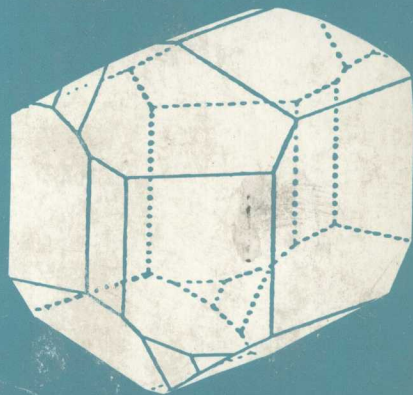
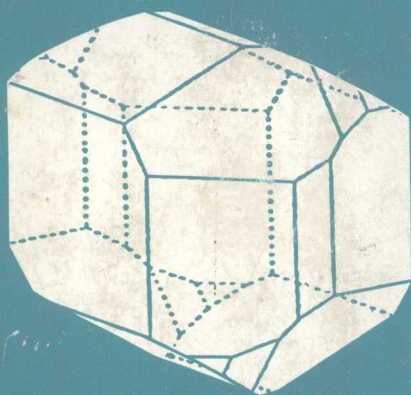
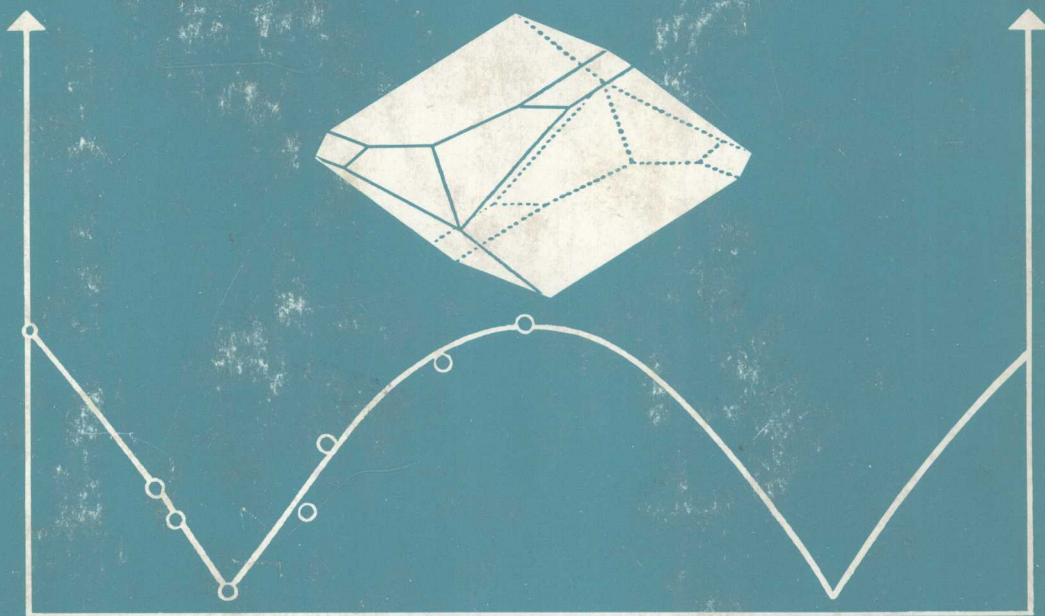


Enantiomers, Racemates and Resolutions



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Enantiomers, Racemates, and Resolutions

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Preface

Experimental stereochemistry and, in particular, the synthesis of chiral stereoisomers enriched in one enantiomer by a variety of methods is the subject of a multitude of contemporary studies. The reasons for the enormous effort in producing optically active molecules are well known to chemists but they bear repeating. Such molecules, whether small or large, have inherent interest, that is, their physical and chemical properties merit study; they are useful adjuvants in the elucidations of chemical reactions and of reaction mechanisms; and, above all, their biological properties have driven chemists to seek them out and to create them for utilitarian purposes.

It would seem that all of this activity would have given rise to several book-length summaries and overviews of the properties of racemates and of their constituent enantiomers and of the principles that underlie their separation from one another. While these optics have indeed been dealt with in review articles, briefly in textbooks as well as in comprehensive multivolume works, to the best of our knowledge no full-length monograph dealing with the properties of enantiomers exists. If this absence was earlier justified by an insufficient understanding and knowledge of racemate properties, this is no longer the case. We believe that a monograph on these subjects is timely, especially in view of the present-day interest and activity in asymmetric synthesis, in enzymatic synthesis, and in chromatographic resolutions.

We have also been concerned to some extent by errors we continue to find in the literature in connection with separation of enantiomers and their purification. These are often conceptual errors that derive from a lack of awareness of cause-and-effect relationships between planned experiments and properties of systems. These errors are in part forgivable; no clear and easily accessible statement of these properties and their consequences exists. Some of these properties have not been known heretofore; reports of others have been scattered in the literature and have not been easy to find. The time is thus ripe for a book in which the properties of enantiomers and racemates are brought together and examined critically.

Characteristics unique to enantiomers manifest themselves principally in the solid, that is, crystalline, state. This has led us to place special emphasis on their properties in this state and to pay special attention to the separation of enantiomers and, by extension, of diastereomers by physical methods, namely, by crystallization

with and without a solvent, and by sublimation. While chromatographic resolutions are indeed treated here, we have placed less emphasis on such methods since the theory of chromatographic techniques is adequately discussed elsewhere.

We have been monitoring and commenting upon developments in nonchromatographic resolutions for well over a decade. In spite of statements and views to the effect that traditional resolution is *passé*, we have yet to witness the predicted demise of even the most classic variant of this useful unit operation in organic chemistry. This is attested to by the very large number of resolutions reported in the contemporary journal literature, and the substantial number of patents dealing with resolutions attests to their considerable economic importance. Yet we have in no way conceived of this book, or any part thereof, as a defense of classical resolution as against the modern chromatographic variants or against other methods of optical activation such as asymmetric synthesis. Indeed, what is wrong with the traditional way of carrying out resolutions is a lack of real understanding of it. It is this very void we attempt to fill. Such an understanding is equally necessary for classical resolutions and for the study of systems enriched in one enantiomer produced by other methods.

The book is divided in two parts. The first treats racemic systems and enantiomers: the nature of the crystals, enantiomer mixtures and their properties and energetics, and solution properties of enantiomer mixtures. The second part treats the resolution of enantiomers: (1) by direct crystallization, (2) by formation and separation of diastereomer mixtures, and (3) experimental aspects of resolutions. While the examples in this book are virtually all organic, the principles are equally applicable to inorganic compounds; the chapters on resolution are therefore also suggestive of approaches to the resolution of inorganic compounds.

The readership for which we have geared this book is research workers in the area of stereochemistry in general, synthetic organic chemists who are concerned with asymmetric synthesis, medicinal and pharmaceutical chemists in universities and in industry, as well as others who must prepare chiral substances in nonracemic form, and graduate students in the corresponding fields. The volume is designed as a sourcebook and general reference and not as a textbook. It contains much that is of practical use to working chemists in the identified fields. The necessary theory is given in a treatment that is rigorous though largely nonmathematical.

This book is the outcome of an unusual collaborative effort between researchers working on both sides of the Atlantic Ocean. Many of the results and interpretations reported herein are original and derive from work carried out at the Collège de France, where studies of optical activity and of chiral substances follow the long tradition which began when J. B. Biot discovered optical activity in organic compounds there in 1815. It will be remembered that it was Biot who required Louis Pasteur to repeat the very first resolution — that of tartaric acid — in his laboratory at the Collège de France. We trust that we may be forgiven an element of pride in our ability to present this work in continuity of the classic studies in stereochemistry.

Finally, we would be remiss if we did not acknowledge the contributions of our associates to the successful completion of this work. Without their efforts this

volume could not have seen light of day. We have in particular greatly benefited from the experimental results (often unpublished) and from the many suggestions and ideas of Drs. Martine Leclercq and Marie-Josèphe Brienne. Mrs. Cécile Bertrand and Mrs. Rosamond Lewis Wilen both labored in more than one capacity over our bilingual manuscripts. It is with considerable pleasure and in the spirit of friendship that we express our thanks to them.

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Contents

PART 1 RACEMATES AND THEIR ENANTIOMER CONSTITUENTS

- 1 Types of Crystalline Racemates 3
 - 1.1 Definitions, 3
 - 1.2 The Crystallization of Racemates and Enantiomers, 5
 - 1.2.1 Chirality and Packing Modes in Crystals, 7
 - 1.2.2 Preferred Space Groups for Crystalline Enantiomers and Racemic Compounds, 8
 - 1.2.3 Enantiomorphous Crystals Derived from Achiral Molecules and from Racemic Compounds, 14
 - 1.2.4 Characterization of Enantiomorphous and Achiral Crystals by Physical Methods, 18
 - 1.3 Relationships Between Arrays of Enantiomers and the Corresponding Racemic Compound in Crystals, 23
 - 1.3.1 Comparison of Crystal Structures of Enantiomers and of the Racemic Compound, 23
 - 1.3.2 Symmetry, Compactness, and Stability: Racemic Compound Versus Conglomerate, 28
- 2 Binary Mixtures of Enantiomers 32
 - 2.1 Characterization of Racemate Types by Means of Binary (Melting Point) Phase Diagrams, 32
 - 2.1.1 Representation of Melting Point Phase Diagrams, 33
 - 2.1.2 Preparation of Mixtures for the Construction of Binary Phase Diagrams, 35
 - 2.1.3 Visual Measurement of Transition Temperatures, 36
 - 2.1.4 Automated Procedures, 37
 - 2.1.5 The Contact Method of Kofler, 40

- 2.2 **Conglomerates, 43**
 - 2.2.1 *The Phase Rule, 43*
 - 2.2.2 *Analysis of the Binary Phase Diagram, 44*
 - 2.2.3 *The Equation of Schröder–Van Laar, 46*
 - 2.2.4 *The Ideality of Enantiomer Mixtures in the Liquid State, 47*
 - 2.2.5 *Inventory of Enantiomer Mixtures That Exist as Conglomerates, 53*
- 2.3 **Racemic Compounds, 88**
 - 2.3.1 *Phase Diagrams, 88*
 - 2.3.2 *Thermodynamic Aspects, 90*
 - 2.3.3 *Comparison of Enthalpies of Fusion and Specific Heats of Racemic Compounds with Those of the Crystalline Enantiomers, 93*
 - 2.3.4 *The Problem of Racemic Compound Stability, 93*
 - 2.3.5 *Quasi-Racemates, 100*
- 2.4 **Pseudoracemates. Solid Solutions of Enantiomers, 104**
 - 2.4.1 *Ideal Solid Solutions, 105*
 - 2.4.2 *Nonideal Solid Solutions of Enantiomers. Pseudoracemates with Minimum Melting Point, 110*
 - 2.4.3 *Nonideal Solid Solutions of Enantiomers. Pseudoracemates with Minimum Melting Point, 112*
 - 2.4.4 *Thermodynamic Properties, 113*
 - 2.4.5 *Thermodynamic Aspects. A Priori Calculation of Pseudoracemate Phase Diagrams, 119*
 - 2.4.6 *Pseudoracemy and Its Relationship to Isomorphism, 120*
 - 2.4.7 *Crystalline Forms of Enantiomers That Cocrystallize, 123*
 - 2.4.8 *Partial Miscibility, 126*
 - 2.4.9 *Quantitative Definition of Similarity, The Coefficient of Isomorphism, 128*
- 2.5 **Polymorphism in Binary Systems, 131**
 - 2.5.1 *Enantiotropy and Monotropy. Transition Temperature, 131*
 - 2.5.2 *Polymorphism Without Alteration of the Nature of the Racemate, 136*
 - 2.5.3 *Polymorphism with Alteration to the Nature of the Racemate, 137*

2.5.4	<i>The Racemic Compound \rightleftharpoons Conglomerate Transformation, 140</i>	
2.5.5	<i>Polymorphism of Chiral Mesomorphs, 144</i>	
2.6	<i>Anomalous Racemates, 147</i>	
2.7	<i>Calorimetric Determination of Enantiomeric Purity, 151</i>	
2.7.1	<i>Principles and Limitations of the Direct Method, 151</i>	
2.7.2	<i>Theory of the Indirect Method, 153</i>	
2.7.3	<i>Application of the Indirect Method, 156</i>	
2.8	<i>Solid–Vapor Equilibria. Sublimation of Enantiomer Mixtures, 159</i>	
2.8.1	<i>Phase Diagrams for Sublimation, 159</i>	
2.8.2	<i>Separation of Enantiomers by Sublimation, 162</i>	
2.9	<i>Liquid–Vapor Equilibria. Distillation of Enantiomer Mixtures, 165</i>	
3.	Solution Properties of Enantiomers and Their Mixtures	167
3.1	<i>Graphic Representation of Ternary Systems, 167</i>	
3.1.1	<i>Quantitative Definitions of Concentration and Solubility, 167</i>	
3.1.2	<i>Representation of Ternary Systems. Generalizations, 168</i>	
3.1.3	<i>Triangular Phase Diagrams, 169</i>	
3.1.4	<i>The Enlargement of Triangular Phase Diagrams, 172</i>	
3.1.5	<i>Other Representations of Solubility Diagrams, 173</i>	
3.1.6	<i>Construction of Solubility Diagrams, 175</i>	
3.2	<i>Solutions of Conglomerates, 178</i>	
3.2.1	<i>Theoretical Phase Diagrams and Experimental Properties, 178</i>	
3.2.2	<i>Solubility Rules for Partially Resolved Mixtures, 181</i>	
3.2.3	<i>Comparison of the Solubilities of Pure Enantiomers and Their Conglomerate, 182</i>	
3.3	<i>Solutions of Racemic Compounds, 192</i>	
3.3.1	<i>Theoretical Phase Diagrams, 192</i>	
3.3.2	<i>Examples of Experimental Phase Diagrams, 194</i>	
3.3.3	<i>Solubility Rules for Partially Resolved Mixtures, 195</i>	
3.4	<i>Solutions of Pseudoracemates, 197</i>	
3.4.1	<i>Theoretical and Experimental Phase Diagrams, 197</i>	
3.4.2	<i>Solubility Rules for Partially Resolved Mixtures, 200</i>	

- 3.5 *Polymorphism in Ternary Systems, 201*
 - 3.5.1 *Description of the Polymorphism of Ternary Systems, 201*
 - 3.5.2 *Polymorphism and Solvation of Crystals, 203*
- 3.6 *Enantiomeric Purity Determination from Solubility Measurements, 207*
 - 3.6.1 *Conglomerates, 208*
 - 3.6.2 *Racemic Compounds, 210*

PART 2 RESOLUTION OF ENANTIOMER MIXTURES

- 4. Resolution by Direct Crystallization 217
 - 4.1 *Separation Based upon the Simultaneous Crystallization of the Two Enantiomers, 217*
 - 4.1.1 *Manual Sorting of the Conglomerate. Triage, 217*
 - 4.1.2 *Simultaneous and Separate Crystallization of Enantiomers, 219*
 - 4.1.3 *Simultaneous and Differentiated Crystallization of Enantiomers, 222*
 - 4.2 *Resolution by Entrainment, 223*
 - 4.2.1 *History and First Examples, 223*
 - 4.2.2 *Description of the Process of Resolution by Entrainment, 224*
 - 4.2.3 *Interpretation Based on Solubility Diagrams, 225*
 - 4.2.4 *Racemates Resolvable by Entrainment, 228*
 - 4.2.5 *The Search for Conditions Favoring Entrainment. The Method of Amiard, 229*
 - 4.2.6 *Derivation of Favorable Conditions for Resolutions by Entrainment from the Ternary Diagram, 232*
 - 4.2.7 *Control of Crystallization Rates, 235*
 - 4.3 *Resolution by Entrainment in a Supercooled Melt, 241*
 - 4.3.1 *Theory, 242*
 - 4.3.2 *Application of the Procedure, 243*
 - 4.4 *Crystallization in Optically Active Solvents, 245*
 - 4.4.1 *Solubility of Pure Enantiomers in Optically Active Solvents, 245*

- 4.4.2 *Resolution Experiments*, 246
- 4.4.3 *Origin of the Preferential Crystallization Phenomenon*, 247
- 4.4.4 *Resolution with Inclusion of an Optically Active Solvent*, 249

5 Formation and Separation of Diastereomers

251

5.1 *Dissociable Compounds and Complexes*, 253

- 5.1.1 *Resolution of Acids*, 257
- 5.1.2 *Resolution of Bases*, 259
- 5.1.3 *Resolution of Amino Acids*, 261
- 5.1.4 *Resolution of Alcohols. Transformation of Alcohols into Salt-Forming Derivatives*, 263
- 5.1.5 *Resolution of Aldehydes and Ketones. Transformation of Carbonyl Compounds into Salt-Forming Derivatives*, 266
- 5.1.6 *Diastereomeric Salts and Resolution of Werner Complexes*, 268
- 5.1.7 *Lewis Acid-Base Complexes*, 273
- 5.1.8 *Crystalline Inclusion Compounds*, 275
- 5.1.9 *Quasi-Racemates*, 282
- 5.1.10 *Physical Properties of Diastereomeric Salts*, 283
- 5.1.11 *Binary Melting Point Diagrams of Diastereomeric Salts*, 289
- 5.1.12 *Solubility Diagrams of Diastereomer Salt Mixtures*, 290
- 5.1.13 *Double Salts*, 295
- 5.1.14 *Cocrystallization of Diastereomeric Salts*, 299
- 5.1.15 *Isolation of the More Soluble Diastereomeric Salt. The Method of Ingersoll*, 301
- 5.1.16 *The Markwald Principle and Reciprocal Resolutions*, 306
- 5.1.17 *Resolution with Nonstoichiometric Quantities of Reagents*, 307
- 5.1.18 *The Method of Pope and Peachey*, 309
- 5.1.19 *Dissociation and Solubility of Salts. Interpretation of "Nonstoichiometric" Resolutions*, 312
- 5.1.20 *Optical Rotations of Diastereomeric Salts and Their Constituents*, 317

5.2	<i>Covalent Compounds, 328</i>	
5.2.1	<i>Covalent Derivatives of Acids, 329</i>	
5.2.2	<i>Covalent Derivatives of Amines, 330</i>	
5.2.3	<i>Covalent Derivatives of Alcohols, Thiols, and Phenols, 332</i>	
5.2.4	<i>Covalent Derivatives of Aldehydes, Ketones, and Sulfoxides, 335</i>	
5.2.5	<i>Resolution of Olefins, Sulfoxides, and Phosphines via Diastereomeric Zerovalent Complexes, 339</i>	
5.2.6	<i>Physical Properties of Covalent Diastereomers and Their Mixtures, 342</i>	
5.2.7	<i>Chromatographic Behavior of Covalent Diastereomers, 348</i>	
5.3	<i>Structure-Property Correlations of Diastereomers, 359</i>	
5.3.1	<i>Rules of Winther and Werner, 359</i>	
5.3.2	<i>Quasi-Enantiomeric Resolving Agents, 362</i>	
6	<i>Crystallization-Induced Asymmetric Transformations</i>	369
6.1	<i>Asymmetric Disequilibrium of a Racemate. Total "Spontaneous Resolution," 371</i>	
6.2	<i>Asymmetric Transformation of Diastereomeric Salts, 373</i>	
6.3	<i>Asymmetric Transformation of Covalent Diastereomers, 376</i>	
7.	<i>Experimental Aspects and Art of Resolutions</i>	378
7.1	<i>Choice of Resolution Method, 378</i>	
7.1.1	<i>Choice of Method as a Function of Scale, 378</i>	
7.1.2	<i>Choice of Method According to the Structure of the Substrate, 379</i>	
7.2	<i>Obtaining Crystalline Diastereomers, 380</i>	
7.2.1	<i>Systematic Trials. Choice of Resolving Agent, 380</i>	
7.2.2	<i>Choice of Crystallization Solvent, 383</i>	
7.2.3	<i>Isolation of the First Crystallization Seeds, 386</i>	
7.2.4	<i>Neutral Salts and Acid (or Basic) Salts, 387</i>	
7.3	<i>Purification of Diastereomers, 389</i>	
7.3.1	<i>Optimal Conditions for Crystallization. Quantity of Solvent, 389</i>	
7.3.2	<i>Crystallization with Seeding, 391</i>	

- 7.3.3 *Influence of Temperature, 392*
- 7.3.4 *Fractional Crystallization, 392*
- 7.3.5 *Use of Optically Impure Resolving Agents, 393*
- 7.4 ***Recovery of Enantiomers from Diastereomers, 396***
 - 7.4.1 *Decomposition of Diastereomeric Salts, 396*
 - 7.4.2 *Decomposition of Covalent Diastereomers, 399*
 - 7.4.3 *Recovery and Purification of Resolving Agents, 403*
- 7.5 ***Monitoring Enantiomeric Purity, 405***
 - 7.5.1 *Analysis of Diastereomer Mixtures, 406*
 - 7.5.2 *Enantiomeric Composition by Means of Diastereomeric Interactions, 410*
 - 7.5.3 *Calorimetric Methods, 416*
 - 7.5.4 *Isotope Labeling, 417*
 - 7.5.5 *Quantitative Enzymatic Analysis, 419*
- 7.6 ***Final Purification. Enrichment of Partially Resolved Enantiomer Mixtures, 423***
 - 7.6.1 *Definitions. Pure and Ultrapure Enantiomers, 423*
 - 7.6.2 *Classical Final Purification, 424*
 - 7.6.3 *Ultrapurification by Zone Melting, 428*
 - 7.6.4 *Chemical Purification, 430*

PART 1

Racemates and Their Enantiomer Constituents

The separation of racemates into their chiral constituents rests upon a number of physicochemical principles and data which are the essential subject of the first part of this volume.

Chemists who are occasionally called upon to reproduce a resolution described in the literature or who have (or will have) succeeded in carrying out a resolution "without problem" may feel that we attach greater importance than is warranted to a particular body of knowledge and to facts that do not appear to be immediately useful.

In fact, the goal of Part 1 is a double one. We wanted first of all to collect data and interpretations which, when understood and applied, would lead those who do encounter difficult resolutions to be less hesitant in facing them. We also wished to describe, in as complete a way as possible, the actual state of an area of physical chemistry which, after having been much worked over at the end of the last century, has for the most part lain fallow over several decades.

Yet the study of the properties of enantiomers and of their mixtures must not be thought of as an abstruse subject falling outside the mainstream of physical chemistry; it is an essential component of contemporary problems of general interest. The problems of molecular packing in solids, of cocrystallization, of polymorphism, and of the thermodynamics of solutions are but specific facets of larger problems which arise from the symmetry properties of the systems which are taken up in this book. The reader ought not to be too surprised to find herein, more often than at first supposed, ideas and notions familiar in other contexts.

Types of Crystalline Racemates

We begin our examination of chiral substances with the definition of terms, follow this with an analysis of those physical properties which distinguish the principal types of racemates, and conclude with a discussion of concepts applicable to racemates and their constituents at the interface of crystallography, symmetry, and thermodynamics.

1.1 DEFINITIONS

Chirality is a concept well known to organic chemists and, indeed, to all chemists concerned in any way with structure. It has numerous implications ranging from those affecting physical properties of matter to those related to biological mechanisms. These implications extend far beyond the borders of "pure" chemistry. Since it is likely that readers concerned with those aspects of chirality examined in this volume may belong to a wide variety of disciplines, we believe that it is worthwhile, if not essential, to define the terminology employed in this book in as precise and unequivocal a manner as possible.

The geometric property that is responsible for the nonidentity of an object with its mirror image is called *chirality*. A *chiral* object may exist in two *enantiomorphic* forms which are mirror images of one another. Such forms lack *inverse symmetry elements*, that is, a center, a plane, and an improper axis of symmetry. Objects that possess one or more of these inverse symmetry elements are superposable on their mirror images; they are *achiral*. All objects necessarily belong to one of these categories; a hand, a spiral staircase, and a snail shell are all chiral, while a cube and a sphere are achiral.

According to Kelvin,¹ "two equal and similar right hands are *homochirally* similar. Equal and similar right and left hands are *heterochirally* similar . . .". All of the foregoing definitions remain valid at the molecular level; there are achiral as well as chiral molecules. The latter exist in two *enantiomeric* forms (the adjective enantiomorphic is more generally applied to macroscopic objects). The term enantiomer is used to designate either a single molecule, a *homochiral collection* of

molecules, or even a *heterochiral collection* that contains an excess of one enantiomer and whose composition is defined by its enantiomeric purity p , or the *enantiomeric excess* e.e. which is equivalent to p .

The oldest known manifestation of molecular chirality is the *optical activity*, or *rotatory power*, the property that is exhibited by the rotation of the plane of polarization of light. The two enantiomers of a given compound have rotatory powers of equal absolute value but of opposite *sign*, or *sense*. One is *positive*, or *dextrorotatory*, while the other is *negative*, or *levorotatory*. The absolute designations of sign are arbitrary inasmuch as they are wavelength, temperature, and solvent dependent, but the relative designations are always valid. That is, a given enantiomer may be (+) at one wavelength and (–) at another. The other enantiomer will always have the opposite sign at the corresponding wavelength.

While we shall use as often as possible the (+) and (–) symbols to designate a pair of enantiomers, we shall occasionally employ the letters *d* and *l* or *D* and *L* for convenience.

The expression *optically active substance* may signify a pure enantiomer or a mixture containing an excess of one of the two. The composition of a mixture of two enantiomers may be characterized by its *optical purity*, which may in turn be determined from the ratio of the optical rotation of the mixture to that of the pure enantiomer. The optical purity (experimental value) is generally equal to the enantiomeric purity, which reflects the real composition. A pure enantiomer is often called *optically pure*.

The *absolute configuration* of a chiral substance is known when an enantiomeric structure can be assigned to an optically active sample of a given sign. We have little need to concern ourselves with absolute configurations as such in this book. Recall that absolute configurations are designated by means of an alphabetic symbolism (*R*, *S* for *rectus* and *sinister*) whose application is determined by the rules of Cahn, Ingold, and Prelog.² However, the *D* and *L* descriptors of Rosanoff³ are still used for carbohydrates. Care should be exercised so as not to confuse these with the sign of the optical activity.

An equimolar mixture of two enantiomers whose physical state is unspecified or unknown is called a *racemate*;⁴ the corresponding adjective is *racemic*, as in a racemic substance, for example. This word is derived from racemic acid, a name used to designate one of the isomeric tartaric acids during the last century and which Pasteur demonstrated to be a mixture of dextro- and levorotatory forms. Racemates, which we generally designate by the symbol (\pm), are evidently optically inactive by external compensation.

The separation of the two enantiomers that constitute a racemate is called a *resolution*, or an *optical resolution*. When the separation is not complete, a mixture is obtained which is often called either a partially resolved racemate or a partially resolved enantiomer.

We shall see that crystalline racemates may belong to one of three different classes. In the first, the crystalline racemate is a *conglomerate*, that is, a mechanical mixture of crystals of the two pure enantiomers. A conglomerate is formed as a result of a *spontaneous resolution*. The expression “racemic mixture” has generally