

ORGANIC STEREOCHEMISTRY

G. HALLAS

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by

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PREFACE

During the last decade or so, considerable progress has been made within the field of stereochemistry. Although recent advances have been covered in review articles and in other specialized publications aimed at graduate level, a gap exists between this treatment and that encountered in standard textbooks of organic chemistry. It is hoped, therefore, that this book will present the essentials of the subject to the undergraduate student.

Whilst the text deals mainly with modern aspects of stereochemistry, the classical background has not been neglected. Reaction mechanisms are not dealt with as such, but it would have been quite unrealistic to attempt to discuss stereochemistry without reference to fundamental organic processes. It is intended that the material will be suitable for degree, Dip. Tech., and Grad.R.I.C. courses. General references are listed at the end of each chapter. A selection of examination questions is also included.

I am especially grateful to my former Professor, Dr. Brynmor Jones, for his Foreword, to Dr. C. C. Barker (University of Hull), who stimulated my interest in stereochemistry, and to Dr. E. Tittensor (Huddersfield College of Technology), who was kind enough to read the entire manuscript, for his constructive comments and criticisms. I should also like to acknowledge my indebtedness to the original literature and to other publications, in particular Professor Eliel's *Stereochemistry of Carbon Compounds* and the series *Progress in Stereochemistry*. It is a pleasure to thank the authorities of the following for permission to quote from their examination papers: the Universities of Cambridge, Hull, Leeds, London, Manchester, Oxford and Sheffield, and the Royal Institute of Chemistry.

G. HALLAS

FOREWORD

In the last fifty years Organic Chemistry has become a vast subject. New knowledge has accumulated at what must appear an alarming rate to undergraduates and postgraduate students. For these reasons comprehensive treatises take so long to prepare that they become somewhat dated even before they can be published. But even more important is the fact that few authors can be equally knowledgeable or indeed equally interested in the various sections of the subject to write a well-balanced and up to date treatise. The day of the wide ranging and voluminous textbook may well be over and increasingly its place may be taken by a series of relatively short monographs designed specially for undergraduates.

In this introduction to *Organic Stereochemistry* Dr. Hallas has written just such a monograph. In this he has been particularly concerned to deal with the modern aspects of his subject, but the classical background has not been overlooked. This concise, lucid and well-planned account should greatly help all who wish to understand and appreciate one of the most fascinating fields of science.

BRYNMOR JONES

Vice-Chancellor
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CHAPTER 1

INTRODUCTION

1.1. Scope of Stereochemistry

Traditionally, stereochemistry is concerned with isomerism in three-dimensional space (stereoisomerism). Stereoisomeric compounds have identical structures but different spatial arrangements of the component atoms (i.e. different configurations). Classical stereochemistry deals mainly with static molecules and their geometry. Nowadays, the scope of the subject extends well beyond this treatment into the field of reaction mechanisms and vital processes. The dynamic aspects of stereochemistry are concerned with the ways in which spatial arrangements influence the behaviour of molecules during chemical reactions.

The customary stereochemical topics will be considered in this book and, although reaction mechanisms will not be dealt with as such, wherever possible the modern dynamic aspects of stereochemistry will be emphasized.

1.2. Historical Development

According to the wave theory of light, a ray of white light behaves as a transverse wave-motion. In other words, the waves of the various wave-lengths vibrate in all directions perpendicular to the direction of transmission of the beam. Monochromatic light, however, is of discrete wave-length but still vibrates in a great many different planes. In 1808 Malus discovered that it was possible to produce plane-polarized light where the vibrations are all in one plane, known as the plane of polarization. Malus found that on passing a ray of light through a calcite (a form of calcium carbonate) crystal the beam was doubly refracted to produce two emergent rays which were polarized in planes perpendicular to each other. A convenient way of producing plane-polarized light is to use a Nicol prism (named after its inventor) which is constructed by carefully bisecting a calcite crystal and cementing the two pieces together. Such a device, called a polarizer, allows only one of the polarized rays to pass through. The prism functions as though it were a slit, transmitting only those

vibrations which are parallel to the slit. Thus, if the polarized ray is viewed through a second Nicol prism, called an analyser, it will pass through with undiminished intensity only when the planes of polarization of the two prisms are parallel. Otherwise, the intensity of the beam is diminished until, when the planes of polarization are perpendicular to each other (the Nicol prisms are said to be crossed), the polarized ray fails to pass through the analyser.

The power of a substance to rotate the plane of polarization of a ray of polarized light, which is passed through it, is called optical activity. This phenomenon was first observed in 1811 by Arago and then in 1813 by Biot, a French physicist, who discovered that certain quartz crystals rotated the plane of polarized light to the right, or clockwise, whereas other quartz crystals turned it to the left, or anticlockwise. In 1815 Biot found that a similar rotation of the plane of polarization was produced by some naturally occurring organic liquids, such as turpentine, as well as solutions of certain organic solids, such as camphor. Moreover, Biot recognized a fundamental difference between these two observations. The rotation produced by quartz can be associated with a specific crystalline structure (optical activity is lost when the crystals are melted), whereas the ability of organic compounds to rotate the plane of polarization must be a property of the individual molecules because optical activity may be observed in the liquid and vapour states as well as in solution.

The mineralogist Haüy noticed that rare specimens of quartz crystals exist in two hemihedral forms which are non-superimposable mirror images of one another. Such pairs of crystals are said to be enantiomorphous and are related to each other as the right hand is to the left hand. In 1821 Herschel established that one form of crystal rotates the plane of polarized light in a clockwise direction, whereas the mirror-image form rotates the plane of polarization in the opposite direction. After an extensive study of optically active compounds (see Chapter 2), Louis Pasteur concluded, in 1860, that optical activity in molecules is caused by an asymmetric arrangement of the component atoms or groups. Pasteur also realized that there is a mirror-image relationship between molecules of the same substance which rotate the plane of polarized light to the right and to the left. Two years previously, Kekulé had introduced the concept of the quadrivalency of carbon, and then in 1874 van't Hoff and Le Bel independently and simultaneously recognized that molecular asymmetry can exist if four different groups are joined to a non-planar

carbon atom. However, it was van't Hoff who actually suggested a tetrahedral arrangement of the four valencies of carbon (see below). This idea received some experimental verification when, in 1913, Bragg demonstrated the tetrahedral distribution of carbon atoms by X-ray analysis of the diamond. Other direct physical techniques, such as electron diffraction and spectroscopy, and also theoretical considerations, confirm van't Hoff's proposal.

Quantum-mechanical calculations indicate that the four bonds which a carbon atom forms in saturated compounds arise from four equivalent sp^3 -hybrid-orbitals which are directed, at an angle of $109^\circ 28'$ to one another, towards the corners of a regular tetrahedron, the carbon atom being situated at the centre. Small deviations from the valency angle of $109^\circ 28'$ occur when the four substituents are not all the same.

1.3. Optical Isomerism

When four different atoms or groups are attached to the same carbon atom (such an atom is often said to be asymmetric), two different structural arrangements may exist, as shown in Fig. 1.1, which are

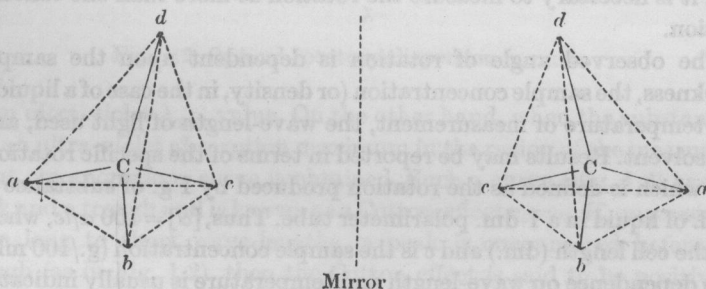


Fig. 1.1. Optical isomers of $Cabcd$.

non-superimposable but which are mirror images of each other. One of the arrangements of $Cabcd$ corresponds to the isomer which rotates the plane of polarized light to the right, and the other arrangement corresponds to the isomer of opposite rotation. If two or more of the atoms or groups attached to a carbon atom are identical, then the object and its mirror image become superimposable and optical activity is lost.

Although the majority of optically active compounds contain at least one asymmetric carbon atom, the presence of asymmetric atoms

is not a necessary condition for the existence of optical activity (see Section 1.3b).

a. Polarimetry. The actual measurement of the angle of rotation, α , of an optically active liquid, gas, or solution is carried out in a polarimeter. Essentially, a simple polarimeter consists of two Nicol prisms, one of which acts as a polarizer with the other functioning as an analyser. Between the two prisms is situated a polarimeter tube which contains the optically active substance. Polarimetric readings may be obtained by visual matching of light intensities, but a more accurate result can be obtained with a photoelectric attachment. A recent development in this field is the recording photoelectric spectropolarimeter which makes it possible to obtain values of α over a range of light wave-lengths and not at just one particular value.

A clockwise rotation of the plane of polarization, as the beam of light traverses the polarimeter tube, is produced by a dextrorotatory substance and has a positive value, whereas a laevorotatory substance gives rise to an anticlockwise rotation which has a negative value. It will be realized that no distinction will appear between rotations of $\alpha + 180n^\circ$ (where n is any integer). To obtain an unequivocal value of α it is necessary to measure the rotation at more than one concentration.

The observed angle of rotation is dependent upon the sample thickness, the sample concentration (or density, in the case of a liquid), the temperature of measurement, the wave-length of light used, and the solvent. Results may be reported in terms of the specific rotation, $[\alpha]$, which is defined as the rotation produced by 1 g. of substance in 1 ml. of liquid in a 1-dm. polarimeter tube. Thus, $[\alpha] = 100 \alpha / lc$, where l is the cell length (dm.) and c is the sample concentration (g./100 ml.). The dependence on wave-length and temperature is usually indicated by subscripts and superscripts respectively. Hence, $[\alpha]_{\text{D}}^{20}$ means the specific rotation of a substance at 20°C . measured at the wave-length of the sodium D line (589 m μ). It is also necessary to state the solvent used and the concentration ($c = \text{g./100 ml.}$). An example is $[\alpha]_{546}^{25} = +78.5^\circ$ ($c = 6.42 \text{ g./100 ml.}$, chloroform). Molecular rotation, $[M]$ or $[\phi]$, is an alternative term to specific rotation and it allows comparisons to be made between compounds of different molecular weight. The molecular rotation of a substance is simply obtained by dividing the product of the specific rotation and the molecular weight by 100 (for convenience).

The variation of optical rotatory power with wave-length, known

as optical rotatory dispersion, was recognized by Biot as early as 1817. This phenomenon can now be readily observed by means of a photoelectric spectropolarimeter which permits plots of optical rotation against wave-length to be made, down to about $210 \text{ m}\mu$. The plot obtained may be a plain curve (Fig. 1.2) where, in this case, a decrease in wave-length leads to a numerical increase in the negative optical rotation. Such a curve can often be expressed mathematically by the Drude equation, $[\alpha] = K/(\lambda^2 - \lambda_0^2)$, where λ is the wave-length at which $[\alpha]$ is observed, K is a constant, and λ_0 corresponds closely

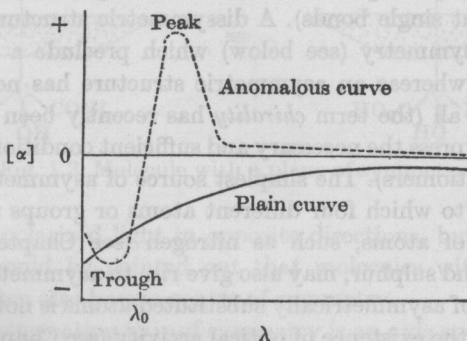


Fig. 1.2. Optical-rotatory-dispersion curves.

to an ultra-violet λ_{max} value. On the other hand, when the substance has an ultra-violet absorption maximum in the region of the measurement, an anomalous curve is obtained. Such a curve (Fig. 1.2) has a peak and a trough and is known as a Cotton-effect curve. If, on passing from long to short wave-lengths, a peak is encountered before a trough (as in Fig. 1.2), then the Cotton effect is said to be positive. When the trough is reached first, the anomalous curve is called a negative Cotton-effect curve. Clearly, Cotton-effect curves do not obey the simple Drude equation since, at wave-length λ_0 , the specific rotation would become infinite. The application of optical rotatory dispersion to configurational studies will be considered in Chapter 3.

It should be realized that the changes of specific rotation associated with temperature, solvent and concentration changes do not involve a change in configuration. These changes can often be related to changes in solvation and in the degree of association or dissociation. A change in the direction of rotation may be observed, as well as a

variation in its magnitude, but this does not imply a change in configuration. For example, the specific rotation of natural tartaric acid, $[\alpha]_D^{20}$, is $+14.40^\circ$ in water ($c = 5 \text{ g./100 ml.}$), whereas in a mixture of ethanol and chlorobenzene (1:1) it is -8.09° . Similarly, the specific rotation of aspartic acid, $\text{HO}_2\text{CCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$, changes from a positive value at room temperature to a negative value at higher temperatures.

b. Dissymmetry and Asymmetry. The necessary and sufficient condition for a molecule to show optical activity is that such a molecule should not be superimposable on its mirror image (allowing for internal rotation about single bonds). A dissymmetric structure lacks those elements of symmetry (see below) which preclude a mirror-image relationship, whereas an asymmetric structure has no elements of symmetry at all (the term *chirality* has recently been reintroduced by Cahn to express the necessary and sufficient condition for the existence of enantiomers). The simplest source of asymmetry is a single carbon atom to which four different atoms or groups are attached. Other kinds of atoms, such as nitrogen (see Chapter 8), silicon, phosphorus and sulphur, may also give rise to asymmetry. However, the presence of asymmetrically substituted atoms is not an essential condition for the existence of optical activity (see Chapters 4 and 7).

To decide whether a given molecule is optically active, superimposability may be ascertained either by constructing models of the molecule and its mirror image or by looking for symmetry elements in the molecule. A molecule that has a plane of symmetry, a centre of symmetry, or an alternating axis of symmetry is superimposable on its mirror image and cannot be optically active.

A plane of symmetry divides a molecule in such a way that the atoms or groups on one side of the plane are mirror images of those on the other side. Although tartaric acid, $\text{HO}_2\text{CCH}(\text{OH})\text{CH}(\text{OH})\text{CO}_2\text{H}$, will be considered more fully in Chapter 2, it is convenient to note here that one form of the acid is optically inactive. Clearly, the configuration shown in Fig. 1.3, *meso*-tartaric acid, has a plane of symmetry. Its mirror image is superimposable on the original molecule after it has been turned upside down. Planes and centres of symmetry are often found in alicyclic compounds (Chapter 6).

A centre of symmetry is a point such that, if a line is drawn from any group to this point and then extended an equal distance beyond the point, it meets the mirror image of the original group. The substituted diketopiperazine shown in Fig. 1.4 has a centre of symmetry

and is therefore optically inactive. At the same time, this *meso*-form may be regarded as a *trans* geometrical isomer (Section 1.4). The corresponding *cis*-isomer, in which both methyl groups are situated on the same side of the ring, is dissymmetric and consequently exists in two optically active mirror-image forms. Such non-superimposable mirror images are called enantiomorphs or enantiomers. They rotate

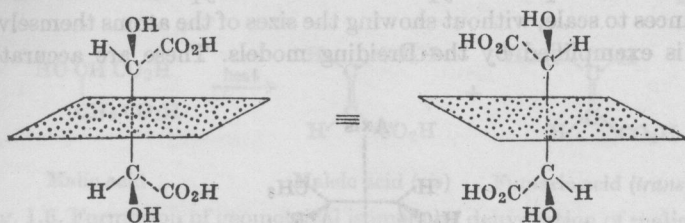


Fig. 1.3. Molecule with a plane of symmetry.

the plane of polarized light in opposite directions, but to the same extent. It should be pointed out that molecules with a plane of symmetry often also have a centre of symmetry.

An n -fold alternating axis of symmetry is an axis such that, when the structure possessing this axis is rotated through an angle of $2\pi/n$ about the axis and then reflected across a plane perpendicular to the axis, an identical structure results. Until fairly recently, no compound was known in which the optical inactivity was due solely to

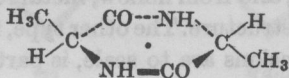


Fig. 1.4. Molecule with a centre of symmetry.

the existence of an alternating axis of symmetry. In 1955 McCasland and Proskow prepared the *N*-spiro-compound (Section 7.3) shown in Fig. 1.5. This molecule, which does not have a plane or a centre of symmetry, is optically inactive because it contains a four-fold alternating axis of symmetry. Thus, the mirror image becomes identical with the object after a rotation of 90° about the axis, followed by reflection across the plane through the N atom (Fig. 1.5). The structure of the molecule is considered in some detail in Chapter 8.

It should be mentioned that the presence of an alternating axis of symmetry is sufficient to prevent optical activity inasmuch as a plane

of symmetry is equivalent to a one-fold alternating axis and a centre of symmetry corresponds to a two-fold alternating axis.

Frequent reference to three-dimensional models leads to a better understanding of stereochemistry. The student is strongly urged to construct his own molecular models as often as possible. Apart from the simple ball-and-stick type models, which are the least expensive, there are two important types of models. One type shows interatomic distances to scale, without showing the sizes of the atoms themselves, and is exemplified by the Dreiding models. These are accurately

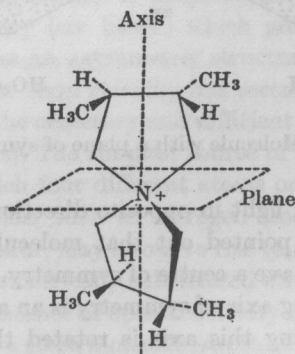


Fig. 1.5. Molecule with a four-fold alternating axis of symmetry.

constructed from solid, and from hollow, metal rods and are best used to illustrate molecular structure. The other type, in which both atomic and interatomic dimensions are to scale, is particularly useful when it is necessary to know whether certain atoms or groups in a given structure interfere with one another. Catalin models are of this type, the atoms, made of a phenolic resin, being joined together by rubber pegs.

1.4. Geometrical Isomerism

The type of spatial isomerism known as geometrical isomerism was recognized by van't Hoff, although his conception of a double bond as being formed by a pair of tetrahedra joined at two corners has been superseded in modern orbital theory (Chapter 5). At the time, there were no instances of such isomerism although it had long been known that malic acid loses water readily when heated to give two substances, maleic acid and fumaric acid (Fig. 1.6). In 1838 Liebig established