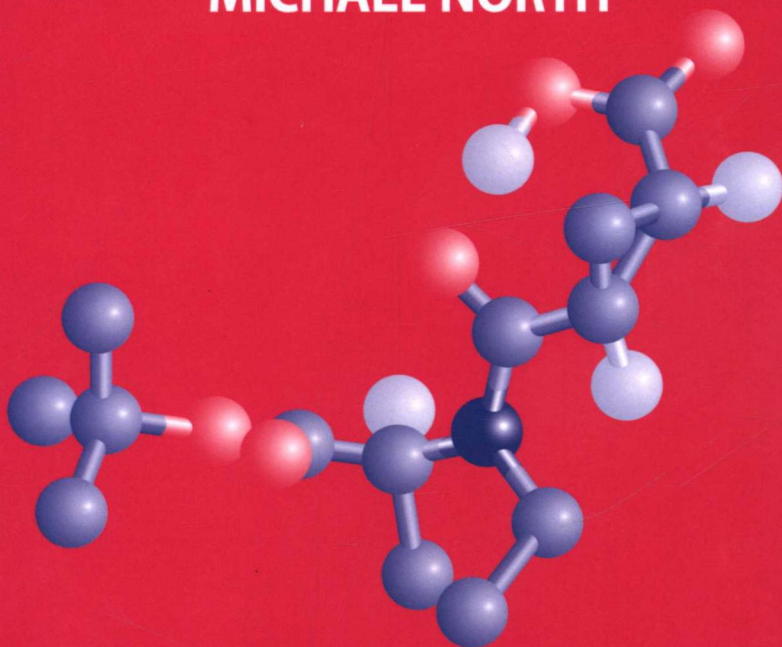


Principles and Applications of Stereochemistry

MICHAEL NORTH



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Stereochemistry is a topic of fundamental importance in chemistry. Thorough understanding of the topic is essential in the comprehension of almost all aspects of modern organic chemistry. Similarly, it is crucial in many biochemical and medicinal disciplines, since the stereoisomers of a compound can have dramatically different biological properties. This book explains how these different properties arise, and what processes can be used to prepare and analyse stereoisomerically pure compounds. The stereochemistry of inorganic and organometallic compounds is a topic which is largely neglected in many undergraduate chemistry courses, but which is likely to increase in importance as these compounds are used as symmetric catalysts in asymmetric synthesis. This aspect of stereochemistry is therefore given prominent coverage.

Throughout the text the most modern stereochemical terminology is used, though reference is also made to other stereochemical descriptors so that the reader will be able to understand older terms which are still widely used. A set of problems at the end of each chapter will further the reader's understanding of how the content can be applied.

Mainly designed as a textbook for undergraduate students and useful reference source for more advanced levels, this book will also be attractive to both academic and professional organic chemists.

Michael North is Senior Lecturer in Organic Chemistry at the University of Wales, Bangor, UK. He has published widely on the stereochemistry of organic compounds and reactions, and is the author of over 50 original publications dealing with conformational analysis and asymmetric synthesis.



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Principles and Applications of Stereochemistry

Foreword

The shapes of molecules control almost every aspect of our lives. They dictate the differences in taste between spearmint chewing gum and caraway seed cake; the difference in elasticity between a rubber band and the gutta percha coating of a golfball and between the toxicity and therapeutic benefit of a drug. Ultimately, they control our heredity.

Since Pasteur's experiments in the 1840s laid the foundations of modern stereochemistry, a huge amount of sophisticated research has been carried out and with it has grown the necessary and complicated jargon required to express the symmetry of molecules and the spatial relationships between the groups that they possess.

Dr North's book has been designed to introduce this area of chemistry to the stereochemical novice and to lead the student with plenty of diagrams and cross referencing from the simplest molecular form to quite sophisticated understanding of topics such as diastereotopicity and catalytic asymmetric synthesis.

Dr North rightly does not flinch from including discussion of energy differences which determine the shapes and ground state populations of flexible and cyclic molecules and he makes constant use of spectroscopic and other quantitative information which not only illuminates his material but has the invaluable add on of making connections to other aspects of molecular behaviour and molecular construction.

E.L. Eliel's volume *The Stereochemistry of Organic Compounds* is the current reference book in this field but at more than 1200 pages does not claim to be a handy student text. Dr North's book fills a wider gap more succinctly and it will be of great value to students from the start of their university courses as well as to their teachers. The inclusion in each chapter of a set of problems is an essential device for checking the understanding of the text and a good set of models will encourage the familiarity essential for a confident grasp of this vital aspect of chemistry.

C.J.M. Stirling, FRS

Preface

Stereochemistry is the relationship between the three dimensional shape of a molecule and its chemistry. It is a topic that falls between the three classical subdivisions of chemistry into organic, inorganic and physical chemistry. Most of the subject is usually taught as part of an organic chemistry course, with molecular symmetry often being split off into a separate physical chemistry course. The stereochemistry of inorganic compounds has been largely neglected in undergraduate chemistry courses, although this is now changing mainly because of the widespread use of organometallic compounds as catalysts for organic reactions. Thus in this text I have tried to bring together the organic, inorganic and physical chemistry aspects of the subject. The book is still dominated by the stereochemistry of organic compounds but the coverage of inorganic stereochemistry probably exceeds the content of most current undergraduate courses.

This book has its origin in a 10 lecture course given to undergraduate chemistry students at the University of Wales, Bangor. Increasingly, students are coming to university to study chemistry and related subjects without having studied mathematics in the preceding years. It is the need to present the topic in as non-mathematical a way as possible that has largely determined the order in which the material is presented. Thus Chapters 1 to 5 are essentially descriptive and require no mathematical ability beyond multiplication and division. The relationship between stereochemistry, symmetry, and group theory is thus delayed until Chapter 6, by which time the reader should have a thorough understanding of the key stereochemical concepts and of why stereochemistry is important. The first eight chapters deal with the stereochemistry of individual molecules and the final two chapters then expand this to show how a knowledge of stereochemistry can be used to predict the outcome of a variety of chemical reactions.

Stereochemistry is sometimes perceived as being a dry and boring aspect of chemistry, probably because of the number of arbitrary definitions and conventions that are associated with stereochemical nomenclature and representations. Throughout this book I have tried to counter this by including numerous real life examples of the applications of stereochemistry, and by including topics such as the origin of enantiomerically pure compounds in nature that would not normally be covered in an undergraduate course. Numbers are used in many different contexts in stereochemistry, and to avoid confusion I have adopted a system of using numbers in a shadow font (*1*, *2*, *3* etc.) to number atoms according to chemical nomenclature, and numbers in a standard font for stereochemical purposes. Much of stereochemistry is concerned with the three

dimensional arrangement of groups. This is often not easily seen in two dimensional representations and the reader would be well advised to purchase a ball and stick type molecular modelling kit such as the inexpensive ORBIT kit. This will allow a three dimensional model of any of the structures discussed in this book to be constructed rapidly, and will greatly aid both the visualization and understanding of the material.

At the end of each chapter, I have included a list of sources of further information which, wherever possible, are books or reviews. A particularly useful, comprehensive and up to date more advanced text is Eliel's *Stereochemistry of Organic Compounds*, and the first reference at the end of each chapter will direct the reader to the appropriate chapter(s) of this book. Also at the end of each chapter are a series of problems based on material covered in the chapter. These problems are of two types: the first being drill type questions usually concerned with arbitrary aspects of nomenclature that can only be memorized by practice. The second type of question are more problem based and designed to test understanding of, and ability to apply, the material covered in the chapter. Answers to these questions have not been included since I feel that this makes it too tempting for students to look at the answers and decide that they could have answered the question without actually doing so. Answers to all of the problems, along with explanations of the answers and two and three dimensional colour versions of many of the diagrams, are, however, available via the internet. Links to the appropriate web pages will be found at: <http://www.bangor.ac.uk/ch/mnhome.htm>.

This book is not a comprehensive coverage of all of chemistry so it has been assumed that the reader has some previous chemical knowledge. In particular, to get the most out of this book, the reader should have previously studied chemical bonding (valence bond and molecular orbital approaches), basic organic reactions, and interpretative NMR spectroscopy. However, where topics such as these which are not immediately related to stereochemistry are required in the text, then a brief review of the area is given and references to further reading are included at the end of the chapter.

A number of my colleagues in Bangor (Professor M.S. Baird, Dr P.K. Baker and Dr J.N. MacDonald) along with external reviewers have assisted in the preparation of this book by reading all or part of the manuscript at various stages of completion and making helpful suggestions as to its improvement. I thank them for their efforts in removing errors from the text, and accept responsibility for any remaining typographical or scientific errors. It would, however, be greatly appreciated if readers could let me know if they find any errors so that these can be corrected in future versions of the book.

Michael North, CChem FRSC
Bangor 1997

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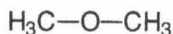
1 Molecular structure and bonding

1.1 Isomerism

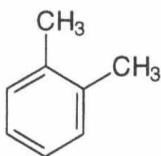
Isomers are different compounds that share the same molecular formula. Common examples include ethanol **1.1** and dimethyl ether **1.2**, both of which have the molecular formula C_2H_6O ; and 1,2-dimethylbenzene **1.3**, 1,3-dimethylbenzene **1.4**, and 1,4-dimethylbenzene **1.5**, all of which share the molecular formula C_8H_{10} . In both of these cases, the connectivity of the atoms is different, i.e. in compound **1.1** the order in which the carbon and oxygen atoms are bonded is C–C–O, whilst in **1.2** the order is C–O–C. Because they differ in the connectivity of their atoms, compounds **1.1** and **1.2** are said to be constitutional isomers (also sometimes called structural isomers), as are compounds **1.3–1.5**.



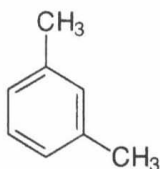
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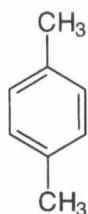
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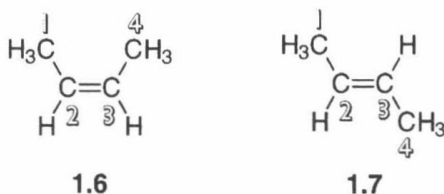


1.5

Constitutional isomers have different chemical and physical properties. This is markedly apparent in the case of isomers **1.1** and **1.2**, since ethanol is a liquid at room temperature and undergoes all the chemical reactions that would be expected for a primary alcohol (dehydration to an alkene, oxidation to an aldehyde or acid etc.). Dimethyl ether **1.2** on the other hand is a gas at room temperature and is unaffected by the reaction conditions and reagents used to dehydrate or oxidize ethanol. This difference in reactivity is to be expected since the two compounds contain different functional groups.

Isomers **1.3–1.5** are more closely related since they contain the same functional groups (two methyl groups attached to a benzene ring), and differ only in the relative positions of these functional groups. Such isomers are often called

positional isomers, but note that positional isomerism is a subclass of constitutional isomerism. Once again the three isomers have different physical properties, for example the boiling points are 144°C, 139°C and 138°C for **1.3**, **1.4** and **1.5** respectively. In general, these three isomers will undergo the same types of chemical reaction (benzylic oxidation for example), but will do so at different rates, again illustrating their different chemical properties.



There is, however, another type of isomerism, one in which all of the atoms in the two isomers **do** have the same connectivity. A familiar example is found in 1,2-disubstituted alkenes such as compounds **1.6** and **1.7**. In both of these isomeric compounds, the order in which the carbon atoms are joined together is C1–C2=C3–C4 and the only difference between them is that in isomer **1.6** the two methyl groups are on the same side of the double bond, whilst in isomer **1.7** the two methyl groups are on opposite sides of the double bond. Any pair of isomers which have the same connectivity of their atoms but which differ in the relative orientation of those atoms are called **stereoisomers**.

Stereoisomers are the topic of this book and the following chapters will investigate the different structural features which are responsible for stereoisomerism, and discuss the chemical, biological and physical consequences of the formation of stereoisomers. Both organic and inorganic compounds can exhibit stereoisomerism, and examples of each will be found throughout this book. Essentially, stereochemistry is concerned with the shapes of molecules, and the consequences of a molecule adopting a particular shape.

Later in this chapter, the way in which the shape of a molecule may be predicted using Valence Shell Electron Pair Repulsion Theory (VSEPR) will be introduced, and the nature of the bonding found in the most common chemical structures will be discussed. At the end of this chapter, the various classifications of stereoisomers will be introduced and these will be discussed in more detail throughout the remainder of this book. However, many of the structures seen later in this chapter are three dimensional, and before they are discussed it is necessary to understand the conventions used when representing three dimensional structures on a two dimensional piece of paper.

1.2 Drawing three dimensional chemical structures

Chemistry is dominated by two structures: the tetrahedron and the octahedron. A tetrahedral structure is found whenever a carbon atom is bound to four groups via four single bonds, whilst many transition metal complexes are octahedral.