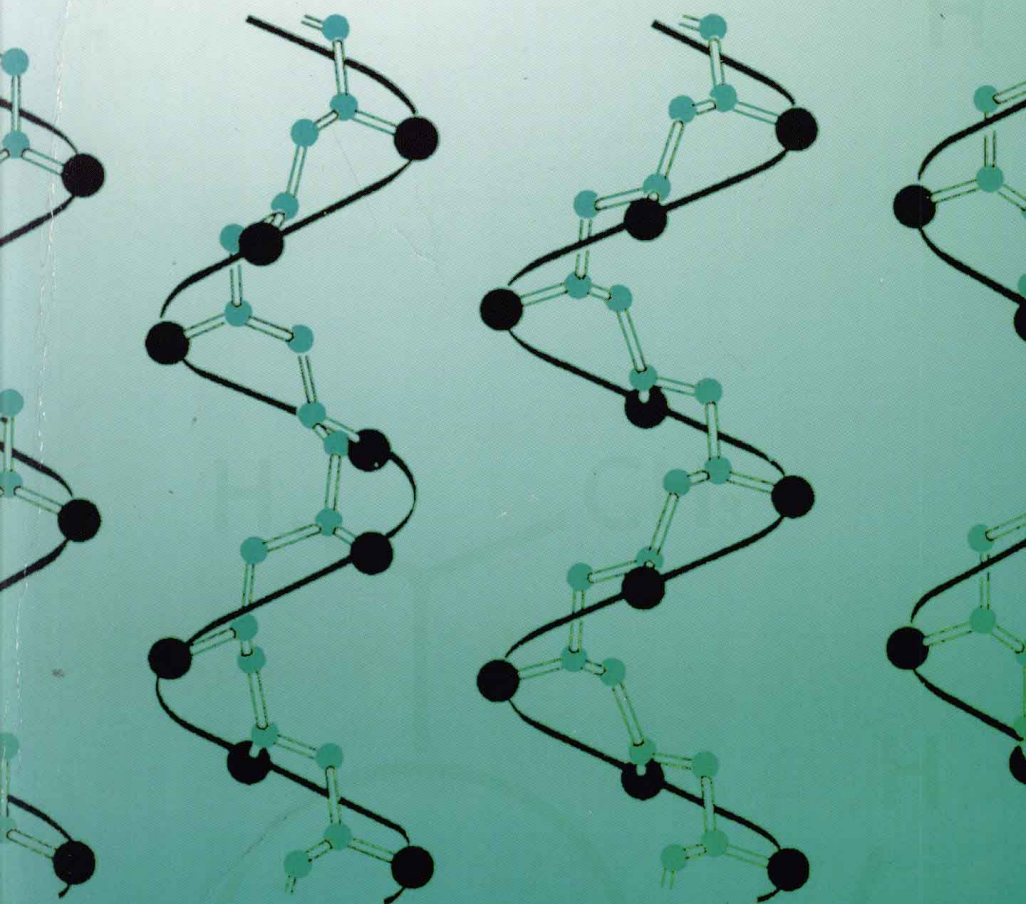


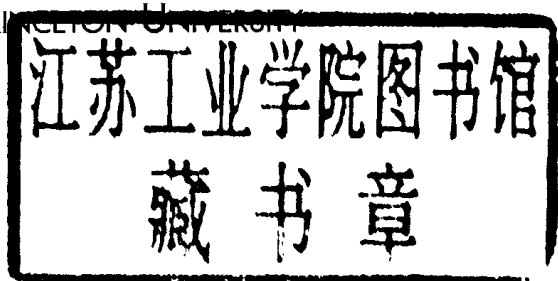
Introduction to Stereochemistry

KURT MISLOW



INTRODUCTION TO STEREOCHEMISTRY

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▪ PREFACE TO THE DOVER EDITION

This book was written in response to the need for a textbook whose chief mission would be to teach that symmetry and chirality are at the heart of stereochemistry. At that time, nearly forty years ago, this subject was mainly taught within a largely empirical and pragmatic framework. With a few laudable exceptions, little if any attention was paid in the textbook literature to the underlying vital connection between chemical structure and symmetry.

To remedy this situation, I employed symmetry elements and point groups in a systematic fashion, a first for organic chemists who had never before been exposed to this approach in stereochemistry textbooks. A classification of asymmetric syntheses and kinetic resolutions provided a novel organizational basis for these processes, whose relevance today is significantly highlighted by the demand of the pharmaceutical industry for enantiopure drugs. Symmetry arguments, which have a distinguished history in stereochemistry, were applied wherever appropriate. In 1848, Louis Pasteur demonstrated the existence of a causal relationship between the handedness of hemihedral sodium ammonium tartrate crystals and the sense of optical rotation of the tartrates in solution. This discovery, which marks the beginning of modern stereochemistry, connected enantiomorphism on the macroscopic scale to enantiomorphism on the molecular scale and thus led to Pasteur's brilliant insight that the optical activity of the tartrates is a manifestation of "dissymétrie moléculaire," or molecular

chirality. Well before the advent of structural theory and the asymmetric carbon atom of Jacobus Henricus van't Hoff, Pasteur recognized that the chiral arrangement of atoms in the molecule is the sole necessary and sufficient condition for enantiomorphism and for its manifestation as optical activity. No recourse to structural theory was needed to arrive at this conclusion, which was based purely on a symmetry argument.

The power of symmetry arguments in stereochemistry is truly formidable. They allow one to predict, for example, that asymmetric molecules of the type Cabcd should have six different bond angles; that carbenium ions in asymmetric molecules are expected to be nonplanar; that symmetry-nonequivalent nuclei should be shifted relative to one another; that there must be a barrier to rotation in ethane; and that chiral products are necessarily produced in the course of asymmetric syntheses and kinetic resolutions. Detailed structural or reaction-mechanistic information is completely unnecessary to arrive at these conclusions; such information is required only where there is a need to determine the direction and magnitude of these effects.

The new book also revisited fundamental aspects of stereoisomerism, including a thorough reexamination of basic definitions. For example, standard textbooks of stereochemistry, even in the early 1960s, defined diastereomers as stereoisomers some or all of which are chiral, but that are not enantiomers. Thus, in accord with this definition, the achiral *cis* isomer of 1,2-dimethylcyclopropane and the chiral *trans* isomer are diastereomers. But the all-*cis* isomer and the *trans* isomer of 1,2,3-trimethylcyclopropane are both achiral. According to the conventional textbook definition of the time, these two isomers could therefore not be diastereomers, yet they are obviously not enantiomers. This and similar inconsistencies are readily resolved by defining diastereomers as stereoisomers that are not enantiomers. Enantiomers are related by symmetry and have exactly the same scalar properties, whereas diastereomers are not related by symmetry and differ in all scalar properties; the only significant distinction between diastereomers and constitutional isomers is that the former have the same constitution (bonding arrangement). This classification, whose compelling logic was not generally appreciated at the time, is now universally accepted.

Stereochemical terminology has been evolving over the years, and Pasteur's "dissymmetry" has been replaced by "chirality." Although this book was the first to introduce the term "chirality" into the chemical textbook literature, Pasteur's terminology was retained for the

most part. No confusion can possibly result, since “dissymmetric” and “dissymmetry” are synonymous with “chiral” and “chirality,” terminology introduced by Lord Kelvin in 1893. The present book also introduced the idea of enantiomeric and diastereomeric groups (nuclei, atoms, faces) in the context of nuclear magnetic resonance (NMR) chemical shifts and enzymatic reactions. In 1967 we reformulated these ideas in the language of topicity, i.e., as enantiotopic and diastereotopic groups. These novel concepts have since been adopted in all organic textbooks.

In the years since this book was written, stereochemistry experienced an enormous intellectual growth and also found widespread industrial application. At the beginning of the new century, stereochemistry has come of age: it is now a mature branch of the chemical sciences, with principles that are solidly grounded and concepts that are well understood. Perhaps this book played a small part in this development: by delineating some of the theoretical underpinning of modern stereochemistry, it changed the way that people thought about this subject.

I believe that this slim volume continues to fill a special role in acquainting the reader with the intellectual beauty of stereochemistry. The exercises, a helpful adjunct to the text that sets this book apart from other stereochemistry textbooks, are intended to further stimulate the reader's interest and broaden an understanding of the subject.

KURT MISLOW

Princeton, N.J.
November 2001

■ PREFACE

MOLECULAR SHAPE, form, and symmetry play a central role in organic chemistry. This book is designed as a short introduction to the conceptual basis of stereochemistry. Emphasis has been placed on the fundamentals of *structural* stereochemistry, as distinct from the dynamic aspects that are more appropriately discussed in the context of reaction mechanisms.

The book is divided into three major sections, dealing with (1) structure and symmetry, (2) stereoisomerism, and (3) the separation and configuration of stereoisomers. The following paragraphs briefly touch on some features of the contents.

In the first section, the student is provided with some feeling for molecular architecture. We consider the ways in which the coordination number of carbon determines bonding geometry and then develop the subject by relating empirical bonding geometries to the hybridization of the central carbon atom. The concept of hybridization, certainly no more than a convenient mathematical fiction, has nevertheless permeated much of the recent literature, and I have included it here without presenting alternative and more "physical" views. This task could be left to the lecturer. The student is introduced at the very beginning to a nonrigorous treatment of symmetry elements and later to point groups, with particular emphasis on the presence or absence of reflection symmetry. I be-

lieve that this approach is most appealing from the point of view of the organic chemist. Following an excursion into the consequences of molecular deformations (as expressed by the relation between changes in geometry and the accompanying changes in energy), the first section is concluded with a brief discussion of the usefulness and limitations of molecular models.

In the second section, I have adopted the view that stereoisomers are most conveniently classified according to (1) symmetry properties and (2) the nature of the barriers that separate the stereoisomers. Consequently, some of the old terms have been given broader meanings (e.g., diastereomer) while others have been given wide berth (e.g., optical isomer). Stereochemistry is an old science (Louis Pasteur was its first practitioner) and terminology has not kept pace with the development of substantive matter. In the present treatment, new terminology and coinages have been freely introduced. In this section, I have also discussed at some length the dependence of optical activity on structure because I believe that this relationship (or at least some features thereof), despite its essential complexity, can in many cases be qualitatively discussed in terms of the powerful viewpoint introduced by A. Moscovitz and W. Moffitt. The second section concludes with a discussion of topological isomerism. The tenets of conformational analysis, introduced early in the book, are applied throughout.

In the third section, I have tried to emphasize the conceptual basis of asymmetric syntheses and kinetic resolutions, and I have classified these reactions in a way that will aid in the systematic exposition of the subject material.

The exercises appended to each of the major sections are designed not only to test understanding of the preceding material but, through the inclusion of new subject matter, to advance the student beyond the descriptive material. Accordingly, the exercises are an integral part of the text; answers are provided.

Because a more complete coverage of the subject has not been possible, many ideas have been presented in abbreviated and simplified form. The student who wishes to go beyond this book is referred to the texts and articles given in the Bibliography at the end of this book.

It is a pleasure to acknowledge the help and stimulation received over the years from my colleagues at New York University. I also owe a debt of gratitude to Professor Jerome A. Berson, who read

the whole manuscript and gave me the benefit of his criticism; many of his suggestions have been incorporated in the final version. I am obliged to Professor Hans Wynberg for permission to include his unpublished results on ethylpropylbutylhexylmethane. Dr. Arnold J. Gordon kindly helped in the critical proofreading of the manuscript.

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Princeton, N.J.
September 1964

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▪ STRUCTURE AND SYMMETRY

1-1 Introduction

MOLECULAR *structure* is a description of the arrangement or distribution of particles in a molecule. We shall elaborate this definition by explaining our use of the terms *description* and *particles*.

A description may take many forms. It may be verbal, or it may be visual—as, for example, through the use of molecular models. The most accurate descriptions are also the most complex: These are the equations which describe the motion of the particles as a function of time and spatial position.

There are two kinds of submolecular particles which are of interest to the organic chemist: the electrons and the nuclei. Wave-mechanical arguments lead to a description of electronic structure as a probability distribution of negative charge, i.e., as a smeared-out charge density cloud. In contrast, the distribution of nuclei in space may be discussed more nearly in classical terms, i.e., we may think of nuclei as particles which vibrate with a very small amplitude around well-defined average positions in space. These vibrations are completely analogous to the quivers executed by two weights connected by a spring: the coulombic and exchange

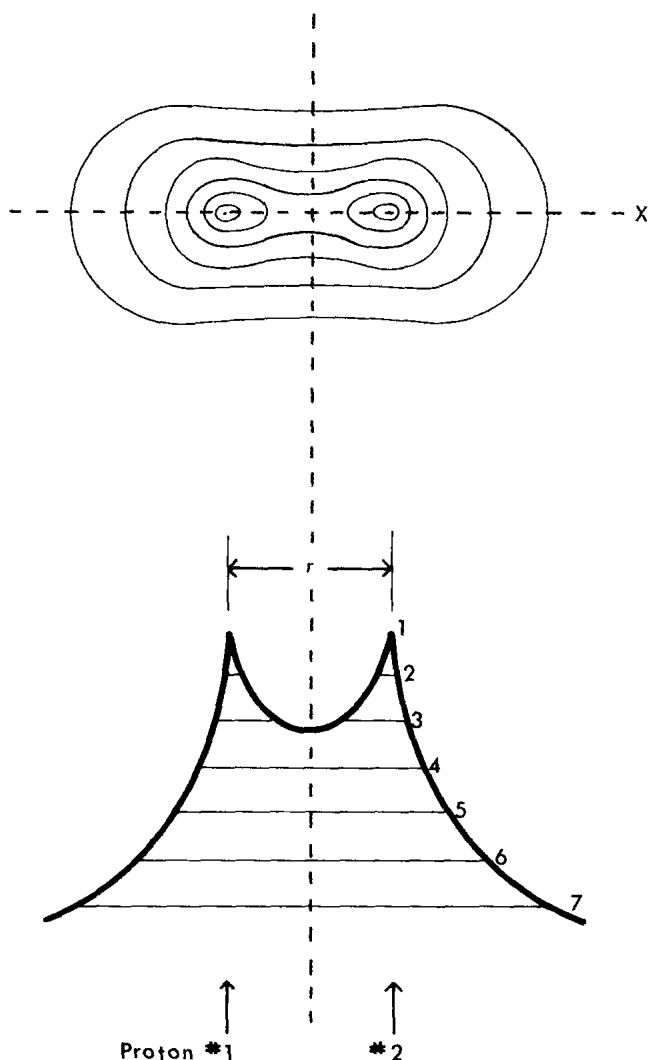


FIGURE 1-1

Schematic representation of electron probability contours in the hydrogen molecule. Electronic charge density decreases in the order $1 > 2 \dots > 7$. Bond length = r . Internuclear axis = x . Above: plane of symmetry through molecule = cross section. Below: plot of electron density against distance along x .

forces in the molecule simply take the place of the mechanical restoring force in the spring.

Compared to organic molecules, the hydrogen molecule is an extraordinarily simple one (in fact, except for its positive ion $[H_2^+]$,

it is the simplest polyatomic molecule conceivable). It might therefore be appropriate to begin our discussion of structure and symmetry by analyzing the case of the hydrogen molecule. In the formation of that molecule, two protons and two electrons have been brought together. The electrons distribute themselves so that the position of the protons assumes an equilibrium value. This distribution of protons and electrons is indicated in Figure 1-1, which shows a cross section of the molecule made by a plane which contains the nuclei. This plane shows contour lines of equal electronic charge density, and the three-dimensional contour surfaces may be developed by rotation around the internuclear line x . Note that well-defined positions are assigned to the protons, whereas the electrons can only be described in terms of the over-all charge density. The molecule may be pictured as a roughly cigar-shaped region of electron density within which the two protons are buried. As shown by the contour lines, the density is highest at points on the x -axis corresponding to the positions of the nuclei, falls off at all distances, but remains high in the region between the nuclei. This region of electron localization between the nuclei coincides in direction with the internuclear line. The outermost contour line shown in diagrams such as these is conventionally chosen to enclose in the neighborhood of 95% of the electron cloud, that is: the probability of finding the electron or electrons within the outermost contour is about 95%.

This description of the distribution of two electrons in the field of the two protons corresponds to the bonding molecular orbital (MO) of hydrogen molecule.

The protons jiggle about but maintain an equilibrium distance r , the *bond length*. The bond length (10.74 Å in this case) refers to the molecular configuration of the vibrating system at a potential energy minimum. The potential energy of the molecule is raised whenever the bond is stretched (say to 10.75 Å) or compressed (say to 10.73 Å), very much as in the analogous case of the two vibrating weights connected by a spring.

We shall now consider symmetry in simple molecules. Every molecule may be classified according to its symmetry, and each particular symmetry class is characterized by the number and type of *symmetry elements* present in such a molecule. For our immediate purposes, the most important such elements are *planes of symmetry*, symbolized by σ , and *simple* (or *proper*) *axes of rotation of order n* (*n -fold axes of symmetry*), symbolized by C_n .

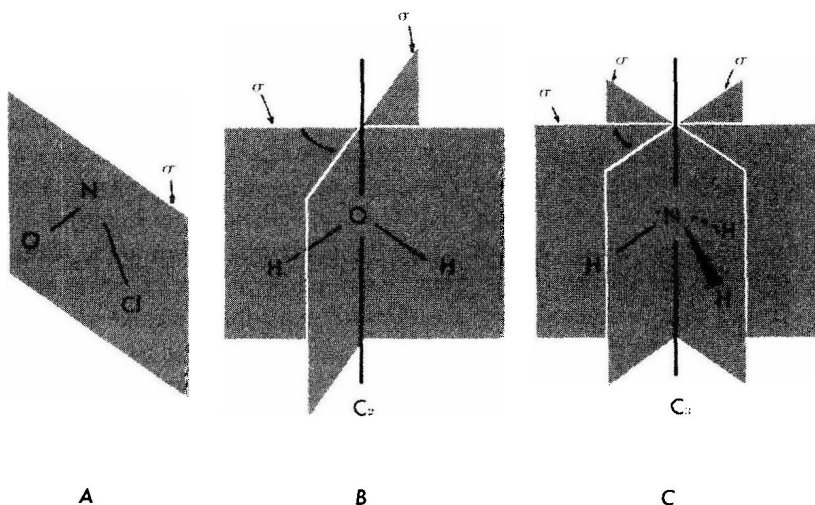


FIGURE 1-2

A molecule with a single plane of symmetry: nitrosyl chloride (A). Two molecules with single axes of symmetry: water (B) and ammonia (C). One of the dihedral angles is shown.

A σ plane is defined as a mirror plane which bisects a geometric figure so that the half of the figure on one side of the plane is exactly mirrored by the half on the other side. Objects like idealized forks, spoons, hammers, and cups have just one plane of symmetry, and so do molecules like nitrosyl chloride (Figure 1-2), bromocyclopropane and vinyl chloride. A C_n axis is defined as an axis which passes through the molecule so that, by a rotation of $360^\circ/n$ around this axis, a three-dimensional arrangement is obtained which is indistinguishable from the original. For example, water has a twofold axis of symmetry and ammonia a threefold axis, as indicated in Figure 1-2. It is important to note that planes and axes of symmetry are often both encountered in the same molecule. For example, while nitrosyl chloride does not have an axis of symmetry (the trivial one-fold axis C_1 is never considered), water and ammonia have, respectively, two and three planes of symmetry (Figure 1-2) which intersect at the C_n axis. The angles between the planes, the *dihedral angles*, have the values 90° and 60° for water and ammonia, respectively.

Let us now apply a similar analysis to the case of the hydrogen molecule. It is readily seen (Figure 1-3A) that there exists an

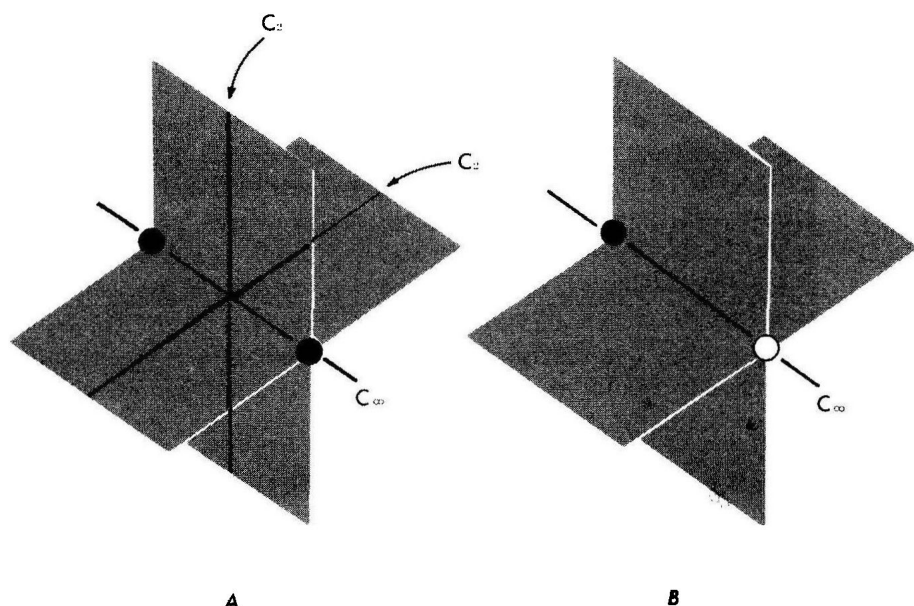


FIGURE 1-3

Some symmetry elements in diatomic molecules. Molecules with cylindrical symmetry have an infinite number of planes of symmetry σ (two are shown) which intersect at the internuclear axis C_{∞} (A), and the same is true of molecules with conical symmetry (B). Cylindrically symmetrical molecules also have a plane of symmetry perpendicular to C_{∞} which contains an infinite number of twofold axes C_2 , two of which are shown in A.

infinite number of σ planes which are identical with the cross section shown in Figure 1-1 and which intersect at the internuclear axis. This axis, which is called the *cylindrical axis*, is also C_{∞} because an infinitesimal rotation suffices to transform the new position into one indistinguishable from the original. In addition to the above-mentioned planes there also exists a σ plane which is perpendicular to the internuclear axis, which bisects the molecule, and which contains an infinite number of C_2 axes. Molecules such as oxygen and carbon dioxide have that kind of symmetry which is called *cylindrical symmetry*. Objects such as idealized hourglasses, footballs (American), and doughnuts also have cylindrical symmetry. *Conical symmetry* is a closely related kind of axial symmetry. In molecules possessing conical symmetry, e.g., hydrogen chloride, there also exists an infinite number of σ planes which inter-