter 11). The compound can exist in three diastereomeric forms (LXV), (LXVI), and (LXVII) (Figure 4.26). In the isomers, the two bridgehead H's are both 'in' (LXV),

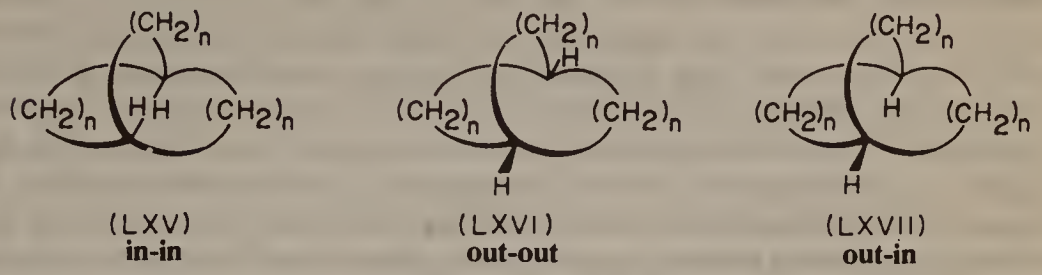


Figure 4.26 'Out-in' isomerism

both 'out' (LXVI), or one 'in' and the other 'out' (LXVII). This type of stereoisomerism is called 'out-in' isomerism (Park and Simmons 1972). Here also, the stereogenicity of the two bridgehead atoms (which are achirotopic) is interlinked and together they form a stereogenic dyad. Depending on the nature of the rings, the two bridgehead atoms may be chiral and so may lead to enantiomerism.

4.7 Summary

1. When four different achiral ligands are bonded to a central atom making a regular tetrahedral arrangement, a five-centre chiral simplex is produced which belongs to C_1 point group and exhibits enantiomerism. The central atom is called a chiral centre. Exchange of a pair of groups reverses the chiral sense of the centre and gives new stereoisomer: an enantiomer if there is no other chiral centre and a diastereomer if there is a second chiral centre. Chirotopicity and stereogenicity are two distinct aspects of an asymmetric centre; the former is defined by its local symmetry and the latter by its bonding connectivity. Examples have been given (in later sections) showing that a compound can be chirotopic but non-stereogenic; alternatively, a compound can be achirotopic but stereogenic. In the majority of cases, however, these two properties are closely linked together in organic stereochemistry.

2. In addition to tetrahedral carbon, various tetracoordinate atoms such as nitrogen, silicon, phosphorus, and arsenic may provide tetrahedral chiral centres with varying degree of configurational stability. Molecules with tricoordinate chiral atoms such as trivalent nitrogen, phosphorus, and sulphur are also well known. A lone pair of electrons on the atom serves as the fourth substituent. Racemisation can occur through inversion at the chiral centre which is relatively easy for the first row of elements but is increasingly difficult for elements in the second and third rows of the periodic table.

3. A chiral compound can be recognised only by establishing a diastereomeric relationship with another chiral substrate or environment. The usual method is to determine the optical rotation, an observable property of a chiral compound, by a polarimeter. The plane-polarised light being constituted of two oppositely circularly

polarised components serves as a chiral environment which interacts differently with the two enantiomers. Optical rotation of a compound is usually expressed as specific rotation $[\alpha]$ or molecular rotation $[M]$ and can be determined with high precision.

4. Two systems of configurational nomenclature, one due to Fischer-Rosanoff using D and L descriptors and the other due to Cahn-Ingold-Prelog (CIP) using *R* and *S* descriptors have been discussed. The former has the advantage of systematically correlating certain types of natural products (e.g., sugars and amino acids) but is of little use elsewhere and is ambiguous. The CIP system is based on the three-dimensional models of molecules and is self-consistent and unambiguous. The four ligands at a chiral centre are first arranged in a priority order following the sequence rule (defined by a number of standard subrules). The molecule is then viewed from the side remote from the lowest priority ligand and if the remaining three ligands (seen according to their priority order) appear in a clockwise direction, the configuration is *R* and if they appear in an anticlockwise direction, the configuration is *S* (the chirality rule). A few empirical and mnemonic methods have been devised which enable one to assign *RS* descriptors to a chiral centre without going through the complexity of the CIP procedure. The nomenclature of certain diastereomeric cyclane derivatives which cannot be readily expressed in terms of *R* and *S* has been discussed.

5. For olefinic diastereomers, an unambiguous system of configurational nomenclature is used according to which a diastereomer having groups of higher priorities on the same side of the double bond is called *Z* isomer and the other with groups of higher priorities on opposite sides is called *E* isomer. Both the systems (*RS* and *EZ*) can be applied to compounds containing multiple stereogenic units.

6. Achiral models of the types: Caabc, Caaab, and Caaaa may be desymmetrised by appropriately bridging pairs of groups which eliminates the σ planes but retain the C_n axis or axes. Such molecules possess central chirality and belong to C_n or D_n point group. CIP nomenclature (*RS*) with suitable modifications is applied to them.

7. The presence of two or more chiral centres increases the number of diastereomers in a predictable manner. Diastereomers having two non-equivalent chiral centres are important for their extensive use in the studies of reaction mechanisms and conformational analysis. Different systems of nomenclature for their relative stereochemistry are known of which a few important ones such as erythro-threo, like-unlike, pref-parf, and syn-anti have been discussed including a latest one by Brewster.

8. Cyclic compounds with multiple chiral centres, equivalent or non-equivalent usually have lesser number of stereoisomers due to (i) increased symmetry of a cyclic structure vis-a-vis its acyclic counterpart and (ii) the absence of certain diastereomers as a result of steric constraint. Certain cyclic molecules have the centre of chirality located not on any atom but in the unoccupied space inside the molecule. A new type of stereoisomerism known as 'out-in' isomerism in certain bicyclo compounds containing large rings is illustrated.

References

1. R.S. Cahn, C.K. Ingold, and V. Prelog, (1966), *Angew. Chem. Int. Edn. Engl.*, **5**, 385.
2. K. Mislow and J. Siegel (1984), *J. Amer. Chem. Soc.*, **106**, 3319.
3. V. Prelog and G. Helmchen (1982), *Angew. Chem. Int. Edn. Engl.*, **21**, 567.
4. G.E. McCasland (1953), *A New General System for the Naming of Stereoisomers*, Chemical Abstract Service, Columbus, Ohio, p.2.
5. J.H. Brewster (1986), *J. Org. Chem.*, **51**, 4751.
6. P.G. Mezey (1986), *J. Amer. Chem. Soc.*, **108**, 3976.
7. K. Mislow and P. Bickart (1976-77), *Israel J. Chem.*, **15**, 1.
8. L. H. Sommer (1965), in *Stereochemistry, Mechanism, and Silicon* McGraw-Hill, New York.
9. R.J.P. Corriu, C. Guerin, and J.J.E. Moreau (1984) in *Topics in Stereochemistry*, vol. 15, Eds. E. L. Eliel, S.H. Wilen, and N.L. Allinger, Wiley, New York.
10. R.L. Shriner (1965) in *Organic Chemistry: An Advanced Treatment*, vol. 1, Ed. H. Gilman, Wiley, London, p. 214-488.
11. K. Ohkubo, Y. Azuma, and M. Okada (1976), *Bull. Soc. Japan*, **49**, 1397.
12. D.W. Slocum, D. Sugarman, and S.P. Tucker (1971), *J. Chem. Educ.*, **48**, 597.
13. R.S. Cahn and C.K. Ingold (1950), *J. Chem. Soc.*, 612; R.S. Cahn, C.K. Ingold, and V. Prelog (1956), *Experientia*, **12**, 81.
14. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
15. G.A. Epling (1982), *J. Chem. Educ.*, **59**, 650.
16. E.L. Eliel (1985), *J. Chem. Educ.*, **62**, 223.
17. M. Kotera (1986), *Bull. Chem. Soc. Japan*, **59**, 639.
18. International Union of Pure and Applied Chemistry (1976): *Rules for the Nomenclature of Organic Chemistry: Section E, Stereochemistry, Pure & Appl. Chem.* **45**, p.11.
19. E.L. Eliel (1971), *J. Chem. Educ.*, **48**, 163; Information Bulletin No. 35, IUPAC, 1969; *J. Org. Chem.*, 1970, **35**, 2849.
20. J.L. Pierre (1971) in *Principles de Stereochimie Organique Statique*, Armand Colin. Paris, p. 103.
21. J.E. Blackwood, C.L. Gladys, K.L. Loening, A.E. Petrarca, and J.E. Rush (1968), *J. Amer. Chem. Soc.*, **90**, 509.
22. B. Testa (1979) in *Principles of Organic Stereochemistry*, Marcel Dekker, New York, p. 60.
23. M.A. Brook (1987), *J. Chem. Educ.*, **64**, 218.
24. F. A. Carey and M.E. Kuehne (1982), *J. Org. Chem.*, **47**, 3811.
25. R. Noyori, I. Nishida, and J. Sakata (1981), *J. Amer. Chem. Soc.*, **103**, 2106.
26. D. Seebach and V. Prelog (1982), *Angew. Chem. Int. Edn. Engl.*, **21**, 654; also ref. 3.
27. S. Masamune, A. Sk. Ali, D.L. Snitman, And D.S. Garvey (1980), *Angew. Chem. Int. Edn. Engl.*, **19**, 557.
28. C.H. Heathcock (1984) in *Asymmetric Synthesis*, vol. 3, Ed. J.D. Morrison, Academic Press, New York; also see, D.A. Evans, J.V. Nelson, and T.R. Taber (1982) in *Topics in Stereochemistry* vol. 13, Eds. N.L. Allinger, E.L. Eliel, and S.H. Wilen, Wiley, New York.
29. F.A.L. Anet, S.S. Miura, J. Siegel, and K. Mislow (1983), *J. Amer. Chem. Soc.*, **105**, 1419.
30. H. Hirschmann and K.R. Hanson (1974), *Tetrahedron*, **30**, 3649.
31. C.H. Park and H.E. Simmons (1972), *J. Amer. Chem. Soc.*, **94**, 7184.
32. H. Dodziuk and M. Mirowicz (1990), *Tetrahedron : Asymmetry*, **1**, 171.

Chapter 5

Stereoisomerism : Axial Chirality, Planar Chirality, and Helicity

5.1 Introduction

In the preceding chapter, stereoisomerism in organic compounds has been discussed on the basis of chiral centres (occasionally, pseudoasymmetric centres) acting as stereogenic units. Two other elements of chirality, namely, axes and planes, also behave as stereogenic units according to CIP system. Appropriately substituted allenes, alkylidenecycloalkanes, spirans, adamantoids, biaryls, *trans*-cycloalkenes, cyclophanes, and their analogues do not contain any formal chiral centre but exhibit stereoisomerism which is attributed to the presence of either a chiral axis (first five cases) or a chiral plane (last two cases). Just as a chiral centre is called a stereocentre, a chiral axis and a chiral plane are called a stereoaxis and a stereoplane respectively to emphasise the stereogenic character of these chiral elements.* Lastly, a molecule may have a helical structure and a helix possesses an inherent chirality being non-superposable with its mirror image. This introduces another element of chirality (stereogenic unit), known as helicity.

5.2 Principles of axial and planar chirality

The general principles on which the concepts of chirality axis and chirality plane are based have recently been refined by Prelog and Helmchen (1982). In this section, a very simplified version of the treatment is given.

5.2.1 Elongated tetrahedron approach

As mentioned earlier, a regular tetrahedron with four distinguishable vertices (structure I in Figure 5.1) represents a three-dimensional chiral simplex. The centre of the tetrahedron which is usually occupied by a tetracoordinate atom, e.g., C in Cabcd is a stereocentre. If this centre is replaced by a linear grouping such as C—C or C = C = C, the tetrahedron becomes elongated (extended) along the axis of the grouping as shown in II and illustrated by an allene, abC = C = Cab. Such

* It may be recalled, however, that Mislow and Siegel (1984) have argued against the factorisation of molecular chirality into elements of chirality such as axes and planes.

an elongated tetrahedron (D_{2d} point group with $3C_2$ axes and 2σ planes) has lesser symmetry than a regular tetrahedron (T_d) and the condition for its desymmetrisation is less stringent. Instead of all the four vertices being distinguishable, only pairs of vertices around the two ends of the axis need to be distinguished (i.e., a ≠ b). The structure (II) thus becomes three-dimensionally chiral and is enantiomorphous with its mirror image (II′). The axis along which the tetrahedron is elongated (shown by the dotted lines) is called the chiral axis or the stereoaxis (exchange of ligands at either of the terminal atoms across the axis reverses the chirality)*. Actually, the elongated tetrahedron II (C_2) is a *desymmetrised* tetrahedron of type Caabb (C_{2v}).

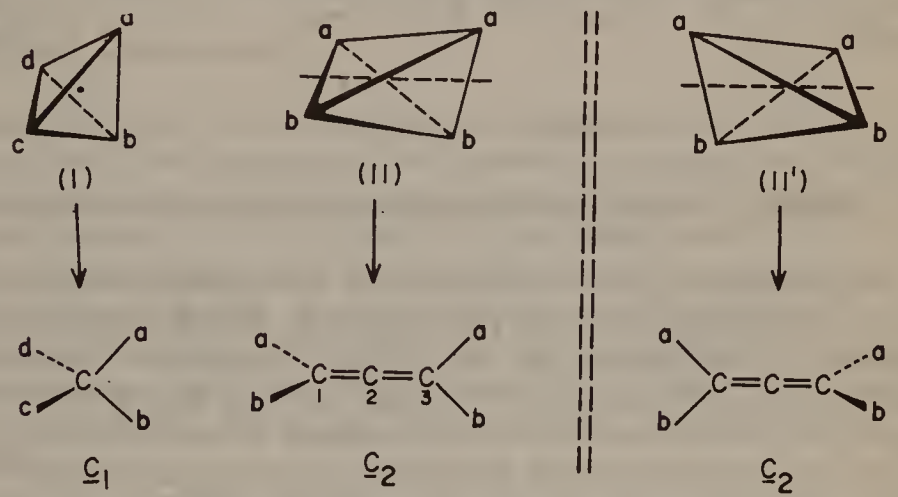


Figure 5.1 Elongated pyramid and chiral axis.

5.2.2 Approach based on two-dimensional chiral simplex

Some aspects of stereochemistry can be conveniently explained on the basis of two-dimensional chiral simplex. An equilateral triangle with three distinguishable vertices is a two-dimensional chiral simplex, i.e., chiral in two dimensions. In the molecular level, a substituted trigonal tricoordinate carbon (as III) (Figure 5.2) represents a two-dimensional chiral simplex (the double bond may be ignored). Two such groupings can combine together either to give (*i*) a composite molecule in which the two planes are brought to coincide (planar combination) or to give (*ii*) a composite molecule in which the two planes are perpendicular to each other (non-planar combination). The planar combination affords two diastereomers, e.g., cis (IV) and trans (V) whereas the non-planar combination affords a three-dimensionally chiral structure (VI) which exists in two enantiomorphic forms similar to structures II and II′. The allene (II) with the two terminal planes at right angle to each other thus has a chiral axis (along C = C = C) which is stereogenic. The biphenyl derivative (VII) in which the two substituted phenyl groups (a ≠ b) are non-planar due to steric reason provides another example, the pivotal bond coinciding with the chiral axis.

*According to Brewster (Chapter 4), the stereogenicity rests on both C-1 and C-3 interdependently, i.e., C-1 is stereogenic because C-3 is and vice versa. Together they form a stereogenic dyad.

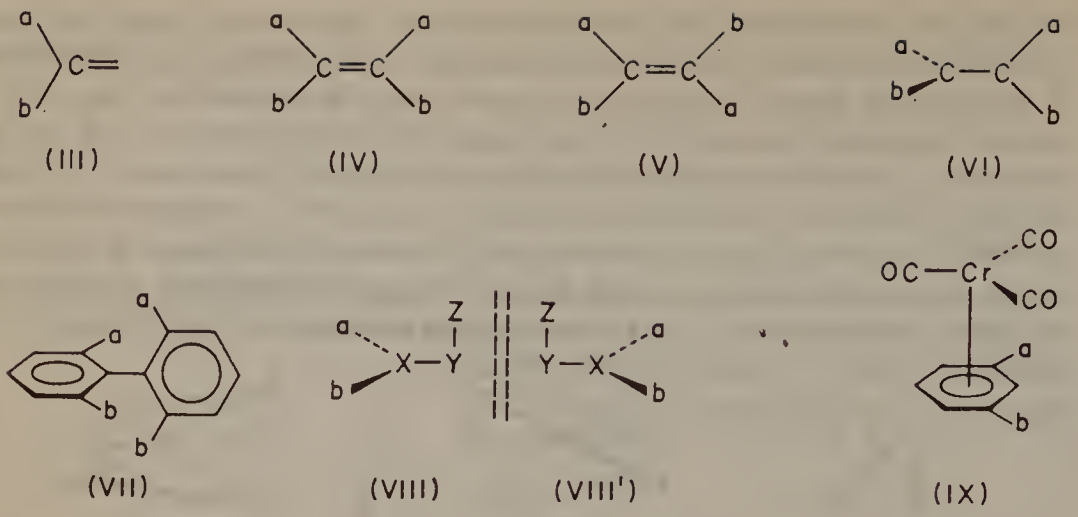


Figure 5.2 Two-dimensional chiral simplex and axis and plane of chirality

A two-dimensional chiral simplex divides the three-dimensional space around it into two half-spaces which are enantiomorphic and so topographically distinguishable. The arrangement of abX—Y in VIII represents a two-dimensional four-point chiral figure (actually X is present there as a ligating centre and is not necessary for two-dimensional chirality). A ligand Z may be added to Y from either of the two enantiomorphic half-spaces (from above or below the abX—Y plane) giving two enantiomorphic structures (VIII) and (VIII'); the latter has been turned upside down to show the mirror image relationship with VIII. In the structure (VIII or VIII'), the four ligands a, b, Y, and Z form the vertices of a tetrahedron of C_s symmetry which can be converted into a three-dimensional chiral simplex of C_1 symmetry simply by differentiating two vertices defined by a and b. A tetrahedral stereogenic unit thus results with a chiral plane specified by abX—Y. The tricarbonylchromium complex of a dissymmetrically substituted benzene derivative (IX) provides a simple example (only one enantiomer is shown). Here, the plane of the aromatic ring is two-dimensionally chiral.

5.3 Stereochemistry of allenes

As early as 1875, van't Hoff pointed out that an appropriately substituted allene should exist in enantiomeric forms. The two end carbon atoms (C-1 and C-3) in allene are sp^2 and the centre carbon atom (C-2) is sp hybridised. The orbital picture is shown in the structure (X) (Figure 5.3); the shaded p orbitals and the unshaded p orbitals separately overlap with each other forming π bonds making the two end groups non-planar. The structure (X) can be projected to a Newman formula (Xa) as shown at the right (viewed with the front groups in a horizontal line). The allenes, of the general formula Cab = C = Cab possess a C_2 axis (shown by the dotted line) but no σ plane and belong to point group C_2. If three or four of the substituents are different as in Cab = C = Cad or Cab = C = Cde, the C_2 axis also disappears and the molecules are rendered totally asymmetric (C_1 point group). This rule applies to all axially chiral molecules.

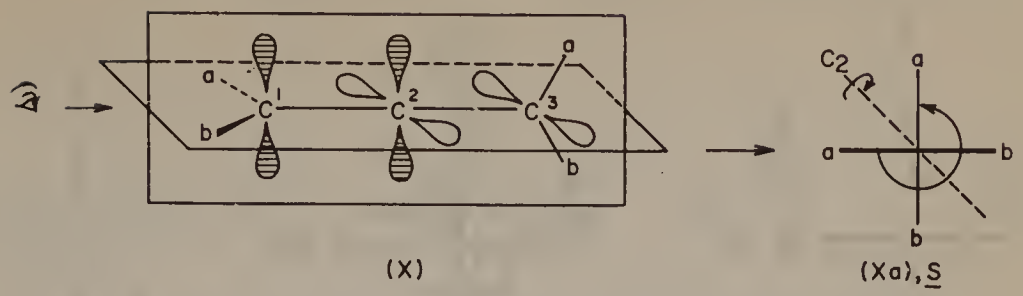


Figure 5.3 Orbital picture of an allene and its projection formula

5.3.1 Optically active allenes

The first optically active allene was prepared by Maitland and Mills (1935) sixty years after van't Hoff's prediction. The problem of resolution was avoided by synthesising the allene through asymmetric transformation. 1,3-Dipheny1-1,3-di-α-naphthyl-2-propen-1-o1 (XI) (Figure 5.4a) was dehydrated with (+)-, (−)-, and (±)- camphor-10-sulphonic acid respectively. With (±)-sulphonic acid, the allene (XII) was obtained as a racemic mixture while with (+)- or (−)-sulphonic acid, the allene was obtained with slight preponderance (~3%) of (+)- or (−)- enantiomer (see Landor 1982). The pure enantiomer in the last two cases could be crystallised out from the mixture and had a specific rotation, $[\alpha]^{17}_{546}$, 437–438°.

Subsequently, the allenic acid (XIII) (Figure 5.4b) was resolved through brucine salt. (−)-Glutinic acid (XIV) and the antibiotic mycomycin (XV) are other examples of optically active allenes which occur in nature. At the right hand side, Newman type projection formulae of the structures X, XII, and XIV (only one enantiomer of each) are shown to be used for configurational nomenclature.

5.3.2 Configurational nomenclature

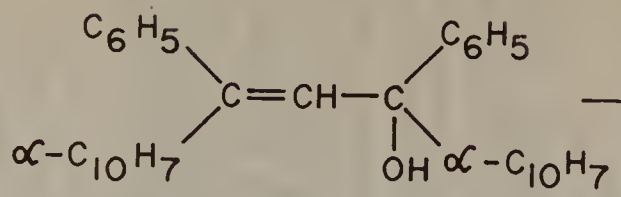
For the assignment of configurational descriptors (CIP system) to allenes and other axially chiral molecules, the standard subrule (0)1 (Chapter 4) is to be considered first. This means that near groups should be given priority over far groups before the other subrules are applied. If a precedes b, then in the projection formula of the allene (Xa), the horizontally placed (front) a and b are to be numbered 1 and 2 and the vertically placed (rear) a and b to be numbered 3 and 4 respectively. The sequence 1 → 2 → 3 gives the configurational descriptor which in this case is *S*. It does not matter from which end the molecule is viewed; for better visualisation, it is advisable to put the front groups on a thick line (horizontal or vertical). This is illustrated in the molecules (XII) and (XIV) both of which have *R* configuration.

It may be noted that interchange of the two geminal groups in these molecules leads to enantiomers.

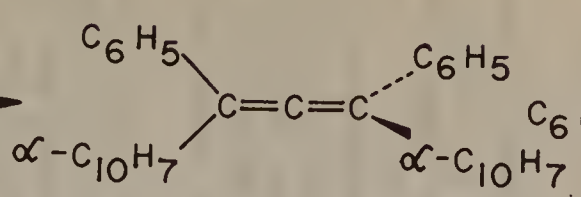
5.4 Stereochemistry of spiranes and analogues

Spiranes, alkylidenecycloalkanes, and adamantanes (also catenanes) when appropriately substituted can be dissymmetric in the same way as allenes. Alkylidenecy-

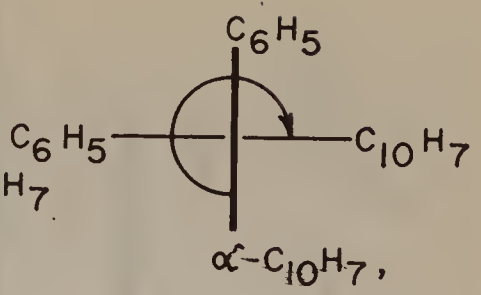
a.



(XI)

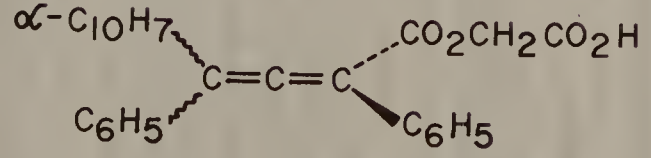


(XII)

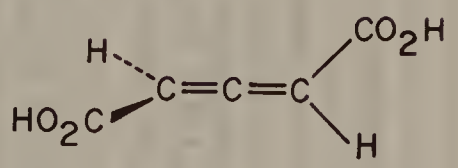


R

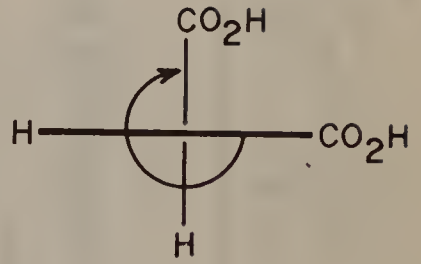
b.



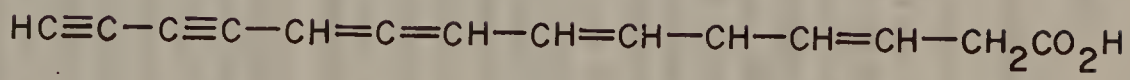
(XIII)



(XIV)



R



(XV)

Figure 5.4 Optically active allenes : synthetic and natural

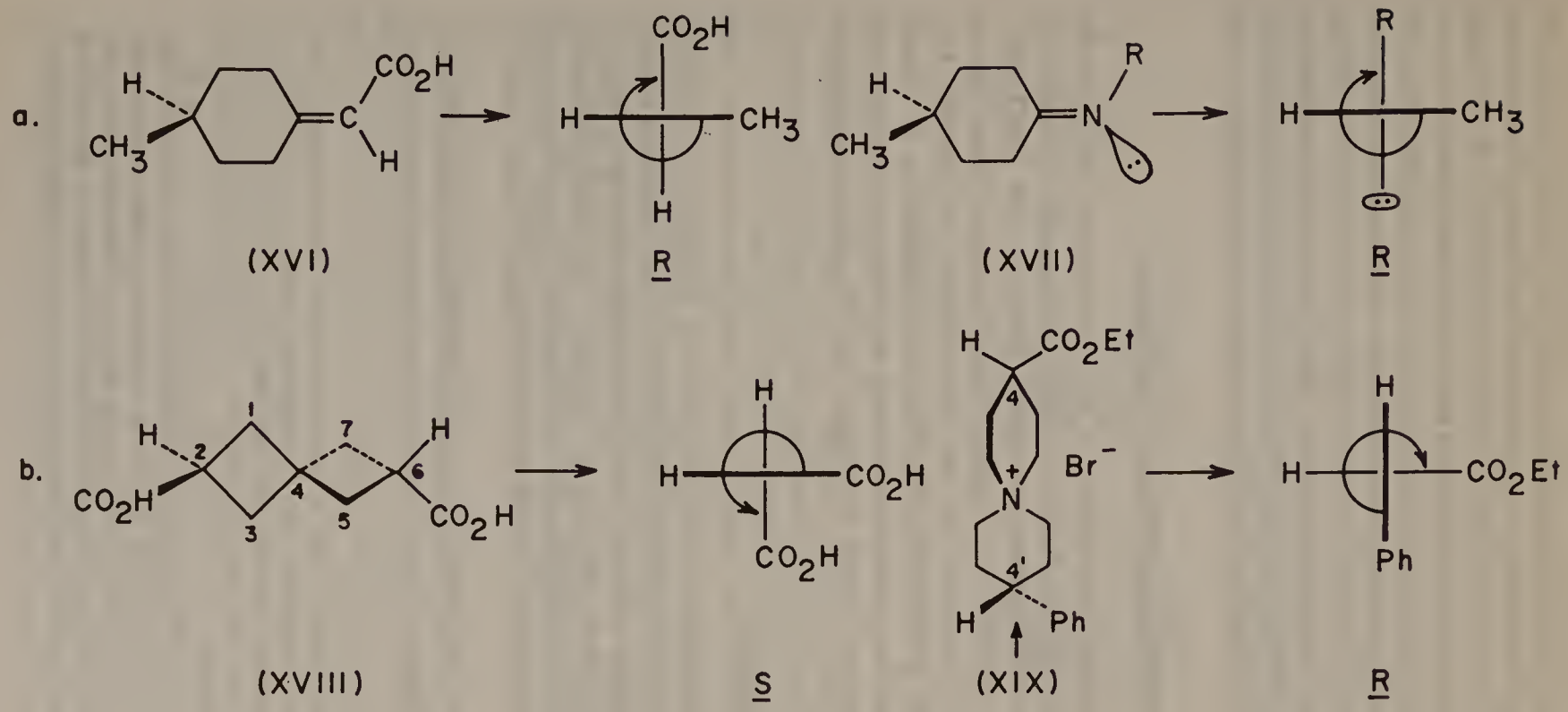


Figure 5.5 (a) Alkylidenecycloalkanes and oximes
(b) Spiranes

cloalkanes (sometimes called hemispiranes) are compounds in which one of the double bonds of allene is replaced by a ring, such as XVI (Figure 5.5a) while in spiranes, such as XVIII (Figure 5.5b) both the double bonds in allene are replaced by rings. The net result is the same, namely, the two terminal methylene planes are perpendicular to each other as in allenes and if pairs of geminal substituents (a, b) are non-equivalent (a $\neq$ b), the compounds would exhibit enantiomerism. The rings are assumed to have rigid planar structure although in reality they may exist in different conformations. The adamantanes (e.g., XXIV) (Figure 5.7) are highly rigid molecules and the diametrically opposite methylene planes are perpendicular to each other so that axial chirality would develop similar to that in allenes with proper substitution.

5.4.1 Optically active alkylidene cycloalkanes (hemispiranes)

4-Methylcyclohexylideneacetic acid (XVI)* is the first molecule without any asymmetric carbon to be resolved (Pope et al 1909). Subsequently, a number of cyclic oximes, semicarbazones, and phenylhydrazones (XVII, R = OH, $NHCONH_2$, and NHPh) have been resolved. The configurational stability of these imino-compounds (as XVII) is, however, low and they racemise on standing. The configurational labels are given by following the same procedure as in allenes. Thus the molecules (only one enantiomer of each) are projected as shown and both XVI and XVII turn out to have *R* configuration. The molecules belong to point group C_1.

5.4.2 Optically active spiranes

Spiro[3,3]heptane-2,6-dicarboxylic acid (XVIII)† is an example of an axially chiral spirane, one of the first of its kind investigated. The configurational symbol *S* is given to this particular structure from the projection formula as shown. Another interesting example is 4-carbethoxy-4′-phenyl-1, 1′-spiro-*bis*piperidinium bromide (XIX) shown in *R* configuration. The quaternary nitrogen acts as a tetrahedral centre. The compounds (XVIII) and (XIX) belong to point group C_2 and C_1 respectively.

It may appear that these compounds (hemispiranes and spiranes) contain one or two chiral centres, for example, C-2 and C-6 of the spirodicarboxylic acid (XVIII).

---

*It is worth noting that a rotation (torsion) of 180° around the double bond in the hemispirane (XVI) converts it into its enantiomer (which also applies to allenes). So this type of enantiomerism is sometimes referred to as geometrical enantiomerism (Eliel 1962, p. 319). In contrast, ethylenes (C = C) or cumulenes (C = C = C = C) with odd number of π bonds, on similar torsion, gives diastereomers (cis and trans isomers).

†Spiro hydrocarbons are named by prefixing the name of the acyclic hydrocarbon containing the same total number of carbon atoms with *spiro* and interposing an expression, within square bracket, denoting the number of atoms (other than the spiro atom) in each ring. Numbering starts at a ring carbon (in case of two unequal rings, the smaller ring is numbered first) adjacent to the spiro atom and proceeds around one ring, through the spiro atom, and thence around the other ring (IUPAC Rules: Rule A-41, 1957).

Their chirality, however, cannot be specified since during sequencing, branches of equal priority meet before their priority is determined. On the other hand, in spiranes such as XX (Figure 5.6), the central atom (C-5) common to both the rings is truly a chiral centre (a case of desymmetrisation of tetrahedral Caabb by bridging unlike ligands) and configurational symbols can be given to them following the sequence rule as applied to compounds with central chirality, see for example, 5,5′-spiro-*bis*hydantoin (Chapter 4). The four ligands attached to C-5 of spiro[4,4]nonane-1,6-dione (XX) should be sequenced as C-1>C-6>C-4>C-9 which settles the configuration as *R*. When a molecule exhibits both central and axial chirality, the former has precedence for configurational nomenclature.

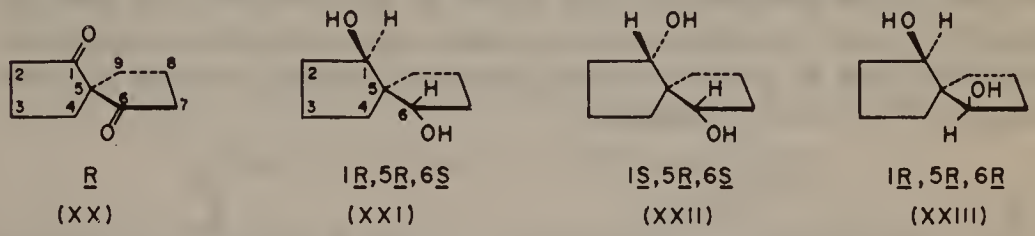


Figure 5.6 Spiranes with more than one chiral elements

In addition to central or axial chirality, a spirane may contain one or more chiral centres at the rings in which case diastereomers would occur. Thus when the dione (XX) is reduced, three diastereomeric diols (XXI)—(XXIII) result each of which is chiral and resolvable (Gerlach 1968). The three enantiomers shown are labeled as 1*R*,5*R*,6*S* (XXI), 1*S*,5*R*,6*S* (XXII), and 1*R*,5*R*,6*R* (XXIII). Reference has been made in Chapter 2 to another spiro-compound, 3,4,3′,4,′-tetramethylspiro [1,1′]dipyrrolidinium *p*-toluenesulphonate (p. 19) which contains five chiral atoms in all (counting the spiro N atom) four of which are equivalent. The molecule exists in four diastereomeric forms; three are chiral (resolvable) while the fourth is meso due to the presence of an S_4 axis (McCasland and Proskow 1956).

5.4.3 **Optically active adamantoids**

Adamantane-2,6-dicarboxylic acid (XXIV) (Figure 5.7) satisfies the condition of axial chirality (C-2 and C-6 methylenes are non-planar and dissymmetrically

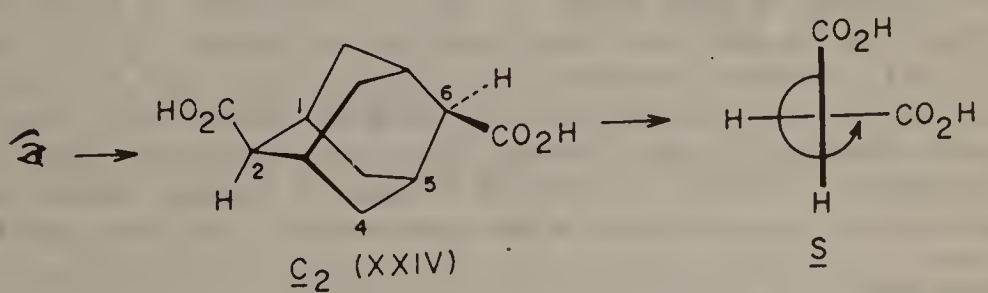


Figure 5.7 Optically active adamantane

substituted) and exists in two enantiomeric forms. The one (XXIV) shown has *S* configuration. In adamantoids, the imaginary chiral axis passes through the two substituted terminal carbon atoms and the geometrical centre of the ring system, which can also be a chiral centre if the bridgehead atoms bear appropriate substituents (see Chapter 4).

5.4.4 Optically active catenanes

A catenane with two (or more) dissimilar rings interlinked with each other may give rise to chirality due to secondary structure*. If the two rings are held with their planes perpendicular to each other as in XXV (Figure 5.8), a catenane may correspond to the structure (II) with respect to the arrangement of four distinguishable groups in the chains. Like other axially chiral molecules, configurational nomenclature may be given from similar projection formula. Thus the particular enantiomer (XXV) has *S* configuration.

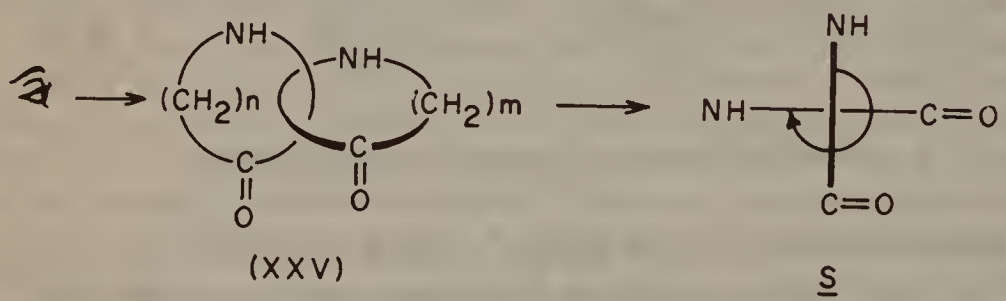


Figure 5.8 Optically active catenanes

5.5 Biphenyl derivatives and atropisomerism

Biphenyl is represented by the structure XXVI (Figure 5.9) in which two phenyl groups are joined by a single bond (sp^2—sp^2), called the *pivotal* bond. The distance between ortho H's in adjacent rings in the planar conformation is appreciably greater (0.29 nm) than twice the van der Waals radius of hydrogen (2×0.12 nm) so that the rotation around the pivotal bond is not impeded by steric factors. A phenyl group which is dissymmetrically substituted, i.e., does not have a vertical plane of symmetry is two-dimensionally chiral and a planar combination of two such groups would lead to two (cis and trans) diastereomers (XXVII) and (XXVIII) belonging to point groups C_{2v} and C_{2h} respectively. A non-planar combination, on the other hand, would give two enantiomers (XXIXa) and (XXIXb) of C_2 symmetry, the arrangement of abab corresponding to the general chiral structure (II). Such molecules are axially chiral with the line joining C-1 and C-1′ as the chiral axis. It is clear, therefore, that in order to have the biphenyls to be enantiomeric (resolvable) an additional condition is necessary, namely the planes of the two aryl groups must be kept non-coincident. This can be done by

*Secondary structure arises out of primary structure through coiling or otherwise, the most common example being the helical structure of proteins.

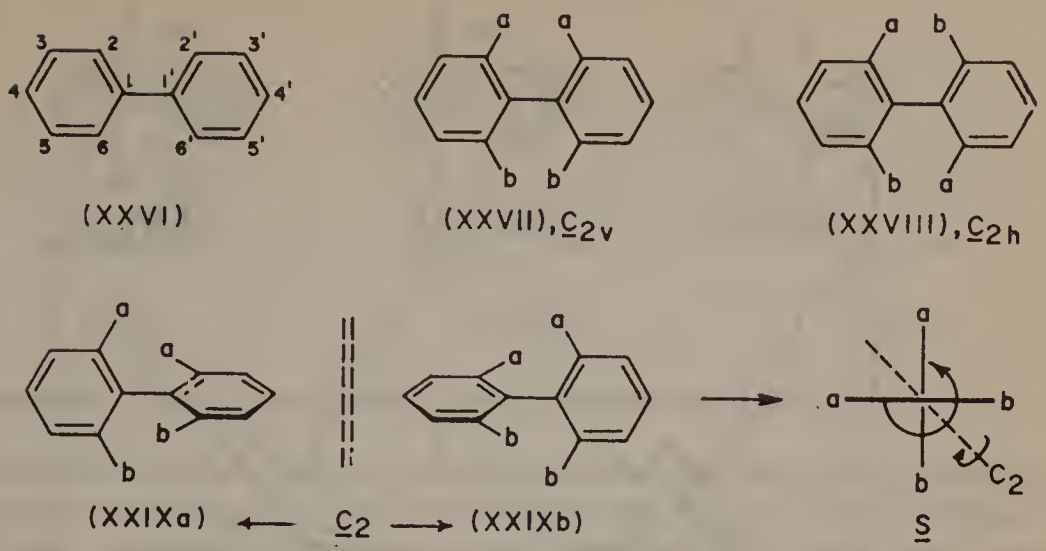


Figure 5.9 Principle of optically active biphenyls

introducing bulky groups in the ortho positions so that the planar conformations are destabilised due to steric repulsion. An approximate energy profile diagram* is shown in Figure 5.10 for a 360° (θ) rotation around the pivotal bond. Since inter-ring resonance is minimum at 90°, the true situation may be that of a double minimum when θ is around 90° and 270° as shown so that the preferred conformations of the enantiomers are those in which the two phenyl planes are approximately but not *exactly* perpendicular to each other.

It may be noted that the two diastereomeric planar conformations (XXVII) and (XXVIII) represent the energy maxima, the one with similar groups on the same side (cisoid) having higher energy than the other with similar groups on opposite sides (transoid). Racemisation, therefore, takes place with greater ease through the transoid configuration. The bulkier the ortho substituents are, the higher is the energy barrier separating the enantiomers and when it exceeds 80-100 kJ mol^{-1}, the stereoisomers may be separable at room temperature. This type of isomerism which owes its existence to restricted rotation around a single bond is known as *atropisomerism* and the isomers are called *atropisomers*. They are actually torsional isomers about single bonds.

The characteristic of atropisomers is that they cannot be represented by any type formula (e.g., XXVII) as in the case of allenes, spiranes, and centrally chiral compounds since the stereochemistry depends on the bulks of the ortho substituents which restrict the rotation about the single bond. Thus even a 2,2′,6,6′-tetrasubstituted biphenyl may be non-resolvable: an example is difluoro-dimethoxy derivative (XXX). On the other hand, biphenyl-2,2′-disulphonic acid (XXXI) with only

*The exact conformation of biphenyl itself is still controversial. X-ray analysis shows the molecule to be almost planar which is expected because of inter-ring resonance and very little of steric repulsion among the inter-ring ortho H's. Electron diffraction in the gas phase shows the two rings at an angle with each other (close to 45°).

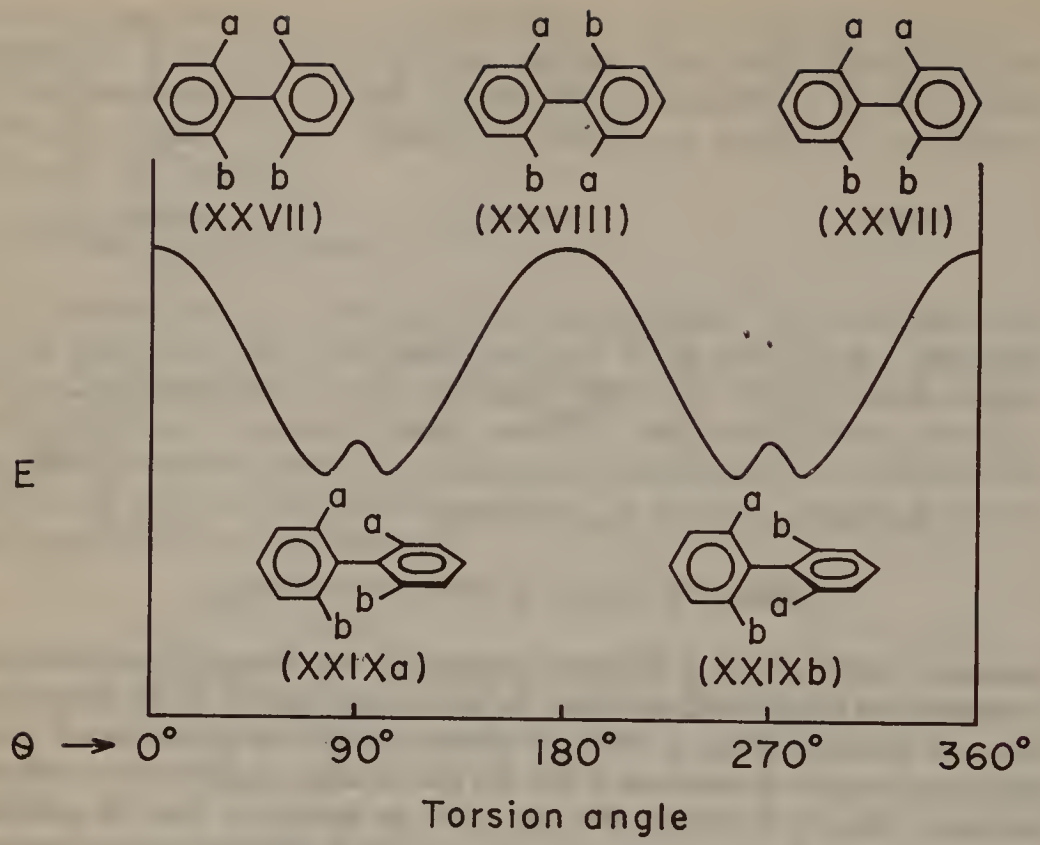


Figure 5.10 Energy profile diagram of biphenyls

two ortho substituents is resolvable because of much higher bulk of SO_3H (Figure 5.11).

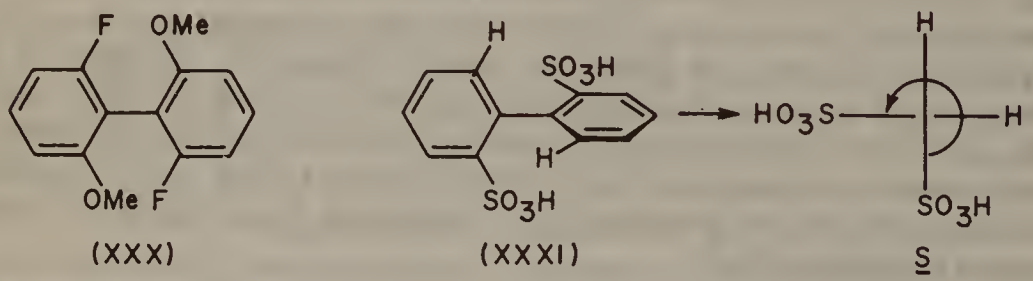
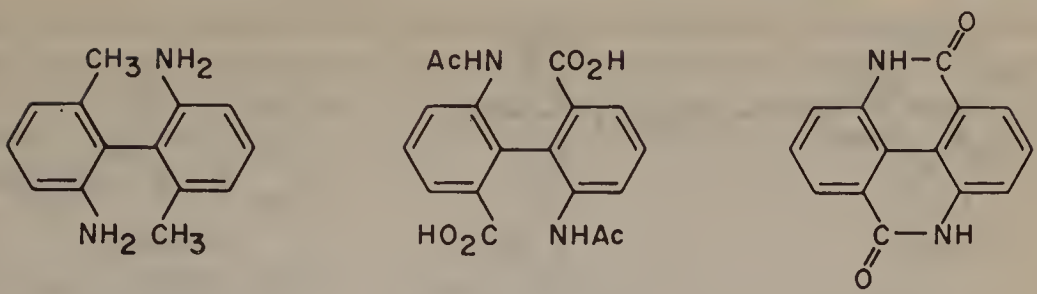


Figure 5.11 A non-resolvable tetra-*o*-substituted and a resolvable di-*o*-substituted biphenyl

In addition to physical proofs such as X-ray diffraction, dipole moment measurement, electronic spectroscopy (UV), NMR etc., direct chemical evidence for the non-planar configuration of the optically active biphenyls is provided by the following examples. The compound (XXXII) as well as the compound (XXXIII) (Figure 5.12) derived from it are resolvable. But the compound (XXXIV) in which the ortho positions are joined by planar rings is non-resolvable because the non-bonded interaction has been converted into a bonded one.

The stereochemistry of the biphenyls has a long history which started with certain wrong assumptions and erroneous experimental data (see Gilman 1943)



(XXXII) (XXXIII) (XXXIV)

Figure 5.12 Disappearance of atropisomerism by formation of ring through ortho positions

and ended up with a new type of stereoisomerism, namely, atropisomerism. In the following subsections, a few important optically active biphenyls, their analogues, and their stereochemical nomenclature are discussed (for a review, see Krow 1977).

5.5.1 Optically active biphenyl derivatives

Dinitrodiphenic acid is the first biphenyl which was resolved. The *S*-enantiomer is shown (XXXV) in Figure 5.13. It is clear from the previous discussion that the resolvability of a biphenyl derivative depends on the sum of the van der Waals group radii of the ortho substituents. This is illustrated in compounds of the type (XXXVI). The carboxylic groups here serve two purposes: they make the phenyl rings dissymmetric, i.e., two dimensionally chiral and provide a handle for resolution (using chiral base). If *R* is fluorine, twice the value of its radius ($0.139 \times 2 = 0.278$ nm) is smaller than that required for overlapping (≈ 0.290 nm) and so the compound (XXXVI, R = F) is not resolvable*. If *R* is methoxyl (radius 0.145 nm), overlapping occurs minimally and the compound racemises readily. On the other hand, if *R* is chlorine (radius 0.169 nm), there is considerable overlap and the two enantiomers are stable configurationally. Thus, depending on the effective bulks of the ortho substituents, the biphenyls can exist in stereoisomers which range from fleeting conformers to stable configurational isomers. The order of steric hindrance produced by various groups appears to be Br>Me>Cl> NO_2>CO_2H>OMe>F which roughly corresponds to the order of the respective van der Waals radii of atoms and groups. In this connection, it is interesting to note that the rate of racemisation of the deuterated compound (XXXVIII) is 1.13 times as fast as that of the undeuterated one (XXXVII)—a fact known as secondary isotope effect. This means that deuterium has a smaller van der Waals radius than hydrogen (because of its lower zero-point vibrational frequency).

4,4′,5,5′,6,6′-Hexahydroxydiphenic acid (XXXIX) is one of the very few naturally occurring biphenyls isolated in optically active form.

Biphenyl atropisomers with only two bulky ortho substituents are also well

*There is some buttressing effect due to the adjacent CO_2H groups.

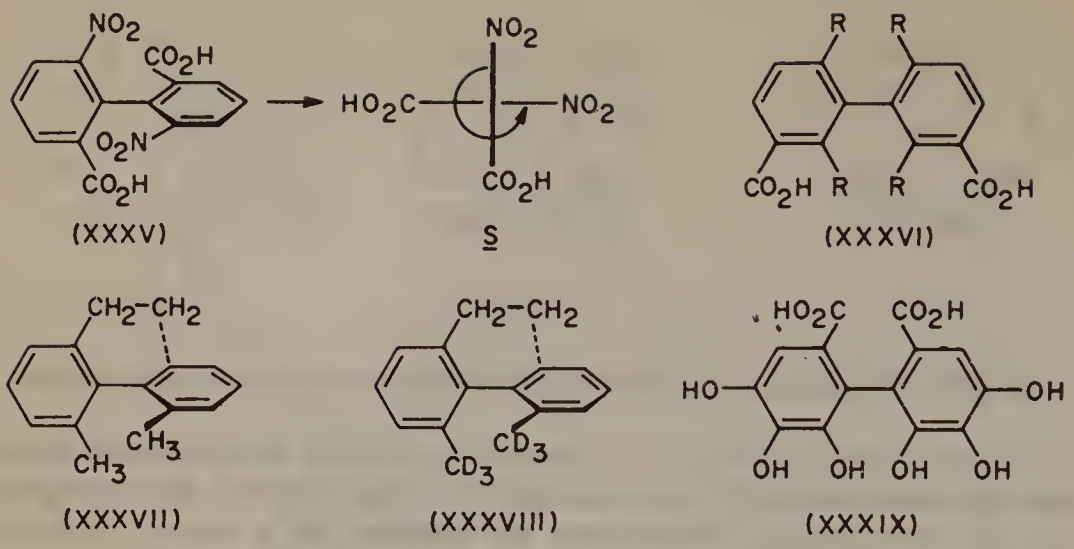


Figure 5.13 Biphenyl atropisomers with varying degree of configurational stability.

known. 2,2′-Di-*t*-butylbiphenyl (XL) (Figure 5.14) prepared from optically active 6,6′-di-*t*-butylbiphenyl-2,2′-dicarboxylic acid by decarboxylation gives highly stable enantiomers. The previously mentioned biphenyl-2,2′-disulphonic acid (XXXI) although resolvable racemises on heating. Even a single bulky group like trimethylarsonium ion in compound (XLI) can give rise to atropisomerism. The (+)-camphorsulphonate of XLI shows mutarotation indicating that a first order asymmetric transformation (see Chapter 7) takes place in solution. The enantiomer (XLI) has the *R* configuration as shown. The 2-H adjacent to 3-Br precedes 6-H.

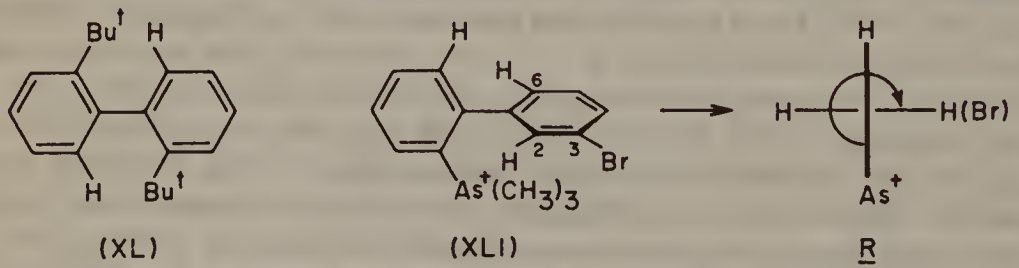


Figure 5.14 Optically active di- and mono-substituted biphenyls

In addition to the bulk of the ortho substituents, the nature and position of other substituents in the rings often play some role in determining the configurational stability of the atropisomers. The effect may be attributed to three different factors: (*i*) A bulky group adjacent to an ortho substituent exerts a buttressing effect. Thus the rate of racemisation of the 3′-nitro-derivative (XLII) is much lower than that of the 5′-nitro-derivative (XLIII) (Figure 5.15). The buttressing effects of some of the groups are in the following order: NO_2>Br>Cl>Me which does not exactly correspond to the order of steric hindrance of these groups. (*ii*) A group at the 4- or 4′-positions (specially a nitro group) retards the racemisation. This effect has been attributed to a change in the entropy of activation (Harris et al 1957). (*iii*) Finally,

the presence of electron-attracting and electron-donating groups (capto-dative groups, e.g., NO_2 and OMe) at 4- and 4′-positions helps interannular resonance so that the pivotal bond assumes more double bond character and the transition state energy is lowered. However, this effect is found to be very small (Oki et al 1971, Nasipuri et al 1977).

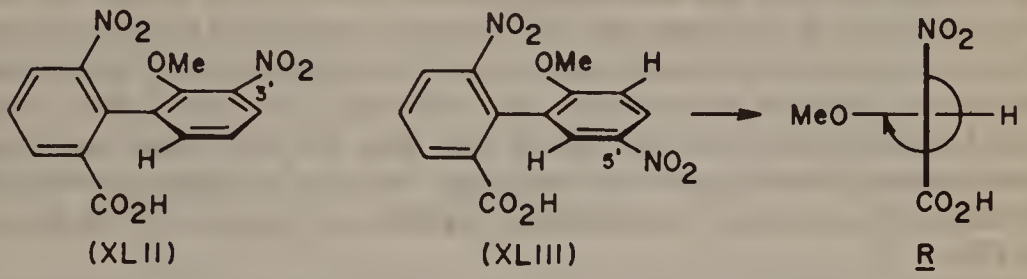


Figure 5.15 Buttressing effect on configurational stability of biphenyls

5.5.2 **Bridged biphenyls**

A large number of biphenyls are known in which the 2- and 2′-positions are bridged with rings of different sizes as XLIV (Figure 5.16). When n is 1, the

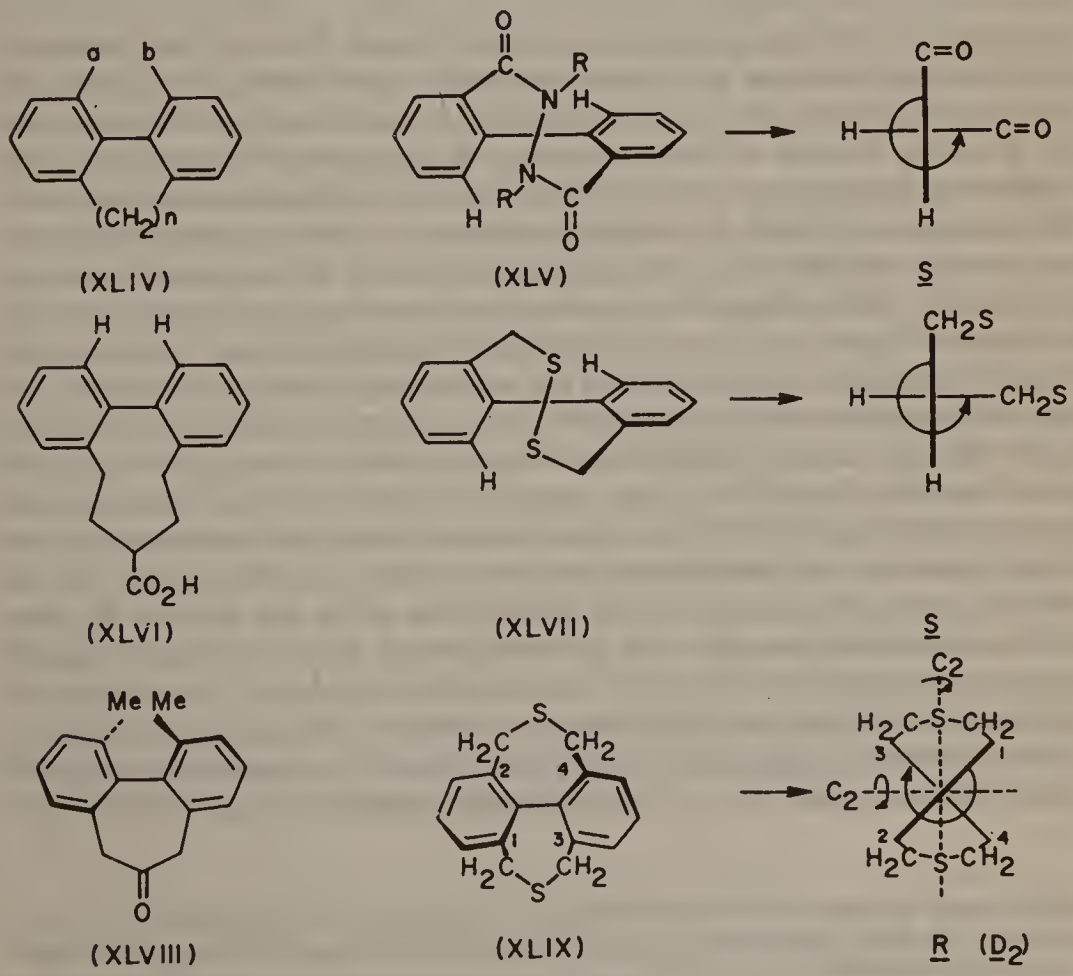


Figure 5.16 Bridged biphenyls and their configurational nomenclature

molecule is a disubstituted fluorene which is planar and does not permit atropisomerism. When n is 2, the molecule is a dihydrophenanthrene and the non-planar six-membered ring can give rise to atropisomerism if the other two ortho positions are substituted with bulky groups, e.g., methyl as in the biphenyl XXXVII, (Figure 5.13); otherwise they slip through the plane readily. When n is greater than 2, the bridged biphenyls give atropisomers irrespective of the bulk of the other two ortho substituents. In these cases, the non-planarity is maintained by the puckering of the rings which in planar configuration suffer from angle strain and non-bonded interactions. Examples are provided by compounds (XLV)—(XLVII). These bridged biphenyls racemise with relative ease since the angle strain and steric interactions in medium rings are not very large. They can be further stabilised by substituting the remaining ortho positions with bulky groups as in the ketone (XLVIII).

A number of biphenyls in which both pairs of ortho positions are bridged have also been prepared in optically active forms. Thus the thioether (XLIX) has been resolved (Mislow et al 1961). Both the rings are puckered (not shown in the structure). The molecule belongs to point group D_2.

5.5.3 Configurational nomenclature of biphenyls

The assignment of configurational descriptors (*R* and *S*) to 2,2′,6,6′-tetra-substituted biphenyls is done in the same way as for other axially chiral molecules (allenes and spiranes). The molecule is viewed from either end of the chiral axis and projection formulae are drawn as shown in the previous Figures. Two points of difference, however, have to be observed in view of certain later modification in CIP nomenclature (1966). In the previous procedure (1956), a biphenyl molecule was viewed from the side of the nearest substituents (not necessarily the 2,6-substituents*) which differed from each other. In the modified system, only the four atoms, C-2, C-6 , C-2′, and C-6′ which correspond to the four vertices of the elongated tetrahedron are considered for sequencing. Instead of looking at the molecule from the outside in (old system), one now looks at it from the inside out so that the cases of axial chirality are in closer consonance with those of central chirality (see also Eliel 1971)†. Concomitantly, the priority order is no longer fixed by the substituents *per se* but by the four ortho carbon atoms themselves after due complementation for quadriligancy (which includes the substituents). In the modified system, the molecule when viewed from either end leads to the same configurational descriptor (*R* or *S*). The difference in the two procedures usually becomes manifest when the rings are substituted at C-3 or C-5 or at both in addition to ortho positions. The following two examples will clarify the situation .

The molecule (L) (Figure 5.17), according to the new system when viewed from the left hand side along the 1—1′ bond gives the projection (A) and when viewed

*Thus if one of the rings contains a substituent at C-3 (or C-5). the old system advises to view the molecule with this ring in front and the 3,5-substituents rather than the 2,6-substituents determine the sequence (see Eliel 1962).

†This system gives chiral axes a minimum effective range.

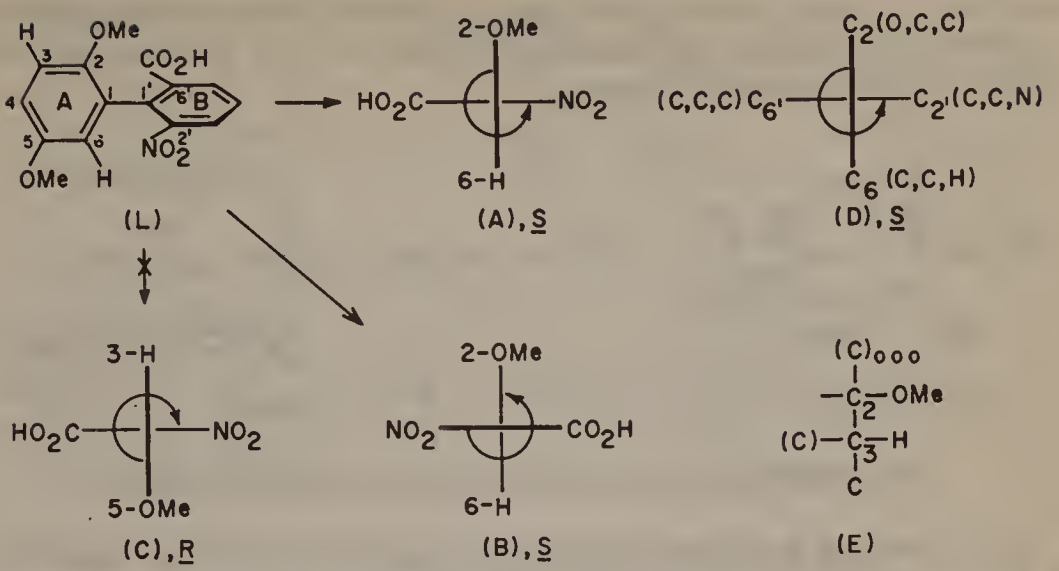


Figure 5.17 Configurational assignment to biphenyls (modified system)

from the right hand side along the 1′—1 bond gives the projection (B). Both the projections conform to *S* configuration. It does not matter which end is taken as the near end, provided that the choice, once made, is adhered to (CIP 1966). According to the older system, the molecule (L) is to be viewed from the side of the 5-substituted ring A only and 3-H and 5-OMe are the fiducial groups. The projected structure* is C which corresponds to *R*.

In the above example, the ortho carbon atoms are sequenced solely by the substituents attached to them. Actually they should be properly complemented to quadriligancy by atoms directly attached to them and by duplicate representation for the double bonds before being sequenced. As an example, the C-2 atom in L after proper complementation would appear as E (the exploration may be continued if necessary). The structure (L) is thus projected as D which shows the ortho carbon atoms in correct priority order (C-2 > C-6 because O > C and $C_2' > C_6'$ because N > C) indicating *S* configuration. For most molecules like the present one, it does not matter whether the sequencing is done by the substituents *per se* or by the properly complemented ortho carbon atoms (the result is the same). But when C-2 and C-6 in a ring are attached to identical atoms and C-3 and (or) C-5 are also substituted as in LI (Figure 5.18), ambiguity arises and the priority order of the ortho carbon atoms has to be determined through exploration around the ring or side chain. Thus in LI, C-6 with a Me group gets precedence over C-2 with a methylol (CH_2OH) group (in contravention to 1956 convention) because an exploration from C-6 around the ring (along the route providing highest precedence) leads to the phenolic hydroxyl group whereas similar explora-

* The same procedure may be adopted for projection if the chiral axis is vertically placed (see Eliel 1962), to give identical results. The alternative method of constructing an elongated tetrahedron, converting it into Fisher projection, and then assigning configuration is cumbersome.

tion from C-2 along the side chain leads to a primary hydroxyl group (see the projection F for details). The structure (LI) conforms to *R* configuration from whichever side the molecule is viewed.

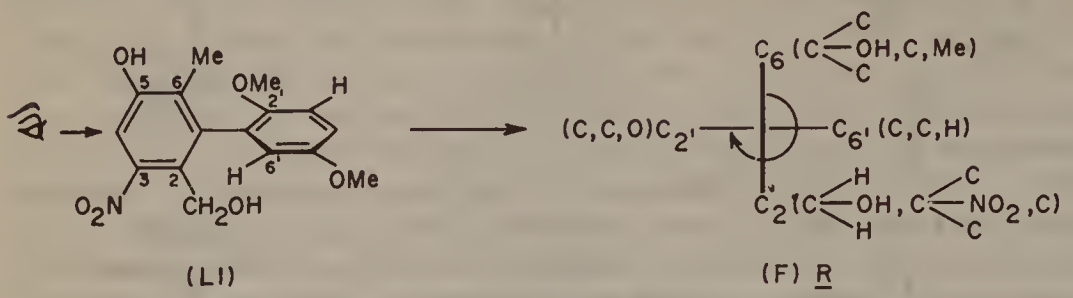


Figure 5.18 Configurational assignment to polysubstituted biphenyls

The 2,2′-bridged biphenyls can be similarly treated as illustrated in Figure 5.16. In the doubly bridged biphenyl (XLIX), all the four ortho carbons are equivalent. In order to assign configuration, any one of them at the near end (front) is referred to as number 1, the second near group is given number 2, and one of the far end groups exploration from which around the ring leads to number 1 is taken as number 3. Thus all the four atoms are sequenced as depicted in the structure (XLIX) and the projection formula shows *R* configuration.

5.5.4 Atropisomerism in compounds other than biphenyls

There are several types of molecules other than biphenyls which show atropisomerism. In all of them, two-dimensional chiral units are linked together through a pivotal bond, rotation around which is hindered due to steric factors. The atoms joined by the pivotal bond are usually sp^2 hybridised. They can be classified under the following headings:

(*i*) One or both of the phenyl groups are replaced by other aromatic or heteroaromatic rings. Thus appropriately substituted N-phenylpyrrole (LII), N,N′-bipyrryl (LIII), 1,1′-binaphthyl (LIV)*, and 3,3′-bipyridyl (LV) (Figure 5.19) are resolvable. The configurational nomenclature of the last-named compound (only one enantiomer is shown) is illustrated with the projected formula.

(*ii*) The two phenyl groups in biphenyls are interposed by a phenylene ring forming para terphenyl derivatives and restricted rotation may arise around two pivotal bonds so that the two terminal phenyl groups are coaxial as well as coplanar. This corresponds to a planar combination of two two-dimensional chiral units and both diastereomerism and enantiomerism may result. Thus the terphenyl derivative (LVI) (Figure 5.20) in which all the eight ortho positions are substituted exists in two achiral diastereomers which can be conveniently described as cis and trans with reference to the two bromine atoms. Both the cis and trans isomers have a plane of symmetry coincident with the plane of the paper; the trans isomer, in

*1,1′-Binaphthyl is itself resolvable (see Chapter 7); each naphthyl group is two-dimensionally chiral and the peri H's provide enough steric hindrance to keep the rings non-planar.

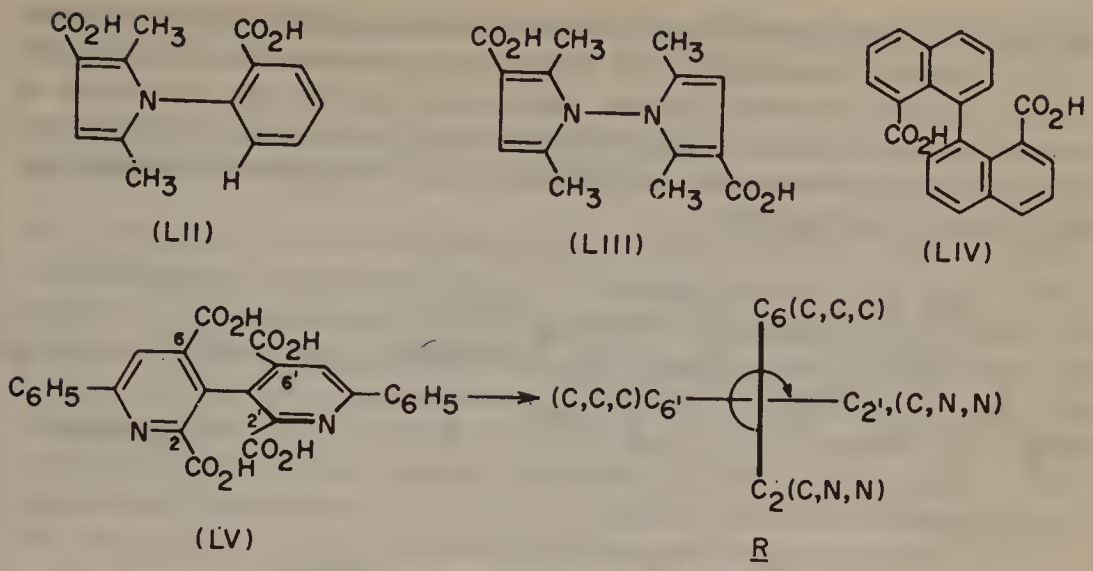


Figure 5.19 Atropisomerism in biphenyl analogues

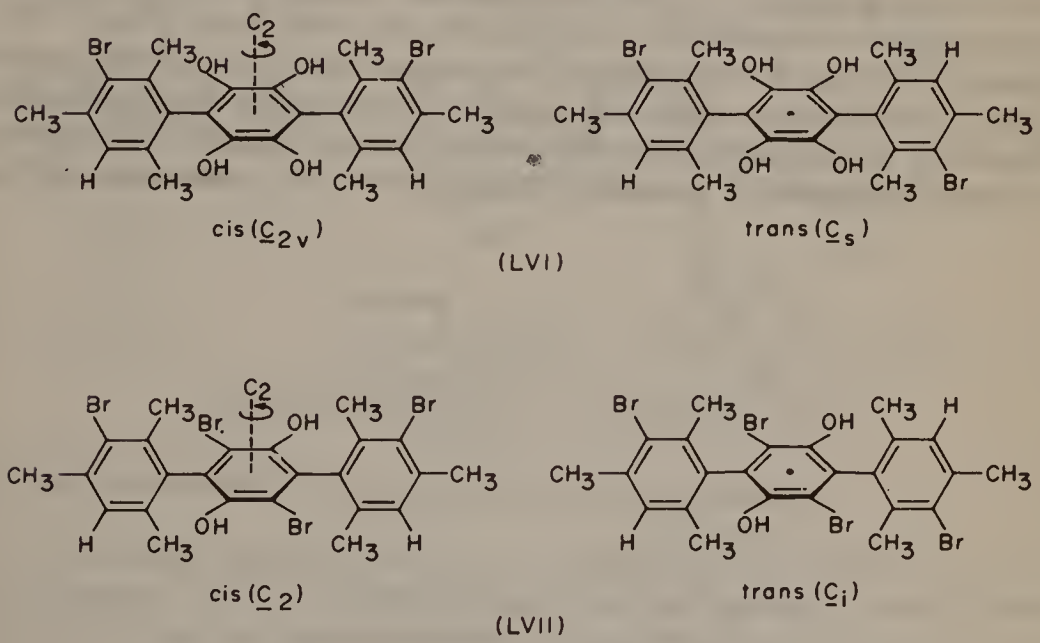


Figure 5.20 Stereoisomerism in terphenyl derivatives

addition, has a centre of symmetry, the mid-point of the central ring (denoted by a dot). They belong to point groups C_{2v} and C_s respectively. In the analogous compound (LVII), the central ring is dissymmetrically substituted which eliminates the σ plane. The cis isomer (C_2) is resolvable but the trans isomer still retains tne centre of symmetry and is a meso compound. The molecule (LVII) thus behaves as if it has two equivalent elements of chirality like tartaric acid.

(*iii*) One of the planar ring is replaced by an acyclic grouping which is two-dimensionally chiral usually due to a dissymmetrically substituted trigonal atom. Molecules of this type may give atropisomers if sufficient steric hindrance is

created around the pivotal bond. Thus the substituted stilbene (LVIII) (Figure 5.21) is capable of resolution. The substituted naphthylamine (LIX) provides another example in which the peri nitro group prevents the substituents at nitrogen* to cross the plane of the naphthalene ring. Assignment of configurational symbols is made following the usual procedure which is illustrated for enantiomer (LIX) having *S* configuration.

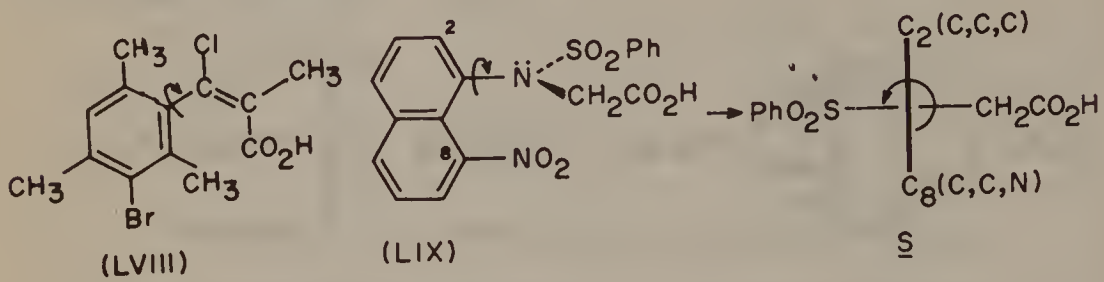


Figure 5.21 Acyclic analogues of biphenyls

An interesting example is provided by the two oximes of 1-acetyl-2-hydroxynaphthalene-3-carboxylic acid. The structures (LX) and (LXI) (Figure 5.22) represent the *E* and *Z* diastereomers of the oxime respectively. In the former, rotation around the aryl—carbon (as shown) is not sufficiently restricted and the compound is not resolvable. But in the latter, the hydroxyl group of the oxime in the planar conformation interferes sufficiently with the substituents of the

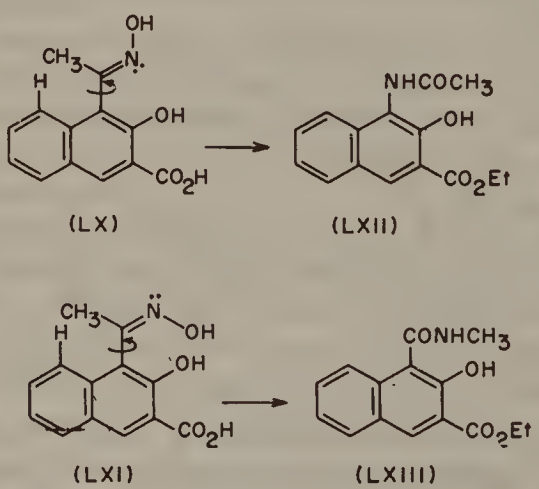


Figure 5.22 Atropisomerism in oximes and Beckmann rearrangement

naphthalene moiety (2-OH and 8-H)† to permit the separation of the two (non-planar) enantiomers. The configuration (*E* and *Z*) of the two oximes is thus settled unambiguously. The *E*-isomer (as ethyl ester) when submitted to Beckmann rearrangement furnishes the acetamide (LXII) while the *Z*-isomer (as ethyl ester)

*Aryl N is nearly planar with very low inversion barrier and so this is truly a case of hindered rotation.

† Peri interaction accounts for the major contribution.

gives the naphthamide (LXIII) which proves that, in Beckmann rearrangements, the substituent anti to the leaving group (e.g. N-OH) migrates.

5.5.5 Atropisomerism around sp^3—sp^3 bond

Atropisomerism so far shown is due to restricted rotation around an sp^2—sp^2 single bond. It has been pointed out before that rotation about an sp^3—sp^3 single bond is restricted to various extent but the energy barrier is usually too low to permit the isolation of any particular conformer (rotamer). In the triptycene type of molecules, however, the barrier to rotation around a 9-substituted bond may be quite high (see also Chapter 12). Thus the compound (as LXIV) (Figure 5.23) has been synthesised and all three possible conformers isolated. The structure (LXIV) represents the meso isomer (C_s) while the structures (LXVa) and (LXVb) represent two enantiomers (C_1). They are fairly stable at room temperature (Oki 1976).

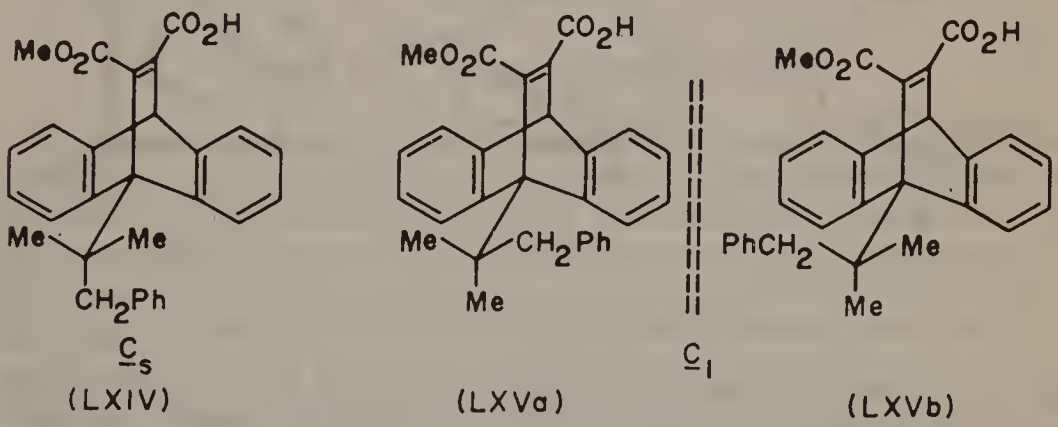


Figure 5.23 Atropisomerism around an sp^3—sp^3 bond

5.6 Stereochemistry of molecules with planar chirality

The geometrical requirement of a molecule having planar chirality has already been discussed. Just as in axially chiral molecules, an exchange of a pair of ligands around the chiral axis leads to an enantiomer, similarly in molecules with a chiral plane, an exchange of ligands across the chiral plane (which in isolation is a two-dimensional chiral simplex) leads to an enantiomer. The configurational stability arises out of restriction imposed by steric factor on the out-of-plane movement of a structural unit and an energy factor is involved as in the biphenyls. Such molecules again cannot be represesnted by any type formula since the isolation of stereo-isomers depends on the bulk of certain groups and the size of the ring. This is also a type of atropisomerism and is exhibited by ansa compounds, cyclophanes, and certain *trans*-cycloalkenes.

5.6.1 Ansa compounds

If two para positions of an aromatic ring are attached to heteroatoms and they are

in turn connected through a polymethylene chain, the compounds are called *ansa* compounds (ansa means handle in Latin). The compounds (LXVI)—(LXVIII) (Figure 5.24) fall under this category. In all of them, the aromatic ring is dissymmetrically substituted (two-dimensionally chiral) and the polymethylene chain can be either above or below the plane of the aromatic ring giving two enantiomeric structures. If the polymethylene chain is small enough, it cannot be swung around the plane (alternatively, the rotation of the ring is hindered) and the two enantiomers will be configurationally stable. Thus the compound (LXVI) with monosubstituted phenylene is resolvable when n is 8, racemises easily when n is 9, but is non-resolvable when n is 10. The disubstituted molecule (LXVII) gives stable enantiomers even when n is 10. The dithio-ether (LXVIII) is extremely stable.

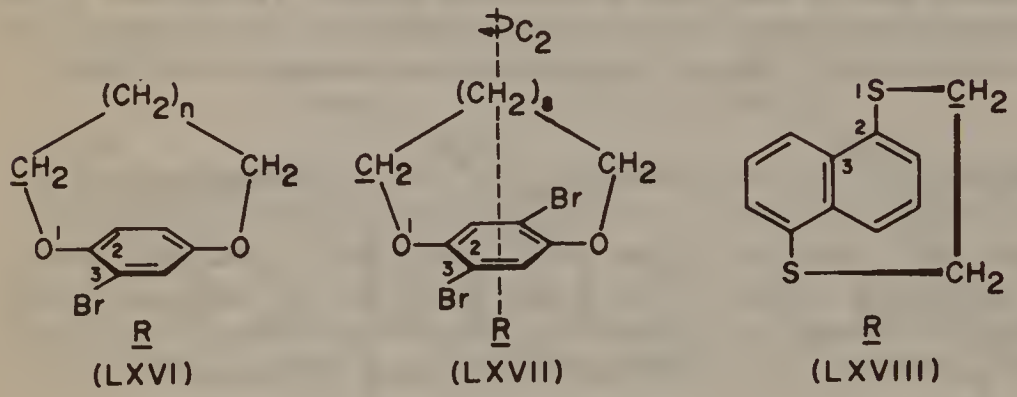


Figure 5.24 Ansa compounds

For the assignment of chirality descriptors to this type of compounds, a pilot atom has to be selected first which is directly bonded to an atom in the chiral plane but itself is not in the plane, i.e., it is the first out-of-plane atom. The pilot atom should be chosen from that side of the plane which is most preferred by the standard subrules. Thus in the case of LXVI, the preferred side of the ring is the one with ortho bromine and the left hand methylene carbon (underlined) is the pilot atom. In case both sides are equivalent, the pilot atom may be chosen from any side. The sequence starts from the first in-plane atom (here oxygen) and continues through atoms in the plane always following the path leading to the more preferred atom. This is indicated in the structure by numerals 1, 2, and 3. Viewed from the pilot atom, if the order 1→2→3 appears in a clockwise direction, the configuration is *R* and if in an anticlockwise direction, the configuration is *S*. Accordingly, the configurational notations of compounds (LXVI), (LXVII), and (LXVIII) are all *R*. The molecules (LXVI) and (LXVIII) belong to point group C_1 while the molecule (LXVII) having a C_2 axis belongs to point group C_2.

5.6. Cyclophanes

Cyclophanes are conceptually similar to ansa compounds. Usually two aromatic rings are joined together by bridging the para positions to give paracyclophanes or the meta positions to give metacyclophanes. The compound (LXIX) (Figure 5.25)

is a simple paracyclophane with one aromatic ring only (resembling an ansa compound) which has been resolved. The pilot atom is the methylene carbon (underlined) on the side of the carboxyl group and the structure (LXIX) has *R* configuration. In more complex paracyclophanes (e.g., LXX), the two benzene rings are arranged one above the other (parallel) and the one with the substituent (CO_2H) cannot make a full turn if the chains are small.

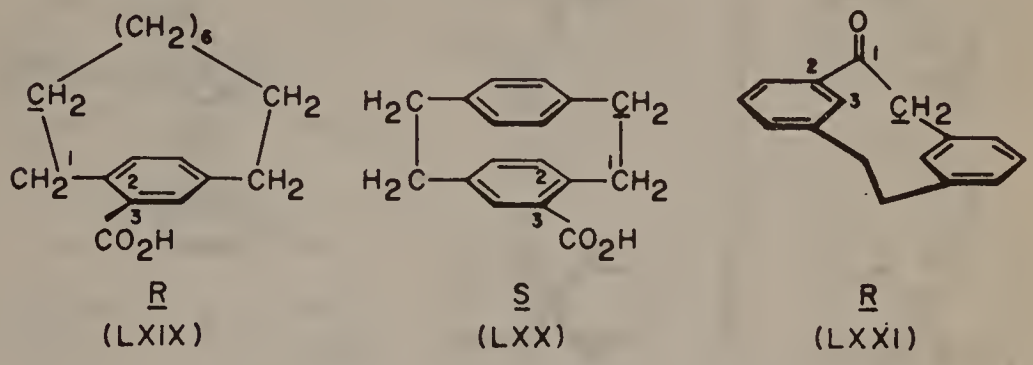


Figure 5.25 Cyclophanes: simple, para, and meta

To have enantiomerism, at least one of the ring must be dissymmetrically substituted or, in the case of the metacyclophanes, the two chains must be non-equivalent as in the structure (LXXI). For the assignment of configuration, the same procedure is adopted. The pilot atoms are underlined and the molecules (LXX) and (LXXI) have configurations *S* and *R* respectively. Paracyclophanes have been reviewed by Cram and Cram (1971) and metacyclophanes by Vögtle and Neumann (1974). The two parallel aromatic π electronic systems interact with each other (π-π transannular interaction) which is exhibited in many of their physical properties particularly in the electronic spectrum.

5.6.3 *trans*-Cycloalkenes

trans-Cycloalkenes provide another type of molecules with planar chirality. The two trigonal carbons and the atoms directly attached to them are in a plane and the polymethylene bridge is skewed in the third dimension. Cyclooctene is the smallest ring* which can accommodate a trans double bond and two conformations (LXXIIa) and (LXXIIb) (Figure 5.26) are possible which are mirror images of each other. The interconversion of the two enantiomers which requires the swinging of the tetramethylene chain over and below the plane of the trigonal atoms (chiral plane) is opposed by ring strain (angle strain) and the two enantiomers have been separated (Cope et al 1963). The molecule has a C_2 axis (passing through the centre of the double bond and bisecting 5-6 bond) and therefore belongs to point group C_2. In passing to higher homologues, the mobility of the polymethylene chain increases and the rotational barrier decreases. *trans*-

**trans*-Cycloheptene has been seen as a fleeting intermediate; the case of *trans*-cyclohexene is more controversial.

Cyclononene exists in optically active form only at −80° and *trans*-cyclodecene is an extremely mobile system. The configurational notation is assigned in the same way as before selecting the pilot atom from any side of the plane. The two enantiomers (LXXIIa) and (LXXIIb) have *R* and *S* configurations respectively*.

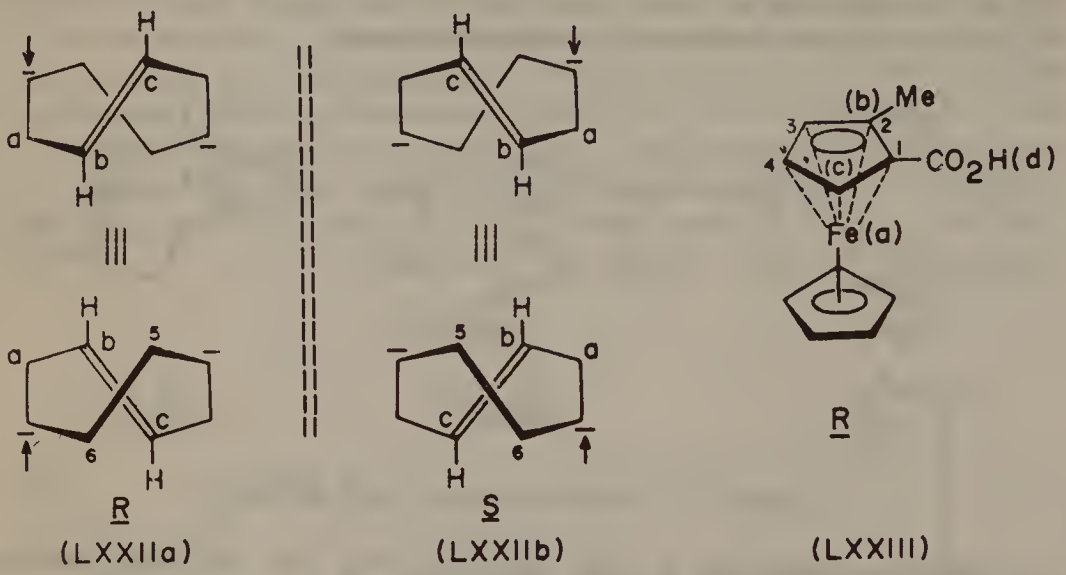


Figure 5.26 *trans*-Cyclooctene and a chiral ferrocene

The ferrocene molecule (LXXIII) (Figure 5.26) with one of the five-membered ring dissymmetrically substituted is a typical example of chiral metallocenes which were previously considered to have planar chirality. In the modified system (1966), they are classified as compounds with chiral centres (see Schlögl 1967). Each of the five carbon atoms of the substituted cyclopentadienyl ring is an asymmetric atom and bonded to the metal. The chirality of any of these centres preferably C-1 (most preferred by standard subrule) specifies the chirality of the molecule. Fe is a, C-2 is b, C-5 is c, and CO_2H is d which makes the configuration of LXXIII *R*. (C-2 and C-5 are bonded to Fe and so get precedence over CO_2H).

5.7 Helicity

A helix is inherently chiral and is non-superposable on its mirror image (see Figure 5.27). A helix may, in fact, be considered as manifesting axial chirality, its axis serving as the chiral axis, although it is more convenient to discuss chirality of this type under the heading of *helicity*. If it has a C_2 axis perpendicular to the axis of the cylinder, the helix is called palindromic†. The assignment of chiral designation to the helix is very simple. If moving from one end to the other along the axis, the

*For better visualisation, it is advised to bring the concerned pilot atom (marked by an arrow) on to the front with the double bond at the back (see the structures at the bottom). The fiducial groups (a,b,c) now appear in a plane away from the spectator point.

†It looks the same from either end.

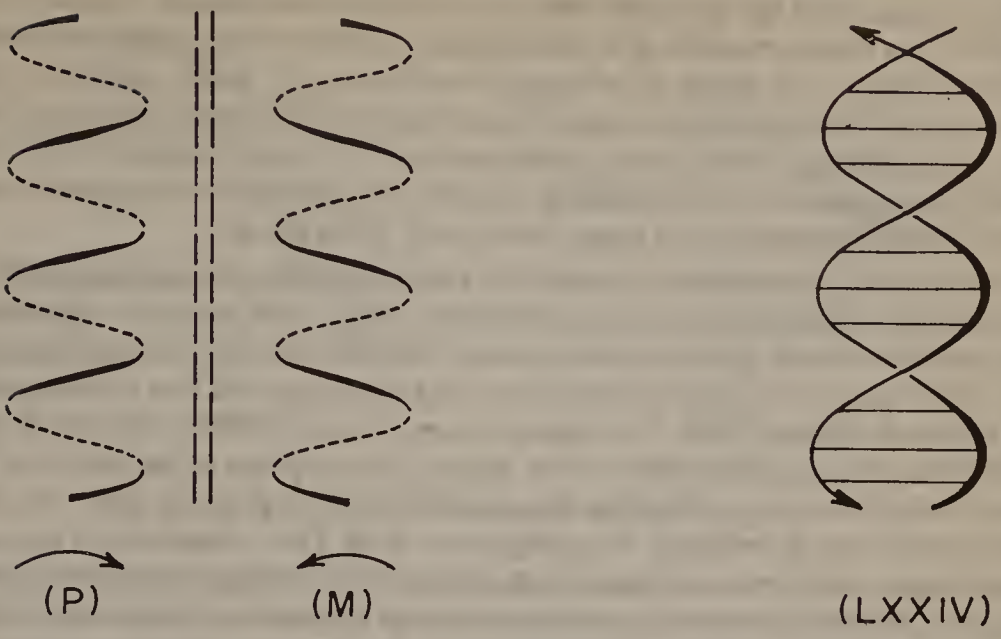


Figure 5.27 Helical structures

helix describes a clockwise direction, it is designated *P* (plus) and if it describes an anticlockwise direction, it is designated *M* (minus). At the molecular level, helicity often arises from secondary structure and is conformational in origin. Thus helical structure has been intensively studied in protein molecules. The polypeptide chain derived from naturally occurring L-amino-acids often coils to form an α-helix which is a *P* helix. Such helices are directed, i.e., two ends are non-equivalent and there is no C_2 axis. The skeleton of a double helix present in the structure of nucleic acids is shown in LXXIV. Although of conformational origin, the helicity is preserved in these molecules by strong intramolecular H-bondings (Goodman et al 1970). Optical rotatory dispersion and circular dichroism (Chapter 15) provide interesting experimental study of polypeptide helicity.

Helicity in molecule may result also from molecular overcrowding. This is manifested in molecules such as helicenes (as LXXV), benzphenanthrenes (as LXXVI), or even phenanthrenes (as LXXVII) (Figure 5.28). These molecules are normally expected to be planar but, due to molecular overcrowding, the ring structures assume a helical shape; the terminal rings and the substituents are in

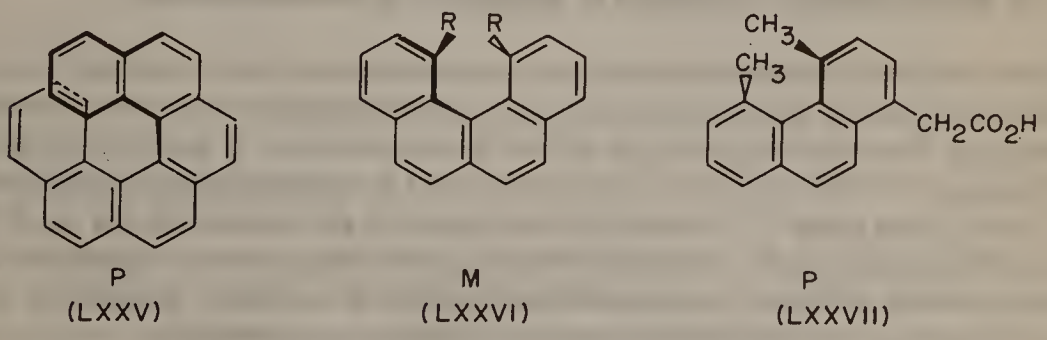


Figure 5.28 Molecular overcrowding

different planes and the molecules exist as two helical enantiomers. Hexahelicene (LXXV) is a classic example of a stable helical molecule with exceptionally high optical rotation, $[\alpha]_D$ being 6200°. Higher helicenes (e.g., hetpa-, octa- etc.) are also known. The chiral designations of the molecules (LXXV)-(LXXVII) are *P, M,* and *P* respectively. The first two molecules have a C_2 axis passing through the central ring junction of the molecules with the two planes of the terminal rings symmetrically oriented around it and belong to C_2 point group.

It is often very convenient to specify the chiral descriptor of conformational or atropisomeric enantiomers such as substituted ethanes and biphenyl derivatives with axial chirality by helical nomenclature (*P* and *M*). The rules are very simple. The substituents are ordered in three in the case of ethanes and two in the case of the biphenyls (Figure 5.29). The highest priority group (CIP) is selected at the front (fiducial group) and related to the highest priority group at the rear. If in so doing, a clockwise turn is described, the configuration is *P*; if, on the other hand an anticlockwise turn is described, the configuration is *M*. This is illustrated in the two enantiomeric conformers of meso tartaric acid (LXXVIIIa) and (LXXVIIIb) (Figure 5.29). For illustrations in the biphenyls, the projection of *S*-dinitrodiphenic acid (Figure 5.13) is reproduced here (XXXV). The two fiducial groups are NO_2 in the front and NO_2 in the rear. Movement from the former to the latter takes

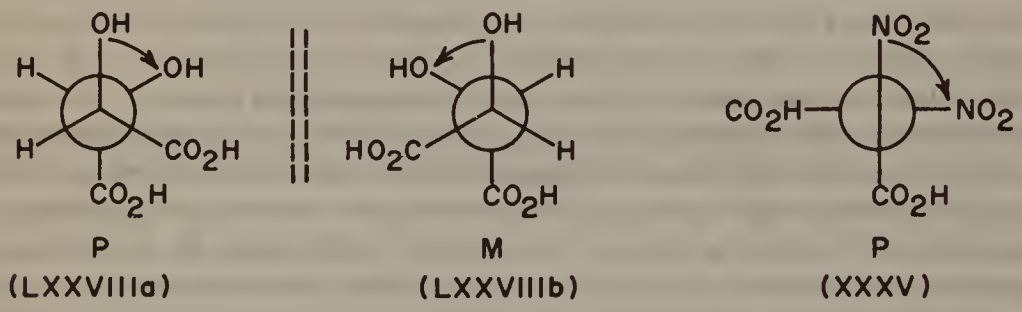


Figure 5.29 P and M nomenclature for acyclic conformers

place in clockwise direction and so it is represented as a *P* helix. The enantiomer is an *M* helix. In the biphenyls, *R* corresponds to *M* and *S* to *P*. In case two ligands are identical as in $ClCH_2CH_2Cl$ and $Cl_2CHCHCL_2$, the unique atoms (Cl in the first and H in the second) are fiducial.

5.8 Miscellaneous examples of molecular stereoisomerism

Some molecules show stereoisomerism (enantiomerism or diastereomerism) due to factors inherent in their structures and may not be categorised under the previous headings. One interesting example of such a chiral molecule is provided by tri-*o*-thymotide (LXXIX) (Figure 5.30) (Newman and Powell 1952) which possesses a C_3 axis (point group C_3). Molecular dissymmetry in this molecule is the result of the three phenyl rings not lying in the same plane (due to steric congestion), as shown in the structure. Its configurational stability is very low. Basically, it is a case of atropisomerism (hindered rotation leading to stereoisomerism).

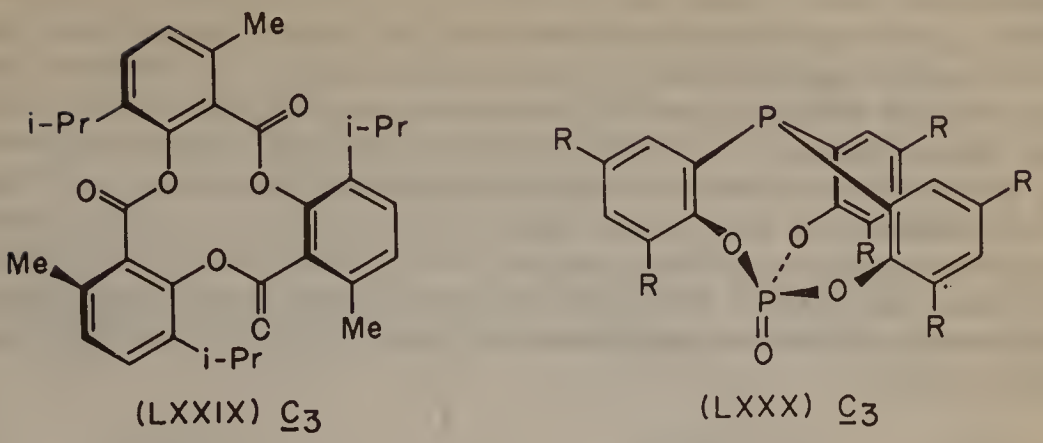


Figure 5.30 Chiral molecules of C_3 point group

Very recently, Sharpless et al (1988) have synthesised an interesting type of chiral monophosphanes of C_3 symmetry represented by the structure (LXXX, R = H, *t*-Bu) which are chiral also for a similar reason. The C_3 axis passes through the two phosphorus atoms and is tilted by about 27° with respect to the planes of the aromatic rings which eliminates the σ planes.

Annulenes are large ring compounds with conjugated (alternate) double bonds which may exist both in cis and trans configuration. Thus the [14]annulenes shown in structures LXXXI and LXXXII (Figure 5.31) have four trans and three cis double bonds (Gaoni and Sondheimer 1964). In each of the structures, four transannular hydrogens overlap with each other leading to two conformational diastereomers which differ in the mode of overlapping. The two forms although separable (on silica gel column impregnated with silver nitrate) are easily interconvertible.

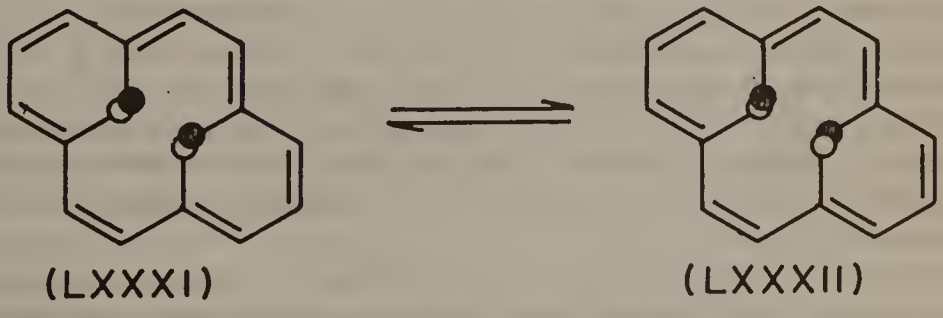


Figure 5.31 Stereoisomers of annulenes differing in the mode of overlap of intraannular H atoms

5.9 Cyclostereoisomerism

A new type of stereoisomerism has been described first by Prelog et al (1964) and later extended by Mislow et al (1986-87) which is based on *cyclic directionality* and is known as cyclostereoisomerism. Compounds exhibiting such stereoisomerism are generally cyclic and contain more than one chiral centre either as a part of the

ring or as side chains. A cycle (constituted of three or more non-linear points in the molecule) is directed if the two directions around the ring are non-equivalent, one of the simple example being that in 2,5-diketopiperazine (LXXXIII) (Figure 5.32) and undirected if they are equivalent as in benzene and cyclohexane. The necessary and sufficient condition for cyclic directionality (Mislow 1986) is the absence of a C_{2n} axis and a σ plane *bisecting* the molecule. If two such molecules have identical chiral framework but differ in ring (cyclic) directionality, they are called cyclostereoisomers which can be further subdivided into cycloenantiomers and cyclodiastereomers depending on whether they are mirror images of each other or not. Cyclic directionality may be of constitutional origin (as in LXXXIII) or of conformational origin (see later).

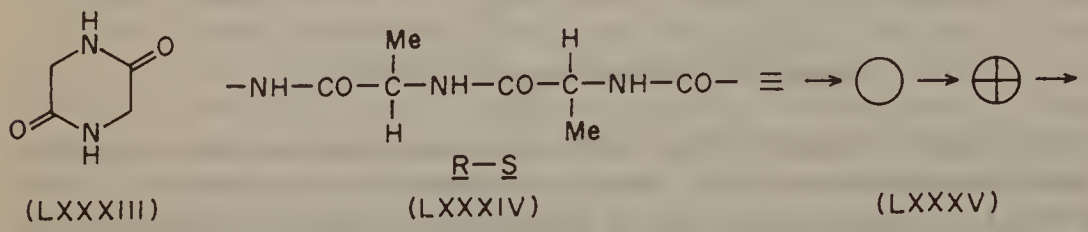


Figure 5.32 Constitutional ring directionality and a short hand notation for a peptide chain

5.9.1 Cyclic directionality of constitutional origin

Cyclooligopeptides (constituted of α-amino acids) provide examples of ring compounds with cyclic directionality. Since the achiral unit chain, NH-CO joining the chiral centres differ in its terminal groups, ring directions along the ring, clockwise and anticlockwise, are non-equivalent giving rise to constitutional ring directionality. If such a cyclooligopeptide is built up of equal numbers of *R* and *S* amino acids of the same kind (monotonic) (the total number of chiral centres becomes 2n), it may show cyclostereoisomerism. A shorthand notation for a two-unit chain (LXXXIV) containing one *R* and one *S* alanine moiety is shown in Figure 5.32 to be used in subsequent discussion. The white circle stands for *R* and the crossed circle for *S* chiral centre while the arrow (→) pointing to the right and the arrow (←) pointing to the left stand for NH-CO and CO-NH respectively (LXXXV). The white circle and the crossed circle are mirror images of each other and so are the arrows.

When the total number of alanine residues (2n) is two, only one arrangement (*R* and *S* doubly linked through peptide chains) is possible which is achiral due to the presence of an S_2 axis (an inversion centre). When $2n = 4$, two different arrangements of the chiral centres, *RRSS* and *RSRS* are possible which are shown by short-hand notations as LXXXVI and LXXXVIII and by detailed structures as LXXXVII and LXXXIX respectively (Figure 5.33). Both of them are achiral, the first having an S_2 axis and the second an S_4 axis*. They are thus two non-resolvable meso diastereomers in the normal sense.

*Because of ring directionality, these structures cannot have any σ plane.

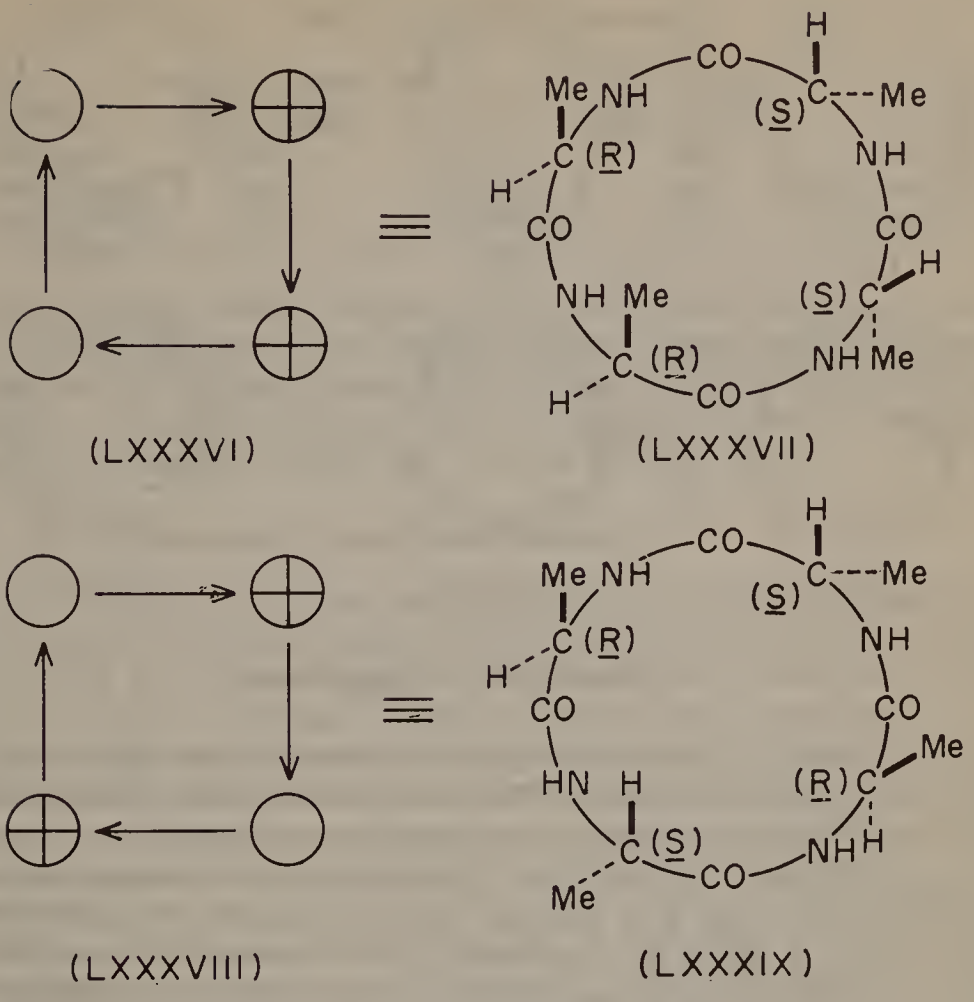


Figure 5.33 Cyclotetraalanyls: two meso isomers

When $2n = 6$, three different arrangements of the chiral centres are possible. The one in which three *R* and three *S* centres are placed consecutively has an S_2 axis and is a meso isomer (structure not shown). The second one with *R* and *S* placed alternately (XC) (Figure 5.34) is also a meso compound (presence of an S_6 axis); its mirror image (XCI) apparently differing in ring directionality* is superposable with the original when rotated by 180° around a horizontal axis. The third one (XCII) does not have any S_n axis and is chiral (point group C_1). Its mirror image (XCIII) shows an unusual structural feature, all the *R* and *S* units are arranged exactly as in the original (XCII); only the ring directionality is different which prevents the two from being superposable (a 180° rotation of XCIII around the horizontal axis makes the ring directionality the same but now the chiral framework is different). The two structures are called *cycloenantiomers* (the stereoisomerism is called *cycloenantiomerism*). Like true enantiomers, they possess identical properties and differ only in optical rotation which is equal but opposite.

* Cyclic directionality and ring directionality are used here synonymously.

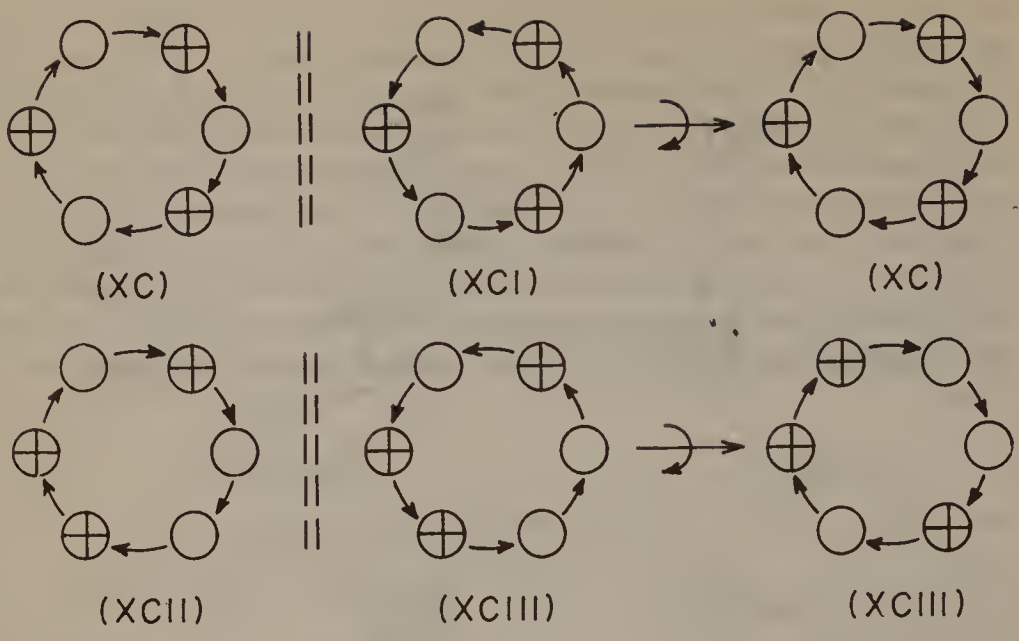


Figure 5.34 Cycloenantiomers

Thus the cyclohexaalanine (XCII) with a clockwise directionality has α_D^{23} of $-25.5°$ while its cycloenantiomer (XCIII) with an anticlockwise directionality has α_D^{23} of $+22.2°$ (the small difference is due to imperfect purification).

With the increase of 2n, the number of stereoisomers also increases and when $2n = 10$, there occur four meso forms, six pairs of cycloenantiomers, and five pairs of enantiomers (a total of 26 stereoisomers). The structures (XCIV) and (XCV) (Figure 5.35) represent a normal enantiomeric pair while the structure (XCVI) represents a member of another enantiomeric pair. Inspection of XCIV and XCVI reveals an interesting fact : their chiral frameworks are identical, only the ring directionality is different. They cannot be cycloenantiomers since they are not mirror images of each other. They are, therefore, called *cyclodiastereomers* and like normal diastereomers, they differ in all their properties. The enantiomer of XCVI is in turn cyclodiastereomeric with XCV. Characterisation of a pair of cyclostereoisomers is thus made on the basis of three criteria : the identity or non-identity of the chiral framework, ring directionality, and mirror image relation, as summarised in Table 1.

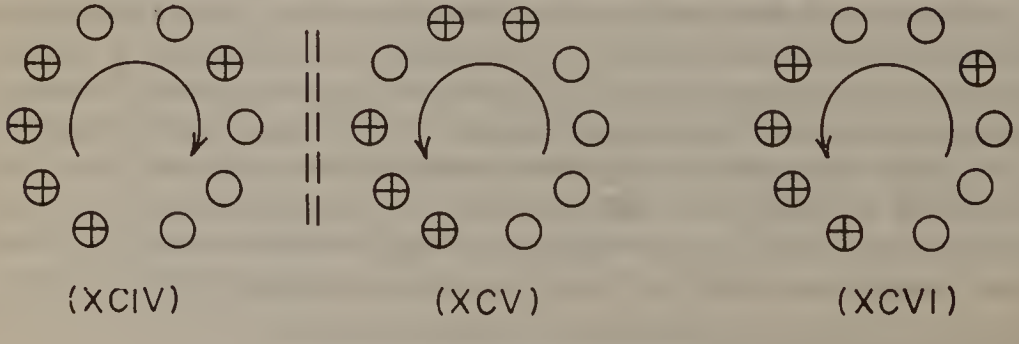


Figure 5.35 Cyclodiastereomers

Table 5.1 Criteria for cyclostereoisomers

Stereoisomers	*Chiral frame*	*Directionality*	*Mirror image*	*Example*
Enantiomers	different	opposite	yes	XCIV & XCV
Cycloenantiomers	same	opposite	yes	XCII & XCIII
Cyclodiastereomers	same	opposite	no	XCIV & XCVI

Since ring directionality can be changed at will by simply turning over the ring, the nature of cyclostereoisomers is best determined by keeping the ring directionality of any two structures opposite and then applying the other two criteria. Compounds which are neither enantiomers, nor cycloenantiomers, nor cyclodiastereomers are normal diastereomers by default, e.g., XCV and XCVI.

5.9.2. Cyclic directionality of conformational origin

Recently, Mislow and coworkers have demonstrated that cyclic directionality may also originate from several conformationally mobile groups arranged around the periphery of an undirected ring and rendered immobile by steric factors. This is best illustrated by examples. 1,2-Diethyl-3,4,5,6-tetraisopropylbenzene (XCVII) (Figure 5.36) on photobromination affords two diastereomers (the two ethyl side chains are converted into two stereogenic α-bromoethyl groups). One of the diastereomers (*R,S*) is shown in its two enantiomeric forms (XCVIII) and (XCIX). In the structures, the white circles stand for Me and the black circles for Br; the tertiary H's are indicated by short lines. It may be noted that the six side chains are interlocked in such a way that the tertiary H's are all arranged in a clockwise or in an anticlockwise fashion giving cyclic directionality. The two enantiomers (XCVIII) and (XCIX) have the same chiral framework (*R,S*) but differ in cyclic directionality and may, therefore, be called *conformational cycloenantiomers*. The second diastereomer (not shown) also exists in two enantiomeric forms, *R,R* and *S,S* which are normal enantiomers. Under condition of rapid rotation of the side chains around aryl-C bonds, the enantiomers of the first diastereomer interconvert into each other; the diastereomer thus becomes a meso isomer similar to *meso*-tartaric acid

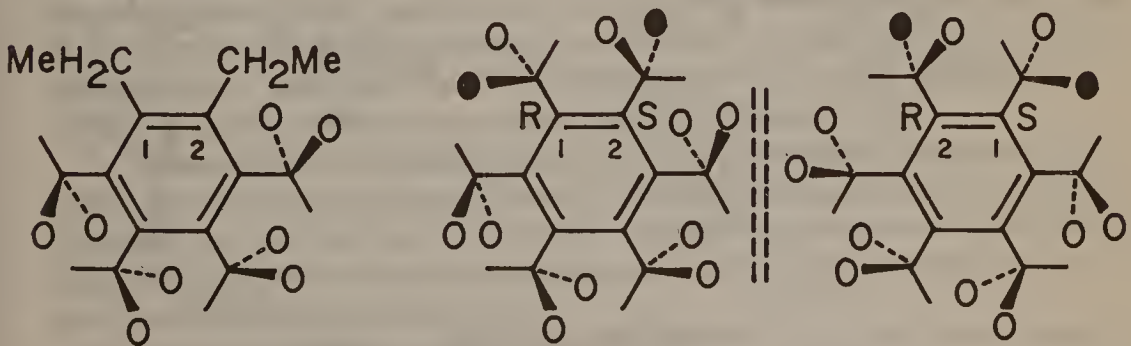


Figure 5.36 Conformational cycloenantiomers

which also exists in two chiral conformers, *P* and *M*. The enantiomers of the second diastereomer, on the other hand, retain their configurational integrity under condition of rapid internal rotation similar to (+)- and (−)- tartaric acid.

5.9.3 Retro-enantio isomers

Yet another interesting type of cyclostereoisomerism is encountered in cyclooligopeptides and analogues consisting of two or more different chiral centres (polytonic). If the configuration of each chiral unit and the ring direction are both reversed for a structure, a new structure results which is essentially a constitutional isomer of the original since the sequence C_1-NH-CO-C_2 has now been replaced by the sequence C_1-CO-NH-C_2, C_1 and C_2 representing two different chiral centres. Two such tripeptides (C) and (CI) are shown in Figure 5.37. The circles of different radii refer to different amino acid residues. Such pairs of compounds are called 'retro-enantio' isomers. They are of biological interest because one can effectively replace the other in a biological (enzymatic) reaction (see Nogradi 1981). This is due to the fact that both of them have the same relative disposition of the side chains and the same conformation of the peptide chain but differ in the ring direction as evident in the two structures (CII) and (CIII). Thus the antimicrobial activities of enniatin, an antibiotic cyclohexapeptide are almost identical with those of its retro-enantio isomer (Shemjakin et al 1969).

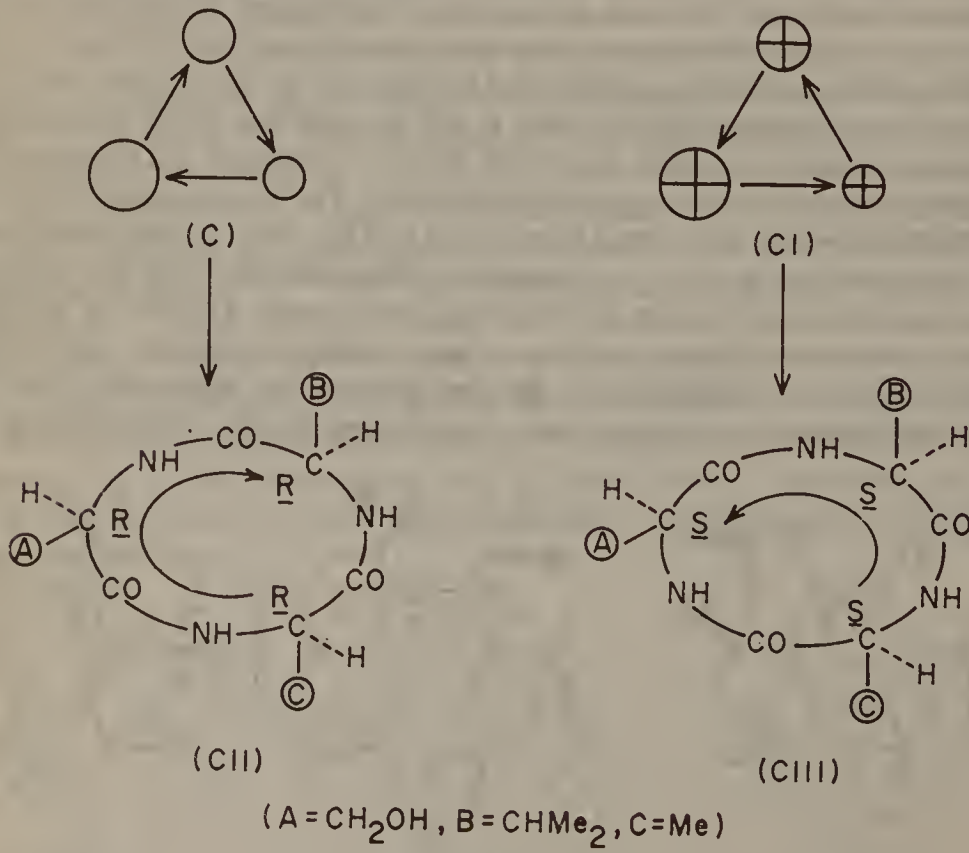


Figure 5.37 Retro-enantio isomerism

5.10 Summary

1. A molecule may be chiral even in the absence of a centre of chirality due to the presence of other elements of chirality such as axes, planes, and helices. The principle of axial chirality is explained on the basis of an elongated tetrahedron, the two adjacent pairs of vertices of which are distinguishable from each other. Such a tetrahedron serves as the model of axial chirality and the line along which the tetrahedron is elongated acts as the chiral axis. At the molecular level, a large number of molecules such as appropriately substituted allenes, hemispiranes, spiranes, adamantoids, biphenyls, and their analogues conform to this model and show enantiomerism due to axial chirality.

2. The three-dimensional stereoisomers based on axial and planar chirality can be conveniently analysed in terms of two-dimensional chiral simplexes as structural units. When two such units undergo planar combination, they lead to planar diastereomers such as cis and trans olefins but when they combine in a non-planar way, three-dimensional structures result which correspond to an elongated tetrahedron previously mentioned and the resulting molecules show enantiomerism.

A two-dimensionally chiral plane divides the three-dimensional space into two distinguishable half-spaces. An atom or a group may be attached to a centre in the chiral plane from either half-space giving two enantiomers. Molecules belonging to this category are said to be chiral due to the presence of a chiral plane.

3. A number of allenes, hemispiranes, spiranes, and adamantoids which are chiral according to the above principles, are discussed. In order to assign configurational symbols to axially chiral molecules, the standard subrule (0) is applied first which states that near groups precede far groups. The molecule is viewed from any end of the axis and the groups near to the observer are numbered 1 and 2 whereas the groups at the far end are numbered 3 and 4 following the priority rule. The order $1 \rightarrow 2 \rightarrow 3$ (clockwise or anticlockwise) gives the configuration as *R* and *S*.

4. Stereoisomerism in biphenyls requires a new principle, namely, hindered rotation around the pivotal bond (the bond connecting the two phenyl groups) and is known as atropisomerism. The two aryl rings must be dissymmetrically substituted (so that they conform to two-dimensional chiral units) and there should be sufficient bulky ortho substituents to prevent them from being planar. A large number of biphenyls of this type have been discussed which exhibit different extent of configurational stability including a few which are singly or doubly bridged (through ortho positions). Terphenyl derivatives with suitable substituents may show both cis-trans isomerism as well as enantiomerism.

5. The assignment of configurational symbol to biphenyls and analogues is done following the same general procedure as recommended for axially chiral molecules. Unlike in the previous practice, however, the fiducial groups are not the ortho substituents *per se* but the four ortho carbons properly complemented to quadriligancy according to the sequence rule.

6. Atropisomerism is also known to occur in compounds with restricted rotation around single bond joining two sp^3 hybridised carbons atoms. Thus a few triptycene type molecules are known which have been isolated in enantiomeric as well as in diastereomeric forms.

7. Molecules with planar chirality include ansa compounds, paracyclophanes, metacyclophanes (in which remote atoms of a phenyl ring are joined by chain or chains), and a few *trans*-cycloalkenes. The enantiomeric forms result due to the position of the methylene chain on either side of the aryl ring or C = C bond, the interconversion between the isomers being prevented by the inability of the chain to swing from one side to the other of the aryl or olefinic plane.

The assignment of configurational descriptors to these compounds is done by first selecting a pilot atom (spectator point) which is the first out-of-plane atom linked to the sequence-preferred end of the chiral plane. The sequencing starts with the first in-plane atom and continues through atoms in the plane along the preferred path. These atoms are numbered respectively 1; 2 and 3 and the order in which they appear when seen from the pilot atom determines the configuration; i.e., *R* for clockwise and *S* for anticlockwise.

8. The α-helix represents a secondary structure of protein molecules arising out of coiling of polypeptide chain and is thus conformational in origin. Certain polycyclic aromatic compounds known as helicenes also assume helical structure due to molecular overcrowding. As a helix is traversed, it describes either a clockwise or an anticlockwise direction and accordingly it is called a *P* (plus) or an *M* (minus) helix. Polypeptide chains formed from L-amino-acids give mostly *P* helices which are held rigidly through intramolecular H-bonding.

Sometimes, it is more convenient to specify the chirality of conformers of acyclic molecules and biphenyl derivatives (having axial chirality) by helical nomenclature. A few illustrations are given.

9. Finally, a new type of stereoisomerism, namely, cyclostereoisomerism based on cyclic directionality (of constitutional or conformational origin) has been discussed.

References

1. V. Prelog and G. Helmchen (1982), *Angew. Chem. Intl. Edn. Engl.*, **21**, 567.
2. K. Mislow and J. Siegel (1984), *J. Amer. Chem. Soc.*, **106**, 3319.
3. S.R. Landor (Ed.) (1982) in *The Chemistry of Allenes*, vol. 3, Academic Press, New York.
4. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds* McGraw-Hill, New York; see R. E. Lyle and G.G. Lyle (1957), *J. Org. Chem.*, **22**, 856; G.G. Lyle and T. Pelosi (1966), *J. Amer. Chem. Soc.*, **88**, 5276.
5. H. Gerlach (1968), *Helv. Chim. Acta*, **51**, 1587.
6. G.E. McCasland and S. Proskow (1956), *J. Amer. Chem. Soc.*, **78**, 5646.
7. H. Gilman (Ed.) (1943) in *Organic Chemistry : An Advanced Treatment*, vol. 1, Wiley, New York; also see, D.H. Hall (1969) in *'Progress in Stereochemistry'* Eds. B.J. Aylett and M.M. Harris, Butterworths, London.
8. G. Krow (1970) in *Topics in Stereochemistry* vol. 5. Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
9. J.W. Brooks, M.M. Harris, and K.E. Howlett (1957), *J. Chem. Soc.*, 1934.
10. M. Oki, H. Iwamura, and G. Yamamoto (1971), *Bull. Chem. Soc. Japan*, **44**, 262,

11. D Nasipuri, P.K. Bhattacharya, and G.T. Furst (1977). *J. Chem. Soc. Perk.* II, 356.
12. K. Mislow and M.A.W. Glass (1961), *J. Amer. Chem. Soc.*, **83**, 2780.
13. E.L. Eliel (1971), *J. Chem. Educ.*, **48**, 163.
14. R.S. Cahn, C.K. Ingold, and V. Prelog (1966), *Angew. Chem. Intl. Edn. Engl.*, **5**, 385.
15. M. Oki (1976), *Angew. Chem. Intl. Edn. Engl.*, **15**, 87.
16. D.J. Cram and J.M. Cram (1971), *Acc. Chem Res.*, **4**, 204.
17. F. Vögtle and P. Neumann (1974), *Top. Curr. Chem.*, **48**. 67.
18. A.C. Cope, C.R. Ganellin, H.W. Johnson, T.V. Van Auken, and H.J.S. Winkler (1963), *J. Amer. Chem. Soc.* **85**, 3276.
19. K. Schögl (1967) in *Topics in Stereochemistry*, vol. 1., Eds. N.L. Allinger and E.L. Eliel, Wiley, New York.
20. M. Goodman, A.S. Verdini, N.S. Choi, and Y. Masuda (1970) in '*Topics in Stereochemistry*', vol. 5, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
21. A.C.D. Newman and H.M. Powell (1952), *J. Chem. Soc.*, 3747.
22. Y. Gaoni and F. Sondheimer (1964), *Proc. Chem. Soc.*, 299.
23. C. Bolm. W.M. Davis, R.L. Hatterman, and K.B. Sharpless (1988), *Angew. Chem. Intl. Edn. Engl.*, **27**, 835.
24. V. Prelog and H. Gerlach (1964), *Helv. Chim. Acta*, **47**, 2288; see also R. Crusse (1966) in *Stereochemie der Kohlenstoffverdunger*, E.L Eliel, Verlag Chemie, Weinheim.
25. K. Mislow (1986), *Chimia*, **40**, 395.
26. M.D. Singh, J. Siegel, S.E. Bialĭ, and K. Mislow (1987), *J. Amer. Chem. Soc.*, **109**, 3397.
27. M. Nogradi (1981) in '*Stereochemistry : Basic Concepts and Applications*', Pergamon Press, Oxford.
28. M.M. Shemjakin, J.A. Ovohinikov, and V.T. Ivanov (1969), *Angew. Chem. Intl. Edn. Engl.*, **8**, 492

Chapter 6

Topicity and Prostereoisomerism

6.1 Introduction

Ligands (atoms or groups in a molecule)* are called homomorphic (Greek *homos* means same and *morphe* means form) if they are indistinguishable when considered in isolation. In the case of atoms, they must be of the same element, e.g., two H or two Br atoms and in the case of groups, they must have the same constitution and configuration, e.g., two Me or two Ph groups or two secondary butyl groups of the same chirality *R* or *S*. Such homomorphic ligands may, however, be distinguishable in an intact molecule if they are bonded to constitutionally different ligating centres in the molecule or if they have different spatial relation with the rest of the molecule. In the former case, the ligands are called *constitutionally heterotopic* (Greek 'topos' means place), as for example, H's at C-2 compared to H's at C-3 in *n*-pentane (Figure 6.1). This type of heterotopicity has no stereochemical relevance and will not be discussed any further. When their spatial relation with the rest of the molecule is different, the ligands are called *stereoheterotopic* as for example, the geminal H's at C-2 (designated H_A and H_B) of *n*-pentane. The Me-C-Pr plane (Me and Pr may be regarded as two distinguishable points) forms a two-dimensional chiral simplex dividing the three-dimensional space into two half-spaces (right and left) which are stereochemically distinguishable (they are enantio-

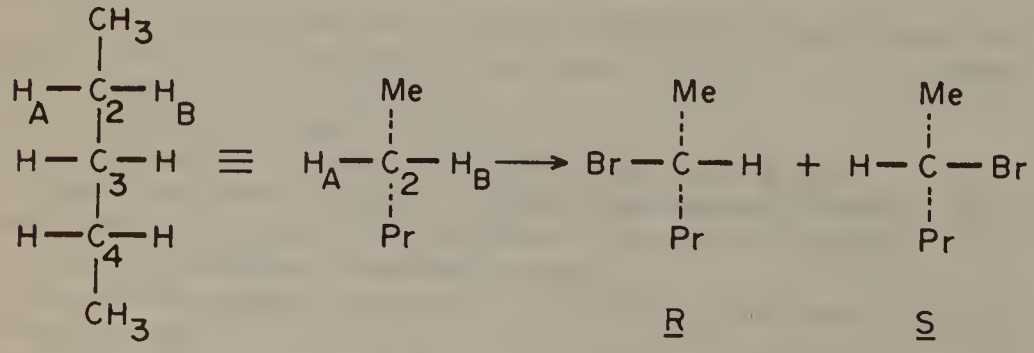


Figure 6.1 Homotopic and heterotopic ligands

*Actually, ligands may be considered as subunits of a molecule.

morphic in the present case) which makes the two H's residing in them stereochemically non-equivalent; i.e., *stereoheterotopic* (actually enantiotopic). The difference becomes more obvious when the two H's are replaced, hypothetically and one at a time, say by Br, giving two enantiomers (as shown). Similar replacement of constitutionally heterotopic ligands would lead to constitutional isomers. If Me or Pr is replaced by a chiral group, the two half-spaces as defined above become diastereomorphous with respect to the plane and bromination at C-2 leads to two diastereomers which also makes the two H's stereoheterotopic (actually diastereotopic). The geminal H's at C-3, on the other hand, are *homotopic*, there being no distinction between the two half-spaces they reside in (Et-C-Et plane is two-dimensionally achiral). Replacement of either of the two H's by Br gives identical product.

A few points emerge from the above illustrations. Molecules having stereoheterotopic ligands exhibit *prostereoisomerism* (provided the ligands can be reacted on) which proves that stereoheterotopicity and prostereoisomerism are two associated phenomena. Prostereoisomerism, in the present case, is attributed to C-2 (or C-4) of *n*-pentane which may be described as a prostereogenic centre. Just as stereoisomerism is discussed in terms of stereogenic elements (centres, axes, and planes), prostereoisomerism may also be described in terms of analogous prostereogenic elements, i.e., prostereocentres, prostereoaxes, and prostereoplanes. The term *chirality* in stereoisomerism should similarly be replaced by the term *prochirality* in prostereoisomerism which would mean that if two homomorphic ligands at a prochiral centre (or axis or plane) be made different, a chiral centre (or axis or plane) would result. A tetrahedrally bonded atom of the general formula Xaabc (where none of the groups a,b, or c is the enantiomer of another) illustrates a typical prochiral centre, e.g., C-2 in *n*-pentane. Just as a stereogenic centre may not necessarily be a chiral centre, a prostereogenic centre may not necessarily be a prochiral centre, i.e., a centre may be prostereogenic without being prochiral (examples will follow). Two faces of appropriate molecules may also be stereoheterotopic and reactions on either face would lead to different stereoisomers.

Stereoheterotopic ligands (or faces) can, in principle, be differentiated by chemical, biochemical, and spectroscopical (particularly, NMR) methods. The principle of stereoselective synthesis (Chapter 13) is based on the differential behaviour of heterotopic groups and faces towards chemical reactions. The concept of stereoheterotopicity has been discussed by Mislow and Raban (1967) and that of prochirality by Hanson (1966). The topic has been recently reviewed (Eliel 1982).

6.2 Topicity of ligands and faces

It may be pointed out that topicity as defined above describes the relationships of two or more homomorphic ligands (or faces) which together constitute a set. Hence, a ligand cannot by itself be called homotopic or heterotopic; in order to use this terminology, a comparison with other homomorphic ligand or ligands present either in the same molecule (internal comparison) or in a different molecule (external comparison) is necessary. These terms are thus similar to the

terms *enantiomeric* and *diastereomeric* used in reference to stereoisomers (Chapter 3).

6.2.1 Homotopic ligands and faces

Two criteria, namely, a substitution (or addition) criterion and (or) a symmetry criterion are employed to determine the topic relationships of homomorphic ligands and faces (only one test suffices).

(A) **Substitution-addition criterion**: Two homomorphic ligands are homotopic if substitution (replacement) of first one and then the other by an atom or a group which is not already attached to the ligating centre gives identical product. By this token, all hydrogen atoms in methylene dichloride, methyl chloride, ethylene, and allene (Figure 6.2a) are homotopic. (Substitution of hydrogen atoms in each set gives a single product). The two methine hydrogens in (+)-tartaric acid (I) [as also in the (−)-enanatiomer] are also homotopic since their respective replacement by deuterium leads to identical product (II) (Figure 6.2b). The last example proves that molecular asymmetry is no bar in having homotopic ligands.

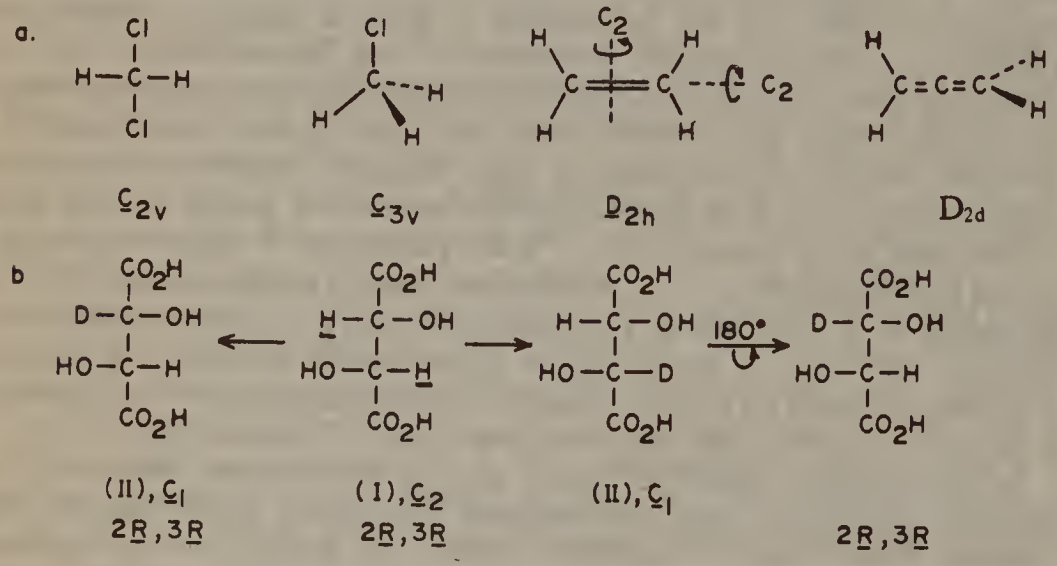


Figure 6.2 Homotopic ligands

For conformationally mobile molecules like cyclohexane (which undergoes ring inversion), the topicity of ligands depends on the time scale of experimental observation. Thus cyclohexane at low temperature is immobilised in the two equivalent chair conformations (IIIa) and (IIIb) in which two types of protons (H_a and H_e are discernible (by low temperature NMR). The twelve hydrogen atoms form two sets of homotopic hydrogens ($6H_a$ and $6H_e$). Replacement of any hydrogen of the same set by deuterium gives identical product. Members of the two sets, H_a and H_e are, however, heterotopic since their replacement gives different products (axial and equatorial isomers).* On the other hand, at room

*See Chapter 10.

temperature, the ring inversion is rapid on the experimental time scale and all the twelve H's become homotopic as in the planar structure (IIIc). Replacement of any one of them, say by Cl, gives a single monochlorocyclohexane.

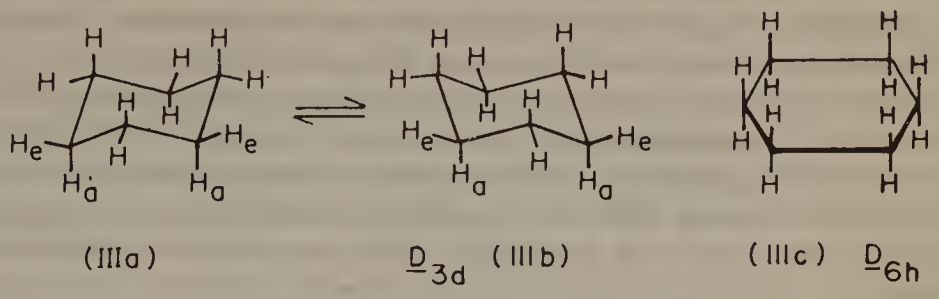


Figure 6.3 Conformation and topicity in cyclohexane

Two faces of a double bond are homotopic if addition to either face gives identical product, e.g., formation of ethanol by addition of MeMgI to either face of formaldehyde (Figure 6.4a). The two faces of the dialkyl sulphide (IV) are homotopic by the same token (oxidation to sulphoxide may be taken as a test reaction here). Alternatively, the two lone pairs may be considered to be homotopic. Things become more complicated when addition takes place at both ends of a double bond as in ethylene, 1,1 -dimethylethylene, and *cis*-2-butene (Figure 6.4b); these molecules all contain two homotopic faces. Confusion may be avoided by using epoxidation as the test reaction as demonstrated for *cis*-2-butene which gives the same epoxide on reaction at either face as shown.

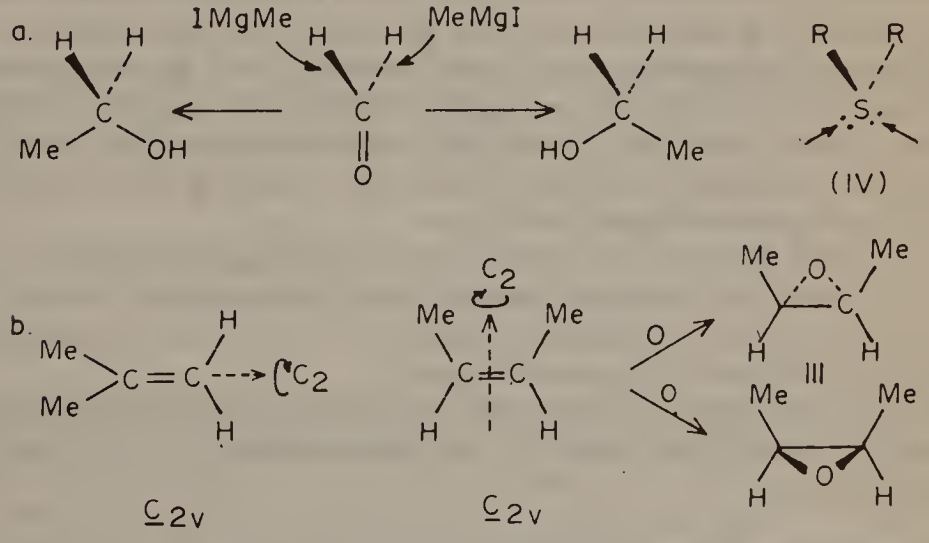


Figure 6.4 Homotopic faces

(B) Symmetry criterion. Ligands are homotopic (by internal comparison) if they can interchange positions by rotation around a simple axis C_n ($\infty > n > 1$). Thus the two hydrogens in methylene dichloride (see Figure 6.2; the point group is shown under each structure), the three hydrogens of methyl chloride, and the four

hydrogens of ethylene can interchange positions through rotations around C_2, C_3, and C_2 axes respectively. In allene, the geminal hydrogens are interchangeable in pairs by rotation around the molecular axis (C_2 axis) while the non-geminal hydrogens are interchangeable through rotation around the two C_2 axes perpendicular to the former. All the four hydrogen atoms are thus homotopic. This proves that if ligands A and B are found homotopic through rotation around one C_n axis and ligands B and C through rotation around another C_n axis, all three (A,B, and C) form a set of homotopic ligands. The two methine protons (as also the two OH and the two CO_2H groups) of (+)-tartaric acid (I) are interchangeable through rotation around a C_2 axis either in the eclipsed conformation or in a staggered conformation (the reader may verify this). These pairs of ligands are, therefore, homotopic.

In the chair conformations (IIIa,b) of cyclohexane (Figure 6.3), the two sets of homotopic ligands H_a and H_e can interchange positions through rotations around the C_3 axis and C_2 axes. All twelve homotopic hydrogens in the planar cyclohexane (IIIc) can interchange positions through rotations around the C_6 axis and C_2 axes.

The following points may be noted:

(*i*) Any achiral or chiral molecule with a C_n axis ($\infty > n > 1$) must contain at least one set (usually two) of homotopic ligands. The presence of a C_n axis in a molecule itself does not ensure that any two ligands are homotopic. The ligands in question must interchange positions by the operation of the C_n symmetry element.

(*ii*) Molecules belonging to non-axial point groups, such as C_1, C_s and C_i (and also $C_{\infty v}$ for a different reason) which do not possess any C_n axis cannot have homotopic ligands.

(*iii*) For conformationally mobile systems, if the structural change is rapid on the time scale of observation, homomorphic ligands (interchanged under condition of fast rotation) are homotopic (e.g., H's in cyclohexane) The same is true for homomorphic ligands which undergo rapid exchange of sites by torsion around a single bond as in CH_3, NR_2, PO_3 etc. (groups which possess rotational symmetry). The three methyl hydrogens in acetic acid are homotopic by the same token although any conformation of CH_3CO_2H belongs to point group C_s which does not allow any homotopic ligands (vide supra).

(*iv*) In a rigid molecule, the number of homotopic ligands belonging to a set cannot be greater than (although it may be equal to) its symmetry number (σ).* The symmetry number of molecules belonging to C_1, C_s, C_i, and $C_{\infty v}$ point groups is 1 and so they cannot have homotopic ligands.

Faces of double bonds, carbonium ions, and molecules with disubstituted atoms capable of accepting a third ligand (e.g., R-S-R) are homotopic if they interchange through a C_2 axis.

6.2.2 Enantiotopic ligands and faces

The origin of stereoheterotopicity of ligands has already been discussed in Section 6.1. The stereoheterotopic ligands are of two types: *enantiotopic* if their positions

*See Chapter 2.

in the molecule are related in mirror-image fashion and *diastereotopic* if their positions do not bear a mirror-image relationship. While the difference between diastereotopic ligands is self evident, that between two enantiotopic ligands is more subtle. Two identical windows symmetrically placed in a symmetrical house front may apparently look the same. But to a person approaching the house, one of them is always at his right and the other always at his left. The two windows may be likened to two enantiotopic ligands attached to the house. A chiral *discriminator* (here a man whose right and left sides are distinguishable) is necessary to differentiate enantiotopic ligands (as in the case of two enantiomers).

Enantiotopic ligands and faces may be recognised by the application of the substitution-addition and symmetry criteria as follows:

(A) Substitution-addition criterion. Two heterotopic ligands are enantiotopic if replacement of first one and then the other by a different achiral ligand gives rise to two enantiomers*. The same goes for addition to enantiotopic faces. Substitution or addition with a chiral group leads to diastereomers and will not be discussed at present. The principle is illustrated by examples (see Figure 6.5a,b).

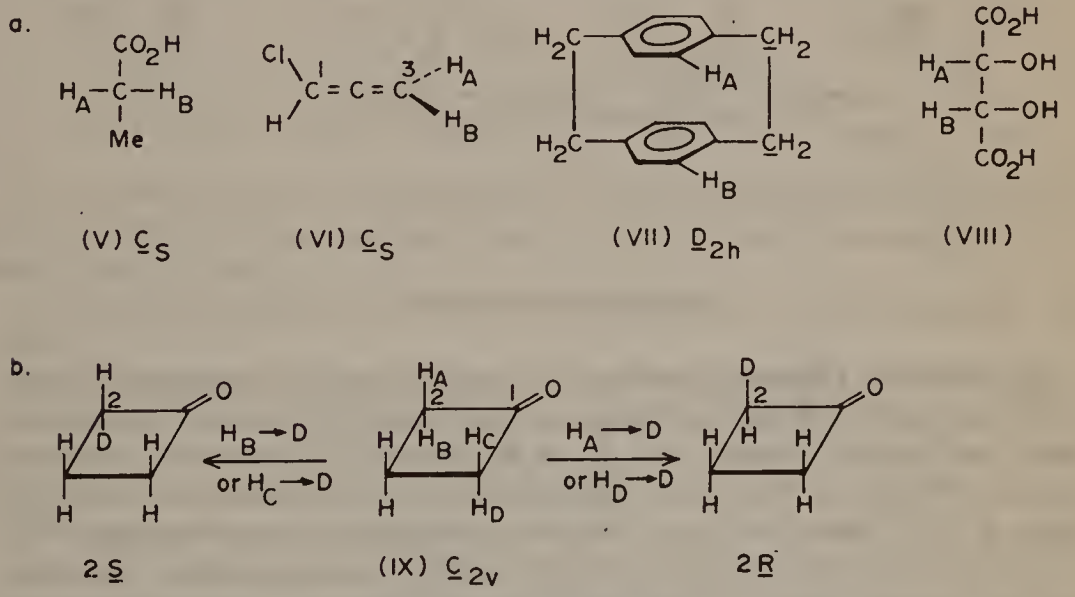


Figure 6.5 Enantiotopic ligands

The cases of propionic acid (V), monochloroallene (VI), and paracyclophane (VII) (only one pair of enantiotopic H's is shown) are easy to understand; replacement of H_A and H_B one at a time with D leads to enantiomers. Molecular chirality of the products is due to the presence of a centre, an axis, and a plane of chirality respectively (see Chapter 5); the molecules (V)—(VII) thus provide examples of a prochiral centre, a prochiral axis and a prochiral plane respectively.

*The test ligand must differ from all other ligands attached to the ligating centre (or axis or plane). Such a prostereogenic element is called a prochiral centre, axis, or plane as the case may be (vide infra).

Substitution of H_A and H_B in *meso*-tartaric acid (VIII, Fischer projection) by D similarly gives rise to two enantiomeric structures. Monoesterification of CO_2H groups and mono-acetylation of OH groups likewise lead to enantiomeric products. The two H's, CO_2H groups, and OH groups are, therefore, enantiotopic. In cyclobutanone (IX), H_A and H_D are homotopic as are H_B and H_C since their substitution by deuterium gives identical products: 2*R* by replacement of H_A or H_D and 2*S* by replacement of H_B or H_C. H_A is, however, enantiotopic with both H_B and H_C while H_D is enantiotopic with both H_B and H_C, since their replacement gives enantiomeric products. This shows that unlike enantiomers, enantiotopic ligands may be more than 2 in number.

Addition of a hydride ion to the right face of acetophenone (X) (Figure 6.6) gives *S*- while addition to the left face gives *R*-phenylmethylcarbinol indicating that the two faces are enantiotopic. Addition of oxygen to the two faces of ethyl methyl sulphide (XI) gives two enantiomeric sulphoxides (shown by the arrows) and hence the two faces of sulphur are enantiotopic. In fact, the two lone electron pairs on sulphur may be regarded as enantiotopic.

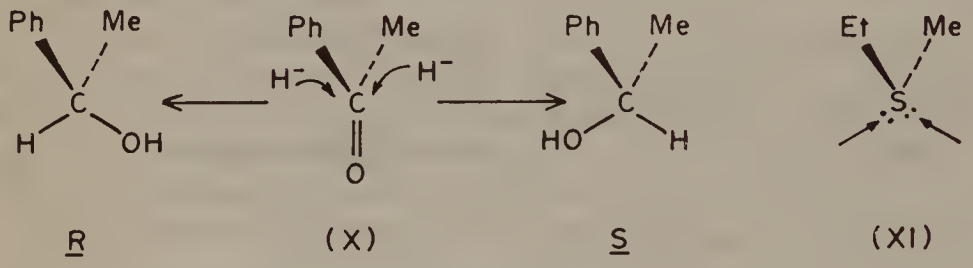


Figure 6.6 Enantiotopic faces

(B) Symmetry criterion. Heterotopic ligands or faces are enantiotopic if they are interchangeable through operation of symmetry of the second kind, i.e., σ planes and S_n axes. Thus H_A and H_B in V, VI, and VII (Figure 6.5) exchange positions through a σ plane, so also the two H's, two OH groups, and two CO_2H groups in VIII. These ligands are, therefore, enantiotopic. In cyclobutanone (IX), H_A and H_B as also H_C and H_D are interchangeable through a σ plane coincident with the molecular plane while H_A and H_C as also H_B and H_D are interchangeable through a σ plane perpendicular to it. Thus each of the four H's in the molecule is enantiotopic with two other H's. On the other hand, H_A and H_D, H_B and H_C as also the two unlabeled H's at C-3 are homotopic since they are interchangeable through the operation of a C_2 axis.*

Enantiotopic ligands may also be interchangeable through the operation of a centre of symmetry (if present). Thus H_A and H_C, H_B and H_D, the two Ph groups, and the two CO_2H groups in α-truxillic acid (XII) are related through a centre of symmetry (*i*) (Figure 6.7). Each pair of ligands is, therefore, enantiotopic. *Meso*-Tartaric acid (VIII, Figure 6.5a) in its stable staggered conformation also contains a centre of symmetry the operation of which makes enantiotopic pairs of ligands

*Homotopicity and heterotocicity are mutually exclusive.

(two H's two OH groups, and two CO_2H groups) interchangeable. Compounds with the general formula (XIII) in which F and ⅁ represent two enantiomeric ligands* have an S_4 axis (a rotation of 90° around the vertical axis leads to XIIIa which on reflection across the molecular plane gives the original molecule). Each of the four hydrogens is interchangeable with two adjacent hydrogens through S_4 operation. Thus H_A is enantiotopic with H_B and H_D, H_B with H_A and H_C and so on. At the same time, alternate pairs of hydrogens (H_A and H_C; H_B and H_D) are homotopic due to the presence of a C_2 ($S_{n/2}$) axis.

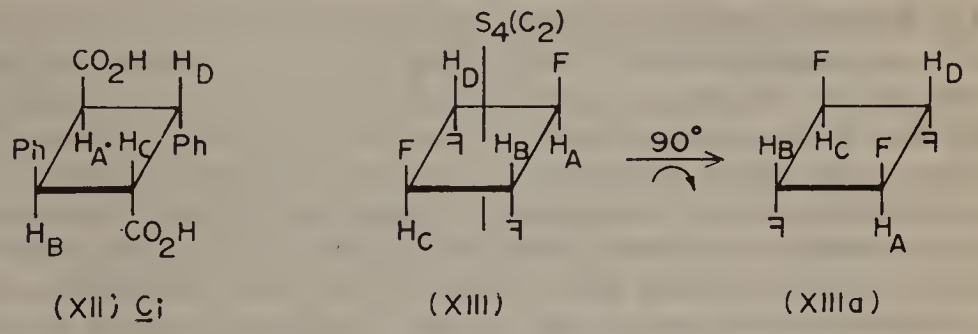


Figure 6.7 Enantiotopic ligands exchangeable through S_n axis

The enantiotopic faces of acetophenone (X) and of ethyl methyl sulphide (XI) (Figure 6.6) are likewise interchangeable through a σ plane coinciding with the plane of the molecules.

The following points are to be noted in connection with enantiotopicity of ligands:

(*i*) Only achiral molecules can have internally enantiotopic ligands (or faces) since the presence of a symmetry element of the second kind is necessary for interchange. This excludes all molecules belonging to chiral point groups C_n and D_n (and also $C_{\infty v}$ and $D_{\infty h}$ for a different reason).

(*ii*) Molecules with enantiotopic ligands may belong to non-axial point groups, e.g., C_1 and C_s (in contrast to molecules containing only homotopic ligands) as well as to axial point groups. Since molecules of axial point groups contain C_n (often C_2) axis, enantiotopic and homotopic ligands may coexist in them (e.g., IX).

(*iii*) Molecules with enantiotopic ligands (and faces) are not only prostereogenic but also prochiral.†

(*iv*) Unlike enantiomers which occur only in pairs, a ligand can be enantiotopic with more than one other ligand.

(*v*) Like enantiomers, enantiotopic ligands or faces cannot be distinguished by achiral reagents or in achiral media but are distinguishable by chiral reagents notably by enzymes and by NMR in chiral media.

(*vi*) Corresponding atoms and groups in enantiomers are enantiotopic by external comparison. Thus the two methyl groups in D- and L-alanine or in (+)-

*They are not homomorphic and therefore cannot be topically related.

†These two adjectives should better be used to qualify centres, axes, and planes (Hanson 1966) rather than molecules, although they often are.

and (−)-lactic acid are enantiotopic because they show mirror-image relationship.

6.2.3 Diastereotopic ligands and faces

Diastereotopic ligands and faces reside in diastereomeric environments and can be distinguished very often simply by an inspection of the molecular structure. However, application of the substitution-addition and symmetry criteria often makes the task easy.

(A) Substitution-addition criterion. The hydrogen atoms H_A and H_B in propene (XIV) and bromocyclobutane (XV)* (Figure 6.8) on substitution (as specified before) give two diastereomeric products in each case and are, therefore, diastereotopic. Even in the original molecules, they can be distinguished, H_A being cis and H_B trans to Me and Br respectively. Two geminal methylene protons (or other homomorphic groups, e.g., Me) adjacent to a chiral centre are usually diastereotopic as in the molecules represented by the general formula (XVI). The replacement criterion leads to two chiral diastereomers differing in the configuration at C-2 which correspond to erythro and threo isomers. The methylene protons H_A and H_B in *trans*-1,2-dibromocyclopropane (XVII) containing two chiral centres are, however, homotopic (inspite of the presence of two chiral centres) since substitution of either of them gives identical products.

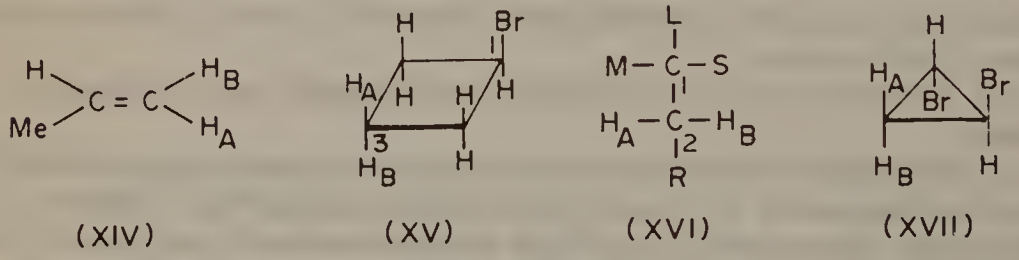


Figure 6.8 Diastereotopic ligands

The two faces of the carbonyl group in a molecule of the general formula (XVIII) (Figure 6.9) containing a chiral centre are diastereotopic since addition of a hydride to the two faces gives different diastereomers: XIX when addition takes place to the left face and XX when addition takes place to the right face. 4-*t*-Butylcyclohexanone (XXI) is an example of an achiral molecule in which the two faces of the carbonyl group are diastereotopic since addition of hydride to the two faces (one at a time) gives two diastereomeric (achiral) products, *trans*-(XXII) and *cis*-(XXIII) 4-*t*-butylcyclohexanol.

(B) Symmetry criterion. Diastereotopic ligands are not related by any symmetry operation and are, therefore, relatively easy to spot. Since the application of the

*The C-3 atom in XV is an example of a prostereogenic centre which is not prochiral while the C-2 atom in XVI is prostereogenic as well as prochiral.

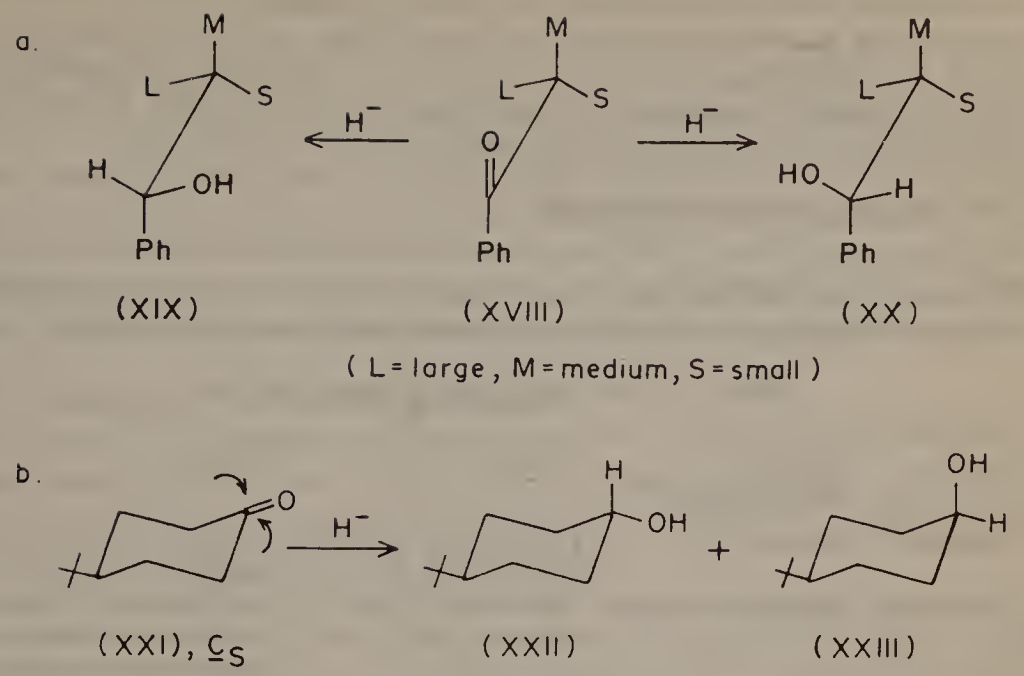


Figure 6.9 Diastereotopic faces

symmetry criterion is already familiar to the reader, instead of taking individual cases a few general observations are made:

(*i*) Chiral molecules belonging to C_1 point group cannot have homotopic ligands (absence of C_n) or enantiotopic ligands (absence of σ and S_n) but they may contain diastereotopic ligands or faces.

(*ii*) Frequently, homomorphic ligands at a carbon atom in chiral molecules are in diastereomeric environments and thus diastereotopic. However, this is not true in all chiral molecules, particularly not in those belonging to a C_n point group (which contain a C_n axis). Thus H_A and H_B in *trans*-1,2-dibromocyclopropane (XVII) (C_2 point group) are interchangeable through a C_2 axis and are homotopic although the methylene group is flanked by two chiral centres. Chirality is thus neither a *necessary nor a sufficient* condition for the presence of diastereotopic ligands. Achiral molecules may have diastereotopic ligands and chiral molecules may not. In fact, molecules belonging to all point groups except $C_{\infty v}$ and $D_{\infty h}$ can have diastereotopic ligands. Similarly, both chiral and achiral molecules can have diastereotopic faces. However, such molecules must be non-planar.

(*iii*) Enantiotopic and diastereotopic ligands often coexist. One of the best examples is citric acid (see later) which belongs to C_s point group and hence cannot have homotopic ligands. The four methylene H's are stereoheterotopic (enantiotopic and diastereotopic).

(*iv*) Like enantiotopic ligands, diastereotopic ligands may be attached to different centres and may be multiple in number. They must not be confused with constitutionally heterotopic ligands.

(*v*) Diastereotopic ligands, in principle, are distinguishable by all physical and chemical (including biochemical) means both in achiral and chiral media. NMR spectroscopy is particularly helpful.

(*vi*) Ligands may be diastereotopic by external comparison as well. Just as two corresponding ligands in enantiomers are enantiotopic, two corresponding ligands in any two diastereomers are diastereotopic. The distinction of diastereotopic ligands by external comparison is a mere formality but the concept may be useful in some cases, e.g., ^{13}C-NMR (see Eliel 1982).

6.2.4 Summary of topic relationships

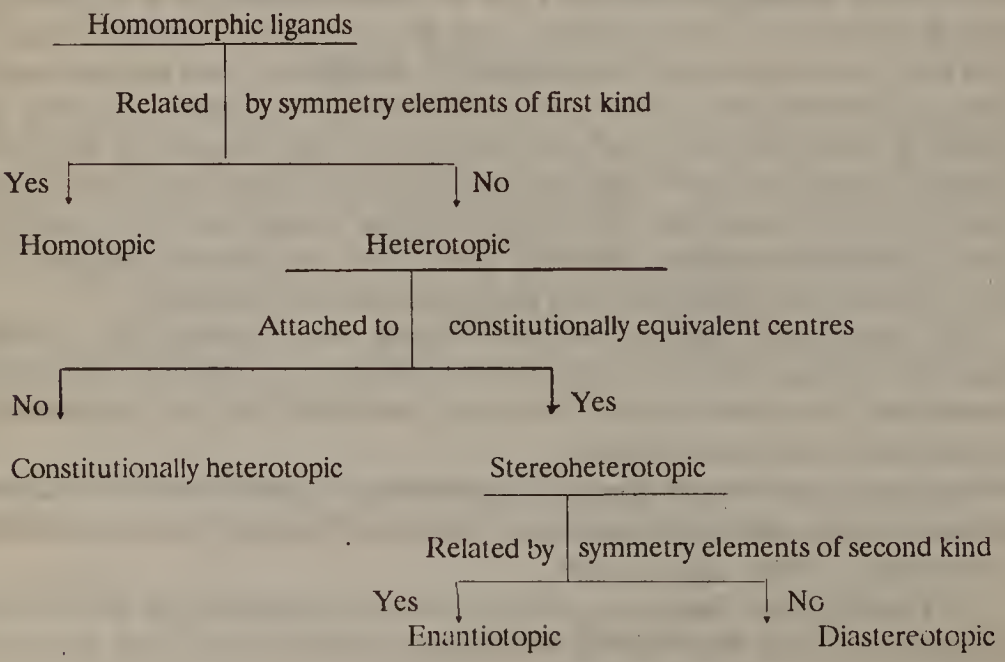
The points so far discussed are summarised in Table 6.1. The table has much in common with that given by Mislow and Raban (1967) and by Eliel (1980).

Table 6.1 Topic relationship of ligands and faces

Topicity	Substitution-addition criterion*	Symmetry criterion	Difference
Homotopic	Identical product	Ligands related through C_n and faces by C_2 axis.	No difference by any method
Enantiotopic	Enantiomeric products	Ligands (faces) related through σ, i, or S_n	Distinguishable, in principle, in chiral media (NMR), by chiral reagents, and enzymes
Diastereotopic	Diastereomeric products	Ligands and faces not related by any symmetry element	Distinguishable, in principle, by all methods

*Substition-addition by achiral groups only is considered.

In view of the interrelationship between topicity of ligands and isomerism in general, it may be instructive to draw a classification diagram for topicity and to compare it with that drawn for isomerism (Chapter 3).



6.3 Nomenclature of stereoheterotopic ligands and faces

Stereoheterotopic ligands differ in their spatial relationships in the same way as stereoisomers differ in the spatial arrangements of their constituent atoms and groups. It is, therefore, desirable that like stereoisomers, such ligands should be given appropriate descriptors. Configurational descriptors such as *R, S, Z, E, cis*, and *trans* which are used to describe stereogenic units may be prefixed with *pro* and used to describe the heterotopic ligands attached to analogous prostereogenic units. Such a system was first introduced by Hanson (1966) and since then has gained wide currency among chemists and especially among biochemists.

6.3.1 Symbols for stereoheterotopic ligands

Since enantiotopic and diastereotopic ligands often coexist and their labeling systems are correlated, the assignment of descriptors to both kinds of stereoheterotopic ligands is discussed under the same headings.

1. Molecules with one prochiral centre. Molecules with a single prochiral centre are represented by the general formula Cabxx and depicted by Fischer plane projection in two perspectives (A) and (B) (Figure 6.10). It is assumed that ligand 'a' has a higher priority than ligand 'b' as determined by the sequence rules (Chapter 4) while ligand X may have any priority lower, higher, or in between with respect to 'a' and 'b'. For the present discussion, it is assumed that X has the lowest priority. In order to assign a descriptor to any of the paired ligands, say X_A, it is arbitrarily given a higher priority than X_B without disturbing the priorities of 'a' and 'b' (the unpaired ligands). The chirality rule is now applied to the hypothetical chiral centre which happens to have *R* configuration (viewed from the side remote from X_B, the lowest ranking group, a→b→X_A describes a clockwise direction). The ligand X_A is called *pro-R* and may be denoted by adding a subscript *R*, as X_R. The other ligand X_B is *pro-S* (denoted by X_S) by default—a conclusion which is alternatively arrived at by adopting the above procedure but

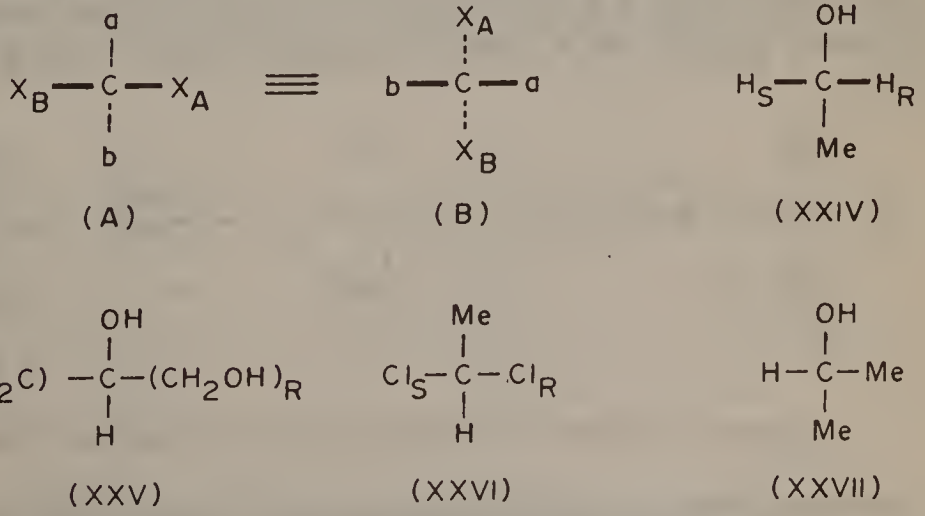


Figure 6.10 A mnemonic for pro-R and pro-S descriptors

elevating the priority of X_B over that of X_A. Visualisation in three dimensions may be avoided if the 'very good' mnemonic is applied to determine the chirality of the hypothetical chiral centre (Chapter 4).

The method is illustrated with three examples (Figure 6.10). In ethanol (XXIV), X = H and the priority order is a>b>X; in glycerol (XXV), X = CH_2OH and the priority order is a>X>b; in dichloroethane (XXVI), X = Cl and the priority order is X>a>b. A common feature is observed in these examples (which cover all three possibilities of priority sequences), namely, when the ligand 'a' (the higher ranking unpaired ligand) is placed at the top in the Fischer projection as in A (called top-a), the right hand ligand (X_A) at the prochiral centre is *pro-R*. A mnemonic may thus be worked out as *Top-right* (conversely *Bottom-left*) meaning that the ligand (at the same prochiral centre) which is on the right of top-a (conversely, on the left of bottom-a) is *pro-R*. When the paired ligands are placed vertically instead of horizontally, the mnemonic *Top-right* is changed to *Right-top* (conversely, *Left-bottom*) as in the projection B meaning that when 'a' is on the right, the adjacent top ligand is *pro-R* and so on (Nasipuri 1989). The mnemonic is valid only when the paired ligands are written linearly (either horizontally or vertically); if they are placed at right angle to each other as in XXVII, the reverse is true. The mnemonic is particularly useful to assign topic descriptors to ligands in molecules with multiple prochiral centres (see later).

An alternative to Hanson's procedure for assigning *pro-R* and *pro-S* symbols is to replace one of the paired ligands (or a part thereof) by a heavy isotope, e.g., H by D (provided such a ligand is not already present at the prochiral centre) and then apply the chirality rule to the now truly chiral centre (Arigoni and Eliel 1969). Since the heavier isotope gets precedence over the lighter one, the assignment is the same as described in the previous paragraph. Two points may be noted in this connection: (i) The subscripts *R* and *S* used for *pro-R* and *pro-S* ligands respectively should not be confused with the configurational descriptors *R* and *S*. A group with *R* chirality may very well be a *pro-S* ligand. (ii) Replacement of a *pro-R* ligand by a fourth different ligand does not necessarily give a product of *R* chirality (as the prefix *pro* appears to signify); see an example in Figure 6.11 for contrary results. However, if the substitution is by a heavier isotope, substitution of *pro-R* ligand does give the *R* enantiomer and that of *pro-S* ligand gives the *S* enantiomer.

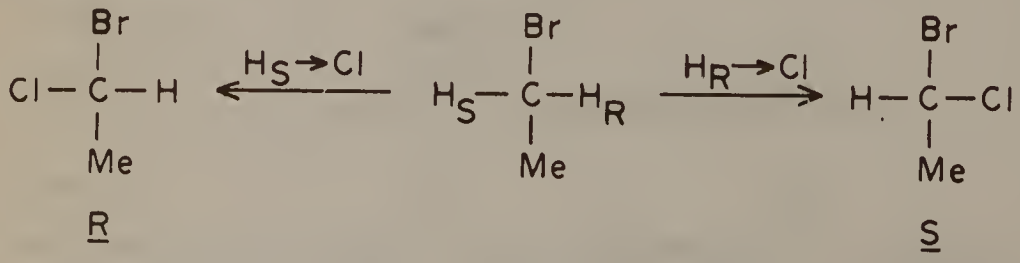


Figure 6.11 Conversion of pro-R ligand into *S* and pro-S ligand into *R* centre

2. Molecules with a pro-pseudoasymmetric centre. The two H's (H_A and H_B) at C-3 of 2,4-dihydroxyglutaric acid (XXVIII) (Figure 6.12) are not homotopic,

neither they are enantiotopic since they are not interchangeable by the symmetry of any kind (homomorphic pairs of ligands at C-2 and C-4 are, however, enantiotopic as in *meso*-tartaric acid). They must, therefore, be diastereotopic and indeed the substitution criterion (replacement of H_A and H_B by D) gives two diastereomers (XXIX) and (XXX) in which C-3 is pseudoasymmetric centre with *r* and *s* configuration respectively (see Chapter 4). The C-3 centre in XXVIII may, therefore, be called a *pro*-pseudoasymmetric centre or perhaps more logically (Mislow and Siegel 1984) a prostereogenic but proachirotopic centre. H_A is *pro-r* (denoted by H_r) and H_B is *pro-s* (denoted by H_S): a conclusion which can also be reached by the application the 'Top-right' mnemonic (C-2 has *R* configuration and so precedes C-4 which has *S* configuration and becomes the fiducial ligand 'a' and H_A which is on the right side is thus *pro-r*).

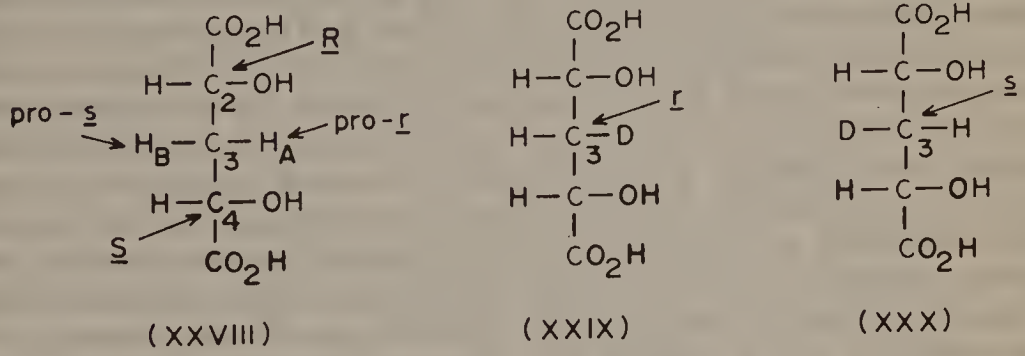


Figure 6.12 A molecule with pro-pseudoasymmetric centre

3. Molecules with more than one prochiral centre. Citric acid with three prochiral centres provides an interesting example in which enantiotopic and diastereotopic H's coexist. All the four methylene H's (see structure **XXXIa**) (Figure 6.13), designated H_A, H_B, H_C, and H_D are distinguishable (by enzymes as well as by NMR under appropriate conditions). The topic descriptors to each of the H's can be assigned very easily with the help of the 'Top-right' mnemonic. The CO_2H group evidently corresponds to the fiducial ligand 'a' both at C-2 and C-4. The top-right and bottom-left mnemonics label the four H's directly or by default, as *pro-S* (H_A), *pro-R* (H_B), *pro-R* (H_C), and *pro-S* (H_D), denoted by the first

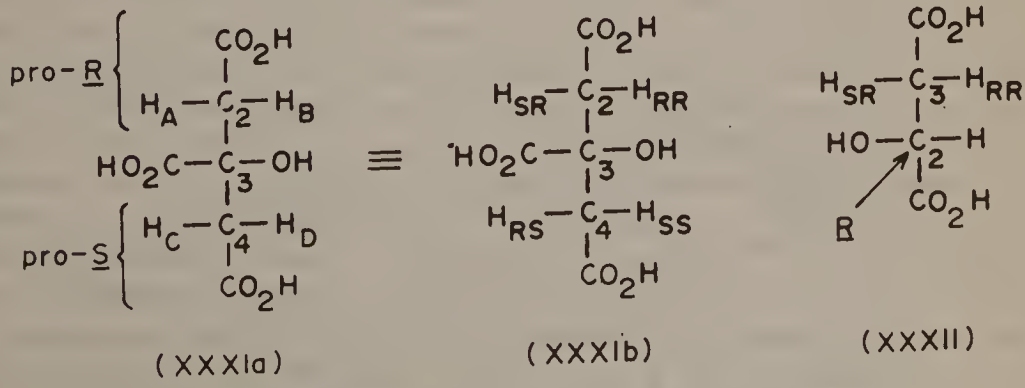


Figure 6.13 Methylene protons in citric acid and malic acid

subscripts of the H's as shown in XXXIb. The C-3 atom is also prochiral, the two CH_2CO_2H being enantiotopic. The OH group at C-3 is the fiducial ligand 'a' and according to right-top mnemonic, the upper CH_2CO_2H is *pro-R* and the lower one is *pro-S*. The subscripts of the groups are now added to the individual subscripts of H's which are thus labeled H_{SR}, H_{RR}, H_{RS}, and H_{SS} (as in XXXIb) respectively. The double indexing system, first used by Retey and Robinson (1982) in a somewhat modified form has the advantage that it makes the topic relationship (enantiotopic and diastereotopic) immediately obvious; thus H_{SR} is diastereotopic with H_{SS} and H_{RR} but enantiotopic with H_{RS}.

4. Molecules with a chiral as well as a prochiral centre. A prochiral centre in a molecule containing one or more chiral elements usually contains diastereotopic ligands which may also be specified by topic descriptors. They are first labeled with appropriate *R* and *S* subscripts following the top-right mnemonic and to these is added the configurational descriptor (*R* and *S*) of the nearest chiral centre with the proviso that when two nearest chiral centres are equidistant, the one in the higher priority branch at the prochiral centre is chosen. The two diastereotopic H's at C-3 of *R*-malic acid (XXXII in Figure 6.13) are thus denoted by paired subscripts as H_{SR} and H_{RR}. It may be noted that the second subscripts of the citric acid H's and the malic acid H's have different connotations the former referring to group prochirality and the latter to central chirality. The two situations are, however, mutually exclusive since a chiral molecule (e.g., malic acid) cannot have enantiotopic ligands (prochiral groupings), there being no reflection symmetry.

5. Molecules with a prochiral axis. Molecules like allenes, biphenyls, and analogues when suitably substituted may have a pair of stereoheterotopic ligands. The usual way to assign topic descriptors to such ligands is to project the molecule on to a plane in the way it is done for determining *R* and *S* chirality (shown for monochloroallene and for a biphenyl in Figure 6.14), preferably with the enantiotopic ligands in the front. To assign topic descriptor to H_A, its priority is elevated

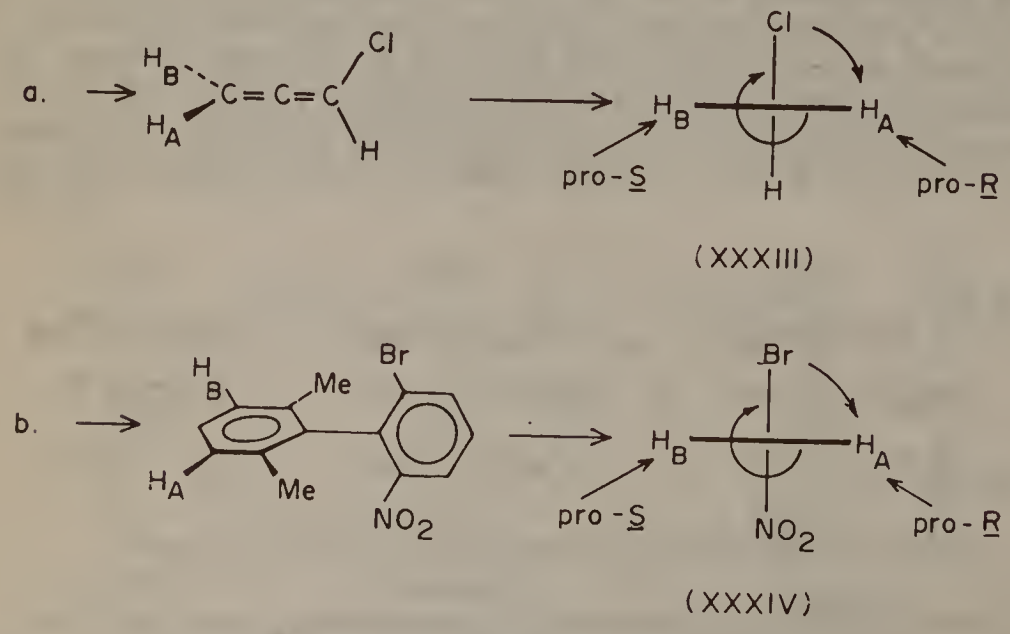


Figure 6.14 Enantiotopic ligands at prochiral axis

over that of H_B (alternatively, H_A may be hypothetically replaced by D). If the configuration of the hypothetical chiral axis is *R* as in XXXIII, then H_A is *pro-R* and is denoted by H_R and so on. Similar procedure is adopted for the biphenyls and illustrated in XXXIV. One may use the top-right mnemonic in these cases as shown by short arrows but it does not offer any advantage. To make the mnemonic operative, the front ligands (be they paired or unpaired) must be placed on the horizontal line so that the arrangement resembles a Fischer projection of a tetrahedral centre. Under this condition, the projection may not be needed since one can immediately see which of the enantiotopic ligands is on the right or on the left of the fiducial ligand (Cl in XXXIII and Br in XXXIV).

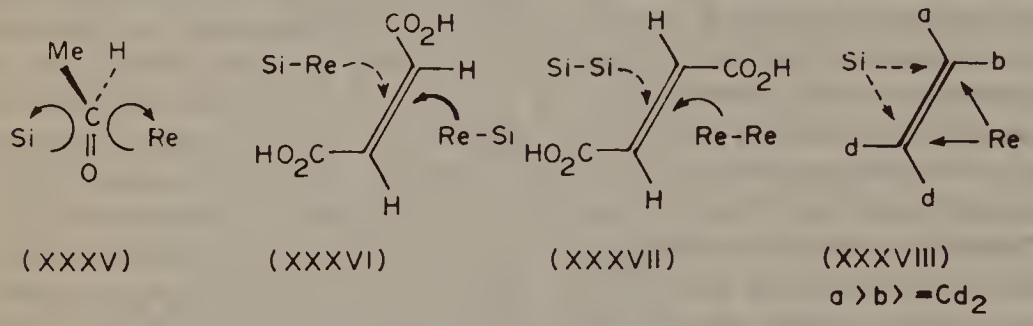
6. Molecules with a prochiral plane. The assignment of descriptors to heterotopic ligands in molecules with a prochiral plane is best illustrated with an example, the paracyclophane (VII) in Figure 6.5a. There are several pairs of enantiotopic H's; only one pair, H_A and H_B is shown (they are not interchangeable by a C_n axis but by a σ plane). To give a descriptor to H_A, it must be given priority over H_B (alternatively, it may be replaced by D) so that the bottom methylene C (underlined) becomes the pilot atom (Chapter 5) and the hypothetical chiral plane has *R* configuration; so H_A is *pro-R* (H_R). Similarly, when H_B is considered, the top methylene C (underlined) becomes the pilot atom and H_B becomes *pro-S* (H_S).

7. Molecules with prostereogenic but proachiral centres. A variety of prostereogenic molecules contain diastereotopic ligands which on substitution give achiral diastereomers, i.e., they do not have prochiral centre or centres. Such ligands may be called *pro-Z, pro-E, pro-cis, pro-trans, pro-endo, pro-exo* etc. depending on the nature of the diastereomers formed on their substitution. The nomenclature is self-evident and need not be discussed further.

8. Re and Si system of nomenclature for ligands. A different system of nomenclature for stereoheterotopic ligands has been proposed by Prelog and Helmchen (1972), somewhat similar to that used to differentiate heterotopic faces by Hanson (vide infra). The tetrahedron represented by CabXX (A in Figure 6.10) is divided into two enantiomorphous halves along the a-C-b vertical plane (a two-dimensional chiral simplex). Each half-space contains three ligands, a, b, and X (in addition to the ligating C atom) which when seen in their priority sequence describe a clockwise or an anticlockwise direction. The half-space in which they are clockwise (the observer must be in the same half-space) is designated *Re* and the other is designated *Si*. The ligands are given the designations of the half-spaces they reside in. Thus X_A in the structure (A) falls in the *Re* half-space (a>b>X) and is designated *Re* (X_{Re}) and so on. When X has the lowest or the highest priority, both Hanson's and Prelog's methods give concordant results. But when X has a priority in between those of the unpaired ligands, disconcordant results are obtained as in glycerol (XXV). Now the half-spaces are to be designated by the direction a → X →b (since a>X>b) rather than a→ b → X (or X→a→b) and the right half-space becomes *Si* in A and X_A is designated *Si*. Hanson's method is already extensively used in the literature and a change of terminology at this stage is undesirable particularly since the correspondence between *pro-R* (or *pro-S*) ligands and products of isotopic substitution of *R* (or *S*) configuration is very convenient in biochemical studies.

6.3.2 Symbols for stereoheterotopic faces

(A) Enantiotopic faces. Enantiotopic faces of molecules are two-dimensionally chiral. Hanson's method for specification of such faces is exremely simple. If the three ligands arranged in priority order appear clockwise in a face, the face is *Re* and if they appear anticlockwise, the face is *Si* as shown in the case of acetaldehyde (XXXV) (Figure 6.15). If the double bond contains two specifiable trigonal atoms, a face may be uniquely defined by two symbols one for each specifiable atom. This is illustrated with maleic acid (XXXVI) (here the two faces are homotopic) and fumaric acid (XXXVII) (the two faces are enantiotopic). Olefins of the type (XXXVIII) in which one terminal contains two equivalent ligands require,* however, only one symbol *Re* or Si depending on the priority



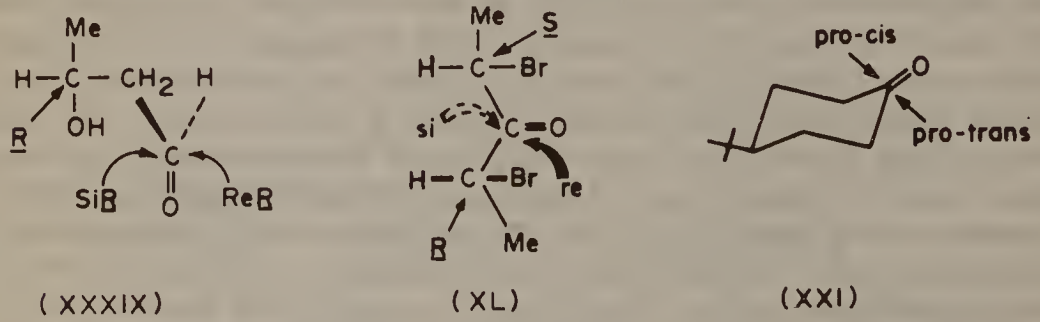
(XXXV) (XXXVI) (XXXVII) (XXXVIII)

Figure 6.15 Nomenclature of heterotopic faces in achiral molecules

order of a, b, and $=Cd_2$ (in the Figure, the priority order is $a > b > =Cd_2$); see also Kaloustian and Kaloustian 1975.

In the case of molecules containing prochiral bivalent atoms such as the dialkyl sulphide (XI) (Figure 6.6), the lone electron pair is regarded as a phantom ligand having the least priority so that the right face of the molecule is *Re* and the left face *Si*.

(B) Diastereotopic faces. The two carbonyl faces of 3-hydroxybutanal (XXXIX) (Figure 6.16) are diastereotopic (presence of a chiral centre). The right face is *Re*



(XXXIX) (XL) (XXI)

Figure 6.16 Nomenclature of heterotopic faces (continued)

*A double bond is important in assigning two-dimensional chirality to a plane.

and the left face is *Si* according to the above procedure to which a further subscript *R* (the chirality descriptor of C-3) may be added so that the double-lettered subscripts *ReR* and *SiR* are truly diastereotopic.

If the trigonal atom is *pro*-pseudoasymmetric as in the general formula G_R-CO-G_S (G_R and G_S are enantiomeric groups), the two diastereotopic faces as in XL may be designated by *re* (upper face) and *si* (lower face); the *R* group gets precedence over *S*. The lower case alphabets are used to indicate reflection-invariance.

The two diastereotopic faces (axial and equatorial) of 4-*t*-butylcyclohexanone (XXI) are designated *pro-cis* and *pro-trans* (upper and lower faces respectively) on the basis that a substituent when added to the upper face becomes cis and when added to the lower face becomes trans with respect to the *t*-butyl group. The actual products of addition may, however, have opposite designations, e.g., trans instead of cis and so on (compare the alcohols obtained on reduction of XXI with hydrides in Figure 6.9).

6.4 Stereoheterotopic ligands and NMR spectroscopy

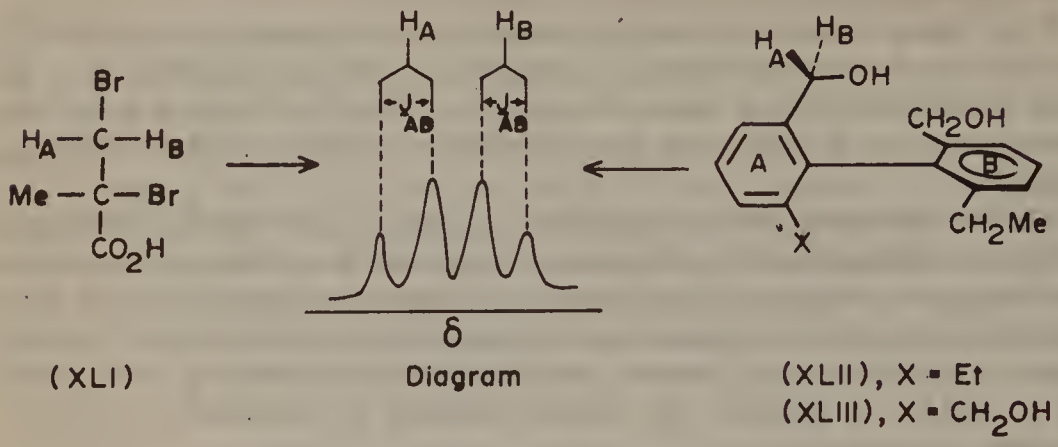
NMR spectrosocopy can distinguish between nuclei which reside in different environments so that they are shielded or deshielded to different extents. Such nuclei differ in their chemical shifts and are called chemical shift non-equivalent or *anisochronous*. Homotopic ligands reside in identical environments and cannot be distinguished by NMR; they show chemical shift equivalence and are called *isochronous*. Enantiotopic nuclei are also isochronous since they reside in environments which are geometrically equivalent and differ only in topography. NMR is an achiral probe and cannot in itself make topographical (chiral) discrimination. Enantiotopic nuclei can be distinguished by NMR only if a diastereomeric relationship be established by using a chiral solvent or a chiral additive with which the substrate forms an *associate* (solvate, complex etc.). Diastereotopic ligands (or nuclei) reside in different environments and are, in principle, always anisochronous. The difference in chemical shifts (anisochrony) is, however, often very small (1 ppm or less) and may even be undetectable in which case, one speaks of chance or accidental isochrony. Use of higher fields or of ^{13}C-NMR instead of ^{1}H-NMR can be helpful in increasing anisochrony, as, especially in ^{1}H-NMR, can a change of solvents.

6.4.1 Diastereotopic ligands and NMR spectroscopy

Different types of diastereotopic nuclei (mostly protons) and their spectral behaviour are discussed under different headings.

1. Geminal ligands adjacent to a chiral centre. Nair and Roberts (1957) first showed that methylene protons adjacent to a chiral centre are chemically non-equivalent. A typical example is the methyl ester of 2,3-dibromo-2-methylpropionic acid (XLI) (Figure 6.17) in which H_A and H_B are anisochronous and appear in the NMR spectrum as an AB-quartet (J_{AB} = 10 Hz) (see diagram). Although the fact

that they are not symmetry related (diastereotopic) is itself a sufficient cause for anisochrony, a conformational factor is also involved (vide infra).

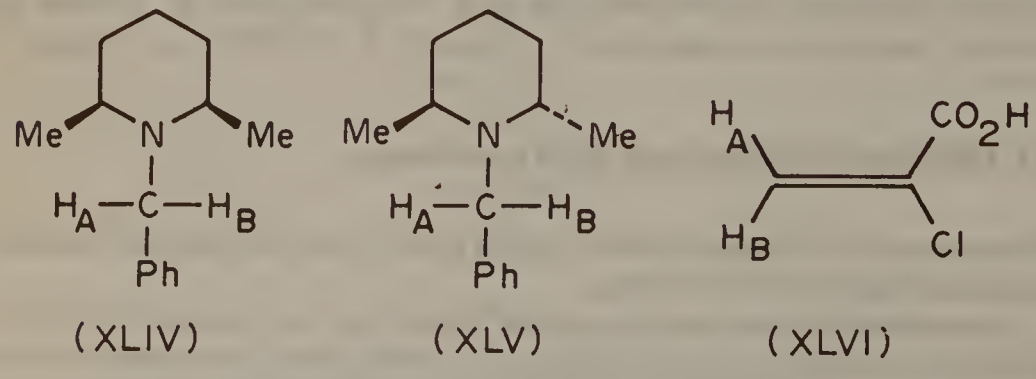


(XLI) (XLII), X = Et (XLIII), X = CH_2OH

Figure 6.17 Non-equivalence of geminal protons

2. Geminal nuclei adjacent to a chiral axis. Appropriately substituted biphenyls possess a chiral axis (Chapter 5) and suitably placed geminal ligands therein may be diastereotopic and anisochronous. Thus the methylene protons in each of the CH_2OH group in the biphenyl (XLII) are diastereotopic (no σ plane bisecting the H_A-C-H_B angle) and so anisochronous. They appear as an AB-quartet (with δ_A and δ_B at 4.05 and 4.20 ppm respectively and $J_{AB} = 12$ Hz) (Meyer and Meyer, 1963). The biphenyls need not be necessarily chiral since chirality is not a necessary condition for diastereotopicity. In the achiral biphenyl (XLIII), the geminal hydrogens in each CH_2OH group in ring A are diastereotopic (absence of σ plane bisecting H_A-C-H_B angle)* and so appear as an AB-quartet. The geminal hydrogens in CH_2OH attached to ring B in XLIII, on the other hand, are enantiotopic (related by a σ plane) and thus isochronous.

3. Diastereotopic ligands in cis-trans isomers. The cis and trans isomers of N-benzyl-2,6-dimethylpiperidine (XLIV and XLV) (Figure 6.18) are classical examples of molecules which are distinguished by NMR. In the cis isomer, the



(XLIV) (XLV) (XLVI)

Figure 6.18 Non-equivalence of geminal protons in cis and trans isomers

*See Jennings (1975).

benzylic protons H_A and H_B are enantiotopic and so isochronous appearing as a sharp singlet at δ 3.70 ppm (isochronous nuclei do not visibly couple with each other). On the other hand. H_A and H_B in the trans isomer are diastereotopic and so anisochronous. They form an AB-quartet centred at δ 3.63 ppm ($J_{AB} = 14$ Hz). (Hill and Chan, 1965).

Another simple example showing geminal anisochrony of this type is 2-chloropropenic acid (XLVI) in which the two terminal hydrogens form an AB-quartet with an appreciable chemical shift difference (0.85 ppm).

4. Diastereotopic ligands in molecules devoid of stereogenic centres. Citric acid (XXXI) (Figure 6.13) and analogous compounds, e.g., $PhCH(OCH_2CH_3)_2$ contain two enantiotopic pairs of hydrogens. H_A & H_C and H_B & H_D (labels as in citric acid). Each pair being isochronous exhibits identical chemical shifts. A member of an isochronous pair (say H_A) is, however, diastereotopic and so anisochronous with a member of the other pair (say H_B) and the NMR spectrum shows them as an AB-quartet (of two protons each) similar to the diagram (Figure 6.17). In the case of $PhCH(OCH_2CH_3)$, the methylene protons are further split by the adjacent methyl hydrogens. The two methyl groups, on the other hand, are enantiotopic and isochronous.

6.4.2 Diastereotopic faces and NMR spectroscopy

The case of (−)-menthyl esters of maleic and fumaric acids (XLVII) and (XLVIII) (Schurig 1977) is a very instructive one. The two faces of the maleate are homotopic (related by a C_2 axis) while those of the fumarate are diastereotopic. The two olefinic protons in each are, however, homotopic (interchangeable through C_2 axes). The esters form complexes with iron tetracarbonyl, $Fe(CO)_4$. The faces of the maleate being homotopic, a single complex is formed (cf. epoxidation). The two olefinic protons are now diastereotopic (by internal comparison) due to the absence of C_2 axis and σ plane. They are thus anisochronous and give rise to an AB-quartet in NMR.

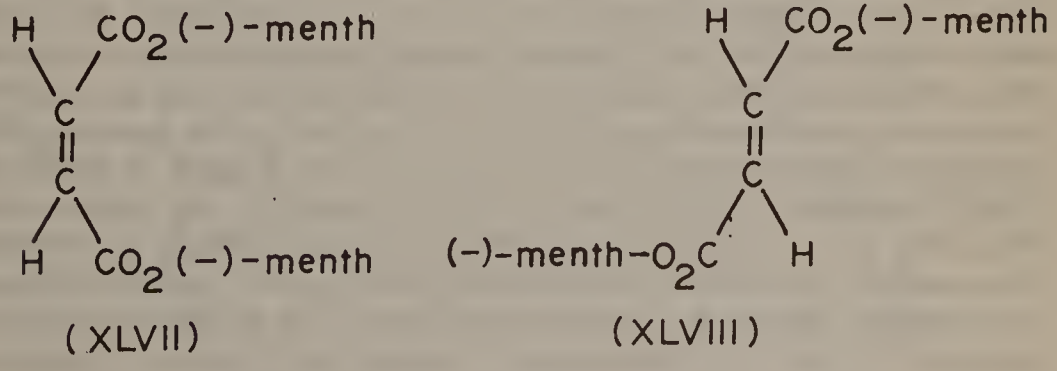


Figure 6.19 Anisochrony arising out of stereoheterotopic faces

The fumarate (XLVIII), on the other hand, gives two diastereomeric complexes in each of which the olefinic protons are homotopic (related by a C_2 axis) and so isochronous. The two olefinic protons in one distereomer are, however, diastereo-

topic with the two olefinic protons of the other diastereomer (by external comparison). The diastereomeric complexes thus give two singlets resulting in two peaks (not necessarily of equal intensity) for the olefinic protons (see Eliel 1982). Thus the two original esters are distinguished by NMR through complexation with faces of different topicity.

6.4.3 Diastereotopic nuclei in conformationally mobile systems

If two diastereotopic nuclei interchange sites at a rate faster than the NMR time scale (determined by the chemical shift difference of the two nuclei)*, they become isochronous due to averaging of the environments around each. Thus the ^{19}F-NMR of 1,1-difluorocyclohexane (XLIX) (Figure 6.20) shows a sharp singlet for the two diastereotopic fluorines because of rapid exchange between the conformers (XLIXa) and (XLIXb). However, at a temperature below −50°C, the rate of exchange becomes appreciably slow on the NMR time scale and they show the expected AB-quartet. On the other hand, in the conformationally rigid molecule (L), the two fluorine atoms are always anisochronous.

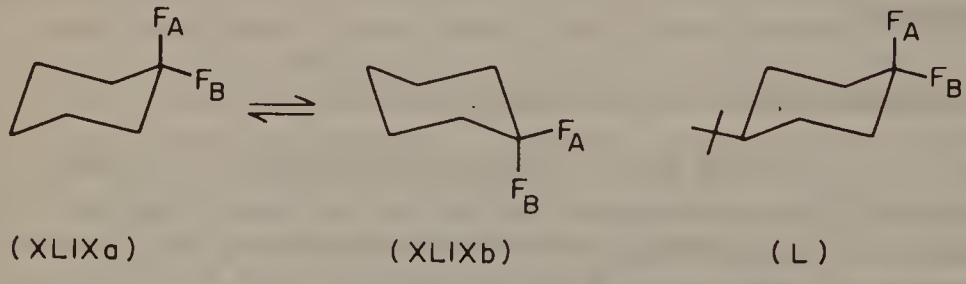


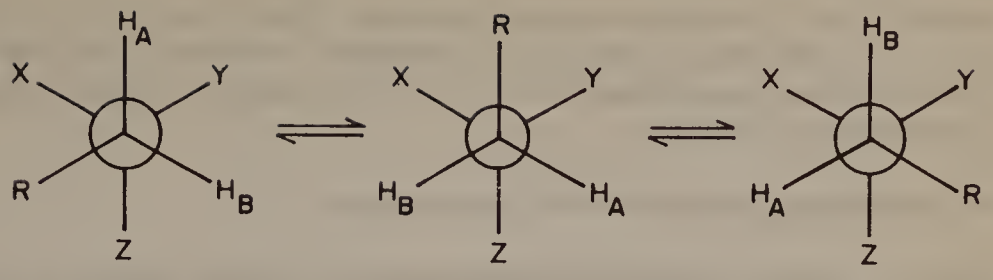
Figure 6.20 Diastereotopic ligands in conformationally mobile system

6.4.4 Intrinsic anisochrony and conformational anisochrony

A conformationally mobile chiral molecule of the type, RCH_AH_B-CXYZ exists usually in three distinct conformations (M), (N), and (O) (Figure 6.21). The effective chemical shift of H_A is given by equation (1) and that of H_B by equation (2) in which n_M, n_N and n_O represent the fractional populations of the respective conformers at a particular temperature and δ_{XY}, δ_{YZ}, and δ_{ZX} the chemical shifts† in conformers with the proton concerned placed between X and Y, Y and Z, and Z and X respectively. Assuming that δ_{XY} for H_A equals δ'_{XY} for H_B and so on (which may not be exactly true) and that the chemical shifts are the weighted average shifts of the contributing conformers (which is possibly true), the difference of the chemical shifts of H_A and H_B can be obtained as the difference between expressions (1) and (2) which primarily depends on the relative populations

*The rate (k) of a process is fast on the NMR scale if $k >> \frac{1}{2}\sqrt{2\pi\Delta\nu}$ where $\Delta\nu$ is the difference in chemical shifts (in Hz) of the exchanging nuclei (see also Chapter 9).

†Actually, these values will vary slightly for the two protons and hence those for H_B are denoted with primes in equation (2).

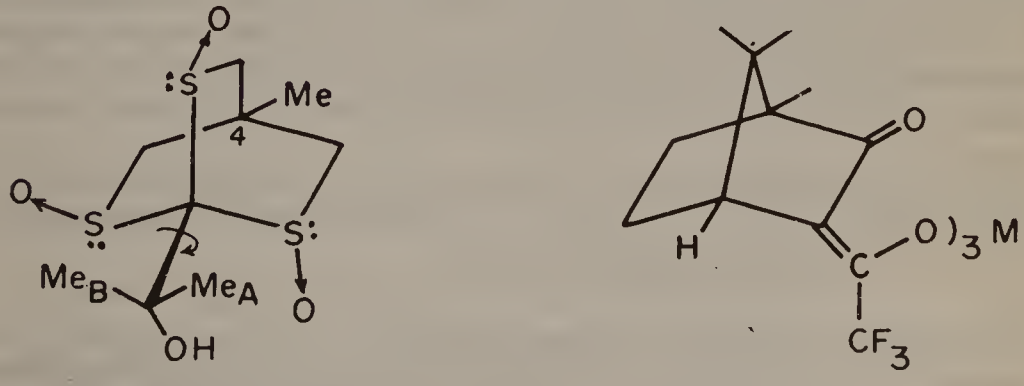


$$\delta_{H_A} = n_M \delta_{XY} + n_N \delta_{YZ} + n_O \delta_{ZX} \quad \ldots\ldots (1)$$

$$\delta'_{H_B} = n_O \delta'_{XY} + n_M \delta'_{YZ} + n_n \delta'_{XZ} \quad \ldots\ldots (2)$$

Figure 6.21 Intrinsic anisochrony in conformationally mobile system

(n_M, n_N, n_O) of the conformers. Now at a high temperature, the three conformers should be almost equally populated and the chemical shift difference ($\delta_A - \delta_B$) should tend to be zero; however, this is not observed in practice. The reason is that the environment of H_A in the conformer (M) with H_A flanked by X and Y is not exactly the same as that of H_B in the conformer (O) with H_B flanked by X and Y since in the former, R is anti to Y while in the latter, R is anti to X. The residual anisochrony at high temperature which is independent of population (also of temperature) is known as '*intrinsic anisochrony*' in contrast to the other component known as *conformational anisochrony* which originates from the difference in conformer populations and is temperature dependent (see Jackman and Sternhell 1969). Intrinsic anisochrony freed from conformational anisochrony at room temperature has been demonstrated using substrates like the bicyclic trisulphoxide (LI) (Figure 6.22) in which the three conformers arising out of rotation around C-C bond (as shown) are equivalent due to the presence of a C_3 axis (passing



δ_{AB} = 0.038 ppm

(LI)

M = Eu, Yb, Pr

(LII)

Figure 6.22 (a) Intrinsic anisochrony, (b) chiral shift reagents

through C-1 and C-4) and so are equally populated. The difference in the chemical shifts of Me_A and Me_B (0.038 ppm in pyridine) is thus solely due to intrinsic anisochrony (Franzen and Binsch 1973). When CH_3 groups are replaced by CF_3, δ_{AB} is 0.282 ppm (^{19}F-NMR).

6.4.5 Enantiotopic nuclei and NMR spectroscopy

Enantiotopic nuclei are isochronous under normal conditions. However, they can develop measurable anisochrony in the presence of chiral solvents and additives with which the substrates form transient *associates**. Thus dimethylsulphoxide (CH_3SOCH_3) contains two (enantiotopic) isochronous Me groups. But when the spectrum is taken in optically active $PhCHOHCF_3$ (with which sulphoxides form some sort of associate), the two Me groups are seen as a doublet separated by 0.02 ppm. Chiral solvents and chiral shift reagents (e.g., LII) are widely used to differentiate between two enantiomers, i.e., between nuclei which are enantiotopic by external comparison and to determine the enantiomeric excess in partially racemic mixtures by quantification of the signals due to two species (see Chapter 8).

6.4.6 Isogamous and anisogamous nuclei

Anisochronous nuclei couple with one another but the isochronous ones do not. Two anisochronous nuclei when coupled with a third nucleus (of the same kind or of different kinds, e.g., ^{1}H, ^{13}C, ^{19}F etc.) have different coupling constants. This property is called spin coupling non-equivalence or *anisogamy* and the nuclei are called *anisogamous* (see Eliel et al 1971). Diastereotopic nuclei are both anisochronous and anisogamous.

Of more immediate interest are certain homotopic or enantiotopic nuclei which do not couple with one another (because of isochrony) but do couple with a third nucleus with different coupling constants, i.e., are anisogamous. The third nucleus must have at least one homotopic or enantiotopic counterpart; otherwise it has to be symmetrically placed with respect to the two isochronous nuclei (symmetry requirement) which would necessarily be isogamous as H_A and H_A', in LIII (with respect to their coupling with F) (Figure 6.23). The simplest system in which

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*The principle is explained as follows. If L_R and L_S are two enantiotopic nuclei (either by internal or external comparison) and A_R is a chiral solvent or additive, two equilibria are established (for the sake of simplicity, substrates are equated with the ligands) :

$$L_R + A_R \overset{k_R}{\rightleftharpoons} L_R - A_R \quad ; \quad L_S + A_R \overset{k_S}{\rightleftharpoons} L_S - A_R$$

The exchange rates (k_R and k_S) are too fast on the NMR time scale so that the chemical shift of L_R is averaged out between that of free L_R and that of the associate L_R-A_R; similarly, the chemical shift of L_S is averaged out between that of L_S and that of the associate L_S-A_R. Since the shifts of the diastereomeric associates L_R-A_R and L_S-A_R are not the same, and also because these associates may not be formed at the same rate ($k_R \neq k_S$), the observed chemical shifts for the two initially enantiomeric species (or enantiotopic ligands) are not the same. The case is different from the one in which relatively stable diastereomeric associates or complexes are formed so that even if the solvent or additive is racemic, two signals are observed for the two diastereomers.

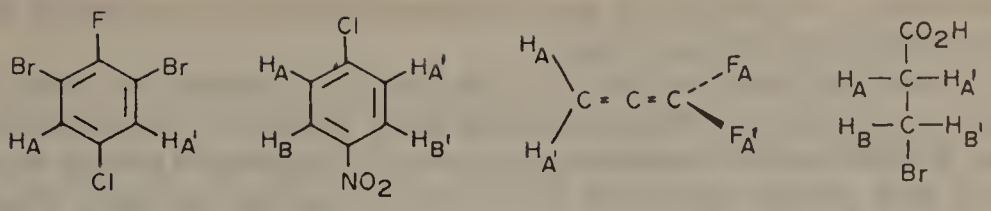


Figure 6.23 Isogamous and anisogamous nuclei

anisogamy of isochronous nuclei is expected must therefore correspond to A_2B_2 or, more precisely, AA′BB′ type such as LIV. In this molecule J_{AB} is not equal to $J_{A'B}$ (nor J_{BA} to $J_{B'A}$) and H_A and $H_{A'}$, as also H_B and $H_{B'}$ are thus anisogamous. Even this cannot be generalised since 1,1-difluoroallene (LV) or CH_2F_2 which corresponds to AA′BB′ type has a pair of H's and a pair of F's which are isochronous as well as isogamous. Some symmetry restriction has to be imposed on such molecules in order to have anisogamy in isochronous nuclei. According to Mislow (cited by Eliel 1982), if in a spin system of the type AA′BB′, substitution of one of the B's by a different nucleus Z leads to a system A_2BZ in which the two nuclei A and A′ are no longer interchangeable by symmetry operation of any kind (C_n or S_n), then B and B′ are anisogamous as in LIV; if, on the other hand, in A_2BZ, two A's are interchangeable by a symmetry operation, then the two B's are isogamous as in LV*. The methylene protons in 3-bromopropionic acid (LVI) are examples of enantiotopic nuclei which are isochronous and anisogamous (the molecule conforms to the above symmetry criterion).

6.5 Prostereoisomerism and stereoisomerism

Molecules with stereoheterotopic ligands and faces are prostereogenic and an appropriate chemical (or biochemical) reaction transforms them into stereoisomers. The stereochemical outcome and the relative rates of reactions depend on the topic relationship of the ligands (or faces), the nature of the reagents (chiral and achiral), and the reaction conditions in general. In reactions with heterotopic ligands or faces, one or the other of the stereoisomers is formed in excess leading to what is known as stereoselective synthesis. The reactions may be discussed under two broad headings: chemical reactions using laboratory reagents and biochemical reactions mediated through enzymes.

6.5.1 Chemical transformations of heterotopic ligands and faces

The differential behaviour of stereoheterotopic ligands and faces provides the basis of many stereoselective reactions which will be discussed in chapters on dynamic

*Replacement of one H_B in LIV by Z makes the two H_A's constitutionally heterotopic and so H_B and $H_{B'}$ are anisogamous (which also holds for H_A and $H_{A'}$). Replacement of either a H or a F atom in LV by Z gives an allene in which the two homomorphic nuclei (F's or H's) are enantiotopic (isochronous) and so both H's and F's in LV are isogamous.

stereochemistry. Here only a few general observations which almost parallel those under NMR spectroscopy are made.

(*i*) Homotopic ligands and faces are identical in all respects and hence any reaction (substitution or addition) involving them, whether it is carried out with chiral or achiral reagents (including environments), gives identical product. In case two or more products are formed, they are obtained in the same ratio from the two ligands or faces. Thus chlorocarbene ($:CCl_2$) adds to either of the two homotopic faces of *cis*-2-butene giving two diastereomeric products; a cyclopropane with all the three substituents cis and a cyclopropane with Cl trans to the two cis Me groups. The ratio of the two is the same for the reaction on either side.*

(*ii*) Enantiotopic ligands or faces with achiral reagents or in achiral environments give rise to two enantiomers via enantiomeric transition states which are of equal energy. The two enantiomeric products are, therefore, formed in equal amounts. If the reagent is chiral or if the reaction is carried out in a chiral medium, two diastereomeric transition states may be formed leading either to two enantiomers or to two diastereomers (under kinetical control) in unequal amounts (see Chapter 13 for details).

(*iii*) Diastereotopic ligands and faces undergo reactions, either with achiral or chiral reagents, through diastereomeric transition states which differ in all their thermodynamical properties and two or more diastereomeric products are formed at different rates and thus in different amounts. Such reactions whether carried out under kinetical or under thermodynamical control are stereoselective to a greater or lesser extent. By changing the reaction conditions and the nature of the reagents, stereoselectivity may be improved even to the extent of 100%.

6.5.2 **Biochemical transformations of heterotopic ligands and faces**

Biochemical transformations are carried out through the agency of enzymes (as catalysts). Enzymes are protein molecules constituted of a large number of optically active amino acids and represent a class of most efficient chiral reagents.† As such they are capable of discriminating between two ligands and faces which are enantiotopic by external comparison (as in enantiomers) or by internal comparison (as in prochiral molecules). Like a true catalyst, an enzyme adsorbs the substrate molecules on its surface and orients them in such a fashion that the reacting group is brought in juxtaposition to the active site present in the enzyme itself (known as a prosthetic group) or in a suitably bound coenzyme. The interactions between the enzyme and substrate are highly specific so that only one out of the two diastereomeric transition states is favoured, the other being almost non-existent due to large difference in free energies of activation. Thus the enzymes usually act on only one of the two enantiomers—a property known as stereospecificity—and in the case of prochiral molecules with only one of the enantiotopic ligands or faces—a property known as stereoselectivity (see Chapter 13 for

*No experimental proof can, however, be given.

†It is usually the secondary and tertiary structures (e.g., right- or left-handed helices) of proteins (rather than the chiral centres) which give rise to the active sites in enzymes and are ultimately responsible for stereospecificity.

terminology). The first kind of reactions is illustrated by the enzymatic hydrolysis of the N-acetyl derivatives of a D,L-pair of amino acids when one of the enantiomer (usually the derivative of the naturally occurring L-isomer) is hydrolysed much faster (sometimes by a factor of 10^4) than the other. The second kind is illustrated by the phosphorylation of glycerol when the *pro*-R hydroxymethylene group is esterified exclusively by adenosine triphosphate (ATP) in the presence of an enzyme (glycerol kinase).

Enzymatic discrimination between enantiomers and between enantiotopic ligands is, in most cases, almost total. For detailed study, the reader is referred to two textbooks (Bentley 1970; Alworth 1982) and many reviews (see Eliel 1982). Two examples of enzymatic discrimination of stereoheterotopic ligands (in addition to the above) are discussed below.

(A) Enzyme mediated reduction of acetaldehyde to ethanol.* Acetaldehyde is reduced to ethanol with yeast alcohol dehydrogenase (YAD) in the presence of the hydride donating coenzyme NADH (reduced form of nicotinamide adenine dinucleotide). In the reverse reaction, ethanol is oxidised to acetaldehyde by the oxidised form of the coenzyme (NAD^+) (Figure 6.24). Several stereochemical possibilities exist in this apparently simple oxidation-reduction sequence. Acetaldehyde has two enantiotopic faces and hydride may be transferred to either face. Ethanol has two enantiotopic hydrogens (H_R and H_S) and either of them may be transferred to NAD^+. NAD^+ has two faces (*Re* and *Si*) and either of them can accept a hydride. Finally, NADH has two enantiotopic hydrogens (H_R and H_S) and either of them may be transferred in the reduction step. The facts which have been established are: (i) Only the *Re* faces of both acetaldehyde and NAD^+ are involved and (ii) only H_R of both ethanol and NADH participates in the reactions. (H or D which are transferred are circled in the Figure). The proofs are as follows (consult the Figure) :

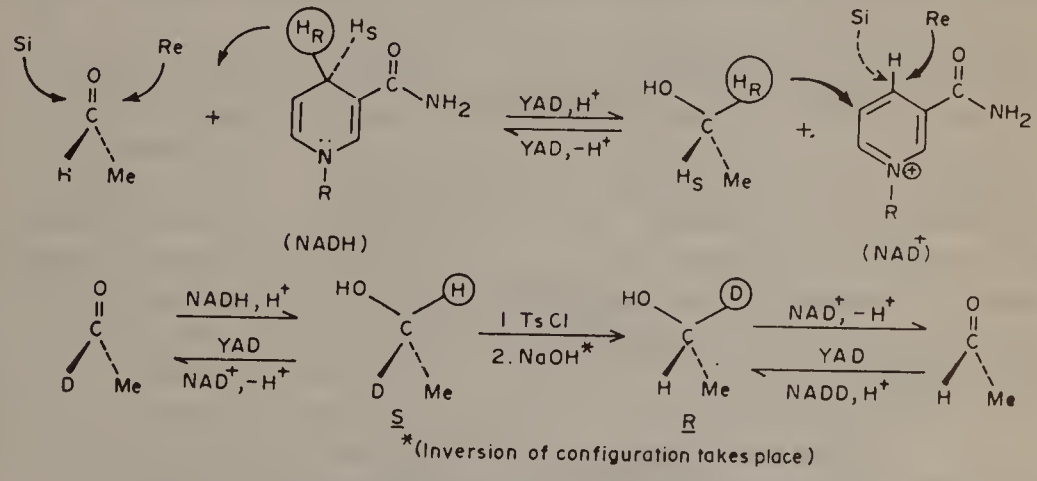


Figure 6.24 Enzymatic transformation of CH_3CHO-CH_3CH_2OH
(R stands for the rest of the molecule)

* See also Eliel (1980).

(*i*) When acetaldehyde-1-*d* is reduced, *S*-ethanol-1-*d* is formed exclusively which proves that the *Re* face of acetaldehyde is attacked.

(*ii*) In the reverse reaction, *S*-ethanol-1-*d* gives back the original deuterated acetaldehyde which means that the circled H (H_R in ethanol) is transferred.

(*iii*) Both the above points have been further confirmed by converting *S*-ethanol-1-*d* into *R*-ethanol-1-*d* and submitting it to NAD^+—YAD oxidation. Acetaldehyde devoid of deuterium is obtained meaning that D (circled) which occupies the position of H_R in ethanol is transferred.

The complete stereoselectivity of this oxidation- reduction process means that the orientations of the substrates, the enzyme's binding sites, and the coenzyme associated with it are such that one of the two diastereomeric transition states for a particular reaction (oxidation or reduction) is favoured greatly over the other so that only one ligand or face is involved in the hydride transfer.

(B) Citric acid cycle (part). Citric acid (XXXI) (Figure 6.25) is a suggested intermediate in the enzymatic conversion of pyruvic acid into 2-oxoglutaric acid (LVIII). On carbonylation of pyruvic acid with labeled C^*O_2, oxaloacetic acid with C* at the top CO_2H group (LVII) is obtained. Acetylcoenzyme-A ($CH_3COSCoA$) converts it into citric acid with the labeled C* in one of the two CH_2CO_2H groups (that this is the *pro-R* group as shown in the Figure has been proved by experiments with tritiated citric acid). 2-Oxoglutaric acid (LVIII) obtained as an isolable product is found to be labeled only at one of the carboxyl group, the one placed at the top of the structure which means that the enzyme has converted only one of the CH_2CO_2H groups, the *pro-S* one (derived from acetylcoenzyme-A) into $COCO_2H$. This is further confirmed when the other carboxyl group is labeled by using CH_3C^*OSCoA in the second step: the 2-oxoglutaric acid now has C* in the botton carboxyl group in the structure (LVIII). This once again proves that an enzyme can discriminate between two enantiotopic ligands (Before this was recognised, doubt had been raised regarding citric acid

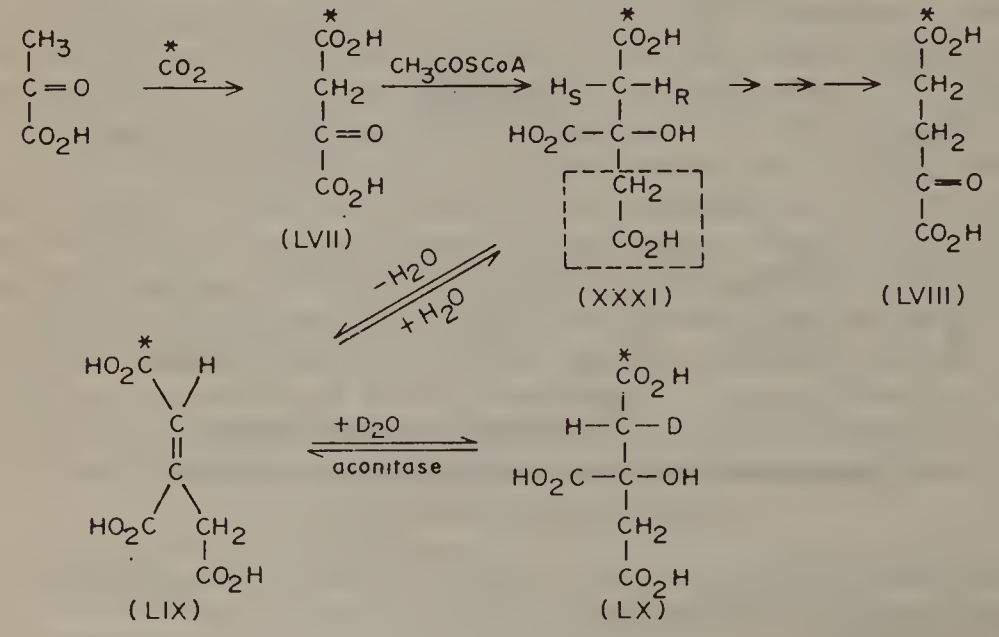


Figure 6.25 Citric acid cycle (a part only)

being an intermediate because of isolation of a singly labeled 2-oxoglutaric acid).

It has been mentioned earlier that the four hydrogens of citric acid are different and so can be distinguished by enzymes. Citric acid is dehydrated reversibly by the enzyme aconitase giving *cis*-aconitic acid (LIX). It has been proved by labeling experiments that it is the *pro-R* hydrogen of the *pro-R* CH_2CO_2H group, i.e., H_{RR} (for nomenclature, see Figure 6.13) which takes part in dehydration (for details, see Arigoni and Eliel 1969). During the enzymatic hydrolysis of *cis*-aconitic acid in D_2O, only one deuterium atom is introduced at the site of H_{RR} to give monodeuterated citric acid (LX).

Before the symmetry criterion was applied to enantiotopic ligands, a mechanistic rationale was given by Ogston (1948) for the ability of enzymes to distinguish between two paired ligands in molecules of the type Cabdd on the basis of three-point contact model (see any biochemistry text). The model, however, while providing a viable kinetic picture, may obscure the intrinsic, symmetry-based difference between heterotopic groups.

6.6 Summary

1. Prostereoisomerism is a property of certain molecules by virtue of which they are capable of giving rise to stereoisomers (enantiomers or diastereomers). Such molecules contain either non-equivalent homomorphic ligands or faces replacement of, or addition to, first one and then the other of which gives stereoisomeric products.

2. Such homomorphic non-equivalent ligands or faces are known as stereoheterotopic; they are further subdivided into enantiotopic and diastereotopic ligands and faces. The former reside in geometrically equivalent molecular environments having mirror-image relationship and replacement or addition gives enantiomeric products. In contrast, diastereotopic ligands or faces reside in diastereomeric environments and on substitution or addition give diastereomers. By default, when ligands or faces reside in completely identical environments, replacement or addition gives rise to a single product; such (equivalent) ligands or faces are called homotopic.

3. The three types of ligands can be distinguished by symmetry criteria also. Homotopic ligands or faces interchange their positions by the operation of symmetry elements of the first kind, i.e., C_n axis. Enantiotopic ligands or faces interchange their positions only by operation of symmetry elements of the second kind, i.e., σ plane, i, and S_n. Molecules with enantiotopic ligands or faces are capable of giving two enantiomers and are known as prochiral. In analogy with chiral or stereogenic elements, the prochiral or prostereogenic elements can be factorised into prostereocentres, prostereoaxes, and prostereoplanes.

4. Descriptors for stereoheterotopic ligands and faces have been devised in close analogy with those used for chiral molecules (*R* and *S*). A ligand is thus called *pro-R* or *pro-S* (and denoted by L_R and L_S respectively) following a certain convention which is consistent with CIP nomenclature and has been explained in the text. A mnemonic has been worked out for the assignment of *pro-R* and *pro-S* symbols to stereoheterotopic ligands.

5. Homotopic nuclei, because of their identical environments have the same chemical shift in NMR and are called isochronous. They are incapable of being distinguished by any physical or chemical method. Enantiotopic ligands are also isochronous by virture of their geometrically equivalent environments. However, their isochrony may be destroyed by creating diastereomeric environments either by taking the spectrum in a chiral medium (solvent) or in the presence of a chiral additive. Ligands in enantiomers (enantiotopic by external comparison) or in prochiral molecules (enantiotopic by internal comparison) may form transient and fast-exchanging associates or complexes with chiral solvents or additives and thereby become anisochronous, i.e., have different chemical shifts. Diastereotopic ligands like diastereomers are always distinguishable in principle and very often in practice. Such nuclei, barring accidental isochrony, are anisochronous.

6. Enzymes can effectively discriminate between enantiomers as well as between enantiotopic ligands and faces. They often react with one of a pair of enantiomers with 100% stereospecificity and with one of the enantiotopic ligands or faces with 100% stereoselectivity. Several examples of enzymatic reactions have been given.

References

1. K. Mislow and M. Raban (1969) in *Topics in Stereochemistry*, vol. 1, Eds. N.L. Allinger and E.L. Eliel, Wiley, New York.
2. K.R. Hanson (1966), *J. Amer. Chem. Soc.*, **88**, 3649; also H. Hirschmann and K.R. Hanson (1971), *Eur. J. Biochem.*, **22**, 301.
3. E.L. Eliel (1982), *Top. curr. Chem.*, **105**, 1.
4. E.L. Eliel (1980), *J. Chem. Educ.*, **57**, 52.
5. D. Nasipuri (1989), *J. Chem. Educ.*, **66**, 483.
6. D. Arigoni and E.L. Eliel (1969) in *Topics in Stereochemistry*, vol. 4, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
7. K. Mislow and J. Siegel (1984), *J. Amer. Chem. Soc.*, **106**, 3319.
8. J. Retey and J.A. Robinson (1982) in *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie, Weinheim.
9. V. Prelog and G. Helmchen (1972), *Helv. Chim. Acta*, **55**, 2581.
10. S.A. Kaloustian and M.K. Kaloustian (1975), *J. Chem. Educ.*, **52**, 56.
11. P.M. Nair and J.D. Roberts (1957), *J. Amer. Chem. Soc.*, **79**, 4565; for F-NMR of analogous compounds, see J.J. Drysdale and W.D. Phillips (1957), *J. Amer. Chem. Soc.*, **79**, 319.
12. W.L. Meyer and R.B. Meyer (1963), *J. Amer. Chem. Soc.*, **85**, 2170.
13. R.K. Hill and T-H. Chan (1965), *Tetrahedron*, **21**, 2015.
14. W.B. Jennings (1975), *Chem. Rev.*, **75**, 307.
15. V. Schurig (1977), *Tetrahedron Letters*, 3977.
16. L.M. Jackman and S. Sternhell (1969) in *Applications of NMR Spectroscopy in Organic Chemistry*, Pergamon Press, Oxford.
17. G.R. Franzen and G. Binsch (1973), *J. Amer. Chem. Soc.*, **95**, 175.
18. G. Binsch, E.L. Eliel, and H. Kessler (1971), *Angew. Chem. Intl. Engl. Edn.*, **10**, 579.
19. R. Bentley (1969) in *Molecular Asymmetry in Biology*, Academic Press, New York.
20. W.L. Alworth (1982) in *Stereochemistry and its Application in Biochemistry*, Wiley, New York.
21. A.G. Ogston (1948), *Nature*, **162**, 963; see also R. Bentley, (1978), *Nature*, **276**, 673.

Chapter 7

Racemisation and Methods of Resolution

7.1 Introduction

Chiral compounds are usually available either in enantiomerically pure (optically active) form, e.g., most of the natural products with one or more chiral centres, or in racemic modification, e.g., those synthesised in the laboratory using achiral substrates, reagents, and media. When an enantiomer is converted into a racemic modification (usually through chemical reactions), the process is known as *racemisation*. Conversely, when a racemic modification is separated into its constituent enantiomers, the process is known as *resolution*. In the latter process, optical rotation is enhanced (a phenomenon called *optical activation*) and equals to that of a pure enantiomer in the case of complete resolution. Racemisation and resolution are thus complementary to each other.

Racemisation is a thermodynamically favourable process (it leads to an increase of entropy, see Chapter 3) and would proceed spontaneously if a convenient pathway is available for the interconversion of the enantiomers. Any mechanism of racemisation, in principle, must operate from either of the enantiomers. Racemisation (in the sense of enantiomerisation) is, therefore, a reversible process, $(+) \rightleftharpoons (-)$, and may formally be regarded as a reaction in which half of one enantiomer undergoes inversion of configuration and the other half retains its configuration, although in fact the two forms remain in dynamic equilibrium in the reaction medium with 50 : 50 population ($\Delta G^\circ = 0$ and so $K = 1$).

If a molecule contains more than one chiral centre and configurational inversion takes place, say reversibly, at one centre only, the product formed is not the enantiomer of the original but a diastereomer, more specifically, an epimer and the process is called *epimerisation*. The two epimers exist in unequal amounts in equilibrium since they differ in their free energies. Epimerisation may be carried out on an enantiomerically pure diastereomer, or on its racemic modification, or on a meso isomer. Racemisation is usually monitored by observing the gradual zeroing of optical rotation. In epimerisation, if rotations of both the epimers are known, the change in optical rotation of the reacting mixture may be used to follow the progress of epimerisation. However, nowadays NMR, particularly ^{13}C-NMR, provides a good probe for monitoring epimerisation of both optically active and inactive stereoisomers.

Resolution of a racemic modification is an altogether different proposition. Since two enantiomers behave identically in achiral environments, they cannot be

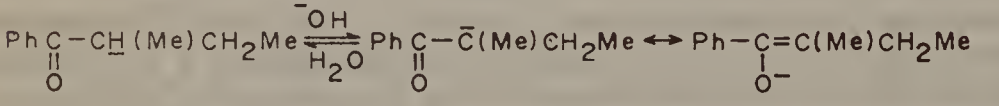
distinguished unless a diastereomeric relationship is established by using chiral reagents, solvents, media etc. Resolution of a racemic modification, therefore, requires a chiral agency in one form or other.

7.2 Mechanisms of racemisation

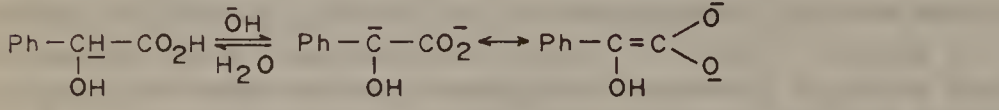
When racemisation is carried out by a chemical reaction, the enantiomer usually has to pass through a symmetrical species*, be it a transition state or an intermediate so that when the molecule is reformed, the two enantiomers are produced with equal facility and in equal amounts. The ease of racemisation depends on the mechanism involved which in turn depends on the nature of the substrates and the reagents employed.

7.2.1 Mechanism involving carbanions

If a ligand at a tetrahedral chiral centre is removed by heterolytic cleavage leaving behind an anionic species, e.g., a carbanion, the latter undergoes rapid inversion so that when the ligand recombines, it can do so either from the same side it left (a homofacial reaction accompanied with retention of configuration) or from the opposite side (a heterofacial reaction accompanied with inversion of configuration). The two approaches are enantiomorphic and so equally facile giving a product which is racemic. Generally, an acidic proton is removed using mild to strong bases such as sodium hydroxide and sodium alkoxides (in appropriate solvents). Two examples are given in equations (1) and (2).



(1)



(2)

The derived anion in each case is stabilised by resonance which facilitates their formation under basic condition. Phenyl *s*-butyl ketone (in eqn. 1) undergoes easy racemisation (with aqueous NaOH), mandelic acid (in eqn. 2) and lactic acid do so much less readily, and atrolactic acid, $PhC(Me)(OH)CO_2H$ with no enolisable H does not racemise at all. The mechanism is the same as that for keto-enol tautomerism, halogenation, and deuterium exchange in enolisable carbonyl compounds.

When the concerned proton is very acidic as in the disulphone (eqn. 3), the

*A tetrahedral chiral centre can change its chirality if two of its ligands are interchanged through chemical transformations. If the interconversion is carried out to 50%, a recemic mixture is obtained without involving an achiral transition state or intermediate.

carbanion may form in appropriate solvents without any base and racemisation takes place spontaneously:

$$(\underline{p})\ MeO\text{-}C_6H_4\text{-}SO_2\text{-}C\underline{H}(Me)\text{-}SO_2Ph \underset{H_3O^+}{\overset{H_2O}{\rightleftharpoons}} (\underline{p})\ MeO\text{-}C_6H_4\text{-}SO_2\text{-}\bar{C}(Me)\text{-}SO_2Ph \quad (3)$$

A mineral acid may also effect racemisation of a ketone containing an α-H through the intermediate enol (eqn.4).

$$-\overset{|}{\underset{|}{C}}H-\overset{|}{\underset{|}{C}}=O + H^+ \rightleftharpoons -\overset{|}{\underset{|}{C}}H-\overset{|}{\underset{|}{C}}=\overset{+}{O}H \rightleftharpoons -\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}-OH + H^+ \qquad (4)$$

7.2.2 Mechanism involving carbonium ions

A group (electron-withdrawing) may be detached from a chiral centre with an electron pair leaving behind a cationic species, e.g., a carbocation which because of its planar structure is achiral. Recombination of the anion, therefore, leads to racemisation. The mechanism operates when the substrate is capable of giving rise to a stable carbocation (benzylic, allylic, or tertiary). The reagents used are Lewis acids such as antimony pentachloride (eqn. 5), aluminium trichloride, and zinc chloride and sometimes a mineral acid (eqn. 6).

$$(+)\ PhCH(Cl)-Me + SbCl_5 \rightleftharpoons PhC^+(H)-Me + SbCl_6^- \rightleftharpoons (-)\ PhCH(Cl)-Me + SbCl_5 \qquad (5)$$

$$R_1R_2R_3CH + 2H_2SO_4 \rightarrow R_1R_2R_3C^+ + HSO_4^- + SO_2 + 2H_2O$$

$$R_1R_2R_3C^+ + R_1R_2R_3CH \rightleftharpoons R_1R_2R_3CH + R_1R_2R_3C^+ \text{ etc.} \qquad (6)$$

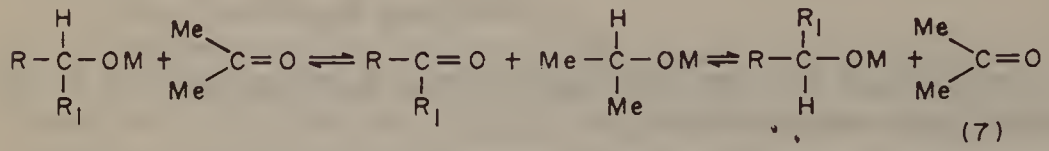
7.2.3 Mechanism involving free radicals

A free radical has a near planar structure (Chapter 4) and if a chiral centre is converted into a free radical pair by homolytic cleavage of a bond, the recombination of the pair would lead to a racemic product. Substrates which produces relatively stable radicals (benzylic, allylic, tertiary) may undergo racemisation through this mechanism under the influence of heat or light Thus α-chloroethylbenzene (in eqn. 5) in enantiomerically pure form when distilled under normal pressure, undergoes extensive racemisation. Hydrogenation-dehydrogenation catalysts, e.g., Pd-C can racemise a chiral centre containing a H atom through radical mechanism.

7.2.4 Mechanism involving stable symmetrical intermediate

In certain cases, the enantiomers (or diastereomers) are interconverted through stable (isolable) achiral intermediates and get racemised (or epimerised). A classical example is provided by Meerwein-Ponndorf-Verley/Oppenauer reduction-oxidation procedure (M-P-V) in which a secondary alcohol in the form of its aluminium

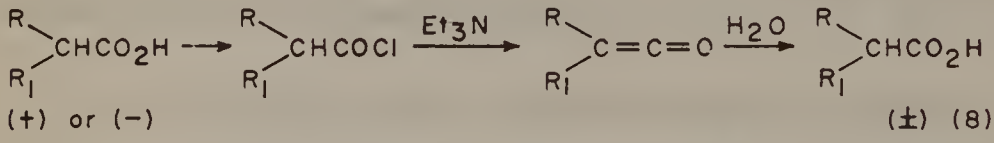
derivative is heated with a trace of a ketone (e.g., acetone). The ketone initiates a reversible oxidation-reduction sequence (eqn. 7) and an equilibrium is established between enantiomers (leading to racemisation) or between diastereomers (leading to epimerisation).



(7)

The method is particularly suitable for equilibration of cyclic secondary alcohols. In the above equation, M stands for dialkoxyaluminium. Sodium, potassium, and lithium alkoxides derived from secondary alcohols (M=Na,K,Li) on prolonged heating in the presence of a trace of a ketone may also establish equilibrium between enantiomeric or epimeric alcohols through an analogous mechanism. A primary alcohol of the type RR_1CHCH_2OH also gets racemised by heating with sodium since the intermediate aldehyde, RR_1CHCHO forms the enolate anion, $RR_1C{=}CHO^-$ before it is converted back into the alcohol.

Sometimes, the acid chloride of an optically active carboxylic acid, during reaction in the presence of a tertiary amine, undergoes racemisation through a ketene (eqn. 8).



(+) or (−) (±) (8)

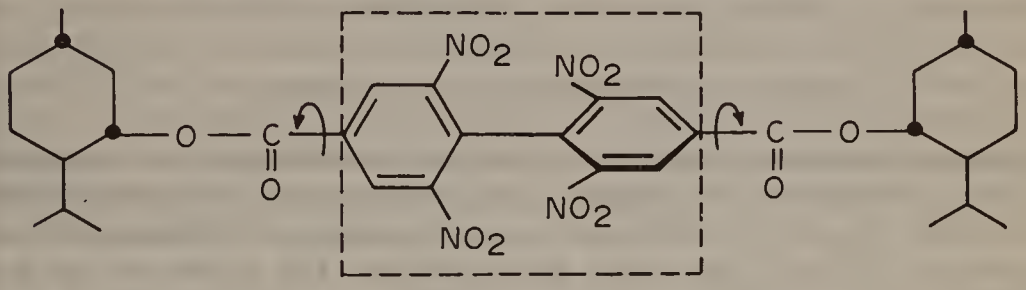
7.2.5 **Racemisation through rotation around bonds**

In the case of conformational enantiomers (Chapter 3), racemisation takes place through rotation around a single bond or bonds and the interconversion usually takes place readily via an achiral conformation. This has been already illustrated for atropisomers, e.g., optically active biphenyls (Chapter 5) in which the configurational stability depends on the steric bulk of appropriately placed substituents. Most of these enantiomeric atropisomers racemise by application of heat which leads to bond stretching and (or) bond bending and helps the non-planar enantiomers to cross the planar transition state.

Cyclic compounds which exist in enantiomeric conformations, e.g., *cis*-1,2-dimethylcyclohexane and *cis*-decalin undergo racemisation through ring inversion (see Chapter 10) apparently without passing through any achiral intermediate or transition state.

Mislow and Bolstad (1954) (see Eliel 1962) have prepared a biphenyl derivative, namely, (+)-menthyl (−)-menthyl 2,6,2′,6′-tetranitrobiphenyl-4,4′-dicarboxylate

(I) (Figure 7.1) which has some interesting structural features. (*i*) The two phenyl rings are prevented from being coplanar by the ortho nitro groups; (*ii*) the two terminals of the molecular axis are attached to two chiral moieties which are mirror images of each other; (*iii*) the non-planar biphenyl unit with its four nitro groups forming the vertices of a tetrahedron (elongated along the molecular axis) eliminates the possibility of the σ plane passing through the centre of the molecule. The net result is that the molecule does not have any element of symmetry (it belongs to C_1 point group) and is thus non-superposable with its mirror image. There is, however, a fourth structural feature; (*iv*) The biphenyl unit (put in a box) as a whole can rotate around two relatively unhindered single bonds joining the phenyl and carboxylate groups. A rotation of 90° converts one enantiomer into the other leading to spontaneous racemisation. The two enantiomers are thus conformational in origin similar to the two gauche conformers of *n*-butane (Chapter 9) with the difference that they do not have to pass through any achiral conformation during enantiomerisation.



(I)

Figure 7.1 Racemisation through rotation around single bonds

7.2.6 Configurational change in substitution reactions

In a nucleophilic substitution reaction, if substitution takes place at a chiral centre, e.g., when Y^- displaces X in $RR_1R_2C\text{-}X$ to give $RR_1R_2C\text{-}Y$, configurational change occurs the nature of which depends on the mechanism. The case is, however, quite distinct from racemisation since a different chiral centre is formed in the place of the original (unless X = Y). Three things may happen: The product may be racemic even though the starting material is optically active; the product may retain the configuration of the original molecule (Y in place of X); or it may undergo an inversion of configuration at the chiral centre. In S_N1 reactions, X^- departs first in a rate-determining step leaving behind a carbonium ion which, as has already been noted, has a planar structure and so extensive racemisation occurs in the product. In S_N2 reactions, the incoming nucleophile (Y^-) initiates the reaction from the back while X^- leaves the molecule from the front (a heterofacial reaction) in a concerted process as shown in Figure 7.2.* The chiral centre thus

*Orbital picture is given in Chapter 12.

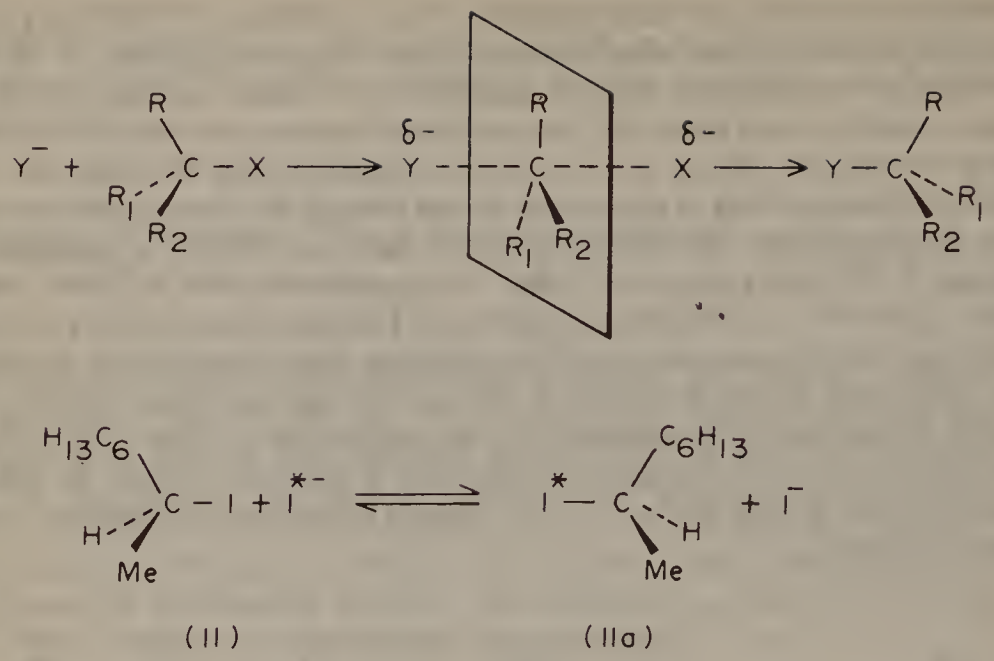


Figure 7.2 Configurational inversion in S_N2 reaction

undergoes an inversion of configuration with respect to the substrate stereochemistry. If X = Y as in the reaction of optically active 2-iodooctane (II) with sodium iodide, the reaction becomes reversible and an equilibrium is set up between the two enantiomers (II) and (IIa) leading to racemisation. The mechanism has been proved by using sodium iodide with radioactive iodine (I*). The rate of incorporation of I* is monitored by radioactivity of the substrate and the rate of racemisation by optical rotation. In the case of S_N2 mechanism, the rate of inversion will be equal to the rate of incorporation of I* which in turn will be half of the rate of racemisation (each inverted molecule forms a racemic pair with an uninverted one). This is found to be true within experimental error.

If the incoming nucleophile forms a part of the outgoing group, as Cl in the chlorosulphite (III) (Figure 7.3), it reacts with the chiral centre from the same side of the leaving group (a homofacial reaction known as S_Ni) and the configuration is retained*. Even before the mechanisms were known, Walden demonstrated the

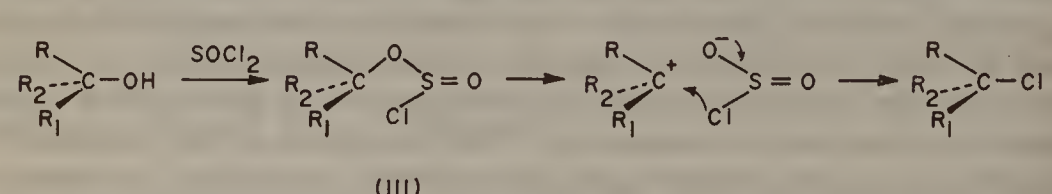


Figure 7.3 Retention of configuration: S_N1 mechanism

* Nucleophilic reaction through neighbouring group participation also leads to retention of configuration (as a result of two successive inversions) which is discussed in Chapter12.

phenomenon of inversion with the help of a few reaction sequences (see Kryger and Rasmussen 1972), one of which is shown in Figure 7.4. (−)-Malic acid on treatment with phosphorus pentachloride gives (+)-chlorosuccinic acid while on treatment with thionyl chloride gives (−)-chlorosuccinic acid. Obviously, in one of the reactions, inversion of configuration has occurred. It is now known that the first reaction goes with inversion (S_N2) and the second with retention (S_Ni) but at

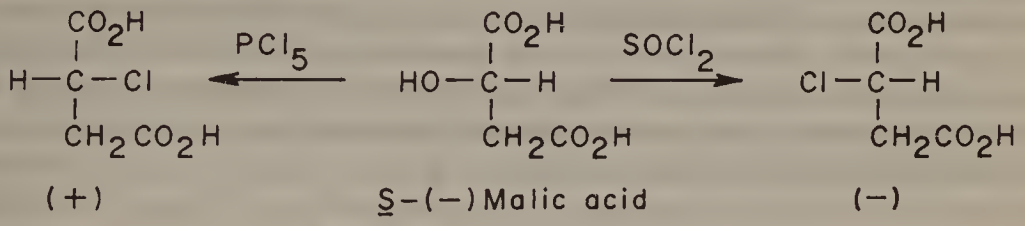


Figure 7.4 An example of Walden inversion

that time it could not be known (sign of rotation is no guide for configuration). A more pertinent example which definitely proves that inversion of configuration accompanies an S_N2 reaction is provided by the sequence of reactions given in Figure 7.5. The (+)-enantiomer of the alcohol (IV) is converted in three steps into the (−)-enantiomer (IVa). Tosylation and hydrolysis of acetate (first and the third steps) do not involve the chiral centre and inversion (designated by a loop), therefore, must have occurred at the second step in which the acetate replaces a tosylate group by S_N2 mechanism.

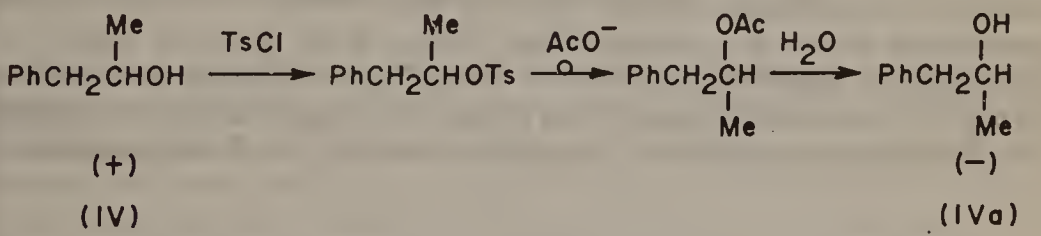


Figure 7.5 Interconversion of enantiomers through Walden inversion

7.3 Asymmetric transformation and mutarotation

A compound with a labile chiral centre can undergo configurational change in solution through any of the mechanisms discussed before and eventually lead to equilibrium. If that is the only chiral centre in the molecule, all that happens under achiral conditions is complete racemisation. If on the other hand, there exists a chiral element in the environment, one or the other of the enantiomers would predominate in equilibrium leading to what is known as 'asymmetric transformation'. The second chiral element may arise from a chiral solvent, a chiral counter ion, or a covalently linked chiral grouping present either in the molecule itself (in which case, it is purely an epimerisation process) or in another molecule used as an additive. What matters is that the chiral element of the environment must interact with (or form a part of) the chiral substrate giving rise to two diastereomeric associates (or complexes) formed in unequal amounts. For example, if a confi-

gurationally labile acid, (±)-A, is mixed with an enantiomerically pure base, (+)-B, in an appropriate solvent, equilibrium is established between two diastereomeric combinations, (+)-A. (+)-B and (−)-A. (+)-B (eqn. 9) and if the latter is more stable than the former, equilibrium will shift to the right, more and more of (−)-A will form from (+)-A, and the solution will be enriched with the species, (−)-A. The same equilibrium will result whether one starts with (±)-A, (+)-A, or (−)-A. A change in optical rotation will follow concomitantly. The transformation is known as *asymmetric transformation* while the change in optical rotation is known as *mutarotation*. Mutarotation is just an experimental observation—phenomenological in nature—and does not have any mechanistic implication. It may be due to a configurational change as in asymmetric transformation: it may also be due to a structural change in solution (vide infra).

$$(+)\text{-A. } (+)\text{-B} \rightleftharpoons (-)\text{-A. } (+)\text{-B} \tag{9}$$

7.3.1 Mutarotation and first order asymmetric transformation

Historically, asymmetric transformation was first observed by Dubrunfaut in 1846 although its significance was understood only much later. A freshly prepared solution of what is now called the α-form of D-glucose in water gradually changes its specific rotation (at 20°C) from the initial value of + 111° to an equilibrium value of + 52.5°. The phenomenon was termed 'mutarotation' by Lowry (1899) and subsequently any spontaneous change in rotation of a compound in solution, irrespective of mechanism, became known as mutarotation. In the case of glucose, mutarotation is due to a configurational change at the anomeric centre (C-1) establishing an equilibrium between α- and β-forms of glucose (two anomers) through the intermediate aldehyde form (Figure 7.6). This is basically an epimerisation process brought about by an amphoteric solvent, e.g., H_2O and is catalysed by

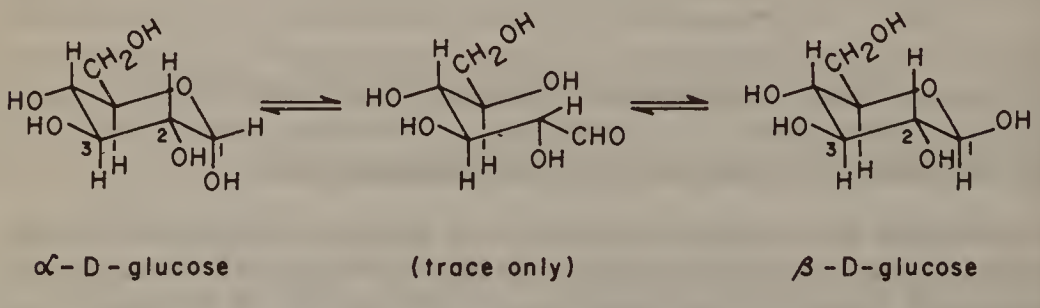


Figure 7.6 First order asymmetric transformation in glucose

acids and bases. The chiral element required for this asymmetric transformation is provided by the rest of the chiral component of glucose. Conformational changes of this type which occur in solution (involving a single phase) is known as *first order asymmetric transformation*. All reducing sugars (excepting a few ketoses) and many of their derivatives undergo first order asymmetric transformation and exhibit mutarotation. In the case of glucose, equilibrium (in water) corresponds to 38% of the α- and 62% of the β-form and can be reached from either side. The

mechanism involves protonation of the oxide ring, deprotonation of 1-OH by base followed by ring opening to the aldehyde form, and its subsequent ring-closure to the original hemiacetal or its epimer by acid catalysis. In consonance with the mechanism, an amphoteric solvent or a combination of acid and base is necessary for mutarotation. Thus in tetramethyl glucose, mutarotation can be arrested by using cresol (a weak acid) or pyridine (a weak base) alone as solvent but goes twenty times faster in the mixture of the two than in water. Hydroxypyridine containing both acidic and basic nuclei is an effective catalyst for mutarotation in sugars.

Mutarotation due to a structural change may be illustrated with gluconolactones a solution of which in water establishes equilibrium between δ-glucono- and γ-gluconolactone through the intermediate gluconic acid (Figure 7.7). In this case, no asymmetric transformation is involved (two compounds in equilibrium are structural isomers).

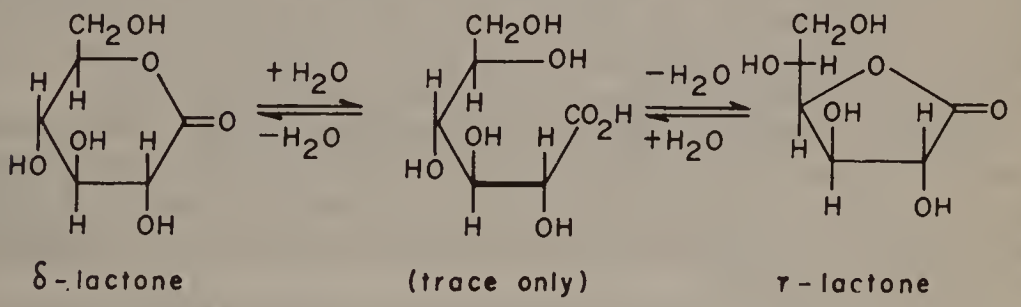


Figure 7.7 Mutarotation due to structural change

First order asymmetric transformation accompanied by mutarotation is exhibited by many biphenyl derivatives and analogues (Chapter 5) in which rotation around the pivotal single bond is moderately restricted so that interconversion between two enantiomeric atropisomers takes place in solution. Such compounds are not resolvable under ordinary conditions but when admixed with appropriate chiral additives, show mutarotation because of first order asymmetric transformation. Thus 3′-bromobiphenyl-2-trimethylarsonium iodide (V) (Figure 7.8) when mixed with (+)-camphorsulphonate (as a salt) in solution shows mutaro-

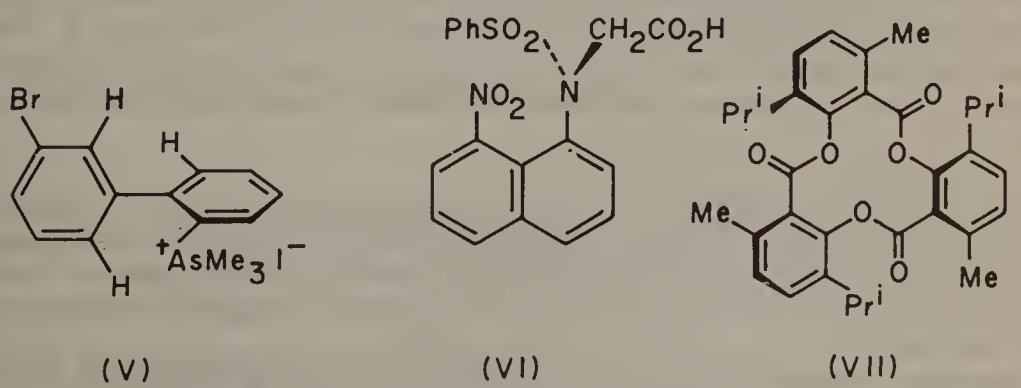


Figure 7.8 Substrates for first and second order asymmetric transformations

tation. Here the chiral counter ion, (+)-camphorsulphonate, discriminates between the readily interconvertible atropisomers of the biphenyl leading to two unequally populated diastereomeric salts. The first order asymmetric transformation* thus involves the establishment of equilibrium between two diastereomeric complexes which have *real* existence in solution (Jamison and Turner 1942).

7.3.2 Second order asymmetric transformation

It may so happen that in an asymmetric transformation, one of the enantiomers or diastereomers actually crosses the phase boundary, i.e., comes out of the solution as crystals or immiscible liquids. This is known as *second order asymmetric transformation* and is of more practical value than the first kind since it can permit sometimes a 100% conversion of a racemic mixture into a pure enantiomer. Many transformations of the first kind may be turned into those of the second kind by changing the conditions, e.g., the solvent. Thus when a solution of glucose in ethanol is concentrated, the less soluble α-form crystallises first and equilibrium is once again established so that finally, only α-form of glucose is obtained. In a similar way, crystallisation of glucose from pyridine gives the β-form only.

Examples of second order asymmetric transformation are again available from compounds which owe their chirality to restricted rotation. Thus (+)-N-benzenesulphonyl-8-nitro-1-naphthylglycine (VI, Figure 7.8) when combined with brucine, may yield either of the diastereomeric salts in almost 100% yield by crystallisation from methanol or acetone.

A few cases of total asymmetric transformation of the second kind are known in which an enantiomer of the substrate itself provides the necessary chiral element. Here one enantiomer may happen to crystallise first providing a seed (the racemic form must necessarily be conglomerate, see Chapter 3) which by virtue of its enantiomorphous structure induces crystallisation of the same form, e.g., (+,+) or (−,−). In the solution, equilibrium shifts towards the enantiomer which is crystallising out leading eventually to total asymmetric transformation. Thus tri-*o*-thymotide (VII, Figure 7.8) when crystallised from benzene separates out as crystalline solvates (a solvent molecule is incorporated into the molecule)† in either enantiomeric form leading to spontaneous resolution. 1,1′-Binaphthyl (Chapter 5) is another interesting compound which undergoes almost total asymmetric transformation both by crystallisation from solvents (or melt) and by heating the solid form below the melting point. The transformation in the solid phase is rather surprising and is due to the existence of two crystal forms: racemic conglomerate (eutectic form) and racemic compound. The former is more stable than the latter

*Pfeiffer and Quehl (1931) first observed asymmetric transformation in chiral coordination complexes by the addition of an anionic, a cationic, or a neutral species into aqueous solution of the complexes and hence the phenomenon is also known as Pfeiffer effect. The term 'order' has nothing to do with kinetics and may be replaced by 'kind' (Kuhn 1932), i.e., asymmetric transformation of first kind and of second kind.

† Such crystals act as good host molecules and often form inclusion complexes preferably with one enantiomer of another chiral molecule and thus provides a method of partial resolution (vide infra).

above a certain temperature (>25°C) and so when the crystals are warmed, the *racemic compound* gets converted into the *eutectic* (apparently, 1,1′-binaphthyl can change its configuration in the solid state). The first single homochiral crystal of the conglomerate that is formed initiates a chain reaction favouring the formation of crystals of its own kind, (+,+) or (−,−), thus leading to almost total asymmetric transformation (see Wilson and Pincock 1975 for details). Free energy necessary for (spontaneous) resolution is provided by the energy gained in the conversion of the less stable crystal form into the more stable one.

7.4 Methods of resolution

The basic principle of resolution of a racemic form is as follows. Enantiomeric discrimination has to be effected by using chiral reagents (resolving agents) or a chiral medium through the establishment of diastereomeric relationships. Unlike racemisation, resolution is not a thermodynamically favourable process and is not expected to occur spontaneously under ordinary circumstances. Most of the natural products, food stuffs, drugs, flavouring agents, perfumes, and other biologically active materials usually show their desirable or beneficial effects in one enantiomeric form only. Thus proteins contain only L-amino acids: the natural (+)-glutamic acid is a flavour-enhancing agent, its (−)-enantiomer is not: of the four possible stereoisomers of chloramphenicol (chloromycetin) having two chiral centres, only one acts as an antibiotic: (+)-morphine is a powerful analgesic. its enantiomer is not. It is necessary.therefore, that the chiral compounds be available in the desired enantiomeric forms. This is possible in two ways: asymmetric synthesis (see Chapter 13) or resolution of racemic modifications synthesised in the laboratory under achiral circumstances. The area of asymmetric synthesis is fast expanding and considerable success has been achieved. But still in the majority of cases, resolution of racemic forms is the only practical method for large scale preparation of optically pure compounds. Depending on the requirements, chiral compounds may be partly resolved (partial resolution) or completely resolved (total resolution). The method of resolution was initiated in 1848 by Pasteur and three of the methods now used are due to him. Since then considerable improvement has been made both in technique and in methodology and it is not possible to cover every aspect of resolution in this text (see Jaques et al 1981, Mason 1982). The principle of the important procedures is discussed followed by illustrative examples.

7.4.1 Mechanical separation: crystallisation method

As pointed out in Chapter 3, racemic modifications may exist in three types of crystalline forms: conglomerate with homochiral assemblies of enantiomers in a single crystal, racemic compounds containing equal number of (+) and (−)-isomers in the unit cell of the crystal, and pseudoracemates with no preference for enantiomers in the crystal structure. In the case of the conglomerate, sometimes the two enantiomorphous crystals are distinguishable visually and can be separated by hand-sorting with the help of a magnifying glass and a pair of tweezers. Pasteur in 1848 crystallised sodium ammonium tartrate by slow evaporation of an aqueous

solution when the temperature happened to be below 27°. He then separated the two types of crystals with distinguishable hemihedral facets. When dissolved in water, they showed optical rotation of opposite directions. The method is applicable only to racemic conglomerates the frequency of occurrence of which although higher than that of pseudoracemates is considerably lower than that of racemic compounds. In crystals of high symmetry, as in 1,1′-binaphthyl, the two sets of enantiomorphous crystalline froms may not be distinguishable visually. The difficulty can occasionally be circumvented by producing big crystals and then checking the rotation of each individual crystal. However, the method is tedious and not of much practical application.

Pasteur's original method has been subsequently modified to preferential crystallisation of enantiomorphous crystals by inoculating a supersaturated solution of the racemic mixture with a crystal of one of its enantiomer or in its absence with an isomorphous crystal of another chiral compound. This method is known as entrainment and the seed crystal is known as *entrainer*. For example, the saturated solution of sodium ammonium tartrate may be seeded with one of its own crystal or a crystal of (−)-asparagine, $NH_2COCH_2CH(NH_2)CO_2H$. Sometimes even a crystal of an achiral molecule can act as an entrainer, e.g., glycine in resolution of asparagine in either enantiomeric form.

The preferential crystallisation depends on the principle that the solubility of the enantiomer is less than that of the racemic form. This method is more effective for salts consisting of charged species than for neutral molecules. One of the compounds which has been resolved on a large scale by this method is *S*-glutamic acid, a racemic mixture of which is synthesised from acrylonitrile (Collet et al 1980). The method is particularly useful for effecting a total resolution from a partially resolved sample available either from asymmetric synthesis or from resolution by other methods. In a rare variation, the crystallisation may be carried out from an optically active solvent or a solution containing an optically active solute, e.g., glucose and tartaric acid.

A very important modification of the method has been developed recently which works on a reverse principle. Instead of using an entrainer, an *inhibitor* is used in minute quantity which retards the growth of crystal of a particular enantiomorphic form by modifying its morphology in a selective way. Thus racemic glutamic acid, threonine, and asparagine are totally resolved using *S*-lysine, *S*-glutamic acid, and *S*-aspartic acid respectively as additives. In each case the *R*-enantiomer crystallises out. Configurational correlation between the separating enantiomer and the chiral additive has been worked out (Chapter 8) and it is found that the fast separating enantiomer and the chiral additive have opposite configurations (Addadi et al 1985).

7.4.2 **Resolution through the formation of diastereomers**

The second method of Pasteur, namely, the formation of diastereomeric salts and their fractional crystallisation, is the best method for resolution and is applicable to a much wider range of compounds. The principle is illustrated here in the resolution of a racemic acid, (±)-A with an optically pure base, (+)-B which

combines with the racemic acid giving two diastereomeric salts (p and n isomers respectively)* .

$$(\pm)\text{-A} + (+)\text{-B} \rightarrow (+)\text{-A}.(+)\text{-B} + (-)\text{-A}.(+)\text{-B}$$

Being diastereomeric, the two salts differ in properties such as solubility, boiling point, and adsorption coefficient. When crystallised from a solvent. one of them, say the p isomer, would separate first and after several crystallisations be available in pure state as judged by the melting point and optical rotation which would attain constant values. Decomposition of the salt with mineral acids would furnish (+)-A in enantiomerically pure form. For successful execution. several conditions should be fulfilled which are enumerated below :

(*i*) The substrate and the resolving agent must have suitable functional groups capable of interacting with each other. It is essential that the configuration of the chiral centres remains unchanged during the formation of the diastereomers as well as during the regeneration of the enantiomers. Salt formation, for this reason, is the most desired reaction. Other reactions involve formation of esters. urathane derivatives, molecular adducts etc. depending on the nature of the substrates.

(*ii*) The resolving agents should be available in enantiomerically pure form. The optical purity of the resolved product cannot, in principle, exceed that of the resolving agent. However, this is not a serious limitation since a partially resolved compound can be further resolved by fractional crystallisation (vide supra).

(*iii*) The resolving agent should be either inexpensive or capable of regeneration at the end of the operation.

(*iv*) The most important criterion is the proper choice of the resolving agent. If the separation be done through fractional crystallisation, the resulting diastereomers should be easily crystallisable and differ in their solubility in a particular solvent. If one of them is less soluble in one solvent and the other in another solvent, then the condition is ideal and both the enantiomers can be separated in pure form. In most cases, the choice is made on a trial and error basis. Some guidelines are available from the study of a large number of salts prepared from fourteen acids and nine bases commonly used (Jaques et al 1981).

(*v*) The choice of solvents is also important and again it must be done on the basis of trial and error. The most usual solvents are water, alcohols, acetone, and ethyl acetate. Temperature also plays a role in crystallisation.

(*vi*) The possibility of double salt formation during crystallisation must be checked and should be avoided by changing solvent or the resolving agent. The double salt, e.g., (+)-A. (+)-B, (−)-A. (+)-B, analogous to an azeotropic mixture in the case of liquids would prevent any further enrichment of a diastereomeric mixture.

Organic acids and bases (amines) are by far the most important groups of compounds which are resolved directly by this method. Organic bases used as resolving agents are the naturally occurring alkaloids such as quinine, brucine, strychnine, ephedrine, cinchonine, and cinchonidine (see Figure 7.9). A large

*A diastereomeric complex in which both the components have the same sign of rotation is sometimes called p (positive) isomer while the diastereomer in which the components have opposite signs of rotation is called n (negative) isomer for convenience.

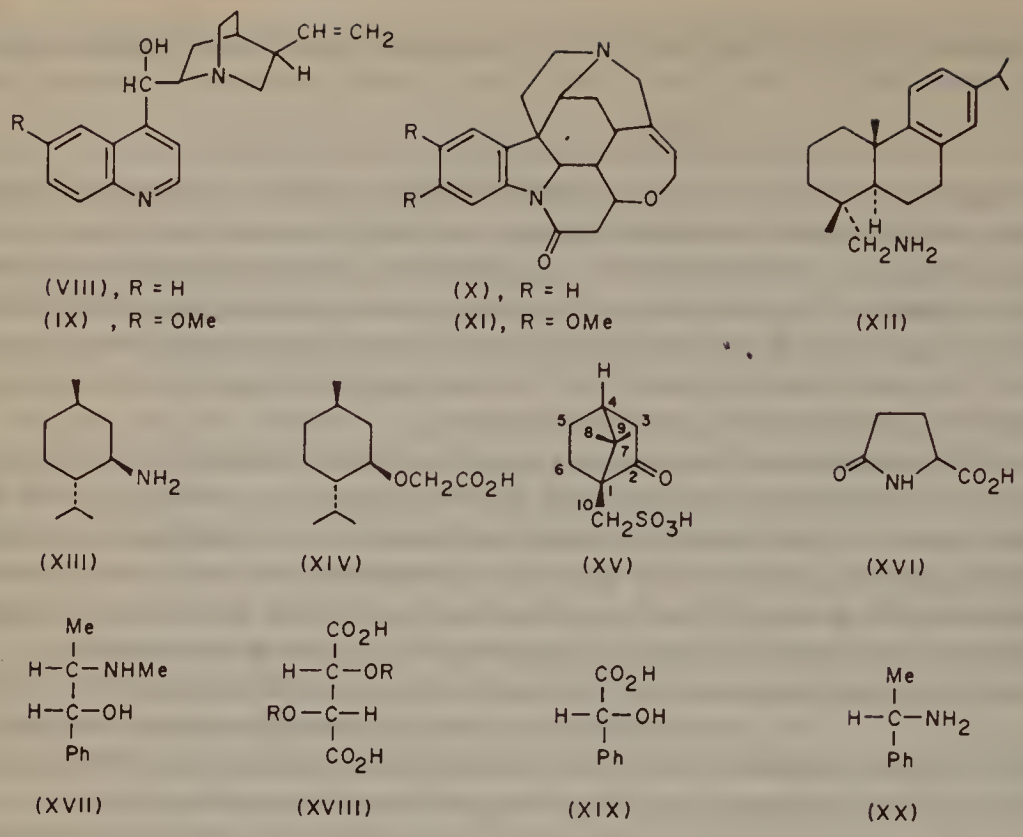


Figure 7.9 Some common resolving agents: cinchonine and cinchonidine (VIII), quinine and quinidine (IX), strychnine (X), brucine (XI), dehydroabietylamine (XII), menthylamine (XIII), menthyloxyacetic acid (XIV), camphor-10-sulphonic acid (XV), pyroglutamic acid (XVI), ephedrine (XVII), tartaric acid dibenzoyl derivative (XVIII), mandelic acid (XIX), and α-phenylethylamine (XX).

number of racemic acids have been successfully resolved with quinine and brucine alone (Wilen 1972). The resolved acids in turn may be utilised for the resolution of chiral amines. A few synthetic amines are also used for resolution of acids of which α-phenylethyl amine, is most important. The advantage of the synthetic bases is that two enantiomeric forms are usually available.

On the other side, the number of enantiomerically pure naturally occurring acids are few. Tartaric acid and its derivatives such as dibenzoyl, diacetyl, and the derived anilic acid are used for resolution of amines. They are cheap and need not be regenerated. Other natural acids such as mandelic acid, malic acid, and camphoric acid are less readily available. Some optically active acids have been prepared from terpenoid ketones and alcohols such as 3-, 9-, and 10-camphor-sulphonic acids and menthyloxy and bornyloxyacetic acids (Figure 7.9). The different types of substrates which are resolved in addition to acids and bases by application of this method are briefly summarised below:

(*i*) **Amino acids**: Amino acids exist in zwitterionic structure and before resolution, either the amino or the carboxyl group should be derivatised. The usual method is to formylate the amino group and then convert the product into diastereomeric salts with optically active bases. The formyl group can be removed under mild hydrolysis condition and no racemisation usually occurs. Other protecting groups are acetyl, benzoyl, tosyl etc. which require more drastic condition for removal.

Alternatively, the carboxyl end of the molecule can be protected by esterification and resolution can be done through salt formation with optically active acids. Many racemic α-amino acids have been successfully resolved by preparing isobutyl or benzyl esters and using dibenzoyl tartaric acid as the resolving agent.

(*ii*) **Alcohols** : Alcohols can be directly converted into diastereomeric esters by reaction with optically active acids. Menthyloxy or bornyloxyacetic acid chloride or acid chloride derived from a steroidal carboxylic acid may be used. Diastereomeric urethanes may be prepared by the reaction of the alcohols with optically active isocyanates. Separation is done usually through crystallisation although column chromatography can also be used. Fractional crystallisation of the esters, in general, is not as satisfactory as that of the ionic salts and the following additional steps are generally used.

The alcohol is first converted into a half ester of succinic acid or phthalic acid by heating with succinic anhydride (Figure 7.10) or with phthalic anhydride respectively. The half esters may then be treated as typical acids and resolved using optically active bases. The resolved half ester is finally hydrolysed or reduced with lithium aluminium hydride (as shown) to set the alcohol free.

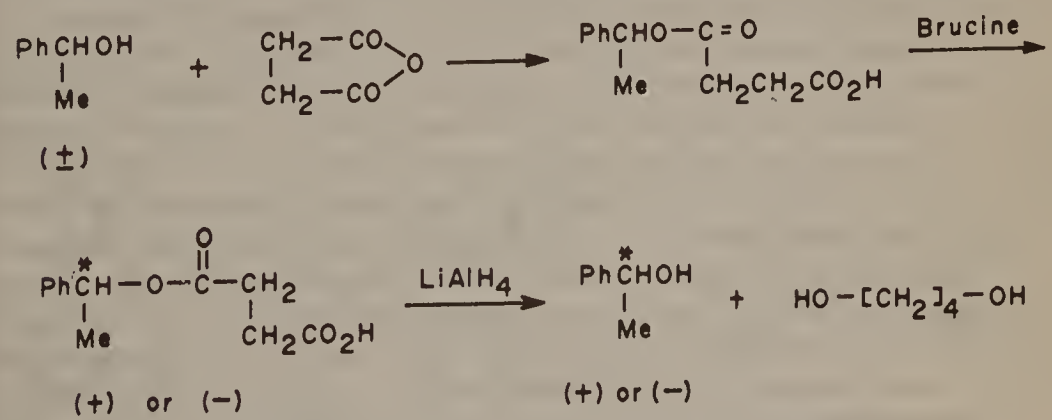


Figure 7.10 Resolution of an alcohol through acid phthalate

(*iii*) **Aldehydes and ketones** : Optically active aldehydes and ketones are generally available synthetically from other chiral compounds and their resolution is seldom needed. For their resolution, derivatisation reagents in optically active form may be used. Some of the resolving reagents are the hydrazide of (+)-mandelic acid. amidohydrazide of (+)-tartaric acid, menthylsemicarbazide etc. Ketones can also be converted into ketals or dithioketals using optically active 2.3-butanediol or 2,3-butanedithiol. In the latter case, after purification by fractional crystallisation, the thioketal can be directly desulphurised by treatment with Raney nickel to the ketone (Corey and Mitra 1962).

(*iv*) Hydrocarbons and aromatic ethers which do not possess any reactive functional group are sometimes resolved through formation of molecular complexes discussed in the next subsection.

7.4.3 Resolution through the formation of molecular complexes

Instead of forming stable salts or covalent compounds with the substrates and the

resolving reagents, it is possible, in a few cases, to have molecular complexes which form easily and decompose easily and thus are ideally suited for resolution. The first observation was again made by Pasteur in the formation of molecular compounds between the amides of (−)-malic acid and of tartaric acid. Digitonin (XXI) (Figure 7.11), a steroidal saponin forms addition complexes with various alcohols, e.g., α-terpineol, isocarvomenthol, and phenolic compounds which can be preferentially crystallised from appropriate solvents and then decomposed to give enantiomerically pure alcohols and phenols. (+)-2-Naphthylcamphylamine (XXII) has been successfully used to resolve N-*s*-butylpicramide.

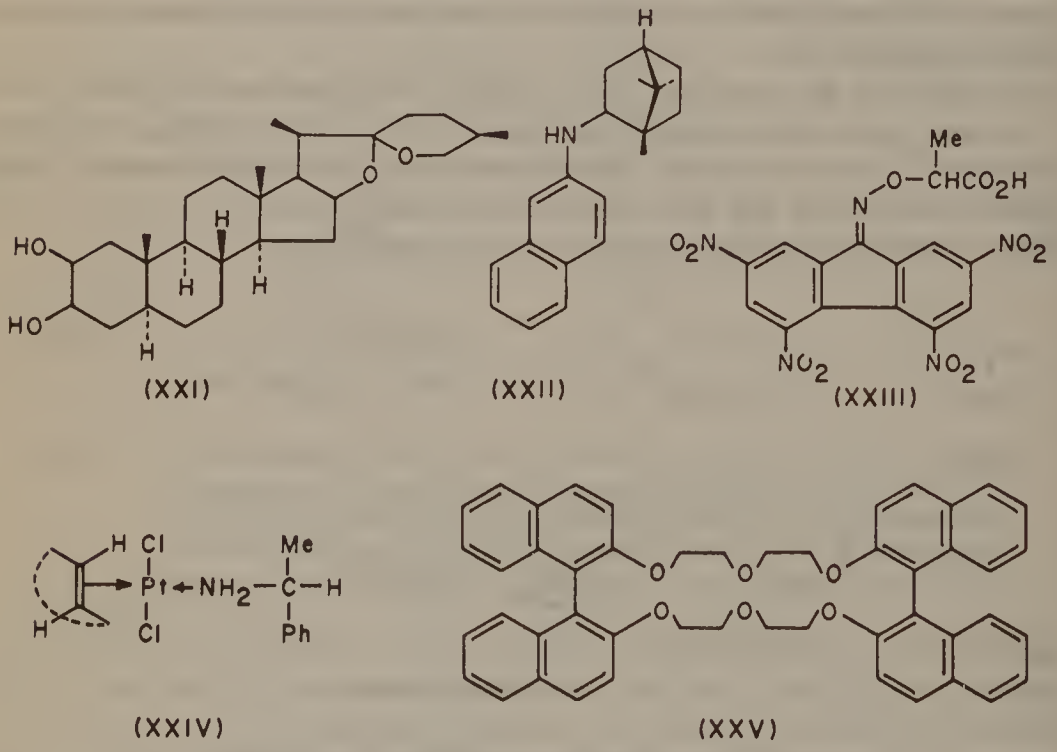


Figure 7.11 Some chiral complexing reagents

α-(2,4,5,7-Tetranitro-9-fluorenylideneaminoöxy)propionic acid (XXIII) (TAPA) forms charge transfer complexes (π-complexes) with many aromatic hydrocarbons including helicenes and aromatic ethers and has been successfully used to resolve naphthyl *s*-butyl ethers and helicenes (Newman and Lednicer 1956). With (+)-TAPA, *P*-(+)-hexahelicene preferentially crystallises out of the solution while the *M*-(−)-isomer forms the stronger complex and remains in solution. *trans*-Cyclooctene (the *E*-isomer) has been resolved through complexation with the platinum (IV) reagent containing *R*-1-phenylethylamino moiety (XXIV). Another interesting example is the enantioselective partitioning between an aqueous phase and a solvent containing a chiral complexing agent such as the chiral crown ether (XXV) (chirality is due to restricted rotation). Chiral alkyl and arylammonium ions have been resolved by the formation of diastereomeric complexes with chiral crown ethers of appropriate cavities (see Cram and Cram 1974).

7.4.4 Resolution by chromatography

The chromatographic method of resolution of racemic mixtures is carried out generally under four different conditions: (*i*) formation of diastereomeric mixtures by derivatisation with optically active reagents and separation by classical chromatography using achiral adsorbents based on the different adsorption coefficients of the diastereomers; (*ii*) direct resolution of the racemic mixtures using chiral adsorbent materials either as solid or as liquid stationary phase; (*iii*) direct resolution on an achiral solid phase using a mobile chiral liquid phase; and finally, (*iv*) direct resolution using an achiral solid stationary phase modified by a chiral reagent. The first method is an alternative to separation by crystallisation of diastereomeric salts. The method is of general use and may be illustrated in the resolution of 2-butanol by forming esters with (−)-mandelic acid followed by chromatography on Dowex-50W-X2 to give both the diastereomeric esters.

The second method, namely, use of chiral stationary solid phase is more interesting. The naturally occurring polysaccharides and their derivatives provide useful chiral stationary phase materials. One, namely, microcrystalline triacetyl cellulose (MCTC) forms a versatile column on which a number of compounds, e.g., racemic olefins, biphenyls, ketones, alcohols, esters, acids, and salts have been resolved (Hesse and Hagel 1976). The problem is its relative unavailability. A number of synthetic chiral polymers have also been used as stationary phase materials. However, the method can hardly be used for total resolution since the solvation of the substrate minimises the disastereomeric relationship and very long column has to be used for effective resolution. An alternative method of preparation of a chiral stationary phase is the adsorption or chemical binding of a resolving agent to an achiral stationary phase, Thus (−)-TAPA (XXIII) adsorbed or covalently bonded to silica gel has been used to resolve chiral aromatic hydrocarbons including helicenes. Chiral crown ethers bonded to silica or organic polymers have been used by Cram and Cram (1978)*. A series of chiral aromatic fluoroalcohols on supporting materials provide a broad spectrum of resolutions by means of high performance liquid chromatography (HPLC) (Pirkle et al 1980).

In the third variation, many cationic chelated metal complexes, e.g., tris-(diamino)metal complexes have been resolved by chromatography on a column of cation-exchange Sephadex (dextran cross-linked with epichlorohydrin) by elution with an aqueous solution of (+)-tartrate. In the fourth variation, an ordinary adsorbent like silica gel is made stereoselective by special treatment with optically active substances, e.g., (+)-tartaric acid and (+)-camphorsulphonic acids which are later removed by elution with solvent leaving behind a 'memory'. When a solution of similarly constituted racemic compound is passed through such treated column, preferential adsorption of the 'like' enantiomer takes place (Curti and Colombo 1952).

Gas chromatography has also been extensively used for analysis as well as separation of enantiomers working on the above principles. The trifluoroacetyl derivatives of optically active amino acids have been used for gas chromatographic

*For chiral crown ethers, see Stoddart, 1987.

resolution of racemic alcohols via the corresponding esters. Paper chromatography can also effect partial resolution; the paper itself (cellulose material) can act as chiral adsorbent or it may be impregnated with solutions of optically active compounds such as camphorsulphonic acids (see Potapov 1979).

7.4.5 Resolution through equilibrium asymmetric transformation

The principle of equilibrium asymmetric transformation has already been discussed. Resolution based on it involves two steps: epimerisation of a diastereomeric species, be it a covalent compound, a salt, or a complex, in solution and precipitation of the predominant epimer (second order asymmetric transformation). If the asymmetric centre undergoing the configurational change can be separated from the rest of the diastereomeric species, only one enantiomer is obtained. In ordinary resolution, the yield of the enantiomer can never exceed 50% (usually 25-30% is good enough) but in asymmetric transformation, the racemic form can, in principle, be completely converted into one of the enantiomers. This is illustrated with an example from Eliel's book (1962). When the racemic form of 2-(*p*-carboxybenzyl)-1-hydrindanone (XXVI) (Figure 7.12) is treated with brucine in acetone solution, one of the diastereomers precipitates in over 90% yield (epimerisation takes place through enolisation). On acidification, the (+)-enantiomer of the ketone (XXVI) is obtained which, however, racemises spontaneously. Similarly, when the (−)-menthyl ester of racemic phenylchloroacetic acid (XXVII) is treated with base, it epimerises (acidic H is underlined), leading to an equilibrium mixture containing esters with 57% of the (−)-acid and 43% of the (+)-acid.

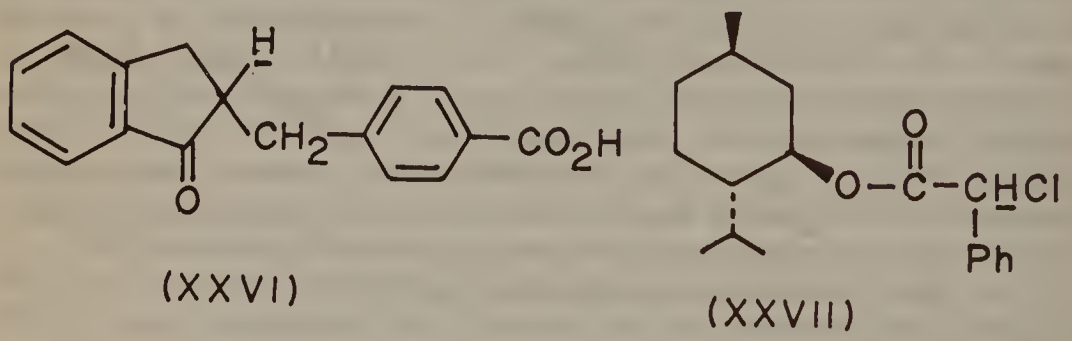


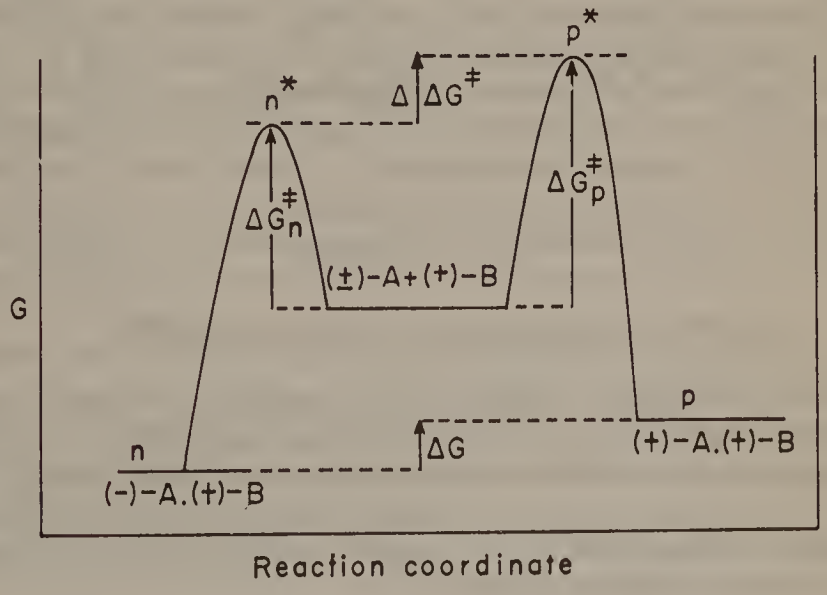
Figure 7.12 Equilibrium asymmetric transformation

7.4.6 Resolution through kinetic asymmetric transformation*

The kinetic asymmetric transformation is based on the principle that one of the diastereomer is formed, destroyed, or transformed selectively by a chemical reaction. This is possible because the activation energies of the two diastereomeric transition states in the reaction of a racemate with a chiral reagent are different and so the two enantiomers react at different rates. There are several variations of the method.

*For a latest review on kinetic resolution, see H.B. Kagan and J.C. Fiaud in *Topics in Stereochemistry* (1988), vol. 18.

(*i*) **Kinetic method of resolution**: If a racemic substrate, i.e., (±)-A is allowed to react with an optically active reagent, i.e., (+)-B, (see the centre of the diagram in Figure 7.13) the reaction proceeds through two diastereomeric transition states, p* leading to the p-diastereomer, (+)-A. (+)-B, and n* leading to the n-diastereomer, (−)-A. (+)-B. Because of diastereomeric relationship, the products as well as the transition states are of different free energies, the differences being ΔG in the ground states of the products and $\Delta\Delta G^{\ddagger}$ in the transition states. If the reaction is carried out in such a way that equilibrium is established between p- and n-diastereomers, the reaction is called *thermodynamically controlled* and the product



$$\Delta G = -RT \ln \frac{p}{n} \cdots\cdots \text{thermodynamically controlled condition}$$

$$\Delta\Delta G^{\ddagger} = -RT \ln \frac{p^*}{n^*} \cdots\cdots \text{kinetically controlled condition}$$

Figure 7.13 Thermodynamically and kinetically controlled reactions.

ratio is governed by ΔG. On the other hand, if the reaction is carried out irreversibly so that equilibration is completely avoided, the reaction is known to be *kinetically controlled* and the product ratio is governed by $\Delta\Delta G^{\ddagger}$ (see equations). In the latter case, the rates of formation of the two products are different; the one formed through lower energy transition state (n* in the the present case) is produced at a faster rate and in greater amount. The principle holds good for any kinetically controlled reaction whether the products are of the same free energy (when they are two enanatiomers) or of different free energies (when they are diastereomers or constitutional isomers). In the present case, it would mean that one of the enantiomers of the substrate, (−)-A would react faster ($\Delta G_n^{\ddagger} < \Delta G_p^{\ddagger}$) and if the reaction is stopped before completion [or if the reactant, (+)-B is taken in insufficient amount], the unreacted substrate would be enriched in (+)-A thus providing a kinetic method of resolution. For example, when (±)-mandelic acid

is esterified with an insufficient amount of (−)-menthol, (−)-menthyl (+)-mandelate (n-diastereomer) is formed in higher proportion leaving behind the unreacted mandelic acid enriched in the (−)-isomer.

The biphenyl ketone (XXVIII)) (Figure 7.14) provides another interesting example of kinetic method of resolution. When the (±)-ketone is partially reduced with *S*-2-octanol (in the presence of aluminium *t*-butoxide), the (+)-ketone is reduced at a faster rate and the unreacted ketone becomes enriched in the (−)-enantiomer (XXIX) (Mislow 1965). The resultant alcohol, in turn, becomes

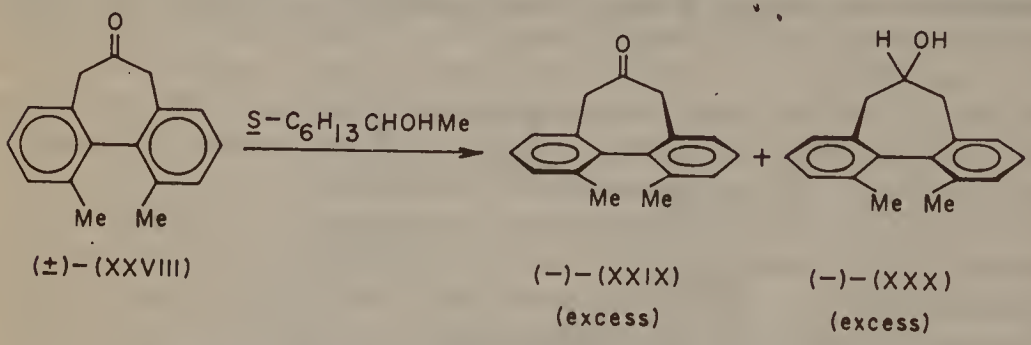


Figure 7.14 Kinetic resolution of a bridged biphenyl ketone

enriched in the (−)-enantiomer (XXX) which is also obtained by the reduction of (+)-XXIX with an achiral reagent, e.g., lithium aluminium hydride. In a somewhat reverse situation, when two moles of (±)-isobornyloxyaluminium dichloride (XXXI) are allowed to react with one mole of (−)-menthone (Figure 7.15), one enantiomer of the reagent is oxidised faster and the product consists of 90% of (+)-camphor (XXXII) (Nasipuri and Mukherjee 1974).

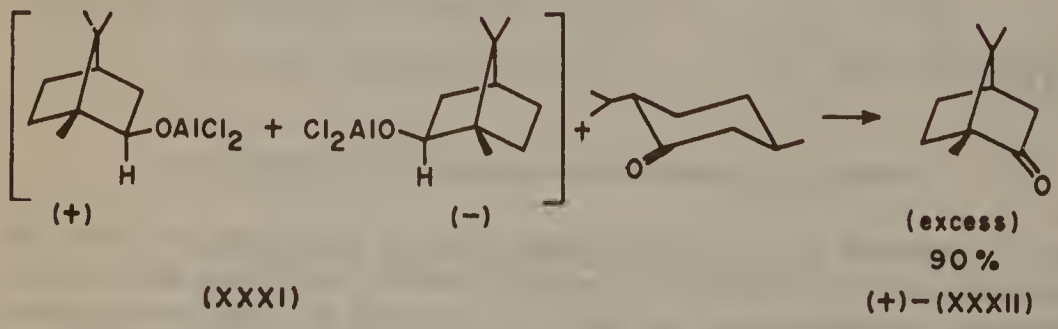


Figure 7.15 Kinetic method of resolution of camphor

These reactions may also be considered as asymmetric synthesis, in the first case, of the alcohol (XXX) and in the second case, of camphor (XXXII). Furthermore, since the difference in the reactivities of the two enantiomers with chiral reagents may ultimately be traced to the difference in the topologies of the reacting molecules (in terms of secondary interactions: steric and electronic), such reactions also provide information regarding the relative configuration of the reacting species (see Chapter 8). In fact, any method of optical activation (which is based on the difference in diastereomeric interactions), is, in principle, capable of establishing

relative configuration provided a precise knowledge of the mechanism of the process is available.

(*ii*) **Kinetic method using diastereomeric substrates**: Instead of using a racemate substrate, a mixture of diastereomers can be used in a reaction with an achiral reagent. The two diastereomers would react at different rates and a partial separation of diastereomers may be effected. Thus the mixed esters derived from (±)-mandelic acid and (−)-menthol on incomplete hydrolysis afford a partial resolution of the mandelic acid in the hydrolysed product and a partial separation of the diastereomeric esters in the unhydrolysed residue.

(*iii*) **Other variations**: Sometimes a reaction may be carried out in the presence of an optically active catalyst. Thus racemic ethyl phenylchloroacetate on incomplete hydrolysis in the presence of cyclodextrin produces (+)-$C_6H_5CH(Cl)CO_2H$. Another variation is the preferential destruction of a chiral centre in a diastereomer. The most common method is to carry out dehydration or dehydrogenation using chiral catalyst. A simple example is the incomplete dehydration of (±)-phenylmethyl carbinol with (+)- or (−)-camphorsulphonic acid when one or the other of the enantiomeric alcohol predominates in the undecomposed substrate. An asymmetric dehydration has already been referred to in Chapter 5 in the synthesis of an optically active allene.

Asymmetric decomposition of appropriate substrate by circularly polarised light is also well known. As early as 1930, Kuhn and Knopf decomposed (±)-α-azidopropionic dimethylamide $MeCHN_3CONMe_2$, with right and left circularly polarised light to obtain a residue of the azide with weakly dextro- and levorotatory azide respectively.

Like asymmetric destruction, asymmetric synthesis may also be used for getting chiral compounds of high optical purity which will be discussed in a later chapter.

7.4.7 Resolution by biochemical transformation

In the kinetic method of resolution discussed above, the chiral reagents may be replaced by microorganisms or enzymes which are often highly stereoselective in their reactions. Pasteur first observed (his third method) that when a solution of the ammonium salt of (±)-tartaric acid is fermented by yeast or a mold (Penicillium glaucum), the natural (+)-form is completely consumed leaving behind the ammonium salt of (−)-tartaric acid.

The biochemical method has found important application in the resolution of (±)-amino acids. Thus an acetylated (±)-amino acid is treated with an enzyme 'acylase I' (hog-kidney acylase) until half the acetyl groups are hydrolysed away. The unhydrolysed acetyl derivative is that of the D-amino acid while the hydrolysed product consists of L-amino acid.

The shortcomings of the biochemical transformation are as follows. (*i*) Very dilute, usually aqueous solutions have to be used for fermentation, thus the product may be hard to isolate; (*ii*) most of the time, that enantiomer is selectively consumed which is biologically important; so frequently, only the unnatural enantiomer is available; (*iii*) it is not always possible to find an appropriate enzyme or microorganism for a particular substrate. In contrast, enzymatic asymmetric synthesis has found much wider application.

7.4.8 Resolution through inclusion compounds

Some compounds crystallise in such a way that a hole is formed inside the crystal which can accommodate another guest molecule without forming any chemical bond. These complexes are known as *inclusion* or *clathrate* compounds. The inclusion of the guest molecule depends on the steric fit inside the crystal lattice and is often very selective. Desoxycholic acid, a steroidal compound forms such crystals in which a particular enantiomer of selected molecules can be included. It has been used for the resolution of camphor.

An interesting case is the crystals of tri-*o*-thymotide (VII in Figure 7.8) which not only separate out from solvents in one particular enantiomorphous form but also sometimes include chiral solvent molecules such as 2-bromobutane in one enanatiomeric variety only, thus effecting partial resolution. Urea, although achiral, forms helical crystals and depending on the helicity can give inclusion compound with either enantiomer of a chiral solvent such as 2-chlorooctane thus causing partial resolution. Chiral crown ethers, previously discussed, can similarly be used to trap enantiomeric cations. These methods, however, are of little practical use.

7.5 Optical purity and enantiomeric excess

The specific rotation, $[\alpha]$, is highest for an enantiomerically pure compound and any contamination with the optical antipode lowers it, usually, proportionately. The optical purity (O_p) of a chiral compound is expressed as the percentage ratio of the rotation observed and the maximum rotation (rotation of a pure enantiomer) and is usually equal to the enantiomeric excess, *ee* (excess of one enantiomer over the other). The following equation (10) shows the relationship :

$$O_p = \frac{[\alpha]_{obsd}}{[\alpha]_{max}} \times 100 = ee = \frac{|\,[R] - [S]\,|}{[R] + [S]} \times 100 \qquad (10)$$

where $[R]$ and $[S]$ represent the mole fractions of the R and S enantiomers so that $[R] + [S] = 1$. The percentages of R and S enantiomers can be calculated from the above equation as follows:

$$\begin{aligned} \%\ \text{of } R \text{ (or } S) &= ee + \%\ \text{of } S \text{ (or } R) \\ &= ee + 100 - \%\ \text{of } R \text{ (or } S) \\ &= \frac{ee + 100}{2} \quad \text{(for the major enantiomer)} \qquad (11) \end{aligned}$$

$$\text{Similarly, } \%\ \text{of } S \text{ (or } R) = \frac{100 - ee}{2} \quad \text{(for the minor one)} \qquad (12)$$

Determination of O_P or *ee* of a chiral compound is an essential part of any resolution method or asymmetric synthesis since it gives the composition of the product. In the majority of cases, polarimetric measurement gives the true values of O_P and *ee* (Lyle and Lyle 1983). However, difficulty arises when the rotation of a pure enantiomer is not known and in the few cases where the rotation is not

linearly related to the concentration as for some compounds which undergo association through H-bonding or otherwise. Moreover, a polarimetric determination of rotation requires the compounds to be chemically pure, e.g., free of solvent and by-product.

One of the simplest way to know whether a compound is enantiomerically pure or not is to crystallise it (if solid) several times and check the constancy of the melting point and optical rotation. Even this method may not be fully reliable since some racemic modifications form solid solutions; also the crystals incorporate unknown quantities of solvent. A second alternative is to procure the optical antipode—preferably by another route—and to see whether it has exactly equal and opposite rotation. Other methods exist and they are mainly based on enantiomeric recognition through establishment of a diastereomeric relationship between a chiral reagent and the enantiomeric pair (Mislow and Raban 1967).

7.5.1 **Isotopic dilution method**

In isotopic dilution method, a known weight of the sample under examination is mixed in solution with a known weight of the racemic modification of the same compound uniformly labeled with an isotope. The racemic form is then separated out, recrystallised, and its isotope content determined. If the original sample was enantiomerically pure, the isotope dilution factor can be calculated from the known relative amounts of the two specimens mixed. If the factor turns out to be less than the calculated value, the compound was not enantiomerically pure. Instead of a racemic form, an optically active mixture may separate out. In either case, appropriate calculation gives the enantiomeric purity of the original sample (Anderson et al 1983).

7.5.2 **Enzymatic method**

Enzymes are usually highly enantiospecific, i.e., they react often with one enantiomer only and are completely inert to the other. If the test sample is treated with an appropriate enzyme and no reaction occurs as indicated by the absence of any change in optical rotation, the sample is enantiomerically pure (incomplete consumption of the enantiomerically pure substrate would also keep the rotation unchanged). Any enhancement or reduction of the original rotation would mean optical impurity. Thus the oxidase of amino acids which oxidises the L-amino acids 1000 times faster than the D-amino acids may be used to test the optical purity of an amino acid sample.

In a non-enzymatic variation, the enzyme may be replaced by an insufficient amount of optically pure reagent. The two enantiomers of the substrate would react with different rates and at the end, the unreacted substrate would be enriched in the less reactive enantiomer accompanied with a change of rotation (see kinetic method of resolution).

7.5.3 **Methods based on gas chromatography**

An analytical gas chromatography (using capillary columns for better resolution) is

conveniently used for determining the enantiomeric purity of a variety of compounds. The compound is first converted into a diastereomeric mixture by allowing it to react with an optically pure reagent, e.g., esterification of an alcohol or acetylation of an amine with an optically pure acid. The composition as determined by gas chromatography using achiral stationary phase gives the enantiomeric ratio of the original sample. High performance liquid chromatography (HPLC) may be used for unstable compounds. Precautions to be taken are: The derivatising reagents should be enantiomerically pure; no racemisation should take place on the column; and finally, the two diastereomers should be separable on the column under the condition of chromatogram. Diastereomeric esters prepared from N-acetyl (or N-trifluoroacetyl) amino acids and (−)-menthol are conveniently separated by gas chromatography.

Alternatively, an optically active stationary phase may also be used and the enantiomers directly separated (see the resolution method) on the column without derivatisation. Here, it is not necessary for the stationary phase to be enantiomerically pure though the degree of separation increases with the optical purity of the stationary phase.

7.5.4 **Methods based on NMR spectroscopy**

NMR spectroscopy is extensively used for the determination of enantiomeric purity. Several variations of the method are known.

1. Use of diastereomers: Since any two corresponding ligands (or nuclei) in two enantiomers are enantiotopic by external comparison, they are isochronous and cannot be distinguished in NMR working under achiral condition. But if the enantiomers are first derivatised with an optically pure reagent (as in the case of gas chromatography), two such ligands will be diastereotopic by external comparison and will have different chemical shifts. One has to select one or more groups in the compound which are clearly discernible in the spectrum. Thus phenylmethylcarbinol whose enantiomeric excess is to be determined is esterified with the acid chloride of optically pure *O*-methylmandelic acid (Figure 7.16). The resultant ester (XXXIII) may be a mixture of diastereomers depending on the optical purity of the original alcohol. The methoxyl peaks of the mandelate moiety can be easily detected in ^{1}H-NMR—one for each of the diastereomers—and their relative intensities would indicate the percentage ratio of enantiomers in the original alcohol.

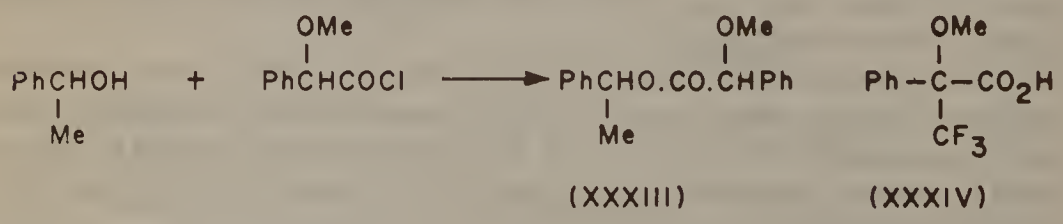


Figure 7.16 NMR method of determination of enantiomeric excess

Optically active α-methoxy-α-trifluoromethyl-α-phenylacetic acid (XXXIV) is a very useful acid for esterification (or acylation) since the products can be

investigated by ^{1}H-, ^{13}C-, and ^{19}F-NMR spectroscopy simultaneously. Mereover, the absence of α-H eliminates the possibility of racemisation. For the method to work satisfactorily, two conditions must be satisfied: the two anisochronous signals be well separated and the derivatising agents be optically pure (see Yamaguchi 1983).

2. Use of Shift reagents. Chiral shift reagents, e.g., XXXV in Figure 7.17 (see also Chapter 6) are also extensively used to determine the enantiomeric excess by NMR. They form diastereomeric complexes with chiral substrates having a variety of functional groups and at the same time, induce increased anisochrony (larger separation of chemical shifts) in the two diastereotopic groups of protons. Here, enantiomeric purity of the shift reagent is not essential; but calibration of the method with racemic material is necessary (see Fraser 1983, Sullivan 1978).

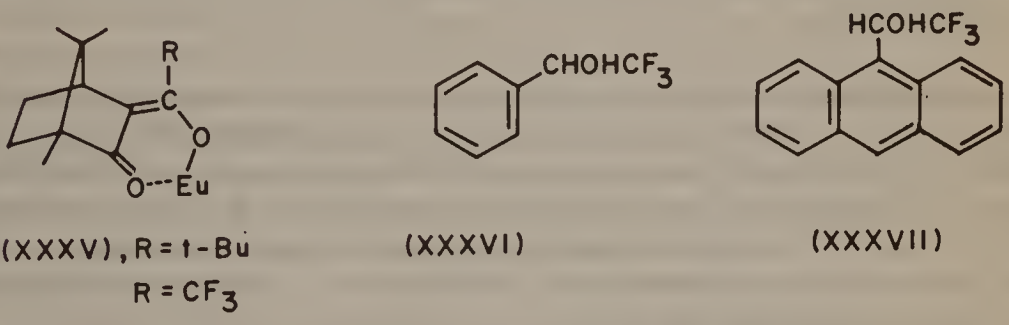


Figure 7.17 Chiral shift reagents and chiral solvating agents (CSA)

3. Use of chiral solvating agents. In yet another variation of NMR method, a 'chiral solvating agent' (CSA) is used which forms diastereomeric solvates with the substrate through weak solvent-solute interaction. The CSA may be either a solvent, or a cosolvent, or even a solid auxiliary (for reason of cost). Two most common CSA's are 2,2,2-trifluoro-1-phenylethanol (XXXVI) and the corresponding anthracyl derivative (XXXVII). The former is available by asymmetric reduction of $PhCOCF_3$ with bornyloxyaluminium dichloride in 68% *ee* (Nasipuri and Bhattacharya 1975) and the latter is available commercially. They interact with a variety of chiral compounds such as alcohols, amines, sulphoxides, phosphines, amine oxides, and epoxides giving diastereomeric solvates (Pirkle et al 1971, 1982) linked through H-bonds (shift reagents also work on the same principle). The association-complexes are unstable (most of the substrate remains uncomplexed at any time) and are in rapid equilibrium exchanging sites constantly. The situation is shown in Figure 7.18 for a racemic sulphoxide and a chiral CSA (XXXVI). Since

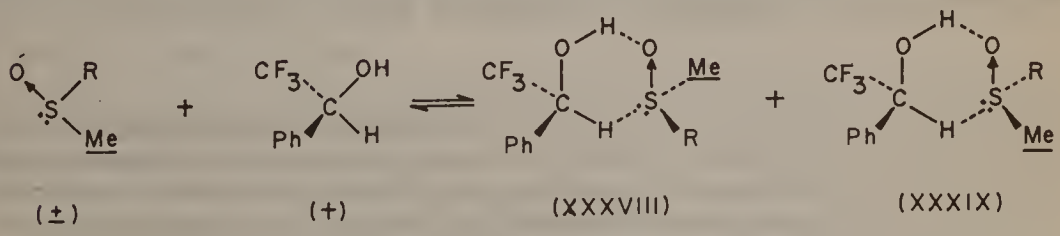


Figure 7.18 Diastereomeric associates with CSA through H-bonding

the site exchange is fast on NMR time scale, the chemical shift of the methyl group for (+)-S (S stands for the substrate) is a weighted average of that in the free (+)-S and that in the association-complex, say XXXVIII. Similarly, the chemical shift of the methyl group in (−)-S is the weighted average of that in the free (−)-S and that in the association-complex (XXXIX). The complexes being diastereomeric will have different values for the chemical shift. The enantiomeric purity of S may thus be determined from the relative intensities of the two peaks.

Here again, it is not necessary that the chiral solvating agent be optically pure; however, the separation of the chemical shifts of the anisochronous group is directly proportional to its optical purity.* With racemic CSA, no separation of peaks is possible because of averaging out of the diastereomeric associates through rapid exchange of enantiomeric ligands.

7.6 Summary

1. Racemisation is a process in which an optically active compound is converted into a mixture containing equal amounts of the two enantiomers with no resultant optical activity. It usually involves a reversible change of configuration at a chiral centre. If the molecule undergoing the change contains more than one chiral centre, a new diastereomer (an epimer) is formed instead of the enantiomer and the process is known as epimerisation. Epimerisation, in principle, always leads to unequal amounts of two epimers.

Depending on the nature of the substrates and the reaction conditions, racemisation may take place through carbanions, carbonium ions, free radicals, or even stable intermediates such as olefins and ketones. A chiral centre which contains an acidic hydrogen, e.g., an α-H in a ketone, racemises easily through the intermediate enol or enolate ion depending on whether it is acid-catalysed or base-catalysed. Atropisomers racemise on heating usually via achiral but occasionally via chiral transition states.

2. Resolution is a process in which pure enantiomers are separated out of the racemic modifications. It leads to optical activation and can be effected only through enantiomeric discrimination which in turn arises out of diastereomeric interaction between a chiral resolving agent and the two enantiomers of the substrate.

3. A compound containing a labile chiral centre may undergo spontaneous configurational change in solution. If there is a second chiral element in the environment such as chiral solvents, chiral additives (auxiliaries), or even other chiral centre (centres) in the molecule itself, one or the other of the enantiomers (or diastereomers) predominates in equilibrium. This is known as first order (or

*The chiral sample itself can serve as its own reference under certain conditions (Horeau et al 1973). If the substrate forms homochiral, (+ , +) or (− , −) and heterochiral, (+ , −) dimeric associates either directly or through an achiral component, e.g., (+)-A-(+) and (+)-A-(−) (where A represents the achiral component) and if fast scrambling of monomeric units among the aggregates occurs, the situation becomes the same as the one for CSA method (Figure 7.18), the two aggregates serving as the two diastereomeric associates (Feringa et al 1985; Pasquier and Marty 1985).

first kind) asymmetric transformation and is accompanied with a change of optical rotation to a steady equilibrium value—a phenomenon known as mutarotation. Mutarotation is exhibited by most of the reducing sugars and their derivatives. It may also be due to a structural change of a chiral compound brought about in solution. Configurationally labile biphenyls and related atropisomers provide interesting examples of first order asymmetric transformation and mutarotation.

If in an asymmetric transformation, one of the diastereomeric species precipitates out of the solution, the equilibrium shifts so as to produce more of the precipitating isomer with the result that the entire amount of the substrate may come out as a single diastereomer. This process is known as second order asymmetric transformation.

4. A large number of methods for resolutions have been known since the time of Pasteur. They include (*i*) mechanical separation and preferential crystallisation, (*ii*) formation of diastereomeric compounds with optically pure reagents and their subsequent separation, (*iii*) formation of molecular complexes with chiral complexing agents, (*iv*) methods based on equilibrium and kinetic asymmetric transformations, (*v*) chromatographic methods using achiral stationary phase and diastereomeric substrates or chiral stationary phase and racemic substrates, and (*vi*) biochemical asymmetric transformation using enzymes and microorganisms. The selection of the most appropriate method depends on the nature of the substrates and the reagents available.

5. The optical purity of a sample (O_p) is defined by the percentage ratio of its specific rotation and that of a pure enantiomer while the enantiomeric excess (*ee*) is the percentage excess of one enantiomer over the other. The conventional method of determining the optical purity (and hence *ee*) of a sample by polarimetric method has now largely been superseded by other methods especially by those based on analytical gas chromatography and NMR spectroscopy. The different variations of these methods have been discussed.

References

1. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
2. K. Mislow and R. Bolstad (1955), *J. Amer. Chem. Soc.*, 77, 6712.
3. L. Kryger and S.E. Rasmussen (1972), *Acta Chem. Scand.*, **26**, 2349.
4. P. Pfeiffer and K. Quehl (1931), *Chem. Ber.*, **64**, 2667.
5. R. Kuhn (1932), *Ber.*, **65**, 49.
6. M.M. Jamison and E.E. Turner (1942), *J. Chem. Soc.*, 437.
7. K.R. Wilson and R.E. Pincock (1975), *J. Amer. Chem. Soc.*, 97, 1474.
8. J. Jaques, A. Collet, and S.H. Wilen (1981) in *Enantiomers, Racemates, and Resolutions*, Wiley, New York.
9. S. Mason (1982) in *Molecular Optical Activity and the Chiral Discrimination*, Cambridge University Press, Cambridge.
10. A. Collet, M.J. Brienne, and J. Jaques (1980), *Chem. Rev.*, **80**, 215.
11. L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil, L.J.W. Shimon, M. Lahav, and L. Leiserowitz (1985), *Angew. Chem. Intl. Edn. Engl.*, **24**, 466.
12. J. Jaques, M. Leclerq, and M. J. Brienne (1981), *Tetrahedron*, 37, 1727.

13. S.H. Wilen (1972) in *Tables of Resolving Agents and Optical Resolutions*, University of Notre Dame Press, Notre Dame, Indiana.
14. E.J. Corey and R.B. Mitra (1962), *J. Amer. Chem. Soc.*, **84**, 2938.
15. M.S. Newman and D. Lednicer (1956), *J. Amer. Chem. Soc.*, **78**, 4765; for a review of helicenes, see R.H. Martin (1974), *Angew. Chem. Intl. Edn. Engl.*, **13**, 649.
16. D.J. Cram and J.M. Cram (1974), *Science*, **183**, 103.
17. G. Hesse and R. Hagel (1976), *Chromatographia*, **9**, 62.
18. D.J. Cram and J.M. Cram (1978), *Acc. Chem. Res.*, **11**, 8.
19. J.F. Stoddart (1987) in *Topics in Stereochemistry*, vol. 17, E.L. Eliel and S.H. Wilen (Eds), Wiley, New York.
20 W.H. Pirkle, D.W. House, and J.M. Finn (1980), *J. Chromatogr.*, **192**, 143.
21. R. Curti and U. Colombo (1952), *J. Amer. Chem. Soc.*, **74**, 3961.
22. V.M. Potapov (1979) in *Stereochemistry*, Mir Publishers, Moscow, p. 87.
23. K. Mislow (1965) in *Introduction to Stereochemistry*, Benjamin, New York.
24. D. Nasipuri and P.R. Mukherjee (1974), *J. Indian Chem. Soc.*, **51**, 171.
25. J.D. Morrison (Ed) (1983) in *Asymmetric Synthesis*, Academic Press, New York:
(a) G.G. Lyle and R.E. Lyle, *Polarimetry*, p. 13.
(b) K.K. Anderson, D.M. Gash, and J.D. Robertson, *Isotope Dilution Technique*, p. 45.
(c) V. Schurig, *Gas Chromatographic Method*, p. 59.
(d) S. Yamaguchi, *NMR Analysis using Chiral Derivatives*, p. 125.
(e) G.R. Weisman, *NMR Analysis using CSA*, p. 153.
(f) R.B. Fraser, *NMR Analysis using Chiral Shift reagents*, p. 173.
26. G.R. Sullivan (1978) in *Topics in Stereochemistry*, vol. 10, E.L. Eliel and N.L. Allinger (Eds.), p. 287, Wiley, New York.
27. M. Raban and K. Mislow (1967) in *Topics in Stereochemistry*, vol. 2, E.L. Eliel and N.L. Allinger (Eds.), Interscience, New York.
28. D. Nasipuri and P.K. Bhattacharya (1975), *Synthesis*, 701.
29. W. Pirkle, R.L. Muntz, and I.C. Paul (1971), *J. Amer. Chem. Soc.*, **93**, 2817; W. Pirkle and M.S. Hoekstra (1976), *J. Amer. Chem. Soc.*, **98**, 1832; also earlier papers.
30. W. Pirkle (1982) in *Topics in Stereochemistry*, vol. 13, N.L. Allinger, E.L. Eliel, and S.H. Wilen (Eds.), Wiley, New York.
31. J.P. Vigneron, M. Dhaenens, and A. Horeau (1973), *Tetrahedron*, **29**, 1055.
32. B.L. Feringa, Ab Smaardijk, and H. Wynberg (1985), *J. Amer. Chem. Soc.*, **107**, 4798.
33. M.L. Pasquier and W. Marty (1985), *Angew. Chem. Intl. Edn. Engl.*, **24**, 315.

Chapter 8

Determination of Configuration

8.1 Introduction

Various problems associated with chiral molecules have been discussed in the previous chapters which include molecular representation, different elements of chirality, and configurational nomenclature. It now remains to determine the configuration of a chiral molecule in the absolute sense. Enantiomers are geometrically equivalent (isometric), have identical scalar properties, and differ only in their topography, i.e., in the sense of chirality. Chirality can never be determined without referring it to another chiral agent. Thus the chirality of a molecule has been defined in terms of right-handedness or left-handedness or with relation to clockwise or anticlockwise direction. These provide arbitrary references based on *common visual experience and common agreement on direction* (Mislow 1965). One can think of two three-dimensional Cartesian coordinate systems, one right-handed and the other left-handed (i.e., mirror images of each other). Enantiomers will have the same x,y,z coordinates if one is placed in the right-handed and the other in the left-handed coordinate system. One of the coordinate systems, say the right-handed one, is accepted as the standard for this world and any configuration (arrangement of atoms or groups) defined with reference to this should be the *absolute configuration.**

Enantiomers differ only in their absolute configuration (if there is a single chiral centre, the two configurations are designated *R* and *S*). But two diastereomers being anisometric differ in the relative steric disposition of atoms or groups, i.e., in their *relative configuration.* Any two selected groups may be nearer to each other in one isomer and farther apart in the other in space. They are designated by various names such as cis and trans, syn and anti, erythro and threo and so on as described in Chapter 4. If they are achiral, relative configuration is sufficient to describe them uniquely as for maleic acid and fumaric acid or for *cis* and *trans*-1,4-dimethylcyclohexane. But if they are chiral, absolute configuration is also necessary to describe them uniquely. Thus 1,2-dimethylcyclohexane having the relative configuration trans (with the two methyl groups placed on the opposite sides of the ring) exists in two enantiomeric forms which differ in their absolute configuration. The configuration of a molecule with multiple chiral centres is

*The reader is referred to an interesting article on the dissymmetric worlds by Abernethy (1972).

usually determined in two stages: the relative configuration of the chiral centres is determined first. Then the absolute configuration at a particular chiral centre is established by a suitable method which automatically fixes the absolute configuration of the rest of the molecule.

8.2 Determination of absolute configuration

The discrimination between enantiomers is possible only through diastereomeric interaction with a chiral agent. Therefore the various physical methods, e.g., UV, IR, and NMR spectroscopy and simple X-ray diffraction which provide achiral probes can give information regarding relative configuration only but are normally useless for the determination of absolute configuration. Three methods for the determination of absolute configuration are at present available: (*i*) method based on optical rotation, circular dichroism, and optical rotatory dispersion (chiroptical properties), (*ii*) method based on anomalous X-ray scattering, and (*iii*) method based on crystals used as probes. The method based on chiroptical properties will be taken up in Chapter 15; here the last two methods are discussed.

8.2.1 Method based on anomalous X-ray scattering

X-ray diffraction measures only the scalar geometrical parameters of a molecule (in the solid state) and therefore cannot ordinarily discriminate between two non-superposable enantiomers which are isometric. This is illustrated graphically with the help of an imaginary linear molecule (a part of a crystal lattice) with two distinguishable ends marked A and B - a one-dimensional chiral simplex. In figure 8.1, A-B and B-A represent the two enantiomers of a molecule. When a parallel

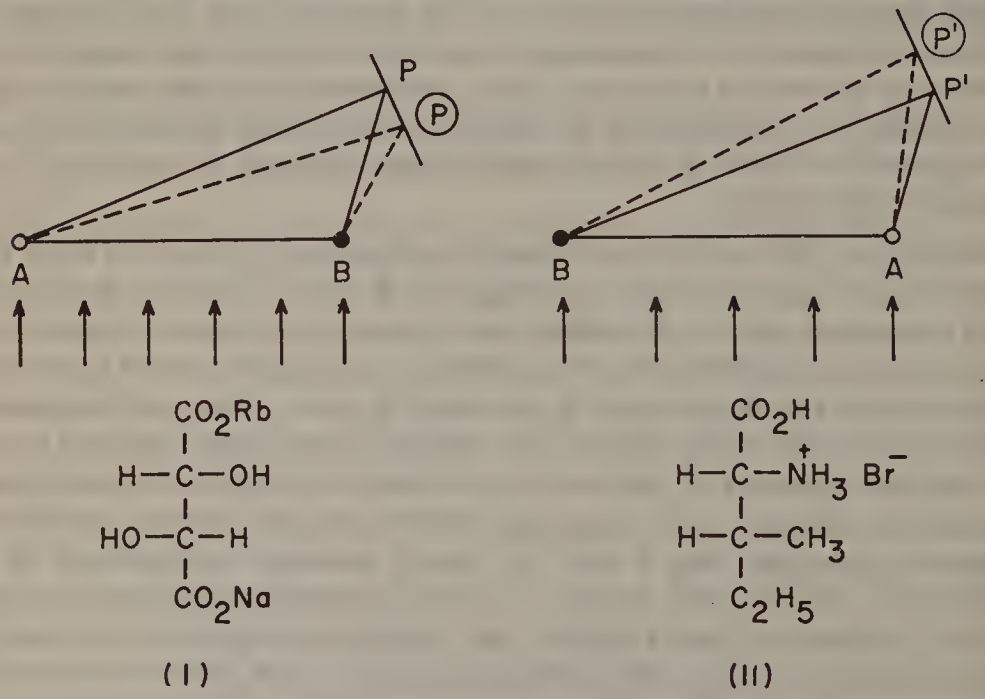


Figure 8.1 Anomalous X-ray diffraction and configuration

beam of X-rays is impinged on the units, scattering takes place at A and B and two sets of diffracted wave fronts starting exactly with the same phase cause interference patterns at the photographic plates P and P′. Since the phase differences of the two interferring waves depend solely on the distances travelled by them from both ends*, the interference patterns are identical for the enantiomers A-B and B-A (note that AP—BP = BP′—AP′)†. The analysis can give only the distance between the two nuclei A and B.

However, when one of the nuclei, say B, is a heavy atom and absorbs partially at the frequency of the X-ray used, i.e., when the wavelength of the X-rays lies near the absorption edge of the heavy atom, anomalous scattering results meaning that the secondary wave front scattered from B undergoes a phase lag (an exception of Friedel's law). The two ends of the molecule A and B can now be differentiated by the X-ray as regards their absolute position in space. Thus in the right hand diagram, the diffracted rays from B has not only to travel a longer distance to reach P′ (BP′>AP′), but has already suffered a phase lag so that the difference in phase with respect to the rays from A is accentuated. On the contrary, in the left hand diagram, the scattered rays from A have to travel a longer distance than the rays from B to reach P but because of an initial phase lag at B, the ultimate phase difference when both the scattered wave fronts reach the photographic plate decreases to that extent (Eliel 1962, Mason 1982). If the phase lag is expressed in terms of reduced velocities, the dotted lines represent the new pathways and the two interference patterns (at circled P and P′) are now substantially different. The enantiomers are thus discriminated and an analysis of the two interference patterns will give their absolute configuration.

In the actual experiment by Bijvoet group (1951), the sodium rubidium salt of (+)-tartaric acid (I) was used along with Kα radiation from zirconium which lies on the absorption edge of rubidium. The result shows that (+)-tartaric acid has the absolute configuration as (I), originally assigned by Fischer on an arbitrary basis. Similarly, (−)-isoleucine hydrobromide (II) was used along with Lα radiation from uranium. Here Br served as the heavy atom and the Lα ray lies on its absorption edge. The result is also in conformity with Fischer's original configurational assignment. Because of this coincidence, the configurations of numerous compounds arrived at through chemical correlation since the time of Fischer remain unchanged. The assignment of absolute configuration by the above X-ray method is unambiguous and has been substantiated by many other workers (Dunitz 1979).

With the development of computerised diffractometers, the X-ray diffraction technique has now become a very powerful tool for the determination of both relative and absolute configuration. The number of molecules the absolute configurations of which have been determined by X-ray diffraction is now almost one thousand.

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*According to Friedel's law, the phase difference between the X-rays (or any other electromagnetic radiation) scattered at different centres (nuclei) in the crystal arises solely from the path difference between the scattering centres since the scattered wave front from each nucleus starts with the same phase.

†Only the full lines in the diagrams are now considered (not the dotted lines).

8.2.2 Crystals as probes for the assignment of configuration

Recently, a group led by Lahav (Addadi et al 1986) has developed a second independent experimental method for configurational assignment to molecules based on correlation of macroscopic morphological asymmetry of crystals with microscopic chirality of the constituent molecules. The principle is best discussed in the light of the mechanism of crystal growth inhibition induced by *tailor-made* additives (see also Chapter 7). A tailor-made additive is a compound which resembles partly the structure of the substrate but is partly modified.

Normally, in pure solvents a crystal grows so that the areas of different faces of it maintain a constant ratio as shown for a hypothetical two-dimensional crystal (III→IV) (Figure 8.2) distinguished by two types of faces A and B. If crystallisation

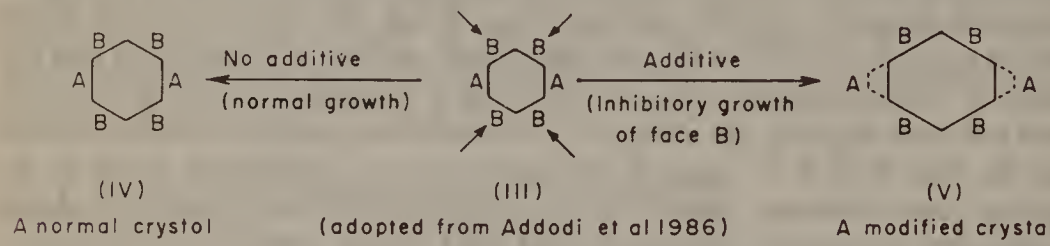


Figure 8.2 Crystal growth in the presence and absence of additives (arrows show binding sites)

is carried out in the presence of an appropriate tailor-made additive, the additive is adsorbed on to one type of faces (say B) (with the unmodified part bound to appropriate sites through ionic and/or hydrogen bond), leaving the other type of face (i.e., A) unaffected. The modified part of the additive sticks out from the B faces and retards further deposition of substrate on them. This adsorption-inhibition mechanism thus leads to a lopsided development of crystals which are elongated in the direction perpendicular to the A faces so that the ratio of the area of B faces to that of A faces increases dramatically (see, III→V). Analysis of such morphological changes of the crystals gives valuable pieces of information on the configuration of the host and guest molecules which are enumerated below.

1. Resolution of conglomerates. If a conglomerate (a racemic mixture, *R,S*) is crystallised from a solvent containing a tailor-made additive (say *S'*, homochiral* with *S*), the additive gets selectively adsorbed on the surfaces of the crystals composed of *S*-enantiomers (*S*-crystals) only, because of similar handedness of the host and the guest molecules. As a result, the rate of growth of *S*-crystals is very much retarded ($k_S \ll k_R$) leading to kinetic resolution. At the same time, the *S*-crystals undergo substantial morphological change (the change is proportional to the concentration of the additive which is usually 0.5% or even less) so as to be easily distinguishable from the *R*-crystals and may be hand-picked. The additive is often occluded in the bulk of the *S*-crystals. This method of resolution has been successfully used in the α-amino acid series (Chapter 7).

2. Assignment of relative configuration. The above phenomena, namely, kinetic

*The terms *homochiral* and *heterochiral* are used here as defined by Ruch. The recent practice, however, is to use 'homochiral' to mean enantiomerically pure (Masamune, see Chapter 3).

resolution, selective morphological change, and selective occlusion, by their very nature, establish relative configuration of the host and guest molecules. Thus if an *S*-additive is used, the *R*-crystals come out of the solution at a faster rate (kinetic resolution), the *S*-crystals are modified (selective morphological change), and the additive enters into the bulk of the *S*-crystals (selective occlusion).* This has been well established in the α-amino acid series.

Instead of the growth of a crystal, one can also study its dissolution which is the reciprocal process. In pure solvents, the dissolution propagates along all directions at the same relative rates but in the presence of a tailor-made additive, the rate of dissolution along the direction perpendicular to the faces binding the additive is appreciably retarded. This leads to the formation of *etch pits* in the affected crystals and their correlation with the *etchants* (additives) gives the relative configuration of the host-guest molecules. Thus the *R*-crystals of asparagine are preferentially etched in the presence of *R*-aspartic acid while the *S*-crystals dissolve smoothly (Addadi et al 1985). *R*-asparagine and *R*-aspartic acid are, therefore, configurationally correlated.

3. Assignment of absolute configuration. A crystal with a polar axis† is so packed that the vector of the constituent chiral molecules A-B (shown as a one-dimensional chiral simplex) tends to align parallel to it (Figure 8.3). Because of the polar nature of the axis, its positive and negative directions are distinguishable in principle (but not by normal X-ray crystallography) and the determination of the

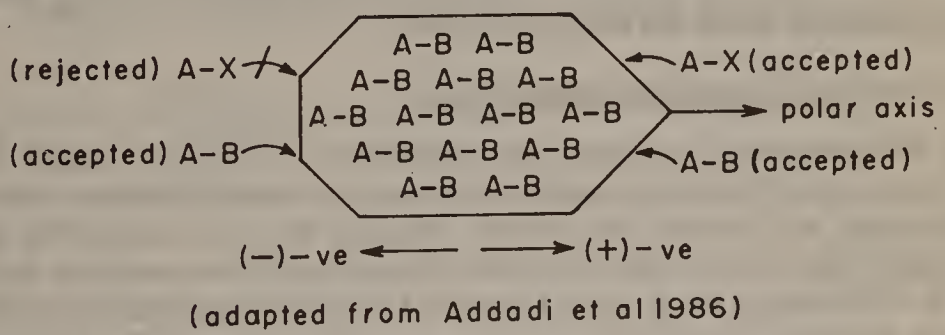


Figure 8.3 Assignment of configuration using crystals as probes

sense of the directionality fixes the absolute configuration of the molecule A-B. In one of the enantiomorphous crystal (see Figure), groups A emerge from the left hand faces and groups B from the right hand faces of the crystal. If the crystal is allowed to grow in the presence of a tailor-made additive, say A-X (A being

*The method is analogous to quasi-racemate method of configurational assignment (section 8.3.3) which operates on the principle that two similarly constituted chiral molecules of opposite chirality (heterochiral, according to Ruch) form a quasi-racemic compound and the corresponding homochiral components a simple mixture. Both the methods involve the replacement of a host molecule by a guest molecule at the lattice sites in a crystal. The only difference is that while the quasi-racemate method relates to a thermodynamic phenomenon which influences the bulk properties of the crystals such as melting point, the present method relates to a kinetic phenomenon, namely, growth on the crystal surface.

†To avoid complication, only crystals with polar axis (chiral crystals) are considered. The treatment of centrosymmetric crystals is necessarily more complex (Addadi et al 1986).

common in both the host and guest molecules), the additive binds on the right hand faces because of the favourable interaction between A and B but not on the left hand faces where no such interaction exists. Growth of the crystals is thus retarded in directions perpendicular to the right hand faces (the opposite happens if the other enantiomorphous crystal with the polar axis in the reverse direction is considered). Analysis of this selective asymmetrical morphological change in the crystals enables one to determine the direction of the polar axis and with it (and in combination with X-ray data) the absolute configuration of the molecule A-B. It is not necessary that the additive be chiral. Even if it is chiral, its chirality has no relevance to the analysis. By employing this method, the absolute configuration of sucrose has been determined by analysing the morphological change in its crystals in the presence of di- and trisaccharides.

8.3 Correlative methods for configurational assignment

Once the configurations of a few molecules are determined by any of the above methods, those of many other molecules may be known by correlation through chemical transformations or by comparison of physical and chiroptical properties. The normal X-ray diffraction itself provides a good correlative method when a piece of known and a piece of unknown configuration are stitched together. A few other methods excepting those using ORD and CD are discussed here. The reader is referred to an extensive compilation of molecules with their absolute configurations by Klyne and Buckingham (1978).

8.3.1 Chemical correlation of configuration

(a) Methods without involving the chiral centre. The normal practice is to carry out a series of chemical transformations on a compound of known absolute configuration, e.g., tartaric acid, without affecting the chiral centre. The new compounds thus obtained will have their configurations corresponding to the old one. A few examples are given in Figures 8.4–8.7; the transformations (not all reagents are shown) and the conclusions are self-explanatory. The important compounds have been put into boxes. In Figure 8.7, (−)-β-methoxyadipic acid has been correlated first with (−)- malic acid of known absolute configuration and then with a product obtained from vitamin D_3 thus establishing the configuration of C–3 in the steroid molecules. Since the relative configuration of steroids has previously been determined, the correlation gives the absolute configuration of this important group of natural products.

(b) Chemical correlation involving diastereomers. In the previous method, the nature of the atoms next to the chiral centre must remain constant and very often, at least a pair of ligands of the two related chiral centres are same, as in glyceraldehyde and tartaric acid. An alternative method was developed by Freudenberg (1953-1955) which is free from these shortcomings and is applicable to molecules of the type R-CHX-R′, common in many natural products. The principle, elegantly explained by Eliel (1962), devolves on the establishment of relative configuration of a particular chiral centre in a molecule (a diastereomer) containing at least one more chiral centre, the configuration of which is known.

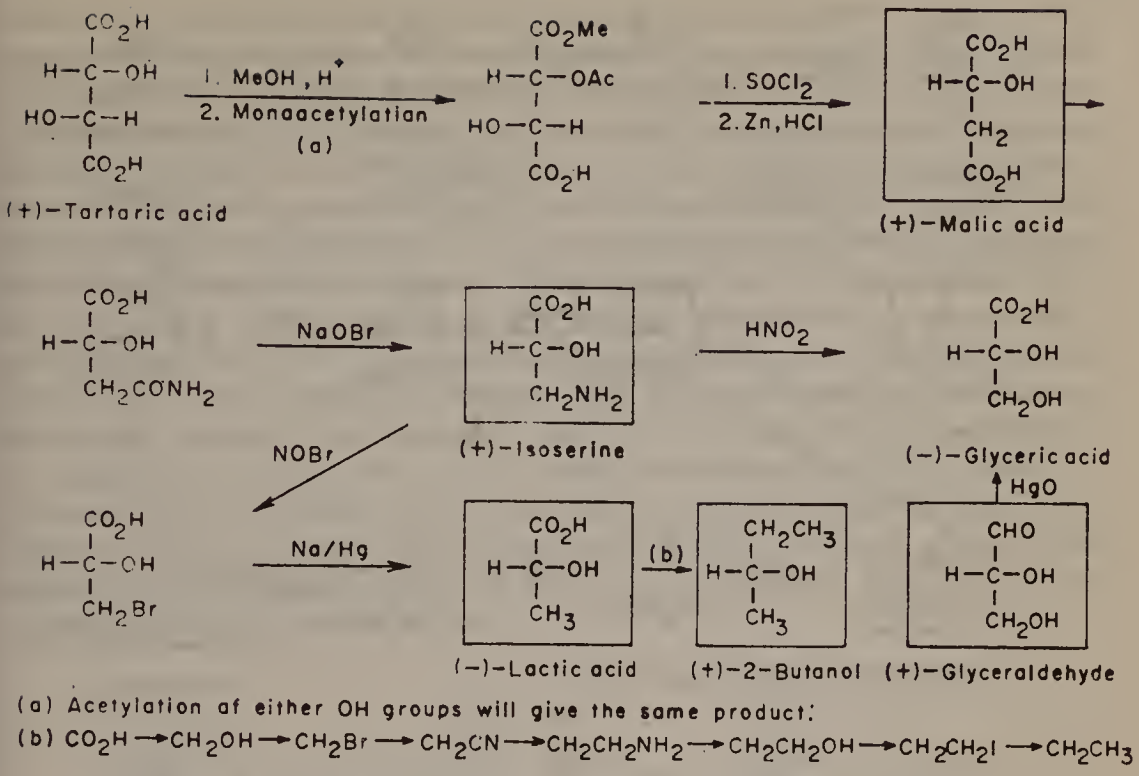


Figure 8.4 Configuration of malic acid. isoserine, glyceraldehyde. and lactic acid

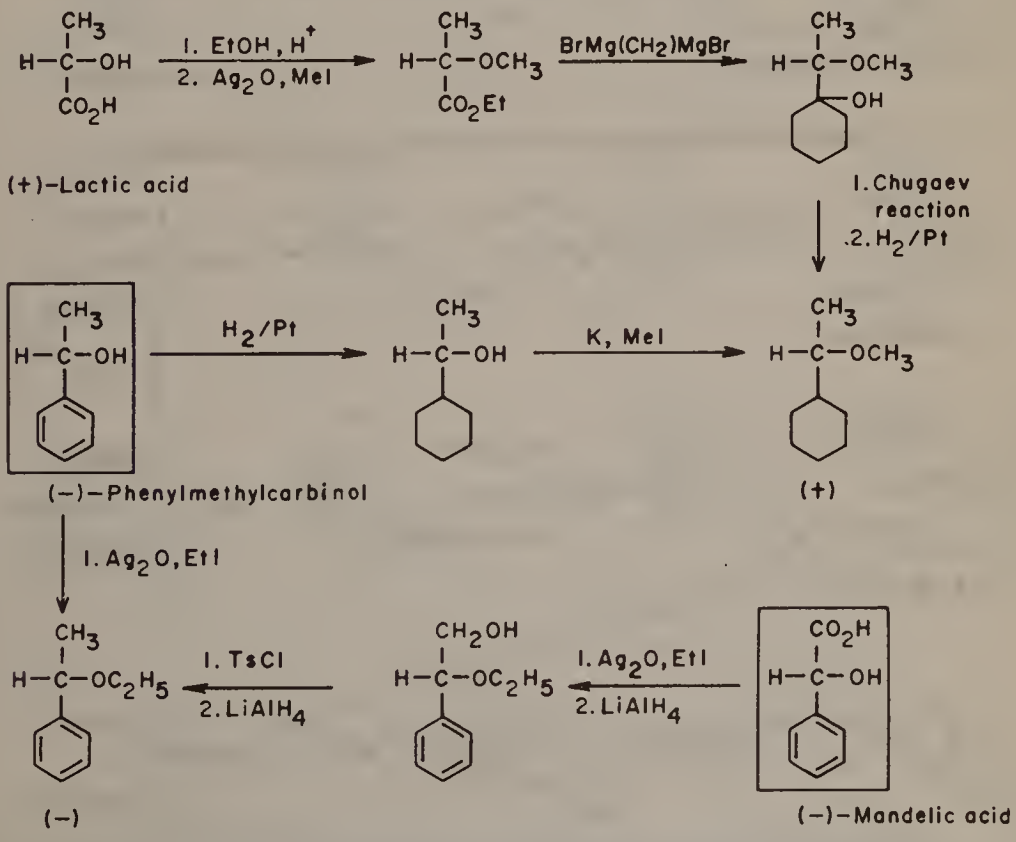


Figure 8.5 Configuration of phenylmethylcarbinol and mandelic acid

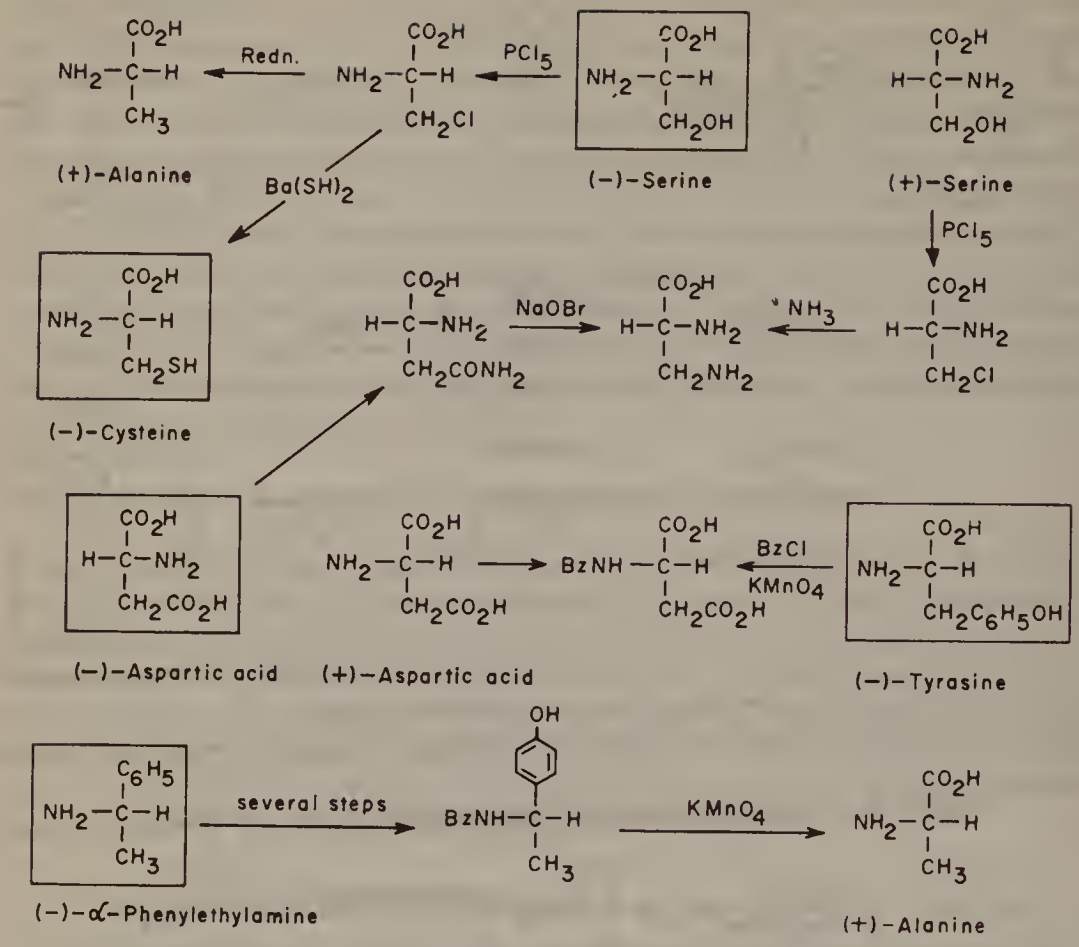


Figure 8.6 Configurational correlation of some amino acids and amines

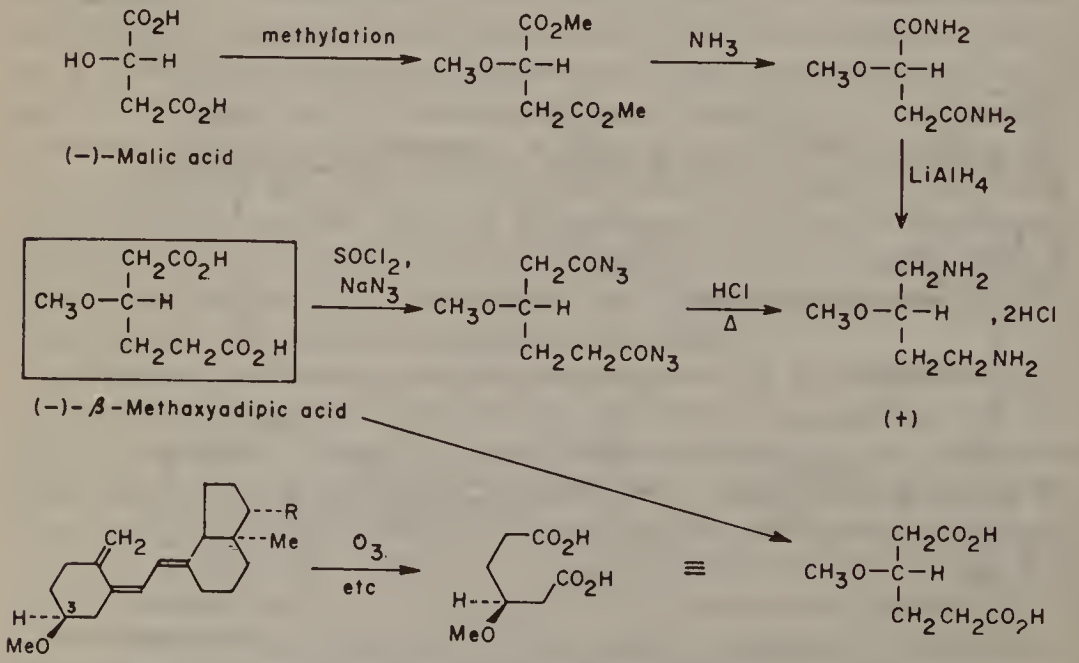


Figure 8.7 Configuration of β-methoxyadipic acid and steroids

Then if the centre can be cleaved in the form of a molecule from the rest of the compound, its configuration follows automatically. The principle is illustrated by dihydroshikimic acid (VII) obtained from shikimic acid (VI) (Figure 8.8) whose configuration at C-3, C-4, and C-5 is known by correlation with D-glucose through conversion into (+)-desoxygluconolactone (VIII)*'. Dihydroshikimic acid (VII) is then degraded through a series of standard reactions (starting with the cleavage of *cis*-3,4-diol) into (+)-3-carboxyadipic acid (IX) which must thus have the *R* configuration. This is converted into *S*-(+)-3-methylhexane (X) ($CO_2H \rightarrow CH_3$). The configuration of a number of compounds such as (−)-2-methylbutan-1-ol (XI), (+)-2-methylbutyric acid (XII), and (+)-3-Methyladipic acid (XIII) can in turn be correlated with that of 3-methylhexane through appropriate chemical transformations. The last-named acid (XIII) is available as a degradation product from (+)-3-methylcyclohexanone (XIV) which is obtained from (+)-pulegone (XV) through a retro-aldol reaction. The configuration of pulegone is thus known and with it, those of a few other monocyclic monoterpenes which are related to (+)-pulegone through chemical transformations also become known.

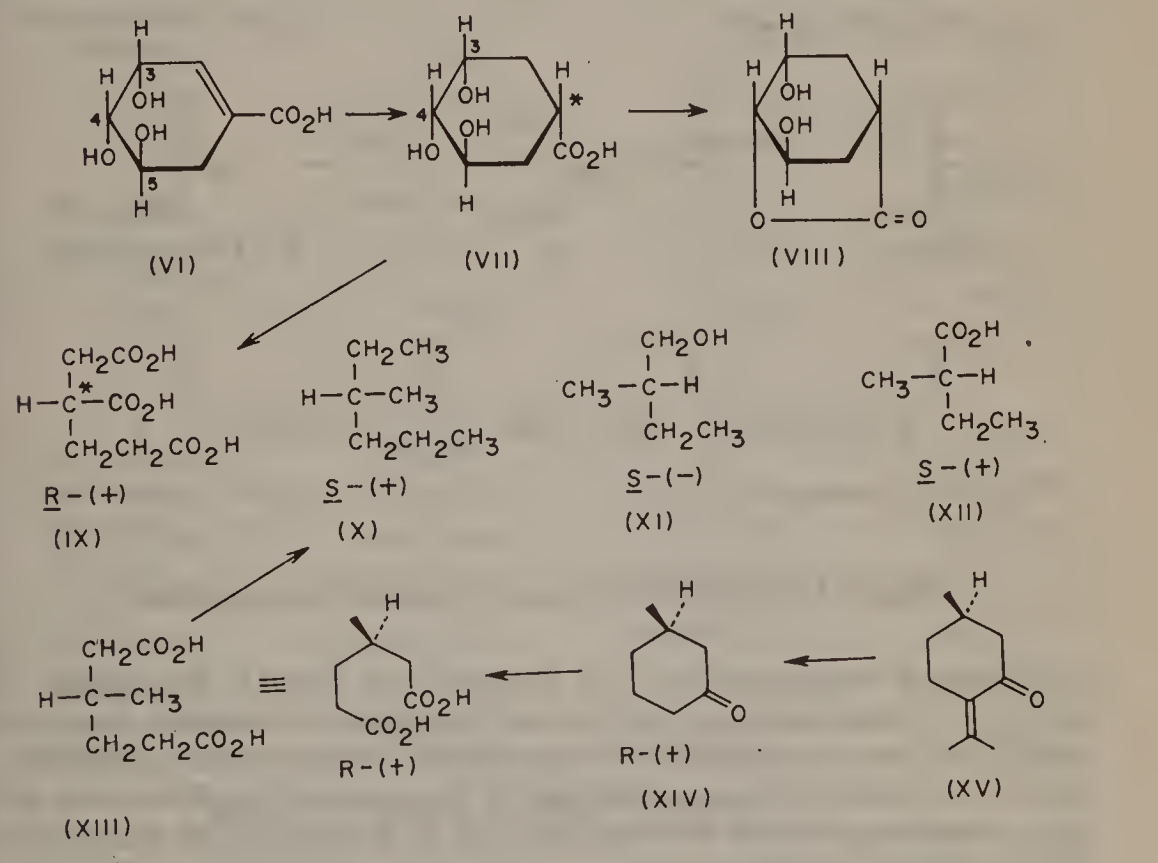


Figure 8.8 Freudenberg's method of chemical correlation

*The configuration of D-glucose has already been related to D-glyceraldehyde (and *S,S*-tartaric acid) by Fischer (see Chapter 4).

(c) Chemical transformation involving the chiral centre. Very often a reaction is carried out at a chiral centre with predictable stereochemistry, such as configurational inversion in S_N2 reactions and retention of configuration in S_Ni reactions or in nucleophilic substitutions involving neighbouring group participation. Some of these reactions are discussed in Chapter 7 and a few others will be discussed in Chapter 12. In such cases where the steric course of the reaction is known with certainty, the configuration of the product can be correlated with that of the substrate and vice versa. A few examples are given in Figure 8.9. Case A is

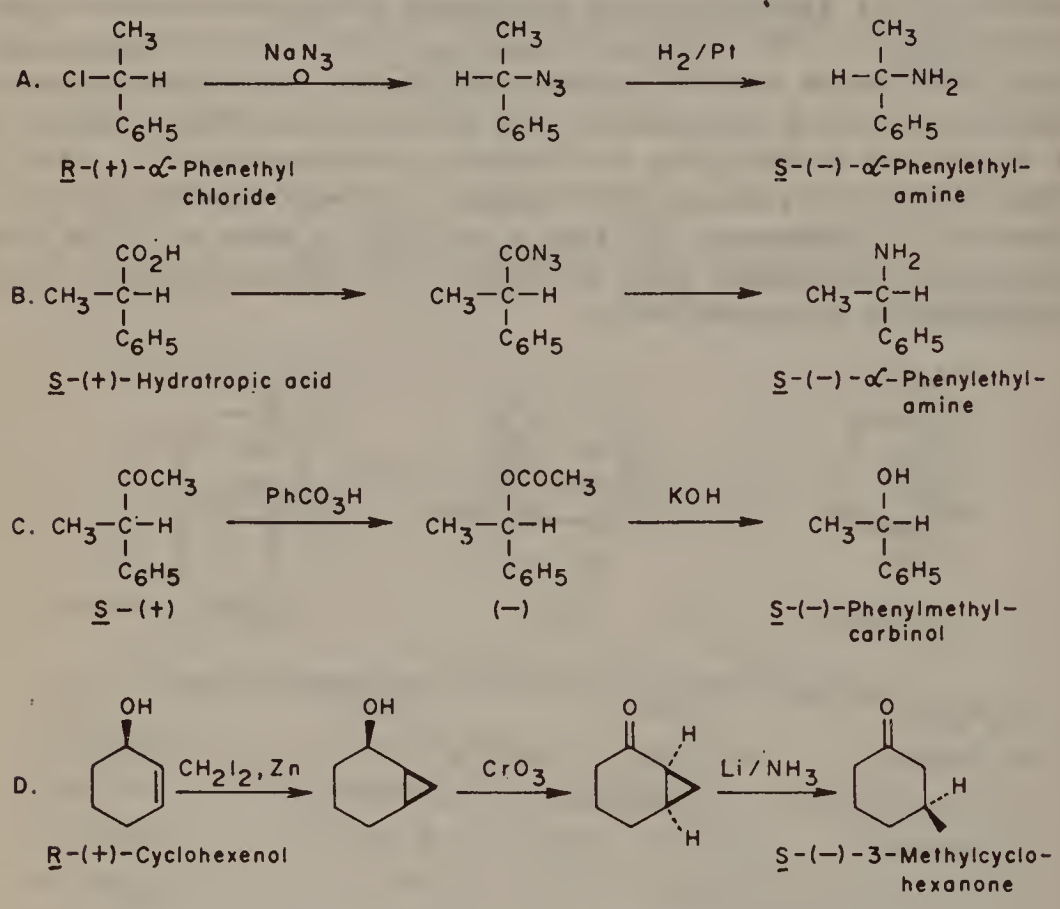


Figure 8.9 Configurational correlation via reactions of known mechanism

an example of Walden inversion (S_N2 reaction); cases B and C are examples of migration of chiral groupings with retained configuration (molecular rearrangements), and case D is an example of stereoselective Simmons-Smith cyclopropylation (it is accepted as a general rule that in the reaction of an allyl alcohol, the cyclopropane ring is formed cis to the allylic OH). In this example, the configuration of (−) -3-methylcyclohexanone is known (vide supra) which settles the configuration of (+)-cyclohexenol as *R*.

(d) Chemical transformations involving predictable change in symmetry. In this method, compounds containing multiple chiral centres are chemically transformed with consequent loss or gain of symmetry, which offers clue regarding the relative configuration. The method is elegantly illustrated by Fischer's work on the relative

configuration of glucose and a few other sugars (for a recent comprehensive account, see Bentley and Popp 1987). The arguments are summarised pointwise below (Eliel 1962).

(*i*) L-(+)-Arabinose is an aldopentose with three chiral centres (acyclic aldehydic form is assumed throughout). By convention (which proved subsequently to be right), the 4-OH is placed on the left of the Fischer projection (XVI) (Figure 8.10). On oxidation, it affords an optically active 2,3,4-trihydroxyglutaric acid which by virtue of its lack of symmetry (no σ plane) must have the 2–OH on the right (as in XVII).

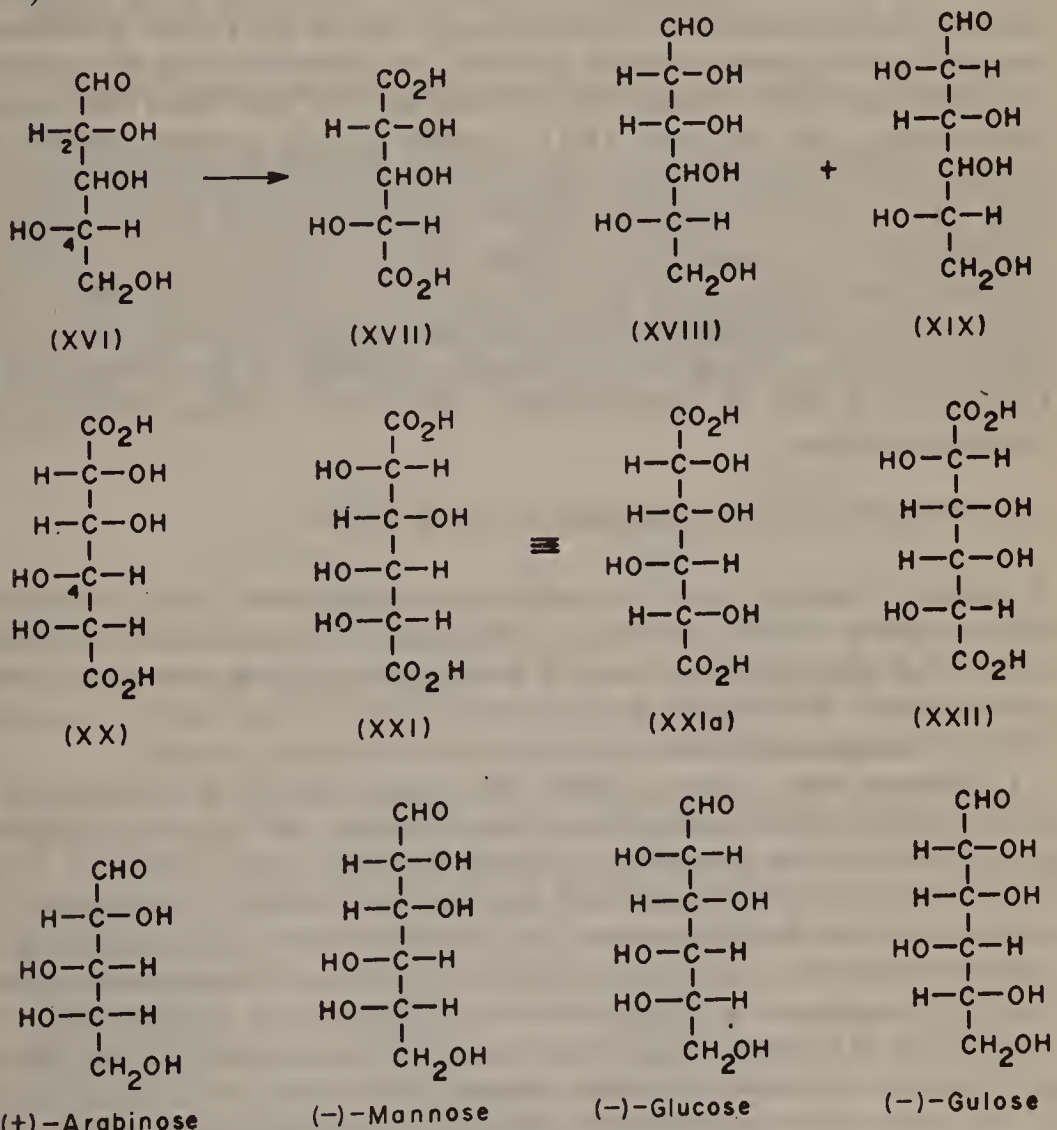


Figure 8.10 Configuration correlation of some sugars

(*ii*) L-(+)-Arabinose on Kiliani synthesis gives two aldohexoses, (−) -mannose and (−) -glucose (optical antipodes of natural dextrorotatory mannose and glucose) which may be represented by the two structures (XVIII) and (XIX), epimeric at C-2. When these two sugars are oxidised with nitric acid, two saccharic acids are obtained both being optically active — a fact which is compatible only with the

structures (XX) and (XXI) (neither of them has a σ plane bisecting the 3-4 bond) In both of them, the 4-OH (equivalent to the 3-OH in arabinose) is on the left.* This settles the relative configuration of arabinose as shown in the bottom row in Figure 8.10.

(*iii*) The next piece of information is supplied by the fact that (+)-gulose, a naturally occurring hexose, on oxidation gives the same saccharic acid as (+)-glucose which means that if the two terminal groups of glucose, namely, CHO and CH_2OH are interchanged, it would give a new sugar, gulose. An equivalent statement is that if the 2-3-4-5 skeleton (the *core*) of glucose (or of the derived saccharic acid) is *inverted*, i.e., rotated through 180° in the Fischer projection, a new core (that of gulose) would be produced. An inspection of the two saccharic acids (XX) and (XXI) indicates that it is true only for XXI which must thus be glucosaccharic acid. The other (XX) in which the core remains unaltered on inversion is mannosaccharic acid. Glucose and gulose are related to each other by what is known as *core inversion* principle. This final evidence settles the relative configuration of (−)-mannose, (−)-glucose, and (−)-gulose which are shown in the bottom row. Gulosaccharic acid (XXIa), on 180° rotation in the plane of the paper, becomes superposable with glucosaccharic acid in conformity with the core inversion principle. Because of the established correlation of the configuration of D-glucose with that of *R*-glyceradehyde, the present configurations may be accepted as absolute.

8.3.2 **Methods based on comparison of optical rotation**

A number of empirical rules for configurational assignment (mostly correlative) based on optical rotation (measured at D line) have been enunciated since the time of van't Hoff. The reliability of some of them is questionable in view of their shaky theoretical basis. Nevertheless, they have been found to be very useful. A summary of these rules are given below.

1. Distance rule (Chugaev 1898). The optical rotation of a compound is primarily determined by the arrangement of atoms and groups (of different polarisabilities) in the immediate vicinity of the chiral centre. Therefore, if two compounds have similarly constituted chiral centres but differ in the structure at a point distant from the chiral centres, they very often show optical rotation of the same sign and even of the same magnitude if they have identical configuration. Thus in a homologous fatty acid series with an α-Me group, e.g., Me $(CH_2)_n$-CH (Me)-CO_2H, of identical configuration, the optical rotations have the same sign for all values of n and their molecular rotations tend to approach a constant value (~28°) as the chain length increases. The rotation gradually decreases as the Me group shifts nearer to the centre of the chain. A generalisation has been made on the basis of the distance rule which states that the secondary alcohols (as XXIII)

*If the 4-OH is placed at the right in the projection formulae of glucose and mannose (the configuration at other centres is already fixed), one of the saccharic acids the one derived from XIX would have been a meso compound (XXII).

and α-hydroxy-carboxylic acids (as XXIV) (Figure 8.11) show dextrorotation and levorotation respectively.* The usefulness of this rule is immediately apparent.

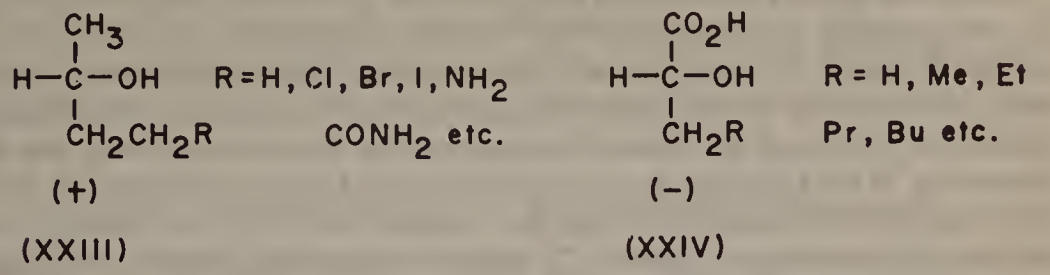


Figure 8.11 Rotational signs of secondary alcohols and α-hydroxyacids (distance rule)

2. Rule of shift or displacement rule. The rule of shift (Freudenberg et al 1923) works on a very similar principle as described above. It states that if two similarly constituted chiral molecules such as (+)-lactic acid and (+)-alanine are converted into a series of analogous derivatives such as acetates, benzoates, amides, ethers etc., each change would produce an appreciable but comparable shift of optical rotation in the same direction. The method is illustrated with the work of Freudenberg in which the configuration of lactic acid and alanine is correlated. (Table 8.1).

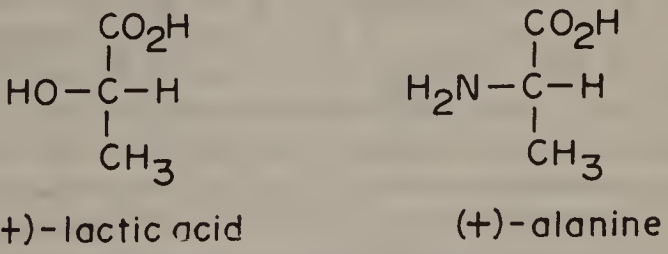


Table 8.1 Configurational correlation of lactic acid and alanine

Derivatives[a]	$[M]_D$ of lactic acid derivatives	$[M]_D$ of alanine derivatives	Direction[b] of shift
Free acid	+ 3.6° (in H_2O)	+ 2.4° (in H_2O)	
Acetyl-ethyl ester	− 80.9°	− 84.0°	− and −
Benzoyl-amide	+ 135.0°	+ 93.0°	+ and +
Benzoyl-ethyl ester	+ 59.5°	+ 107.0°	+ and +
Benzoyl-methyl ester	+ 43.5°	+ 15.0°	+ and +
Tosyl-ethyl ester	− 123.0°	− 104.0°	− and −

[a]OH and NH_2 are similarly derivatised. [b]Occasional exceptions do occur.

3. Rule of optical superposition. The rule of optical superposition was first stated by van't Hoff in 1894 and operates on the basic assumption that if a molecule contains more than one chiral centre. the overall optical rotation may be considered as the algebraic sum of the contribution of each individual chiral

*The sign of the rotation may. however. be reversed in the hydroxyacid series if R = Ph or groups which absorb in the near UV.

centre.* A more recent version of the rule is: *Like functional groups in like surroundings make like contributions to optical rotation* (Mayo 1959).

One of the oldest application of this rule is due to Hudson (1909) who used it for the successful determination of the relative configuration of C-1 (anomeric carbon) in aldoses. He proceeded with the assumption (which subsequently proved to be correct) that in the D-aldoses, the α-anomers (the anomers are, by definition, epimeric at C-1) have the higher dextrorotation (or lower levorotation) than the β-anomers. In the L-aldoses, the α-anomers have the higher levorotation (or lower dextrorotation). The structures of the four isomers (α-D, β-D, α-L, and β-L) of aldohexoses are shown in Figure 8.12 both in normal chair forms† (at the top) and in Fischer projections (at the bottom; 1-OH is shown as 1-OR).

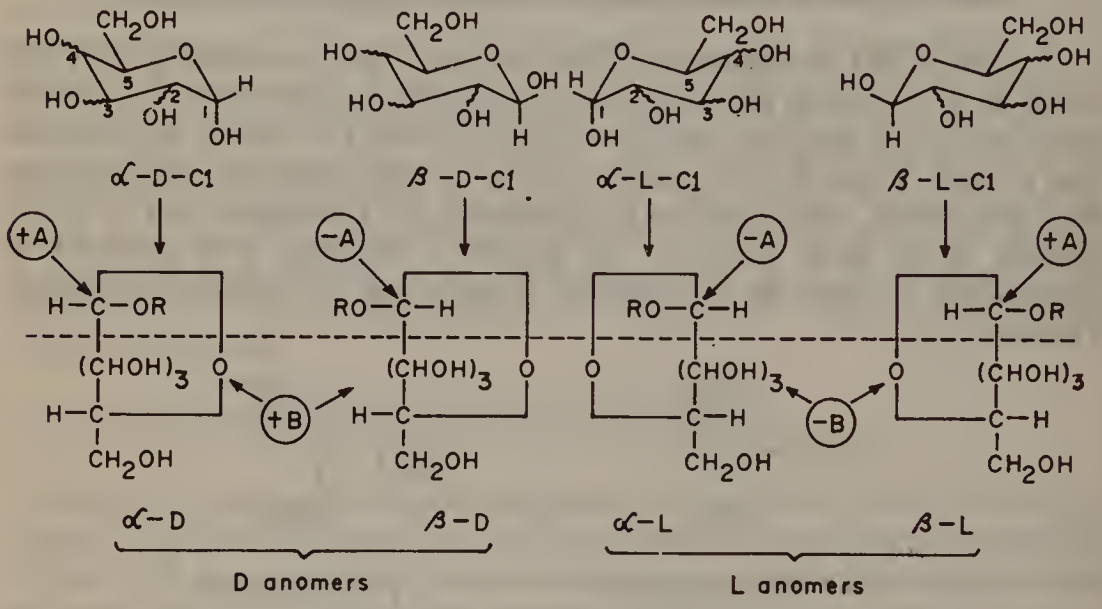


Figure 8.12 Hudson's isorotation rules

The optical rotation of a sugar or its derivatives is regarded as the sum of two quantities: one due to C-1 centre and the other due to the rest of the molecule (the dotted line divides the molecules into the two specified segments). The contributions are + A and − A for C-1 and + B and − B for the rest of the molecule (+ for righthanded and − for lefthanded disposition of 1-OR and 1-5 oxide ring in Fischer projections). Two rules known as Hudson's *isorotation rules* are now formulated as follows:

(*i*) For a pair of α- and β-anomers, the sum of the molecular rotations will be approximately constant (2B) and will be characteristic of a particular sugar (or its derivatives). It will be independent of HC_1-OR.

*The obvious drawback of the rule is that it ignores the interaction of two vicinal chiral centres which may affect each other's contribution to rotation.

†The normal pyranose chair is designated C1 (the inverted chair is designated 1C). The normal chair is also designated $^4C_1$ meaning that C-4 is at the top and C-1 at the bottom of the chair, similarly, the inverted chair is designated $^1C_4$. These conformational notations may be prefixed with D, L and α, β as the case may be. Hudson's rules are applicable to the Fischer projections of C1 forms.

(*ii*) The difference of molecular rotations of an anomeric pair (α and β) will also be another constant (2A) which will be characteristic of the anomeric centre (HC_1-OR), but independent of the rest of the molecule.

The first rule may be illustrated by the data recorded in Table 8.2 for three anomeric pairs of D-glucopyranosides (including D-glucose itself) (see Finar 1975).

Table 8.2 Molecular rotations of α and β D-glucose and two glucosides

OR =	$[M]_\alpha$ (exptl)	$[M]_\beta$ (exptl)	2B value ($M_\alpha + M_\beta$)	2A value ($M_\alpha - M_\beta$)
OH	+ 202	+ 34	+ 236	+ 168
OCH_3	+ 309	− 66	+ 243	+ 375
OC_2H_5	+ 314	− 69	+ 245	+ 383

The 2B values for glucose and its 1-derivatives are reasonably constant (rule 1) which proves two things: (*i*) the assignment of configuration at C-1 is correct; (*ii*) the same type of ring structure (pyranose) is present in free glucose as well as in the glucosides. The chemical evidence for pyranose structure in glucose is mainly based on the degradative work on methyl glucoside. The application of the isorotation rule correlates the structure of glucose with that of methyl glucoside (NMR provides still better evidence).

The 2A values depend on the nature of R (characteristic of HC_1-OR) and so they should be compared for different sugars with the same HC_1-OR. Agreement here is not so good (see Gilman 1943) except for D-glucose and D-galactose which have 2A values of + 168 (see Table 2) and + 176 respectively. The reason may be traced to a vicinal effect (interaction between C-1 and C-2) which is almost the same for glucose and galactose (the 2-OH has the same configuration in both).

4. Method based on molecular rotation difference. The principle of the method is the same as of optical superposition. The rule has been developed by Barton and Klyne (1948) from a large number of data available in the steroid field. According to this rule, the molecular rotation of a steroid (or a polyterpenoid) may be described as the sum of the contribution made by the parent hydrocarbon, e.g., cholestane, androstane, pregnane etc. and the contribution made by any other functional group or groups (including double bond) present in the molecule. The parent hydrocarbons such as cholestane, androstane, and pregnane have molecular rotation values, + 91°, + 5°, and + 52° respectively in the 5α series and + 97°, + 11°, and + 58° respectively in the 5β series. The shift in molecular rotation due to a substituent is known as the Δ value which depends on the position and orientation of the substituent.* Thus Δ values for 6-α-OH and 6-β-OH are + 55° and − 50° respectively which means that 6-α-hydroxycholestane and 6-β-hydroxycholestane would have molecular rotations (+ 91 + 55)° and (+ 91 − 50)°

*For the Δ values to be additive, the functional groups must not be too close to each other; the double bonds must not be conjugated.

respectively which is approximately correct. An application of this rule is illustrated by the determination of the position of the double bond in cholestene formed by dehydrohalogenation of 3-chlorocholestane. The double bond could be either between C-2 and C-3 or between C-3 and C-4 (Figure 8.13). The molecular rotation of the actual product is + 248° which conforms to that of 2, 3-cholestene (the Δ values of 2-3 and 3-4 double bonds are added to 91°). This optical rotation difference method is now largely superseded by CD and ORD methods.

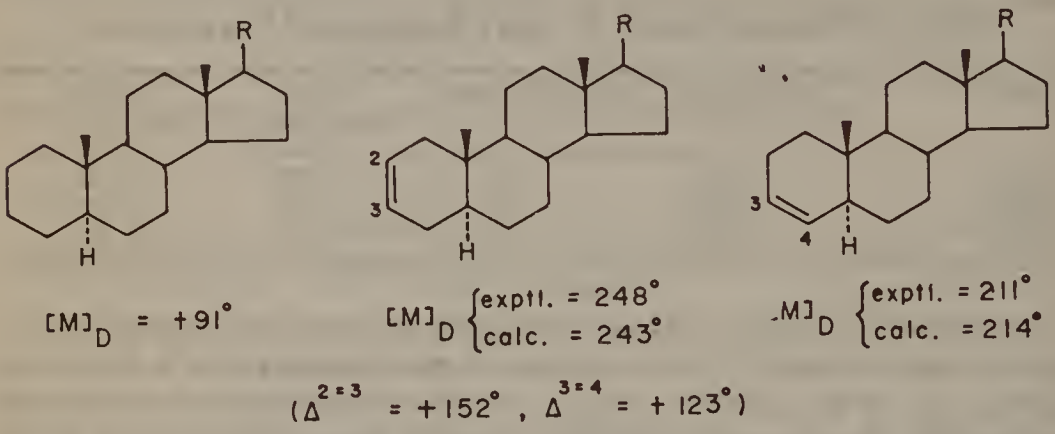


Figure 8.13 Application of molecular rotation difference in structure determination

5. Mills' rule for epimeric cyclohex-2-en-1-ols. Mills (1952) examined the rotations of a few epimeric pairs of terpenoid and steroidal allyl alcohols of known configuration and came out with a rule which is as follows: the more levorotatory epimer has the configuration (XXV) corresponding to that of *S*-glyceraldehyde and the more dextrorotatory one has the opposite configuration (XXVI) corresponding to that of *R*-glyceraldehyde (Figure 8.14).

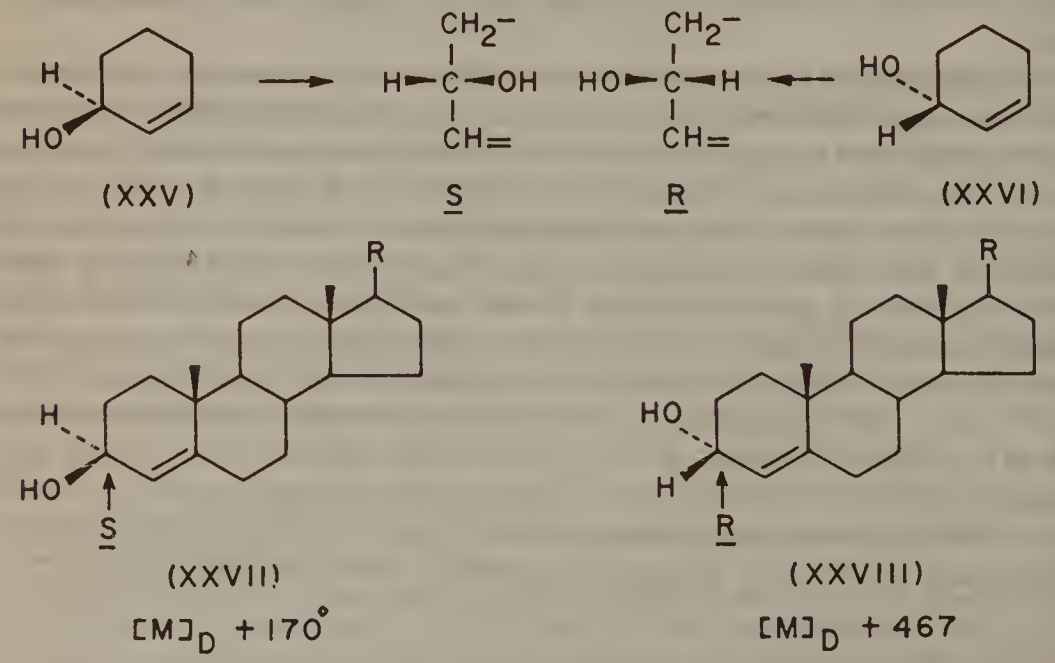


Figure 8.14 Application of Mills rule

The difference in rotations between the epimers is usually high and is increased by esterification. Examples in the steroid field are given by cholestan-β-3-ol (XXVII) and cholestan-α-3-ol (XXVIII) which have molecular rotations $+170°$ (less positive) and $+467°$ (more positive) respectively. The former is configurationally related to *S*-glyceraldehyde and the latter to *R*-glyceraldehyde.

8.3.3 The method of quasi-racemate

It has earlier been mentioned (Chapter 3) that two structurally similar chiral molecules of opposite configuration (i.e., heterochiral), sometimes form quasi-racemic compounds which can be easily characterised by their mixed melting point diagram. This provides a method of configurational correlation of two species which may not be chemically transformed into each other. The method (originally due to Fredga 1941) is very simple and the least time consuming but in order to succeed requires some conditions to be fulfilled: (*i*) The compounds to be compared should be chemically very similar; (*ii*) they must not be too small and are usually polar; (*iii*) both the enantiomers of at least one of the components (A and B) must be available so that one can check whether (+)-A and (+)-B form a quasi-racemic compound and (+)-A and (−)-B form a simple mixture or the reverse; (*iv*) the method is not applicable if both the combinations form molecular compounds (rare) or if both form simple mixture (more common). The method has been reviewed (Fredga 1960).

A classical correlation achieved by this method is between malic acid and methylsuccinic acid. They do not form quasi-racemic compounds by themselves. (−)-Malic acid is first converted into (+)-ethyl xanthate derivative (XXIX) (Figure 8.15) and the latter is found to form a quasi-racemic compound with

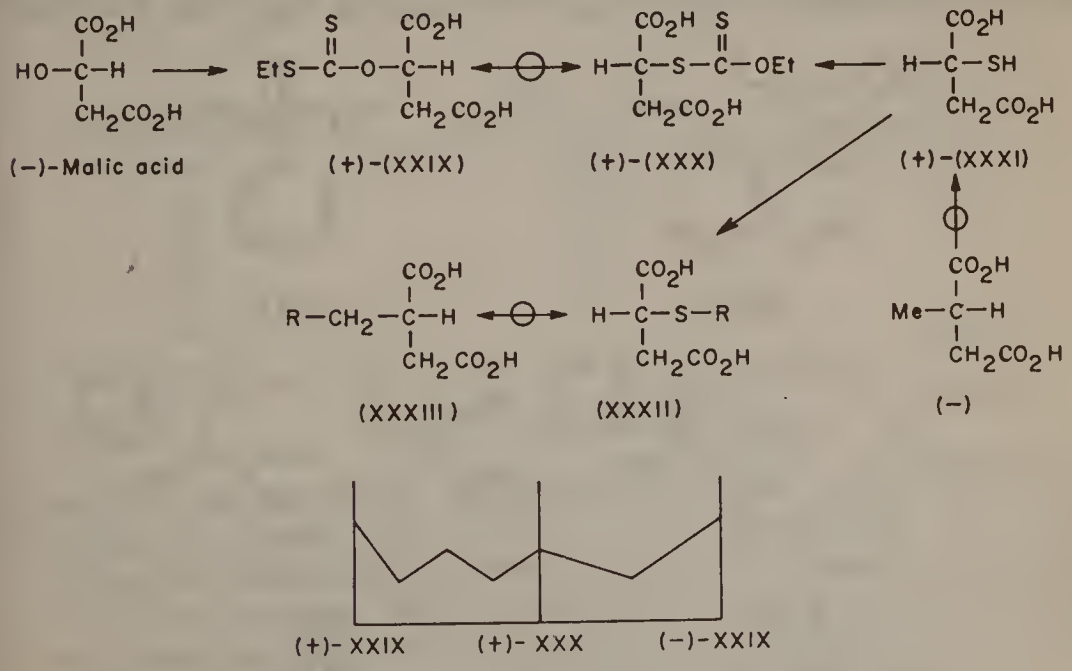


Figure 8.15 Configurational assignment by quasi-racemate method (double-headed arrows with circles denote quasi-racemic compounds)

(+-ethyl thionecarbonate (XXX) of (+)-2-thiolsuccinic acid (see the melting point diagram below). The configuration of 2-thiolsuccinic acid (XXXI) is thus known. The thiol in turn forms a quasi-racemic compound with (−)-methylsuccinic acid whose configuration thus follows. The thiol (XXXI) can be converted into S-alkylated thiolsuccinic acids (XXXII) many of which form quasi-racemic compounds with higher alkylsuccinic acids (XXXIII) and the correlation is continued.

8.3.4 Correlative method based on NMR spectroscopy

NMR spectroscopy (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR etc.) offers an achiral probe and has been extensively used for the determination of relative stereochemistry of diastereomers (see later). In conjunction with an optically active solvent or additive with which the chiral substrate forms transient diastereomeric associates (or solvates), NMR spectroscopy may also discriminate between enantiomers as discussed in Chapter 6. Here the problem is twofold: A particular nucleus (say, H) or a group of nuclei (say, CH_3) must be distinguished in the spectra with detectable anisochrony for the two diastereomeric solvates and secondly, each diastereomeric solvate must be capable of being correlated with the spectral data. For an example, N-ethyl-N-methyl-1-naphthylamine-N-oxide when dissolved in *S*-(+)-2,2,2-trifluoro-1-phenylethanol forms two transient diastereomeric solvates, *S,S* (XXXIV) and *R,S* (XXXV) (Figure 8.16) the conformations of which are fixed by interaction at two points; a H-bonding between N→O and OH and a weak bond between the π-electron cloud of the naphthalene nucleus and the acidic carbinyl H of Ph-C*H*OHCF$_3$. An inspection of the two structures (XXXIV and XXXV) shows that the N-Et group in the former is cis to the phenyl ring and its protons are, therefore, shielded by aromatic ring current relative to those of the N-Et group

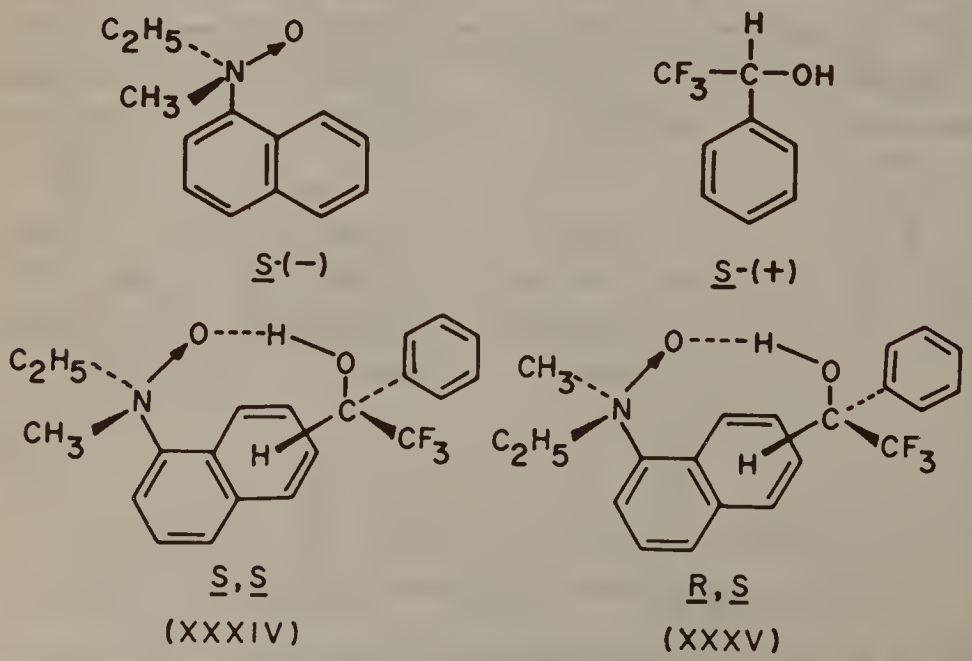


Figure 8.16 Formation of diastereomeric solvates

in XXXV which is trans to the phenyl ring. Actually, in XXXIV, N-ethyl (methylene) protons are 0.02 ppm upfield; the two solvates, *S,S* and *R,S* are thus distinguished (Pirkle et al 1971). A sample of the amine-N-oxide enriched with the levo-enantiomer is then examined in the same solvent and it is found that the *S,S* additive predominates (N-Et signal at the higher field is more intense) which fixes the levo enantiomer with the *S*-configuration. The method depends on the correct interpretation of the structures of the additives and so is suggestive rather than confirmative.

8.3.5 Correlation based on asymmetric synthesis

When a new chiral centre is created in a molecule which already contains one or more, two diastereomers are formed in unequal amounts. The reaction is known as asymmetric synthesis and the existing chiral centre (or centres) is said to bring about asymmetric induction. A few empirical rules have been proposed, depending on the substrates, which correlate the configuration of the newly created chiral centre in the preponderant diastereomer with that of the existing one. Only the qualitative aspect of these rules is discussed here (see Chapter 13 for more quantitative treatment).

1. Cram's rule. When a ketonic group attached to a chiral centre (e.g., $RCOCR_LR_MR_S$ in which L, M. and S stand for large, medium, and small respectively) undergoes nucleophilic addition with organometallic or metal hydride reagents, two diastereomeric products result, erythro and threo of which one predominates. The relative configuration of the predominant isomer is predicted by 'Cram's rule' based on some arbitrary models (Cram and Elhafez 1952; see Eliel 1983). In the *open chain* model (XXXVI), the C=O group is flanked by two smaller groups (R_S and R_M) with the large group (R_L) nearly eclipsed with R (Figure 8.17). The metallic part of the reagent gets complexed with C=O and the

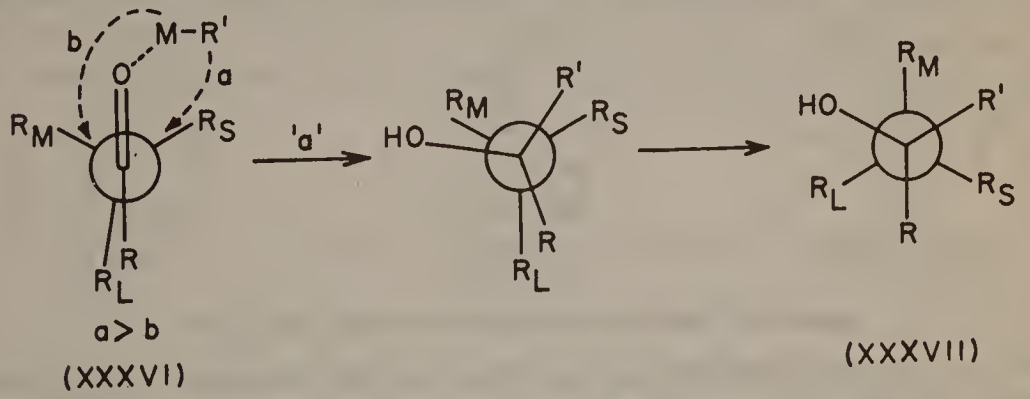


Figure 8.17 Cram's open chain model

carbanion equivalent of alkyl (R′) or H is transferred to the trigonal carbon from the side of R_S (route a) in preference to that of R_M (route b) to give XXXVII. Although no mechanistic rationalisation has been claimed, it is reasoned that C=O being complexed with the reagent becomes effectively the bulkiest group and is thus better placed between R_S and R_M. Two examples are given in Figure 8.18 which illustrate the rule and are self-explanatory. It may be noted that

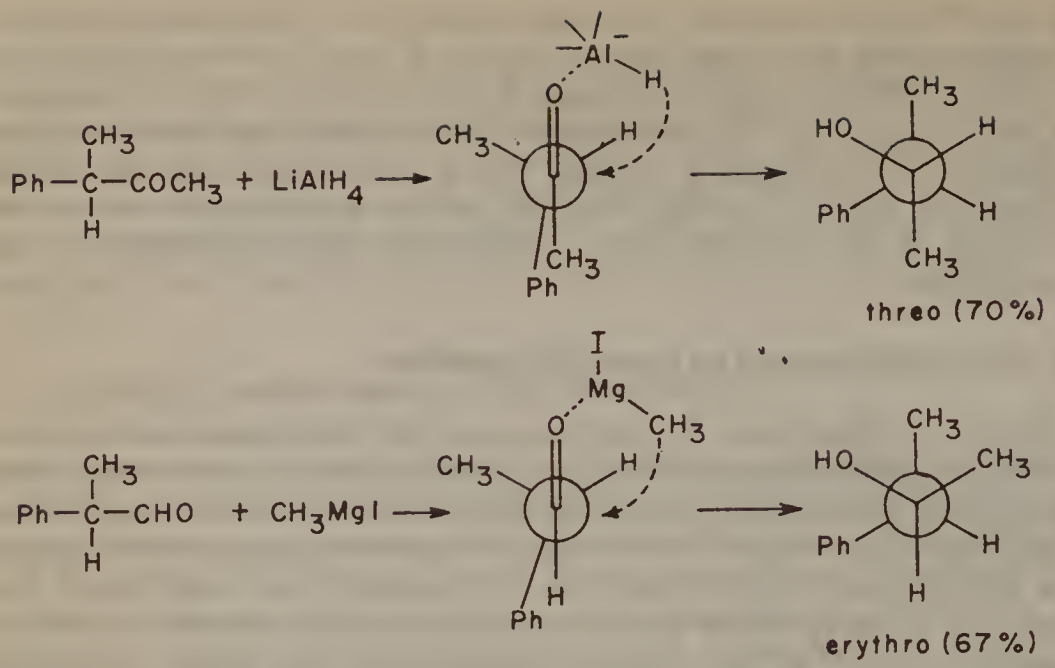


Figure 8.18 Application of Cram's rule; examples

although only one enantiomer of the substrate is shown, the rule is equally applicable to racemic substrate in which case, the products are also racemic.

The model although correctly predicts the stereochemical course of the reactions, often fails to give quantitative assessment of the asymmetric induction in terms of steric interactions. From mechanistic consideration, a few alternative models have been suggested (see Eliel 1983) of which the Felkin-Anh model (Anh 1980) has gained consensus. In this model, two reactive conformations (XXXVIII) and (XXXIX) (Figure 8.19) have been considered in which either the largest (R_L) or

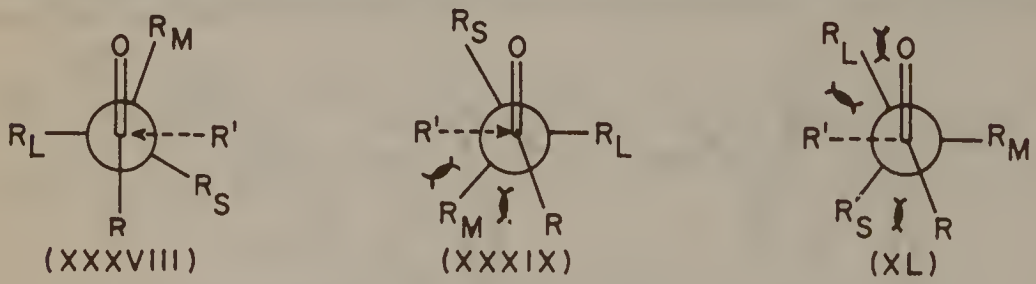


Figure 8.19 Felkin-Anh model-an alternative to Cram's model

the most electron-withdrawing group (which provides the greatest σ^*-π^* overlap with the carbonyl π^* orbital) at Cα is placed at right angle to the C=O double bond. Between the two, the first with R_M opposing C=O and R_S gauche to R is usually preferred. The non-bonded interactions which involve R′ and R_S (rather than R′ and R_M as in XXXIX) are thus minimised. The model predicts the same stereochemistry as Cram's but provides a more quantitative assessment of 1,2-asymmetric induction. A third conformation (XL) may make some contribution but is generally ignored (unfavourable steric interactions).

If the chiral centre in the ketone contains an α-group such as OH, NH_2, and

OMe which is capable of coordinating with the reagents, the stereochemistry of the product is predicted by Cram's rule based on a rigid (chelate) *cyclic model* (XLI) (Figure 8.20) in which the metallic part of the reagent is doubly coordinated to

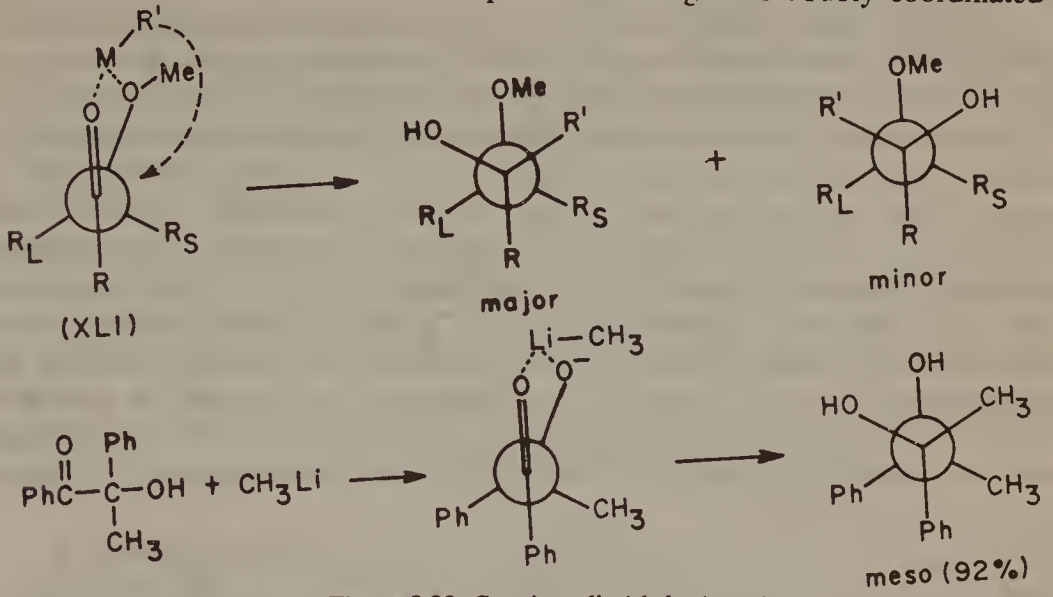


Figure 8.20 Cram's cyclic (chelate) model

form a five-membered ring. The nucleophile preferentially approaches the electrophilic carbon from the side of R_S (an example follows). If the chelating group is R_M (which is often the case), the cyclic model predicts the same stereochemistry (qualitatively) as the open chain model; but if it is R_S or R_L opposite stereochemistry follows. Asymmetric induction through chelate model is usually high.

If a strongly electronegative group, e.g., a halogen atom is present at Cα, yet another model, a *dipolar* one is suggested for prediction of the stereochemistry. The dipoles of the carbonyl bond and the C-X bond oppose each other and so they are placed anti as in the model (XLII) (Figure 8.21). The dipole repulsion is thus minimised, the electrophilic character of the carbonyl carbon increases, and

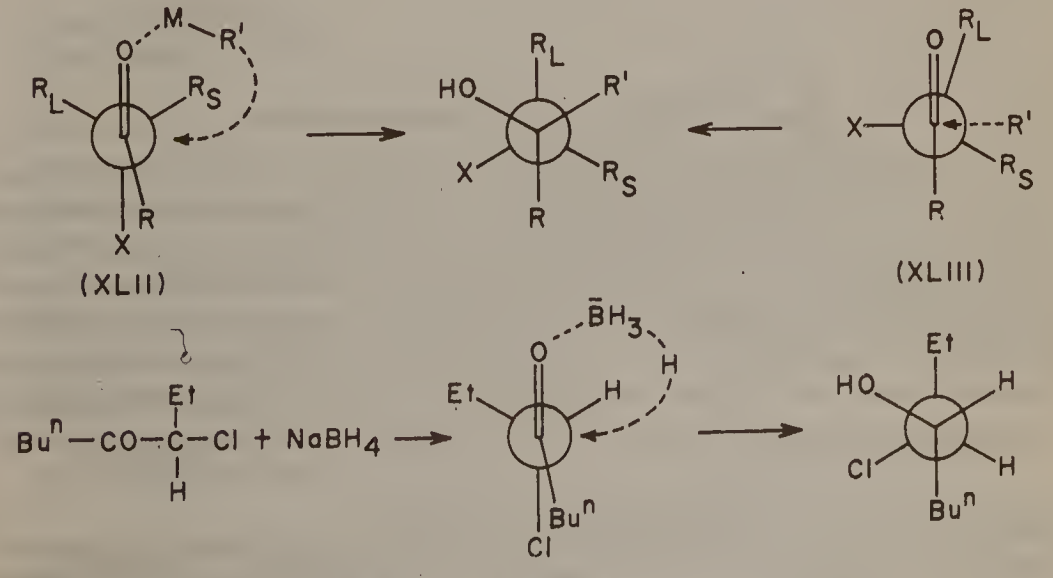


Figure 8.21 Cram's dipolar model

the nucleophile adds from the side of R_S giving the major product as shown. The Felkin-Anh model (XLIII) in which the electron-withdrawing X is placed perpendicular to C=O bond also predicts the same stereochemistry. An example follows.

2. Prelog's rule. Prelog's rule which correlates the configurations of chiral alcohols with those of α-hydroxyacids, especially mandelic acid and atrolactic acid is the outcome of generalisation of the results of asymmetric synthesis carried out by McKenzie group in the early part of the century. When phenylglyoxylic acid is esterified with an optically active alcohol, e.g., (−)-menthol and the ester is reduced with sodium amalgam (or with sodium borohydride), mandelic acid enriched in one of its enantiomers, in this case, *R*-(−), is obtained after complete hydrolysis of the product (see Morrison and Mosher 1971). The reduction step has now been replaced by Grignard addition of methylmagnesium halide so that configurationally stable atrolactic acid is produced. Prelog's rule correlates the configuration of the hydroxyacid, i.e., atrolactic acid with that of the alcohol as follows. The ester of phenylglyoxylic acid is so written that the two carbonyl groups are antiperiplanar as in XLIV (Figure 8.22) and the large group R_L(C-4) at

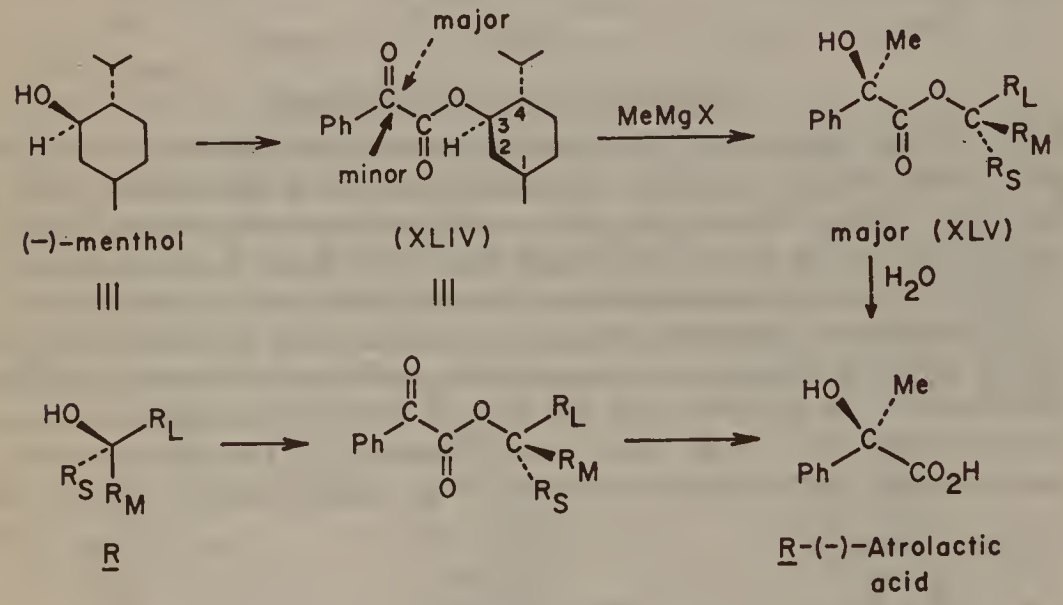


Figure 8.22 Prelog's model and the atrolactic acid rule

thc chiral centre of the alcohol moiety is on the same side of the ketonic carbonyl (PhCOCOOC*-L lies in a plane)*. R_S(H) and R_M (C-2) are in the back and front of the plane respectively†. Methylmagnesium bromide approaches the electrophilic carbon (of the ketonic C=O) from the side of R_S more easily than from the side of R_M. The preferred diastereomer is thus XLV which on complete hydrolysis affords atrolactic acid enriched in *R*-(−)-enantiomer. The carbinyl carbon in menthol has *R* configuration and it follows that obtention of *R*-(−)-atrolactic acid from the above sequence of reactions (esterification of an alcohol with phenylglyoxylic acid,

*As in Cram's rule. this is a formal and not a mechanistic assumption.

†Alternative conformation with R_S in place of R_L may also be considered in which case, it is a choice between the approach from R_M side versus that from the R_L side. The former is preferred and the same stereochemistry results.

Grignard addition of MeMgX, and subsequent complete hydrolysis of the product) settles the configuration of the chiral alcohol as *R*. Similarly, if *S*-(+)-atrolactic acid is obtained, the configuration of the alcohol is *S*. This is illustrated with two steroidal alcohols, 7α- and 7β-hydroxycholestane (Figure 8.23). The asymmetric induction is usually moderate (10-30%) but is sufficient for the correlation of configuration. Since the configuration of atrolactic acid is known, the method gives the absolute configuration of the chiral alcohols.

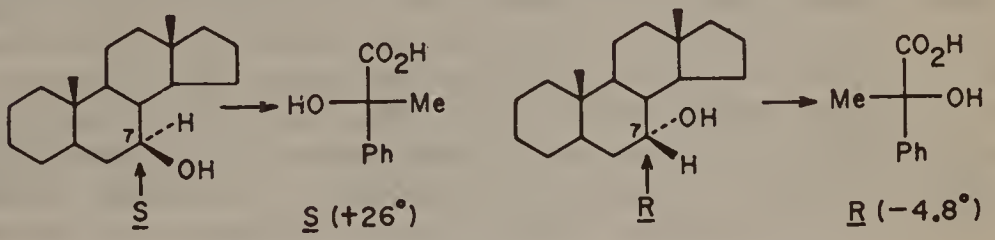


Figure 8.23 Configuration at C-7 of steroids (Prelog's rule)

3. Horeau's method. Horeau (1962) has developed another empirical method for the correlation of configuration of secondary alcohols based on the principle of kinetic resolution. A secondary alcohol, enantiomerically pure or enriched, is treated with an excess of (±)-α-phenylbutyric anhydride (XLVI) (Figure 8.24).

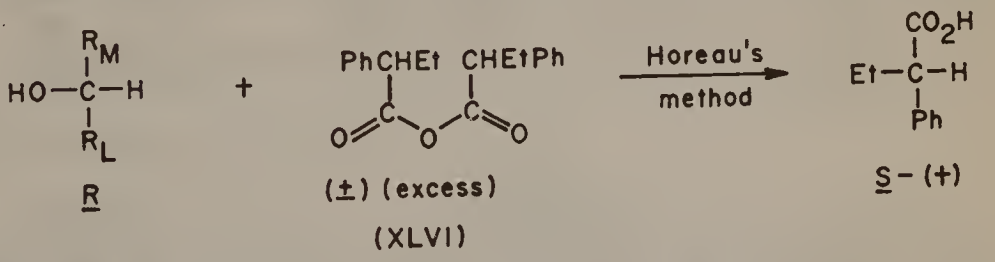


Figure 8.24 Horeau's method of configurational correlation

The residual anhydride is hydrolysed and the optical rotation of the resultant α-phenylbutyric acid measured. The rule states that an alcohol with *R-configuration gives an excess of S*-(+)- phenylbutyric acid (the CIP priority assumes $R_L > R_M$) and so on. No rationalisation has been attempted and the rule is strictly empirical. The method has the advantage that if no optically active alcohol is available, the racemic alcohol itself may be treated with optically active α-phenylbutyric anhydride taken in insufficient amount. The unreacted alcohol is recovered and its rotation measured. The rule is now reversed: if the anhydride of *S*-(+)-phenylbutyric acid is used, the unreacted alcohol would have the *R* configuration. The method is sensitive and can even be used to determine the configuration of 2-propanol-1,1,1-d_3($CH_3CHOHCD_3$).

8.4 Configuration of molecules with axial and planar chirality

Configurations of molecules with axial and planar chirality, e.g., biphenyls, allenes, sprianes, *trans*-cycloalkenes etc. are difficult to correlate with that of a molecule

with a centre of chirality. The problem has been tackled only during the late fifties and sixties using methods based on asymmetric synthesis, specific molecular rearrangements, and comparison of chiroptical properties (see Krow 1970 for a review). A few illustrative examples are discussed in the following subsections.

8.4.1 Configuration of biphenyls and analogues

The biphenyls were the first non-centrodissymmetric molecules to be investigated for their absolute configuration by correlative methods. The method of Mislow et al based on kinetic resolution has already been mentioned in Chapter 7 (Figure 7.14) in which considerations of non-bonded interactions in the transition states (TS) of the asymmetric hydride transfer reactions correlate the configuration of a singly or doubly bridged biphenyl ketone with that of the optically active secondary alcohol used. Thus when a racemic mixture of *o,o'*-dinitro-1,2,3,4-dibenz-1,3-heptadien-6-one (XLVII) is reduced with *S*-(+)-methyl-*t*-butylcarbinol, (Figure 8.25) the *R*-enantiomer reacts faster than the *S*-enantiomer. In the case of

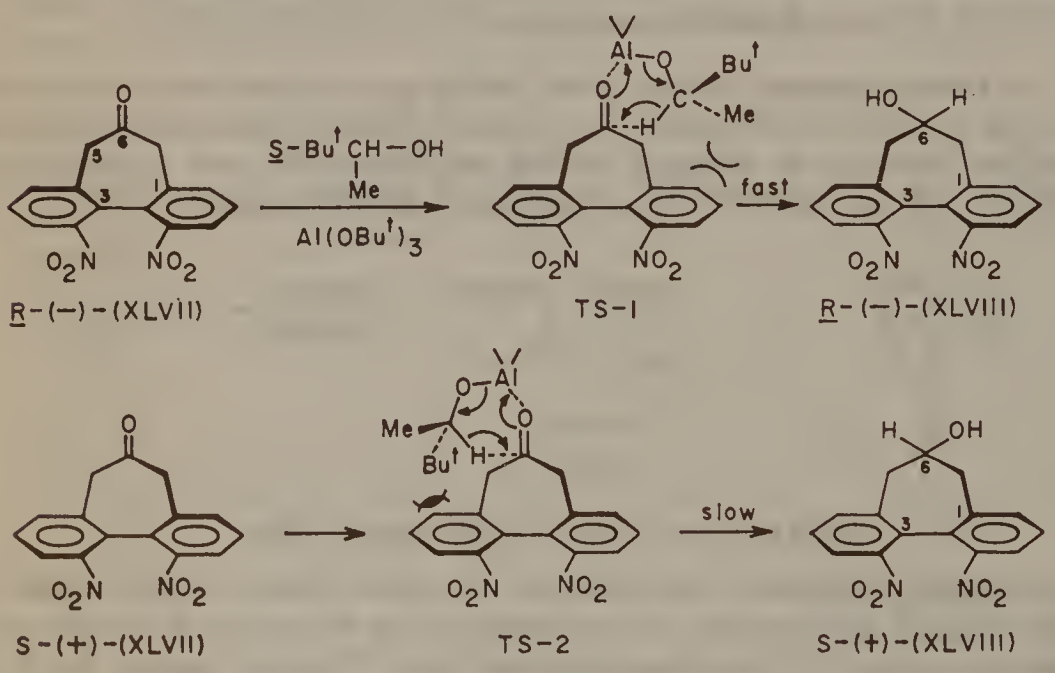


Figure 8.25 Configurational correlation of biphenyls by asymmetric synthesis

the latter, the *t*-Bu group interacts with the adjacent phenyl ring sterically (as shown) making TS-2 of higher energy than TS-1. If the reaction is stopped before completion, the residual ketone is enriched with the (+) -enantiomer which thus must have the *S*-configuration. From the kinetic resolution of a number of singly and doubly bridged biphenyl ketones as described above, a generalisation has been made that incomplete reaction with *S*-(+)-methyl-*t*-butylcarbinol or with *S*-(+)-2-octanol leads to an enrichment of the *S*-enantiomer of the biphenyl ketones, provided that the configurational nomenclature (*R* and *S*) of the biphenyls corresponds to that of XLVII.

The two enantiomeric alcohols (XLVIII), *R* from *R*-ketone and *S* from *S*-ketone can in turn be configurationally correlated by the atrolactic acid method:

The phenylglyoxylic ester from the *R*-alcohol gives an excess of *R*(−)-atrolactic acid and that from the *S*-alcohol gives an excess of *S*-(+)-atrolactic acid following Prelog's rule. It may be noted that C-6 in the alcohol (XLVIII) is chirotopic but non-stereogenic (see also Chapter 7). The two faces of the ketone (XLVII) are homotopic (related by C_2 axis) by internal comparison but enantiotopic by external comparison between the two enantiomeric ketones.

Once the configurations of a few biphenyls such as XLVII are known, those of many others may be correlated through the conventional chemical transformations (Figure 8.26) (Eliel 1962).

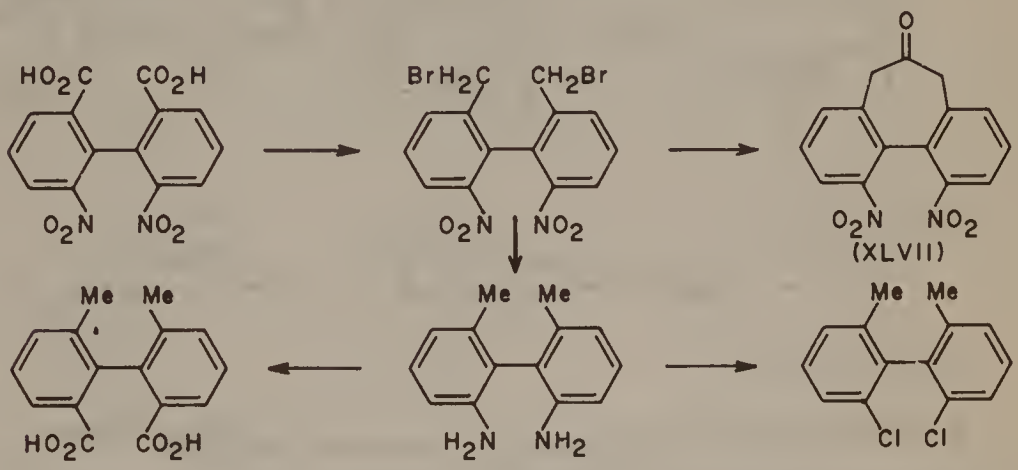


Figure 8.26 Configurational correlation of biphenyls through chemical transformations.

8.4.2 Configuration of chiral allenes

Several methods are available for correlating the configuration of allenes with that of centrodissymmetric molecules (Krow 1970, Morrison and Mosher 1971). A few are mentioned below.

1. Rearrangement of propargyl alcohol. The configuration of methyl-*t*-butylethynylcarbinol (XLIX) (Figure 8.27a) has been determined by the atrolactic acid method. The *R*-(−)-enantiomer* (C ≡ CH > Bu^t) is treated with thionyl chloride when an internal nucleophilic displacement reaction with rearrangement (S_Ni') takes place. The resultant 3-*t*-butyl-3-methyl-1-chloroallene is levorotatory and assuming that the rearrangement is highly stereoselective, its configuration is *R* (an apparent violation of Lowe's rule, see Chapter 15).

2. Claisen-type rearrangement. Vinyl propargyl ethers (e.g., L) prepared from propargyl alcohols of known configuration (as determined by the atrolactic acid

* In the original experiment (Landor et al 1963, 1965), the sign of rotation of the acetylenic alcohol (XLIX) was wrong, (+) instead of (−), because of kinetic resolution during hydrolysis in Prelog's method which in turn gave a wrong configurational assignment to the chloroallene, *R*-(+) instead of *R*-(−). This has been recently rectified by Eliel and Lynch (Tetrahedron Letters, 1987, **28**, 4813). Since the correct experiment has not been done so far, the Scheme in Figure 8.27a is hypothetical: nevertheless, it illustrates the principle (see Elsevier and Mooiweer, *J. Org. Chem.*, 1987, **52**,1536 for other evidence).

method) have also been used to establish the configuration of chiral allenes through Claisen-type rearrangements as shown in Figure 8.27b.

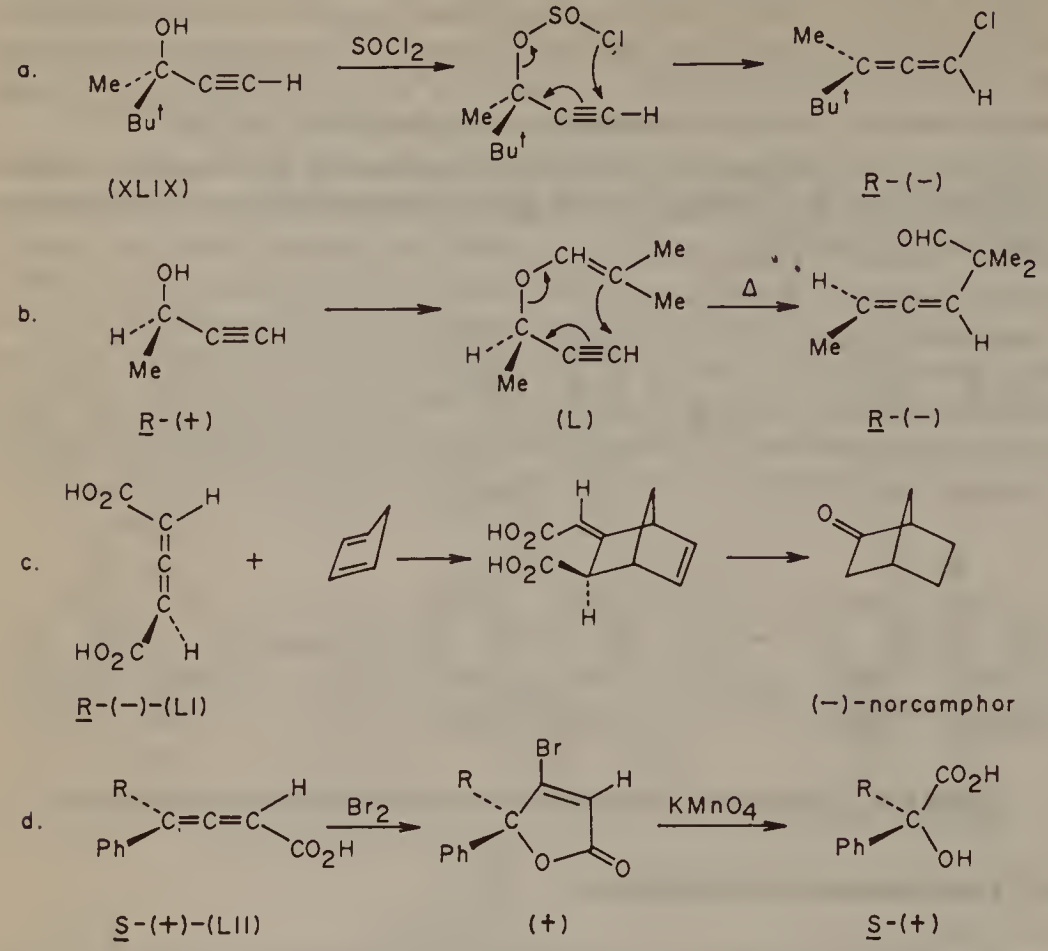


Figure 8.27 Configurational correlation of allenes

3. Diels-Alder reaction. The configuration of (−)-glutinic acid (LI) has been correlated to that of (−)-norcamphor through the sequence of reactions shown in Figure 8.27c which consists of a Diels-Alder reaction followed by degradation. The exo-syn structure of the adduct is confirmed through the formation of an anhydride.

4. Conversion of allenic acids into bromolactones. The configuration of a series of (+)-phenylallenecarboxylic acids (LII) (Figure 8.27d) has been confirmed as *S* by converting them into bromolactones and then into α-hydroxy-acids of known absolute configuration.

8.4.3 Configuration of alkylidenecycloalkanes

No general method for the determination of configuration of the alkylidenecycloalkanes is available. The strategy varies from substrate to substrate and is illustrated here with two examples.

1. 4-Methylcyclohexylideneacetic acid. Gerlach (1966) determined the absolute

configuration of 4-methylcyclohexylideneacetic acid-α-*d* (LIII) (Figure 8.28) by a combination of catalytic hydrogenation, asymmetric synthesis, and chemical transformations. The (+)-form of LIII is reduced catalytically (cis addition of

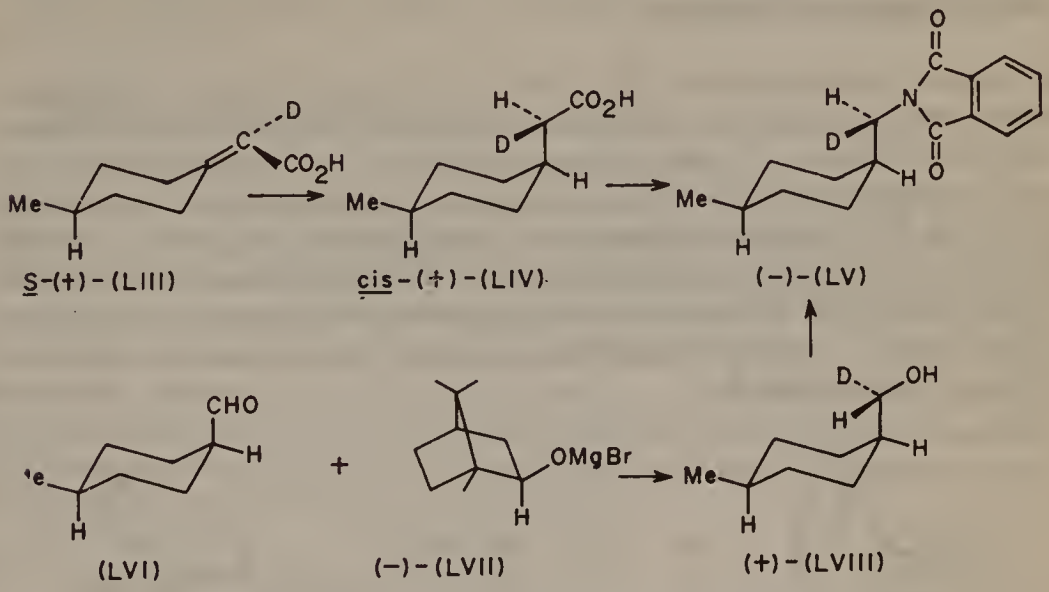


Figure 8.28 Configuration of 4-methylcyclohexylideneacetic acid-α-d

hydrogen) to give a mixture of the cis and trans isomers which are separated. The cis isomer (LIV) which happens to be dextrorotatory is converted into the phthalimide derivative (LV). In another reaction, *cis*-4-methylcyclohexanecarboxaldehyde (LVI) is asymmetrically reduced with (−)-isobornyloxymagnesium bromide (LVII) to give the alcohol (LVIII) enriched in the (+)-enantiomer. From analogy of other reductions with this reagent, the configuration of the new chiral centre is fixed as *S*-(LVIII). This is converted through a known sequence of reactions (including one with Walden inversion) into the phthalimide derivative (LV), identical with the one obtained in the first reaction sequence. The configuration of (+)-4-methylcyclohexylideneacetic acid-α-*d* is thus settled as *S*, i.e., LIII.

2. Configuration of 1-benzylidene-4-methylcyclohexane. (+)-3-Methylcyclohexanone of known configuration (vide supra) is converted into the benzylidene derivative (−)-(LIX) (Figure 8.29), the *E* configuration of which is confirmed by spectral data. The carbonyl group is then reduced by $LiAlH_4$-$AlCl_3$ which does not interfere with the rest of the stereochemistry (Brewster et al 1966). (+)-1-

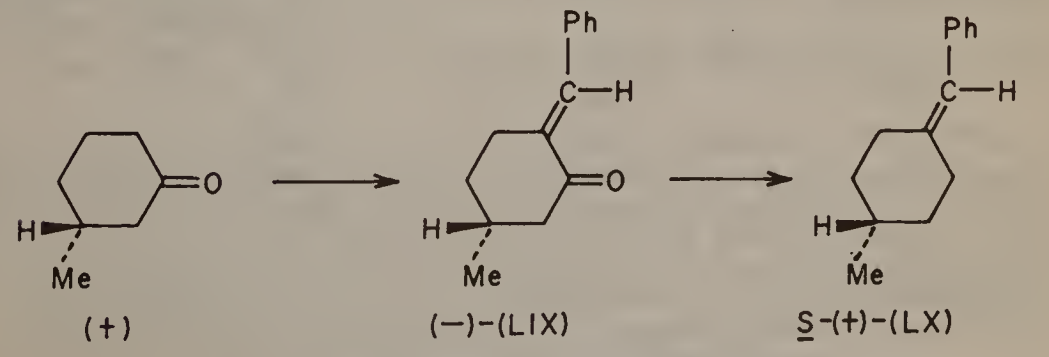


Figure 8.29 Configuration of 1-benzylidene-4-methylcyclohexane

Benzylidene-4-methylcyclohexane (LX) thus obtained must have the *S* configuration.

8.4.4 Configuration of spiranes

The absolute configuration of only a few chiral spiranes has been determined. Gerlach (1968) prepared *trans, trans*-spiro [4,4] nonane-1,6-diol (LXI) and resolved it. The chiral centres at C-1 and C-6 are related by a C_2 axis and may therefore be treated as a single chiral unit. The (−)-enantiomer, represented by the type formula LXII (Figure 8.30) is then treated with (±)-2-phenylbutyric anhydride (an excess) and the residual anhydride hydrolysed to get *S*-(+)-2-phenylbutyric acid which according to Horeau's rule indicates *R*-configuration at C-1 and C-6. The diol on oxidation gives a (−)-dione which thus must have the configuration shown in LXIII, i.e., *S* (see Chapter 5).

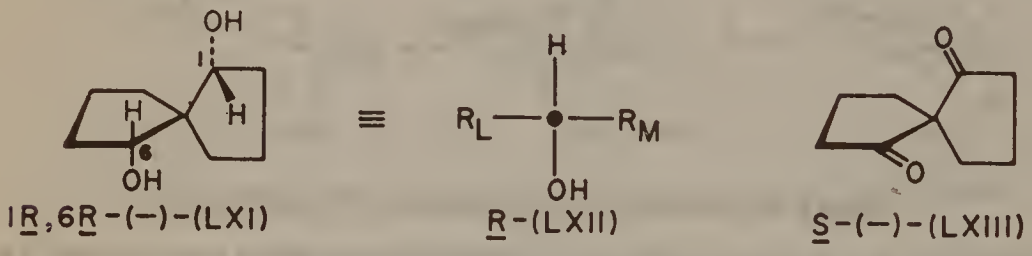


Figure 8.30 Configuration of a spirane

8.4.5 Configuration of trans-cycloalkenes

Configurational correlation of *trans*-cycloalkenes with that of a centrodissymmetric molecule is illustrated with *trans*-cyclooctene (Cope and Mehta 1964). The (−)-enantiomer (LXIV) is oxidised with osmium tetroxide to give a *cis*-diol stereoselectively (Figure 8.31) with the two OH groups away from the methylene side chain.

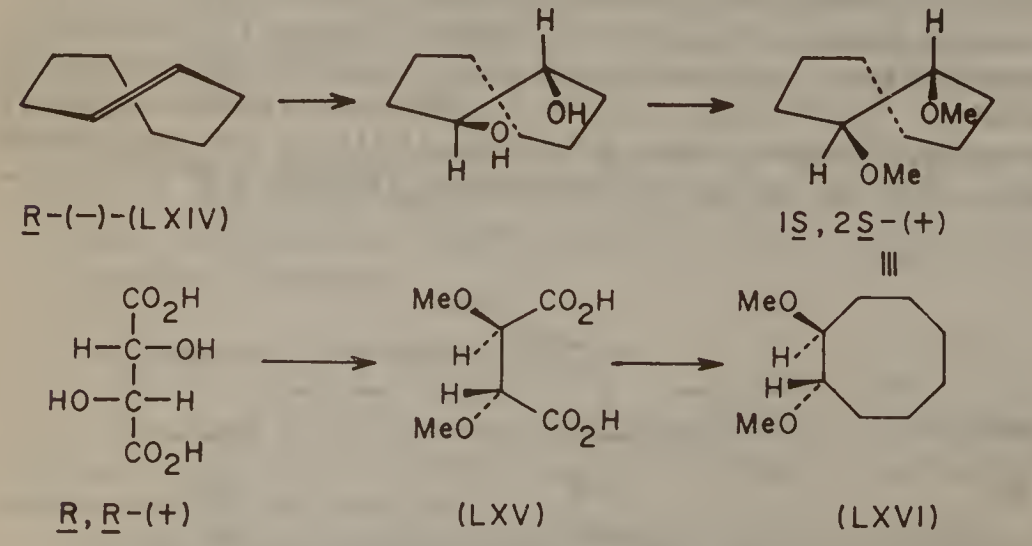


Figure 8.31 Configuration of *trans*-cyclooctene

The diol on methylation gives the dimethyl ether (LXVI) which has been correlated with (+)-tartaric acid via its dimethyl ether (LXV) (through synthesis). The (−)-*trans*-cyclooctene must therefore have the *R* configuration.

For the configurational correlation of metallocenes, reference is made to Falk and Schogl (1968).

8.5 Relative configuration of diastereomers

Diastereomers comprise a large variety of stereoisomers such as *E* and *Z* in compounds with dissymmetrically substituted double bonds, cis and trans in substituted carbocyclic and heterocyclic compounds, exo and endo in bridged ring compounds, erythro and threo (syn and anti) in compounds with multiple chiral centres, and so on. Two such diastereomers differ in their relative configuration and unlike enantiomers, can be distinguished by their physical and chemical properties and by UV, IR, NMR, and X-ray diffraction. Their relative configuration can thus be determined by a comparison of their physical and chemical properties as well by the above mentioned spectral methods.

8.5.1 Comparison of physical properties

In early times when NMR methods were not available, the relative configuration of many natural products has been determined by a comparison of their physical properties such as boiling point (b.p.), melting point (m.p.), density (d), refractive index (n_D), dissociation constant (pK_a), and dipole moment (μ). A few empirical rules have been worked out and used extensively.

1 Auwers-Skita rule. One of the earliest rules which correlates b.p., d, and n_D with the relative configuration (cis and trans) of monocyclic compounds is due to von Auwers and Skita. The rule has undergone several modifications and in its present form (known as the *conformational rule*) states that between two alicyclic epimers which do not differ appreciably in dipole moment, the one with the highest enthalpy* has the higher b.p., d, and n_D. The rule may be rationalised in terms of higher molecular volume of the trans isomer which is directly responsible for its lower d and n_D. The relationship of molecular volume with enthalpy and b.p is not so obvious (see Eliel 1962). The rule finds application in determining the relative configuration of many monocyclic monoterpenes such as menthones. The rule regarding the b.p. does not hold for alkylcyclohexanols in which the formation of H-bond influences the b.p.

2. van Arkel or dipole rule. When two isomers differ appreciably in dipole

*In its original form, the rule states that the cis isomer has the higher values for the properties (b.p., d, and n_D) which is usually correct because in most cases, the cis isomer has the higher enthalpy. However, according to the conformational theory, the epimer with the higher number of equatorial substituents (see Chapter 10) has the lower enthalpy and it may not be necessarily trans. Thus for 1, 3-dimethylcyclohexane, the cis isomer with two equatorial Me is more stable than the trans with one equatorial and one axial Me. Hence the trans isomer has the higher b.p. (124.5° versus 120.1°) higher d_4^{24} (0.7806 versus 0.7620), and higher n_D^{25} (1.4284 versus 1.4206).

moment, van Arkel rule or the *dipole rule* is applied which states that the isomer with the higher dipole moment (μ) possesses the higher b.p., d, and n_D. Thus the cis isomer of 1,2-dichloroethene (ClCH = CHCl) has a higher dipole moment than the trans and its b.p., d, and n_D are higher than those of the trans (this, however, also conforms to the Auwers-Skita rule). In the case of 1-chloro-1-propene (MeCH = CHCl) and crotononitrile (MeCH = CHCN), the trans isomers have the higher dipole moment and also the higher physical constants (b.p., d, n_D), contrary to Auwers-Skita rule.

3. Comparison of boiling points. More recently, the boiling points of a series of structurally related compounds have been correlated with that of the parent molecule and the number and nature of the substituents present (Kellie and Riddell 1972) in accordance to the equation:

$$T_x = T_o + \Sigma\, a$$

in which T_x is the calculated b.p. of a compound in the series, T_o is the b.p. of the parent compound, the Σ **'a'** is the summation of contributions of different substituents. The contribution (**a**) for an equatorial methyl in cyclohexane is + 19.1 and for an axial methyl is + 23.0 with additional increments of + 4.2, + 3.1, and − 5.7° for vicinal e,e-dimethyl, vicinal e,a-dimethyl, and geminal dimethyl respectively. The calculated b.p. of 1,2-*trans*-dimethylcyclohexane (with two vicinal e-Me) is thus 123.9°. (81.5 + 2×19.1 + 4.2), the b.p. of cyclohexane being 81.5°. The experimental value is 123.4° in close agreement (all b.p.s are under atmospheric pressure).

4. Comparison of melting point and pK_a value. Between a pair of cis and trans isomers, the trans has usually the higher m.p., the lower solubility in inert solvents, and in acids, the lower dissociation constant (K_a)*. In this respect, there is significant resemblance among the cis and trans isomers of the olefins and ortho and para isomers of benzene. Thus *E*-crotonic acid and *p*-toluic acid have both the higher m.p.s and the lower K_a values compared to *Z*-crotonic acid and *o*-toluic acid (Figure 8.32). However, these properties by themselves can hardly be used for the determination of relative configuration unambiguously.

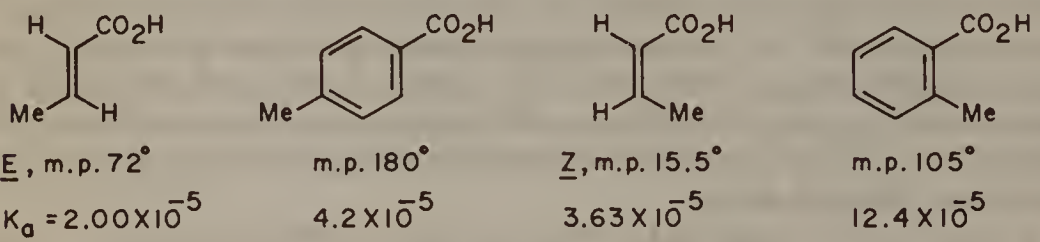


Figure 8.32 Melting points and K_a values of *E* and *Z* isomers vis-a-vis those of ortho and para isomers

*In dicarboxylic acids such as maleic and fumaric acid, the first dissociation constant is higher for the cis but the second one is higher for the trans (see Eliel 1962 for related Bjerrum's law) because of a proximity effect (CO_2^- is H-bonded to CO_2H in maleic acid after first dissociation).

5. Dipole moment. In molecules like XHC=CHX where X is a single atom or a group with conical symmetry, the net dipole moment of the trans isomer is zero while the cis usually has an appreciable dipole moment (see 1,2-dichloroethene in Figure 8.33). When the substituents (X) are different but of the same polarity (e.g., Cl and Br), the trans isomer has a smaller dipole moment than the cis. When, however, the groups have non-coplanar dipole moment or are of opposite polarity (e.g., Cl and Me), the difference in dipole moments may be very slight or even be opposite in direction (see chloropropene in Figure 8.33). Except for clear-cut cases, one cannot depend on the dipole moment measurements alone.

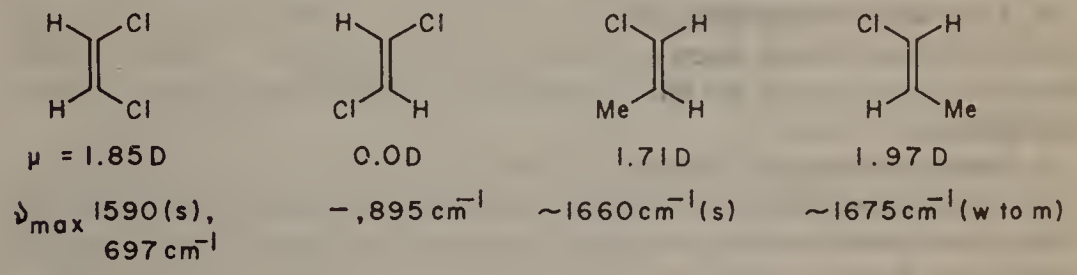


Figure 8.33 Dipole moments and IR data of *E* and *Z* isomers

6. Electronic spectra. The electronic spectra (UV and visible) may sometimes be used to distinguish between the cis and trans (*Z* and *E*) isomers in olefinic compounds where the double bond is in extended conjugation with other groups. The classical examples are trans (*E*) and cis (*Z*) isomers of stilbene (Figure 8.34). Both the position of the absorption maxima (λ_{max}) and the absorption coeffficients (ϵ) differ appreciably. In *cis*-stilbene, the two phenyl rings are not quite planar due to steric reason and resonance is appreciably inhibited.

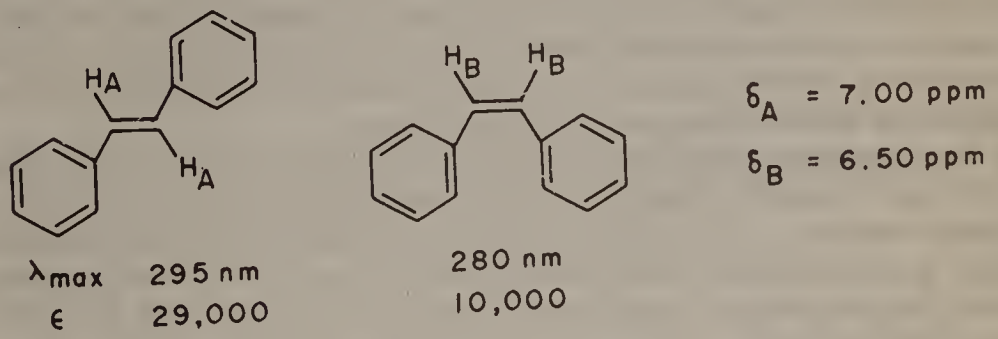


Figure 8.34 UV spectral and NMR data of *cis* and *trans*-stilbene

7. Infrared and Raman spectra. In IR, the intensity of the C=C stretching frequency (1650-1680 cm^{-1}) and the position of the =C-H out-of-plane vibration (970-690 cm^{-1}) differ significantly in the cis and trans isomers of substituted olefinic compounds. To observe the C = C stretching frequency, it is essential that the transition should be accompanied by a change in dipole moment. The trans isomer of XCH = CHX does not incur any change in dipole moment in the transition and so does not absorb (or absorbs only feebly) in the above region where the cis

isomer shows a strong band. In unsymmetrically substituted olefins of the type R-CH = CHR′, the C = C band of the cis isomer (1660 cm^{-1}) is more intense than that of the trans isomer (1675 cm^{-1}) (Figure 8.33) The absorption band for C = C is less diagnostic in trisubstituted olefins such as XYC = CHZ unless two groups, either X or Y and Z are strongly polar as in 1,2-dichloropropene (CH_3-CCl = CHCl) (the *Z* isomer has a strong band at 1614 while the *E* isomer has a weak band at 1615 cm^{-1})

Raman spectra show strong C = C absorption both for the trans and cis isomers at 1668-1671 and 1654-1657 cm^{-1} respectively and may be used for configurational assignment. Both the isomers must be available.

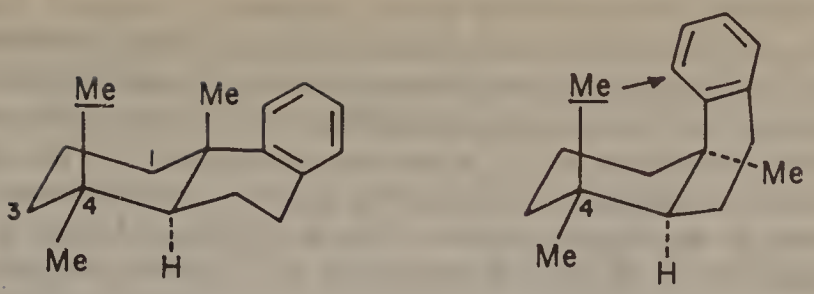
8. X-ray and electron diffraction. X-ray and electron diffraction give the actual distances between various atoms and groups as already mentioned. When applicable, these techniques provide the most unambiguous methods for determining relative configuration.

9. Mass spectrometry. In mass spectrometry, molecules are bombarded with very high energy (10-70 eV) electron beams and so mass spectra, in general, cannot discriminate between stereoisomers to the extent required for configurational assignment. However, often the trans isomers give molecular ion peaks of higher intensity than the cis isomers; intensities of fragments are also higher for the trans (see Green 1976).

8.5.2 Methods based on NMR spectroscopy

The remarkable development in the technique of NMR spectroscopy in recent years has greatly helped in assigning relative configuration to all types of diastereomers. Three basic pieces of information are available from ^{1}H-NMR regarding the structure of a molecule: (*i*) the chemical environment around a proton (or protons) in terms of its chemical shift (δ); (*ii*) the number of chemically equivalent protons from the relative intensity of the peaks; (*iii*) and the number and steric disposition of neighbouring protons from the splitting pattern and spin-spin coupling constant (*J*) respectively. The chemical shift and the coupling constant give valuable information regarding the relative stereochemistry of diastereomers.

1. Chemical shift and relative configuration. Electrons associated with certain atoms (e.g., Cl and Br), bonds (e.g., C=C and C≡C), and groups (e.g., C=O and aryl) exert long range shielding effects on neighbouring protons. Since these effects depend very much on the relative steric disposition of the two interacting systems, they are different for any two diastereomers. Protons which are coplanar or near coplanar with an aromatic ring or C=C and C=O groups are deshielded and protons which lie above them are shielded. Thus in *trans*-stilbene (Figure 8.34), each of the two olefinic protons (H_A) are deshielded by both the aromatic rings whereas in the cis isomer, each of them (H_B) is deshielded by only one adjacent aromatic ring. H_A's therefore appear at a lower field than H_B's (δ7.00 and 6.50 respectively). The shielding due to an aromatic ring current is best shown in the trans and cis isomers of podocarpa-8,11,13-triene (Figure 8.35). In the trans isomer (LXVII), the axial 4-Me is far away from the aromatic ring whereas in the cis isomer, the axial 4-Me is almost directly above it and so is considerably shielded by the ring current (δ1.00 in LXVII and 0.35 in LXVIII).

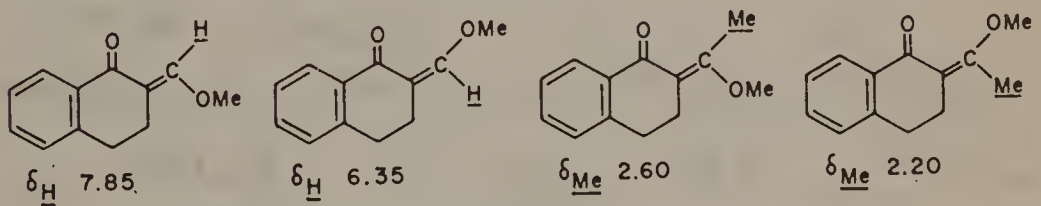


δ_{Me} 1.00 (LXVII)

δ_{Me} 0.35 (LXVIII)

Figure 8.35 Shielding effect of an aromatic ring

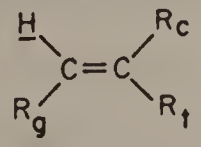
The deshielding of an olefinic proton and an allylic methyl by a cis carbonyl group is shown in Figure 8.36 which is self-explanatory (Nasipuri et al 1972). It may be noted that excepting the X-ray technique, no other method can ordinarily distinguish between these pairs of diastereomers.



δ_H 7.85 δ_H 6.35 δ_{Me} 2.60 δ_{Me} 2.20

Figure 8.36 Deshielding effect of C=O group

Pascual et al (see Pasto and Johnson 1969) have worked out an empirical equation correlating the chemical shifts of an olefinic proton in a substituted ethylene. shown in Figure 8.37 where δ_E is the chemical shift of ethylene protons (5.28 ppm) and Z_i is the $\Delta\delta$ contribution of R_g (g for geminal), R_c (c for cis), and R_t (t for trans) to be added to give the overall chemical shift (δ). The values of four substituents depending on their position are given in the Table. Using the values for Ph, the calculated chemical shifts* of the *cis*- and *trans*-stilbene are δ 7.00 and 6.53 respectively which are in good agreement with the experimental (Figure 8.34).



$$\delta = \delta_E + \sum_i z_i$$

R	gem	cis	trans
Alkyl	0.44	−0.26	−0.29
C=O	1.10	1.13	0.81
OR	1.18	−1.06	−1.28
Aryl	1.35	0.37	−0.10

Figure 8.37 Empirical correlation of chemical shifts in trisubstituted ethylenes

* Contribution of H (g, c, and t) is nil ; δ is measured in CCl_4.

In cyclohexanes, an equatorial proton appears at a slightly lower field ($\Delta\,\delta = 0.4 - 0.5$ ppm) than an axial proton due to C − C bond anisotropy which is often used to determine the relative stereochemistry of substituted cyclohexane derivatives. Thus the carbinyl proton in LXIX and LXX (Figure 8.38) resonates at δ 3.93 in the cis (e-*H*) and at 3.37 in the trans isomer (a-*H*). On the other hand, protons attached to an axially oriented carbon appear at a slightly lower field than those attached to an equatorial carbon. Thus in LXXI and LXXII, a-CH_2 and e-CH_2 resonate at δ 2.74 and 2.53 respectively. In ^{13}C-NMR, the chemical shift difference between an axially placed carbon and an equatorially placed carbon is much more pronounced (Slothers et al 1974) and so more reliable for stereochemical assignment. The axial carbon resonates at a much higher field than an equatorial one due to a γ-effect arising out of two gauche interactions with two γ-carbon atoms of the ring. The large difference in the chemical shifts in the side-chain methylene carbons in LXXI and LXXII determines their configurations unambiguously (Nasipuri et al 1979). An axial carbonyl group in a cyclohexane ring often deshields the axial 3-H and 5-H appreciably as in LXXII in which the two axial protons appear at δ 2.24 (the usual chemical shift of cyclohexane methylene

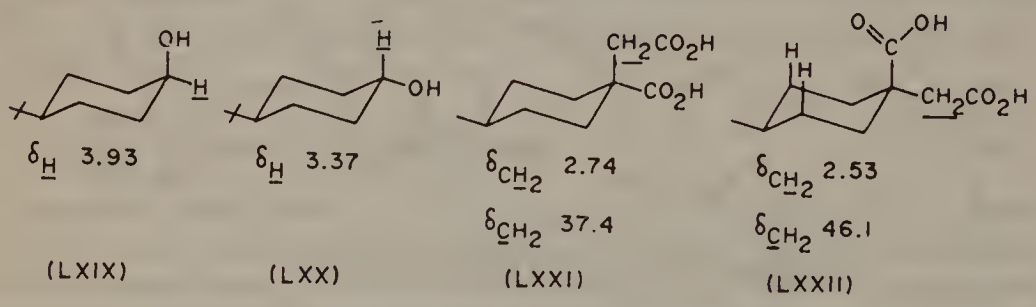


Figure 8.38 Different shieldings of axial and equatorial nuclei

protons is around δ 1.50). This observation may also be helpful for stereochemical assignment in appropriate cyclohexane system. (Nasipuri et al 1979).

2. Coupling constant and relative configuration. The coupling constant (*J*) between two protons depends on several factors : the number of bonds separating them, the nature of the neighbouring substituents, and the dihedral angle (θ) in the case of vicinal protons. The relationship between dihedral angle and J_{vic} is given by the Karplus equation, one of its simplest modification of which is shown below (see also Chapter 10):

$$J_{CH\text{-}CH} = 10\cos^2\theta$$

For θ of 0°, 60°, 90°, and 180°, the approximate values of *J* are 10, 2.5, 0, and 10 Hz respectively (*J* decreases almost linearly from about 8-10 Hz at 0° to about 0 Hz at 90° and then increases to about 10 Hz at 180°). This is illustrated for the trans and cis isomers of 4-*t*-butylcyclohexylacetate (LXXIII) and (LXXIV) in

Figure 8.39 which have vicinal H's with $\theta = 180°$ (a,a) and 60° (e,e and e,a).* Similar splitting is also observed for olefinic protons in the *Z*- and *E*-isomers. The *J* values are usually 4-12 Hz for the cis arrangement and 12-18 Hz for the trans

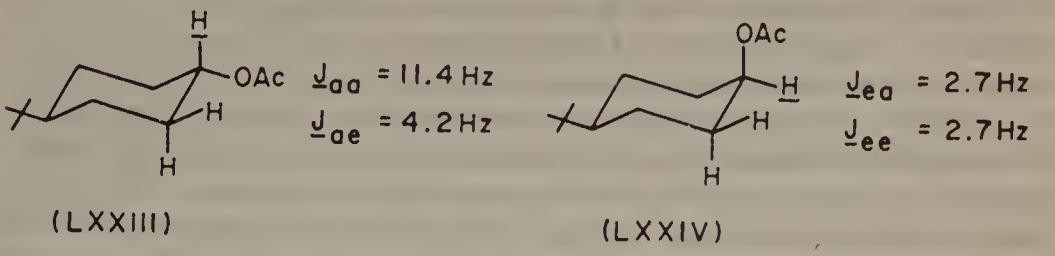


Figure 8.39 Coupling between vicinal protons in cyclohexanes

arrangement of protons with respect to the double bond (see Figure 8.40). Because of overlapping *J* values, the spectra of both the isomers must be available to reach an unambiguous conclusion.

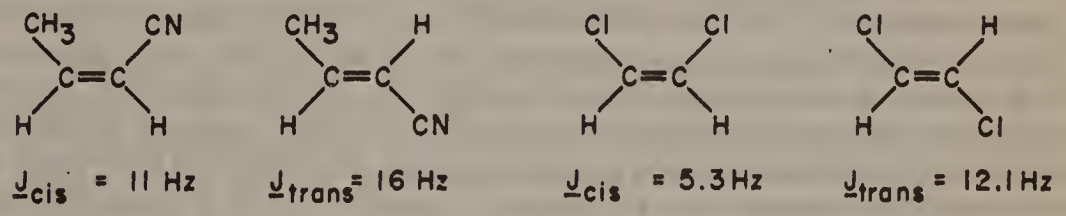


Figure 8.40 Coupling constant (J_{HH}) in *Z* and *E* isomers

In the case of acyclic diastereomers, e.g., threo and erythro, the dihedral angle does not have any fixed value because of conformational mobility. The preferred conformers of each diastereomer must be determined and the weighted average of their coupling constants may be compared (see Chapter 9). In rare cases, the diastereomers may be converted into cyclic compounds as shown in Figure 8.41;

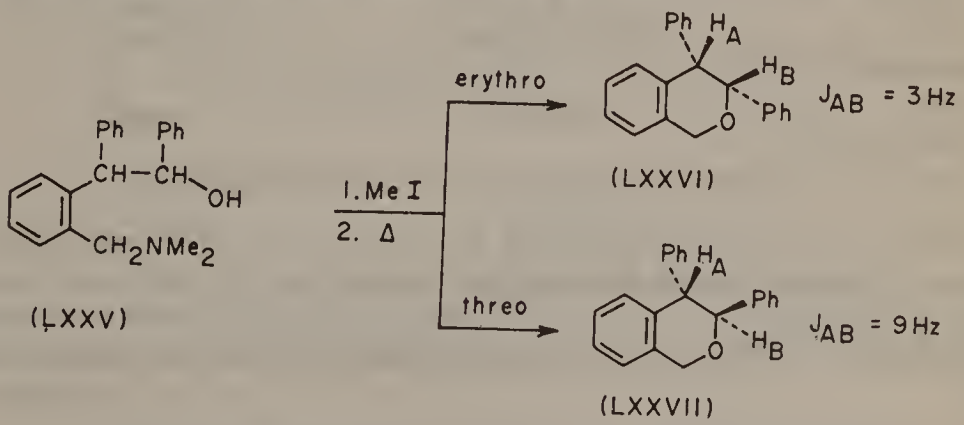


Figure 8.41 Conversion of acyclic diastereomers into cyclic diastereomers.

* J_{ae}, J_{ea}, J_{ee}, are not equal because the cyclohexane ring is a little flattened (see Chapter 10) so that $\theta_{ea}=56°$ and $\theta_{ee}=64°$; hence $J_{ee}<J_{ea}$. The J_{ea}, in the axial isomer is depressed by the antiperiplanar polar effect of the acetate oxygen.

the erythro and threo isomers of LXXV on treatment with methyl iodide followed by heat are converted into LXXVI and LXXVII respectively in which H_A and H_B have different steric disposition distinguishable by J_{AB}.

3. Nuclear Overhauser effect. If two nuclei have different chemical shifts and are close in space e.g., H_A and H_B in LXXVI (but not in LXXVII) and if the molecule is simultaneously irradiated with the radio frequency ν_A (the resonance frequency of H_A) while recording the NMR spectrum, two things happen : The peak of H_A disappears due to saturation and the peak of H_B (now an uncoupled singlet) is enhanced in intensity (10-50%) due to increased spin-spin relaxation. The technique is called double irradiation and the effect is called *nuclear Overhauser effect* (NOE). The NOE decreases rapidly with increasing distance between the two interacting nuclei and may be used to determine the relative stereochemistry in suitable compounds (Bell 1972). Thus the two chromans (LXXVI) and (LXXVII) may be distinguished by double irradiation with ν_A which would increase the peak intensity of H_B in LXXVI but not in LXXVII (H_B would be decoupled in both the cases).

4. Use of shift reagents. Some paramagnetic reagents like hexacoordinated chelate complexes of europium and praseodymium form labile molecular associates with electron-donating polar groups such as OH, C=O, and NH_2 and bring about large changes in the chemical shifts (downfield for ΔEu and upfield for ΔPr) of protons (or carbons in ^{13}C-NMR) (Hofer 1976). The shifts known as lanthanide-induced shifts (LIS) are inversely proportional to the third power of the distance of the nuclei from the lanthanide and provide a sensitive method of ascertaining the relative distance of various groups and atoms from the complexation site. One such common reagent is the dipivaloylmethanato complex (Figure 8.42). Thus when the reagent (M = Eu) is added to borneol and isoborneol respectively,

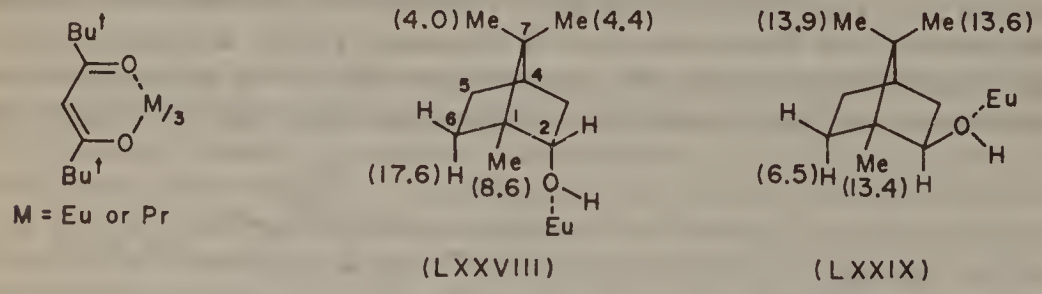


Figure 8.4.2 Shift reagents and lanthanide-induced shifts

downfield shifts are induced practically to all the protons in the molecules but more so to those near to OH. Shifts (in ppm) induced on 1-Me, 6-H, and 7-Me are shown in the Figure (for 1 : 1 molar complex) which may be used to determine the configuration. Chiral shift reagents and their uses have been discussed elsewhere.

8.5.3 Chemical methods

Two classical methods for the determination of relative configuration are based on ring-closure and ring-opening. Ring closure involving two functional groups which

are on the same side of a double bond or a ring is always more facile than when they are on opposite sides (the ring formation may not take place at all in the latter case). Ring opening always gives a product in which the two newly released functional groups are on the same side (cis) of a double bond or a second ring. The classical examples for the ring-closure method are the formation of an anhydride from maleic acid and not from fumaric acid (on drastic condition, it does form an anhydride but not of its own but of maleic acid) and the spontaneous cyclisation of coumaric acid (LXXX) to coumarin. The isomeric coumarinic acid (LXXXI) does not cyclise without first being isomerised (Figure 8.43). The conclusions are obvious.

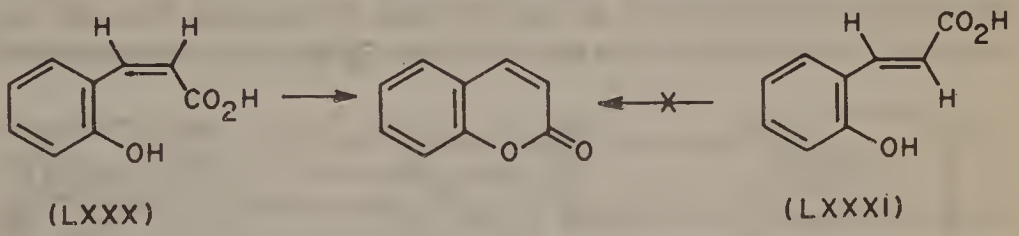


Figure 8.43 Relative configuration by ring-closure method

Only the cis isomers of 1,3- and 1,4-cyclohexanedicarboxylic acids form the anhydrides; the trans isomers do not. Both the cis and trans isomers of 1,2-cyclohexanedicarboxylic acids give their own anhydrides but the cis does so more readily. In this case, the functional groups in both the isomers are proximal (e,a and e,e). On the other hand, *cis*-cyclohexane-1,2-diol forms cyclic ketal but the *trans*-diol does not (see Chapter 10).

Benzene and *p*-benzoquinone on oxidation give maleic acid confirming its *Z*-configuration. In a more interesting example, 3,4,5-triphenyloxazole (LXXXII) (Figure 8.44) has been opened up by ozonolysis followed by hydrolysis to give the *Z* isomer of benzil monoxime (LXXXIII). This on Beckmann rearrangement gives the anilide of benzoylformic acid (A) and not the diphenylurea (B) which proves that the rearrangement involves anti migration.

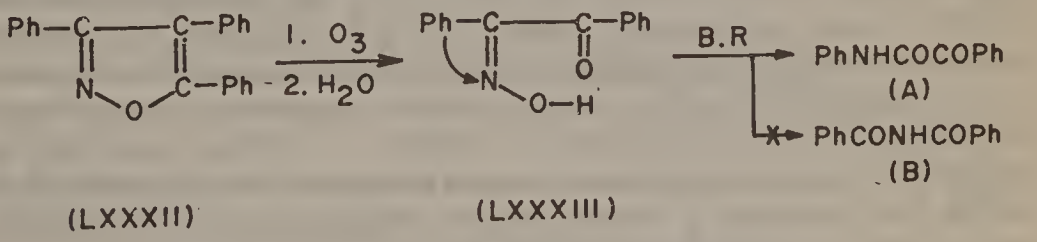


Figure 8.44 Relative configuration by ring opening method

Chemical transformations which distinguish two diastereomers will be discussed in Chapter 12.

8.5.4 Symmetry consideration

One or more members of a set of diastereomers may be meso due to the presence of reflection symmetry. In such cases, the methods of resolution may be adopted to

distinguish the active isomer (the failure to resolve does not necessarily prove that the isomer is inactive since when one method fails, another may succeed). In such cases, NMR method, particularly the application of ^{13}C-NMR is often very helpful. Thus 2,5-dimethylcyclopentane-1-carboxylic acid exists in three diastereomeric forms : two meso (meso-1 and meso-2) and one (±) (Figure 8.45). In principle, the active form is resolvable. But one can distinguish the three from their ^{13}C-NMR spectra. In the two meso forms, both the Me groups are chemically equivalent (isochronous) and so appear as a single peak of intensity two. In meso-1, the two Me and the CO_2H groups are on the same side and as a result, the methyl carbon appears at a higher field (γ effect) than in meso-2 in which the two Me and the CO_2H groups are on opposite sides. In the active form, the two Me groups are anisochronous and so give rise to two signals each of intensity one.

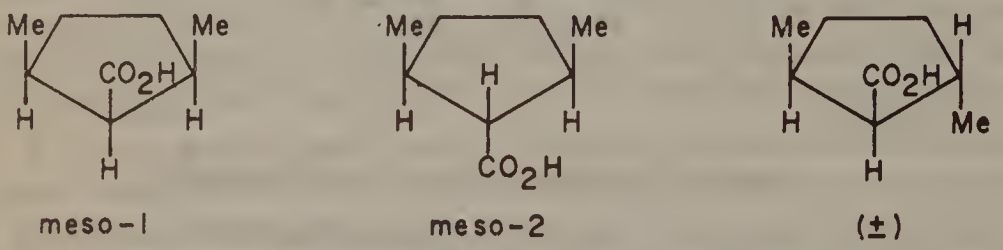


Figure 8.45 Relative configuration and symmetry

8.6 Summary

1. Three methods are available for the determination of absolute configuration of chiral molecules : method based on chiroptical properties, method based on anomalous X-ray scattering, and method based on the use of cyrstal growth as a probe. The last two methods are discussed in this chapter.

2. Once the absolute configurations of a few molecules, e.g., tartaric acid are known, a number of correlative methods may be adopted which include chemical transformations without involving the chiral centre, reactions at the chiral centre following known stereochemical course, e.g.. S_N2, NGP, S_Ni etc., correlation through diastereomers, and reactions involving change of symmetry in the products.

3. In addition, the correlative methods include comparison of optical rotations and molecular rotation differences (a number of empirical rules have been improvised). The formation of quasi-racemic compounds involving similarly constituted chiral molecules of opposite chirality (heterochiral) often provides a very simple method for correlating configurations.

4. Asymmetric synthesis using a chiral substrate helps to establish a correlation between the configuration of the newly created chiral centre and that of the existing one. Several empirical and semiempirical rules have been worked out, such as Cram's rule, Prelog's rule, and Horeau's rule which have been discussed.

5. A few methods for the correlation of configurations of molecules having axial and planar chirality such as biphenyls, allenes, and spiranes with those of centrodissymmetric molecules have been summarised.

6. Diastereomers differ in relative configuration as well as in all their physical

and chemical properties. Physical properties such as dipole moment, boiling point, refractive index, density, dissociation constant, and melting point have been employed (and several empirical rules worked out) for the determination of the relative configuration of diastereomers (cis and trans, *Z* and *E*). The application of spectral methods such as IR, Raman, UV, and mass in configurational assignment has been discussed. Special emphasis has been given on the NMR methods because of their extensive and versatile use.

7. Finally, a few chemical methods, particularly, those based on ring-closure and ring-opening have been discussed.

References

1. K. Mislow (1965) in *Introduction to Stereochemistry*, Benzamin, New York.
2. J.L. Abernethy (1972), *J. Chem. Educ.*, **49**, 455.
3. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
4. S.F. Mason (1982) in *Molecular Optical Activity and the Chiral Discrimination*, Cambridge University Press, Cambridge.
5. J.M. Bijvoet, A.F. Peerdeman, and A.J. van Bommel (1951), *Nature*, **168**, 271.
6. J.D. Dunitz (1979) in *Methods of Crystal Structure Analysis*, Cornell University Press, Ithacca, p. 143.
7. L. Addadi, Z. Berkovitch-Yellin, I. Weissobuch, M. Lahav, and L. Leiserowitz (1986) in *Topics in Stereochemistry*, vol. 16, Eds. E.L. Eliel, S.H. Wilen, and N.L. Allinger, Wiley, New York.
8. L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil., L.J.W. Shinon, M. Lahav, and L. Leiserowitz (1985), *Angew. Chem. Intl. Edn. Engl.*, **24**, 466.
9. W. Klyne and J. Buckingham (1978) in *Atlas of Stereochemistry : Absolute Configurations of Organic Molecules*, Chapman and Hall, London; also see J. Buckingham and R.A. Hill (1986) for a supplementary volume.
10. K. Freudenberg and W. Hohmann (1953), *Ann.*, **584**, 54; K. Freudenberg and W. Lwowski (1955), *Ann.*, **594**, 76.
11. R. Bentley and J.L. Popp (1987), *J. Chem. Educ.*, **64**, 15.
12. L.A. Chugaev (1898), *Chem. Ber.*, **31**, 360, 1775.
13. K. Freudenberg, F. Brauns, and H. Siegal (1923), *Chem. Ber.*, **56**, 193.
14. P. de Mayo (1959) in *Mono- and Sesquiterpenoids*, Interscience, New York.
15. I.L. Finar (1975) in *Organic Chemistry*, vol. 2, Lowpriced Edn. ELBS, Longman, London.
16. H. Gilman (Ed) (1943) in *Organic Chemistry : An Advanced Treatise*, vol. 2, Wiley, London.
17. D.H.R. Barton and W. Klyne (1948), *Chemistry & Industry*, 755.
18. J.A. Mills (1952), *J. Chem. Soc.*, 4976.
19. A. Fredga (1960), *Tetrahedron* **8**, 126.
20. W.H. Pirkle, R.L. Muntz, and I.C. Paul (1971), *J. Amer. Chem. Soc*, **93**, 2817.
21. D.J. Cram and F.A. Abd Elhafez (1952), *J. Amer. Chem. Soc.*, **74**, 5828.
22. E.L. Eliel (1983) in *Asymmetric Synthesis*, vol. 1, Ed. J.D. Morrison, Academic Press, New York.
23. N.T. Anh (1980), *Top. Curr. Chem.* **88**, 185.
24. J.D. Morrison and H. Mosher (1971) in *Asymmetric Organic Reactions*, Prentice Hall, Englewood Cliffs, New Jersey.

25. A. Horeau (1962), *Tetrahedron Letters*, 506, 965.
26. G. Krow (1970) in *Topics in Stereochemistry*, vol. 5, Eds. E.L. Eliel, and N.L. Allinger, Wiley, New York.
27. R.J.D. Evans and S.R. Landor (1965), *J. Chem. Soc.*, 2553.
28. H. Gerlach (1966), *Helv. Chim. Acta*, **49**, 1291.
29. J.H. Brewster and J.E. Privett (1966), *J. Amer. Chem. Soc.* **88**, 1419.
30. H. Gerlach (1968), *Helv. Chim. Acta,* **51**, 1587.
31. A.C. Cope and A.S. Mehta (1964), *J. Amer. Chem. Soc.* **86**, 1268.
32. H. Falk and K. Schlögl (1968), *Angew. Chem. Intl. Edn. Engl,* **7**, 383; also K. Schlögl (1967) in *Topics in Stereochemistry*', vol. 1, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
33. G.M. Kellie and F.G. Riddell (1972), *J.C.S. Chem. Commn.*, 42.
34. M.M. Green (1976) in *Topics in Stereochemistry*, vol. 9, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
35. D. Nasipuri, A. Mitra, K.K. Biswas, and D.N. Roy (1972), *Indian J. Chem.*, **10**, 897.
36. D. Pasto and R. Johnson (1969) in *Organic Structure Determination*, Prentice-Hall, Englewood Cliffs, New Jersey.
37. N.K. Wilsop and J.B. Slothers (1974) in *Topics in Stereochemistry*, vol. 8, Eds. E.L. Eliel and N.L. Allinger, Wiely, New York; also see J.B. Slothers (1972) in *Carbon-13 NMR Spectroscopy*, Academic Press, New York.
38. D. Nasipuri, S.K. Konar, S.N. Natschke, and E.L. Eliel (1979), *Indian J. Chem.,* **17B**, 127.
39. R.A. Bell and J.K. Saunders (1973) in *Topics in Stereochemistry*, vol. 7, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
40. O. Hofer (1976) in *Topics in Stereochemistry*, vol. 9, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.

Chapter 9

Conformations of Acyclic Molecules

9.1 Introduction

The discussion has so far been confined mostly to static stereochemistry in which the molecules are pictured more or less as having fixed, rigid, and time-invariable structures. In reality, all molecules exhibit intramolecular motions such as deformation of bond angles, bond stretching and compression, and rotation around one or more single bonds all of which add a temporal dimension to the molecular geometry. As a consequence, a compound is hardly expected to have a fixed geometry independent of time; instead, it exists in a dynamic equilibrium with a number of continuously changing energy-preferred conformations which differ from one another in the degree of rotation around one or more single bonds (dihedral angles) and in some cases also in bond angles and bond lengths. They are distinct molecular species separated by energy barriers and are called *conformers* (also *rotamers*) which are basically stereoisomers (Chapter 3) in as much as they differ only in the spatial disposition of atoms and groups. Although incapable of independent existence at ambient temperature, they are separable in principle, at low temperature and certainly detectable or observable by physical methods. Depending on their relative population and the energy barriers separating them, the conformers influence the physical and chemical properties of a compound. In fact, it is the discrepancy between the theoretically calculated values and experimental values of entropy and heat capacity in ethane (Pitzer 1936) that led to the prediction of their existence in the first place. A study of the physical and chemical properties of a compound in terms of various conformations of the pertinent ground states, transition states, and excited states (in the case of molecular spectroscopy) is known as *conformational analysis*. With conformational analysis, one thus passes from the realm of static stereochemistry into the realm of dynamic stereochemistry, the two branches complementing each other in modern stereochemistry.

Historically, certain aspects of conformational theory were recognised long ago by different workers. Wislicenus (1888) represented the product of addition of chlorine to crotonic acid, ($CH_3CHClCHClCO_2H$) by three different eclipsed conformations; Sachse (1890) and Mohr (1918) postulated the chair and boat conformations of cyclohexane and their interconversion; Hermans (1924) studied the influence of conformation and configuration on reaction of acyclic diols; Boeseken (1928) recognised the differential behaviour of two diastereomeric butane-2,3-diols on the conductivity of boric acid; Weissberger and Wolf (1930)

independently suggested restricted rotation around C-C bond in 1,2-dichloro-1,2-diphenylethane from the study of dipole moment; and Kohlrausch (1936) recognised two distinct types of bonds in cyclohexane from the analysis of Raman spectra. X-ray diffraction experiments on hexachlorocyclohexane indicated a chair conformation. However, it was Hassel (1943) by his electron diffraction experiments and Barton (1950) by his conformational analysis of cyclohexane stability and reactivity who laid the foundation of modern conformational theory for which they were jointly awarded the Nobel prize in 1969. Since then, there has been an exponential growth of the subject mainly in view of its tremendous importance in reaction mechanism and in understanding enzymatic behaviour and properties of macromolecules.

9.2 Molecular mechanics and conformation

The rates and equilibria of reactions are governed by three major factors : steric effects, electrostatic effects, and resonance effects, the three interacting with each other in some cases (Westheimer 1956). The calculations for determining the steric effects in a molecule are relatively easy and have been successfully used to predict the conformation and energetics of molecules in which steric effects are dominant. The overall steric strain or steric energy (E_s) of a molecule, according to molecular mechanics, may be expressed in terms of four energy functions associated with four basic structural parameters, namely, bond angle (α), bond length (l), torsion angle (θ)*, and the distance (r) between non-bonded atoms in the molecule as shown in the equation below :

$$E_s' = E(\alpha) + E(l) + E(\theta) + E(r) \qquad (1)$$

where $E(\alpha)$ is the energy due to bond angle deformation, $E(l)$ is the strain due to bond stretching and compression, $E(\theta)$ is the torsional strain, and $E(r)$ is the non-bonded interaction arising from van der Waals forces (Chapter 1).

A molecule tends to adopt the conformations which correspond to the lowest energy levels and it does so by adjusting the above four geometric parameters within certain range such that the steric strain is minimised ($E_s = E_{min}$). If the energy E_{min} for a molecule can be computed, the optimised values of α, l, θ, and r may be estimated, and the precise geometry of the molecule and its steric requirements as well as its energy in that geometry be known which in turn can be correlated with chemical equilibria and reaction rates. The functions (equation 1) are, however, only approximate and the partitioning of the overall energy among the different deformations is somewhat artificial and adopted mainly as a matter of convenience (Mislow 1965).

9.2.1 Molecular deformations and steric strain

The potential energy functions for the different types of molecular deformations are derived from classical mechanics. The bond angle bending (a scissoring

* Synonymous with dihedral angle (θ) defined in Chapter 1 but more specific (see later).

motion) and the bond stretching and compression are both vibrational motions and are governed by Hooke's quadratic laws as in equations (2) and (3) :

$$E(\alpha) = \frac{k\alpha}{2}(\alpha - \alpha_0)^2 \approx 0.04(\alpha - \alpha_0)^2 \text{ kJ mol}^{-1} \text{ degree}^{-2} \quad (2)$$

where $k\alpha$ is the bond bending force constant and α_0 is the optimal and α the actual bond angle. $E(\alpha)$ is the measure of angle strain and is approximately 0.04 kJ mol^{-1} for a 1° deformation of α from its optimal value. $E(l)$ is given by

$$E(l) = \frac{k_l}{2}(l - l_0)^2 \approx 145 \times 10^3 (l - l_0)^2 \text{ kJ mol}^{-1} \text{ nm}^{-2} \quad (3)$$

where k_l is the bond-stretching force constant, l_0 the optimal and l the actual bond length. It is a comparatively hard energy function requiring approximately 3.6 kJ mol^{-1} for a bond stretching (or compression) of 0.005 nm.

The variation of potential energy with torsion angle, on the other hand, is almost sinusoidal and is given by the following approximate equation :

$$E(\theta) = \frac{1}{2} E_0 (1 + \cos n\theta) \quad (4)$$

where E_0 is the torsional energy barrier and n the periodicity, i.e., the number of times a given conformation recurs during a complete rotation. For ethane (see Chapter 1), the energy barrier is 12.0-12.5 kJ mol^{-1} and is purely torsional in origin there being hardly any non-bonding interaction in the eclipsed conformation. This value may be used as standard when computing the torsional strain in acyclic hydrocarbons with respect to torsion around C-C single bond. For other types of bonds, different values (see Table 9.4) for the energy barrier are to be used.

The van der Waals potential function for non-bonded interactions contains two terms (equation 5) and is more difficult to evaluate since the constants A and B depend on the nature of the interacting nuclei although the van der Waals atomic radii (r) can be determined with some degree of accuracy.

$$E(r) = -\frac{A}{r6} + \frac{B}{r12} \quad \text{or} \quad -\frac{A}{r6} + B e^{-\mu r} \quad (5)$$

The first term is attractive in nature (lowers the energy) and the second term is repulsive. As a result, when two atoms approach each other in space, the interaction between them is very small but attractive at large distances, becomes increasingly attractive (due to London or dispersion forces) as the distance decreases, reaches an energy minimum at the van der Waals distance, and then becomes increasingly strongly repulsive for distances less than the sum of the van der Waals atomic radii (r). This is shown graphically by the well known Morse-type potential diagram* (Figure 9.1). It is the non-bonded interaction between two atoms within van der Waals atomic radii which is so important in organic stereochemistry and is known by different names such as steric hindrance, steric repulsion, steric compression, and non-bonded interaction. Since the energy rises very steeply with decrease of r, a molecule having atoms within touching distance tries to relieve some of the non-bonded interaction by changing other geometric

* Morse potential usually refers to bonded atoms but applies equally here.

parameters. The bond length deformation is also governed by a hard energy function and is therefore quite limited; in contrast bond angle deformation is relatively easy and occurs commonly but its effect on stereochemistry (except for small ring compounds) is not immediately apparent. On the other hand, the torsion angles undergo considerable change to accommodate any external strain and in doing so drastically affect the interatomic relationships; this is obviously very significant in stereochemistry. It is, therefore, the interplay between the torsional strain and the non-bonded interaction (both attractive and repulsive) which mainly determines the conformational behaviour of molecules. Other pertinent factors such as electrostatic forces, dipole-dipole interactions, and H-bonding will be considered later. In the following subsections, the conformations of ethane, propane, substituted propanes, and *n*-butane are discussed qualitatively in terms of torsional strain and non-bonded interaction. For quantitative treatment of molecular mechanics, reference is made to a recent book by Burkert and Allinger (1982).

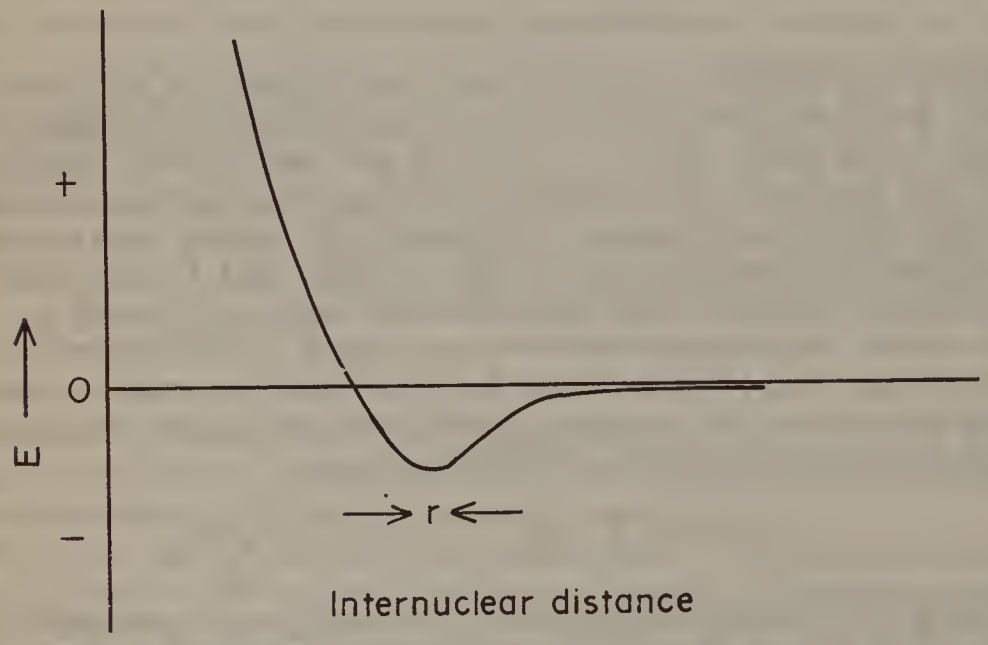


Figure 9.1 van der Waals potential energy function

9.2.2 Conformation of ethane, propane, and *n*-butane

The potential energy diagram of ethane has already been depicted in Chapter 1 There are three equivalent energy minima corresponding to the staggered conformations (E_s) and three equivalent energy maxima corresponding to the eclipsed conformation (E_e) (Figure 9.2) with torsion angles 60°, 180°, − 60° and 0°, 120°, − 120° (with respect to a fixed pair of H's at C-1 and C-2) respectively. The important cases are those in which rotation around a single bond gives rise to three (as in the case of alkanes) or two (as in the case of biphenyls) or six (as in toluene or nitromethane or acetaldehyde) energy minima (Cahn et al 1966).

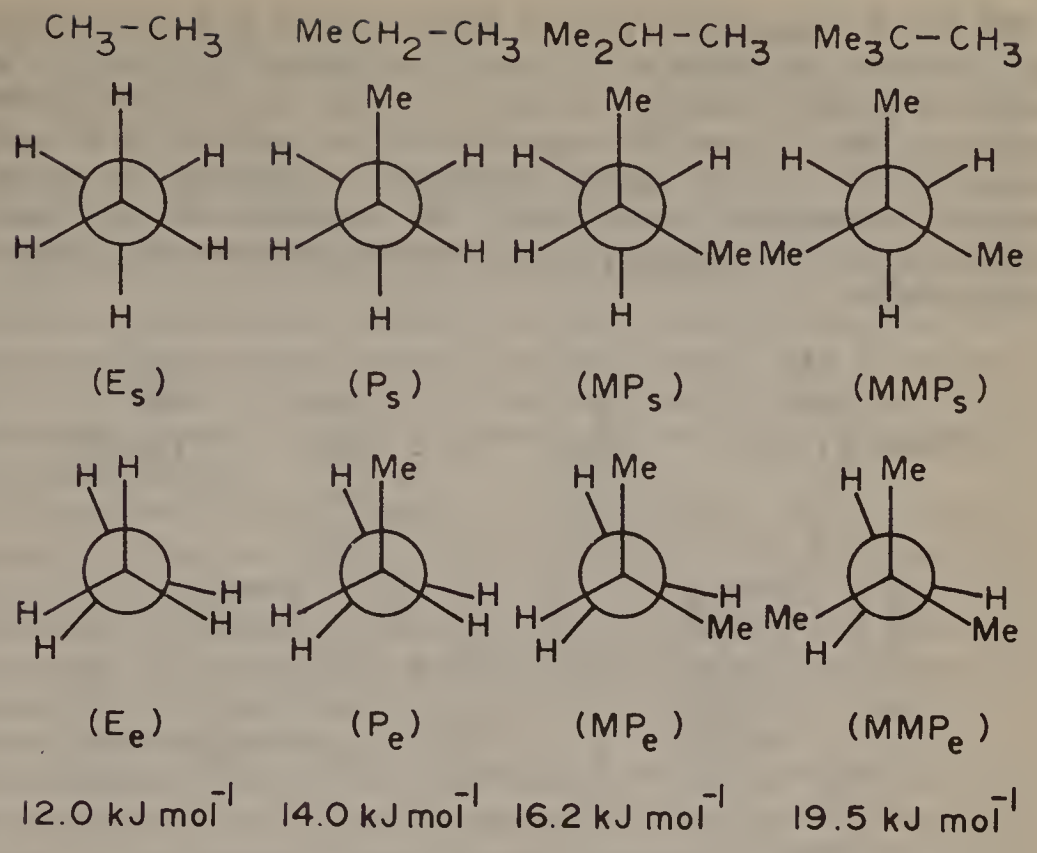


Figure 9.2 Conformations of ethane, propane, 2-methylpropane, and 2, 2-dimethylpropane

The energy barrier in ethane is 12.0-12.5 kJ mol^{-1}, approximately 4 kJ mol^{-1} per H-H eclipsing and has been said to be due to torsional (Pitzer) strain. For ethane, the distance between the pairs of eclipsed H's is 0.23 nm against the van der Waals atomic radii of 0.24 nm. The steric interaction in the eclipsing is thus trivial and at best accounts for only 10% of the total energy barrier. The origin of the major part of torsional strain is still controversial (may be due to an electronic factor). In the case of propane, the energy barrier, i.e., the difference in energies between the conformations P_e and P_s is 14.0 kJ mol^{-1}, 2.0 kJ mol^{-1}, higher than that for ethane*. Since the skew H-H and Me-H interactions (as in P_s) are generally ignored, the value of 2.0 kJ mol^{-1} is attributed to a Me-H eclipsing. In 2-methylpropane (isobutane), there are two such Me-H eclipsings and the energy barrier increases to 16.2 kJ mol^{-1}, (see MP_s and MP_e) and in 2, 2-dimethylpropane, there are three Me-H eclipsings and the energy barrier rises to 19.5 kJ mol^{-1}, (see MMP_s and MMP_e). Thus for every Me-H eclipsing there appears to be a non-bonding interaction of approximately 2.0 kJ mol^{-1}

The three conformers in each of the molecules differ by torsion angles of 120° among each other and are homomeric (periodicity = 3). In each set, they correspond to energy minima and are arbitrarily given zero potential energy.

---

*E, P, MP, and MMP stand for ethane, propane, 2-methylpropane, and 2,2-dimethylpropane and s and e for staggered and eclipsed conformations respectively in Figure 9.2.

The case of *n*-butane is more complex. Rotations around the 1-2 and 3-4 bonds give homomeric conformers as in propane (Me replaced by Et) and are not considered. Rotation around the 2-3 bond, on the other hand, gives three distinct conformers, which is typical of a large number of such molecules. In the energy diagram (Figure 9.3a), the different conformers are represented by Newman projection formula (dot indicates methyl). The conformers with their specific designations* are shown separately (Figure 9.3b). The salient features are discussed in details below.

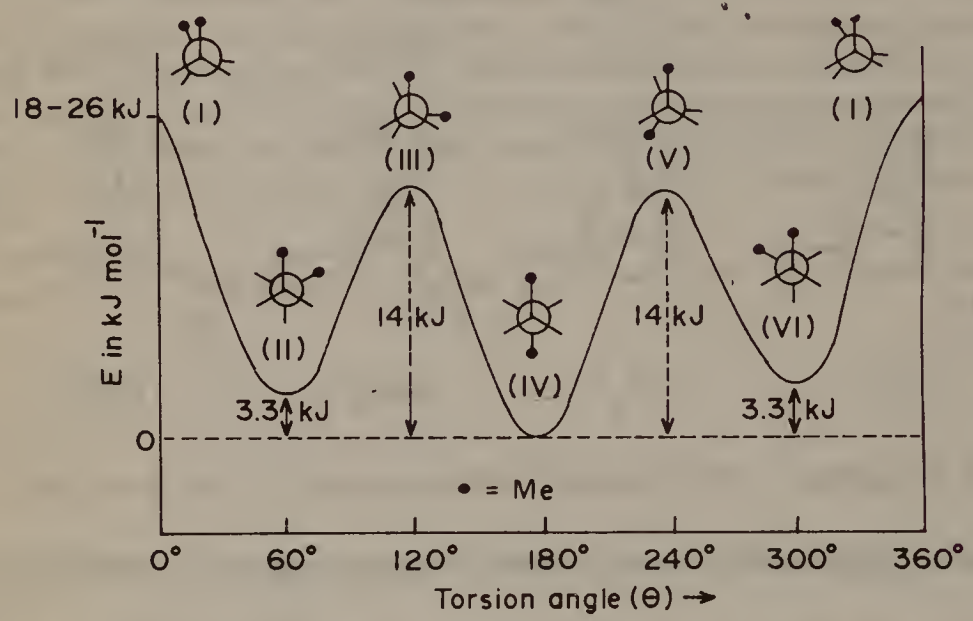
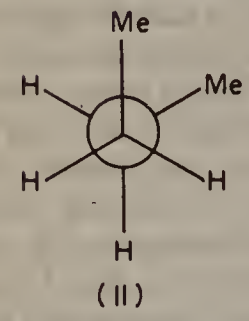
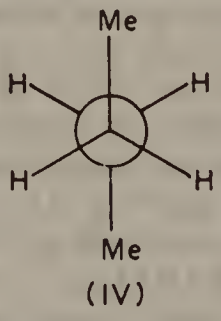
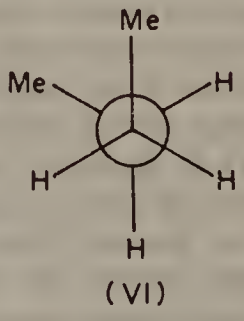


Figure 9.3a Potential energy diagram of *n*-butane

b.







1. Desgn.	P-gauche (+) sc	anti (±) ap	M-gauche (−) sc
2. Symm.	C_2 point group $\sigma = 2$ C_2 axis	C_{2h} point group $\sigma = 2$ C_2 axis, σ plane	C_2 point group $\sigma = 2$ C_2 axis

Figure 9.3b Conformers of *n*-butane

* Desgination based on torsion angles is discussed later.

1. Energy barriers: *n*-Butane exhibits a potential energy diagram with three maximum energy conformations (I), (III), and (V) of which the first with two eclipsed Me's and two pairs of eclipsed H's has predictably the highest potential energy, 18.0-26.0 kJ mol^{-1}. It has a σ plane and is achiral. The conformations (III) and (V) are non-superposable mirror images of each other having torsion angles of $+120°$ and $-120°$ respectively with an energy of 14 kJ mol^{-1}, very similar to that of an eclipsed propane. They contain a pair of Me-H and one H-H eclipsed interactions. Since non-bonded interactions increase inversely as the high power of the distance, the interactions between two large groups (L) far exceeds that between a large and a medium group (M) so that in general, L-L + S-S is greater than 2 M-S (S stands for small). The lower barrier height (14 kJ mol^{-1}) is the effective energy barrier in *n*-butane because the conformers tend to interconvert via the path of least energy.

2. Conformers: The three energy minima conformations (II), (IV), and (VI) constitute the three conformers of which the one (IV) with the two methyls oppositely placed ($\theta = 180°$) is called *anti* and is the most stable. Here torsional strain is absent and, as already pointed out, the H-H and Me-H skew interactions are very small. The potential energy of IV is arbitrarily taken as zero and those of others are calculated relative to it. It has a centre of symmetry, a C_2 axis, and a σ plane and belongs to C_{2h} point group.

The conformers (II) and (VI) with torsion angles of $+60°$ and $-60°$ respectively are non-superposable mirror images of each other and form an enantiomeric pair. They have a C_2 axis passing through the mid-point of the 2-3 bond and bisecting the dihedral angle between the two methyls and belong to C_2 point group. They are called *gauche* or *skew* conformers and their absolute configuration may be conveniently designated *P* and *M* in terms of helical chirality. They are equienergetic and have a potential energy of 3.3 kJ mol^{-1} above that of IV which is commonly known as the *butane gauche* interaction* and plays an important part in conformational analysis. In more general terms, the difference in potential energies between the most stable conformer of a molecule and a designated less stable one is called *conformational energy*. Since the torsional strain in gauche conformers is nearly zero, the gauche interaction originates from the non-bonded interaction between the two gauche methyls whose distance falls within the van der Waals group radii.

In general, the gauche interaction gets appreciable relief at the cost of some torsional strain by increase of the torsion angle by a few degrees. For example, electron diffraction experiments indicate a value of $63 \pm 8°$ for the torsion angle in gauche butane. Allinger (1974) actually put forward a hypothesis that while the non-bonded interactions between the gauche methyls can be minimised by a change of torsion angle and bond angle deformations, the H-H gauche interactions which are almost ubiquitous cannot generally be significantly reduced by any kind of molecular distortions and the origin of conformational energy both in acyclic

* The best experimental values for butane gauche interaction appear to be 2.10-2.93 kJ mol^{-1} in the liquid or solution phase and 3.68-4.2 kJ mol^{-1} in the gas phase (Rosenthal et al 1982). A recently determined value from *trans*-1,2-dimethylcyclohexane (in liquid phase) is 3.10 ± 0.38 kJ mol^{-1} (Eliel et al 1984).

and cyclic compounds might thus be traced to gauche H-H rather than gauche Me-Me interactions. The idea, however, did not gain any currency.

Any conformation intermediate between eclipsed and gauche is called *skewed* and its energy depends on its position on the potential energy diagram.

3. Population of conformers : The equilibrium population of any two conformers is given by the well known reaction isotherm (equation 6),

$$\Delta G^\circ = -RT\ln K \quad (6)$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (7)$$

where ΔG° is the free energy change in the standard state (Gibbs free energy) and is constant at a given temperature, and K (the equilibrium constant) expressed as the ratio of the more stable to the less stable conformers (ΔG° is thus negative). The standard free energy change is related to the enthalpy difference through an entropy term (equation 7). In many cases, ΔS° is small enough to be neglected, in which case the free energy change may be equated with the difference in enthalpy. In the present situation, however, the gauche conformers have a statistical advantage of 2, thus increasing the entropy by Rln2 (which may also be ascribed to an entropy of mixing of two enantiomeric gauche forms). The free energy difference is thus reduced by RTln2 which at 25° is 1.7 kJ mol^{-1} giving the value of 1.6 kJ mol^{-1} for ΔG° (with $\Delta H^\circ = 3.3$ kJ mol^{-1}). This corresponds to a population ratio of 1 : 2 for gauche and anti forms (the symmetry number for all the conformers is 2 and so is not taken into consideration). Accordingly, at room temperature, *n*-butane contains 66% of the anti (IV), 17% of *P*-gauche (II), and 17% of *M*-gauche (VI), the last two forming a racemic mixture.

As the temperature increases, the population of the less stable conformer increases and eventually becomes equal to that of the stabler conformer. On the other hand, at low temperature, the stable anti conformer prevails to a much greater extent and may become the only form detectable. At very low temperatures, the rate of interconversion is also very slow. If ΔG° exceeds 10 kJ mol^{-1}, the stabler isomer constitutes over 98% of the total at room temperature, (K = 49) and such an equilibrium is called *anancomeric* (Antenius et al 1966) or conformationally biased and the molecule constitutes an anancomeric system (see Chapter 10) even though the rate of interconversion remains facile. Table 9.1 gives the conversion of a few conformational free energies into percentage populations of the stabler isomer using equation (6).

Table 9.1 Conformational free energies and the populations of the stabler isomer at 300 K[a].

ΔG°		% of	ΔG°		% of
kJ mol^{-1}	kcal mol^{-1}	stabler isomer	kJ mol^{-1}	kcal mol^{-1}	stabler isomer
0	0	50	3.4	0.82	80
0.5	0.12	55	4.3	1.03	85
1.0	0.24	60	5.5	1.30	90
1.5	0.37	65	7.3	1.74	95
2.1	0.50	70	9.6	2.31	98
2.7	0.65	75	11.4	2.72	99

[a]For data covering a wide range of temperature, see Gordon and Ford (1972).

4. The shape of the diagram : The variation of potential energy with torsion angle is approximately sinusoidal. Vibrational spectra as well as molecular mechanics calculations prove conclusively that the energy minima conformations correspond to the staggered forms and the energy maxima to the eclipsed forms. Since the non-bonded interactions increase very rapidly inside the van der Waals distance, it might have been expected that very sharp peaks would occur as the molecule rotates towards the eclipsed conformation bringing the atoms within contact distance. However, the process is also accompanied with deformations of bond angles having a soft energy function which take place in such a manner as to lower and round off the peaks. In any case, the high energy portions of the potential diagrams are rather poorly defined (Wilson 1972) and their nature remains obscure.

9.3 Klyne-Prelog terminology for torsion angles

Torsion angles play an important part in discussions of stereochemical problems and so the terminology relating to them must be precise as far as possible. While the different terms so far used such as eclipsed (opposed), gauche (skew), anti, and skewed are quite adequate for specifying the conformations of molecules when both the atoms flanking the bond are tetrahedral, some of the terms lose their significance in describing conformations where one or both the atoms are trigonal. The torsion angle is no longer a multiple of 60° but can have intermediate values. In fact, even for the tetrahedral compounds, in most cases the torsion angles are different from the idealised values. A general and detailed method of nomenclature has been worked out by Klyne and Prelog (1960) to describe steric relationship across a single bond in a molecule or part of a molecule. The rules are discussed below.

1. Torsion angle although used interchangeably with dihedral angle has a slightly different connotation. Thus while dihedral angle is the angle between two *planes* defined by A-X-Y and X-Y-B in molecules of the type A-X-Y-B, the torsion angle is the angle subtended by A and B *across* the bond X-Y. In contrast to dihedral angle, torsion angle has a directional property, (+) when measured in a clockwise direction and (−) when measured in an anticlockwise direction starting from the front substituent A and ending at the rear substituent B. It may be measured from 0° to 360° continuously following a clockwise direction but the general practice is to express it by the smaller angle prefixed by (+) or (−). In subsequent discussions, torsion angle (θ)* will be used most of the time.

2. For specifying torsion angle, it is necessary to specify two fiducial (reference) groups one from each set of substituents across the bond and this is done according to the Conformation Selection Rule (Cahn et al 1966) which are : (*i*) If all substituents in a set are different, the sequence rule preferred group is selected.

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* Dihedral angle is usually designated by the Greek letter theta (θ) whereas torsion angle is designated by various Greek letters, e.g., τ (tau), ω (omega), ϕ (phi), and even θ. IUPAC Nomenclatrue (1974) recommends the use of θ and ω for torsion angle. In this text, θ is used in most cases both for dihedral angle and for torsion angle where the sign of the angle is not important. For ring torsion angle, however, ϕ is used following Bucourt (1974) where the signs of torsion angles are important.

(*ii*) If two in a set are identical, the non-identical group is chosen irrespective of the sequence rule. (*iii*) If all the substituents in a set are identical, that which makes the smallest torsion angle is chosen.

3. The fiducial group at the front atom is preferably placed at the top of the Newman projection formula and the torsion angle is described in terms of three pairs of self-explanatory designations : (*i*) (+) and (−) for a rotation of 0° to 180° in clockwise and anticlockwise directions respectively; (*ii*) syn for a value of 0°-90° and anti for a value of 90°-180° in both directions; and (*iii*) periplanar meaning approximately planar and clinal meaning inclined. The conformations bear the designation of the torsion angle expressed within ±30°. Six such combinations for *n*-butane type of molecules are possible and they are listed in Table 9.2 along with the current nomenclature. The sign of torsion angle in any conformation remains unchanged whether the molecule is viewed from the fornt or from the rear; in the first case, it is measured from A to B and in the second, from B to A, A and B being the two fiducial groups.

Table 9.2 Designations of conformations based on torsion angle

Torsion angle (θ)	Designation	Symbol	Reference to *n*-butane	θ as a multiple of 60°
0° ± 30°	± syn-periplanar	± sp	eclipsed (I)	0
+ 60° ± 30°	+ syn-clinal	+ sc	gauche (II), P	1
+ 120° ± 30°	+ anti-clinal	+ ac	eclipsed (III)	2
180° ± 30°	± anti-periplanar	± ap	anti (IV)	3
− 120° ± 30°	− anti-clinal	− ac	eclipsed (V)	4
− 60° ± 30°	− syn-clinal	− sc	gauche (VI), M	5

The advantages of this system are : The torsion angles are expressed within a range, which is more realistic since often their exact values are not known; the (+) and (−) signs immediately show the direction of a torsion angle; it is applicable to any molecule or a part of a molecule typified by a segment A-X-Y-B whether X and Y are tetrahedral or other than tetrahedral; and finally, it may be used with advantage to describe partial conformation of polymer chains and ring compounds. A few illustrations of different types are given in Figure 9.4.

meso-1,2-Dichloro-1,2-diphenylethane (stilbene dichloride) exists in three conformers (VIIa), (VIIb), and (VIIc) (Figure 9.4a) which have torsion angles of 180°, − 60°, and + 60° (the fiducial groups are the *Cl* atoms) and are designated (±) ap, (−) sc, and (+) sc respectively. Of the three, (±) ap is the most stable conformer, the bulky phenyl groups being anti (see discussion on dipole moment). Similarly, the (1*S*,2*S*) enantiomer of the optically active form exists in three conformers (VIIIa), (VIIIb), and (VIIIc) which are designated (−) sc, (+) sc and (±) ap respectively. Here probably the conformer (VIIIb) is more stable (see Eliel and Brunet 1986 for conformational analysis of stilbene dibromides).

Propionaldehyde is an example in which the rotation to be considered is around an sp^3-sp^2 bond. It exists in three conformations in each of which either H or Me is

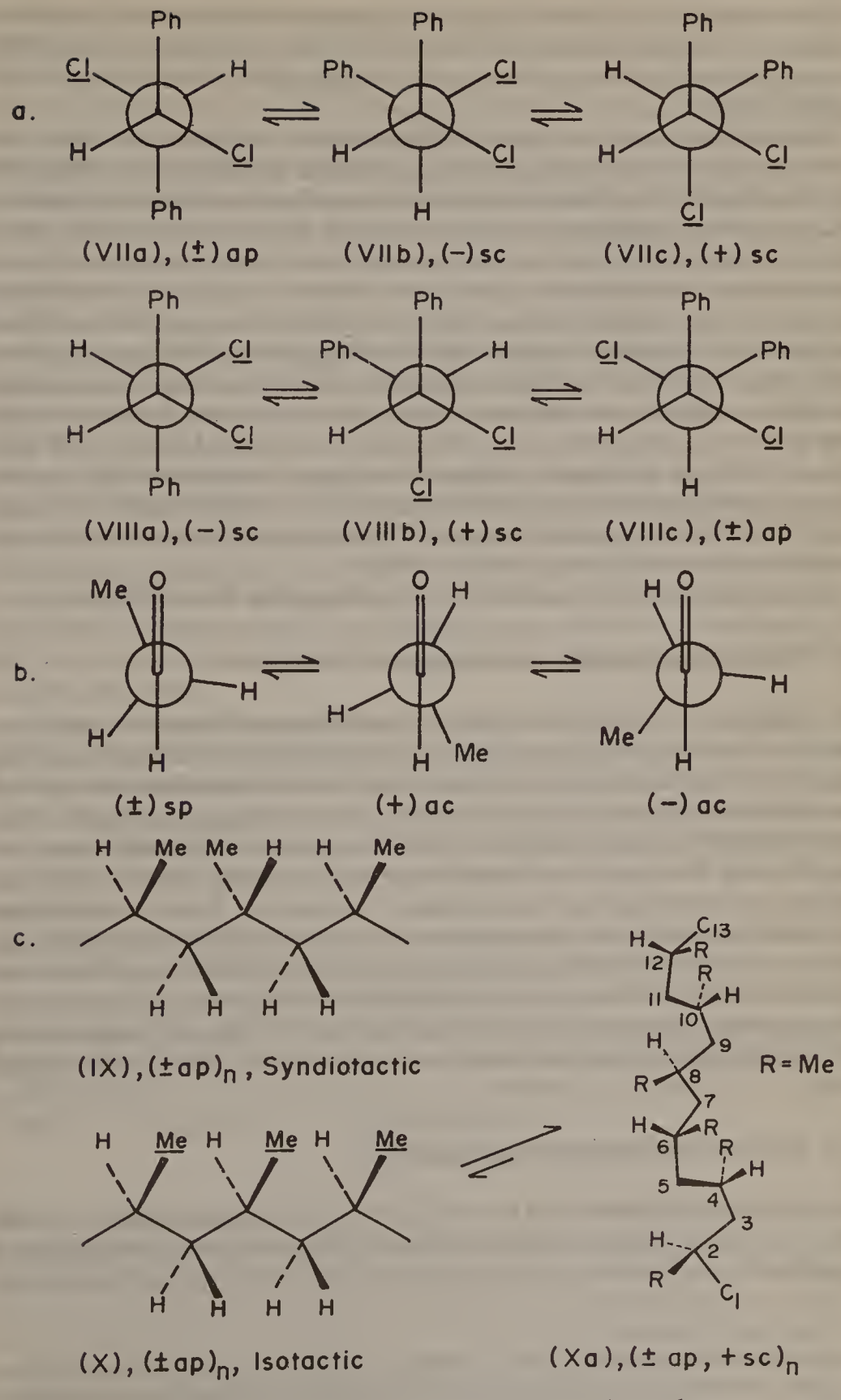

Figure 9.4 Klyne-Prelog nomenclature for torsion angles

eclipsed with the C = O bond*. The fiducial groups are oxygen and Me and the designations of the three conformers (Figure 9.4b) from left to right are respectively (±) sp, (+) ac, and (−) ac with torsion angles of 0°, + 120°, and −120° approximately.

Polypropylene forms two types of linear chains, syndiotactic in which the consecutive chiral centres have opposite chirality and isotactic in which they have the same chirality. The former exists layered in an all antiperiplanar conformation (IX, Figure 9.4c), represented by $(\pm \text{ ap})_n$ or $(180°)_n$, the C-C bonds in the chain serving as the fiducial groups. The isotactic chain when represented by all antiperiplanar conformation (X) incurs severe non-bonded interactions among the syn methyl groups which is avoided by assuming a helical conformation in which the torsion angles alternate between 180° and + 60° or 180° and − 60° as one proceeds along the chain; the former arrangement constitutes an *M* helix and the latter a *P* helix. An approximate diagram of the *M* helix is shown in the structure (Xa) which may be designated $(180°, + 60°)_n$ or $(\pm \text{ ap}, + \text{ sc})_n$. In the diagram, the torsion angles are successively 180° (around C_2-C_3), + 60° (around C_3-C_4), 180° (around C_4-C_5), + 60° (around C_5-C_6), and so on. The C_7 is the translational repeat of C_1, C_8 of C_2 etc., three monomeric units making a complete 360° turn (Goodman 1967).

Torsion angles in cyclic compounds will be discussed in the next chapter.

9.4 Physical methods for conformational analysis

The properties of a compound exhibiting conformational isomerism cannot be defined on the basis of any single rigid structure. Instead, they are determined by the nature of the contributing conformers, their relative populations (which in turn are determined by their enthalpy, entropy, and free energy), and finally, their kinetic stability (which is decided by the energy barrier separating them). Information on these points is available from many sources: study of pertinent physical properties such as thermodynamic parameters, dipole moments, and chiroptical properties; instrumental methods based on diffraction experiments and spectroscopy; and study of chemical properties including chemical equilibrium and chemical kinetics. In this section, the discussion will be mainly confined to the conformational information derived from the study of physical properties and instrumental methods (see also Wyn-Jones and Pethrick 1969, Orville-Thomas 1974).

9.4.1 Physical and thermodynamic properties

Thermodynamic properties such as enthalpy, entropy, and heat capacity, physical properties such as densities, refractive indices, and dipole moments, and chiroptical properties (in the case of chiral molecules) are influenced by conformation in a

*Actually, a set of three and a set of two substituents should lead to $3 \times 2 = 6$ energy minima. However, only conformations with H or Me groups eclipsed with C=O correspond to low-energy.

predictable manner and their measurements serve as good probe for conformational analysis.

1. Thermodynamic method. A classical method for conformational study (very rarely done these days) is to determine experimentally the various thermodynamic parameters of a compound calorimetrically and compare them with the theoretically calculated values. The calculations require spectroscopic assignment of all vibrational frequencies except the torsional ones, a knowledge of the moments of inertia of the molecule as a whole, and also the moments of the oscillating groups about the torsional axis. The difference between the experimental and the calculated values serves to determine the energy barriers. Thus in ethane, the discrepancy between the calorimetric and spectroscopic entropy led to the prediction of an energy barrier of 12.0 kJ mol^{-1}. The method is best suited for molecules with relatively low energy barriers ($\approx$ 20 kJ mol^{-1}) and the results are in good agreement with those derived from microwave spectroscopy (Aston and Fritz 1959; Millen 1962).

The calorimetric method also provides valuable information on the relative stability of configurational isomers from heat of combustion data (rarely applicable to rapidly interconvertible conformers). Thus the heats of combustion of cycloalkanes give a quantitative idea of ring strain. The method has also been used to measure the difference in enthalpy between a cyclohexane chair and a cyclohexane boat conformer (Chapter 10). It has helped to assign the correct configuration as well as the correct conformation to *cis*- and *trans*-1, 3-dimethylcyclohexanes (see conformational rule).

Another thermodynamic method commonly used is to establish an equilibrium between two diastereomers through chemical means. The ratio of the two diastereomers in the equilibrium mixture can be accurately determined by gas chromatography or by spectroscopic method. The free energy difference ($\Delta G°$) can then be calculated from equation 6. The other thermodynamical parameters such as enthalpy and entropy changes can be computed from the value of K at different temperatures.

2. Dipole moment. Dipole moment measurements have been used for structural determination over a long period (Sutton 1955). The dipole moment is a vector quantity and if the moments of the individual groups in a molecule are known, the molecular geometry may be ascertained from the measurement of the overall dipole moment. In the case of a compound showing conformational isomerism, the dipole moment (μ) of the molecule (experimental) is related to the dipole moments of the conformers by the following equation :

$$\mu^2 = n_a\mu_a^2 + n_g\mu_g^2 \text{ (for two conformers)} \qquad (8)$$

where n_a and n_g are the mole fractions of the two conformers (anti and gauche or any such pair) and μ_a and μ_g are the dipole moments of the conformers. Thus 1,2-dichloroethane ($ClCH_2-CH_2Cl$) exists in anti and gauche forms. The dipole moment of the anti form is assumed to be zero (it may actually have a small amount due to libration) since the two C-Cl dipoles are oppositely directed, but that of the gauche has a value of approximately 3.2 D (calculated with reference to ethyl chloride). 1,2-Dichloroethane in the gaseous state at 22° has a dipole

moment of 1.12 D corresponding to 88% of the anti and 12% of the gauche conformers (equation 8). Examples from the cyclic system will be given in the next chapter.

Dipole moment measurements of diastereomers often provide valuable information regarding their relative configuration as well as the preferred conformation. Thus *meso*-1,2-dichloro-1,2-diphenylethane has a dipole moment of 1.27 D while that of the optically active form is 2.77 D which is considerably higher. The preferred conformation for the meso form is evidently the (±) ap (VIIa) (Figure 9.4a) with the pairs of Ph and Cl oppositely placed so that the dipole moment is relatively low. The active isomer is mostly a mixture of two conformers (VIIIa) and (VIIIb) both with the two Cl gauche. The overall dipole moment is thus considerably higher. The relative contribution of the conformers in each isomer may be determined in theory from the calculated dipole moment of each conformer.

3. Study of some common bulk properties. The correlation of some common physical properties such as boiling point, density, and refractive index with molecular geometry has already been discussed and a number of rules, namely, von Auwers-Skita rule, (or conformational rule) and van Arkel rule have been formulated. Other physical properties such as Kerr constants, pK values, polarographic reducibilities, acoustic relaxation etc. have also been used for conformational analysis (Eliel et al 1965)*. The chiroptical properties of the chiral molecules will be discussed in a subsequent chapter (Chapter 15).

9.4.2 Spectroscopic methods

Different diffraction and spectroscopic techniques can identify the conformers as distinct rigid species and thus provide more precise information on their geometry and also on the thermodynamic and kinetic parameters concerning their interconversion. Because of the low energy barriers, the average life period of most conformers is very short. For an energy barrier of 20 kJ mol^{-1}, the rate of interconversion (k) as calculated from the Eyring equation (see below) is approximately 10^9 sec^{-1} at room temperature. In the equation,

$$k = \underline{K}\,(k_B T/h)e^{-\Delta G^{\ddagger}/RT} = \frac{RT}{Nh}\,e^{-\Delta G^{\ddagger}/RT} \qquad (9)$$

K is the transmission coefficient (often assumed to be unity), k_B the Boltzmann constant, h the Planck constant, N the Avogadro's number, $\Delta G^{\ddagger}$ the activation energy, R the gas constant, and T the temperature in degrees Kelvin. In order to *see* the conformers as rigid molecular species, the time scale of observation provided by a particular instrumental technique must be commensurate with the rate of interconversion of the system under observation and the concentration of each species must be high enough for the instrumental sensitivity. In Table 9.3, the time scales (time constants) for some of the instrumental methods are given (Muetterties 1965, Bassindale 1984).

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*For conformational change associated with electrode reactions, see D.H. Evans and K.M. O'Connell (1986) in *Electro Analytical Chemistry*, Ed. A. Bard, vol.14, p.113, Marcel Dekker, New York.

Table 9.3 Time scale of some diffraction and spectroscopic techniques

Technique	Time scale, sec.$^{-1}$	Technique	Time scale, sec^{-1}
Electron diffraction	10^{-20}	Visible	10^{-14}
Neutron diffraction[a]	10^{-18}	IR-Raman	10^{-14}
X-ray diffraction[a]	10^{-18}	Microwave spectroscopy	10^{-10}
UV spectroscopy	10^{-15}	NMR[b]	10^{-1}-10^{-9}

[a] The methods are applicable to solid and not really comparable with others.
[b] Time scale sensitivity depends on the system under investigation and temperature.

As evident from the data in Table 9.3, the time scale of all the techniques (except NMR) mentioned above compares favourably with the rate of interconversion of ground state conformers. The techniques are briefly discussed below.

1. X-ray diffraction. The X-ray diffraction of a compound gives the complete structure showing all the interatomic distances, bond angles, and conformational details very accurately (Robertson 1955). The drawback of the method is that compounds can be examined only in the crystalline state (*good crystals*). Organic chemists deal with compounds in liquid state or in solution and the information derived from X-ray experiments is thus of limited application. Moreover, in the solid state, a compound usually exists exclusively in its most stable conformation, e.g., anti form in 1,2-dichloroethane. Only in rare cases, isomorphous crystals are obtained (as for $Br_2CH\text{-}CHBr_2$) consisting of either of the anti and gauche conformers in the lattice so that geometric parameters of both the forms are available.

X-ray diffraction technique is frequently used to study the existence of boat or twist form and any other abnormality in a compound. The geometry of medium ring compounds such as derivatives of cyclononane, cyclodecane, cyclododecane etc. has been studied by X-ray diffraction (Chapter 10).

2. Electron diffraction. It is the electron diffraction (ED) experiments by Hassel and his school which first confirmed the chair conformation of cyclohexane. Like X-ray diffraction, ED gives the complete structure of a conformer but in the gaseous state. For a compound showing conformational isomerism, a set of interatomic distances for each conformer may be available so that the geometry as well as the relative population of the conformers (and hence the conformational free energy) can be inferred. The technique is limited to small molecules and gives information only in the gaseous state where intermolecular forces are absent and the results may, therefore, be different from those in the condensed state.

3. Neutron diffraction. Neutron diffraction (ND) has been used to determine the energy barrier of some simple molecules which may not be amenable to IR and Raman spectral analysis due to forbidden transition. Neutrons with very small energy when collide with a conformer in the first torsional excited state take up the extra energy and move with slightly enhanced speed which can be detected and used to determine the barrier height. The usual ND technique, however, applies to

solid and is complementary to X-ray diffraction but locates H's which X-ray does not do well at all.

4. Infrared and Raman spectroscopy. Infrared (IR) and Raman spectra are obtained when transition takes place in molecules from a ground vibrational or rotational state to a higher excited state by absorption of electromagnetic radiation in the frequency region, 25 - 4000 cm^{-1}. The requirements for IR and Raman spectroscopy are slightly different. For IR spectra, the dipole moment of the vibrating system must be different in the ground and the excited states while for Raman spectra, polarisation must change in going from one state to the other. In some respects, the two vibrational spectroscopies are thus complementary to each other. The spectra can be obtained in the gaseous, liquid, or solid state.

IR and Raman spectra can be analysed for molecules from the symmetry class to which they belong and the total structures (for simple molecules) can be determined. A non-linear molecule containing n atoms gives a maximum number of 3n−6 fundamental frequencies. Therefore, if a simple molecule like 1,2-dibromoethane ($BrCH_2$-CH_2Br) shows more than the expected lines, a mixture of conformers is indicated and the relative intensities of the lines give their approximate population. Thus in the solid state, dibromoethane shows lines characteristic of the anti conformer only. As it is converted into liquid, lines appear for the gauche conformer as well. A careful analysis of the two superposed spectra at different temperatures provides information regarding internal rotation of the molecule (Mizushima 1954).

In the case of complex molecules, the usual practice is to utilise the characteristic bands of certain groups such as C-X (X = halogen, OH, O-COR etc.) provided that the vibrational frequencies of the C-X bond in the two conformers (say anti and gauche) are sufficiently different (this is usually true for equatorial and axial C-X bonds). If the mole fractions of the two conformers are n_a and n_g respectively, the equilibrium constant K is given by the equation.

$$K = \frac{n_g}{n_a} = \frac{A_g \alpha_a}{A_a \alpha_g} \qquad (10)$$

where A_g and A_a are the measured extinctions (intensities of lines) and α_g and α_a are the molar extinction coefficients of the two conformers, gauche and anti. The values of molar extinction coefficients of conformers, however, are generally not known. In the case of cyclic systems, rigid or conformationally biased molecules may be taken as reference, their extinction coefficients being used for the mobile conformers. One way of getting around the difficulty is to measure the extinctions at different temperatures and to use van't Hoff equation according to which

$$\frac{\Delta H^\circ}{R}\left[\frac{1}{T_1} - \frac{1}{T_2}\right] = \ln\frac{K_2}{K_1}; \quad K_1, K_2 \text{ being equilm. constants at } T_1, T_2$$

$$= \ln\left[\frac{A_a}{A_g}\right]_{T_2} - \ln\left[\frac{A_a}{A_g}\right]_{T_1} \qquad (11)$$

In equation (11), the terms involving the molar extinction coefficients are eliminated and ΔH° can be determined from the ratio of the two extinctions at two different

temperatures (K_1 and K_2 being the equilibrium constants at T_1 and T_2 in Kelvin respectively). A graphical method can also be employed using data at several temperatures.

Intramolecular H-bonding plays a very important part in conformational preference. Since the average energy of a H-bond is around 8.0-20.0 kJ mol^{-1} (Chapter 1), it frequently dominates over the other factors when it occurs. IR spectroscopy can clearly distinguish between the H-bonded O-H and non-H-bonded O-H frequencies. Thus the intramolecularly H-bonded O-H frequency appears at lower region around 3590 cm^{-1} and the non-H-bonded O-H frequency, around 3630 cm^{-1} ($\Delta\nu \simeq 40$ cm^{-1}). If a compound contains two conformers one capable of forming H-bond (-O-H··X) and the other not, they can be distinguished by IR. The strength of the H-bond is indicated by $\Delta\nu$; the higher the value, the stronger is the H-bond. This value provides additional information as regards the structure of the conformers and will be illustrated in due course.

5. Microwave spectroscopy. Microwave spectroscopy (range $\nu = 10 - 10^{-1}$ cm^{-1}) is concerned with the transitions between rotational states arising out of molecular collisions. The spectrum of a compound consisting of two or more conformers gives torsional frequencies of each individual conformer the analysis of which gives information regarding the structures, the torsion angle, dipole moment, barrier to internal rotation etc. (Wilson 1972). The barrier heights are measured by two techniques: a frequency method applicable to low-energy barriers but extremely sensitive and an intensity method less accurate but applicable to relatively high energy barrier. The two techniques are thus complementary to each other.

Microwave spectroscopy gives complete structural data but is applicable only for simple molecules with relatively high vapour pressure. The compounds must have some dipole moment even if it is as low as in propane. The barrier energies to internal rotation of some typical molecules as determined by microwave spectroscopy are listed in Table 9.4 (see also Lowe 1968). A few data available from thermodynamic methods are also incorporated for comparison.

6. Ultraviolet spectroscopy. Ultraviolet (UV) absorption spectroscopy may be used for conformational analysis in cases where the compound under consideration contains a chromophore capable of interacting electronically with an adjacent group in a particular conformation. This happens in cyclohexanone derivatives with an α-substituted halogen (or a similar electron acceptor group) in axial disposition where the antibonding π^* carbon orbital of the carbonyl function containing an electron in the excited state overlaps with a vacant orbital (usually 3s) of the electronegative group (see Chapter 10). This leads to a bathochromic shift in the axial conformer.

The n-π^* transition (leading to weak absorption) in a carbonyl moiety or other similar chromophore in a chiral molecule is asymmetrically perturbed and used in optical rotatory dispersion and circular dichroism measurement for configurational correlation (Chapter 15).

In conjugated systems such as biphenyls and analogues, both the absorption maxima and extinction coefficients are affected in a predictable fashion as the molecules are twisted around the pivotal bonds (Chapter 5) from a planar to a

Table 9.4 Barriers to internal rotation

Molecules	Barrier energy(microwave)		Barrier energy (thermodynamic)	
	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}
CH_3-CH_3	-	-	11.3-12.5	2.7-3.0
CH_3-CH_2F	13.8	3.3	-	-
CH_3-CHF_2	13.3	3.18	-	-
CH_3-CH_2Cl	14.9	3.57	11.3-19.6	2.7-4.7
CH_3-CH_2Br	14.9	3.57	-	-
CH_3-CH_2I	13.5	3.33	-	-
CH_3-OH	4.5	1.07	6.7	1.6
CH_3-O-CH_3	10.5	2.50	-	-
CH_3-SH	5.3	1.26	6.3	1.5
CH_3-NH_2	8.1	1.94	7.9	1.9
CH_3-CHO	4.8	1.15	4.2	1.0
CH_3-CO_2Me	4.8	1.17	-	-
CH_3-$CH=CH_2$	8.3	1.98	8.15	1.95
CH_3-SiH_3	7.1	1.70	-	-
CH_3-NO_2	0.025	0.006	-	-

(Adapted from E.B. Wilson in Advances in Chemical Physics, Interscience, New York, 1959, Vol.II, p. 370).

non-planar conformation. Thus the UV spectra of simple biphenyl and 2,2′-dimethylbiphenyl show λ_{max} 240 nm (ϵ 19,000) and 224 nm (ϵ 700) respectively. The hypsochromic shift and the lowering of extinction coefficient in the latter are due to steric inhibition of resonance indicating non-planar conformation.

7. Nuclear magnetic resonance spectroscopy. NMR has proved to be one of the most powerful techniques for conformational analysis and may be conveniently used either at room temperature or at low temperature depending on the system but requires barrier above 20 kJ mol^{-1} to be useful (unless one uses indirect methods - average J or δ values). Some of the applications of NMR have already been discussed in connection with configurational assignments (Chapter 8). In a conformational equilibrium, the molecules are constantly changing their shape without affecting the overall concentrations of the conformers at any moment. The question arises whether NMR can 'see' conformers as discrete species or as time-averaged non-rigid structures. This depends on the rate of interconversion and the time scale of observation which for NMR is decided by the substrate under consideration. The following equilibrium may be considered in which the two exchanging species contain only one observable proton with chemical shifts of ν_A and ν_B and coupling constants of J_A and J_B respectively (coupling may be due to any other nucleus in the species). The inverse of $\Delta\nu_{AB}$ gives a measure of the NMR time scale and if the rate constant (k) of the process is of similar order of magnitude as $\Delta\nu_{AB}$, typically 10^{-1} to 10^5 sec^{-1} (Binsch 1968), the system is amenable to NMR study (^{13}C-NMR permits a wider range) and precise information regarding the thermodynamic parameters of the rate process may be available from NMR. Molecules with an internal barrier energy of 20-100 kJ mol^{-1} are

ideally suited for this purpose; below this, the problem can be tackled efficiently by microwave spectroscopy and above this, the exchanging species are separable and their interconversion can be studied by classical methods. Three different situations may arise depending on the exchange rate and the NMR time scale available:

$$AH_A \rightleftharpoons BH_B$$

(*i*) The exchange rate is slow on the NMR time scale in which case the spectrum is a superposition of two independent spectra, one of AH_A and the other of BH_B, with their characteristic chemical shifts and coupling constants. The relative intensities of ν_A and ν_B peaks give the ratio of the two exchanging species and hence the conformational free energy at the temperature of observation. In this case, the average life of the species (τ) is much higher than $1/\Delta\nu_{AB}$.

(*ii*) The exchange rate is fast on the NMR time scale (τ is shorter than $1/\Delta\nu_{AB}$) in which case, the conformers (exchanging species) are seen as non-discrete species with intermediate structures and the chemical shifts and coupling constants are the weighted average of their values in AH_A and BH_B. The chemical shift (ν) and the coupling constant (J) in the spectrum are given by the following equations where n_A and n_B represent the mole fractions of the two exchanging species. If ν_A and ν_B are known, the relative population and the conformational free energy can be determined from the measurement of ν since $n_A + n_B = 1$. Two methods are generally used to obtain these values: taking the spectra of rigid model compounds in which two protons are in similar environments as in AH_A and BH_B; or taking the spectrum at very low temperature so that the exchange rate is slow on the NMR time scale and individual values of chemical shifts can be seen (see Chapter 10).

$$\nu = n_A \nu_A + n_B \nu_B$$

$$J = n_A J_A + n_B J_B$$

$$\text{(In general, } \nu = \sum_i n_i \nu_i \text{ and } J = \sum_i n_i J_i$$

(*iii*) The exchange rate is comparable with the NMR time scale (τ and $1/\Delta\nu_{AB}$ are of similar order of magnitude) in which case, a broad ill-defined spectrum is generally obtained. The shape of the spectrum changes significantly with temperature and the kinetic parameters are obtained by a complete line shape analysis as a function of temperature (Binsch 1968).* A simple and common practice is to measure $\Delta\nu_{AB}$ from a spectrum at sufficiently low temperature and then to find out the coalescence temperature, T_c, i.e., the temperature at which the two peaks just coalesce to a broad singlet. Below this, the peak is resolved and above this, the peak becomes sharper. The exchange rate (k_c) at the coalescence temperature can be calculated from equation (12) or (13) which when combined with Eyring equation (9) gives the value of $\Delta G_c^{\ddagger}$ at T_c.

In the absence of any spin-spin coupling, equation (12) is used and equation (14) gives the free energy of activation. In the case of analysis of a spectrum in which the protons in question show geminal coupling (such geminal non-equivalence

*This technique is known as dynamic nuclear magnetic resonance (D-NMR)

$$k_c = \frac{1}{2}\pi\sqrt{2}\,\Delta\nu_{AB} \tag{12}$$

$$\text{or}\quad k_c = \pi\left[(\Delta\nu_{AB}^2 + 6J_{AB}^2)/2\right]^{\frac{1}{2}} \tag{13}$$

$$\Delta G_c^{\ddagger} = RT_c\,(23.7 + 2.3\log T_c/\Delta\nu_{AB}) \tag{14}$$

$$\text{or}\quad \Delta G_c^{\ddagger} = RT_c\,(23.7 + 2.3\log T_c/k_c) \tag{15}$$

arises due to lack of symmetry which in turn may arise from restricted rotation), the exchange rate, k_c is given by equation (13), the values of ν_{AB} and J_{AB} being determined by the positions of the peaks in the AB-quartet (for some simple systems, see Nasipuri et al 1977). $\Delta G^{\ddagger}$ is then obtained from equation (15)*. The topic has been reviewed (Oki 1984).

The technique is equally applicable to ^{13}C-NMR with the added advantage that $\Delta\nu$ is very much larger (sometimes by a factor of 10) so that species with faster exchange rate may be studied. Two examples from acyclic molecules (Abraham and Loftus 1979) are discussed here. 2,2,3,3-Tetrachlorobutane exists in three conformers: anti (XIa), *P*-gauche (XIb), and *M*-gauche (XIc) (Figure 9.5). The last two are enantiomeric and so have identical NMR spectra. In both the anti and gauche conformers, the two methyl groups are isochronous for reason of symmetry (C_2 axis). In the anti form, they are flanked by two chlorine atoms and so are slightly more deshielded than their counterparts in the gauche forms. At $-50°$C, the two methyl signals are well-separated ($\Delta\nu = 4.2$ Hz at 60 MHz) and their relative intensity (the downfield peak is more intense) gives a value of 0.7 kJ mol^{-1} for the conformational free energy; i.e., $\Delta G_g - \Delta G_a = 0.7$ kJ mol^{-1}. The two peaks coalesce at $-30°$ to a broad singlet and the application of equation (13) gives a value of 56.0 kJ mol^{-1} for the free energy barrier of internal rotation.

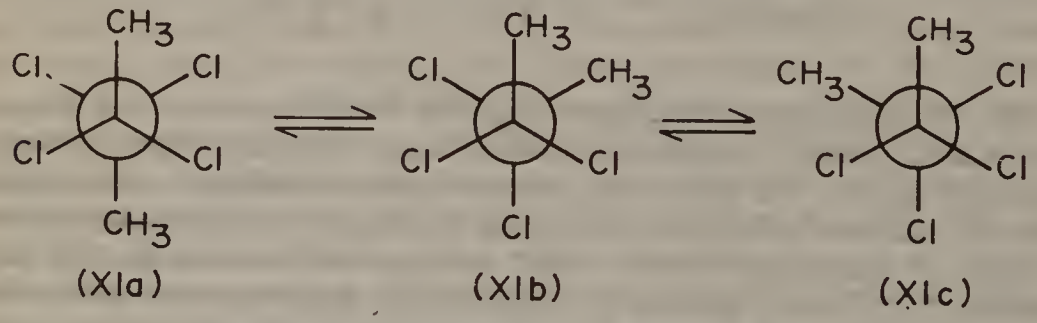
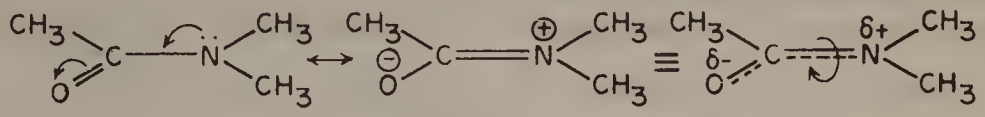


Figure 9.5 Conformations of 2.2.3.3-tetrachlorobutane

N,N-Dimethylacetamide (XII) (Figure 9.6) is a classic example of restricted rotation around a C-N bond which has a partial double bond character due to resonance as shown. The two methyl groups attached to N are anisochronous, the one syn to the oxygen atom being slightly more deshielded. At room temperature, the two methyl singlets are well-separated ($\Delta\nu = 10.5$ Hz at 60

*The equation holds for two equally populated conformers, e.g., enantiomers.

MHz). The coalescence temperature is 65°C and an approximate $\Delta G^{\ddagger}$ value of 74.0 kJ mol^{-1} is calculated from these data. It may be noted that the internal rotation of the molecule does not bring about any change in conformation. In ^{13}C-NMR, $\Delta\nu$ is 75.6 Hz (at 25.2 MHz) and the coalescence temperature is 80°C giving almost the same value for $\Delta G^{\ddagger}$.



(XII)

Figure 9.6 Restricted rotation in N, N-dimethylacetamide

9.5 Conformations of a few acyclic molecules

In this Section, the conformations of a few selected acyclic molecules will be discussed. So far, the general impression has been that the anti conformer is always more stable than the gauche. This is true as long the interactions between two groups are principally steric in nature. As will be seen in the sequel, other factors such as electrostatic effect, dipole-dipole interaction, and H-bonding also have considerable influence on the preferred conformation of a compound and may very well change the order of stability.

9.5.1 Conformations of alkanes

For straight chain hydrocarbons containing more than four carbon atoms, rotational isomerism takes place around more than one C-C bond (such molecules are called multiple rotors) and the nature and number of conformers may be considered in terms of constituent *n*–butane units. Generation of an anti conformation around an additional C–C bond does not increase the energy of the molecule but the formation of a gauche unit adds up approximately 3.3 kJ $mol^{-1}$of energy. While rotation around any single bond gives rise to three conformers as in *n*-butane, subject to symmetry consideration, no additional isomers are formed by rotation around bond connecting any terminal methyl group. As a result of various combination of anti and gauche orientations (three for a single rotor), the number of conformers increases. The increase in number, however, does not follow a geometrical progression; firstly, if the molecule has end-over-end symmetry, there is degeneracy; secondly, some conformers are sterically excluded. Thus in *n*-pentane, there are two bonds, 2-3 and 3-4 rotation around which produces conformers. Out of possible nine (3 ×3), only six conformers can exist because of degeneracy (due to end-over-end symmetry) which are shown in Figure 9.7 and designated *meso*-anti-anti or (±ap, ±ap) (XIIIa), (±)-anti-gauche or (±ap, +sc) (XIIIb) (its enantiomer: ±ap,–sc), (±)-gauche-gauche or (+sc, +sc) (XIIIc) (its enantiomer:–sc,–sc,), and *meso*-gauche-gauche or (−sc, +sc) (XIIId). The last-named conformer, however, has synparallel methyls and is of high energy (ca 16 kJ mol^{-1}) which leaves only *five* conformers appreciably populated. The anti-anti

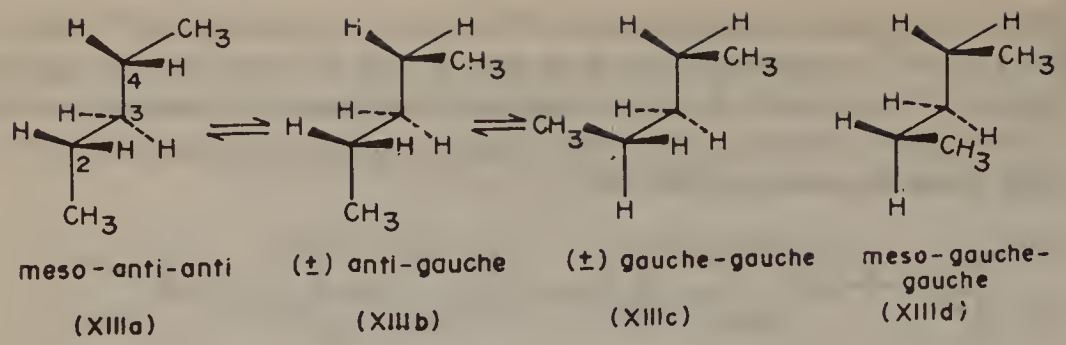


Figure 9.7 Conformations of *n*-pentane

conformer is given an arbitrary zero energy and the other two conformers (XIIIb) and (XIIIc) have 3.3 and 6.6 kJ mol^{-1} of energy respectively. Newman projection formulae are inadequate to represent these conformers; instead, zigzag extended sawhorse formulae are used. Normal paraffins from C_4 to C_{12} have been studied both in solid and liquid states by Raman and IR spectroscopy (Mizushima 1954). In the crystalline state, often a single conformer, the all-anti form is found but in the liquid or gaseous state, equilibrium among various anti-gauche combinations is established. As the chain length increases, e.g., in *n*-cetane, the statistical probability of having an all-anti conformation in the liquid or vapour state becomes very small and conformers with one or more gauche orientations predominate.

The conformations of branched chain alkanes are examined on a similar basis. In these cases, however, in addition to steric factor, bond angle deformations also play an important part. The cases of propane, 2-methylpropane, and 2,2-dimethylpropane have already been discussed. 2,3-Dimethylbutane provides an interesting case. It exists in an achiral anti (XIVb) and two enantiomeric gauche forms (XIVa) and (XIVc) (Figure 9.8) and all three conformers appear to be equally populated at all temperatures as evidenced from Raman, IR, and NMR spectra. The conformational free energy is, therefore, zero and the total concentration of the gauche form is twice that of the anti. Similar preference of gauche conformers is also observed in 1,1,2,2-tetrachloro- and 1,1,2,2-tetrabromoethanes (see later). This has been ascribed to a widening of the Me-C-Me and X-C-X angles (Thorpe-Ingold effect) which is easy in gauche but difficult in anti conformers (where it produces

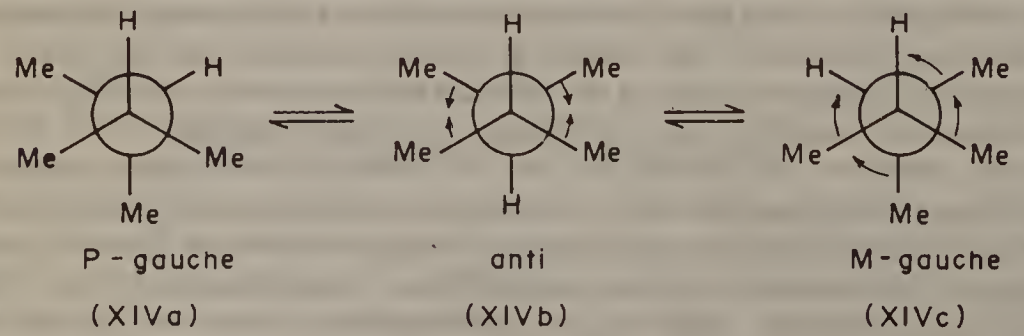


Figure 9.8 Conformations of 2.3-dimethylbutane

Me-Me steric compression evident from the directions of arrows shown in Figure 9.8). There are two rotational barriers in these molecules. For 2,3-dimethylbutane, the values are 18.0 and 33.0 kJ mol^{-1}, the higher one corresponding to two Me-Me eclipsings and one H-H eclipsing. Since rotation takes place through the path of least resistance, the gauche-gauche interconversion cannot take place directly (it necessitates crossing the higher energy barrier) but goes through the intermediacy of the anti form.

9.5.2 Conformations of halogenoalkanes

The conformations of a large number of halogenoalkanes have been studied by Raman, IR, and microwave spectroscopy and in some cases also by dipole moment measurements. Several points are of interest. The energy barriers in ethyl halides (CH_3-CH_2X, X = F, Cl, Br, and I) are remarkably similar in magnitude (around 14-15 kJ mol^{-1}, Table 9.4) despite considerable difference in the size of the halogens. It appears that the effect of the increasing size is compensated by the correspondingly increasing bond lengths as the halogen changes from F, Cl, Br to I. The slightly higher values of the barrier heights compared to ethane (12.0 kJ mol^{-1}) are consistent with the increased van der Waals radii of halogens compared to hydrogen. The extra energy is thus a result of a steric effect rather than of electronic origin.

n-Propyl chloride exists in an anti and two enantiomeric gauche conformers (Figure 9.9). In the liquid and gaseous states, the gauche conformers (XVb) and (XVc) predominate, the conformational free energy being 2.5 kJ mol^{-1} in favour of the gauche as determined by microwave spectroscopy. Electron diffraction experiments show a torsion angle of 65-70° between Me and Cl in the gauche form. It is thought that, in this geometry, the two groups are at a distance where van der Waals attractive forces (London forces) rather than repulsive ones predominate so that the gauche conformer is preferred over the anti (XVa). Even when Me is replaced by Et as in *n*-butyl chloride, the gauche orientation (with respect to the C_1-C_2 bond) is slightly favoured ($\Delta G° = 1.3$ kJ mol^{-1}). These are interesting examples where the gauche forms are favoured due to van der Waals forces of attraction.

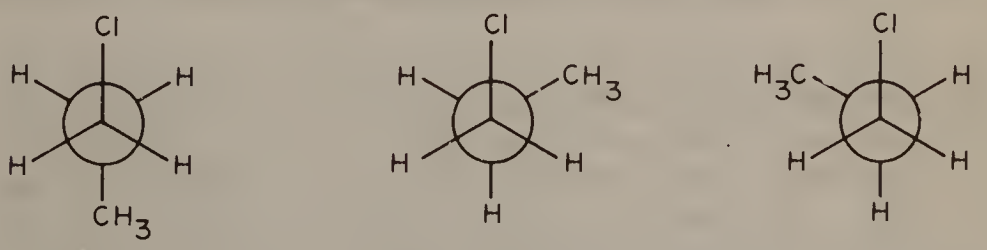


Figure 9.9 Conformations of *n*-propyl chloride

The conformations of 1,2-dihalogenoethanes (Figure 9.10) have been extensively studied by various physical methods especially by dipole moment measurement, Raman, IR, and microwave spectroscopy. In the gaseous state at 22°C, 1,2-dichloro- and 1,2-dibromoethanes contain 73 and 85% of the anti conformers respectively as against 67% for *n*-butane. The higher stability of the anti form (as XVIa) in comparison to *n*-butane is due to a combined effect of a steric factor (larger in the bromide than in the chloride) and an electronic interaction (dipole-dipole repulsion). In the liquid state or in polar solvents, on the other hand, the electrostatic repulsion decreases considerably due to the high dielectric constant of the medium and the ratio of gauche conformers (XVIb) and (XVIc) increases. In dichloroethane, the two conformers (anti and gauche) are almost equally populated in the liquid state whereas in dibromoethane, the gauche population is 35% corresponding to a conformational free energy of 3.5 kJ mol^{-1} in favour of the anti. Similarly, for 1,2-chloroflouro-, 1,2-bromofluoro-, and 1,2-fluoroiodoethane, the anti forms predominate in the gaseous state but the gauche forms become more in the liquid state. The barrier height in 1,2-dichloroethane (approximately 12.5 kJ mol^{-1}) is very similar to that in ethane which means that H-H and H-Cl eclipsing interactions are similar in nature and that there is little H/Cl steric effect.

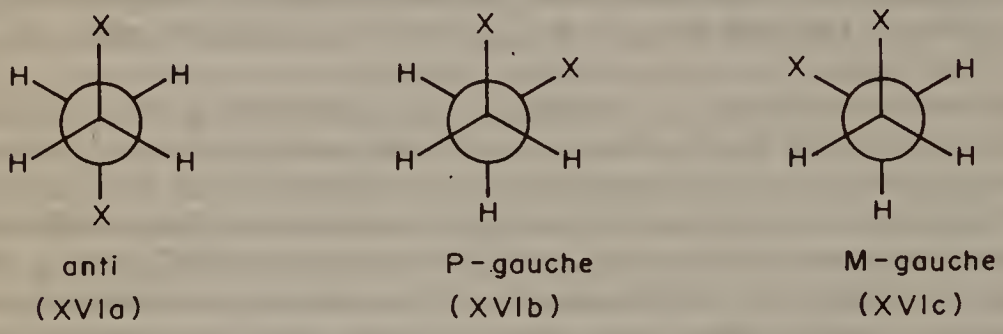


Figure 9.10 Conformations of 1,2-dihalogenoethanes

As the number of halogen substituents is increased, the barrier energy gradually increases from 15.5 kJ mol^{-1} in ethyl chloride to 50-60 kJ mol^{-1} in hexachloroethane; the 1,1,2,2-tetrachloro-and 1,1,2,2-tetrabromoethanes (Figure 9.11) have the additional feature that they exhibit preference for gauche conformations

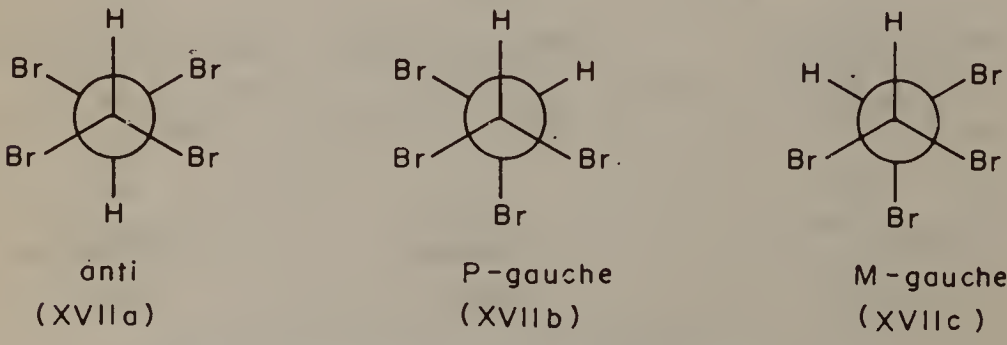


Figure 9.11 Conformations of polyhalogenoalkanes

(XVIIb) and (XVIIc) over the anti (XVIIa). Moreover, the tetrabromo-derivative gives two isomorphous crystals (depending on conditions) one containing the anti and the other containing the gauche conformer exclusively so that both forms can be studied by X-ray diffraction experiments.

9.5.3 Conformation and intramolecular hydrogen bonding

Intramolecular H-bonding between two vicinal groups confers an appreciable amount of stability (8-20 kJ mol^{-1}) to a conformer. For effective intramolecular H-bonding to occur, the donor and the acceptor groups (Chapter 1) must be close to each other which is possible only in the eclipsed or gauche conformation. In the eclipsed conformation, however, the atoms come within contact distance, so van der Waals repulsive forces come into play and make the conformation unstable. The gauche conformations with a torsion angle of 60-70° between the interacting groups are ideally suited for intramolecular H-bonding. The anti conformer with the two groups oppositely placed as in XVIIIa (Figure 9.12a) does not permit the formation of such a bond.

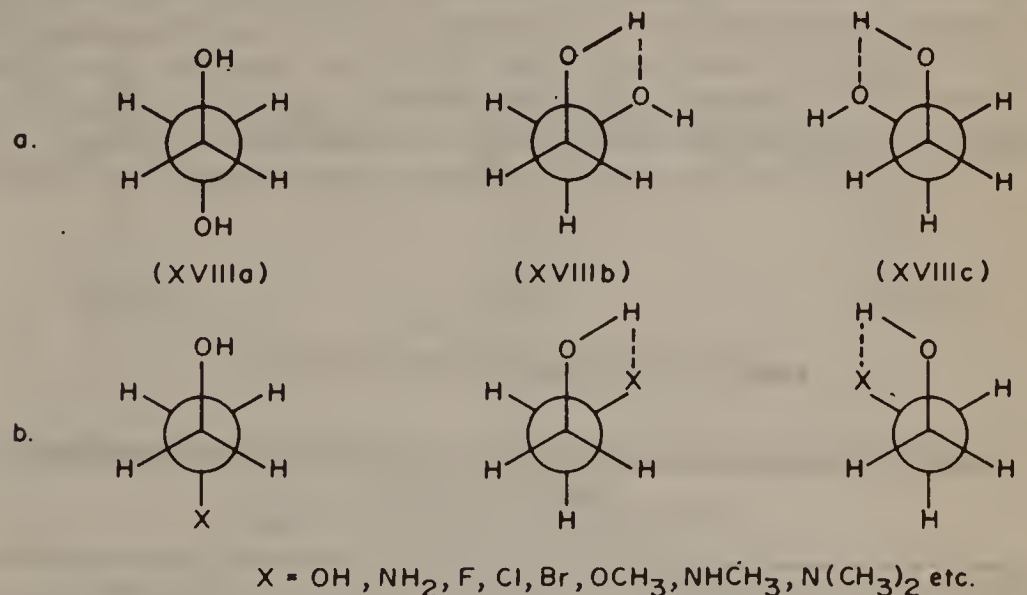


Figure 9.12 Conformations and H-bonding

As already stated, the vibrational frequencies of the free and bonded O-H are sufficiently different ($\Delta\nu \approx 40\ cm^{-1}$) to permit their separate detection in dilute solution*. Ethylene glycol exists almost exclusively in the H-bonded gauche forms (XVIIIb) and XVIIIc). IR (in CCl_4) shows a frequency difference of 32 cm^{-1} (3644 cm^{-1} for unbonded and 3612 cm^{-1} for the bonded OH). 2-Chloroethanol (ethylene chlorohydrin) exists exclusively in the H-bonded gauche form in the solid state; in the liquid and gaseous state, an equilibrium is set up with 15% of the anti and 85% of the gauche conformers ($\Delta G°=4.0$ kJ mol^{-1}). In general, 2-substituted ethanols of the type, X-CH_2-CH_2-OH where X = OH, NH_2, F, Cl, Br, OCH_3,

*To ensure the absence of intermolecular H-bonding.

$NHCH_3$, $N(CH_3)_2$ etc. (Figure 9.12b) all have the preferred gauche conformations with OH and X forming intramolecular H-bonds. Usually the dihedral angle is slightly greater than 60°.

9.5.4 Conformations of 1-substituted 3,3-dimethylbutanes

The conformations of a large number of monosubstituted 3,3-dimethylbutanes of the general formula $(CH_3)_3CCH_2\text{-}CH_2X$ (XIX) (Figure 9.13) around the 1-2 bond have been studied by ^{1}H-NMR (Whitesides et al 1967) and the conformational energies (ΔE) determined for different groups. The anti form (XXa) is in all cases more stable than the gauche (XXb) and the ΔE values (Table 9.5) thus give the relative magnitude of gauche interactions for different substituents. Since the gauche interaction in these cases essentially arises from steric factors, the values are also indicative of the effective size of the groups. Some of the interesting features are: (*i*) CH_3 and OH have similar interactions and so similar effective size (this is in variation with cyclic compounds). (*ii*) The conformational energy* in the

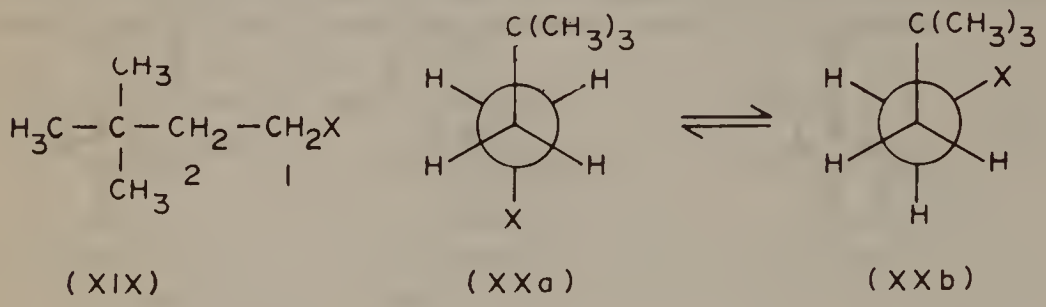


Figure 9.13 Conformations of $(CH_3)_3C\text{-}CH_2CH_2X$

Table 9.5 Conformational energies of some 1-substituted 3,3-dimethylbutanes[a]
$(CH_3)_3CCH_2\text{-}CH_2X$

X =	ΔE, kJ mol^{-1}	X =	ΔE, kJ mol^{-1}
H	0.00	NH_2	4.53
CH_3	2.94	CO_2H	4.48
C_6H_5	6.93	CO_2Me	3.70
F	2.60	$O\text{-}C_6H_5$	2.50
Cl	4.51	$O\text{-}SO_2C_6H_4Br(p)$	2.50
Br	5.49	SMe	6.16
I	6.76	$S\text{-}C_6H_5$	6.21
OH	3.07	SCN	6.29
CN	3.49	$CONH_2$	5.37

[a] Taken from G.M. Whitesides, J.P. Sevenair, and R.W. Goetz, *J. Amer. Chem. Soc.*, 1967, **89**, 1135.

*These conformational energies should not be confused with conformational free energies of substituents in cyclohexane discussed in the next chapter.

halogen series increases as the size of the halogen increases from fluorine, chlorine, bromine to iodine which is expected. (*iii*) The effective size is determined mainly by the first atom through which the substituent is linked as evidenced from the fact that SCH_3, SCN, and SC_6H_5 have similar conformational energy and so also have $O\text{-}C_6H_5$ and $O\text{-}SO_2C_6H_4Br$ (*p*).

9.5.5 Conformation around sp^3-sp^2 and sp^2-sp^2 bonds

Rotation around an sp^3-sp^2 bond such as in acetaldehyde and in propionaldehyde (Figure 9.14) should lead to six (3×2) energy minima conformations, three of which (XXIa), (XXIb), and (XXIc) are shown for propionaldehyde in which the carbonyl oxygen is eclipsed with hydrogens and methyl. It has been shown by ^{1}H-NMR spectra that these are the preferred conformers (Karabatsos and Fenoglio 1970). The other three conformers with the aldehydic hydrogen eclipsed are not present in any detectable amount. The conformational free energy of propionaldehyde is approximately 3.8 kJ mol^{-1} in favour of the conformer (XXIc) in which the methyl group is nearly eclipsed by the carbonyl oxygen (actually, the torsion angle is around 10°). This is true for all aliphatic aldehydes and also for alkenes with a terminal methylene group, e.g., propene (C=O replaced by C= CH_2). The rotational barrier in these molecules is relatively low, around 6.0-10.0 kJ mol^{-1}. Propionaldehyde has two energy barriers of 6.3 and 8.8 kJ mol^{-1}.

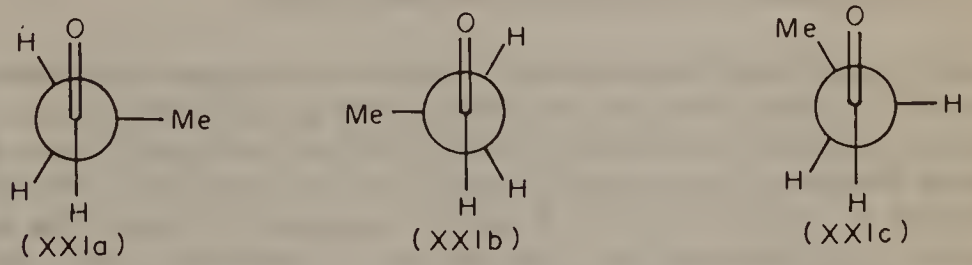


Figure 9.14 Conformations of propionaldehyde

Compounds containing sp^2-sp^2 bonds belong to conjugated system and hence such bonds possess some double bond character. The molecules are planar and exist in two conformations, transoid (*s*-trans) and cisoid (*s*-cis), as shown for 1,3-butadiene (XXIIa) and (XXIIb) (Figure 9.15). For steric reasons, the *s*-trans (*s*

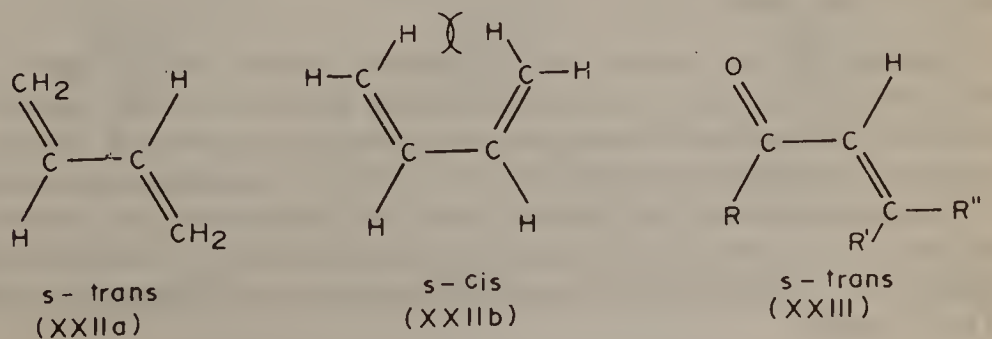


Figure 9.15 Conformations of 1,3-butadiene

refers to single bond) isomers are preferred over the *s*-cis. For 1,3-butadiene, the conformational free energy is approximately 10.5 kJ mol^{-1} and the energy barrier is almost double that value. All α,β-unsaturated aldehydes and ketones prefer to assume the transoid conformation (XXIII). Furfuraldehyde is another interesting molecule (Figure 9.16) which exists in the transoid form (XXIVa) in the liquid state or in polar solvents but changes to the cisoid conformation (XXIVb) in the gaseous state probably due to the dominating polar repulsive interaction between the two oxygen atoms in the *s*-trans form. Restricted rotation around C-N single bond as in the amide (XXV) has already been discussed.

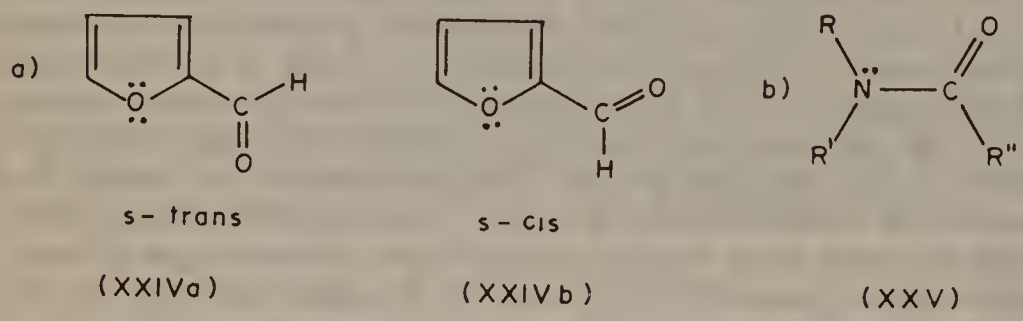


Figure 9.16 (a) Conformations of furfuraldehyde (b) Substituted amide

9.5.6 Conformations around carbon-heteroatom bonds

Rotation around single bond between sp^3-hybridised carbon and other atoms such as Si, N, O, S etc. is also not quite free and leads to conformers. In the case of trivalent and divalent atoms (N, O, and S), the lone electron pairs serve as the missing substituent. The relatively low energy barrier (7.1 kJ mol^{-1}) in CH_3-SiH_3 compared to ethane (Table 9.4) is due to the longer C-Si bond. The energy barriers for CH_3OH and CH_3NH_2 are respectively 4.5 and 8.3 kJ mol^{-1} which are approximately one third and two thirds of the value for ethane (12.0 kJ mol^{-1}). This may be accounted for from the number of H-H eclipsing in the transition states which is one for methanol, two for methylamine and three for ethane. The rotational energy barrier in the C-N bond rises more steeply with increase of substituents than in C-C bond. Thus there is hardly any change in the energy barrier from ethane to propane but the barriers for CH_3NH_2 and CH_3NHCH_3 are 8.3 and 15.0 kJ mol^{-1} respectively. The same is true for C-O bond (see CH_3OH and CH_3OCH_3, Table 9.4).

In general, the free electron pair is effectively smaller than hydrogen or any other substituent and so is preferentially placed gauche to a bulky group. The preferred conformations of some pertinent molecules are shown in Figure 9.17. Compounds containing two pairs of free electrons (or one pair of free electrons and one polar group) on two adjacent atoms exist in conformations in which the lone pairs and/or polar groups are gauche to each other (e.g., the case of H_2O_2 in Figure 9.17c). This is known as *gauche effect* (Wolfe et al 1972) (see also Chapter 10 for its origin).

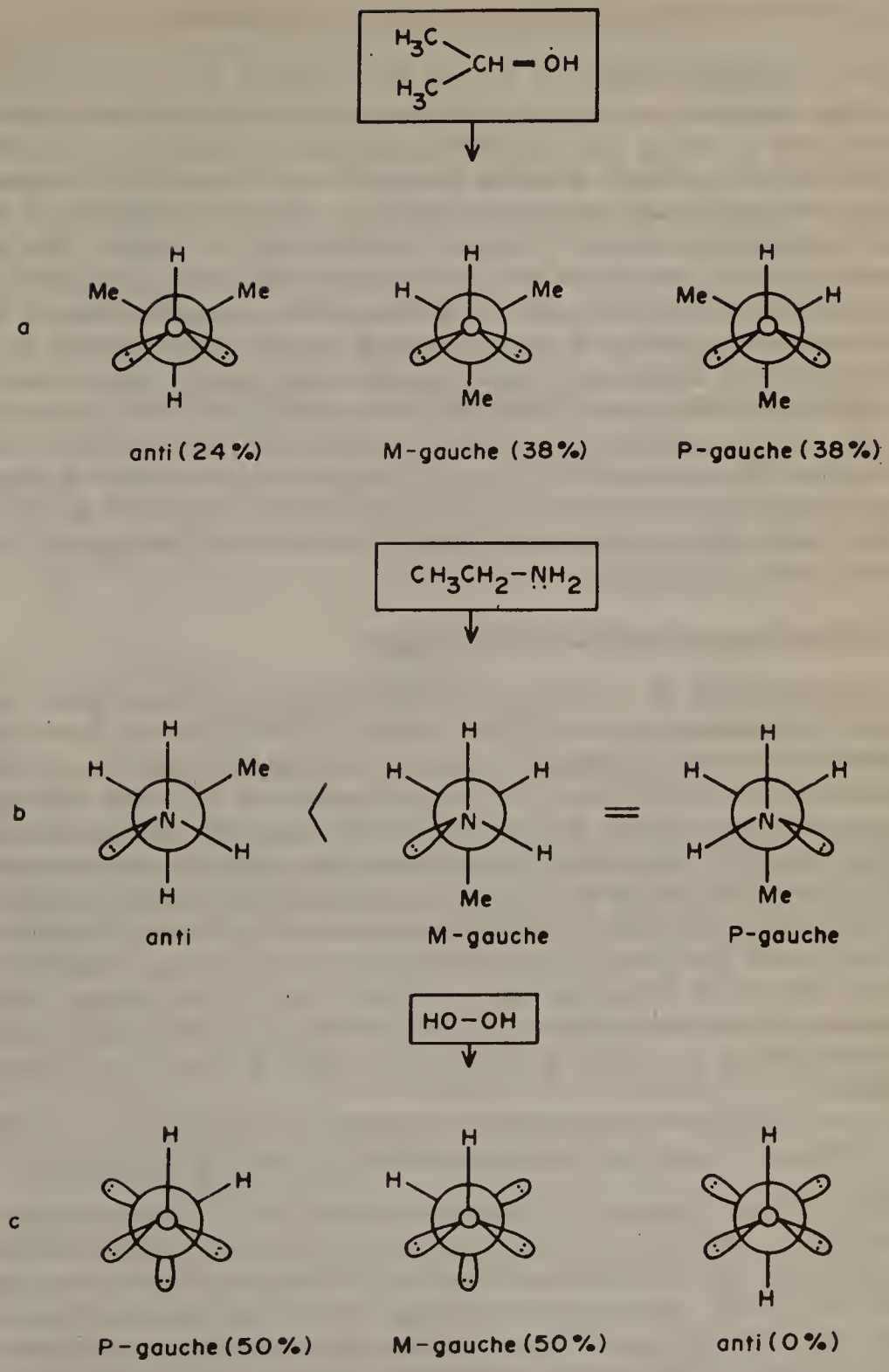


Figure 9.17 Conformations around C-O, C-N, and O-O bonds

9.6 Diastereomers: configurations, and conformations

From the preceding sections, it is clear that depending on the steric factors, electronic interactions, and secondary linkages such as H-bonding, certain molecules usually exist in one or more preferred conformations (conformers). It is these conformers which primarily determine the ground state behaviour of a compound, namely, its physical and spectroscopic properties, chiroptical parameters, if any, and thermodynamic stability. Chemical properties such as reaction rates and reaction pathways, on the other hand, depend both on the ground state and on the transition state conformations and will be discussed in a subsequent chapter. The conformational effects can be best appreciated through the comparison of the properties of two diastereomers usually a meso and an optically active isomer or an erythro and a threo isomer. Depending on the configuration, each isomer exists in one or more preferred conformations and it is the difference in their conformational features which in the long run distinguishes the two isomers as regards their physicochemical properties. This is illustrated in this section with the help of a few typical pairs of diastereomers through comparison of their physical properties and chemical equilibria.

9.6.1 Diastereomers with two vicinal halogens

The conformations of 1,2-dichloro-1,2-diphenylethane (dichlorostilbene) have already been discussed in terms of dipole moment. In NMR, the meso isomer with preferred conformer VIIa (Figure 9.4a) is expected to show a higher J_{HH} coupling constant than the active forms with preferred conformers VIIIa and VIIIb (see Karplus equation, Chapter 8)* which helps to distinguish between the two diastereomers. The computation of steric interactions in the preferred conformers of each isomer predicts that the meso is more stable than the active form assuming that the order of the gauche interactions are as follows: Ph/Ph>Ph/Cl>Cl/Cl. In general, a meso compound is thermodynamically more stable than the active one (in the absence of H-bonding) and an erythro than a threo isomer. When computing the free energy of an isomer with multiple conformers, due allowance must be made for the entropy of mixing ($\Delta S°$), which is given by the following equation:

$$\Delta S°_{mix} = -2.303\ R(n_1 \log n_1 + n_2 \log n_2 + n_3 \log n_3 \text{ etc.}) \qquad (16)$$

where n_1, n_2, n_3 etc. are the mole fractions of the contributing conformers.

Another pertinent example of a dihalogeno compound is 2,3-dibromobutane, the meso form of which exists predominantly in the anti conformation (XXVIa) (Figure 9.18). The two gauche conformers (XXVIb) and (XXVIc) with four consecutive gauche interactions are relatively unstable. On the other hand, the three conformers of the active form (only one enantiomer is shown) (XXVIIa), (XXVIIb), and (XXVIIc) are all substantially populated. The following values of gauche interactions are used to calculate the enthalpies of the different conformers: Me/Me = 3.3 kJ mol^{-1}, Me/Br = 0.8 kJ mol^{-1}, Br/Br = 3.0 kJ mol^{-1} (in the

*The experimental J value will be a weighted average of J values of the contributing conformers.

liquid state). The relative enthalpy and respective population (assuming $\Delta S = 0$) as estimated from these interactions are shown for each conformer. It may be readily

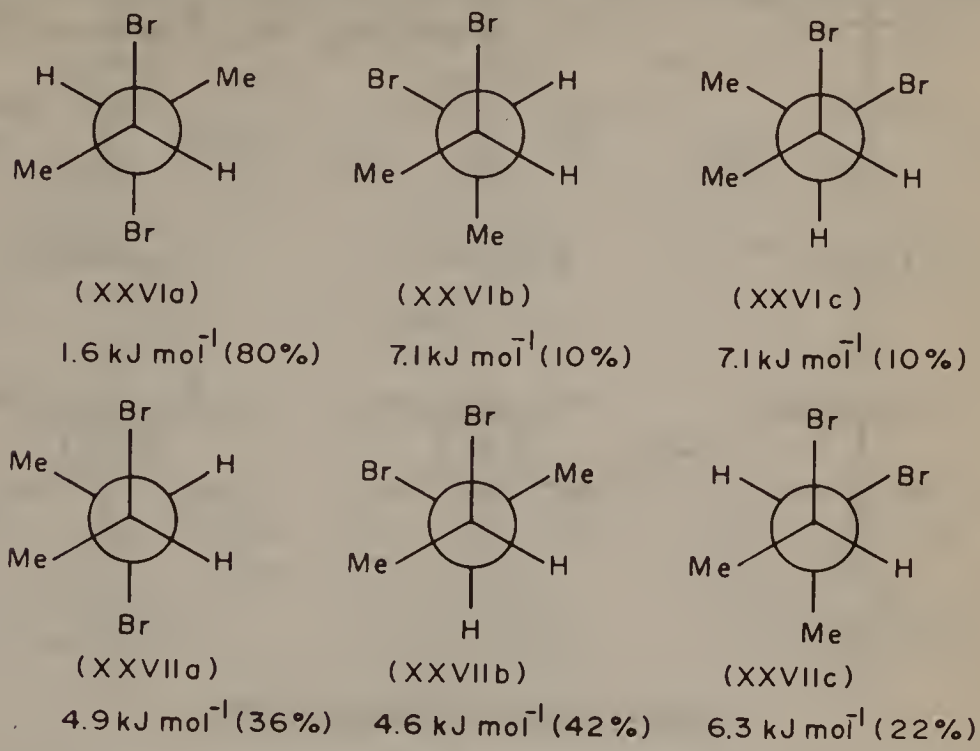


Figure 9.18 Conformations of 2.3-dibromobutanes

seen that the anti conformer (XXVIa) which constitutes approximately 80% of the meso form is energetically preferred over all the others so much so that the meso is more stable than the active form despite the fact that the latter derives an entropy advantage being a mixture of two almost equienergetic gauche conformers (XXVIIa,b).

9.6.2 Diastereomers with two vicinal hydroxyl groups

Butane-2,3-diol exists in two diastereomeric forms, the meso XXVIII and the racemic XXIX (Figure 9.19, only one enantiomer is shown). In both, the gauche conformers predominate because they permit the formation of intramolecular H-bond. The two gauche conformers of the meso (XXVIIIa) and (XXVIIIb) are enantiomeric and so are equally populated. The active isomer also consists of two H-bonded gauche conformers which are unequally populated, the one (XXIXb) with the two methyls anti being preferred over the other (XXIXa) and presumably also over the two gauche conformers (XXVIIIa,b) of the meso form. The IR spectra of the two diastereomers show that the intramolecular H-bonding in the meso is weaker than that in the active (or racemic) form. The difference between the free and the H-bonded O-H stretching frequencies ($\Delta\nu$) which is a measure of the strength of the H-bond is 42 cm^{-1} for the meso and 49 cm^{-1} for the racemic (it is 32 cm^{-1} for ethylene glycol). This is due to the closing up of the two hydroxyl groups in forming the intramolecular H-bond which is sterically unfavourable in

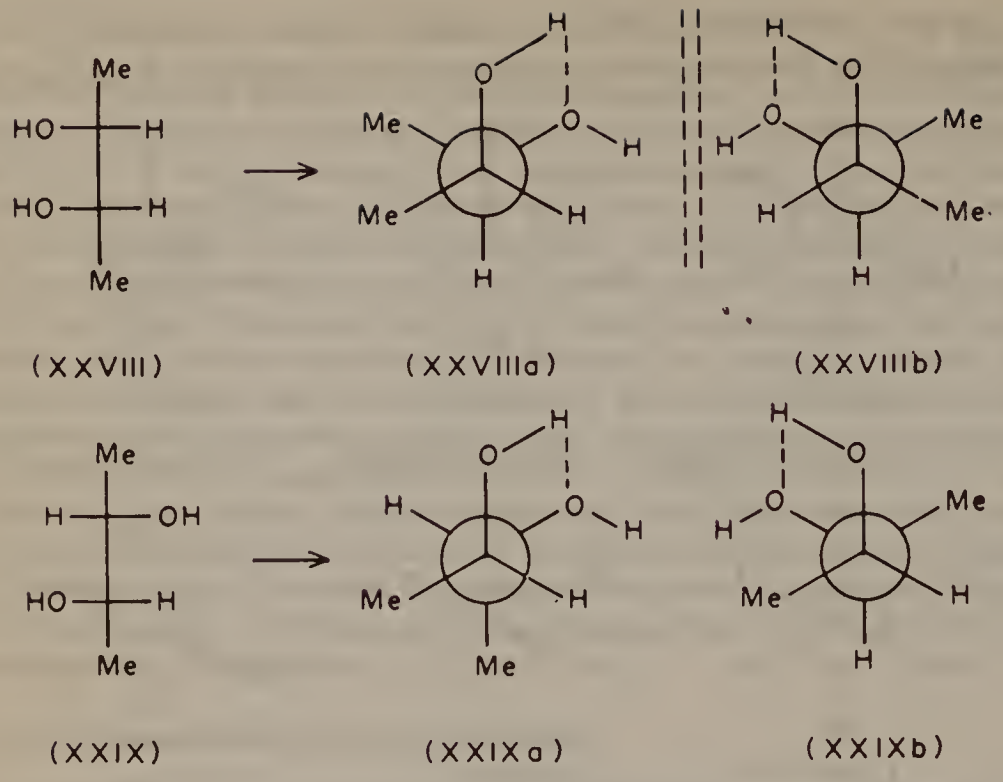


Figure 9.19 Conformations of butane-2,3-diols

the enantiomeric conformers (XXVIIIa,b) since it draws the two gauche methyls closer but is favourable in the diastereomeric conformers (XXIXa) and (XXIXb) since it increases the torsion angles between the two methyls in the former and between methyl and hydroxyl groups in the latter. It is further observed (Eliel 1962) that as the methyl groups are replaced by bulkier alkyl groups, $\Delta\nu$ increases for both the diastereomers but much more so in the racemic than in the meso forms. Since the intramolecular H-bond is always stronger in the active (and racemic) forms, they are more stable than the meso isomers.

9.6.3 Diastereomers with vicinal hydroxyl and amino groups

The conformations of the diastereomeric amino alcohols of the type, PhCH(OH)-CH(NR_2)Ph have been studied by NMR (Munk et al 1968) and one of the compound, 2-(N,N-dimethylamino)-1,2-diphenylethanol ($NR_2 = NMe_2$) is discussed here to illustrate the use of NMR in conformational analysis. The threo isomer (only one enantiomer is considered) can have three conformers (XXXa), (XXXb), and (XXXc) (Figure 9.20) of which the last one (anti) may be ruled out because of severe steric interactions, e.g., Ph/Ph + Ph/NMe_2 as well of its inability to form intramolecular H-bond. The preferred conformers are, therefore, the two gauche forms (XXXa) and (XXXb) the first with H_a and H_b anti and the second with H_a and H_b gauche. Values of 11.0 Hz for J_{anti} and 2.6 Hz for J_{gauche} in this system have been assumed. The experimental value for the coupling constant in the threo isomer is 10.5 Hz which means that the conformer (XXXa) occurs to the extent of

more than 90% ($J_{ab} = 11.0 \times n_{anti} + 2.6 \times n_{gauche}$). The predominance of the conformer (XXXa) over the other (XXXb) is presumably due to a severe steric interaction between Ph and NMe_2 in the latter. The approximate nature of the calculation should, however, be understood.

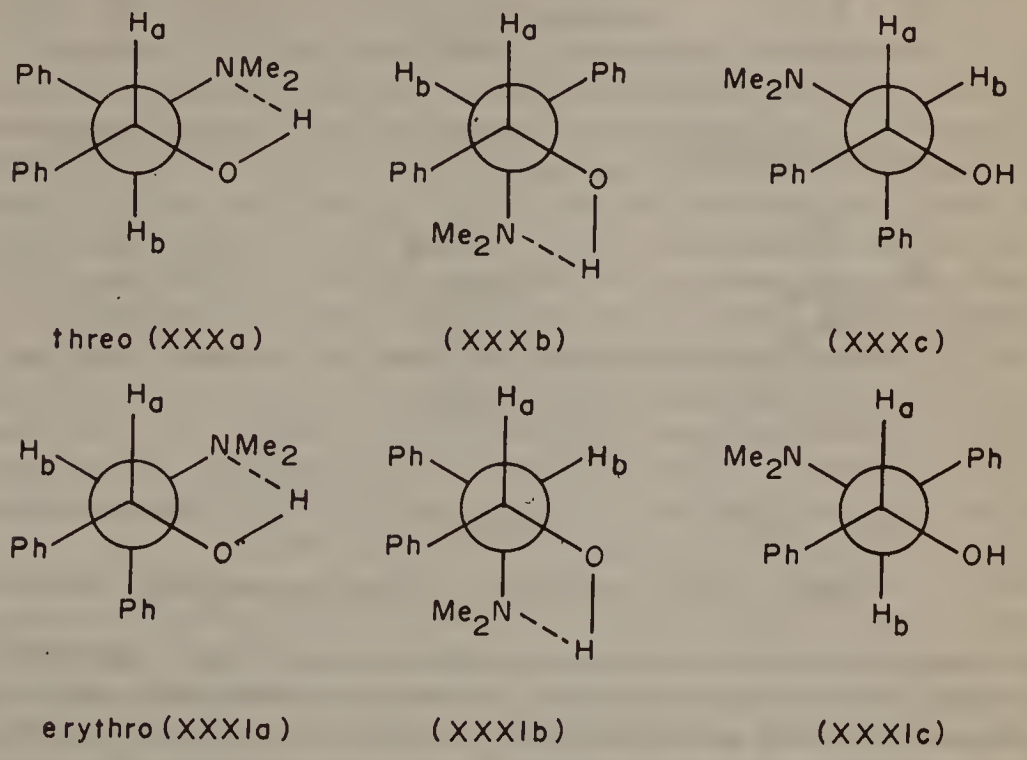


Figure 9.20 Conformations of amino alcohols

In the erythro isomer, all the three conformers contribute more or less to the equilibrium population. The anti conformer (XXXIc), although incapable of forming an intramolecular H-bond, is not as bad sterically as its counterpart (XXXc) in the threo isomer (absence of Ph/Ph gauche interaction). The NMR spectrum shows a coupling constant of 4.4 Hz which corresponds to approximately 25% of the anti (XXXIc) and 75% of the sum of the gauche forms (XXXIa) and (XXXIb). Computation of relative stability of the two diastereomers is not easy but can be done essentially through comparison of conformer XXXa of the threo with conformer XXXIa of the erythro structure which suggests that the threo isomer is thermodynamically more stable.

(−)-Ephedrine (XXXII, R = Me), an important alkaloid of medicinal value and its diastereomer, *ψ*-(−)-ephedrine (XXXIII, R = Me) belong to erythro and threo series respectively. Here also, the gauche conformers with intramolecular H-bonding are more stable than the anti in each isomer (Figure 9.21). Following the same argument as before, it is possible to say that the threo isomer (*ψ*-ephedrine) is more stable than the erythro isomer (ephedrine). Two conformational observations have helped to settle their relative configuration.

(*i*) It has been observed that N-carbobenzyloxy-*nor*-*ψ*-ephedrine (XXXIII, R = $OCOCH_2Ph$) readily rearranges in the presence of mineral acids to the O-

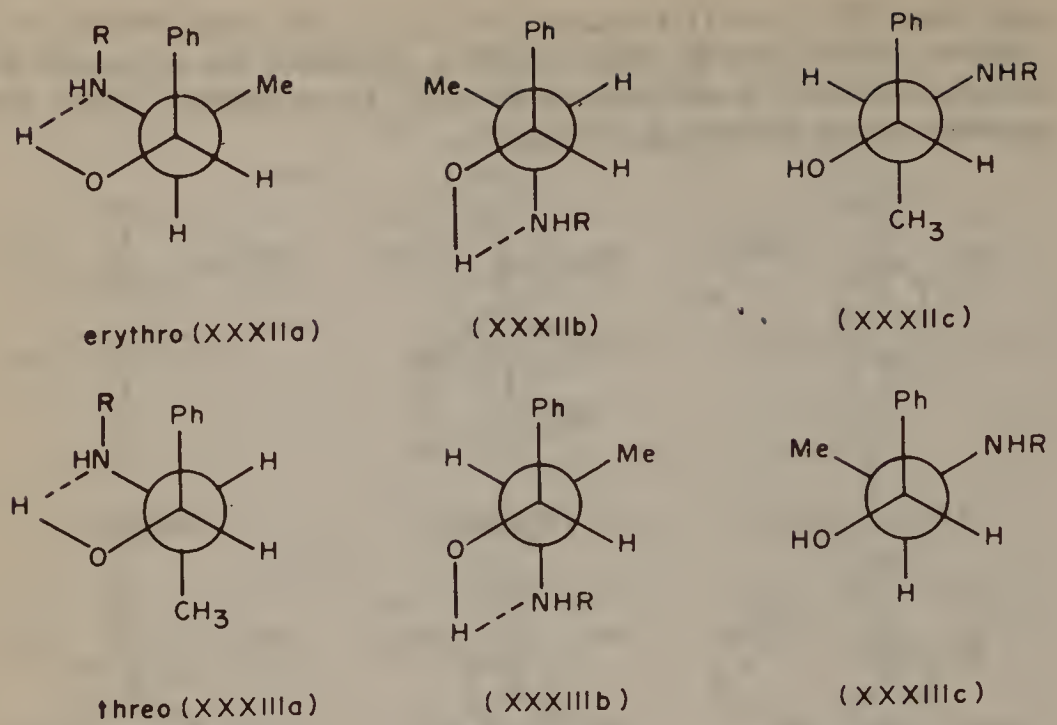


Figure 9.21 Conformations of ephedrine and ψ-ephedrine

carbobenzyloxy-derivative while such rearrangement is not facile in the analogous *nor*-ephedrine series. This can best be explained on the assumption that *nor*-ψ-ephedrine (from which ψ-ephedrine is derived) has the threo configuration since its most preferred conformation (XXXIIIb) permits the formation of the cyclic intermediate involving O and N more easily than either of the conformers (XXXIIa) and (XXXIIb) of the erythro structure. In the former, such an operation reduces the Ph-Me interaction by pulling these groups apart while, in the latter, it increases the Ph-Me interaction by drawing them closer to each other. Although the argument is based on ground state conformations, it is equally valid for the transition states.

(*ii*) Ephedrine is a slightly weaker base (pK_a 9.14) than ψ-ephedrine (pK_a 9.22). It may be easily seen that the conjugate acid of the threo conformer (XXXIIIb, $NHR = N^+H_2Me$) can form an effectively stronger H-bond through the acidic proton than the erythro conformer (XXXIIb, $NHR = N^+H_2Me$) for reasons discussed for butane-2,3-diols. The observation is thus consistent with the erythro structure of ephedrine and the threo structure for ψ-ephedrine. The structural assignment has been confirmed by X-ray (Phillips 1954).

9.7 Summary

1. When a part of a molecule is rotated around a single bond, innumerable conformations result of which only a few correspond to energy minima and are called conformers or rotamers. They differ from one another mostly in the dihedral angles. They are a kind of stereoisomers existing in dynamic equilibrium, easily interconvertible, and, in principle (but often not in fact), isolable under appropriate

conditions. They can, however, be detected and distinguished by many physical methods. The relative population of the conformers depends on the difference in their free energies; whereas the ease of their interconversion depends on the energy barrier which separates them and is usually low. A study of physico-chemical properties of a compound in terms of its conformations in the ground and transition states is known as conformational analysis.

2. The energy of a conformer may be computed from the different types of strains present in the molecule such as deformation of bond lengths, deformation of bond angles, torsional strain, and non-bonded interactions and is minimised by suitable adjustment of the pertinent geometrical parameters. The variation of dihedral (torsion) angle brings about by far the most important change in molecular geometry and is most significant from the stereochemical point of view.

3. The various aspects of the conformations of *n*-butane are discussed in detail as a model in which only steric interaction operates. It exists in three conformers, an anti and two enantiomeric gauche forms with dihedral angles of 180° and 60° respectively. The anti conformer is arbitrarily given zero potential energy while the gauche form has a potential energy of 3.3 kJ mol^{-1} being due to a Me-Me gauche interaction. The gauche conformer is favoured by an entropy of mixing (R1n2) which reduces the difference in free energies between the gauche and the anti to 1.5—1.7 kJ mol^{-1} (conformational free energy) corresponding to a relative population of 66% of anti, 17% of *P*-gauche, and 17% of *M*-gauche at room temperature. There are two energy barriers; the lower one (14 kJ mol^{-1}) arising out of two Me-H eclipsings and one H-H eclipsing is equal to that of propane and very close to that of ethane (12.0 kJ mol^{-1}). A detailed system of nomenclature of different conformations has been worked out by Klyne and Prelog based on torsion angle which is also used to describe partial conformation of polymer chain and of a ring compound.

4. Certain physical properties, e.g., thermodynamic data, dipole moments, chiroptical parameters etc. are predictably influenced by conformation and the measurements of such properties in turn are utilised for conformational analysis of pertinent molecules. Among the physical methods, diffraction experiments such as X-ray, electron, and neutron diffractions and various spectroscopic methods such as IR, Raman, microwave, UV, and NMR are used to determine the relative population of the conformers (and hence the conformational free energy), their geometries, and also the kinetic parameters of the interconversion process. All these physical techniques have their own time scales of observation. When these are commensurate with the rate of interconversion of the conformers, the conformers can be examined as discrete species.

5. A few typical acyclic molecules such as long chain and branched chain alkanes, mono-, di-, and polyhalogenoalkanes, 1-substituted 3,3-dimethylbutanes, ethylene glycol, and 2-halogenoethanols have been discussed. Although the anti conformer is ordinarily more stable than the gauche, the presence of certain interactions such as dipole-dipole repulsion, van der Waals attractive force (London force), and formation of intramolecular H-bond may very well reverse the stability order. By virtue of the high stability conferred by intramolecular H-bonding, its occurrence in gauche conformer is a very important consideration in

conformational analysis. In fact, such intramolecularly H-bonded gauche forms are often the predominant conformers.

The preferred conformations of a number of molecules having restricted rotation around sp^3-sp^2 and sp^2-sp^2 bonds are also discussed.

6. The effect of conformation on the physicochemical properties is best understood through comparison of a diastereomeric pair of compounds. Each diastereomer exists in one or more preferred conformations and the difference in properties of the two isomers may be assessed by a comparison between the pertinent sets of conformers. This has been illustrated with the help of a few pairs of diastereomers with vicinal groups which interact electronically (dihalogeno compounds) or through formation of intramolecular H-bonding (glycols and amino alcohols).

References

1. H. Sachse (1890), *Ber.*, **23**, 1368.
2. E. Mohr (1918), *J. Prakt. Chem*. **98**, 315.
3. P.H. Hermans (1924), *Z. Physik Chem.*, **113**, 337.
4. J. Boeseken and R. Cohen (1928), *Rec. Trav. Chim.*, **47**, 839.
5. A. Weissberger and R. Sangewald (1930), *Z. Physik Chem.*, 133.
6. K.L. Wolf (1930), *Trans. Faraday Soc.*, **26**, 315.
7. D.H.R. Barton (1950), *Experientia,* **6**, 316; see also, D.H.R. Barton and O. Hassel (1971), in *Topics in Stereochemistry*, vol. 6, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
8. F.H. Westheimer (1956), in *Steric Effects in Organic Chemistry*, Ed. M.S. Newman, Wiley, New York.
9. K. Mislow (1966), in *Introduction to Stereochemistry*, W.A. Benjamin, New York.
10. U. Burkert and N.L. Allinger (1982), in *Molecular Mechanics*, ACS Monograph No. 177, Amer. Chem. Soc., Washington, DC.
11. R.S. Cahn, C.K. Ingold and V. Prelog (1966), *Angew. Chem. Int.* Edn. Engl., **5**, 385
12. L. Rosenthal, J.F. Rabolt and J. Hummel (1982), *J. Chem. Phys.*, **76**, 817.
13. M. Manoharan and E.L. Eliel (1984), *Tetrahedron Letters*, **24**. 453.
14. M. Antenius, D. Tavernier, F. Borremans (1966), *Bull. Soc. Chim, Belges,* **75**, 396.
15. A.J. Gordon and R.A. Ford (1972), in *The Chemists' Companion,* Wiley, New York.
16. E.B. Wilson (1972). *Chem. Soc. Rev.*, **1**, 293.
17. W. Klyne and V. Prelog (1960), *Experientia,* **16**; 521.
18. IUPAC (1974), Rules for the Nomenclature of Organic Chemistry, Section E, Stereochemistry, *Pure & Appl. Chem.*, **45**, 11-30.
19. R. Bucourt (1973), in *Topics in Stereochemistry*, vol. 8, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
20. E.L. Eliel and E. Brunet (1986), *J. Org. Chem.*, **51**, 1902.
21. M. Goodman (1967), in *Topics in Stereochemistry* vol. 2, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
22. R.A. Pethrick and E. Wyn-Jones (1969), *Quart. Rev.*, **23**, 301; E. Wyn-Jones and R.A. Pethrick (1970), in *Topics in Stereochemistry*, vol. 5, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
23. W.J. Orville-Thomas (1974), in *Internal Rotation in Molecules*, Wiley, New York.
24. J.G. Aston and J.J. Fritz (1959), in *Thermodynamics and Statistical Thermodynamics*, Wiley, New York.

25. D.J. Millen (1962), in *Progress in Stereochemistry*, vol. 3, Eds. P.B.D. de la Mare and W. Klyne, Butterworth, Washington.
26. L.E. Sutton (1955), in *Determination of Organic Structures by Physical Methods*, vol. 1, Eds. E.A. Braude and F.C. Nichod, Academic Press, New York.
27. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison (1955), in *Conformational Analysis*, Interscience, New York.
28. E.L. Mutterties (1965), *Inorg. Chem.*, **4**, 769.
29. A. Bassindale (1984), in *The Third Dimension in Organic Chemistry*, Wiley, New York.
30. J.M. Robertson (1955), in *Determination of Organic Structures by Physical Methods*, vol. 1, Eds. E.A. Braude and F.C. Nachod, Academic Press, New York.
31. S. Mizushima (1954), in *Structures of Molecules and Internal Rotation*, Academic Press, New York.
32. J.P. Lowe (1968), Prog. *Phys. Org. Chem.*, **6**, 1.
33. G. Binsch (1968), in *Topics in Stereochemistry*, vol. 3., Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
34. D. Nasipuri, P.K. Bhattacharya, and G.T. Furst (1977), *J. C. S. Perkin* II, 356.
35. M. Oki (1984), in *Methods of Stereochemical Analysis: Application of Dynamic NMR in Organic Chemistry*, vol. 4, Ed. A. P. Merchand, VCH, Deerfield, Florida.
36. R.J. Abraham and P. Loftus (1978), in *Proton and Carbon-13 NMR Spectroscopy* Wiley, New York.
37. G.J. Karabatsos and D.J. Feloglio (1970), in *Topics in Stereochemistry*, vol. 5. Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
38. S. Wolfe (1972), *Acc. Chem. Res.*, **5**, 102.
39. E.L. Eliel (1962), in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
40. M.E. Munk, M.K. Meilahn, and P. Fraklin (1968), *J. Org. Chem.* **33**, 3480.

Chapter 10

Conformations of Cyclic Systems: Monocyclic Compounds

10.1 Introduction

Conformational theory was initiated by Barton mainly on the basis of his studies of cyclohexane derivatives (steroid system) and since then the conformational analysis of the cyclic compounds has developed into a most sophisticated area of stereochemistry which in turn has helped to understand many physicochemical phenomena including biogenesis of natural products. The cyclohexane ring is unique in character since it exists, in most cases, in two well defined chair conformations separated by relatively high (ca 40 kJ mol^{-1}) energy barrier. The interconversion, however, is still too rapid to permit isolation of the conformers at ambient temperature although they can be frozen out at low temperature. In contrast, rings higher than six-membered exist in a large number of conformers some of which are equienergetic and separated by very low energy barrier and only a few may be frozen out at low temperature.

10.1.1 Early history

Although the non-planar configuration of cyclic compounds such as cyclohexane is predictable from the tetrahedral theory of Le Bel and van't Hoff, its acceptance was long delayed due to the popularity of Baeyer's strain theory (1885) according to which all ring compounds are supposed to be planar and suffer (to a greater or lesser extent) from angle strain arising out of deviation from the natural valency angles. The strain theory was apparently supported by the facts that the 3- and 4-membered rings in which angle strain is maximum are most unstable (also most reactive), 5- and 6-membered rings in which angle strain is small or negligible are readily formed, and rings of higher members (>7) in which angle strain is again appreciably high (Table 10.1) are difficult to form. It is now understood that the ease of ring formation is of kinetic origin and not necessarily pertinent to thermodynamic stability. A 3-membered ring is easy to make because the geometry of the acyclic precursor (planar with two terminal atoms very close to each other) is favourable for cyclisation (entropy effect). It is also easy to break because of the inherent Baeyer and Pitzer strains in the system. The formation of a 4-membered ring is difficult because of its unfavourable transition state with all the hydrogens as well as the terminal carbons on both sides of the incipient ring eclipsed. The

non-bonded interactions and torsional strain are considerably reduced in the transition states leading to 5- and 6-membered rings due to the puckering of the chain which explains their easy formation. The larger rings are difficult to make because of an unfavourable entropy factor, the probability of having both ends of the acyclic intermediate within bonding distance being very small. The overall strain in a cyclic molecule in the absence of electronic effects and secondary linkages originates from three factors: Baeyer (angle) strain, Pitzer (torsional) strain, and non-bonded interactions.

From the experimental point of view, the heat of combustion of a ring compound per methylene group (H_c/n) may be taken as a reliable guide to the relative stability of different ring systems. In Table 10.1, H_c/n values for 3- to 16-membered cycloalkanes minus that for an acyclic methylene group ($H_c = 658$ kJ mol^{-1}) are given along with angle strain. Prelog and Brown (see Eliel 1962) have classified the ring compounds into four categories: *small* rings (n = 3-4), *common* or *normal* rings (n = 5-7), *medium* rings (n = 8-11), and *large* rings (n > 11). The data in the Table show that the small rings are highly strained in accordance with Baeyer's theory. These rings are planar or nearly so and the predominance of angle strain is understandable. Other rings avoid most of the angle strain and some of the torsional strain by puckering the chain and are relatively strain-free. The medium rings possess some residual strain mainly due to transannular interactions (non-bonded interactions across the ring), which in some instances, is evaded by considerable enlargement of the bond angles from the normal value. The heat of combustion of cyclohexane is minimum and equal to that of acyclic alkanes which is not compatible with a planar structure. In view of all these considerations, Baeyer's concept of planar rings had to be abandoned.

Table 10.1 Heats of combustion of a methylene group in $(CH_2)_n$ over that of an acylic methylene group

$(CH_2)_n$ n =	angle strain[a]	H_c/n—658 (kJ mol^{-1})	$(CH_2)_n$ n =	angle strain[a]	H_c/n—658 (kJ mol^{-1})
3	24°44′	38.6	10	− 17°16′	5.0
4	9°44′	27.4	11	− 18°54′	4.2
5	0°44′	5.4	12	− 20°16′	1.25
6	− 5°16′	0.0	13	− 21°25′	1.7
7	− 9°33′	3.8	14	− 22°25′	0.0
8	− 12°46	5.0	15	− 23°16′	0.4
9	− 15°16′	5.9	16	− 24°00′	0.4

[a] ½(109°28′ − α); the factor of ½ comes about because the strain is spread over two bonds; (180n − 360)°/n = the internal angle of an n-sided polygon.

Already in 1890, Sachse pointed out the possibility of two forms of cyclohexane, chair and boat both of which are completely free of angle strain but the suggestion was not generally accepted since numerous attempts to isolate additional isomers predicted on the basis of these structures failed. Mohr (1918) attributed the failure to rapid interconversion of the two forms and suggested the possibility of separation of two stereoisomers of decalins, a trans with double chair and a cis with double

boat configuration. In 1925, Hückel indeed isolated the two isomers of decalin, although, as well be seen later, both isomers contain only chair forms. Boeseken (1921) realised the necessity for the chair conformation of cyclohexane ring from the results of his investigations with *cis*-cyclohexane-1,2-diol. The chair conformation of cyclohexane was finally confirmed by Hassel (1947) with his electron diffraction experiments and by Barton (1950) with his conformational analysis setting a land-mark in organic stereochemistry.

10.2 Conformations of cyclohexane

X-ray and electron diffraction experiments clearly prove that cyclohexane exists almost exclusively in the chair conformation. An examination of the model (Dreiding, Fieser, or Prentice-Hall) of the cyclohexane chair shows that it is devoid of any kind of strain. In an ideal chair, the bond angles are 109°28′, i.e., $E_\alpha = 0$; there is no bond length distortion, i.e., $E_l = 0$; all the bonds are staggered ($\theta = 60°$), i.e., $E_\theta = 0$, and there is no non-bonded interaction. In fact, the chair form lies at the bottom of a deep energy well and any deviation therefrom is strongly resisted by internal forces. The structure is rigid and the rigidity can be felt even in the model which unlike that of *n*-butane resists easy rotation around single bonds.

10.2.1 Characteristics of the chair conformation

The characteristics of the cyclohexane chair are best described under the following headings:

1. Geometry. The electron diffraction experiments of cyclohexane in the gaseous phase (Geise et al 1971) show the following geometric parameters:

C—C bond length = 0.1528 nm (152.8 pm)
C—H bond length = 0.1119 nm (111.9 pm)
C—C—C bond angle = 111°05′ (instead of 109°28′)
Dihedral angle (as shown in Ia) = 56° (instead of 60°)

The increased C—C—C bond angle makes the chair conformation slightly flattened* so that the dihedral angles between adjacent C—C bonds are 56° and the vertical C—H bonds (axial) are not exactly parallel to the C_3 axis but lean outwards from it by 7°. The chair form is drawn in three different perspectives (Figure 10.1). The structure (I) shows the conventional drawing of the chair with the C_3 axis vertical and the six carbon atoms distributed in two parallel horizontal planes, 1-3-5 in one and 2-4-6 in the other separated by a distance of 0.05 nm. Any consecutive four carbon atoms form a gauche butane unit and since there are six such units (1-2-3-4, 2-3-4-5, 3-4-5-6 etc.), the enthalphy of cyclohexane chair may be computed as 3.3×6 or 19.8 kJ mol^{-1} with respect to a hypothetical all-anti chair conformation†

In the structure (Ia), two pairs of *n*-butane units (2-3-4-5 and 2-1-6-5) are seen in Newman projection with dihedral angle of 56° in each. The structure (Ib) shows

*The flattening brings a balance between angle and torsional strains thus minimising the energy of the system.

†For various reasons, the calculation may be spurious as well as hypothetical (see Schleyer et al 1970).

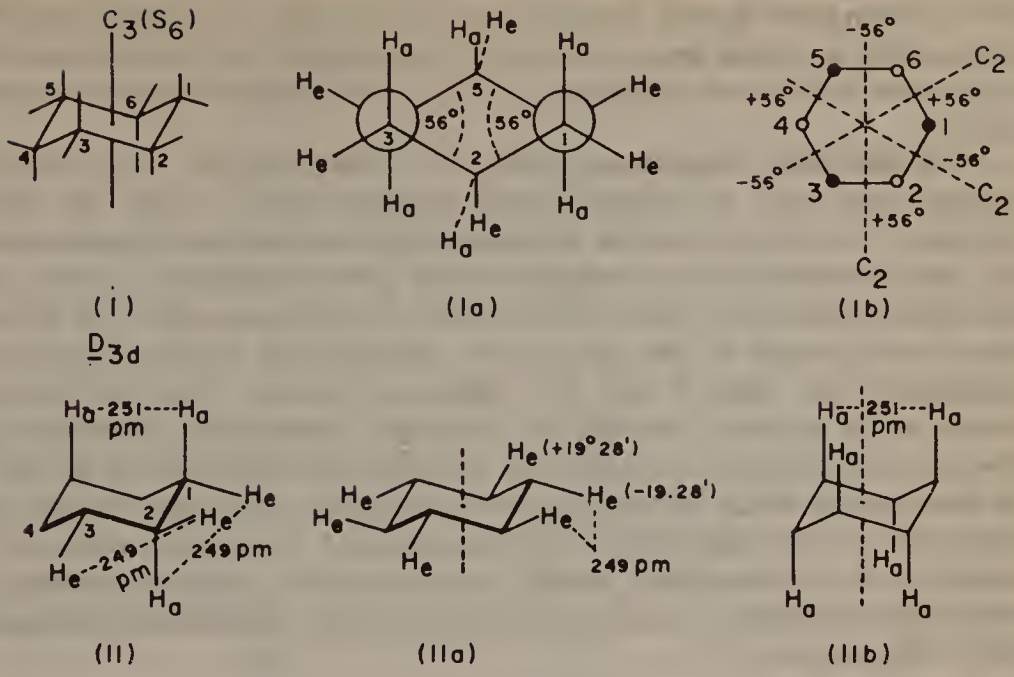


Figure 10.1 Geometry of cyclohexane chair

the six carbon atoms alternately up (•) and down (o) with signs of torsion angles* between pairs of adjacent carbon atoms according to Klyne-Prelog convention.

2. Symmetry. The vertical axis passing through the centre of the chair is a C_3 as well as an S_6 axis. In addition, there are three C_2 axes bisecting pairs of opposite sides and also a centre of symmetry. Then there are three vertical σ planes passing through diagonal carbon atoms. The cyclohexane chair thus belongs to point group D_{3d}.

The symmetry number (σ) is 6 counted thrice for 120° rotation around C_3 and once each for 180° rotation around the three C_2 axis (see Chapter 2).

3. Equatorial and axial bonds. Two types of C-H bonds are discernible in the cyclohexane chair: six are distributed around the periphery of the ring making alternately $+19°28'$ and $-19°28'$ angle with the horizontal plane of the molecule and the remaining six are approximately parallel with the vertical C_3 axis again alternatively up and down as shown separately in the two structures (IIa) and (IIb). The former are called equatorial (e) and the latter axial (a) bonds (Barton et al 1953). The approximate distances between different pairs of adjacent hydrogens are shown which are within 249-251 pm, greater than twice the van der Waals radius of hydrogen (120 pm). Thus there is no non-bonded interaction in the cyclohexane chair and since these distances occur twenty four times in the molecule, the stability of the chair conformation is readily understood.

The interaction between 1e,2e and 1e,2a substituents is known as 1,2-interaction while that between 1a,3a is known as 1,3-interaction or synaxial interaction. One significant difference between the two types of interactions is that while the 1e,2e

*To designate a torsion angle, three bonds in succession involving four connected atoms have to be considered (Bucourt 1974), e.g., $\phi_{a,\,b,\,c}$ where a, b. and c are bonds. Ordinarily, the position of the central bond, i.e., b is indicated. Models will be helpful to understand the diagram (Ib).

and 1e,2a bonds are skewed, the 1a,3a bonds are parallel. As a result, when H is substituted by a bulkier group with longer bond length, the 1,2-interaction does not increase in the same proportion as the 1,3-interaction which is thus more severe.

4. Cis and trans isomerism. When two substituents are 1a,2a, they are typically trans since the dihedral angle between them is 180°. By default, substituents 1e,2e are also trans but the dihedral angle between them is approximately 60°. The cis orientation at the adjacent carbon atoms can be only 1e,2a or 1a,2e with dihedral angle of 60° (more precisely 56°). It will be seen later that the trans isomer exists mostly in the diequatorial conformation (1e,2e). Thus in the cyclohexane chair, there is very little difference between 1,2-cis and 1,2-trans isomers as far as steric proximity is concerned. Considerable differences are, however, realised in practice particularly in the ring-forming ability of the two cis and trans groups which is explained on the basis that an attempt to bring 1e,2a substituents (cis) in a plane flattens the ring reducing 1,3-interaction while such an attempt on 1e,2e substituents pushes the axial groups inwards increasing 1,3-interaction considerably. Cis and trans isomerism in other disubstituted cyclohexanes will be discussed later.

10.2.2 **Ring inversion**

The six axial and six equatorial protons form two sets of chemically non-equivalent (diastereotopic) nuclei with different chemical shifts in NMR, the axial protons appearing at a slightly higher field (ca 0.4—0.5 ppm). However, the NMR spectrum of cyclohexane at ambient temperature shows a sharp singlet which means that the two sets of protons exchange sites at a rate faster than the NMR time scale. The conformational change involved is known as ring inversion, ring reversal, or flipping of the ring and is accompanied with the interchange of 1-3-5 and 2-4-6 carbon planes leading to an inverted chair*. No change in the relative configuration ever occurs during the ring inversion, i.e., substituents which are α remain α and substituents which are β remain β; also cis remains cis and trans remains trans; similarly, *R* centres remain *R* and likewise for *S*.

1. Conformational itinerary in chair inversion. The most obvious way a chair can undergo inversion is through a planar cyclohexane ring. However, this involves a great deal of energy (> 125 kJ mol^{-1}) and is, therefore, very unlikely. According to Hendrickson (1961, 1967), the most plausible transition state is one (III) in which four carbon atoms lie in a plane with the other two alternately above and below the plane (Path A, Figure 10.2). The chair conformer may be suitably

*For simple cyclohexane itself, the ring inversion is a case of degenerate isomerisation since there is no net change in the chemical structure—a null reaction. Such homomeric transformations in which identical ligands are interchanged between distinguishable chemical and/or magnetic environments have been given the general name of topomerisation (Eliel et al 1971). The nomenclature may further be extended based on the topic relationship of the exchanging groups. Thus the exchange of homotopic, enantiotopic, and diastereotopic groups may be referred to as homo-, enantio-, and diastereotopomerisations respectively. In cyclohexane, the hydrogen atoms which interchange sites are diastereotopic and the ring inversion process is a case of diastereotopomerisation.

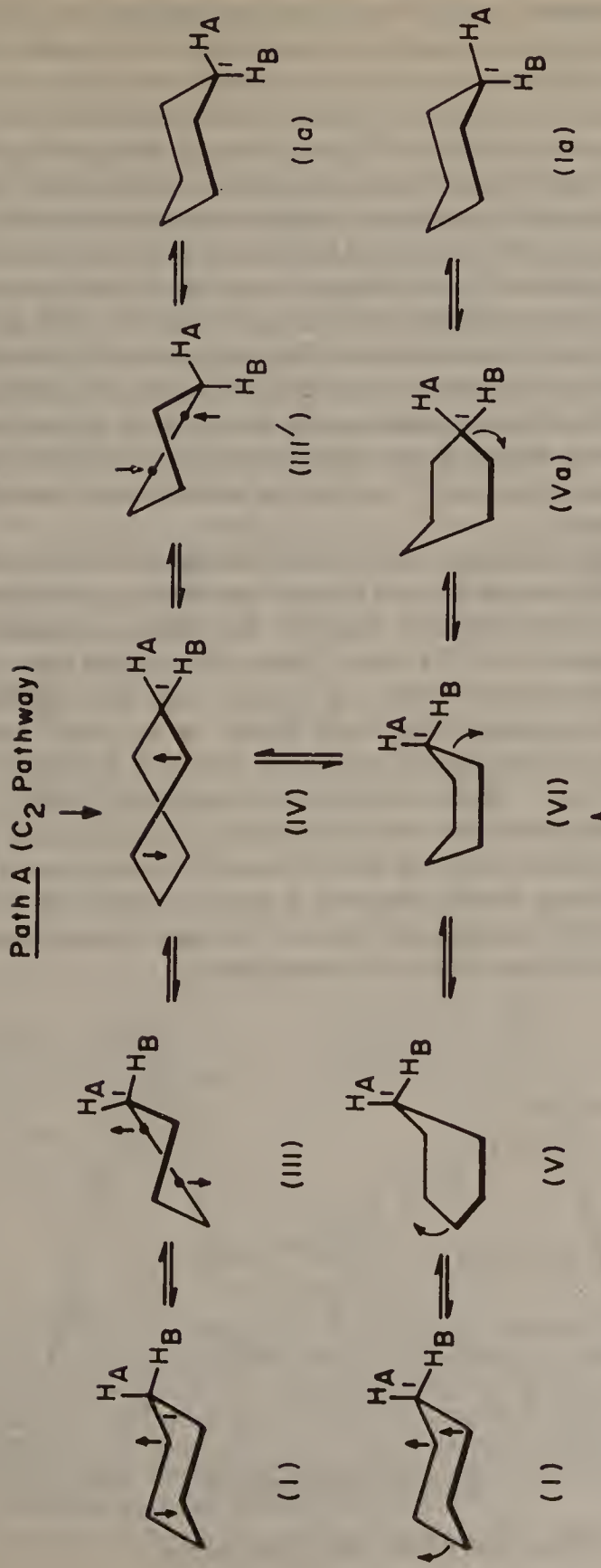


Figure 10.2 Conformational itinerary of cyclohexane

twisted in the directions shown by the arrows to get the transition state (III). There occurs extensive bond angle deformation accompanied by increased torsional strain and the energy of the transition state is computed as 46.0 kJ mol^{-1} which agrees fairly well with that (42-43 kJ mol^{-1}) found experimentally (see later). The transition state conformation (III) has a C_2 axis but no σ plane and belongs to point group C_2 (chiral). Further change along the direction of the arrows leads to the 'twist-boat' conformation (IV) which does not have any angle strain but suffers from some residual torsional strain. Lying in a high energy valley, it corresponds to an energy minimum (23 kJ mol^{-1} with respect to the chair) and is actually a conformer. Three such indistinguishable twist-boats are possible; they are interconverted into one another by pseudorotation. The conformer (IV) can either go back to the original chair through the transition state (III) or be converted into the inverted chair (a topomer of the original) equally well through the enantiomeric transition state (III'). This is shown in the energy diagram (A) in Figure 10.3 and is called the C_2 pathway, since the C_2 axis of the ground state chair form is retained along this pathway.

An alternative pathway (B in figure 10.2) is also possible in which the chair is twisted to an envelope-like transition state (V) with five of the carbon atoms in a plane and the sixth one either above or below it. According to calculation, its energy is only slightly higher (ca 47.3 kJ mol^{-1}) than the transition state (III) (ca 46.0 kJ mol^{-1}) and so this pathway cannot be entirely ruled out. Conformation (V) has a σ plane and so is achiral and leads directly to an energy minimum conformation (VI) which is the classical boat. The latter has a slightly higher energy (by ca 3.7 kJ mol^{-1}) more than the twist-boat and exists in three interconvertible homomeric forms. The boat intermediate in its turn can go back to the original chair or its topomer—through two equivalent transition states (V) and (Va) respectively—with equal facility. Pathway B may be called a σ pathway, since both V and VI retain the symmetry plane of the chair ground state. The energy diagram is shown in Figure 10.3 by the dotted lines.

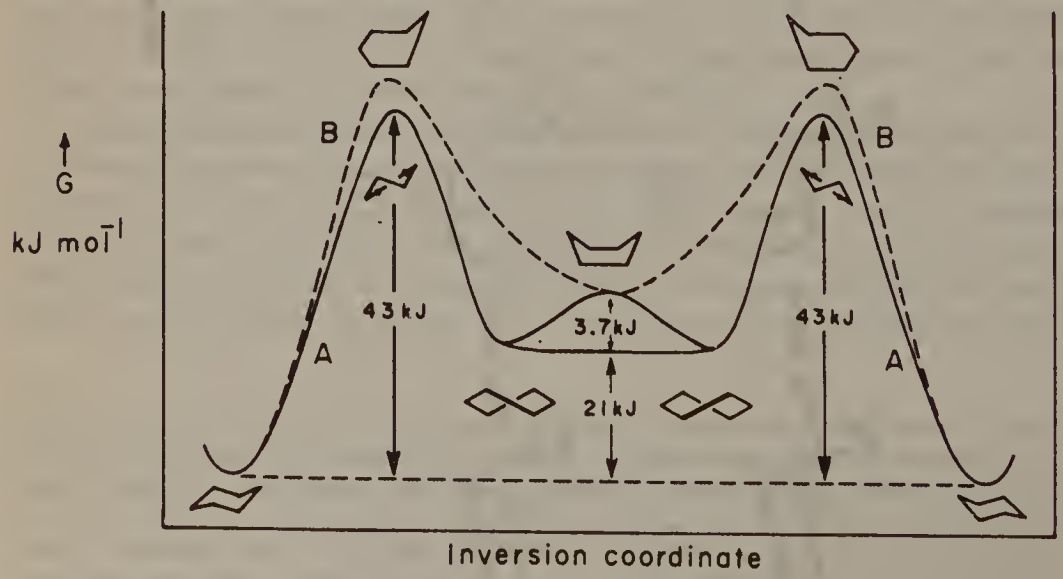


Figure 10.3 Energy profile of ring inversion

In principle, the two pathways (A and B) are mutually exclusive, i.e., the ring inversion takes place either through a twist-boat or through a true boat. However, once a twist-boat or a true boat is formed, they undergo interconversion through pseudorotation* before they are converted back into the chair forms. The entire range of conformations between a true boat and a twist-boat are called *flexible forms* and depending on the nature of substituents, one or the other may be stabilised. The boat form is of slightly higher energy and may be regarded as the transition state of the pseudorotation process. The twist-boat is of lowest energy and the term *flexible* form generally refers to it (in contrast, the chair forms are *rigid* conformers of cyclohexane not interconvertible by pseudorotation). The transition state in path A, i.e., III is a half-chair while that in path B, i.e., V is a half-boat which also suggestes that path A is energetically preferred.

2. The flexible conformers. The boat (B) and the twist-boat (TB) are the two extremes of the flexible forms of cyclohexane. The boat conformation is shown in three different perspectives in Figure 10.4. The conventional boat (VI) with a C_2 axis and two σ planes (point group C_{2v})† shows the following types of bonds: normal equatorial and axial at C-1 and C-4, designated linear (lin) and perpendicular (perp) respectively (one of the perp bonds is also designated flagpole, abbreviated as fp and the other bowsprit abbreviated as bs), four boat-equatorial

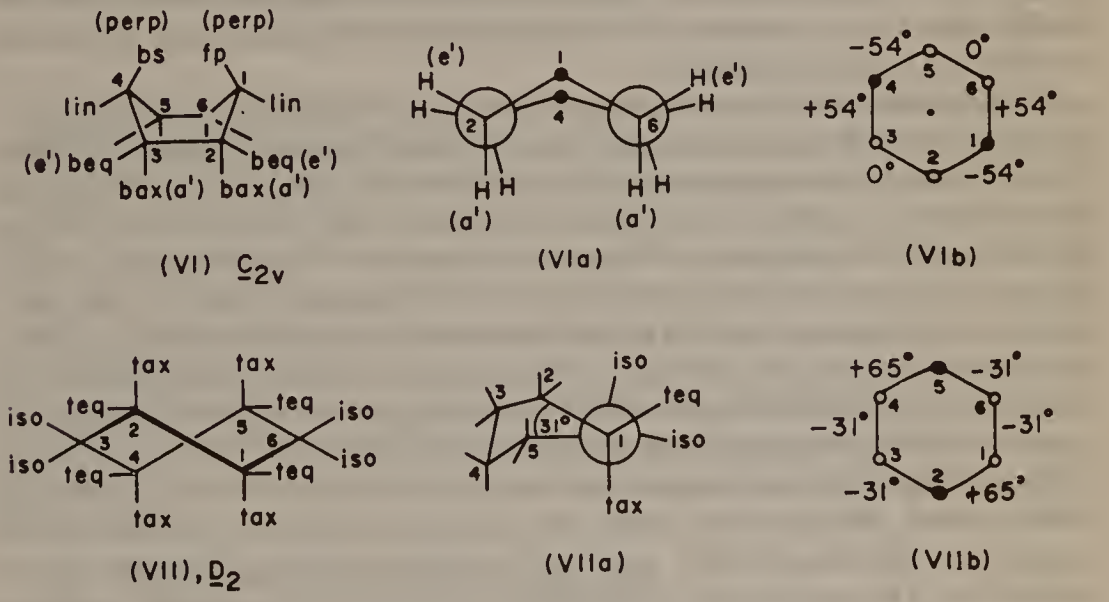


Figure 10.4 Geometry of flexible forms

*The term *pseudorotation* was originally adopted by Pitzer to describe the rotation of the out-of-plane displacements in a puckered cyclopentane ring. It is now used to describe a variety of conformational changes in cyclic systems which are low-energy processes and do not involve bond angle variations but only changes in torsional strain and other non-bonded interactions, as in transformations of the flexible forms of cyclohexanes (but not the chair-chair interconversion) and interconversions of mobile forms of higher cycloalkanes. The rotation is limited to an oscillation of dihedral angles within certain limits without ever making a complete turn (180°).

†It may be noted that symmetry has been reduced relative to the chair both in the boat and in the twist boat.

(beq. or ψ-e, or e′) on C-2, C-3, C-5, and C-6 which are eclipsed in pairs, and four boat -axial (bax. or ψ-a, or a′) on the same four carbon atoms also eclipsed in pairs. The boat consists of four gauche butane and two eclipsed butane units and the strain may be computed as $4\times3.3+2\times18.0=49.2$ kJ mol^{-1} (minimum) or $4\times3.3+2\times26.0=65.2$ kJ mol^{-1} (maximum). The difference in enthalpies between the chair and boat forms is thus 29.4 kJ mol^{-1} (minimum) or 45.4 kJ mol^{-1} (maximum), the enthalpy of the chair being 19.8 kJ $mol.^{-1}$. In addition, the two perpendicular H's at C-1 and C-4 is only 183 pm away giving rise to a non-bonded interaction, known as flagpole-bowsprit interaction. Structure VIa shows the two eclipsed butane units in Newman projection and structure VIb shows the torsion angles according to Klyne-Prelog convention.

If the fp and bs H's are pulled a little apart, the twist-boat results in which the fp-bs interaction is minimised and the conformation becomes more stable. It belongs to point group D_2 ($2\times C_2$) and is chiral. The different bonds are shown in the structure (VII) in which tax, teq, and iso stand for twist-axial, twist-equatorial, and isoclinal (the two geminal bonds are equivalent) respectively. The structure (VIIa) shows one butane unit in Newman projection and the structure (VIIb) shows the torsion angles according to Klyne-Prelog convention. Although the boats and twist-boats (flexible forms) are of high energy, they have favourable entropy due to more degrees of freedom than the chair and the population of the flexible form is approximately 1 in 1000 at ambient temperature quite insufficient for detection by physical methods.

3. Determination of barrier energy. The axial and equatorial protons of cyclohexane form two broad and complex (due to spin-spin coupling) bands in NMR at -100°C and below separated approximately by 0.45 ppm which coalesce to a broad singlet at -66.7° (at 60 MHz). The free energy of activation ($\Delta G^{\ddagger}$) as determined by the coalescence temperature (Chapter 9) is found to be $42.2 + 0.4$ kJ mol^{-1} (Jensen et al 1962). In order to avoid complexity due to spin-spin coupling, cyclohexane-d_{11} (C_6HD_{11}) has been used for variable temperature NMR with deuterium-decoupling so that two sharp signals one due to the axial and the other due to the equatorial proton are obtained (Figure 10.5a) at low temperature (Anet et al 1967). The coalescence temperature is found to be -61.4° (at 60 MHz) corresponding to the free energy of activation of 43.2 kJ mol^{-1}. A complete line shape analysis (which requires measurements of line-widths at different temperatures) gives the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as 45.1 kJ mol^{-1} and 11.7 JK^{-1} mol^{-1} respectively. The large entropy of activation arises from the fact that the transition state (as III) can adopt as many as six (three for simple cyclohexane) conformations giving considerable amount of entropy of mixing. Substituents in the ring do not substantially raise the barrier energy and the usual range of barrier height is 42–50 kJ mol^{-1}.

Anet et al (1975) heated cyclohexane to 800°C when the population of twist-boat form rose to 25% and then suddenly cooled the sample to -253°C on a cesium iodide plate so that all the conformers were frozen*. From the study of kinetics of twist-boat-chair interconversion by IR, the free energy of activation is found to be

*The procedure is known as matrix separation (see butadiene).

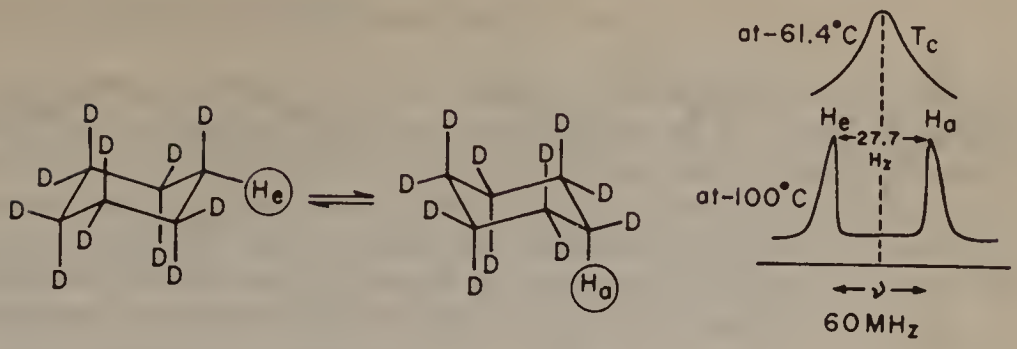


Figure 10.5a Ring inversion of cyclohexane-d_{11}

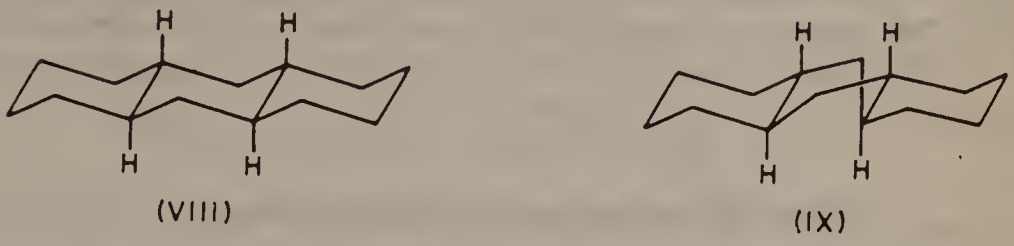


Figure 10.5b Energy of chair and boat forms

22 kJ mol^{-1} which marks the position of the twist-boat conformer almost half-way up the energy path to the transition state of chair-chair conversion. The entropy of activation is 16 JK^{-1} mol^{-1}. The difference in enthalpies between a chair and twist-boat form of cyclohexane has also been determined (Johnson et al 1963) from heat of combustion data of trans-syn-trans (VIII) (all-chair) and trans-anti-trans (IX) (with the central ring as twist-boat) isomers of perhydroanthracenes (Figure 10.5b). By taking due consideration of the heat of vaporisation of each isomer and the destabilising effect (ca 2.5 kJ mol^{-1}) of the two terminal rings on the flexible form, ΔH came up to a value of 20.1 kJ mol^{-1}. The difference in free energies of the twist-boat and the true boat has been computed by Hendrickson to be around 3.7 kJ mol^{-1}. All these values are shown in the energy profile diagram (Figure 10.3).

10.2.3 Stabilisation of the flexible conformers

It is evident from the previous discussion that the chair form of cyclohexane is ordinarily the most stable conformer. It may be understood, however, that under certain conditions the boat or the twist-boat can be stabilised in preference to the chair. In some molecules, the configurational requirement is such that the chair form is not possible, as in IX and X. Other factors such as formation of intramolecular H-bond (as in XI) or electronic effects (as in XII) also favour the formation of the flexible conformers. Finally, structural features of some molecules force them to exist exclusively in one or the other of the cyclohexane conformers. Examples are fixation of chair form in adamantane (XIII), fixation of boat form in pentaasterane (XIV), and fixation of twist form in twistane (XV) (Figure 10.6).

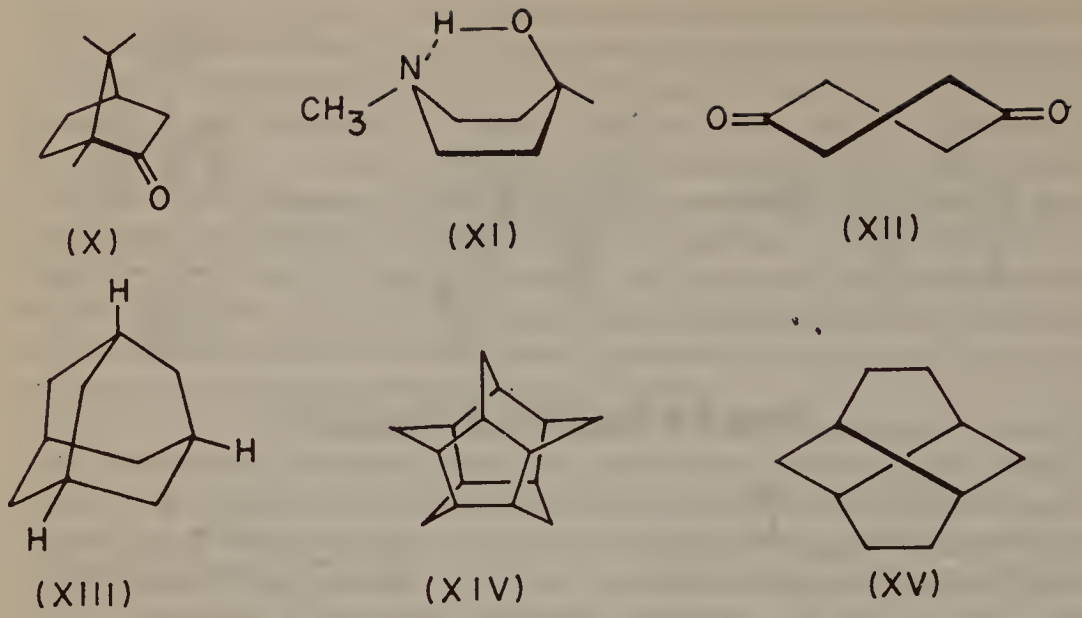


Figure 10.6 Rigid molecules from cyclohexane conformers

10.3 Conformations of monosubstituted cyclohexanes

Monosubstituted cyclohexanes exist in two non-equivalent diastereomeric chair conformations, one with the substituent in the equatorial position (conformer E) and the other with the substituent in the axial position (conformer A), shown for methylcyclohexane by the structures (XVIa) and (XVIb) or (XVIc) (Figure 10.7) respectively. The following points are to be considered in connection with monosubstituted cyclohexanes.

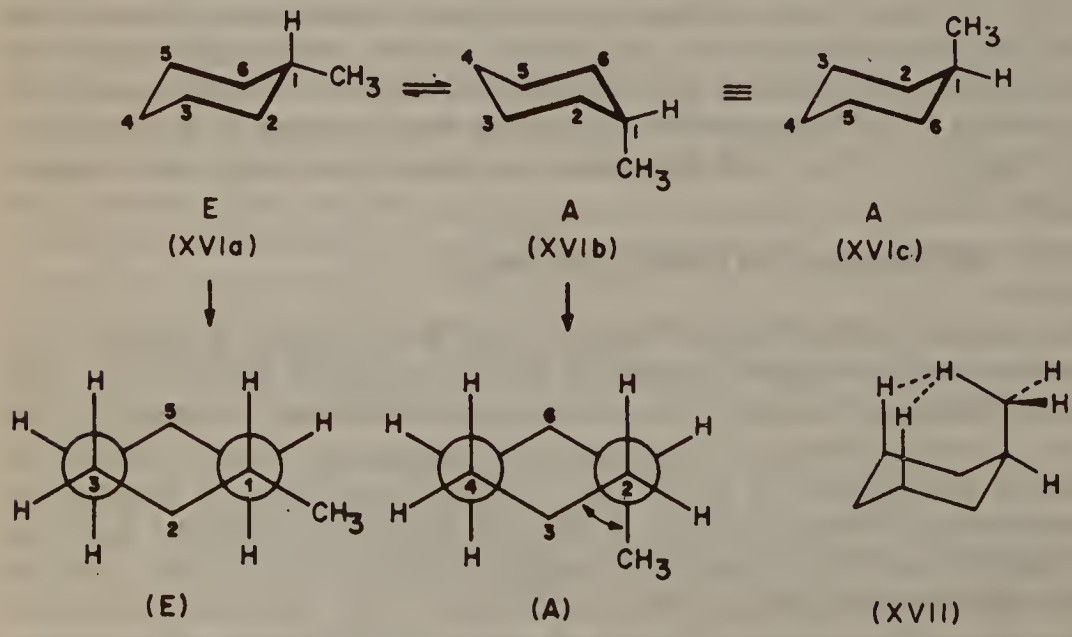


Figure 10.7 Conformers of methylcyclohexane

10.3.1 Transition states and intermediates

Energy barrier of ring inversion in substituted cyclohexanes remains practically unaffected. The number of possible transition states and the flexible forms (there are six different carbon atoms to which the substituent can be attached), however, increases because of the loss of symmetry in the molecule. The energy profile diagram is similar to that of cyclohexane ring inversion (Figure 10.3) except for the fact that the two chair conformers have different enthalpies and free energies and the rates of interconversion are different from the two sides.

10.3.2 Conformational free energy

The most significant fact from the point of view of conformational analysis is that the two diastereomeric chair forms are of unequal free energy and so are differently populated, the equilibrium constant K being given by the equation :

$$\Delta G^\circ = -RT \ln K \qquad \text{where } K = \frac{[E]}{[A]} \tag{1}$$

ΔG° which is usually negative is the difference of free energy between the equatorial and axial conformers and $-\Delta G^\circ$ is known as conformational free energy of the substituent (sometimes known as A-value). It determines the equatorial preference of the substituent in the substituted cyclohexane which is based on steric ground as explained before* (in some cases, electronic factor may also operate) and is best exemplified by methylcyclohexane. Thus the equatorial conformer (XVIa) does not have any additional gauche butane interaction, the two new butane units, e.g., Me-C_1-C_2-C_3 and Me-C_1-C_6-C_5 (shown by thick lines) having anti orientation. On the other hand, the axial conformer (XVIb) has two additional gauche interactions involving Me-C_1-C_2-C_3 and Me-C_1-C_6-C_5. In the partial Newman projection (E) (Figure 10.7) for the equatorial conformer, no extra gauche interaction is seen whereas in the one (A) for the axial conformer, an extra gauche interaction is observed (the second gauche can be seen in the projection along 1-6 bond). The overall steric interactions may also be evident from the inspection of the structure (XVII) in which the axial methyl protons are very near (183 pm) to the synaxial protons. When the methyl group is equatorially placed, no such interaction exists. Based on the number of additional gauche interactions, the difference in enthalpy of the two conformers is 6.6 (2×3.3) kJ mol^{-1}. If ΔH is equated to ΔG ($\Delta S \approx 0$), the value corresponds to a population of equatorial conformer over 90% (actually 95% as found by NMR) at ambient temperature. The conformational free energies ($-\Delta G^\circ$ values) of a number of

*According to a suggestion of Allinger (Wertz and Allinger 1974), it is the tertiary hydrogen which has a preference for the axial position which leaves the substituent in the equatorial position by default (equatorial hydrogen effect). The arguments—which are based on the assumption that while a gauche methyl interaction can be substantially relieved by ring flattening and deformation of bond angles, the gauche H-H interaction cannot get any such relief and this ultimately becomes the deciding factor—are too much involved and since there has been dispute over them, are not discussed here (see also Chapter 9).

common substituents are listed in Table 10.2 (Hirsch 1967). The values are variable; the data in the table show averages.

Table 10.2 Conformational free energies ($-\Delta G°$) in kJ mol^{-1} for some common substituents

Substituent.	$-\Delta G°$	Substituent.	$-\Delta G°$	Substituent.	$-\Delta G°$	Substituent.	$-\Delta G°$
F	0.63	OH	2.18[a]	NH_2	5.03[a]	CH_3	7.50
Cl	1.80	OH	3.65[b]	NH_2	6.70[b]	C_2H_5	8.10
Br	1.59	OCH_3	2.51	NO_2	4.60	$CH(CH_3)_2$	9.00
I	1.80	OC_2H_5	2.96	CO_2H	5.65	$C(CH_3)_3$	20.00
CN	0.71	$OCOCH_3$	2.51	CO_2Me	5.32	C_6H_5	12.60

[a]in aprotic solvent. [b]in protic solvent.

The following points are of interest in the context of the data in Table 10.2:

1. In the halogen series, F has the least effective bulk as expected. The conformational free energies of Cl, Br, and I are almost equal which is due to the fact that as the size of the halogens increases, the bond length also increases and with it the distance from the synaxial hydrogens. Secondly, with larger atomic volumes, the atoms become more polarisable and easier to deform and the van der Waals attractive forces (dispersion forces) also become more prominent near the contact distance. To generalise, the elements of the first two rows in the Periodic Table with relatively short bonds to carbon and low polarisability of their electrons show larger $-\Delta G°$ values than the heavier elements with longer bonds to carbon and higher polarisability of electrons.

2. It is the number and nature of substituents at the first atom connected to the ring which are more important. Substituents at the next atom (as in OCH_3, OC_2H_5, OTs, $OCOCH_3$) do not affect the effective bulk very much (see also Chapter 9).

3. For the same reason, the $-\Delta G°$ value of CH_3 and C_2H_5 (and to some extent i-C_3H_7) do not differ to the extent expected on the basis of their space-occupying volumes. On the other hand, the value increases sharply for *t*-butyl which has the highest effective bulk in the series. In the case of ethyl and isopropyl, the syndiaxial interaction may be minimised by turning the α-hydrogen inwards which is not possible for the *t*-butyl group. The high conformational energy of *t*-butyl ensures that the group has an almost total preference for equatorial disposition so that the ring system becomes anancomeric (Chapter 12).

4. Groups like OH, NH_2, NHMe etc. which form H-bonds have different $-\Delta G°$ values in protic and aprotic solvents.

5. Although not intrinsic in the definition, the $-\Delta G°$ values are approximately additive so that they may be used for di- or polysubstituted cyclohexanes.

10.3.3 Isolation and characterisation of conformers

Although at ambient temperature the interconversion of cyclohexane conformers is very fast, at $-100°C$ or below it is slow enough so that the two conformers of a substituted cyclohexane can be studied independently by NMR. Thus at $-115°C$,

the methine proton of chlorocyclohexane resolves into two sets of signals, the one at δ4.50 ppm (broad singlet) being due to the equatorial and the other (multiplets) at δ3.80 ppm being due to the axial proton (Figure 10.8). The equatorial proton is coupled with adjacent methylene protons which are all gauche (with low coupling constants) (see Chapter 9) and so gives a broad signal while the axial proton is coupled with both equatorial and axial protons (with high coupling constants) and gives well resolved multiplets (Jensen et al 1966, 1969). Their relative intensity provides the conformational free energy at $-115°$. At $-150°C$, the equatorial conformer crystallises out and the mother liquor can be decanted off thus effecting a separation of the two conformers. The solid when redissolved in a better solvent at very low temperature gives the NMR spectrum of the equatorial conformer (δ3.80 ppm) while the mother liquor gives largely the NMR spectrum of the axial conformer (δ4.50 ppm) recorded for the C*H*Cl proton.*

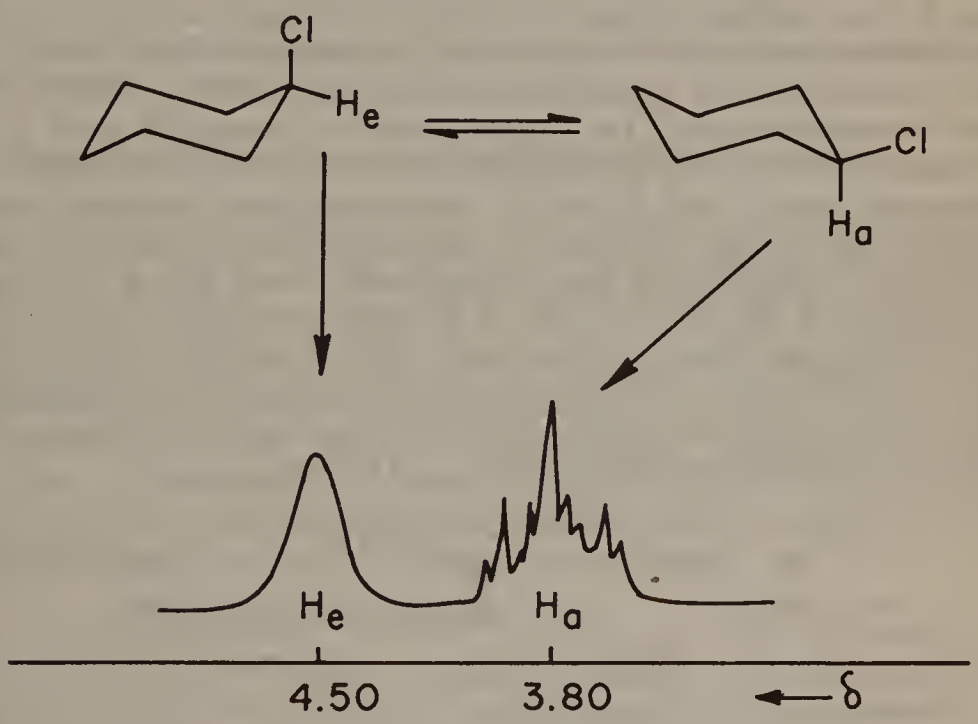


Figure 10.8 Low temperature NMR spectrum of conformers of chlorocyclohexane

Even though separation of two conformers is not always possible, their relative population, rate of interconversion, and the thermodynamic parameters of the exchange process may be studied by NMR. It has been computed (Jensen et al 1969) that equatorial chlorocyclohexane has a half-life of 22 years at $-160°$, 23 minutes at $-120°$, 0.25 second at $-60°$, and 10^{-5} second at 25°C.

*In IR, even at ambient temperature, the two C-Cl bonds can be distinguished. Thus liquid chlorocyclohexane exhibits two C-Cl stretching frequencies, 684.5 and 731 cm^{-1} for the axial and equatorial bonds respectively. Crystalline chlorocyclohexane gives only the 731 cm^{-1} band characteristic of the equatorial bond.

10.3.4 Determination of conformational free energy

The principle of conformational analysis by physical methods including different spectroscopic techniques has already been discussed in a previous chapter. Because of conformational simplicity, its application in cyclohexane system is more straightforward. A particular property, be it physical or chemical, is determined by some suitable means for each of the two conformers and the same property is measured for the conformationally mobile system at a given temperature. Three values, P_a (for axial), P_e (for equatorial), and P (for the mobile) are thus obtained and the equilibrium constant K may be determined by the relation :

$$K = \frac{P_a - P}{P - P_e} = \frac{[E]}{[A]} \qquad (2)$$

This is direct method (it does not require any reference compound) and P may be chemical shifts (δ) in NMR or stretching frequencies (cm^{-1}) in IR. The case of chlorocyclohexane discussed above is a typical example in which δ_a and δ_e are determined directly. The conformational free energies of most of the substituents have been determined by NMR using the low-temperature method.

In certain cases P_a and P_e may be determined from appropriate model compounds (see Chapter 12). Thus *cis*- and *trans*-4-*t*-butylcyclohexyl bromides (XVIIIa) and (XVIIIb) which are conformationally biased (Figure 10.9) show chemical shifts of 198 and 160.5 Hz (at 60 MHz) respectively for α-H while bromocyclohexane shows a chemical shift of 191.5 Hz (Eliel 1959). Putting the values in the equation (2) and assuming that the presence of the *t*-butyl group does not affect the chemical shifts, K is found to be 4.8 corresponding to 83% of equatorial population ($-\Delta G°_{Br} = 3.8$ kJ mol^{-1}).*

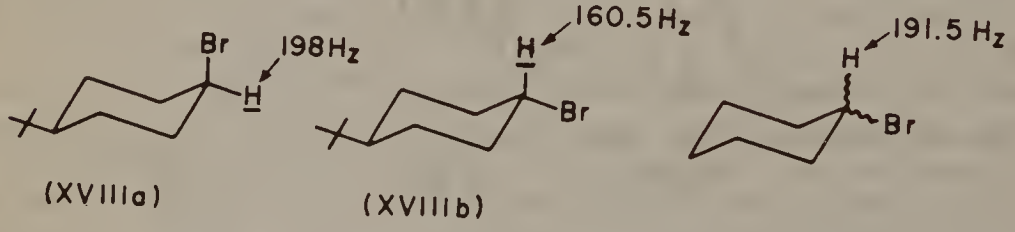


Figure 10.9 Determination of K from conformationally biased molecules

A similar kinetic method substituting P by rate constants in equation (2) will be discussed in Chapter 12.

A chemical method is often used in which two diastereomers are equilibrated and the equilibrium concentration of each is determined. If during equilibration, one of the groups remains unaltered in position, then the conformational free energy of the second group can be calculated from the equilibrium constant. Thus the *cis*- and *trans*-4-*t*-butylcyclohexanols (XIXa) and (XIXb) (Figure 10.10) are

*—$\Delta G°$ values depend very much on the method used and in the case of polar compounds, also on solvent (see Eliel et al 1965).

equilibrated by heating with Raney nickel in refluxing benzene. In the product which is analysed by gas chromatography, the *t*-butyl group always remains in the equatorial position. The equilibrium constant for the reaction (28% of XIXa and 72% of XIXb) gives a value of $-\Delta G°_{OH}$ of 2.9 kJ mol^{-1} (Eliel and Schroeter 1965) in benzene solution.

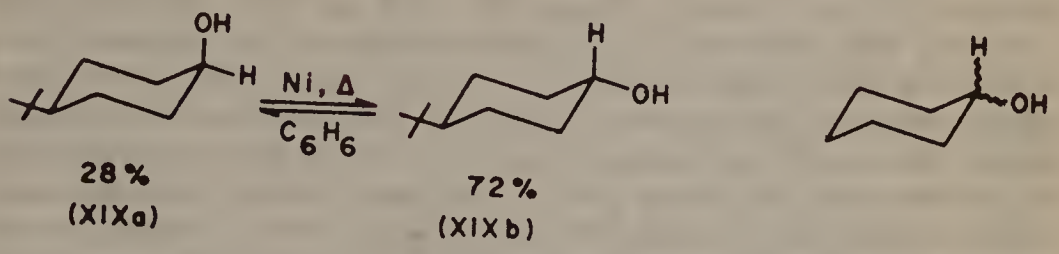


Figure 10.10 Equilibration of 4-*t*-butylcyclohexanols

The various methods used for determining the conformational energies have been reviewed (Jensen and Bushweller 1971).

10.4 Conformations of di- and polysubstituted cyclohexanes

The principle of conformational analysis as applied to monosubstituted cyclohexanes may be extended to di- and polysubstituted cyclohexanes. Two additional points, however, have to be considered. These compounds generally exist in two or more diastereomeric forms and each of them is capable of existing in two (sometimes even more) conformers. It is desirable to examine each pair of conformers of a diastereomer in terms of symmetry, enthalpy, entropy, and free energy and to ascertain the preferred conformation. Comparison is then made between the diastereomers through the preferred conformer or conformers of each. Secondly, the substituents may interact among themselves sterically or otherwise and these interactions must be included in the analysis.

10.4.1 1,1-Disubstituted cyclohexanes

The case of 1,1-disubstituted (geminally substituted) cyclohexanes is relatively simple. They do not exhibit any configurational isomerism but exist in two interconvertible conformers (XXa) and (XXb) (Figures 10.11) separated by an energy barrier usually of the same order of magnitude as the cyclohexane ring inversion. When X and Y are the same as in 1,1-dimethylcyclohexane, the two conformers are identical (topomers). When X and Y are different as in 1-methylcyclohexanol, the two conformers are diastereomers and present in unequal amounts. In principle, the ratio of the two conformers should correspond to the difference in the conformational free energies of the two substituents. However, in reality, this seldom happens; although the conformer with the bulkier substituent in the equatorial position often predominates, there is a levelling effect, the preferred conformer being considerably less populated than expected. Thus 1-methylcyclohexanol exists as a 70 : 30 mixture of axial (XXIa) and equatorial (XXIb) conformers in dimethyl sulphoxide at 35° corresponding to a free energy difference

of 2.0 kJ mol^{-1} whereas the actual difference between $-\Delta G°$ values of Me and OH is around 3.5 kJ mol^{-1}. In some cases, the opposite conformer may predominate. Thus in 1-methyl-1-phenylcyclohexane, the conformer (XXIIa) with axial phenyl and equatorial methyl is preferred over the other (XXIIb) with equatorial phenyl and axial methyl by 1.33 kJ mol^{-1} inspite of the appreciable difference of $-\Delta G°$ values of Ph and Me which are 12.6 and 7.5 kJ mol^{-1} respectively and would lead to an opposite conclusion. The explanation is as follows. The phenyl ring in XXIIa is so oriented (see structure XXIII) that it interacts minimally with the axial 3-H and 5-H. There may be some interactions between the ortho H's and the adjacent equatorial H's. In the conformer (XXIIb), on the other hand, the phenyl group in its usual bisecting orientation would interact strongly with the methyl H's (see structure XXIV). Therefore, it must rotate to confront the ring (see structure XXV) but now there appear strong interactions between the ortho H's and the adjacent e-H's (Eliel 1985). The lack of additivity of $\Delta G°$ values in geminally substituted cyclohexanes is also demonstrated by other examples (see Eliel et al 1965).

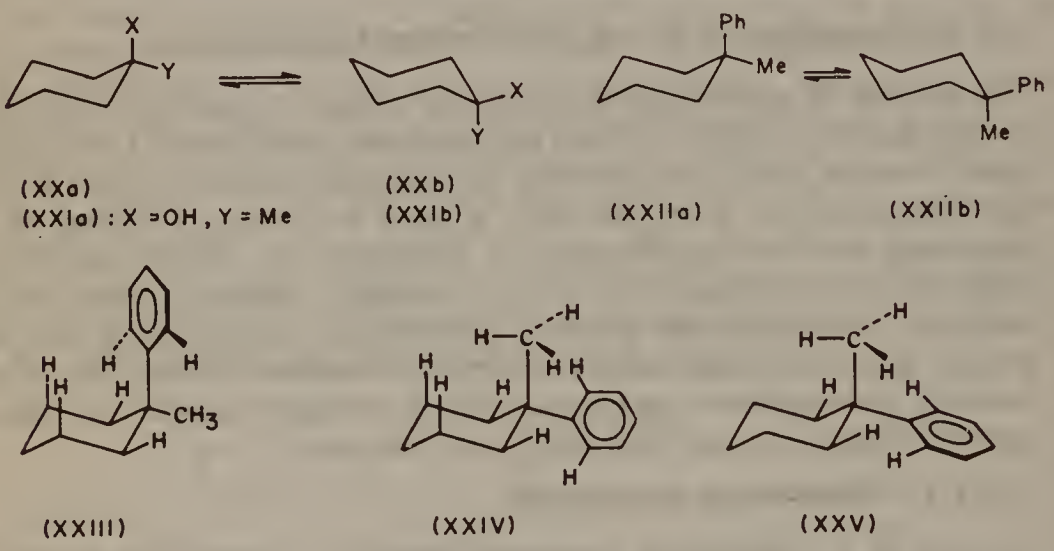


Figure 10.11 Conformations of geminally substituted cyclohexanes

10.4.2 **Disubstituted cyclohexanes**

Non-geminally disubstituted cyclohexanes exist in three sets of positional (constitutional) isomers, e.g., 1.2-, 1,3-, and 1,4-isomers. Each set constitutes a cis-trans pair of diastereomers each of which in turn exists in two interconvertible chair conformers. In addition, depending on symmetry property, a particular isomer may exhibit enantiomerism. These points are illustrated with the dimethylcyclohexanes. In Figure 10.12, all the isomers are drawn first in planar structures and then in chair conformations. In the case of resolvable (±)-pair, only one enantiomer is shown.

1. 1,2-Dimethylcyclohexanes. *cis*-1,2-Dimethylcyclohexane exists in two energetically equivalent axial-equatorial (a,e) and equatorial-axial (e,a) conformations.

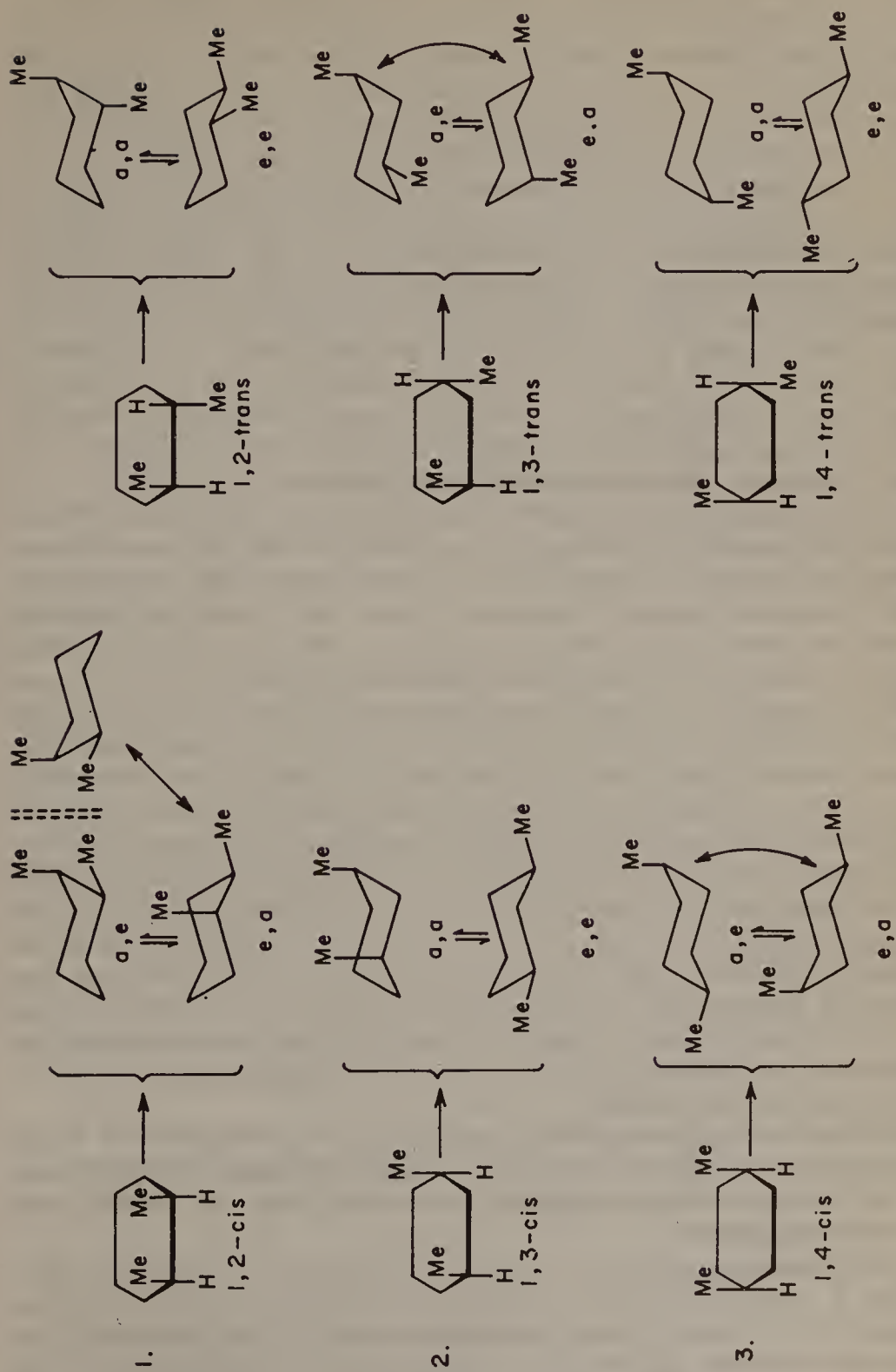


Figure 10.12 Configurations and conformations of dimethylcyclohexanes (the double-headed arrows indicate identity and the reversible arrows ring inversion)

They are non-superposable mirror images of each other and constitute a pair of readily interconvertible enantiomers. Thus while the planar structure shows the cis isomer as a meso compound, the chair conformation shows it as a non-resolvable racemic mixture. This, however, contributes a positive entropy of mixing (see below). The second major deviation from the planar structure is in the dihedral angle between the two vicinal methyls which is 0° (true cis) in the planar structure but 60° (gauche) in the chair conformation. Either of the chair conformers contains three gauche butane interactions (two for one axial methyl and one for e,a-dimethyl) corresponding to a potential energy of 11.2 kJ mol^{-1} (with respect to a hypothetical structure with no extra interaction).* The entropy of such compounds originates from three sources: (i) entropy due to symmetry number ($-R\ln\sigma$), (ii) entropy due to mixing of conformers, and (iii) entropy due to a (±)-mixture ($R\ln 2$). For the cis-1,2 isomer (C_1 symmetry), σ is 1 and so its contribution to entropy is nil; the second and the third factors happen to be the same : the two conformers being enantiomeric contribute an entropy of mixing, $R\ln 2$. The thermodynamic data, calculated and experimental, are listed in Table 10.3.

trans-1,2-Dimethylcyclohexane likewise exists in two chair conformations - diaxial (a,a) and diequatorial (e,e) - which are non-equivalent and like the planar structure are chiral (C_2 symmetry). Unlike the 1,2-cis, the 1,2-trans isomer occurs in two distinct enantiomers forming a resolvable (±)-pair. The diequatorial conformer contains one butane gauche interaction (due to e,e-dimethyl) while the diaxial conformer contains four (two for each axial methyl) which makes the former preferred over the latter by three gauche interactions (11.2 kJ mol^{-1}) corresponding to a 99 : 1 mixture at 25°C (ΔS is ignored). For comparison purposes, therefore, the trans isomer is represented by the diequatorial conformer with an arbitrary enthalpy of 3.75 kJ mol^{-1}. It is thus more stable than the cis isomer by 7.5 kJ mol^{-1} (two gauche interactions) which is in agreement with experimental data derived from heats of combustion (Table 10.3). The chair conformation differs from the planar structure in one significant point : the dihedral angle between the two methyl groups in the planer structure is 180° (true trans), but that in the diequatorial conformer is 60° (gauche), almost the same as in the cis isomer. This explains the fact that both the *cis*-and *trans*-cyclohexane-1,2-dicarboxylic acids form their own anhydrides. The entropy of the 1,2-trans isomer arises from all the three sources : its symmetry number is 2, it is a (±)-mixture, and it is a 99 : 1 mixture of e,e and a,a conformers.

When the two substituents in the cyclohexane ring are different, both the cis and trans isomers are resolvable, the trans isomer exists in a diequatorial conformation, and the cis isomer in equatorial-axial conformation with the bulkier group predominantly equatorial.

2. 1,3-Dimethylcyclohexanes. In the case of the 1,3-cis isomer, the planar structure as well as the two chair conformers (a,a and e,e) are achiral (due to the presence of a σ plane) which makes this isomer a meso compound. The diequatorial conformer has no gauche interaction while the diaxial has two (one for each axial methyl) corresponding to an enthalpy of 7.5 kJ mol^{-1} and in

*Following Eliel et al (1965), a gauche butane interaction is given a value of 3.75 kJ mol^{-1} (0.9 kcal mol^{-1}).

addition, a 1,3-diaxial Me/Me interaction which contributes an additional energy of 15.5 kJ mol^{-1}. The enthalpy of the diaxial conformer is thus 23.0 kJ mol^{-1} higher than that of the diequatorial making the former almost non-existent (1 in 10,000 at 25°). The trans isomer, on the other hand, exists in two superposable e,a-conformations with two gauche interactions corresponding to an enthalpy term of 7.5 kJ mol^{-1} and is less stable than the cis isomer by the same amount. Thus unlike in the 1,2- (also in the 1,4-) series, the 1,3-cis is more stable than the 1,3-trans isomer - a fact which is not at all evident in the planar configuration. Besides, the distance between the two methyls in the preferred e,e-conformation of the cis isomer is greater than in the e,a-conformer of the trans isomer. Nevertheless, the relative orientation of the substituents remains unaltered, the cis isomer having them always on the same side of the ring (both up or both down) and the trans isomer having them on opposite sides of the ring (one up and the other down). The higher thermodynamic stability of the cis isomers in both 1,3-dimethylcyclohexane and 3-methylcyclohexanol has been experimentally verified (see also Auwers-Skita rule). It is to be noted that 1,3-trans isomer exists in a resolvable (±)-pair. Ring inversion only converts (+) into (+) and (−) into (−) enantiomers and is a topomerisation process. Regarding the evaluation of entropy, all the contributing factors are nil for the cis isomer : σ is 1 and there is no mixture of enantiomers or conformers. For the trans isomer, the only contribution to entropy is due to (±)-mixture (Rln2).

The two substituents in the preferred diequatorial 1,3-cis isomer are quite far apart. However, if necessity arises, the cis isomer can adopt the diaxial conformation by ring inversion bringing the substituents within reacting distance as in the formation of an anhydride from *cis*-1,3-cyclohexanedicarboxylic acid or in the formation of intramolecular H-bond in *cis*-1,3-cyclohexanediol.

When the two substituents are different, both the cis and trans isomers are resolvable; the former exists in a preferred diequatorial conformation and the latter in an equatorial-axial conformation with the bulkier group predominantly in the equatorial position.

3. 1,4-Dimethylcyclohexanes. The analysis of the cis and trans isomers of 1,4-dimethylcyclohexane is done in a similar fashion. The cis isomer exists in two identical e,a- and a,e-conformations and the trans in two non-equivalent e,e- and a,a-conformations of which the latter is destabilised by four gauche interactions (15.0 kJ mol^{-1}). The vertical plane passing through C-1 and C-4 is a σ plane and so all the conformers are achiral (even when the two substituents are different). The trans isomer is preferred over the cis isomer by two gauche interactions or 7.5 kJ mol^{-1} (the cis isomer has two gauche interactions while the trans has none). The cis isomer has all the entropy terms nil while the trans isomer has a symmetry number 2 due to the presence of a C_2 axis bisecting 2-3 and 5-6 bonds which decreases its entropy by Rln2.

When both the substituents are different, the 1,4-trans isomer has the diequatorial conformation while the cis isomer exists in two unequally populated e,a-conformers, the one with the bulkier equatorial group predominating.

It may be pointed out that the use of a planar ring for cyclohexane of point group D_{6h} provides a simpler way of determining the number and the nature

Table 10.3 Conformations, interactions, enthalpies, entropies, and free energies of non-geminal dimethylcyclohexanes[a]

Isomers	Prefd. confn.	No. of gauche (difference)	ΔH_{calcd} (kJ mol^{-1})	ΔH_{exptl} (kJ mol^{-1})	Entropy ($JK^{-1}mol^{-1}$) contribution from: $R\ln\sigma$	(±)	e,e+a,a	Total	ΔS_{exptl} (ΔS_{calcd})	ΔG^{b}_{exptl} (25°C) (ΔG^{b}_{calcd}) (kJ mol^{-1})
cis—1,2	e,a	3			0	5.8	0	5.8		
		(2)	7.5	7.80					3.00[c]	6.9
trans—1,2	e,e	1			−5.8	5.8	0.46	0.46	(5.34)	(5.78)
cis—1,3	e,e	0			0	0	0	0		
		(−2)	−7.5	−8.20					−5.19	−6.65
trans—1,3	e,a	2			0	5.8	0	5.8	(−5.8)	(−5.64)
cis—1,4	e,a	2			0	0	0	0		
		(2)	7.5	7.95					5.00	6.50
trans—1,4	e,e	0			−5.8	0	0.13	−5.6	(5.6)	(5.70)

[a] The numerical values indicate the difference between cis and trans isomers (for sources of information, see Eliel 1962).
[b] ΔG has been calculated from ΔH and ΔS.
[c] The large deviation is probably due to interference with methyl rotation (cog-wheeling) which has not been taken care of.

(diastereomeric and enantiomeric) of stereoisomers which are not immediately evident from the chair conformations. Adoption of planar projection formulae for non-rigid molecules undergoing rapid conformational change has been justified by symmetry-based arguments (Leonard et al 1975)*.

10.4.3 A few atypical disubstituted cyclohexanes

The conformational free energies of substituents in cyclohexanes under ideal conditions are expected to be additive; this is found to be true for the dimethylcyclohexanes as evidenced by the excellent agreement between the experimental and calculated values of the thermodynamic parameters (Table 10.3). The additivity rule is observed for substituents other than methyl particularly in 1,4-disubstituted and to a lesser extent in 1,3-disubstituted cyclohexanes. However, discrepancy arises in the 1,2-disubstituted cyclohexanes because of increased interaction between the two substituents (proximity effect). Thus there is a clear discrepancy between the experimental and calculated entropy difference in the cis-trans isomers of 1,2-dimethylcyclohexanes (Table 10.3).

Other factors which interfere with the additivity rule are the presence of polar groups leading to dipole-dipole interaction and the formation of intramolecular H-bond. Even the presence of a bulky group such as *t*-butyl, commonly used as a 'holding' group may cause appreciable change in the conformational situation by distortion of the ring as well as by through-space and through-bond effects (see Buys and Eliel 1970). A few examples are given below to show the various effects other than steric in conformational analysis.

1. Dipole-dipole interaction. The trans isomers of 1,2-dihalocyclohexanes which have been thoroughly investigated (by IR and NMR spectroscopy as well as measurement of dipole moments) provide examples of the effect of dipole-dipole interactions on conformation. In these compounds, the diaxial conformer which is almost non-existent in the dimethyl series is substantially populated sometimes more so than the diequatorial one. The percentage of diaxial conformers increases across the series : Cl < Br < I. In the diaxial forms (XXVIa), (Figure 10.13a) the two dipoles are oppositely placed ($\theta = 180°$), the dipole moment is nearly zero, and there is no electrostatic interaction between them. On the other hand, in the diequatorial conformers (XXIb), the two dipoles are oriented at a dihedral angle of 60° (the same as in the cis isomer) and there is considerable electrostatic repulsion which destabilises the diequatorial conformers. The opposing effects of steric interaction and dipole-dipole repulsion are evident in the equilibration of 4-*t*-butyl-1,2-dibromocyclohexane. The equilibrium mixture consists of almost equal amounts of the two diastereomers : the diaxial (XXVII) and diequatorial (XXVIII) forms. For *trans*-1,2-dibromocyclohexane itself, the relative population of a,a- and e,e-conformers depends on the state of aggregation and the nature of solvents as shown in Table 10.4.

*The conversion of the chair of cyclohexane into the other leads to a permutation group whose combinational properties are identical with D_{6h}, the point group of the planar structure.

Table 10.4 Relative population of a,a- and e,e-conformers in *trans*-1,2-dibromocyclohexane

State of aggregation	% of a,a-conformer	% of e,e-conformer
Liquid	65	35
Gaseous	95	5
In CCl_4	84	16
In C_6H_6	52	48

In solution, the relative population of the two conformers depends on the solvent polarity, the diequatorial form being more stabilised by increasing solvent polarity. The dipole moment of the trans isomer changes with solvents but that of the cis isomer remains reasonably constant. *trans*-1,2-Dichlorocyclohexane exists exclusively in the e,e-conformation in crystal, shows some a,a-conformer in the liquid, but in the gaseous state, the a,a-form predominates. The ring inversion parameters (a,a⇌e,e) in dihalides are $\Delta H^{\ddagger} = 42.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -12.0 \pm 8\,JK^{-1}$ (Ehrhardt and Vaughan 1981).

2. Effect of H-bond. The effect of intramolecular H-bonding in stabilising the diaxial conformation of *cis*-cyclohexane-1,3-diol has already been mentioned. Both the *cis* and *trans*-cyclohexane-1,2-diols show intramolecular H-bonding which is slightly stronger in the cis than in the trans isomer (the shift of OH stretching frequency from that of free OH being 38 and 33 cm^{-1} respectively). In the *trans*-2-halocyclohexanol, the diequatorial conformer (XXIXa) is stabilised through intramolecular H-bonding and the diaxial conformer (XXIXb) has the advantage of the absence of electrostatic repulsion between the two dipoles (Figure 10.13b). A compromise is reached and the two conformers are almost equally populated.

3. Cis preference for 1,2-disubstituted cyclohexane. A rare example of cis-preference is recorded (Pasto and Rao 1969) for 2-*t*-butylcyclohexanols which on equilibration with Raney Ni give a preponderance of the cis (XXX) over the trans (XXXI) isomer corresponding to $\Delta G_{296}°$ of 2.3 kJ mol^{-1}, ΔH of 3.3 kJ mol^{-1} and ΔS of 3.6 JK^{-1} mol^{-1} (from cis to trans). The relatively low ΔS precludes the existence of any flexible form. This is probably due to the interaction of a Me in the *t*-butyl group with OH although it is not clear why this is less in the cis isomer.

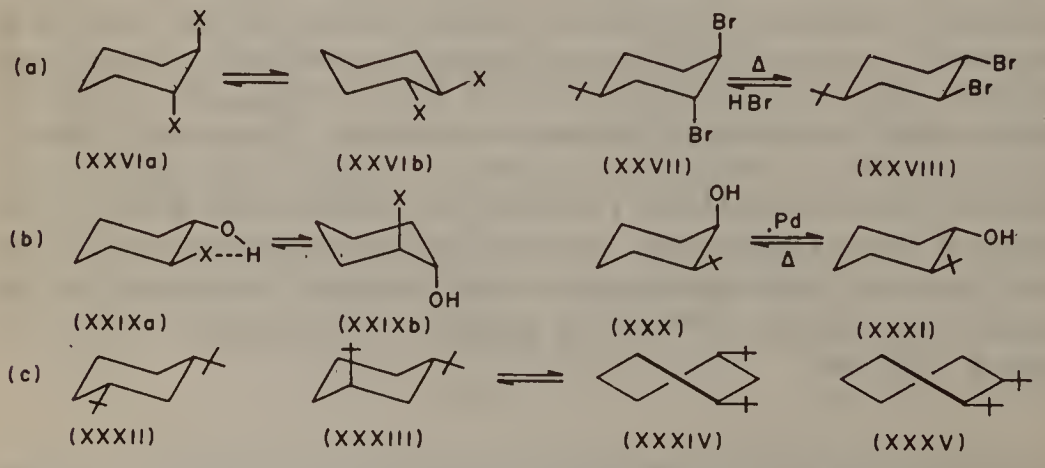


Figure 10.13 Effect of dipole moment, H-bonding, and bulky substituents on conformation

4. Twist-boat conformers. In some cases, the presence of two or more bulky groups like *t*-butyl may destabilise the normal chair and one or more of the flexible forms predominate. Thus the cis isomer of 1,3-di-*t*-butylcyclohexane exists in chair conformation (XXXII) with both the *t*-butyl groups placed in equatorial positions. But in the trans isomer, one of the *t*-butyl groups has to be placed in an axial position which would make the chair conformer (XXXIII) highly strained (Figure 10.13c). The steric interaction can be substantially reduced in the flexible conformation (XXXIV). The cis and the trans isomers are equilibrated by heating with Pd (Allinger and Freiberg 1960) and the thermodynamic parameters are as follows: $\Delta H = 25.0$ kJ mol^{-1}, $\Delta S = 20.5$ JK^{-1} (from trans to cis). The high value of ΔS is consistent with the flexible form for the trans isomer and that of ΔH also agrees with the calculated value (difference in chair and twist forms) which is approximately 22.0 kJ mol^{-1}. More recently, the cis isomer of 1,2-di-*t*-butylcyclohexane has been shown by low temperature NMR (Kessler et al 1968) to exist as an equilibrium mixture of a chair and a number of flexible conformers (as XXXV).

5. Reflex effect. If two or more substituents are placed in 1,3-diaxial positions in cyclohexane, a considerable amount of steric interaction results. To avoid the steric strain, the ring flattens on the side of the substituents and in so doing, the axial positions on the other side of the ring become congested. Thus the strain on one side of the ring is reflected on the other side and this effect is known as the *reflex effect* (Ourisson et al). The reflex effect also interferes with the normal conformational analysis and will be discussed in connection with polysubstituted cyclohexanones (Section 10.5.1).

10.4.4 Conformation of polysubstituted cyclohexanes

The conformational analysis of polysubstituted cyclohexanes is rendered more difficult because of the increased number of interactions among the substituents. A few typical examples are discussed here which have been studied through chemical equilibrium between two or more diastereomers at different temperatures. The preferred conformation of each diastereomer is evaluated on the basis of various interactions and the experimental thermodynamic parameters compared with the calculated values. In general, the conformers with the higher number of equatorial substituents are more stable.

1. 1,3,5- Trimethylcyclohexanes. 1.3.5- Trimethylcyclohexane is capable of existing in two meso diastereomers, the cis represented by the formula (XXXVI) and the trans by XXXVII (Figure 10.14). The alternative conformers obtained by ring inversion are too unstable due to 1,3-diaxial Me-Me interaction and may be ignored. Their equilibria at different temperatures have been studied by heating with palladium. The values of $\Delta H_{25}°$ and $\Delta S_{25}°$ are 8.8 kJ mol^{-1} and 9.6 JK^{-1} mol^{-1} respectively which agree fairly well with the calculated values (ΔH corresponds to two gauche butane interactions in the trans, i.e. 7.5 kJ mol^{-1} and ΔS corresponds to Rln3 or 9.2 JK^{-1} mol^{-1} in favour of the cis isomer which has a symmetry number 3 in contrast to 1 for the trans isomer). The conformations of 1,2,3-trimethylcyclohexanes have been studied by ^{13}C-NMR (Dalling and Grant 1972).

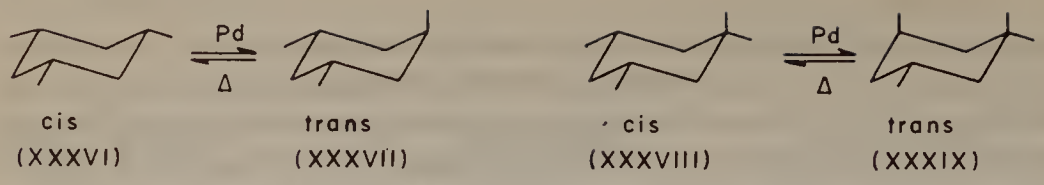


Figure 10.14 Equilibration of tri- and tetramethylcyclohexanes

2. 1,1,3,5-Tetramethylcyclohexanes. 1,1,3,5-Tetramethylcyclohexane exists in a meso cis form (XXXVIII) and a resolvable (±)-trans form (XXXIX) (Figure 10.14) and their chemical equilibrium at different temperatures has been studied (Allinger and Miller 1961). The cis isomer has the preferred triequatorial conformation (XXXVIII), the inverted conformation with three methyls in synaxial position being too unstable. The trans isomer (XXXIX) on ring inversion leads to an equivalent conformation. From the temperature-dependent equilibria, the values of $\Delta H°$ and $\Delta S°$ (at 300°C) are found to be 15.5 kJ mol^{-1} and 6.9 JK^{-1} mol^{-1} respectively, the cis isomer being more stable than the trans. Both the cis and trans isomers have two gauche butane interactions. But the latter (XXXIX) has, in addition, a 1,3-diaxial Me-Me interaction. The difference in their enthalpies, 15.5 kJ mol^{-1} thus corresponds to the last-named interaction—a value which is generally accepted. Although this severe interaction may lead to some distortion in the geometry, the molecule essentially retains the chair form as evidenced by the entropy change (6.9 as against a calculated value of 5.8 JK^{-1} mol^{-1}).

The equilibration of the cis and trans isomers of 3,3,5-trimethylcyclohexanols (using aluminium isopropoxide) gives a value of 10.0 kJ mol^{-1} for the 1,3-diaxial interaction between Me and OH (Eliel and Haubenstock 1961).

3. Menthols. 2-Isopropyl-5-methylcyclohexanol (menthols) contains three asymmetric centres and exists in 4 (±)-pairs, known as menthol (XL), neomenthol (XLI), isomenthol (XLII), and neoisomenthol (XLIII) (Figure 10.15, only one enantiomer of each is shown). The first two and the last two form epimeric pairs and can be equilibrated with aluminium isopropoxide. They are written in order of their thermodynamic stability, menthol with all the groups equatorial being the most stable and neoisomenthol with Me and OH axially disposed being the least stable. The bulkiest isopropyl group remains equatorial in all these conformations although in the case of neoisomenthol, there may be substantial population of the inverted conformer. The four diastereomeric menthyl amines are similarly analysed.

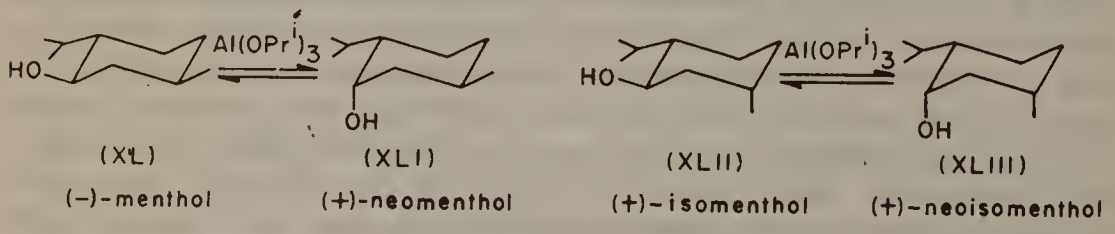


Figure 10.15 Configurations and conformations of menthols

4. 1-Phenyl-2-aminocyclohexanol. The cis isomer of 1-phenyl-2-aminocyclohexanol exists in two conformers (XLIVa) and (XLIVb) (Figure 10.16) both

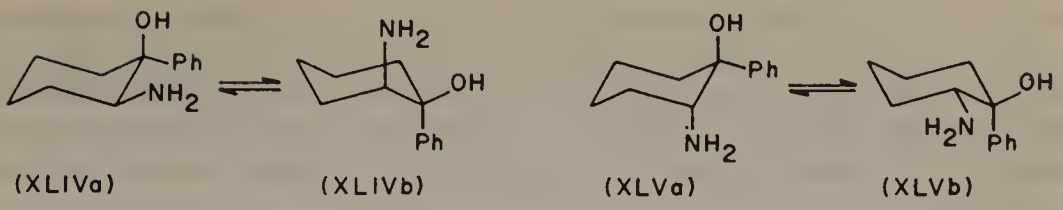


Figure 10.16 Conformers of *cis*- and *trans*-1-phenyl-2-aminocyclohexanols

capable of forming intramolecular H-bond between OH and NH_2 with OH stretching frequency lower than 3600 cm^{-1}. Although the former (XLIVa) has the bulky Ph group equatorial, the conformer is very congested,. The other conformer (XLIVb) with axial Ph interacting minimally with 3-H and 5-H (see Section 10.4.1) may, therefore, predominate. For the trans isomer, however, the conformer (XLVa) with Ph equatorial is clearly preferred over the other (XLVb). Indeed the isomer does not show any trace of intramolecular H-bonding.

5. 1,2,4,5-Tetramethylcyclohexanes. 1,2,4,5-Tetramethylcyclohexane exists in five diastereomeric forms (Table 10.5). Their chemical equilibrium at different temperatures has been determined (Werner et al 1970). Their enthalpies and relative populations are given in the Table which approximately correspond to the calculated values (interactions are shown).

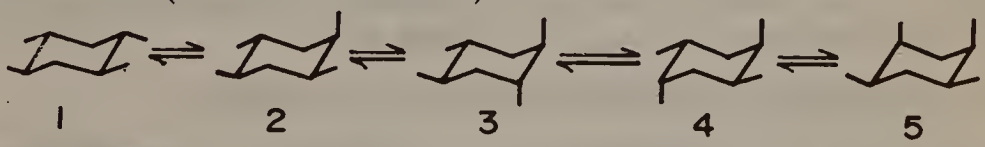


Table 10.5 Conformations of 1,2,4,5-tetramethylcyclohexanes

Conformers: (preferred)	1	2	3	4	5
% at 300°C	53.2	35.1	9.3	1.9	0.5
Δ H° (kJ mol^{-1})	0 *	+ 7.9	+ 12.1	+ 16.3	+ 23.4
Interactions	2g	4g	5g	6g	4g + syn-1,3-Me_2

*The arbitrary base value includes two gauche interactions which are offset in the computation of all $\Delta H°$values)..

It is interesting to know how the increasing substitution affects the barrier energy of cyclohexane ring inversion. 1,1-Dimethylcyclohexane has almost the same $\Delta G^{\ddagger}$ value (42.6 kJ mol^{-1} at 298 K) as cyclohexane itself while 1,1,4,4-tetramethylcyclohexane has a slightly higher $\Delta G^{\ddagger}$ value (47.7 kJ mol^{-1} at 211 K). All-*cis*-1,2,4,5-tetramethylcyclohexane has a barrier to ring inversion of 51.8 kJ mol^{-1} at 261 K and all-*cis*-1,2,3,4;5,6-hexamethylcyclohexane has a barrier of 71.8 kJ mol^{-1} at 338 K which shows that in general two or three alkyl substituents do not increase the barrier energy very much but when the number of substituents is higher, the barrier increases appreciably. Sometimes, even two groups increase the barrier if they are sufficiently bulky. Thus *cis*-1,2-di-*t*-butylcyclohexane has a barrier of 68.1 kJ mol^{-1} at 310 K. The ring inversion parameters are available in a recent text (Oki 1984).

6. Hexachlorocyclohexanes. 1,2,3,4,5,6- Hexachlorocyclohexane in principle should exist in eight configurational isomers one of them being resolvable and the

rest meso. Five of them, designated α (a,a,e,e,e,e), β (e,e,e,e,e,e), γ (a,a,a,e,e,e), δ (a,e,e,e,e,e), and ϵ (a,e,a,e,a,e) (only preferred conformations are indicated), have been investigated by electron diffraction experiments in the gas phase (Hassel et al).There has been close agreement between the experimentally determined enthalpies and those obtained by calculation. The γ isomer is the insecticide gammexane.

7. Inositols. Of the polyhydroxycyclohexanes known as cyclitols, the inositols are most well known because they occur in nature. Like hexachlorocyclohexanes, inositols exist in eight isomeric forms all of which are known and their configurations determined by spectroscopic data and chemical reactions (see Eliel et al 1965). The following points are to be noted:

(*i*) Seven of the isomers are meso and the eighth one (a,a,e,e,e,e,) is resolvable giving a total of nine stereoisomers.

(*ii*) In the case of two isomers (a,e,a,e,a,e) and (a,a,a,e,e,e), the ring inversion gives the same conformation. In the case of one (a,e,a,a,e,e), the two conformers are non-superposable mirror images of each other which makes this isomer non-resolvable (±) -pair.

(*iii*) The higher the number of e-OH, the higher is the stability and the preferred conformer of any isomer is selected on that basis. For isomers with three a-OH groups, the two conformers are equally populated. The number of isomers are predictable from the planar structure (Leonard et al).

10.5 Cyclohexane ring with one and two sp^2 carbons

Introduction of an sp^2-hybridised carbon into a cyclohexane ring brings about several changes: one or more valence angles are increased, the ring slightly flattens in the vicinity of the sp^2 carbon decreasing torsion angles and increasing torsional strain, and finally, the steric interactions among the substituents and between the substituents and the ring change perceptibly. As a result, there is an overall increase in enthalpy of cyclohexanes with an sp^2 hybridised ring atom relative to simple cyclohexanes. Cyclohexanone with one sp^2 carbon has been most thoroughly investigated and illustrates the above points.

10.5.1 Cyclohexanone ring system

In the absence of any complicating factor, cyclohexanone exists almost exclusively (99% at 25°) in the chair form (XLVIa) which on inversion gives a topomer (XLVIb). A small amount (ca 1% at 25°) remains in the flexible forms (XLVIc) and (XLVId) (Figure 10.17). The conformational aspects of cyclohexanones are discussed under the following headings.

1. Geometry. The geometry of the cyclohexanone chair differs slightly from that of cyclohexane:

CH_2- CH_2 bond length = 0.1545 nm (154.5 pm)
CH_2- CO bond length = 0.151 nm (151.0 pm)
C-CO-C bond angle* = 116°

*It is less than 120° which means that flattening is resisted by torsional strain and angle strain does develop.

The torsion angles between pairs of adjacent carbon atoms are given for each conformation according to Klyne-Prelog convention (Bucourt 1974) which shows flattening of the ring at the site of the carbonyl group. The chair form (XLVIa) has only a vertical σ plane passing through C-1, and C-4 and belongs to point group C_s while the flexible forms belong to chiral point groups C_1 and C_2. Due to flattening, the e-H's at C-2 and C-6 in XLVIa are partially eclipsed with the carbonyl oxygen ($\theta = 4.3°$) while the a-H's lean slighlty outwards. The combined effect of angle strain and torsional strain slightly destabilises cyclohexanone relative to cyclohexane. The lower thermodynamic stability of cyclohexanone is manifest in the equilibrium of cyclohexanone cyanohydrin ($sp^2 \rightleftharpoons sp^3$) which lies more towards the cyanohydrin side than that of di-*n*-octyl ketone (K is 70 times as great) *. Similarly, the lower kinetic stability of cyclohexanone is manifest in the fact that it is reduced with sodium borohydride at a rate 355 times as fast as di-*n*-hexyl ketone. These manifestations of strain have long been known; the term I-strain (internal strain) has been coined by Brown for this (see later).

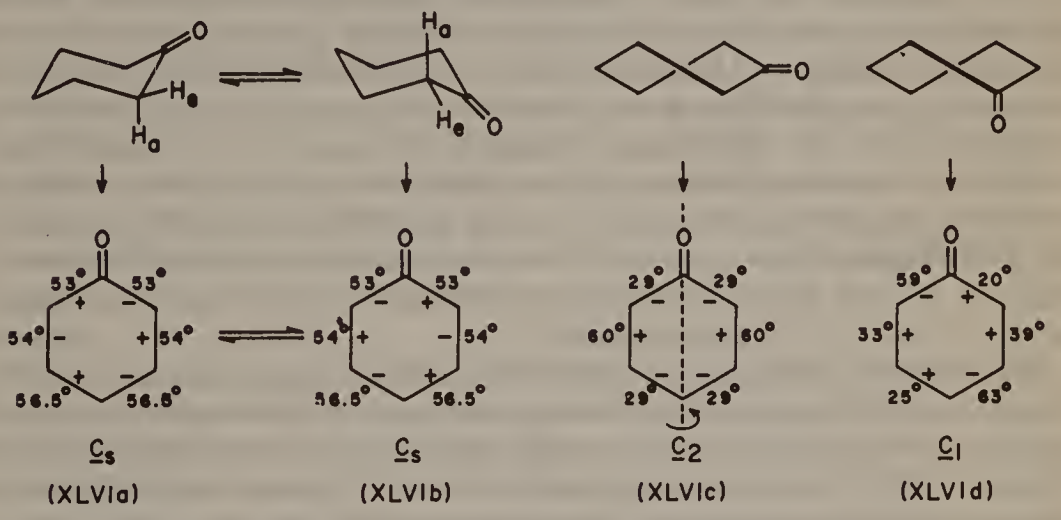


Figure 10.17 Conformation and geometry of cyclohexanone

In comparison to cyclohexane, the flexible forms here are slightly more stabilised due to the absence of eclipsing of adjacent e-H's with the carbonyl oxygen in the twist-boat forms (XLVIc) and (XLVId) and due to the partial absence of eclipsing between cis H's in the boat forms. Of the two twist-boats, the one (XLVIc) is stabler than the other (XLVId), their respective enthalpies (calculated) being 13.4 and 16.7 kJ mol^{-1} above that of the chair form which are considerably lower than that in the cyclohexane system (22.2 kJ mol^{-1}). The two boat conformers (not shown), one a C_s boat and the other a C_1 boat have slightly higher energy. The flexible forms may be substantially populated in cyclohexanones with bulky substituents, more so than in analogous cyclohexanes (Allinger et al 1966).

2. **Ring inversion.** Because of lower torsional barrier around an sp^3-sp^2 carbon

*The presence of one or more axial substituents, however, reverses the direction of the equilibrium due to 1,3-diaxial interaction (see Eliel 1962, p. 243).

bond than an sp^3-sp^3 one, the free energy of activation for the ring inversion in cyclohexanone is considerably lower than in cyclohexane. The $\Delta G^{\ddagger}$ value at $-170°C$ has been experimentally determined as 20.5 kJ mol^{-1}; $\Delta S^{\ddagger}$ has been estimated as 5.85 JK^{-1} mol^{-1} which gives a value of 21.1 kJ mol^{-1} for $\Delta H^{\ddagger}$ (Jensen and Beck 1968). Thus the flexible forms lie more than half way up to the transition state for chair-chair interconversion*. Pseudorotation among the flexible forms of cyclohexanone is more facile than in cyclohexane and the transition states are not all equivalent.

3. 2-Alkyl- and 3-alkylketone effect. In cyclohexanone, the equatorial H's at C-2 and C-6 are partially eclipsed and if either of them is replaced by an alkyl group, the interaction between it and the carbonyl oxygen may destabilise the e-conformer decreasing the energy difference between the axial and the equatorial conformers in comparison to that in cyclohexane. This decrease is known as 2-alkylketone effect, measured by the difference of $-\Delta G°_R$ in cyclohexane and $-\Delta G°_R$ in cyclohexanone. Equilibrium data of 2-alkyl-4-*t*-butylcyclohexanones (XLVII) and (XLVIII) (Figure 10.18a) and of 2,6-dialkylcyclohexanones should, in principle, give an estimate of these values. When R = Me, this value is nil, in fact, slightly negative (-2.0 kJ mol^{-1}). This is comprehensible because the methyl group in equatorial position is too far to have any appreciable steric interaction with C=O; on the other hand, eclipsing of Me and C=O is electronically favourable as evidenced from the preferred conformation of propanal in which Me and C=O are eclipsed. When R=Et, a value of 2.90-3·20 kJ mol^{-1} is obtained for 2-alkylketone effect and when R = i-Pr, the value is increased to 7.1 kJ mol^{-1}. When R = *t*-Bu, the molecule exists predominantly in twist-boat conformation in which *t*-Bu/C=O eclipsing is avoided.

In a 3-alkylcyclohexanone, the axial conformer is likewise stabilised over the equatorial conformer with respect to their counterparts in cyclohexane to the extent that one 1,3-interaction between the axial alkyl group (R) and axial H is missing (Figure 10.18b). This decrease in $-\Delta G°$ value of R is known as 3-alkylketone effect which is equivalent to one butane gauche interaction (3.75 kJ mol^{-1}) when R = Me. In practice, the equilibrium data of cis-trans isomers of 3,5-dimethylcyclohexanones give a value of 1.7 kJ mol^{-1}, only half the expected value. An average of 2.0-2.5 kJ mol^{-1} is generally accepted for the 3-methylketone effect. In menthone, the 2-isopropylketone effect and the 3-methylketone effect cooperate with each other to stabilise the diaxial conformer (XLIXb) with respect to the diequatorial (XLIXa) so much so that in solvent of low polarity e.g., isooctane, the former prevails (see CD spectrum in Chapter 15).

Eliel et al (1965) have also defined a 4-alkylketone effect which arises due to the leaning of the axial H's at C-2 and C-6 in cyclohexanone slightly outwards so that an axial alkyl at C-4 will have lesser interaction with them. This effect has been invoked to explain the higher rate of chromic acid oxidation of 4,4-dimethylcyclohexanol as compared to that of cyclohexanol and also the larger

*A somewhat lower inversion barrier has been reported (Anet et al 1973) from the study of coalescence temperature in ^{1}H-NMR spectrum of cyclohexanone-3,3,4,5,5,-d_5 which is 16.7 kJ mol^{-1} at $-183°C$.

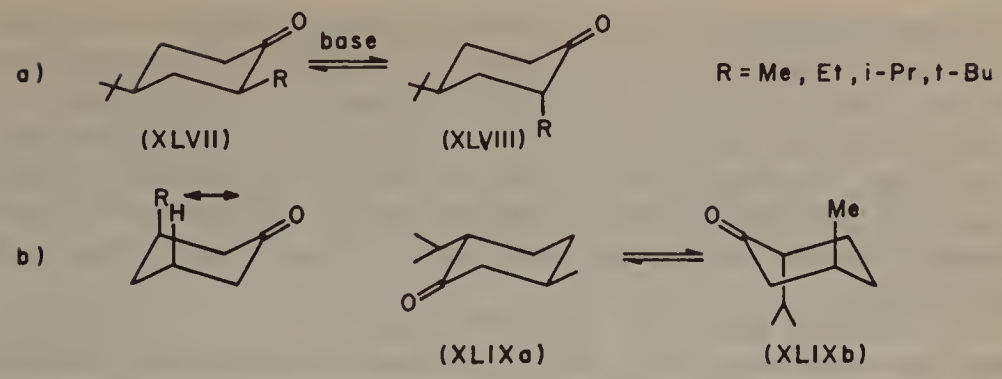


Figure 10.18 (a) 2-Alkylketone effect: (b) 3-alkylketone effect

dissociation constant of 4,4-dimethylcyclohexanone cyanohydrin compared to that of cyclohexanone cyanohydrin.

4. 2-Halocyclohexanones. Cyclohexanones with a polar group such as halogens at C-2 pose a special problem. In addition to the steric interaction in the equatorial conformer due to partial eclipsing, there also exists a dipole-dipole interaction between the two almost parallel dipoles C-X and C=O, further destabilising the equatorial conformer. Since the dipole-dipole interaction is solvent dependent, the population of the conformers is affected by solvent polarity. Equilibrium data of 2-bromo-4-*t*-butylcyclohexanones (XLVII and XLVIII, R = Br) (Figure 10.18a) show that the axial isomer predominates to the extent of 78% in carbon tetrachloride (solvent of low polarity) but only to the extent of 63% in dioxane (solvent of high polarity). The polar effect is less for chlorine than for bromine.

The case of the cis and trans isomers of 2,6-dibromocyclohexanone is interesting. They are equilibrated by heating with HBr giving predominantly the trans isomer (LI), the repulsion of the C-Br and C=O dipoles preferring an orthogonal arrangement rather than the all-parallel arrangement of the three dipoles in the cis isomer (L) (Figure 10.19). The corresponding 3,3,5,5-tetramethyl-2,6-dibromocyclohexanones (LII) and (LIII), on the other hand, on similar equilibration give mainly the cis isomer (LII) despite the unfavourable dipole-dipole interaction and without any apparent steric advantage. This and many analogous observations are explained on the basis of 'reflex effect' (Ourisson 1963) according to which the presence of bulky axial groups on one side of the ring causes some deformation by opening of the axial bonds. This in turn causes a *pinching* of the axial groups or H's on the other side of the ring. As a result, the axial bromine in LIII will have a more severe synaxial interaction with 4-H_a which reverses the stability order.

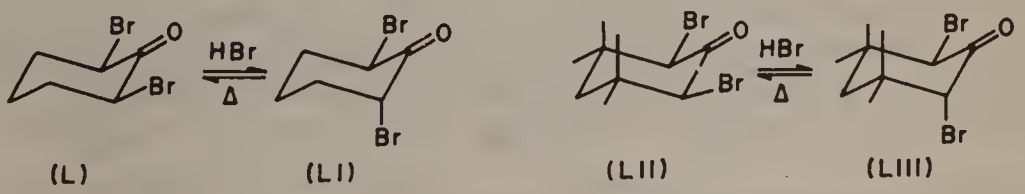


Figure 10.19 Reflex effect in bromocyclohexanones

5. Spectral properties. Electronic interaction between the polar α-substituents and the carbonyl group in cyclohexanones is also reflected in some spectroscopic properties. Thus in IR, the C=O stretching frequency (ν_{CO}) is increased in the equatorial conformer by the nearly parallel dipole of the equatorial halogens by about 20 cm^{-1}. In contrast, the axial halogens which are almost perpendicular to the carbonyl plane hardly affect ν_{CO}. This spectroscopic behaviour may be used to distinguish between isomers with axial and equatorial halogens adjacent to a carbonyl group.

In the electronic spectra, the axial polar bond, C-X (X = Cl, Br, OH, OAc) brings about some bathochromic shift to the carbonyl absorption at 280-290 nm (due to n-π^* transition). This is because the near parallel orientation of the polar bond with respect to the π-orbital of C=O causes an appreciable delocalisation involving the σ and π-electrons. On the other hand, in the equatorial isomers, there occur small hypsochromic shifts. The bathochromic shifts for axial Cl, Br, OH, and OAc are respectively 22, 28, 17 and 10 nm while the hypsochromic shifts for the equatorial substituents are 7, 5, 12, and 5 nm respectively.

It may be relevant to mention that the axial proton at the α-carbon is easier to abstract by a base since the σ-electrons of the axial C-H bond maintain a continuous overlap with the π-electrons of C=O during the formation of the enolate anion. The reverse, i.e., protonation of the enolate ion also takes place from the axial direction for the same reason (see Chapter 12).

10.5.2 Alkylidenecyclohexanes

In alkylidenecyclohexanes (as LIV) (Figure 10.20), C=O is replaced by C=C R′R″ Assuming the same geometry as in cyclohexanone, in the equatorial conformation (LIVa), the allylic segment, R′-C_α=C_β-C_γ-R is near coplanar so that R and R′ are almost eclipsed giving rise to a 1,3-diaxial interaction, perhaps a little worse because of the shorter C=C bond in between. This interaction is designated $A^{1,3}$- or allylic 1,3-strain for the sake of semantic simplicity (see Johnson 1968) since the groups involved are at 1 and 3 positions of an allylic system (see also $A^{1,2}$ strain in the next section). The numbering should not be confused with that of the cyclohexane ring in which sp^2 carbon is numbered 1. The axial conformation (LIVb), in comparison, has two R/H synaxial interactions and an almost equivalent R′/2-H_e interaction. Depending on the size of R and R′, the axial conformer may, therefore, be the preferred one. A stereochemical theorem has been enunciated as follows (Johnson and Malhotra 1965). *If in the allylic system as LIV, R and R′ are medium to large groups, the axial conformer (LIVb) is preferred over the equatorial (LIVa).* When R = R′ = Me, the distance between them is 245 pm in

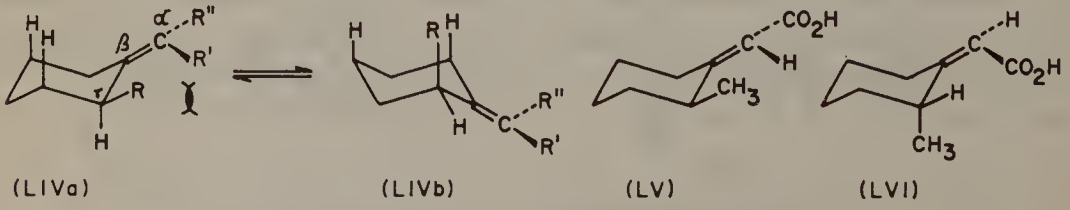


Figure 10.20 Alkylidenecyclohexane : $A^{1,3}$ strain

LIVa and $A^{1,3}$-strain is approximately 32 kJ mol^{-1}; after allowing for two gauche interactions (7.5 kJ mol^{-1}) in LIVb and one cis butene interaction (5.5 kJ mol^{-1}) (due to interaction of α-Me and γ-H_e) the difference in energy between the equatorial and axial conformers is 19.0 kJ mol^{-1} in favour of the latter. A recent value is, however, much smaller, 11.0 kJ mol^{-1} for the all methyl compound (LIV, R = R′ = R″ = Me) (Allinger et al 1968). The $A^{1,3}$-strain is illustrated with 2-methylcyclohexylideneacetic acid, the syn conformer of which exists largely with Me axial (LVI) (due to $A^{1,3}$-strain) but the anti conformer has the Me equatorial (LV) (NMR study).

10.5.3 Cyclohexene

The conformation of cyclohexene with two sp^2 carbons has long been known to be a half-chair (LVII) (Figure 10.21), which is confirmed by X-ray crystallographic data of cyclohexene derivatives and also by electron diffraction studies of cyclohexene in the vapour phase. The torsion angles as shown are supported by theoretical calculations and show considerable flattening of the ring near the double bond. The following characteristic features of cyclohexene geometry may be mentioned:

1. The C-1, C-2, C-3, and C-6 atoms are in a plane as are the two vinylic hydrogens. The other two ring carbons C-4 and C-5 are disposed alternately up and down (or down and up) with respect to this plane.

2. The structure (LVIIa) has a C_2 axis bisecting the double bond (no σ plane) and belongs to point group C_2 (chiral). The two enantiomeric structures (LVIIa) and (LVIIa′) are, however, interconvertible by inversion of the ring* and so form an inseparable (±)-pair. They are shown in a different perspective by the structures (LVIIb) and (LVIIb′).

3. The homoallylic carbons (C-4 and C-5) have almost normal equatorial and axial bonds, the latter slightly leaning towards the centre of the ring. They are designated e and a respectively. The axial and equatorial character of the bonds at the allylic carbons, however, is considerably modified; a dihedral angle of 44° (60°−16°) has been calculated for H_e-C_6-C_1-H (and H_e-C_3-C_2-H) and the two equatorial bonds at C-3 and C-6 are called pseudoequatorial (e′). This leaves a dihedral angle of 76° (60° + 16°) for H_a-C_6-C_1-H and H_a-C_3-C_2-H and the two axial bonds are called pseudoaxial (a′).

4. The interconversion of the two half-chair forms probably goes through a transition state which may be represented by the boat conformation (LVIII). The experimental barrier energy is 22.2 kJ mol^{-1} ($\Delta G^{\ddagger}$ as determined by ^{1}H-NMR from the coalescence of 4-H and 5-H of cyclohexene-d_6 at −164°). The calculated value of enthalpy for the boat (LVIII) is 25.0 kJ mol^{-1}. The barrier energy is very sensitive to substituents at C-4 and C-5 which is consistent with the boat as the transition state.

5. $A^{1,2}$-Strain (allylic 1,2-strain). Johnson and Malhotra (see Johnson 1968) have postulated a second theorem which states that in a cyclohexene of the type (LIX)

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*The process is called enantiomerisation (see also interconversion of *cis*-1,2-dimethylcyclohexane).

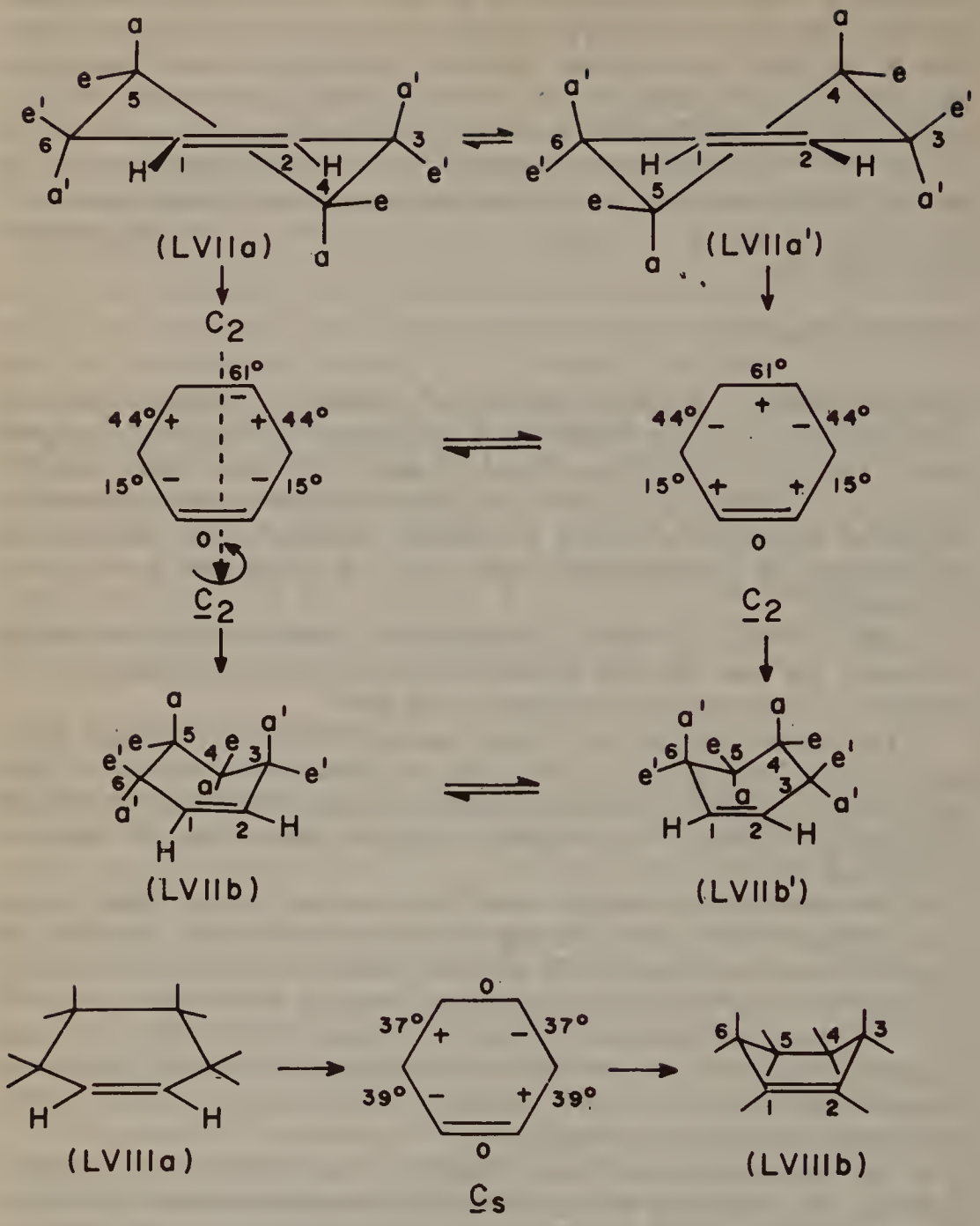


Figure 10.21 Conformations of cyclohexene

(Figure 10.22), if R and R′ are moderately large, they will interfere sterically with each other in the equatorial conformer (LIXa) to such an extent that the axial conformer (LIXb) will be preferred. As already stated, the dihedral angle between 6-e-substituent and 1-substituent is considerably less than the normal value of 60°. When both the substitutents are Me, an enthalpy difference of 1.5 kJ mol^{-1} (approximately) has been calculated in favour of the axial conformer (which contains a 1,3-diaxial Me/H interaction) corresponding to a mixture of 64:36 at ambient temperature (see also Allinger et al 1978). $A^{1,2}$-strain is not a powerful effect and becomes manifest only when the groups are bulky e.g., Ph. Thus the enamine (LX) and 1-phenyl-6-*t*-butylcyclohexene (LXI) exist predominantly in the axial conformers (NMR evidence).

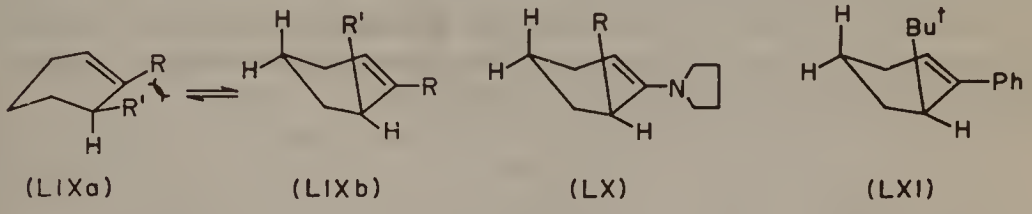


Figure 10.22 Allylic 1,2-strain

10.5.4 Cyclohexane-1,4-dione

The spectroscopic data (IR and Raman) of cyclohexane-1,4-dione show conclusively that it exists in a single, non-chair conformation both in the liquid and in the solid state. Four flexible conformers (LXIIa)—(LXIId) (Figure 10.23) are possible of which the last one (LXIId) is the most stable. The dipole moment of cyclohexane-1,4-dione is very small but non-zero.

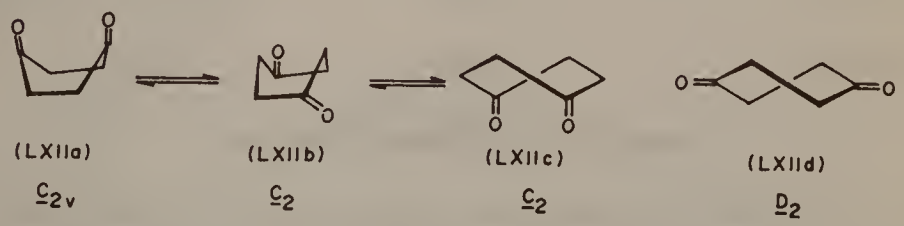


Figure 10.23 Conformations of cyclohexane-1,4-dione

10.6 Carbocycles other than cyclohexane

As stated elsewhere, carbocyclic rings may be divided into four categories: small rings (3- and 4-membered), common rings (5- to 7-membered), medium rings (8- to 11-membered), and large rings (12-membered and above). The cyclopropane ring is necessarily planar and there is no question of conformation, stereoisomers being confined to rigid diastereomers and enantiomers. Conformational heterogeneity starts with the cyclobutane ring, becomes well defined in cyclohexane, and grows more complex in medium and large rings.

10.6.1 Cyclobutane

Cyclobutane may be represented by two extreme conformations: a planar one (LXIIIa) (point group D_{4h}) and a puckered one (LXIIIb) (point group D_{2d}) (Figure 10.24). The former has the pairs of adjacent H's eclipsed and suffers from torsional as well as angle strain. The puckering of the ring with one carbon atom either above or below the plane of the other three relieves some of the torsional strain and non-bonded interaction at the expense of angle deformation (increased angle strain). Raman spectra and electron diffraction experiments (also X-ray data of substituted cyclobutanes) confirm the puckered conformation (LXIIIb) with an angle of puckering α (the angle between C_1-C_2-C_3 and C_3-C_4-C_1 planes) of approximately 35° (the torsion angles are alternately $+25°$ and $-25°$). A geometrical consequence of puckering is the existence of two types of bonds very similar to equatorial and axial bonds in cyclohexane.

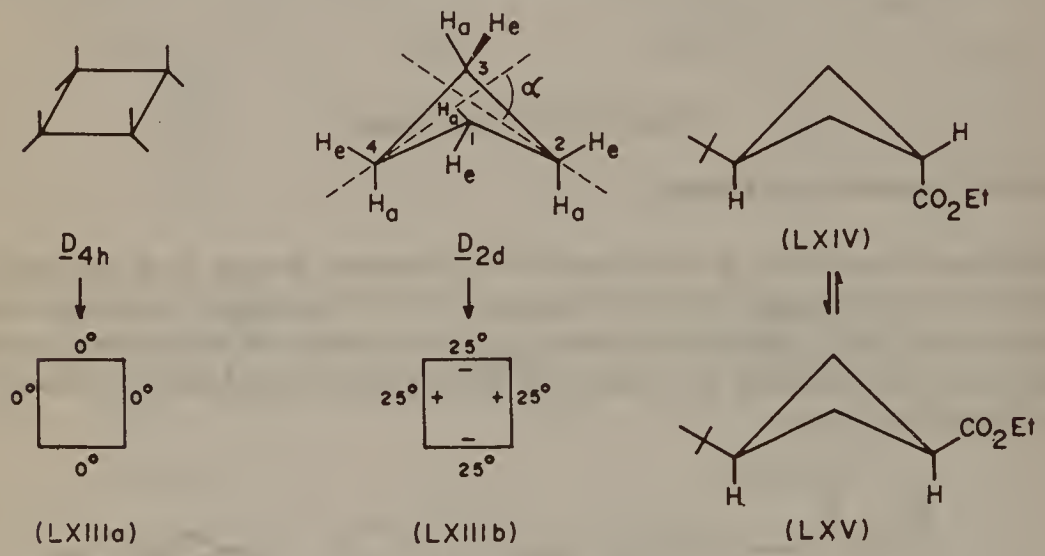


Figure 10.24 Conformations of cyclobutane

The inversion of the ring resembles the wing motion of a butterfly and evidently goes through the planar transition state (LXIIIa) interchanging the equatorial and axial bonds in the process. The energy barrier, however, is very low, around 6.0 kJ mol^{-1} as determined by Raman spectra and may be as low as 4.5 kJ mol^{-1} in some instances. Substituents are preferably placed in equatorial positions, as in cyclohexanes. Thus bromocyclobutane exists predominantly in the equatorial form with very little of the axial conformer, Disubstituted cyclobutane such as the 1,2-dicarboxylic acids show diastereomerism (cis and trans isomerism), the trans having diequatorial and the cis having equatorial-axial substituents. Base-catalysed equilibration of the cis and trans isomers of the dimethyl esters of 1,2-cyclobutanedicarboxylic acid yields a 90:10 mixture (in favour of the trans) at 65° comparable to the 93:7 mixture for the corresponding cyclohexane derivatives. Like cyclohexanes, *cis*-1,3-disubstituted cyclobutanes are more stable than the trans isomers, their conformations as e,e and e,a respectively being confirmed by electron diffraction

experiments. As in cyclohexanes, the *t*-butyl group may be used as a *holding* group and equilibration of the trans and cis isomers of 3-*t*-butylcyclobutane-1-carboxylates (LXIV) and (LXV) gives a preponderance of the latter with a $\Delta G°$ value of 2.5 kJ mol^{-1} at 100°. Because of the occurrence of the cyclobutane ring in many natural products and of its formation in cycloaddition reactions, the conformational analysis of this ring system is important (Moriarty 1974). Replacement of a CH_2 group by a heteroatom reduces the barrier energy as in oxetane, thietane etc.

10.6.2 Cyclopentane

The planar conformation of cyclopentane (D_{5h} point group) is highly strained because of eclipsing interactions among adjacent H's even though angle strain is almost nil. Two puckered conformations which retain some residual symmetry, one known as envelope (LXVIa) and the other known as half-chair (LXVIb) (Figure 10.25) are preferred. The former has a plane of symmetry (C_s point group) and the latter has a C_2 axis (C_2 point group) with torsion angles as shown (Bucourt 1974). The C_s conformer has four carbon atoms in a plane with the fifth either above or below the plane. The C_2 conformer has three carbon atoms (joined by thick lines) in a plane with the fourth and fifth alternately up and down. The shape of cyclopentane is, however, not fixed; the up and down movement rotates round the carbon atoms like ripples on water interconverting a total of ten envelope forms and ten half-chair forms which are of almost equal energy and are separated from one another by very low energy barriers. This movement is known as pseudorotation, the barrier energy being lower than RT (2.5 kJ mol^{-1} at room temperature). Compared to the half-chair and envelope conformations, the planar form is less stable by about 20 kJ mol^{-1}; it is not a transition state nor an intermediate in pseudorotation.

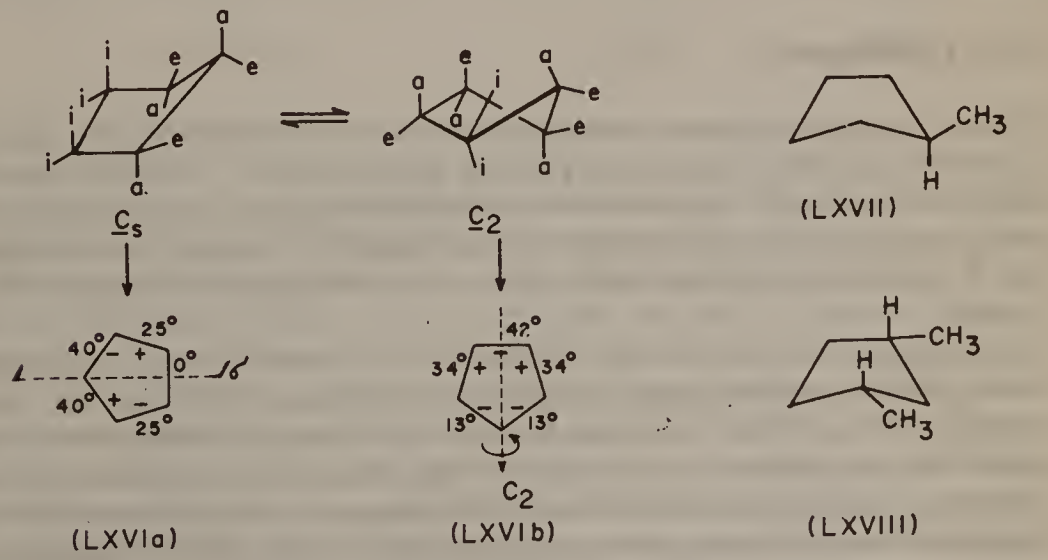


Figure 10.25 Conformations of cyclopentane

The geometry of the half-chair and envelope forms suggests three types of bonds or substituents, equatorial (e), axial (a), and isoclinal (i) as shown. Depending on

the nature of substitution, the chair or the envelope form may be more stable. In monosubstituted cyclopentanes, e.g., methylcyclopentane, Me is in the equatorial position at the tip of the envelope (LXVII). The cis and trans isomers of 1,2-dimethylcyclopentane exist, respectively, in e,a and e,e (envelope) conformations, the difference in enthalpy between the two being 7.15 kJ mol^{-1} which is slightly less than that for the dimethylcyclohexanes (7.8 kJ mol^{-1})*. The case of the cis and trans isomers of 1,3-dimethylcyclopentane is interesting since as in the 1,3-dimethylcyclohexanes, the cis isomer (e,e) (LXVIII) is more stable than the trans (e,a) by 2.25 kJ mol^{-1}. This is a direct demonstration of the non-planar structures of cyclopentane derivatives since a planar structure should have a higher energy for the cis.

When one of the ring carbon atom is sp^2 hybridised as in cyclopentanone or is replaced by atoms such as O, S, and N, eclipsing interactions with substituents on two adjacent carbon atoms disappear. The more favourable conformation in this situation is the half-chair form (LXVIb) with the carbonyl carbon or heteroatom in the middle of the three atom-plane (i.e., on the C_2 axis). The substituents at the two non-planar atoms are staggered and the eclipsing interactions among the three atoms in the plane are also minimised. Dipole moment measurements in the 2-halogenocyclopentanone indicate an angle of 77° between halogen and C=O which is close to that calculated for the half-chair but quite different from that calculated for the envelope form.

Cyclopentanone is reduced by sodium borohydride at a much slower rate than acyclic ketones or cyclohexanone. Apparently, the relief of angle strain in the sp^2 to sp^3 change is less than sufficient to compensate for the increased torsional strain in cyclopentanol which implies a negative I-strain in cyclopentanone (relative to cyclohexanone). The cyanohydrin equilibrium also lies on the side of cyclopentanone.

10.6.3 **Cycloheptane**

With the increase of ring size in carbocycles (cycloheptane and above), the number of possible conformers increases due to the greater degree of freedom. Usually, more than one 'family' of conformers are possible. In general, the members of a family pseudorotate into one another whereas a member of one family is converted into a member of the other family by ring inversion (usually a higher energy process).

Cycloheptane exists in two sets (families) of conformers, one set consisting of chair (LXIXa) and twist-chair (LXIXb) forms (Figure 10.26) and the other consisting of boat (LXIXc) and twist-boat (LXIXd) forms, separated by an energy barrier of approximately 35.0 kJ mol^{-1} (less than that in cyclohexane ring inversion). The two enantiomeric twist-chair conformers (LXIXb) and (LXIXb') (there are seven such enantiomeric pairs) appear to be the preferred conformers and pseudorotate into each other with the true chair (LXIXa) as the transition

*This may not be very meaningful since the cis and trans isomers may have different ring conformation.

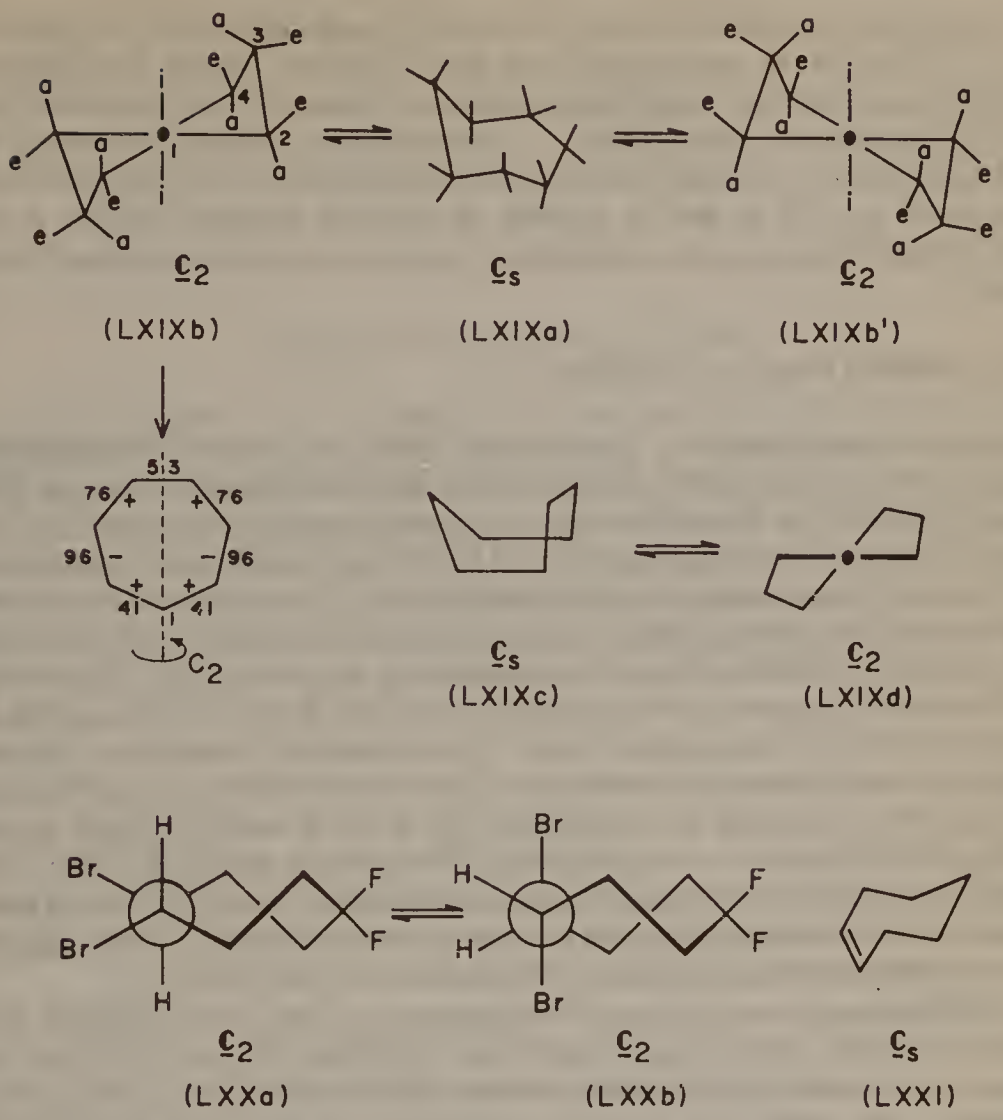


Figure 10.26 Conformations of cycloheptane and cycloheptene

state (energy barrier ≈8.0 kJ mol^{-1}). The interconversion is very rapid and only a single proton peak is seen in ^{1}H-NMR even at very low temperature.

In the twist-chair conformation, four different types of carbons (C-1, C-2, C-3, and C-4) and seven different types of hydrogens (two on C-1 being isoclinal) are discernible. Pair of hydrogen atoms on carbons other than C-1 (which is on the C_2 axis) are designated equatorial (e) and axial (a). In general, a substituent is placed preferably in an equatorial position either at C-2, C-3, or C-4 (almost equivalent in energy). The pseudorotation process and interconversion of chair-boat forms may be slowed down by the introduction of appropriate substituents. Thus the proton decoupled ^{19}F-NMR spectrum of *trans*-1,2-dibromo-5,5-difluoro-cycloheptane (LXX) gives two singlets one for each conformer (the geminal F's are homotopic and so do not couple) with relative intensities of 26:74 at — 114° (Knorr et al 1967) which can be rationalised by the twist-chair conformations (LXXa) and (LXXb).

Cycloheptanone probably exists as a mixture of conformers with C=O either at C-1, C-2, or C-7. In cycloheptene, the presence of the double bond inhibits pseudorotation and the most stable conformer apprears to be the chair form (LXXI) belonging to point group C_s. Conformational complexity is reduced by introducing geminal dimethyl groups, or by replacing one or more CH_2 groups by heteroatoms e.g., O, S, and N resulting in increased torsional barriers, or by incorporating rigid groups such as a double bond or an aromatic ring (see Riddell 1980).

10.6.4 Medium rings: conformations

The medium-sized rings (8- to 11-membered) show some unusual conformational features which are not present in the common and large rings. The strain per CH_2 group (Table 10.1) in the medium ring compounds is appreciably higher (5.0—5.9 kJ mol^{-1}) than in the seven-membered (3.8 kJ mol^{-1}) and in the twelve-membered (1.3 kJ mol^{-1}) ring compounds which bracket them. The conformations of these rings are such that some of the H's are directed inside the rings (intraannular H's) and some are directed outside (extraannular or peripheral H's). The former substituents (H's) interact with one another sterically across the ring leading to what is known as transannular strain. The transannular interactions become manifest in many physical and chemical properties of the medium ring compounds. It is, however, erroneous to assume that the strain is solely confined to the transannular interactions—they contribute at best a minor part to the total strain. Actually, the non-bonded interactions are largely relieved by deformation of bond angles and torsion angles giving rise to angle and torsional strains. Three medium ring compounds are discussed below (for a review, see Dale 1976).

1. Cyclooctane. Three families of conformations exist in cyclooctane ring system: a highly symmetrical crown form (LXXIIa) (Figure 10.27) of D_{4d} symmetry (alternatively, an extended crown), the boat-chair form (LXXIIb) of C_s symmetry, and thirdly, the relatively unstable tub or boat form (not shown). Previously, the extended crown form was believed to be the stablest conformer. More recent ^{1}H-NMR data (Anet and Basus 1973) are consistent with cyclooctane existing as a 95:5 mixture of boat-chair (LXXIIb) and crown (LXXIIa) conformations with $\Delta H°=7.94$ kJ mol^{-1}, $\Delta S°=4.0 \pm 4.0$ JK^{-1} mol^{-1}, and $\Delta G^{\ddagger}=46.8$ kJ mol^{-1} at $-45°$ (boat-chair to crown). The boat-chair form is also supported by the X-ray study of crystalline derivatives of cyclooctane (Srinivasan and Srikrishan 1971). The free energy of activation for ring inversion (boat-chair to boat-chair) as determined by dynamic NMR using cyclooctane-d_{14} is 33.9 kJ mol^{-1} at $-111.5°$ (Anet and Hartman 1963). Intraannular H's at C-1, C-4, and C-6 on the upper side and at C-3, C-5 and C-7 on the lower side of the ring lead to transannular interactions shown by dotted triangles.

^{1}H-NMR spectra of oxocane (one CH_2 in cyclooctane replaced by O) at low temperature are consistent with the boat-chair conformation in which the intraannular H at C-1 is replaced by a pair of electrons belonging to oxygen. The boat-chair conformation for azocane (one CH_2 replaced by NH) is also established by ^{1}H- and ^{13}C-NMR with a free energy of activation of 30.5 kJ mol^{-1} at $-120°$.

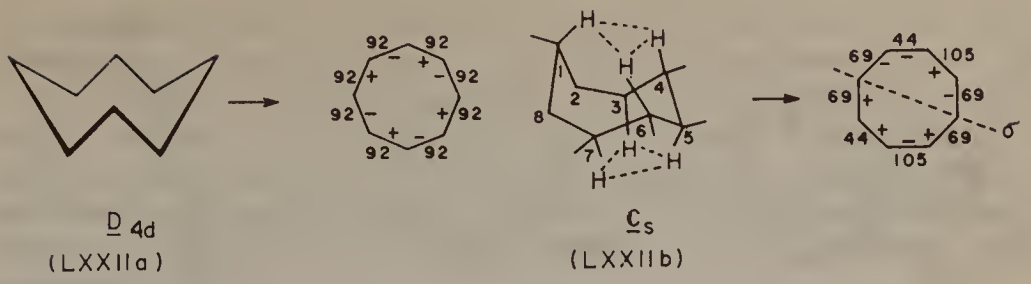


Figure 10.27 Conformations of cyclooctane

2. Cyclononane. Two main families of conformations have been calculated for cyclononane: a twist-chair-boat (LXXIIIa) and a twist-boat-chair (LXXIIIb) (Figure 10.28) belonging to point groups C_2 and D_3 respectively. A chair form (LXXIIIc) with C_s symmetry has also been considered. The ^{13}C-NMR spectrum at −162° shows two distinct types of carbons in the ratio of 2:1 (Anet and Wagner 1971) which is consistent with the twist-boat-chair form (D_3) and inconsistent with any conformation of lower symmetry. The activation energy ($\Delta G^{\ddagger}$) of 25 kJ mol^{-1} at — 162° is also found to be reasonable for a process in which exchange between two sites occurs.

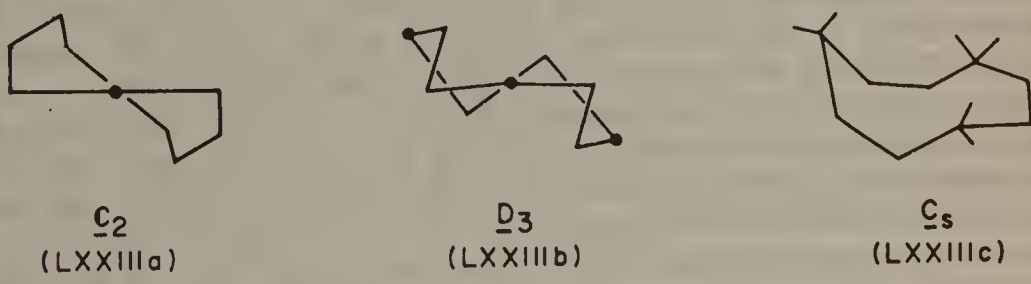


Figure 10.28 Conformations of cyclononane

3. Cyclodecane. Cyclodecane is a typical example in which all the conformational features of the medium rings are exhibited. X-ray crystallographic studies (see Dunitz 1968) have established the boat-chair-boat conformation (LXXIV) shown in two different perspectives (Figure 10.29) for cyclodecane in the solid state. Electron diffraction experiments (Hilderbrandt et al 1973) also show it as the major conformer in the gas phase along with some twist-boat-chair conformation. The following are the characteristic features of this boat-chair-boat conformation:

(*i*) The conformation has a plane of symmetry perpendicular to the C_2 axis (passing through the centres of 3-4 and 8-9 bonds) and belongs to point group C_{2h}. The σ plane passes through C-1 and C-6 and contains the axial and equatorial H's on these carbons.

(*ii*) The torsion angles around the ring are approximately staggered, i.e., torsional strain is minimum. The C-C-C angles are slightly opened up to minimise the transannular interactions (see below) with an average value of 117°.

(*iii*) Unlike cyclohexane which contains only one type of carbon and two types of hydrogens, cyclodecane in this conformation has three different types of carbons

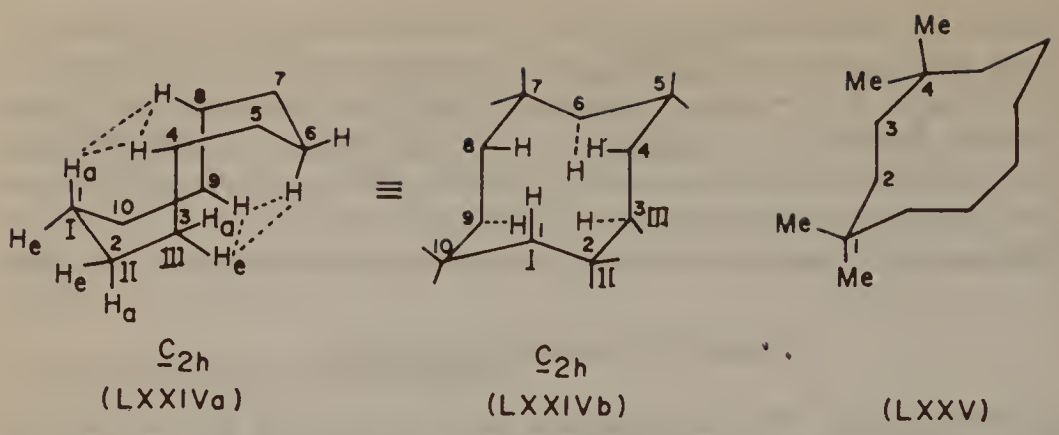


Figure 10.29 Conformations of cyclodecane

and its hydrogens can occupy six different positions. Of the three types of carbons, type I has e-H peripheral and a-H intraannular (e.g., C-1); type II has both a-H and e-H peripheral (e.g., C-2); and type III has a-H peripheral and e-H intraannular (e.g., C-3). Out of twenty H's, fourteen are peripheral and six are intraannular. Of these six, three are attached to C-1, C-4, and C-8 and the other three at C-3, C-6, and C-9 (each set shown by a dotted triangle in LXXIVa and also separately in LXXIVb). The members of a triad are within a distance of 190-200 pm and are thus responsible for the transannular interactions in cyclodecane. The fourteen peripheral H's belong to four different types and are relatively unhindered.

(*iv*) An inspection of the conformation (LXXIVa) or (LXXIVb) with the help of appropriate models will establish its resemblance to the diamond lattice (a part of it) which is constituted of cyclohexane chairs. The axial and equatorial bonds are thus similar in nature to those in cyclohexane. They are differentiated because they are attached to non-equivalent carbon atoms and because some of them are extraannular and some intraannular. In fact, a monosubstituted cyclodecane may exist in seven different conformers : three enantiomeric pairs (R at II-a, II-e, and III-a) and one meso (R at I-e). Other conformers are not appreciably populated.

(*v*) In cyclodecane and other medium ring compounds, pseudorotation which interconverts the members of a family of conformers can be inhibited in several ways. The introduction of one or more geminal dimethyl groupings, for example, stabilises only those conformers in which they are placed on carbons of type II (with no intraannular bond), e.g., 1,1,4,4-tetramethylcyclodecane (LXXV)*. Replacement of one or more CH_2 groups by sterically less demanding heteroatoms, such as O, S, NH, and C=O stabilises the conformations in which these atoms are at more hindered carbons, i.e., types I and III.

10.6.5 Medium rings : some unusual properties

The medium ring compounds show a few unusual physical and chemical properties (some are due to transannular interactions or proximity effect). They are disucssed below.

*Numbering in LXXIV and LXXV are different: C-1 and C-4 in LXXV correspond to C-10 and C-7 (or C-2 and C-5) in LXXIVb.

1. Accommodation of a trans double bond. The medium and large rings can accommodate a trans double bond. In cycloheptene, the trans (*E*) isomer exists only as a reaction intermediate (isolated as a Diels-Alder adduct). In cyclooctene, the *E* isomer has been prepared and resolved (although not very stable). The stability of the *E* isomer increases with increase of ring size : in cycloundecene, *E* and *Z* isomers are of comparable stability* and in still higher cycloalkenes, the *E* isomer is more stable than the *Z*. The smallest ring in which a triple bond can exist is 8-membered.

2. Accommodation of an anti butane unit. Cyclooctane is the smallest ring which can accommodate an anti butane unit and thereafter, as the ring size increases, the strain in having an anti butane unit decreases and its number also increases. In large rings, the majority of butane units exist in this conformation. One interesting outcome is that the classical distinction between a cis and a trans isomer based on proximity of groups disappears. As in the acyclic compounds, two vicinal substituents can have any torsion angle between 0° to 180° without causing much strain in either of the cis or the trans isomers. This is best illustrated with the help of cis-trans pairs of a series of cycloalkane-1,2-diols which are capable of forming intramolecular H-bonds. The strength of the H-bonds can be measured by the difference in O-H stretching frequencies of the non-bonded and bonded hydroxyl groups which in turn gives a measure of the ease with which the two OH groups can be brought into a plane or near-plane. In cyclopentane-1,2-diol, the cis isomer forms the strongest intramolecular H-bond ($\Delta\nu = 61$ cm^{-1}) and the trans isomer does not form any which is expected. In 6- to 9-membered ring glycols, the cis isomers show stronger intramolecular H-bond than the trans isomers, in the 10-membered ring, the two isomers form H-bond almost equally, and in larger rings, the trans isomers form stronger intramolecular H-bonds than the cis isomers. The situation now becomes similar to that of acyclic glycols, e.g., butane-1,2-diols (Chapter 9) which show stronger H-bond in the (±)-form (equivalent to the trans isomer in large rings) than in the meso form (equivalent to the cis isomer in large rings).

The rates of cleavage of cyclic 1,2-glycols which usually proceeds through a 5-membered cyclic intermediate, follow a very similar pattern : they are higher for the cis isomers in common rings but the reverse is observed in medium and large rings in which the trans isomer reacts faster.

3. Conformational mobility and ring inversion. The presence of transannular interactions in medium ring compounds increases the energy barriers both to pseudorotation and to ring inversion particularly with increase of substitution and hence reduces the conformational mobility to a large extent. Thus while the barrier to ring inversion in cyclohexane changes only moderately with the nature and degree of substitution, that in medium ring compounds is very much dependent on them. The ring inversion energy ($\Delta G^{\ddagger}$) for cyclononane is 25.0 kJ mol^{-1} which rises to 37.5 kJ mol^{-1} for 1,1-dimethyl- and to 83.5 kJ mol^{-1} for 1,1,4,4-tetramethylcyclononane.

4. I-Strain. The concept of I-strain was invoked (Brown 1957) to explain the relative ease with which a change of bond hybridisation, sp^2 to sp^3 (addition to

*Stability should not be confused with ease of resolvability.

C=O) or sp^3 to sp^2 (oxidation of -CHOH- to C=O, S_N1 and S_N2 reactions) takes place in ring compounds. The change may refer to the formation of a transition state or of a product leading to a kinetic effect or a thermodynamic effect respectively. In addition to angle strain and torsional strain, steric strain arising out of transannular interactions may also contribute to I-strain. In 3- and 4- membered rings, a change from sp^2 to sp^3 is favourable (angle strain is relieved at the expense of some torsional strain). In 5-membered ring, a change from sp^3 to sp^2 is easier since it removes considerable amount of torsional strain and the increase in angle strain is slight. In cyclohexane, there is little bond opposition and the change from sp^2 to sp^3 is very facile. For the medium rings and to some extent for 7-membered ring, the major source of I-strain is transannular interactions with concomitant deformation of bond angles and torsion angles which may be removed at least partly in a change from sp^3 to sp^2 due to a decrease in the number of intraannular H's. The situation of I-strain in different ring systems may be summed up as follows (Table 10.6).

Table 10.6 Relative ease of change in hybridisation in different rings (I-strain)

Ring size	Facile process	Relief of major strain
3-and 4-membered	$sp^2 \rightarrow sp^3$	angle strain
5-membered	$sp^3 \rightarrow sp^2$	torsional strain
6-membered	$sp^2 \rightarrow sp^3$	angle strain, torsional strain
7-to 11-membered	$sp^3 \rightarrow sp^2$	transannular strain
12-membered and higher	No appreciable difference in either change.	

To illustrate the effect of I-strain in medium ring compounds, it may be pointed out that while cyclohexanone cyanohydrin hardly dissociates, cyclodecanone does not form a cyanohydrin at all. The rate of reduction of cyclodecanone (sp^2 to sp^3) with sodium borohydride is the lowest among cyclic ketones. The rates of solvolysis of the tosylates derived from cycloalkanols, which goes through the carbonium intermediate (sp^3 to sp^2) are highest for medium ring compounds. The rates of S_N2 reaction (sp^3 to sp^2) between cycloalkyl bromides and lithium iodide also follow the same trend. The large ring compounds resemble open chain compounds and are not amenable to I-strain treatment.

5. Spectral properties. When a functional group such as C=O comes into proximity with another transannular group capable of interacting with it, there is expected a change in the spectral character of both. Thus the medium ring amino ketones (A) (Figure 10.30) have a nucleophilic (:N-Me) and an electrophilic (C=O) group across the ring. Partial neutralisation of the two takes place which leads to a lowering of carbonyl frequency (IR). an unexpectedly nigh dipole moment, and a decrease of reactivity of the carbonyl group. If the amino ketone contains a chiral centre, there is observed an appreciable weakening of the Cotton effect in the region of 300 nm (C=O absorption).

More dramatic changes are observed when the amino ketones (A) are protonated to give ammonium salts (as C). The carbonyl frequency around 1700 cm^{-1} disappears in some cases presumably due to the formation of bicyclic compounds

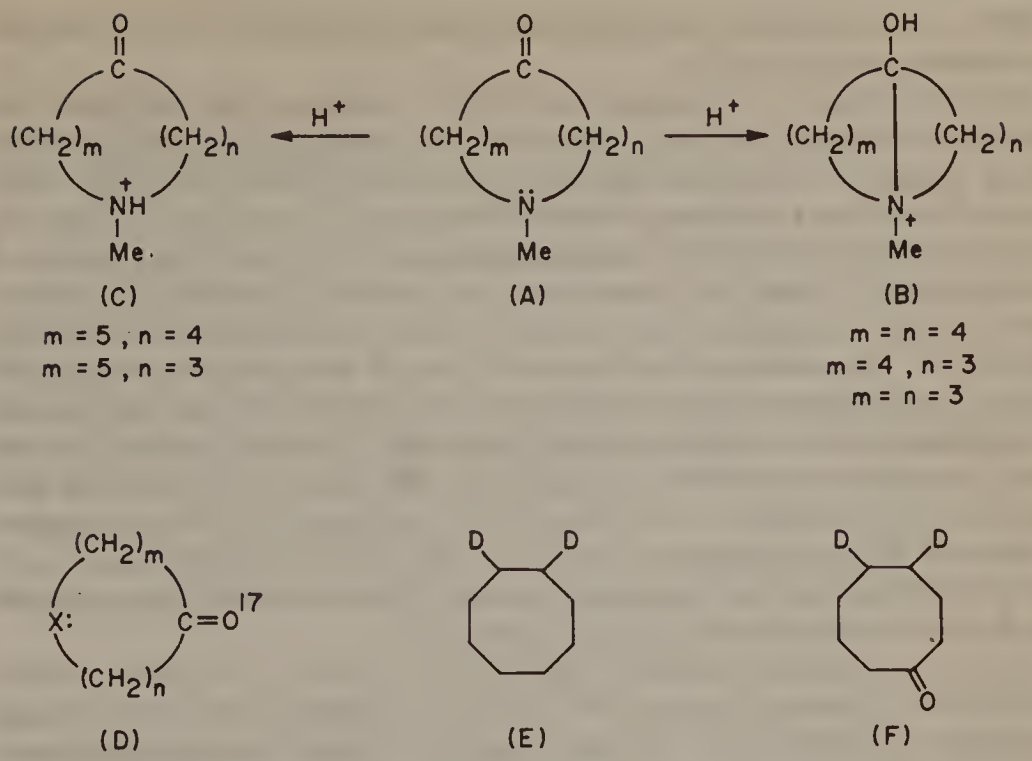


Figure 10.30 Transannular interactions in medium rings

(as B). Thus 8-, 9-, and 10-membered ring amino ketones (A) form respectively bicyclo-[3.3.0], [4.3.0], and [4.4.0] compounds (as B in Figure 10.30). The 11-membered ring amino ketone (A, m = 5, n = 4) does not cyclise to the bicyclo [5.4.0] compound under this condition but instead gives salt (C) which shows C=O absorption.

The medium ring ketones themselves have the C=O frequency around 1690 cm^{-1} which is considerably lower than the normal value (1710—1715 cm^{-1}). Prelog attributed this shift to a transannular H-bond involving 5-H or 6-H in the case of cyclooctanone. However, later work with deuterated compounds (E) and (F) (Allinger and Maul 1968) showed that the C-D stretching frequencies in the two compounds are identical thus eliminating the possibility of H-bonding. The lower stretching frequency for the medium ring ketones is presumably a result of C-CO-C bond angle expansion.

In the amino ketones (as A) or other heterocyclic medium ring ketones (as D), there is a characteristic change in the chemical shift of ^{17}O of the carbonyl group in ^{17}O-NMR due to transannular interaction. Hydration of the carbonyl group as measured by deuterium exchange between the ketone and H_2O is also appreciably slower than in the corresponding six-membered ring ketones with a heteroatom on the other side of the ring, again due to a transannular interaction.

The electronic spectra of paracyclophanes are also affected by transannular interactions (Eliel 1962, p. 261).

6. Transannular reactions. Two groups of workers (Prelog et al and Cope et al) working respectively on cyclodecane and cyclooctane systems have shown that groups across the medium rings which are within reacting distances are often

involved in rearrangement and neighbouring group participation. A few examples are recorded in Figure 10.31.

The trans isomer of cyclodecene (LXXVI) on oxidation with performic acid followed by acid-catalysed ring opening of the protonated epoxide (LXXVII) affords a number of products including cyclodecane-1,6-diol (LXXVIII) which can only result from a transannular hydride transfer as shown (Figure 10.31a). The normal product, cyclodecane-1,2-diol is also formed along with a small amount of *trans*-1-decalol (a result of transannular ring closure). Evidently, the normal backside attack (S_N2 type) by the nucleophile directly at the reaction site is partially prevented by the transannular methylene H's. As an alternative, the nucleophile (HCO_2^-) directs its attack on the transannular carbon which becomes activated by a concomitant hydride transfer across the ring to give LXXVIII. Similarly, *cis*- and *trans*-cyclooctenes on oxidation with performic acid followed by hydrolysis give *cis*- and *trans*-cyclooctane-1, 4-diols respectively. This transannular hydride transfer is observed in cycloundecene but not in cyclohexene, cycloheptene, and cyclododecene (at least not in any significant amount). The transannular rearrangements like all other rearrangements are highly stereospecific.

Acetolysis of cyclodecyl tosylate with labelled carbon (*) (LXXIX) (Figure 10.31b) gives cyclodecyl acetates (LXXX) and (LXXXI) with the acetoxy group positioned at C-5 and C-6 showing that transannular hydride transfer has occurred.

Similarly, bromination (an electrophilic addition reaction) of *cis*-cyclodecene (LXXXII) gives *cis*-1,6-dibromocyclodecane (LXXXIII) (Figure 10.31c). The reaction is assumed to go through a cyclic bromonium ion and Br attacks on the transannular methylene group with a simultaneous transfer of a hydride to the bromonium ion.

An interesting transannular pinacol rearrangement is observed when cyclodecane-1,6-diol (LXXXIV) is treated with acids. A hydride (or deuteride) is transferred from the transannular carbinol carbon giving cyclodecanone or cyclodecanone-6-*d* (LXXXV).

10.6.6 **Large ring compounds**

The member of the first large ring compounds, cyclododecane is solid at room temperature and its conformation has been studied by X-ray crystallography (Dunitz and Shearer 1960) which is depicted by schematic diagram in Figure 10.32. For rings larger than cyclododecane, conformational information is rather scanty; however, the following points are important.

1. The large rings are much more flexible and because of free rotation about C-C bonds, the formal distinction between cis and trans isomers in di- and polysubstituted molecules disappears.

2. It is difficult to freeze the molecules in any definite conformation. IR spectral data suggest that the large rings exist in conformations similar to the arrangement of carbon atoms in small pieces of diamond lattice. This means that most of the butane units have zig-zag (anti) conformations but since a completely zig-zag conformation does not permit ring formation, there must exist a few gauche butanes which will turn the chain into a *square* or a *rectangle*.

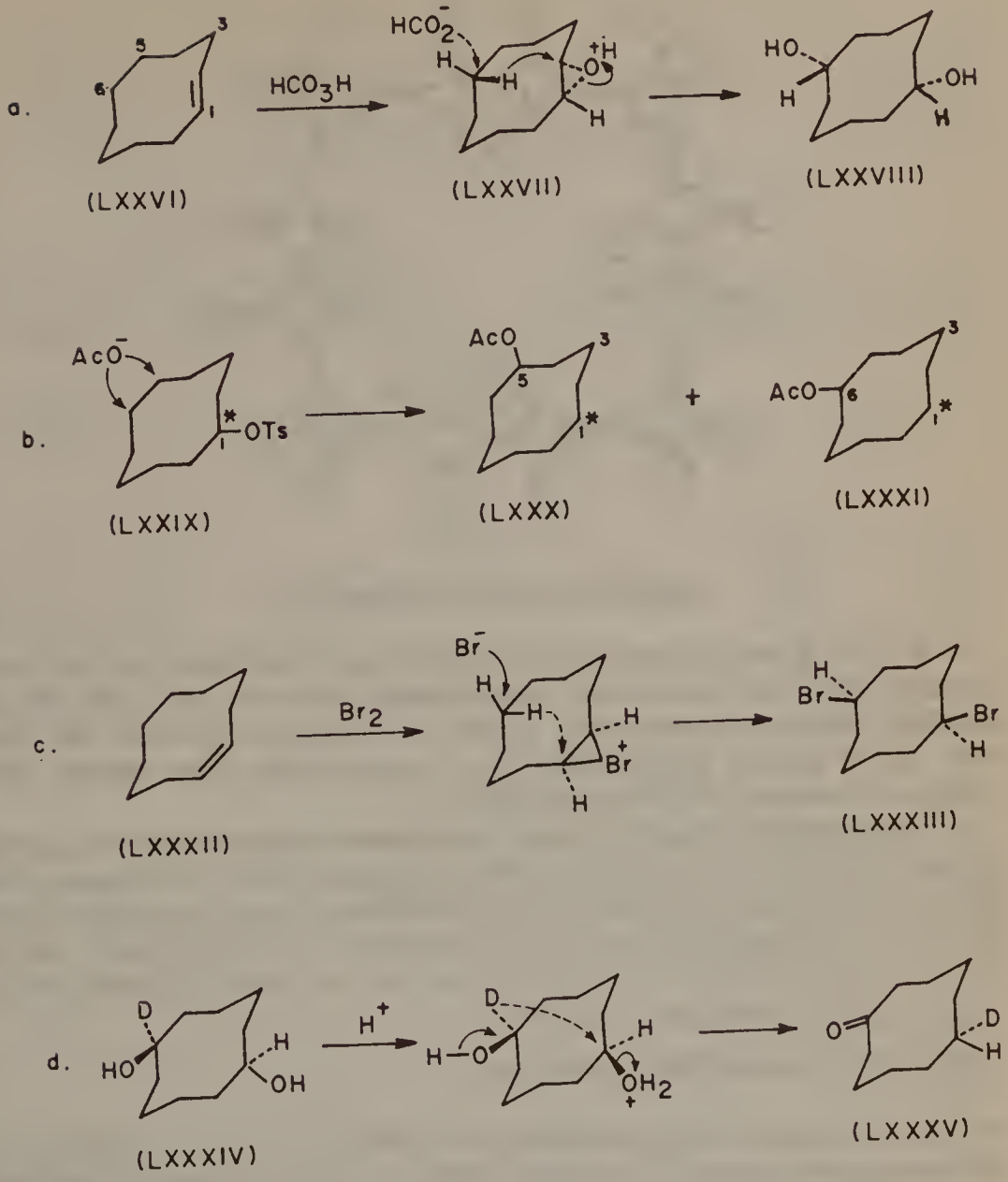


Figure 10.31 Some transannular chemical reactions

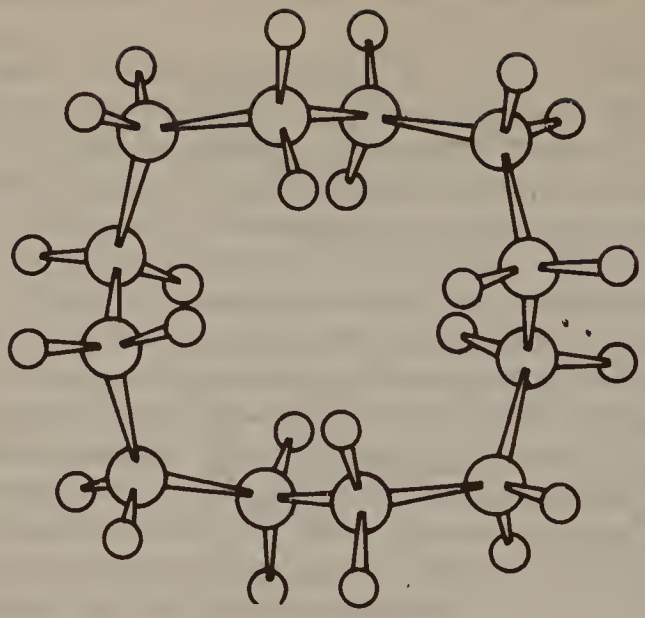


Figure 10.32 Structure of cyclododecane

3. It is now generally accepted that the large rings (20-membered and up) form rectangles with two large zig-zag carbon chains parallel to each other (as in paraffins) instead of squares which would leave a large intraannular hole. The latter would prevent intramolecular (also intermolecular) close packing thus reducing favourable van der Waals attraction.

4. The rectangular shape of the large rings necessitates that at least eight gauche butane units (at four corners) are present compared to six in cyclohexane. The enthalpies of the large ring compounds per methylene group are thus slightly lower than that of cyclohexane as proved experimentally for the 17-membered ring. In acyclic chains, a favourable entropy term increases the number of gauche butane units but the free energies are minimised.

10.6.7 Rings with multiple double bonds

The smallest cyclic diene is cyclobutadiene (LXXXVI) (Figure 10.33) which inspite of the conjugated double bonds is too unstable to exist in free state but has been isolated as a silver nitrate complex and also using the matrix technique at low temperature. According to Hückel's rule (see below), cyclobutadiene is antiaromatic. Cyclopentadiene (LXXXVII) is quite stable with a more or less planar conformation. The derived anion (LXXXVIII) which contains 6π electrons in a planar cyclic system possesses aromatic character (and so is relatively stable) according to Hückel's rule which states that if a planar monocyclic arrangement of trigonal atoms each contributing a p-orbital to the resultant π-system possesses $(4n + 2)$ π electrons (n being an integer), it gains extra stabilisation and the system is known as aromatic. If such a planar arrangement contains $4n$ π electrons, it is relatively unstable and is called antiaromatic.

Both 1,3- and 1,4-cyclohexadienes are known, the latter existing as a flattened boat form (LXXXIX). Cycloheptatriene is non-planar having boat-like con-

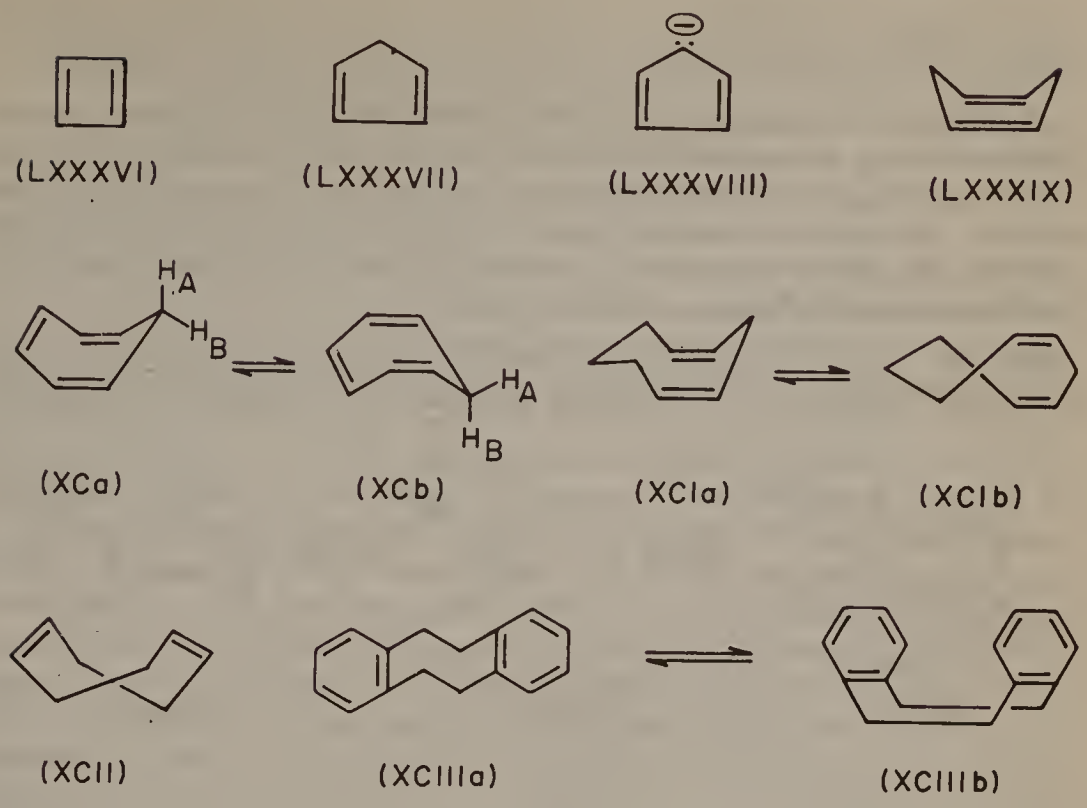


Figure 10.33 Rings with two and three double bonds

formations (XC) in which the two allylic hydrogens are non-equivalent but interchangeable by ring inversion. ^{1}H-NMR spectrum of cycloheptatriene-7-*d* shows a ring inversion (XCa→XCb) barrier of 23.8 kJ mol^{-1} at 120.6 K (the decoalescence temperature, see Oki 1984). Barriers to conformational change in cycloheptadienyl systems have not been studied.

The *cis,cis*-1,3-and *cis,cis*-1,4-cyclooctadienes have non-planar conformations, and both of them show a barrier to ring inversion of approximately 33.5 kJ mol^{-1} at −100°C. Two interconvertible conformations, a relatively rigid boat-chair (XCIa) and a mobile twist-boat (XCIb) are suggested for *cis,cis*-1,4-cyclooctadiene from force-field calculations. A twist-boat conformation (XCII) has also been suggested for *cis,cis*-1,5-cyclooctadiene. In contrast, dibenzo-1,5-cyclooctadiene is known to exist in a chair (XCIIIa) and a boat (XCIIIb) conformation with $\Delta G^{\ddagger}$ (chair to boat) of 42.6 kJ mol^{-1} at −72° and $\Delta G^{\ddagger}$ (boat to boat) of 31.45 kJ mol^{-1} at −115°C.

Cyclooctatetraene (an antiaromatic [8]annulene) presents some interesting features:

(*i*) Electron diffraction experiments indicate a non-planar tub (or boat) form (as XCIVa) (Figure 10.34) in which the bonds are localised (geometrical parameters shown). The non-planar conformation not only minimises angle strain but also avoids antiaromaticity of a 4n π electron system.

(*ii*) Ring inversion (RI) (tub to tub) takes place presumably through a transition state resembling the planar structures with D_{4h} symmetry. For substituted cyclo-

octatetraene (as XCIV) which is chiral in tub form, ring inversion leads to racemisation; XCIVa and XCIVa′ are enantiomers and so are XCVa and XCVa′.

(*iii*) Valence isomerisation also proceeds simultaneously giving two tautomeric forms which are distinguishable for substituted cyclooctatetraenes; XCIVa and XCVa are tautomers. Valence isomerisation or bond shift (BS) requires a planar transition state with D_{8h} symmetry, possibly the delocalised antiaromatic form (as XCIV-XCV)*. The activation energy of BS is, in general, higher than that of RI (for an exception, see Paquette and Wang 1988).

The free energies of activation of both RI and BS processes have been determined by Anet et al (1984) by dynamic NMR using 1-(1-hydroxy-1-

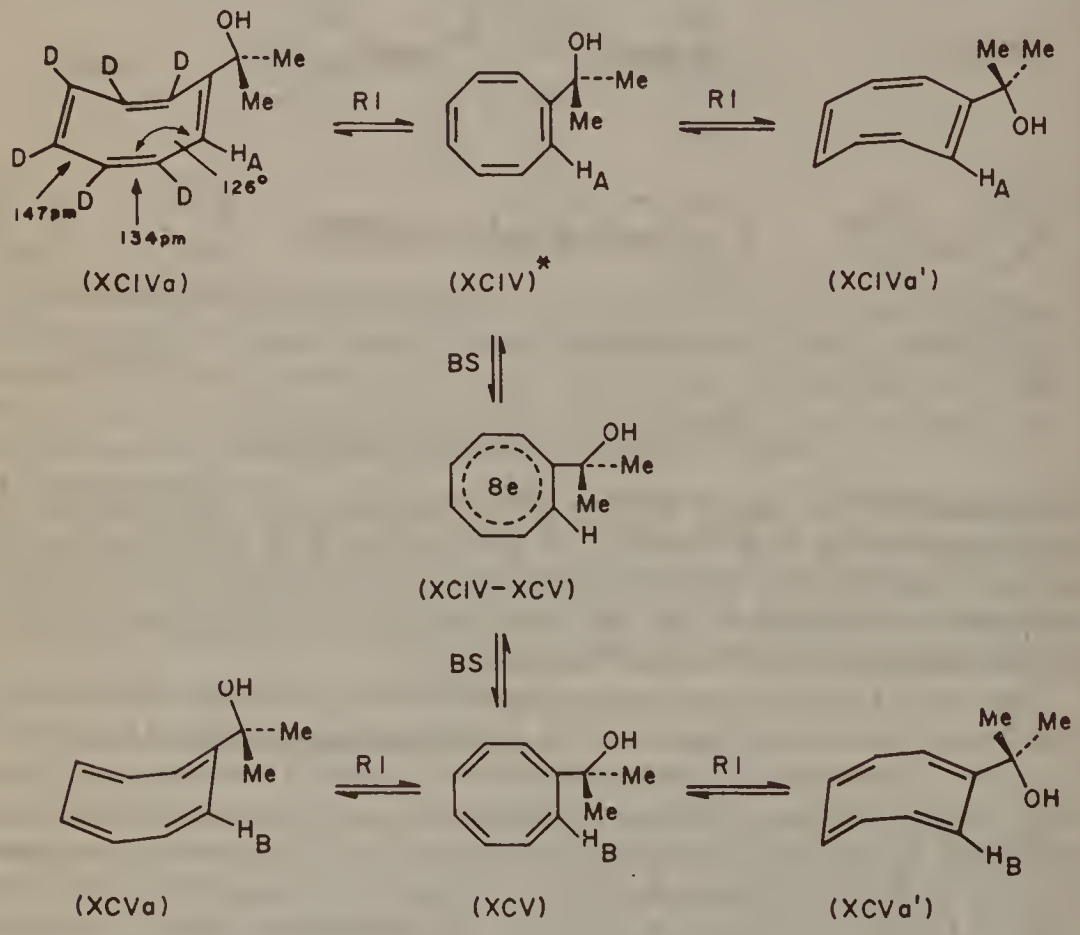
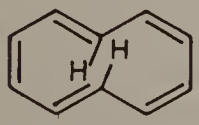


Figure 10.34 Ring inversion and bond shift in cyclooctatetraene

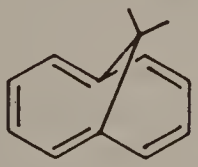
*Controversy exists regarding whether one can distinguish between a planar delocalised $4n\pi$ structure and the two planar bond alternate structures (see Paquette and Wang 1988 for relevant literature) and whether the former can exist at all even as a transition state. One can assume, perhaps logically, that the stable tub forms with localised bonds first pass over to the localised planar structures (XCIV & XCV), the resultant angle deformations constituting the activation energy. Ring inversion takes place before the nuclei can reorganise into a regular octagon. Bond shift, however, can take place only after the nuclear reorganisation leading to a higher energy antiaromatic structure (CXIV-CXV) (see also Carey and Sandburg 1986).

methylethyl)cyclooctatetraene-3,4,5,6,7,8-d_6 (XCIV and XCV). Bond shift is accompanied with the exchange of H_A and H_B protons whereas ring inversion leads to the exchange of the two diastereotopic Me groups. Low temperature NMR spectra show that the coalescence of the methyl signals takes place earlier (at–2°C at 60 MHz) than that of the olefinic protons (at 41°C) which gives values for ΔG^*_{RI} and ΔG^*_{BS} as 61.4 kJ mol^{-1} (at −2°C) and 72.7 kJ mol^{-1} (at 41°C) respectively.

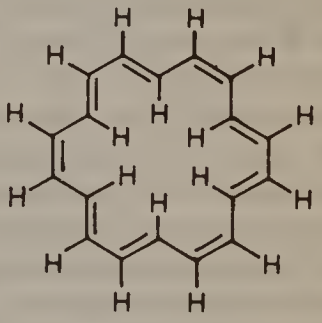
The next higher annulene is [10]annulene, cyclodecapentaene which with five double bonds and ten π electrons can be aromatic according to Hückel's rule. The only isomer which can adopt a planar configuration with minimal strain is the *trans,cis,trans,cis,cis*-pentaene but even this suffers from a severe non-bonded interaction between the two intraannular H's (shown in XCVI) (Figure 10.35). It assumes, therefore, a non-planar structure and thus cannot have aromatic character. When the transannular interaction is removed by introducing a bridge as in XCVII, a diamagnetic ring current is observed in NMR spectrum characteristic of aromatic system. Other larger annulenes are known and aromatic character is or is not observed in them depending on the number of π electrons. Thus [14]annulene is perceptibly aromatic but [16] annulene is not and [18] annulene (XCVIII) is again aromatic. The internal cavity in the last-named compound is large enough to accommodate the six intraannular H's and the angle strain is also nil. The NMR spectrum indicates the presence of a ring current which heavily shields the intraannular H's (chemical shift at -3δ) and deshields the extraannular H's (chemical shift at 9δ). Such systems are known as diatropic. X-ray crystallography of [18] annulene shows it to be nearly planar with twelve inner C-C bonds of 138 pm and six outer C-C bonds of about 142 pm. The resonance energy is about 155 kJ mol^{-1} almost the same as in benzene. Higher annulenes, whether they behave as polyenes or as aromatic system are essentially planar and can accommodate both cis and trans double bonds.



(XCVI)



(XCVII)



(XCVIII)

Figure 10.35 The [10] and [18] annulenes

10.7 Conformational analysis of heterocycles

Replacement of one or more CH_2 groups in cycloalkanes by heteroatoms leads to heterocyclic compounds the conformations of which differ from those of the corresponding alicycles to the extent the geometry of the rings is changed by the

heteroatoms. The different structural parameters that are affected are bond lengths (C-X or X-Y versus C-C where X and Y are heteroatoms), bond angles (C-X-C versus C-C-C), and van der Waals radii (CH_2 versus X and Y). The values of these parameters for some common heteroatoms along with those of carbon are given in Table 10.7.

Table 10.7 Bond lengths, bond angles, and van der Waals radii

Heteroatom (X)	Bond length (C-X)	Bond angle (C-X-C)	van der Waals radii
CH_2	154 pm (C-C)	113° (C-C-C)	200 pm (for CH_3)
N	148 pm	112°	150 pm
O	142 pm	110°	140 pm
S	181 pm	100°	185 pm

It may be seen that these values are not very much different for N and O heterocycles from those for cyclohexane. Other factors which play important role in heterocycle conformations are electrostatic interactions, orbital interactions, preferred torsion angles about C-X and X-Y bonds, formation of intramolecular H-bonds with ring heteroatoms, and finally pyramidal inversion at heteroatoms. The topic is too extensive to give it even a moderate coverage. Reference is made to a few review articles (Eliel 1972, Lambert 1971, Lambert and Featherman 1975), and monographs (Armarego 1977, Riddell 1980).

10.7.1 Three-membered heterocycles

In contrast to cyclopropane derivatives which have rigid planar structures, three-membered heterocycles containing a tricoordinate atom, e.g., N and S (as in sulphoxides), can undergo configurational changes through pyramidal inversion. While the energy barriers of N-inversion in acyclic compounds are low, ($\Delta H^{\ddagger}$ is 24-25 kJ mol^{-1} for NH_3 and 34.4 kJ mol^{-1} for Me_3N, as determined by IR), those for aziridine and its derivatives are usually much higher. Thus for aziridine itself, the energy barrier as determined by dynamic NMR (methylene protons are non-equivalent at low temperature) is 72.4 kJ mol^{-1} at 68°. The relatively high barrier is ascribed to a highly strained transition state involving an sp^2 hybridised nitrogen (for which the normal valency angle is 120°) constrained to an endocyclic bond angle of approximately 60°. As the normal bond angle is increased in passing from three-membered to seven-membered heterocycles, the free energy of activation for N-inversion gradually decreases (Figure 10.36). (In the case of six-membered ring, a bridged piperidine is taken to avoid the complication due to ring inversion). The energy barrier, however, depends very much on the nature of the substituent on nitrogen (as shown for aziridines). The following points are important in conformational analysis of aziridines:

(*i*) For the substituted aziridines, that conformer (invertomer) is more stable which has the R group in N-R (R = H or alkyl) anti to the ring substituent. Thus 2-1′-naphthylaziridines exist predominantly in the anti conformation (XCIX)

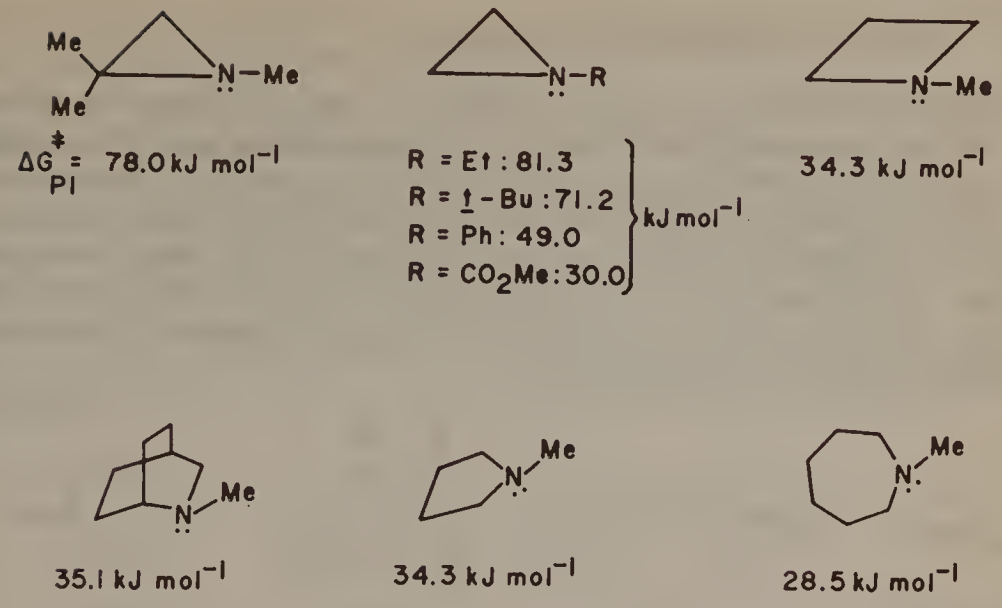


Figure 10.36 Energy barriers to N-inversion in N-heterocycles

(Figure 10.37) and *cis*-2,3-diphenylaziridine in conformation (C). The analysis is made on the basis of coupling constants in the *H*-C-N*H* (^{1}H-NMR) or in the *H*-C-^{15}*N* (^{15}N-NMR) fragments. Advantage is also taken of the fact that 2-H and 3-H syn to N-R are relatively shielded, the extent of shielding decreasing in the order: N-Me > N-Et > N-*i*-Pr > N-*t*-Bu.

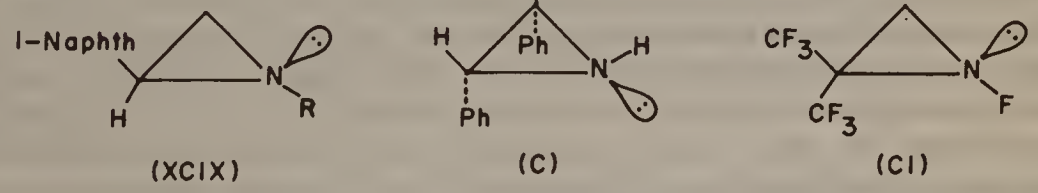


Figure 10.37 Some relatively stable invertomers of aziridines

(*ii*) The energy barrier to N-inversion (hence the stability of invertomers) decreases with increase in the bulk of the N-alkyl group presumably because of ground state compression. The barrier is notably reduced when the substituent is Ar, acyl, or carboalkoxyl (see values in Figure 10.36).

(*iii*) When N is substituted by halogen, the barrier to N-inversion increases considerably and in several cases isolation of invertomers is possible. Thus 1-fluoro-2,2-*bis*(trifluoromethyl) aziridine (CI) is one of the most conformationally stable compound which does not invert even at 190°C. The increase in barrier caused by electronegative substituents is seen in four- and five-membered heterocycles also and is presumably due to enhanced p-character of the bonds to N.

(*iv*) Appropriate solvents stabilise the ground state conformers through H-bonding and/or solvation and thus increase the energy barrier in heterocycles in general. The relative population of the conformers may also be affected.

10.7.2 Four and five-membered heterocycles

Four-membered heterocycles (CII, X = NH, O, S, SiH_2 etc.) (Figure 10.38) can undergo ring inversion (CIIa to CIIb) as in cyclobutane as well as pyramidal inversion. Because of their low molecular weights and appreciable dipole moments, these heterocycles can be studied by microwave spectroscopy. The ring inversion process is accompanied with low free energy of activation (Moriarty 1974): 5.28 kJ mol^{-1} for azetidine (CII, X = NH), 0.4 kJ mol^{-1} for oxetane (CII, X=O), 3.14 kJ mol^{-1} for thiatane (CII, X = S), and 5.28 kJ mol^{-1} for siletane (CII, X = SiH_2) as against 6.2 kJ mol^{-1} for cyclobutane.

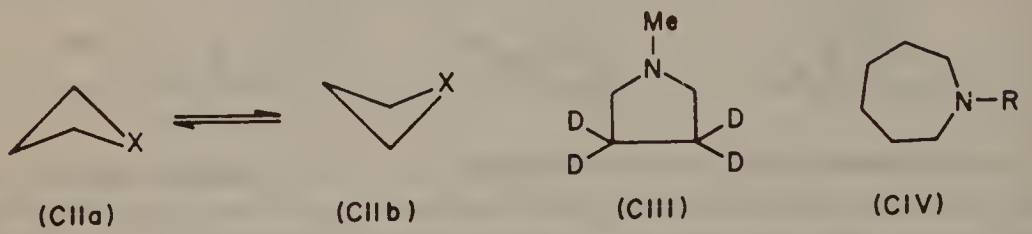


Figure 10.38 Four, five, and seven-membered heterocycles

Five-membered heterocycles such as tetrahydrofuran and pyrrolidine pseudorotate among the various half-chair and envelope forms (which may lack C_2 and C_s symmetry due to the presence of the heteroatom) just as cyclopentane. Ring inversion in five-membered heterocycles is, therefore, too rapid to be studied by NMR. However, the pyramidal inversion is much slower and may be studied by low temperature NMR. As already stated, electronegative substituents increase the energy barrier in four- and five-membered heterocycles also. Thus the free energy of N-inversion in N-methylazetidine is 41.8 kJ mol^{-1} which is increased to 56.1 kJ mol^{-1} in N-chloroazetidine. Similarly, the free energies of activation in N-methylpyrrolidine-d_4 (CIII) and in N-chloropyrrolidine are 34.7 and 43.1 kJ mol^{-1} respectively. The same trend is maintained in seven-membered N-heterocycles (azepins); N-methylazepin and N-chloroazepin (as CIV) show energy barriers of 28.5 and 37.7 kJ mol^{-1} respectively.

10.7.3 Six-membered heterocycles

The conformation of six-membered heterocycles, particularly those containing N and O atoms is of special interest because of the existence of these ring systems in natural products: piperidine in alkaloids and tetrahydropyran in sugars. Nitrogen in piperidine and oxygen in tetrahydropyran are considered to be sp^3 hybridised the lone pairs of electrons (one on N and two on O) replacing the missing substituents. The important conformational features of these two ring systems along with a few related heterocycles are briefly discussed.

1. Molecular geometry. The six-membered N and O (also S) heterocycles exist almost exclusively in chair conformation which has been proved for piperidine derivatives by X-ray crystallography and for tetrahydropyran derivatives by microwave spectroscopy. In piperidine, the ring torsion angles (53-56°) are very

similar to those in cyclohexane. Because of somewhat shorter C-O and C-N bonds (Table 10.7), the chair forms of piperidine and tetrahydropyran are expected to be slightly more puckered than cyclohexane which is also true for thiane since the effect of the longer C-S bond is compensated by the smaller C-S-C bond angle (ca 100°).

Lambert (1967, 1971) has developed a method based on Karplus equation (see Chapter 8) which indicates the nature of the ring structure (chair or deformed chair) of six-membered heterocycles. Karplus equation (shown below) is difficult to apply to heterocyclic systems owing to the unknown value of A which is different for different *H*-C-X-*H* or *H*-X-Y-*H* segments and also depends on substituents. If the ratio J_{trans}/J_{cis} is used, the constant cancels out giving a R-value as follows:

$$J \text{ (cis or trans)} = A \cos^2 \theta_c \text{ or } A \cos^2 \theta_t$$

$$R = \frac{J_{trans.}}{J_{cis}} = \frac{A \cos^2 \theta_t}{A \cos^2 \theta_c} = \frac{\cos^2 \theta_t}{\cos^2 \theta_c}$$

For six-membered ring compounds, a R-value of 2 indicates almost a perfect chair, As the value decreases (approaching 1), the ring chair is assumed to be flatter. On the other hand, an increased R-value (>2) indicates a more puckered chair

The R-values (around 2) provide additional support to the chair conformation for piperidine and tetrahydropyran. The boat form is approximately 20 kJ mol^{-1} higher for piperidine and 16 kJ mol^{-1} higher for tetrahydropyran.

2. Barrier to ring inversion. Torsional interactions along X-X or X-Y bonds are usually higher than those along C-C bond but are less along C-X bonds†. The effect is reflected in the free energy of activation for inversion of different heterocyclic ring systems (Table 10.8). As in cyclohexane, ring inversion takes place through the intermediate twist-boat forms and since this conversion involves torsion along bonds, the higher the torsional interaction, the higher is the activation energy.

Table 10.8 Free energy of activation for ring inversion of six-membered heterocycles[a].

Ring system	$\Delta G^{\ddagger}$ (kJ mol^{-1})	T (°C)
Cyclohexane	43.2	−67.0
Piperidine	43.6	−62.5
Tetrahydropyran (oxane)	39.8	−80.0
Thiane	37.7	−93.0
1,3-Dioxane	40.6	—
1,2,4,5-Tetraoxane	62.8	—

[a]Mostly taken from Lambert and Featherman (1975)

*R values of cyclohexanone, cyclohexa-1,4-dione, 1,4-dioxane, and cyclohexane twist-boat are 1.72, 1.29, 2.20, and 1.20 respectively which are consistent with their conformations.

†Thus torsional potentials of CH_3-CH_3, CH_3-OH, CH_3-NH_2, and HO-OH are 12.0, 4.5. 8.3, and 29.0 kJ mol^{-1} respectively.

3. Pyramidal inversion. The conformational analysis of six-membered heterocycles is complicated by the fact that ring inversion and pyramidal inversion go side by side and are often competitive. In general, ring inversion is slower than pyramidal inversion. For piperidine itself, the two inversions bring about the same conformational changes: N-H_e to N-H_a and vice versa. For tetrahydropyran, both the processes are degenerate isomerisation (as in cyclohexane). Inversion at O is inconsequential in any case since it interchanges the positions of the two lone pairs of electrons only. The difference in ring inversion and pyramidal inversion can be seen in 1,3-dimethylpiperidine (Figure 10.39). Ring inversion (RI) leads to conformational isomers, the configuration (cis and trans) remains unaltered. On the other hand, pyramidal inversion (PI) converts a cis isomer into a trans isomer and vice versa. Since both RI and PI occur concomitantly at ambient temperature, an equilibrium is reached among the four conformers shown. Since in conformational analysis, one hardly distinguishes the mechanisms which bring the conformational change provided they are low energy processes, a change in definition of conformation is indicated.

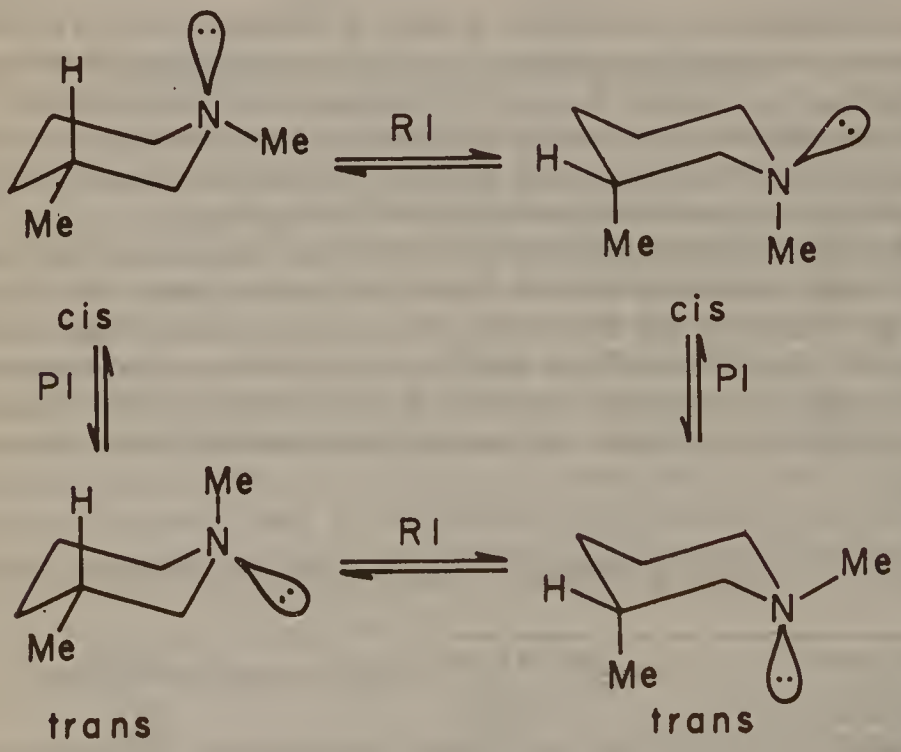


Figure 10.39 Ring inversion and pyramidal inversion in piperidine

Originally, conformations of a molecule are defined as the various arrangements of its atoms in space which differ only in rotation around single bond or bonds (i.e., in dihedral angles) and are easily interconvertible. This definition has already undergone some modification in dealing with the conformers of cyclohexanes in which interconversion of two conformers requires not only a change in dihedral angles but also moderate changes in bond angles and bond lengths. If inversion at a tricoordinate atom is regarded as a conformational change as it often is, then a

more fundamental change in the definition should be introduced. Riddell (1980) has proposed a definition according to which *conformations are stereoisomers that can be interconverted either by rotation around bonds of order approximately one with any concomitant small distortion at bond lengths and angles or by inversion at a three coordinate centre in the molecule or by pseudorotation on phosphorus.* While this definition is followed in this text, a distinction is still retained between a conformation and a conformer the former referring to any arrangement permitted by the definition and the latter referring only to energy minima ones.

Coming back to ring inversion and pyramidal inversion, 1,3,5-trimethylhexahydro-1,3,5-triazine (CV) (Figure 10.40) provides an interesting example in which the two processes can be distinguished by dynamic ^{1}H-NMR (Sutherland et al 1967). At ambient temperature, both the inversions are very fast on the NMR time scale and as a result, the three Me groups are isochronous (due to N-inversion) and so are the three CH_2 groups (due to ring inversion). The NMR shows a time-averaged spectrum with two singlets in the ratio 3:2. As the temperature is lowered, ring inversion first comes to slow exchange limit showing the CH_2 protons as an AB-quartet coalescing at -5° corresponding to a $\Delta G^{\ddagger}_{RI}$ of 54.5 kJ mol^{-1} (the three Me's remain still isochronous). At temperature below −140°, the methyl signals are resolved into two singlets in a ratio of 1:2 (the ring methylene protons also split up into two AB-quartets in the same ratio). Evidently, the molecules are frozen into the stable conformer with two Me's equatorial and one axial (the all-equatorial conformer with three synaxial lone pairs is destabilised by serious electrostatic or other interactions). The coalescence temperature for the methyl signals is−123°C corresponding to a $\Delta G^{\ddagger}_{PI}$ value of 30.0 kJ mol^{-1}.

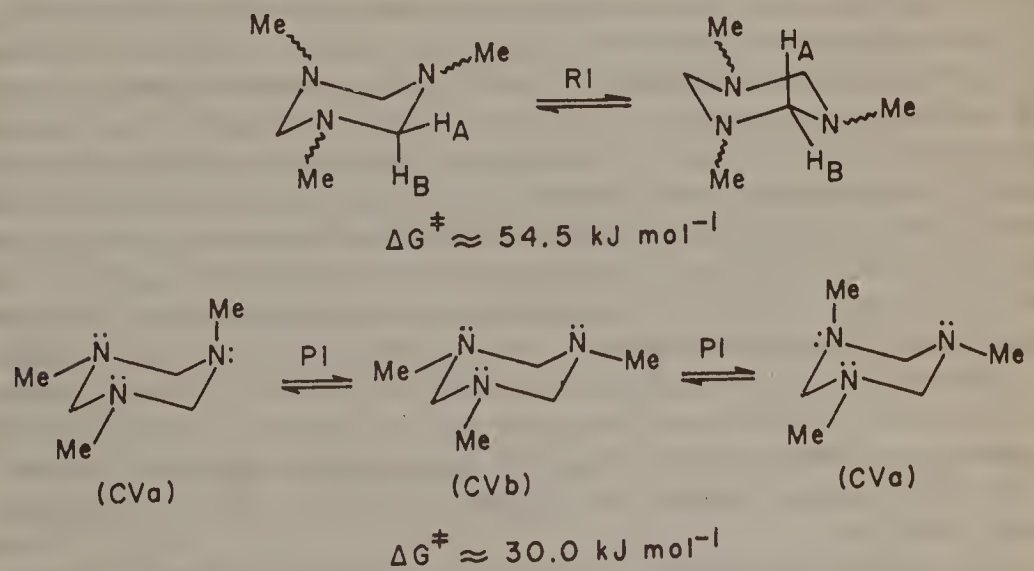


Figure 10.40 Ring inversion and N-inversion in 1,3,5-trimethylhexahydro-1,3,5-triazine

4. 1,3-Synaxial interaction. Because of increased puckering of the chair form in six-membered heterocycles, the 1,3-synaxial interaction between appropriate substituents is expected to increase. However, in the heteroatoms (O, S, and N), one or two H atoms are replaced by lone pairs of electrons which are effectively less

bulky. This reduces the non-bonded 1,3-diaxial interactions considerably in the heterocycles compared to cyclohexane. This is illustrated in *cis*-2-methyl-5-*t*-butyl-1,3-dioxane (CVI) (Figure 10.41) which exists preferentially in the conformation (CVIb) with the bulky *t*-Bu group axial (Eliel and Knoebner 1968). In addition, the decreased C-O bond length in 1,3-dioxane ring brings the axial 2-Me closer to the synaxial H's at C-4 and C-6 destabilising the conformation (CVIa).

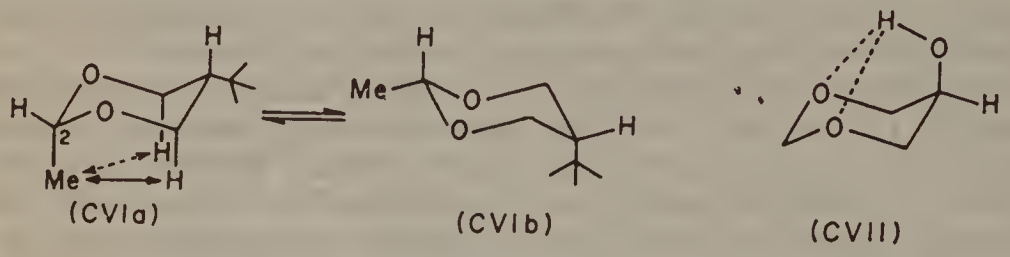


Figure 10.41 Conformational preference in 1,3-dioxanes

5. **Intramolecular H-bonding.** The ring heteroatoms may be involved in forming intramolecular H-bonds with one or more OH (or NH_2) groups present in the molecule thereby affecting the conformational situation. Thus 5-hydroxy-1,3-dioxane (CVII) (Figure 10.41) exists in the preferred conformation with OH axial in order to form H-bond with the ring O atoms. The effect of solvation of ring heteroatoms or formation of intermolecular H-bonds with appropriate solvents also alters the conformational equilibrium.

6. **Conformational free energy.** A value of 7.1 kJ mol^{-1} for conformational free energy of N-Me in piperidine was arrived at from the measurements of dipole moment which has now been replaced by a much higher value (10.5-12.6 kJ mol^{-1}) by using a novel technique (trapping method). The method (Robinson et al 1977) consists of introducing N-methylpiperidine (vapour or solution in a water-immiscible solvent) with a *holding* group (so that ring inversion is prevented) on to the surface of a non-volatile inorganic acid. Since the reaction is effectively irreversible, goes with retention of configuration, and is faster than N-inversion, the ratio of the two diastereomeric piperidinium salts (determined by NMR) corresponds to the ratio of the two conformers in the original equilibrium (brought about by N-inversion) (CVIII and CIX, Figure 10.42). The higher value (ca 11.3 kJ mol^{-1}) for $-\Delta G°$ of N-Me is rationalised on the basis of the shorter C-N bond which brings the axial N-Me closer to the axial H's at C-3 and C-5. In contrast, $-\Delta G°$ of Me placed at C-3 and C-5 is substantially less (6.3 kJ mol^{-1}) which is obviously due to the absence of one synaxial H as shown in structure CX. The conformational free energy of Me at C-4 is again slightly higher (8.3 kJ mol^{-1}) which is attributed to 'pinching' in of C-2 and C-6 because of increased puckering of the chair form.

Conformational free energies of Me groups placed at different positions of tetrahydropyran (Eliel et al 1982) are as follows:

2-Me, 11.97 kJ mol^{-1}; 3-Me, 5.98 kJ mol^{-1}; 4-Me, 8.16 kJ mol^{-1}.
(Temperature range : 163-183 K; solvent: CD_2Cl_2).

7. **Nitrogen lone pair in piperidine.** There has been some controversy regarding the conformational preference of the lone electron pair and H at N in piperidine.

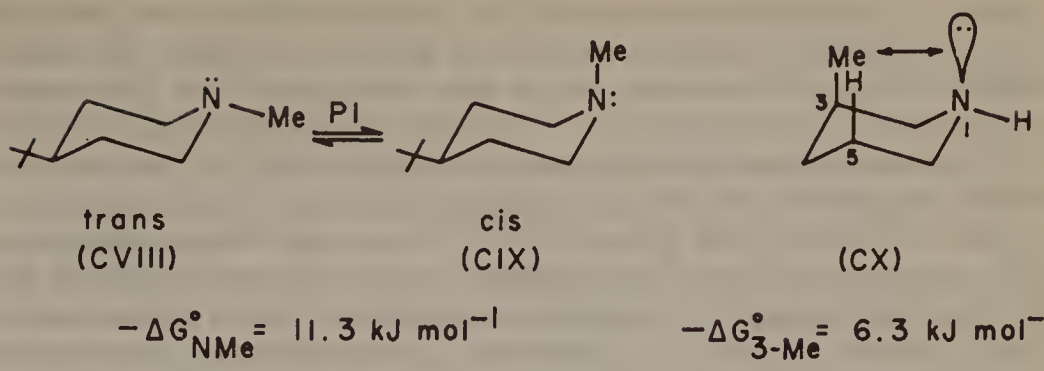


Figure 10.42 Conformational free energies of Me in piperidines

Earlier physical data (Kerr constant and molecular polarisability) appeared to support the preferred conformation with N-H axial. Later work (Katritzky et al, Eliel et al, and others) has conclusively proved that both in the gas phase and in solution, the conformer with N-H_e is preferred. Evidence is as follows : (*i*) The microwave spectrum of piperidine (vapour phase) is consistent with an equilibrium of N-H_e (60%) and N-H_a (40%) forms at 25°C. (*ii*) The dipole moment of 4-*p*-chlorophenylpiperidine suggests that the N-H_e conformer is more stable by approximately 2.2 kJ mol^{-1}. (*iii*) NMR spectral measurements at low temperature exhibit two conformers at −172°C for piperidine with ΔG° of 1.5 kJ mol^{-1} in favour of the N-H_e form. (*iv*) The IR spectrum distinguishes two N-H frequencies in the first overtone region and indicates an enthalpy preference of 2.1 kJ mol^{-1} in favour of the N-H_e form.

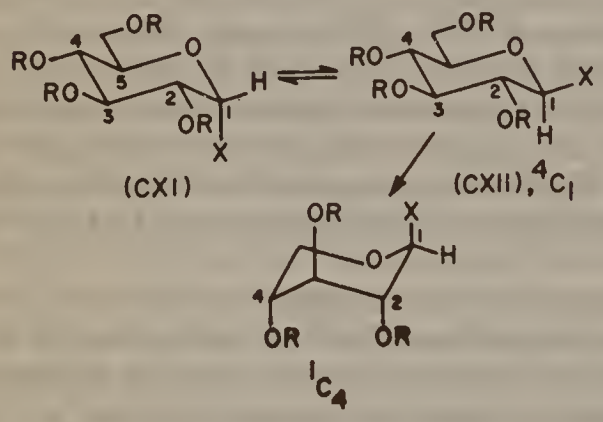
When N-H in piperidine is replaced by N-R, the conformer with equatorial R and axial lone pair is always strongly preferred. This has been proved by low temperature NMR from the relative shielding of equatorial and axial α-H's and by IR spectra of piperidine, N-methylpiperidine, and N-*t*-butylpiperidine by the observation of Bohlmann bands. In ^{1}H-NMR, the axial lone pair shields selectively the adjacent axial H's (ca 0.5 ppm) presumably because of the interaction of nitrogen p orbital with the antibonding orbital of C-H_a bond antiperiplanar to it. As a result, the already upfield shift of an axial H (ca 0.5 ppm) with respect to an equatorial H is increased to approximately 1.0 ppm, i.e., $\Delta\delta_{a,e} \approx 1.0$ ppm for geminal H's at α-C. This upfield shift has been observed for N-Me and N-*t*-Bu piperidines (Lambert and Keske 1966) supporting the equatorial disposition of N-alkyl groups.

In IR, the observation of Bohlmann bands in the region 2700-2800 cm^{-1} is an indication that the lone pair is antiperiplanar to at least one adjacent H (axial) which is possible only if the lone pair is axially oriented. Usually, two such antiperiplanar (one at C-2 and the other at C-6) axial H's give strong Bohlmann bands.

10.7.4 Stereoelectronic effects in heterocycles

The presence of one or more heteroatoms in the ring may give rise to stereoelectronic effect in many cases which considerably affects the conformational

situation in heterocyclic compounds. The anomeric effect is one such effect observed long time back in pyranose sugars and their derivatives. The effect is defined as the extra preference for an axial orientation of an electronegative substituent at the anomeric carbon over and above that normally expected from its conformational free energy (see Paulsen 1975 and Kirby 1983 for reviews). A few examples are given in the equilibration (anomerisation which is an epimerisation process) of CXI and CXII (Figure 10.43). The anomeric effect is quantitatively defined as the sum of the free energy difference for the equilibrium in Figure 10.43 and the conformational free energy of the substituent (X), in cyclohexane, i.e., $-\Delta G^{\circ}_{X}$) assuming that the latter value remains unaltered in the heterocycles, (which is not often correct). Thus 94% of axial isomer in the equilibrium of tetra-*O*-acetyl-D-glucosyl chloride* (last entry) corresponds to a free energy difference of 7.3 kJ mol^{-1} ($G_e^{\circ} - G_a^{\circ}$); $-\Delta G^{\circ}_{Cl}$ is 1.8 kJ mol^{-1} which makes the anomeric effect of Cl approximately 9.1 kJ mol^{-1}. A few characteristics of the anomeric effect and one or two related effects are discussed below followed by a rationalisation of the facts.



R	X	% of CXI
H	OH	36 (25°C in H_2O)
H	OMe	67 (25°C in MeOH)
Ac	OAc	86 (25°C in AcOH)
Ac	Cl	94 (25°C in MeCN)

Figure 10.43 Anomeric effect in pyranose sugars

1. Ring system and anomeric effect. Although tetrahydropyran and pyranose derivatives have been widely investigated for the anomeric effect, other ring systems such as thiane, 1,3-dioxane, and furanose (to a lesser extent) are known to exhibit the effect.

2. The effect of substituent. The anomeric effect depends very much on the nature of the electronegative substituents. The magnitude of the anomeric effect decreases in the following order:

$$\text{Halogens} > PhCO_2 > AcO > AcS > RO > RS > HO > NH_2 > CO_2Me > N^+$$

In fact, for compounds (as CXI and CXII) with N-pyridinium for X, the anomeric

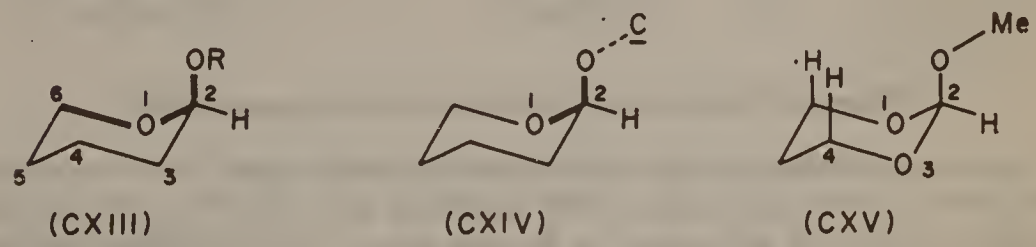
*The anomeric effect also affects the conformational equilibrium in an anomer. In CXI, the $^4C_1$ conformer (C-4 up and C-1 down) is stabilised both by the axial preference for X and equatorial preference for the other substituents. In CXII, the two factors oppose each other. In fact, in tri-*O*-acylpentapyranosyl halides (as CXII, CH_2OR replaced by H), the high equatorial preference of CH_2OR is absent, and the inverted all-axial $^1C_4$ conformer (C-1 up and C-4 down) actually predominates.

effect is negative, i.e., the equatorial isomer is more populated than expected from its space occupying bulk. This is known as the reverse anomeric effect and is characteristic of substituents attached to the anomeric C through a positive nitrogen (for explanation, see later).

3. **Effect of bulk.** In the case of an alkoxy group (X = OR), an increase in bulk of R (from Me, Et, Pr, *i*-Pr, to *t*-Bu) has very little effect on the magnitude of the anomeric effect.

4. **Solvent polarity.** There is a clear indication that the anomeric effect is lower in more polar solvents. This suggests electrostatic interaction at least as a minor contributor to the anomeric effect. The effect is more prominent when solvent is changed from water to an organic one.

5. **Exo-anomeric effect.** The axial preference of a 2-substituent (as OR) in tetrahydropyran actually means the preference for a gauche conformation of the C(6)-O-C(2)-O fragment over the antiperiplanar one (shown in CXIII by thick line, Figure 10.44). The same gauche preference is also expected for a O-C(2)-O-*C* fragment in the compound (CXIV) and has been experimentally verified both for equatorial and axial isomers of CXIV. For steric reasons, O-*C* bond moves away from the ring (as shown). This is equally true for acyclic molecules and the gauche preference for conformations about a carbon-heteroatom bond in the general formula R-X-C-Y has been termed as generalised anomeric effect (Lemieux 1971 and Eliel 1972).



(CXIII) (CXIV) (CXV)

Figure 10.44 Exo-anomeric and double anomeric effects.

6. **Double anomeric effect.** 1,3-Dioxanes substituted at C-2 with electronegative groups show a double anomeric effect. Thus the axial methoxy-derivative (CXV) is very much preferred over the equatorial isomer inspite of the fact that the synaxial interactions of the axial OMe with 4-H and 6-H are very severe due to a puckered chair form of 1,3-dioxane.

7. **Anomeric effect versus gauche effect.** Reference has been made to a 'gauche effect' in Chapter 9 which prefers a conformation in which the lone pair and/or polar groups are gauche to each other. This is known as 'attractive' gauche effect and does not seem to work in systems showing anomeric effect. Thus in CXVI (Figure 10.45), Cl is axial (anomeric effect) although according to the gauche effect, it would be preferably equatorial (in the axial conformer, only one oxygen lone pair is gauche to the polar C-Cl bond but in the equatorial conformer, the C-Cl bond being placed in between the two oxygen lone pairs is gauche to both)*.

*In CXVI, the lone pair of electrons shown (in p orbital) is antiperiplanar to the C-Cl bond; the second lone pair is gauche to it by default.

A common explanation of both the effects has been suggested as follows. The systems which show the anomeric and gauche effects have always a non-bonding lone pair antiperiplanar to the polar C-X bond. A stereoelectronic factor is thus clearly indicated. It may be accepted that the major contribution to the anomeric effect (and also to the gauche effect) comes from the interaction of the p orbital of the heteroatom (i.e., oxygen) with the antibonding σ orbital of C-X bond (n-σ^* interaction as shown in CXVI), its magnitude depending on the donor capacity of the heteroatom and the acceptor capacity of the C-X bond (Kirby 1983). In valence bond concept, it is a case of resonance involving a double bond between O and C-2 and no bond between C-2 and X which, if correct, predicts a shorter bond length for C-O and a longer bond length for C-X. This has been experimentally verified (X-ray crystallography) in appropriate compounds*.

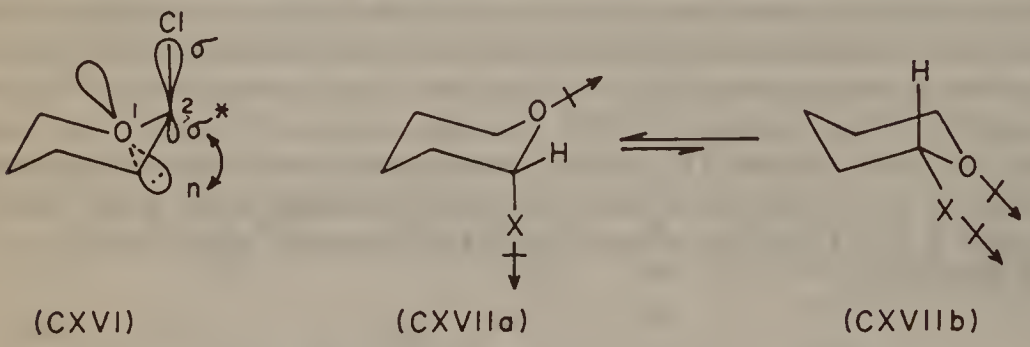


Figure 10.45 Stereoelectronic and electrostatic factors in anomeric effect

Dipole-dipole interaction also contributes (to a minor extent) to the anomeric effect (see its solvent dependence). The equatorial form (CXVIIb) with parallel dipoles is destabilised with respect to the axial form (CXVIIa) in which the two dipoles are divergent. In the case of pyridinium-type substituents, the attractive interaction of the dipoles cooperates with the high conformational energy of the substituent giving the 'reverse' anomeric effect.

8. Rabbit-ear effect. In 1,3-Diheterocycles such as tetrahydro-1,3-oxazine (CXVIII) (Figure 10.46a), the conformation in which the two lone pairs are syn-1,3-diaxial (CXVIIIa) is destabilised with respect to the other conformer (CXVIIIb). This was known as the 'rabbit-ear effect' for obvious reason. This effect, however, may be regarded as nothing but an endo-anomeric effect, explained by stabilising overlap between the p orbital of N and the antibonding orbital of the endo C-O bond which are antiperiplanar (shown by thick line) in the conformation (CXVIIIb). This effect is lacking in the other conformer (CXVIIIa).

9. Repulsive gauche effect (hockey sticks effect). In 1,4-dioxane (CXIX), the conformer with axial X (Figure 10.46b) is favoured although to a lesser extent than in related tetrahydropyran. This is due to the anomeric effect (X is an electronegative substituent). But in the corresponding 1,4-oxathiane (CXX), the

*When no polar bond exists as in hydrazines and peroxides, the antiperiplanar arrangement of vicinal lone pairs is unfavourable (see Chapter 9) and an attractive gauche effect operates.

equatorial conformer (CXXa) is very much favoured over the axial one (CXXb). This phenomenon previously known as the *hockey sticks effect* is now called the *repulsive gauche effect*. Both groups of workers in this field (Zefirov, Eliel) agree that the *repulsive gauche effect* arises out of non-bonded repulsion between the p orbitals of the large substituents X and Y in the unit X-C-C-Y which is absent when they are antiperiplanar (as in CXXa), maximal when they are synperiplanar (as in CXXb), and medium when they are gauche. The effect is much higher in the case of S than O because of the larger size of the outer atomic orbital of the former leading to more electronic overlap.

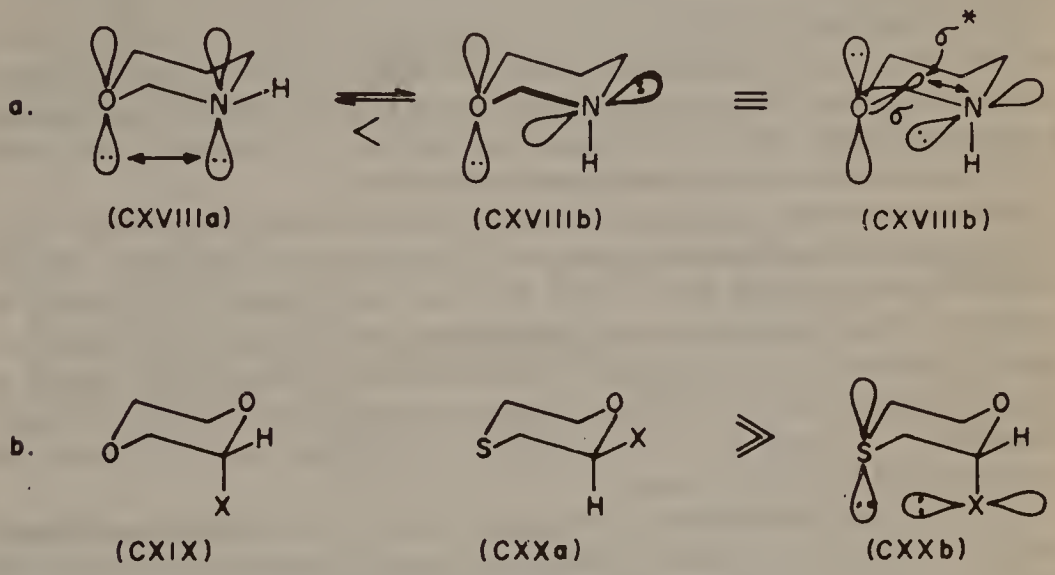


Figure 10.46 (a) Rabbit-ear effect and (b) hockey sticks effect

10.8 Summary

1. The different ring systems are classified into four categories: small (3- and 4-membered), normal (5- to 7-membered), medium (8- to 11-membered), and large (12-membered and above). The cyclopropane ring is necessarily planar whereas the larger rings are puckered to a more or lesser extent so that the different non-bonded interactions are optimised. Conformational heterogeneity starts with cyclobutane, becomes well defined in cyclohexane, and grows more complex in medium and large rings.

2. Cyclohexane exists almost exclusively in a chair form in which angle strain, torsional strain, and non-bonded interactions are minimised. Two types of bonds (or H's) are distinguishable, equatorial and axial, which exchange sites by ring inversion—a process characterised by an energy barrier of 43 kJ mol^{-1}. The ring inversion takes place through a number of intermediates ranging from boat to twist-boat conformations (collectively known as flexible forms) which undergo rapid interconversion among one another through pseudorotation.

3. A substituent in cyclohexane prefers to adopt the equatorial conformation in which steric interaction is minimum. The difference in free energy between an equatorial and an axial conformer is known as the conformational free energy

($-\Delta G°_R$ or A-value) of the substituent (R) and determines the equatorial preference of R. The $-\Delta G°$ values for a large number of substituents have been determined by a number of physical as well as chemical methods.

4. The conformations of 1,2-, 1,3-, and 1,4-dimethylcyclohexanes have been discussed in terms of enthalpy, entropy, and free energy. The differences in enthalpies are calculated on the basis of gauche butane interactions present in a conformer. The calculated thermodynamical parameters are in good agreement with those experimentally determined. In general, a diequatorial conformer is preferred over an equatorial-axial conformer which in turn is preferred over a diaxial conformer.

Factors other than steric which influence conformation are dipole-dipole interaction, the presence of H-bonds, bulky substituents deforming the normal chair form, and the reflex effect. The conformational analysis of polysubstituted cyclohexanes is done along similar lines. In most cases, that conformer (or isomer) is more stable which has the largest number of equatorial substituents.

5. When one or more sp^2 carbon atoms are introduced in a cyclohexane ring, a few changes in the conformations take place. The molecules become flatter near the trigonal atoms increasing the torsional strain and angle strain. With respect to cyclohexane, these molecules such as cyclohexanone and cyclohexene are, therefore, thermodynamically and kinetically less stable*. Several, characteristic features of these ring systems such as 2-alkyl-, 3-alkyl-, and 4-alkylketone effects (in cyclohexanones), $A^{1,3}$-strain (in cyclohexylidine derivatives), and $A^{1,2}$-strain (in cyclohexenes) have been discussed.

6. Of the other alicyclic rings, cyclobutane exists in two rapidly equilibrating puckered conformations with e- and a-like bonds. Cyclopentane displays two unique conformations: one an envelope form (C_s symmetry) and the other, a half-chair form (C_2 symmetry) (both rapidly interconverting among a number of equivalent conformers through pseudorotation). With the increase of ring size from cycloheptane onwards, the number of possible conformers increases due to a greater degree of mobility. Usually more than one 'family' of conformers exist; the members of a family pseudorotate into each other whereas one 'family' is separated from another by a substantial energy barrier. Conformations of medium rings in which transannular interactions play a major role have been discussed. The large rings are strain-free and simulate in part the structure of diamond. They can accommodate trans double bonds as well as anti butane units.

Large ring compounds with two or more double bonds are interesting because they can give both conformational and configurational (*E* and *Z*) isomers. Some of them, specially the annulenes with consecutive double bonds, have extra stability due to aromaticity following Hückel's $4n + 2$ rule.

7. Saturated heterocycles display both similarities to and differences with the corresponding carbocycles. In piperidine and other N-heterocycles, conformational changes are brought about both by ring inversion and by pyramidal inversion at N, the latter being generally energetically more facile.

Certrain six-membered heterocycles display unusual conformational behaviour, as exemplified by the anomeric effect and gauche effect which are mostly stereoelectronic in origin.

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*It is not, however, reasonable to compare the stabilities of structurally different molecules.

References*

1. W. Hückel (1925), *Ann.*, **441**, 1.
2. H.J. Geise, H.R. Buys, and F.C. Mijlhoff (1971), *J. Mol. Struct.* **9**, 447.
3. P.V. Schleyer, J.E. Williams, and K.R. Blanchard (1970), *J. Amer. Chem. Soc.*, **92**, 2372.
4. R. Bucourt (1974) in *Topics in Stereochemistry*, vol. 8., Eds E.L. Eliel and N.L. Allinger, Wiley, New York.
5. D.H.R. Barton, O.Hassel, K.S. Pitzer, and V. Prelog (1953), *Science,* **119**, 49.
6. G. Binsch, E.L. Eliel, and H. Kessler (1971), *Angew. Chem. Int. Edn. Engl.,* **10**, 570.
7. J.B. Hendrickson (1961), *J. Amer. Chem. Soc.,* **83**, 4537; (1967), *J. Amer. Chem Soc.,* **84**, 7047.
8. F.R. Jensen, D.S. Noyce, C.H. Sederholm, and A. J. Berlin (1962), *J. Amer. Chem. Soc.,* **84**, 386.
9. F.A.L. Anet and A.J.R. Bourn (1967), *J. Amer. Chem. Soc.,* **89**, 760.
10. M. Squillacota, R.S. Sheridon, O.L. Chapman, and F.A.L. Anet (1975), *J. Amer. Chem. Soc.,* **97**, 3244.
11. J.L. Margrave, M.A. Frisch, R.G. Bautista, R.L. Clarke, and W.S. Johnson (1963), *J. Amer. Chem. Soc.,* **85**, 546.
12. H.A. Hirsch (1967) in *Topics in Stereochemistry*, vol. 1, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
13. F.R. Jensen and C.H. Bushweller (1966), *J. Amer. Chem. Soc.,* **88**, 4279; (1969), *J. Amer. Chem. Soc.,* **91**, 3223.
14. E.L. Eliel (1959), *Chem. and Ind.,* 568.
15. E.L. Eliel and S.H. Schroeter (1965), *J. Amer. Chem. Soc.,* **87**, 5031.
16. F.R. Jensen and C.H. Bushweller (1971), *Adv. Alic. Chem.,* **3**, 139.
17. E.L. Eliel (1985), *J. Mol. Struct.,* **126**, 385.
18. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison 1965) in *Conformational Analysis*, Wiley Interscience, New York.
19. E.L. Eliel (1962) in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
20. J.E. Leonard, G.S. Hammond, and H.E. Simmons (1975), *J. Amer. Chem. Soc.,* **97**, 5052.
21. H.R. Buys and E.L. Eliel (1970), *Tetrahedron Letters*, 2779:
22. W.C. Ehrhardt and W.E. Vaughan (1981), *J. Chem. Phys.,* **74**, 5479.
23. D.J. Pasto and R.D. Rao (1969), *J. Amer. Chem. Soc.,* **91**, 2790.
24. N.L. Alinger and L.A. Freiberg (1960), *J. Amer. Chem. Soc.,* **82**, 2393.
25. H. Kessler, V. Gusowski, and M. Hanack (1968), *Tetrahedron Letters*, 4665.
26. D.K. Dalling and D.M. Grant (1972), *J. Amer. Chem. Soc.,* **94**, 5318.
27. N.L. Allinger and M.A. Miller (1961), *J. Amer. Chem. Soc.,* **83**, 2145.
28. E.L. Eliel and H. Haubenstock (1961), *J. Org. Chem.,* **26**, 3504.
29. H. Werner, G. Mann, M. Muhlstadt, and H.J. Kohler (1970). *Tetrahedron Letters*, 3563.
30. M. Oki (1984) in *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Deerfield Beach, Florida.
31. N.L. Allinger, M.M. Blatter, L.A. Freiberg, and F.M. Karkowski (1966), *J. Amer. Chem. Soc.,* **88**. 2999.

*The first few references are already given in Chapter 9.

32. F.R. Jensen and B.H. Beck (1968), *J. Amer. Chem. Soc.,* **90**, 1956.
33. F.A.L. Anet, G.N. Chmurny, and J. Krane (1973), *J. Amer. Chem. Soc.,* **95**, 4423.
34. B. Waegell, P. Pouzet, and G. Ourisson (1963), *Bull. Soc. Chim. France*, 1820; and earlier papers.
35. F. Johnson (1968), *Chem. Rev.,* **68**, 375.
36. N.L. Allinger, J.A. Hirsch, M.A. Miller, and I.J. Tymniski (1968), *J. Amer. Chem. Soc.,* **90**, 5773.
37. R.M. Moriarty (1974) in *Topics in Stereochemistry*, vol. 8, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
38. R.Knorr, C. Ganter, and J.D. Roberts (1967), *Angew. Chem. Int. Edn. Engl.,* **6**, 556.
39. F.G. Riddell (1980) in *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, London.
40. J. Dale (1976) in *Topics in Stereochemistry*, vol. 9, Eds. E.L. Eliel, and N.L. Allinger, Wiley, New York; also see J. Dale (1966), Angew. Chem. Int. Edn. Engl., **5**, 100; F.A.L. Anet (1973), *Top. Chem.,* **45**, 169.
41. F.A.L. Anet and V.J. Basus (1973), *J. Amer. Chem. Soc.,* **95**, 4424; for a review, see F.A.L. Anet (1974), *Fortschritte,* **45**, 169.
42. R. Srinivasan and T. Srikrishnan (1971), *Tetrahedron,* **27**, 1009.
43. F.A.L. Anet and J.S. Hartman (1963), *J. Amer. Chem. Soc.,* **85**, 1204.
44. F.A.L. Anet and J.J. Wagner (1971), *J. Amer. Chem. Soc.,* **93**, 5266.
45. J.D. Dunitz (1968) in *Perspective in Structural Chemistry*, vol. 1 Wiley, New York.
46. R.L. Hindebrandt, J.D. Weiser, and L.K. Montogomery (1973), *J. Amer. Chem. Soc.,* **95**, 8598.
47. H.C. Brown and K. Ichikawa (1957), *Tetrahedron*, **1**, 221.
48. N.L. Allinger and J.J. Maul (1968), *Tetrahedron*, **24**, 4257.
49. A.C. Cope, M.M. Martin, and M.A. McKervey (1966), *Quart. Rev.,* **20**, 119.
50. J.D. Dunitz and H.M.M. Shearer (1960), *Helv. Chim. Acta,* **43**, 18.
51. L.A. Paquette and T-Z Wang (1988), *J. Amer. Chem. Soc.,* **110**, 3663.
52. F.A.L. Anet, A.J.R. Bourn, and Y.S. Lin (1964), *J. Amer. Chem. Soc.,* **86**, 3576.
53. F.A. Carey and R.J. Sundberg (1986) in *Advanced Organic Chemistry, Part A: Structures and Mechanisms*, Plenum/Rosetta, New York.
54. J.B. Lambert and S.I. Featherman (1975), *Chem. Rev.,* **75**, 611.
55. E.L. Eliel (1972), *Angew, Chem. Int. Edn. Engl.,* **11**, 739.
56. J.B. Lambert (1971) in *Topics in Stereochemistry*, vol. 6, Eds. N.L. Allinger and E.L. Eliel, Wiley, New York.
57. W.L.F. Armarego (1977) in *Streochemistry of Heterocyclic Compounds*, Part I & II, Wiley, New York.
58. J.B. Lambert (1967), *J. Amer. Chem. Soc.,* **89**, 1836; (1971), *Acc. Chem. Res.,* **4**, 87, also see H.R. Buys (1970), *Rec. Trav. Chem.,* **89**, 1244.
59. J.M. Lehn, F.G. Riddell, B.J. Price, and I.O. Sutherland, (1967), *J. Chem. Soc.,* (B), 387.
60. P.J. Crowley, M.J.T. Robinson, and M.G. Ward (1977), *Tetrahedron,* **33**, 925; and earlier papers.
61. E.L. Eliel, K.D. Hargrave, K.M. Pietrusiewicz, and M. Manoharan (1982), *J. Amer. Chem. Soc.,* **104**, 3635.
62. J.B. Lambert and R.G. Keske (1966), *J. Amer. Chem. Soc.,* **88**,
63. H. Paulson (1975), Die Starks—Starch, **27**, 397.
64. A.J.B. Kirby (1983) in *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer Verlag, W. Germany.

65. R.U. Lemieux (1971), *Pure Appl. Chem.*, **25**, 527.
66. E.L. Eliel (1972), *Angew, Chem. Int. Edn. Engl*, **11**, 739.
67. N.S. Zefirov (1977), *Tetrahedron*, **33**, 3193, (1976), **32**, 1211.
68. For some general references, see C. Romers, C. Altona, H.R. Buys, and E. Havinga (1969) in *Topics in Stereochemistry*, Vol. 4., Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.

Chapter 11

Conformations of Cyclic Systems: Fused Ring and Bridged Ring Compounds

11.1 Introduction

Polycyclic compounds (bi-, tri-, tetracyclic etc.) with one or more atoms common between two rings may be classified into three categories: spiranes in which any two rings are joined through a single common atom (their stereochemistry has been discussed in Chapter 5), fused or condensed ring compounds in which any two rings have two common atoms (which are necessarily adjacent), and bridged ring compounds in which any two rings (or more) are joined through two non-adjacent atoms and necessarily contain more than two common atoms. The special features which characterise the stereochemistry of these compounds are: (*i*) The sizes of the rings permitting, any two rings may be joined through cis fusion or trans fusion giving rise to diastereomers (cis and trans), each of which should be submitted to conformational analysis separately. (*ii*) Since the rings are interlinked, there may be, in many systems, considerable amount of conformational restraint, i.e., the systems would be less flexible. (*iii*) Finally, any conformational deformation of one ring may be transmitted to the others through the ring junctions—a phenomenon known as conformational transmission.

11.2 Fused bicyclic systems

The conformations of a few typical fused bicyclic systems such as decalin, octalin, and hydrindane are discussed first in detail because the information derived therefrom would help to analyse the conformations of the higher polycyclic systems.

11.2.1 Bicyclo[4.4.0]decane (decalin)

Conformational analysis of bicyclo[4.4.0]decane or decalin is amenable to a more quantitative treatment than any other bicyclic system. Like 1,2-dimethylcyclohexane (to which it bears a formal analogy, each ring being 1,2-disubstituted), decalin exists in two diastereomeric forms: a cis form in which the two rings are cis fused and a trans form in which the two rings are trans fused. They are shown in Figure 11.1 in planar formula, in perspective formula, and in Newman projection formula

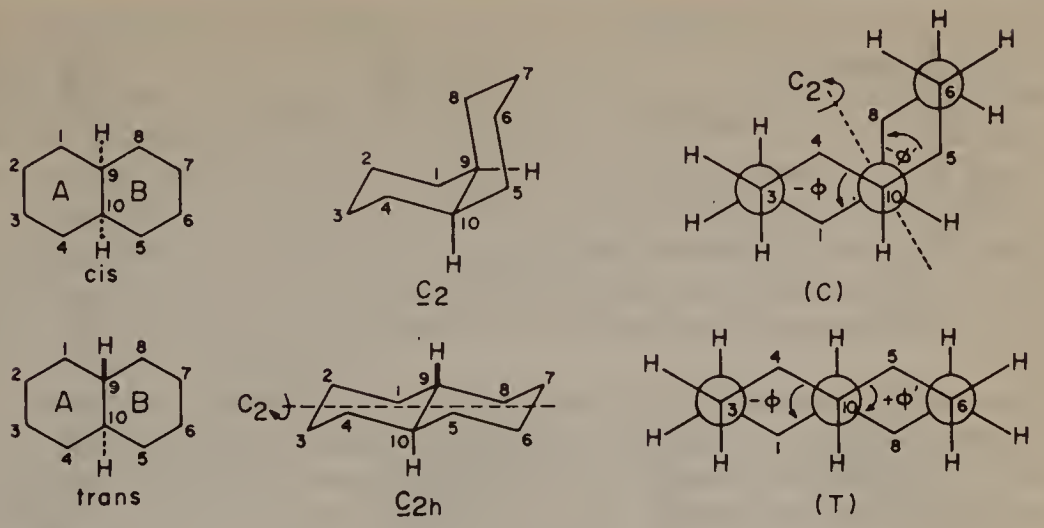


Figure 11.1 *cis*-Decalin and *trans*-decalin

viewed along the 10-9 bond. The last-named formula shows the torsion angle (ϕ) in each ring across the common central bond, known as torsion angle of junction (Bucourt 1974). The planar structures may be simplified by replacing the bridgehead H atom above the plane of the rings (denoted by thick line) with a dot. It may be noted that the trans isomer cannot exist in planar form since it necessitates spanning of two 1,2-trans bonds (torsion angle 180°) by a tetramethylene chain. The isolation of *cis*- and *trans*-decalins thus constitutes a convincing proof for the puckered structure. The salient features of the two-chair conformations of decalins are best discussed under the following headings.

1. Geometry. The cyclohexane units in both *cis*- and *trans*-decalins exist in chair conformation, the previously assumed two-boat conformation for *cis*-decalin being discarded on energy ground as well as by electron diffraction experiments. Torsion angles around all C-C bonds including the common bond of the rings are approximately 55-56°, the same as in cyclohexane. *trans*-Decalin in which the two rings are fused through e,e bonds has a rigid structure and cannot undergo ring inversion which would lead to a highly strained a,a ring fusion. On the other hand, *cis*-decalin in which the rings are fused through a,e bonds can invert by interchanging a,e bonds in the ring junction as shown in Figure 11.2. The two interconvertible structures Ia and Ib (= Ia′) are mirror images of each other and *cis*-decalin thus exists as a (±)-pair similar to *cis*-1,2-dimethylcyclohexane.* Unlike *trans*-decalin which is more or less flat, *cis*-decalin has a folded structure with a convex and a concave side so that steric interactions are distributed unequally on the two sides.

*The structure (Ia) is called the steroid conformation (because of its resemblance with the A/B rings of 5β steroids) whereas the structure (Ib) is called non-steroid. In *cis*-decalin itself, the two are enantiomeric but in substituted *cis*-decalins, they may be diastereomeric and unequally populated (see 1- and 2-decalones). It may be noticed that although Ia and Ia′ (= Ib) are mirror images of each other, ring A of Ia corresponds to ring B in Ia′ and ring B of Ia to ring A of Ia′.

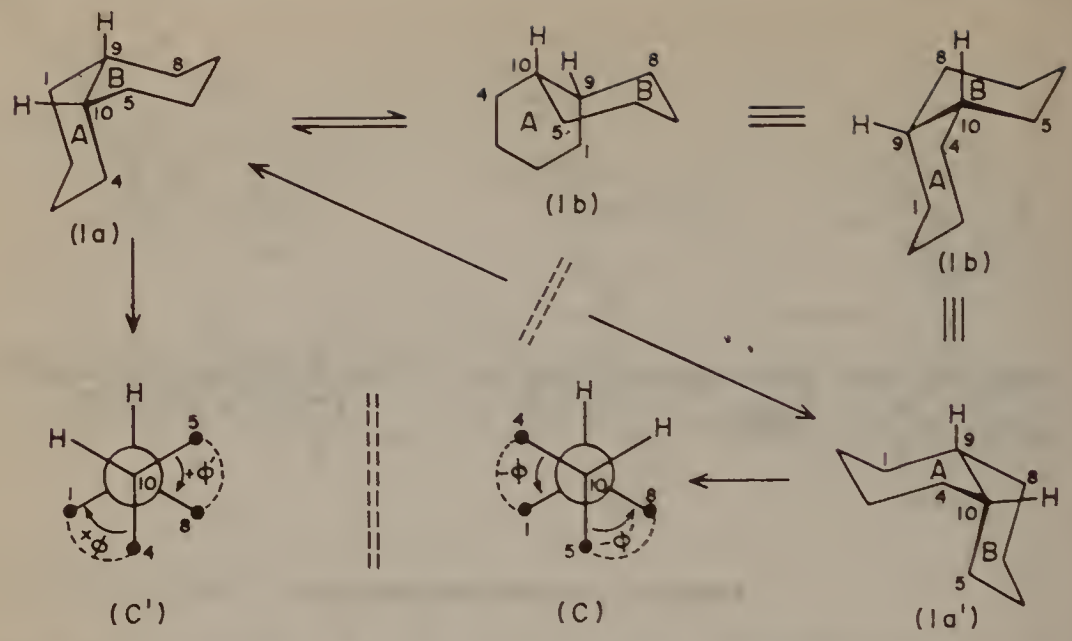


Figure 11.2 *cis*-Decalin: ring inversion and torsion angles of junction

2. Torsion angles of junction. A *torsion angle of junction* is the torsion angle (ϕ) in each ring which has the common bond as its central bond (Bucourt 1974) as shown in Newman projection in Figure 11.1 (T stands for *trans*- and C for *cis*-decalin). Those in the two enantiomeric forms of *cis*-decalin are once again shown in abbreviated structures C and C′ (Figure 11.2). Usually, their values are 55° so that $\phi + \phi'$ equals 110°. For the trans isomer, their signs are opposite and fixed while for the cis isomer, their signs are identical and they can be changed simultaneously. Thus in the structure (T), if the molecule is rotated around the 10-9 bond in an anticlockwise direction, the torsion angle of junction in ring A closes up but that in ring B opens up — a process not energetically favourable (ring B becomes more puckered). On the other hand, in the structure (C) or (C′), a decrease of torsion angle of junction in ring A follows a similar decrease of its counterpart in ring B and if the process is continued, C is finally converted into C′ and vice versa (C and C′ are mirror images of each other). Such a concerted change in torsion angles of junction is energetically quite feasible which explains the ring inversion in *cis*- but not in *trans*-decalin. Further use of torsion angle of junction will be illustrated later.

3. Symmetry. The two-chair conformation of *trans*-decalin (Figure 11.1) has a centre of symmetry (mid-point of the 9-10 bond) and is achiral. In addition, it has a C_2 axis passing between C-2 and C-3, C-9 and C-10, and C-6 and C-7 and a σ plane perpendicular to the C_2 axis and passing through the ring junction. Its symmetry number (σ) is, therefore, 2 and it belongs to point group C_{2h}. The two-chair conformation of *cis*-decalin has no reflection symmetry but has a C_2 axis passing through the midpoint of the 9-10 bond and bisecting the dihedral angle between 9-H and 10-H (the dotted line in Figure 11.1). It is, therefore, chiral, has a symmetry number of 2, and belongs to point group C_2. As already stated, the two conformers of *cis*-decalin are enantiomeric but interconvertible at a rate too fast for the NMR time scale.

4. Entropy. Both *cis*- and *trans*-decalins have symmetry number 2 which contributes an entropy term of -Rln2 to each. In addition, *cis*-decalin has an entropy of mixing (being a racemic mixture), equal to Rln2 or 5.8 $JK^{-1}mol^{-1}$. Thus the difference in entropies of the cis and trans isomers is 5.8 $JK^{-1}mol^{-1}$ in favour of the cis. The experimental value is, however, quite small, approximately 2.3 $JK^{-1}mol^{-1}$ (in liquid) suggesting that there is more ordering in *cis*-decalin than in *trans*-decalin in the liquid state. It belies the popular idea that *cis*-decalin is more flexible than *trans*-decalin which would increase rather than decrease the difference in entropies of the *cis* and *trans* isomers. The ability of ring inversion of a system should not be confused with its flexibility.

5. Enthalpy and free energy. One can count the number of gauche butane units in *cis*- and *trans*-decalin arising out of carbon atoms from two different rings and then calculate the difference in enthalpies in terms of gauche interactions. In *trans*-decalin, since each ring is joined through e-bonds, no additional gauche unit exists (the single gauche in diequatorial *trans*-1,2-dimethylcyclohexane happens to be intraannular and so is not counted). In *cis*-decalin, three such gauche units exist, namely, 1-9-8-7, 1-9-10-5 and 3-4-10-5 as shown in the structure below (Figure 11.3). The difference of enthalpy is, therefore, equal to three gauche interactions*, i.e., 10.05 kJ mol^{-1} which is in good agreement with the experimental values ranging from 8.8 to 11.4 kJ mol^{-1} (determined by temperature dependence of equilibrium between cis and trans isomers and heat of combustion data). The relevant physical properties. e.g., boiling point, density, and refractive index have higher values for the cis isomer according to the Auwers-Skita (conformational) rule (b.P. 193°C/743 mm and 184.50°C/747 mm; d_4^{20} 0.895 and 0.870; n_D^{20} 1.4811 and 1.4697; the first values refer to the cis and the second to the trans isomer).

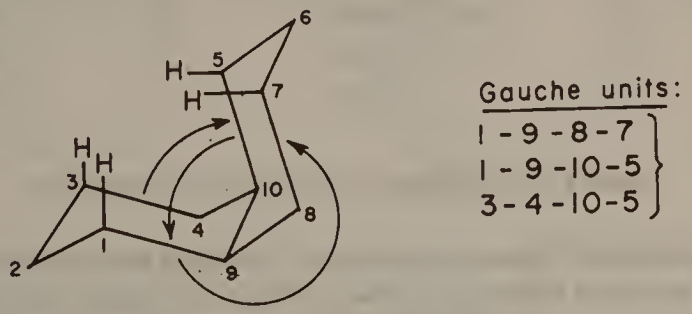


Figure 11.3 Gauche butane interactions in *cis*-decalin

The difference of free energies as determined from ΔH and ΔS is approximately 10.0 kJ mol^{-1} which agrees semiquantitatively to the equilibrium data of *cis*- and *trans*-1-decalones (the comparison may not be strictly valid because of 2- and

*Following W.S. Johnson, a value of 3.35 kJ mol^{-1} has been assumed for a gauche butane interaction in polycyclic systems.

3-alkylketone effects in decalones). The position of equilibrium of the 1-decalones corresponds to 5-10% of the cis isomer.

6. Ring inversion in cis-decalin. *cis*-Decalin and related system undergo ring inversion similar to cyclohexane which can be studied by ^{1}H-NMR. In rigid *trans*-decalin, the equatorial and axial protons are distinguishable and appear as two broad bands due to spin-spin coupling. On the other hand, in *cis*-decalin, the equatorial and axial protons are averaged out due to flipping of the rings and appear as a narrow band at ambient temperature. This can, however, be split up into two broad bands at low temperature and the coalescence temperature gives a value of 53.6 kJ mol^{-1} at -18°C in CS_2 for the free energy barrier of ring inversion. 2,2-Difluoro-*cis*-decalin exhibits a barrier of 51.5 kJ mol^{-1} at -30°C in ^{19}F-NMR. *cis*-Decalin has thus considerably higher barrier energy than cyclohexane and *cis*-1,2-dimethylcyclohexane ($\Delta G^{\ddagger}$=42.0 kJ mol^{-1} at -60°C).*

7. Effect of an angular methyl group. Introduction of a methyl group at one of the bridged carbon atoms gives rise to additional gauche interactions : *four* in the trans isomer (II) (two with respect to each ring, Me being axial to both) and *two* in the cis isomer (III) (Me being axial to one ring only) (Figure 11.4). The original difference of three gauche interactions in *cis*- and *trans*-decalins is thus reduced to one in 9-methyldecalins in favour of the trans isomer which is thus more stable than the cis isomer by 3.35 kJ mol^{-1}. This is more or less supported by the experimental values of enthalpy difference as determined by temperature dependence of cis-trans equilibrium and by heat of combustion data, ΔH ranging from 2.5 to 8.4 kJ mol^{-1}.

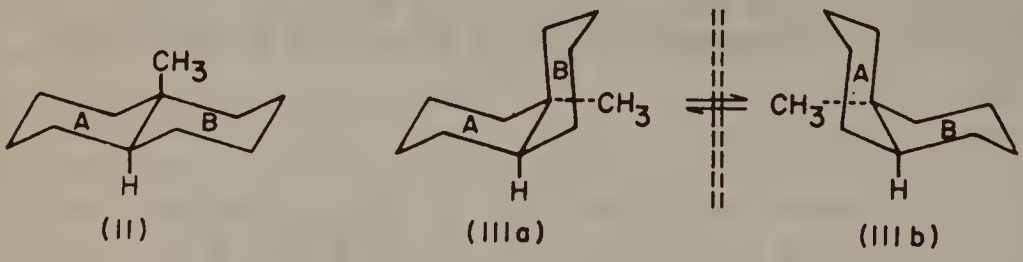


Figure 11.4 *cis*-9-Methyldecalin and *trans*-9-methyldecalin

trans-9-Methyldecalin (II) does not have any C_2 axis but possesses a σ plane passing vertically along the 9-10 bond. It is thus achiral and belongs to point group C_s. The cis isomer, on the other hand, is devoid of any symmetry element and belongs to point group C_1. However, the two enantiomers (IIIa) and (IIIb) are interconvertible by ring inversion and *cis*-9-methyldecalin is a (±)-mixture having an entropy term higher than the trans isomer by Rln2 (5.8 JK^{-1} mol^{-1}). Experimentally, the entropy term favours the cis isomer but not to the extent expected theoretically - a behaviour which appears to be intrinsic in the decalin system.

cis-9-Methyldecalin exhibits a ring inversion barrier of 52.8 kJ mol^{-1}, similar in

*Many of the ring inversion data are available in a monograph by Oki (1985).

magnitude to that in *cis*-decalin. *cis*-9,10-Dimethyldecalin displays a much higher ring inversion barrier (61.2 kJ mol^{-1}).

11.2.2 Decalones and decalols

As long as the rings in decalin system are not substituted other than at bridgeheads, the trans isomers are always achiral having a σ plane vertical to the common bond and the cis isomers although chiral exist as unresolvable racemic mixtures. Introduction of a substituent at any other carbon creates three chiral centres, two at the bridgeheads and one at the point of substitution and the number of stereoisomers increases. When a carbonyl group is introduced to give 1- or 2-decalone, the two bridgehead carbons become chiral and both the *cis*- and *trans*-decalones exist as resolvable (±)-pair. Thus *trans*-1-decalone can be resolved into two enantiomers (IV) and (IV′) (Figure 11.5) which have fixed conformations. In the case of *cis*-1-decalone, each of the enantiomers undergoes ring inversion to a non-equivalent conformer. The enantiomers (Va) and (Va′) have the steroid conformation while Vb and Vb′ have the non-steroid conformation. Both *cis*- and *trans*-1-decalones can be easily equilibrated by treatment with base into a mixture in which the latter predominates ($\Delta G°$ is around 10.0 kJ mol^{-1}) to the extent of 90-95%. The ring inversion barrier in *cis*-decalones is appreciably higher than that ir cyclohexanone. Thus ^{19}F-NMR spectra of 6,6-difluoro-*cis*-2-decalone at low temperatures indicate a free energy of activation for ring inversion of 39.9 kJ mol^{-1} in comparison to 16.75 kJ mol^{-1} for cyclohexanone. The effect of a 10-Me substituent on the energy barrier is negligible ($\Delta H^{\ddagger} = 41.0$ kJ mol^{-1}; $\Delta S^{\ddagger} = 20.0$ JK^{-1} mol^{-1} for *cis*-10-methyl-1-decalone).

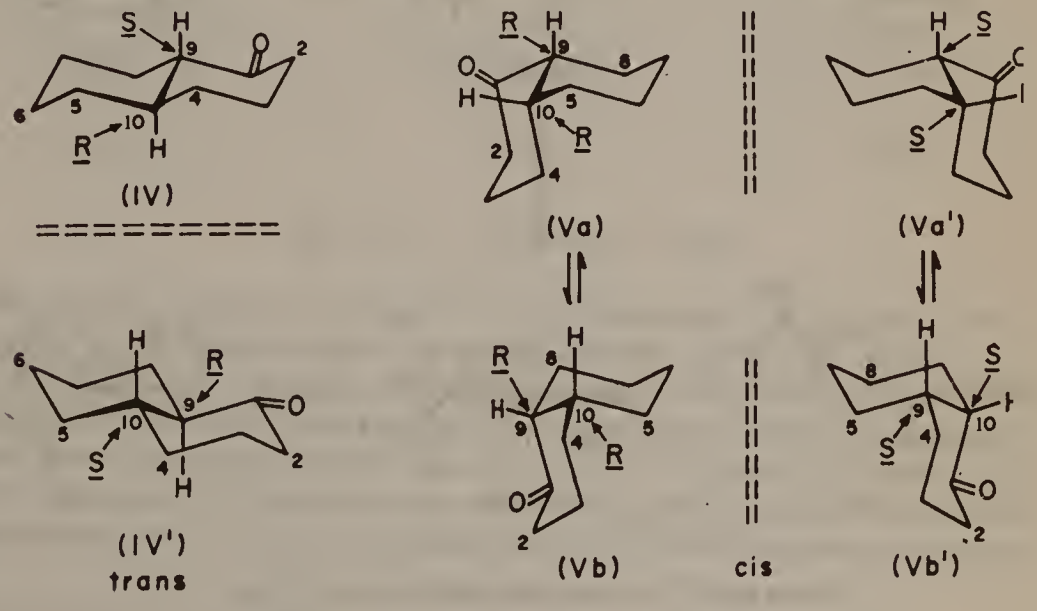


Figure 11.5 *cis*-1-Decalone and *trans*-1-decalone

When decalones are reduced to decalols, a third chiral centre is created and the number of stereoisomers correspondingly increases. Each enantiomer of *trans*-1-decalone would give an axial and an equatorial alcohol resulting in a set of four

stereoisomers. The same is true in principle when *cis*-1-decalone is reduced to decalol but here each of the four stereoisomers exists in two conformations so that altogether eight conformational isomers result. For the *trans*-decalols, conformational analysis is easy, the equatorial alcohol being preferred over the axial. But for the *cis*-decalols, each isomer is a mixture of two conformers with OH axially and equatorially oriented and the axial-equatorial character of OH in a particular isomer would depend on the relative population of the two conformers. The number of isolable isomers is predictable from planar structures (Leonard et al).

11.2.3 **Octahydronaphthalenes (octalins)**

Depending on the position of the double bond, there are four octalins : $\Delta^{9,10}$-octalin which has the double bond at the junction with the two cyclohexene rings in half-chair conformation, $\Delta^{1,9}$-octalin which has ring A in deformed half-chair form and ring B in deformed chair form, and finally, $\Delta^{1,2}$-octalin and $\Delta^{2,3}$-octalin which have the double bond away from the ring junction with ring A in flexible half-chair conformation and ring B in chair conformation. The last three systems are of conformational interest and are discussed below.

1. $\Delta^{1,9}$-Octalin. $\Delta^{1,9}$-Octalin (VI) (Figure 11.6) has a chiral centre at C-10, exists as a (±)-pair, and belongs to point group C_1: Ring A is fused with ring B through a fixed 9-8 bond and a flexible 10-5 bond which may be either

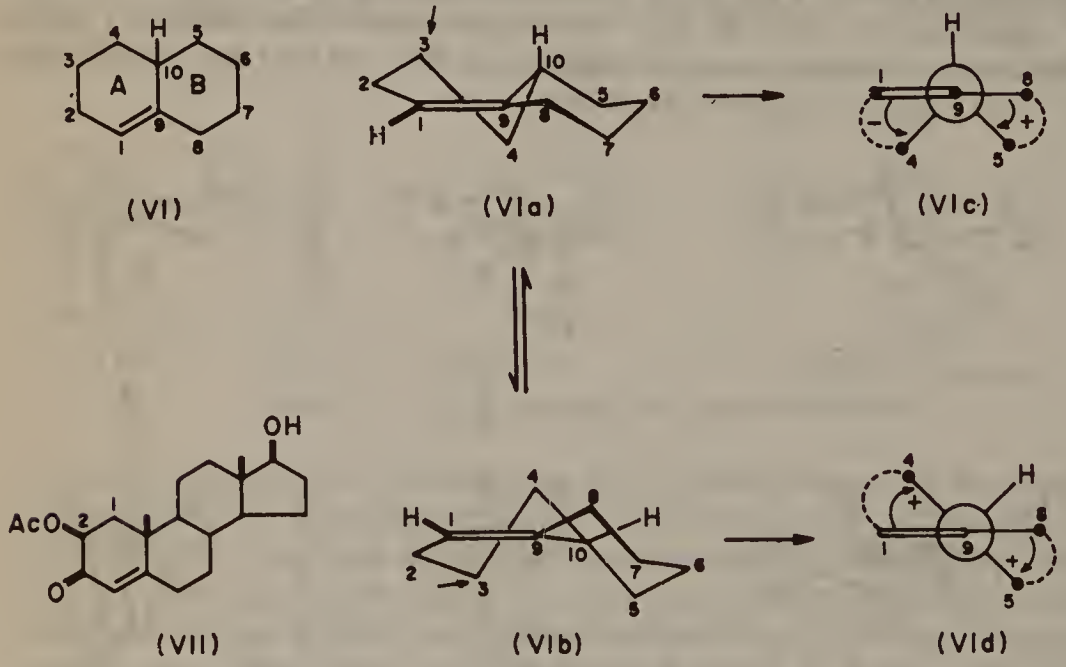


Figure 11.6 $\Delta^{1,9}$-Octalin: quasi-trans and quasi-cis fusion

pseudoequatorial as in VIa or pseudoaxial as in VIb, the two conformers being non-equivalent but interconvertible by ring inversion. Their Newman projections (VIc) and (VId), viewed along C-9 and C-10, show torsion angles of junction. The first conformer (VIa) is flat, almost like *trans*-decalin but lacking its rigidity with

torsion angles of junction of opposite signs, again like *trans*-decalin. It is, therefore, called a *quasi*-trans form. The second conformer (VIb) is folded and like *cis*-decalin, torsion angles of junction are of the same sign. It is called *quasi*-cis conformer. The terms *quasi*-trans and *quasi*-cis refer here to conformational and not to configurational isomers*. A priori, octalin (VI) should exist predominantly as the *quasi*-trans form (VIa) unless some steric situation such as an axial group at C-3 (shown by arrow) makes it unstable due to 1,3-syndiaxial interaction. This is the case with 2 β-acetoxytestosterone (VII) (C-2 in VII corresponds to C-3 in VI) in which acetoxy group is found to be equatorial (see arrow in VIb).

2. The $\Delta^{1,2}$- and $\Delta^{2,3}$- octalins. $\Delta^{1,2}$- Octalin (VIII) and $\Delta^{2,3}$--octalin (IX) (Figure 11.7) in their trans configuration have the torsion angles of junctions as shown. Compared to *trans*-decalin (as T on the left hand side), the torsion angle in the saturated ring of $\Delta^{1,2}$-octalin has undergone an opening of 10° (from + 55° to + 65°) while the same in the saturated ring of $\Delta^{2,3}$-octalin has been reduced by 6° (from + 55° to 49°).† This means that a double bond at the 2-3 position is more favourable than a double bond at the 1-2 position in *trans*-decalin. The calculated enthalpy difference between the two octalins is approximately 3.0 kJ mol^{-1} which compares favourably with an experimental value determined by equilibration of isomers of octalin. It is pertinent to note that opening of a torsion angle in cyclohexane chair is energetically less preferable than closing of a torsion angle of the same magnitude. Incidentally, this may explain the tendency of *trans*-2-decalone to enolise to give a 2,3-double bond rather than a 1,2-double bond.

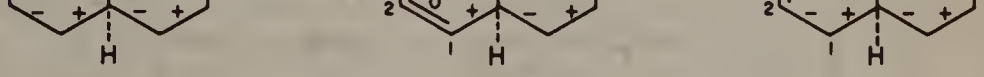


Figure 11.7 $\Delta^{1,2}$-Octalin and $\Delta^{2,3}$-Octalin

The relative stability of $\Delta^{1,2}$- and $\Delta^{2,3}$-*cis*-octalins cannot be evaluated from a consideration of torsion angles of junction (Bucourt 1974). The presence of a double bond in a *cis*-decalin system minimises the gauche interactions previously mentioned. If the double bond is at the 1-2 position in *cis*-decalin, it decreases two of the three gauche interactions (consult diagram in Figure 11.3) while if the double bond is at the 2-3 position, only one of the gauche interactions is decreased which makes *cis*-$\Delta^{1,2}$-octalin more stable than *cis*-$\Delta^{2,3}$-octalin (a result opposite to

*Perhaps *quasi*-trans and *quasi*-cis be better replaced by transoid and cisoid respectively.

†To assign the signs of torsion angles of junction, one should follow the sequence of the signs of the torsion angles of a ring in a clockwise fashion. A β axial substituent (at bridgeheads) is preceded by (+) and followed by (−) and the reverse for an α axial substituent (Bucourt 1974). One must also keep in mind that the signs of torsion angles around successive C-C bonds in cyclohexane chair alternate and that in the case of a trans fusion, both angular substituents are axial.

that for the *trans*-octalins). This may explain the tendency of *cis*-2-decalone to enolise towards C-1 instead of C-3.

11.2.4 Fused bicyclic systems with nitrogen

Decahydroquinoline (X) and quinolizidine (XII) are the two most important fused bicyclic systems containing an N atom. Their stereochemistry is of interest because of their occurrence in various alkaloids, e.g., lupinine, reserpine, and yohimbine. Decahydroquinoline (also decahydroisoquinoline) exists as trans (X) and cis (XI) diastereomers similar to decalin, as shown in Figure 11.8 with the difference that it contains two chiral centres and each isomer is resolvable accounting for a total of four stereoisomers. In addition, pyramidal inversion at N can take place giving rise to invertomers (Xa) and (Xb). As in the case of piperidine, N-H_e is preferred. Like *cis*-decalin, the cis isomer exists in two conformers, steroid (XIa) and non-steroid (XIb) interconvertible by ring inversion. They are, however, not mirror images of each other as in *cis*-decalin but have their enantiomeric counterparts. The conformer (XIb) is more stable than the other (XIa) because CH_2 synaxial to lone pair on N is better than CH_2 synaxial to H at C. Although inversion at N takes place, N-H_e or N-R_e is preferred.

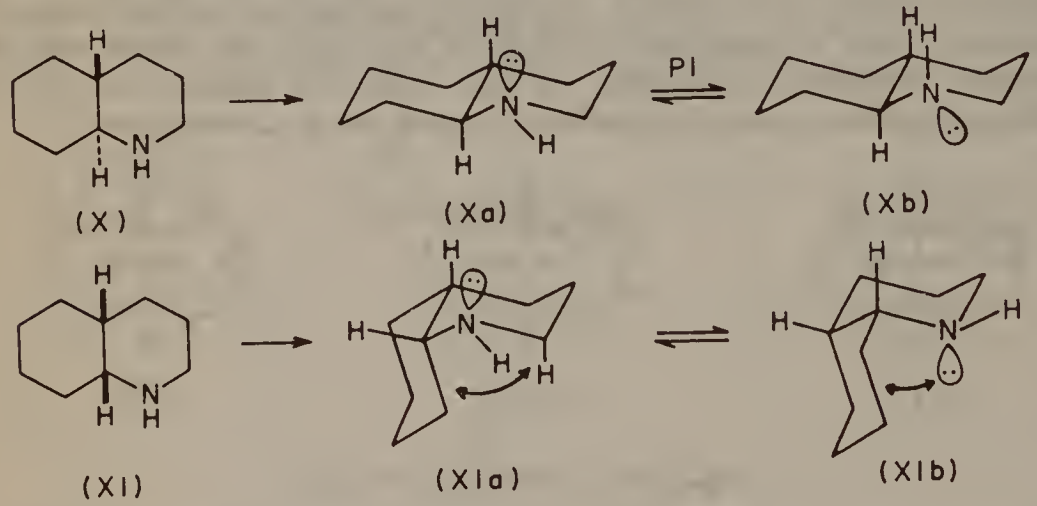


Figure 11.8 Decahydroquinoline

Quinolizidine (XII) is achiral (presence of a σ plane) and exists in a trans and a cis form. They are, however, interconvertible by inversion at nitrogen and may be called either conformational isomers or configurational isomers.* The trans form (XIIa) on inversion at N can give either the cis conformer (XIIb) or its mirror image (XIIb′) as shown in Figure 11.9. The two enantiomers are in turn interconvertible by ring inversion . Thus all the three conformers (XII: a,b,b′) are in dynamic equilibrium. The trans conformer (XIIa) is more stable than the cis (XIIb) by an energy term of 18.5 - 20.0 kJ mol^{-1} (determined by irreversible quaternisation of nitrogen discussed before) which is considerably higher than in decalin series. This is quite expected because the conformational free energy of Me in N-methylpiperidine is ~11.3 kJ mol^{-1} (Chapter 10). The trans fused quino-

* Actually, they should better be called conformational diastereomers.

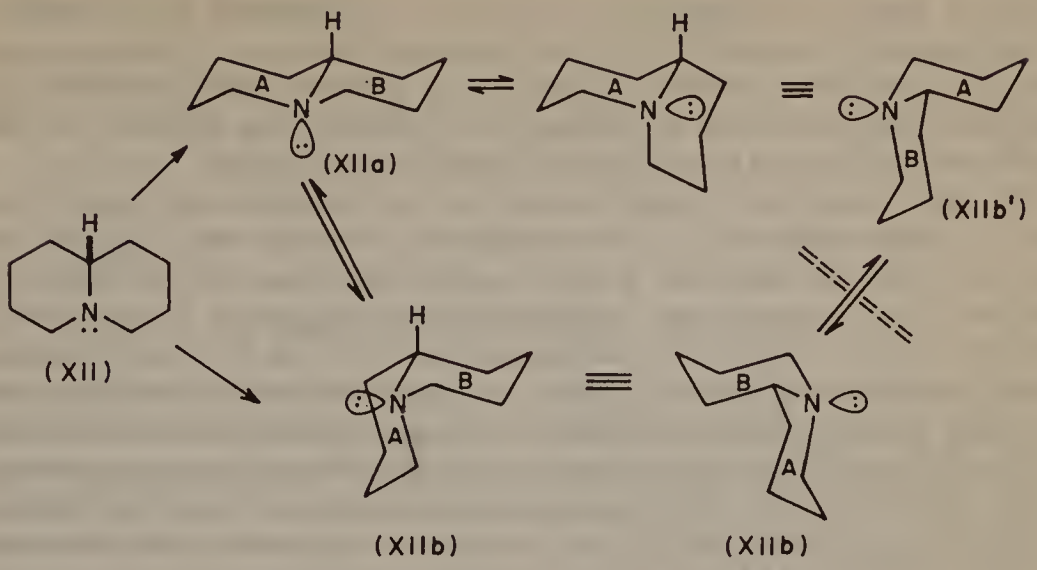


Figure 11.9 Quinolizidine (dotted line represents mirror)

lizidines are characterised by the presence of Bohlmann bands in IR (around 2700-2800 cm^{-1}) which are either absent or very weak in the cis fused isomers.

11.2.5 **Bicyclo[4.3.0]nonane (hydrindane)**

Next to decalin, bicyclo[4.3.0]nonane, commonly known as hydrindane is the most important bicyclic system because of its occurrence in steroids (rings C and D). Like decalin, hydrindane also exists in two diastereomeric forms. cis and trans which are shown in Figure 11.10 in planar (XIII) and (XIV) and puckered (XIIIa) and (XIVa) forms. The planar structures show two equivalent chiral centres (the bridgehead carbons) predicting the trans isomer as a (±)-pair and the cis isomer as a meso compound. Actually, *cis*-hydrindane in which one axial and one

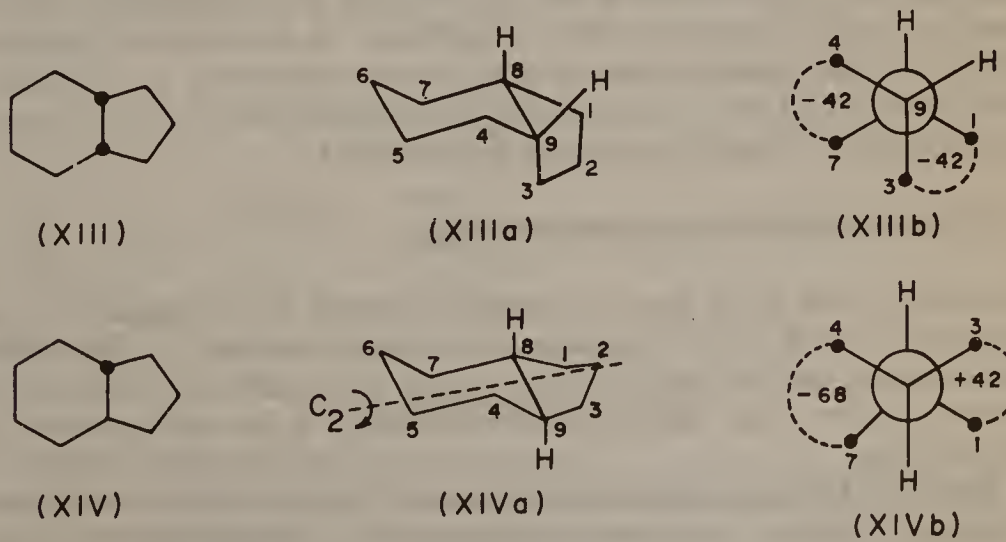


Figure 11.10 Hydrindanes (only one enantiomer of each diastereomer shown)

equatorial bond of cyclohexane are engaged in cyclopentane ring formation (XIIIa) is chiral (C_1 point group) but like *cis*-decalin exists as a (±)-mixture, the two enantiomers being interconvertible by ring inversion. *trans*-Hydrindane in which two equatorial bonds are engaged in cyclopentane ring formation is rigid (XIVa), has a C_2 axis but no reflection symmetry (C_2 point group).

The trans isomer has a slightly smaller heat of combustion (by about 5 kJ mol^{-1}) in vapour phase and so is only marginally stabler than the cis isomer. On the other hand, the latter has a higher entropy (by about 9.5 $JK^{-1}mol^{-1}$)—apparently, in the trans isomer, pseudorotation in cyclopentane is considerably restricted—and as a result, at a temperature below 466 K, the trans isomer is slightly more abundant but above that the cis isomer predominates at equilibrium. The small enthalpy difference between *cis*- and *trans*-hydrindanes compared to decalins is due to relatively flat cyclopentane ring in which ring torsion angles may reach a maximum of 42° only without creating much strain. The idealised values of the torsion angles of junction in *cis*- and *trans*-hydrindanes are shown in structures (XIIIb) and (XIVb). In the latter, the torsion angle of junction in the cyclohexane ring shows a considerable opening (from 55° to 68°) which is quite unfavourable (it makes the chair form much more puckered). The situation in *cis*-hydrindane is not so bad, the reduction of torsion angle of junction slightly flattens the cyclohexane chair. That the cyclohexane ring in hydrindanes exists in chair form (slightly deformed) is evidenced from the oxidation rates of cis and trans isomers of 2-oxahydrindane-*cis*-5,6-diols (Eliel 1962, p. 277) with lead tetraacetate which correspond roughly to those of the *cis*-and *trans*-cyclohexane-1-2-diols (OH's staggered) but not to those of the cyclopentane-1.2-diols (OH's nearly eclipsed).

The small enthalpy difference between *cis*- and *trans*-hydrindanes is further reduced by introduction of substituents. Thus in the case of 8-methylhydrindane and 1-hydrindanone, the cis isomers are more stable than the trans isomers (much more so in 1-hydrindanone).

The free energies of activation for ring inversion in *cis*-hydrindane and its derivatives are also much lower than in *cis*-decalins, as determined by dynamic NMR studies. The average barriers to ring inversion (determined by ^{19}F-NMR) are 30.5 and 31.8 kJ mol^{-1} for *cis*-6,6-difluorohydrindane and *cis*-6,6-difluoro-8-methylhydrindane respectively (Lack and Roberts 1968).

11.2.6 **Fused bicyclic systems with small rings**

Either one or both of the rings in bicyclic compounds may be small (3- or 4-membered) in which case two phenomena are usually observed: (*i*) The systems become strained and (*ii*) the cis isomers become more stable than the trans; in extreme cases, the latter may even be non-existent. A few such systems are discussed below.

1 Bicyclo[3.3.0]octane. Bicyclo[3.3.0]octane (XV) (Figure 11.11) in which two cyclopentane rings are fused through adjacent atoms is known under the trivial name, pentalane and can still exist in cis and trans forms. The cis fusion takes place through two nearly eclipsed bonds and is relatively easy. The trans fusion which

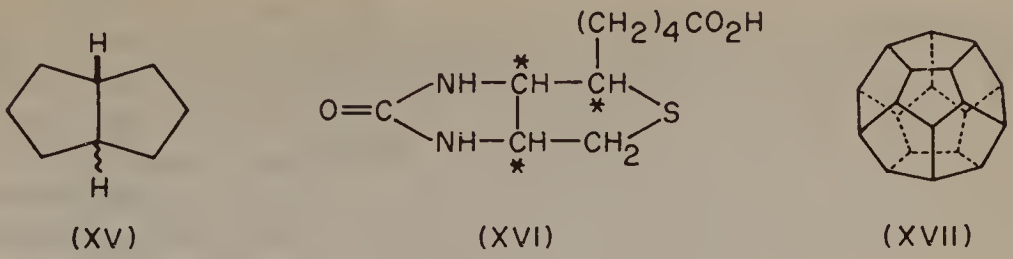


Figure 11.11 Bicyclo[3.3.0]octane and analogues

requires spanning of two oppositely oriented bonds by a $(CH_2)_3$ chain leads to deformation of the cyclopentane rings. The enthalpy of formation of the trans-isomer is about 25 kJ mol^{-1} higher than that for the cis isomer. Biotin (XVI) is a naturally occurring compound with two cis fused 5-5 heterocyclic rings. Dodecahedrane (XVII), a synthetic hydrocarbon exhibiting the highest known symmetry, I_h ever imagined for any organic molecule is built up of twelve cis fused (all-syn) five-membered rings (six pentalane units).

2. Bicyclo[3.2.0]heptane and related systems. The next lower homologue is bicyclo[3.2.0]heptane (XVIII) (Figure 11.12) which exists only in the cis form. Bicyclo[4.2.0]octane is stable in the cis form (XIX) although the trans form is known. If the other ring is 7-membered or larger, the trans fusion becomes easier and may be even stabler than the cis fusion. The naturally occurring sesquiterpene, caryophyllene (XX) provides an example in which not only the ring junction but also the endocyclic double bond is trans oriented. Bicyclo[2.2.0]hexane (XXII) is also known (in cis form) as one of the products of photolysis of bicyclo[3.2.0] heptanone (XXI).

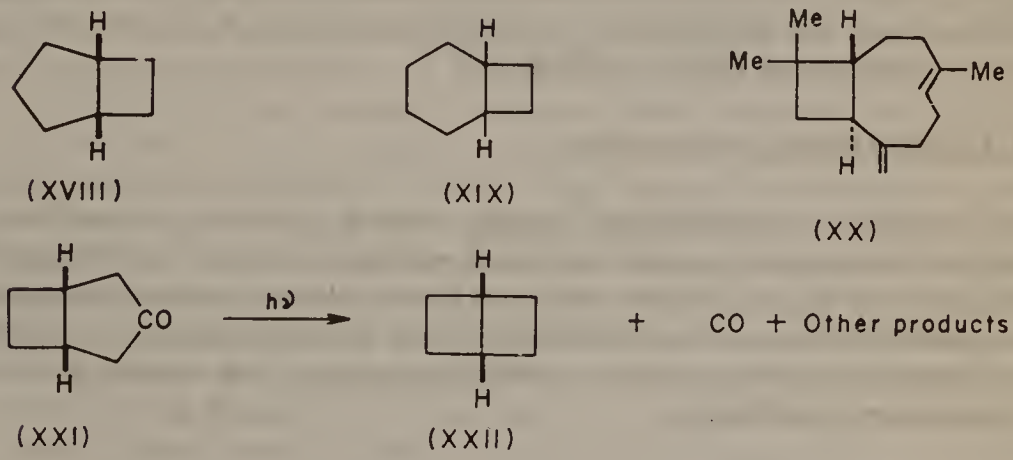


Figure 11.12 Fused 4-ring systems

3. Fused 3-membered ring systems. Bicyclic compounds containing a cyclopropane ring or an epoxide ring are quite well known both in natural and synthetic products. The smallest possible bicyclic carbocycle is bicyclo[1.1.0]butane (XXIII) formed by photo-chemical reaction of 3-diazobutene (Figure 11.13). It can exist only in cis form having a folded structure (XXIIIa) in which the methylene

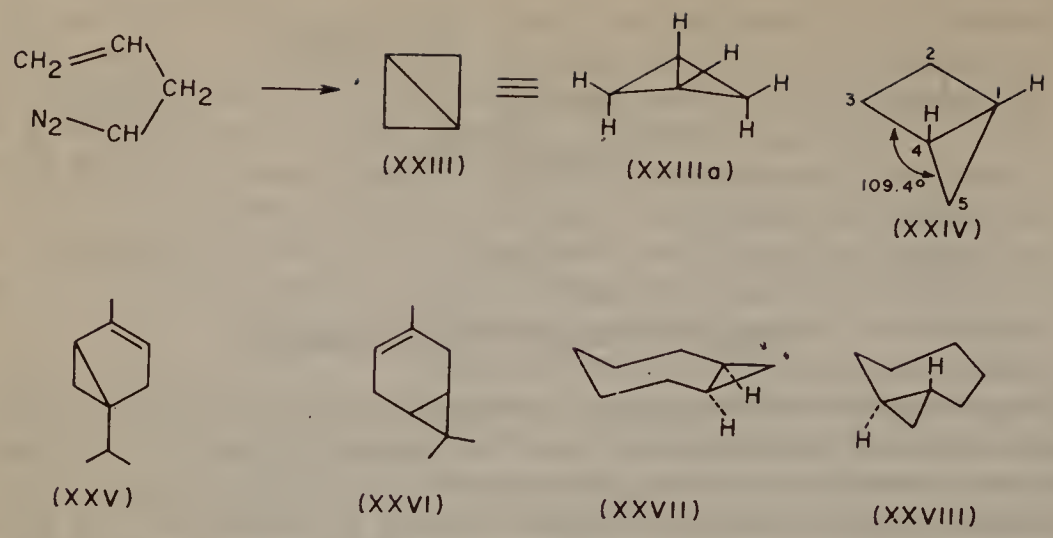


Figure 11.13 Fused 3-ring systems

protons fall under two categories, exo and endo as in bridged compounds (see later). The next higher homologue is bicyclo[2.1.0]pentane (XXIV) which has been studied by electron diffraction. It has a folded structure with an angle of 109.4° between the planes of the two rings and has an unusually long 2-3 bond (162.2 pm) and an unusually short 1-4 bond (143.9 pm). Bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane skeletons are found in monoterpenes, thujane and carane derivatives respectively, e.g., α-thujene (XXV) and car-3-ene (XXVI). Only cis isomers are possible in these systems. However, in bicyclo[5.1.0]octanes and higher homologues, both cis and trans isomers are possible, e.g., XXVII (cis) and XXVIII (trans).

Fused bicyclic compounds with small rings (see Seebach 1965 for a review) are highly strained: the strain energy in bicyclobutane (XXIII) is 270 kJ mol^{-1} and that in bicyclopentane (XXIV) is 230 kJ mol^{-1}.

11.3 Fused polycyclic systems

The principles of conformational analysis adopted in bicyclic systems can be extended to polycyclic systems. Additional problems, however, arise because of interactions among non-adjacent rings which also influence the relative stabilities and chemical behaviour of the stereoisomers. Three polycyclic systems are discussed here, namely perhydrophenanthrene, perhydroanthracene, and steroids (perhydrocyclopentenophenanthrenes).

11.3.1 Perhydrophenanthrenes

Perhydrophenanthrene with three cyclohexane rings fused consecutively to an angular arrangement illustrates most of the stereochemical principles involved in polycyclic systems. It constitutes the A, B, and C rings of steroids and triterpenoids. In addition to the terms cis and trans which define the stereochemistry of ring junctions, two other terms *cisoid* (synonymous with *syn* and abbreviated here as *c*)

and *transoid* (synonymous with *anti* and abbreviated here as *t*) (IUPAC Commission 1974) are used which define the steric relations (syn and anti respectively) of the nearest bridgehead atoms* (H's in the present examples) belonging to two different rings which are not fused together. Two other points would help to understand the stereochemistry of these systems: (*i*) If any two 6-membered rings are trans fused, the entire system becomes rigid like *trans*-decalin and no ring inversion can take place. (*ii*) The number and nature of stereoisomers may be determined from the planar structures (Leonard et al 1975).

The perhydrophenanthrene molecule contains two equivalent pairs of chiral centres (the four bridged carbons). It thus belongs to ABBA type and can exist as four (±)-pairs and two meso forms. Their relative configurations have been determined by the classical work of Linstead and coworkers through conversion of perhydrophenanthrones (as XXIX) into perhydrodiphenic acids (as XXX) (Figure 11.14a). The stereochemistry of the latter has been worked out from the study of catalytic hydrogenation of diphenic acid giving cis isomers followed by preferential epimerisation of the derived diesters and monoesters with sodium methoxide. Thus the three stereoisomeric acids obtained initially from catalytic hydrogenation are equilibrated to the other three isomers (Figure 11.14b).

Conformational analysis of the six diastereomers and their relative stabilities have been worked out by Johnson (1951) and more recently by Allinger and coworkers (1971). Johnson's method is based on counting gauche butane interactions and allowing 3.35 kJ mol^{-1} for each while Allinger et al obtained molecular geometries and energies by using molecular mechanics. Johnson's method which is similar to that used for decalins is discussed here. Both give nearly the same results except for two cases which are pointed out later. The six diastereomers are shown in Figure 11.15 in planar structures and in three-dimensional perspective formulae along with the number of gauche interactions and approximate energies calculated therefrom. The trans-*transoid*-trans isomer (trans-*t*-trans) is the most stable in which the central ring is fused with the other two rings by four equatorial bonds (A). Unlike *trans*-decalin, however, it has one gauche interaction resulting from H's on C-4 and C-5 (to be designated henceforth as 4,5-interaction). It may be remembered that two adjacent e,e or e,a methyl groups in cyclohexane form a gauche butane unit and so this interaction is present in all isomers except in the rare case where the ring residues are joined to the central ring by two adjacent axial bonds. The 4,5-interaction is best seen in the conformation (B) which happens to be the mirror image of A shown in different perspective. The chirality or otherwise of these molecules can be judged by looking for a vertical plane of symmetry passing through the 9-10 and the 12-13 bonds in the planar structures. Its absence in trans-*t*-trans, cis-*t*-trans, cis-*c*-trans, and cis-*t*-cis makes them resolvable and its presence in cis-*c*-cis and trans-*c*-trans makes them meso. The cis-*t*-trans (C) has a *cis*-decalin unit characterised by three gauche interactions. In addition, it has the 4,5-interaction (the first digit in the count indicates its presence or absence) and

*The term 'nearest atoms' means those which are linked together either directly or through smallest number of atoms (see, for example, nomenclature in Figures 11.15 and 11.16). When a choice remains, the pair containing the lower-numbered atoms is selected.

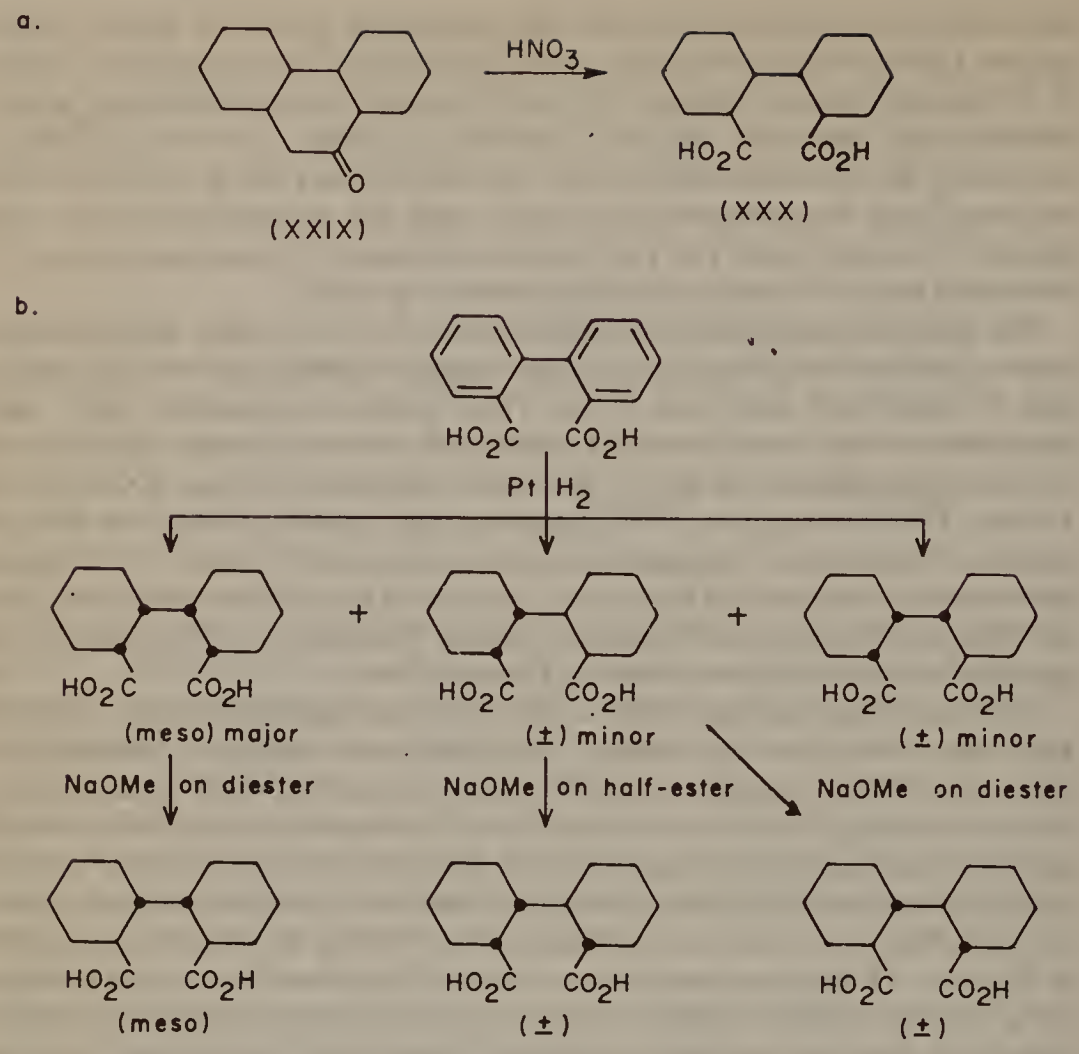


Figure 11.14 Stereochemistry of perhydrodiphenic acids (see Eliel 1962, p. 283)

so the energy is 13.4 kJ mol^{-1} (4 × 3.35). The same goes for the cis-*c*-trans isomer (D), the 4,5-interaction being due to a,e-substitution. The cis-*t*-cis isomer (the central ring diequatorially substituted) having two cis ring junctions can undergo inversion and exists as a mixture of two conformers (E) and (F) which are non-equivalent.* There are two *cis*-decalin units in each totalling six gauche interactions and in E, the 4,5-interaction is also present. The conformer (F) with six gauche interactions is thus preferred having an energy of approximately 20.1 kJ mol^{-1}. The cis-*c*-cis isomer also exists as a mixture of two conformers (G) and (G′) which happen to be mirror images of each other. While the planar structure has a plane of symmetry, the puckered structure has none and so is chiral. Like *cis*-decalin, it is an inseparable (±)-mixture and the term 'meso' is really not applicable. In addition to having two *cis*-decalin units, the conformation (G) has a 1,3-syndiaxial interaction which usually introduces in simple system an interaction term of 22.6

*It is once more pointed out that only cis-cis isomers can exist in two conformers due to ring inversion.

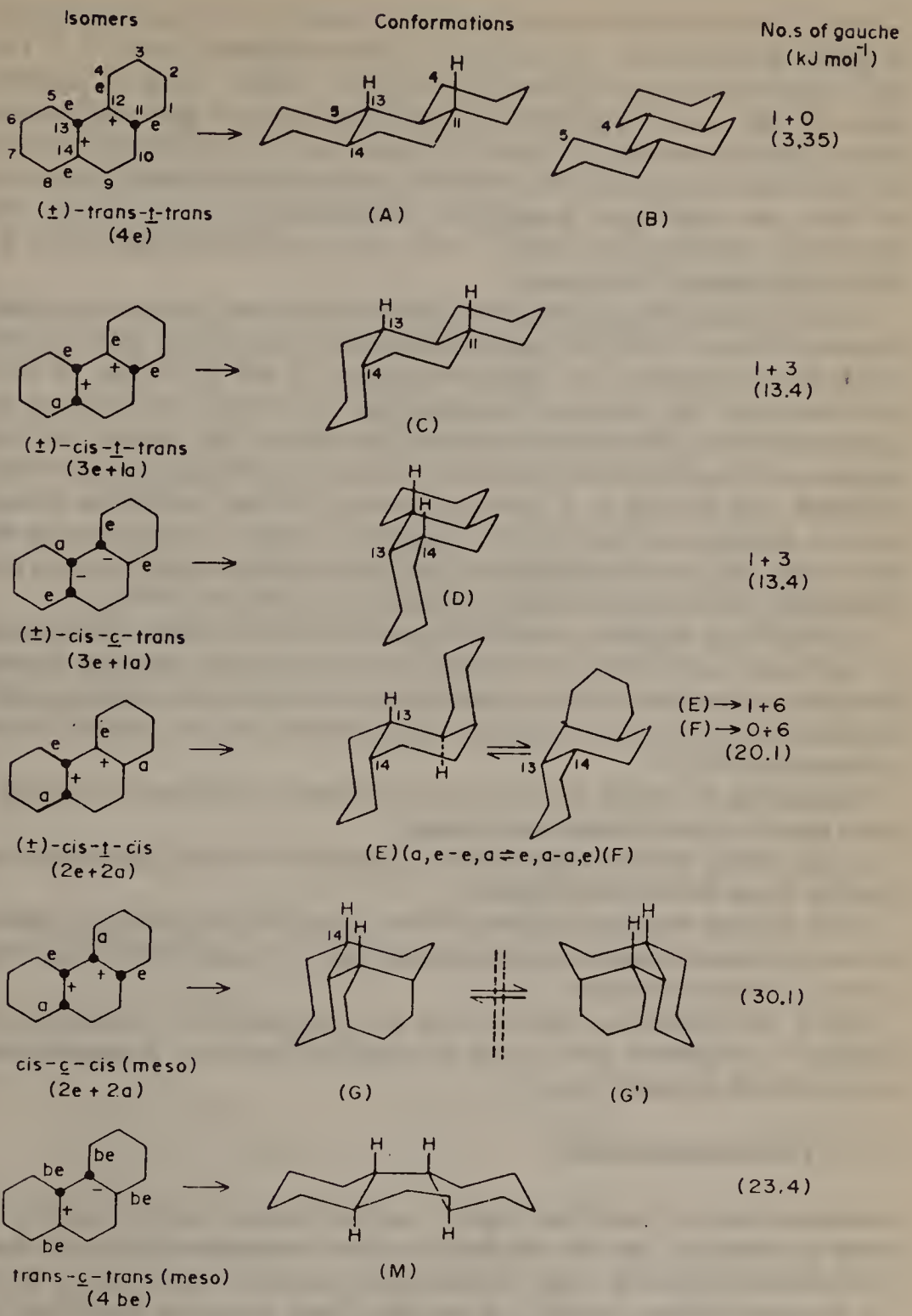


Figure 11.15 Conformations of perhydrophenanthrenes

kJ mol^{-1}. This along with two other gauche interactions (6.7 kJ mol^{-1}) should give an energy of 29.3 kJ mol^{-1} to this isomer. Johnson suggested a value of 30.1 kJ mol^{-1} while Allinger et al calculated a value of 37.7 kJ mol^{-1} being the highest in this series. The trans-*c*-trans isomer (the last one) cannot have both ring junctions trans and at the same time 12-H and 13-H cisoid in an all-trans conformation. For this, the central ring must assume a boat or a twist-boat conformation (as M) with the other two rings fused through four boat-equatorial bonds. Johnson has estimated an energy of 23.4 kJ mol^{-1} while Allinger et al have computed for it a slightly higher energy, 29.4 kJ mol^{-1}.

The torsion angles of junctions in the central ring have signs shown in the planar structures (Figure 11.15). The signs are determined from the rule that a β axial substituent is preceded by (+) and followed by (−)* and the reverse for an α axial substituent (the reference bridgehead axial C-H bonds are shown in the puckered structures). In the first five isomers, the signs are the same for each ring junction across bonds which are alternate (1,3) in a cyclohexane ring and are thus consistent with it being in a chair conformation. In the trans-*c*-trans isomer, however, the signs are opposite which suggests a non-chair conformation for the central ring. The use of torsion angles of ring junctions in studying the nature of a cyclohexane ring is specially helpful in steroidal system (Bucourt 1974).

The data so far available on the relative stabilities of the isomers, mainly from the equilibrium study of perhydrophenanthrones, agree with the calculated energies. Preliminary measurements of the composition of a perhydrophenanthrene sample equilibrated over palladium catalyst are also consistent with the calculated values (Allinger et al 1971).

Summarising the results, one can see that the above conformational analysis is based mainly on the following three premises:

(*i*) The system with the larger number of equatorial bonds of the central ring involved in ring fusions is more stable.

(*ii*) In the cases when two axial bonds of the central ring are used in ring fusion, 1,2- and 1,4-diaxial arrangements are preferred over 1,3-diaxial which suffers from a severe 1,3-diaxial interaction.

(*iii*) If the central ring cannot satisfy the configurational requirement by adopting a cyclohexane chair, a boat or twist-boat form for it is assumed with correspondingly increased energy.

11.3.2 Perhydroanthracenes

Perhydroanthracenes can be very similarly analysed stereochemically with only two points of distinction. The rings are fused in a linear arrangement so that the terms cisoid and transoid are no longer determined by the steric relations of 1,2 but by 1,3 bridgehead atoms. Secondly, all the four chiral centres are equivalent, the system corresponds to an AAAA type so that the number of stereoisomers is less. Perhydroanthracene exists in five diastereomeric forms: meso-trans-*c*-trans, (±)-cis-*c*-trans, meso-cis-*t*-cis, (±)-trans-*t*-trans, and meso-cis-*c*-cis (Figure 11.16), mentioned in order of their relative stabilities. The stereochemical symbols have the same significance as in perhydrophenanthrenes. The cis-*c*-trans isomer may as

* When seen in a clockwise direction.

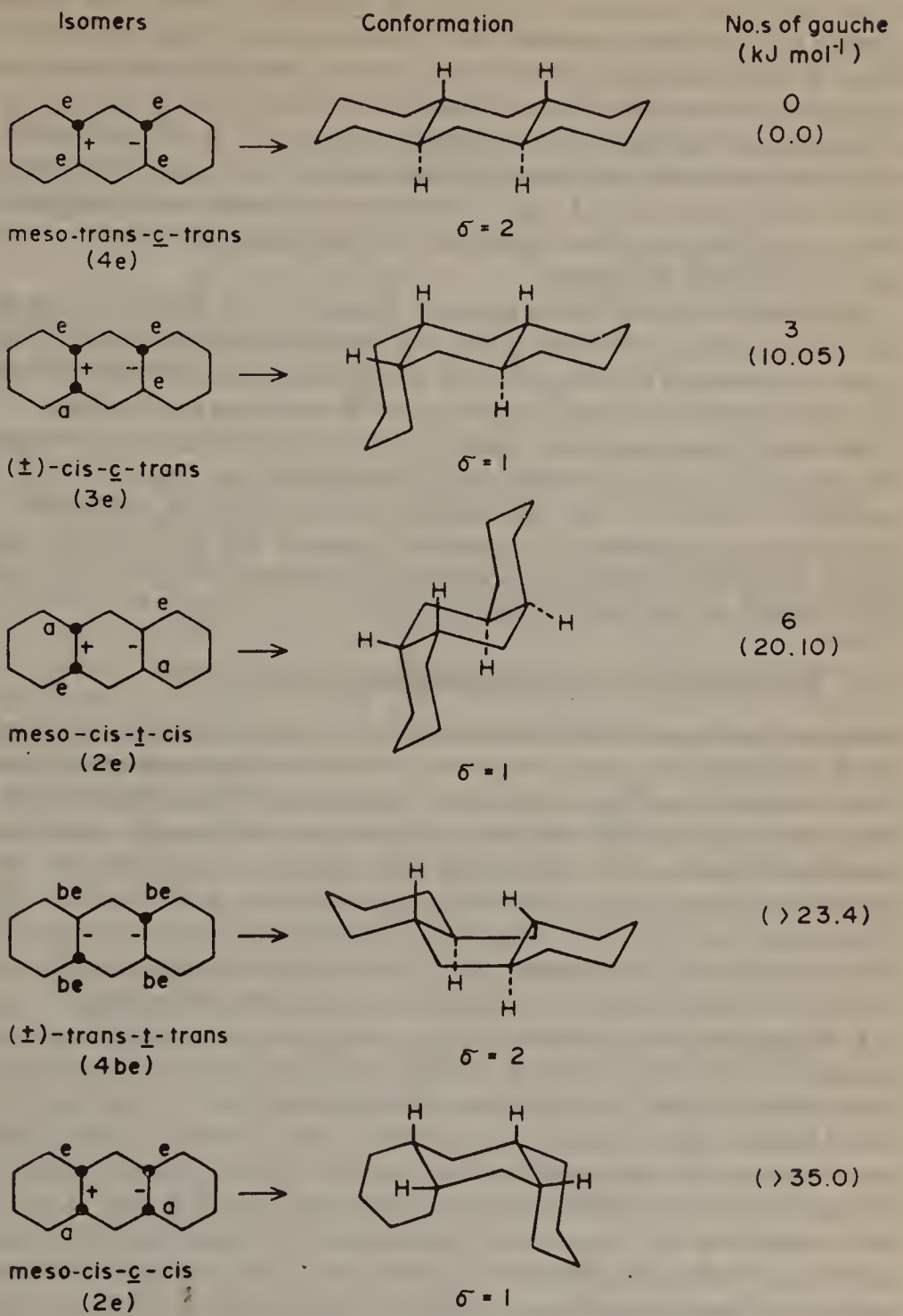


Figure 11.16 Conformations of perhydroanthracenes

well be called cis-*t*-trans isomer depending on whether one looks at the bridgehead atoms in the clockwise or anticlockwise direction. In this system, the trans-*c*-trans isomer is the most stable isomer having no extra gauche butane interaction (cf. trans-*t*-trans perhydrophenanthrene which contains one). The cis-*c*-cis isomer with a 1,3-syndiaxial interaction and two gauche interactions is the least stable. The trans-*t*-trans isomer has the central ring in a boat or twist-boat conformation and has an energy over 23.4 kJ mol^{-1}. The two cis-cis isomers on ring inversion give the same conformers: they are achiral even in chair conformations (cis-*t*-cis is of C_i and cis-*c*-cis is of C_s symmetry).

The respective signs of torsion angles of junctions in the central ring are shown following the same convention. In this case, since the two common bonds are 1,4, a chair conformation for the central ring would require opposite signs. The similar signs in the trans-*t*-trans isomer suggests a boat or twist-boat conformation.

The energy terms have been calculated using force-field method (Allinger and Wuesthoff 1971) and also experimentally determined from the composition of an equilibrium mixture of the hydrocarbons as a function of temperature. The experimental and calculated (in parenthesis) values of $\Delta H°$ are as follows: trans-*c*-trans, 0.00 (0.00); cis-*c*-trans, 11.55 (10.96); trans-*t*-trans, 17.37 (24.52); cis-*t*-cis, 23.35 (23.27); cis-*c*-cis, 36.58 (34.02) kJ mol^{-1}.

11.3.3 Steroids: perhydrocyclopentenophenantherene system

Steroids belong to one of the most important class of naturally occurring compounds which are biologically active. They have a perhydrophenanthrene moiety joined to a five membered ring. The substituted steroids because of their rigid structures have been extensively used for the study of reactions with specific stereochemical requirements such as E2 elimination and molecular rearrangements and for verification of many physicochemical theories especially in spectroscopy (IR, UV, NMR, and mass). The stereochemistry of steroids is discussed in many textbooks (Fieser and Fieser 1959; Gilman 1945). Only the basic conformational aspect of the steroidal ring system is presented here under the following headings.

1. Nomenclature. The different carbon atoms in the steroid nucleus are numbered as shown in the planar structure (XXXI) and a few mother systems have their trivial names (Figure 11.17). In most of the natural steroids, the four rings are joined through trans fusion giving a rigid and more or less flat structure (XXXII). In a few cases, the rings A and B are cis fused as shown in structure (XXXIII); but the molecules are still rigid. Compounds with rings A and B trans belong to 5α series while those with rings A and B cis belong to 5β series. The groups or atoms pointing upwards (in the direction of 10-Me and 13-Me) are called β whereas the groups or atoms pointing downwards (away from 10-Me and 13-Me) are called α (an arbitrary configurational nomenclature). The β groups are denoted by thick lines and the α groups by dotted lines in the planar structures. These designations have nothing to do with the axial or equatorial nature of the groups. Since, however, both configuration and conformation of a substituent in steroid nucleus are fixed, a given α (or a β) substituent must be either axial or equatorial, depending on the carbon atom at which it is located. Thus in the 5α series, 1-α-OH is axial, 2-α-OH is equatorial, 3-α-OH is axial, and 4-α-OH is equatorial. By default, the β-OH on these carbon atoms has the opposite conformation. In the 5β

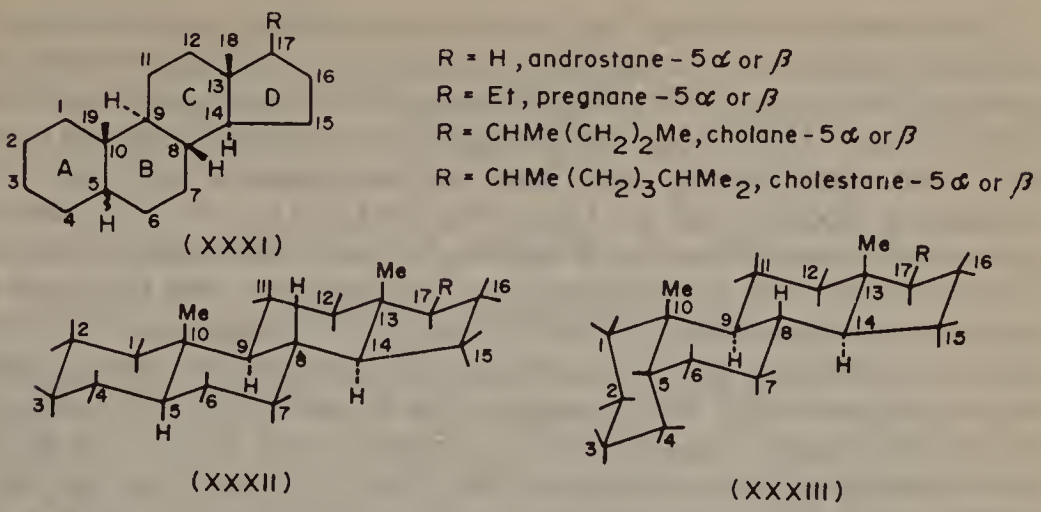


Figure 11.17 Numbering in steroids and conformations of A/B-trans and A/B-cis ring compounds

series, 1-α-OH is equatorial, 2-α-OH is axial, 3-α-OH is equatorial, and 4-α-OH is axial and so on. The two sets of designations are best seen in the steric formulae (XXXII) and (XXXIII). The remaining portion of the molecules is the same in 5α and 5β series. Ring D, however, may have different conformations depending on the substitution pattern and the axial and equatorial nature of a substituent varies accordingly, although its configuration (α or β) remains the same regardless of conformational change.

2. Stereochemistry of rings A and B. The six bridgehead carbons of steroid nucleus are chiral and the number of possible stereoisomers is, therefore, 2^6 i.e., 64 or 32 (±)-pairs. Any substituent at a non-bridgehead ring atom doubles the number. However, in natural steroids, the B/C and C/D ring junctions are always (with a few exceptions) trans fused which reduces the number of stereoisomers. The all-trans configuration of 5α steroids has been confirmed by X-ray analysis of cholesteryl iodide (with a 5,6-double bond).

The 5α steroids are more stable than the 5β steroids since the latter contain three additional gauche butane interactions characteristic of a *cis*-decalin moiety. This is consistent with the observation that cholestan-4-one and cholestan-6-one on equilibration show 99% and 88% of the A/B trans isomers respectively. As in the perhydrophenanthrene system, both 5α and 5β steroids have a gauche butane interaction among H's on C-1 and C-11. The axial H on C-11 is further sterically hindered by a synaxial interaction with 13-Me.

All the three cyclohexane rings exist in chair conformation as expected. However, in some exceptional cases, ring A may adopt a boat or twist-boat conformation as in 2α-bromo-2β-methylcholestan-3-one mainly to avoid 1,3-interaction between the axial Me and 10-Me in the chair form, and of course, the twist-boat in a cyclohexanone is not so unstable as in a cyclohexane.

In all natural steroids, the substituents on C-9 and C-10 have transoid arrangements as also, with a few exceptions, the substituents on C-8 and C-14. The 5α series thus belongs to a *trans*-5,10-*transoid*-9,10-*trans*-8,9-*transoid*-8,14-*trans*-13,14 and the 5β series to a *cis*-5,10-*transoid*-9,10-*trans*-8,9-*transoid*-8,14-*trans*-13,14 configuration. The absolute configuration is as shown (Chapter 8).

3. Conformation of D ring. The conformation of the five membered ring in 14α steroids (rings C/D trans fused) is still controversial. Three conformations are considered, two envelope forms (XXXIV) and (XXXV) and one half-chair form (XXXVI) (Figure 11.18). From the consideration of angle strain, torsional strain, and 1,3-interaction involving axial 13-Me and β-hydrogens at C-15 and C-16, conformation (XXXIV) with C-13 above the C-14, C-15. C-16, C-17 plane is preferred for an unsubstituted ring D and also for ring D substituted at C-17β (as in normal steroids with 17-side-chains). For 17-ketosteroids, ring D appears to exist in the second envelope form (XXXV) which has C-14 below the C-13, C-17, C-16, C-15 plane and the C = O plane at C-17 bisecting the valency angles between the two 16-H's. This is supported by the fact that the IR spectra of 16α- and 16β-bromo-17-ketosteroids show an identical shift (12 cm^{-1}) in the IR carbonyl stretching frequency (Hanack 1965, Eliel et al 1965). The half-chair conformation (XXXVI) with C-13 above and C-14 below the C-15, C-16, C-17 plane is favoured for 16-ketosteroids in which α and β H's at C-15 and C-17 have pseudoaxial or pseudoequatorial character as shown. The assignment is based on the shift of carbonyl frequency by halogen substitution of a′-H or e′-H. The problem is particularly tricky because of the conformational transmission effect (see below) which may alter the situation.

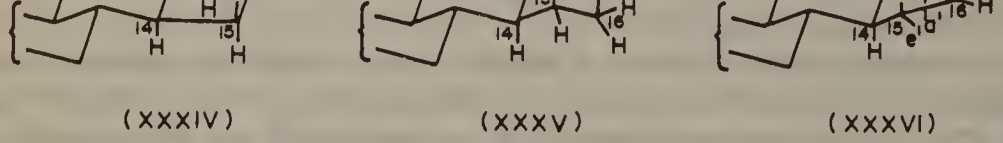


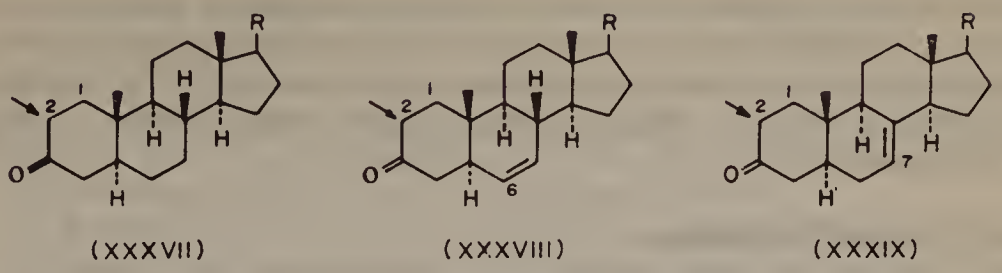
Figure 11.18 Conformation of D ring of steroids

It may be remembered that for 8-methylhydrindane, the cis isomer is more stable than the trans. However, in the steroidal system, the 14α (trans) series appears to be more stable than the 14β (cis) series as established from the study of 15-ketosteroids (equilibration data and optical rotatory dispersion are consistent).

4. Orientation of substituents. As in a cyclohexane derivative, any substituent other than H prefers to adopt an equatorial position in the steroidal system. Thus a steroid alcohol may be equilibrated to a composition in which the equatorial isomer predominates, e.g., 3-α-cholestanol to 3-β-cholestanol. Vicinal axial dibromides rearrange to diequatorial configuration.

5. Conformational transmission. Conformational transmission which exhibits itself in altering the properties of a molecule at a reactive site remote from the point where some deformation has occurred either by a specific substitution or by introduction of one or more trigonal atoms was first observed by Barton and is quite well known in the steroids and other polycyclic compounds. An explanation in terms of change in torsion angles of junction (Bucourt 1974) has already been suggested for this effect. A few illustrations* are given (Figure 11.19) from steroid

*Reflex effect previously discussed is also a kind of short range conformational transmission effect.



(XXXVII) (XXXVIII) (XXXIX)

Figure 11.19 Conformational transmission

chemistry. Benzaldehyde condenses with a methylene group (shown by arrows) adjacent to a carbonyl under base catalysis and the rate of formation of the benzylidene derivative may be determined by observation of an absorption band at 292 nm. 3-Ketosteroids (as XXXVII) such as cholestan-3-one, stigmastan-3-one, and 17β-hydroxyandrostan-3-one show a comparable rate of formation, 182, 180, and 188 respectively (relative to an arbitrary value of 100 for lanost-8-en-3-one) Cholest-6-en-3-one (XXXVIII), on the other hand, has a much higher rate of 645 which is due to a conformational transmission effect. If the double bond is shifted to position 7 as in XXXIX, the rate suddenly drops down to 43.

Conformational analysis of other polycyclic systems such as triterpenes, and alkaloids (Eliel et al 1965, p. 256) follow a similar pattern.

11.4 Bridged ring systems

When two rings are fused through non-adjacent atoms, more than two atoms become common to the rings and bridged ring systems result. They differ from fused ring systems previously discussed in that unless one or both of the rings are large ($\geq$7-membered), only cis fusion is possible and the number of stereoisomers is diminished (actually halved) from what is expected. Such systems are characterised by their relative rigidity, particularly when the rings are small and a substituent or a functional group is held with a fixed topology. They provide excellent models for investigating the stereochemistry and mechanism of many reactions. A good many natural products, both alicyclic and heterocyclic, possess bridged ring systems. A few are discussed, emphasis being laid on bicyclo[2.2.1] heptane and bicyclo[2.2.2]octane because of their importance in stereochemical studies.

11.4.1 Bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane

Bicyclo[1.1.1]pentane (Figure 11.20) is the smallest bridged ring system possible

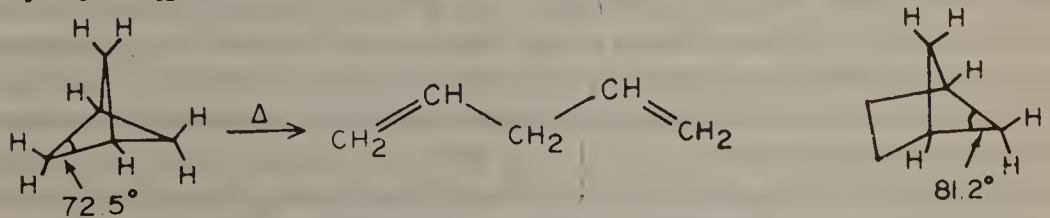


Figure 11.20 Bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane

and has been synthesised. The two bridgehead carbons are brought to close proximity (ca 200 pm) because of very small endocyclic valency angles (72.5°) It is unstable and converted into 1,4-pentadiene on heating at 300°C. The next higher homologue is bicyclo[2.1.1]hexane with the smallest endocyclic valency angle of 81.2° (Figure 11.20).

11.4.2 Bicyclo[2.2.1]heptane

The most common bridged ring system is bicyclo[2.2.1]heptane (XL) (Figure 11.21), known by the trivial name norbornane, so called because of its relation with natural terpene bornane. The characteristics of this system are discussed under the following headings.

1. Geometry. In this system, C-1 and C-4 of cyclohexane are joined by a methylene bridge forcing it to adopt a boat conformation. The smallest endocyclic valency angle is 93.0°. The system is also considerably strained because of two eclipsed butane units in the boat, although the fp-bs interaction in the boat is absent. Norbornane has a C_2 axis and two mutually perpendicular vertical σ planes and belongs to point group C_{2v}. Depending on the nature of substituents in the ring system, there may be slight twisting of the molecule along the 1-4 axis as shown in the projection formula on the right.

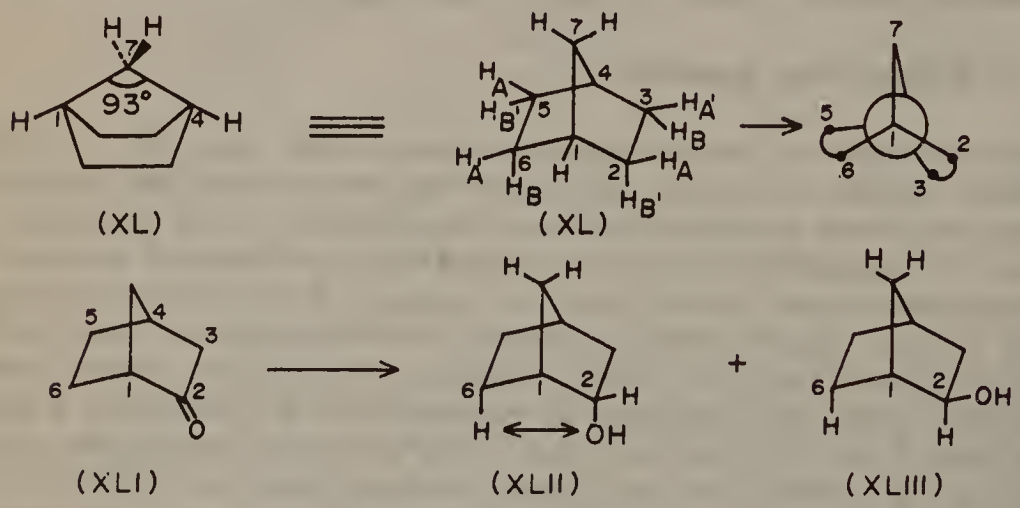


Figure 11.21 Bicyclo[2.2.1]heptanes

Six types of H's are discernible* in norbornane of which those situated at C-2, C-3, C-5, and C-6 and designated H_A, H_A', H_B, and H_B' are stereochemically relevant. H's with subscripts A and A′ have boat-equatorial orientation and are called exo whereas H's with subscripts B and B′ have boat-axial orientation and are called endo. They are diastereotopic and their replacement by a substituent gives exo and endo diastereomers respectively. H_A and H_A' (as also H_B and H_B'), on the other hand, are enantiotopic, their replacement giving enantiomeric products. Thus monosubstitution at any of these four methylene carbons gives a total of four stereoisomers: (±)-exo and (±)-endo although this creates three chiral centres, two at the bridgeheads and one at the point of substitution. This is because in the

*They are discussed in detail in Subsection 11.4.3.

present case, trans-bridging is not possible and the number of isomers is halved. Introduction of a carbonyl function in the ring (except at C-7) gives norbornan-2-one (XLI), known as norcamphor (in these systems, 'nor' signifies the absence of one or more methyl groups) which contains two chiral centres, C-1 and C-4 but exists only as one (±)-pair. Reduction of norcamphor gives (±)-*endo*-(XLII) and (±)-*exo*-norborneol (XLIII) (only one enantiomer is shown).

2. Relative stability of isomers. In general an exo isomer is more stable than an endo isomer. Thus when norborneol is equilibrated (Meerwein-Ponndorf-Oppenauer method), *exo*-norborneol predominates to the extent of 80%. This is because in the endo-isomer, OH has an unfavourable interaction with the endo-H at C-6. The situation, however, is reversed when C-7 holds a gem-dimethyl group as in borneols (Figure 11.22) of which *exo*-2-borneol (isoborneol) (XLVI) is less stable than *endo*-2-borneol (borneol) (XLV) (the latter predominates in the equilibrium composition to the extent of 71%). In this series, the steric interaction between the overhanging 7-Me and the exo-OH in isoborneol is greater than that between the endo-OH and the endo-6-H in borneol.

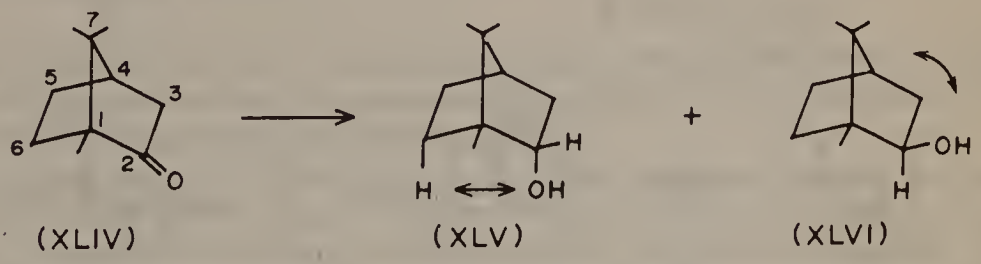


Figure 11.22 Camphor, borneol and isoborneol

3. Relative rate of formation of isomers. In the reduction of norcamphor with lithium aluminium hydride (kinetically controlled), norborneol (XLII), the less stable epimer is formed in excess (89%). This is because of a steric approach control which favours the approach of the reagent from the less hindered exo side. For the same reason, when camphor (XLIV) is reduced with lithium aluminium hydride, isoborneol (exo-alcohol) is formed to the extent of 90%. In this case, the exo approach is more hindered due to the pendant Me group at C-7.

4. Norbornyl cation. The norbornane derivatives have played an important role in elucidating the mechanism of solvolytic reactions and in building up the concept of non-classical carbonium ion of Winstein. A short account relevant to stereochemistry is given here; for details, texts on reaction mechanisms may be consulted (Carey and Sundberg 1986; Lowry and Richardson 1987).

Both *exo*- and *endo*-norbornyl brosylates (Figure 11.23) (Bs = *p*-bromobenzenesulphonyl) undergo acetolysis to acetates and the facts are: (i) the exo isomer solvolyses 350 times faster than the endo isomer; (ii) both exo and endo brosylates give exclusively the exo acetate; and (iii) an optically pure exo brosylate gives 100% racemic and an optically pure endo brosylate gives 93% racemic exo acetate. According to Winstein and coworkers, in the exo isomer the 1-6 σ bond lends an *anchimeric* (also called synartetic by Ingold) assistance to remove OBs by a backside attack giving directly a non-classical carbocation (XLVII) while the endo isomer first dissociates into the classical carbocation (actually carbenium ion)

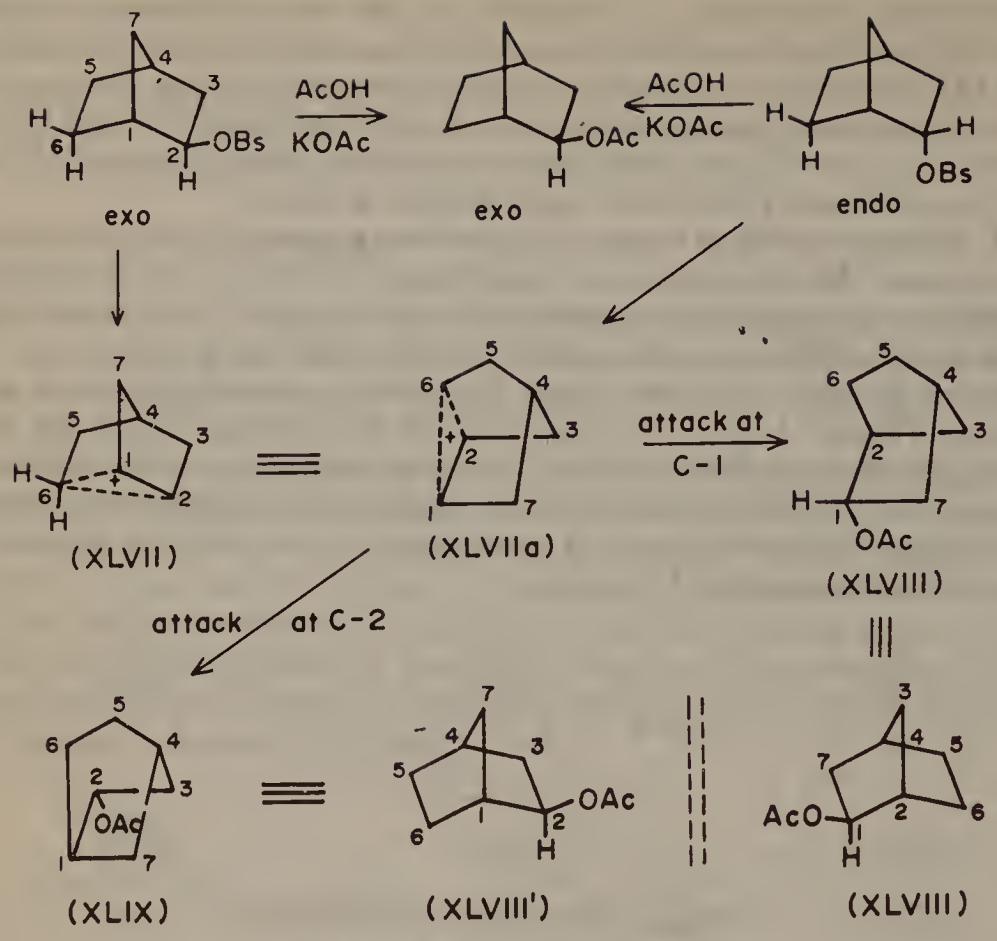


Figure 11.23 Reactions of norbornyl cation

which then delocalises to the non-classical one (XLVII = XLVIIa). This explains the enhanced rate (anchimeric acceleration) for the exo isomer. The non-classical carbocation is the common intermediate (assumed to be stabler than the localised carbocation) which is achiral (see XLVIIa) and can be attacked by solvent molecule equally at C-1 and C-2 which are related by a σ plane. The products of the two attacks XLVIII and XLIX are thus the two enantiomers of *exo*-2-norbornyl acetate (attack can be made only from the exo side due to the cage structure). This explains the exclusive formation of the exo isomer in completely racemic form.* Although no change in carbon skeleton has occurred, some carbon atoms have interchanged their positions (see the numbering of the two enantiomeric acetates). In fact, solvolysis of norbornyl brosylate labelled at 2 and 3 positions with ^{14}C shows the labels not only at C-1, C-2, C-3, and C-7 as expected from the above mechanism but also at C-5 and C-6. Apparently, 1,2-hydride shifts occur in the classical carbocations.

Although the concept of non-classical carbonium ion explains all the stereochemical outcome of the solvolysis reactions, it is strongly contended by H.C. Brown who prefers the two enantiomeric classical carbocations with +ve charge

*In the *endo*-brosylate, S_N2 mechanism operates to some extent which accounts for incomplete racemisation (93%).

localised at C-1 and at C-2 (the former arising from a rearrangement) as reaction intermediates. Among other arguments (see Winstein 1972; Brown 1977), Brown has pointed out that the exclusive formation of the exo products is due to a steric approach control, the concave endo side of the classical norbornyl cation hindering the endo approach. Regarding the high exo/endo rate ratio, Brown suggests that an endo substituent experiences steric hindrance to ionisation by three endo-H's. Not withstanding these arguments, the concept of non-classical ions in reaction mechanism has proved to be very useful (see also Deslongchamps 1983). The non-classical norbornyl cation in superacid media has actually been indicated by ^{1}H- and ^{13}C-NMR studies as well as by Raman spectra although its presence under solvolytic conditions is still controversial.

5. Occurrence. The biocyclo[2.2.1]heptane system occurs in many bicyclic monoterpenes, e.g., camphor, borneol, isoborneol (mentioned earlier), fenchene, fenchone, camphene etc. (see any text book on terpenes).

11.4.3 Bicyclo[2.2.2]octane

Bicyclo[2.2.2]octane (L) is an interesting bridged ring system (Figure 11.24) in which 1,4-positions of a cyclohexane boat are joined by an ethylene bridge. The system is discussed under the following headings.

1. Geometry. In its idealised form, the system has all the adjacent methylene protons eclipsed. It has one C_3 axis, three C_2 axes, and four σ planes (3 vertical and 1 horizontal) and belongs to point group D_{3h}. Angle strain is negligible but a considerable amount of eclipsing interactions exist which may be partly relieved by twisting the molecule around the 1-4 axis (7-15°) in either direction. The σ planes disappear in the twist forms which have D_3 symmetry and exist as rapidly interconverting enantiomers.

2. Topic relationship of hydrogens. In bicyclo[2.2.2]octane (L), three types of H's are distinguishable. The first two types are represented by H_A and H_A', (six of

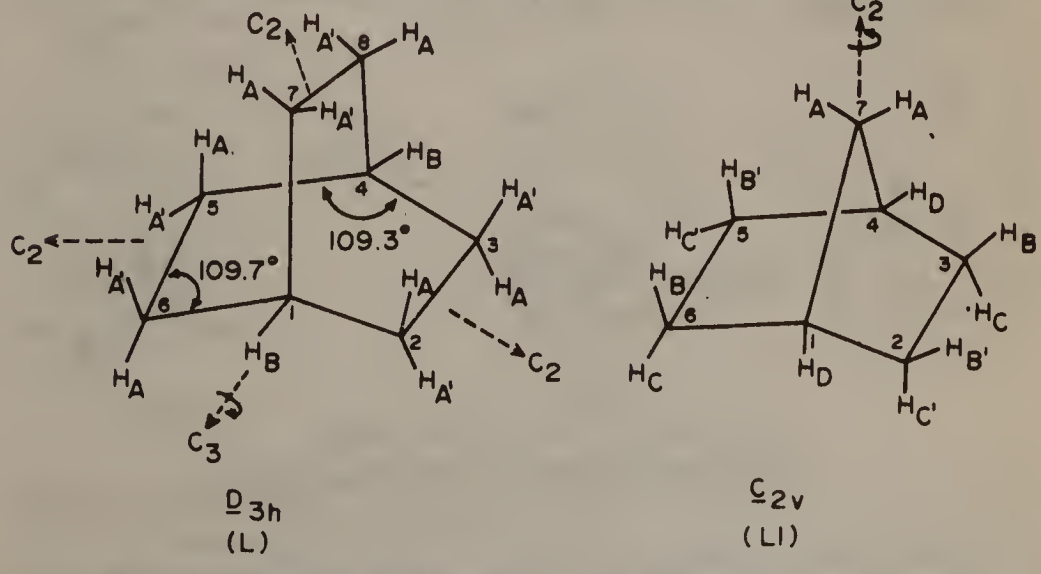


Figure 11.24 Bicyclo[2.2.2]octane and bicyclo[2.2.1]heptane: Topic relationship of hydrogens

each) located at the methylene carbons; all H_A's are homotopic as are all H_A,s (exchangeable by the C_3 axis or the three C_2 axes). Each type, however, is enantiotopic with the other (related by σ planes). There is no distinction between endo and exo and substitution at any methylene carbon can give only two enantiomers. The two bridgehead hydrogens H_B belong to the third type; they are homotopic with each other (related by a C_2 axis) but constitutionally heterotopic with the remaining twelve hydrogens.

In contrast, bicyclo[2.2.1]heptane (LI) (with lesser symmetry) has six types of distinguishable hydrogens: (*i*) Type H_A consists of two hydrogens located at the bridging carbon which are homotopic with each other but constitutionally heterotopic with the remaining ten hydrogens. (*ii*) Types H_B and H_B' (the four exo hydrogens) are enantiotopic with each other (two H_B's and two H_B''s are, however, homotopic). (*iii*) Types H_C and H_C' (the four endo hydrogens) are related in the same away to each other as H_B's and H_B''s. The exo and endo hydrogens are diastereotopic. (*iv*) The two hydrogens H_D on the bridgeheads constitute the sixth type; they are homotopic with each other but constitutionally heterotopic with the remaining hydrogens. Hydrogens with identical subscripts (in both the ring systems) are homotopic, hydrogens with the same subscripts but primed and unprimed are enantiotopic, and hydrogens bearing different subscripts are constitutionally heterotopic or diastereotopic (so anisochronous in ^{1}H-NMR).

3. Bicyclo[2.2.2]octyl cation. Bicyclo[2.2.2]octyl brosylate (LII) (Figure 11.25) exists as a (±)-mixture (one enantiomer is shown). The classical carbocation (LIII) derived from the brosylate is achiral (unlike the norbornyl cation which is chiral) and on participation of 1-6 σ bond may give rise to the non-classical carbonium ion (LIV)* which, in contrast to that in the norbornyl system, is chiral. Here also, solvent molecules can attack either at C-2 or C-1 giving, respectively

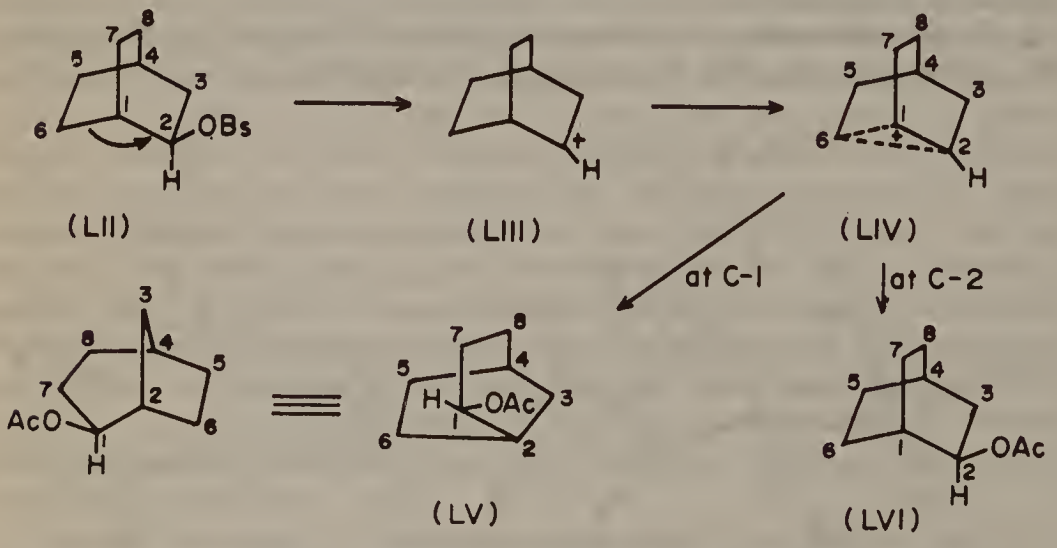


Figure 11.25 Solvolysis of bicyclo[2.2.2]octyl brosylate

*The non-classical carbonium ion can also be formed directly from the brosylate precursor by neighbouring σ bond participation.

bicyclo[2.2.2]octyl acetate (LVI) with retention of configuration and bicyclo[3.2.1] oct-*exo*-1-yl acetate (LV) with rearrangement. If the brosylate is optically pure, the non-classical carbonium ion would be in a single enantiomeric form (provided its formation from the former takes place through a concerted process and not via the achiral classical carbocation) and both the end products would be optically active. This is what actually happens predominantly (Walborsky et al 1961). Thus the concept of non-classical carbonium ion gives an elegant explanation of the stereochemical course of this reaction.

11.4.4 **Other bridged ring systems**

A large variety of bicyclo[l.m.n]alkanes is known for different values of l, m, and n. Bicyclo systems with single carbon bridge between two rings (n = 1) always suffer from some angle strain. Bicyclo[3.1.1]heptane (LVII) (Figure 11.26) in which 1,3-diaxial bonds of a cyclohexane chair are linked through a CH_2 group is isomeric with norbornane and occurs in the natural monoterpenes related to pinane (LVIII). The higher homologues are bicyclo[3.2.1]octane (LIX) and bicyclo [3.3.1]nonane (LX). The latter can exist in three conformations, chair-chair (LXa), boat-chair (LXb), and boat-boat (LXc) of which the chair-chair conformation (LXa) appears to be favoured by 6.0—10.4 kJ mol^{-1} (Allinger et al 1971a). The distance between 3-H and 7-H has been calculated as 220 pm. The major non-bonded interactions (among H's) are shown in the various structures.

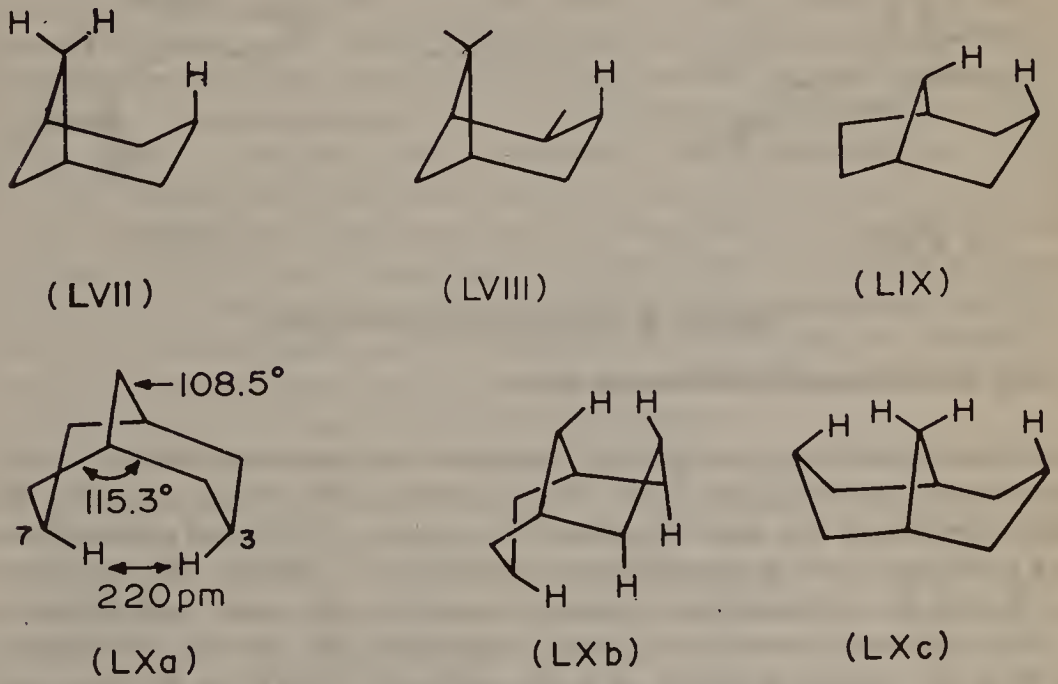


Figure 11.26 Some bicyclo[l.m.n]alkanes

Bicyclo systems with a mininum of two-carbon bridge between two rings (i.e., n≥2) do not have any appreciable angle strain. Of these, bicyclo[3.3.2]decane (LXI) (Figure 11.27) can exist in three conformations. Both calculated and

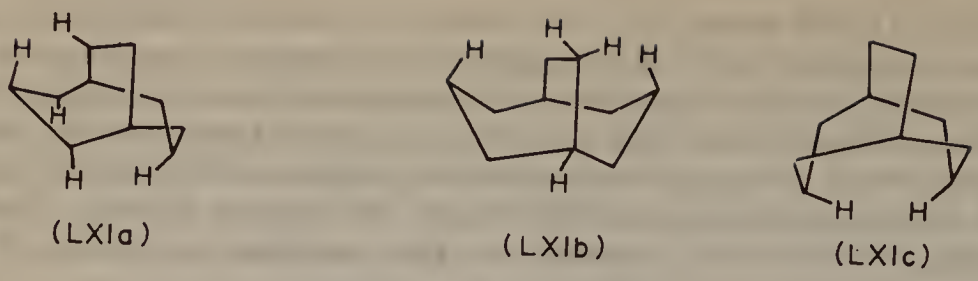


Figure 11.27 Bicyclo[3.3.2]decane

experimental results indicate that there is no single energy minimum geomertry for them but all these conformers coexist differing at most by 0.5 kJ mol^{-1} (Engler et al 1972). These molecules thus constitute another class of flexible ring systems in which the actual conformations depend on the nature of the substituents rather than on the carbon skeleton.(cf. cyclopentane)

Bicyclo[3.3.3]undecane (LXII), a still higher homologue (Figure 11.28), known by the trivial name manxane* is another interesting system. All the middle methylene protons are equivalent in ^{1}H-NMR which is consistent with the symmetrical structure (LXII) belonging to point group D_{3h}. The endo-exo protons (H_A and H_B) are exchanged by inversion of all the three rings which has a barrier energy of aproximately 40 kJ mol^{-1} at -60°C.

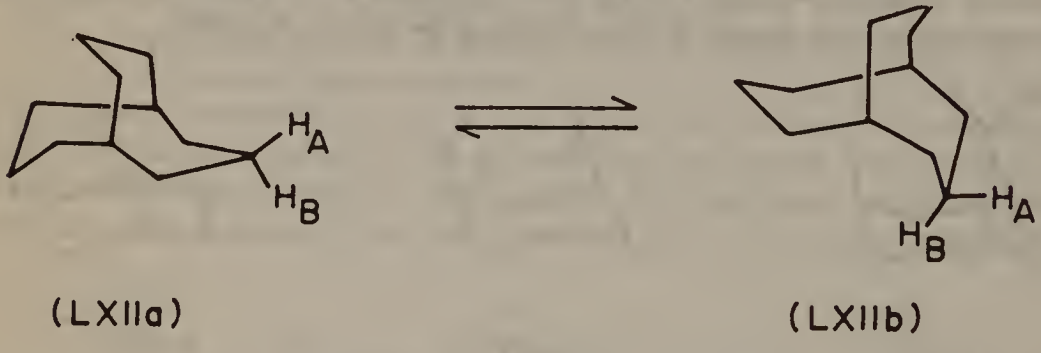


Figure 11.28 Bicyclo[3.3.3]undecane (manxane).

11.4.5. **Bicyclo systems with hetero atoms**

Many heterocyclic analogues of bicyclo compounds are known and some also exist in naturally occurring compounds. Thus tropane (LXIII) which constitutes the parent ring system of a series of alkaloids. e.g., tropine (LXIV) and pseudotropine (LXV) (Figure 11.29) is a derivative of 8-azabicyclo[3.2.1]octane. The chair forms (as shown) are preferred. But the energy required to flip to the boat forms (as LXVI) is not large as evidenced by a facile migration of the benzoyl group from O to N in the benzoyl derivative of norpseudotropine (LXVI). In the boat conformation of norpseudotropine, N-H and 3-OH come close to each other. This rearrangement also proves the syn configuration of 3-OH (with respect to bridging N). In the N-benzoate of the epimeric nortropine (LXVII) (with anti 3-OH) no

*The triskelion is in the coat of arms of the Isle of Man, hence the name.

benzoyl migration takes place. The relative stabilities of the chair and boat conformations also depend on the nature of the substituents.

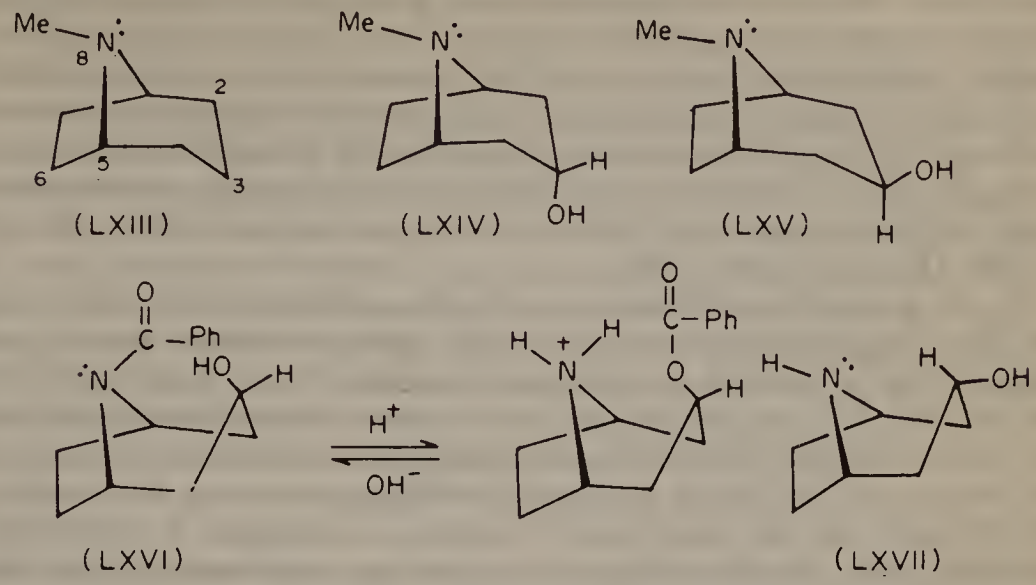


Figure 11.29 8-Aza-bicyclo[3.2.1]octane

11.4.6 Tri- and polycyclo systems

In bicyclo systems, the number of bridgehead atoms is two. If these two atoms are joined by a single bond, tricyclo systems result with three rings sharing the two bridgehead atoms. These compounds have propeller-like structures and are called propellanes. The smallest member, tricyclo[1.1.1.0]pentane (LXVIII) (Figure 11.30) has recently been synthesised (Wiberg and Walker 1982). The propellane, tricyclo $[3.2.1.0^{1,5}]$octane (LXIX) has three-, four-, and five-membered rings in a single system and looks very similar to bicyclo[3.2.1]octane (LIX in Figure 11.26) with C-1 and C-5 joined by a single bond. However, there is one very important difference: while the fourth valencies of C-1 and C-5 in LIX are directed outwards, those in LXIX are drawn in to form a single bond so that all the four valencies of the two bridgehead carbons are extended on the same side! This necessarily causes considerable angle strain and makes the system unstable.

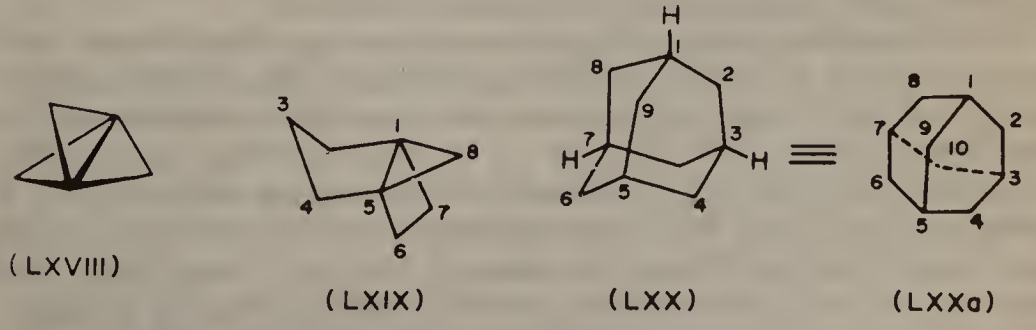


Figure 11.30 Propellanes and adamantane

In a second variation, tricyclo compounds may be formed with four bridgehead atoms. One interesting example is adamantane (LXX) so named because of its resemblance with part of the diamond structure. It has a rigid structure with a high degree of symmetry having four C_3 axes, three C_2 axes, and six σ planes (same as methane) and belongs to point group T_d. This hydrocarbon has a very high melting point (270°C) inspite of its relatively low molecular weight. The structure has been confirmed by X-ray diffraction and also by synthesis. If the number of bridgehead atoms are further increased (some of them may be single atoms counted twice), higher polycyclo systems result (for some esoteric hydrocarbons of these types, see le Noble 1974 and Ferguson 1969).

For the nomenclature of tricyclo or polycyclo compounds (Reddy 1987), first the largest ring (*main* ring) possible from the skeleton is written; secondly, the longest bridge is identified and the numbering starts from a bridgehead atom moving along the longest bridge; three basic segments (bridges) are obtained and the system is described as for bicyclo compounds; finally, the remaining connections are defined with the help of the number of bridging atoms (in the remaining bridges) and using the numberings of carbons so connected as superscripts. According to this procedure, adamantane has the main ring 8-membered as in the projected formula (LXXa) with a basic bicyclo[3.3.1]-system. Application of the final rule gives the full name as tricyclo[3.3.1.$1^{3,7}$]decane. In the case of two equivalent ways, the one involving the lower numbers is chosen.

11.5 Summary

1. Polycyclic systems are divided into three categories: two or more rings may be joined through a single common atom (for a pair of rings) to give spiro-compounds; they may be joined through two (adjacent) atoms which are common to both the rings to give fused ring or condensed ring compounds; and finally, any two rings may be joined through non-adjacent atoms so that more than two atoms are common giving rise to bridged ring compounds. The principle of conformational analysis in polycyclic systems is the same as for monocyclic systems except for the fact that in most cases, there is considerable restraint on the flexibility of the ring systems, the conformation of one ring being dependent on the other to which it is linked. Any conformational deformation of one ring may be transmitted to the other through the ring junction (conformational transmission).

2. Conformational analysis of bicyclic systems has been illustrated with the cis and trans isomers of decalin (decahydronaphthalene). The geometry, enthalpy, entropy, and torsion angle of junction of each isomer have been discussed. The trans isomer is more stable than the cis in decalin, by three gauche butane interactions ($\sim$10.0 kJ mol^{-1}). Introduction of an angular methyl reduces the difference to one gauche. The cis and trans isomers of hydrindane have similarly been treated. Here the difference in enthalpy is less but the trans isomer is still preferred although in 8-methylhydrindane or in 1-hydrindanone, the cis isomer is more stable. Decahydroquinoline and quinolizidine have been analysed similarly. In these compounds, pyramidal inversion at N also takes place.

3. Conformational analysis has been continued with fused bicyclic compounds

with small rings. In these systems, the cis isomer is usually more stable than the trans unless one of the rings is larger than 8-membered.

4. Conformational analysis of polycyclic fused ring compounds has been illustrated with perhydrophenanthrenes, perhydroanthracenes, and steroids (perhydrocyclopentenophenanthrenes). The analysis is based on the different steric interactions previously discussed. A few generalisations have been made. Thus the isomer with the larger number of equatorial bonds of the central ring involved in ring fusion is more stable; in case two axial bonds of the central ring are involved in ring fusion, 1,2- and 1,4-diaxial arrangements are preferred over 1,3-diaxial; finally, if the central ring cannot satisfy the configurational requirement by adopting a cyclohexane chair, a boat or a twist-boat form is assumed with corresponding increase in enthalpy. The preferred conformation of the cyclopentane ring (D-ring) of the steroids has been discussed in terms of envelope and half-chair forms. A few examples of conformational transmission in steroid molecules are given.

5. Several bridged bicyclo systems represented by the general formula bicyclo [1.m.n] alkanes in which 1, m, and n have values greater than zero have been discussed. Because of bridging, the number of isomers in most of these systems is halved. Two such systems, namely, bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane have been given special emphasis because of their importance in elucidating reaction mechanisms and in building up the concept of non-classical carbocations.

6. Finally, a number of other bicyclo systems, both alicyclic and heterocyclic (e.g., tropane) and a few polycyclo bridged systems such as propellanes and adamantanes have been discussed.

References

1. R.Bucourt (1974), in *Topics in Stereochemistry*, vol 8, eds. E.L. Eliel and N.L. Allinger, John Wiley & Sons, New York.
2. M. Oki (1985), in *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, vol 4, chapter 7, VCH Publishers Inc., Deerfield Beach, Florida.
3. J.E. Leonard, G.S. Hammond and H.E. Simmons (1975), *J. Amer. Chem. Soc.*, **97**, 5052.
4. E.L. Eliel (1962), in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
5. R.E. Lack and J.D. Roberts (1968), *J. Amer. Chem. Soc.*, **90**, 6997.
6. D. Seebach (1965), *Angew. Chem.* **77**, 119.
7. IUPAC: Rules for the Nomenclature in Organic Chemistry, Section E: Stereochemistry (1974), *Pure & Appl. Chem.*, **45**, 11-30.
8. W.S Johnson (1951), *Experientia*, **7**, 315; *J. Amer. Chem. Soc.*, (1953), **75**: 1498.
9. N.L. Allinger, B.J. Gordon, I.J. Tyminisky, and M.T. Wuesthoff (1971), *J. Org. Chem.*, **36**, 2051.
10. L.F. Fieser and M. Fieser (1969), in *Steroids*, Asia Publishing House, Bombay.
11. H. Gilman (1945), in *Organic Chemistry: An Advanced Treatise*, vol 2, John Wiley & Sons, London.
12. M. Hanack (1965), in *Conformational Theory*, Academic Press, New York.
13. E.L. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison (1965), in *Conformational Analysis*, Wiley Interscience, New York.

14. F.A. Caiey and R.J. Sundberg (1986), in *An Advanced Organic Chemistry*, 2nd edn, Part A, Plenum-Rosetta, New York.
15. T.H. Lowry and K.S. Richardson (1987), in *Mechanism and Theory in Organic Chemistry*, 3rd edn, Harper and Row, New York.
16. S. Winstein (1972), in *Carbonium Ions*, vol 3, eds. G.A. Olah and P.v.R. Schleyer, Wiley-Interscience, New York; also see G.D. Sergent in the same Text.
17. H.C. Brown (1977), in *Nonclassical Ion Problem*, Plenum, New York.
18. H.M. Walborsky, M.E. Baum, and A.A. Youssef (1961). *J. Amer. Chem. Soc.*, **83**, 988.
19. N.L. Allinger, M.T. Tribble, M.A. Miller, and D.H. Hertz (1971a), *J. Amer. Chem. Soc.*, **93**, 1637.
20. E.M. Engler, L. Change and P.v.R. Schleyer (1972), *Tetrahedron Letters*, 2525.
21. K.B. Wiberg and F.H. Walker (1982), J. Amer. Chem. Soc., **104**, 5239.
22. W.J. le Noble (1974), in *Highlights of Organic Chemistry: An Advanced Textbook*, Marcel Dekker Inc., New York.
23. L.N. Ferguson (1969), *J Chem. Educ.*, **46**, 404.
24. P.A. Reddy (1987), *J Chem. Educ.*, **64**, 400.

Chapter 12

Dynamic Stereochemistry I : Conformation and Reactivity

12.1 Introduction

Dynamic stereochemistry is concerned with stereochemical studies of any rate process, be it a chemical reaction involving bond-breaking and bond-making (usually a high energy process) or simply a conformational transformation involving interconversion of conformers (usually a low energy process). It correlates the stereochemistry of starting materials and products in terms of transition states and intermediates. Conformational changes in molecules have already been discussed in the previous chapters with occasional reference to chemical reactions. In this and two subsequent chapters, those aspects of dynamic stereochemistry will be discussed which are concerned with chemical reactions only. correlating conformation and reactivity on one hand and leading to stereoselective synthesis on the other. It has been long recognised that diastereomers differ significantly in their chemical reactions with respect to relative rates and sometimes even in the nature of products. No consistent explanation can be given to these phenomena on the basis of classical stereochemistry. The conformational theory not only provides a rationale to these observations but also predicts the relative reactivity of stereoisomers. The principles of conformational analysis so far discussed are applied in this chapter to study the effect of conformation on chemical reactivity. Some older literature (Eliel et al 1965, Hanack 1965) on conformational analysis and a few recent taxtbooks on reaction mechanism (e.g., Lowry and Richardson 1987) may be consulted.

12.2 Selection of substrates

Substrates which are used for the study of conformation-reactivity correlation may be divided into *three* categories which are discussed below along with the types of information they provide.

12.2.1 Conformationally rigid diastereomers

Conformationally rigid diastereomers in which the reacting groups are locked into two different orientations, e.g., equatorial and axial provide a direct relationship between conformation and reactivity. Compounds with two or more cyclohexane rings linked through trans ring junctions (and which therefore cannot undergo ring

inversion) fall under this category. Thus in *trans*-2α-decalol (I) and *trans*-2β-decalol (II) (Figure 12.1a), the OH group is equatorial and axial respectively and remains so during any chemical reaction. Employing these two diastereomers, reaction rates can thus be measured for an equatorial (k_e) and an axial (k_a) OH group. They may be used as standard for conformationally well defined substituents.

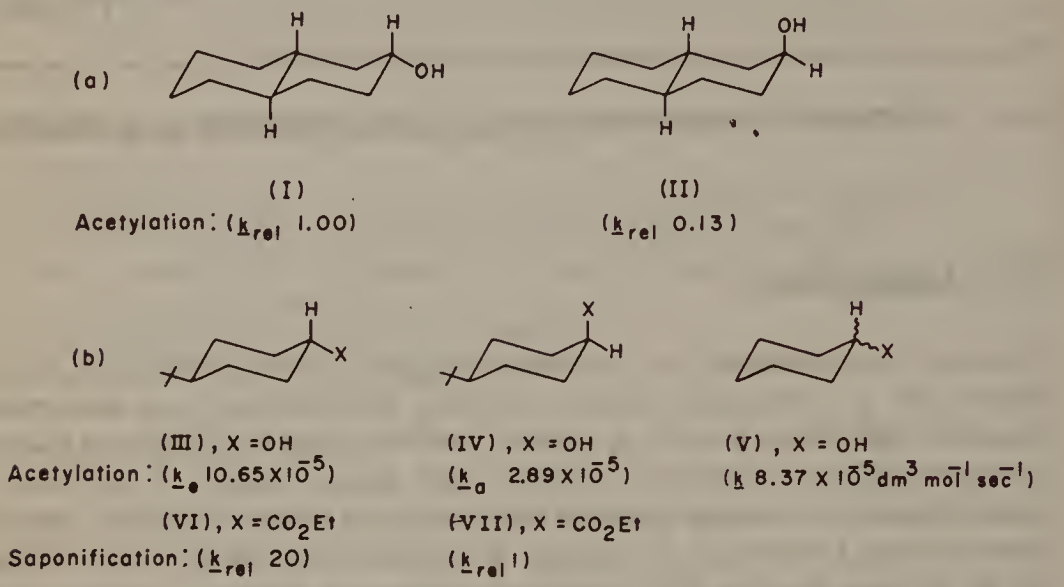


Figure 12.1 (a) Conformationally rigid and (b) anancomeric systems with reaction rates (relative or specific) of axial and equatorial isomers

A second type of substrate which serves the same purpose is represented by cyclohexane derivatives with a bulky group such as *t*-butyl (Winstein and Holness 1955). Because of high preference for equatorial disposition of this group, the equilibrium is displaced almost completely to the side in which *t*-butyl is equatorial (the population of the axial conformer is approximately 1 in 10,000 at ambient temperature) and the system is essentially conformationally homogeneous. The trans and cis isomers of 4-*t*-butylcyclohexanols (III) and (IV) (Figure 12.1b) are examples of this type*. The two epimers show reactions typical of an equatorial and of an axial OH (or any other group to be studied). Such a system is called a conformationally *biased* or more technically an *anancomeric* system. The same reactivity for an equatorial or for an axial substituent is expected, in theory, in the two systems, i.e., rigid and anancomeric, but is seldom observed in fact. The reason for the deviation (which is usually only minor) may lie in an additional 3-substituent in the *trans*-decalins and in the possible deformation of the cyclohexane ring geometry by the presence of the bulky *t*-butyl group. The anancomeric system is more commonly used for conformational analysis because of its ready acces-

*Unlike the conformationally rigid systems, these molecules, however, can undergo facile ring inversion, i.e., their near conformational homogeneity is thermodynamically, not kinetically based. With increase of temperature, the unfavoured conformer becomes more and more populated. In some reactions this less stable conformer may be the only reactive species due to stereoelectronic reasons and as the reaction proceeds, equilibrium is continuously reestablished to maintain a steady supply of this conformer. The rate of the reaction is, however, low because of its low concentration.

sibility. *cis*-3,5-Dimethyl- and 3,3,5-trimethylcyclohexane derivatives provide other anancomeric systems.

Studies of these systems reveal that reactions at exocyclic positions, i.e., not involving any ring carbon generally proceed at a faster rate for the equatorial than for the axial isomer. Thus the saponification rate of the trans isomer of ethyl 4-*t*-butylcyclohexanecarboxylate (VI) in 70% ethanolic sodium hydroxide is 20 times as fast as that of the cis isomer (VII). Rates of acetylation of cyclohexanols (III), (IV) and (V) in pyridine at 25°C are shown in Figure 12.1b. The equatorial isomer reacts 3.7 times as fast as the axial isomer while the unsubstituted cyclohexanol react at an intermediate rate.

Acyclic molecules rarely exist in rigid conformations except in exceptional cases when a particular conformer is fixed in a crystal matrix or exists as an atropisomer due to steric hindrance around a single bond. The conformation-reactivity relationship in such systems is usually studied with the help of diastereomers (see below).

12.2.2 Conformationally mobile diastereomers

For conformationally mobile substrates, both cyclic and acyclic, the relative specific reaction rates of any two diastereomers depend on the corresponding rates for all the constituent conformers and their populations in the equilibrium mixture of each diastereomer. For cyclohexane derivatives, the specific reaction rates of the equatorial and axial conformers are often available from conformationally rigid or anancomeric system (as discussed above). But for acyclic molecules, these rates are generally not available and the analysis is less quantitative. Two situations often arise which simplify the treatment: (*i*) One of the conformers in each diastereomer is highly populated so that comparison of reactivities may be confined to those conformers provided the lesser populated conformers are not exceptionally reactive. (*ii*) Some reactions have specific stereoelectronic requirements and only a certain conformer of each diastereomer satisfies them. In such situations, only the pertinent conformer needs to be considered.

An example of the first kind is provided by 2,3,4-triphenylbutyric acid (Lednicer and Hauser 1958). The compound exists as two diastereomers, threo (VIII) and erythro (IX) (Figure 12.2). The preferred conformations of the threo and the erythro isomers are represented by VIIIa and IXa respectively each of which has two gauche interactions between the bulky groups while the others (not shown) have three (due to placement of four adjoining bulky groups) and so contribute very little to the equilibrium population. The preferred threo structure (VIIIa) has the CO_2H group very close to the $PhCH_2$ group at C-4 and so cyclises (with anhydrous HF) mainly to the tetralone (X). On the other hand, the erythro structure (IXa) has the carboxyl group adjacent to the Ph group at C-3 and so gives a preponderance of the indanone (XI)*.

Iodide-induced debromination of *meso*- and (±)-2,3-dibromobutane (an E2 reaction) provides an example of the second kind. The stereoelectronic factor

*The argument is valid only if the rates of cyclisation of VIIIa and IXa are equal which in this case is probably true. Otherwise the product ratio is governed by the Curtin-Hammett principle (Section 12.3).

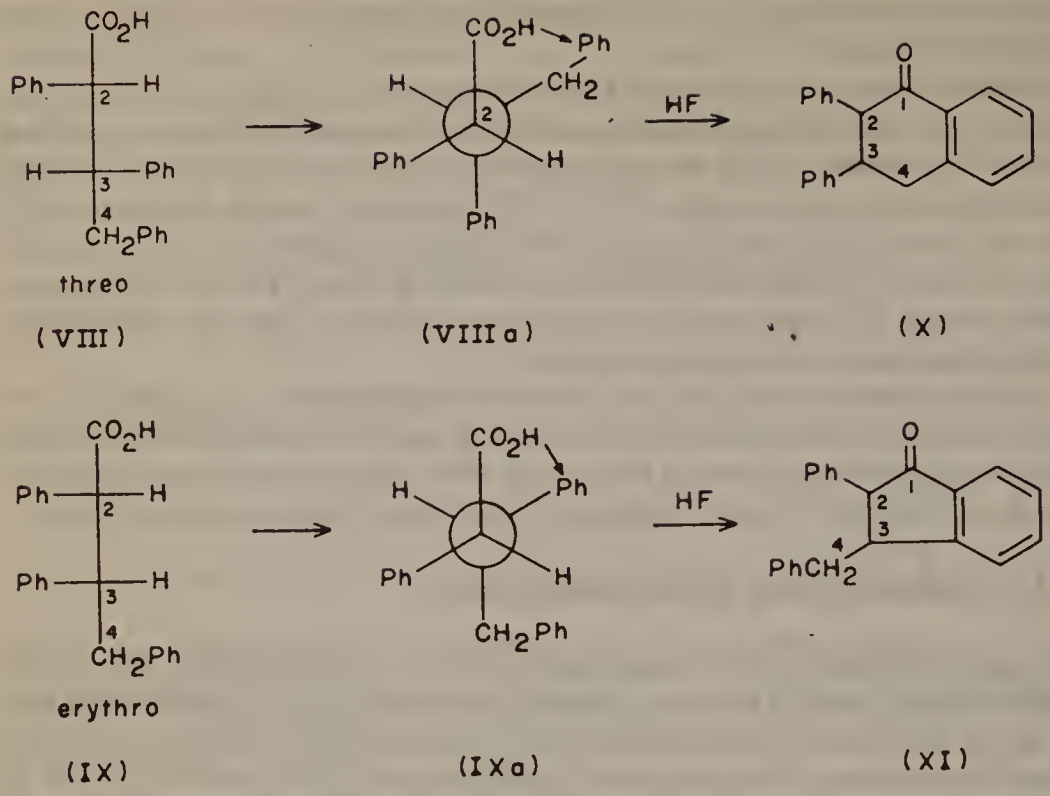


Figure 12.2 Ring-closure of threo and erythro isomers of 2,3,4-triphenylbutyric acid

requires that the two Br atoms must be antiperiplanar in the reacting conformers—a condition which is satisfied by the conformer (XIIa) of the meso isomer (XII) and the conformer (XIIIa) of the (±)-form (XIII) (Figure 12.3). The reaction has to go through them irrespective of their ground state stability. According to the

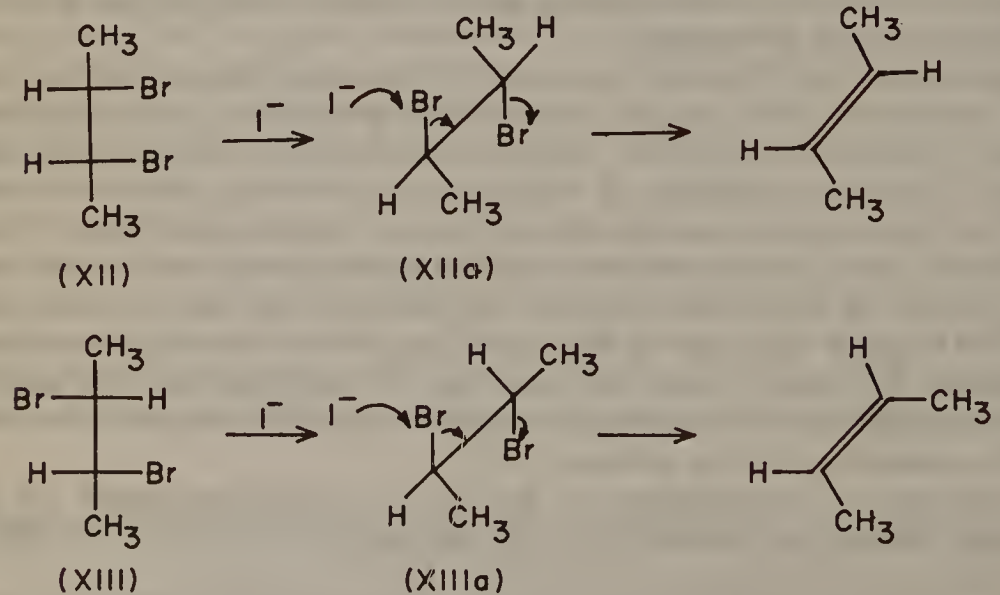


Figure 12.3 Debromination of *meso*- and (±)-2,3-dibromobutane

accepted mechanism, the former (XIIa) gives preponderantly the trans and the latter (XIIIa) preponderantly the cis isomer of 2-butene. The rate of the reaction of the meso form is 2.3 times as fast as the rate of the active isomer (only one enantiomer is shown). It appears that the slower rate of the active form (XIII) is due to a higher energy trantion state in which the two methyl groups are partially eclipsed*.

12.2.3 A single substrate with two or more conformers

The overall specific reaction rate (k) of a substrate consisting of a number of conformers in mobile equilibrium depends both on the ground state population of the conformers and on their specific reaction rates (Winstein-Holness 1955) as given by the equation:

$$k = \sum_i n_i k_i \qquad \ldots\ldots\ldots (1)$$

where n_i is the mole fraction of i-th conformer and k_i is its specific reaction rate. The equation (and its various modifications) is applicable to a system in which the conformational interconversion is much faster than the reaction so that the conformer population remains unaltered throughout the reaction. Three types of conformers are possible—homomeric, enantiomeric, and diastereomeric (Chapter 3). Homomeric conformers behave identically (as regards rate and product) under all conditions and so need not be considered. Enantiometric conformers also behave identically under achiral conditions but differently under chiral conditions whereas diastereomeric conformers always behave differently. The products can be related to the reacting conformers provided they are non-equilibrating (unlike the reactants). A few examples are given below illustrating the difference in the reactivities of enantiomeric and diastereomeric conformers.

cis-1,2-Di(hydroxymethyl)cyclohexane, which exists as two enantiomeric conformers (XIV) and (XIV'), (Figure 12.4a) on enzymatic oxidation gives an

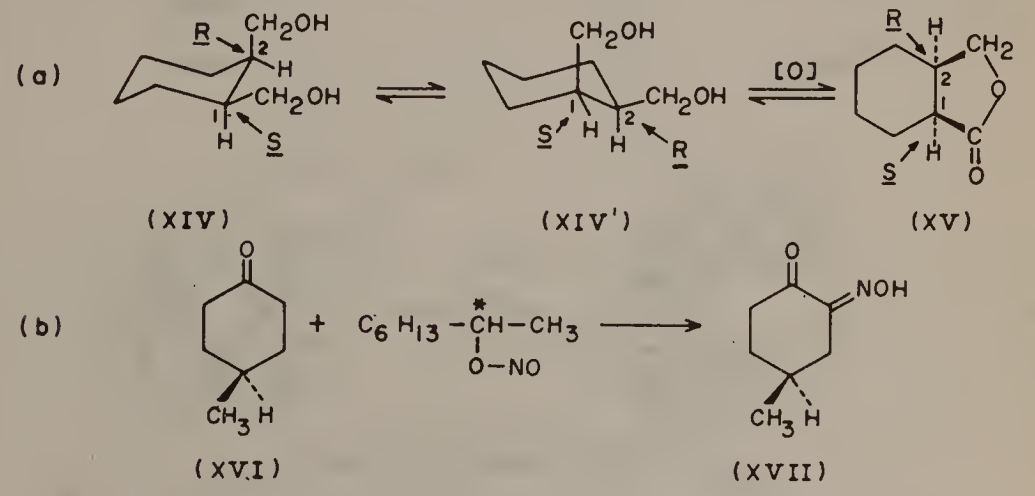


Figure 12.4 (a) Enzymatic conversion of *cis*-1,2-dihydroxymethylcyclohexane
(b) Conversion of 4-methylcyclohexanone into optically active 2-oximino-derivative

*For an alternative possibility, see Eliel et al 1965.

optically active lactone of the configuration (XV) (1*S*, 2*R*) (Goodbrand and Jones 1977). If it is assumed that the enzyme (a chiral reagent) forms a complex only with one enantiomer (XIV′) and further that it preferentially oxidises its axial CH_2OH to CO_2H, the exclusive formation of the lactone (XV) is explained. As the reactive enantiomer is consumed, it is replenished by the mobile equilibrium and, at the end, the entire substrate is converted into the lactone (XV)—a case of second order asymmetric transformation (Chapter 7). An alternative explanation, however, cannot be excluded according to which the conformationally mobile *cis*- diol may be looked upon in its time-averaged planar conformation. The two CH_2OH groups are now enantiotopic and can be preferentially reacted upon by any chiral reagent, e.g., an enzyme. An analogy is found in the reaction of 4-methylcyclohexanone (XVI) (Figure 12.4b) which is achiral in both of its conformations (due to the presence of a σ plane). But when it reacts with optically active 2-isooctyl nitrite, it gives a 2-oxyimino-derivative (XVII) enriched in one of its enantiomers. Here also, the two methylene groups at 2- and 6-positions are enantiotopic and therefore react at different rates with a chiral reagent.

Two other reactions which display enantiomeric preference in more uncontroversial terms are: (i) formation of an optically active erythro isomer of 1-(4-methylbenzoyl)-1,2-dibromo-2-(4-methylphenyl)ethane (XIX) by the (anti) addition of gaseous or liquid bromine to a chiral single crystal of 4,4-dimethylchalcone (XVIII) (Figure 12.5a) (one of the enantiomeric conformation of the achiral

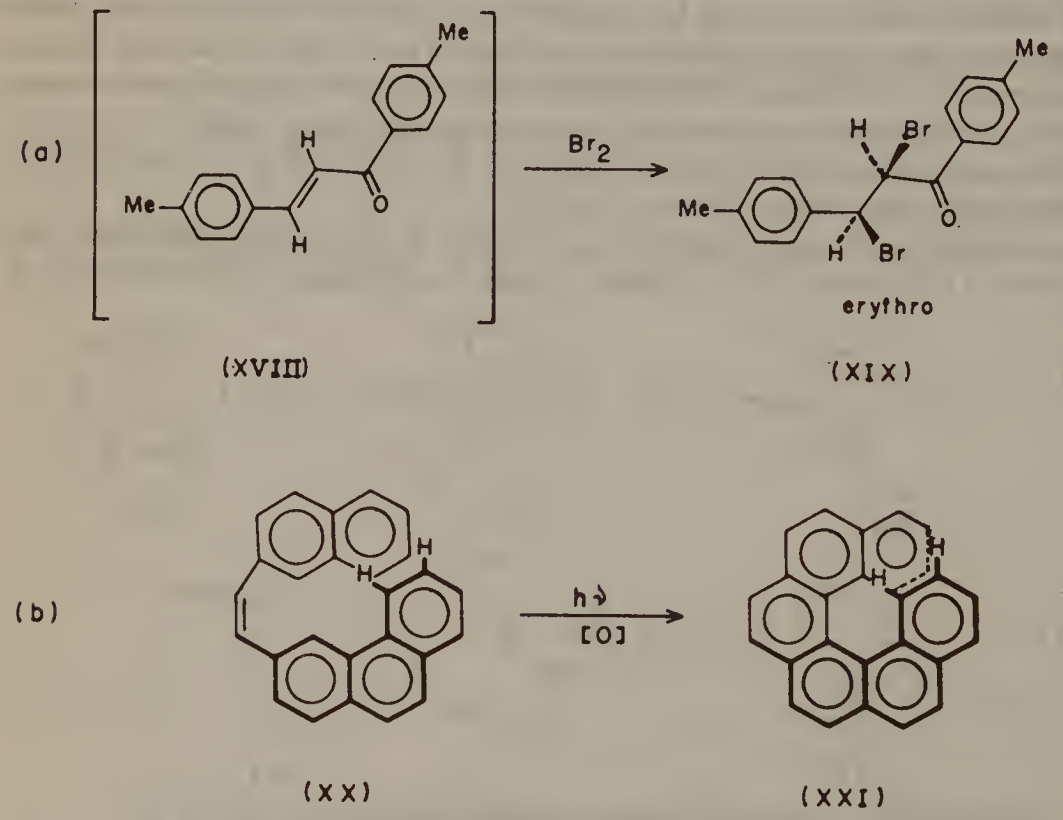


Figure 12.5 Conversion of enantiomeric conformers into optically active products

chalcone is stabilised in the crystal matrix) (Penzion and Schmidt 1969) and (ii) formation of an optically active hexahelicene (XXI) through photochemical oxidative ring-closure of the stilbene (XX) (Figure 12.5b). The stilbene exists as two enantiomeric helical conformations (*P* and *M*) which are cyclised by circularly polarised light (of 410 nm) at different rates. The helicity of the polarised light controls the helicity of the enantiomerically enriched helicene (Buchardt 1974).

Diastereomeric conformers should, in principle, react through diastereomeric transition states to give either diastereomeric or constitutionally different products*. When the products are non-equilibrating and the rate of equilibration of the conformers in the starting material is faster than the reaction rate, the products can be correlated to the reacting conformers both with respect to their ground state population and free energies of activation of the reactions. This aspect of conformational analysis is discussed in Section 12.3; only one example, the dehydration of malic acid into a mixture of maleic acid and fumaric acid (two diastereomers) is given here. The two methylene H's (H_A and H_B) in malic acid (XXII) (Figure 12.6) are diastereotopic and each can be made antiperiplanar with the leaving OH group in the two diastereomeric conformations (XXIIa) and (XXIIb) giving respectively maleic acid (XXIII) and fumaric acid (XXIV).

The observations apply to reactions which are kinetically controlled. In thermodynamically controlled reactions, the product ratio is determined by the ground

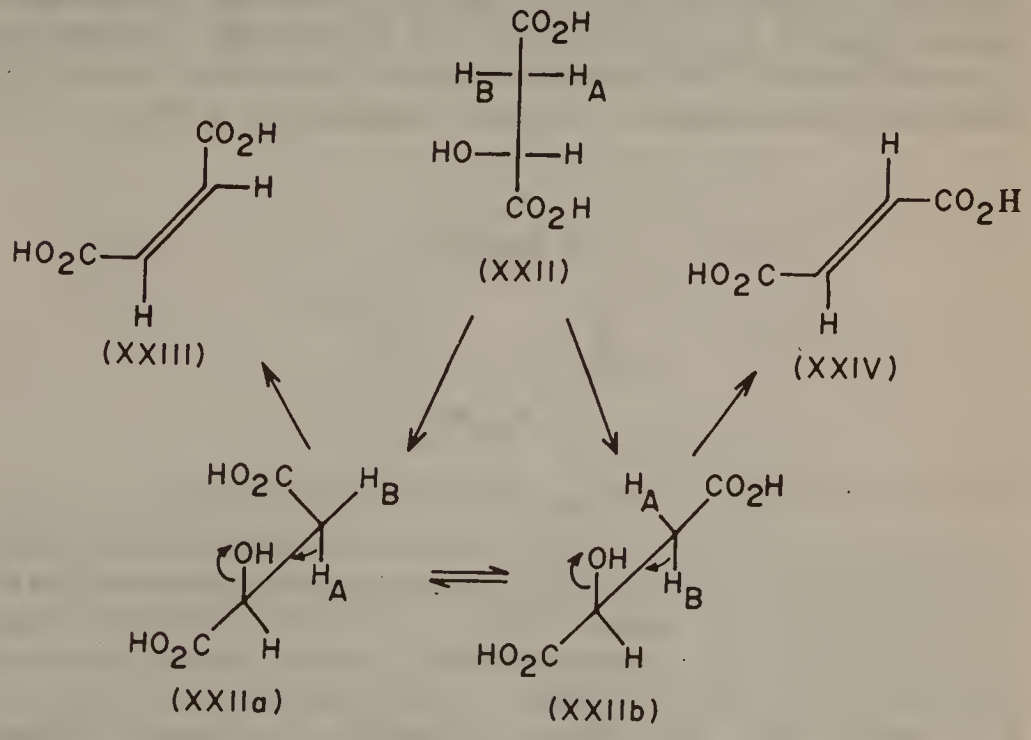


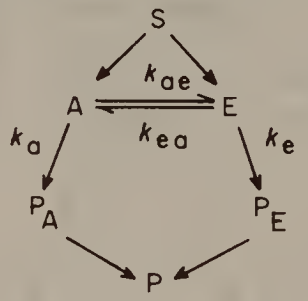
Figure 12.6 Dehydration of malic acid

*Homomeric products may also be obtained from two diastereomers when the reaction is stereodestructive. i.e., if the stereocentre is destroyed as in the oxidation of cyclohexanols into cyclohexanones.

state free energy difference of the products concerned. Unless otherwise stated, all subsequent discussions relate to kinetically controlled reactions.

12.3 Quantitative correlation between conformation and reactivity

So far, the conformation-reactivity correlation has been discussed more or less in qualitative terms although reference has been made occasionally to the Curtin-Hammett principle and a rate equation. The Curtin-Hammett principle was proposed in the early fifties and so named by Eliel (1962), while the rate equations were derived in the mid fifties by two groups of workers (Winstein and Holness 1955; Eliel and Ro 1956) independent of each other and might better be called Winstein-Eliel equations*. The Curtin-Hammett principle primarily correlates the product distribution with the transition state energies for two different reaction pathways followed by two different *conformers* of a substrate giving non-equilibrating products and points out the inappropriateness of equating the product ratio with the equilibrium constant (K) of the ground state conformers. The Winstein-Eliel rate equations correlate the overall observed specific reation rate (k) of a substrate (the so called empirical rate constant since it refers to the reaction of more than one conformer) with the specific reaction rates of individual conformers irrespective of whether the products are equilibrating or non-equilibrating. At one time, these equations were extensively used to determine the conformational free energies. Together, the Curtin-Hammett and Winstein-Eliel treatments give a quantitative analysis of the conformation-reactivity relationship. Both apply to the same kinetic system represented in the most simplified form, as follows:



$$K = \frac{[E]}{[A]} = \frac{k_{ae}}{k_{ea}} \quad \text{and} \quad k_e,\ k_a \ll k_{ae},\ k_{ea}$$

In the system, E and A refer to two conformers of a substrate (S) (for example, the equatorial and axial conformers of a monosubstituted cyclohexane) and k_e and k_a are their specific rate constants leading to two different products P_E and P_A, respectively, which may equilibrate (allowed in Winstein-Eliel system) or may not equilibrate (Curtin-Hammett system). P refers to the total product while k_{ae} and k_{ea} are specific rates of conformational interconversion. A restriction is imposed on the system, namely, that the rate of interconversion of conformers (k_{ae}, k_{ea}) is

*In the literature, equation (1) is generally known as Winstein-Holness equation. But since there is no basic difference between this equation and the one derived by Eliel's group, it seems more appropriate to refer to the equations as the Winstein-Eliel equations from the names of the two main authors of the two originating laboratories.

much faster than their reaction rates (k_a, k_e)—an assumption which is generally but not universally true.

12.3.1 Winstein-Eliel equations

Winstein and Holness (1955) first developed an equation correlating the overall empirical reaction rate constant (k) of a conformationally mobile substrate (S) with the specific rate constants of the individual conformers. Thus the total rate of product formation may be written as:

$$\frac{d[P]}{dt} = \frac{d[P_E]}{dt} + \frac{d[P_A]}{dt}$$

Since conformer E gives rise to product P_E and conformer A to product P_A, the equation may be rewritten as:

$$k\{[E] + [A]\} = k_e[E] + k_a[A]$$

Or

$$k = k_e \frac{[E]}{[E] + [A]} + k_a \frac{[A]}{[E] + [A]}$$

$$= k_e n_e + k_a n_a \ldots\ldots\ldots (1)$$

(where n_e and n_a are respective mole fractions of E and A conformers)

In a somewhat more analytical approach (Eliel 1960), a similar equation correlating all three specific rate constants and the equilibrium constant (K) is derived:

Given $[S] = [E] + [A]$ $K = \frac{[E]}{[A]}$ or $[E] = K[A]$

Hence $k[S] = k\{[E] + [A]\} = k_e[E] + k_a[A]$

Replacing [E] by $K[A]$,

$$k\{K[A] + [A]\} = k_e K[A] + k_a[A]$$

Or

$$k = \frac{k_e K + k_a}{K + 1}, \text{ or } K = \frac{k_a - k}{k - k_e} \quad \ldots\ldots (2)$$

Concentration terms of other co-reacting species (as in bimolecular reactions) cancel out on division and so do not enter into the equations*

The Winstein and Eliel equations can be interconverted one into the other and both can be used to determine the value of K from three parameters, k (determinable directly) k_e, and k_a (determinable indirectly from reference compounds). Thus the specific reaction rates of acetylation of the three cyclohexanols (III), (IV), and (V) (Figure 12.1b) give the conformational equilibrium constant, K_{OH} at 25°C for cyclohexanol through the following equation:

$$K_{OH} = (2.89 - 8.37)/(8.37 - 10.65) = 2.4$$

If one of the conformers does not react because of stereoelctronic reason, its specific rate, k_e or k_a ($= 0$) is omitted from equation (2). Thus in E2 elimination

*The reactions must involve the same kinetic expression.

of cyclohexyl tosylate, the equatorial conformer cannot have the tosyl group antiperiplanar with an adjacent hydrogen and so is unable to react—a fact also confirmed by the lack of reactivity of *trans*-4-*t*-butylcyclohexyl tosylate (XXV) (Figure 12.7) under similar condition. The cis isomer (XXVI), on the other hand, reacts with a specific rate of 7.1×10^{-3} l mol^{-1} sec^{-1} at 75°. The specific rate constant of cyclohexyl tosylate (XXVII) itself is 2.4×10^{-3} (same unit). According to equation (2), the value of K is calculated as follows: $K = (7.1 - 2.4)/2.4 = 2.0$ (Eliel and Lukach 1957).

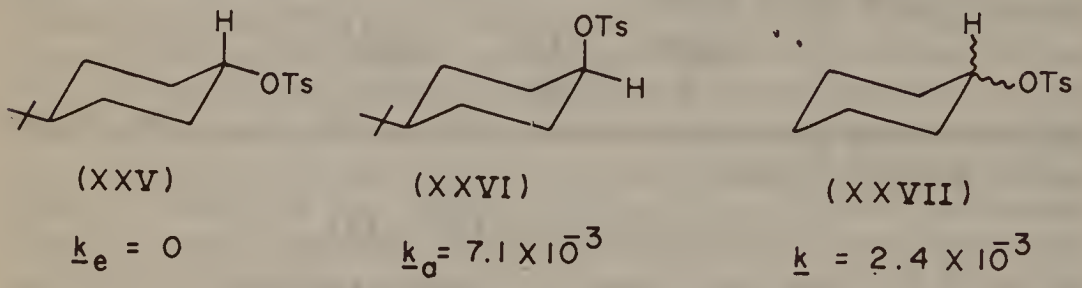


Figure 12.7 Elimination reaction of cyclohexyl tosylates

The kinetic method of conformational analysis for which the equations were originally derived has become now obsolete since the true values of k_e and k_a are difficult to determine, most of the models giving unreliable data. Conformational equilibria nowadays are more directly and precisely determined by ^{1}H- and ^{13}C-NMR spectroscopy working at high fields and low temperature (Chapter 10). However, molecular properties other than chemical reactivities such as chemical shifts, coupling constants, pK values, dipole moments etc. may also be used in the Winstein-Eliel equations although the doubtful element regarding the use of appropriate reference compounds still remains in its practical application.

12.3.2 Curtin-Hammett principle

The Curtin-Hammett principle applies to a conformationally heterogeneous starting material with the additional restriction that the products must be non-equilibrating. The latest definition of the principle proposed by IUPAC Commission (Gold 1983) is given below (see also Seeman 1986):

In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation, whereas the products do not interconvert) the product composition is not solely dependent on the relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states. It is also true that the product composition is formally related to the relative concentrations of the conformational isomers (i.e., the conformational equilibrium constant) and the respective rate constants of their reactions: these parameters are generally—though not invariably—unknown.

The principle is explained with the help of an energy diagram (Figure 12.8) for reactions of a substrate (S, with the same specification as in the former diagram) in

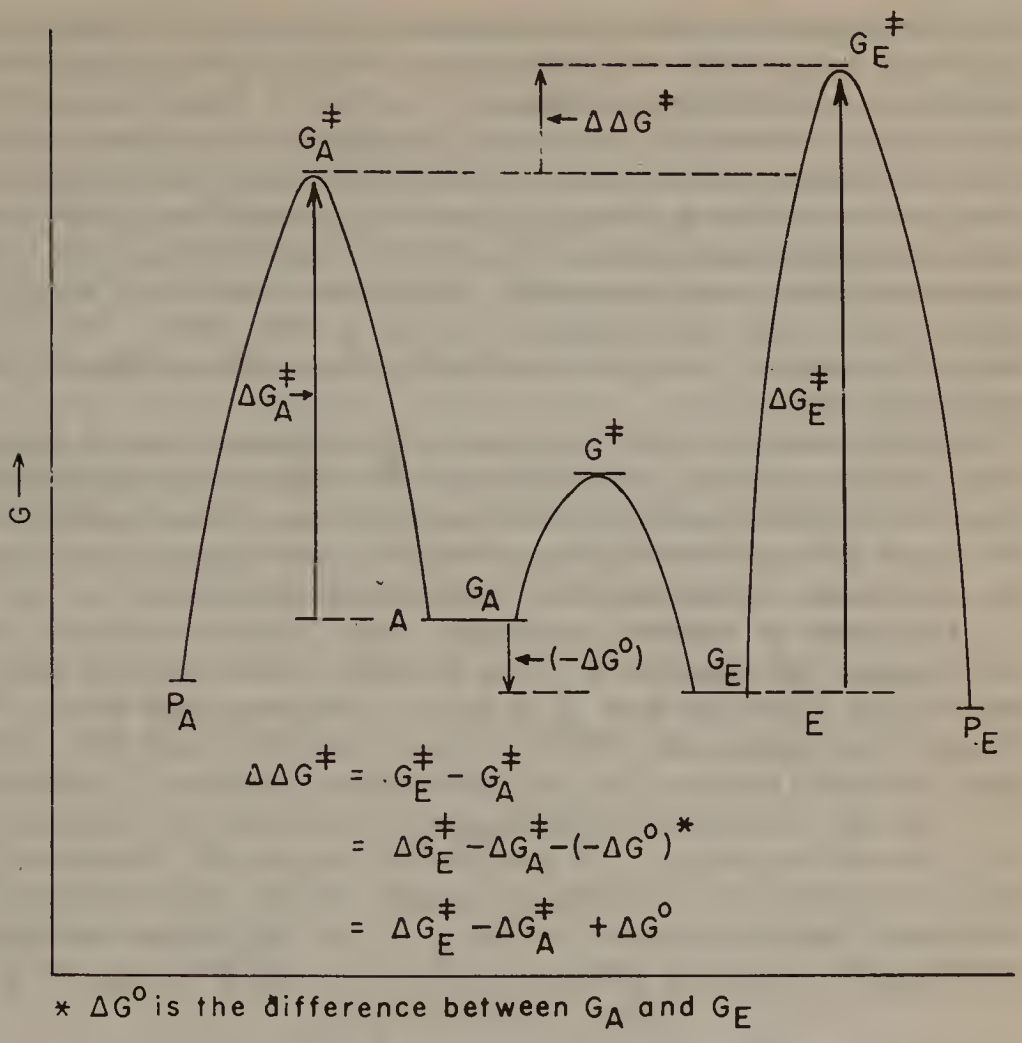


Figure 12.8 Energy diagram for a Curtin-Hammett system

which the more stable conformer (E) reacts through the higher energy transition state. The quantitative relationship between product ratio and transition state energies is derived through the following equations:

$$\frac{d(P_E)}{dt} \Big/ \frac{d(P_A)}{dt} = \frac{k_e[E]}{k_a[A]} = \frac{k_e}{k_a} K \qquad \ldots\ldots (3)$$

$$\text{or } \frac{[P_E]}{[P_A]} = K\frac{k_e}{k_a} \qquad \ldots\ldots (4)$$

Thermodynamics and Eyring equation give the following values for K, k_e, and k_a:

$$K = e^{-\Delta G^{\circ}/RT} \qquad k_e = ATe^{-\Delta G_E^{\ddagger}/RT} \qquad k_a = ATe^{-\Delta G_A^{\ddagger}/RT}$$

Substituting these values in equation (4), one obtains,

$$\frac{[P_E]}{[P_A]} = e^{(-\Delta G^{\circ} - \Delta G_E^{\ddagger} + \Delta G_A^{\ddagger})/RT}$$

$$= e^{-(\Delta G_E^{\ddagger} - \Delta G_A^{\ddagger} + \Delta G^{\circ})/RT} \qquad \ldots\ldots (5)$$

$$= e^{-(G_E^{\ddagger} - G_A^{\ddagger})/RT}$$

$$= e^{-\Delta\Delta G^{\ddagger}/RT} \text{ (see Figure 12.8)} \qquad \ldots\ldots (6)$$

The final equation (6) shows that the product ratio is solely dependent on the difference in energies of the two transition states and is completely independent of the difference in ground state stabilities of the conformers. However, in equations (4) and (5), K as well as $\Delta G°$ are involved. The difference in absolute free energy of transition states is generally difficult to assess experimentally. On the other hand, conformational equilibrium constant (K) can be determined accurately and in many cases, specific rate constants of the conformers may also be available at least approximately from model compounds. In this sense, equation (4) which is a modified form of the Curtin-Hammett equation is more realistic. The Curtin-Hammett principle and its various extensions have been reviewed (Seeman 1986, 1983; Zefirov 1977).

In most of the reactions which correspond to Curtin-Hammett systems, the more stable conformer gives the major product and it is difficult to prove whether the product ratio results from the conformer population ratio or from the difference in free energies of the two transition states. Two illustrations are given here in which the more abundant product arises from the less abundant conformer.

1. Elimination in dimethyl-s-butylamine oxide. Suitably substituted amine oxides eliminate hydroxylamine on heating, through a 5-membered cyclic transition state involving a hydrogen atom cis or gauche to the amine oxide moiety. N,N-Dimethyl-*s*-butylamine oxide (XXVIII) (Figure 12.9) gives, along with 1-butene (major product), a mixture of *cis*- and *trans*-2-butene in a ratio of 1:2 (Cope et al 1957). The two conformers (XXVIIIa) and (XXVIIIb) satisfy the requirement of the cis-elimination giving *cis*- and *trans*-2-butene respectively. From steric consideration, the conformer (XXVIIIb) is less stable than the other (XXVIIIa), (see interactions NMe_2/Me in b and Me/Me in a). The predominant formation of *trans*-butene thus cannot be attributed to the ground state population but to the

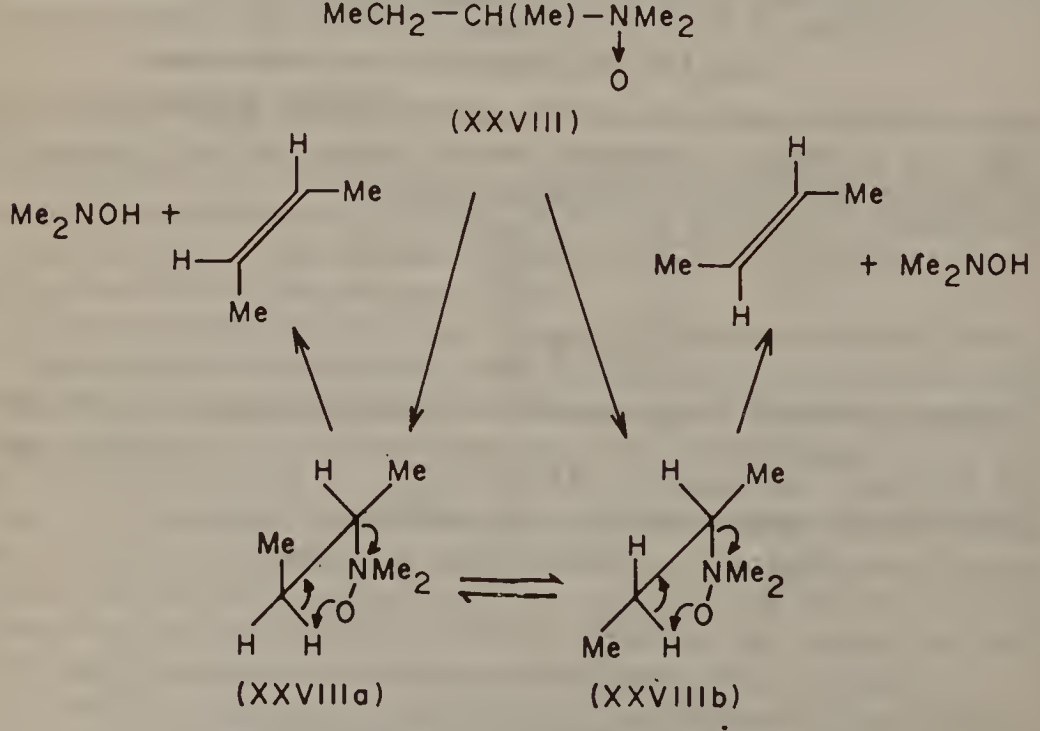


Figure 12.9 Elimination in N,N-dimethyl-*s*-butylamine oxide

relative stability of the transition states the one giving *cis*-2-butene being less stable due to an eclipsing interaction between the two methyl groups*.

2. Quaternisation of tropanes. Tropanes (e.g., XXIX) are more sterically hindered on the side of the piperidine ring than on the side of the pyrrolidine ring and the conformer (XXIXb) is less stable than the conformer (XXIXa) (Figure 12.10). On quaternisation with $^{13}CH_3I$, however, the former reacts faster giving a preponderance of XXXI over XXX which means that the transition state with the attacking group on the less hindered pyrrolidine side is preferred (see Seeman 1983).

The preferential formation of one of the diastereomers by nucleophilic addition to acyclic carbonyl compounds discussed under Cram's rule and Prelog's rule (Chapter 8) may also be regarded as examples of the Curtin-Hammett principle in a broader sense. However, here one reactive conformation gives two products.

In a few cases, by combining the Winstein-Eliel equations and the Curtin-Hammett relationship, it has been possible to determine the specific reaction rates of two individual conformers (see Seeman 1986).

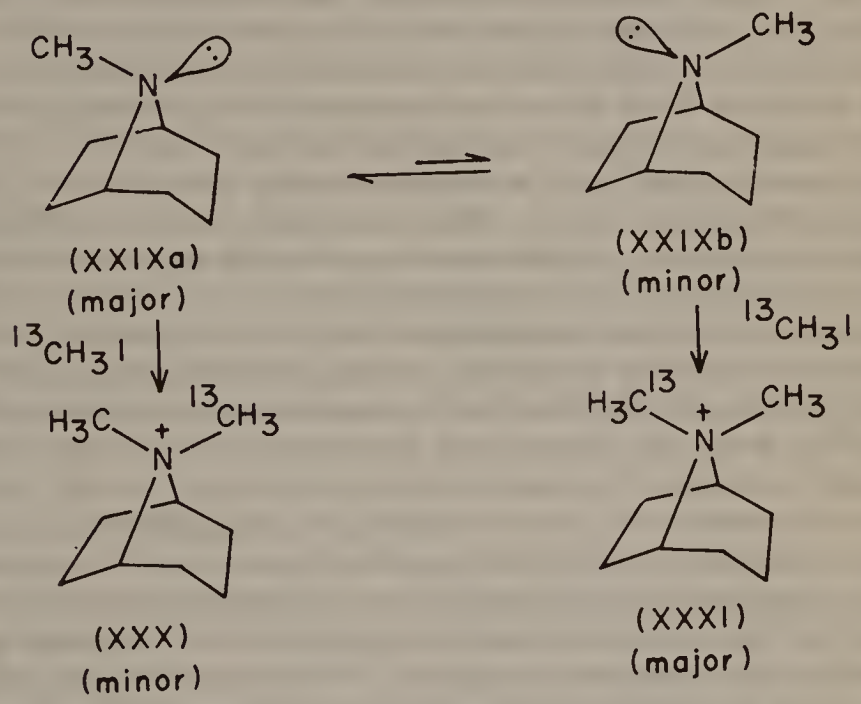


Figure 12.10 Methylation of tropane

Systems in which the rate of conformational interconversion is slow relative to the rate of a chemical reaction are rare but not non-existent. The trapping of N-alkylpiperidines (with a holding group) by the reaction with inorganic acids

*The situation appears to be similar to that encountered in the debromination of the *meso*- and (±)-2,3-dibromobutane. However, the Curtin-Hammett principle applies strictly to conformational diastereomers and not to configurational diastereomers.

discussed in Chapter 10 provides such examples to which the Curtin-Hammett principle is not applicable.

Two situations may be mentioned in order to dispel any confusion in understanding the Curtin-Hammett principle. In the case where $\Delta G_A^{\ddagger} = \Delta G_E^{\ddagger}$, the specific reaction rates of conformers A and E are the same and the product ratio would reflect the ground state population of the conformers. In the other case, $G_A^{\ddagger}$ may be equal to $G_E^{\ddagger}$ and then according to equation (6), the product ratio would be 1. Since the absolute value of free energy of a transition state is never known, it is the ratio of the products which gives information on the transition state energy and not the other way round.

12.4 Conformation, reactivity, and mechanism : cyclic systems

It is clear from the previous discussions that the difference in reactivities between any two stereoisomers or conformers depends on the transition states through which they react. Two factors are generally of importance in determining the stability of a transition state: a *steric factor* and a *stereoelectronic factor*. In the broader sense, the steric factor not only includes van der Waals repulsive interaction (steric hindrance) but also strains arising out of bond angle and bond length distortions. Other factors such as torsional strain, electrostatic interactions, H-bonding etc. also depend very much on the steric disposition of atoms and groups concerned and may be considered along with the steric factor. The stereoelectronic factor, on the other hand, arises from the delocalisation of electrons (usually a pair, bonded or non-bonded) or, in terms of orbital theory, out of overlap of orbitals in the transition states. It is so named because such delocalisation (or orbital overlap) depends very much on the *steric* disposition of the *electrons* concerned (or orbitals holding them). The stereoelectronic effects manifest themselves in the form of certain stereoelectonic requirements which must be fulfilled before the reaction can take place*. Thus in S_N2 reactions, the incoming nucleophile, the centre undergoing substitution, and the leaving group must be collinear; in E2 reactions, the four reacting centres involved must be coplanar with the two leaving groups preferably anti to each other across the C-C bond (i.e., antiperiplanar); in molecular rearrangements, the migrating group is anti to the leaving group; in a nucleophilic addition to a carbonyl group, the nucleophile approaches with an angle of 110° to the carbonyl plane; and so on. The rationale for these stereoelectronic requirements may be better understood in terms of molecular orbital theory (Klopman 1974; Deslongchamps 1983). Thus in the transition state of an S_N2 reaction, the central carbon atom is considered to be sp^2 hybridised with its three fixed substituents (R, R_1, R_2) occupying the three sp^2 orbitals. The remianing p orbital has one lobe (the right half in Figure 12.11a) overlapping with the orbital of the leaving group and the other lobe (the left half) overlapping with the orbital of the incoming nucleophile. Molecular rearrangements,

*The stereoelectronic effects like steric effects also operate in the ground state affecting the thermodynamic stability of the products (see anomeric effect, Chapter 10).

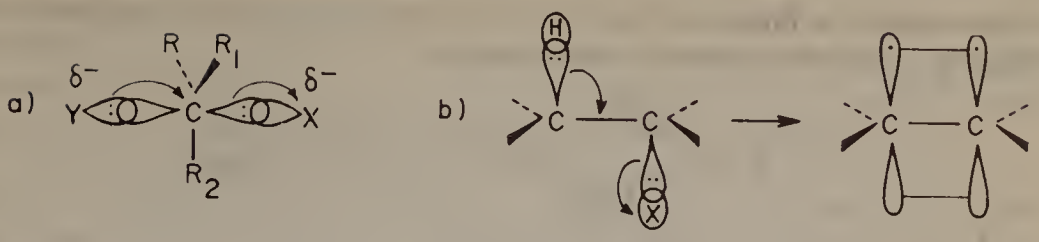


Figure 12.11 (a) S_N2 transition state; (b) E2 transition state

which in most cases simulate intramolecular S_N2 reactions, are subject to a similar stereoelectronic control, the migrating group attacking from the back side of the leaving group. In E2 reactions, coplanarity of the four reacting centres is required to maintain a continuous overlap between the bond orbitals of the two leaving groups (H and X in Figure 12.11b) which ultimately become the π system of the double bond. Both anti and syn eliminations take place the latter being less facile probably due to an unfavourable interaction between the two leaving groups. When the leaving groups are held gauche to each other, an E2 reaction is extremely difficult (lack of coplanarity). On the other hand, in the thermal cis elimination which proceeds through a five-membered cyclic transition state, the groups to be eliminated must be cis or gauche.

Briefly stated, the stereoelectronic factor refers to the conformational requirements of the groups directly involved in the reaction while the steric factor refers to the conformational requirements of the non-reactive groups. The former determines the feasibility of a reaction and pertains to its mechanism and the latter determines the extent of steric hindrance or of steric assistance, if any, in the reaction and thus pertains to its reactivity. Conformation plays an important part in both factors. Cyclic molecules, particularly cyclohexane derivatives with their well defined conformations, provide good substrates for the study of interrelationship of conformation, reactivity, and mechanism.

12.4.1 **Reactions involving exocyclic atoms**

Reactions such as saponification of an ester or esterification of an alcohol do not involve any ring atom but are confined to exocyclic atoms or groups. In these reactions, the stereoelectronic factor has little relevance; only steric and other factors operate. In general, an equatorial substituent is less hindered than an axial one and so is more reactive as illustrated in Section 12.1. In ester hydrolysis, the rate determining step is the formation of an intermediate tetrahedral complex by nucleophilic addition to the trigonal carbon (see next page). This increases the effective bulk of the ester group and at the same time imparts a negative charge to it which in turn increases the degree of solvation. The steric requirement of the group thus becomes markedly greater in the transition state than in the ground state. As a result, the difference in free energies of the axial and equatorial isomers is enhanced in the transition states than in the ground states and the axial isomer reacts at a slower rate than the equatorial isomer. The situation is shown

diagramatically in Figure 12.12a and is a typical case of steric hindrance. The following points may be noted in this connection :

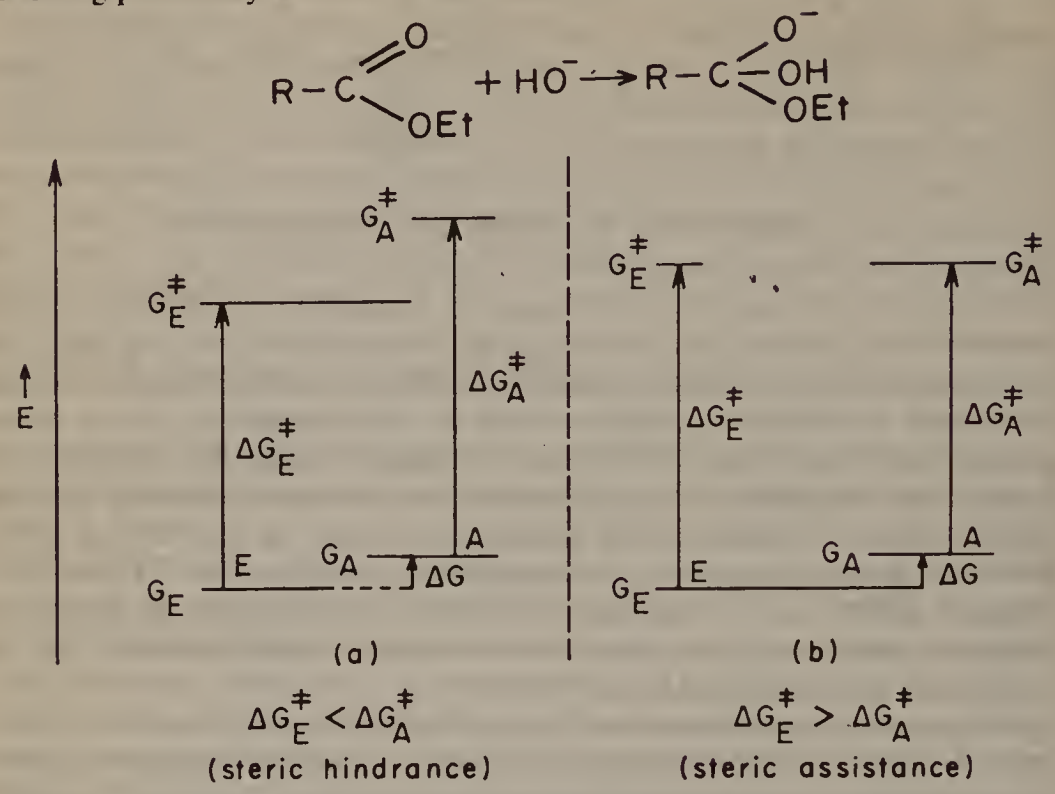


Figure 12.12 Energy diagrams: (a) steric hindrance; (b) steric assistance

(*i*) The difference in the rates of a reaction for an equatorial and an axial isomer is diminished as the site of crowding moves away from the ring. Thus k_{trans}/k_{cis} for the sponification of 4-*t*-butylcyclohexanecarboxylates and of 4-*t*-butylcyclohexyl acetates is 20 and 6.7 respectively (in the latter, C=O is one atom removed from C-1).

(*ii*) Substituents at other positions of the ring especially an axial group at C-3. usually affect the relative rates of reaction of the equatorial and axial isomers. Two examples of opposite character are discussed below.

In the two epimeric esters (XXXII) and (XXXIII) (Figure 12.13) belonging to

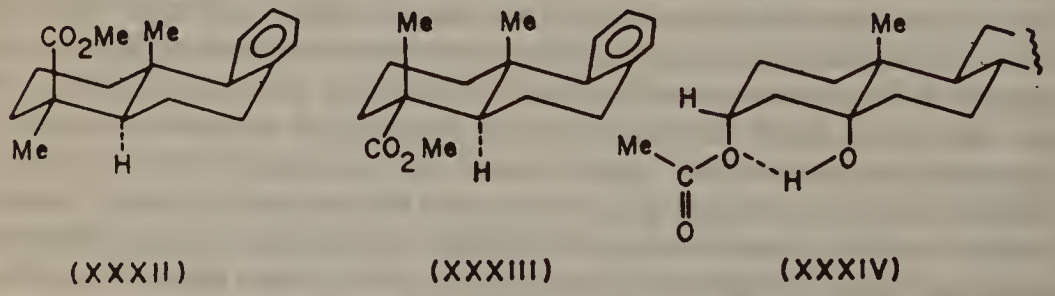


Figure 12.13 Effect of synaxial interaction in saponification

the podocarpane and abietane series of diterpenes respectively, CO_2Me is axial in one and equatorial in the other. The already slow rate of reaction of the axial carbomethoxyl group in XXXII is still further reduced by a synaxial interaction of

the angular methyl. The two esters can thus be very easily identified and even be separated from each other by preferential hydrolysis. In fact. it is a common practice to assign configuration of a carboxyl or a hydroxyl group in many natural products from a study of the relative rates of esterification and saponification.

In 3α-acetoxy-5α-hydroxycholestane (XXXIV, partial structure), the acetoxy group is synaxial to the hydroxyl group permitting the formation of an intramolecular H-bond. The H-bond would be much stronger in the transition state where the other oxygen develops partial negative charge during hydrolysis. As a result, the free energy of activation is considerably decreased for 3α-acetoxy than for 3β-acetoxy derivative and the former (axial) hydrolyses faster.

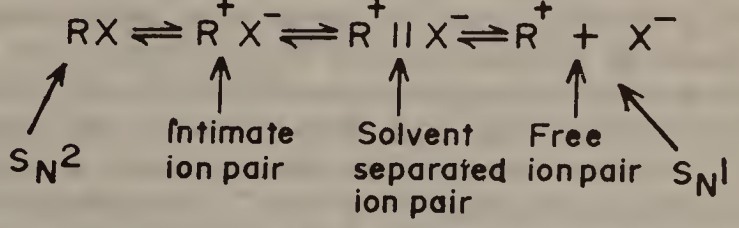
Substituents at the adjacent positions in the ring also affect the relative rates. For example : the saponification of an e-CO_2R is retarded more by an adjacent e-Me than by an a-Me; an e-Me retards the rate of an adjacent e-CO_2Me much more than that of a-CO_2Me (Hellbergand and Peiffer 1968).

(*iii*) Finally, there are situations in which the difference in the ground state free energies of an axial and an equatorial isomer is greater than that in the transition state. Figure 12.12b explains such a situation graphically where the transition state energies are comparable in magnitude in both the diastereomers. The axial isomer with its higher ground state energy would react at a faster rate. This is known as steric assistance or steric acceleration. Examples of such reactions at exocyclic positions are rare (see Eliel et al 1965).

12.4.2. **Nucleophilic substitution reaction at ring carbon**

Other reactions to be discussed involve one or more endocyclic carbon atoms; the nucleophilic substitution is one of them. The effect of conformation on reactivity in substitution reactions is discussed under four headings depending on the mechanisms involved.

1. S_N1 reaction. The nucleophilic substitution reactions are believed to follow a unified ion-pair mechanism in which S_N1 and S_N2 form the two extremes as shown with the substrate RX in a varied states of dissociation.



If a reaction takes place between RX and a nucleophile (or a solvent) through the S_N1 end of the mechanistic continuum, a common carbocation (as XXXV) is formed from both the axial and equatorial isomers (Figure 12.14). The energy diagram corresponds to Figure 12.12b and the axial isomer having a higher ground state energy reacts faster. The steric strain of the axial isomer is relieved in the transition state providing steric assistance. Thus solvolysis (acetolysis, formolysis, and ethanolysis) of the 4-*t*-butylcyclohexyl tosylates gives a ratio of k_{cis}/k_{trans} varying from 4.0 to 2.3 which correspond to a $-\Delta G°$ value of 2.6-3.4 kJ mol^{-1} for OTs group in fair agreement with values determined by other methods. The above

picture is, however, oversimplified and the carbocation (XXXV) is very seldom free from the counter anion as evidenced by the fact that the products of solvolysis from the two epimers are not the same. Walden inversion usually accompanies the reactions and the axial isomer gives a fair amount of elimination products through E1 mechanism. Nevertheless, there appears to exist a direct correlation between reactivity and the steric congestion of the leaving group in the ground state.

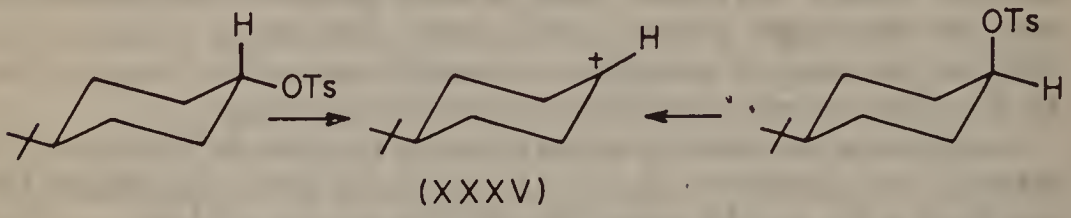


Figure 12.14 Transition state of an S_N1 reaction (cyclohexyl system)

2. S_N2 reactions. The transition state of an S_N2 reaction involves a pentacoordinated carbon atom to which the leaving group (X) and the incoming group (Y) are partially bonded (Figure 12.11). The main interaction is between Y and the two axial H's in XXXVIa and between X and the two axial H's in XXXVIb for the trans and cis isomers (Figure 12.15) respectively. If Y is bulkier than X,

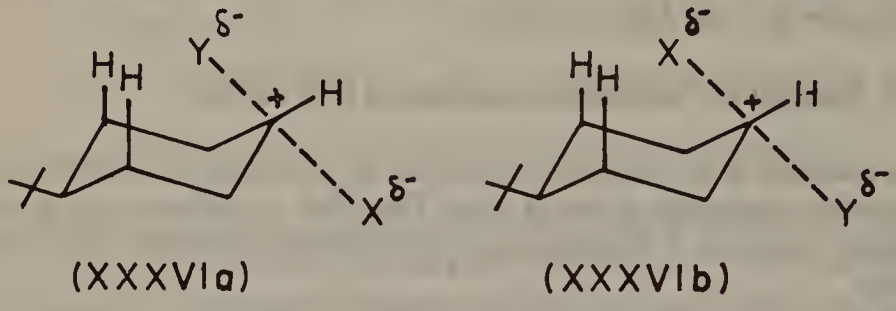
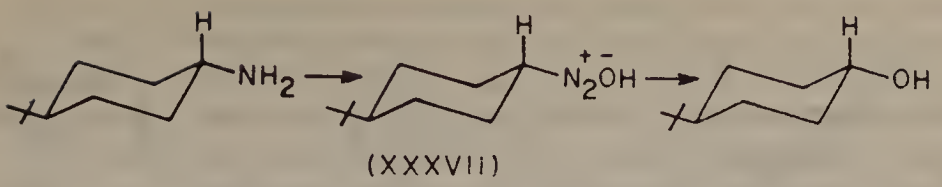


Figure 12.15 Transition states of an S_N2 reaction (cyclohexyl system)

XXXVIa is of higher energy than XXXVIb and the equatorial isomer reacts at a slower rate*. It may also be noted that because of the higher ground state energy of the axial isomer, the activation energy of the axial isomer is still further reduced. Thus for the 4-*t*-butylcyclohexyl bromides (XXXVI, X = Br). the cis isomer reacts approximately 60 times faster than the trans isomer with sodium thiophenate ($Y = PhS^-$) in aqueous ethanol. If the incoming group and the leaving group happen to be the same (displacement of I^- by I^{*-}), the difference of free energy of activation would be equal to the difference in ground state free energy.

3. S_Ni reactions. In an S_Ni reaction, the nucleophile forms a part of the ion pair and attacks the reacting centre from the same side of the leaving group with retention of configuration. The amine-nitrous acid reaction in which NH_2 is replaced by OH (see ion-pair XXXVII in Figure 12.16) has been studied extensively and it has been observed that equatorial amines usually give equatorial alcohols almost exclusively (sometimes admixed with a small amount of the axial

*Of course, the C···X and C···Y distances in the transition states are also to be taken into account.

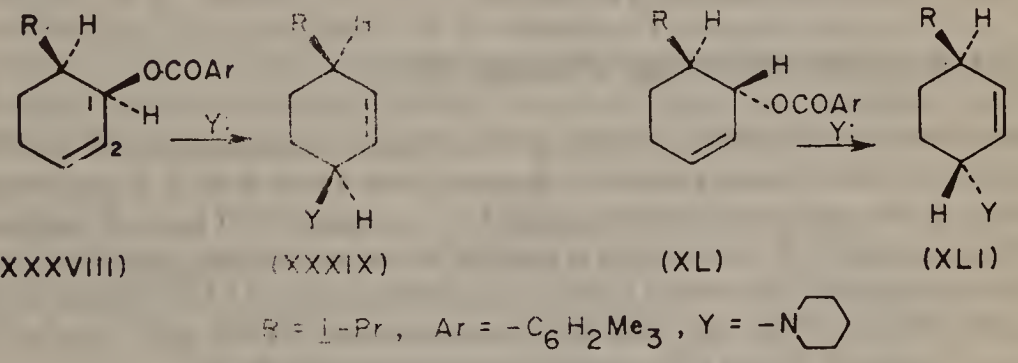


(XXXVII)

Figure 12.16 Stereochemistry of amine-nitrous acid reaction

isomers). Thus menthylamine (e-NH_2) gives menthol (e-OH), carvomenthylamine (e-NH_2) gives carvomenthol (e-OH), and 1β (or 2α)-amino-*trans*-decalin (e-NH_2) gives *trans*-1β (or 2α)-decalol (e-OH) all in high yields. The reaction of an axial amino group, on the other hand, often leads to a mixture of olefins (due to a facile E2 elimination), axial alcohols, and equatorial alcohols indicating that no single mechanism operates.

4. S_N2' reactions. An allylic substrate, e.g., R-CH = CH-CH_2-X often undergoes substitution reaction with allylic rearrangement through an S_N2' mechanism.* All evidences point out that the incoming nucleophile approaches γ-C from the side syn to the leaving group. Thus the 6-alkyl-2-cyclohexenyl mesitoates react with piperidine stereospecifically, the cis isomer (XXXVIII) giving the cis (XXXIX) and trans isomer (XL) giving the trans cyclohexene (XLI) (Figure 12.17) (Stork and the Kreft 1977; also see Magid 1980). The stereochemical results may be explained on the basis of the following stereoelectronic arguments:



(XXXVIII) (XXXIX) (XL) (XLI)

R = i-Pr , Ar = $-C_6H_2Me_3$, Y = $-N$

Figure 12.17 Stereochemistry of S_N2' reaction

The cyclohexenyl system (the cis isomer) exists in two conformers (XLIIa) and (XLIIb) (Figure 12.18) with the leaving group X pseudoaxial and pseudo-equatorial respectively. In the former, the syn attack proceeds from the antiparallel direction (so called because Y---C and C—H_a' are antiparallel) and leads to a chair-like transition state (XLIIIa) in which the Y---C bond is antiperiplanar to an electron pair at C-2 which in turn is antiperiplanar (or nearly so) to C-X bond - the stereoelectronic requirement of the E2 reaction. The product has the anticipated cis stereochemistry (as XLIV). A syn attack on the other conformer (XLIIb) takes place in parallel direction (so called because Y---C and C—H_a' are parallel) and leads to a twist-boat transition state (XLIIIb) which also fulfills the antiperiplanar stereochemistry and gives the same cis product (XLIV')†. The mechanism although

*Substitution with allylic rearrangement through an S_Ni' mechanism also occurs.

†A priori, the antiparallel approach leading to a chair transition state is favoured.

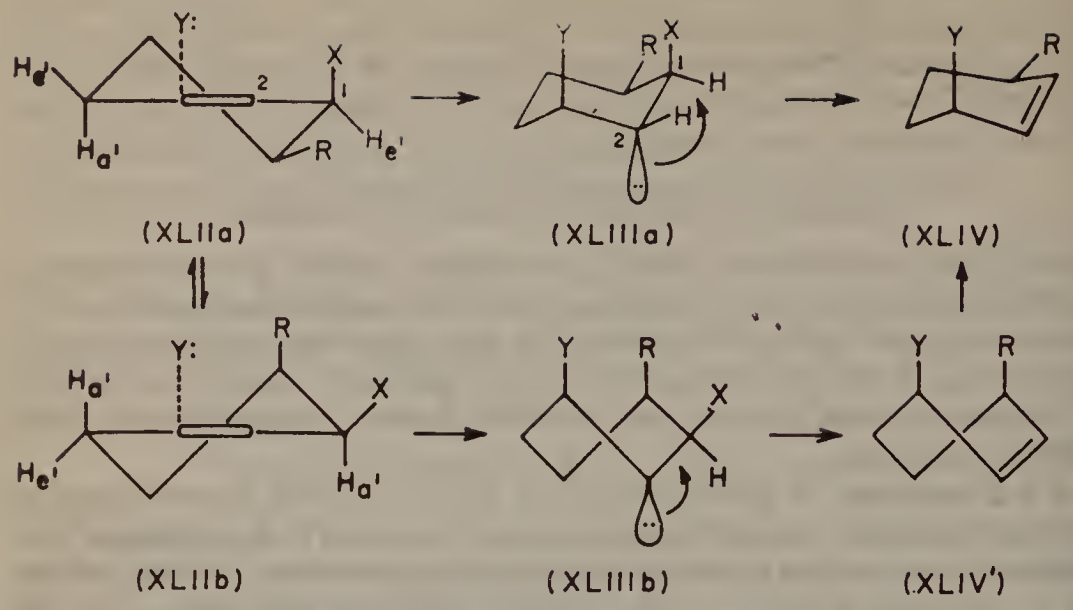


Figure 12.18 Transition states in S_N2' reaction

shown in a non-concerted fashion is very possibly a concerted one. The anti attack, on the other hand, would fail to comply with the stereoelectronic requirements described above. A frontier orbital analysis (Chapter 14) also supports the syn attack (Lowry and Richardson 1987).

12.4.3 Formation and cleavage of epoxide ring

The formation of epoxides (oxiranes) from vicinal bromohydrins (Br may be replaced by other leaving groups) by treatment with a base is an S_N2 reaction and subject to the same stereoelectronic control, i.e., oxygen of OH has to be collinear with and anti to C-Br bond which is possible for the cyclohexane derivatives only if they are diaxial. Thus *trans*-1β-bromo-2α-hydroxydecalin (XLV) (Figure 12.19) is converted smoothly into *trans*-1α,2α-epoxydecalin (XLVI) while the 1α,2β-isomer (with both Br and OH equatorial) reacts extremely slowly.

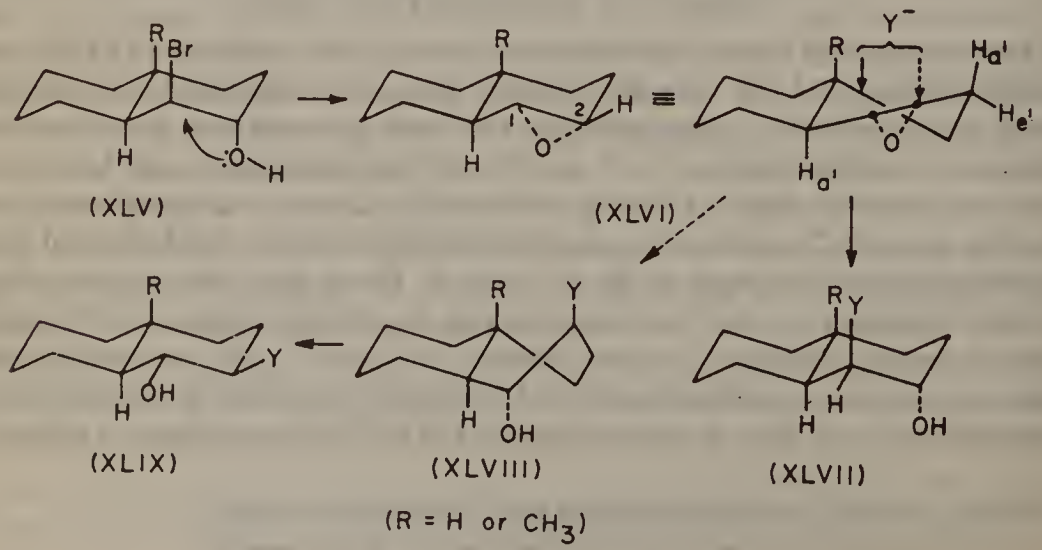


Figure 12.19 Stereochemistry of epoxide ring opening

The reverse process, namely, nucleophilic opening of the epoxide ring is also an S_N2 reaction with the difference that the leaving group stays attached to the molecule. The nucleophile (Y^-) must approach either of the oxirane carbons from the rear side of the oxide linkage (β face of XLVI). Such an approach at C-1 of XLVI is antiparallel (shown by a full arrow) and at C-2 is parallel (shown by a dotted arrow). The former leads to a chair-like transition state and gives the diaxial product (XLVII) which in turn can be converted into the starting epoxide by base. The parallel approach, on the other hand, leads to a twist-boat transition state (XLVIII, see the dotted arrow) and finally gives the diequatorial product (XLIX). The chair-like transition state is generally favoured over the twist-boat and XLVII is formed preferentially. However, if R = Me, a synaxial interaction is set up between Me and Y in the antiparallel approach and the other isomer (XLIX) may predominate. Thus both stereoelectronic factor and steric factor control the nature of products in the ring opening of unsymmetrical epoxides. In the acid-catalysed epoxide ring opening, the ether oxygen is first protonated and the conjugate base of the acid or a solvent molecule then reacts to give the trans-diaxial product (as XLVII).

In the case when Y^- is an intramolecular nucleophile, a new ring is formed while the epoxide ring is opened and the ease of such cyclisation depends on the ability of the side chain containing the nucleophile to maintain a collinear approach. Models show that the formation of a six-membered ring through such opening of an epoxide (L to LII) permits a better collinear approach of the nucleophile than the formation of an analogous five-membered ring (LI to LIII) (Figure 12.20). It has been indeed observed by Stork et al (1974) that the reaction is much faster in the former reaction. In the case when the nucleophilic end of a chain attacks the oxirane carbon to which the chain is attached, a cyclobutane is

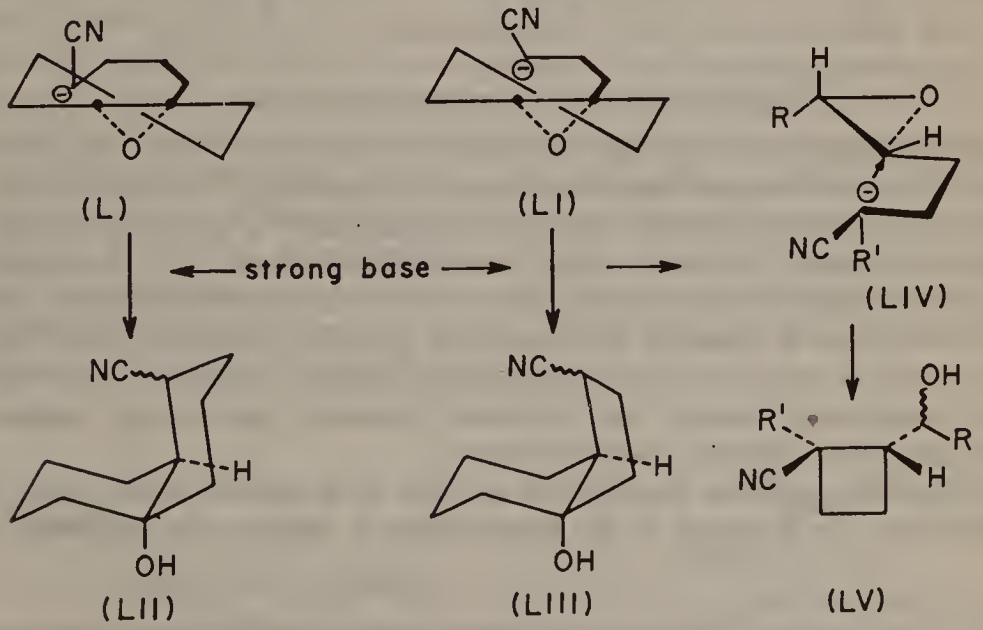


Figure 12.20 Intramolecular ring-closure through epoxide ring opening (some structures are reconstructed with permission from Deslongchamps, *Stereoelectronic effects in organic chemistry*, Pergamon Press, 1983).

formed in preference to a cyclopentane through a spiro-type transition state (LIV to LV)*. The stereochemistry of the products is such that CN (which becomes an effectively bulky group due to complexation with metal ion) is trans with respect to the alcoholic side chain (see Deslongchamps 1983 for discussion).

12.4.4 **Addition reactions to double bonds**

Addition reactions to double bonds are also subject to stereoelectronic control and are discussed under different headings.

1. Electrophilic addition. In an electrophilic addition reaction, an electron deficient species such as Br^+ (it may even be a radical) adds to the double bond forming a cyclic intermediate, e.g., bromonium ion. A nucleophile (often the anionic counterpart of the eletrophile) opens up the ring approaching from the side opposite to the electrophile (similar to the ring opening of a protonated epoxide) and a trans diaxial product results in the case of cyclohexene derivatives. This is demonstrated by the conversion of 2-cholestene (LVI) (Figure 12.21) into 2β,3α-

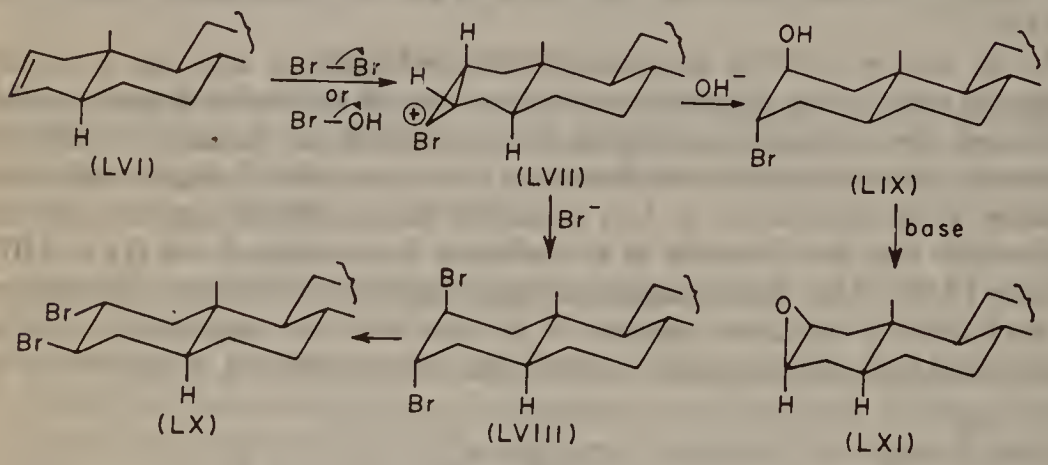


Figure 12.21 Stereochemistry of addition reactions

dibromocholestane (LVIII) and into 2β-hydroxy,3α-bromocholestane (LIX) by treatment with bromine and hypobromous acid respectively. The intermediate bromonium ion LVII) is common in both the reactions. The diaxial dibromide (LVIII) is isomerised to the more stable diequatorial dibromide (LX) on heating presumably through the same intermediate (LVII). The bromohydrin (LIX) on treatment with base is smoothly converted into the 2β, 3β-epoxide (LXI) as expected. Minute quantities of the diequatorial addition products are always obtained conceivably through the twist-boat transition state which explains isomerisation of the dibromide mentioned above.

2. Nucleophilic addition. Nucleophilic addition to an isolated double bond is very rare since the π system of the double bond is electron-rich. However, in

*All the three ring-closures mentioned above are allowed by Baldwin rules (1976) and are designated respectively as 6-Exo-Tet, 5-Exo-Tet, and 4-Exo-Tet (the numeral denotes the ring size that is going to be formed. the term exo or endo denotes whether the bond being broken is exocyclic or endocyclic with respect to the newly formed ring. and Tet, Trig, and Dig refer to the state of hybridisation undergoing the nucleophilic attack).

enone systems in which the double bond is polarised by the presence of an electron-withdrawing carbonyl group, 1,4-addition of nucleophiles is facile (e.g., Michael reaction). Such reactions are controlled by both the stereoelectronic factor and the steric factor. A cyclohexenone (as LXII) (Figure 12.22) may be represented

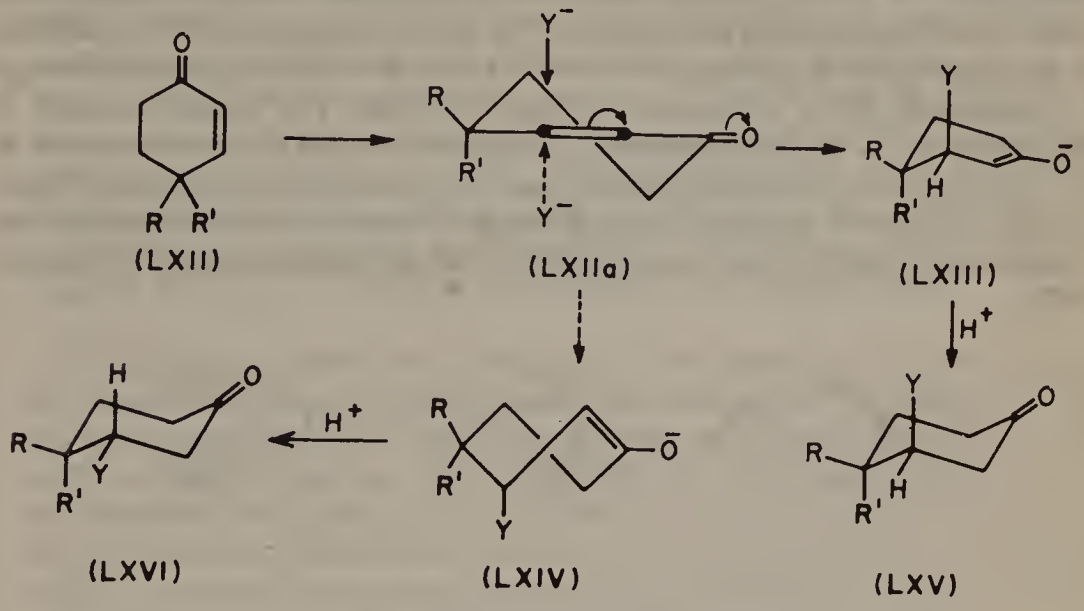


Figure 12.22 Stereochemistry of 1,4-addition

by the half chair conformation (LXIIa) with R′ pseudoaxial (in the inverted conformation, R is pseudoaxial). To maintain a continuous overlap with the extended π system, the nucleophile Y^- must approach the β-carbon perpendicular to the enone plane. The antiparallel approach (shown by the full arrow) leads to a chair-like enolate ion (LXIII) while the parallel approach (shown by the dotted arrow) leads to a twist-boat enolate ion (LXIV). In the absence of any compelling steric effect, the former provides a more facile pathway and the product with axial Y (LXV) is formed in a kinetically controlled reaction in preference to the one with equatorial Y (LXVI). Numerous hydrocyanation reactions (Nagata and Yoshioka 1977) and conjugate additions of Grignard reagents and organocopper reagents (Posner 1972) appear to follow this stereochemical principle. To cite but one example, 5-methylcyclohex-2-enone on treatment with lithium dimethylcuprate gives 3,5-dimethylcyclohexanones, the trans isomer predominating to the extent of 98% in the product (House and Fischer 1968) (Figure 12.23).

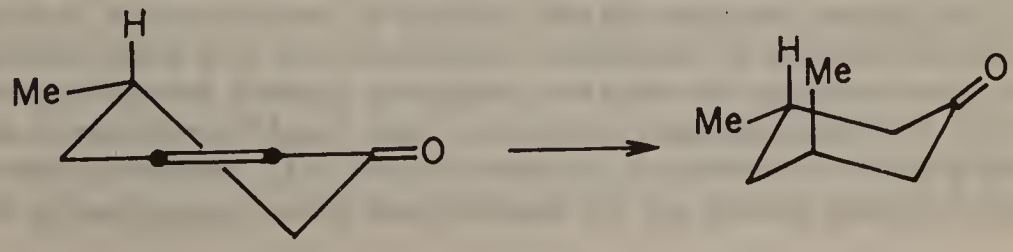


Figure 12.23 1,4-Addition to cyclohexenone

3. Cis addition via cyclic intermediates. If the addition of the reagents takes place through a cyclic intermediate or transition state, the product must have the entering groups cis to each other. One such example is the selective oxidation of a cyclic olefin to a *cis*-1,2-glycol with osmium tetroxide or less efficiently with aqueous alkaline potassium permanganate. The reaction is equivalent to the addition of the components of hydrogen peroxide to a double bond and proceeds through five-membered cyclic intermediates (Figure 12.24a). The second example is hydroboration* of an olefin followed by oxidative removal of boron as shown in the conversion of methylcyclohexene into *trans*-2-methylcyclohexanol (Figure 12.24b)—a reaction equivalent to the addition of water to a double bond in anti-Markownikoff fashion. Boron attaches itself to the less substituted carbon (Jackson 1972).

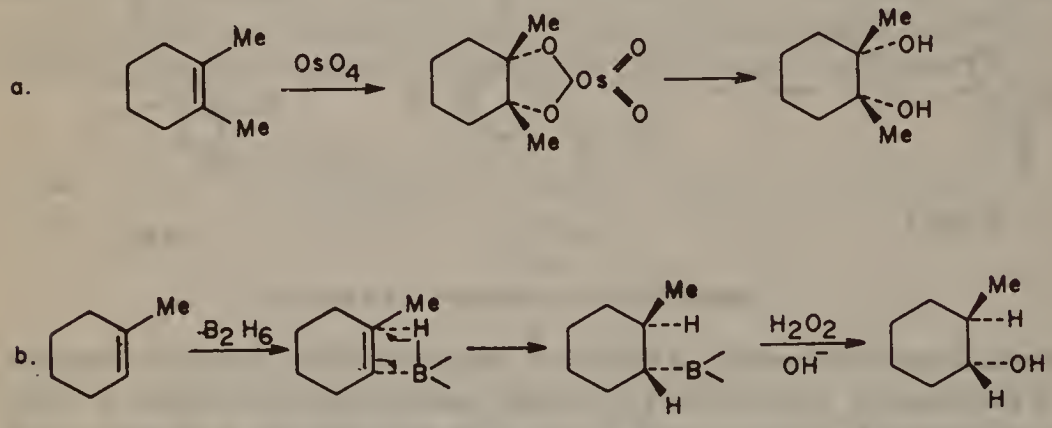


Figure 12.24 (a) cis-Hydroxylation (osmylation); (b) hydroboration

12.4.5 Elimination reactions

Three types of elimination reactions are discussed here to illustrate the conformation-reactivity relationship : E2 elimination (ionic), cis elimination (pyrolytic), and 1,4-elimination leading to molecular fragmentation.

1. E2 elimination. A few elimination reactions and their stereoelectronic requirements have already been mentioned in previous discussions. Like the nucleophilic substitution reactions, the elimination reactions also go through a broad spectrum of mechanisms with ElcB and El forming the two extreme ends. In ElcB (elimination, unimolecular, conjugate base), the C-H bond is broken first in the H-C-C-X fragment (see Figure 12.11b) followed by elimination of X^- from the resultant carbanion. In El (elimination, unimolecular), the C-X bond dissociates first to give a carbonium ion which then eliminates a β-proton. Between these two extremes, intermediate mechanisms operate in which H and X are eliminated with a varying degree of concertedness, collectively known as E2 (elimination, bimolecular)† As already pointed out, the stereoelectronic factor requires that the two

*Orbital symmetry consideration supports a non-concerted mechanism.

†For further subclassification of elimination reactions, see Lowry and Richardson (1987).

leaving groups, e.g., H and X must be either antiperiplanar or synperiplanar and the elimination is accordingly designated anti or syn. The anti elimination in general is the preferred mode although the syn elimination is often competitive and may even be dominant depending on the nature of substrates, nucleophiles, leaving groups, and solvents (Sicher 1972; Bartsch and Zavada 1980). The syn elimination is favoured: (*i*) when the transition state possesses considerable anionic character as in ElcB, (*ii*) when a synperiplanar arrangement is possible but an antiperiplanar arrangement is not, (*iii*) when the base is not free but exists as an ion pair, and (*iv*) when a syn hydrogen is more acidic. Other conditions being equal, the tendency for syn elimination is greater when 1,2-disubstituted olefins are formed rather than trisubstituted ones, when the leaving groups are ammonium or sulphonium rather than Cl, Br, and tosyl, and when the solvents are weakly dissociating.

Cyclohexyl derivatives show preference for anti elimination probably because the chair form can easily accommodate an antiperiplanar arrangement of the leaving groups (1,2-diaxial) while synperiplanar arrangement with a torsion angle of 0° is difficult to achieve. The classical example of E2 reactions differentiating the reactivities of an epimeric pair of substrates is dehydrochlorination of menthyl and neomenthyl chloride with sodium ethoxide. The former (LXVII) (Figure 12.25) in its stable conformation cannot fulfill the antiperiplanarity requirement and so has to be inverted to its unstable conformation (LXVIIa). The latter has Cl

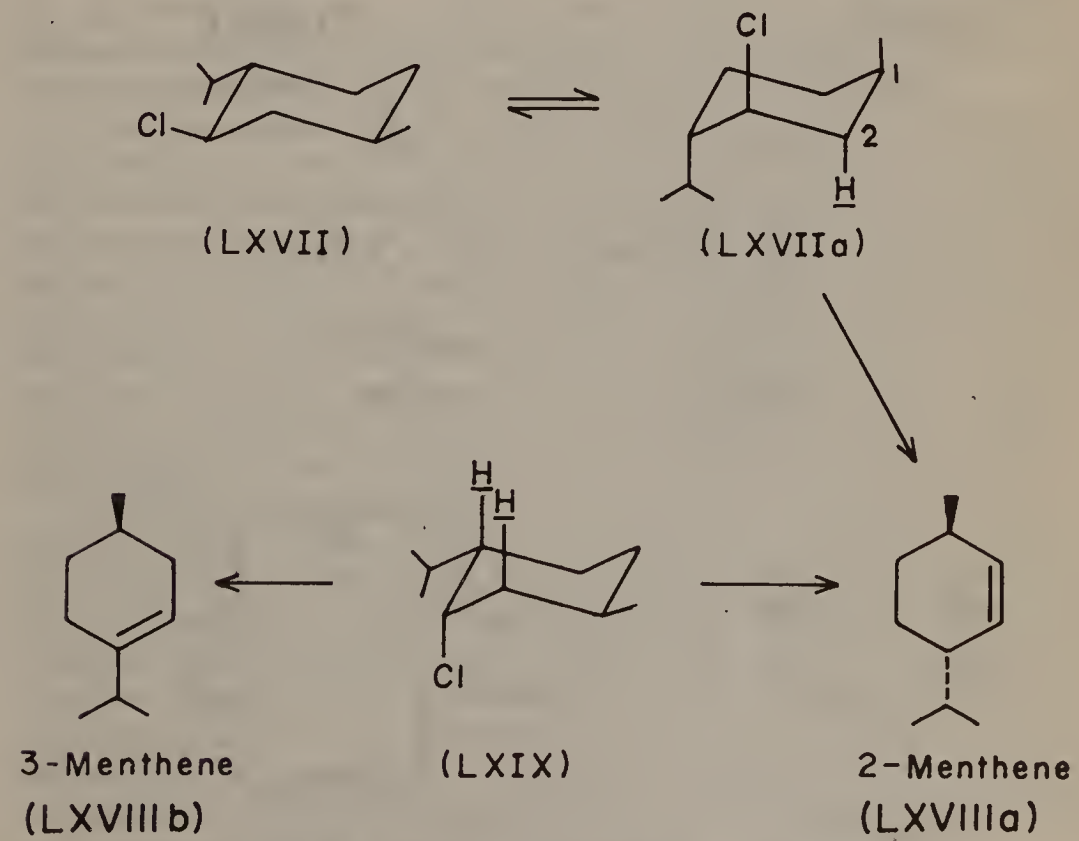


Figure 12.25 E2 Elimination of menthyl and neomenthyl chloride

antiperiplanar only with the axial H at C-2 and gives a single product, 2-menthene (LXVIIIa) (Hofmann product—least substituted olefin). On the other hand, in neomenthyl chloride (LXIX), the axial Cl is antiperiplanar to two adjacent axial H's and so gives two products, 3-menthene (LXVIIIb) (Saytzeff product, 75%) and 2-menthene (25%). Moreover, the reaction rate is much slower for menthyl chloride which is understandable from the very low concentration of the reactive all-axial conformer (LXVIIa) in the equilibrium (cf Winstein-Eliel equations).

In the cyclopentane derivatives, on the other hand, two adjacent cis groups can easily adopt a synperiplanar arrangement but it is comparatively difficult for two trans groups to adopt an antiperiplanar arrangement. The syn elimination is, therefore, preferred. 2-Phenylcyclopentyl tosylate provides an interesting example in which both syn and anti eliminations compete with each other. In the cis isomer (LXX) (Figure 12.26), the acidic proton at C-2 is antiperiplanar to the tosyl group and 90% of 1-phenylcyclopentene (LXXII) is formed by treatment with potassium *t*-butoxide in *t*-butanol—a clear case of predominant anti elimination. The trans isomer (LXXI) in which 2-H is synperiplanar with the tosyl group on similar

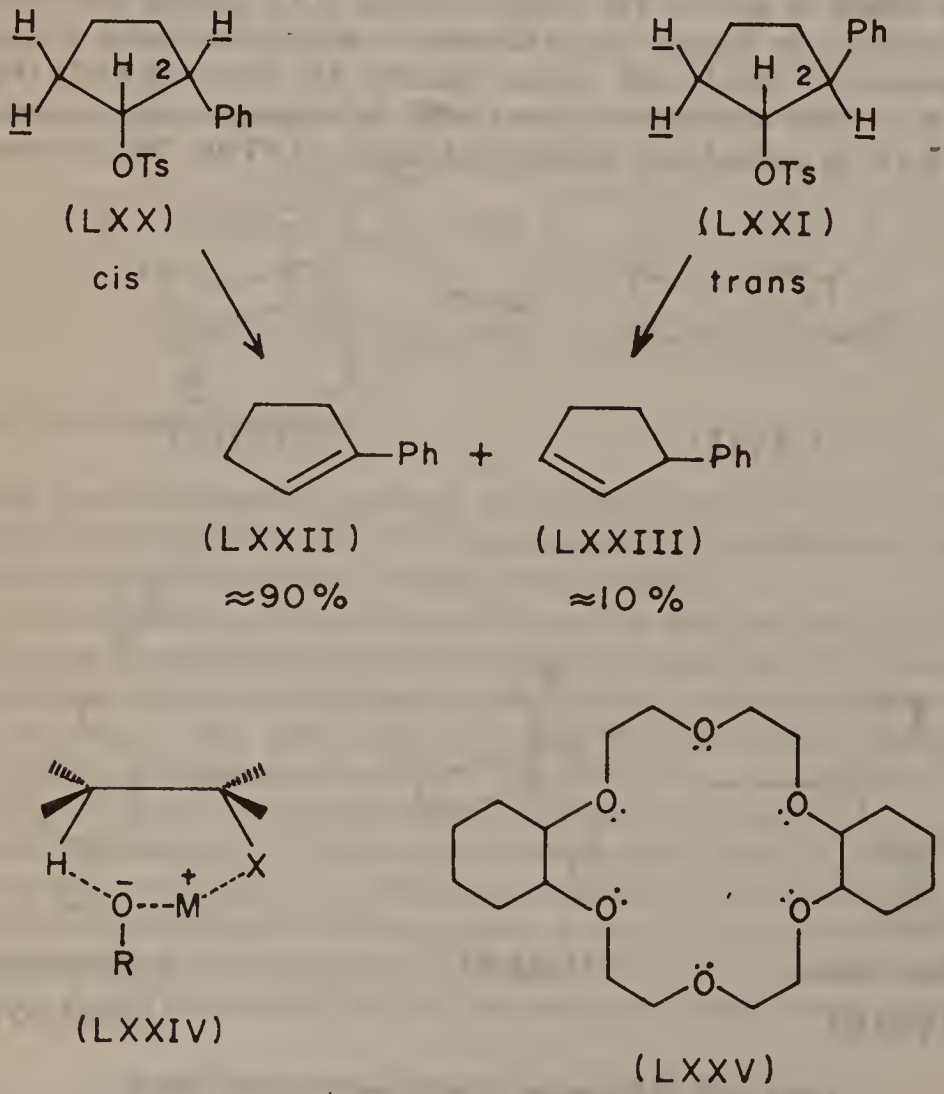
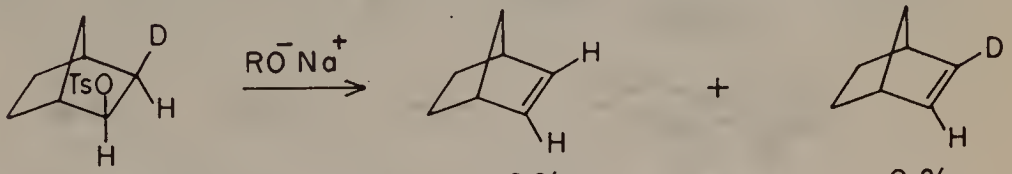


Figure 12.26 Syn and anti elimination in 2-phenylcyclopentyl tosylate

treatment gives almost an identical mixture—90% of LXXII and 10% of LXXIII—this time a clear case of syn elimination. The greater reactivity of the 2-H proton is definitely one of the controlling factors. During the elimination of the trans isomer (LXXI), if the crown ether (LXXV) is added which binds K^+ ion in its inner cavity and sets the alkoxide ion free, the percentage of LXXII (product of syn elimination) drops to 30 (Bartsch et al 1974). This means that an ion pair (specially in a weakly ionising solvent) helps the syn elimination by simultaneously pulling out the β-H and removing X through complexation with K^+ as shown in the structure LXXIV.

In certain rigid bicyclo systems, e.g., bicyclo[2.2.1]heptanes and bicyclo[2.2.2] octanes, the arrangement for anti elimination is prohibited and only the syn mode of elimination can operate. Thus elimination of deuterated norbornyl tosylate (LXXVI) (Figure 12.27) with the sodium salt of 2-cyclohexylcyclohexanol (Brown



(LXXVI) No crown ether: 98% 0%
Crown ether : 70% 30%

Figure 12.27 Elimination in norbornyl system

and Liu 1970) gives 98% of undeuterated norbornene. Here also when an appropriate crown ether is added, deuterated norbornene (30%) is formed via anti elimination supporting the participation of ion pair in syn elimination.

2. Pyrolytic cis elimination. Pyrolysis of acetate ester, methyl xanthate ester, and tertiary amine oxide with the formation of olefins and elimination of acetic acid, COS and MeSH, and dimethylhydroxyl amine respectively is believed to involve a cyclic transition state (Figure 12.28a). In cyclohexane system, this necessitates an axial-equatorial alignment of the eliminating groups. This is illustrated by the product compositions from the methyl xanthate esters (Chugaev reaction) derived from menthol (LXXVII) and neomenthol (LXXVIII). These isomers give preponderantly 3-menthene and 2-menthene respectively (Figure 12.28b), opposite to the result encountered in base-induced E2 elimination. Elimination of dimethylamine oxide (Cope reaction) appears to be more stereospecific (Figure 12.28c).

3. 1,4-Elimination (fragmentation). 3-Aminoalcohol derivatives of the type (LXXIX) (Figure 12.29) in which the p orbital of N with a lone pair is antiperiplanar to 3-2 bond which in turn is antiperiplanar to the leaving group (OTs) can undergo a concerted 1,4-elimination leading to the fragmentation* of the molecule as shown. The epimeric structure (LXXXI) cannot be so converted into the amino olefin (LXXX) which shows that the stereoelectronic requirements in the reaction (known as Gröb fragmentation, Gröb 1969) are very stringent. Gröb fragmentation of monotosylates of 1,3-glycols in appropriately aligned conformations has been used in many syntheses. Thus the two epimeric monotosylates of 1,3-glycols (LXXXII) and (LXXXIV) (Figure 12.30) on treatment with a

*Fragmentation here leads to ring-cleavage.

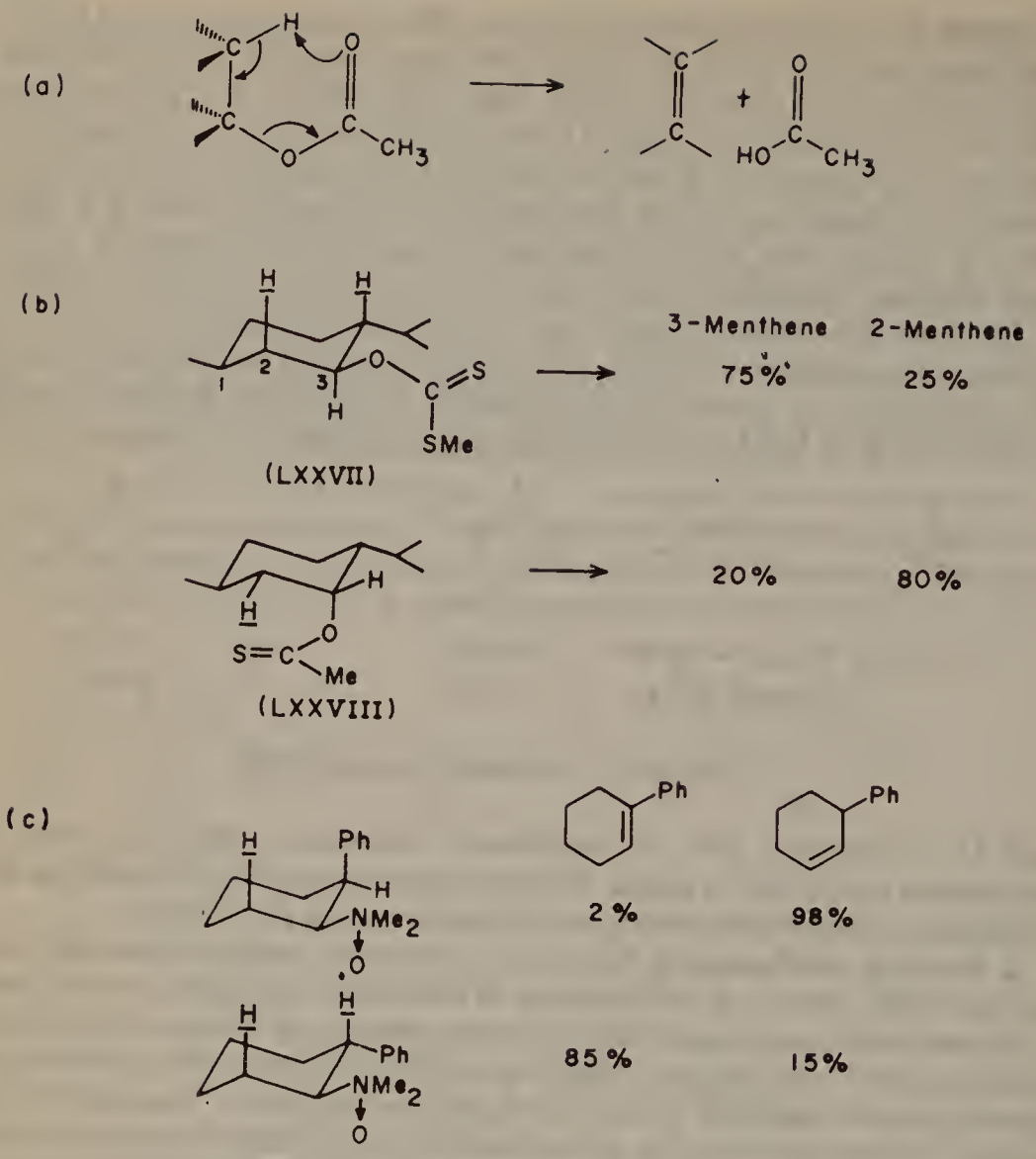


Figure 12.28 Pyrolytic cis elimination

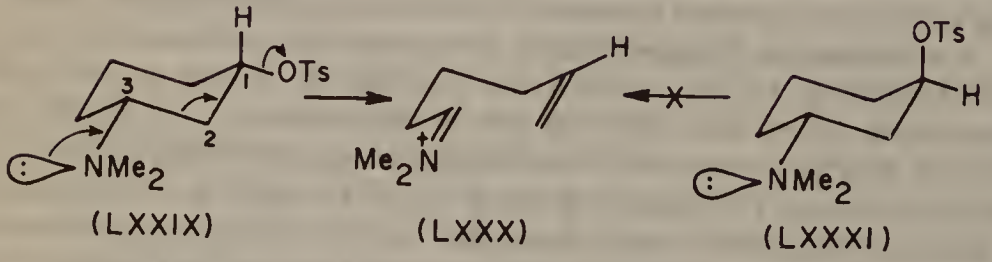


Figure 12.29 Gröb fragmentation

strong base are converted into medium ring unsaturated ketones (LXXXIII) and (LXXXV) respectively (Corey et al 1964). Here the flexibility of the cyclopentane ring permits the tosyl group in both the epimers to be approximately antiperiplanar with the bridging C-C bond. It is also immaterial whether the ring junction is cis or trans fused. The epimer with the angular Me and the tosyl group cis gives the trans olefin while the other gives the cis olefin. The former has been utilised for the synthesis of caryophyllene and the latter for the synthesis of isocaryophyllene.

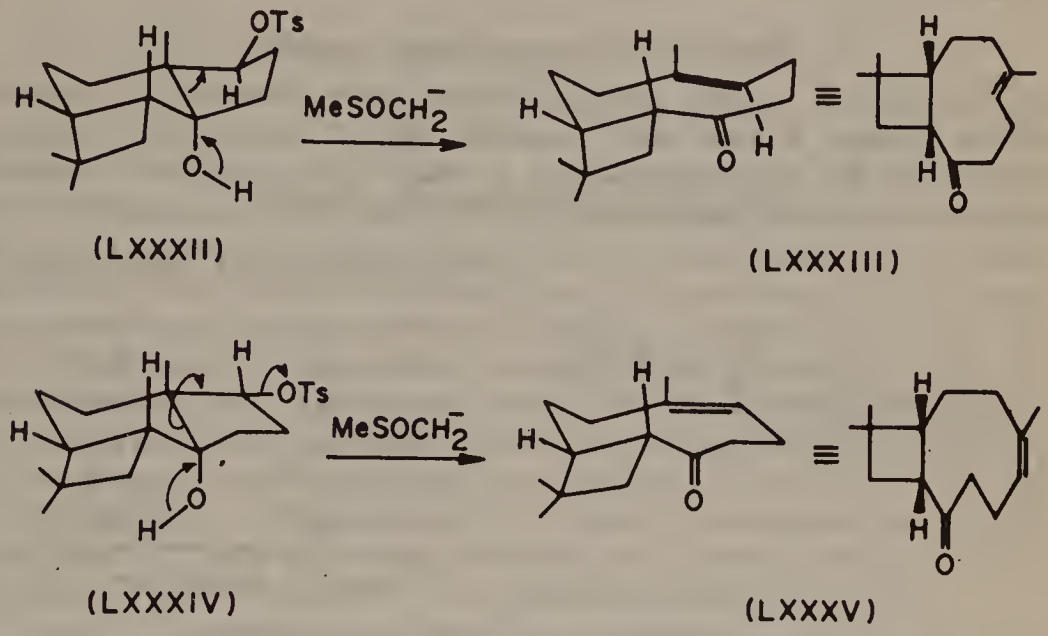


Figure 12.30 Fragmentation of monotosylate of 1,3-glycol

12.4.6 Chromic acid oxidation of cyclohexanols

The chromic acid oxidation of a secondary alcohol to a ketone is believed to go in two steps: the rapid formation of a chromate ester followed by its rate-determining decomposition into the ketone, a chromite ion, and a proton as shown:

$$R_2CHOH + HCrO_4^- + H^+ \rightleftharpoons R_2CH\text{-}O\text{-}CrO_2\text{-}OH + H_2O$$

$$R_2CH\text{-}O\text{-}CrO_2\text{-}OH \rightarrow R_2C{=}O + HCrO_3^- + H^+$$

It has been well established both in substituted cyclohexanols (Eliel et al 1966) and in steroidal alcohols (Schreiber and Eschenmoser 1955) that the axial alcohols are oxidised at a faster rate than the equatorial ones by a factor of 3 to 6 (sometimes even more). The relative rates of oxidation of a few typical cyclohexanols are shown in Figure 12.31 which illustrate the point. At the first sight, it

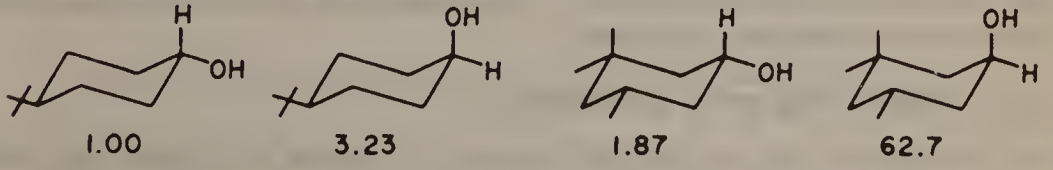
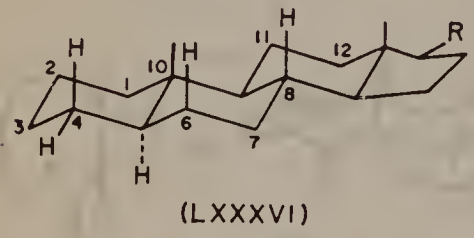


Figure 12.31 Relative rates of chromic acid oxidation of cyclohexanols

may appear that the ease with which the carbinol hydrogen* is abstracted by the solvent (H_2O) or by chromate oxygen should determine (see Figure 12.32) the

Figure 12.32 Mechanism of chromic acid oxidation

rate, i.e., the axial alcohols are more readily oxidised because the equatorial carbinol hydrogen is more easily accessible. That this contention is wrong is proved by the fact that cholestan-4α-ol in which 4β-H suffers from a synaxial interaction with 10-Me (see structure LXXVI, Figure 12.33) is oxidised twice as



(LXXXVI)

Position of OH (e/a)	Relative rate
3β-ol (e)	1.0
3α-ol (a)	3.0
6α-ol (e)	2.0
6β-ol (a)	36.0
11α-ol (e)*	14.0
11β-ol (a)*	> 900

*Pregnane derivatives

Figure 12.33 Relative rates of oxidation of steroidal alcohols

fast as cholestan-3β-ol. Experiments with the steroidal alcohols show that when either or both of the OH and the carbinol H are sterically hindered, the reactivity increases (for further examples, see Eliel et al 1965). It suggests that the relief of steric strain in the transition state in going from the chromate ester to the ketone is responsible for the fact. The difference in free energies between the axial and equatorial chromate esters in the ground state exceeds that between the respective transition states due to the more ketone-like structure of the latter. Thus it is a typical case of steric assistance and the energetics correspond to the diagram in Figure 12.12b.

The relative rates of chromic acid oxidation of a few chosen steroidal alcohols are given in Figure 12.33. When a hydroxyl group is too much hindered sterically as in 3,28-diacetoxy-6β-hydroxy-18β-olean-12-ene (the part structure is similar to LXXXVI with a gem-dimethyl group at C-4 and an axial Me at C-8 so that 6-β-OH is subjected to three synaxial interactions), the rate of esterification becomes slower and the rate of oxidation much faster. In such a case, esterification is the rate determining step (as evidenced by the absence of a deuterium isotope effect) and the order of reactivity is reversed.

12.4.7 Neighbouring group participation

If a substrate of an S_N reaction happens to contain a nucleophilic group

*Carbinol H refers to the one attached to the hydroxylated C.

appropriately positioned, it often participates in the reaction by removing the leaving group through an intramolecular S_N2 mechanism and giving a cyclic intermediate. The latter then reacts with the external nucleophile (or solvent) by another S_N2 process and the internal nucleophile returns to its original position,* the net result being a nucleophilic substitution in two steps as shown in Figure 12.34. This is called neighbouring group participation which is associated with two

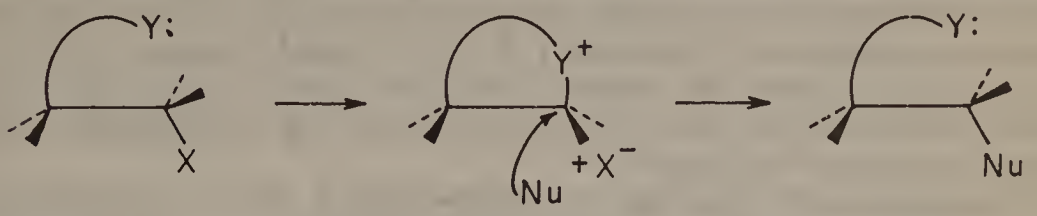


Figure 12.34 Neighbouring group participation

distinctive features: (*i*) an enhancement of rate (at least by a factor of 10, usually much more) which is known as anchimeric (synartetic) assistance and (*ii*) retention of configuration at the reacting carbon if it happens to be a chiral centre (this is a result of two consecutive inversions). Such participation is particularly favourable when the intermediate in the first step forms a 3- or a 5-membered ring and least so when it forms a 4-membered ring (see Capon and McManus 1976 for a review). The participating species may be a group with a lone pair, the π-electrons of a double bond, or even the σ electrons of a single bond. Since the participating group must have definite geometric orientation with respect to the leaving group, conformation plays an important role in neighbouring group participation.

1. Participation of an internal nucleophile. A classic example of neighbouring group participation in a cyclic system is the acetolysis of 2-acetoxycyclohexyl tosylate, both the (LXXXVII) and the trans (LXXXVIII) isomers (Figure 12.35) of

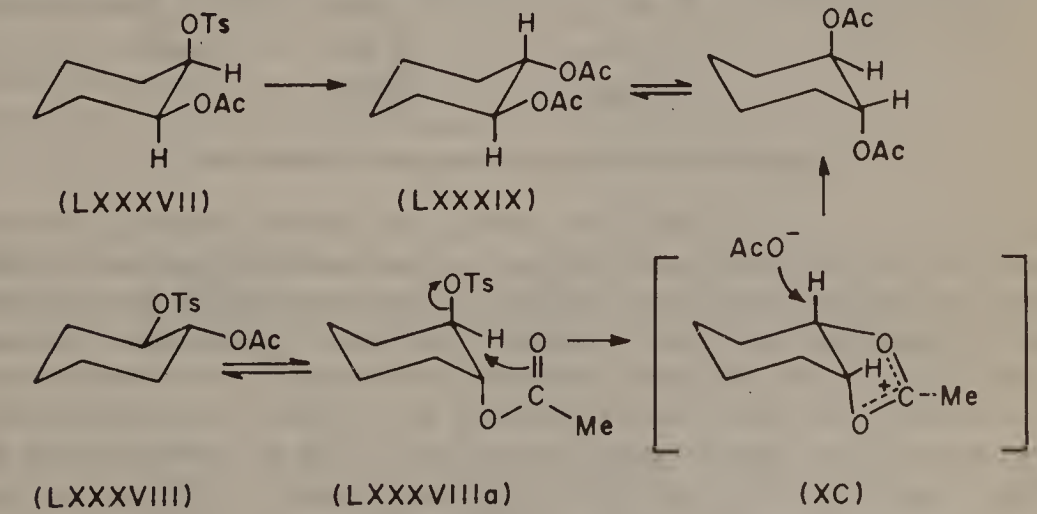


Figure 12.35 Neighbouring group participation in *trans*-2-acetoxycyclohexyl tosylate

*If the internal nucleophile does not return to its original position, molecular rearrangements occur (see the next section).

which give *trans*-1,2-diacetoxycyclohexane (LXXXIX) the former by direct S_N2 reaction and the latter through neighbouring group participation. In the diaxial conformer (LXXXVIIIa) of the trans isomer, the acetoxy group is suitably disposed to remove the tosyl group by an intramolecular S_N2 reaction to give an intermediate acetoxonium ion (XC) with cis fused 6,5-rings. This exists as a rapidly interconvertible enantiomeric pair (cf. *cis*-hydrindane) and a nucleophilic attack by acetate ion at either ring junction gives the trans diacetate. Thus if an optically active trans isomer (LXXXVIII) is used, a racemic mixture of the diacetate is formed. The reactivity of the *trans isomer* is almost 700 times greater than that of the *cis isomer* despite the very low concentration of the reactive conformer in the former.

2. Participation of π-electrons of a double bond. A pair of π-electrons of a double bond can help in removing a leaving group if suitably oriented. The relative rates of acetolysis of the three norbornane derivatives (XCI), (XCII), and (XCIII) are shown in Figure 12.36. The anti tosylate (XCII) reacts 10^{11} times faster than

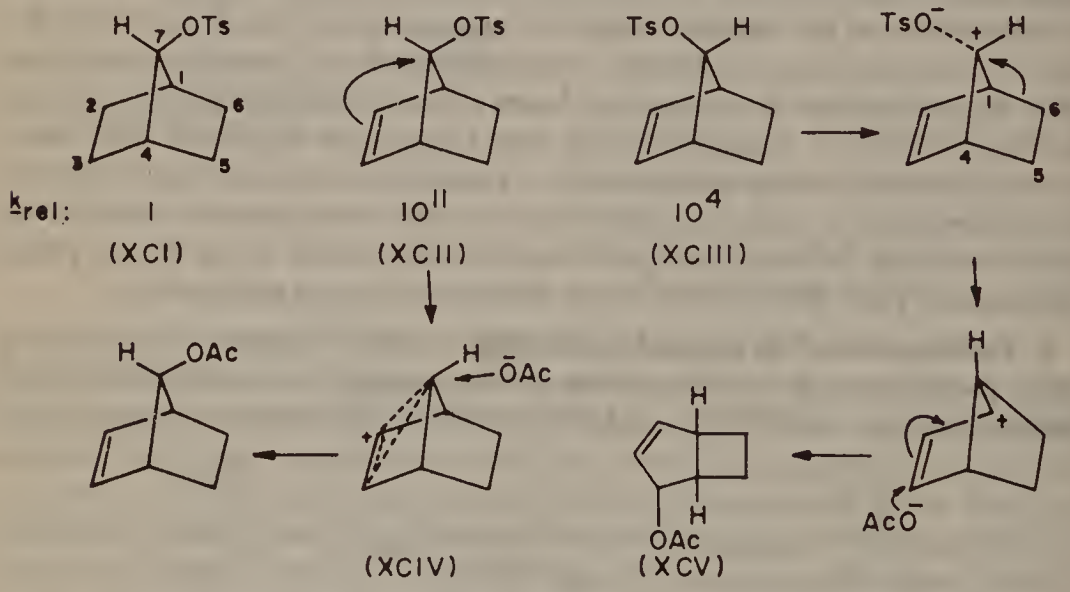


Figure 12.36 Participation of π-electrons of a double bond

the reference norbornyl tosylate (XCI) which proves that the removal of the tosyl group (the rate determining step) is subject to strong anchimeric assistance by the double bond and the resulting non-classical carbonium ion (XCIV) can react only from the right hand side giving an acetate with retained configuration. The syn isomer (XCIII), on the other hand, dissociates (without anchimeric assistance) into a homoallylic carbocation which rearranges to an allylic one and the latter subsequently leads to the bicyclic acetate (XCV). The 10^4 times reactivity of XCIII compared to XCI is probably due to participation of σ electrons of two allylic 1-6 and 4-5 bonds (see the upper right hand structure).

The π-electrons of an aromatic ring also participate under suitable conditions and form intermediate phenonium ions which will be discussed in the next Section.

3. Participation of a σ bond electrons. Participation of an electron pair of a σ bond particularly in bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane systems in

helping to remove a leaving group with anchimeric assistance has already been discussed in Chapter 11.

12.4.8 **Molecular rearrangement**

Molecular rearrangement is a very common occurrence in organic chemistry and literature is replete with examples of various types (P.de Mayo 1963). The discussion here is confined to those rearrangements which lead to ring contraction and ring expansion. The requirements are the presence of a carbon atom (C_α) with a leaving group (the migration terminus), a migrating group (in this case, a part of the ring) at C_β (the migration origin), and preferably an electron-donating substituent at C_β, e.g., OH which would help to detach the migrating group (as in XCVIa). If C_α is outside the ring, a ring expansion occurs, if it is inside the ring, a ring contraction occurs, and if C_α and C_β belong to two rings, both a ring contraction and a ring expansion occur. The process may be concerted (as is very often the case) or it may be non-concerted, i.e., the carbocation (at C_α) is first formed followed by 1,2-shift of the migrating group. The migrating group, if chiral, retains its configuration, the migration terminus undergoes inversion (the rearrangement being an S_N2 process) to an extent depending on the degree of concertedness, and the migration origin if it remains tetrahedral undergoes inversion. As in neighbouring group participation, the migrating group and the leaving group must be antiperiplanar (or approximately so) although in non-concerted molecular rearrangements, this requirement is not stringent. Three examples are given which show that the results of such rearrangements depend very much on the conformation of the substrate.

1. Deamination of 2-aminocyclohexanol. Deamination with nitrous acid usually gives rise to a very reactive (*hot*) carbocation and any rearrangement associated with it is facile. In such cases, the activation energy may be comparable to that for conformational inversion and the ground state population of conformers may control the product ratio (contrary to the Curtin-Hammett principle). *cis*-2-Aminocyclohexanol exists in two conformations (XCVIa) and (XCVIb) (Figure 12.37). In the first, e-NH_2 is anti to an endocyclic bond (1-6) and its deamination

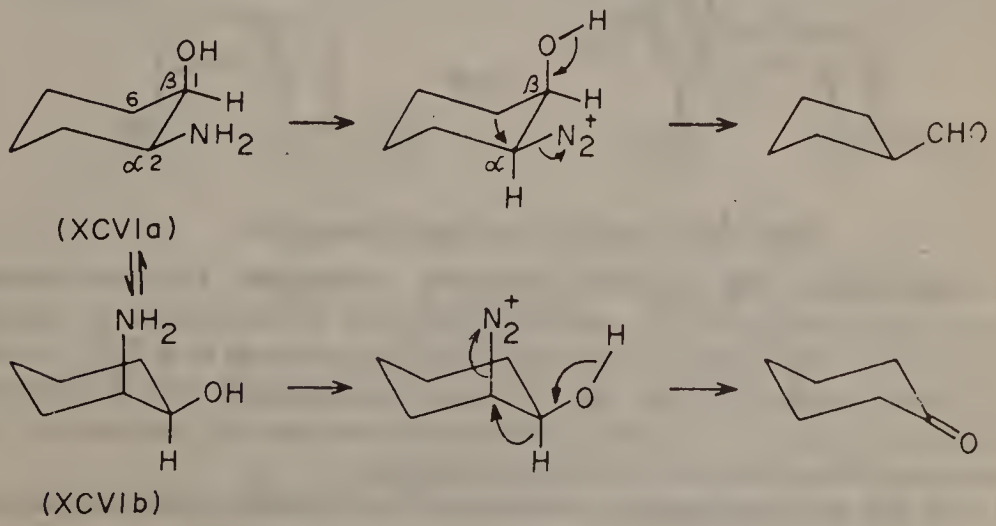


Figure 12.37 Deamination of *cis*-2-aminocyclohexanol

accordingly gives cyclopentanecarboxaldehyde—a product of ring contraction. The second conformer has the NH_2 group antiperiplanar to the carbinol H which undergoes a 1,2-hydride shift, the process being assisted by the concomitant movement of the O-H σ electron pair. The product is cyclohexanone. In the trans isomer, the conformer (XCVIIa) (Figure 12.38) has the NH_2 group anti to the 1-6 bond (as in XCVIa) and so a ring contraction results. The diaxial conformer

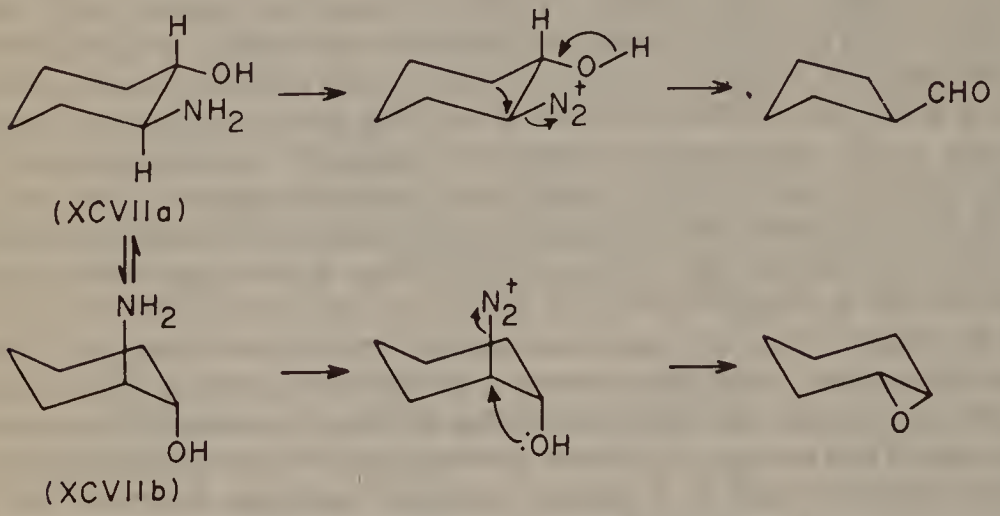


Figure 12.38 Deamination of *trans*-2-aminocyclohexanol

(XCVIIb) is not expected to have any appreciable population and the anticipated epoxide is not detected. If a *t*-butyl group is attached at C-4, all the four structures would be rigid and non-interconvertible and for each of them, only a single product, i.e., cyclopentanecarboxaldehyde, cyclohexanone, or epoxide is obtained (Cherest et al 1965) depending on which atom or bond is antiperiplanar to the C-N bond. Woodward's synthesis of a prostaglandin intermediate is an elegant application of this rearrangement (1973) (Figure 12.39).

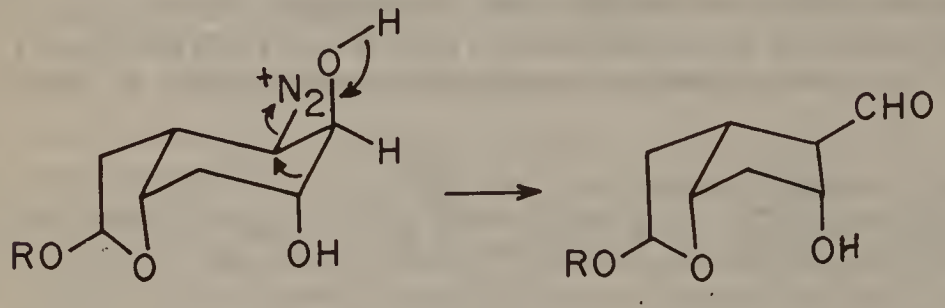


Figure 12.39 Synthesis of a prostaglandin intermediate

2. Concomitant ring expansion and ring contraction. The two epimeric tricyclic chloronitriles (XCVIII) and (XCIX) (Figure 12.40) provide an example of a concerted ring expansion and ring contraction (Yamada et al 1977). As the C-Cl bond is broken by Ag^+, the C-C bond antiperiplanar with it undergoes 1,2-shift assisted by the movement of the oxygen lone pair of OMe and the two epimers give two products (C) and (CI) respectively.

3. A double rearrangement. In certain cases, two successive rearrangements may take place. Deamination of *syn*- and *anti*-2-bornenyl-7-carbinyl amines (CII) and

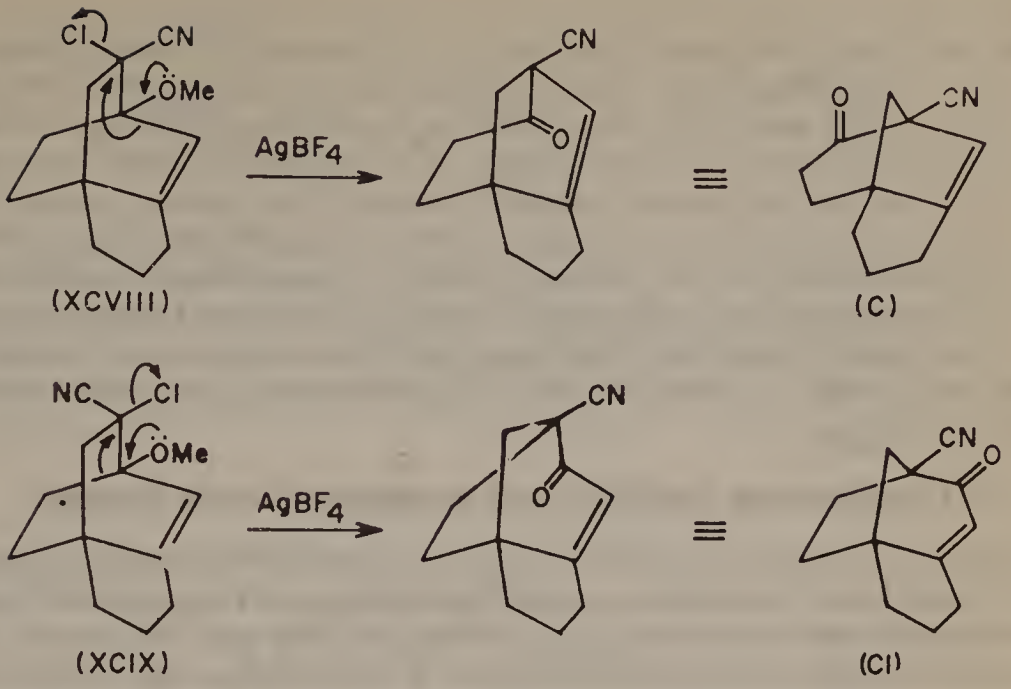


Figure 12.40 Concomitant ring expansion and ring contraction (reconstructed with permission from Deslogchamps, *Stereoelectronic effects in organic chemistry*, Pergamin Press, 1983).

(CIII) (Figure 12.41) appears to give the same rearranged carbocation shown as ion pairs (CIV) and (CIVa) (the double bond is not properly positioned to participate in the formation of the carbocation). This can undergo two reactions: (*a*) a second 1,2-shift with concomitant solvolysis to give the bicyclic allylic alcohol (CV) and (*b*) participation of the π-electrons to form a σ bond giving the tricyclic saturated alcohol (CVI). Surprisingly, the product ratio depends on the

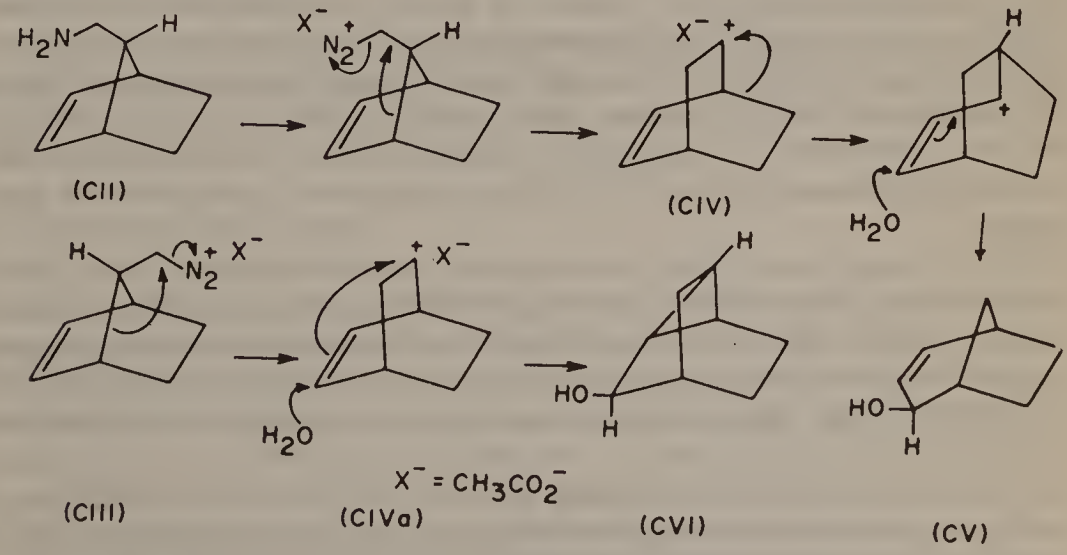


Figure 12.41 Double rearrangement: a memory effect

stereochemistry of the starting amines, the syn isomer (CII) giving more of CV and the anti isomer (CIII) giving more of CVI—a phenomenon known as *memory effect* (Berson 1968; Collins 1975). Evidently, the two carbocations (CIV) and (CIVa) are not exactly equivalent: either as proposed by Collins (and perhaps more plausibly), they exist as two ion pairs (X^- in the Figure is acetate ion) so that the syn and the anti sides are unequally blocked by the counter anions, or as proposed by Berson, they are twisted in such a fashion that in CIV, the cationic centre leans towards the anti direction favouring a σ bond migration and in CIVa, it leans towards the syn side favouring the attack by π-electrons. These explanations are based on the assumption of carbonium ion intermediates and are not valid if the whole process is concerted in which case stereoelectronic factors might account for the difference.

12.5 Conformation, reactivity, and mechanism: acyclic systems

Except for atropisomers, acyclic molecules have relatively free rotation around a C-C single bond. As a result, one or more conformations of a molecule may satisfy the stereoelectronic requirements of a reaction and more than one product may result (Curtin-Hammett system). For a pair of diastereomers, one conformer in each may satisfy the stereoelectronic requirements in which case the reactivities have to be compared between those conformers only. A few reactions are reported to illustrate the conformation-reactivity relationship in acyclic systems.

12.5.1 Addition reactions

The difference in stereochemical behaviour of two diastereomeric substrates towards addition reactions is illustrated with two examples: bromination (anti addition) and *bis*-hydroxylation (syn addition) of maleic and fumaric acid (Figure 12.42). To take the bromination case first, maleic acid has two homotopic faces and so a single achiral bromonium ion intermediate (A) (Figure 12.42a) is formed. The two anti approaches of Br (shown by arrows) are enantiomeric and so are equally probable giving (±)-dibromosuccinic acid. In contrast, the two faces of fumaric acid are enantiotopic and so addition of Br^+ gives chiral bromonium ion in two enantiomeric forms (C and its mirror image, C′) (Figure 12.42b). The two anti approaches of Br are related by a C_2 axis and so give a single product, in this case *meso*-dibromosuccinic acid. The other intermediate C′ also gives the meso product*.

The *bis*-hydroxylation (with permanganate) follows a different steric course because of syn addition. The cyclic intermediate from maleic acid (B) is achiral having a σ plane and since it directly leads to the product, the resulting tartaric acid must also be achiral, i.e., meso. On the other hand, fumaric acid leads to two enantiomeric cyclic intermediates (D and D′) in equal amounts and since the

*The formation of the meso product is due to the fact that the intermediates (C and C′) also contain a Br atom. If the attacking nucleophile is other than Br^-, e.g., MeO^-, the two intermediates (C and C′) would give opposite enantiomers (a chiral intermediate is expected to give a chiral product) and the product would be a racemic mixture. For further clarification, see neighbouring group participation in 3-bromo-2-butanol.

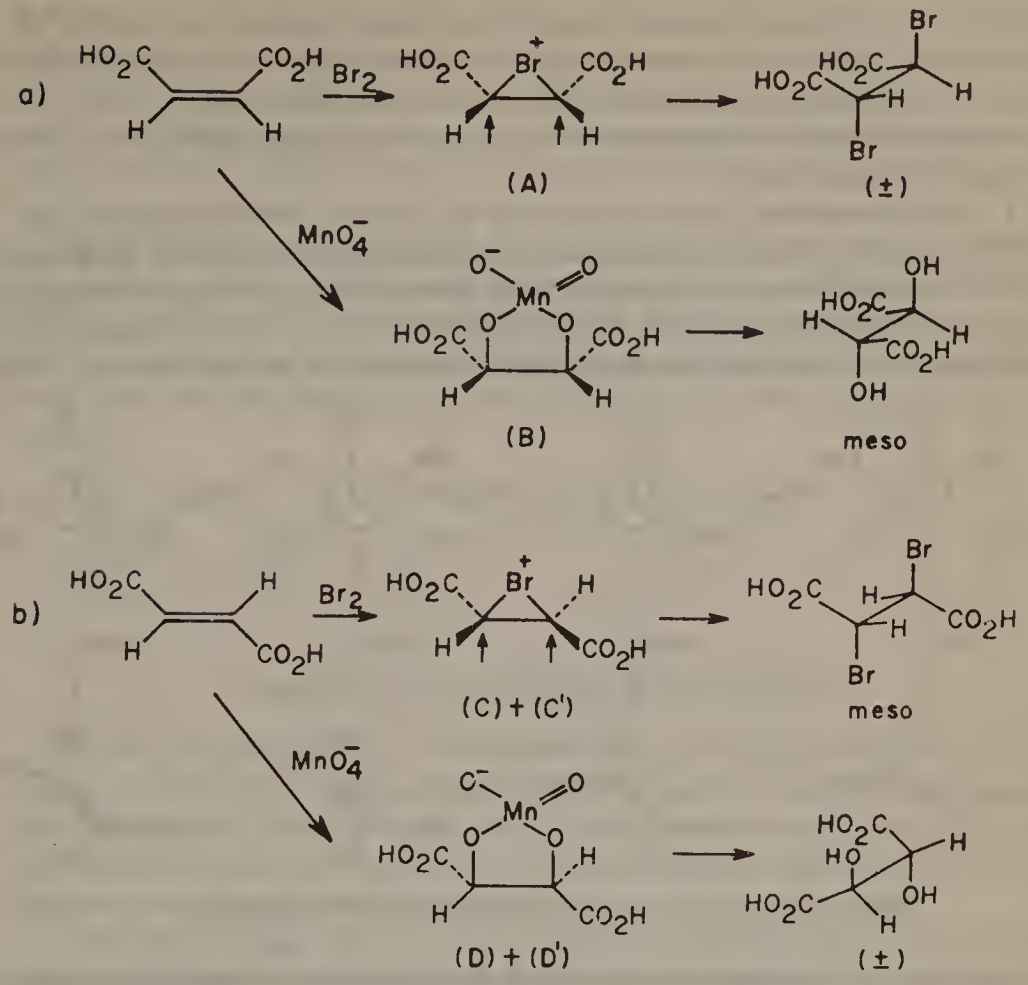


Figure 12.42 Bromination and *bis*-hydroxylation of maleic and fumaric acid (C′ is the mirror image of C and D′ of D; only one of each enantiomeric pair is shown)

stereochemistry is maintained in the product, the resultant tartaric acid is a racemic mixture of two optically active forms. These two examples, however, are not relevant to conformation-reactivity relationship.

12.5.2 Elimination reactions

In acyclic system, anti elimination is preferred particularly with good leaving groups such as Cl and OTs but syn elimination is not uncommon and may be the preferred mode with bulky and poor leaving groups such as onium. Interestingly, syn elimination gives predominantly the trans olefins while the cis olifins are obtained exclusively through anti elimination (syn-anti dichotomy). Finally, there is the problem of orientation of the double bond which is governed by two rules: the Hofmann rule and the Saytzeff rule, the former predicting the formation of the least substituted olefins from onium salts and the latter predicting the most substituted olefins from halides. This dichotomous situation may be rationalised from a knowledge of the position of the transition state in the mechanistic

continuum previously discussed which can predict whether the acidity of the eliminating proton or the relative stability of the olefins is the controlling factor. This is not, however, relevant to the present discussion and is better left for textbooks on reaction mechanisms. Only the stereochemical aspects of E2 eliminations are discussed below.

1. Anti elimination. The anti mode of E2 elimination in the system, e.g., R-CHX-CH_2-R (X = Cl or Br) has been proved by dehydrobromination of deuterated 2-bromobutane. The pure erythro isomer of 2-bromobutane-3-*d* may be represented in four conformations in which H or D is either syn or anti to Br. These are shown in Figure 12.43, the first two giving *trans*-2-butene and the last two *cis*-2-butene

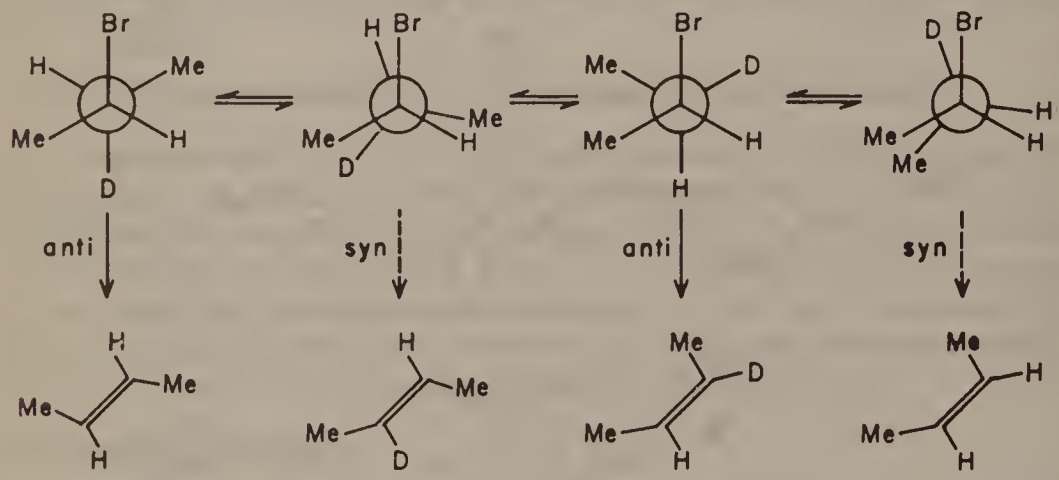


Figure 12.43 Anti and syn elimination in *erythro*-2-bromobutane-3*d*

by anti and syn eliminations as shown. It is seen that anti elimination would give undeuterated *trans*-butene and deuterated *cis*-butene which is actually the case (Bartsch 1971; see also Sicher 1972). Syn elimination would give opposite results and so is disproved.

A few examples of E2 elimination in acyclic system have already been given. One of the most common system studied is represented by the general formula, R-CH_2-CHX-R (CVII) with two diastereotopic geminal H's (cf. dehydration of malic acid) and either can be placed antiperiplanar with X (X = Br) as shown (Figure 12.44), giving trans olefin by removal of H_A and cis olefin by removal of H_B. The relative stability of the cis and trans olefins will be reflected in the

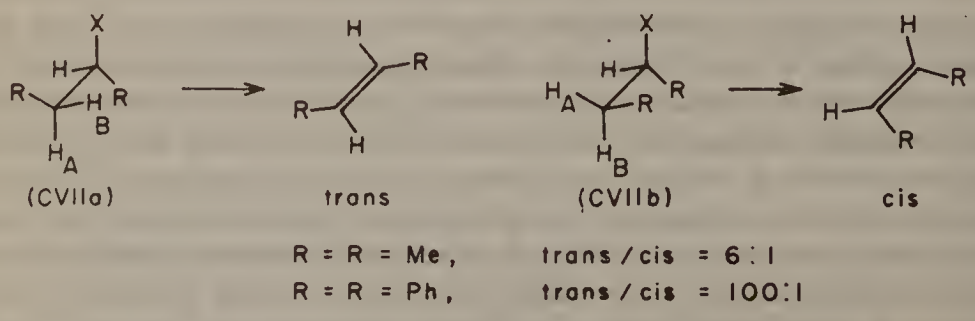


Figure 12.44 Anti elimination in diastereomeric RCH_2-CHX-R

respective transition states which in turn will control the product ratio (Curtin-Hammett principle). In accordance with this, the trans/cis ratio varies from 6:1 (when R = Me) to 100:1 (when R = Ph) due to what is known as *cis-effect* (purely steric in origin). The same ratio (100:1) is obtained when 1,2-diphenylethyl triethylbenzoate (CVII, R = Ph, X = triethylbenzoyloxy) is treated with potassium *t*-butoxide in *t*-butanol.

The 'cis-effect' due to eclipsing of two Ph groups is more dramatically shown in dehydrochlorination of the (±) and meso forms of stilbene dichloride (CVIII) and (CIX) (Figure 12.45). The former can easily attain the transition state (no cis-effect) and on heating with pyridine at 200°C gives the stable *trans*-chlorostilbene. In the latter, the 'cis-effect' is too severe in the transition state and no reaction takes place.

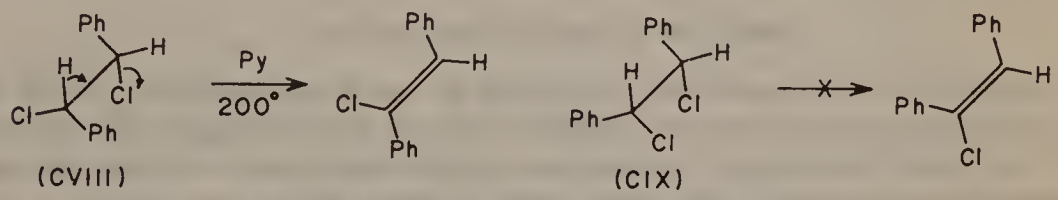


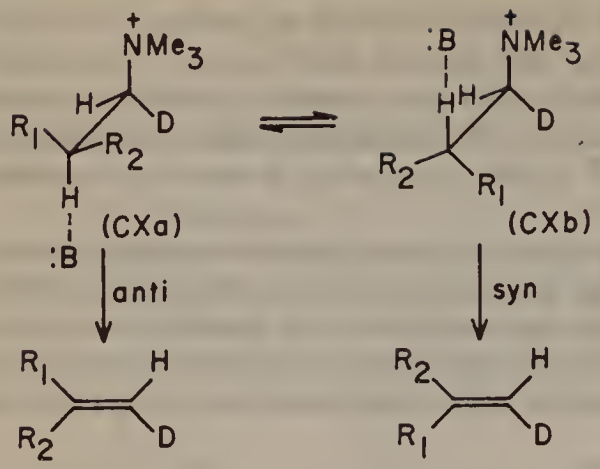
Figure 12.45 Dehydrochlorination of dichlorostilbenes

It is not necessary that a C-H bond be always involved in the elimination. It may be a Br atom as in iodide-induced debromination of vicinal dibromides (p. 342). The C-H bond may also be replaced by a C-M bond as in organometallics such as M-CHR-CHR-OH (M = HgI, Ph_3Pb, Ph_3Sn, and Ph_3Si). The elimination usually follows the anti mode and is quite facile.

2. Syn elimination. It has already been pointed out that the syn elimination may also compete with or even prevail over the anti elimination depending on the nature of the leaving group, the reagent, and the solvent. A poor leaving group (e.g., onium group), a strong base (bulky), and a poorly dissociating solvent favour the syn elimination. In cases where both the syn and anti eliminations take place with the formation of two diastereomeric products (e.g., cis and trans), it has been observed that the syn elimination leads predominantly to the trans product while the anti elimination leads mainly to the cis product. The phenomenon known as syn-anti dichotomy* has been rationalised on the basis of stereochemical arguments (Bailey and Saunders 1970, also Sicher 1972) which are not completely unambiguous. Since the syn elimination goes through an eclipsed transition state, the preferential formation of trans product (which minimises the cis-effect in the transition state) is understood.

The effect of steric factor in controlling the syn-anti modes of elimination has been demonstrated by Tao and Saunders (1983) using onium compounds, $R_1R_2CHCH_2N^+Me_3$ (Figure 12.46). Using HO^-/DMSO-H_2O at 80°, the syn elimination

*The syn-anti dichotomy can sometimes be used with practical advantage in effecting stereoselective synthesis. Thus dehydrochlorination of chlorocyclodecane by potassium *t*-butoxide in dimethyl sulphoxide gives 97% of *cis*-cyclodecene (via anti elimination) while dehydrochlorination by lithium dicyclohexyl amide (strong and bulky base) in hexane (non-polar solvent) gives 96% of *trans*-cyclodecene (via syn elimination). (Traynham et al 1967).



R_1	R_2	% syn
Ph	Pr^i	68.5
Ph	Me	26.5
Bu^n	D	<5.0

Figure 12.46 Competitive syn-anti elimination

is predominant (see the attached Table) when R_1 and R_2 are both bulky. If both or either of them are small, the anti elimination prevails. Apparently the conformations (CXa) and (CXb) represent the transition states (reactant-like) for the anti and syn eliminations respectively. The former with the bulky NMe_3 group gauche to R_1 and R_2 becomes gradually destabilised with respect to the latter as R_1 and R_2 increase in bulk (see Lowry and Richardson 1987).

3. Stereoconvergent elimination. There are a few examples in which both diastereomers on elimination give the same product and at approximately the same rate. This is suggestive of a common intermediate, the formation of which is the rate determining step. Thus the threo and erythro isomers of (1,2-diphenylpropyl) trimethylammonium salt (Figure 12.47) react with *t*-butoxide in *t*-butanol to give *trans*-1-methylstilbene. Apparently, the β-H is first eliminated to give a carbanion (ElcB mechanism) which can undergo rapid isomerisation at α-C followed by elimination to the more stable *trans*-1-methylstilbene (see Sicher 1972).

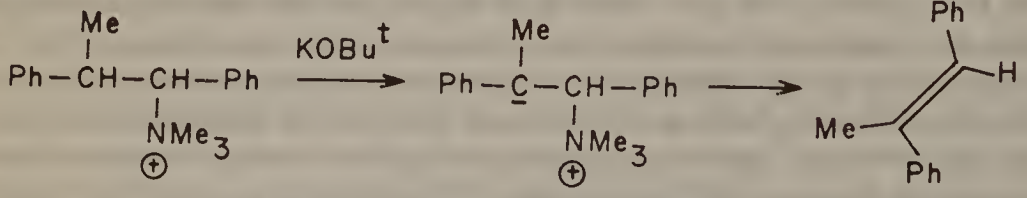


Figure 12.47 Stereoconvergent elimination

12.5.3 Neighbouring group participation and molecular rearrangements

Because of high conformational flexibility in acyclic molecules, if one member of a pair of diastereomers (with two chiral centres) undergoes neighbouring group participation, the other also does so (for exception, see N→O migration in norephedrines). Since neighbouring group participation and molecular rearrangement are subject to the same stereoelectronic control, the two processes often go together and sometimes cannot even be distinguished if the two chiral centres bear identical pairs of non-reacting ligands as in RCHZ-CHXR (Z and X are partici-

pating and leaving groups respectively). A few examples are discussed in which pairs of diastereomers undergo both neighbouring group participation and molecular rearrangement.

1. Participation of a lone pair of electrons. Bromination of 3-bromo-2-butanol with HBr provides a classical example of neighbouring group participation with a lone pair of electrons. The OH group is protonated and then removed by the backside attack of bromine forming bromonium ion intermediates. The one (E) from the threo isomer (Figure 12.48a) is achiral with C-2 and C-3 enantiotopically related so that subsequent nucleophilic attack by Br^- gives a racemic mixture of 2,3-dibromobutane. The other (F) from the erythro isomer (Figure 12.48b) is

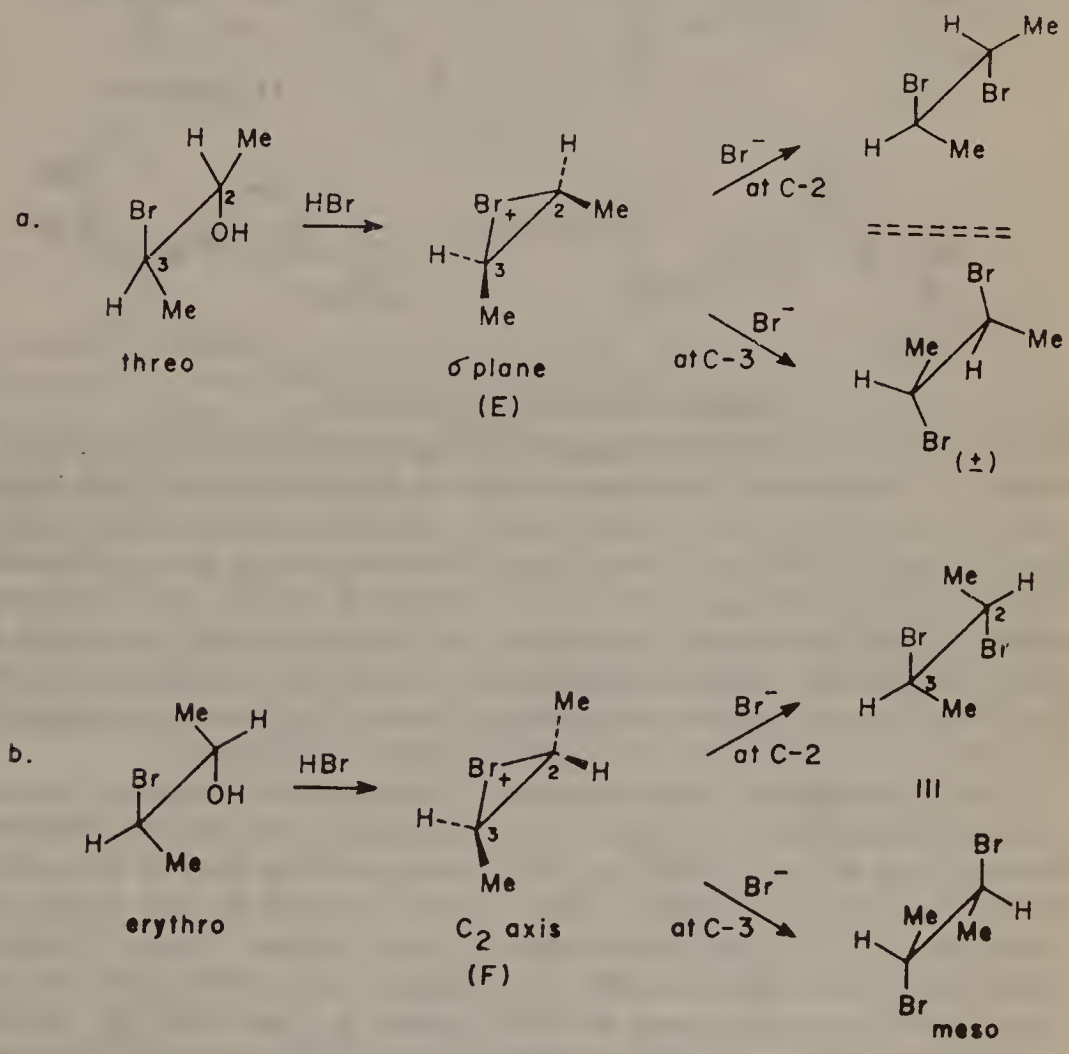


Figure 12.48 Participation of bromonium ion

chiral but C-2 and C-3 are related by a C_2 axis so that subsequent nucleophilic attack by Br^- gives the identical product, *meso*-2,3-dibromobutane (cf. bromination of maleic and fumaric acids). Although on account of symmetry, no distinction can be made between C-2 and C-3, attack on C-2 may formally be considered a neighbouring group participation while reaction at C-3 is formally a molecular rearrangement (Br migrates from C-3 to C-2). In the former, configurations at the chiral centres are retained—a characteristic of neighbouring group participation—

but in the latter, configurations at both the chiral centres are inverted—a characteristic of molecular rearrangement although in the present example, the two processes are chemically and stereochemically equivalent. It may be noted that the optically active forms of threo-bromohydrin also give the racemic mixture of the active dibromide, since the reaction proceeds via an achiral intermediate.

Acetolysis of 3-methoxy-2-bromobutane (Figure 12.49) in the presence of silver acetate in acetic acid follows the same pattern with some difference. The oxonium

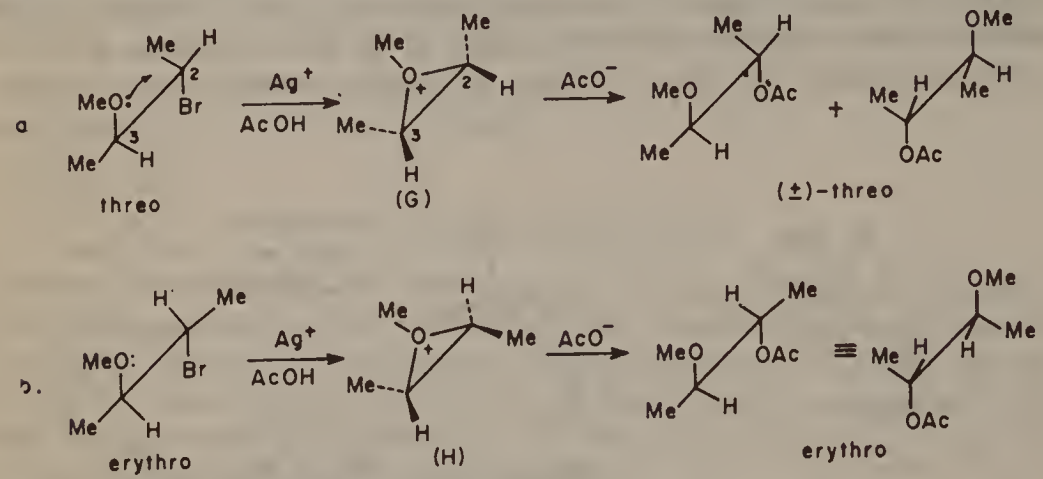


Figure 12.49 Participation of oxonium ion

ion (G) from the threo isomer is achiral and that (H) from the erythro isomer is chiral. The former gives a racemic mixture of *threo*-3-methoxy-2-butyl acetate while the latter gives a single erythro isomer. However, in this case the erythro product is chiral (it has two non-equivalent chiral centres) and its stereochemistry follows from that of the starting material. If the latter is optically pure, the product will be optically pure and if it is racemic, the product will also be racemic. As before, neighbouring group participation and molecular rearrangement go side by side (50:50) and their stereochemical effects (retention and inversion respectively) are evident in the pairs of product structures given for each reaction.

2. Aryl participation : phenonium ion. The concept of phenonium ion as a reaction intermediate (in the same way as bromonium ion) was first originated from the work of Cram (1949)* and later placed on a firm basis by the work of Winstein, Schleyer, and Brown (who at first contested it) (see Lowry and Richardson 1987). (2*S*,3*S*)-*threo*-3-Phenyl-2-butyl tosylate (Figure 12.50a) on solvolysis in acetic acid gives 96% of a racemic mixture of threo acetate (the remaining 4% is erythro isomer formed by direct S_N2 reaction). The (2*R*,3*S*)-erythro isomer (Figure 12.50b) on similar treatment gives only (2*R*,3*S*)-erythro-acetate. The results are explained on the basis of two phenonium intermediates, an achiral one (J) (with a σ plane) for the threo isomer and a chiral one (K) (with a C_2 axis) for the erythro isomer. The arguments are the same as those made for the solvolysis of 3-methoxy-2-bromobutane and need not be repeated.

From the nature of the two phenonium intermediates (J) and (K), it is expected that the threo isomer should react at a slower rate than the erythro (the presence of

*Nevel et al (see Cram 1956), however, first suggested this phenomenon (1939).

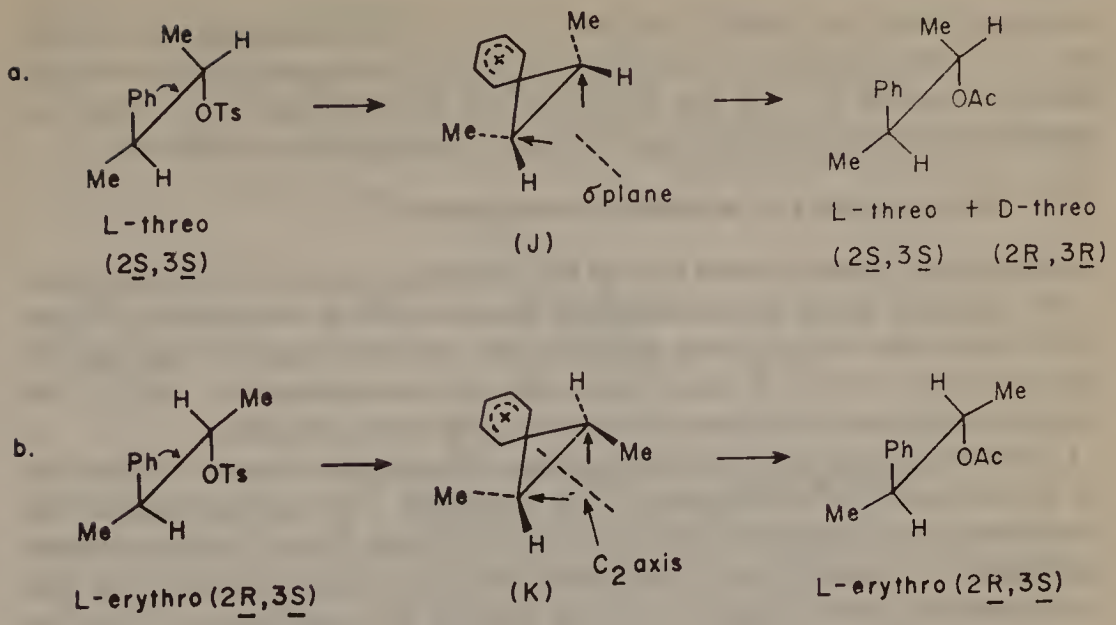


Figure 12.50 Participation of phenonium ion

cis-effect in J). However, the two react almost at the same rate. It is suggested that *the transition states leading to these phenonium ions would appear to be much nearer in geometry to the starting material than to bridged ion and the eclipsing of groups in going to the cis-bridged ion probably occurs after the transition state has been passed* (Cram 1956). No appreciable anchimeric assistance is observed. consistent with this hypothesis.

The results of solvolysis of the tosylates derived from 2-phenyl-3-pentanol and 3-phenyl-2-pentanol are also explained on the basis of phenyl participation (Eliel 1962, p. 148). Both erythro and threo isomers of these substrates give phenonium ion intermediates which are not only chiral but have C-2 and C-3 constitutionally heterotopic, e.g., L (Figure 12.51) derived from a threo isomer. As a consequence, any

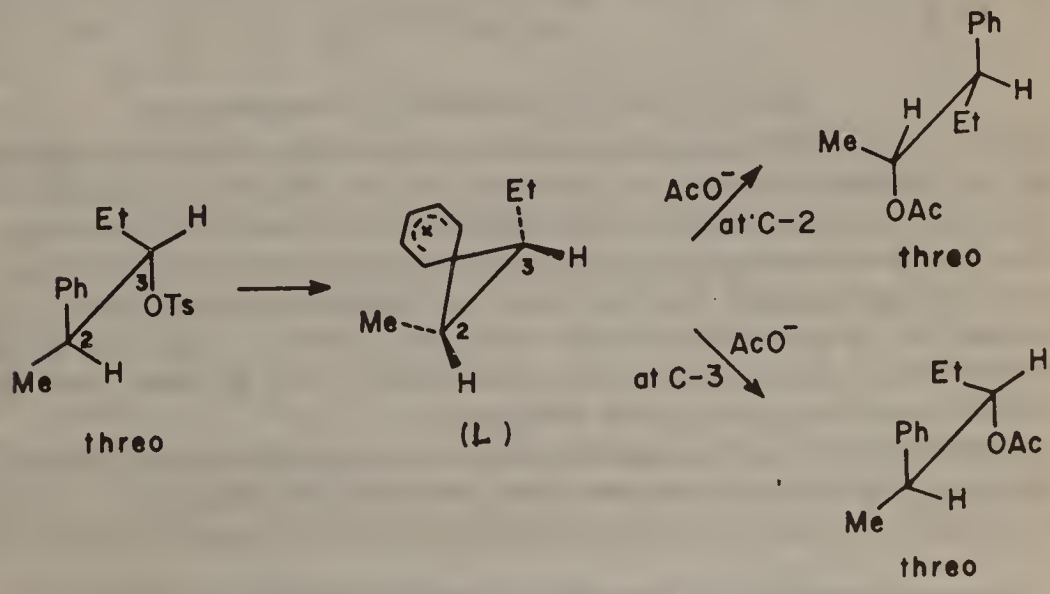


Figure 12.51 Acetolysis of *threo*-2-phenyl-3-pentyl tosylate

active threo or erythro isomer would give two active and constitutionally isomeric threo or erythro products as shown for one of the threo isomers in Figure 12.51. Moreover, attacks at C-2 and C-3 may not be equal and the extents of neighbouring group participation and molecular rearrangement are different.

12.5.4 Stereochemistry of molecular rearrangement

Reorganisation of bonding takes place at three centres in a molecular rearrangement: at the migrating group, at the migration terminus, and at the migration origin. Acyclic molecules of appropriate structures can provide information regarding the stereochemistry at each of these points after the rearrangement is over. A few illustrations are given to elucidate the following stereochemical points.

1. Stereochemistry in the migrating group. All available evidence indicates that the stereochemistry of the migrating group is retained. This is also consistent with the molecular orbital theory according to which the same lobe of molecular orbital that binds the migrating group to the migration origin also participates in the new bond formation. Three examples are given to prove the point (Figure 12.52). The

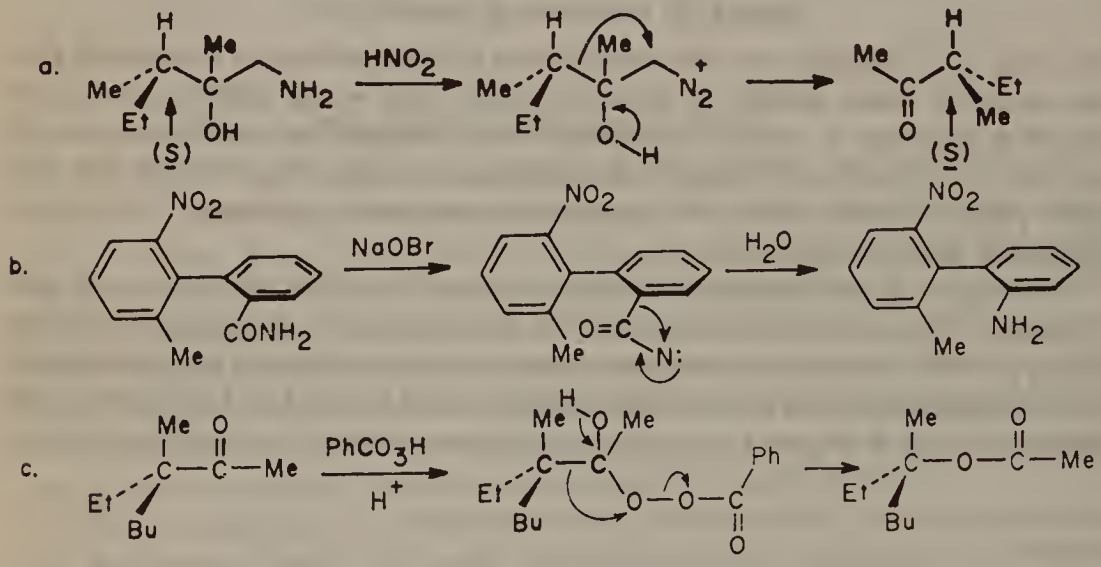


Figure 12.52 Retention of configuration in the migrating group

first one (*a*) is a semi-pinacol rearrangement in which a chiral alkyl group migrates from one carbon to another, the second one (*b*) is a Hofmann degradation in which an atropisomeric biphenyl group migrates from a carbon atom to a nitrogen atom (retention of configuration here proves conclusively that the amide carbon is never completely detached from the phenyl ring during the rearrangement)*, and the third one (*c*) is a Baeyer-Villiger oxidation in which a chiral alkyl group migrates from a carbon atom to an oxygen atom. In all the three cases, the configuration of the migrating group is retained.

2. Stereochemistry at the migration origin. If the migration origin is chiral and remains so after rearrangement and if the migration and attachment of a new nucleophile at the migration origin are concerted, there ought to be inversion at the

*It is immaterial if the nitrene is not an intermediate (which is controversial) as long as the migration of the aryl group is concerted with the removal of Br^- from -N-Br.

migration origin. An example is found in the solvolysis of the tosylate of *R*-3-methyl-2-phenylbutan-1-ol (Figure 12.53) (Kirmse and Gunther 1978). The expected major product, 3-methyl-1-phenylbutan-2-ol arising from 1,2-phenyl shift (through a phenonium ion) shows an inversion of configuration at the migration origin. However, in the majority of cases a substantial amount of racemisation occurs at the migration origin.

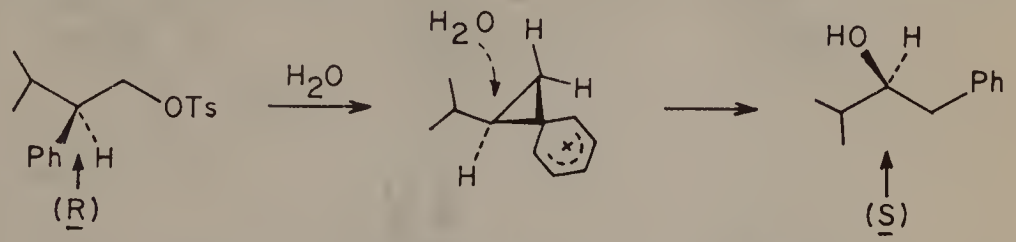


Figure 12.53 Inversion of configuration at the migration origin

3. Stereochemistry at migration terminus. An inversion of configuration is clearly expected at the migration terminus since the migrating group approaches from the side opposite to the leaving group (an S_N2 process). This has been amply demonstrated in molecular rearrangements discussed in the previous subsection in connection with neighbouring group participation.

However, there are two extreme cases in which inversion at the migration terminus may be accompanied with varying degrees of retention: (*i*) If the leaving group is removed before the migration starts giving rise to a very reactive carbocation (which often happens in deamination of amines), the migrating group migrates from whatever position it occupies in the most stable ground state conformation of the substrate and inversion, retention, or both may follow. (*ii*) In the other extreme, if the carbocation so formed is very stable, say through resonance, there would be enough time for the C_α-C_β bond to rotate and to form more than one transition states, the relative stabilities of which would determine the stereochemistry of the migration terminus. The first point is illustrated by the deamination of optically active 1-phenyl-1-phenyl-C^{14}-2-amino-1-propanol (CXI) (Figure 12.54a). The experimental results show that about 90% of the product is $Ph^*CHMeCOPh$ arising out of Ph^* migration accompanied with inversion and 10% is $PhCHMeCOPh^*$ arising out of Ph migration accompanied with retention.† An explanation is given on the basis that the ground state of the molecule is almost entirely populated by the conformer (CXIb) in which the two bulky Ph groups have an H atom in between. The other two conformers (CXIa) and (CXIc) have Me and NH_2 respectively separating the two Ph groups. The intermediate nitronium ion (M) undergoes a rapid elimination of N_2 and the reactive carbocation so formed immediately collapses with concomitant anti migration of Ph^* and syn migration of Ph, the former being preferred. This provides a unique case where a single conformer gives rise to two products.

An example of the other extreme is provided by deamination of *threo*-1-amino-1-phenyl-2-(4-methylphenyl)-2-propanol (Figure 12.54b) (see Lowry and Richardson 1987). Two intermediates could be written involving tolyl participation, one with Ph and Me trans and the other with Ph and Me cis. The former is prefe.red

†For retention and inversion, Me, H sequence (clockwise or anticlockwise) should be compared.

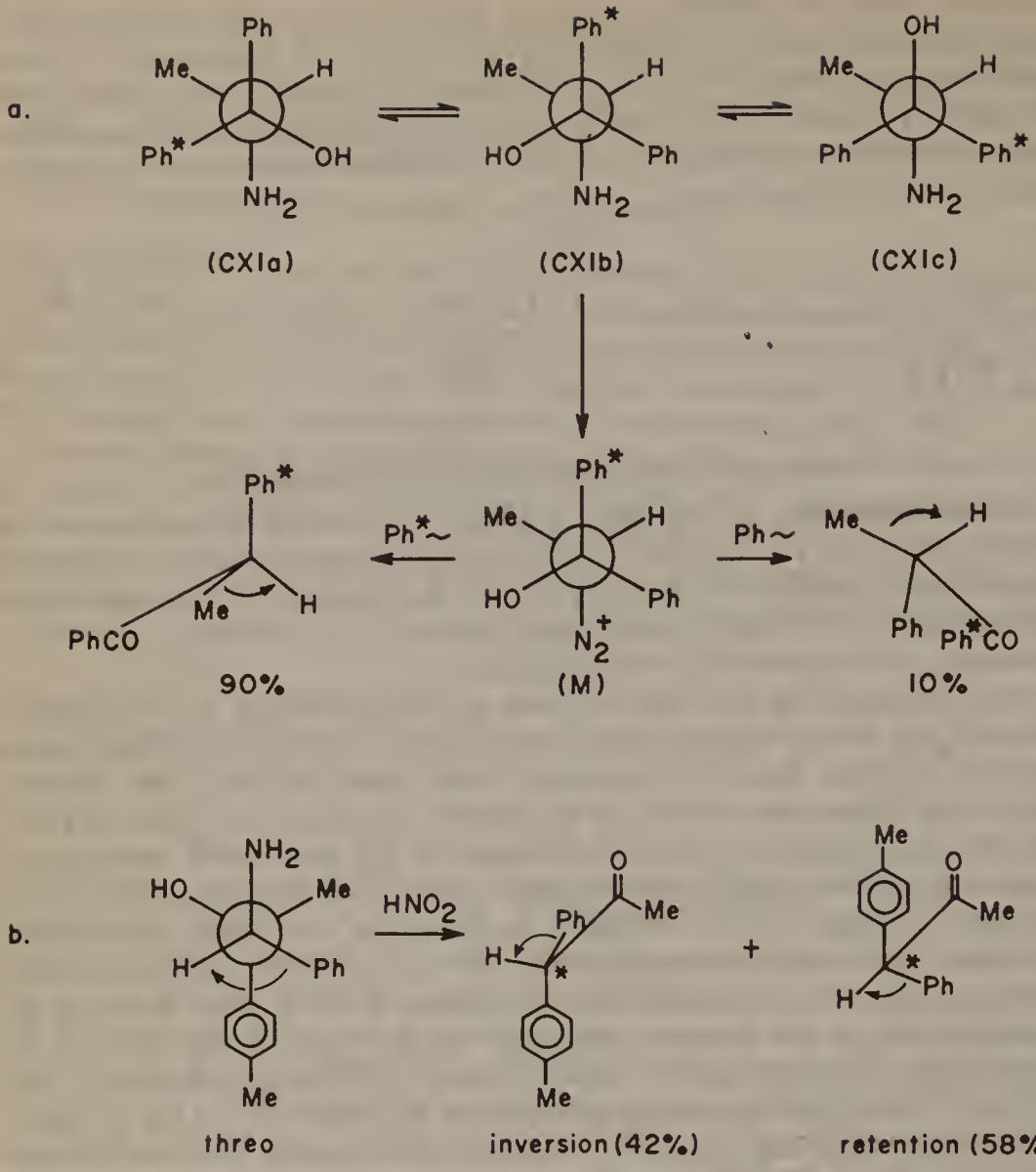


Figure 12.54 Deamination of 2-amino-alcohols

and leads to retention of configuration while the latter is unfavoured and gives inversion (the ratio of retention to inversion is 58:42). The configuration at C-1 is known by the Ph→H direction (clockwise or anticlockwise as shown.).

12.6 Conformational atropisomers and reactivity

For some time in the past, a few conformational isomers have been isolated in diastereomeric forms, their stability being due to restricted rotation about one or more single bonds (atropisomerism). Although these molecules contain one or more rings, the functional group is located in the acyclic part and they may be considered as the counterparts of rigid and anancomeric cyclohexane systems previously discussed. 9-Arylfluorene derivatives in which the aryl group is either 2,6-disubstituted phenyl or 2-substituted 1-naphthyl have high rotational barrier

(> 100 kJ mol^{-1}) about the single bond joining the two rings and provide such examples. Thus in 9-(2,6-dimethylphenyl)fluorene (CXII) (Figure 12.55), the two Me groups cannot interchange their positions because of restricted rotation and so are distinguishable (diastereotopic). One side of the upper Me group (joined by a thick line) is effectively blocked by the fluorene ring; in comparison, the lower Me

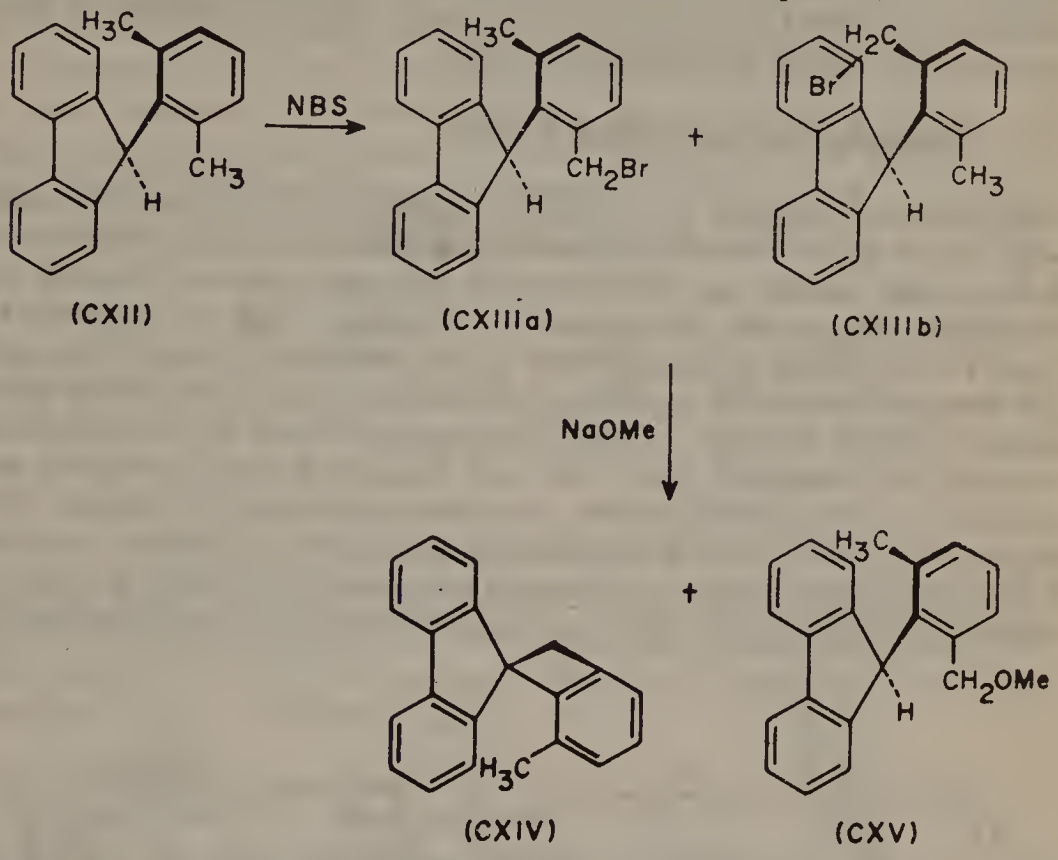


Figure 12.55 Configurational diastereomers and reactivity in 9-arylfluorenes

group is unhindered. They may be termed *ap*-Me (antiperiplanar with 9-H) and *sp*-Me (synperiplanar with 9-H) respectively. When the compound is brominated with N-bromosuccinimide under kinetic control, the less hindered *sp*-Me is brominated at a faster rate than the *ap*-Me giving predominantly the *sp*-isomer (CXIIIa), the ratio of CXIIIa and CXIIIb being 2.2:1 (see Oki 1984 for a review and for other references). Then again, the Br atom in CXIIIb is much more hindered than that in CXIIIa. An S_N2 reaction, therefore, takes place more slowly in CXIIIb than in CXIIIa. In fact, the dibromo compound (as CXII both Me groups replaced by CH_2Br) can undergo preferential methanolysis at the *sp*-CH_2Br. When the monobromides (CXIIIa) and (CXIIIb) are separately treated with sodium methoxide, a mixture of the spiro compound (CXIV) (formation of a carbanion at C-9 followed by an intramolecular S_N2 reaction) and the methyl ether (CXV) (direct displacement) is obtained. The *sp*-isomer (CXIIIa) gives predominantly the methyl ether (CXV) and the *ap*-isomer (CXIIIb) predominantly the spiro compound (CXIV). This is consistent with the fact that CH_2Br is less hindered and 9-H more hindered in CXIIIa while the reverse is true for the other isomer (CXIIIb).

12.7 Formation and reactions of enols and enolates

Enols and enolates derived from ketones are basically nucleophilic and quite a few important organic reactions such as protonation (or deuteration), halogenation, alkylation, acylation, and aldolisation (all are electophilic addition to enolic and enolate double bond) are mediated through them. The stereochemistry of these reactions is best studied in cyclohexanone system.

12.7.1 Protonation and halogenation of enols

It has been long recognised that enolisation of unhindered cyclohexanones either with a base or an acid involves the preferential abstraction of an α-axial proton and in the reverse reaction, e.g., ketonisation of enols with proton or bromine, the electrophile occupies the axial position in the product. This was attributed by Corey (1953-1956) to a stereoelectronic factor, namely, an overlap of the axial C-H bond orbital with the π orbital of the carbonyl group in enolisation and a similar overlap of the empty p orbital of the electrophile with the delocalised enol π orbital in ketonisation. Later Valls and Toromanoff (1961) proposed two pathways for electrophilic addition to cyclohexanone enols or enolates. Two perpendicular attacks both satisfying the stereoelectronic requirement (see also p. 358) are envisaged known as antiparallel and parallel (abbreviated as ap and p respectively) (Figure 12.56). In the antiparallel attack, as the bond between Cα

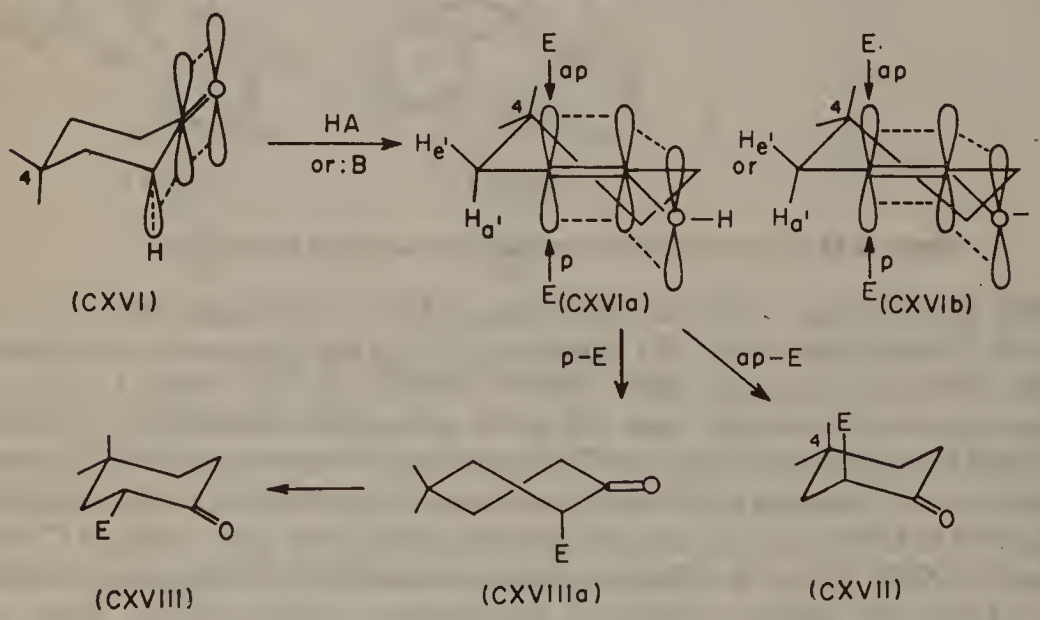
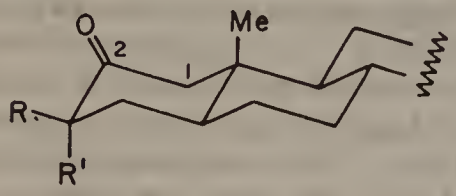


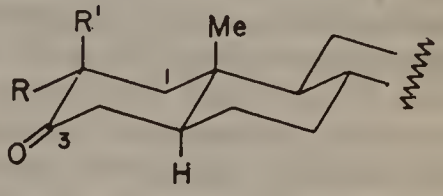
Figure 12.56 Electrophilic addition to double bond of enols and enolate ion

and the electrophile (E) starts forming, the enolate half-chair (CXVIa or CXVIb) moves towards a chair-like transition state which gives the product (CXVII) with E axially oriented. In the parallel attack, the enolate half-chair moves towards a twist-boat transition state leading to a product (CXVIIIa) which finally flips to a chair conformation (CXVIII) with E equatorially oriented. Three points may be noted : (*i*) In the absence of any steric factor, the ap- and p-approaches to the

enolate double bond are almost equally feasible. If there is no appreciable bond formation in the transition state, it would resemble the enolate structure (CXVIa) and there should not be much discrimination between the antiparallel and parallel attacks. (*ii*) If there occurs substantial bond formation in the transition state, it would be more chair-like or twist boat-like and the relative proportion of antiparallel and parallel attacks would depend on the difference in strain energy between the chair and twist-boat forms the former often being preferred as indeed the case for protonation and bromination of enols derived from unhindered cyclohexanones. (*iii*) If there is an axial substituent at C-4, the antiparallel approach would be subject to a synaxial interaction and the parallel approach through twist-boat transition state would prevail. Thus bromination of 2-ketosteroids (CXIX, R = R′ = H) (Figure 12.57) gives preponderantly axial bromo compound (CXIX, R = H, R′ = Br)



(CXIX)



(CXX)

Figure 12.57 Bromination of 2-keto-and 3-ketosteroids

while that of 3-ketosteroids (CXX, R = R′ = H) gives a substantial amount (ca 40%) of equatorial bromide (CXX, R′ = H, R = Br). In the former, there is no steric hindrance to antiparallel approach while in the latter, the 10-Me group introduces a synaxial interaction to it.

12.7.2 Alkylation of enolate ions

Alkylation of an enolate ion by alkyl halides or equivalents is complicated by the fact that a fair amount of dialkylated product is produced and that the initial product may undergo equilibration under basic condition. However, in majority of cases, it is observed that a mixture of monoalkylated products comprising almost equal amounts of equatorial and axial isomers is obtained (see House 1972) which means that the antiparallel and parallel attacks are almost equally feasible and that the transition state involves very little C-C bond formation. Two general observations are made : (*i*) If the antiparallel approach is subject to a synaxial interaction, the parallel approach prevails with the formation of an equatorial isomer. (*ii*) If there exists an alkyl group at the α-C atom, the propensity of axial alkylation is very much increased (see steriod synthesis in Chapter 13). It may be noted that in α,α-disubstituted cyclohexanones, there is no possibility of equilibration and the product is strictly of kinetic control.

In this respect, the stereochemistry of angular methylation of 2-furfurylidene *trans*-1-decalone (Figure 12.58) is instructive. Assuming a half-chair transition state, the usually favourable antiparallel approach of MeI is subject to two synaxial interactions with 5-H and 7-H and as a result, the parallel approach is preferred leading to an excess of the cis isomer (furfurylidene group is introducted to prevent reaction at C-2).

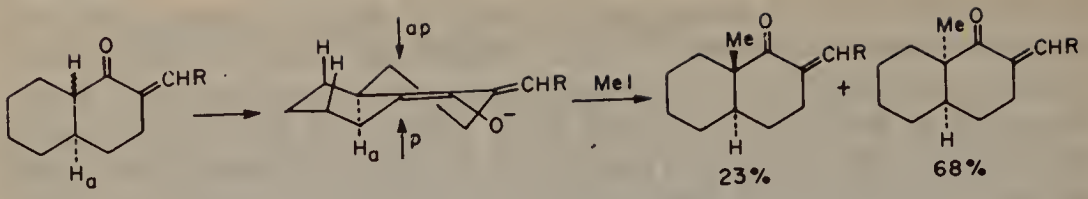


Figure 12.58 Stereochemistry of angular methylation of 1-decalone

12.7.3 Alkylation of cyclohexanone enamines

In contrast to the enolate ions, the enamines derived from cyclohexanones exhibit a higher propensity for giving axial products. The antiparallel approach is preferred indicating substantial bond formation in the transition state. Thus the enamine of 4-*t*-butylcyclohexanone on alkylation gives a high percentage of axially alkylated product (Figure 12.59a), 70% for R = Me, 90% for R = *n*-Pr (Karady et al, 1965). Because of steric reason, the enamine of a 2-substituted cyclohexanone is formed preferentially with the double bond between C-1 and C-6 and to avoid $A^{1,2}$-strain C-alkyl assumes a pseudoaxial orientation (Figure 12.59b). Alkylation, therefore, takes place at C-6 and there is no possibility of dialkylation (see Cook 1968).

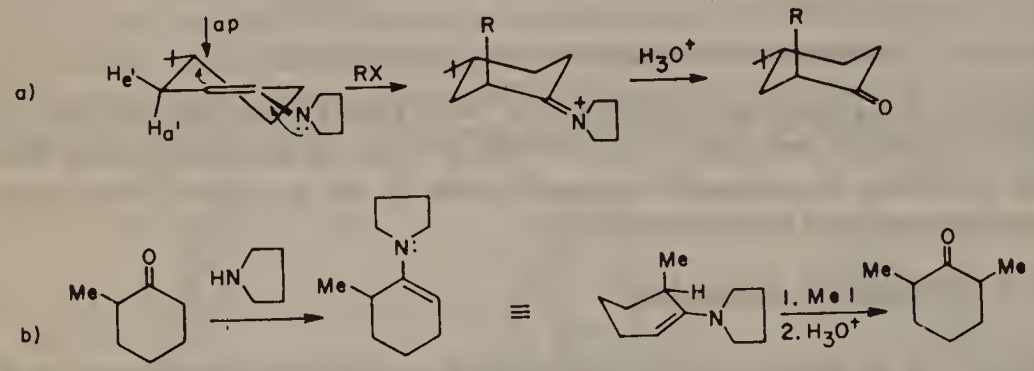


Figure 12.59 Alkylation of cyclohexanone enamines

12.7.4 Enolisation and bromination of an exocyclic ketone

In the case of an exocyclic cyclohexyl ketone, e.g. R-C_6H_{10}COR', the α-H may be axial or equatorial and in either orientation, the C-H bond can be parallel to the π orbital of the carbonyl group and an enol with an exocyclic double bond would result. Electrophilic addition to the double bond would normally give ring substituted product, the approach of the electrophile being controlled by the steric factor alone. The following series of reactions illustrates a few stereochemical principles (Figure 12.60). 1-Acetylcyclohexene (CXXI) undergoes 1,4-addtion with phenylmagnesium bromide to give the bromomagnesio complex (CXXII) which exists in two diastereomeric forms, (*Z*) and (*E*) differing in the configuration of the double bond as proved by their conversion into the acetates (CXXIII). The two acetates (as CXXIII, Me = Ph) have been separated and the axial orientation of the phenyl in each is confirmed by ^{1}H-NMR (the splitting pattern of the benzylic proton being consistent with an e-H split by adjacent a-H and e-H) (Malhotra and Johnson 1965). The

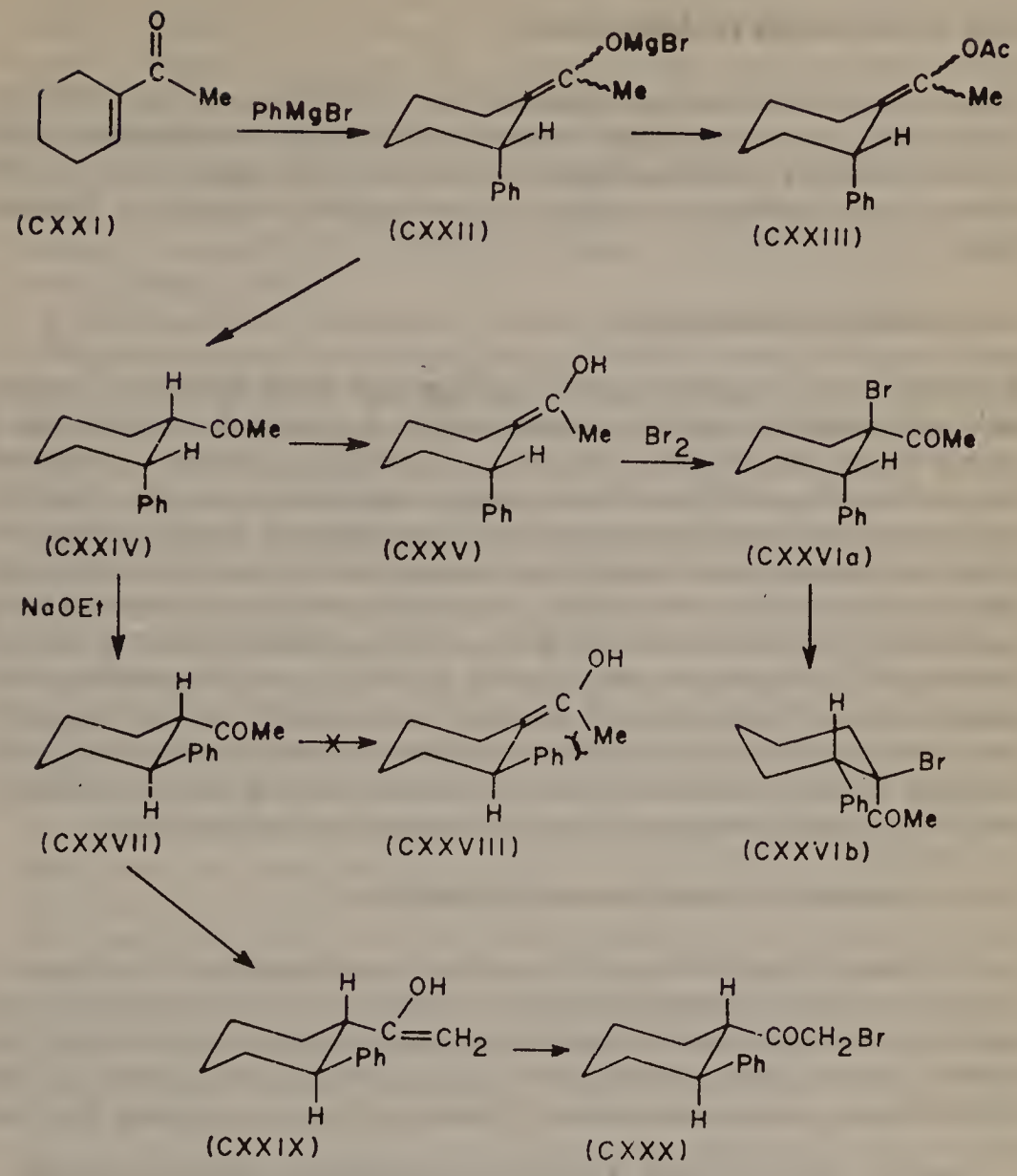


Figure 12.60 Bromination of exocyclic ketone

axial conformer is preferred because it avoids $A^{1,3}$-strain (Chapter 10). Protonation of the complex (CXXII) takes place from the axial side giving the cis ketone shown here in its less stable conformation (CXXIV). It readily enolises (by acid) to give the enol (CXXV) with the Ph group axial, again to avoid $A^{1,3}$-strain. On bromination, the enol gives the bromo derivative (CXXVIa) which flips to the stable conformation (CXXVIb). The cis ketone (CXXIV) on treatment with sodium ethoxide is epimerised to the more stable trans ketone (CXXVII) which can enolise in two ways, either by the removal of axial ring proton or one of the methyl protons to give CXXVIII and CXXIX respectively. The former is unstable again due to $A^{1,3}$-strain and the latter is formed exclusively which on bromination gives the bromoacetyl derivatives (CXXX). When COMe in CXXXVII is replaced by COPh, no bromination takes place.

12.8 Reduction of cyclohexanones

The reduction of substituted cyclohexanones under kinetically controlled conditions gives usually a mixture of axial and equatorial alcohols, the stereochemistry of the products depending on various factors, e.g., nature of the reagents, nature of the substrates, and the reaction conditions. A few common methods are discussed below.

12.8.1 Catalytic hydrogenation

A cyclohexanone is hydrogenated to a cyclohexanol in the presence of catalysts such as Pt and Ni in acidic or neutral medium. It is generally assumed that a catalyst absorbs the substrate from its less hindered side forming a π-bonded intermediate (House 1972) and then transfers hydrogen to that side. Since the equatorial side of a cyclohexanone carbonyl is less hindered, catalytic reduction in strongly acidic medium in which the cyclohexanols are detached from the catalyst surface as soon as they are formed (i.e., the products do not get a chance of being equilibrated), gives mainly the axial alcohol. This is generally known as the von Auwers-Skita hydrogenation rule. However, reduction in neutral medium ensures a longer contact of the alcohols with the catalyst surface and the thermodynamically more stable equatorial alcohol predominates.Thus rapid reduction of 4-*t*-butylcyclohexanone with active catalysts (Ni or Pt) in acidic medium gives 80% of the axial alcohol but the stereoselectivity decreases as the reaction time is increased.

12.8.2 Reduction of cyclohexanones with hydrides

In 1953, Barton formulated a general principle that unhindered cyclohexanones on reduction with lithium aluminium hydride or sodium borohydride afford the more stable equatorial alcohols while hindered cyclohexanones give the less stable axial alcohols. This has been substantiated by many subsequent experiments in simple cyclohexanones and steroidal ketones (Table 12.1) but no consensus has been

Table 12.1 Stereochemistry of reduction of cyclic ketones with $LiAlH_4$ in ether (Group A : unhindered ketones; Group B: hindered ketones)

	Ketone	Stable alcohol	Percentage
Group A:	4-Methylcyclohexanone	trans (*e*)	81
	3-Methylcyclohexanone	cis (*e*)	88
	2-Methylcyclohexanone	trans (*e*)	70
	4-*t*-Butylcyclohexanone	trans (*e*)	90
	Menthone	trans (e)	79
	3-Cholestanone	3-β-ol (*e*)	91
Group B:	3,3,5-Trimethylcyclohexanone	cis (*e*)	45 (29)[a]
	Camphor	endo	10
	Norcamphor	exo	11
	11-Oxosteroids	11-α-ol (*e*)	22

[a]A significantly lower percentage (29%) has been obtained by a rapid mixing technique (McMahan et al 1981).

reached regarding the factors responsible for it. The problem is rendered difficult by lack of definite proof for the exact mechanism of the reactions which may vary with the change of reagents. The structure of the cyclohexanones is another variable parameter which may change from a normal chair to a twist-boat depending on the nature of the substituents. The topic has been reviewed from time to time (Eliel and Senda 1970, Yamada and Koga 1970, Brewster 1972, Boone and Ashby 1979, Wigfield 1979). A summary of different hypotheses so far advanced has recently been published (Nasipuri et al 1984). Some of them are briefly discussed below.

1. Steric approach control and product development control. Dauben et al (1956) first explained the stereochemistry of hydride reduction of cyclohexanones in terms of two concepts: steric approach control (SAC) and product development control (PDC). SAC is a purely steric postulate involving competitive attacks from a favoured (unhindered) and unfavoured (hindered) side (equatorial and axial respectively) while PDC is an energy consideration involving the relative stability of the products. It is suggested that for unhindered ketones, the approach of the hydride on the two sides of the carbonyl group in a cyclohexanone is about equally favoured and the transition state reflects the steric requirement of the product. Thus the more stable equatorial alcohol is formed preponderantly—a result of PDC. On the other hand, for hindered ketones like 3,3,5-trimethylcyclohexanone, steric approach control becomes more important and the axial attack* which is sterically hindered (through synaxial interaction with the 3-Me group) is considerably reduced. The two concepts are better illustrated with an example: the reduction of cyclohexanones with sodium borohydride (Wigfield 1979) which goes through an acyclic mechanism (Figure 12.61). Of the two transition states (CXXXIa) and (CXXXIb) from an unhindered cyclohexanone, the former arising from equatorial attack is less favoured because of the developing interaction between C-O---H and the two axial H's at C-3 and C-5. The relative stability of the equatorial versus axial alcohols is thus reflected on the relative stability of the transition states (product development control). Of the two transition states (CXXXIIa) and (CXXXIIb), the former is favoured because the latter suffers from a synaxial interaction between the axial 3-Me and the incoming nucleophile (BH_4^-) and SAC leads to a preferential formation of the axial alcohol. The two terms, SAC and PDC have subsequently undergone modifications, the former being replaced by *steric strain control* (SSC) and the latter by *product stability control* (PSC) (Brown and Deck 1963) in order to give more emphasis on the transition state rather than on events prior to that. The terms SSC and PSC refer in a relative sense to the position of the transition state along the reaction coordinate. The former applies to a reactant-like or early transition state and the latter to a product-like or a late transition state.

The role of steric approach control on the stereochemical course of a reaction has never been in doubt but that of product development control has always been controversial despite evidence by Wigfield (1979) in sodium borohydride reduction

*It is now well established that the nucleophile approaches the carbonyl carbon along a vector at an angle close to 110° with the carbonyl bond.

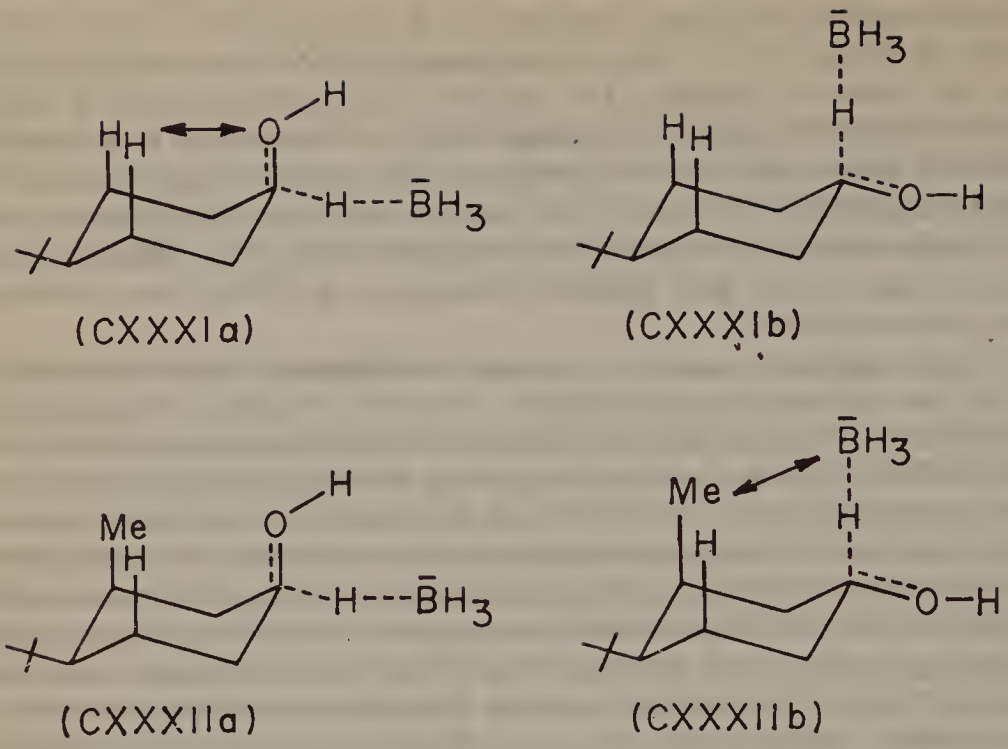


Figure 12.61 Product development control versus steric approach control

and by Rei (1979) in lithium aluminium hydride reduction of a number of cyclohexanones, cyclopentanones, and bicyclic ketones. The last-named worker came to a conclusion that while the stereochemical course of reactions of ketones with methyllithium is little affected by PSC, that of reductions with lithium aluminium hydride is dictated simultaneously and linearly by both SSC and PSC. Some of the observations which go against PSC are : (*i*) Reduction of ketones with hydrides are highly exothermic and so, according to Hammond's postulate, the transition states are expected to be reactant-like and not product-like. (*ii*) The deuterium isotope effect (k_H/k_D) in borohydride/borodeuteride reduction of cyclohexanones with varying degrees of steric hindrance (Wigfield and Phelps 1970) is almost constant inspite of the widely different ratios of the equatorial and axial alcohols which means that the extent of bond making and bond breaking in the transition state is almost the same for hindered and unhindered cyclohexanones—a fact incompatible with the PSC concept. (*iii*) Very often, a higher proportion of an equatorial alcohol is obtained in lithium aluminium hydride reduction than what corresponds to thermodynamic equilibrium, e.g., 90% versus 80% in the 4-*t*-butylcyclohexanone system. (*iv*) The comparative rate studies of a number of sterically hindered ketones using 4-*t*-butylcyclohexanone as a standard (Eliel and Senda) show that while the relative rate constants so determined support the concept of SSC, they display little effect of PSC. (*v*) Finally, PSC itself is of steric origin so that the stereochemical control of these reductions ultimately devolve on the overall steric situation in the transition state and the specific contribution of PSC is hard to determine.

2. Steric factor involving C-2 and C-6 axial hydrogens. Richer (1965) and subsequently Marshall and Carroll (1965) put forward a suggestion that the axial

H's at C-2 and C-6 offer steric resistance to the equatorial approach of a nucleophile which may compete effectively with that offered by the axial H's at C-3 and C-5 to the axial approach. Their relative magnitude would depend on the exact position of the transition state in the reaction coordinate (Figure 12.62).

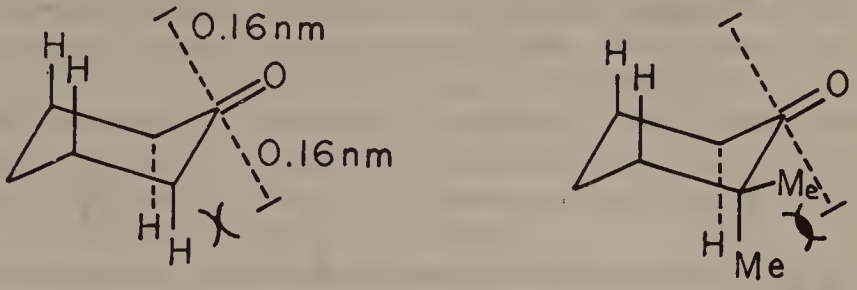


Figure 12.62 Steric interaction of axial H's at C-2 and C-6

If C···Nu is shorter than 0.16 nm, the equatorial approach would be more hindered as for the reduction with hydride reagents. Apart from the fact that the exact nature of the transition state is never known, this new steric effect is not evident in the reduction of 2,2-dimethylcyclohexanone where one axial H is replaced by an axial Me.

3. Torsional strain. At present, perhaps the most satisfactory and widely accepted alternative to PSC is the torsional strain which arises between the semi-formed bond of the nucleophile and the two axial C-H bonds (at C-2 and C-6) during the equatorial approach of the nucleophile (Cherest and Felkin 1968). Two factors are now postulated which compete with each other: the steric interaction of the incoming nucleophile with the 3,5-diaxial groups in the axial attack and torsional strain (similar to that in eclipsed ethane) as defined above in the equatorial attack. In the absence of any compelling steric hindrance, the effect of torsional strain prevails over the steric effect leading to preponderant axial attack with the formation of equatorial alcohols, as in hydride reductions of unhindered cyclohexanones. On the other hand, if there is one bulky axial substituent at C-3 or C-5 (or at both) the steric effect prevails reversing the steric course. This is shown in Figure 12.63 by appropriate transition states drawn in two perspectives. This is also in accord with the observation of Eliel and Senda that the stereochemistry of reduction is not changed appreciably by the introduction of a geminal dimethyl group at C-2 (Figure 12.62) because the torsional strain is relatively insensitive to the bulk of the substituent. The theory has the added advantage that it also successfully explains the stereochemistry of reduction of acyclic ketones (see Chapter 8).

Quite recently, Houk et al (1988) have supported Felkin's theory both from the calculation of molecular mechanics as well as by some experimental results.

4. Alternative theories. A few other suggestions have also been made. Nguyen Anh (1977) working on models for asymmetric induction in acyclic systems performed *ab initio* calculations (STO-3G) on various geometries of transition states for nucleophilic attack and came to the conclusion that antiperiplanarity between the newly formed bond and other bonds already present is desirable. This can be achieved in axial attack on cyclohexanones but not in equatorial attack.

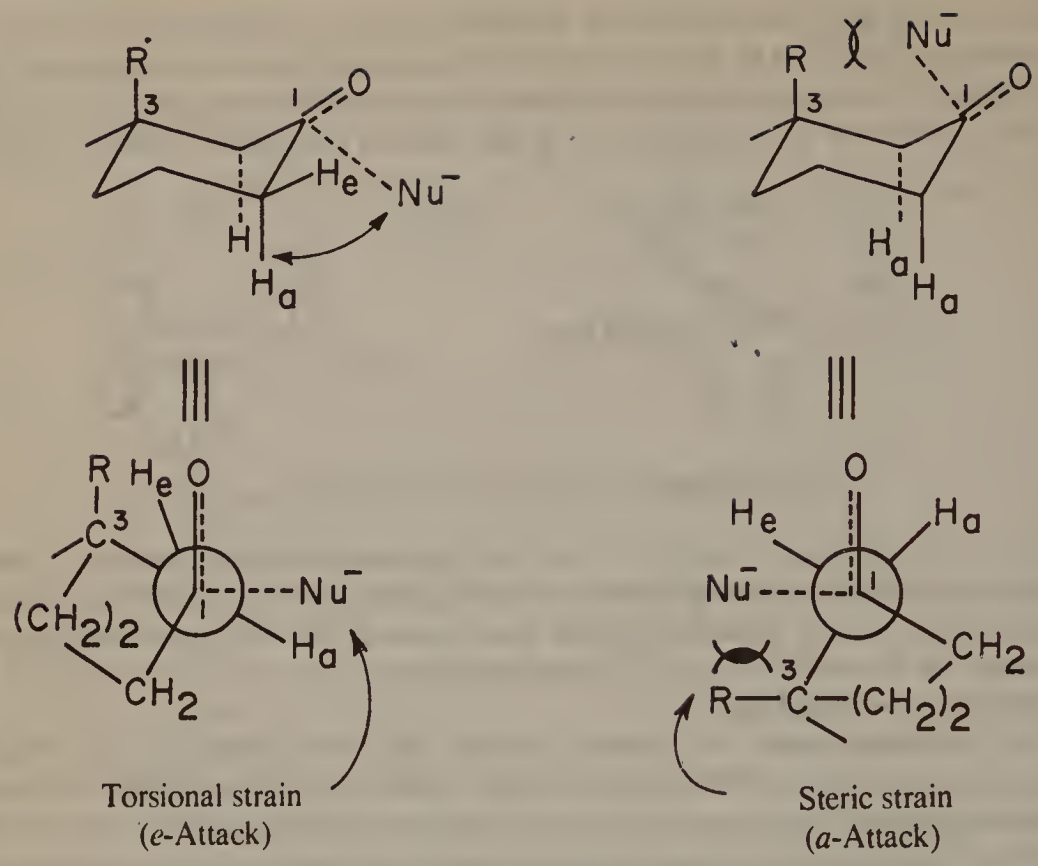


Figure 12.63 Torsional strain versus steric strain

This new interpretation basically agrees with the outcome of Felkin's model but for a different reason.

Finally, Cieplak (1981) has suggested that the stereochemistry of nucleophilic addition to cyclohexanones is determined by a combination of steric and stereoelectronic factors. The steric factor as usual favours the equatorial approach. The stereoelectronic factor arises from the fact that the axial C-H bonds next to the carbonyl group are better electron donors than the 2-3 and 5-6 σ bonds. As a result, the transition state with the incipient bond axially oriented is preferred over the one with the incipient bond equatorially oriented,* (a consequence of stereoelectronic effects).

12.8.3 **Meerwein-Ponndorf-Verley and related reactions**

Meerwein-Ponndorf-Verley (M-P-V) reduction is a classical reaction in which a

*This is apparently due to development of σ^* orbital associated with the incipient bond (and consequent stabilisation of the transition state) by electron donation from two C-H bonds in the case of axial attack and two C-C bonds in the case of equatorial attack. In a recent paper (Cieplak et al 1989), experimental findings show that the stereoelectronic control of π-facial diastereoselection is enhanced (favouring axial attack) if the transition states are electron-defficient as when there is an electronegative substituent, e.g., CF_3 in the substrates (at C-3 of cyclohexanone) or in the reagent, e.g., sodium tri-isopropoxyborohydride. Working on 7-norbornanone system, G. Mehta (private communication) has demonstrated similar stereoelectronic effects by introducing electron-releasing or electron-withdrawing groups in the endo positions which do not interfere with steric factors.

hydride is transferred from aluminium isopropoxide (or any other secondary alkoxide) to a carbonyl carbon. An equilibrium is set up and the reaction is completed either by using an excess of the reagent or by distilling off the acetone formed. The reverse reaction, i.e., oxidation of aluminium alkoxides with a ketone is known as Oppenauer oxidation. Since the reaction is thermodynamically controlled, at least upon prolonged reaction time, the product ratio, in the case of two epimeric alcohols, gives their relative thermodynamical stability which is of interest in conformational analysis. The results of reduction of a few typical cyclic ketones under M-P-V equilibrium condition (with aluminium isopropoxide-isopropyl alcohol-acetone) are recorded in Table 12.2 along with the data of metal-ammonia reduction to be discussed in the next subsection.

The reduction may also be carried out under kinetic control by using an excess of the reagent (aluminium alkoxides) and a short reaction time and under such circumstances the less stable isomer is formed as a result of steric approach control. A few analogous reactions are known such as reduction with sterically hindered Grignard reagents (a case of β-H transfer) which are kinetically controlled and are associated with high stereoselectivity*.

Table 12.2 Stereochemistry of reductions of a few cyclic ketones by M-P-V and by Li-NH_3

Ketones	Percentage of more stable alcohols with :	
	M-P-V equilibration	Li-NH_3[a]
4-*t*-Butylcyclohexanone	79	98-99
4-Methylcyclohexanone	70	99
3-Methylcyclohexanone	—	94-95
2-Methylcyclohexanone	—	99
3,3,5-Trimethylcyclohexanone	94	99
2-Norbornanone (norcamphor)	80	9-32
Camphor	71	79-90

[a]Huffman and Charles 1968

12.8.4 Reduction of cyclic ketones with dissolving metals

Saturated cyclic and acyclic ketones are reduced to alcohols by alkali and alkaline earth metals dissolved in lower alcohols (M + ROH) or better in liquid ammonia (M + NH_3). The latter reaction is known as Birch reduction and is of great synthetic utility because of its vesatile use (Birch and Subba Rao 1972). The products almost in all cases are the more stable alcohols (Table 12.2, last column), one notable exception being norbornan-2-ol in which the less stable endo isomer is formed in excess. Lithium in liquid ammonia is also a method of choice for stereoselective reduction of cyclic α,β-unsaturated ketones to saturated ketones. Here also the more stable trans products are formed in the majority of cases.

*See Nasipuri and Saha (1990) for the stereochemistry and mechanism of reduction of cyclic ketones with Grignard reagents.

1. Reduction of saturated cyclic ketones. The mechanism of Birch reduction (and reduction with alkali metals in alcohols) of a saturated ketone is shown in Figure 12.64. The initially formed ketyl radical (A) arising out of a single electron transfer is believed to be planar at the carbonyl site and is resonance stabilised with 70% of the unpaired electron density located on carbon (House 1972, p.156). This on protonation (in the presence of a proton donor, e.g., ROH) gives a hydroxy carbon radical (B) in which pyramidalisation has occurred to a considerable

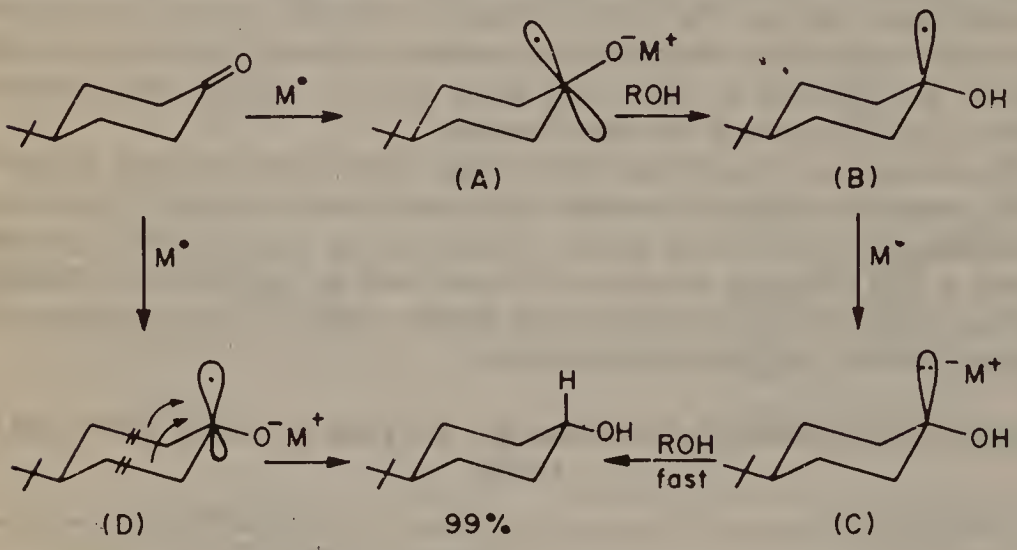


Figure 12.64 Mechanism of reduction of cyclohexanones with dissolving metals

extent. The hydroxy group (or OM) is oriented almost exclusively in the equatorial position. The radical (B) collects another electron and forms the anion (C) which undergoes a fast protonation to give the trans alcohol in 99% yield. The assumptions intrinsic in the mechanism are that the hydroxy radical (B) has a sufficient life time to adopt the more stable conformation and that the protonation of C (with retention of configuration) is fast in comparison to conformational inversion. Two inadequacies of this mechanism may be pointed out: Formation of 99% of equatorial alcohol appears to overemphasise the thermodynamic stability of the hydroxy-radical (B) (compare with the value of 79% when the electron is replaced by H in Table 12.2) and secondly, 2-norbornanone gives an excess of the less stable endo isomer (a non-conforming case). Recently, Pradhan (1986) has proposed an alternative suggestion based on Fukui's frontier molecular orbital (FMO) approach. According to this, the 2-3 and 5-6 σ bonds (HOMO's) are favourably disposed to interact with the singly occupied C-O π^* orbital (SOMO) in the radical anion (A) with the result that appreciable pyramidalisation occurs in the ketyl radical and the orbital is extended in the axial direction as shown in D. This stereoelectronic effect provides a kinetic preference for the axial attack by an electron or a radical at the carbonyl carbon and has been termed Fukui effect (Fukui 1975). In the case of 2-norbornanone (Figure 12.65), the interaction of the 1-7 σ bond orbital (marked) with the C-O π^* orbital causes an orbital extension along the exo direction producing the endo alcohol. It so happens that in the hydroxyradicals (as B and E), the OH group is antiperiplanar or nearly so with the interacting σ bonds.

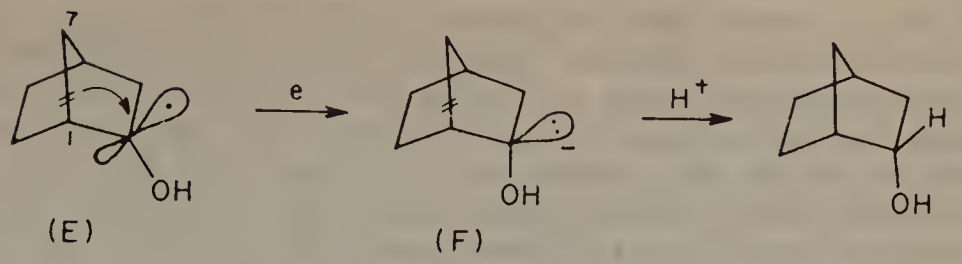
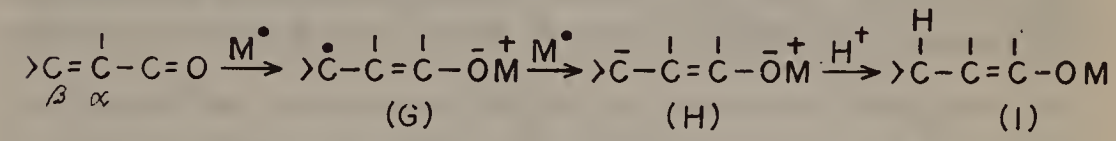


Figure 12.65 Reduction of 2-norbornanone

2. Reduction of α,β-unsaturated cyclohexenones. The stereochemistry of reduction of 1(9)-octalin-2-ones and a few 3.4-disubstituted cyclohexenones with lithium in liquid ammonia is discussed. When an alcohol is used as proton donor, the first-formed saturated ketones are reduced to alcohols and may be oxidised back to the saturated ketones.

The mechanism of reduction of α,β-unsaturated ketones with metal-amine may be represented by the following steps:



The radical anion (G) formed by a single electron transfer on further addition of an electron gives the dianion (H) (or its metallated form). The carbanion centre of the latter is then protonated in such a way that the developing C-H bond overlaps with the remainder of the π system of the dianion giving the enolate salt (I) which is later converted into ketone. The stereoelectronic factors operating in the carbanion (H) would determine the stereochemistry. Thus the dianion derived from 1(9)-octalin-2-one (CXXXIII, R = R′ =H) on two successive addition of electrons can exist in three conformations (J), (K), and (L) (Figure 12.66). Of these, the first

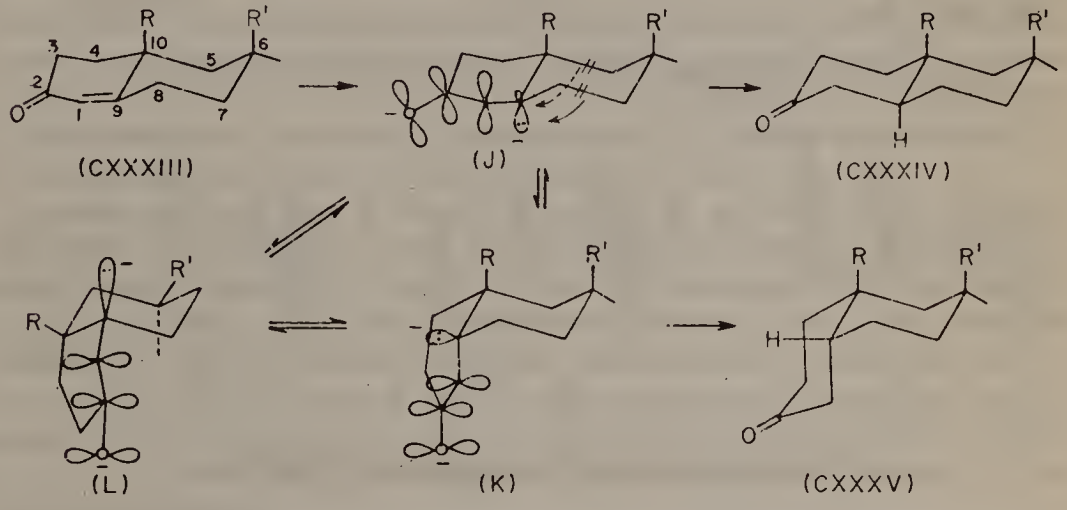
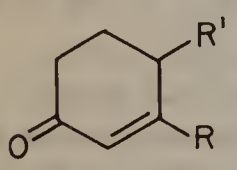


Figure 12.66 Stereochemistry of metal-NH_3 reduction of 2-octalones

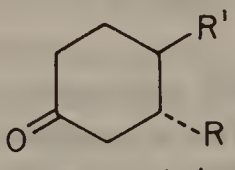
two are stereoelectronically allowed (the p orbital at C_β overlaps with the extended π orbital) and so are preferred giving *trans*- and *cis*-decalones (CXXXIV) and (CXXXV) respectively. A steric factor, however, destabilises the dianion (K)

and the trans isomer is formed to the extent of 99%. This phenomenon in which C_β-H bond is formed axial to the ring containing the carbonyl group is known as '*axial protonation*' rule (Stork and Darling 1960) and happens irrespective of whether the product is a *cis*- or a *trans*-decalone.* Here also, thermodynamic stabilisation by steric effects appears to be overemphasised : A 99 :1 ratio of the *trans*- and *cis*-decalone is hardly expected on the basis of the relative stability of the dianions (J) and (K) as judged from the non-bonded interactions (see also the footnote). A search for kinetic preference for the axial attack on the dianions seems to be in order. Pradhan (1986) has suggested that the same Fukui effect, namely, the orbital extension at the radical centre as a result of σ bond interaction is responsible for the stereochemistry of the products. Thus the p orbital at C-9 in the dianion (J) or more properly in the precursive radical anion gets an extension along the α-face (axial direction) because of the interaction with the two marked endocyclic σ bonds (HOMO's) and thus provides a strong kinetic preference for the axial protonation.

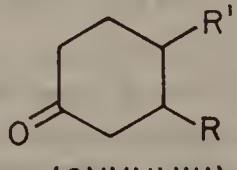
The stereochemical results for a few 3,4-disubstituted cyclohex-2-enones (CXXXVI) are shown in Figure 12.67. The results can be explained with the help of three structures (M), (N), and (O) for the dianions (Figure 12.68). When both



(CXXXVI)



(CXXXVII)



(CXXXVIII)

R = R' = Me	86%	14%
R = R' = Et	56%	44%
R = Ph, R'=Me	6%	94%
R = R' = Ph	2%	98%

Figure 12.67 Stereochemistry of reduction of 3,4-disubstituted cyclohexenones

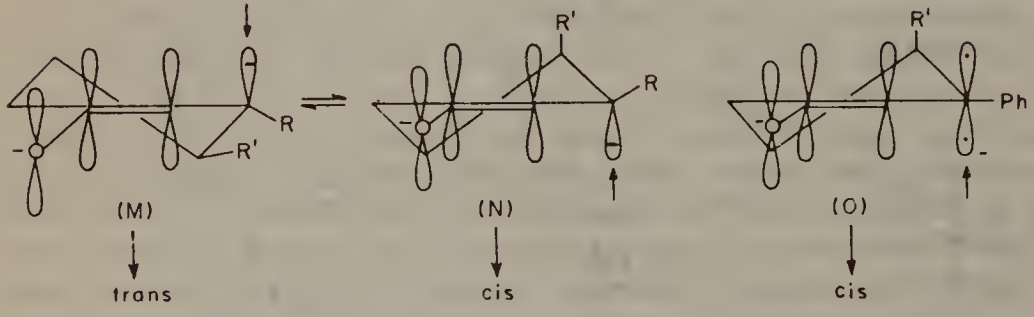


Figure 12.68 Dianionic species from 3,4-disubstituted cyclohexenones

*Usually, the axial protonation leads to the more stable *trans*-decalone. However, the trans isomer may not necessarily be the more stable in all cases. Thus the octalone (CXXXIII, R = Me, R′ = OMe) on reduction gives the trans isomer (CXXXIV, R = Me, R′ = OMe) via the dianion (as J) (axial protonation). But this is certainly less stable than the cis isomer with a non-steroid structure (produced via the dianion, as L) in which 1,3-diaxial interaction is absent (Caine 1976).

R and R′ are alkyl, the first two structures control the ratio of trans (CXXXVII) and cis (CXXXVIII) products, the trans being favoured due to steric reason. It may be observed that there is no Fukui effect. i.e., no kinetic preference for the formation of the dianions. A combination of stereoelectronic and steric factors determines the stereochemistry and there is no overwhelming preference for the trans isomer. When R is phenyl, electron delocalisation in the dianion extends to the phenyl group forcing a coplanarity at β-C atom (as in O). In such a structure, there would arise $A^{1,2}$-strain if R′ is bulky and placed in the equatorial position. Consequently, the dianion assumes the conformation (O) with R′ axially oriented and the cis product predominates depending on the size of R′ (see also Caine 1976).

12.9 Summary

1. Dynamic stereochemistry correlates the stereochemistry of starting materials and products in a kinetically controlled rate process through the transition state geometry. The study of conformations on reactivity reveals one aspect of dynamic stereochemistry which has been discussed in this chapter with the help of three types of substrates: (*i*) conformationally rigid or anancomeric cyclohexanes which provide information on the relative rates of reactions of an axial or an equatorial conformer: (*ii*) a pair of conformationally mobile diastereomers in each of which only one of the conformers is reactive due to stereoelectronic reasons; (*iii*) a single substrate existing in two or more energy preferred conformations which give different non-equilibrating products.

2. Two quantitative treatments are available correlating conformation and reactivity in systems in which conformational interconversion is faster than the reaction rates. One is the Winstein-Eliel equation(s) which quantifies the empirical reaction rate of the conformationally mobile substrate in terms of the specific reaction rates of the individual conformers and their relative population. The second is the Curtin-Hammett principle which correlates the ratio of the products (which are different for different conformers and also non-equilibrating) with the difference in the free energies of the respective transition states. The ground state population of the conformers does not have any direct relation with the product ratio.

3. Some reactions such as S_N2, E2, addition to a double bond, molecular rearrangement, neighbouring group participation, and molecular fragmentation are subject to stereoelectronic control, i.e., certain specific arrangements of the reacting centres are necessary before the reactions can take place. Very often, only one conformer of each diastereomer fulfills the stereoelectronic requirements and in such cases, the steric factors in the reactive conformers determine the relative reactivities of the diastereomers. This has been illustrated with various examples using both acyclic and cyclic substrates. A few conclusions, arrived at are enumerated under 4-7.

4. Esterification of alcohols and saponification of esters go at a slower rate for the axial than the equatorial isomers—a case of steric hindrance. Nucleophilic substitution at a ring atom goes at a faster rate for the axial isomers, particularly, in S_N1 reactions—a case of steric assistance. Electrophilic addition to an endocyclic

double bond or opening of an epoxide ring in cyclohexane gives trans 1,2-diaxial products. E2 eliminations go faster for that diastereomer in which the transition state with the two leaving groups antiperiplanar suffers from a lesser 'cis-effect'- again a case of steric hindrance. Chromic acid oxidation of an axial alcohol (more hindered) is faster than that of an equatorial alcohol—a case of steric assistance (steric strain is relieved in the axial chromate intermediate through conversion into ketone).

5. In E2 reactions, anti elimination is more common than syn although both modes of elimination are stereoelectronically feasible. The actual mode of elimination (when both syn and anti modes are possible) depends on a number of factors. Thus a poor leaving group e.g., onium groups, a strong and bulky base, and a poorly dissociating solvent favour the syn elimination. When both anti and syn elimination take place, the cis olefins are produced mainly through the anti and trans olefins through the syn mode of elimination. This is known as syn-anti dichotomy.

6. Molecular rearrangements require specific arrangements of the groups involved and so are very much conformation dependent. As a consequence, two diastereomers very often give two entirely different products. This has been illustrated by various examples from cyclic and acyclic systems. In molecular rearrangements. the migrating group retains its configuration, the migration origin usually undergoes inversion (if it retains the tetrahedral chiral character), and the migration terminus also undergoes inversion. The extent of retention and inversion of configuration, however, depends on the degree of concertedness of the rearrangements.

7. Neighbouring group participation in nucleophilic displacement reactions is characterised by an acceleration of reaction rate and retention of configuration at the reacting centre. Examples have been given to illustrate the participation of a lone pair of electrons, electrons belonging to a double bond, and even σ bond electrons. Participation of an aryl group (phenonium ions) is particularly interesting. Two diastereomers behave differently in these reactions and conformation of the reactive species plays an important role.

8. In 9-arylfluorenyl derivatives, conformational isomers (atropisomers) have been isolated and their reaction rates studied. These compounds provide examples showing difference in reactivity in two acyclic conformers (analogous to axial and equatorial conformers).

9. A few reactions such as protonation. halogenation, alkylation, and acylation which are mediated through intermediate enols or enolate ions derived from ketones have been studied with particular reference to the cyclohexanone system. Two approaches of the electrophiles, antiparallel and parallel both fulfilling the stereoelectronic requirements (overlap of the empty p orbital with the enolate π orbital) have been considered. The former leads to a chair-like transition state giving axial substitution and is usually favoured. The parallel approach, on the other hand, proceeds through a twist-boat transition state and is more strained. The presence of a compelling steric effect, however, can reverse the situation and an equatorially substituted product may be formed through parallel attack. The effect of allylic strain in bromination of an exocyclic ketone and in alkylation of cyclic enamines has been discussed.

10. The stereochemistry of reductions of cyclohexanones specially with metal hydrides has been discussed in terms of various factors such as product stability control (PSC), steric strain control (SSC), torsional strain, and orbital intractions. The high percentage of equatorial alcohols in the reduction of unhindered cyclohexanones has been attributed to a torsional strain involving the axial bonds at C-2 and C-6 and partial bond of the incoming nucleophile from the equatorial side. The axial approach is thus favoured. On the other hand, if there is an axial substituent at C-3 or C-5, the steric factor dominates and an equatorial approach leading to axial alcohols is preferred.

11. The reduction of cyclic ketones by dissolving metals or by alkali metals in liquid ammonia (Birch reduction) leading almost exclusively to the equatorial or more stable alcohols (except for the case of norcamphor) has been discussed in the light of the existing mechanisms: formation of a hydroxy ketyl radical, its conversion into a dianion, and subsequent protonation. The very high equatorial-axial ratio (99:1), however, indicates a stereoelectronic effect providing a kinetic preference for the axial attack which has now been discussed in terms of a Fukui effect (interaction of appropriately placed σ bonds with the SOMO of the ketyl radical) which helps to extend the SOMO in an axial direction. This also explains the atypical behaviour of norcamphor and the preponderant axial protonation of the dianions derived from octalones.

References

1. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison (1965), in *Conformational Analysis*, Interscience, New York.
2. M. Hanack (1965), in *Conformational Theory*, Academic Press, New York.
3. T.H. Lowry and K.S. Richardson (1987), in *Mechanism and Theory in Organic Chemistry*, 3rd. Edn., Harper & Row, New York.
4. S. Winstein and N.J. Holness (1955), *J. Amer. Chem. Soc.*, **77**, 5562.
5. D. Lednicer and C.R. Hauser (1958), *J. Amer. Chem. Soc.*, **80**, 3409.
6. H.B. Goodbrand and J.B. Jones (1977), *J.C.S. Commun.*, 470.
7. K. Penzien and G.M.J. Schmidt (1969), *Angew. Chem. Int. Ed. Engl.*, **8**, 608.
8. O. Buchardt (1974) in *Photochemistry with Circularly Polarised Light, Angew. Chem. Int. Ed. Engl.*, **13**, 412.
9. E.L. Eliel (1962), in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
10. E.L. Eliel and R.S. Ro (1956), *Chem. Ind.*, 251.
11. E.L. Eliel (1960), *J. Chem. Educ.*, **37**, 126.
12. V. Gold (1983), *Pure Appl. Chem.*, **55**, 1281.
13. J.I. Seeman (1986), *J. Chem. Educ.*, **63**, 42.
15. J.I. Seeman (1983), *Chem. Rev.*, **83**, 83.
16. N.S. Zefirov (1977), *Tetrahedron*, **33**, 2719.
17. A.C. Cope. N. A. LeBel, H.H Lee, and W.R. Moore (1957), *J. Amer. Chem. Soc.*, **79**, 4720.
18. G. Klopman (1974), in *Chemical Reactivity and Reaction Paths*, Wiley, New York.
19. P. Deslongchamps (1983), in *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford.
20. L.H. Hellbergand and R. Peiffer (1968), *Tetrahedron Letters*, 645.
21. G. Stork and A.F. Kreft (1977), *J. Amer. Chem. Soc.*, **99**, 3850, 8373.

22. R.M. Magid (1980), *Tetrahedron,* **36**, 1901.
23. G. Stork, L.D. Cama, and D.R. Coulson (1974), *J. Amer. Chem. Soc.,* **96**, 5268.
24. J.E. Baldwin (1976), *J.C.S. Commun.*, 738.
25. W. Nagata and M. Yoshioka (1977), *Hydrocyanation of Conjugated Carbonyl Compounds* in *Organic Reactions*, vol. 25, Wiley, New York.
26. G.H. Posner (1972), in *Organic Reactions*, vol. 19, Wiley, New York.
27. H.O. House and W.F. Fischer (1968), *J. Org. Chem.,* **33**, 949.
28. R.A. Jackson (1972) in *Mechanism: An Introduction to the Study of Organic Reactions*, Clarendon Press, Oxford.
29. J. Sicher (1972), *Angew. Chem. Int. Edn. Engl.,* **11**, 200.
30. R.A. Bartsch and J. Zavada (1980), *Chem. Rev.,* **80**, 453.
31. R.A. Bartsch, E.A. Mintz, and R.M. Parlman (1974), *J. Amer. Chem. Soc.,* **96**, 4249.
32. H.C. Brown and K.J. Liu (1970), *J. Amer. Chem. Soc.,* **92**, 200.
33. C.A. Gröb (1969), *Angew. Chem. Int. Edn. Engl.,* **8**, 535.
34. E.J. Corey, R.B. Mitra, and H. Uda (1964), *J. Amer. Chem. Soc.,* **86**, 485.
35. E.L. Eliel, S.H. Schroeter, T.J. Brett, F.J. Biros and J.C. Richer (1966), *J. Amer. Chem. Soc.,* **88**, 3327.
36. J. Schreiber and A. Eschenmoser (1955), *Helv. Chim. Acta,* **38**, 1529.
37. B. Capon and S.P. McManus (1976), in *Neighbouring Group Participation*, Plenum Press, New York.
38. P. de Mayo (1963), in *Molecular Rearrangements* Vols I & II, Interscience, New York.
39. M. Cherest, H. Felkin and J. Sicher (1965), *J. Chem. Soc.*, 2513.
40. R.B. Woodward, J. Gosteli, I. Ernest, R.J. Friary, G. Nestler, H. Raman, R. Sitrin, Ch. Suter, and J.K. Whitesell (1973), *J. Amer. Chem. Soc.,* **95**, 6853.
41. Y. Yamada, M. Kimura, H. Nagaoka, and K. Ohnishi (1977), *Tetrahedron Letters*, 2379.
42. J.A. Berson (1968), *Angew. Chem. Int. Edn. Engl.,* **7**, 779.
43. C. J. Collins (1975), *Quart. Rev. Chem. Soc.,* **4**, 251.
44. R. A. Bartsch (1971), *J. Amer. Chem. Soc.,* **93**, 3683.
45. D. S. Bailey and W. H. Saunders (1970), *J. Amer. Chem. Soc.,* **92**, 6905.
46. J. G. Traynham, D. B. Stone, and J. L. Couvillio (1967), *J. Org. Chem.,* **32**, 510.
47. Yu-I, Tao and W. H. Saunders (1983), *J. Amer. Chem. Soc.,* **105**, 2183.
48. D. J. Cram (1956), in *Steric Effects in Organic Chemistry*, ed. M. S. Newman, Chapter 5, Wiley, New York.
49. T. P. Nevel, E de Salas, and C. L. Wilson (1939), *J. Chem. Soc.,* 1188.
50. W. Kirmse and B. R. Gunther (1978), *J. Amer. Chem. Soc.,* **100**, 3620.
51. M. Oki (1984), *Acc. Chem. Res.,* **17**, 154.
52. E. J. Corey (1953), *Experientia,* **9**, 329 ; E. J. Corey and R. A. Sneen (1956), *J. Amer. Chem. Soc.* , **78**, 154.
53. J. Valls and E. Toromanoff (1961), *Bull. Soc. Chem. France*, 758.
54. H. O. House (1972), in *Modern Synthetic Reactions*, 2nd Edn., W. A. Benjamin, Menlo Park, California.
55. S. Karady, M. Lenfant and R. E. Wolff (1965), *Bull. Soc. Chem. France*, 2472.
56. A. G. Cook (1968), in *Enamines : Their Synthesis, Structure, and Reactions*, Marcel Dekker, New York.
57. S. K. Malhotra and F. Johnson (1965), *J. Amer. Chem. Soc.,* **87**, 5493.
58. E. L. Eliel and Y. Senda (1970), *Tetrahedron*, **26**, 2411.
59. S-I Yamada and K. Koga (1970), in *Selective Organic Transformations*, ed. B. S. Thyagarajan, vol. 1, Wiley, New York.

60. J. R. Boone and E. C. Ashby (1979), in *Topics in Stereochemistry*, Eds. E. L. Eliel and N. L. Allinger, vol. 11, Interscience, New York.
61. D. C. Wigfield (1979), *Tetrahedron*, **35**, 449.
62. D. Nasipuri, M. Datta Gupta, and B. Manapatra (1984), *Proc. Indian Natn. Sci. Acad.*, **50A**, 47.
63. R. J. McMohon, K. E. Wiegera and S. G. Smith (1981), *J. Org. Chem.*, **46**, 99.
64. W. G. Dauben, G. J. Fonken and D. S. Noyce (1956), *J. Amer. Chem. Soc.*, **78**, 2579.
65. H. C. Brown and H. R. Deck (1965), *J. Amer. Chem. Soc.*, **87**, 5620.
66. M-H Rei (1979), *J. Org. Chem.*, **44**, 2760.
67. D. C. Wigfield and D. J. Phelps (1970), *J. C. S. Chem. Commun.*, 1152.
68. J. C. Richer (1965), *J. Org. Chem.*, **30**, 324 , J. A. Marshall and R. D. Carroll (1965). *J. Org. Chem.*, **30**, 2748.
69. M. Cherest and H. Felkin (1968), *Tetrahedron Letters*, 2205.
70. D. Mukherjee, Y-D. Wu, F. R. Fronczek and K. N. Houk (1988), *J. Amer. Chem. Soc.*, **110**, 3328.
71. T. A. Nguyen and O. Eisenstein (1977), *Nonv. J. Chem.*, **1**, 61.
72. A. S. Cieplak (1981), *J. Amer. Chem. Soc.*, **103**, 4540.
73. J. W. Huffman and J. T. Charles (1968), *J. Amer. Chem. Soc.*,**90**, 6486.
74. A. J. Birch and G. S. R. Subba Rao (1972), in *Advances in Organic Chemistry, Methods and Results,* Ed. E. C. Taylor, vol. 8, Wiley-Interscience, New York.
75. S. K. Pradhan (1986), *Tetrahedron*, **42**, 6351.
76. K. Fukui (1975), in *'Theory of Orientation and Stereoselection*, Springer Verlag, West Germany.
77. G. Stork and S. D. Darling (1960), *J. Amer. Chem. Soc.* , **82**, 1512.
78. B. Caine (1976), in *Organic Reactions* vol. 23, John Wiley, New York.
79. A.S. Cieplak, B.D. Tait, and C.R. Johnson (1989), *J. Amer. Chem. Soc.*, **111**, 8447; and references therein.
80. D. Nasipuri and A. Saha (1990), *Indian J. Chem.*, **29B**, 471, 474.

Chapter 13

Dynamic Stereochemistry II : Stereoselective Reactions

13.1 Introduction

One of the major objectives of a synthetic organic chemist is to synthesise an organic compound containing multiple chiral centres in a single specific stereoisomeric form—in the case of a natural product, the one that occurs in nature and in the case of a physiologically active compound, the one that is the most active. It is also desirable that the stereochemical transformations be carried out in a predictable manner so that the synthesis can be used to establish the configuration of the molecule. During the last few decades, there has been tremendous development in synthetic methodologies with particular emphasis on stereoselective synthesis a full discussion of which is clearly beyond the scope of this book (see Morrison 1983-1985; Nógradi 1987). A few basic principles along with relevant illustrations are discussed.

The stereochemistry at a chiral centre during a reaction is fixed either by conducting the reaction under kinetic control in which case the stereoselectivity depends on the difference in the free energies of the respective transition states or by carrying out the reaction under thermodynamic control in which case the stereoselectivity depends on the difference in the free energies of the products. Both methods are used in practice although the kinetic method is by far the more common while the thermodynamic method is used occasionally in cases where a chiral centre can be easily epimerised so that the desired stereoisomer is formed almost exclusively. In the present discussion, emphasis is given to stereoselection through kinetically controlled reactions.

13.2 Stereoselectivity : classification, terminology, and principle

There is some confusion in the literature regarding the terminology of stereoselective reactions. A detailed account of the system of classification is given below.

13.2.1 Classification and terminology

Two broad types of stereoselectivity are generally encountered in organic reactions. In the first, a single substrate with a prostereogenic element (Chapter 6) gives preferentially one or the other of two (or more) stereoisomers and in the second,

two stereochemically different substrates (diastereomers or enantiomers) react, usually under identical conditions, at different rates (one may not react at all) to give stereochemically or even constitutionally different products. Following a proposal of Zimmerman, Eliel (1962) has designated the first type of reactions as *stereoselective* and the second type as *stereospecific*. The preferential formation (90%) of equatorial *trans*-alcohol by reduction of 4-*t*-butylcyclohexanone with lithium aluminium hydride is an example of stereoselectivity while the formation of *trans*-2-butene and *cis*-2-butene by debromination of *meso*- and (±)-2,3-dibromobutane respectively (Chapter 12) is an example of stereospecificity. It may be noted that stereospecific reactions are also highly stereoselective in the sense that a diastereomeric starting material often gives almost exclusively a single stereoisomeric product. Considered in broader perspective, stereoselectivity according to this definition refers to product selectivity and stereospecificity refers to substrate selectivity. This difference in the definitions is, however, seldom maintained in practice and the two terms are often used synonymously. The confusion may be avoided if the two types of selectivity is brought under the common terminology, e.g., *stereoselectivity* which is then preceded by *product, substrate*, or *substrate-product* depending on the situation as suggested by Testa (1979) and elaborated by Nógradi (1987). This appears to be more consistent with the trends of biochemistry and pharmacology. Furthermore stereoselectivity without any qualifying term may be used to denote product stereoselectivity (more important for organic chemists) so that it retains its original connotation and the term stereospecificity stripped off its controversial meaning may be used synonymously with stereoselectivity as is often done in the literature. Thus the subdivisions may be made as follows.

1. Substrate selectivity. Depending on whether the substrates are diastereomers or enantiomers, substrate stereoselectivity may be further subdivided into substrate diastereoselectivity and substrate enantioselectivity. Enzymes, which very often react with one enantiomer only, thus show total substrate enantioselectivity. Except for enzyme reactions, ordinary chemical reactions using chiral reagents, catalysts, or medium are not generally of high substrate enantioselectivity while substrate diastereoselectivity particularly of reactions with stereoelectronic control is often very high as shown by examples in Chapter 12.

Another type of selectivity may be mentioned in this connection for substrates which are capable of reacting at more than one centre (polydent molecules) but react at one centre with a higher rate than at the others. This is known as *regioselectivity*. Thus 2-methylcyclohexanone on base induced alkylation gives mostly 2,2-dimethylcyclohexanone and only a little of 2,6-dimethylcyclohexanone. C-Alkylation versus O-alkylation of β-keto-esters provides another example in which the ratio of the products depends on various factors.

2. Product selectivity. Product selectivity refers to cases where a single substrate is capable of giving two or more products but one is formed predominantly. When the products are stereoisomers, e.g., diastereomers or enantiomers, the selectivity is called product stereoselectivity or more precisely, product diastereoselectivity and product enantioselectivity as the case may be. Accepting the suggestion made before, the word 'product' may be dropped and they are referred to simply as diastereoselectivity and enantioselectivity.

The stereoselectivity is expressed as the percentage of the more abundant stereoisomer whether they are enantiomers or diastereomers. Thus the diastereoselectivity of reduction of 4-*t*-butylcyclohexanone with lithium aluminium hydride is 90%. Alternatively, it may also be expressed as stereoisomeric excess, or more precisely, as diastereomeric excess, *de* and enantiomeric excess, *ee* depending on the situation. The second method is generally followed in enantioselective reactions since the value of *ee* directly corresponds to the extent of asymmetric induction and also to the analytical values derived from optical rotation data and from NMR data (see Chapter 7).

A new system of nomenclature for stereoselective reactions has been proposed (Izumi and Tai 1977) based on the symmetry of the substrate under the general heading of stereodifferentiating reactions. The system is, however, cumbersome and has not yet got any currency. Moreover, the terms *stereoselectivity* and *stereospecificity* have become so much part and parcel of organic synthesis that it is advisable to retain them with as little modification as possible.

13.2.2 **Principle of stereoselectivity**

For a reaction to be stereoselective, the substrate must have prostereogenic elements, which in turn depends on the symmetry or more specifically on the topicity of the reacting groups or faces. As pointed out in Chapter 6, only stereoheterotopic (enantiotopic and diastereotopic) groups and faces on appropriate modification give rise to stereoisomers (enantiomers and diastereomers).

The principle of stereoselectivity whether it refers to diastereoselectivity or enantioselectivity in a kinetically controlled reaction is the same: The two stereoisomers must be formed through two diastereomeric transition states. By virtue of their diastereomeric nature, they would differ in their free energies and thus give products in different amounts. The greater is the difference in the free energy, the higher is the stereoselectivity. A difference of 10 kJ mol^{-1} at ambient temperature leads to the formation of the preferred isomer in about 98% yield. The stereoelectronic factor, the steric factor, and other electronic effects (including the participation of chelate and hydrogen bonds) are all to be considered in designing a highly stereoselective reaction. The strategy of such a synthesis has to be decided on an individual basis and no fixed guide line can be given.

Two diastereomeric ligands or faces by their very nature give two diastereomeric transition states on reaction even with an achiral reagent*. Potential chirality and dissymmetry of the reagent in such cases may increase the number of possible transition states and products. Reactions with such substrates can only be diastereoselective. In order to create diastereomeric transition states from substrates containing enantiotopic faces or enantiotopic ligands, the reagents (catalysts, solvents, or the medium) have to be chiral. In the transition states, the developing chirality (*R* or *S*) at the prochiral centre or face of the substrate along with the fixed chirality of the reagent (*R* or *S*) would give rise to two diastereomeric combinations thus

*In the case of addition to an sp^2 hybridised prochiral centre, the entering ligand must be different from the ligands already present at the centre. This is also true for substitution.

fulfilling the requirement of a stereoselective synthesis. If the reagent or the auxiliary chiral associate separates or is detached from the product at the end of the reaction, the reaction would be enantioselective. On the other hand, if the chiral moiety remains attached to the product, it would be a case of diastereoselectivity.*

The principle of enantioselective reaction stated above is illustrated with the help of energy diagrams (Figure 13.1). Acetophenone has two enantiotopic faces *Re* and *Si* as shown and an organometallic hydride represented by H-M(L) (M = metal, L = organic ligand or ligands) can approach the trigonal carbon from either face through two transition states TS-1 and TS-2. If L is achiral (case A), the transition states become non-superposable mirror images of each other and so equienergetic. *R*- and *S*-alcohols are thus formed in equal amounts giving a racemic mixture and the energy diagram corresponds to that in the upper right. Enantioselectivity is non-existent. But if L is chiral (case B), the two transition states are no

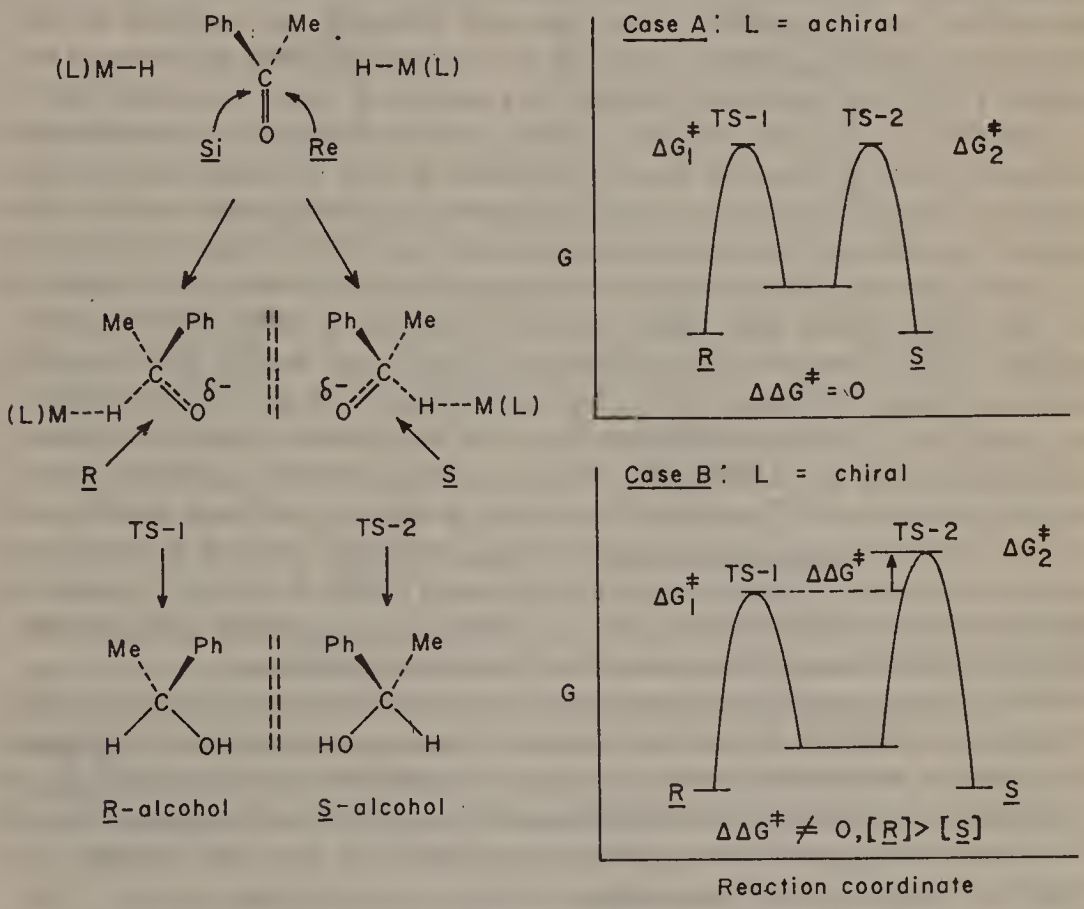


Figure 13.1 Principle of enantioselective reaction

* An illuminating example of the latter class is the addition of methylmagnesium iodide to the ester of phenylglyoxylic acid and an optically active alcohol (see Prelog's rule in Chapter 8). The reaction is diastereoselective since one of the diastereomeric products (which contain two chiral centres) is formed preferentially. However, on hydrolysis, the alcoholic component is detached and atrolactic acid is obtained in an enantiomeric excess which, if hydrolysis is quantitative, is equal to the diastereomeric excess in the first reaction. The overall process is thus enantioselective.

longer enantiomeric but diastereomeric. The energy diagram (lower right) now shows a difference in free energies between the two transition states ($\Delta\Delta G^{\ddagger}$) and the enantiomers are formed in unequal amounts, the *R*-alcohol predominating in the case shown. The reaction is thus enantioselective; the stereoselectivity is achieved through the formation of two diastereomeric transition states. It may be noted that the ground state energies of the products are the same and so under thermodynamically controlled condition, the product would be racemic.

13.2.3 Asymmetric synthesis and asymmetric induction

Two terms which are commonly used in connection with stereoselective synthesis are asymmetric synthesis and asymmetric induction. According to the original definition (Marckwald), an asymmetric synthesis is a reaction which produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of any analytical (separation) process. According to a broader definition by Morrison and Mosher (1971), an asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules (having either enantiotopic or diastereotopic groups or faces) is converted into a chiral unit in such a manner that unequal amounts of stereoisomers are produced. Asymmetric syntheses thus comprise both enantio- and diastereoselective reactions with the proviso that a new *chiral centre* is created. In many enantioselective syntheses, this is often done at the expense of an old one in which case the asymmetric synthesis is called self-immolative (Mislow 1965). When the products are diastereomers, they may be either optically active or racemic. Confusion arises when reactions give two achiral diastereomers, e.g., reduction of 4-*t*-butylcyclohexanone to *cis*- and *trans*-4-*t*-butylcyclohexanols. According to the above definition, this is not an asymmetric synthesis but the analogous reduction of 2-methylcyclohexanone is since an additional chiral centre is being created in the process. In spite of this ambiguity, the term is extensively used and a series of volumes edited by Morrison (1983-) is entitled, *Asymmetric Synthesis*. In this text, the term will be replaced by more precise terms, enantioselective and diastereoselective reactions as and when appropriate.

The somewhat parallel term *asymmetric induction* defines the extent of asymmetry induced at a prochiral centre of the substrate either by the chirality of the reagent or by one or more chiral centres present in the substrate molecule itself*. In an enantioselective reaction, asymmetric induction is equal to the enantiomeric excess (*ee*) and in diastereoselective reactions (giving rise to a new chiral centre), it is equal to the diastereomeric excess (*de*).

13.2.4 Double diastereoselection and double asymmetric induction

In diastereoselective reactions, the asymmetric induction (*de*) remains the same whether the substrate is enantiomerically pure (homochiral†) or racemic provided

*Many authors seem to have used this term in a merely qualitative or semi-quantitative way.
†According to Masamune (see Chapter 3).

the reagent is achiral. The situation is, however, different if the reagent is optically pure. The effect of various combinations of substrates and reagents (achiral or chiral) is best discussed with an example, e.g., the reduction of 2-methylcyclohexanone (see Nögradi 1987) with H-donating reagents. The ketone exists in two enantiomeric froms *S* and *R* (Figure 13.2). When either of them is reduced with an achiral reagent, e.g., lithium aluminium hydride, two diastereomers are formed, a trans (1*S*, 2*S* from *S*-ketone and 1*R*, 2*R* from *R*-ketone both designated *l* according to Prelog-Seebach) and a cis (1*R*, 2*S* or 1*S*, 2*R* designated *u*), the former predominating. The asymmetric induction or diastereomeric excess (*de*) is given by the equation:

$$\text{Asymmetric induction} = de = \frac{[l] - [u]}{[l] + [u]} \times 100$$

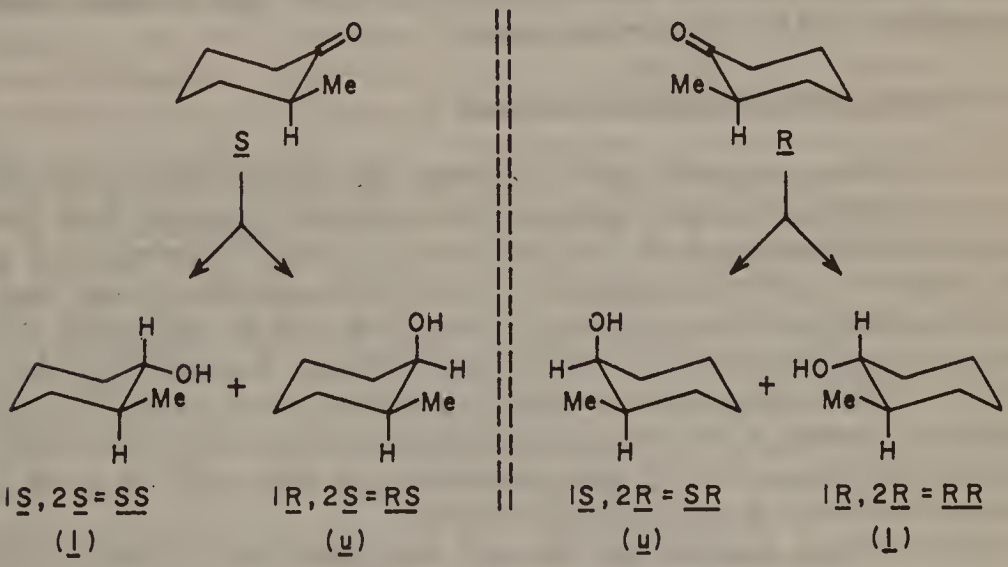


Figure 13.2 Example of double diastereoselection

This holds for both enantiomers of the ketone and therefore for the racemic ketone as well which proves the first point. Two further situations have to be considered. (i) The substrate is enantiomerically pure (say the *S*-ketone in the left hand diagram) and the reducing agent is chiral, either *R* and *S*. With the *R*-reagent, the transition state for the formation of the trans isomer (*l*) may be represented by *SS-R* (chirality *R* of the reagent being added to the topographical descriptors of the product) and with the *S*-reagent, the transition state may be represented by *SS-S*. The two transition states are diastereomeric and so the asymmetric induction or diastereoselection (*de*) will be different when the *S*-ketone (or the *R*-ketone) is reduced with reagents of opposite chirality. The diastereoselectivity in each combination of the substrate and reagent (*SR* or *SS*) may be considered in terms of two contributions: one due to the inherent diastereoface selectivity of the substrate and the other due to the inherent diastereoface selectivity of the reagent leading to what is known as *double asymmetric induction*, or *double diastereoselection* (Masamune, Heathcock). The two contributions may operate synergistically for one combination reinforcing the overall diastereoselectivity or may

oppose each other reducing the diastereoselectivity.* An almost similar situation arises if the chirality of the reagent is kept fixed (say *R*) and the that of the substrate is varied (*S* or *R*). The transition states for the *l* isomer is now *SS-R* or *RR-R* (diastereomeric). The same argument holds for the formation of the *u* isomers, the transition states being *RS-R* and *SR-R*. (ii) In the second situation, the substrate is racemic (*S*- and *R*-ketone) and the reagent is optically pure (say of *R*-chirality). Here again, the *l* isomers (trans) can be formed through transition states *SS-R* and *RR-R* which are not enantiomeric as in the case of an achiral reagent but diastereomeric and so the two enantiomeric trans isomers (*SS* and *RR*) will form in unequal amounts. The same is necessarily true for the *u* isomers (cis), i.e., *RS* and *SR* will form unequally so that both the trans and cis isomers will have *enantiomeric excess* (four stereoisomers are now formed all in unequal amounts). In such cases, it is a general rule that the *ee* value of a diastereomer is inversely proportional to its diastereoselectivity, i.e., the more abundant isomer (here the trans) will have the lower *ee* excess.

13.2.5 Strategy of stereoselective synthesis

While synthesising an optically active compound with multiple chiral centres (say, a natural product), one usually synthesises the compound in racemic form fixing the relative configuration at all the chiral centres through diastereoselection and then applies the resolution technique. It is sometimes preferable to start with a resolved compound (at an early stage) or better still with an appropriate chiral synthon† (chiron approach) or its equivalent reagent (see Warren 1978; Fuhrhop and Penzlin 1983), which may be available either from natural sources (Hanessian 1983) or by synthesis. If possible, an enantioselective reaction may be employed in one of the steps to get optically pure intermediate. Modern trends are to use the chiron approach and/or enantioselective reactions.

Diastereoselective reactions are discussed here under two headings, acyclic diastereoselection and cyclic diastereoselection, followed by enantioselective reactions. No sharp distinction can, however, be maintained between diastereoselection and enantioselection which very often go side by side.

13.3 Acyclic stereoselection

Acyclic molecules are conformationally more mobile than cyclic and stereoselectivity is, therefore, more difficult to attain in the former. Nevertheless, the first

*Since the starting ketone is optically active, the products in all cases are optically active.

†A target molecule is hypothetically broken down into a few smaller fragments called synthons which are usually reactive intermediates derivable from reagents known as *equivalent reagents*. The process is called a *disconnection* (a retrosynthesis) and each step in it a *transform* which is indicated by a double-lined hollow arrow. The synthesis of ethylbenzene is thus depicted as follows:

$$PhCH_2CH_3 \Longrightarrow \underset{\text{(Synthons)}}{PhCH_2^{+} + \bar{C}H_3}$$

The equivalent reagents for the synthons are benzyl chloride and methyllithium respectively.

rationalisations of asymmetric induction were worked out for reactions in acyclic system, e.g., Cram's rule and Prelog's rule (Chapter 8). During the last decade and a half, tremendous developments have been made in acyclic stereoselection, the main incentive being provided by the isolation of a group of macrolide antibiotics, e.g., erythronolides which contain contiguous chiral centres in a macro ring. The topic of acyclic stereoselection has been extensively reviewed (Eliel and Otsuka 1982, Heathcock 1982-1984, Evans et al 1982, Evans 1984, Masamune et al 1985, Mukaiyama 1982, Morrison 1983-1985). In most cases, both diastereoselection and enantioselection are accomplished simultaneously.

13.3.1 **Addition of nucleophiles to carbonyl compounds**

Addition of nucleophiles specially carbanions to carbonyl compounds is one of the most common method to generate a new C-C bond. A simple achiral carbanion equivalent such as R^- (including H^-) gives rise to stereoisomers on addition to a carbonyl compound when the latter has two enantiotopic or diastereotopic faces. In the former case, enantiomers are formed and enantioselectivity can be achieved only by using chiral auxiliaries or a chiral medium. In the latter case, diastereomers are formed in different amounts with varying degrees of stereoselectivity.

1. 1,2-Asymmetric induction. If the chiral centre in the substrate is adjacent to the carbonyl group, the stereochemical course of nucleophilic addition follows Cram's rule (see Chapter 8) based on either the open-chain model (I) or the cyclic or chelate (rigid) model (II) (Figure 13.3). Stereoselectivity through the open-chain model (non-rigid) is not usually high except for a few cases where R′ is bulky. On the other hand, the chelate model can give high stereoselectivity depending on the extent of chelation which in turn is determined by the nature of the chelating group, metal, and solvent (Eliel 1983). Thus Still and McDonald (1980) obtained almost complete diastereoselectivity in Grignard addition to R-CHOX-COMe where X = methoxyethoxymethyl or similar bident chelating groups.

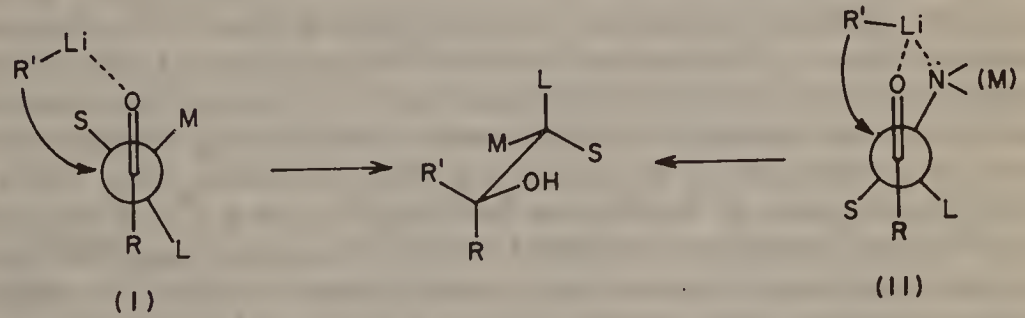


Figure 13.3 Cram's open chain and cyclic models

Recently, Sato et al (1984) have achieved high diastereoselectivity in Grignard reactions and hydride additions with substrates (III) which do not contain a chelating group but have a bulky trimethylsilyl moeity as a part of the L group

(Figure 13.4). The syn compound (Cram product)* is obtained in over 99% yield. When it is oxidised to the ketone (IV) and the latter reduced with metal hydrides, the anti diastereomer. again the Cram product, is obtained almost exclusively. The same substrate (III) is thus used for the stereoselective synthesis of both syn and anti diastereomers of β-methylhomoallyl alcohols; the silyl group is removed by NaH (for syn-anti nomenclature, see Chapter 4).

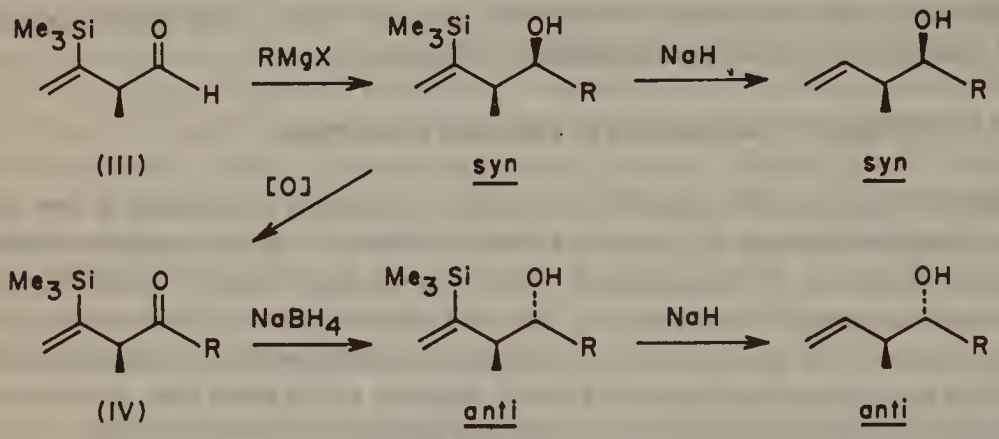


Figure 13.4 Diastereoselective formation of β-methylhomoallyl alcohols

Two of the substituents at the chiral centre may be parts of a ring and in such cases, if one of the adjacent endocyclic atom is chelating, a highly diastereoselective addition to the exocyclic ketone may occur. This is illustrated by two groups of workers who have used a chiral ring system as chiral adjuvant later to be removed to yield almost totally enantiomerically pure products.

Eliel et al (1981) have prepared the bicyclic chiral adjuvant (V) from commercially available (+)-pulegone (Figure (13.5). The derived lithium derivative is obtained entirely in the equatorial form (e-Li at C-2) due to stereoelectronic reason and reacts with an aldehyde with retention of configuration again giving entirely the equatorial diastereomer. The corresponding ketone (VI) undergoes Grignard addition to give exclusively the alcohol (VII) according to Cram's chelate model (chelation occurs between hard Mg and hard O). Cleavage of the oxathiane leads to the α-hydroxyaldehyde(VIII)from which the corresponding tertiary alcohol, glycol, and hydroxyacid may be obtained in 90-99% enantiomeric purity. This is a case of double transfer of chirality—the first transfer occurs at C-2 of the chiral adjuvant (during lithiation) and the second transfer occurs during Grignard addition. The chiral adjuvant can be reconstituted from the products of cleavage. An elegant and highly enantioselective (*ee*>98%) synthesis of both *R*- and *S*-mevalonolactone has been achieved by employing this method (Frye and Eliel 1985).

*The reader is advised to verify that the products correspond to Cram's model. A guide line may be provided thus: If after addition, the main chain remains undiminished in length (as in the reduction of IV). the relative configuration of the Cram product is anti whereas if the chain length is increased (e.g.. Grignard addition to III), the relative configuration is syn. In the latter case, the chain has to be reoriented.

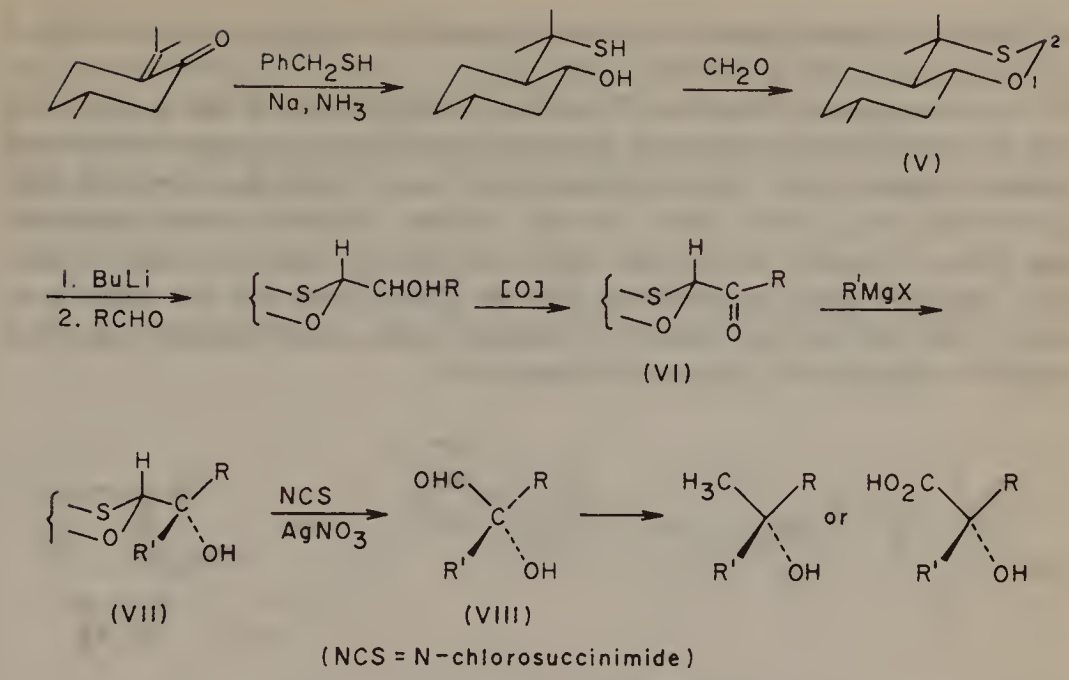


Figure 13.5 Diastereoselective addition to 2-acyl-1,3-oxathianes and enantioselective synthesis of tertiary alcohols

A very similar highly enantioselective synthesis of hydroxyaldehydes starting with 2-anilinomethylpyrrolidine (IX) (Figure 13.6) derived from commercially available proline has been reported by Mukaiyama et al (1978). The bicyclic phenyl ketone (X) on Grignard addition gives almost a single diastereomer (as shown)* which on acidic hydrolysis yields the enantiomerically pure α-hydro-

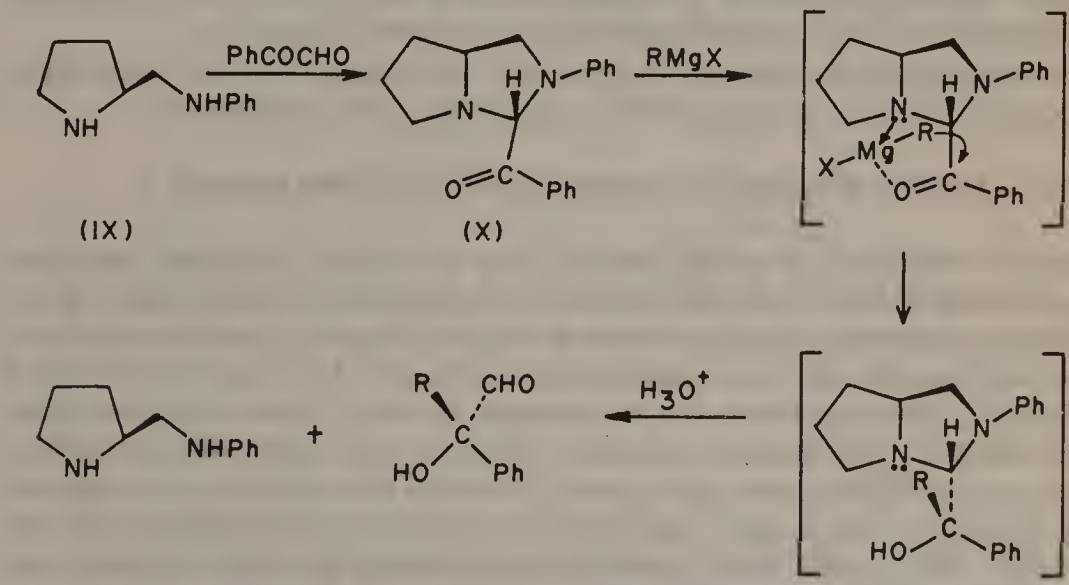


Figure 13.6 Enantioselective synthesis of α-hydroxyaldehyde from 2-anilinomethyl-pyrrolidine

*MgX coordinates with the aliphatic, not the aromatic nitrogen during the reaction with the ketone (X) which has a *cis*-exo configuration. This explains the stereochemistry according to Cram's rigid model.

xyaldehydes and the anilinomethylpyrrolidine back. Phenylglyoxal may be replaced by alkylglyoxals in the above series of reactions.

2. 1,3-Asymmetric induction. When the carbonyl group is two bonds away from the chiral centre, asymmetric induction particularly in reaction with metal hydrides is usually low. Recently, Reetz and Jung (1983) have reported high diastereoselectivity (>90%) in the addition reaction of chiral β-alkoxyaldehydes using titanium reagents through the chelated six-centred chair-like model (Figure 13.7). The alkyl group is transferred from the β-face (from the side opposite to methyl at the chiral centre) rather than from the α-face of the chelated ring (for a review of organotitanium reagents, see Reetz 1982).

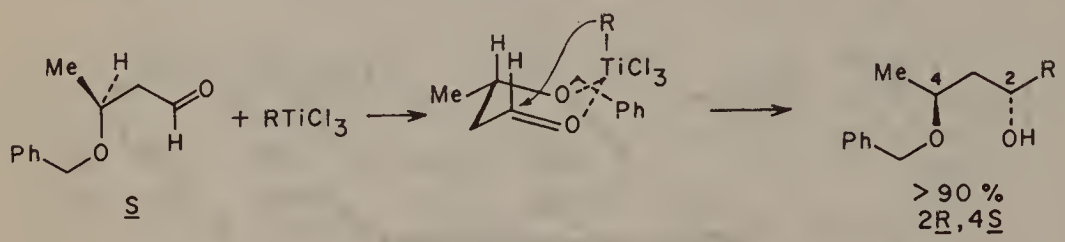


Figure 13.7 1,3-Asymmetric induction

3. 1,4-Asymmetric induction. Metal hydride reactions with and Grignard additions to glyoxylic esters $RCOCO_2R^*$ (R^* is the chiral moiety of an alcohol) illustrate examples of 1,4-asymmetric induction whose course has been rationalised by Prelog's rule (Chapter 8). Asymmetric induction in these reactions is usually low to moderate. However, high asymmetric induction (98%) has been observed when (-)-8-phenylmenthyl glyoxylate is used as the substrate. Presumably the bulky phenyl group blocks one diastereoface of the carbonyl group effectively (Whitesell et al 1982). Prelog's model may be consulted (Chapter 8).

A carbonyl group separated by more than three bonds from the chiral centre does not show much stereoselectivity in nucleophilic addition reactions.

13.3.2 Addition of enolate to a carbonyl group : the aldol reaction

In aldol reactions*, an enolate derived from a carbonyl compound undergoes nucleophilic addition to another carbonyl compound usually an aldehyde, to give a β-hydroxy-aldehyde or ketone, known as an aldol. Depending on the symmetry of the two reactants, the two centres joined by the new C-C bond may be chiral (Figure 13.8a) giving rise to four stereoisomers or two (±)-pairs of diastereomers. The number of diastereomers increases if either or both of the aldehyde and the enolate contain additional chiral centres. Often high stereocontrol can be achieved by choosing proper reactants and reaction conditions; thus the aldol reaction has emerged as a powerful tool for stereoselective synthesis of acyclic molecules with contiguous chiral centres.

*For a review, see Nielsen and Houlihan (1968).

1. Achiral aldehydes and achiral enolates. An achiral aldehyde and an achiral enolate each with two enantiotopic faces can combine in two modes: an unlike mode (*ul*) in which combination takes place between *Si* and *Re* (or *Re* and *Si*) faces of the reactants and a like mode (*lk*) in which combination takes place between *Re* and *Re* (or *Si* and *Si*) faces (Figure 13.8b and 13.8c). The former

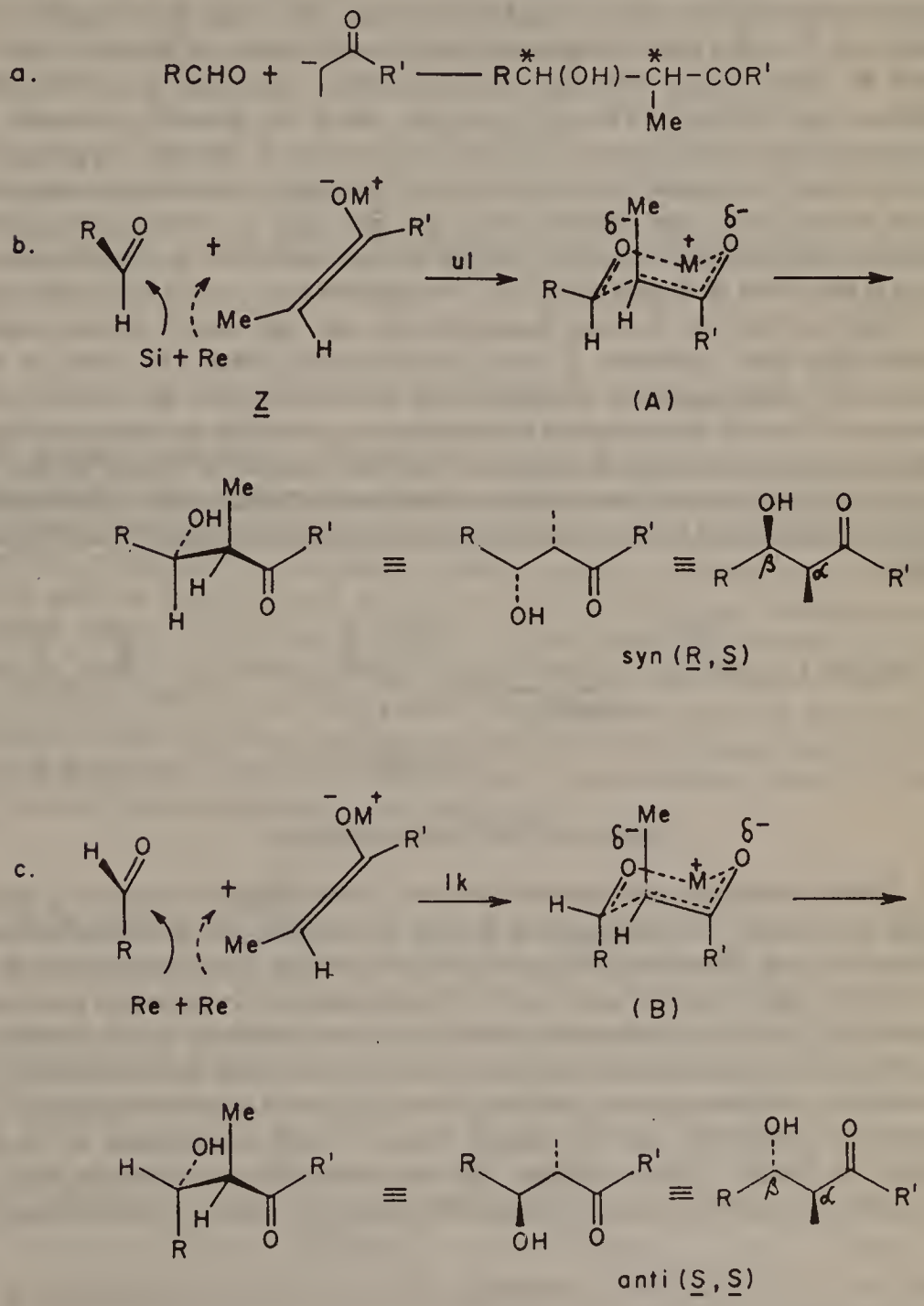


Figure 13.8 Transition states for aldol reations: Zimmerman-Traxler model

leads to a syn and the latter to an anti diastereomer irrespective of the geometry of the enolate (*Z* or *E*)*. Following a chair-like six-centre arrangement in the transition state (Zimmerman and Traxler 1957), the formation of the syn isomer from a *Z*-enolate takes place through the model (A) and that of the anti isomer through the model (B). If R and R′ are large or moderately so, a 1,3-synaxial interaction would disfavour B with respect to A (which has only a R/Me gauche interaction) and the syn isomer would predominate. The extent of stereoselectivity which may be called aldol diastereoselectivity would depend on the steric bulk of R and R′ and is usually very high. This argument is valid only if the following conditions are fulfilled. (*i*) The aldol reactions which are generally reversible be performed under kinetic control† (*ii*) The transition state is chair-like, as proposed, with the metal coordinated to both the carbonyl oxygens-a reasonable assumption except when Lewis acid catalysts, e.g., BF_3 are used in which case acyclic transition states become operative. (*iii*) The enolate must exist in *Z*-configuration which is true when R′ is very bulky, e.g., *t*-Bu and the like. For the *E*-enolates also, the transition state (A) is more favourable but with Me and H of the enolate interchanging their positions. it now gives the anti isomer. In most of the synthetically useful reactions, *Z*-enolates are involved so that the relative configuration at the two newly created chiral centres is syn (*aldol syn stereoselection*). A typical example is shown in Figure 13.9 for the reaction of lithium enolate of ethyl *t*-butyl ketone with benzaldehyde. Reactions effected under equilibrating condition usually lead to anti isomers (anti stereoselection) because of their higher stability.

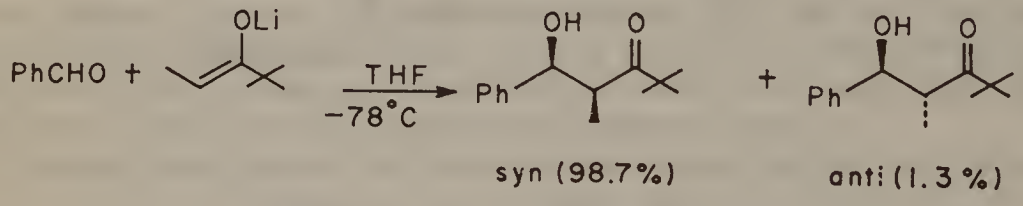


Figure 13.9 Aldol syn diastereoselection

2. Chiral aldehydes and achiral enolates. If the aldehyde contains a chiral centre, the number of diastereomers formed by addition of an achiral enolate increases to four. However, aldol syn stereoselection for *Z*-enolates reduces it to two: syn,syn and syn,anti (Figure 13.10). The two faces of the carbonyl group are diastereotopic and the diastereoface selectivity of the aldehyde would determine the ratio of the two isomers. In the absence of any polar group in the aldehyde, the diastereoface selection may be predicted from the Cram's open-chain model (1,2-asymmetric induction) and the syn,syn isomer would predominate as in the example in Figure 13.10a. Although the stereoselectivity is moderately high, it would be considerably reduced if the aldol reaction is repeated several times in

*This is due to the fact that as the enolate changes from *Z* to *E*, the face also changes from *Re* to *Si*, a case of double interchange.

†The kinetic control in most cases is maintained through chelation of the aldol with metal cations or boron in aprotic solvents. Lithium and boron enolates are particularly effective.

succession to form a long chain with alternating alkyl and hydroxy substituents. A double asymmetric induction can boost the stereoselectivity as will be seen later. The diastereoface selectivity of an aldehyde with respect to different enolates, however, may not always conform to Cram's rule as illustrated for *S*-2-cyclohexyl-propionaldehyde (Figure 13.10b) which gives anti-Cram product in excess.

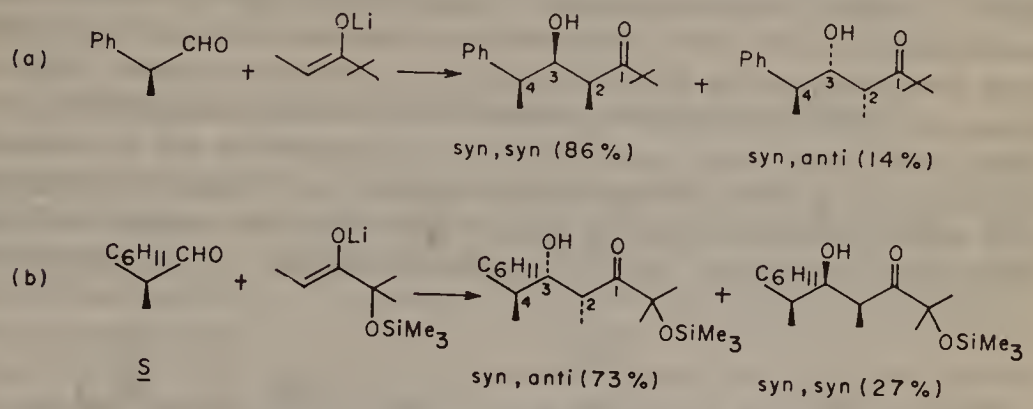


Figure 13.10 Diastereoface selectivity of chiral aldehydes

3. Achiral aldehydes and chiral enolates. The situation is very similar to that discussed above if a chiral enolate reacts with an achiral aldehyde. Two diastereomers are formed, their relative amounts being determined by the diastereoface selectivity of the enolate. Very often, a chiral auxiliary is attached to the enolate which may be later removed so that the end products are enantiomerically enriched. In the first example, (Figure 13.11a) the dibutylboron enolate is derived from an amide containing a chiral centre. The reaction proceeds with high diastereoselection and with still higher enantioselection and the product on hydrolysis yields 3-hydroxy-2-methylcarboxylic acid of high optical purity. In the other example, benzaldehyde is condensed with a chiral enolate (Figure 13.11b); but here the diastereoselectivity is only moderate.

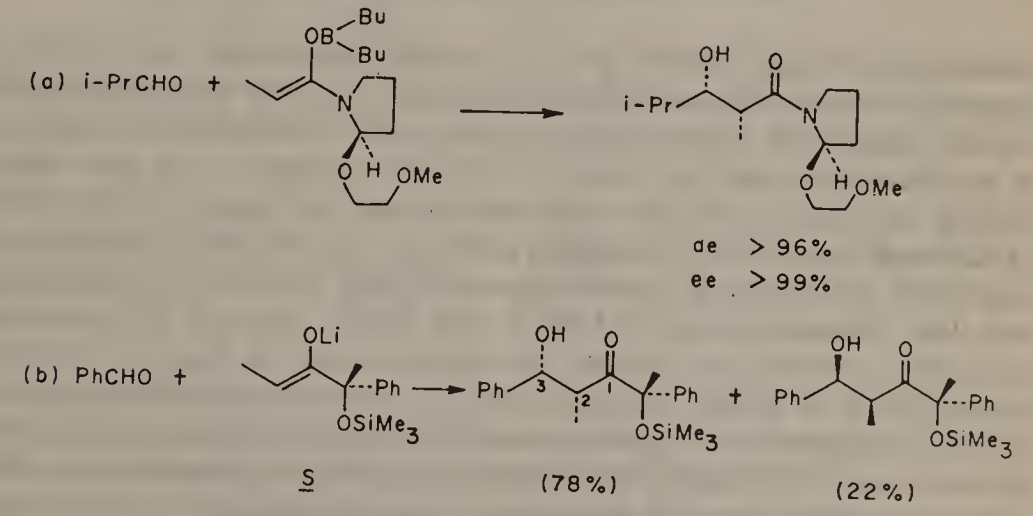


Figure 13.11 Diastereoface selectivity of chiral enolates

4. Chiral aldehydes and chiral enolates. The stereochemistry of the addition of a chiral enolate to a chiral aldehyde is much more complex. Several factors operate jointly and control the overall stereoselectivity. Eight (±)-pairs of diastereomers are possible if the chiral components are taken as racemates which are reduced to only two as shown in Figure 13.12 if the chirality of the two components is fixed and if a completely syn configuration is assumed at C-2 and C-3 centres (aldol diastereoselection). The combined diastereoface selectivities of the two components would then determine the absolute configuration at these two centres. This is a typical case of double asymmetric induction (double stereoselection). If the two existing chiral centres work synergistically, the stereoselectivity will be enhanced and if they work at cross purposes, the stereoselectivity will be reduced. A study of a few related examples can help to predict which of the two isomers (XII) and (XIII) should predominate. Thus 1.2-asymmetric induction in *S*-2-cyclohexylpro-

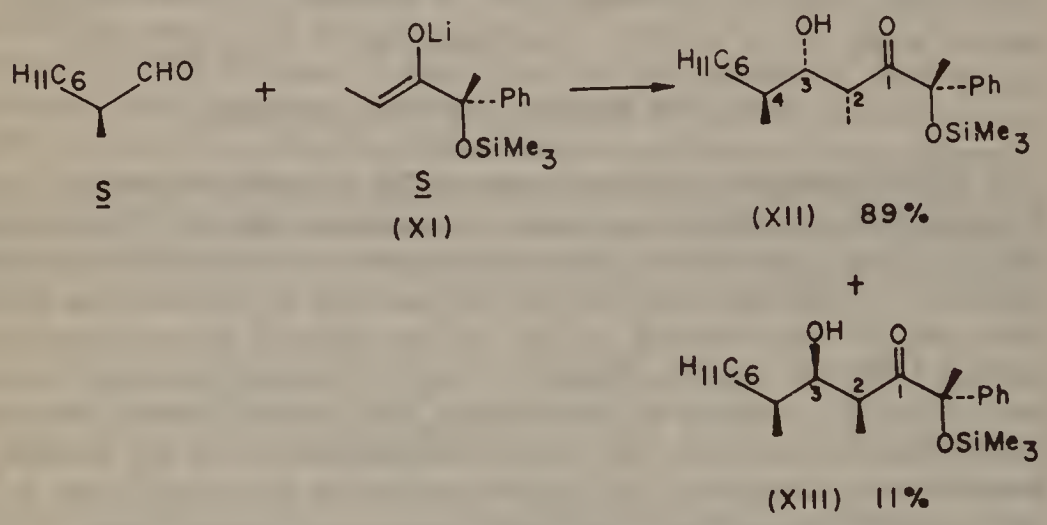


Figure 13.12 Double asymmetric induction (double diastereoselection)

pionaldehyde (Figure 13.10b) gives a 3-α-OH configuration (as in XII) preferentially. Similarly, the reaction of the *S*-enolate (XI) with benzaldehyde gives a 2-α-Me configuration (Figure 13.11b) again as in XII. The diastereoface selectivities of the *S*-aldehyde and the *S*-enolate (XI) thus cooperate with each other in forming the isomer (XII) but neither gets its way in forming the other isomer (XIII) which explains the predominant product as XII. In a cross combination, i.e., *S*-aldehyde and *R*-enolate, the two stereoselectivities work in opposition giving a very low diastereoselection (1:1.5). It also follows that the stereochemically cooperative reactants (in this case, the aldehyde and the enolate of the same chirality, *R* or *S*) would react faster than the stereochemically non-cooperative reactants (components of opposite chirality) so that if the racemic aldehyde (*RS*) is allowed to react with the racemic enolate (*RS*), condensation would occur almost exclusively between *R* and *R* and between *S* and *S* components and very little of cross combination (between *R* and *S* or between *S* and *R*) would take place. Such a situation has actually been observed by Heathcock who initially called it a case

of *mutual kinetic resolution*. Since however, there is no actual resolution, he later agreed to rename it* as a case of *mutual kinetic enantioselection*.

With a few chiral boron enolates, the diastereoface selectivity may be so high that it completely outweighs the moderate asymmetric induction or the diastereoface selectivity of the chiral aldehydes. In such cases, by changing the chirality of the boron enolates, either diastereomer may be obtained in high purity (see Carruthers 1986).

13.3.3 Addition of allylmetal and allylboron compounds to carbonyl

Allylmetal and allylboron compounds add to a carbonyl group through reactions very similar to an aldol condensation, -OM (M = metal) of the enolate being replaced by -CM or -CB (B = boron) in which the metal and boron are the potential leaving groups. The reaction is associated with an allylic rearrangement. The mechanism of the reaction both with *E*- and *Z*-allyl derivatives is shown in Figure 13.13. In the absence of any Lewis acid catalyst, e.g., BF_3, the transition state may be depicted by the chair-like structures (C) for the *E*- and (D) for the Z-allyl compounds with the metal or boron coordinated to carbonyl oxygen. Here also, two modes of attacks are possible: one between like (*Re-Re* or *Si-Si*) and the other between unlike faces (*Re-Si* or *Si-Re*). For the *E*-allyls, the two enantiomeric like approaches through transition state (as C) is favourable because in it, R of the aldehyde occupies an equatorial position whereas in the unlike approaches (not shown), it would occupy an axial position and give rise to a synaxial interaction with one of the ligands at boron (or metal). It fixes the relative stereochemistry at C-3 and C-4 as anti (cf. aldol diastereoselection). For the *Z*-allyls, a similar argument favours an approach of unlike faces and syn isomer is formed through the transition state (D). If a ketone is used (H = R), the stereochemistry cannot be

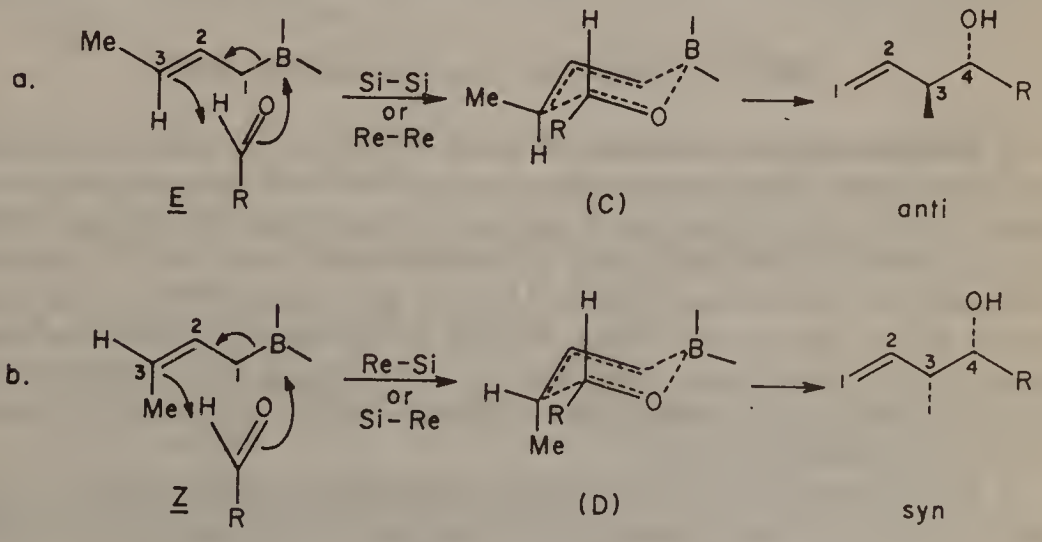


Figure 13.13 Mechanism for addition of allyl boron derivatives

*Heathcock in 'Topics in Stereochemistry' in press; his suggestion is kindly communicated to the author by Professor E.L. Eliel.

predicted so easily. Lewis acid catalysed additions go through acyclic transition states and the syn isomer is formed irrespective of the geometry of the allyl components. A few examples of diverse nature are enumerated.

1. Enantioselective synthesis. Allylboranes or allylboronic esters with chiral ligands are specially efficient for inducing high asymmetry at the carbinol carbon. Thus (−)-diisopinocampheyl- (abbreviated as IPC)-(dimethylallyl)borane (Figure 13.14) reacts with 3-methylcrotonaldehyde to give (−)-artemisia alcohol (XIV) in 96% enantiomeric excess (Brown and Jadhav 1984).

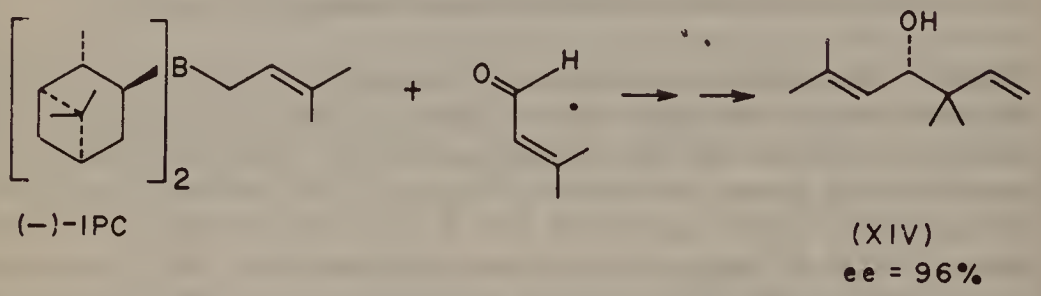


Figure 13.14 Enantioselective synthesis of artemisia alcohol

The use of optically active tartaric esters of allylboronic acid is specially interesting because its two faces are homotopic and induce asymmetry in the same direction*. Homoallyl alcohols (XV) (Figure 13.15) are obtained with 71-87% *ee*'s (Roush and Halterman 1986).

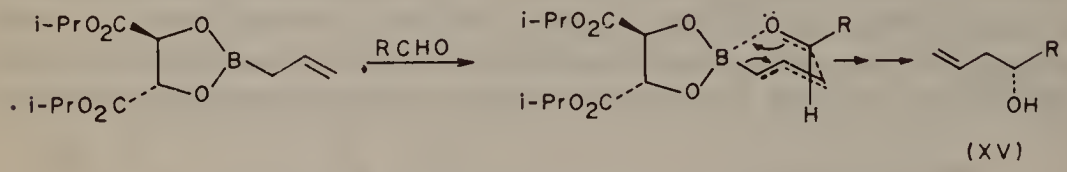


Figure 13.15 Enantioselective synthesis of homoallyl alcohols

2. Diastereoselective synthesis. If either or both of the aldehyde and allyl derivative contain chiral centres, diastereomers are formed with varying degrees of stereoselectivity. The special case of boosting the stereoselectivity through double stereoselection is worth mentioning. *S*-2-Methylbutanal reacts with (−)-phenylbornanediol-*E*-crotylboronate (Figure 13.16) to give mainly (92%) the anti,syn isomer (XVI). On the other hand, reaction of the *R*-aldehyde with the same reagent gives a gross mixture. With the (+)-*Z*-crotyl reagent the syn,anti isomer is obtained in 95% diastereomeric excess—again a case of cooperative double stereoselection (Hoffmann et al 1982).

3. Diastereoselective synthesis of either of the diastereomers. Recently, Yamamoto (1986) has achieved diastereoselective synthesis of both diastereomers from a single substrate using allylic and allenic organometallic reagents for reaction with

*Statistical advantage due to C_2 axis has been discussed recently by Isaksson et al (1988).

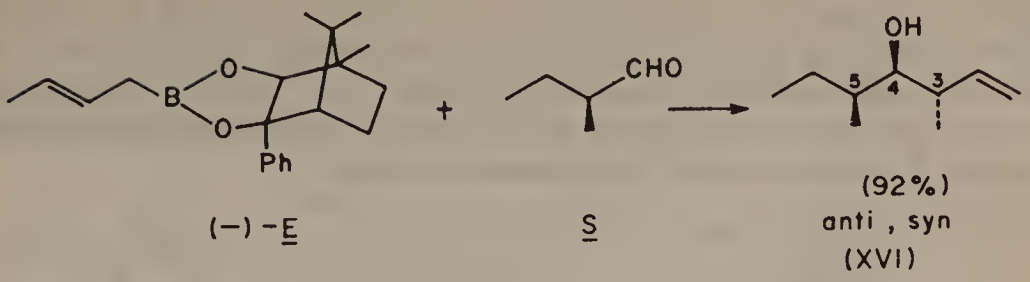


Figure 13.16 Double stereoselection with allylboronate

pyruvate (Figure 13.17). The *E*-allylic reagent, particularly with M = 9-borabicyclo [3.3.1]nonyl (9-BBN), gives almost exclusively the anti hydroxyester (XVII). The stereoselectivity increases with the bulk of R and is maximum for 2,6-di-*t*-butyl-4-methylphenyl. The stereochemistry follows from the previously discussed cyclic transition state. The allenic reagents, on the other hand, react by an acyclic mechanism giving mainly the syn acetylenic compound which on partial hydrogenation over Lindlar catalyst followed by protodesilylation gives the syn hydroxyester (XVIII). Thus by changing the reagents (actually, one of the reactants), two diastereomers are produced from the same substrate with high diastereomeric excess.*

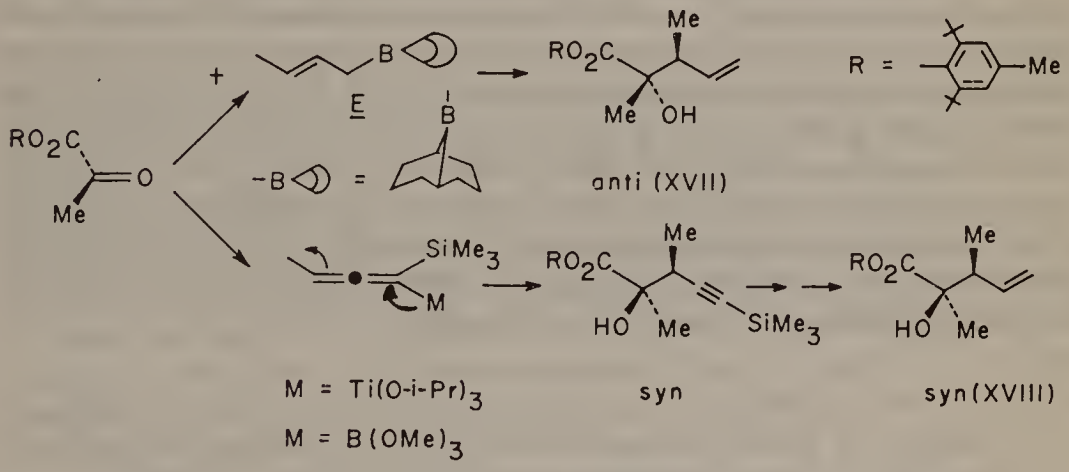


Figure 13.17 Diastereodivergent control with allylic and allenic organometallics

13.3.4 Stereoselective transformations of C = C bond

A C=C bond may be modified in several ways to give new chiral centres. Two such modifications are discussed below from stereochemical point of view.

1. Hydroboration: formation of an alcohol. Hydroboration of an olefin takes place in a syn fashion with boron being attached to the less substituted carbon and the adduct on oxidative deboronation gives an alcohol. If the double bond is

*The syntheses are said to take place under *diastereodivergent control*, two diastereomers being formed from the same substrate through two different routes. The terminology, however, seems to be quite unnecessary and meaningless.

adjacent to a chiral centre, addition takes place to the less hindered diastereotopic face with moderate to high diastereoselection. Thus in the hydroboration of the terminal double bond in the ester (XIX) (Figure 13.18), disiamyl borane reacts from the side anti to 4-Me giving 4.6-syn product (XX) predominantly (87%) (Evans et al 1982)—a case of 1,3-asymmetric induction.

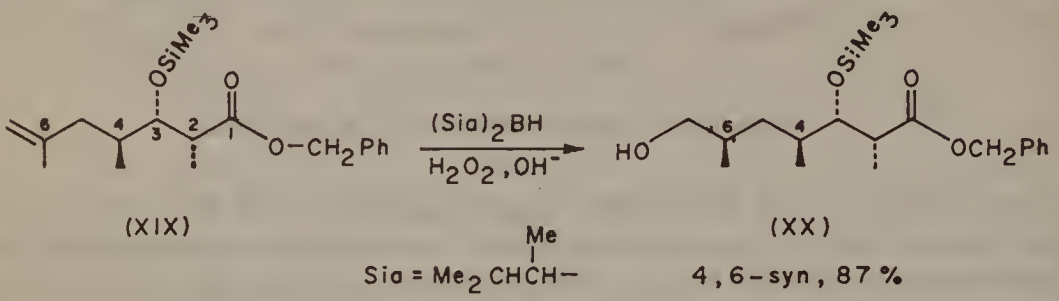


Figure 13.18 Diastereoselective hydroboration of double bond

2. Perhydroxylation: formation of a vicinal diol. Several methods of hydroxylation of olefins are available giving 1,2-glycols. Oxidation with either osmium tetroxide (osmylation) or potassium permanganate furnishes a syn glycol (Chapter 12). Oxidation with peroxy-acids which goes through an epoxide (oxiran) intermediate gives an anti glycol — a result of epoxy ring opening. A third method using iodine and a silver salt (Prévost reaction) similarly goes through a cyclic iodonium ion followed by neighbouring group participation (route 'a') to give an anti glycol (Figure 13.19). If the reaction is carried out in the presence of moisture, the intermediate acylium ion (XXI) is directly hydrolysed (route 'b') and a syn glycol results (Woodward's modification). All these reactions are substrate stereoselective giving syn or anti glycols depending on the geometry of the olefins. Thus in syn-hydroxylation with potassium permanganate, maleic acid and fumaric acid give *meso*- and (±)-tartaric acid respectively (see p. 375).

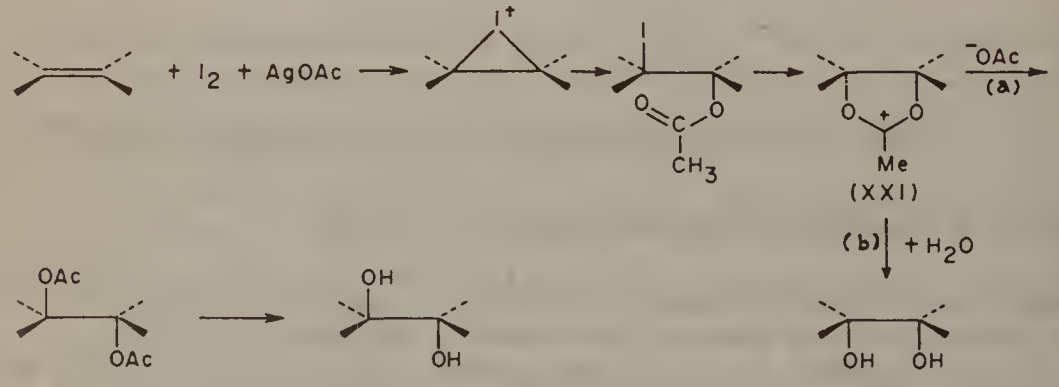


Figure 13.19 Prévost reaction and its modification

Osmium tetroxide oxidation and Woodward's modification of the Prévost reaction both giving syn glycols are complementary to each other in the sense that they show opposite diastereoselectivity in the final product. The former gives the sterically less hindered syn glycol whereas the latter gives the sterically more

hindered syn glycol, as illustrated by syn-hydroxylation of 2,3-cholestene (Figure 13.20). The first ring intermediate in both reactions is formed on the less hindered α-side but since the Prévost oxidation takes place through one more cyclic intermediate, the stereochemistry is ultimately reversed.

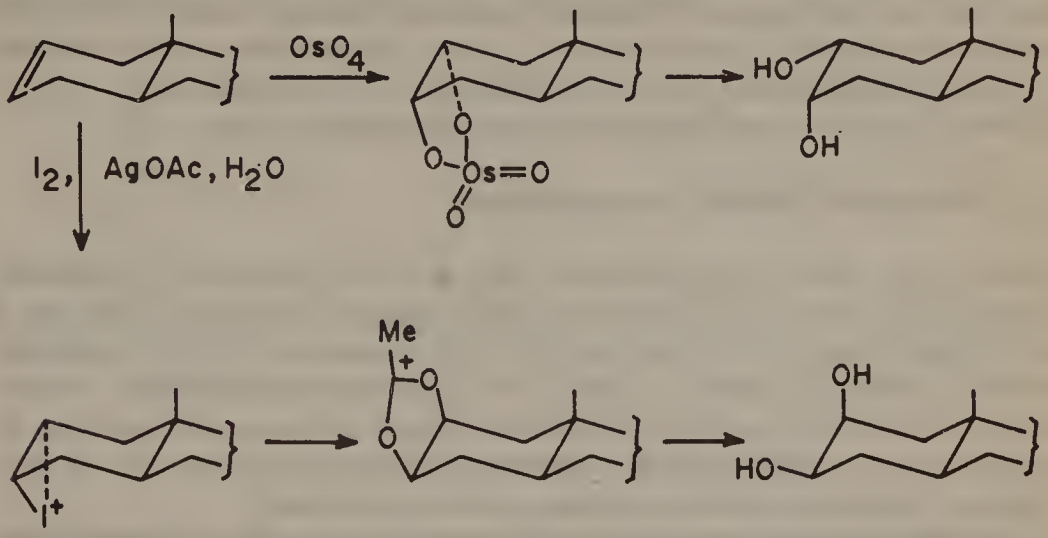


Figure 13.20 Diastereoface selectivity in OsO_4 oxidation and in Prevost-Woodward oxidation.

Recently, almost total enantioface selectivity in osmium tetroxide oxidation has been achieved by using a chiral diamine with D_2 symmetry (Tomioka et al 1987). The diamine (XXII) (Figure 13.21) has a C_2 axis along the N-C-C-N chain (in addition to a vertical C_2 axis). The two faces of the heterocyclic rings are thus homotopic and either face is stereochemically equivalent with respect to a particular enantiotopic face of the reacting olefin. The activated complex may be represented by the structure (XXIII) in which osmium is chelated to the two nitrogen atoms and for steric reasons, the *Re-Si* face of *trans*-1-phenylpropene is exposed to oxidation. *1S-2S*-1-Phenylpropane-1,2-diol is formed in over 99% enantiomeric excess. The enantioselective cis vicinal dihydroxylation of olefins has been further improved recently by Sharpless group (1988) by carrying out the osmylation in the presence of N-methylmorpholine-N-oxide. (NMO) and chiral cinchona alkaloid derivatives (as catalysts). The advantages are rate enhancement and increased catalyst turnover numbers in comparison to the chelating chiral diamines.

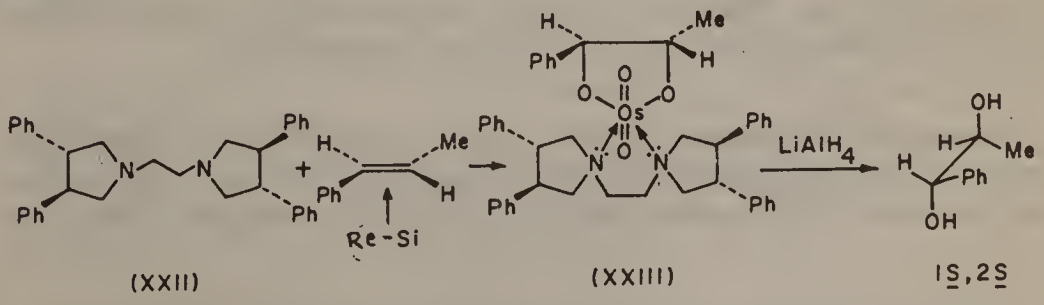


Figure 13.21 Enantioface selectivity of OsO_4 oxidation using chiral diamine

13.4 Diastereoselection in cyclic systems

Many natural products, e.g., terpenes, steroids, and alkaloids are cyclic compounds with multiple chiral centres. Their total syntheses, particularly those achieved during the last four decades, illustrate the various strategies used in designing stereoselective reactions in cyclic systems. A few compilations of these syntheses are available (Ranganathan et al 1970, ApSimon 1972, Fleming 1973). A brief discussion is given here with reference to some broad reaction types.

13.4.1 Nucleophilic addition to cyclic ketones

By far the most extensive study has been made on the stereochemistry of additions of nucleophiles, especially hydrides, to cyclohexanones, cyclopentanones, and a few bicyclo ketones. Factors responsible for stereoselection in cyclohexanones have already been discussed in Chapter 12. There are two possibilities: stereoselective formation of axial (less stable) alcohols and stereoselective formation of equatorial (more stable) alcohols. Considerable success has been had in both directions, especially in hydride reductions, which are discussed.

1. Formation of axial alcohols. The secondary axial alcohols are generally less stable and therefore must be formed under kinetic control using bulky reagents which prefer to approach the carbonyl group from the less hindered equatorial side (*steric approach control*). A large number of reagents are now available which are highly stereoselective in this respect. The results of reduction of five substituted cyclohexanones with just three of such reagents are shown in Table 13.1 (see Nögradi 1987 for other reagents).

Table 13.1 Stereoselective formation of axial alcohols[a]

Cyclohexanones (substituents)	Li (*s*-Bu)$_3$BH[b] (XXIV)	Li (Siam)$_3$BH[c] (XXV)	IsoB-OAlCl$_2$[d] (XXVI)
4-*t*-Bu	96.5	99.0	92.0
4-Me	90.0	98.0	90.0
3-Me	94.5	99.0	92.0
2-Me	99.3	99.0	98.0
3.3,5-Me$_3$	99.0	99.0	98.0

[a]Figures indicate percentage yields of axial alcohols under optimum conditions. [b]Brown and Krishnamurthy (1972); [c]Krishnamurthy and Brown (1976). [d]Eliel and Nasipuri (1965)

The structures of the reagents (XXIV), (XXV), and (XXVI) along with lithium B-isopinocampheyl-9-borobicyclo[3.3.1]nonyl hydride* (XXVII), a related trialkylborane derivative, are shown in Figure 13.22. The last two reagents (XXVI) and

*For various review articles on borane derived reagents, see a compiled volume, *Selections from Aldrichimica Acta* (1984) published by Aldrich Chemical Company.

(XXVII) are also available in enantiomerically pure form and therefore may be used for both diastereoselective and enantioselective reductions. Stereoselectivity for methylcyclohexanones is higher at low temperature (e.g., at −78°C) at which they become anancomeric. The reagent (XXVI) has been particularly useful for the preparation of axial alcohols from steroidal and triterpenoid ketones (Nasipuri et al 1976).

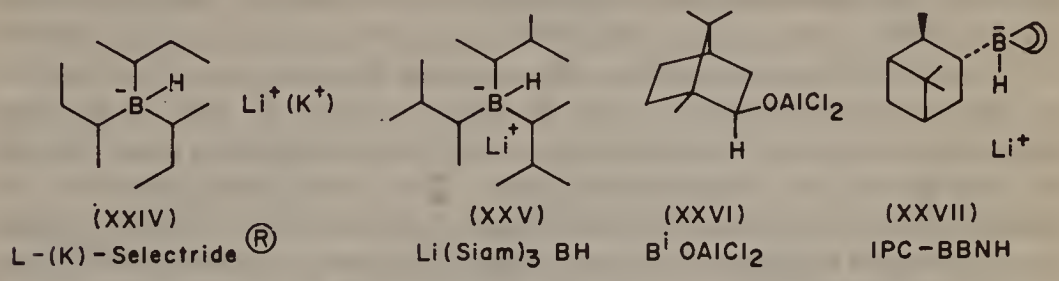


Figure 13.22 Some stereoselective H-transfer reagents

2. Formation of equatorial alcohols. The thermodynamically more stable equatorial alcohols are best prepared by dissolving metal reduction of cyclohexanones (Chapter 12). Alternatively, reduction with *mixed hydride* ($LiAlH_4$-$AlCl_3$) under equilibrium condition (Eliel et al 1967) gives almost exclusively the equatorial alcohols for all the ketones shown in Table 1. Apparently, $OAlCl_2$ solvated with ether molecules has a very high thermodynamic equatorial preference (cf. Meerwein-Ponndorf-Verley reduction in Chapter 12).

Two recent methods for the preparation of equatorial alcohols from cyclohexanones in high excess include: reduction with *t*-butylmagnesium chloride using methylalumino derivative of *bis*-(2,6-di-*t*-butyl-4-methylphenoxide) (Yamamoto 1985) (Figure 13.23a) and reduction with fluorenyloxyaluminium dichloride (Nasipuri et al 1984) (Figure 13.23b). The latter reaction is believed to go through radical intermediates and the stereochemistry is rationalised on the basis of a single electron transfer (SET) mechanism. (1990).

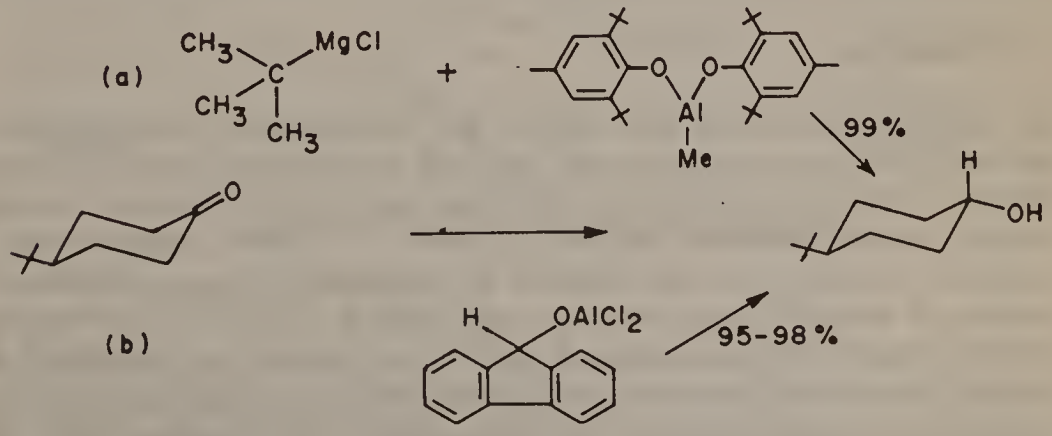


Figure 13.23 Stereoselective reduction of cyclohexanones

13.4.2 Catalytic hydrogenation

Both heterogeneous and homogeneous catalytic hydrogenations are extensively used for reduction of C = C bonds often with high stereoselectivity depending on the nature of catalysts, solvents, and the substitution pattern. In general, the substrate is adsorbed with its less hindered face toward the catalyst surface and addition of hydrogen takes place from that side in a cis fashion. The mechanism is, however, much more complex (House 1972). In some cases, groups like CH_2OH, CHO, and CO_2H show haptophilic effect meaning that they remain anchored on the catalyst surface sufficiently long to allow hydrogen to add on the same molecular face (*proximofacial addition*) to which they are attached rather than the side opposite to them (*distofacial addition*). Thus in the hydrogenation of the tetrahydrofluorene derivatives (XXVIII) (Figure 13.24) when R = CH_2OH, proximofacial addition of hydrogen takes place giving 95% of the *cis* product (XXIX) but when R = $CONH_2$, no haptophilic effect operates and the distofacial addition is preferred due to a steric factor (Thompson and Wong 1985).

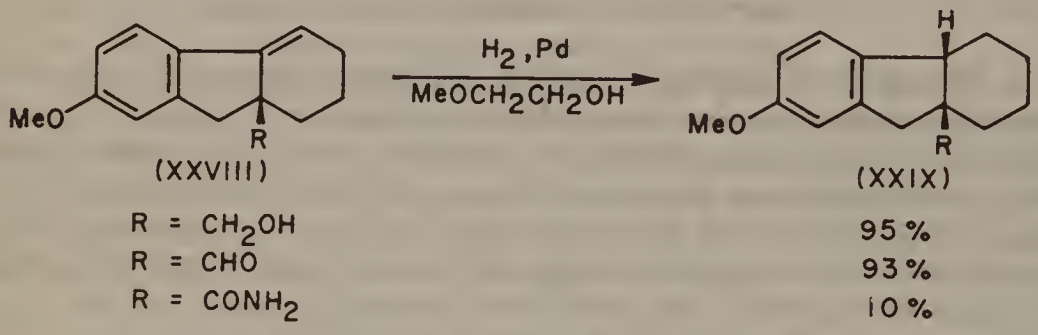


Figure 13.24 Haptophilic stereocontrol in catalytic hydrogenation

Many rhodium-phosphine homogeneous catalysts have been used for stereoselective reduction of cyclic olefins. Thus 3-methylcyclohex-2-en-1-ol and 4-methylcyclohex-3-en-1-ol are reduced in the presence of a rhodium-phosphine-boron tetrafluoride complex to give 98% of the corresponding *trans*-methylcyclohexanols (Evans and Morrisey 1984).

13.4.3 Alkylation

The stereoelectronic factor that controls the stereochemistry of alkylation of enolates derived from cyclohexanones has been discussed in Chapter 12. In the absence of any serious steric factor, alkylation leads to axially alkylated product through chair-like transition state and alkylation at a carbon already having a substituent is often more stereoselective in this respect. Thus in Woodward's synthesis of steroids (1951), when the side chain at C-10 in the intermediate (XXX) (Figure 13.25, only rings B and C are shown) was introduced by cyanoethylation the major product was the unnatural isomer (XXXIa) with methyl occupying the equatorial position. In a later synthesis by Veluz et al (1960), the alkylation sequence was reversed and methylation of XXXII gave the natural isomer (XXXIIIa) with axial methyl preponderantly.

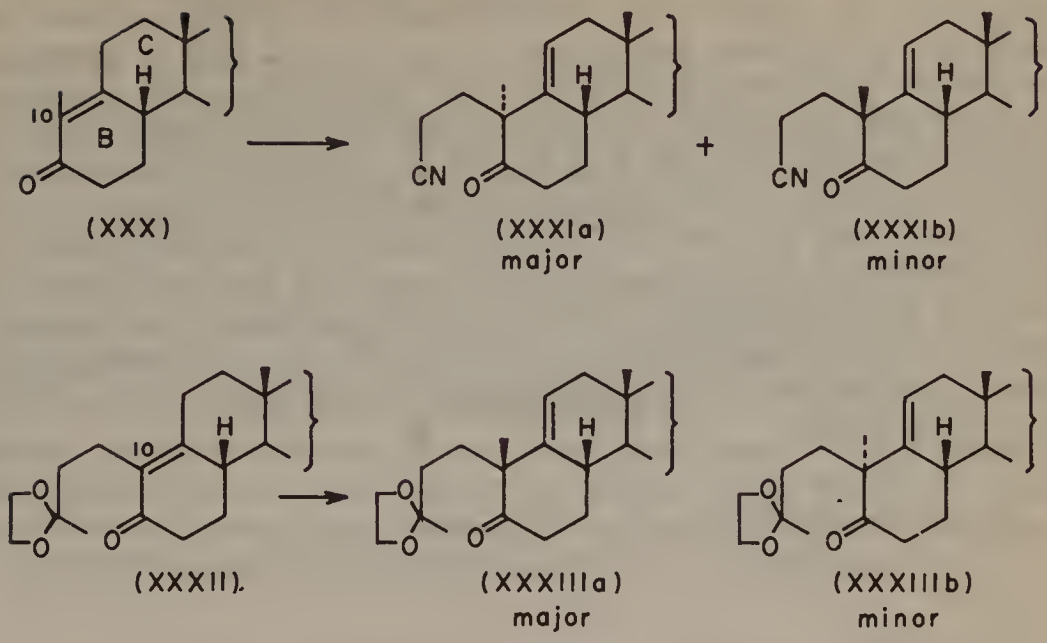


Figure 13.25 Stereochemistry of alkylation at C-10 in steroids

On the other hand, in the synthesis of dehydroabietic acid (Stork and Schulenberg 1962), the steric factor controlled the stereochemistry of alkylation of the dienolate (XXXV) derived from a similarly substituted cyclohexenone (XXXIV) (Figure 13.26). Here the approach of the alkylating agent (ethyl bromoacetate) from the β-side in a chair-like transition state was effectively blocked by a 1,3-synaxial interaction with 10-Me and the product was the desired keto-ester (XXXVI) which was transformed into dehydroabietic acid.

Stereoselective Michael addition to cyclohexenone system is also well known. Thus addition of lithium methylcuprate to 5-methylcyclohexenone gives 99% of *trans*-3,5-dimethylcyclohexanone (House and Fischer 1968).

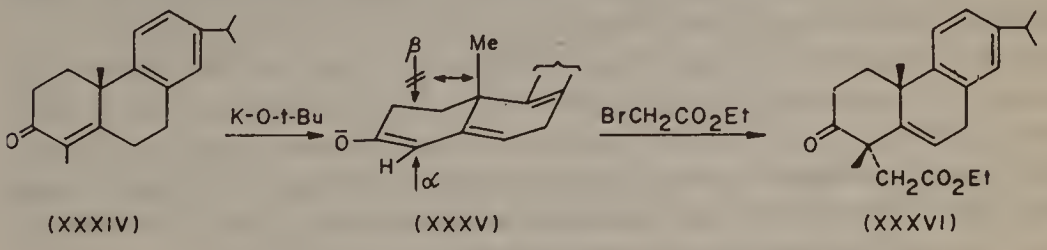
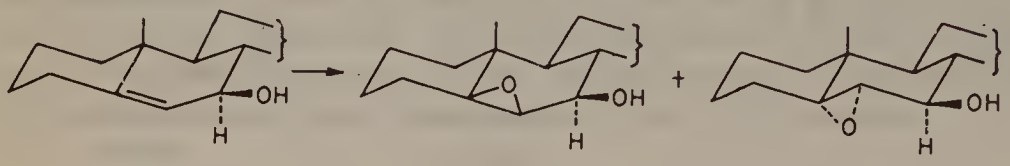


Figure 13.26 Steric effect in alkylation stereochemistry

13.4.4 Diastereoselective oxidation

Substrate selective oxidation of cyclohexanols with chromic acid, in which axial alcohols react faster than equatorial ones, has been discussed in Chapter 12. Stereoselective vicinal dihydroxylation or epoxide formation has also been discussed for acyclic olefins in Section 13.3.4 and this is equally applicable to cyclic olefins. In connection with the latter, a highly stereoselective epoxidation of allylic or

homoallylic cyclic alcohols with *t*-butylhydroperoxide (TBHP) catalysed by vanadium or molybdenum, used as $V(acac)_2$ and $Mo(CO)_6$ must be mentioned (see Sharpless and Verhoeven 1979 for a brief review). Presumably, vanadium coordinates with both the allylic OH and *t*-Bu-O-OH and oxygen is transferred to the double bond almost completely from the side cis to allylic OH (proximofacial addition). The comparative stereoselectivity of TBHP and *m*-chloroperbenzoic acid (MCPBA) is shown in Figure 13.27 for epoxidation of 7β-hydroxycholest-5, 6-ene (XXXVII). The reaction resembles the Simmons-Smith reaction (Simmons et al 1973) in which the cyclopropane ring (formed by the addition of zincmethylene iodide to a double bond) is cis to the allylic OH group. Homoallylic and bishomoallylic alcohols also undergo epoxidation through proximofacial addition but to a lesser extent.



(XXXVII)

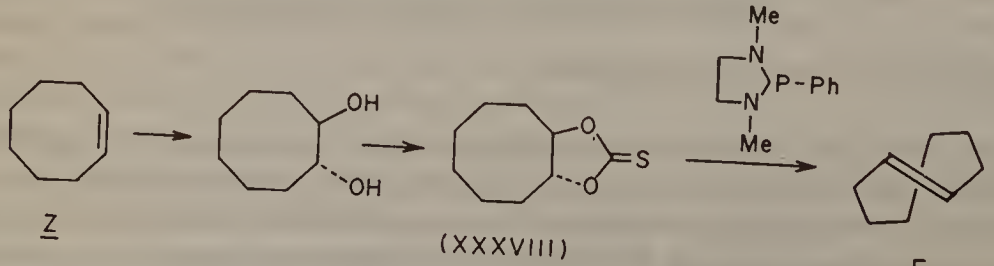
TBHP + V(acac)$_2$	100	:	~ 0
MCPBA	~60	:	~40

Figure 13.27 Stereoselective epoxidation of cyclic allyl alcohol

Osmium-catalysed TBHP oxidation of an olefin also provides a good method for syn dihydroxylation and serves as an alternative to osmium-catalysed similar oxidation with N-methylmorpholine N-oxide (VanRheenen et al 1976). TBHP has the advantage that it is easily available and more stable than the peroxy-acids.

13.4.5 Stereoselective formation of a double bond

Just as a double bond can be oxidised stereoselectively to *cis*- or *trans*-1,2-diols, the diols may also be converted into the corresponding olefinic compounds stereoselectively. The reaction, which is equally applicable to acyclic diols, is shown for a cyclic diol. Thus *Z*-cyclooctene (Figure 13.28) on hydroxylation with peroxy-acids is converted into a trans diol which on reaction with thiophosgene gives the cyclic thionocarbonate (XXXVIII). The latter on treatment with triethyl phosphite or better with 1,3-dimethyl-2-phenyl-1,3-diazo-2-phospholidine (Corey and Hopkins 1982) gives *E*-cyclooctene with complete stereoselectivity. If the diol is resolved before the reaction, one can get enantiomerically pure *E*-cyclooctene.



Z

(XXXVIII)

E

Figure 13.28 Stereoselective conversion of a *trans*-1,2-diol into *trans*-olefin

13.4.6 Stereoselective cyclisation of polyenes

One of the synthetic strategies for polycyclic systems is a concerted cyclisation of appropriately substituted acyclic polyenes according to what is known as Stork-Eschenmoser hypothesis (see Bartlett 1984 for a review). Such a synthesis is known as biomimetic synthesis because of its resemblance to biogenetic processes. Wm. Johnson's group (1971) has improved this method by introducing a functional group capable of generating a cationoid centre at one end of the chain which causes the cyclisation to proceed in a particular direction and prevents random cyclisation. This is illustrated by Johnson's synthesis of progesterone by acid-catalysed cyclisation of the monocyclic tetraene (XXXIX) (Figure 13.29). The allylic carbinol carbon in the cyclopentene ring froms a carbonium ion which triggers the cyclisation, with the two inner double bonds (with *E* geometry) undergoing addition at both ends in anti fashion so that the correct relative configuration is attained in the product (XL). The latter, after a few transformations, is converted into (±)-progesterone (XLI).

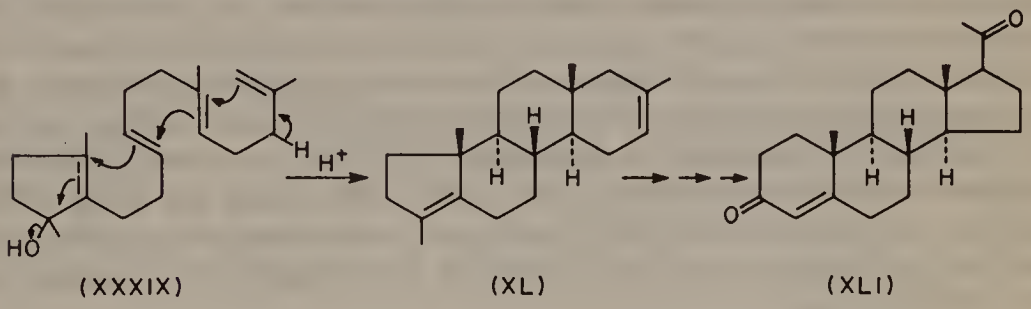


Figure 13.29 Stereoselective cyclisation of polyene

Alternatively, the terminal double bond of a polyene chain is preferentially epoxidised. The epoxide on acid catalysis generates an oxonium ion which then sets up a guided concerted cyclisation. A simple example is given in the synthesis of pallescensin A (Figure 13.30) where three chiral centres are formed with fixed relative configuration in a single step (Nasipuri and Das 1979).

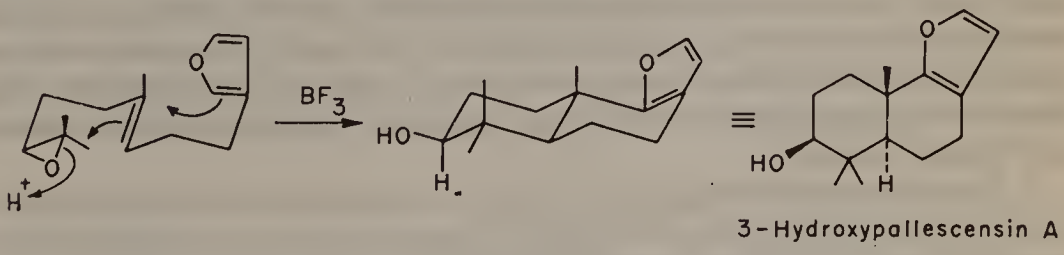


Figure 13.30 Concerted cyclisation of an epoxy-olefin

13.4.7 Miscellaneous reactions

Many other reactions with varying degrees of diastereoselectivity are known.

Molecular rearrangements, neighbouring group participations, and fragmentation reactions which depend on specific conformational requirements have been discussed in Chapter 12. Functionalisation of a distant group is another class of reactions which are very much substrate selective. The Barton reaction (Hesse 1969) is one such important reaction in which a hydroxyl group is used to oxidise a saturated carbon four bonds away through a nitrite ester (via a free radical mechanism). Proximity of the reacting groups, as in 1,3-synaxial orientation, is a prerequisite.

13.5 Enantioselective synthesis

The principle of enantioselective or asymmetric synthesis has been enunciated, and a few highly enantioselective reactions have been discussed in the previous sections. The following criteria should be generally fulfilled in any good asymmetric synthesis (Eliel 1974). (*i*) The reagents (or chiral auxiliaries) must be of high (preferably 100%) optical purity and be easily available (or recyclable). (*ii*) The product must be easily separable from the reaction mixture. (*iii*) The chirality of the reagents should be such that it would give the desired enantiomer in excess. (iv) The enantioselectivity must be high to have practical applicability. (v) Finally, the mechanism of the reaction should be preferably known so that the configuration of the preponderant enantiomer is predictable. The topic has been extensively discussed in several texts (Morrison and Mosher 1971; Kagan and Fiaud 1978; Morrison 1983-1985; Nógradi 1987) and in many review articles one of the latest being due to ApSimon and Collier (1986). A few examples are given here for some typical reactions.

13.5.1 Reduction with chiral hydride donors

A large number of chiral reagents have been developed which reduce (acyclic) prochiral ketones and α-deuterated aldehydes by the transfer of hydrogen with varying degrees of enantioselection. A simple example is provided by the kinetically controlled Meerwein-Ponndorf-Verley reduction of isohexyl methyl ketone with *S*-2-butanol (Figure 13.31). According to Whitmore's six-membered planar cyclic mechanism, two transition states (TS-1 and TS-2) are possible and the one (TS-2) with the larger groups on the opposite sides of the plane is preferred giving an excess of *S*-2-octanol. The asymmetric induction in the reaction is, however, very low (Morrison and Mosher 1971). A few analogous reactions with better enantioselection are discussed.

1. Sterically hindered Grignard reagents. Sterically hindered Grignard reagents instead of undergoing nucleophilic addition transfer a β-H to a carbonyl function and chirality can be induced in the alcohols if hydrogen is transferred from a chiral centre. Mosher and Morrison have prepared a few such reagents of which *S*-2-phenylbutylmagnesium chloride (*S*-PBMgCl) (XLII) (Figure 13.32) is the most enantioselective. The highest enantioselection (82%) has been reported for the reduction of isopropyl phenyl ketone (Table 13.2). Trialkylaluminium (XLIII) and dialkylzinc (XLIV) have also been used for reduction of ketones but the stereo-

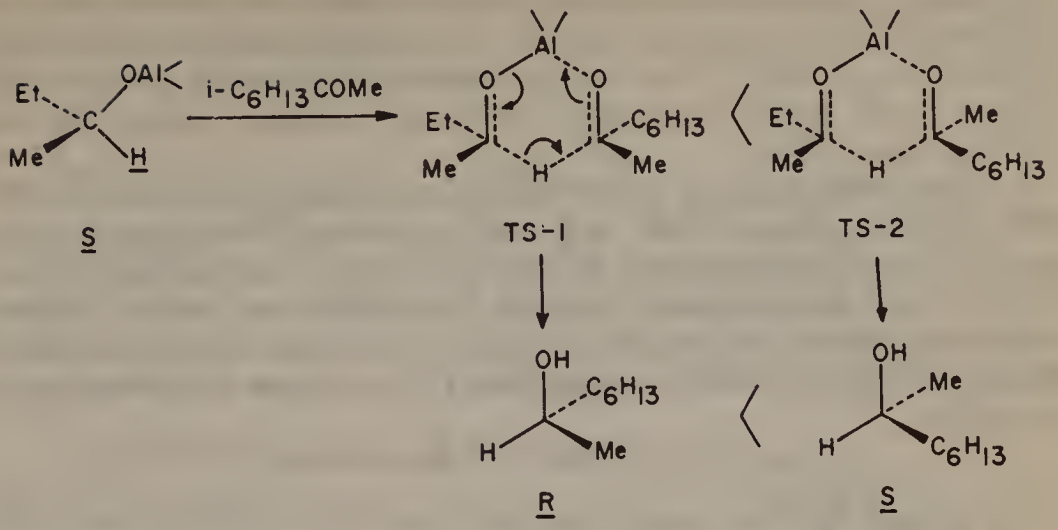


Figure 13.31 Cyclic transition state for hydride transfer

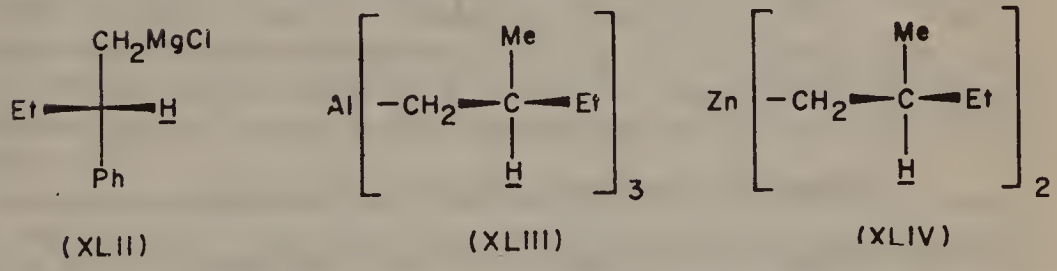


Figure 13.32 Chiral Grignard reagents, trialkylaluminium, and dialkylzinc

selectivity is usually very low (Giacomelli et al 1974). Moreover, the reagents are difficult to prepare and the synthesis is self-immolative, the chiral alkyl groups being converted into achiral alkenes.

2. Bornyloxyaluminium dichlorides. In a modified M-P-V-type of reactions, (−)-isobornyloxy (B^1OAlCl_2) (XLV) and (−)-bornyloxyaluminium dichlorides ($BOAlCl_2$) (XLVI) (Figure 13.33) have been used to reduce a variety of carbonyl compounds with enantioselection ranging from moderate to high (30-90%) (Table 13.2). Reactions take place at low temperature, are virtually irreversible, and give good results particularly with aralkyl and amino ketones (see Nasipuri et al 1984 for a review). A new acyclic transition state model has been proposed in the place

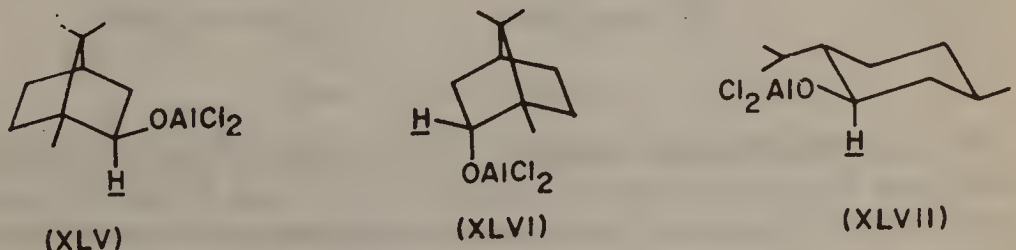
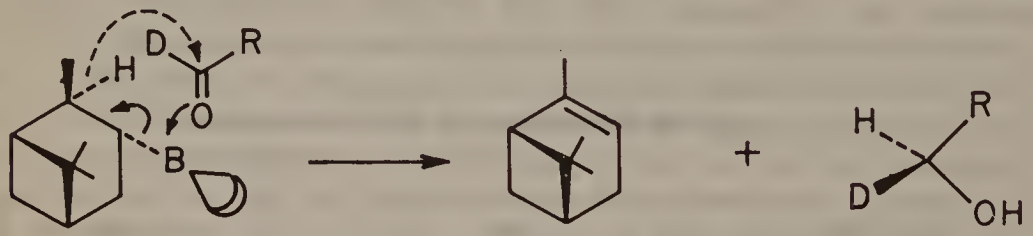


Figure 13.33 Chiral alkoxyaluminium dichlorides

of Whitmore's model which explains a few discrepancies observed in these and some allied reactions (Nasipuri et al 1971). The chiral alcohols, e.g., borneols are commercially available. (−)-Menthyloxyaluminium dichloride ($MenOAlCl_2$) (XLVII) is less reactive but reduces trifluoromethyl phenyl ketone with high enantioselection (77%).

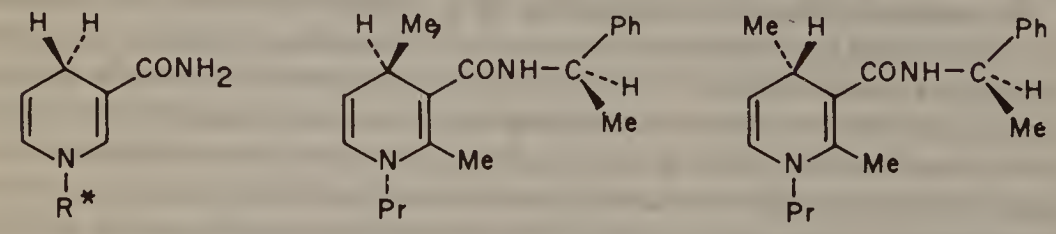
3. Chiral trialkylboranes. B-(3α-Pinanyl)-9-borabicyclo[3.3.1]nonane or IPC-BBN (XLVIII) (Figure 13.34), with the trade name Alpine-borane®, easily prepared from 1,5-cyclooctadiene, borane, and α-pinene, is an extremely efficient enantioselective reducing agent (Midland 1979, 1983) and reduces aliphatic, allylic, and aromatic aldehydes and α,β-unsaturated ketones. Benzyl-α-*d* alcohol is obtained in 100% enantiomeric excess (Table 13.2). α-Pinene is eliminated which is recyclable.



(XLVIII)

Figure 13.34 Alpine-borane or IPC-BBN as reducing agent

4. NADH models. The coenzyme NADH (the hydrogenated form of nicotinamide adenine dinucleotide) (XLIX. partial structure) is a highly enantioselective hydride donor. A few mimics containing the dihydronicotinamide moiety have been prepared, e.g., La and Lb (Figure 13.35). The reagents reduce a number of ketones in the presence of magnesium perchlorate with high (and opposite) enantioselection (70-99%) (see Ohno and Ushida 1986 for a review).

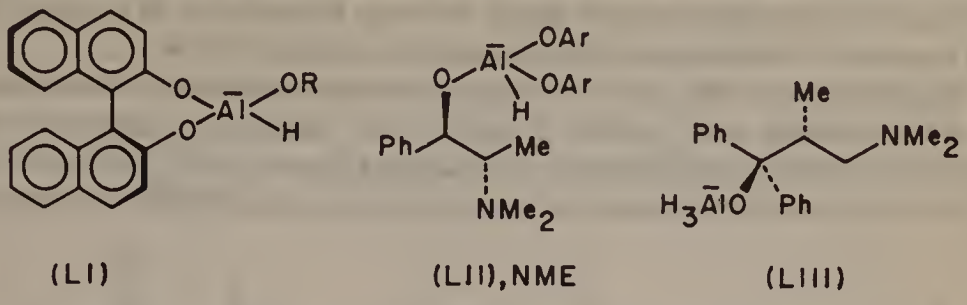


(XLIX) (La) RR-Me_2PNPH (Lb) SR-Me_2PNH

Figure 13.35 NADH models

5. Chiral metal hydride complexes. Lithium aluminium hydride and sodium borohydride have been modified by replacing one or more H atoms by organic chiral molecules with different functionalities and used for enantioselective reduction of ketones (see Haubenstock 1982 for a review). The chiral auxiliaries include 2,2′-dihydroxy-1,1′-binaphthyl, N-methylephedrine, Darvon alcohol (a drug) among

others giving reagents, LI (*S*-BINAL-H), LII (Ar = 3,5-dimethylphenyl; NME), and LIII. (Figure 13.36). Of these. *S*- or *R*-BINAL-H is highly enantioselective (Table 13.2) (Noyori et al 1979).



(LI) (LII), NME (LIII)

Figure 13.36 Lithium aluminium hydride modified with chiral auxiliaries

Some sugar derivatives of lithium aluminium hydride and sodium borohydride are also known but their enantioselectivity is rather poor.

6. Miscellaneous reagents. Lithium and potassium chiral alkoxides (with an α-H) have also been used for enantioselective reduction of ketones but enantioselectivity in general is not high (Morrison and Mosher 1971).

Mono- and dialkyl boranes such as $IPCBH_2$ and IPC_2BH also do not give good results in enantioselective reduction of ketones. However, the enantioselectivity is very much improved by using a chiral borane-amino alcohol complex (Itsuno et al 1983).

A few data (not necessarily the best) are compiled in Table 13.2 for enantioselective reduction of aryl alkyl ketones and aldehydes with the reagents discussed above.

Table 13.2 Enantioselective reductions of some carbonyl compounds

Entry No.	Substrate	Reagent*	Formula	ee (%)	Configuration
1.	PhCDO	(+)-IPC-BBN	(XLVIII)	100	*S*
2.	PhCDO	*S*-BINAL-H	(LI)	82	*S*
3.	PhCDO	(−)-EOMgBr	(as XLVI)	64.5	*R*
4.	PhCOMe	(+)-IPC-BBN	(XLVIII)	83	*S*
5.	PhCOMe	*S*-BINAL-H	(LI)	95	*S*
6.	PhCOMe	(−)-NME	(LII)	84	*R*
7.	PhCOPr^i	*S*-PBMgCl	(XLII)	82	*S*
8.	PhCOPr^i	(−)-B^{i}OAlCl$_2$	(XLV)	84	*R*
9.	PhCOPr^i	*S*-BINAL-H	(LI)	71	*S*
10.	PhCOCF$_3$	(−)-BOAlCl$_2$	(XLVI)	68	*S*
11.	PhCOCF$_3$	(−)-MenOAlCl$_2$	(XLVII)	77	*S*
12.	PhCOCF$_3$	NADH model	(L)	70	*R*

*Names of the reagents are abbreviated as in the text. Most of the references are given in the text: for the rest, the review articles cited may be consulted.

13.5.2 Enantioselective hydroboration

Chiral alkylated boranes and boronic esters have been successfully used for asym-

metric synthesis (see Matteson 1986; Srebnik and Ramchandran 1987). Two such methods, namely, reactions of aldehydes with allylic boranes and boron enolate condensations have already been discussed in the previous sections. One of the major reaction is hydroboration of olefins followed by oxidation to alcohols. This and a reaction of 1-chloromethylboronic esters are discussed below.

1. Hydroboration with mono- and diisopinocampheylboranes. α-Pinene undergoes hydroboration with borane to give either monoisopinocampheylborane ($IPCBH_2$) or diisopinocampheylborane (IPC_2BH) (Figure 13.37). The former is a very good enantioselective reagent for hydroboration of trans alkenes, trisubstituted

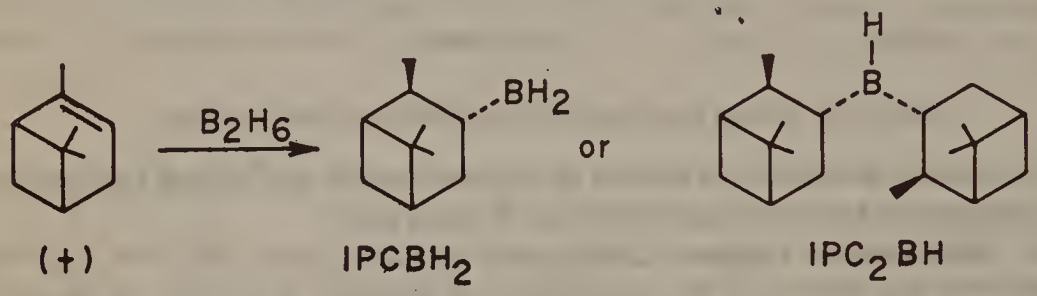


Figure 13.37 Preparation of mono- and di-isopino-campneyl borane

alkenes, and 1-substituted cycloalkenes (see Brown and Jadhav 1983). Two examples are shown in Figure 13.38a. IPC_2BH, on the other hand, does not work very well with these substrates but reacts with symmetrical cis olefins with high enantioselection as illustrated in Figure 13.38b.

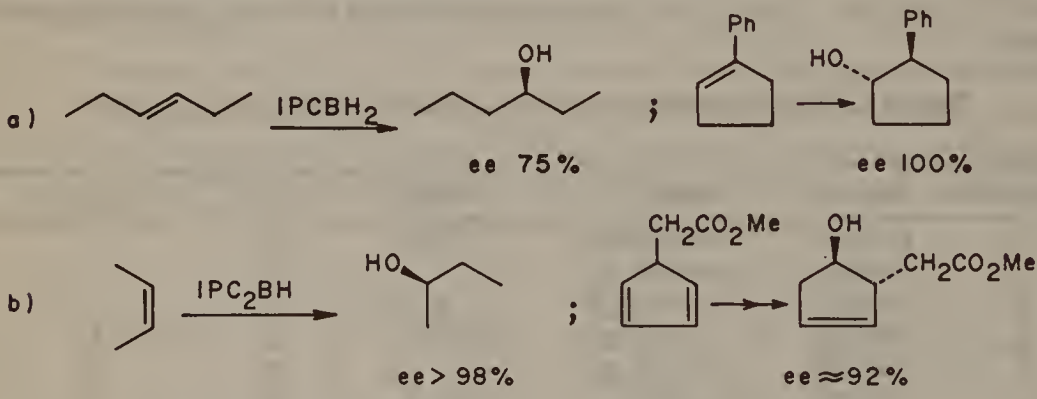


Figure 13.38 Enantioselective reduction with $IPCBH_2$ and IPC_2BH

2. Reaction of 1-chloromethylboronic esters. A novel method has been worked out by Matteson and coworkers (Matteson 1986) for the formation of two or more adjacent chiral centres with absolute stereocontrol starting from 1-chloroalkylboronic esters (Figure 13.39). 1-Alkyl-(2,3-butanediyl)boronate (LIV) with two homotopic faces on treatment with dichloromethyllithium gives a complex which under the catalysis of zinc chloride rearranges to 1-chloroalkylboronate (LV). Addition of an alkyl anion (R′Li or R′MgX) gives the alkylated product (LVI) with inversion of configuration at the side chain carbon. This on oxidative deboronation gives the tertiary alcohol (LVII) in high optical purity. The reaction

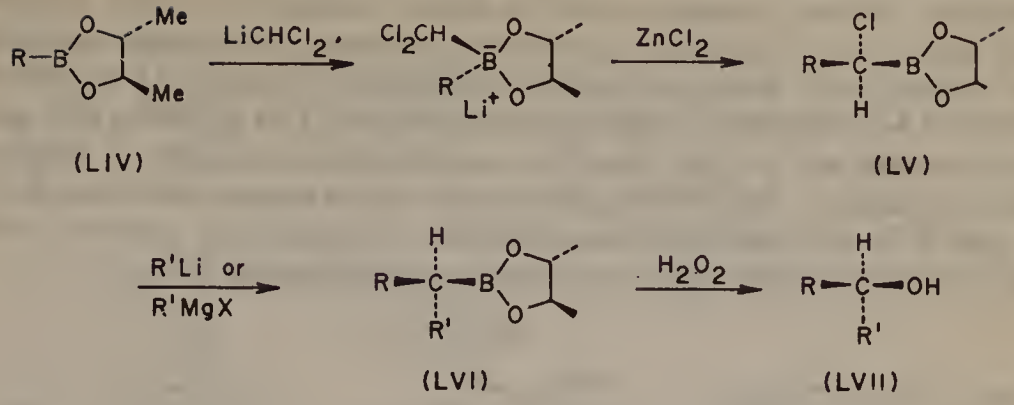


Figure 13.39 Reactions of 1-chloroalkyl-(2,3-butanediyl)-boronate

sequence can be repeated on the penultimate product (LVI) so that a second chiral centre is created adjacent to the first.

13.5.3 Enantioselective catalytic hydrogenation

Both heterogeneous and homogeneous catalytic hydrogenations have been employed for enantioselective reduction of a double bond (C = C, C = O, and C = N).

1. Heterogeneous catalysis. Harada et al (1978) have used tartaric (2*R*, 3*R*) acid-modified Raney nickel (MRN) to reduce methyl acetoacetate to methyl *R*-3-hydroxybutyrate in 88% enantiomeric excess (Figure 13.40a). The method is simple and inexpensive but is not of general applicability. A chiral adjuvant may also be used; thus α-ketoacids are condensed with chiral amines, e.g., *S*-α-aminobenzylamine and the resultant Schiff bases hydrogenated (with concomitant hydrogenolysis) to give α-amino acids (Figure 13.40b) with moderate enantioselection (Harada 1982).

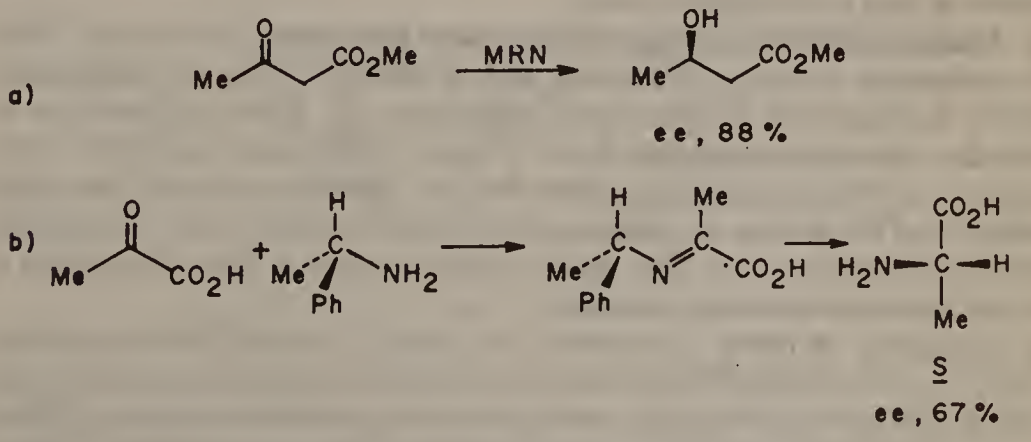


Figure 13.40 Enantioselective heterogeneous catalysis

2. Homogeneous catalysis. After the introduction of Wilkinson's first homogeneous catalyst, chlorotris(triphenylphosphine)rhodium in 1966, there has been tremendous development in this area and a large number of chiral phosphorus-

complexed rhodium catalysts (soluble in organic solvents) have been prepared either with a chiral phosphorus or phosphorus containing chiral organic auxiliaries (see Nögradi 1987). Three such catalysts are shown in Figure 13.41: *R,R*-DIOP (LVIII), *S,S*-CHIRAPHOS (LIX), and *R,R*-DIPAMP (LX) all having a C_2 axis. These catalysts are specially good for enantioselective reduction of N-acetyl (benzoyl) enamines. Thus N-acetylaminoacrylic acid is reduced with them in 56, 79, and 95% *ee* respectively. Enantioselective synthesis using optically active transition metal complexes has recently been reviewed (Brunner 1988).

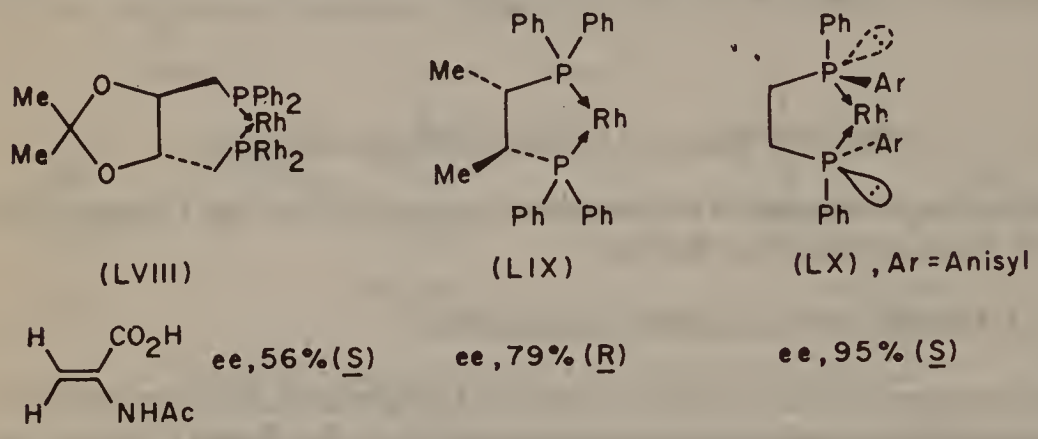


Figure 13.41 Enantioselective homogeneous catalysts

Addition of a silicon hydride (hydrosilylation) to a C=C, C=O, and C=N bond is also done catalytically (see Bosnich and Fryzerk 1981).

13.5.4 Enantioselective synthesis via hydrazones

Hydrazones derived from chiral hydrazines have been used for enantioselective synthesis at least in two different ways.

1. Diastereoselective hydrogenation of cyclic hydrazones. Corev et al (1970) have synthesised a number of α-amino acids in 96-99% *ee* through diastereoface selective hydrogenation of chiral cyclic hydrazones, e.g., LXII prepared from N-amino-2-α-hydroxyethylindoline (LXI) (Figure 13.42). Hydrogenation (with aluminium amalgam) takes place from the side opposite to methyl (distofacial addition) and the product on hydrogenolysis affords α-amino acids. The indoline derivative eliminated in the final step is recycled as shown. Both enantiomers of the indoline-amine have been prepared.

2. Alkylation of chiral hydrazones. *S*-1-Amino-2-methoxymethylpyrrolidine (LXIII), known as SAMP and its enantiomer known as RAMP, prepared from *S*- and *R*-prolines respectively have been used as chiral auxiliaries in a very efficient enantioselective alkylation of ketones and aldehydes (Figure 13.43) (Enders 1984). The derived hydrazone (LXIV) from 3-pentanone on treatment with lithium diisopropylamide (LDA) gives a complex (LXV) in which lithium is coordinated to both the carbanionic centre and the methoxyl group. As a result, the alkylating reagent approaches from the proximofacial side (with respect to CH_2OMe) and gives almost exclusively LXVI. Treatment with methyl iodide and hydrolysis of the

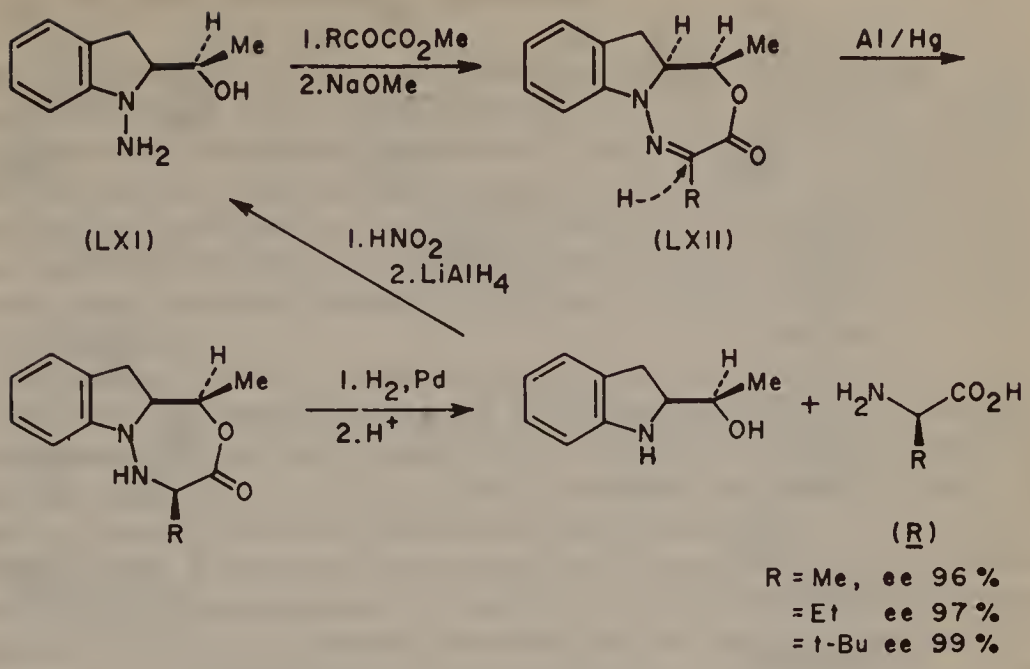


Figure 13.42 Enantioselective synthesis via cyclic hydrazones

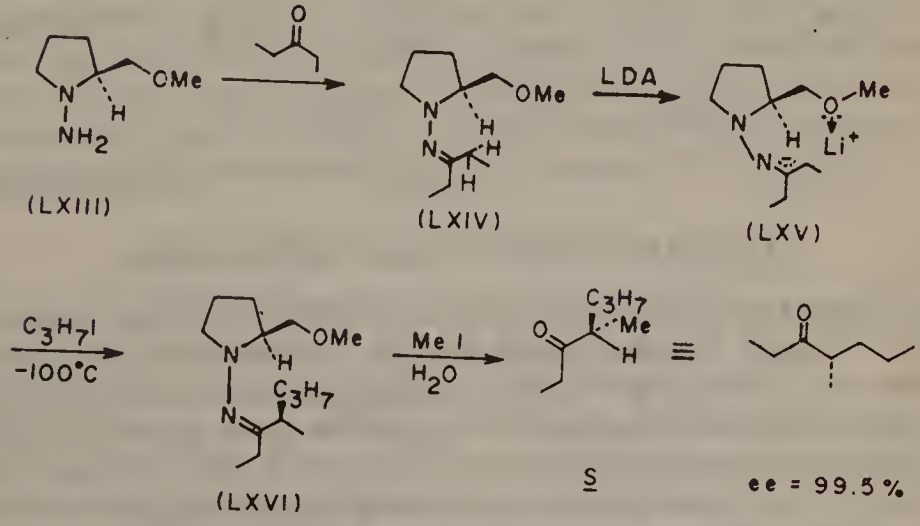


Figure 13.43 Enantioselective alkylation of ketones via hydrazones

methoiodide gives *S*-4-methyl-3-heptanone in over 99% *ee* which is the alarm pheromone of the leaf-cutting ant *Atta texana*. The reagent is recyclable. The stereoselection here does not depend on any steric factor but on the disposition of a metal atom (e.g., lithium) which directs the reagent to a specific face of the substrate. This is popularly known as *second generation stereoselective* method.

13.5.5 Enantioselective alkylation through oxazolines

Meyers and coworkers (Meyers et al 1979) have developed a very efficient and

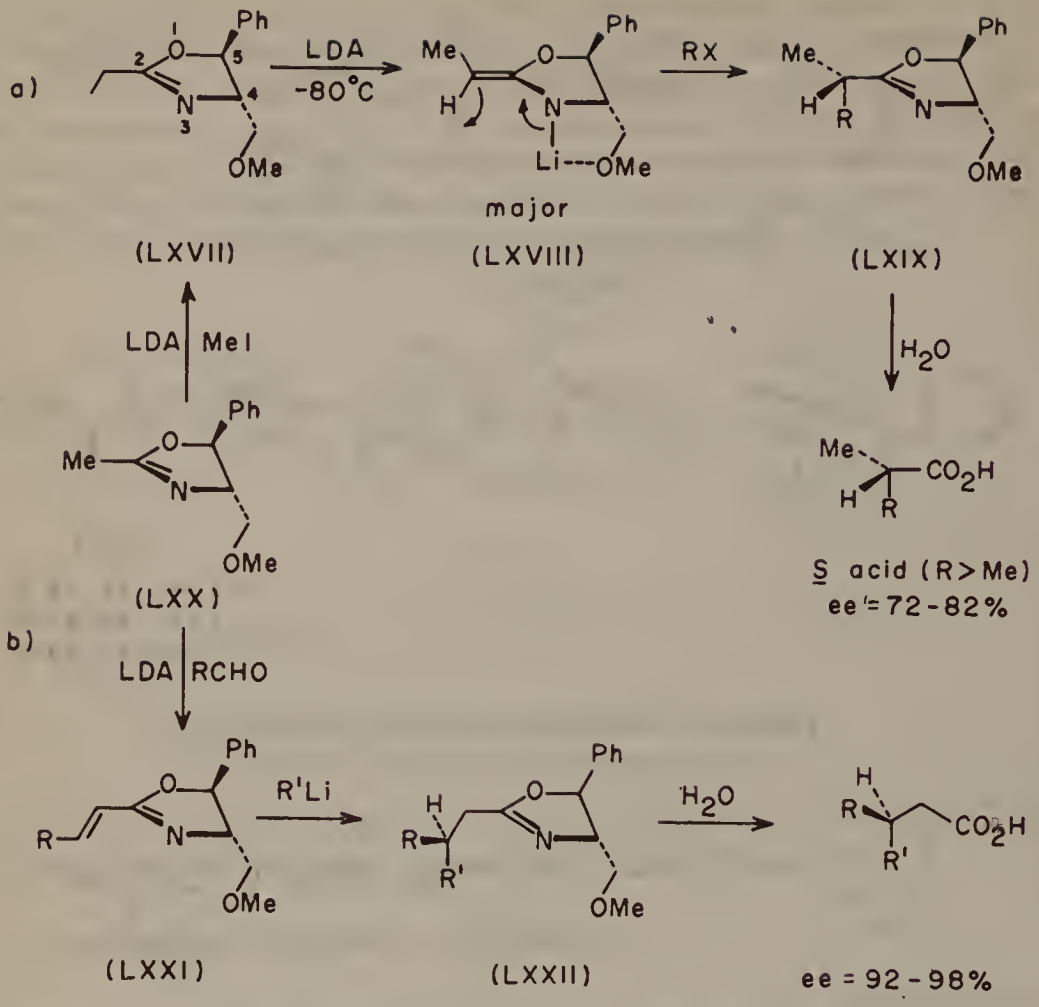


Figure 13.44 Enantioselective synthesis via chiral oxazolines

versatile method for enantioselective synthesis of substituted aliphatic acids through alkylation of chiral oxazolines which serve as a masked carboxylic group. The oxazoline, e.g., LXVII (Figure 13.44) (prepared from commercially available 1*S*, 2*S*-1-phenyl-2-amino-1,3-propanediol) on lithiation forms the complex (LXVIII) with lithium held below the plane of the ring by the methoxyl group. Alkylation takes place from the side of lithium (proximofacial addition) giving the alkylated product (LXIX) which on hydrolysis affords *S*-acid in 72-82% ee. This is also a second generation enantioselective reaction although the Ph group at C-5 may have exerted some steric effect as well. The original phenylaminopropanediol is recovered for recyclation. The 2-methyl-derivative (LXX) is also used as the starting material in which case the reaction sequence is extended by one more alkylation step. By reversing the alkylation order, both enantiomers of the 2,2-disubstituted acetic acids (R and Me interchangeable) may be obtained.

In a modified approach, the oxazoline (LXX) is converted into the 2-vinyl derivative (LXXI) which undergoes Michael addition to give the β-alkylated product (LXXII), again with very high diastereoselection, which on hydrolysis affords 3,3-disubstituted propionic acids in 92-98% ee (see Lutomski and Meyers 1984 for a review).

13.5.6 Sharpless enantioselective epoxidation

The highly strained epoxide ring is an important component of many natural products including insect pheromones and also serves as a valuable synthon. Although a few enantioselective syntheses of epoxides from allyl alcohols using molybdenum and vanadium catalysts were known, the most remarkable stereoselection was achieved in this field by Sharpless and Katsuki (1980) using titanium-catalysed epoxidation with tartaric esters as chiral ligands. The topic has been recently reviewed (Pfenninger 1986; also see Morrison series) and is briefly summarised here.

The method consists in treating an allyl alcohol (mono-, di-, or tri-substituted as LXXIV) with *t*-butylhydroperoxide in the presence of titanium (IV) isopropoxide and optically active diethyl (or di-isopropyl) tartrate. It is presumed that two molecules of isopropyl alcohol are released from titanium forming the ten-membered intermediate (LXXIII) which has a fluxional structure there being a rapid exchange of coordination of titanium with two out of four carbonyl groups at a time. The structure possesses C_2 symmetry and is thus ideal for enantioselection. The allyl alcohol and *t*-butylhydroperoxide displace the two remaining isopropoxide groups forming a chiral matrix in which the substrate is rigidly fixed. The absolute configuration of the preponderant epoxide is predictable from the model (LXXIV) with the CH_2OH group of the allylic alcohol written on the lower right in the rectangular plane. With (−)-diethyl tartrate (DET), oxygen approaches the double bond from the top giving the epoxide (LXXV) while with (+)−DET (natural), oxygen approaches from the bottom giving the other isomer (LXXVI). The enantioselection is very high (over 91-95%) and either of the enantiomers can be prepared. Details are available in a recent reference (Gao et al 1987).

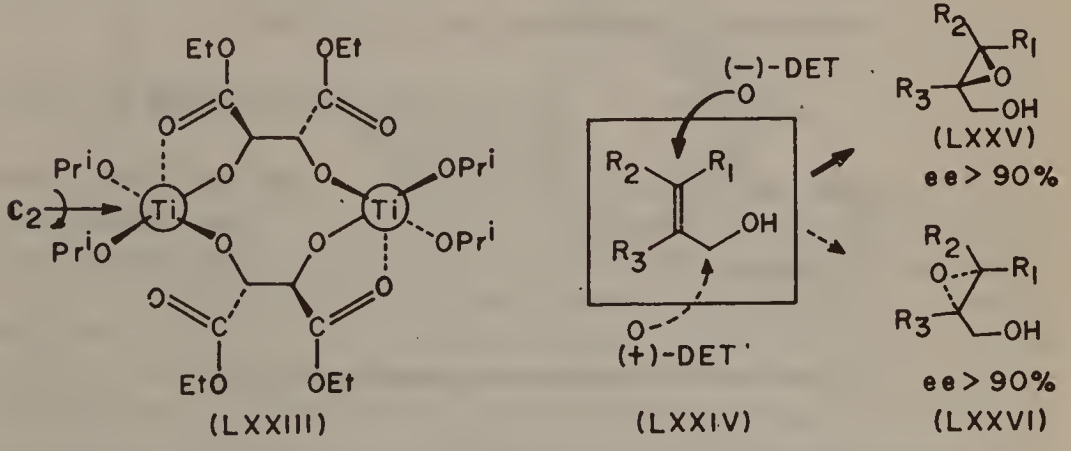


Figure 13.45 Sharpless reagent and epoxidation of allylic alcohols

13.5.7 Miscellaneous enantioselective syntheses

A few assorted enantioselective reactions are described below (see ApSimon and Collier 1986).

1. **Phase transfer catalysis.** Use of chiral phase transfer catalysts such as crown

ethers. ammonium salts. and phosphonium compounds should, in principle, give rise to enantioselection. However, in general the enantioselectivity is poor. Recently, Dolling et al (1984)* have carried out a very efficient enantioselective alkylation of a 2-phenylindanone (LXXVII) catalysed by benzyl cinchoninium cation (Figure 13.46). It is assumed that the quinuclidine ring lies behind the plane of the indanone enolate permitting π-interaction between the benzyl group of the catalyst and the 2-phenyl group and at the same time 9-OH provides a directive handle through H-bonding so that the back side approach of the alkylating agent (MeCl) is effectively prohibited and *S*-(+)-2-methylindanone is formed.

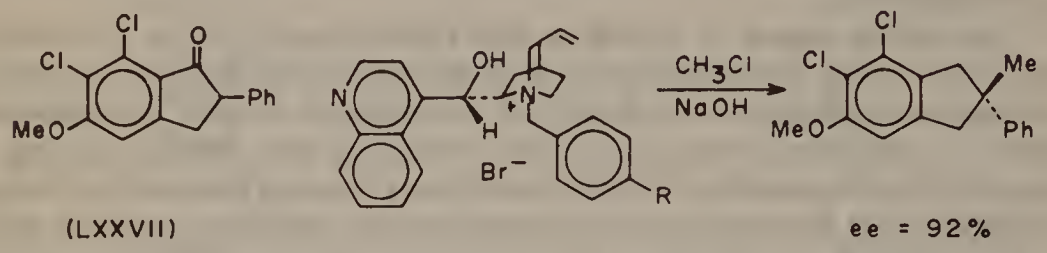


Figure 13.46 Enantioselective alkylation with chiral phase transfer catalyst

2. Intramolecular aldol condensation. Intramolecular aldol condensations under the catalysis of a chiral base sometimes proceed with high enantioselectivity. An example is found in *S*-proline catalysed cyclisation of the cyclopentan-1,3-dione (LXXVIII) to the bicyclic ketone (LXXIX) in 93% *ee* (Hajos and Parrish 1974) (Figure 13.47). The two carbonyl groups in the cyclopentane ring are enantiotopic and are distinguished by the chiral catalyst.

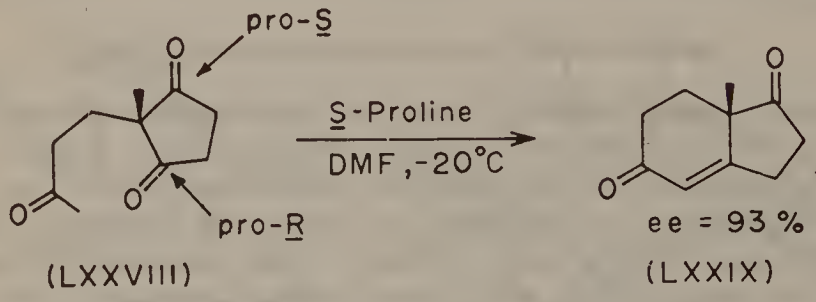
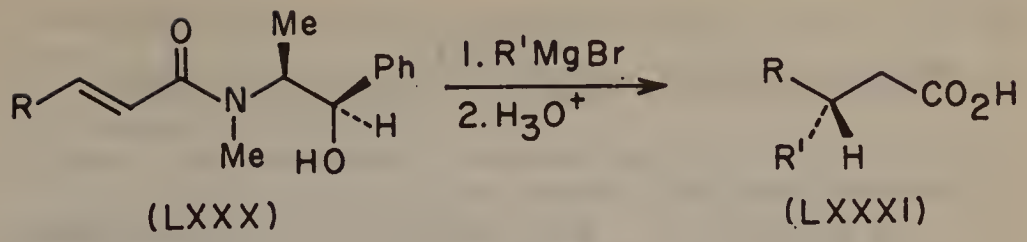


Figure 13.47 Enantioselective intramolecular aldol reaction

3. Michael addition. Michael additions in the presence of chiral amines (as catalysts) show various degrees of enantioselectivity. Mukaiyama and Iwasawa (1981) have achieved good enantioselection by using a chiral base as an adjuvant. Thus α,β-unsaturated amides (LXXX) derived from ephedrine (Figure 13.48) on Grignard addition and subsequent hydrolysis afford 3,3-disubstituted propionic acids (LXXXI) in 79-99% enantiomeric excess.

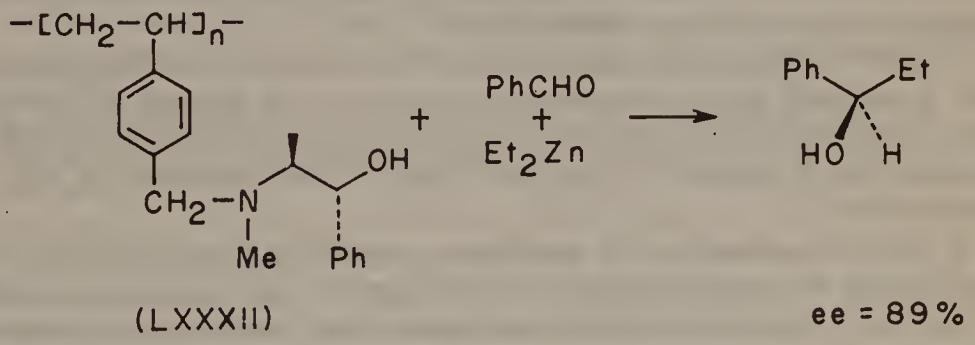
*This synthesis was pioneered by Wynberg (for a review, see Wynberg 1986).



(LXXX) (LXXXI)

Figure 13.48 Enantioselective Michael addition

4. Polymer-bound chiral catalysts. A few examples are known in which a polymer-bound chiral catalyst has been used to effect enantioselective reactions. One of the recent methods involves the reaction of 1*R*.2*S*-ephedrine with chloromethylated polystyrene to give the basic catalyst (LXXXII) which promotes asymmetric addition of dialkylzinc to aldehydes (Soai et al 1988) (Figure 13.49). The highest asymmetric induction (89%) has been achieved in the synthesis of phenylethylcarbinol from benzaldehyde and diethylzinc.



(LXXXII) ee = 89%

Figure 13.49 Polymer-bound ephedrine as a chiral catalyst

13.5.8 Asymmetric amplification

Finally. there is the case of asymmetric amplification—the ultimate method of asymmetric synthesis—in which the *ee* of the product far exceeds the *ee* of the chiral auxiliary used. Recently, Oguno et al (1988) have shown that benzaldehyde on reaction with diethylzinc under the catalysis of some sterically constrained chiral amino alcohols, e.g., LXXXIII-LXXXV (Figure 13.50) gives 1-phenylpropanol in high optical purity. In one instance. the use of the amino alcohol (LXXXIII) with 10.7% optical purity furnished 1-phenylpropanol of 82% enantiomeric purity. The required amino alcohols may be prepared by enantioselective reduction of the corresponding amino ketones (Nasipuri et al 1983). The principle of non-linear effect in asymmetric induction was first discussed by Horeau (1969) and is based on the fact that a bidendate metal (e.g., Zn) may form two types of complexes with chiral ligands (L_R and L_S): two enantiomeric forms L_R-M-L_R and L_S-M-L_S and a meso form L_R-M-L_S. Being diastereomeric, the two types of metal complexes induce different rates for the formation of the two enantiomers and thereby bring about asymmetric amplification.

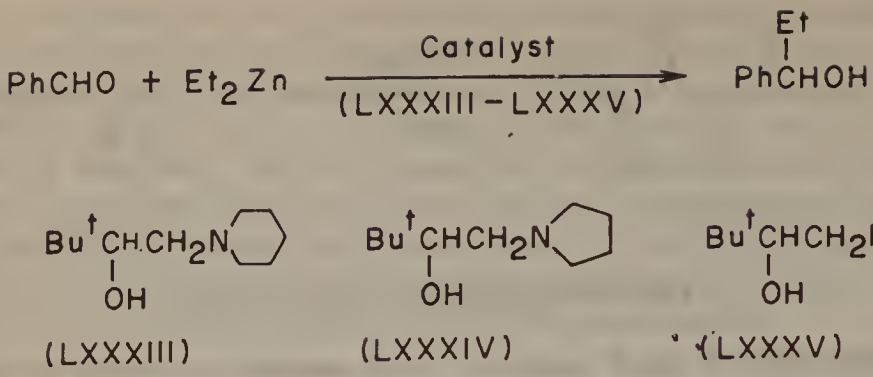


Figure 13.50 Asymmetric amplification

13.6 Summary

1. Stereoselectivity has been classified under two broad categories : substrate stereoselectivity and product stereoselectivity each being further subdivided into enantioselectivity and diastereoselectivity.

2. Diastereoselection and enantioselection in kinetically controlled reactions can only be achieved through diastereomeric transition states differing in free energies. For enantioselective reactions, where the products are mirror images of each other, this condition is attained by using chiral reagents, chiral auxiliaries, or even chiral environments.

3. Acyclic stereoselection, in which great progress has been made during the last two decades, has been discussed for various reactions such as nucleophilic addition to carbonyl compounds, aldol condensation, and reactions of allylmetal and allylboron compounds. Stereoselectivity has been rationalised with the help of appropriate models wherever possible. The principle of double stereoselection or double asymmetric induction in which an otherwise moderate stereoselection is boosted by a matched asymmetric induction by an adjoining chiral centre or centres has been illustrated with examples.

4. Diastereoselection in cyclic compounds is discussed mainly on the basis of axial and equatorial disposition of a substituent and has been illustrated by reactions such as nucleophilic addition to cyclohexanones, catalytic hydrogenation, hydroboration, alkylation, oxidation, and cyclisation of polyenes.

5. Enantioselective reactions are likewise reviewed under various reaction types such as reduction with chiral hydride donors, hydroboration, heterogeneous and homogeneous catalytic hydrogenation, alkylation of chiral hydrazones and oxazolines, Sharpless epoxidation. and miscellaneous reactions.

References

1. J.D. Morrison (Ed) (1983-85), in *Asymmetric Synthesis*, Academic Press, New York.
2. M. Nögradi (1987), in *Stereoselective Synthesis*, VCH, Weinheim.
3. E.L. Eliel (1962), in *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York.
4. B. Testa (1979), in *Principles of Organic Stereochemistry*, Marcel Dekker, New York.

5. Y. Izumi and A. Tai (1977), in *Stereo-differentiating Reactions*, Academic Press, New York.
6. J.D. Morrison and H.S. Mohser (1971), in *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, New Jersey.
7. K. Mislow (1966), in *Introduction to Stereochemistry*, W.A. Benjamin, New York.
8. S. Warren (1978), in *Designing Organic Synthesis: A Programmed Introduction to the Synthon Approach*, Wiley, New York.
9. J. Fuhrhop and G. Penzlin (1983), in *Organic Synthesis : Concepts, Methods, and Starting Materials*, Verlag Chemie, Weinheim.
10. S. Hanessian (1983), in *Total Synthesis of Natural Products : The Chiron Approach*, Pergamon Press, Oxford.
11. E.L. Eliel and S. Otsuka (Eds.) (1982) in *Asymmetric Reactions and Processes in Chemistry*, ACS Symposium Series, No. 185.
12. C.H. Heathcock (1982), in ref. 11.
13. C.H. Heathcock (1984), in *Comprehensive Carbanion Chemistry*, Eds. E. Bunce and T. Durst, Elsivier, Amsterdam, p. 177-238; also in *Asymmetric Synthesis* (1984), (Ed. J.D. Morrison), vol. 3, Academic Press, New York.
14. D. Evans, J.V. Nelson, and T.R. Taber (1982), in *Topics in Stereochemistry*, vol. 13, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
15. S. Masamune, W. Choy, J.S. Petersen, and L.R. Sita (1985), *Angew. Chemi. Intl. Edn. Engl.*, **24**, 1.
16. T. Mukaiyama (1982) in *Organic Reactions*, vol. 28. p. 203. Wiley, New York.
17. E.L. Eliel (1983) in *Asymmetric Synthesis*, vol. 2, Ed. J.D. Morrison, Academic Press, New York.
18. W.C. Still and J.H. McDonald (1980), *Tetrahedron Letters*, **21**, 1031.
19. F. Sato, M. Kusakabe, and Y. Kokayashi (1984), *J.C.S. Chem. Commn.*, 1130.
20. E.L. Eliel and J.E. Lynch (1981), *Tetrahedron Letters*, **22**, 2855.
21. S.V. Frye and E.L. Eliel (1985), *J. Org. Chem.*, **50**, 3402.
22. T. Mukaiyama, Y. Sakito, and M. Asami (1978), *Chem. Letter*, 1253.
23. M.T. Reetz and A. Jung (1983), *J. Amer. Chem. Soc.*, **105**, 4833.
24. M.T. Reetz (1982), *Top. Curr. Chem.*, **106**, 1.
25. J.K. Whitesell, A. Bhattacharya, and K. Henke (1982), *J.C.S. Chem. Commn.*, 988.
26. A.T. Neilsen and W.J. Houlihan (1968), in *Organic Reactions*, vol. 16, p. 1, Wiley, New York.
27. H. Zimmerman and M. Traxler (1957), *J. Amer. Chem. Soc.*, **79**, 1920.
28. W. Carruthers (1986) in *Some Modern Methods of Organic Synthesis*, Cambridge University Press, Cambridge.
29. H.C. Brown and P.K. Jadhav (1984), *Tetrahedron Letters*, **25**, 1215.
30. W.R. Rausch and R.L. Halterman (1986), *J. Amer. Chem. Soc.*, **108**, 294.
31. R.W. Hoffmann, H.J. Zeiss, W. Ledner, and S. Tabsche (1982).*Chem. Ber.*, **115**, 2357; R.W. Hoffmann (1982), *Angew. Chemi. Intl. Edn. Engl.*, **21**, 555.
32. R. Isaksson, H. Wennerstrom and O. Wennerstrom (1988), *Tetrahedron*, **44**, 1697.
33. Y. Yamamoto (1986), *J. Org. Chem.*, **51**, 886.
34. D.A. Evans, J. Bartroli, and T. Godel (1982), *Tetrahedron Letters*, **22**, 4577.
35. K. Tomioka, M. Nakajinia, and K. Koga (1987), *J. Amer. Chem. Soc.*, **109**, 6213.
36. E.N. Jacobsen, I. Marko, W.S. Mungall, G. Schroder, and K.B. Sharpless (1988), *J. Amer, Chem. Soc.*, **110**, 1968.
37. N. Anand, J.S. Bindra, and S. Ranganathan (1970), in *Art in Organic Synthesis*, Holden-Day, San Francisco.
38. J.W. ApSimon (1972) in *Techniques of Chimistry*, vol. IV, Ed. A. Weissberger, Wiley, New York.

39. I. Fleming (1973), in *Stereoselective Organic Syntheses*, Wiley, London.
40. H.C. Brown and S. Krishnamurthy (1972), *J. Amer. Chem. Soc.*, **98**, 7159.
41. S. Krishnamurthy and H.C. Brown (1976), *j. Amer. Chem. Soc.*, **98**, 3383.
42. E.L. Eliel and D. Nasipuri (1965), *J. Org. Chem.*, **30**, 3809.
43. D. Nasipuri, P.R. Mukherjee, S.C. Pakrashi, S. Datta, And P.P. Ghosh-Dastidar (1976), *J.C.S. Perkin I*, 321.
44. E.L. Eliel, R.J.L. Martin, and D. Nasipuri (1967), *Organic Synthesis*, **47**, 16.
45. K. Maruoka, M. Sakurani, and H. Yamamotao (1985), *Tetrahedron Letters*, **26**, 3853
46. D. Nasipuri, M. Datta Gupta, and S. Banerjee (1984), *Tetrahedron Letters*, **25**, 5551.
47. H.O. House (1972) in *Modern Synthetic Reactions*, W.A. Benjamin, London.
48. H.W. Thompson and J.K. Wong (1985), *J. Org. Chem.*, **50**, 4270.
49. D.A. Evans and M.M. Morrisey (1984), *J. Amer. Chem. Soc.*, **106**, 4270.
50. G. Stork and J.W. Schulenberg (1962), *J. Amer. Chem. Soc.*, **84**, 284.
51. H.O. House and W.F. Fischer (1968), *J. Org. Chem.*, **33**, 949.
52. K.B. Sharpless and T.R. Veroeven (1979), *Aldrichimica Acta*, **12**, No. 4.
53. H.E. Simmons, T.L. Cairns, S.A. Vladuchick, and C.M. Hoiness (1973), in *Organic Reactions*, vol. 20, Wiley.
54. V. VanRheenen, R.C. Kelly, and D.Y. Cha (1976), *Tetrahedron Letters*, 1973.
55. E.J. Corey and P.B. Hopkins (1982), *Tetrahedron Letters*, **23**, 1979.
56. P.A. Bartlett (1984) in *Asymmetric Synthesis*, vol. 4, Ed. J.D. Morison. Academic Press, New York.
57. D. Nasipuri and G. Das (1979), *J.C.S. Perkin* I, 2776.
58. R.H. Hesse (1969), in *Advance in Free-radical Chemistry*, vol. 3.
59. E.L. Eliel (1974), *Tetrahedron*, **30**, 1503.
60. H.B. Kagan and J.C. Fiaud (1978), in *Topics in Stereochemistry*, vol. 10, Eds. E.L. Eliel and N. Allinger, Wiley, New York.
61. J.W. ApSimon and T.L. Collier (1986), *Tetrahedron*, **42**, 5157.
62. G. Giacomelli, R. Menicagli, and L. Lardicci (1974), *J. Org. Chem.*, **39**, 1757.
63. D. Nasipuri, A.K. Samaddar, and M. Datta Gupta (1984), *Proc. Indian Acad. Sci. (Chem. Sci.)*, **93**, 801.
64. D. Nasipuri, C.K. Ghosh. P.R. Mukherjee, and S. Venkataraman, (1971), *Tetrahedron Letters*, 1587.
65. M.M. Midland, A. Tramonland and S.A. Zderic (1979), *J. Amer. Chem. Soc.*, **101**, 2352.
66. M.M. Midland (1983), in *Asymmetric Synthesis*, vol. 2, Ed. J.D Morisson, Academic Press, New York.
67. A. Ohno and S. Ushida (1986) in *Mechanistic Models of Asymmetric Reduction*, Springer-Verlag, Berlin.
68. H. Haubenstock (1982), in *Topics in Stereochemistry*, vol. 14, Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.
69. R. Noyari, T. Tomino, and Y. Yamimoto (1979), *J. Amer. Chem. Soc.*, **101**, 3129.
70. S. Itsuno, A. Hirao, S. Nakahama, and N. Yamazaki (1983), *J.C.S. Perkin I*, 1673.
71. D.S. Matteson (1986), *Synthesis*, 973.
72. M. Srebnik and P.V. Ramachandran (1987), *Aldrichimica Acta*, **20**, Nos. 1 and 9.
73. H.C. Brown and P.K. Jadhav (1983), in *Asymmetric Synthesis* vol. 2, Ed. J.D. Morisson, Academic Press, New York.
74. K. Harada (1982), in *Asymmetric Reactions and Processes in Chemistry*, Eds. E.L. Eliel and S. Otsuka, ACS, No. 185.
75. B. Bosnich and M.D. Fryzerk (1981), in *Topics in Stereochemistry*, Ed. G.L. Goeffrey, series Eds. E.L. Eliel and N.L. Allinger, Wiley, New York.

76. H. Brunner (1988), in *Topics in Stereochemistry*, vol. 18, Eds. E.L. Eliel and S.H. Wilen, Wiley, New York.
77. E.J. Corey et al (1970), *J. Amer. Chem. Soc.*, **92**, 2476, 2488.
78. D. Enders (1984), in *Asymmetric Synthesis*, vol. 3, Ed. J.D. Morisson, Academic Press. New York.
79. K.A. Lutmoski and A.I. Meyers (1984), in *Asymmetric Synthesis*, vol. 4, Ed. J.D. Morisson, Academic Press, New York.
80. T. Katsuki and K.B. Sharpless (1980), *J. Amer. Chem. Soc.*, **102**, 5974.
81. A. Pfenninger (1986), *Synthesis*, 89.
82. Y. Gao, R.M. Hanson J.M. Klunder, S.Y. Ko, H. Masamune, and K.B. Sharpless (1987), *J. Amer. Chem. Soc.*, **109**, 5765.
83. U. Dolling, P. Davis, And E.J.J. Grabowski (1984). *J. Amer. Chem. Soc.*, **106**, 446.
84. H. Wynberg (1986) in *Topics in Stereochemistry*, vol. 16, Eds. E.L. Eliel, S.H. Wilen, and N.L. Allinger, Wiley, New York.
85. Z.G. Hajos and D.R. Parrish (1974), *J. Org. Chem.*, **39**, 1615.
86. T. Mukaiyama and N. Iwasawa (1981), *Chem. Letters*, 913.
87. K. Soai, S. Niwa, and M. Watanabe (1988), *J. Org. Chem.*, **53**, 926.
88. N. Oguni, Y. Matsuda, and T. Kaneko (1988), *J. Amer. Chem. Soc.*, **110**, 7877.
89. A.K. Samaddar, S.K. Konar, and D. Nasipuri (1983), *J.C.S. Perkin I*, 1449.
90. A. S Cieplak, B.D. Tait, and C.R. Johnson (1989), *J. Amer. Chem. Soc.*, **111**, 8447.
91. F. Toda and K. Mori (1989), 'Enantioselective Reductions of Ketones in Optically Active Host Compounds with a BH_3-ethylenediamine Complex in the Solid State', *JCS Chem. Commn.*, 1245.
92. E.N. Jacobsen, I. Marko, M.B. France, J.S. Svendsen, and K.B. Sharpless (1989), 'Kinetic Role of the Alkaloid Ligands in Asymmetric Catalytic Dihydroxylation', *J. Amer. Chem. Soc.*, **111**, 737.
93. P.R. Carlier and K.B. Sharpless (1989), 'Studies on the Mechanism of Asymmetric Epoxidation' - A Ligand Variation Approach', *J.Org. Chem.*, **54**, 4016.
94. I. Ojima, N. Clos, and C. Bastos (1989), 'Recent Advances in Catalytic Asymmetric Reactions Promoted by Transition Metal Complexes', *Tetrahedron*, **45**, 6901.
95. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori (1989), 'Asymmetric Diels-Alder Reaction Catalysed by Chiral Titanium Reagents', *J. Amer. Chem. Soc.*, **111**, 5340.
96. C. Siegel and E.R. Thornton (1989), 'Asymmetric Aldol Reactions. A Titanium Enolate Giving Very High Diastereofacial Selectivities', *J. Amer. Chem. Soc.*, **111**, 5722.
97. E. J. Corey (1990), 'Katsuki-Sharpless Oxidation', *J. Org. Chem.* **55**, 1693.
98. D. Nasipuri and A. Saha (1990), 'Stereechemical Evidence for Single Electron Transfer Mechanism: Reduction of Cyclic Ketones by Alkoxy and Alkyl Metal Halides', *Indian J. Chem.*, **29B**, 471, 474.

(References 91 to 98 are later addition)

Chapter 14

Dynamic Stereochemistry III : Pericyclic Reactions

14.1 Introduction

The stereochemistry of reactions so far discussed is based on selective transformation of stereoheterotopic faces and ligands distinguished by intramolecular symmetry. In addition, there is a group of reactions known as pericyclic reactions the stereochemistry of which depends on the symmetry of the interacting molecular orbitals (MO's) and not on the overall symmetry of the molecules. These reactions are concerted, do not follow any ionic or radical pathway, remain unaffected by polar solvents, radical initiators (or inhibitors) and catalysts,* and take place thermally or photochemically. They are further characterised by the facts that at least one component of the reactants and the products is unsaturated and the changes in bonding take place through reorganisation of electrons (pairwise) within a closed loop of interacting orbitals (hence the name pericyclic). The Diels-Alder reaction, e.g., condensation of butadiene and a substituted ethene (Figure 14.1) provides a classic example in which the 4 π-electrons of butadiene and the 2 π-electrons of ethene reorganise through a set of interacting MO's to the 4 σ and 2 π-electrons of cyclohexene.

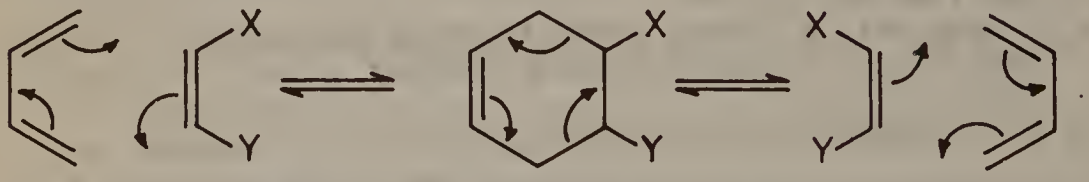


Figure 14.1 A Diels-Alder (cycloaddition) reaction

The curved arrows do not mean that pairs of electrons move in a certain direction (they can move in either direction as shown) but are useful to show the changes in bonding. Woodward and Hoffmann (1965, 1970) first rationalised the outcome of these reactions with the help of certain rules known as Woodward Hoffmann rules) based on the principle of conservation of orbital symmetry which may be briefly stated as follows: In the pericyclic reactions, a set of MO's of the reactants are transformed into a corresponding set of MO's of the products through a concerted process. If during the transformation, the symmetry of the concerned

*Exceptions are some acid-catalysed Diels-Alder reactions.

orbitals is conserved, i.e., the orbitals remain in phase* and thus maintain some degree of bonding throughout the process (giving a concerted character), the reaction involves a relatively low energy transition state and is called symmetry-allowed. On the other hand, if the orbital symmetry is destroyed by bringing one or more orbitals out of phase, the transition state energy becomes very high due to an antibonding interaction and the reaction is symmetry-forbidden (if it occurs, it will be non-concerted). While considering the symmetry of the relevant MO's, the slight perturbation by a substitution (e.g., Me) which may interfere with molecular symmetry is generally ignored since the mechanism of the reaction remains the same. All pericyclic reactions may be regarded as cycloaddition reactions or their retrogressions (see later) although for the sake of convenience, they are subdivided into several categories : electrocyclic, cycloaddition, sigmatropic, cheletropic, and group transfer reactions.

The pericyclic reactions are highly, sometimes even totally, diastereoselective under kinetically controlled conditions and are therefore of special interest in synthetic chemistry. For the same reacting system, thermal and photochemical reactions give opposite stereochemistry. Three different approaches with different degrees of sophistication have been made to explain the results : (i) the method of correlating orbitals in relation to certain symmetry elements which are preserved throughout the reactions (Woodward-Hoffmann), (ii) the method based on aromaticity and antiaromaticity of the transition state according to Hückel's MO theory (Zimmerman and Dewar), and (iii) the frontier molecular orbital (FMO) method in which only the interaction between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) is considered (Woodward-Hoffmann, Fukui). The frontier orbital approach is the simplest and is capable of explaining the stereochemistry of all pericyclic reactions. It is therefore adopted in the present text (see Fleming 1976). For a detailed discussion of the topic, the reader is referred to various texts (Lowry and Richardson 1987, Woodward and Hoffmann 1970, Gill and Willis 1974, Lehr and Marchand 1972, Gilchrist and Storr 1979, Marchand and Lehr 1977, Fukui 1975).

Three main types of pericyclic reactions: electrocyclic reactions, cycloadditions, and sigmatropic rearrangements are considered in this chapter with special emphasis on their stereochemical features. Since they will be treated only by the FMO approach, the importance of the frontier MO's is briefly explained. When two molecules (or appropriate segments thereof) approach each other (in a reaction), pairs of filled MO's which are close in energy interact to give pairs of hybrid MO's, one bonding and the other antibonding. The energy gained by a bonding orbital is always slightly less than the energy lost by the antibonding one so that the energy of the system increases slightly (four electrons are to occupy the two hybrid MO's) and the cumulative effect constitutes the major part of the activation energy of the reaction. At the same time, the HOMO of one molecule interacts with the LUMO of the other but since there are only two electrons (usually), they are accommodated in the bonding hybrid orbital lowering the activation energy to

*See Streitweiser (1961) and Orchin and Jaffe (1967) for symmetry and phase of orbitals.

an appreciable extent.* A third factor, namely, coulombic interaction, has also to be considered when dealing with charged reacting species. The three effects combinedly account for the activation energy of a reaction. In order to have appreciable interaction of the HOMO's and LUMO's which is the major consideration in pericyclic reactions, they must be of comparable energies and above all must belong to the same symmetry type.

14.2 Electrocyclic reactions

An electrocyclic reaction is one in which the two termini of a conjugated polyene shown by the double-lined semicircle† (Figure 14.2a) (k indicates the number of trigonal carbon atoms and also the number of π-electrons) are joined through a single bond, the net change being the conversion of a π-bond into a σ-bond or the reverse, i.e., the conversion of a σ-bond into a π-bond with concomitant ring-opening. Actual examples are given in the interconversion of 1,3-butadiene and cyclobutene and of 1,3,5-hexatriene and cyclohexadiene (Figure 14.2b).

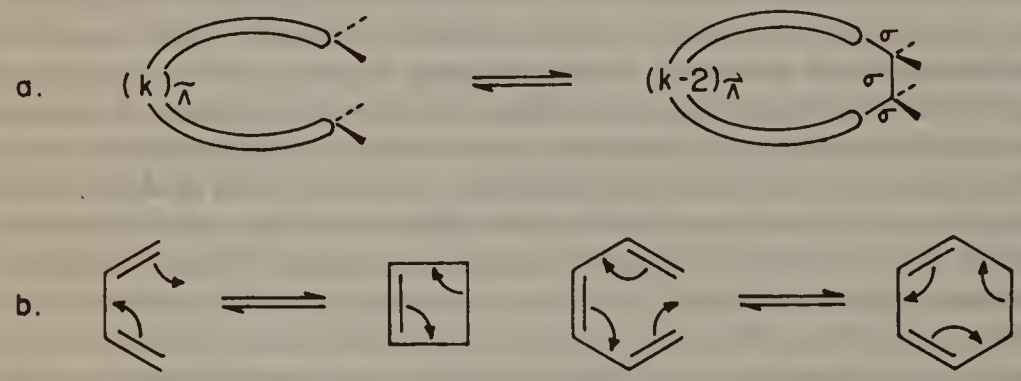


Figure 14.2 Electrocyclic reactions: 4π-system and 6π-system

14.2.1 Frontier molecular orbital (FMO) approach

In electrocyclic reactions, only one reactant, i.e., a polyene or in the reverse reaction, a cycloalkene is involved and in the frontier orbital approach, only the HOMO of the polyene need be considered. For convenience, each π-MO of a polyene is shown as a combination of localised p orbitals (sometimes, the signs of the lower lobes are not shown) with the understanding that adjacent lobes of the same sign (phase) overlap and adjacent lobes of opposite signs produce a node in the resulting MO. The four π-MO's of butadiene thus appear as in the diagram (Figure 14.3a) and are designated ψ_1 to ψ_4. Based on the free electron model (FEM), a simplified mechanical device has been worked out to enable one to get the number and position of the nodes in the MO's of higher polyenes in the

*This is also true of atomic orbitals and easiesr to grasp; thus H + H = H_2 but He + He→no reaction.

†In these reactions, the polyenes are depicted in all-*s*-cis conformation as well as (when applicable) cis configuration. For small polyenes at least these conformation and configuration are required for cyclisation.

increasing order of their energy. The trigonal carbon atoms are represented by dots joined by single bonds of equal length to form a straight line which is elongated on both sides by one half of a bond. The two termini of the line are then joined by multiples of half waves as shown in Figure 14.3b. The points at which the wave

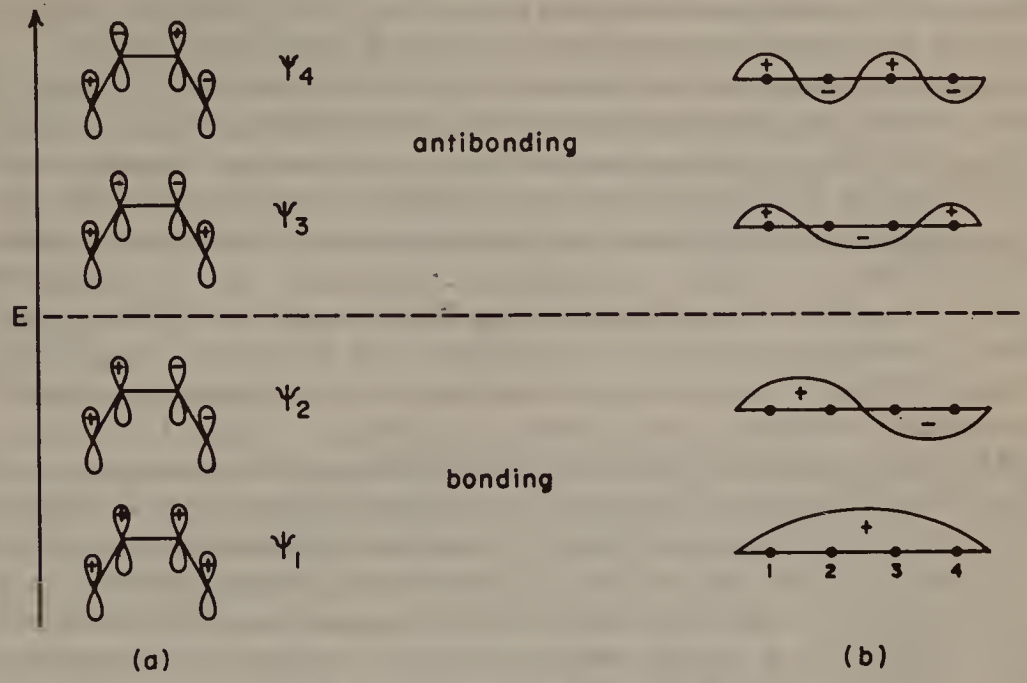


Figure 14.3 Molecular orbitals of 1,3-butadiene

intercepts the line (excluding the two termini) represent the nodes the number of which increases with the increasing energy of the MO's. The sign inside each half wave refers to the sign of the upper lobes of the composite p orbitals; the left hand diagram thus corresponds to the right hand diagram.

The 4 π-electrons of butadiene are accommodated in the two bonding MO's, ψ_1 and ψ_2 so that ψ_2 is the HOMO. It is quite evident that the overlap of the terminal π-lobes of the same sign, (+ +) or (− −), forming a σ bond is possible only by a conrotatory motion (rotation of 90° of two terminal bonds in the same direction) either clockwise (as shown in Figure 14.4) or anticlockwise. A disrotatory motion in the HOMO (rotation of the bonds in opposite directions), on the other hand, leads to an antibonding interaction (σ^*). In thermal electrocyclic reactions of a 4 π-electron system, therefore, only conrotatory motion is allowed and the stereo-

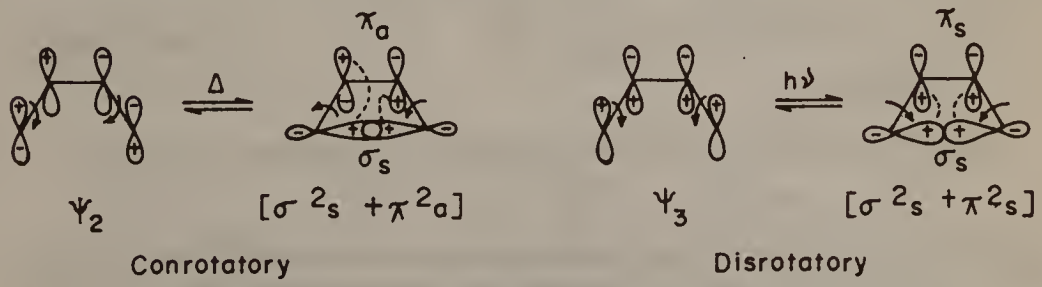


Figure 14.4 Electrocyclic conversion of butadiene into cyclobutene and vice versa

chemistry follows accordingly. On photoexcitation of butadiene, one of the π-electrons is transferred to ψ_3 which thus becomes the HOMO. An inspection of the MO shows that a disrotatory motion leads to an overlap of sp^3 orbitals of the same phase and a different stereochemistry follows.

Electrocyclic reactions, particularly the ring opening of unsaturated cycloalkenes to polyenes, e.g., cyclobutene to butadiene (the reverse of the above reaction) may be regarded as cycloadditions in which a σ bond and a π bond (or a conjugated system) constitute the two components in the addition reactions. Some notations which are used in cycloaddition reactions may be defined here to indicate the mode of additions. If a component undergoes addition (forms bonds) on the same face, it is called a *suprafacial* component while if a component undergoes addition on opposite faces, it is called an *antarafacial* component. The two modes of additions are known as suprafacial and antarafacial respectively. Following this definition, conrotation involves an antarafacial and disrotation a suprafacial interaction between the two termini of the reacting species in electrocyclic reactions. In the thermal conrotatory ring opening of cyclobutene (Figure 14.4), the σ-HOMO of the σ component interacts with the π-LUMO of the π-component with in-phase overlap, the former behaving as a suprafacial component and the latter as an antarafacial one (see the dotted lines). The reaction is designated $[_\sigma 2_s + _\pi 2_a]$ (s and a stand for supra- and antarafacial respectively). Alternatively, the same reaction may be considered in terms of interaction between the σ-LUMO, i.e., σ^* and the π-HOMO, i.e., π and thus designated $[_\sigma 2_a + _\pi 2_s]$. Similarly, the disrotatory photochemical ring opening of cyclobutene (right hand diagram) in which the σ-HOMO and the π-LUMO* both interact suprafacially is designated $[_\sigma 2_s + _\pi 2_s]$. Alternatively, if the interaction between the σ-LUMO and the π-HOMO is considered,* it may be designated $[_\sigma 2_a + _\pi 2_a]$.

The treatment is extended to 1,3,5-hexatriene-cyclohexadiene interconversion shown in Figure 14.5 (k = 6). The HOMO of the triene is represented by ψ_3 which on disrotation leads to an in-phase overlap and so disrotatory ring closure is thermally allowed. In the reverse ring opening, the σ-HOMO interacts with the LUMO (ψ_3) of the butadiene unit both with suprafacial mode and the reaction

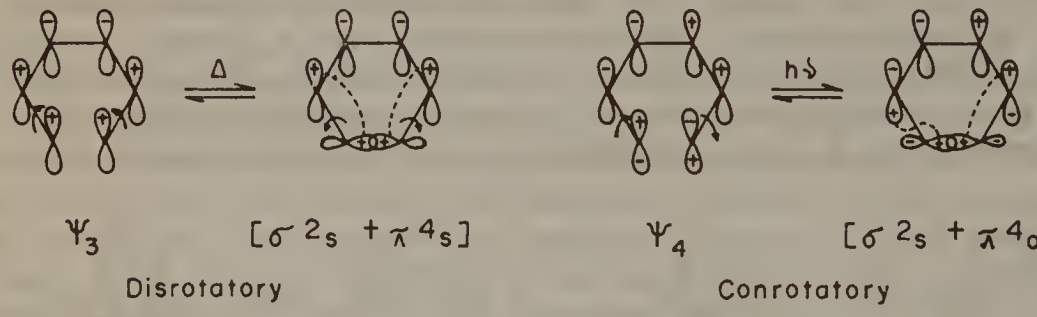


Figure 14.5 Electrocyclic conversion of hexatriene into cyclohexadiene and vice versa

*If a reacting component contains a singly occupied molecular orbital (SOMO), it may act both as a HOMO and a LUMO since it is electron donating as well as electron accepting. In $\pi \rightarrow \pi^*$ excitation, both π and π^* are SOMO, i.e., SOMO-1 and SOMO-2 and relevant interactions may occur between σ-HOMO and SOMO-1 and between σ-LUMO and SOMO-2.

type is $[_{\sigma}2_s + {}_{\pi}4_s]$. In the first excited state, ψ_4 corresponds to the HOMO of the triene and a conrotation leads to an in-phase overlap and so photochemical ring closure (or ring opening) in the 6 π-electron system is conrotatory. The reverse reaction is designated $[_{\sigma}2_s + {}_{\pi}4_a]$ and is a result of the interaction of the σ-HOMO with the SOMO-1 of butadiene. The following two rules which are easily derivable from the nodal properties of polyenes and polyenyl ions (Woodward and Hoffmann 1970) may be stated for all electrocyclic reactions :

(*i*) The thermal electrocyclic reactions of a k π-electron system are conrotatory for k = 4n and disrotatory for k = 4n + 2, (n = 0,1,2 etc.).

(*ii*) For photochemical reactions involving the first excited state, the relationships are reversed.

Examples with stereochemical consequences follow.

14.2.2 Stereochemistry

The stereochemistry of an electrocyclic reaction follows from the conrotatory or disrotatory mode of ring closure (or ring opening) as permitted by the system under consideration and the condition of reaction (thermal or photochemical). For each mode of rotation, there are two distinct possibilities, which occasionally interfere with the product stereoselectivity. In cases where the two possibilities of a mode give the same product due to an inherent symmetry of the system or one possibility is forbidden by molecular geometry or by steric interaction in the transition state, almost total diastereoselectivity results. A few illustrations are given involving different ring systems.

1. Four-membered rings. As already stated, the electrocyclic ring opening of cyclobutenes is thermally conrotatory and photochemically disrotatory. The reverse reaction, namely, ring closure of butadienes to cyclobutenes is not thermodynamically favourable, the dienes being more stable than the cyclobutenes by some 50 kJ mol^{-1}. Figure 14.6 shows that the thermal ring opening of *cis*-3,

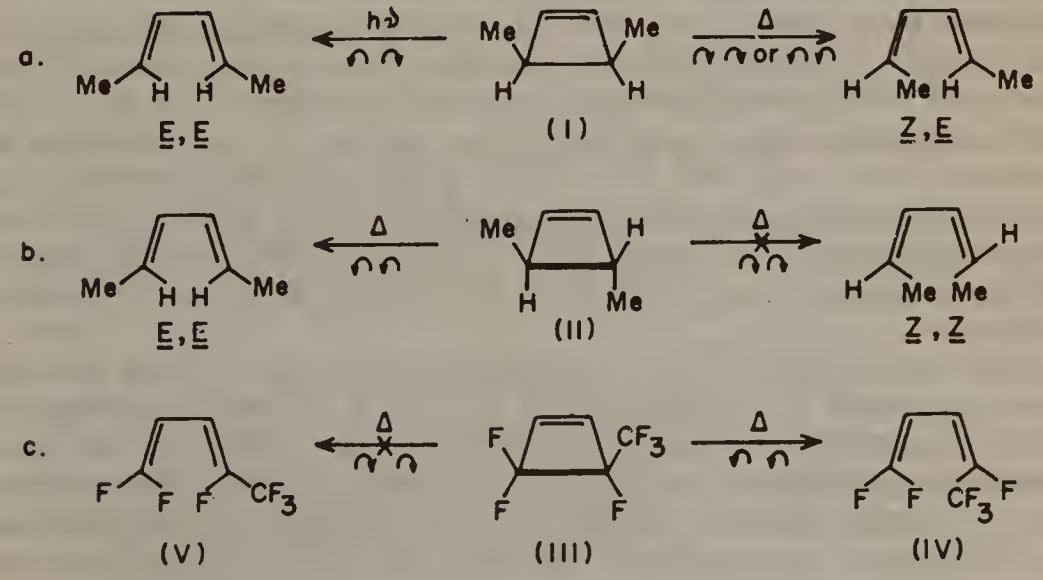


Figure 14.6 Stereochemistry of electrocyclic reactions: cyclobutenes to butadienes

4-dimethylcyclobutene (I) by either of two possible conrotatory motions gives *Z,E*-1,4-dimethylbutadiene while the photochemical ring opening gives the *E,E* isomer only through a single disrotatory motion in which the substituents (Me) move outward (the inward movement incurs excessive steric repulsion). Similarly, the *trans*-cyclobutene (II) on thermal ring opening gives only *E,E*- and not *Z,Z*-butadienes (examples a and b respectively). However, the outward (or inward) movement of a substituent is not controlled by steric factor alone but also by its electronegativity. Thus a π-donor substituent such as F shows a high preference for outward rotation (Dolbier et al 1986) as illustrated by the ring opening of fluorinated cyclobutene (III) in which IV is formed in preference to V (example c).

2. Six-membered rings. In hexatrienes-cyclohexadienes interconversion (k=6), the reactions are thermally disrotatory and photochemically conrotatory. The various transformations of *E,Z,E*-(VI) and *Z,Z,E*-(VII) isomers of 1,6-dimethyl hexatriene are shown in Figure 14.7 (a and b).* Points to be noted are: (*i*)

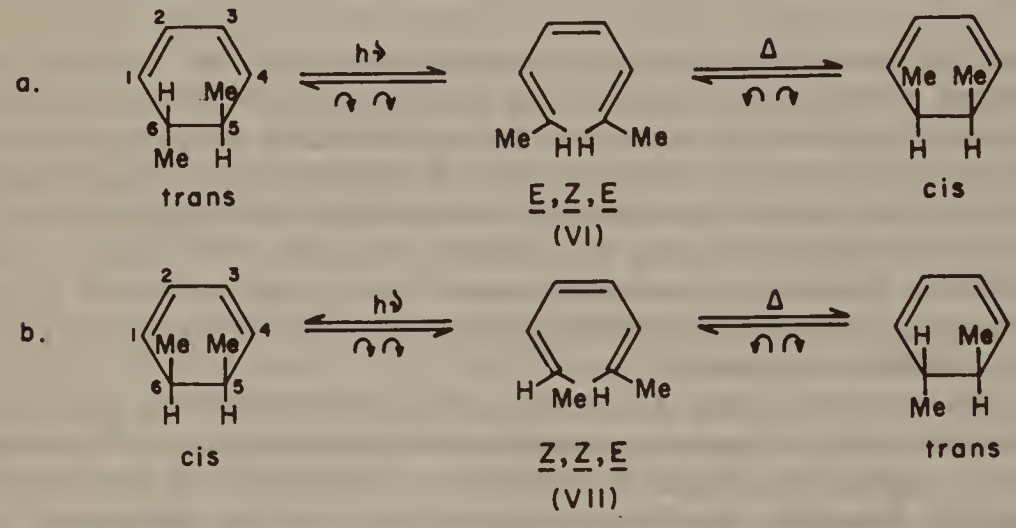


Figure 14.7 Stereochemistry of electrocyclic reactions: hexatrienes to cyclohexadienes

Disrotatory thermal ring opening of the cis isomer of 5,6-dimethylcyclohexadiene follows only one pathway with both the alkyl groups moving outwards and forming two terminal trans double bonds (same as in cyclobutenes). (*ii*) Disrotatory ring closure of any polyene brings the two outer and the two inner substituents at the termini close to each other, i.e., to the same side (cis) of the newly formed σ bond. Conrotatory ring closure does the opposite. (*iii*) The polyene must be so disposed as to bring the two termini (see X in Figure 14.8) within reacting distance which precludes any trans double bond in a polyene except at the terminal positions.

When the two substituents of the cyclohexadiene form parts of a ring as in the bicyclic compound (VIII) (Figure 14.8), point (*i*) is no longer valid and the thermal ring opening takes place by the alternative path of disrotation, with both substituents moving inwards, giving an all-cis cycloalkatriene (IX). This is because there is no longer any steric repulsion and two trans double bonds cannot be accommodated in rings unless they are large. This is well documented in the

* Cyclohexadienes are thermodynamically quite stable.

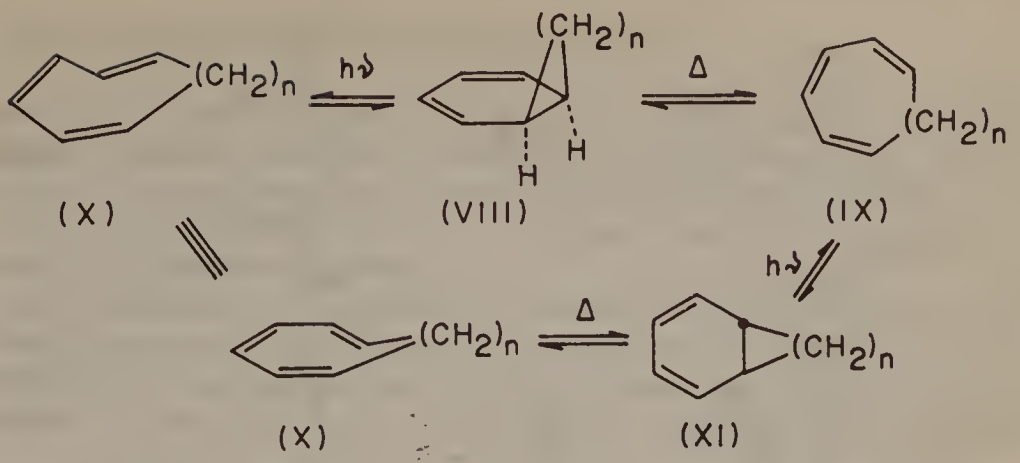


Figure 14.8 Electrocyclic reactions: bicyclic cyclohexadienes to cycloalkatrienes

interconversion of norcaradiene (VIII, n = 1) and cycloheptatriene (IX, n = 1) (Maier 1967) (the equilibrium favours the cycloheptatriene). For n>1, interconversion among VIII and other compounds, e.g., X and XI is possible. The thermal and photochemical transformations in the vitamin D series, e.g., XII (Figure 14.9) (Havinga et al 1960) further illustrate the stereochemistry of these electrocyclic reactions.

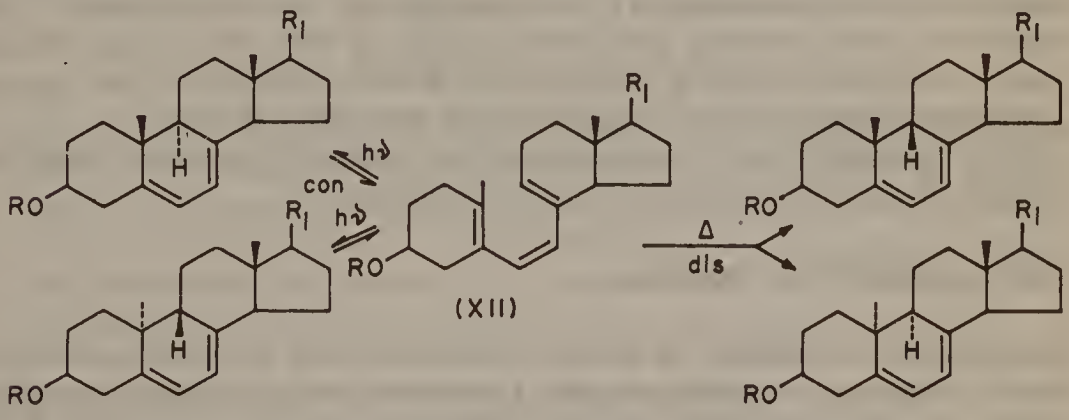


Figure 14.9 Interconversion of cis-hexatrienes into vitamin D

Eight-membered and higher even-membered rings may be treated in a similar fashion and are not included here.

3. Three- and other odd-membered rings. Even-membered rings undergoing electrocyclic ring opening are neutral closed-shell molecules while the odd-membered rings by necessity must be cations, anions, or radicals. A cyclopropyl cation opens up to an allylic cation, a 2 π-electron system ($k = 4n+2$, $n = 0$) through a thermal disrotatory mode and a cyclopropyl anion to an allylic anion (4 π-electron system) through a thermal conrotatory mode. Direct proof for these modes of ring opening may be available from NMR study of the allylic cations formed from 2,3-dimethyl-1-chlorocyclopropanes at low temperatures in strongly acidic medium. Indirect proof is obtained from the relative rates of solvolysis of the two isomeric tosylates (XIII) and (XIV) (Figure 14.10). It is argued that the

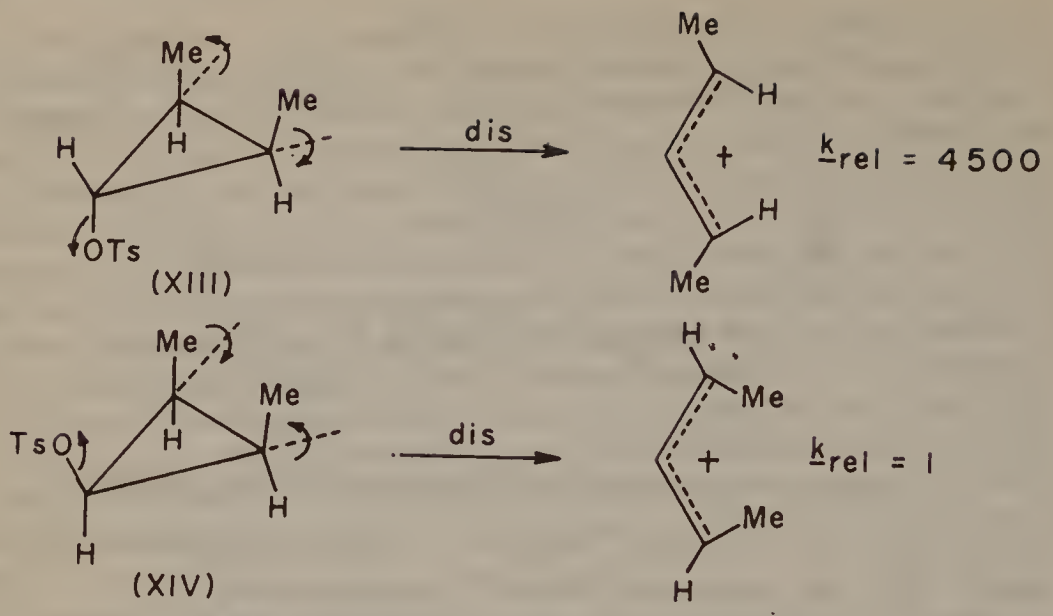


Figure 14.10 Disrotatory ring opening of cyclopropyl cations

formation of cyclopropyl cation and its opening to allyl cation are concerted and that the disrotatory rupture of the σ bond must take place in such a way that it lends an anchimeric assistance to C-OTs bond cleavage by a backside attack. This requires an outward rotation of the methyl groups in XIII which is easy and an inward rotation of the methyl groups in XIV which is difficult for steric reason. The relative acetolysis rates of XIII and XIV are 4500 and 1 at 150°C.

For a treatment of other odd-membered ring systems, the reader is referred to Woodward and Hoffmann (1970), Gills and Willis (1974).

14.3 Cycloaddition reactions

In cycloaddition reactions, the termini of two (or more) π-systems combine to form σ bonds and an additional ring. The reverse process is known as cycloreversion or retro-cycloaddition (see the Diels-Alder reaction. Figure 14.1). If the number of π electrons in the two components is m and n respectively, the cycloaddition is called [m + n] addition. A complete nomenclature such as $[_{\pi}m_s + _{\pi}n_a]$ is used to indicate the nature of the participating electrons* and the mode of addition (supra- or antarafacial) on each component. Depending on whether the two components belong to different molecules or the same, the cycloaddition may be inter- or intramolecular. Cycloaddition reactions constitute an important class of C-C bond forming reactions which are used for the synthesis of many complex molecules.

*The participating electrons are of three types depending on the nature of orbitals they occupy : σ, π, and ω. Electrons occupying a single interacting atomic orbital (as in carbene.) are known as ω-electrons and the orbitals as ω orbitals (Woodward and Hoffmann 1970).

14.3.1 Frontier molecular orbital (FMO) approach

Although the Woodward-Hoffmann treatment based on the conservation of orbital symmetry offers an instructive explanation for cycloaddition reactions, the frontier molecular orbital (FMO) approach based on HOMO-LUMO interaction provides a useful and simple mnemonic device predicting the same results and covering all aspects of cycloaddition reactions.

The cycloaddition of butadiene and a substituted ethylene is a typical example of the Diels-Alder reaction (Figure 14.1). The HOMO of butadiene (ψ_2) and the LUMO of ethylene (π^*) as also the LUMO of butadiene (ψ_3) and the HOMO of ethylene (π) are shown in Figure 14.11 (a and b respectively) with their planes

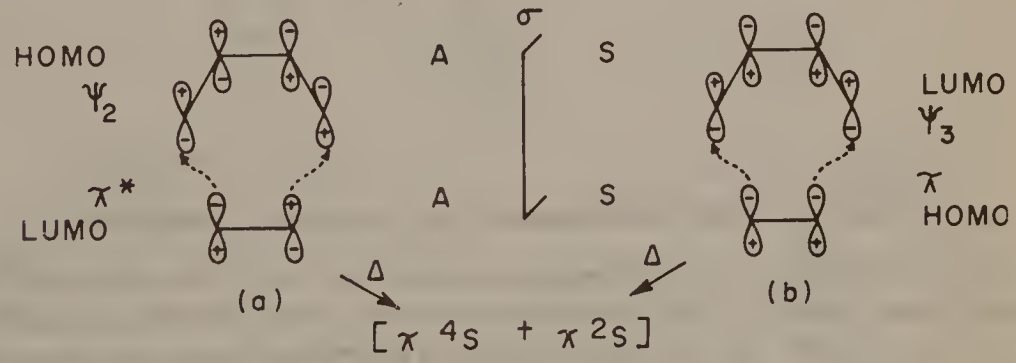


Figure 14.11 HOMO-LUMO interaction in [4 + 2] cycloaddition

parallel. It is at once clear that in both combinations, there are bonding interactions at the termini. Moreover, the pairs of HOMO-LUMO belong to the same symmetry classification (both antisymmetric, A, in the former and both symmetric, S, in the latter) with respect to a σ plane which is also the only symmetry element of the butadiene-ethylene combination (also, ψ_2 and π^* are symmetry correlated with respect to a C_2 axis while ψ_3 and π are so with respect to a σ plane). The $[\pi 4_s + \pi 2_s]$ addition is thus thermally or symmetry allowed. The suprafacial (or antarafacial) interactions are shown by dotted lines. Since suprafacial-suprafacial (s,s) and antarafacial-antarafacial (a,a) combinations give the same prediction, $[\pi 4_a + \pi 2_a]$ addition is also thermally allowed and proceeds simultaneously although less effectively. In a photochemical reaction, the reverse is true, i.e., $[\pi 4_s + \pi 2_a]$ or $[\pi 4_a + \pi 2_s]$ addition takes place (combination of HOMO-LUMO is either SOMO-2 of ethylene and ψ_3 of butadiene or ψ_2 of butadiene and SOMO-1 of ethylene*). To summarise, in a 6 π-electron system (m + n = 6) $[\pi 4_s + \pi 2_s]$ and $[\pi 4_a + \pi 2_a]$ are thermally allowed and $[\pi 4_s + \pi 2_a]$ and $[\pi 4_a + \pi 2_s]$ are photochemically allowed.

Similar treatment of the cycloaddition of two butadiene molecules - an 8 π-electron (m + n = 8) system (Figure 14.12) shows that $[\pi 4_s + \pi 4_a]$ addition (see the dotted lines in a) is thermally allowed while $[\pi 4_s + \pi 4_s]$ is photochemically allowed (also concomitantly, a [4 + 2] cycloaddition may take place). A [6 + 2] addition behaves in the same fashion but it is accompanied by a more facile

*For SOMO-1 and SOMO-2, see footnote on p. 450.

[4 + 2] addition. The cycloaddition of hexatriene and butadiene (m = 6, n = 4)—a 10 π-electron system—behaves exactly in the same way as the [4 + 2] addition (Figure 14.12b).

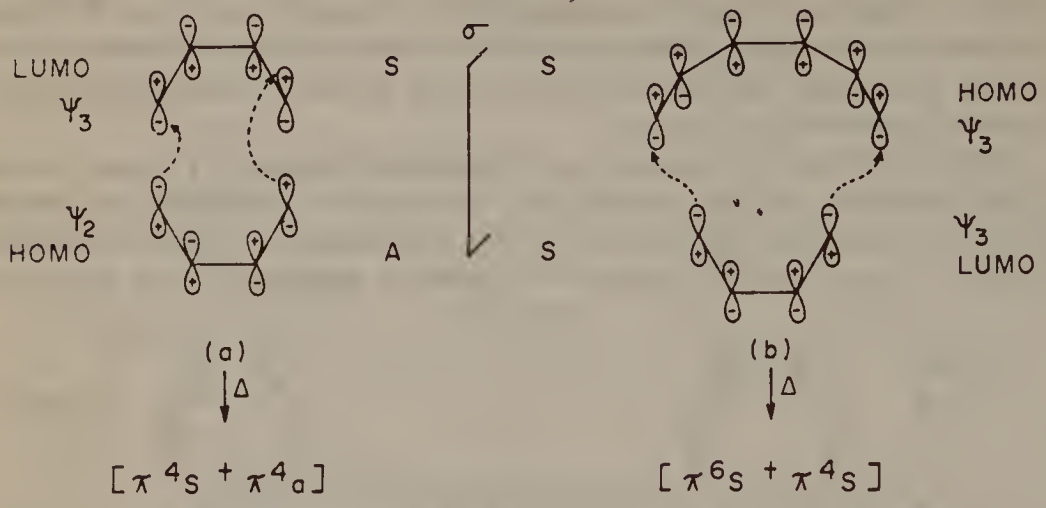


Figure 14.12 HOMO-LUMO interaction in [4 + 2] and [6 + 4] cycloaddition

In the cycloaddition of two ethylene molecules (m + n = 4) to cyclobutane, the ground state HOMO-LUMO combination does not permit thermal (s,s) addition (a in Figure 14.13). The (s,a) addition which is thermally allowed goes through an orthogonal transition state (d) (only the upper lobes of the p orbitals of the horizontal ethylene are shown) giving the product (e = f). Even in this disposition, the overlap is only minimal and worsened by the interfering effect of the

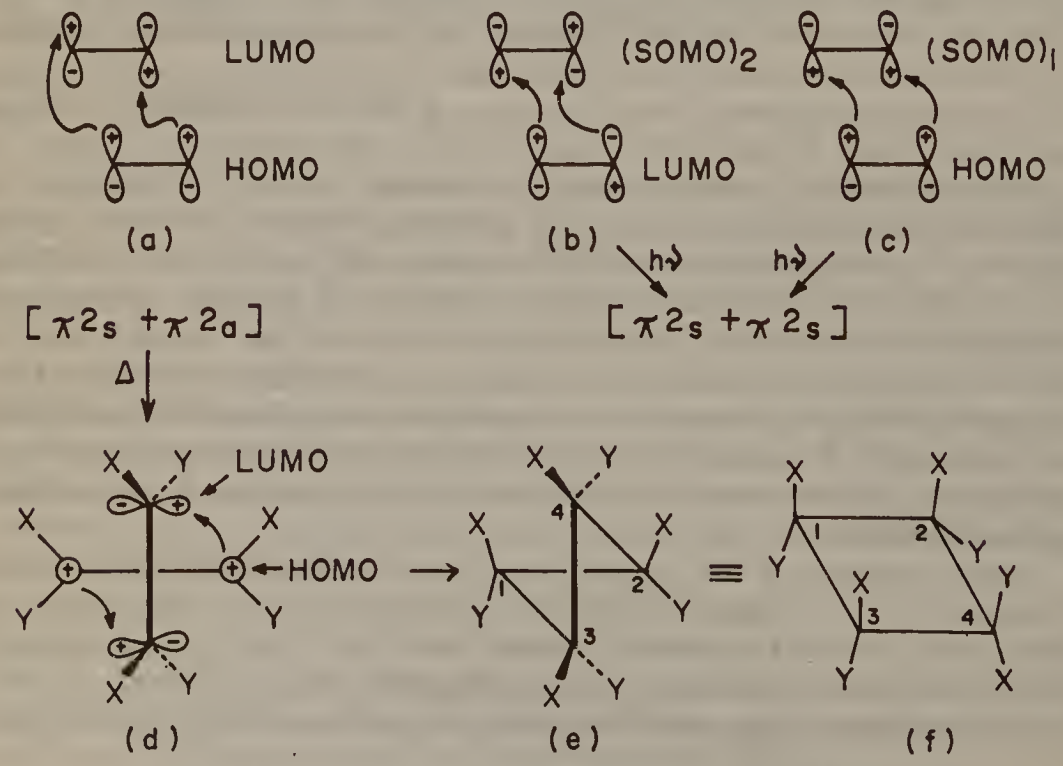


Figure 14.13 HOMO-LUMO interaction in [2 + 2] cycloaddition

substituents (X and Y). Thermal $[\pi 2_s + \pi 2_a]$ additions are thus very rare (see later). Photochemical $[\pi 2_s + \pi 2_s]$ and the equivalent $[\pi 2_a + \pi 2_a]$ additions are, however, allowed (see b and c in Figure 14.13).

In the final example, the cycloaddition of an olefin and a singlet carbene (XV in Figure 14.14), another [2 + 2] electron system is shown. The HOMO of the carbene, a σ orbital (or an ω orbital) with two electrons, adds antarafacially through a non-linear π-approach (A) to the same side (suprafacial) of the LUMO of the olefin (Figure 14.14). It is thus a $[\omega 2_a + \pi 2_s]$ addition. The alternative linear and more symmetrical σ approach (B) is ruled out since it leads to an antibonding interaction.

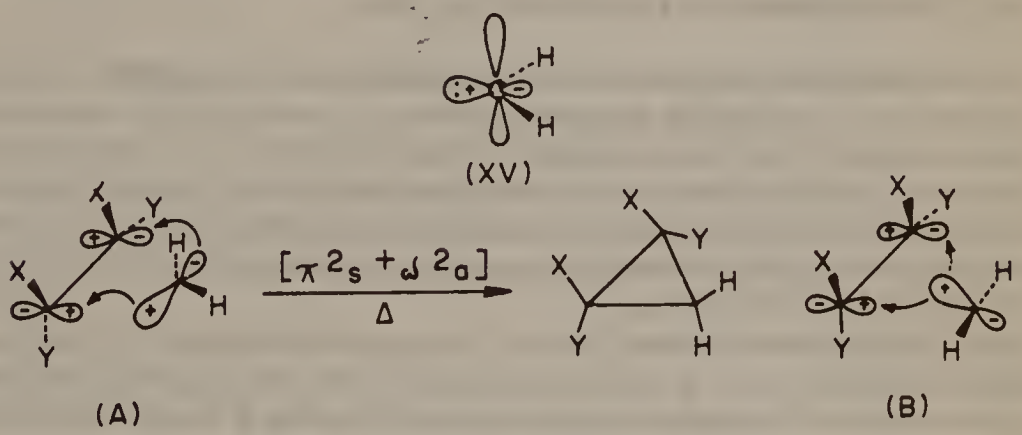


Figure 14.14 Addition of carbene to an olefin

Ionic species such as allylic, pentadienyl, and heptatrienyl cations and anions also participate in cycloaddition reactions as π-components. Neutral 1,3-dipoles—a three atom 4 π-electron system—similarly undergo [2 + 4] cycloaddition with olefins.

14.3.2 Generalised Woodward-Hoffmann rule

The above observations lead to the prediction that the reacting π-systems with a total number of 4q + 2 electrons (2,6,10 etc) undergo thermal (s,s) cycloaddition while those with 4r electrons (4,8 etc.) undergo thermal (s,a) and photochemical (s,s) cycloaddition. They conform to the generalised Woodward-Hoffmann rule* which states that a ground state pericyclic change is symmetry allowed (and so facile) when the total number of $(4m + 2)_s$ and $(4n)_a$ components (say, X and Y respectively) is odd. Thus in the cycloaddition of butadiene and ethylene, ethylene serves as the $(4m + 2)_s$ component and butadiene as the $(4n)_a$ component, i.e, X = 1 and Y = 0 making the total odd and the thermal ground state addition is symmetry allowed. A few relevant points emerge from the above discussion:

(*i*) For a two component cycloaddition, the maximum number of modes of addition is 2^2 (for n components, it is 2^n): (s,s), (s,a), (a,s), and (a,a).

*Should not be confused with Woodward-Hoffmann selection rules which are many and refer to individual pericyclic reactions.

(*ii*) Only in the (s,s) mode of addition, the two π-systems approach in parallel planes. In all other modes of addition, the components approach orthogonally.

(*iii*) Configuration of groups at the two termini of a suprafacial component is retained while that on an antarafacial component is inverted.

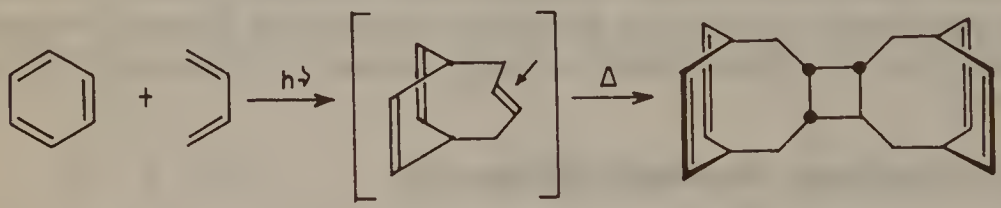
(*iv*) For either m or n greater than 2, there are two modes of (s,s)-additions, the substitution pattern permitting, one giving endo product and the other giving exo product (to be illustrated later).

(*v*) The $[\pi 4_s + \pi 2_s]$ addition is most facile closely followed by $[\pi 4_a + \pi 2_a]$ addition.

14.3.3 Stereoselectivity in cycloaddition reactions

Cycloaddition reactions when concerted are almost totally stereoselective and the stereochemistry is decided by the mode of addition as permitted by the Woodward-Hoffmann rules. Since these reactions proceed by way of cyclic transition state with loss of degrees of freedom. they are characterised by high negative entropy of activation.* A few intramolecular cycloadditions and intermolecular cycloadditions with only two components (which are more common than those with multiple components) are discussed here.

1. [2 + 2] Addition. Thermal $[\pi 2_s + \pi 2_a]$ cycloadditions leading to cyclobutanes are rare because of the geometrical restraint in the orthogonal transition state discussed before. If the double bond in the reacting species is twisted about its axis so that the two p orbitals are no longer parallel (and coplanar) as in the compound (XVI) (Figure 14.15), obtained by the photochemical $[\pi 4_s + \pi 4_s]$ addition of



(XVI) (XVII)

Figure 14.15 Thermal [2 + 2] cycloaddition of olefins (the arrow shows the twisted double bond)

benzene and butadiene, there is better overlap of the FMO's and the addition becomes facile. In fact. the intermediate adduct (XVI) spontaneously dimerises to the product (XVII) with the expected stereochemistry (see Figure 14.13) of a $[\pi 2_s + \pi 2_a]$ addition (Kraft and Koltenburg 1967).

Ketenes and cumulenes with one or more sp hybridised carbon atoms which lack a pair of interfering substituents at one of the reacting termini also undergo thermal [2 + 2] cycloaddition with olefins with relative ease. The former (ketenes and cumulenes) behave as antarafacial and the latter (olefins) as suprafacial components. Two stereochemical features are usually observed: The olefin expectedly

*Average values of $\Delta S^{\ddagger}$ for Diels-Alder reactions are around—35 JK^{-1} per mole and for sigmatropic rearrangements are around—50 JK^{-1} per mole.

retains its configuration but the adduct is the one which is sterically more congested. The latter fact may be rationalised from the orthogonal transition state (the central structure in Figure 14.16) which is so formed that the sp carbon (less hindered) of the ketene is directed towards the more hindered side of the olefinic

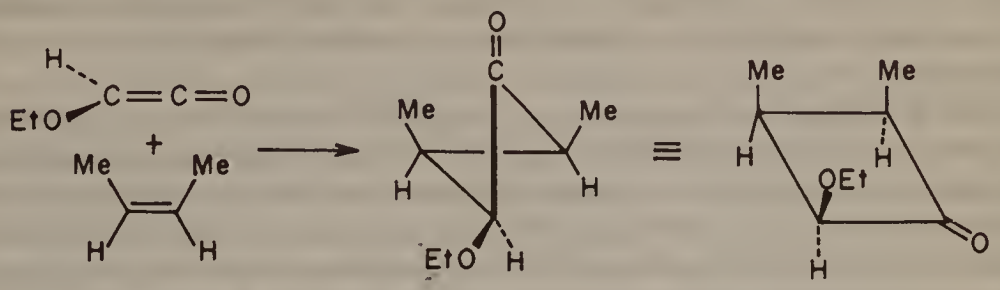


Figure 14.16 Preferred transition state of [2 + 2] cycloaddition of a ketene

double bond (i.e., C=O of the ketene and the two Me's of *cis*-2-butene are on the same side). As a result. the kinetically controlled product of the addition becomes sterically more hindered (OEt ends up on the same side as the Me's). The stereochemistry thus reflects the stability of the transition state and not that of the product.

Many of these cycloaddition reactions proceed through biradical (non-concerted) mechanism particularly with chloro,fluoro-olefins. A few synthetically useful photochemical [$_{\pi}2_s + _{\pi}2_s$] additions are known (see Figure 14.17 for an example).

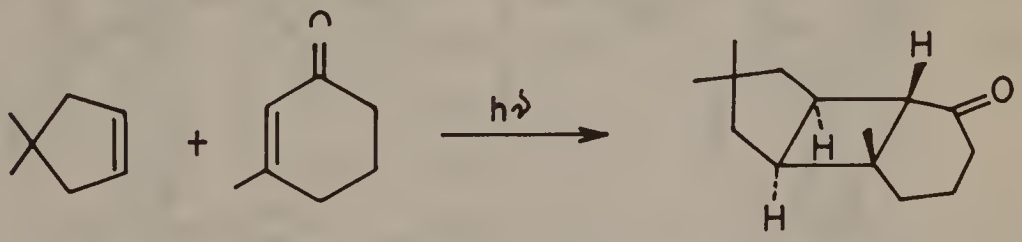


Figure 14.17 Photochemical [2 + 2] cycloaddition of olefins

2. [4 + 2] Addition: the Diels-Alder reaction. The Diels-Alder reaction is the best known [$_{\pi}4_s + _{\pi}2_s$] cycloaddition and proceeds stereoselectively, syn with respect to both the diene and dienophile as expected of a concerted (s,s) mode of addition. The concerted nature of the addition of butadiene and ethylene has recently been confirmed using suitably deuterated components (Figure 14.18), the

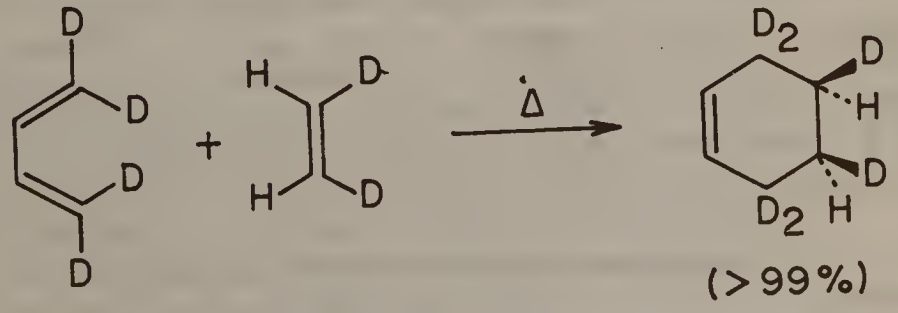


Figure 14.18 Evidence of concerted character of [4 + 2] addition

product being almost exclusively (> 99%) the cis isomer (Houk et al 1986). It is beyond the scope of the present text to discuss the Diels-Alder reaction in any detail. A few characteristic features are presented with appropriate examples.

a. The diene must be able to react in the *s*-cis conformation; thus any structural feature such as bulky substituents at the terminal carbons or the existence of a ring or rings which interfere with achieving the *s*-cis conformation inhibits or retards the reactions.

b. The LUMO of the dienophile and the HOMO of the diene are generally closer in energy than the I UMO of the diene and the HOMO of the dienophile. The relevant interaction is thus between the former pair and any structural feature which raises the energy of the diene HOMO, e.g., electron donating substituents and lowers the energy of the dienophile LUMO, e.g., electron accepting substituents makes the reaction much faster. Thus maleic anhydride reacts with butadiene at a much faster rate than ethylene. In an interesting example, a double bond made strongly dienophilic by an adjacent carbonium ion has been used in an intramolecular Diels-Alder (IMDA) reaction (Gassman and Oingleton 1986) (Figure 14.19a)*. The Diels-Alder reaction in an aqueous medium in the presence of β-cyclodextrin also enhances the intramolecular addition to a furan ring (a diene) (Figure 14.19b) (Grootaert and DeClerq 1986). (For hetero-Diels-Alder reactions. see Schmidt 1986).

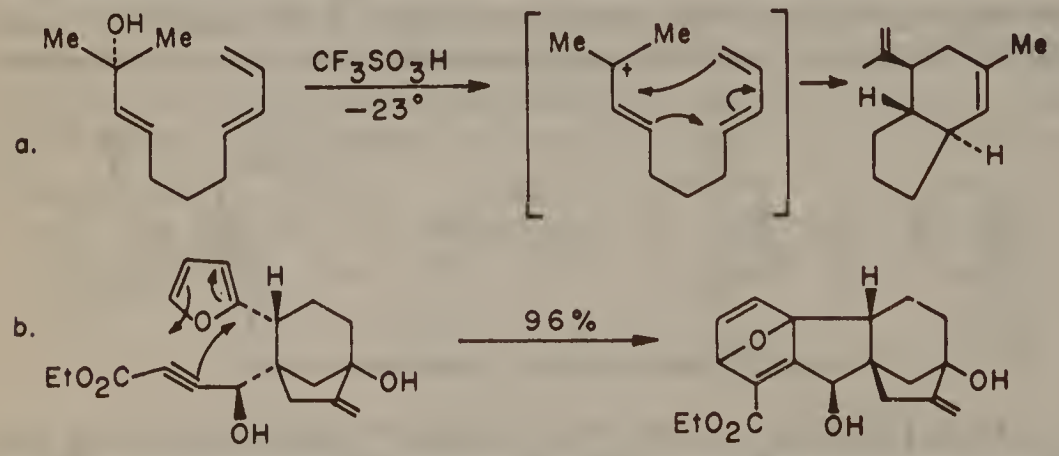


Figure 14.19 Enhancement of reaction rate in cycloaddition

c. Regioselectivity in Diels-Alder reactions is another characteristic property. Thus 1-methoxybutadiene reacts with acrolein (Figure 14.20) to give exclusively

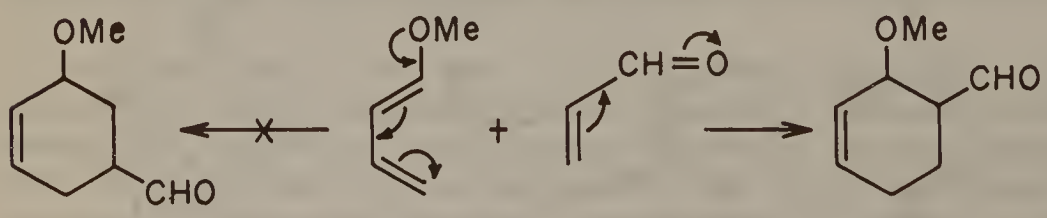


Figure 14.20 Regioselectivity in the Diels –Alder reaction

*Syn (suprafacial) addition of trans olefin gives trans ring junction.

the ortho but not the meta adduct. Although in many cases, the regioselectivity may be determined from the consideration of electrophilic and nucleophilic centres at the two components (see the curved arrows in Figure 14.20), regioselectivity is primarily determined by the coefficients of HOMO and LUMO orbitals at the termini (see Fleming 1976).

d. One of the most important characteristics of Diels-Alder reactions is the 'endo rule' or endo selectivity. When both the diene and dienophile are substituted, the endo isomer is the major kinetically controlled product even though it may be thermodynamically less stable than the exo isomer (into which it may be converted by prolonged heating). This is due to a secondary interaction between non-bond-forming orbital lobes of like sign in the frontier MO's. In the reaction between cyclopentadiene and acrolein (Figure 14.21), this interaction is shown by dotted

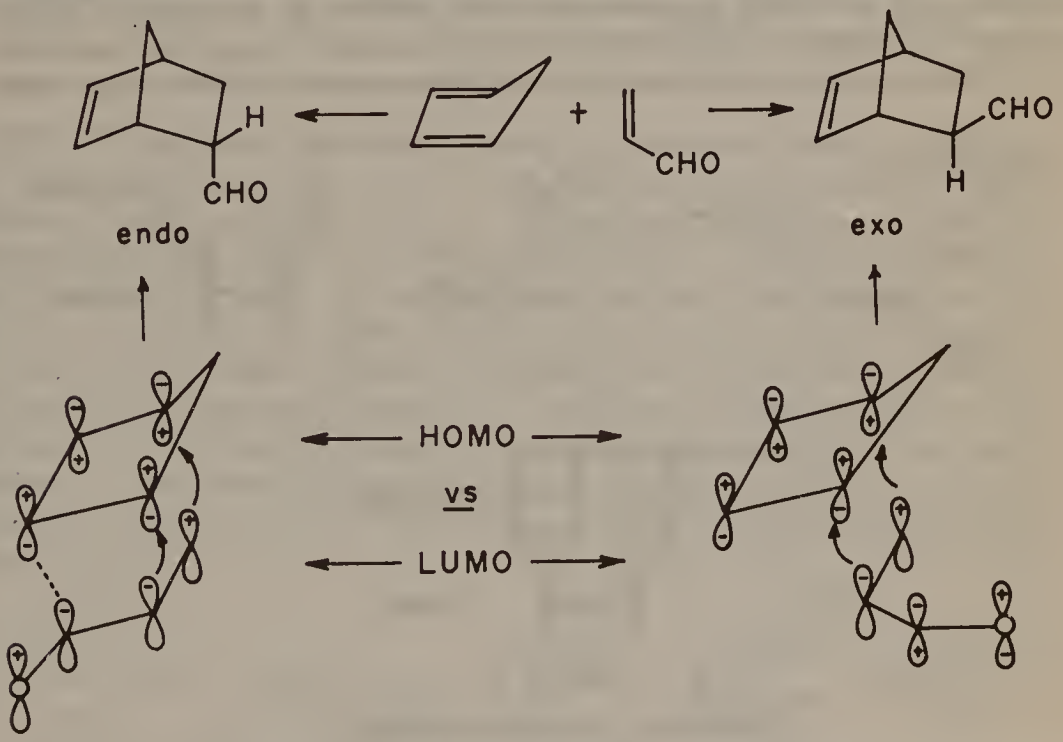


Figure 14.21 Endo selectivity in the Diels-Alder reaction

line which is clearly absent in the formation of the exo product. For the thermally allowed [$_{\pi}6_s + {}_{\pi}4_s$] cycloaddition, this interaction has an antibonding character so that the exo isomer is the kinetically controlled product (vide infra).

e. Site selectivity (where alternative sites are available) is illustrated in an intramolecular Diels-Alder reaction shown in Figure 14.22 giving a product which is ultimately converted into brexane-2-one (XX) (Nickon and Stern (1985). Due to [1,5] sigmatropic shifts of H (see later), the side chain in the cyclopentadiene may approach any of the five carbon atoms but it participates in the form (XVIII) with the side chain at C-5 giving the product (XIX) exclusively.

A large number of reviews are available for the various aspects of Diels-Alder reactions (for references, see Lowry and Richardson 1987). The retro-Diels-Alder reaction is reviewed by Lasne and Ripoll (1985).

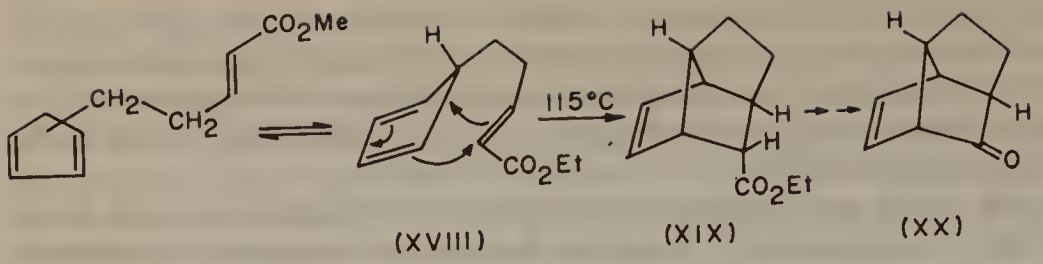


Figure 14.22 Site selectivity in the Diels-Alder reaction

3. [4 + 2] Addition: dipolar cycloaddition. A variety of dipolar reagents such as diazomethane. nitrous oxide. nitrile oxide, and even ozone reacts with alkenes (dipolarophiles). These 1.3-dipolar additions are thermally allowed [4 + 2] cycloadditions and are highly stereoselective (syn addition to olefins)*. A typical example is the reaction of diazomethane with ethyl acrylate to give dihydropyrazole (XXI) (Figure 14.23a). Following the FMO approach, the LUMO of an olefin

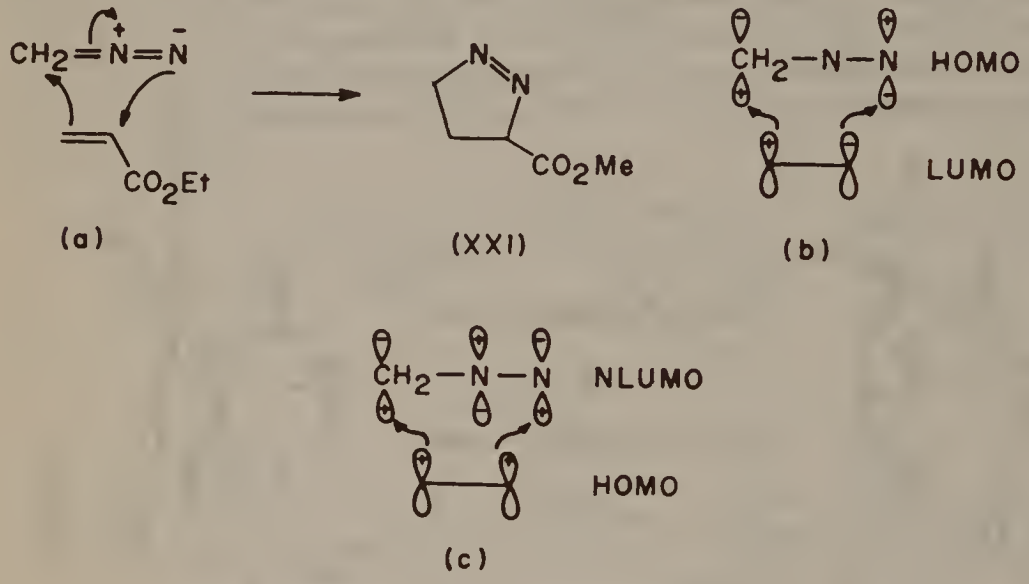


Figure 14.23 1,3-Dipolar cycloadditions

interacts with the HOMO of diazomethane both suprafacially as shown (diagram b). For the linear dipoles. the LUMO has a node on one of the terminal atoms and hence for the alternative combination. the 'next lower unoccupied molecular orbital' (NLUMO) of the dipole and the HOMO of the olefins are considered (diagram c).

Thermal conrotatory opening of an aziridine ring to a 1.3-heterodipole and its subsequent trapping by a 1,3-dipolarophile (dimethyl acetylenedicarboxylate) provide examples of the stereochemistry of both the electrocyclic and cycloaddition reactions (Figure 14.24). Apparently, the rate of interconversion of the intermediate dipoles (by $C{=}N^+$ rotation or carbanion inversion) is slow compared to the rate of 1,3-dipolar addition and so the overall reaction sequence is stereoselective.

*For synthetic applications of dipolar cycloaddition reactions. see Oppolzer 1985 and also Padwa 1984.

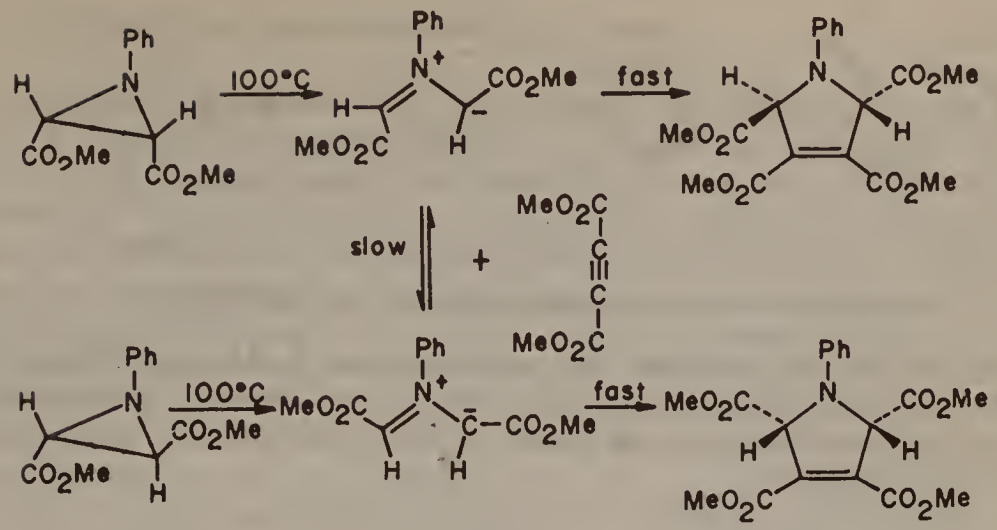


Figure 14.24 Conrotatory ring opening followed by 1,3-dipolar addition

4. [4 + 2] Addition : cheletropic reaction. A cheletropic reaction is a cycloaddition in which one component interacts through a single atom, i.e., with ω electrons. The previously discussed $[_\omega 2_s + _\pi 2_s]$ addition of a carbene to olefins is a cheletropic reaction. If the olefin is replaced by a diene, it will be a 6 π-electron system and thermal $[_\pi 4_s + _\omega 2_s]$ addition would take place. Although the reaction is not known for carbene addition, sulphur dioxide does react with a diene, e.g., *E,E*-1,4-dimethylbutadiene (Figure 14.25a) to form stereoselectively the *cis*-sulphone (XXII). The reverse reaction, i.e., exclusion of sulphur dioxide from the sulphone is more facile. Similarly, *E,Z*-1,4-dimethylbutadiene gives the *trans*-sulphone or vice versa. One can envisage a disrotatory motion in the diene component bringing the two methyl groups to their respective configuration (Figure 14.25b).

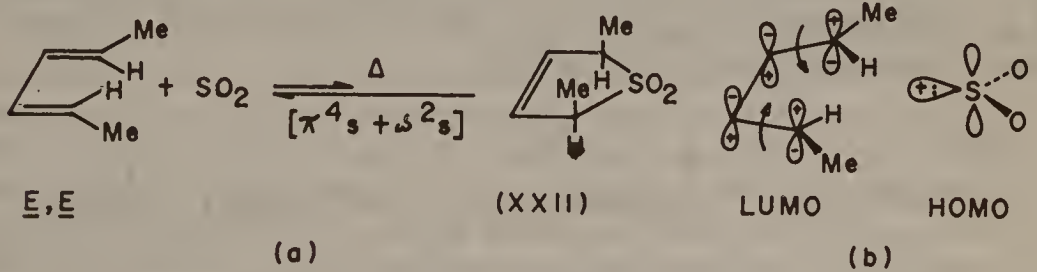


Figure 14.25 A [4 + 2]cheletropic reaction

5. Higher cycloadditions. Among the higher cycloadditions, photochemical $[_\pi 4_s + _\pi 4_s]$ addition of butadiene to benzene has already been mentioned. [6 + 4] Cycloadditions are very few and go thermally by the (s,s) mode, as illustrated in the addition of cyclopentadiene and tropone (XXIII) (Figure 14.26). Two points are of interest : The product is exclusively the exo isomer which is due to an unfavourable secondary interaction between lobes of unlike signs in the HOMO-LUMO combination in forming the endo transition state (the reader may verify it)*. Secondly, a $[_\pi 6_s + _\pi 4_s]$ addition takes place in preference to a $[_\pi 4_s + _\pi 2_s]$

*Exception to the endo rule.

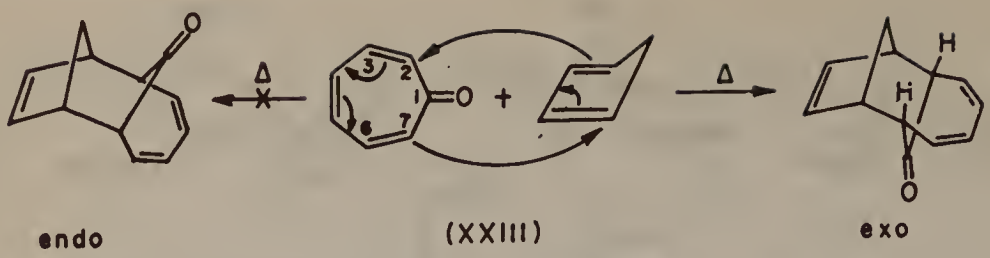


Figure 14.26 [6 + 4]Addition showing exo selectivity and peri selectivity

addition between the butadiene unit and the enone double bond (both are thermally allowed). This phenomenon, known as periselectivity, is explained by the fact that the coefficients of the frontier orbitals of the LUMO of tropone are highest at C-2 and C-7.

14.4 Sigmatropic rearrangements

Sigmatropic rearrangements are pericyclic reactions in which a σ-bonded atom or group migrates from one end of a π-system to the other (equivalent to the migration of a σ bond) in an uncatalysed intramolecular process, as shown in the general structures (XXIV)-(XXVI) (Figure 14.27). The migrating bond in the starting material is depicted with a thick line with both of its termini (one attached to R) labeled with number 1. In the product (XXVI), the migrated bond (also shown with a thick line) has one of the termini still attached to R (and so labeled with number 1) but the other terminus has moved over to a carbon numbered *j* ($j = 2n + 1$). Such migrations are referred to as a [1,*J*] shift (R has actually moved from C-1 to C-*j*), e.g., a [1,5] sigmatropic shift in pentadiene system (Figure 14.27a). If both the termini of the bond move, say one from 1 to *i* and the other from 1 to *j*. the migration is referred to as a [*i*, *j*] shift, e.g., the [3.3] sigmatropic shift in a diallylic system (Figure 14.27b). The rearrangements are necessarily associated with reorganisation of the π-system.

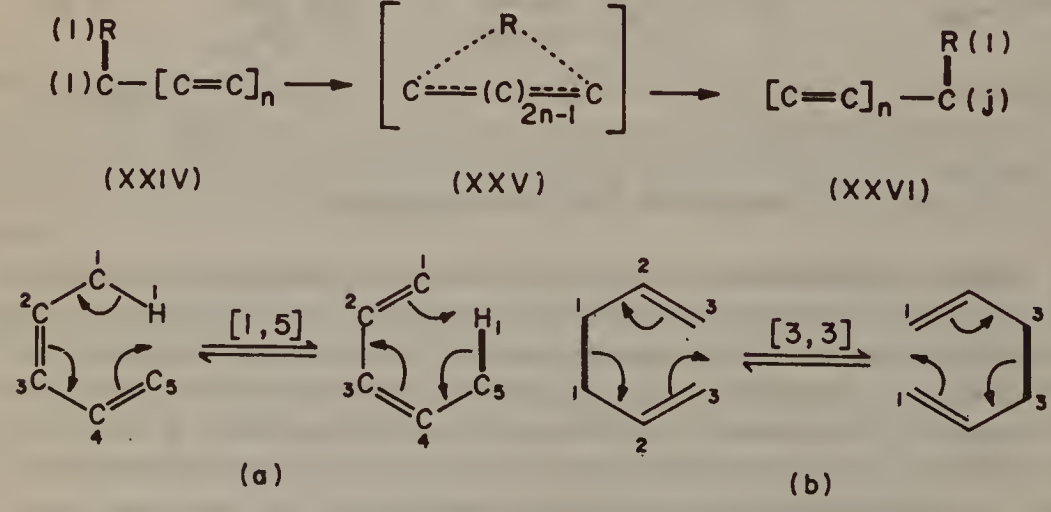


Figure 14.27 Sigmatropic rearrangement: nomenclature

14.4.1 Frontier molecular orbital (FMO) approach

A sigmatropic rearrangement may be regarded as a cycloaddition of the C-R bond and the remaining π-framework (sometimes even more than two components are involved) of a molecule and so may be treated in terms of the HOMO-LUMO interaction. Thus in the pentadiene molecule, the LUMO (Ψ_3) of the butadiene unit and the HOMO of the C-H bond (σ) (Figure 14.28a) interact with an in-phase overlap between the termini allowing a thermal suprafacial migration of H from one end of the chain to the other. A similar combination of HOMO-LUMO in an allylic system (Figure 14.28b) shows that the σ orbital can have bonding

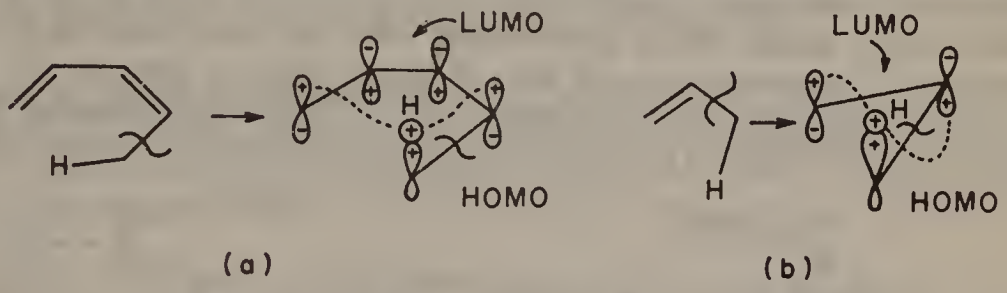


Figure 14.28 Sigmatropic rearrangement as cycloaddition

interactions through lobes on opposite faces of the π-LUMO. Thermal [1,3] migration can thus occur only antarafacially. However. in three or five carbon chains. such antarafacial interaction becomes geometrically difficult and does not occur. Photochemical [1,3] sigmatropic migration involves interaction between the SOMO-1 of ethylene and the σ orbital of C-H permitting suprafacial overlap and quite a few such migrations are known.

A modified frontier orbital analysis (Woodward-Hoffmann) based on correlation of orbital symmetry provides an easier approach to the sigmatropic rearrangements and is commonly used. On the assumption that one electron of C-H (or C-R) bond is associated with the π-framework and the other with H (or R), a transition state (as XXV in Figure 14.27) is envisaged. For concerted migration. the orbitals which hold R and the π-framework together must have the correct symmetry so that the new bond can form in a continuous manner. In [1.5] sigmatropic rearrangement of the pentadiene system. the imaginary transition state consists of a pentadienyl radical and a hydrogen atom (with 5 and 1 electrons respectively). Their HOMO's (for H, it can only be s) are shown in Figure 14.29a. The orbitals have the same symmetry classification (both S with respect to the σ plane) and undergo in-phase overlap suggesting suprafacial migration. A similar analysis for [1.3] sigmatropic migration in allylic molecule (Figure 14.29b) suggests antarafacial

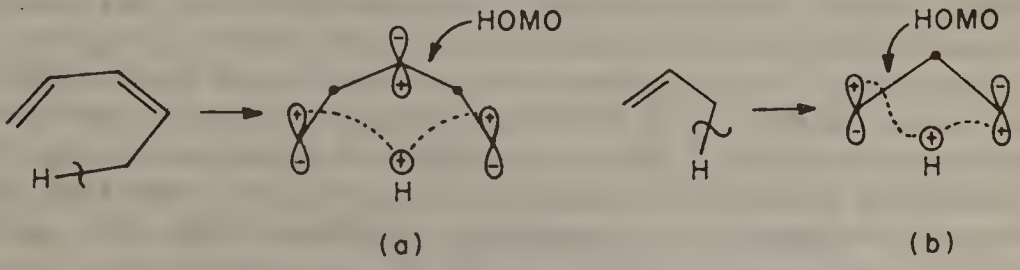


Figure 14.29 Frontier orbital analysis (Woodward-Hoffmann)

migration (the orbitals are symmetry correlated with respect to a C_2 axis) which, however, cannot take place due to lack of flexibility of the carbon chain. It is understood that in a suprafacial migration, the π-system remains planar and the symmetry classification of orbitals must be done with respect to a vertical σ plane. In an antarafacial migration, the two termini of the π-system are placed one above the other giving a slightly helical shape to the π-HOMO and the orbitals must be symmetry classified with respect to a C_2 axis.

An H atom can form a bond through its ls orbital (2p orbitals are of very high energy) only having a single lobe. Consequently, it can move between lobes of same sign but not of opposite signs. This means that an H can migrate only suprafacially with respect to itself. Other atoms such as C, N, and S can use their p and d orbitals having lobes of opposite signs. They can interact either solely with one lobe, i.e., suprafacially or with lobes of opposite signs, i.e., antarafacially with respect to themselves. This is illustrated in the [1,7] sigmatropic migration of an alkyl group (R = Cabc) in a heptatriene system (Figure 14.30). The frontier orbital

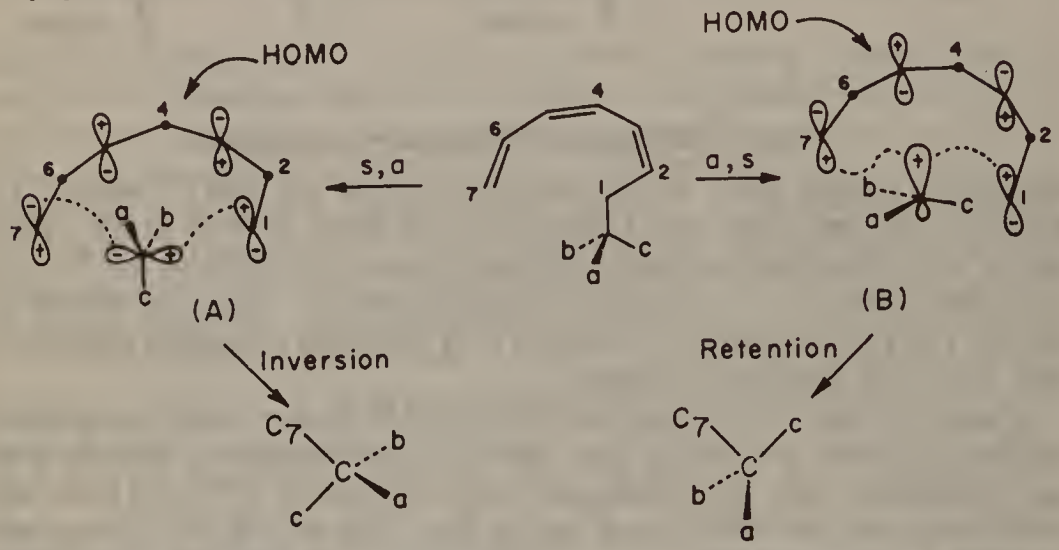


Figure 14.30 [1,7]Sigmatropic rearrangement : (A) suprafacial-antarafacial and (B) antarafacial--suprafacial

analysis shows two arrangements (A) and (B) for the HOMO's of the heptatrienyl radical and the C-radical. In A, the π-system acts as the suprafacial component both the upper terminal lobes undergoing in-phase overlap. The C-radical acts as the antarafacial component with the two lobes of opposite signs interacting with the π-HOMO in a non-linear π-approach (its HOMO has assumed a p orbital configuration). In B, the π-system acts as an antarafacial component and the σ orbital of the C-radical as a suprafacial component interacting with a single lobe in a linear σ approach. Since a seven carbon chain has sufficient flexibility to act as an antarafacial component, both migrations are thermally allowed. Two points are worth mentioning : (i) Orbital symmetry rules are obeyed in both the arrangements. Thus the two HOMO's in A are antisymmetric with respect to the vertical symmetry plane while in B, they are symmetric with respect to a C_2 axis.*(ii) Rearrangement suprafacial with respect to the migrating group takes place with retention of configuration but rearrangement antarafacial with respect to the

*Substituents are ignored; only orbitals are considered.

migrating group takes place with inversion of configuration at the migrating centre. The migrating alkyl group (-Cabc) in A shows an orbital configuration similar to that of a carbon in S_N2 reaction undergoing Walden inversion.

It may be noted that in the allylic system (Figure 14.29b), if H is replaced by an alkyl group, it could undergo a [1,3] sigmatropic rearrangement, suprafacial on the π-system and antarafacial (and so associated with Walden inversion) on the alkyl group. In the [1.5] shift, however. it would act as a suprafacial component (Figure 14.29a) with retention of its configuration. All these conclusions have been experimentally verified.

14.4.2 **Stereochemical course in sigmatropic rearrangements**

Based on symmetry consideration of the orbitals in the transition state of a sigmatropic reaction, Woodward and Hoffmann (1970) formulated a number of selection rules to explain the stereochemical course of different [1,*j*] and [*i*,*j*] shifts. The following guide lines (which are the essence of the selection rules) may be helpful.

1. The most common sigmatropic rearrangements involve the migration of H which is typically a [1,*j*] shift. In such reactions, the HOMO of the π-component determines the mode (suprafacial or antarafacial) of migration in the ground state. If the HOMO ends up with the termini having lobes of identical phase (sign) on the same face, suprafacial rearrangement is allowed. If the lobes are of opposite phases, the rearrangement is antarafacial. In photochemical rearrangements, the LUMO of the π-component has to be considered and the situation is reversed.

2. In order to identify the HOMO, the number of participating electrons (which are delocalised in the transition state) must be known. The [1, *j*] and [*i*, *j*] sigmatropic shifts involve $(1 + j)$ and $(i + j)$ interacting nuclei respectively and the same number of participating electrons if the values are even. If the values are odd, the reactions take place through ionic species and the number of participating electrons would be one less for cations and one more for anions. One of the electrons is accommodated in an H orbital and the rest in the π MO's. The HOMO's may then be constructed according to the mechanical device previously discussed.

3. When the HOMO's of the π-component are drawn for [1,*j*] sigmatropic reactions, it will be seen that the allowed rearrangements in the neutral species (thermal) are antarafacial for [1,3] shifts, suprafacial for [1.5] shifts. and again antarafacial for [1,7] shifts. For ionic species, the [1,2] shift in the cations is suprafacial (e.g., 1, 2-carbonium ion rearrangements), the [1,2] shift in the anion is antarafacial, the [1, 4] shift in the cations is antarafacial. and the [1,4] shift in the anions is suprafacial. For geometrical reasons, antarafacial modes in [1,2], [1,3], [1,4], and even to a certain extent, [1,5] shifts are very uncommon (due to insufficient orbital overlap).

4. When carbon is the migrating atom, all [1, *j*] rearrangements can take place suprafacially with respect to the π-component both in thermal and photochemical reactions. This is because when the π-HOMO has termini with lobes of the same phase on the same face, the ligand carbon interacts with single sp^3 lobe (suprafacial with respect to itself and so with retention of configuration) but when the HOMO

has termini with lobes of opposite phases, carbon interacts with both lobes using its p orbital (antarafacial with respect to itself and so with inversion of configuration). The retention and inversion of configuration at a migrating carbon atom may be given by a selection rule as follows: suprafacial $(1,j)$ migrations of an alkyl group proceed with inversion thermally and with retention photochemically in systems where $j=4n-1$ whereas the situation is reversed in systems where $j=4n+1$. If the carbon migrates antarafacially (with respect to the π-component), all the predictions are reversed.

5. For $[i,j]$ sigmatropic rearrangements, (both i and j greater than 1), the selection rules (Woodward-Hoffmann) are given below. As in carbon migration, topological distinctions must be made with respect to both the π-components.

1. $(i+j)=4q$:	Antara-supra or supra-antara in ground state Supra-supra or antara-antara in excited state
2. $(i+j)=4q+2$:	Supra-supra or antara-antara in ground state Antara-supra or supra-antara in excited state

14.4.3 **Stereoselectivity in sigmatropic rearrangements**

Sigmatropic rearrangements like cycloaddition reactions are highly stereoselective, the stereochemical course being dictated by the pericyclic selection rules (vide supra). A few examples are discussed.

1. [1,*j*] Shifts. Thermal [1,5] migration of H is equivalent to a $[\sigma_s^2 + \pi_s^4]$ cycloaddition and is very common. One of the best examples is the rearrangement of monosubstituted cyclopentadienes, e.g., monomethyl derivative (Figure 14.31)

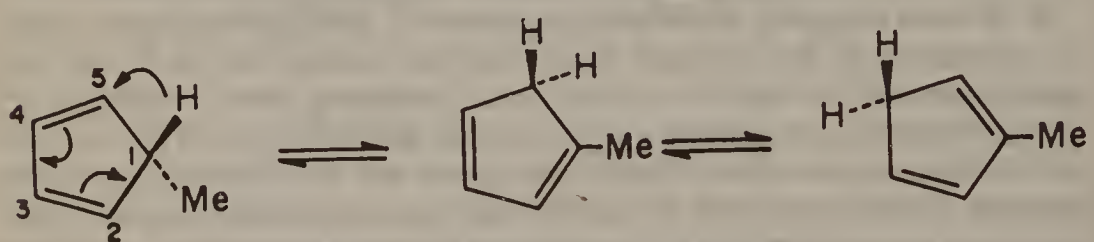


Figure 14.31 [1,5]H-shift in cyclopentadiene

in which H migrates in preference to the methyl group and so fast that at room temperature only a single methyl peak is seen in ^{1}H-NMR.

The stereochemistry of the suprafacial [1,5] migration of H is illustrated with an acyclic 1,3-diene (XXVII) (Figure 14.32) containing a chiral grouping at one of the terminals. The diene exists in two *s*-cis conformations as shown each giving a distinct product with the stereochemistry expected of a suprafacial migration. Chirality is transferred from C-1 to C-5 (Roth et al 1970).

As stated before, thermal [1,3] shifts of carbon (in an alkyl group) can take place suprafacially on the π-component with inversion of configuration at the migrating centre. This has been well documented in an extensive study by Berson (1968, 1972). Pyrolysis of *endo*-bicyclo[3,2,0]hept-2-en-7-methyl-6-yl acetate (XXVIII) (Figure 14.33) gives *exo*-methyl-*exo*-norbornyl acetate (XXX). The HOMO of the allyl system interacts with the two opposite lobes of the the p orbital of C-7 in an (s,a) mode. In a similar experiment. 7-Me is replaced by D and a

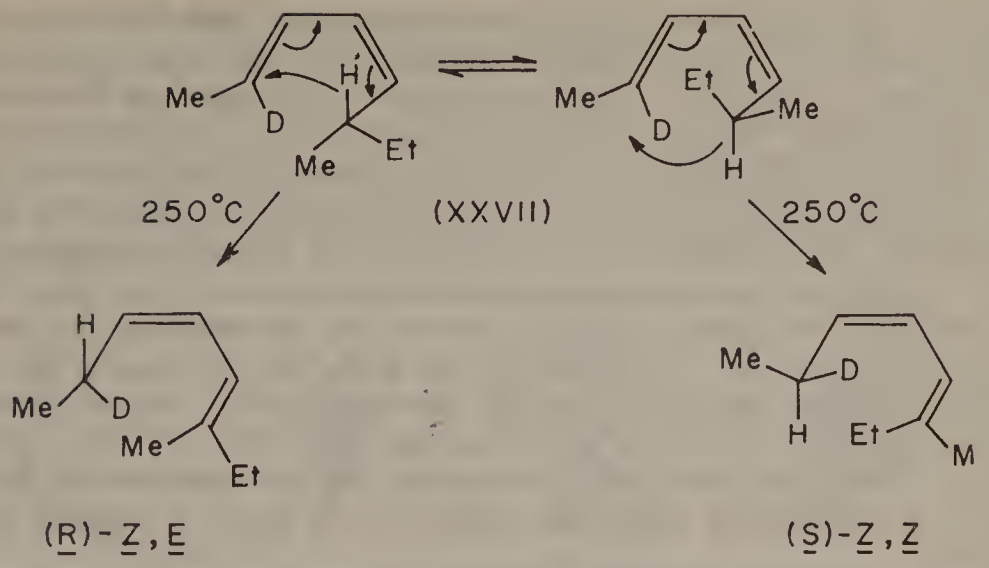


Figure 14.32 Stereochemistry of [1,5] suprafacial H migration

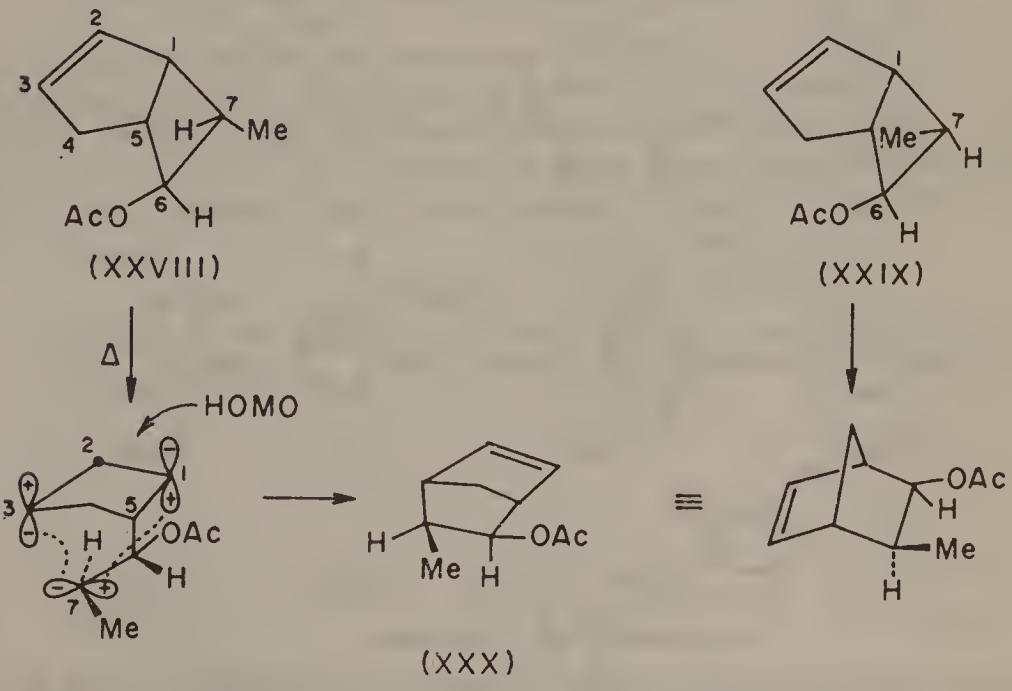


Figure 14.33 Thermal [1,3] shift of carbon with inversion

product with analogous stereochemistry (XXX, Me = D) is obtained. In order to have effective overlap, C-7 has to rotate in a clockwise direction which in the isomeric compound (XXIX) requires that Me should pass under the endo side of the ring. This steric effect prevents the reaction from occurring by a symmetry allowed route. The same product (XXX) is obtained by a symmetry forbidden (more strenuous) and probably non-concerted mechanism.

2. 'Walk' rearrangements. In bicyclo[n.1.0] systems, if the larger ring is so constituted as to permit the [1,*j*] shift of the apical carbon of the three membered

ring, then a succession of [1.*n*] sigmatropic rearrangements takes place and the three membered ring 'walks' (circumambulates) around the larger ring. Such rearrangements are known as 'walk rearrangements' (Woodward and Hoffmann 1970, Klarner 1984).* The migration must necessarily take place suprafacially with respect to the larger ring (on the same side as the cyclopropane ring) but may be either suprafacial or antarafacial on the migrating group as permitted by the selection rules. In the former case, the migrating carbon retains its configuration but its two substituents alternate their positions as endo and exo. In the latter, the configuration of the migrating carbon is inverted with the result that the endo group remains endo and the exo remains exo throughout the changes. As an example of this, the bicyclo[2.1.0] pentenyl derivative (XXXI) (Figure 14.34a) undergoes thermal [1, 3] shift to give the stabler isomer (XXXII). The orbital picture is shown in the middle which is consistent with the stereochemistry, i.e., inversion at the migrating centre and retention of the endo-exo status of the substituents.

In the corresponding bicyclo[4.1.0]heptadienyl derivative (XXXIII) (Figure 14.34b), a thermally allowed [1.5] sigmatropic rearrangement (see the orbital

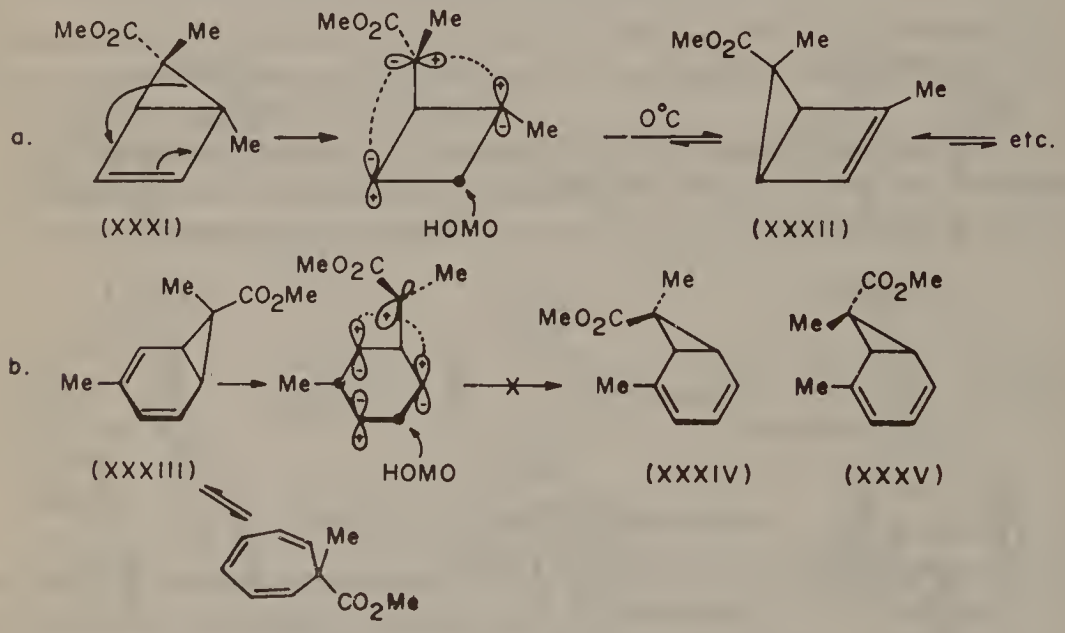


Figure 14.34 Walk rearrangement

diagram) is expected to give the isomer (XXXIV) in which the configuration of the migrating carbon is retained and the substituents have changed their endo-exo positions. However, in actual practice, the isomer (XXXV) is observed — a product of the forbidden path. It has been suggested that in such cases, the 'principle of least motion' (which apparently restricts the motion of a migrating species to the minimum) takes precedence over the pericyclic selection rules (Klärner 1984, Carpenter 1985). In the bicyclo[6.1.0]nonatrienyl derivatives, the walk rearrangement takes place again with inversion at the migrating centre following pericyclic rules.

*Such cyclopropane ring is known as peripatetic ring.

3. [*i, j*] Shift: the Cope rearrangement. Of the [*i, j*] sigmatropic rearrangements, the most common is the Cope rearrangement (see Rhoads and Raulins 1975 for a review). The prototype of this [3,3]shift has been shown in the degenerate rearrangement of 1,5-hexadiene (Figure 14.27b). It may be regarded as a $[\sigma_s^2 + \pi_s^2 + \pi_s^2]$ cycloaddition with the participation of six electrons. In accordance with the frontier orbital analysis adopted so far, two imaginary transition states (A) and (B) (Figure 14.35) may be envisaged both allowing supra-supra thermal inter-

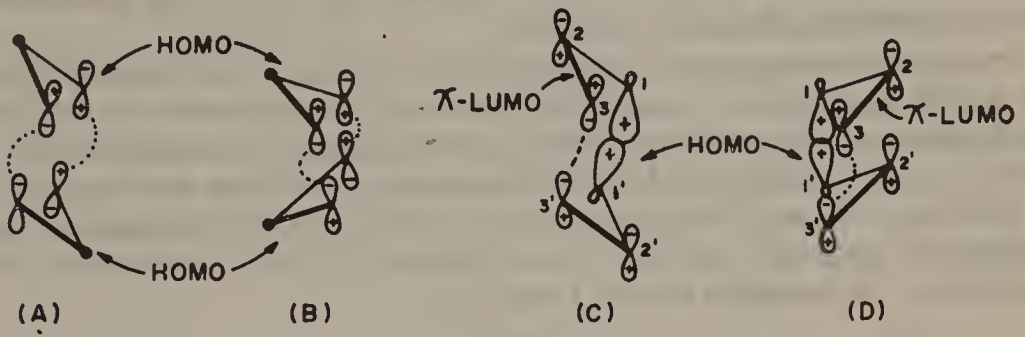


Figure 14.35 Chair-like and boat-like transition states in the Cope rearrangement.

conversion. That the chair-like arrangement (A) is preferred over the boat-like one (B) has been established by Doering and Roth (1963) from the stereochemistry of pyrolysis products of (±)- and *meso*-3,4-dimethylhexa-1,5-diene (Figure 14.36). The former gives a mixture of *E,E* and *Z,Z* dienes while the latter gives selectively the *E,Z* isomer consistent with the chair-like transition state. The preponderance of

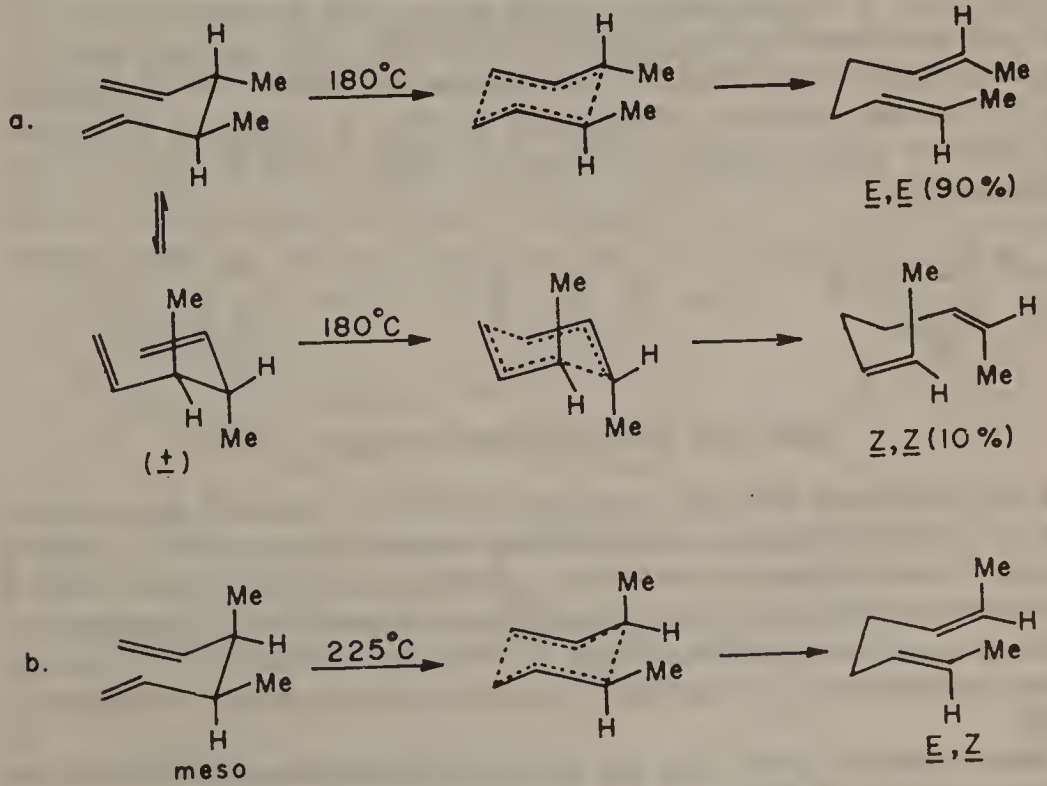


Figure 14.36 Stereoselectivity in the Cope rearrangement

the *E,E* isomer in the pyrolysis of the (±)-form emphasises that the diequatorial chair-like arrangement is preferred.

The chair-like arrangement in the transition state of [3,3] migration is also supported by consideration of secondary interaction in the HOMO-LUMO approach. Thus 1,5-hexadiene may be divided into two components, an ethylene moiety (C_2-C_3) and a butadiene equivalent (C_1-C_1'-C_2'-C_3') and their LUMO and HOMO as π^* and ψ_2 respectively are shown in (C) and (D) (Figure 14.35). It may be noticed that in the boat-like arrangement (D), there is an antibonding secondary interaction between C-2 and C-2′.

The thermal rearrangements of optically active 1,5-dienes show that the products are of high optical purity - a fact which proves the concerted nature of the Cope rearrangement and its possible use in the transfer of chirality to a remote centre.

In the case of 3-hydroxy-1,5-dienes, the product of the Cope rearrangement is an aldehyde or ketone. The reaction is known as the oxy-Cope rearrangement and is effectively irreversible (see Marvell and Whalley 1971 and Swaminathan 1984 for reviews). An example is given in Figure 14.37.

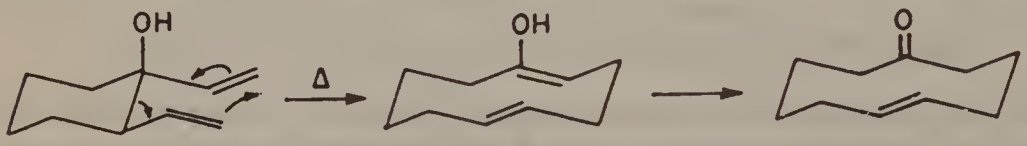


Figure 14.37 An oxy-Cope rearrangement

4. [*i, j*] Shift: the Claisen rearrangement. One of the oldest [3,3] sigmatropic rearrangements known, was discovered by Claisen and is very similar to the Cope rearrangement. In this the migrating σ bond has one of its terminals attached to O (or to N) as in allyl vinyl ethers and allyl phenyl ethers. The topic has been aptly reviewed (Tarbell 1944, Rhoades 1963, Hansen and Smith 1969, Thyagarajan 1967). The same chair-like transition state as above is involved in the product formation. A typical example is shown in Figure 14.38 for ortho Claisen rearrangement.

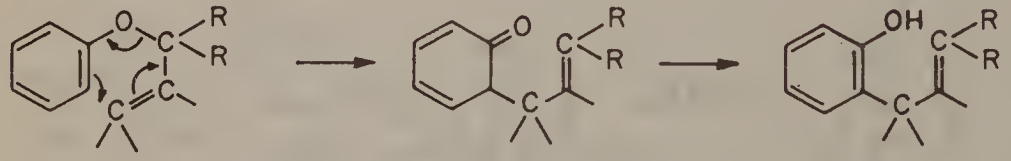


Figure 14.38 The ortho Claisen rearrangement

If the double bond of the allyl group forms part of a cyclohexane ring, a mixture of *e*- and *a*-isomers is obtained, the latter being favoured (Figure 14.39a) - probably a result of stereoelectronic control (axial approach) (Ireland and Varney 1983). If the double bond of the allyl group is exocyclic, the stereochemistry depends on the nature of the six-membered ring (Figure 14.39b,c), e.g., carbocyclic (where *e*-vinyl is less preferred) and pyranose (where *e*-vinyl is the sole product) (Tulshian et al 1984).

Several variations of the Cope and the Claisen rearrangements are known such as the ene reaction (both inter- and intramolecular) (Hoffmann 1969, Oppolzer and

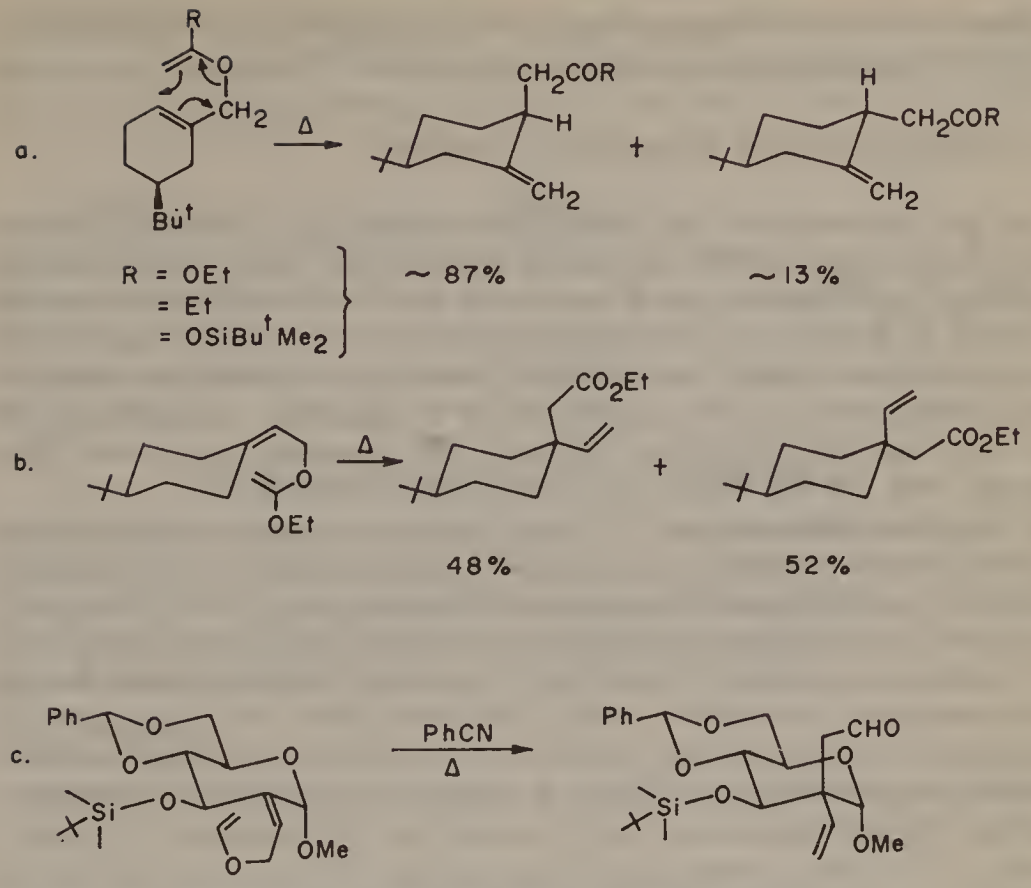


Figure 14.39 Claisen rearrangement of cyclic allyl ethers

Snieckus 1978), the Claisen orthoester rearrangement, the amino-Claisen rearrangement, the Carroll rearrangement, and the Ireland-Claisen rearrangement (Gill and Willis 1974).

5. Other [*i,j*] Shifts. Among other [*i*, *j*] shifts, mention may be made of [2,3] rearrangements which take place in anions, ylides, or other isoelectronic species. That the rearrangements go through a suprafacial mode over the allyl group has been shown by the reaction of the lithium salt (XXXVI) (Figure 14.40). Its two

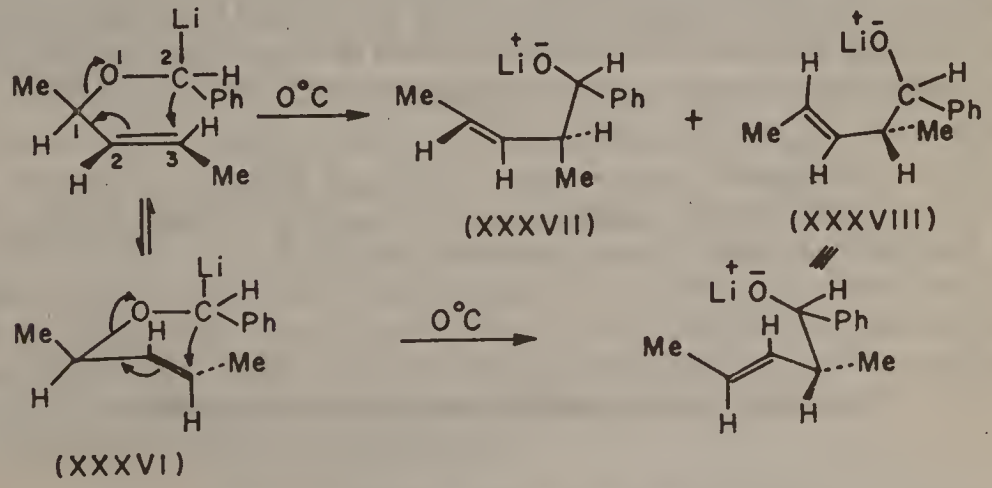


Figure 14.40 [2,3]Sigmatropic rearrangement

conformations give two rearrangement products (XXXVII) and (XXXVIII) as expected of suprafacial migration (Baldwin and Patrick 1971).

14.5 Enantioselectivity in pericyclic reactions

Of the pericyclic reactions, the cycloaddition especially the Diels-Alder reaction has been sucessfully used for asymmetric synthesis with high enantioselectivity. Sigmatropic rearrangements can be used in the transfer of chirality from one end of a chain to the other end. Since the transition states of pericyclic reactions are well-ordered and compact, the asymmetric induction in cycloaddition (where a chiral auxiliary is used) and the chirality transfer in sigmatropic rearrangements are often very high (for reviews, see Nogradi 1987, Apsimon and Collier 1986, Oppolzer 1984, and Hill 1984). Only a few examples are given here.

1. The Diels-Alder reaction. If a chiral auxiliary is introduced either in the dienophile (more common) or in the diene (less common) in a Diels-Alder reaction. high diastereoselectivity-cum-enantioselectivity may result. This is well documented by the reaction of cyclopentadiene with an acrylic ester derived from chiral alcohols, e.g., menthol, borneol etc. The reaction has the advantage that the endo-selectivity is very high (> 95%). Corey and Ensley (1975) have used 8-phenylmenthol (available from pulegone) to have almost complete diastereoselectivity-enantioselectivity (> 99%) in a titanium chloride-catalysed Diels-Alder reaction* (Figure 14.41).

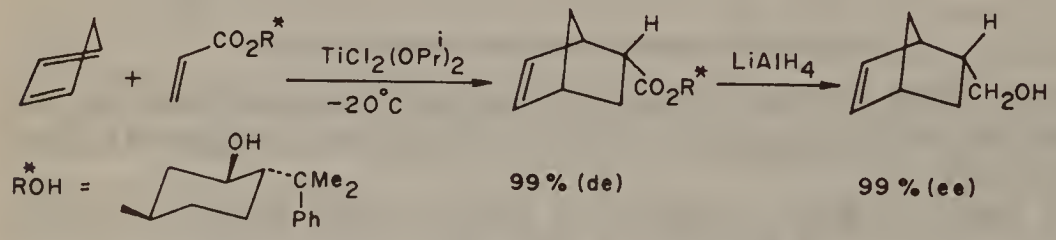


Figure 14.41 An enantioselective Diels-Alder reaction

In a similar reaction of the acrylic ester (XXXIX) with cyclopentadiene, almost total enantioselectivity has been achieved in the final product (XL) (Figure 14.42). Here the bulky side chain at C-2 effectively blocks the approach of the diene from the *Re* side (the two faces of acrylate are diastereotopic) (Oppolzer et al 1982).

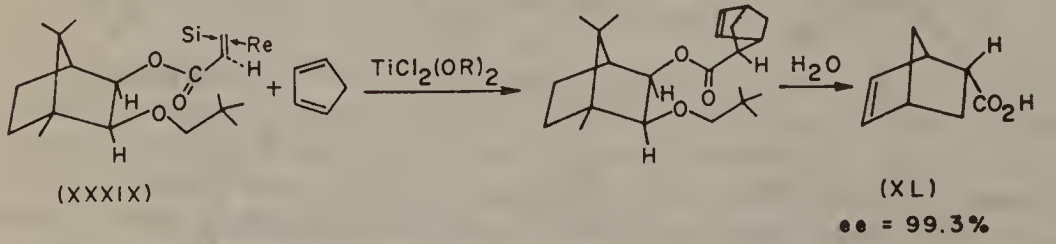


Figure 14.42 Enantioselective Diels-Alder reaction - a second example

*Stereoselectivity is usually very high in acid-catalysed Diels - Alder reactions.

2. Sigmatropic rearrangement. The principle of chirality transfer in [3,3] sigmatropic rearrangements with the help of frontier orbital analysis has already been explained. A simple example is given in Figure 14.43. Because of the rigidity

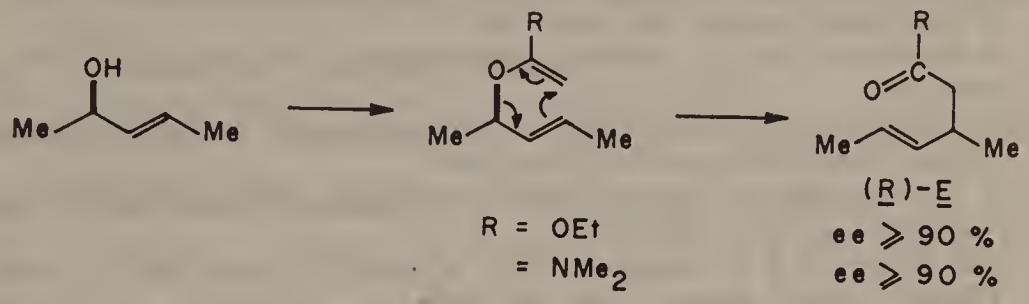


Figure 14.43 Chirality transfer in the Claisen rearrangement

of the chair-like transition state through which these reactions take place, the chirality transfer is almost complete (see Bennett 1977, Ziegler 1977). The stereochemistry of [2,3] sigmatropic rearrangements has been reviewed (Hoffmann 1979). Space does not permit any further discussion on this topic.

14.6 Summary

1. Pericyclic reactions are reactions in which the bond-making and bond-breaking is a concerted (but not necessarily synchronous) one-step process. They do not involve any ionic or radical intermediates, remain unaffected by solvent polarity, and take place only thermally or photochemically (except for certain Diels-Alder reactions which are catalysed by acid).

2. The stereochemical course of pericyclic reactions has been explained by the principle of conservation of orbital symmetry (Woodward-Hoffmann). An alternative simpler approach, namely, a frontier molecular orbital (FMO) approach (Woodward Hoffmann, Fukui) has been adopted in the present text which equally explains all aspects of the reaction topology. In this approach, the interaction between the HOMO and LUMO of the two reacting components are considered in the context of some imaginary transition states. If the orbital symmetry permits bonding interaction between them, the reaction is symmetry allowed, otherwise it is symmetry forbidden.

3. In principle, all pericyclic reactions may be regarded as cycloaddition reactions (intra- or intermolecular); but, for convenience, the reactions are classified into several categories of which only three namely, electrocyclic reactions, cycloaddition reactions, and sigmatropic rearrangements are discussed.

4. In view of the well ordered transition states of these reactions, they are highly, sometimes even totally, diastereoselective. Several other types of selectivity such as regio-, site-, and peri-selectivity are also observed. In cycloaddition reactions, the use of chiral auxiliaries permit enantioselectivity (medium to high). In sigmatropic rearrangements, transfer of chirality from one end of a π-system to the other takes place with high efficiency.

References

1. R.B. Woodward and R. Hoffmann (1970) in '*The conservation of Orbital Symmetry*', Verlag-Chemie/Academic Press, New York.
2. A. Streitweiser (1961), in '*Molecular Orbital Theory for Organic Chemists*', Wiley, New York.
3. M. Orchin and H.H. Jaffe (1967), in '*The Importance of Antibonding Orbitals*', Mohan Primlani, Oxford, and IBH, New Delhi.
4. I. Fleming (1976), in '*Frontier Orbitals and Organic Chemical Reactions*', John Wiley & Sons, London, New York.
5. T.H. Lowry and K.S. Richardson (1987), in '*Mechanism and Theory in Organic Chemistry*', 3rd edn., Harper & Row, New York.
6. G.B. Gill and M.R. Willis (1974), in '*Pericyclic Reactions*', Chapman and Hall, London.
7. R.E. Lehr and A.P. Marchand (1972), in '*Orbital Symmetry*', Academic Press, New York.
8. T.L. Gilchrist and R.C. Storr (1972), in '*Molecular Orbitals in Organic Chemistry*', Cambridge University Press, Cambridge.
9. A.P. Marchand and R.E. Lehr, eds. (1977), in '*Pericyclic Reactions*', Academic Press, New York.
10. K. Fukui (1975), in '*Theory of Orientation and Stereoselection*', Springer-Verlag, Berlin.
11. W.R. Dolbier, H. Koroniak, D.J. Burton, and P. Heinze (1986), *Tetrahedron Lett.*, **27**, 4387.
12. G. Maier (1967), *Angew. Chem. Int. Ed. Engl.*, **6**, 402 (a review).
13. E. Havinga, R.J. de Kock, and M.P. Rappold (1960), *Tetrahedron*, **11**, 278, see also ref.1.
14. K. Kraft and G. Koltenburg (1967), *Tetrahedron Lett.*, 4357.
15. K.N. Houk, Y. -T. Lin, and F.K. Brown (1986), *J. Amer. Chem. Soc.*, **108**, 554.
16. P.G. Gassman and D.A. Oingleton (1986) *J. Org. Chem.*, **51**, 3075.
17. W.M. Grootaert and P.J. Declerq (1986), *Tetrahedron Lett.*, **27**, 1731.
18. R.R. Schmidt (1986), *Acc. Chem. Res.*, **19**, 250.
19. A. Nickon and A.G. Stern (1985), *Tetrahedron Lett.*, **26**, 5915.
20. M.C. Lasne and J.-C. Ripoll (1985), *Synthesis*, 121.
21. W. Oppolzer (ed) (1985), *Tetrahedron*, **41**, 3447.
22. A. Padwa (ed) (1984), '*1, 3-Dipolar Cycloadditions Chemistry*', Wiley, New York.
23. W.R. Roth, J. Konig, and K. Stein (1970), *Chem. Ber.*, **103**, 126.
24. J.A. Berson (1968), *Acc. Chem. Res.* (1972), **5**, 506; also (1968), **1**, 152.
25. F. -G. Klärner (1984), '*Topics in Stereochemistry*', vol. 15, p.1.
26. B.K. Carpenter (1985), *J. Amer. Chem. Soc.*, **107**, 5730.
27. S.J. Rhodhes and N.R. Raulins (1975), '*Organic Reactions*', **22**, 1.
28. W. von E. Doering and W.R. Roth (1963), *Angw. Chem. Int. Edn. Engl.*, **2**, 115.
29. E.N. Marvell and W. Whalley (1971) in '*The Chemistry of the Hydroxyl group*', ed. S. Patai, part 2, p. 738, Interscience, New York; S. Swaminathan (1984), *Indian J. Chem.* **23B**, 99.
30. D.S. Tarbell (1944), '*Organic Reactions*', **2**, p.1.
31. S.J. Rhoades (1963) in '*Molecular Rearrangements*' Ed. p. de Mayo, Part 1, p. 655, Interscience, New York.
32. J.J. Hansen and H. Schmidt (1969), *Chem. Brit.*, **5**, 511.
33. B.S. Thyagarajan (1967), '*Adv. Heterocycl. Chem.*', **8**, 143.

34. R.E. Ireland and M.D. Varney (1983), *J. Org. Chem.*, **48**, 1829.
35. D.B. Tulshian. R. Tseng, and B. Fraser-Reid (1984), *J. Org. Chem.*, **49**, 2347: also *Tetrahedron Lett.*, **25**, 4579.
36. J.E. Baldwin and J.E. Patrick (1971), *J. Amer. Chem. Soc.*, **93**, 3556.
37. M. Nogradi (1987), '*Stereoselective Synthesis*', VCH Publishers, Chapter 7, Weinheim, Germany.
38. J.W. ApSimon and T.L. Collier (1986), *Tetrahedron*, **42**, 5157.
39. W. Oppolzer (1984), *Angw. Chem. Intl. Edn. Engl.*, **23**, 876.
40. R.K. Hill (1984), '*Asymmetric Synthesis*' vol.3., ed. J.D. Morrison, Academic Press, Orlando, Florida.
41. E.J. Corey and H.E. Ensley (1975), *J. Amer. Chem. Soc.*, **97**, 6905.
42. W. Oppolzer, C. Chapnis, G.M. Dao, D. Reichlin, and T. Godel (1982), *Angw. Chem. Intl. Edn. Engl.*, **23**, 4781.
43. G.B. Bennett (1977), *Synthesis*, 589.
44. F.E. Ziegler (1977), *Acc. Chem. Res.*, **10**, 227.
45. R.W. Hoffmann (1979), *Anqw. Chem. Intl. Edn., Engl.*, **18**, 563.
46. H. M. R. Hoffmann (1969), *Angw. Chem. Intl. Edn., Engl.*, **8**, 556.
47. W. Oppolzer and V. Snieckus (1968), *Angw. Chem. Intl. Edn. Engl.*, **17**, 476

Chapter 15

Molecular Dissymmetry and Chiroptical Properties

15.1 Introduction

It has already been mentioned that when a plane-polarised (henceforth to be called linearly polarised or LP) monochromatic light wave passes through a dissymmetric medium, the plane of polarisation rotates giving an optical rotation, α - a chiroptical property exhibited by nearly all chiral molecules. Optical rotations of two enantiomers are equal in magnitude but opposite in sign. This enantiomeric discrimination by a linearly polarised electromagnetic wave occurs due to the fact that although itself symmetrical, an LP wave in which the electrical field vector (E) oscillates in a plane defined by xy* (whose projection is a line) along the direction of propagation (y axis), is the resultant of two chiral components - a right circularly polarised (RCP) ray and a left circularly polarised (LCP) ray (whose projections on xz plane are circles) (Figure 15.1). Because of opposite chiralities, these rays establish

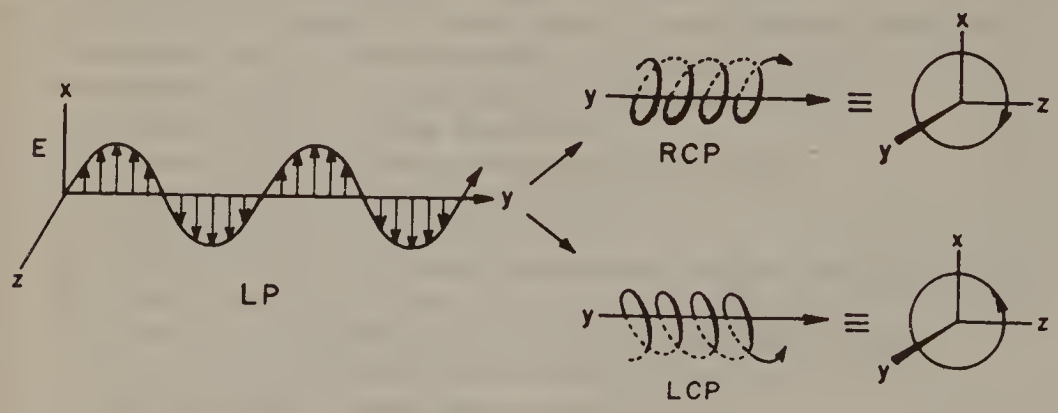


Figure 15.1 Linearly polarised light and circularly polarised rays (E = electric field vector)

diastereomeric relationship with any particular enantiomer and so interact differently. If the nature of the interaction between the radiation field and the enantiomeric molecules which differ in the arrangement of atoms or groups of unequal polarisabilities (the interaction probably takes the form of a helical oscillation of charge in

*The magnetic field associated with electromagnetic waves lies perpendicularly to the electric field and its vector is modulated in yz plane in Figure 15.1.

the molecule) is correctly established, it is possible to correlate optical rotation with the absolute configuration of the chiral molecule under consideration. Appropriate theories have been worked out since the time of Drude but their applications are as yet limited to very simple molecules and are not wholly reliable (Brewster 1967, Mason 1982 and references cited therein). Optical rotations are also associated with manifestation of other chiroptical phenomena such as optical rotatory dispersion (ORD) and circular dichroism (CD), the theoretical study of which offers a better prospect for the determination of absolute configuration. In the present treatment which is necessarily inadequate for lack of space, more emphasis has been laid on the latter aspect than on the former.

15.2 Polarised lights and chiroptical properties

Before considering the correlation of chiroptical properties with molecular dissymmetry, it is necessary to understand the nature of polarised lights, their behaviour in dissymmetric medium, and the manifestation of chiroptical phenomena.

15.2.1 Linearly and circularly polarised lights

While in linearly polarised light, the electric field vector changes its magnitude sinusoidally in a plane along the direction of propagation. in circularly polarised light, the magnitude of the vector remains constant but its direction changes continuously in a helical fashion (its projection in two dimension being a circle) either in a clockwise (RCP) or in an anticlockwide (LCP) direction as shown in Figure 15.1. A RCP ray and an LCP ray having the same amplitude ($E_R = E_L = E$) may combine to produce an LP wave as illustrated in diagram (I) in Figure 15.2. The vector of the LP wave at A is maximum being the sum of E_R and E_L (i.e.,

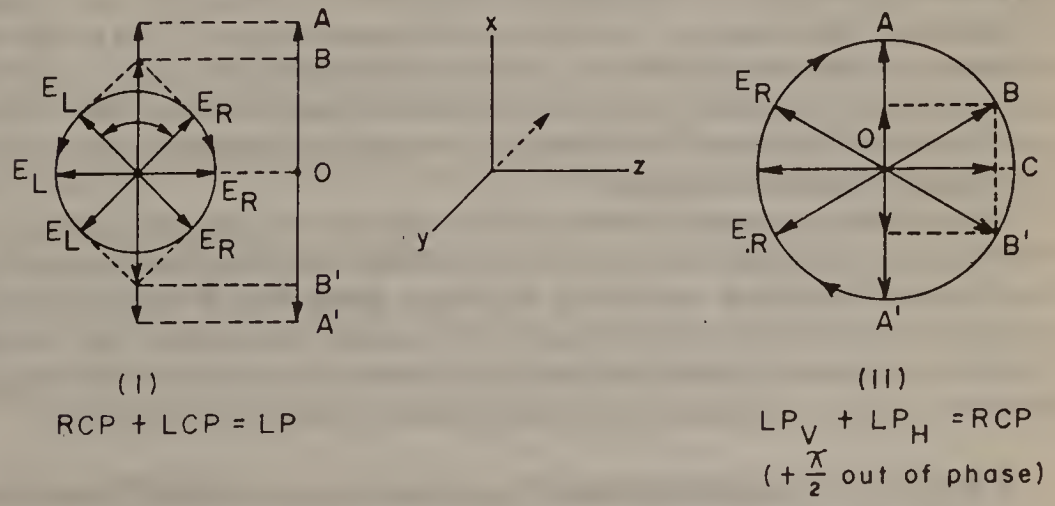


Figure 15.2 I. Combination of RCP and LCP rays in phase to give LP wave
II. Combination of two mutually perpendicular LP waves (with same E), quarter wavelength out of phase leading to CP rays

2E), decreases at B as E_R and E_L rotate in opposite directions.* becomes zero at O when E_R and E_L are oppositely directed, grows increasingly negative as at B′, and reaches the negative maximum (-2E) at A′ when E_R and E_L are again in conjunction. The upward movement takes place in a similar fashion so that the tip of the vector oscillates in a plane (xy) whose projection is a line A-B-O-B′-A′ along x axis, the y axis being the line of progagation.

In a somewhat similar fashion, a circularly polarised ray (RCP or LCP) may be generated from two concurrent linearly polarised waves of equal magnitude with their planes of polarisation at right angle to each other (LP_V and LP_H where V and H refer to vertical and horizontal respectively) and having a phase difference of $\pm \pi/2$ (a quarter of a wave length) as shown in diagram (II) in Figure 15.2. The resultant electric field vector is always the same : OA when the LP_V vector is maximum and the LP_H vector is nil, OB when both have intermediate values; OC when the LP_V vector is nil and the LP_H vector is maximum. and so on. The tip of the resultant vector thus describes a helix (whose projection is a circle) giving rise to a circularly polarised wave, RCP if $\pi/2$ is positive and LCP if $\pi/2$ is negative.

15.2.2 **Circular birefringence and circular dichroism**

When a light beam travels through a medium (which undergoes electronic transition at a certain wavelength), two things happen as a result of the interaction between its electromagnetic field and the valence electrons of the medium. (*i*) The velocity of light, v changes and with it, the refractive index, n (= c/v; c = velocity of light in vacuum). (*ii*) The intensity of the emergent light diminishes due to absorption. Both the phenomena are interrelated and are contributions of electronic transition. They are wavelength dependent: Absorption is at maximum at λ_{max}; the refractive index increases as the wavelength decreases but rapidly falls to a minimum in the absorption region (abnormal dispersion). At λ_{max}, there is no effect on refractive index ($n = 1$). The changes in dispersion and absorption over a range of wavelength (covering λ_{max}) are shown in the diagram (Figure 15.3a) in which k represents the absorption coefficient. Along side are also given (Figure 15.3b) an optical rotatory disperison (ORD) curve with a positive Cotton effect and a positive circular dichroism (CD) spectrum (to be discussed subsequently) to show their apparent similarity in pattern.

When a linearly polarised light beam passes through a dissymmetric medium, its two circularly polarised components show different refractive indices ($n_L \neq n_R$) and different absorption coefficients ($k_L \neq k_R$) giving rise to two chiroptical properties of a chiral medium, known as circular birefringence and circular dichroism respectively. Although these two properties are interrelated (see Krönig-Kramers transform in Djerassi 1960), their effects are best treated separately.

1. Effect of circular birefringence. If n_L is greater than n_R, the RCP component

*E_R and E_L are shown by arrows as they move along the circle describing equal angles but in opposite directions. The resultant vector is worked out from the respective parallelograms.

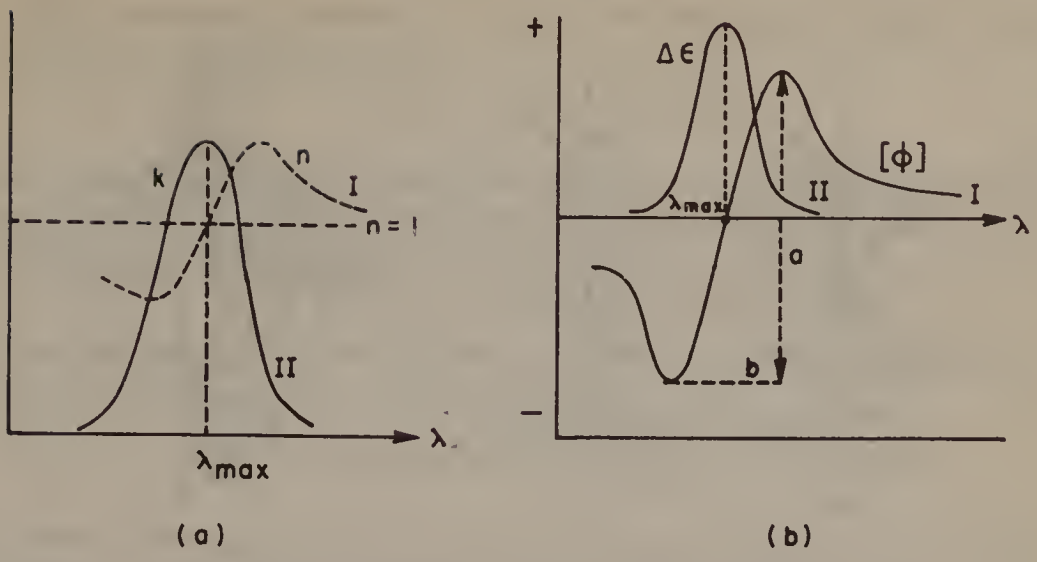


Figure 15.3 (a) Dispersion (I) and absorption (II) as a function of λ: (b) ORD curve with a positive Cotton effect (I) and a positive CD spectrum (II).

of an LP wave travels faster than the LCP one in the chiral medium (diagram III in Figure 15.4). The resultant vector of E_R and E_L no longer oscillates in the original plane defined by A-O-A′ but in a new plane defined by B-O-B′ inclined at an angle α away from the x axis. The plane (and also α), however, changes continuously as the ray proceeds (along y axis) resembling a twisted ribbon. The angle of rotation (α) in degrees for traversing a path of 1 cm is given by equation (1) :

$$\alpha = \frac{180}{\lambda}(n_L - n_R) \qquad (1)$$

$$[\alpha]_\lambda^T = \frac{\alpha \times 10}{C} \; ; \; [\Phi]_\lambda^T = \frac{[\alpha]_\lambda^T \times M}{100} \qquad (2)$$

The specific rotation $[\alpha]_\lambda^T$ may be calculated by multiplying the rotation by 10 (for a path length of 1 dm) and dividing by C (concentration of the sample in g/ml). Molecular rotation $[\phi]_\lambda^T$ is obtained from the specific rotation by the usual method (equation 2). Their values vary with the temperature and wavelength used.

It may be observed from the above discussion that if the RCP component travels faster, the medium is dextrorotatory (α is + ve). If the LCP component travels faster, the medium is levorotatory*. The difference in the refractive indices (eqn.1) is usually very low, a few parts per million but since the denominator (λ) has a still lower value, the rotation can be appreciable.

*This is in accordance with the convention of physicists who look in the direction of the light ray. Chemists. on the other hand, measure the rotation by viewing against the source of light and hence it is oppositely signed : positive (dextrorotatory) if E_L travels faster than E_R and negative (levorotatory) if E_R travels faster than E_L. The chemists' convention is used almost universally except for mathematical treatment when physicists reverse the sign of appropriate functions.

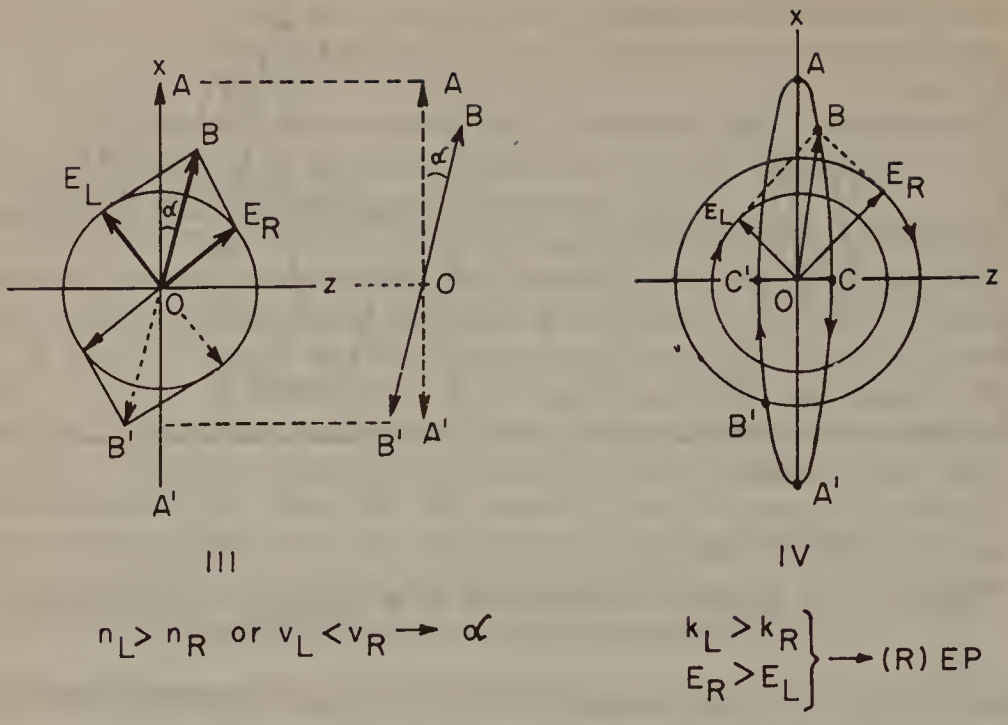


Figure 15.4 (III) : Optical rotation due to circular birefringence.
(IV) : Elliptically polarised ray due to circular dichroism.

2. Effect of circular dichroism. As a result of circular dichroism, the two circularly polarised components of the LP wave will be absorbed to different extents. If the LCP component is absorbed more strongly, i.e., $k_L > k_R$, its electric field vector E_L will be smaller than E_R as shown in the diagram IV (Figure 15.4). When they are in phase, the resultant vector is OA; after a small interval, their new positions are OE_L and OE_R respectively (as projected on xz plane) and the resultant vector is OB (the angular velocity of the two components is the same). The tip of the resultant vectors thus traces a flattened helix whose projection on xz plane is an ellipse (A, B, C, A′, B′, and C′ are few points on it). Such a ray is called elliptically polarised (EP) characterised by a major axis A-O-A′ and a minor axis C-O-C′. (Like circularly polarised ray, this also may be right-handed or left-handed elliptically polarised).

The ellipticity is defined by an angle Ψ (in radian) so that $\tan\Psi$ represents the ratio of the minor to the major axis of the ellipse. For small difference of k_L and k_R, Ψ for unit length (1 cm)* is given by the simplified equation :

$$\Psi = \tfrac{1}{4}(k_L - k_R) \qquad (3)$$

Employing a similar procedure as in optical rotation, the specific ellipticity of the medium may also be defined (for a length of 1 dm and concentration C in g/ml) as follows :

$$[\Psi]^T_\lambda \text{ (in degrees)} = \frac{\Psi}{C} \cdot \frac{1800}{\pi} \qquad (4)$$

*Like α, Ψ also changes continuously as the ray travels through the medium.

Finally, the absorption coefficient, k is related to the molecular extinction coefficient, ϵ through the following equations :

$$I = I_0 \times e^{-kl} = I_0 \times 10^{-\epsilon C' l} \qquad (5)$$

Here I_o and I refer to the initial intensity of light and intensity after travelling through length l and C′ refers to concentration in gmol/l. The relationship may be simplified by converting equation (5) into equation (6) :

$$k = 2.303 \times \epsilon \times C' = 2.303 \times \epsilon \times C \times 1000/M \qquad (6)$$

Combining equations (3), (4), and (6), the specific ellipticity may be expressed in terms of molecular extinction coefficient as follows:

$$[\Psi]^T_\lambda \text{ (in degree)} = \frac{1800 \times 2.303 \times C \times 1000}{4 \times C \times \pi \times M} (\epsilon_L - \epsilon_R)$$

Molecular ellipticity $[\theta]^T_\lambda$ may now be defined in the same way as molecular rotation of a medium by introducing a factor of M/100 as expressed in equation (7):

$$[\theta]^T_\lambda = \frac{1800 \times 2.303 \times C \times 1000 \times M}{4 \times C \times \pi \times M \times 100} (\epsilon_L - \epsilon_R)$$

$$\approx 3300 \times \Delta\epsilon \qquad (7)$$

The difference in the molecular extinction coefficients of the RCP and LCP rays ($\Delta\epsilon$) is called differential dichroic absorption. Instrumentally, one can measure either the ratio of the minor to the major axis (and hence Ψ) or the differential dichroic absorption ($\Delta\epsilon$). Since circular birefringence and circular dichroism occur simultaneously, the resultant wave represented by B-O-B′ in diagram (III) is actually elliptically polarised with its major axis coincident with B-O-B′. However, the ellipticity is extremely small (except near the absorption band) and there is no meaningful distinction whether one treats the resultant wave as linearly polarised or elliptically polarised.

15.2.3 **ORD and CD curves : Cotton effect**

In addition to optical rotation, the combination of circular birefringence and circular dichroism gives rise to another important chiroptical phenomenon, namely, the Cotton effect which usually becomes manifest when one observes the change of optical rotation [α] or [ϕ] with wavelength (λ), commonly known as optical rotatory dispersion (ORD). If the measurement is restricted to wavelengths away from the absorption maximum (λ_{max}), a plain curve results (see the first portion of curve I in Figure 15.3b) showing a steady increase (or decrease) of optical rotation with decrease of wavelength. It may cross or may not cross the zero-rotation line*. In the absorption region, however, the curve becomes *anomalous* : The rotation rises sharply to a maximum (peak), then quickly drops down to zero near about λ_{max}, goes down to a minimum (trough), and then rises again slowly giving an S-shaped curve (represented by curve I in Figure 15.3b). Such an ORD curve is

*A plain curve which does not cross the zero-rotation axis and is devoid of maxima or minima within measurable range is called a normal curve (Djerassi 1960).

called an anomalous or a Cotton effect curve and is said to exhibit a Cotton effect (CE) which is characterised by an amplitude (a) and a width (b), as shown in the diagram. If in the curve, the peak is at higher wavelength than the trough (as shown), the Cotton effect is positive whereas if the trough is at higher wavelength, the Cotton effect is negative. Molecular amplitude (A) which is a measure of asymmetric perturbation of the electronic transition is experssed in terms of molecular rotations $[\phi]_p$ and $[\phi]_t$ at the peak and the trough respectively as follows :

$$A = \frac{[\Phi]_p - [\Phi]_t}{100} \qquad (8)$$

A plain curve can be described mathematically by equation (9), known as Drude equation in which λ is the wavelength at which the specific rotation is measured, λ_o corresponds to a wavelength close to the absorption maximum, and k is an empirical constant.

$$[\alpha] = \frac{k}{\lambda^2 - \lambda_o^2} \qquad (9)$$

With the improvement of instrumental technique, one can now measure either the molecular ellipticity or differential dichroic absorption and thus plot either $[\theta]$ or $\Delta\epsilon$ versus wavelength to give what is known as a CD spectrum which forms a near Gaussian curve as shown in Figure 15.3b (curve II). In the CD spectra, $\Delta\epsilon_{max}$ very nearly coincides with the absorption maximum λ_{max} in the UV region and is related to the molecular amplitude (A) in ORD by the following approximate equation :

$$A = 40.\ \Delta\epsilon_{max} \qquad (10)$$

The ORD and CD curves are both equivalent with respect to their implications in organic stereochemistry. Like ORD, the CD curves can be either positive or negative (a positive ORD usually gives a positive CD and a negative ORD a negative CD). By convention, if $\epsilon_L > \epsilon_R$, $[\theta]$ is positive and so is the CD spectrum (curve II in Figure 15.3b). A CD curve always encompasses the Cotton effect and the area under a CD curve when integrated gives a measure of the rotational strength (R_K) of the chromophore undergoing chiral transition. Its magnitude is related to the induced electric and magnetic dipoles (μ_e^K and μ_m^K):

$$R_K = \mu_e^K . \mu_m^K \qquad (11)$$

Between an ORD and a CD curve, the latter provides some advantages; thus the CD maximum very nearly coincides with λ_{max}. The ORD curve is associated with a background curve (known as skeletal curve) due to transitions at a distant wavelength which may interfere with the determination of the sign of the Cotton effect. CD curves are free from such background effect and if a compound has more than one absorption maximum, the CD extrema are usually well separated. Nowadays, ORD has been almost completely replaced by CD. Earlier data were confined to ORD measurements because of technical difficulty in measuring CD. ORD in the far UV is also difficult to measure because of low light transmission.

15.3 Application of CD and ORD : comparison method

CD and ORD curves, particularly those showing one or more Cotton effects are

extremely useful for providing structural and configurational (including conformational) information. Two procedures are generally adopted : (*i*) A comparison method in which the dispersion curve of a compound of unknown configuration is compared with those of reference compounds of similar structure with known absolute configuration and (*ii*) a semiquantitative approach based on comparison of experimental parameters (sign of the Cotton effect, its amplitude, and position) with those estimated from certain empirical or semiempirical rules. A completely theoretical approach which permits the calculation of rotational strength of the optically active transition of the chromophore is still far from being perfect. A large amount of literature is available since 1960 on this topic (Djerassi 1960; Crabbé 1965, 1967; Snatzke 1967, 1968; Snatzke and Snatzke 1973). A recent review (Kirk 1986) deals with the chiroptical properties of carbonyl compounds.

15.3.1 Use of plain curves

Optical rotations of chiral compounds are generally reported for the wavelength 589 nm (sodium D-line) which is quite far from the UV region where electronic transitions of most organic compounds take place. As a result, values of specific rotations at this wavelength are usually not very high, sometimes even so low as to evade detection so that an enantiomer may be mistaken for a racemic modification*. Specific rotations measured at wavelengths in the shorter range (in a plain curve) undergo manyfold increment (10 to 1,000 times as one approaches the absorption maximum) which makes the enantiomeric purity assay of an optically active compound (e.g., a natural product or a bio-organic specimen) much more precise. If a chiral compound remains inactive throughout the measurable wavelengths, it is almost certainly a racemic modification.

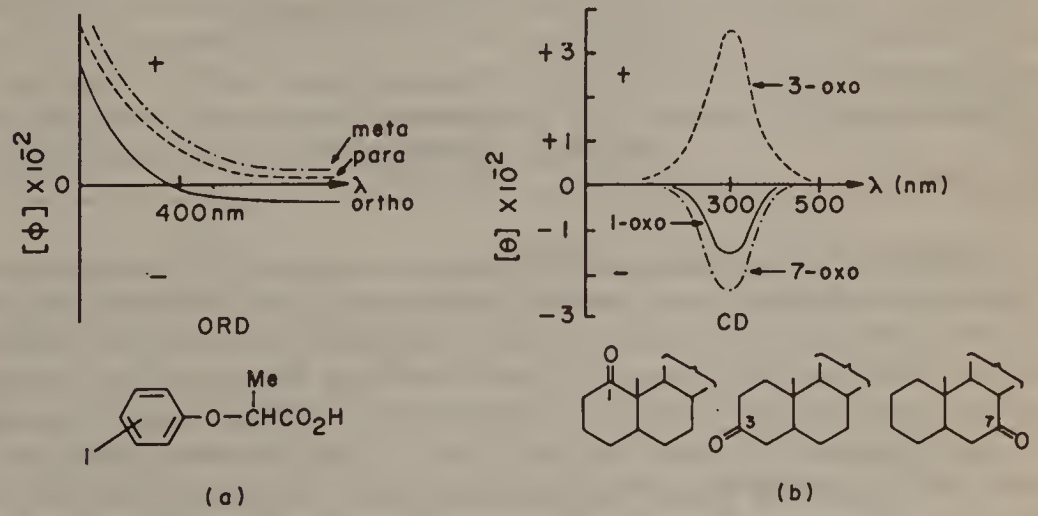


Figure 15.5 (a) ORD curves of *o*-, *m*-, and *p*-iodophenoxypropionic acid
(b) CD curves of 1-oxo-, 3-oxo-, and 7-oxosteroids

*Optical rotation is very low (or nil) when there is no chromophore as in all-alkyl compounds, e.g., CRR′R″R‴.

Then again, a plain dispersion curve for certain molecules—starting from the D-line—may cross the zero-rotation axis so that they show levorotation at the D-line but dextrorotation at shorter wavelengths or the reverse. In such cases, a comparison of specific rotations at the D-line of a set of similarly constituted chiral molecules having the same absolute configuration but one having a plain curve crossing the zero-rotation axis and the others not may lead to misleading conclusion. This is illustrated for the ortho, meta, and para isomers of α-(iodophenoxy)propionic acid (Figure 15.5a). The ortho isomer shows non-conforming levorotation at the D-line although all three have the same absolute configuration, *R* (Djerassi 1960).

15.3.2 CD and ORD curves with Cotton effects

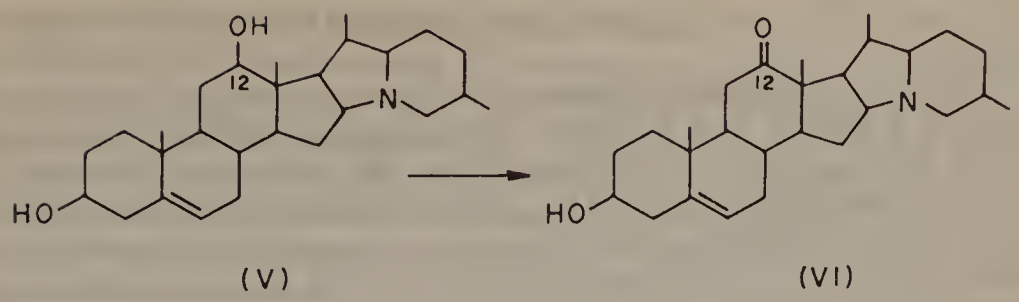
ORD and CD curves showing one or more Cotton effects are more useful and have a variety of applications as shown below.

1. Functional group analysis. Sometimes the characteristic bands of a functional group in conventional spectroscopy (e.g., IR and UV) may be complicated due to overlapping bands. The Cotton effect appears approximately at the absorption maximum (λ_{max}) in UV/visible region and thus provides correct information regarding the functional group. The absorption maxima of a few common chromophores are given in Table 15.1.

Table 15.1

Chromophoric function	λ_{max} (nm)	Chromophoric function	λ_{max} (nm)
Ketone	280-300	Lactone	215-235
α,β-Unsaturated ketone	330-360	α,β-Unsturated lactone	250-260
	230-260		
Carboxylic acid	215-220	Amides and lactam	220-235
α,β-Unsaturated acid	~250	Conjugated diene	~270
Ester	215-220	Substituted phenyl	250-280
Nitro compound	~270	Sulphoxide	~210

2. Position of a functional group. Sometimes the position of a functional group (which is a chromophore or a potential chromopnore) may be ascertained if the skeletal structure of the compound under investigation is more or less common with that of an appropriate reference molecule. Among the polycyclic compounds, steroidal ketones of known absolute configuration have been studied extensively for their chiroptical properties and they often provide important references for polycyclic compounds with carbonyl chromophores. The shapes of the CD curves of 1-oxo-, 3-oxo-, and 7-oxo-5α-steroids are shown in Figure 15.5b. The 3-oxo (as well as 2-oxo) derivatives (e.g., 2- and 3-oxocholestanone) exhibit a positive Cotton effect, while the 1-oxo and 7-oxo derivatives show a negative Cotton effect. 11-Oxo and 12-oxosteroids both show a positive Cotton effect but the 12-oxo derivatives much more strongly so. This fact has been utilised to determine the position of the hydroxyl group in rubijervine (Pelletier and Locke 1957), a steroidal alkaloid (V) (Figure 15.6). It is preferentially oxidised to rubijervone-12 (VI), the

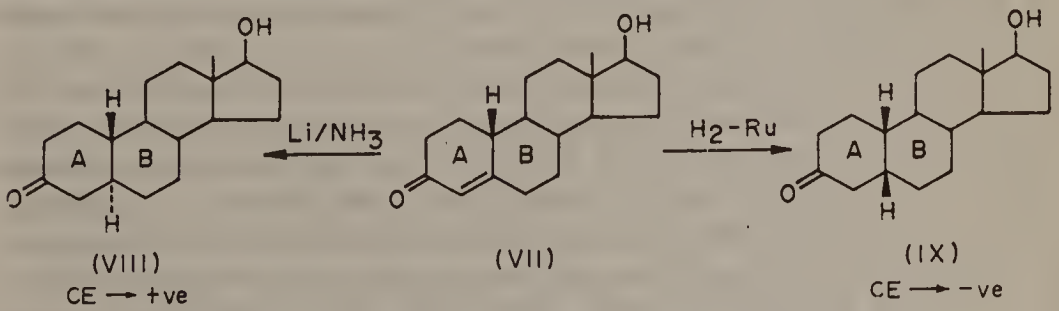


(V) (VI)

Figure 15.6 Rubijervine and rubijervone

ORD curve of which resembles that of a 12-oxosteroid rather than that of an 11-oxosteroid. A change in ring system containing the carbonyl group may, however, also change the sign of the Cotton effect. Thus while both *R*-3-methylcyclopentanone and *R*-3-methylcyclohexanone exhibit a positive Cotton effect, *R*-3-methylcycloheptanone and *R*-3-methylcyclononanone exhibit a negative Cotton effect.

3. Determination of configuration. Assignment of configuration by comparison of CD and ORD curves depends on two principles : ORD and CD curves for enantiomeric structures are exact mirror images of each other across the abscissa (wavelength). Secondly, if the three-dimensional structures of two molecules in the immediate vicinity of the chromophore are identical (with respect to configuration), their CD and ORD curves are expected to give Cotton effects of the same sign (even if the ORD curves are plain, they would correspond in shape). If the structures are antipodal, quasienantiomeric, the signs of the Cotton effects will be opposite. By way of an example, 19-nortestosterone (VII) (Figure 15.7) when reduced with chemical reagents (Li-NH_3) gives an isomer which is diastereomeric with the one obtained by catalytic hydrogenation (H_2-Ru). The first isomer has an ORD curve resembling that of an A/B trans 3-oxosteroid, e.g., cholestan-3-one (with a positive Cotton effect) while the second shows an ORD curve resembling those of 3-oxo-5β-steroids (with a relatively weak negative Cotton effect). Thus the isomers have structures (VIII) and (IX) respectively.



(VIII) (VII) (IX)

CE → +ve CE → −ve

Figure 15.7 Cotton effects (CE) of 5α- and 5β-nordihydrotestosterone

Configurational assignment by the comparison method, however, should be made with caution since structural variations such as the presence of geminal dimethyl at nearby carbon atoms (e.g., C-4 in 3-cholestanone), of unsaturation, of polar groups. as well as ring strain close to the chromophore may change the sign

of the Cotton effect from that of the parent compound (see Kirk 1986 for further details).

4. Study of conformational changes. If a molecule exists in more than one conformer in solution, each conformer will have its own ORD or CD curve and the sign and magnitude of the Cotton effects will change with the change of conformer population caused either by a change of solvent polarity or by a change of temperature. A typical example is found in (−)-menthone which exists as two conformers (Xa) and (Xb) as shown in Figure 15.8. In water (a solvent of high polarity), only a positive Cotton effect CD curve is observed; in methanol (a solvent of moderate polarity), two Cotton effects one positive and the other negative appear; and in isooctane (a non-polar solvent), the negative Cotton effect is very much pronounced. In solvents of intermediate polarity, both the CE's are seen in different proportions (Djerassi et al 1965). This type of curves having two

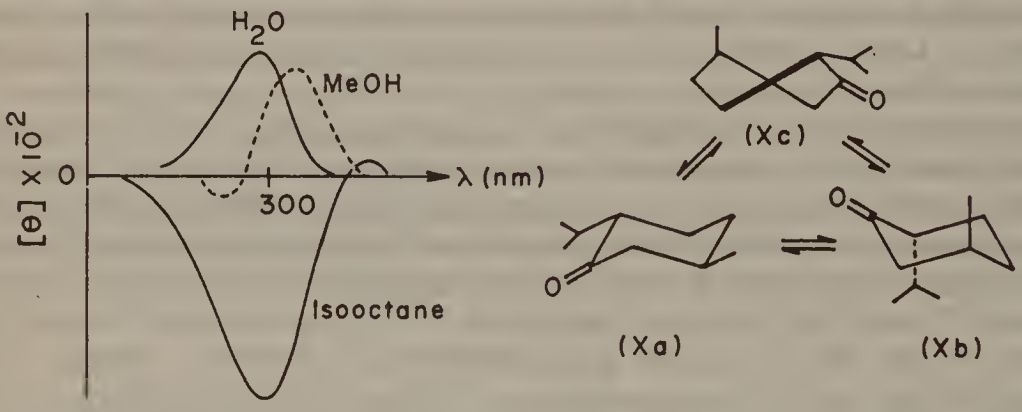


Figure 15.8 CD spectra and conformational changes in (−)-menthone with change of solvent polarity

CD maxima of opposite signs is called 'bisignate' (Klyne and Kirk 1973). In this particular case, the two CE's are presumably due to the two conformers in equilibrium, the diequatorial (Xa) which predominates in a polar solvent (probably a solvation effect) and the diaxial (Xb) or the twist form (Xc) which predominates in a non-polar solvent. The diaxial conformer in menthone is stabilised by the synergistic operation of a 2-alkylketone effect in Xa and of a 3-alkylketone effect in Xb although the function of the polarity of the solvents is not quite clear. The bisignate curves are commonly observed in halocyclohexanones, e.g., (+) − *trans*-2-chloro-5-methylcyclohexanone (see Eliel 1962) the conformational equilibrium of which is very sensitive to solvent polarity (due to the presence of two dipoles). Variation of temperature also produces a similar effect. Thus at low temperature, the diequatorial form of menthone predominates but its population decreases as the temperature is raised. The signs of the CE's may be related to the two conformers by the application of the octant rule (vide infra). It is also to be noted that in bisignate curves, the individual maxima (due to $n \rightarrow \pi^*$ transition) are widely separated (ca 30 nm).

5. Structure of polypeptides and proteins. CD and ORD spectra provide important information regarding the secondary structures of polypeptides, proteins, and nucleotides (Johnson 1985). Only a few points are mentioned here to give some

qualitative idea. The α-helical and β-pleated forms of proteins show different and fairly large CD extrema around 220 nm while the random coil has still different and much weaker Cotton effect. The formation of an α-helix is a cooperative phenomenon in which a large number of weak H-bonds are involved. It does not form if the polypeptide chain is too short (less than a heptamer) and the transition of a random coil to an α-helix with increase of the chain length may be observed in CD and ORD spectra. For a quantitative analysis, some reference compounds are necessary, such as the three (α-helix, β-sheet, and random coil) forms of poly-L-lysine whose ORD and CD curves are known. The α-helix shows strong negative bands (actually, two humps near 220 nm), the β-sheet (with strong H-bonds) both parallel and antiparallel shows a strong single negative band at 220 nm, and the random coil (without regular H-bonds) shows a weak positive band in this region. The CD or ORD curve of a protein under investigation is compared with these reference curves and calibrated (as regards the percentage of secondary structures) accordingly. Variations in secondary structures in proteins and polypeptides with the change of pH and of solvents of different H-bond forming ability may also be studied in this way.

15.4 Empirical and semiempirical rules

Optically active chromophores are broadly classified into two types: chromophores which are inherently dissymmetric because of their intrinsic (often twisted) geometry, e.g., biphenyl atropisomers, helicenes, twisted 1,3-dienes etc. and chromophores which are inherently symmetrical but are asymmetrically perturbed by their chiral surroundings, e.g., a carbonyl group (of local C_{2v} symmetry) in a steroid molecule. The former type shows high optical rotations, high moleculer amplitudes in ORD, and high dichroic difference in CD spectra. Both types (there is a range of intermediate cases) are, in principle, amenable to theoretical treatment as regards their chiroptical properties. The latter type has, however, been investigated more thoroughly, particularly the carbonyl chromophore. Many chiral natural products are ketones or contain groups easily convertible into a ketonic function (e.g., secondary OH). The carbonyl $n \rightarrow \pi^*$ transition absorbs at 280-300 nm, a range of wavelengths which is easily accessible and relatively free from the interference of other chromophores. Moreover, its extinction coefficient is low ($\epsilon \approx$ 20 near 290 nm) so that enough light is transmitted even at λ_{max} to permit easy measurement of ORD and CD. Numerous empirical rules having some theoretical basis have been formulated to correlate the sign of the Cotton effect with its chiral environment. In some of the approaches the space around the chromophore is divided into sectors (quadrants, sextants, or octants) by means of the nodal and symmetry planes of the chromophore and the contribution of a substituent towards the sign of the Cotton effect is assigned depending on its location in the sectors (sector rules). If either the configuration or conformation of a compound is known, the other can be determined by these rules. Some such rules are discussed in the sequel.

15.4.1 The axial haloketone rule

The axial haloketone rule (Djerassi and Klyne 1957) may be regarded as the

precursor of the more general octant rule (vide infra). The rule applies when there is an axial halogen (Cl, Br, and I, but not F*) next to the keto group of a cyclohexanone moiety (see Figure 15.9). One looks at the carbonyl group which is so placed that it occupies the head of the chair (or boat) closest to the observer. If the halogen (X) appears at the observer's right (as in the Figure), the compound will show a strong positive Cotton effect and if it appears at the left, a strong negative Cotton effect is expected. One can also project the molecule into four quadrants defined by a horizontal plane B passing through C-6, C-1, and C-2 and a vertical plane A dividing the cyclohexanone across C=O and C-4 in analogy with the octant rule and label the four quadrants with (+) and (−) as shown, meaning that a substituent in a (+) sector contributes to the positive CE and the reverse applies to a substituent in a (−) sector. The halogen (X) in the projected

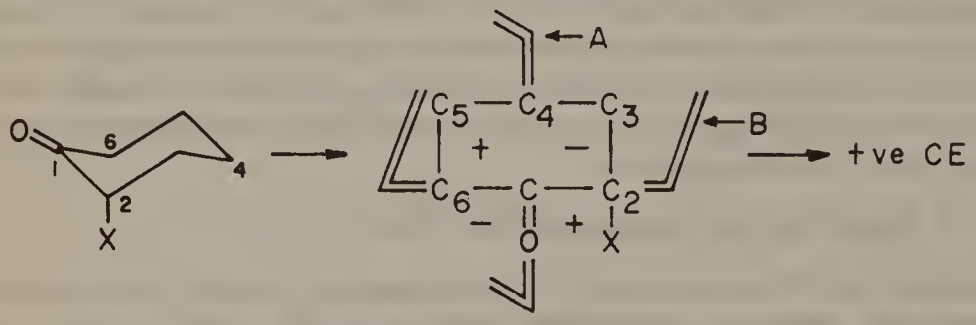


Figure 15.9 Axial haloketone rule

structure is in the lower right quadrant, a (+) sector and hence the CE is positive. In the enantiomeric structure, it would be in the lower left quadrant, a (−) sector, showing a negative CE. The contribution of an axial α-halogen (except F) to the rotational strength of the carbonyl chromophore is so high that in most cases, it outweighs any opposing effect of other substituents (thus it may reverse the sign of the CE of the unhalogenated parent compound). The absorption maximum and with it also the CD maximum undergo bathochromic shifts (20-30 nm) after axial bromination. An elegant application of the axial haloketone rule is illustrated in the determination of the absolute configuration of (−)-*trans*-1-decalone (Djerassi and Staunton 1961). This enantiomer may correspond to either structure XIa or XIb (R=H) (Figure 15.10). On bromination it gives (+)-*trans*-2-bromo-1-decalone with Br in the axial position (as evidenced by IR and UV) which shows a strong positive CE. Looking at the two structures XIa and XIb (R = Br), it is easy to see that the first would give a positive CE (Br is on the right) and the second a negative CE (Br is on the left). The configuration of (−)-*trans*-1-decalone thus corresponds to XIa (R = H).

In another instance, the application of axial haloketone rule proves that the A ring of some substituted 2-bromo-3-ketosteroids exists as a boat. Thus the kinetically controlled bromination of 2α-methyl-3-cholestanone (XII) (Figure 15.11) gives a 2-substituted tertiary bromo compound with Br axially oriented (spectral evidence) which shows a -ve CE. The normally expected product (XIII) with axial bromine would have a strong +ve Cotton effect (Br is on the right hand side if the chair is held with C=O at the top). The only structure which conforms

*Polarisability of F is low while those of Cl, Br, and I are high (compared to H).

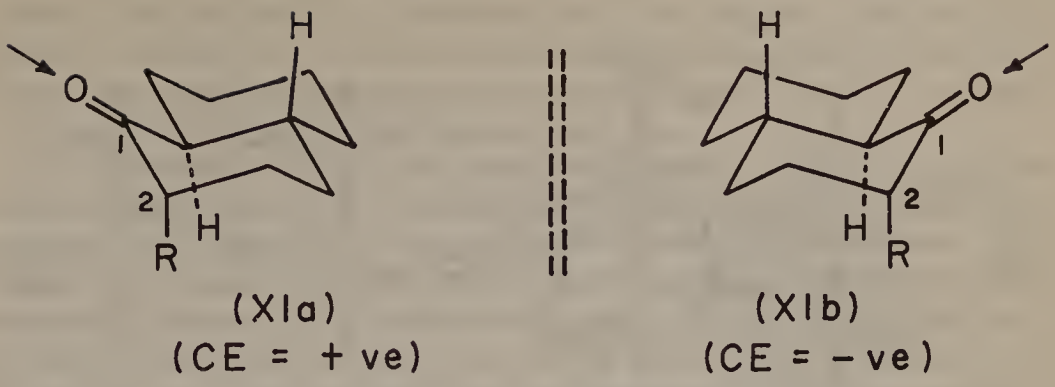


Figure 15.10 Absolute configuration of *trans*-1-decalone

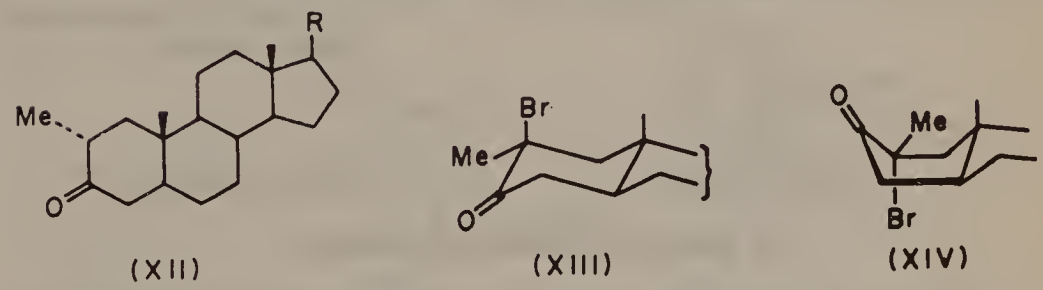


Figure 15.11 Boat conformation of ring A in steroids

to the -ve CE is XIV - a diastereomer of XIII with ring A in boat conformation (Br is now α but axial). Bromination presumably takes place by a parallel attack through twist-boat transition state because of the steric effect of 10-Me (see Chapter 12) and the initially formed boat (or twist-boat) structure (XIV) does not flip to the chair with equatorial bromine since this is destabilised by Me/Me syndiaxial interaction and also by an unfavourable dipole-dipole interaction between carbonyl group and C-Br bond.

15.4.2 The octant rule

The octant rule was first formulated by Moffitt et al (1961) for correlation of the sign of the CE of chiral cyclohexanone derivatives with their absolute configuration. In its simplest form, the space around the C=O group is divided into eight sectors (octants) with the help of three orthogonal planes, A, B, and C defined by xy, zy, and xz respectively (Figure 15.12). The vertical plane A bisects the cyclohexanone chair and the horizontal plane B contains the C=O moiety and the two attached carbons C-2 and C-6. They are also the symmetry planes of the isolated C=O group of C_{2v} symmetry. They divide the space into four quadrants (the cyclohexanone moiety is oriented with C-1 at the head and closest to the observer as in the axial haloketone rule) designated as upper left (UL), upper right (UR), lower left (LL), and lower right (LR) as shown in the right hand diagram in Figure 15.12*. The quadrants are labeled with (+) and (−) signs in such a way that they are mirror images across the symmetry planes A and B.

*The line of vision (y axis) is now perpendicular to the plane of the paper passing through O.

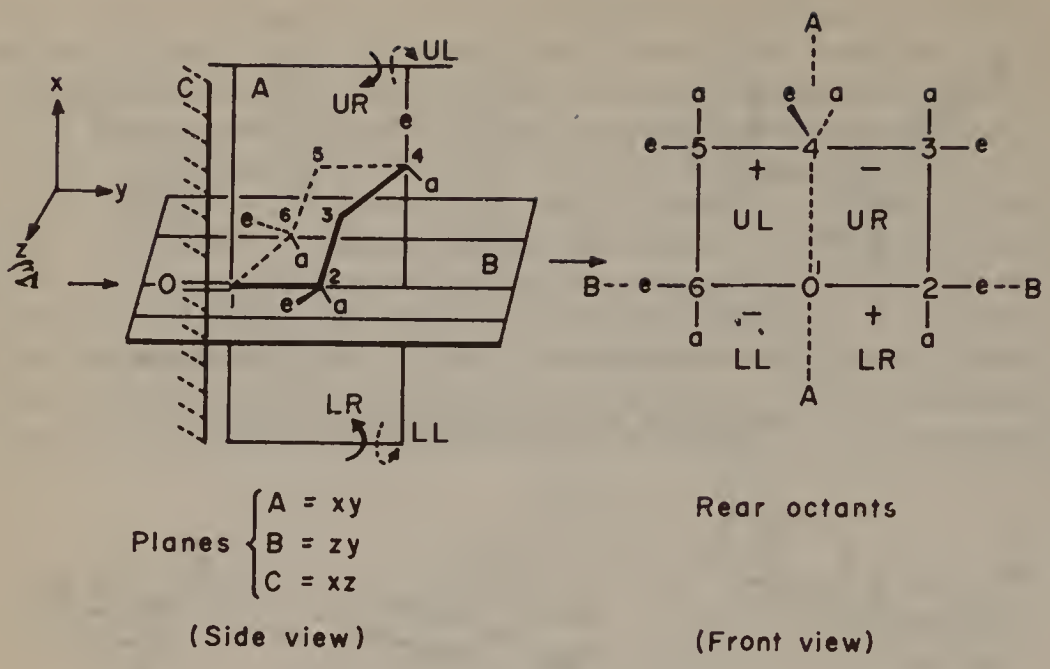


Figure 15.12 Diagrams for the octant rule

Contributions of substituents lying in different sectors towards the sign of the Cotton effect are considered according to the following rules:

(*i*) Substituents lying in the coordinate planes contribute negligibly* and are usually ignored.

(*ii*) Substituents lying in the (+) sectors (UL and LR) make a positive contribution and substituents lying in the (−) sectors (UR and LL) make a negative contribution to the CE. This is generally true for substituents which are more polarisable than an H atom. Such substituents conforming to the octant rule are termed *consignate* and a very few others, such as F, which have lower polarisability than H and do not conform to the octant rule are termed *dissignate* (Klyne and Kirk 1973).

(*iii*) Axial substituents at C-2 and C-6 which are close to the chromophore contribute much more strongly than those situated farther away. Equatorial substituents at C-2 and C-6 (the carbon atoms are numbered in an anticlockwise direction; the actual numbering would depend on the compound under consideration) do not contribute much as they lie in plane B. (This together with the high polarisability of the halogens Cl, Br, and I explains the axial haloketone rule).

(*iv*) The four quadrants described so far constitute the set of the *rear* (away from the observer) octants. On the left hand side of the plane C (not shown), there is another set of four *front* quadrants which are mirror images of the former. Thus substituents lying in them contribute oppositely, i.e., their contributions to the sign of the CE are exactly opposite to those shown in the diagram. Only rarely is a part of some molecules found in these quadrants.

*In fact, the boundary surfaces defined by the orthogonal planes may not be strictly accurate so that substituents lying near the planes sometimes behave anomalously. In a refined model, the xz plane C slightly caves toward the y axis to give a concave surface (Lightner et al 1986).

These rules, although empirical in nature, hold for a large number of steroidal ketones of known absolute configuration with rare exception. The octant rule, therefore, provides a very simple alternative to the other methods described in Chapter 8 for the determination of absolute configuration. A few typical examples are discussed on the various applications of the rule.

1. Conformation. If in a conformationally mobile molecule, the absolute configuration is known, the preferred conformation can be ascertained by the application of the octant rule. An example is (+)-3-methylcyclohexanone, known to have the *R* configuration (XV) (Figure 15.13). According to the octant rule, the equatorial conformer (XVa) should have a positive Cotton effect (3-Me is in the UL octant) while the axial conformer (XVb) would display a negative Cotton effect (3-Me is in the UR octant). Since the ketone actually shows a positive CE, the equatorial conformer predominates (in accordance with the principle of conformational analysis).

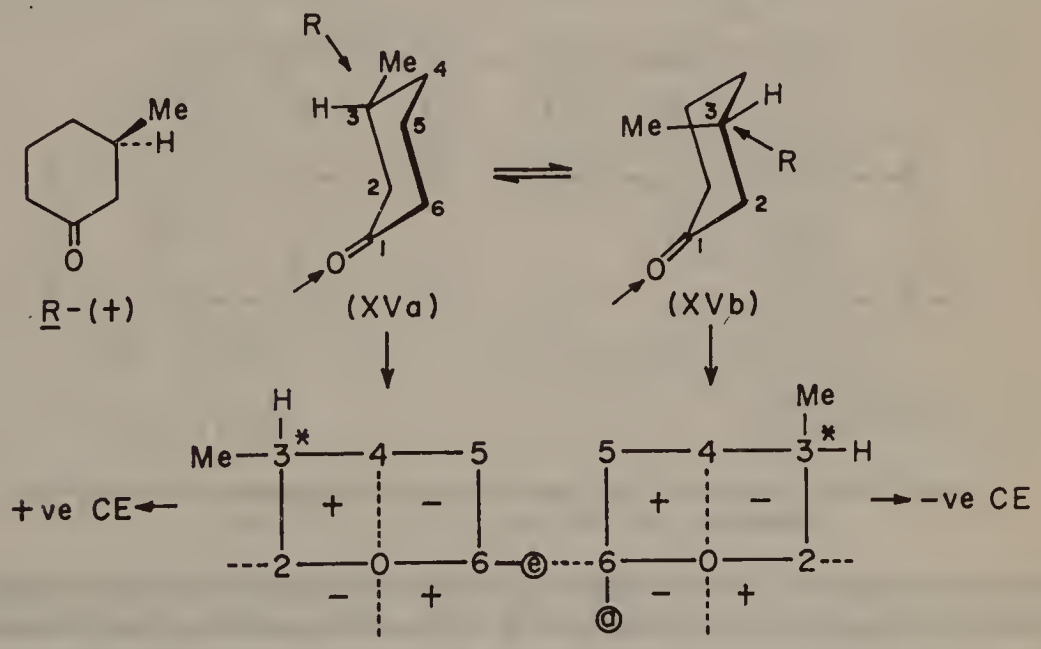


Figure 15.13 Application of the octant rule to *R*-(+)-methylcyclohexanone [and (−)-menthone (the circles holding an isopropyl group)]

(−)-Menthone in the diequatorial conformation (Xa in Figure 15.8) gives an almost identical projection as XVa with an equatorial isopropyl group at C-6 (shown by a circle). It would thus show a positive CD spectrum the contribution of *i*-P_r being nil; but the diaxial conformer (Xb) resembles XVb with an additional axial isopropyl group in a negative sector (circled) and would show a strong negative CD spectrum. The observed CD spectra are consistent with (−)-menthone having a preponderance of diequatorial conformation in water and a preponderence of diaxial conformation in isooctane.

(+)-*cis*-10-Methyl-2-decalone may exist in either of the two conformations, a steroid one (XVIa) and a non-steroid one (XVIb) (Figure 15.14). By the application of the octant rule, it is seen that the former should give a negative CE (ring B being in the negative sector), while the latter a positive CE (ring B being in the positive

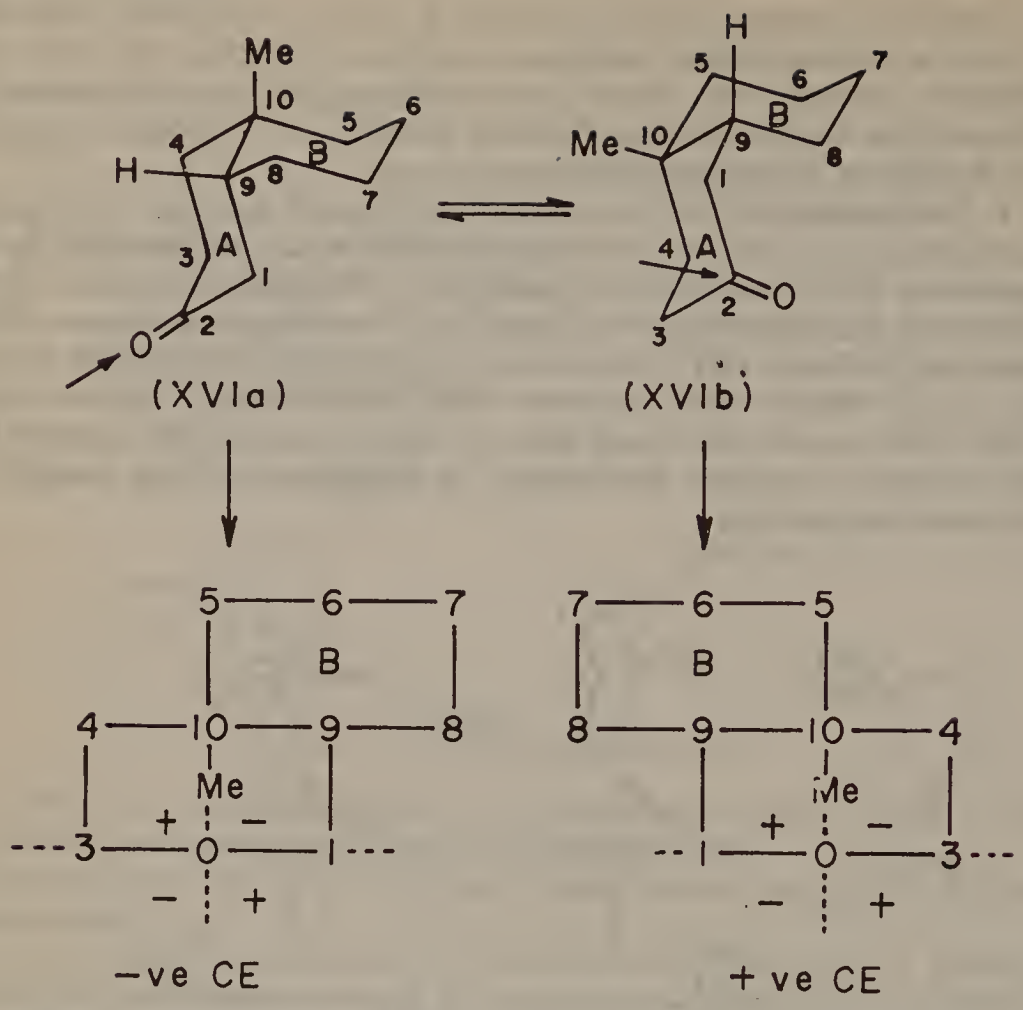


Figure 15.14 Application of the octant rule: steroid conformation of *cis*-10-methyl-2-decalone

sector). Actually it gives a negative CE and so has the steroid conformation, additionally supported by the fact that its ORD curve resembles closely that of a 3-oxo-5β-steroid, e.g., coprostan-3-one. In all the three cases, the absolute configuration is accepted as known.

2. Configuration. *trans*-10-Methyl-2-decalone (XVII) (Figure 15.15) exists in a unique rigid conformation. The absolute configuration of the (+)-enantiomer

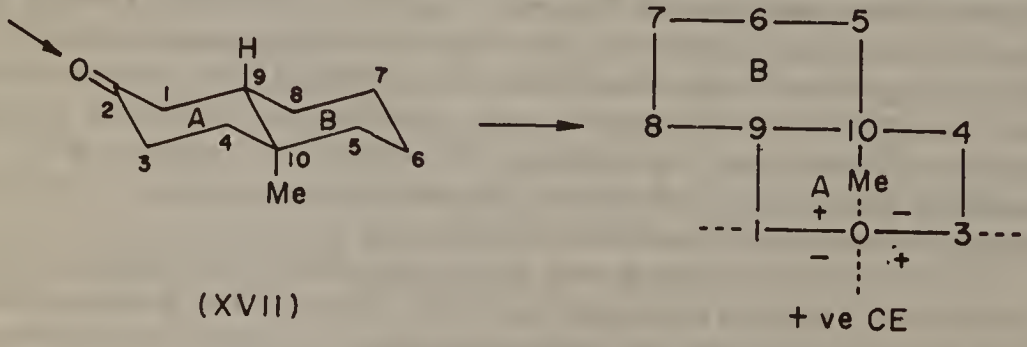


Figure 15.15 Application of the octant rule: configuration of *trans*-10-methyl-2-decalone

which shows a positive CE is thus XVII in accordance with the octant rule (ring B in the projection lies in the positive sector). The mirror image configuration would predict a negative CE.

3. Steroidal ketones. The validity of the octant rule has been tested by its application in many steroidal ketones of known absolute configuration. In Figure 15.16, the structure of 3-cholestanone is projected according to the octant rule. The following procedure must be adopted for proper projection: The structure is so written that the carbonyl group points upwards (towards the observer): C-2 and C-4 are then written as seen and the cyclohexanone rectangle is constructed by

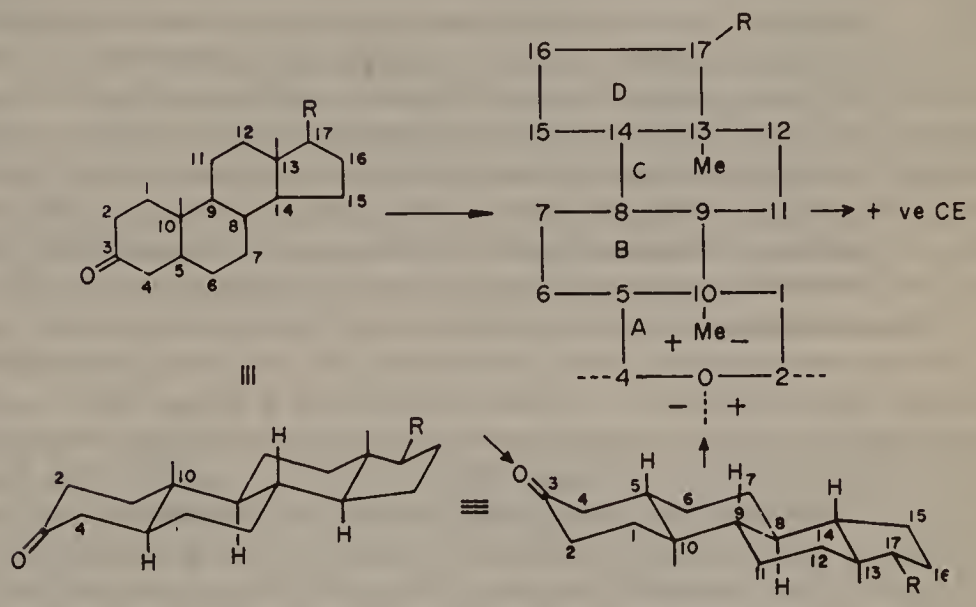


Figure 15.16 Application of the octant rule: 3-cholestanone

placing the diagonally opposite carbon (C-10) just above O. The remaining rings are drawn by following the sequence of numbering. Since the preponderance of atoms is in the UL octant, the CE is predicted to be positive in accord with observation.

For other cyclic ketonic systems such as cyclopentanones and cycloheptanones, the application of the octant rule often becomes ambiguous because of the changed ring conformation. A flexible cyclopentanone exhibits a CE which is the weighted average of values calculated for all conformers.

For aliphatic ketones, polyketonic compounds, and other analogous chromophores, the reader is referred to Crabbé (1965) and Kirk (1986).

15.4.3 Helicity rule

Four atoms of the same element or of different elements linked by three non-linear bonds may be twisted along the central bond to give two (*a* and *b*) or more sets of helical arrangements which are non-superposable mirror images of each other as shown in Figure 15.17. Such a system represents the simplest chiral unit. An

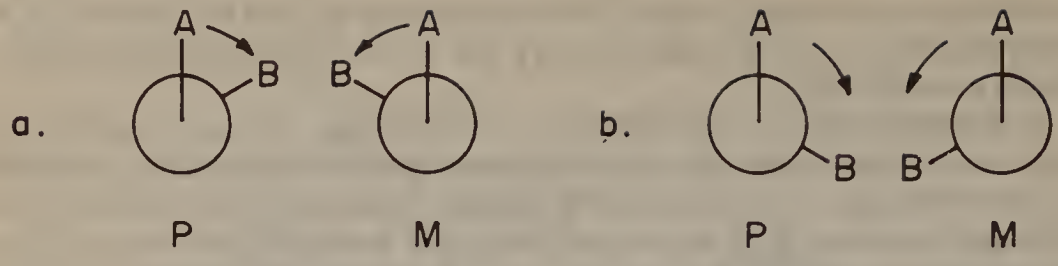


Figure 15.17 Twisted chiral forms of A-C-C-B unit

example at the molecular level is provided by HO-OH which exists in two gauche ($\theta \approx 90°$) conformations (as *a*, A=B=H) along the O-O bond in the solid state. Many of the theoretical models are based on the general rule that in such a system, an electron following a right handed (*P*) helical path (defined by the sigma framework) during the transition contributes to positive rotation while an electron following a left handed (*M*) helical path contributes to negative rotation. This is known as the helicity rule and is exemplified by a number of conjugated systems for $\pi \rightarrow \pi^*$ transitions. Since the chirality is inherent in the chromophore, these compounds illustrate inherently dissymmetrical chromophores mentioned earlier.

1. Conjugated dienes. Depending on the structural feature of the molecule, both a cisoid (*s*-cis) and a transoid (*s*-trans) diene may be skewed forming either a *P* or an *M* helix. The contribution of a chiral skewed diene is so high that it usually overrides the effects of other chiral centres (in practically all such compounds, there is always a chiral centre or even more). The helicity rule is applied to the lowest energy $\pi \rightarrow \pi^*$ transition in dienes around 230-260 nm. The skewed dienes are represented by structures similar to those in Figure 15.17 (set *a* corresponds to a cisoid and set *b* to a transoid diene with C-A and C-B replaced by C = C or C = O). The validity of the rule has been proved by the ORD curves of a number of 2,4-dienes (XVII) and 1,3-dienes (XVIII) (Figure 15.18) derived from steroids, the former giving a strong positive CE and the latter a strong negative CE. The results suggest *P* helicity in 2,4-dienes (XVII) and *M* helicity in 1,3-dienes (XVIII) which can be confirmed from the models. Conversely, knowing the absolute configuration of the steroids, the helicity of the respective dienes can be derived (Charney 1979). These two are cisoid dienes.

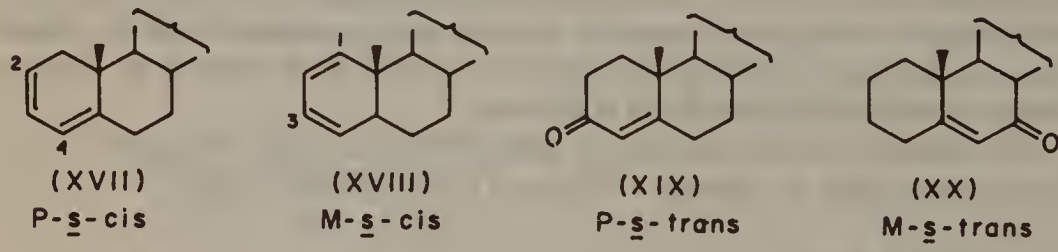


Figure 15.18 Helicity in dienes and enones

The helicity rule also applies to transoid dienes. the hetero-atom analogues of which are illustrated by α,β-unsaturated ketones (XIX) and (XX) again derived from steroids. Their helicity corresponds to that shown in Figure 15.17b with an obtuse dihedral angle separating the C = C and C = O bonds. The CD curve of

cholest-4-en-3-one (XIX) in hexane shows a positive CE (at ~ 250 nm) while cholest-5-en-7-one (XX) shows a negative CE in that region confirming *P* and *M* helicity respectively in the enone component of the two ketones (Snatzke and Snatzke 1973). In each case, a weak $n \rightarrow \pi^*$ band (at 300-350 nm) appears with opposite signs (see Kirk 1986).

2. **Helicenes.** The absolute configuration of helicenes (tetra, penta, hexa, and hepta)* appropriately substituted if necessary, which are characterised by very high optical rotations follows the helicity rule which means that helicenes with *P* helicity are dextrorotatory and give a positive CE and the reverse for helicenes of *M* chirality.

3. **Biaryl atropisomers.** CD spectra as related with the absolute configuration of some biaryls have been investigated by Mason and Seal (1974). *S*-Binaphthyl of *P* helicity (see Chapter 5) and *P*-pentahelicene are both dextrorotatory and their CD spectra are of similar nature which suggests that the helicity rule (see also Lowe's rule below) may work here as well. Theoretical treatment by these workers (Mason 1982) gives a more precise correlation between the CD spectra and absolute configuration of certain biaryls which depends on the dihedral angle between the two aryl rings.

15.4.4 Lowe's rule

The idea of an asymmetric screw pattern of polarisability at a chiral centre (Brewster 1959) has been utilised by Lowe (1965) to work out an empirical rule for assigning the absolute configuration of optically active allenes. The method consists in projecting the allene by placing the more polarisable substituent in the vertical axis uppermost. If in so doing, the more polarisable substituent in the horizontal axis lies on the right, a clockwise screw pattern of polarisability results and the allene is dextrorotatory as illustrated for compound (XXI) in Figure 15.19 which also shows the polarisability order of a few substituents. Levorotation results from an anticlockwise screw pattern of polarisability. All the dissymmetric fungal allene metabolites represented by the general formula XXII (R = H or Me) thus have their absolute configuration correlated with their rotations. Provided the group R′ does not exhibit conformational asymmetry (vide infra), (+)-XXII will have the *S* configuration and (−) -XXII the *R* configuration.

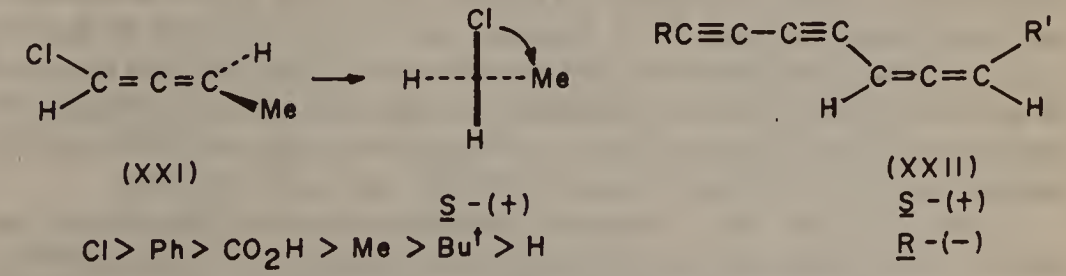


Figure 15.19 Lowe's rule for the configuration of allenes

*The smallest unsubstituted helicene with an appreciable optical stability is pentahelicene. Tetrahelicenes are achiral in the absence of appropriate substituents.

15.4.5 Empirical rules involving the benzene chromophore

Next to the carbonyl chromophore, the benzene ring is perhaps the most well investigated chromophore but its theoretical treatment is understandably much more complex. A few empirical rules have been proposed and used since the time of Freudenberg.

1. Benzoate rule. Freudenberg (1933) first showed that the acid phthalate of a secondary alcohol represented by the configuration XXIII (S = small and L = large) in Figure 15.20 is more dextrorotatory than the parent alcohol. Later this phthalate rule has been incorporated into the more general benzoate rule (Brewster 1961) which is based on the assumption that in the Newman projection of the benzoate (XXIV). the planar benzoyl group because of its high effective bulk is placed between H and S. A clockwise asymmetric screw pattern (S has a higher polarisability than H) results in increased dextrorotation. The reverse effect takes place in the enantiomeric configuration. This rule which covers Mills' rule (see Chapter 8) does not apply to all cases; exceptions occur when L is more bulky and at the same time more polarisable than S and when the carbinyl carbon is flanked by two CH_2 groups. The benzoate rule eventually led to the benzoate sector rule (Nakanishi et al 1968).

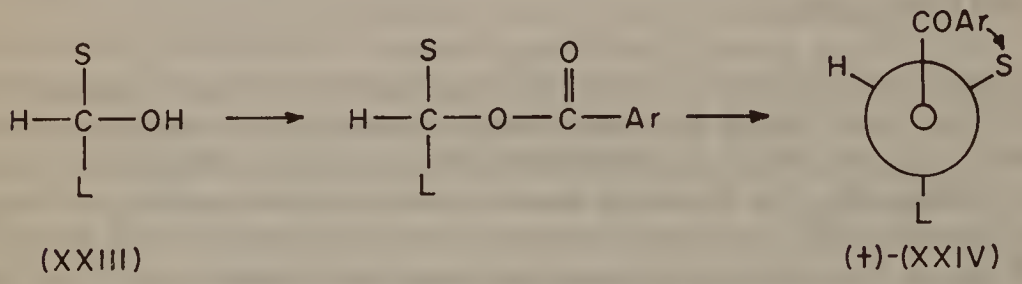


Figure 15.20 The benzoate rule

2. Benzene (sector) quadrant rule. A substituted benzene has several UV absorption maxima and usually exhibits three Cotton effects in the region 220-300 nm. The lowest energy transition around 300 nm resulting in the α-band or ^1L_b band has been used by Japanese workers (Kuriyama et al 1967) to formulate a quadrant rule. The substituted benzene must have a C_{2v} local symmetry so that the electric-dipole transition moment (μ_e in R_K)* for the 290 nm band is along the C_2 axis (local) shown in Figure 15.21. The molecule is so projected that the benzene ring is placed in a horizontal plane in front (indicated by thick line) and the rest of the molecule lies in the four rear quadrants (the signs indicate the contribution of a substituent in each quadrant). The rule is based on the observed ORD and CD curves of lycorine and related compounds of which one example is given.

α-Lycorene (XXV) when projected according to the above specification has most of its components lying in the lower left rear quandrant (a model is useful), a negative sector, and accordingly it should have a negative CE. The experimental value of $[\theta]_{max}$ at 294 nm is −3070. Other examples will be found in the original literature.

3. Snatzke's sector rules. Benzene derivatives substituted as above have

* See p 484

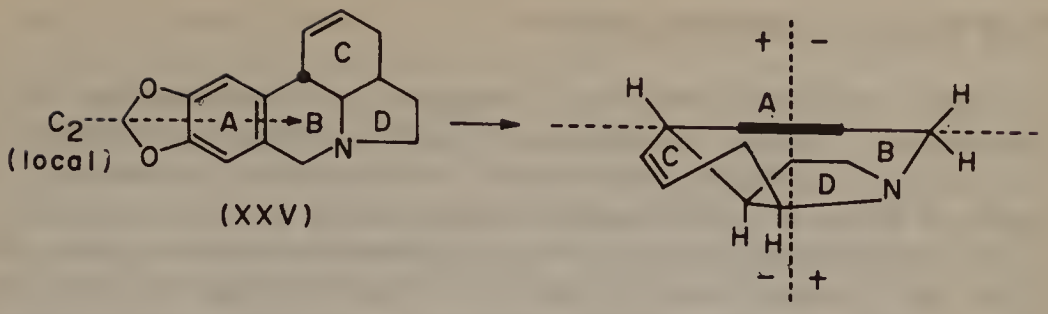


Figure 15.21 Benzene quadrant rule (according to Kuriyama et al)

alternatively been considered by Snatzke et al (1971) in terms of several chiral spheres: the first sphere is the phenyl ring itself (in this case, achiral), the second sphere is the chirally disposed cyclohexene (half chair) ring which has been subdivided into four sectors. The projection and the signs of each quadrant are shown in Figure 15.22 (A and B). It may be noted that the conformation of the cyclohexene ring (second sphere) usually determines the sign of the CE in CD spectra, positive in A and negative in B. The validity of the rule is tested in an authentic compound (XXVI) whose projection C (with obligatory diequatorial fusion at C-2,3) predicts a negative CE at 290 nm which corresponds to observation. The rule finds important applications in the determination of absolute configuration of many isoquinoline alkaloids (morphine etc) with an N atom at the position marked by an arrow. In all these compounds the CE due to the ^1L_a band (at shorter wave length) very often has the opposite sign to that due to the ^1L_b band. Further subdivision of the sectors has been made to show the contribution of the third chiral sphere. The diagram shown in the lower right (D) in Figure 15.22 applies to the tetralin moiety or its heterocyclic analogue (N at the arrowed position. Yet another segmentation has been made to take care of monosubstituted benzene derivatives with chiral centre (s).

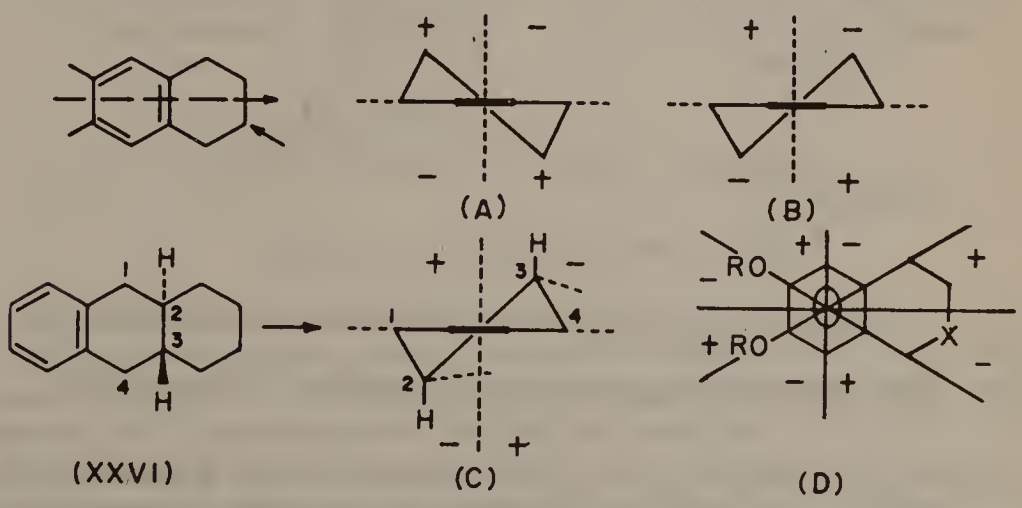


Figure 15.22 Benzene sector rules (according to Snatzke et al)

For a sector rule applicable to aromatic compounds with chiral substituents, see Angelis and Wildman (1969).

15.4.6 The exciton chirality method

Nakanishi and Harada (1969) have developed an empirical method for the determination of absolute configuration of 1,2-glycols through the CD spectra of their dibenzoates (dibenzoate chirality rule)*. The 230 nm band in an unsubstituted dibenzoate is due to an intramolecular charge transfer transition in which the electric transition moment is approximately parallel to the C-O bond of the ester. In the case of vicinal dibenzoates, the two chromophores form a chiral screw pattern, either right-handed or left-handed as shown in the case of $2\alpha,3\beta$-dibenzoyloxycholestane (XXVII) (Figure 15.23). The result of the interaction of the two chromophores is the splitting of the Cotton effect (Davydov splitting) into two: The first CE appears at 233 nm, the second one at 219 nm. Their intensities are the same but their signs are opposite. The sign of the first CE (at 233 nm) corresponds to the helicity rule previously discussed, the right handed screw pattern giving a positive CE and the left handed one a negative CE (as in XXVII). Together they resemble an anomalous ORD curve. The method is applicable to benzoates of 1,2-glycols (OH may be alcoholic or phenolic) or even of 1,2,3-triols as in sugar derivatives (for a review, see Harada and Nakanishi 1972). Other chromophores usually do not interfere in this region. If they do, the position of the CE's may be shifted by appropriate para substitutions (in Bz). The principle holds good for any pair of chromophores provided the direction of the electric moments is known. For application to cyclic 1,2,3-triols, see Wiesler and Nakanishi (1989), (see also refs 41 and 42 at the end).

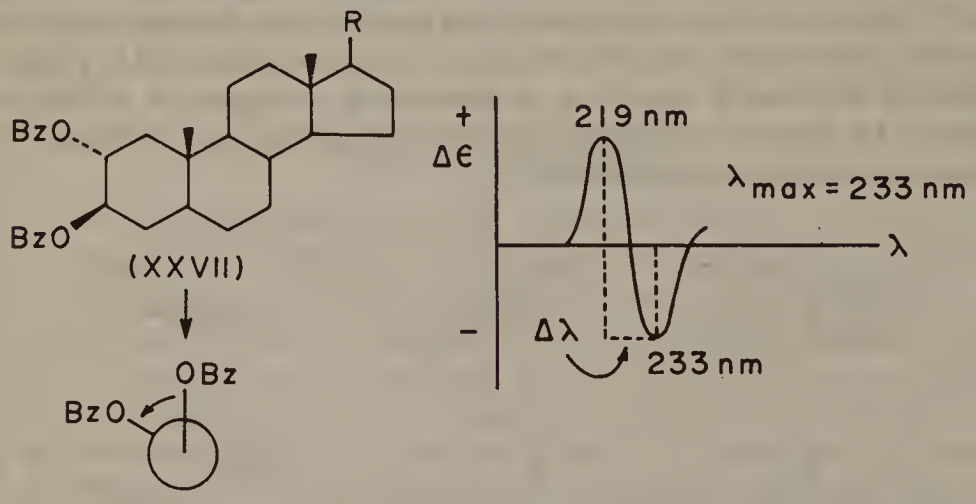


Figure 15.23 Split Cotton effects due to two interacting vicinal benzoates

15.5 Optical rotation and group polarisability - a correlation

Ever since the 1930's, models have been proposed (Drude, Freudenberg, Born. Kuhn, Kirkwood, Eyring, Whiffen, and others) to provide a theoretical basis of optical activity in dissymmetric molecules. In the simplest concept, two electrons

*This has subsequently been termed as 'the exciton chirality method' (Harada and Nakanishi 1972).

or electronic systems vibrating in two mutually perpendicular directions, interact differently with the RCP and LCP components of an LP wave ($n_R \neq n_L$) and thus give rise to optical rotation. However, attempts to correlate optical rotation on the basis of molecular parameters have not yet been very successful*. During 1959-1961, Brewster made an approach for calculating the sign and magnitude of optical rotation based on two independent contributions, namely, atomic asymmetry (configurational contribution) and conformational asymmetry (conformational contribution). Later in 1967, Brewster has modified his treatment of conformational asymmetry and succeeded in certain cases to correlate optical rotation with polarisabilities of atoms and groups.

15.5.1 Atomic asymmetry

Atomic asymmetry refers to a simple chiral centre represented by Cabcd (see Figure 15.24) in which four groups of different polarisabilities (and without any conformational alternative) are joined to a carbon atom. Such a compound is dextrorotatory if the polarisability order a>b>c>d is clockwise as in A and levorotatory if the polarisability order is anticlockwise as in B when Cabcd is shown as a Fischer projection with groups a and c on the horizontal line (pointing to the observer). The polarisability of an atom or group is derived from the atomic refraction (Vogel 1948) of the atoms attached to the chiral centre and is in many cases determined empirically. The order of polarisabilities of a few common atoms and groups are given in Figure 15.24. The rule is illurstrated with one example, *R*-phenylmethylcarbinol which corresponds to a right-handed arrangement (A) and so is dextrorotatory (it may be argued that Ph and OH have conformational alternatives).

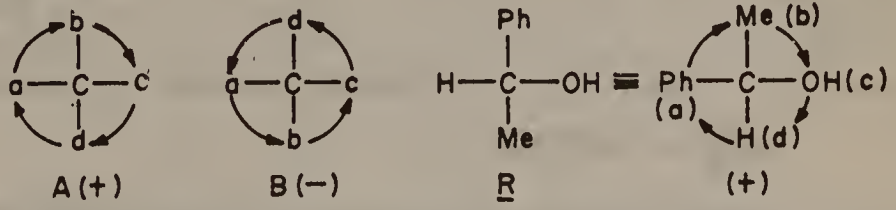


Figure 15.24 Atomic asymmetry (Brewster's rule)

The contribution of atomic asymmetry to optical rotation is usually low unless one or more of the ligands absorb in the near UV region (C=O, Ph etc.). Thus the molecular rotation of cyclohexylmethylcarbinol is only 9° but that of phenylmethylcarbinol is 63°. There is another factor which also contributes to optical rotation in compounds where two groups at the chiral centre form a linkage, such as a H-bond giving cyclic structures. This is illustrated with the general formulae (C) and

*Part of the problem is that $[\alpha]_D$ really originates from the long wavelength tail of one or several of UV Cotton effects.

(D) (Figure 15.25) in which X is oxygen (as in α-hydroxy acids) or nitrogen (as in α-amino acids). If a has higher polarisability than b. the configuration (C) would contribute to positive rotation and the configuration (D) to negative rotation: these contributions should be added to that due to atomic asymmetry. The latter may act in the same direction or in the opposite direction. Thus *R*-lactic acid (XXVIII) should, according to atomic asymmetry, be dextrorotatory but levorotation is predicted from the cyclic (H-bonded) structure (which corresponds to D). As a result, *R*-lactic acid is weakly levorotatory (in water) and the sign of its rotation changes with the solvent and concentration.* In *R*-mandelic acid (XXIX), both the atomic asymmetry and the cyclic structure (as shown) contribute negatively and so the levorotation is high.

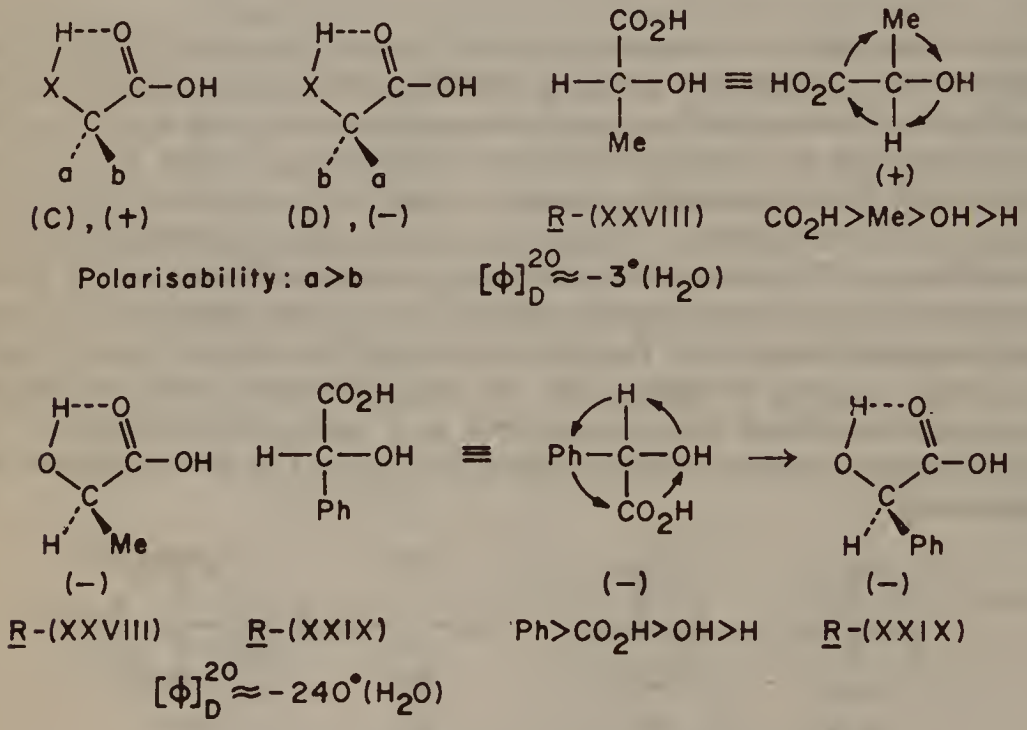


Figure 15.25 Configurational contribution due to H-bond formation

15.5.2 **Conformational asymmetry**

If two or more groups are attached to a chiral centre through identical atoms as in $C_2H_5CH(CH_3)C_3H_7$, Brewster's rule for atomic asymmetry cannot be used since the identical atoms will have the same polarisability and no appreciable rotation is expected. The contribution to optical rotation in such molecules is entirely due to conformational asymmetry which becomes manifest due to conformational mobility. If one considers the Newman projection (XXX) of an unit A-C-C-B (C represents carbon) (Figure 15.26) twisted along the C-C bond, it forms a helical turn, in this case a right-handed one. The length of the helical path is given by the summation

*Its esters and salts are dextrorotatory.

of the three bond lengths A-C, C-C, and C-B, i.e, $(d_1 + d_2 + d_3)$ which may be considered as a spiral homogeneous conductor along which electron moves. To this model, is now added a second molecular parameter, namely, the polarisability of the bonds C-A and C-B (to be determined by the bond refractions). One can calculate the contribution of the helical unit to molecular rotation, (+) for right-handed and (−) for left-handed helix, through equation (12) in which $\Sigma\Delta R_D$ stands for the sum of refractions of bonds.

$$[\Delta\phi]_{AB} = 251 \times \frac{d_1 d_2 d_3}{(d_1 + d_2 + d_3)^2} (\Sigma\Delta R_D) \qquad (12)$$

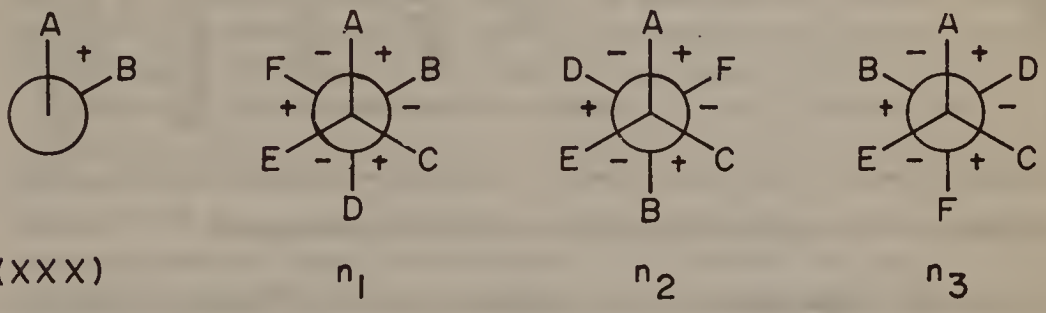


Figure 15.26 Conformational asymmetry (Brewster)

In a complete conformation, six such helical units exist (see Figure 15.26) and the total contribution of a particular conformation (say n_1) is given by the summation of the six individual components :

$$[\phi] = [\Delta\phi]_{AB} - [\Delta\phi]_{BC} + [\Delta\phi]_{CD} - [\Delta\phi]_{DE} + [\Delta\phi]_{EF} - [\Delta\phi]_{FA} \qquad (13)$$

The molecule itself is a mixture of three conformers whose mole fractions are given by n_1, n_2 and n_3 respectively so that $n_1 + n_2 + n_3 = 1$ (due to steric reason, one or the other may be very little populated and ignored) so that the net contribution to molecular rotation is given by equation (14) :

$$[\phi]'_D = n_1[\phi]_1 + n_2[\phi]_2 + n_3[\phi]_3 \qquad (14)$$

Yet another parameter, the refractive index of the solvent (n) in which the rotation is measured has to be considered and accordingly a correction factor f(n) is introduced as defined below:

$$f(n) = \frac{(n^2+2)^2}{9n} \qquad (15)$$

The actual molecular rotation $[\phi]_D$ is thus given by the final expression :

$$[\phi]_D = f(n) \times (n_1[\phi]_1 + n_2[\phi]_2 + n_3[\phi]_3) \qquad (16)$$

The solution of equation (16) depends primarily on the solution of equation (12) which contains the bond lengths (calculated on the basis of atomic radii according to Pauling) and ΔR_D values (known experimentally or calculated from the atomic refractions following Vogel). Values for the mole fractions of the conformers, n_1, n_2, and n_3 are computed from conformational analysis (not easy) and the molecular rotation of the compound may be determined both in sign and

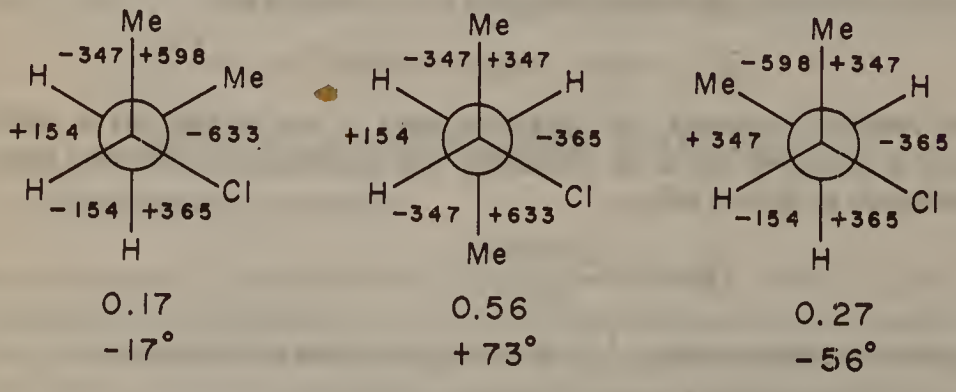
magnitude. For ready reference, the rotational contributions of a number of helical units (A-C-C-B) as determined by equation (12) are given in Table 15.2.

Table 15.2 Rotational contribution of helical unit (as XXX).

A	B = H	F	OH	NH_2	CH_3	Cl	SH	Br	I
H	154	159	225	297	347	365	480	483	698
F		168	240	319	376	398	528	531	775
OH			314	395	453	478	609	615	860
NH_2				477	537	566	700	707	957
CH_3					598	633	767	777	1037
Cl						672	813	823	1100
SH							956	971	1125
Br								988	1270
I									1570

(Adapted from V.M. Potapov 1979 in *Stereochemistry*, Mir Publishers, Moscow).

The method is illustrated with the calculation of the molecular rotation of 2-chlorobutane which exists as three conformers, shown in Figure 15.27 with their respective mole fractions. The rotational contribution of each helical unit (Table 15.2) is inserted in the corresponding sextant. The computed values have been put under each conformer. The value of n at 20°C is 1.40 which gives a value of 1.24 for the correction factor f(n). The calculated value of $[\phi]_D$ turns out to be + 28.2° which is in excellent agreement with the maximum value recorded, + 30.0°. One good point of this rule is that it is applicable to those chiral molecules which cannot ordinarily be investigated by ORD and CD methods (lack of appropriate chromophore). It gives uncertain results when one of the group is Ph and is not applicable to vicinal dibromides.



$$[\phi]_D = 1.24\,[-17 \times 0.17 + 73 \times 0.56 - 56 \times 0.27] = 28.2°$$

Figure 15.27 Application of Brewster's rule

15.6 Origin of chirality

The origin of chirality in the earth is one of the most intriguing problems, yet to be

solved quite satisfactorily. Moreover, it is related to another most fundamental problem, namely, the origin of life (the major functional biomolecules being chiral). The topic is too complex to be treated in the present discussion in which only a brief outline of some of the theories is given. The earlier ones are reviewed by Elias (1972) and the recent ones by Mason (1988) and Bonner (1988).

Pasteur who first initiated the concept of dissymmetry in organic molecules was convinced that some chiral natural forces, perhaps some element in the sunlight or a magnetic field, are responsible for the generation of the first chiral molecule. His initial attempts to influence optical rotation by artificial means, e.g., by growing crystals in a powerful magnetic field or by carrying out reactions in rapidly rotating vessels and even in reflected (mirror image) sunlight, however, failed. Nevertheless, as will be seen in the sequel, he was probably right in his belief.

Fischer during his diastereoselective synthesis in the sugar series came out with a *key and lock* principle meaning that in a chemical reaction, a steric fit between the reactants would determine the course of the reaction and provide a method for stereoselective (and enantioselective) synthesis. While this is true and generally accepted, it cannot explain the formation of the first chiral molecule(s) in nature which is necessary for subsequent propagation of chirality through this mechanism. A number of theories such as asymmetric catalysis by chiral quartz, asymmetric synthesis (or decomposition) by circularly polarised light, stereospecific autocatalysis in complex systems (Akabori), the accidental formation of a chiral 'Adam' molecule (Mills), spontaneous resolution, and a few others were advanced most of which depend on a chance factor or a high degree of coincidence.

One observation was very significant in this connection. D-tyrosine is preferentially destroyed, with respect to L-tyrosine, when an alkaline solution of the two is exposed to the β-radiation (which gives rise to circularly polarised ray. Bremsstrählung, when slowed down). It is known that sunlight at the twilights is circularly polarised (to the extent of 0.5%), although the sign is opposite at sunrise and sunset so that the overall effect is nil. In fact, according to the principle of parity conservation (Curie 1894, Wigner 1927), the forces of nature of the type conceived exist in mirror-image pairs, e.g., a parallel or an antiparallel electric and magnetic field generated by a right-handed or a left-handed helical charge displacement, and so are even-handed on a time and a space average.

Lee and Young (1956) for the first time pointed out that the parity conservation rule is violated in the weak nuclear interactions as in the β-decay (emission of a β-electron or a β-positron) of radionucleides (^{60}Co to ^{60}Ni and ^{58}Co to ^{58}Fe). The electron showed an intrinsic left-handedness and the positron an intrinsic right-handedness (considered in relation to their respective preferred antiparallel and parallel modes and the directions of the spin axis and linear momentum) (see Wu et al 1957). Later in the unified electromagnetic theory, this effect (together with another weak neutral current interaction involving neutral and charged massive bosons) is known as electroweak interaction. The electroweak interaction discriminates between binding energy of the electronic state (stationary and transitional) of the two enantiomeric forms of a molecule so that they differ by a very small amount of energy, of the order of 10^{-14} J mol^{-1} as in L-peptides and D-peptides, L-α-amino acids and D-α-amino acids (Mason and Tranter 1984-85).

This corresponds to an excess of about 10^6 molecules of L-forms in the racemate. Obviously, this energy (ΔE_{ew}) is very small and needs amplification.

An amplification mechanism was suggested as early as 1953 (Frank) according to which in an open non-equilibrium racemic reaction, each enantiomer autocatalyses its own formation but inhibits that of its enantiomer from an achiral substrate giving a racemic product. However in such a system, if the substrate concentration reaches a critical point, the steady state is destroyed and the reaction switches to a particular channel favouring either the formation of L or that of its antipode D. The direction depends entirely on chance in the absence of any extraneous factor. The electroweak interaction although weak is sufficient to direct the reaction path towards the formation of the energy-preferred enantiomer and thus might have provided the biomolecular handedness in the prebiotic period. Afterwords, the self-replication of biomolecules takes over and the chirality continues to be preserved.

15.7 Summary

1. Linearly polarised (LP) light actually consists of two circularly polarised (right-handed and left-handed) rays which by virtue of their chirality interact differently with a chiral medium. The interaction involves the valence electrons which take part in electronic transition and exhibits itself in the form of two chiroptical properties, namely, circular birefringence and circular dichroism which means that the chiral medium will have different refractive indices (hence different velocities) and different absorption coefficients for the two circularly polarised components of the LP light. Optical rotation is also an outcome of these phenomena.

2. The optical rotatory dispersion (ORD) and circular dichroism (CD) curves are obtained by plotting specific or molecular rotation and molecular ellipticity (or differential dichroic absorption) respectively against the wavelength. They show a Cotton effect at or near the wavelength of the maximum absorption (UV/visible). In principle, an appropriate interpretation of the Cotton effect (its sign and magnitude) in terms of the dissymmetric environment of the chromophore (which is responsible for asymmetric perturbation of the electronic transition) should give information about the absolute configuration. Thus optical rotation and configuration may be correlated.

3. Optically active chromophores are classified into two types : intrinsically dissymmetric (biphenyls, helicenes, twisted dienes etc.) and intrinsically symmetric but asymmetrically perturbed by chiral environments (e.g., a C=O group in a chiral molecule). The former type shows very high optical rotation and gives prominent ORD and CD spectra.

4. A number of empirical and semiempirical rules for the assignment of absolute configuration to a chiral molecule from ORD and CD studies have been formulated most of which are based on dividing the space around the chromophore into sectors and assigning characteristic signs (+ or −) to them meaning that substituents residing in these sectors contribute positively or negatively to the Cotton effect. Of these, the octant rule involving the $n \rightarrow \pi^*$ transition of a carbonyl

group is the most thoroughly investigated one and has been used here for the determination of configuration and conformation of many ketonic compounds. A few other rules relating to other chromophores (the phenyl chromophore in particular) have been discussed. Lowe's rule for determining the configuration of chiral allenes is worth mentioning.

5. Brewster's rule based on atomic asymmetry and conformational asymmetry has been also discussed and illustrated. This rule applies to rotation measured at the D line.

6. The different theories of the origin of chirality in the natural products including biomolecules have been summarised. The latest theory involving the electroweak (nuclear) interaction appears to provide the most plausible rationale. However, a definite answer to this problem seems to be quite remote.

References

1. J.H. Brewster (1967), in *Topics in Stereochemistry*, vol. 2, Eds. N.I.. Allinger and E.L. Eliel, Interscience, New York.
2. S.F. Mason (1982), in *Molecular Optical Activity & Chiral Discriminations*, Cambridge University Press, Cambridge.
3. C. Djerassi (1960), in *Optical Rotatory Dispersion*, McGraw Hill, New York including the chapter by Mosecowitz.
4. P. Crabbe' (1965), in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, London.
5. P. Crabbe' (1967), *Tetrahedron*, **23**, 3449-3503.
6. G. Snatzke (1967), in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Heydon & Sons, London.
7. G. Snatzke (1968), *Angew. Chem. Intl. Engl. Edn.*, **7**, 14-25.
8. G. Snatzke and F. Snatzke (1973), in *Fundamental Aspects and Recent Developments in ORD and CD*, Eds. F. Ciardelli and P. Salvadori, Heydon, London.
9. D.N. Kirk (1986), *Tetrahedron*, **42**, 777.
10. E.L. Eliel (1962), in *Stereochemistry of Carbon Compounds*, McGraw-Hill. New York.
11. W.C. Johnson Jr. (1985), in *Methods of Biochemical Analysis*, vol. 31, Ed. D. Glick, p. 61, John Wiley, New York.
12. K.M. Wellman, P.H.A. Laur, W.S. Briggs, A. Moscowitz, and C. Djerassi (1965), *J. Amer. Chem. Soc.*, **87**, 66.
13. W. Klyne and D.N. Kirk (1973) in ref. 8, p. 89.
14. C. Djerassi and W. Klyne (1957), *J. Amer. Chem. Soc.*, **79**, 1506.
15. C. Djerassi and J. Staunton (1961), *J. Amer. Chem. Soc.*, **83**, 736.
16. W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi (1961), *J. Amer: Chem. Soc.*, **83**, 4013.
17. E. Charney (1979) in *The Molecular Basis of Optical Activity, Optical Rotatory Dispersion, and Circular Dichroism*, Wiley, New York.
18. W. Klyne and D.N. Kirk (1973), *Tetrahedron Letters*, 1483.
19. D.A. Lightner, T.D. Bouman. W.M.D. Wijekoon, and A.E. Hansen (1986), *J. Amer. Chem. Soc.*, **108**, 4484.
20. S.F. Mason, R.H. Seal, and D.R. Roberts (1974), *Tetrahedron*, **30**, 1671.
21. J.H. Brewster (1959), *J. Amer. Chem. Soc.*, **81**, 5475.

22. G. Lowe (1965), *J.C.S. Chem. Commn.*, 411.
23. J.H. Brewster (1961), *Tetrahedron*, **13**, 106.
24. N. Harada and K. Nakanishi (1968), *J. Amer. Chem. Soc.*, **90**, 7351; N. Harada, M. Ohashi, and K. Nakanishi, *ibid.*, **90**, 7349.; also see ref. 41
25. K. Kuriyama, T. Iwata, M. Moriyama, K. Kotera, Y. Hamada, R. Mitsui, and K. Takeda (1967), *J. Chem. Soc.* (B), 46.
26. G. Snatzke and P.C. Ho (1971), *Tetrahedron*, **27**, 3645.
27. G.G. De Angelis and W.C. Wildman (1969), *Tetrahedron*, **25**, 5099.
28. N. Harada and K. Nakanishi (1969), *J. Amer. Chem. Soc.*, **91**, 3939.
29. N. Harada and K. Nakanishi (1972), *Acc. Chem. Res.*, **5**, 257.
30. A.I. Vogel (1948), *J. Chem. Soc.*, 1833.
31. W.E. Elias (1972), *J. Chem. Educ.*, **49**, 448.
32. S.F. Mason (1988), *Biochemical Pharmacology*, **37**. 1.
33. W.A. Bonner (1988) in *Topics in Stereochemistry*, vol. 18. Eds. E.L. Eliel and S.H. Wilen, Interscience, New York.
34. E. Wigner (1927), *Z. Phys.*, **43**, 624.
35. P. Curie (1894), *J. Phys.*, **3**, III, 393.
36. T.D. Lee and C.N. Yang (1956), *Phys. Rev.*, **104**, 254.
37. C.S. Wu, E. Ambler, R.W. Hayward, D.D. Hoppes, and R.P. Hudson (1957), *Phys. Rev.*, **105**, 1413.
38. F.C. Frank (1953), *Biochim. Biophys. Acta*, ii, 459.
39. S.F. Mason and G.E. Tranter (1984), *Mol. Phys.*, **53**, 1091.
40. G.E. Tranter (1985), *Mol. Phys.*, **56**, 825.
41. W.T. Wieslar and K. Nakanishi (1989), 'A Simple Spectroscopic Method for Assigning Relative and Absolute Configuration in Cyclic 1,2,3-Triols', *J. Amer. Chem. Soc.*, **111**, 3446.
42. H. Uzawa, Y. Nishida, H. Ohrui, and H. Meguro (1990), 'Application of the Dibenzoate Chirality Method to Determine the Absolute Configuration of Glycerols and Related Acyclic Alcohols', *J. Org. Chem.*, **55**, 116; and references therein.

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