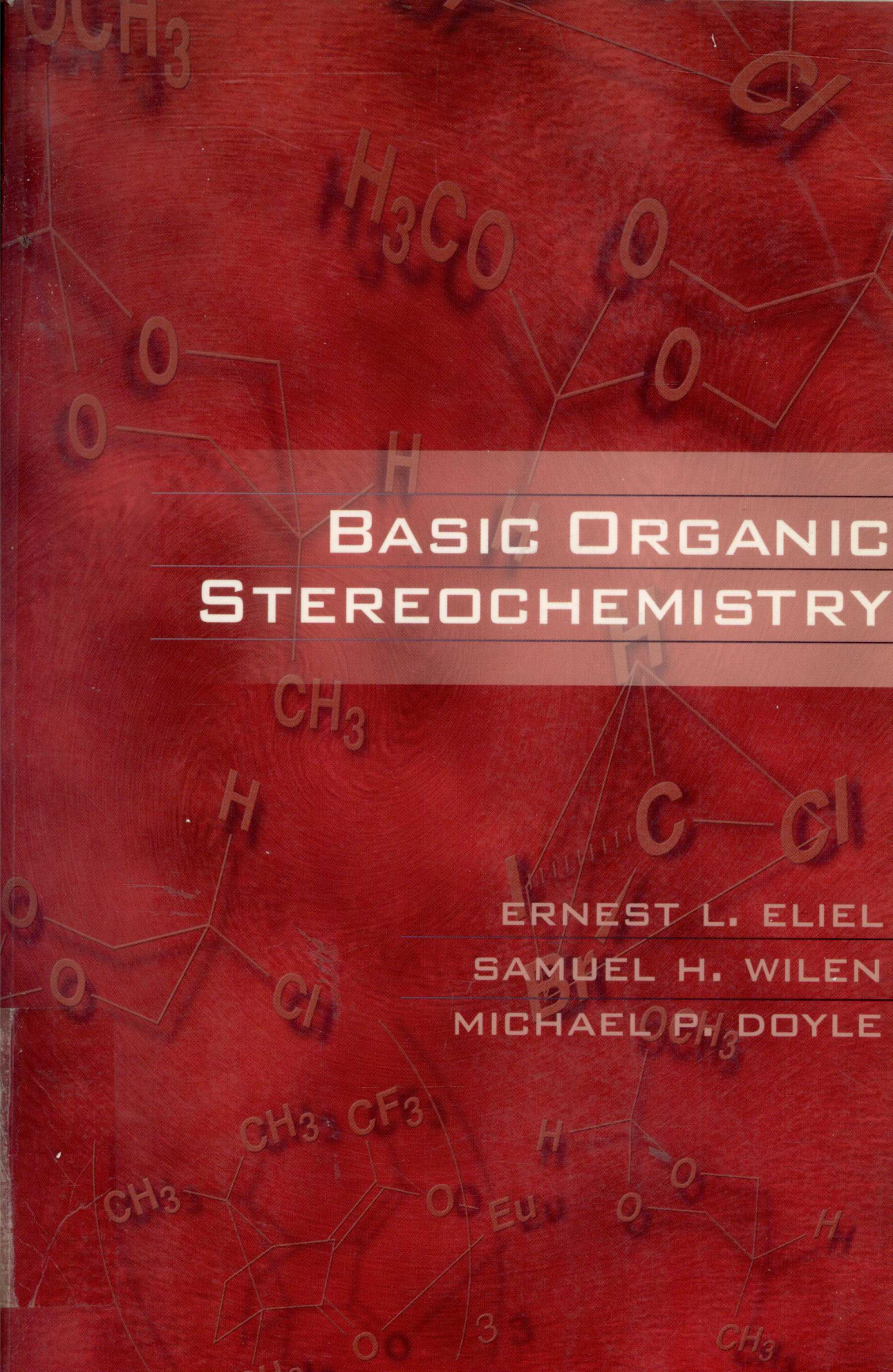

Basic Organic Stereochemistry

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BASIC ORGANIC STEREOCHEMISTRY

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PREFACE

In 1994 John Wiley & Sons, Inc. published *Stereochemistry of Organic Compounds* co-authored by one of us (E.L.E) with the late Samuel H. Wilen, with a chapter on stereoselective synthesis by Lewis N. Mander. This comprehensive volume was well received in spite its length of 1267 pages. The book serves well as a reference text and a refresher resource for established chemical scientists, and also as a reliable source of stereochemical information for graduate students, but seems too extensive to be used in a semester course. Yet stereochemical thinking is increasing in importance not only in the core area of chemistry, but also in the more recently developed areas of molecular science, such as in materials chemical science and chemical biology. Thus a systematic training in the often-perplexing area of stereochemistry is more than ever necessary, both at the advanced undergraduate and the at the beginning graduate level.

The present volume represents a substantially abbreviated version of the 1994 book, to nearly half of its original length, making it more suitable for teaching the subject at the college level. To achieve the reduction, we have had to omit the chapter on stereoselective synthesis by Professor Mander, not only because of its original size, but also because that particular area of stereochemistry has so grown in the last six years that an adequate chapter would no longer fit into the confines of a general stereochemistry text. (A number of books in this area have appeared since 1994, including a three-volume series dating from 1999.) We have also omitted the glossary since a glossary has now been issued by IUPAC (see Ref. 1 in Chapter 2); moreover, pertinent terms can be traced through the index. We have also omitted most of the original text that was set in smaller font, and we have substantially condensed all other material. We hope and trust, however, that the essential tenets of stereochemistry have been preserved.

Most of the citations have been taken from the 1994 book, although in a few areas of rapid development they have been supplemented with more recent references. We acknowledge that with the availability of such a large body of references, we have succumbed to the temptation to include more citations than is usual in a textbook; in doing so we have given preference to review articles and books. The references may be of use when the teacher wishes to assign a detailed study of a particular area to individual students, or when the topic forms the basis of a separate seminar.

If, when using this book in the classroom, a choice of topics has to be made, we recommend Chapters 1–6, 8–10, and selective material from Chapter 11. The students can read Chapter 7 independently and Chapters 12 and 13 are of a more advanced nature. This book may serve a specific course on stereochemistry or may assist in the development of major components in an even broader subject sequence. The text will be a valued resource in enabling students to understand critical elements in stereochemical concepts, ideas, analysis, techniques, terminology, and history.

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INTRODUCTION

1-1. SCOPE

Stereochemistry (from the Greek *stereos*, meaning solid) refers to chemistry in three dimensions. Since most molecules are three-dimensional (3D), stereochemistry, in fact, pervades all of chemistry. It is not so much a branch of the subject as a point of view, and whether one chooses to take this point of view in any given situation depends on the problem one wants to solve and on the tools one has available to solve it.

There is little question that, today, the third dimension has become all-important in the understanding of problems not only in organic, but in physical, inorganic, and analytical chemistry as well as biochemistry, so that no chemist can afford to be without a reasonably detailed knowledge of the subject.

It has become customary to factorize stereochemistry into its static and dynamic aspects. *Static stereochemistry* (perhaps better called stereochemistry of molecules) deals with the counting of stereoisomers, with their structure (i.e., molecular architecture), with their energy, and with their physical and most of their spectral properties. *Dynamic stereochemistry* (or stereochemistry of reactions) deals with the stereochemical requirements and the stereochemical outcome of chemical reactions, including interconversion of conformational isomers or topomers (cf. Chapter 2); this topic is deeply interwoven with the study and understanding of reaction mechanisms. Like most categorizations, this one is not truly dichotomous and some subjects fall in between; for example, quantum mechanical treatments of stereochemistry may deal with either its structural or its mechanistic aspects; spectroscopic measurements may fathom reaction rate as well as molecular structure.

1-2. HISTORY

Historically, the origins of stereochemistry stem from the discovery of plane-polarized light by the French physicist Malus[1] in 1809. In 1812 another French scientist, Biot,[2] following an earlier observation of his colleague Arago,[3] discovered that a quartz plate, cut at right angles to its crystal axis, rotates the plane of polarized light through an angle proportional to the thickness of the plate; this constitutes the phenomenon of

optical rotation. Some quartz crystals turn the plane of polarization to the right, while others turn it to the left. Three years later, Biot[4] extended these observations to organic substances, both liquids (such as turpentine) and solutions of solids (such as sucrose, camphor, and tartaric acid). Biot recognized the difference between the rotation produced by quartz and that produced by the organic substances he studied: The former is a property of the crystal; it is observed only in the solid state and depends on the direction in which the crystal is viewed, whereas the latter is a property of the individual molecules and may therefore be observed not only in the solid, but in the liquid and gaseous states as well as in solution.

With respect to the question of the cause of optical rotation, the French mineralogist Haüy[5] had already noticed in 1801 that quartz crystals exhibit the phenomenon of hemihedrism. Hemihedrism (cf. Section 6-4.c) implies inter alia that certain facets of the crystal are so disposed as to produce nonsuperposable species (Fig. 1.1, **A** and **B**), which are related as an object to its mirror image. (Such mirror-image crystals are called "enantiomorphous," from the Greek *enantios* meaning opposite and *morphe* meaning form.) In 1822, Sir John Herschel[6] observed that there was a relation between hemihedrism and optical rotation: All the quartz crystals having the odd facets inclined in one direction rotate the plane of polarized light in one and the same sense, whereas the enantiomorphous crystals rotate polarized light in the opposite sense.

It was, however, left to the genius of Louis Pasteur to extend this correlation from the realm of crystals, such as quartz, which rotate polarized light only in the solid state, to the realm of molecules, which rotate both as the solid and in solution. [The naturally occurring *dextro*-tartaric acid, henceforth denoted as (+)-tartaric acid, rotates the plane of polarized light to the right; see Section 1–3.] In 1848 Pasteur[7] had succeeded in separating crystals of the sodium ammonium salts of (+)- and (−)-tartaric acid from the racemic (nonrotating) mixture in the following way. When the salt of the mixed (racemic) acid which is found in wine caskets, was crystallized by slow evaporation of its aqueous solution, large crystals formed, which, to Pasteur's surprise and delight, displayed hemihedric facets similar to those found in quartz (Fig. 1.1). By looking at these crystals with a lens, Pasteur was able to separate the two types (with their

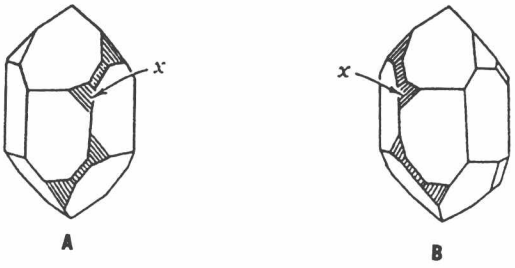

Figure 1.1. Hemihedrism of quartz crystals. [Reprinted with permission from Fieser, L. F. and Fieser, M. *Organic Chemistry*, 3rd ed., Heath, Lexington, MA, 1956.]

dissymmetric facets inclined to the right or left) by means of a pair of tweezers. When he then separately redissolved the two kinds of crystals, he found that one solution rotated polarized light to the right [the crystals being identical with those of the salt of the natural (+)-acid], whereas the other rotated to the left. [(−)-Tartaric acid had never been encountered up to that time.]

Pasteur[8] soon came to realize the analogy between crystals and molecules: In both cases the power to rotate polarized light was caused by dissymmetry, that is, the nonidentity of the crystal or molecule with its mirror image, expressed in the case of the ammonium sodium tartrate crystals by the presence of the hemihedric faces. Similarly, Pasteur postulated, the molecular structures of (+)- and (−)-tartaric acids must be related as an object to its mirror image; he pictured them as nonsuperposable helices of opposite sense. The two acids are thus enantiomorphous at the molecular level; we call them enantiomers. [The ending *-mer* (as in isomer, polymer, and oligomer, from the Greek *meros* meaning part) usually refers to a molecular species.]

In 1874 van't Hoff[9] in Utrecht, The Netherlands and Le Bel[10] in Paris, France independently and almost simultaneously proposed the structural base for enantiomerism in a substance of the type Cabcd: the four substituents are arranged tetrahedrally around the central carbon atom to which they are linked. van't Hoff, who had worked with Kekulé and whose views were based on structural theory, specified the 3D arrangement quite precisely: The four linkages to a carbon atom point toward the corners of a regular tetrahedron (Fig. 1.2) and two nonsuperposable arrangements (enantiomers) are thus possible.

We call the model corresponding to a given enantiomer (e.g., Fig. 1.2, **A**) and the molecule that it represents "chiral" (meaning handed, from Greek *cheir*, hand) because, like hands, the molecules are not superposable with their mirror images. The term chiral was first used by Lord Kelvin[11] in 1893, was rediscovered by Whyte[12] and was firmly reintroduced into the stereochemical literature by Mislow[13] and by Cahn, Ingold, and Prelog,[14] who define a model as chiral when it has no element of symmetry (plane, center, alternating axis; cf. Chapter 4) except at most an axis of rotation. A certain amount of confusion or ambiguity has arisen in the use of the term. When a *molecule* is chiral, it must be either "right-handed" or "left-handed." But if a *substance*

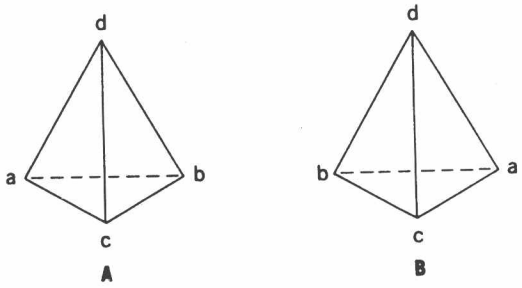

Figure 1.2. Tetrahedral carbon.

or sample is said to be chiral, this merely means that it is made up of chiral molecules; it does not necessarily imply that all the constituent molecules have the same "sense of chirality" (*R* or *S*, or *M* or *P*; cf. Chapter 5). We may distinguish two extreme situations (plus an infinite number of intermediate ones): (a) The sample is made up of molecules that all have the same sense of chirality (homochiral molecules). In that case the sample is said to be chiral and "nonracemic." This serves to distinguish this case from the opposite situation, where (b) the sample is made up of equal (or very nearly equal) numbers of molecules of opposite sense of chirality (heterochiral molecules), in which case the sample is chiral but racemic. Thus the statement that a macroscopic sample (as distinct from an individual molecule) is chiral is ambiguous and therefore sometimes insufficient; it may need to be further stated if the sample is racemic or nonracemic. Lack of precision on this point has led to some confusion, for example, in the titles of articles where the synthesis of a chiral natural product is claimed, but it is not clear whether the investigator simply wishes to draw attention to the chirality of the pertinent structure or whether the product has actually been synthesized as a single enantiomer (i.e., an assembly of homochiral molecules, which should not, however, be called a homochiral sample).

The situation is even slightly more complex than so far implied. There is little ambiguity about the meaning of "chiral, racemic": Chiral, racemic means that (within the limits of normal stochastic fluctuations) the sample is made up of equal numbers of molecules of opposite sense of chirality. But in a "chiral, nonracemic" sample there can be some molecules of a sense of chirality opposite to that of the majority; that is, the sample may not be enantiomerically pure (or *enantiopure*). Experimental tests as to whether a sample is enantiopure or merely *enantioenriched* will be discussed in Section 6-5.

It immediately follows from van't Hoff's hypothesis that in an alkene, where the tetrahedra are linked along one edge (Fig. 1.3) cis–trans isomerism is possible (see Chapter 9) and already in 1875 van't Hoff[9b] predicted the stereoisomerism of allenes, not actually observed in the laboratory until 1935 (cf. Chapter 13).

The hypothesis of van't Hoff and Le Bel has stood with but minor modifications until today. Both the visualization of molecules by X-ray and electron diffraction and the interpretation of vibrational [infrared (IR) and Raman] spectra have confirmed that carbon is, indeed, tetrahedral. Quantum mechanical calculations[15,16] concur in predicting a much lower energy for tetrahedral methane than for (hypothetical) methane of *planar geometry*.

van't Hoff[9a] had already pointed out that if CX_2Y_2 were planar (or, for that matter, square pyramidal), two isomers should exist but only one is found. For a detailed discussion see Wheland.[17]

Figure 1.3. Tetrahedral representation of alkenes and allenes.

1-3. POLARIMETRY AND OPTICAL ROTATION

It was mentioned in Section 1-2 that the discoveries of polarized light and optical rotation led to the concept of molecular chirality, which, in turn, is basic to the field of stereochemistry. Polarized light and optical rotation are therefore usually given considerable play in elementary treatments of stereochemistry. In the present text we take the view that the central theme of stereochemistry is molecular architecture, notably including chirality, and the resultant fits (as of a right hand with a right glove or of an enzyme with its natural substrate) or misfits (as of a right hand with a left glove or of an enzyme with the enantiomer of its natural substrate). In this theme, polarimetry and optical rotation are important as diagnostic tools for chirality but not central to its existence. We shall therefore treat polarimetry only briefly at this point, assuming that the nature of polarized light and the workings of a polarimeter are already familiar to the reader.

The observed angle of rotation of the plane of polarization by an optically active liquid, solution, or (more rarely) gas or solid is usually denoted by the symbol α. The angle may be either positive (+) or negative (–) depending on whether the rotation is clockwise, that is, to the right (*dextro*) or counter-clockwise, that is, to the left (*levo*) as seen by an observer *toward whom* the beam of polarized light travels. (This is opposite from the direction of rotation viewed *along* the light beam.) It may be noted that no immediate distinction can be made between rotations of $\alpha \pm 180\,n°$ (n = integer), for if the plane of polarization is rotated in the field of the polarimeter by ±180°, the new plane will coincide with the old one. In fact α, as measured, is always reported as being between –90° and +90°. Thus, for example, no difference appears between rotations of +50°, +230°, +410°, or –130°. To make the distinction. one must measure the rotation at least at one other concentration. Since optical rotation is proportional to concentration (see below), if solutions of the above rotations were diluted to one-tenth of their original concentrations, their rotations would become +5°, +23°, +41°, and –13°, values that are all clearly distinct. Readings taken at two different concentrations almost always determine α unequivocally. An alternative for solutions and the method of choice for pure liquids is to measure the rotation in a shorter tube. In the above cases, if a tube of a quarter of the original length [e.g., 0.25 decimeters (dm) instead of 1 dm] is used, the rotations as recorded become +12.5°, +57.5°, –77.5° (equivalent to +102.5°), and –32.5°, again all clearly distinguishable. [Note that halving the tube length (e.g., from 1 to 0.5 dm) would have left the ambiguity between the first and third observation (+25° vs. +205° = 180° + 25°) and between the fourth and second (–65° and +115° = 180° – 65°).]

Biot discovered that the observed rotation is proportional to the length ℓ of the cell or tube containing the optically active liquid or solution and the concentration c (or density in the case of a pure liquid): $\alpha = [\alpha] \cdot c \cdot \ell$ (Biot's law). The value of the proportionality constant $[\alpha]$ depends on the units chosen; in polarimetry it is customary to express ℓ in decimeters, because the cells are usually 0.25, 0.5, 1, or 2 dm in length, and c in grams per milliliter (g mL^{-1}) or (and this is preferred for solutions) in g100 mL^{-1}. Thus