Reviews

Stereochemistry of optically active compounds. Problems and prospects

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The review is concerned with the fundamental ideas and concepts of chiral stereochemistry, *i.e.*, of the stereochemistry dealing with optically active compounds, from the asymmetric synthesis to the basics of mathematics, including characterization of the principal results and the current state of this branch of science.

Key words: stereochemistry, chirality, achirality, symmetry groups, optical activity, polyhedra, geometry, topology.

Introduction

The past century was marked by prosperity of stereochemistry. From the 19th century, it has inherited the discovery of optical activity exhibited by compounds in crystals and solutions; the notions of racemates, enantiomers, and diastereomers and the first procedures for resolution of racemates into enantiomers, which have been realized in practice by Pasteur; the acceptance of rotation of the polarization plane and circular dichroism spectroscopy as methods for investigating optically active compounds and the discovery of the Cotton effect; a large number of optically active natural compounds, which provided the basis for numerous syntheses of novel optically active compounds in complete agreement with Berthelot' aphorism ("organic chemistry creates its own subject"); the first evidence for the relationship between stereochemisty (optical activity) and reaction mechanisms (Walden inversion); the van't Hoff—Le Bel tetrahedral model of the carbon atom; and, finally, the name of this branch of science.[1] Hence, stereochemistry started from optically active compounds, which remain to be its heart.

Early in the 20th century, Werner extended stereochemistry, which has arised as the three-dimensional geometry of organic (hydrocarbon) molecules, to octahedral metal complexes. Later on, the stereochemisty was extended to the overall molecular world, gained the universal character, gave rise to the doctrine of internal molecular dynamics (conformational analysis), served as an important tool in studying reaction mechanisms, established interrelations with a number of physicochemical methods, and received serious mathematical support.

Chiral molecules hold a central position in stereochemistry. This is in no way associated with the fact that they are more widespread than achiral molecules. The reasons are that the concept of chirality introduces a wealth of ideas into stereochemistry, which actually revolutionize this branch of science, and that enantiomerically pure compounds play an important role in the chemistry of living organisms.

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"Chiral stereochemistry" is a simplified term for the description of the area of stereochemistry dealing with chiral molecules in the nonracemic form, *i.e.*, with molecules whose enantiomeric purity differs from zero, to put it differently, with optically active molecules. However, the term "optical activity" is more restricted in the sense that it assumes the employment (at least potentially) of only one method, *e.g.*, measurements of rotation of the polarization plane, whereas other methods for evaluating the enantiomeric purity are also available. The notion of chirality has a clear mathematical basis and is not associated with a particular method of investigation. The term "chirality" alone ensures only that the object (molecule) is non-superimposable with its mirror image. A slight deviation from the exact meaning of this term is acceptable with reserve of nonracemic molecules. One must strictly distinguish between the cases when the term "chiral" means actually "optically active" ("enantiomeric") and when it is used in its own original sense.

The present review surveys the development of the main concepts and achievements in the *chiral stereochemistry* over the last 100 years and is concerned with all its divisions, from the practice of the synthesis of optically active compounds to mathematical aspects. Since the problem is, evidently, very complex, each area will be considered as briefly as possible and some aspects will be only listed. Particular preference will be given to theoretical problems, which are more complex than synthetic aspects. Besides, complication of synthetic purposes as well as the employment of new methods remain within the same paradigm, whereas application of new mathematical concepts implies a substantial increase in the degree of novelty. The names of the major participants of the stereochemical history, with rare exception, can be found in the references rather than in the text of the review (lest the review resemble the funeral list and the reader's attention be attracted away from the essence of the matter).

Over a long period of time, stereochemistry comprised a small part of the general chemical courses. Later on, monographs on the general problems of stereochemistry and (as this branch of science was developed) on its particular divisions were published. More recently, other publications (series, journals) devoted purely to stereochemical problems appeared[2—17] (see also Section 16).

In the first half of the 20th century, stereochemistry was not differentiated although its main directions became evident. The idea of optical activity in the absence of the asymmetric carbon atom was realized. Thus, the following compounds were synthesized: enantiomeric 1,2-disubstituted allenes[18] for which the above possibility has been predicted by van't Hoff; geometrically analogous methylenecyclohexanes,[19] spiranes,[20] and, finally, biaryls containing substituents, which hinder the aryl—aryl rotation;[21] and aromatic *ansa*-compounds in which rotation about bonds is also hindered.[22] It was also established that not only carbon atom but also other tetravalent elements, *viz.*, nitrogen and phosphorus in oxides of tertiary amines and phosphines and nitrogen in ammonium salts, have tetrahedral structures and can serve as asymmetric centers.[23] Moreover, the three-coordinate sulfur atom in sulfonium salts and sulfoxides[24] and the three-coordinate nitrogen atom in the structurally rigid cyclic structures of Tröger base can act as asymmetric centers.[25]

At the same time, first attempts have been made to correlate the value and the sign of optical rotation with the structures of enantiomeric molecules. Empirical regularities were searched for successively in curves of optical rotatory dispersion and in circular dichroism curves[26] in which the values and signs of the Cotton effects are easier to analyze. Based on comparison of the signs of optical rotation, predominantly qualitative correlations were made for relative configurations of related optically active molecules.[27] Here it is necessary to understand the relationship between the stereochemistry, on the one hand, and the kinetics and the reaction mechanism, on the other hand. First regularities have been stated; for example, it has been reasoned that the bimolecular nucleophilic substitution at the carbon atom occurs with inversion of its configuration[28] (Walden inversion).

Simultaneously, theorists examined the possibility to predict *the sign and value* of optical rotation from the molecular structure. The general equation for the optical rotation derived from quantum mechanics[29] appeared to be difficult to apply to real molecular structures. Several approaches, which were developed taking into account certain approximations, are only of limited utility: the one-electron model,[30] the coupled oscillator model,[31] and the dynamic polarization model.[32]

Early in the 20th century, chiral stereochemistry went beyond the scope of organic chemistry and demonstrated its general character. This happened when Werner[33] proposed the octahedral model of the central metal atom in complexes of cobalt and other transition metals and applied this model to the explanation of their geometrical and optical isomerism. This investigation provided a radical extension of the concept compared to, for example, the asymmetric nitrogen or phosphorus atoms, because it accounted for the different geometry of the coordination center (an octahedron instead of a tetrahedron). Further generalization was made in the second half of the 20th century owing to the advancement of organometallic chemistry.

The first half of the 20th century was marked by discoveries and investigations of new reactions applicable, in principle, to optically active compounds as well as by isolation of new natural compounds. The stereoselective synthesis of natural compounds was an important problem facing organic chemists. Since many compounds are optically active and their molecules often bear more than one asymmetric centers, chemists considered it the matter of honor to synthesize natural

enantiomers with as high optical purity as possible. In the case of compounds exhibiting pronounced biological activities, one of the goals was to prepare non-natural stereoisomers as well. These studies played an important role in the development of the organic synthesis. Of numerous investigations, which often strike by the ingenuity and experimental art, the syntheses of famous compounds received due recognition of the chemical community just because these compounds are universally known. These are the syntheses of strychnine,[34] morphine,[35] quinine,[36] and steroids.[37—39] All diastereomers of some steroids, in particular, of estrone, were synthesized.[40] In most of these syntheses, which would presently be called *chiroselective*, either natural enantiomers were used or chemical resolution of racemates at a particular stage was employed. In the second half of the 20th century, considerable progress was made toward the directed synthesis (see Sections 14 and 15).

Complication of compounds under investigation not only in the purely structural but also in the stereochemical aspects generated a need for the adequate description of molecular structures. Because of this, the nomenclature acquired great importance. It appeared that a molecule is rather difficult to unambiguously describe. First investigations, which were concerned with molecules possessing many asymmetric centers, were carried out in the field of the chemistry of carbohydrates. For these compounds, E. Fischer devised a nomenclature.[41] However, this nomenclature was inapplicable to other classes of compounds. In addition, the range of optically active compounds without asymmetric centers was gradually extended, which called for the development of new principles. Shortly thereafter this task was accomplished based on the concept of chirality.

At that time, the notion of *the asymmetric synthesis* was formulated, which involves the preparation of two enantiomers of a particular compound in non-equal amounts from an *achiral* (as we presently would say) compound (however, this useful term had been unavailable) through an intermediate diastereomer.[42,43] Later on, empirical rules were stated for several special cases of intramolecular induction of the newly formed asymmetric carbon center under the effect of the already available optically active group, the important role of the steric factor being revealed.[44—46]

An asymmetric agent can also be external, *i.e.*, can be an asymmetric catalyst. First asymmetric catalysts were heterogeneous. Thus, metal (copper, nickel) deposited on a crystal surface of optically active quartz promoted asymmetric dehydration of alcohols and, as a result, the alcohol residue, which was not subjected to dehydration, exhibited weak optical rotation.[47]

Circularly polarized light or the asymmetric crystal surface were also considered as external asymmetric agents. This version involving a non-chemical asymmetric agent was called the *absolute asymmetric synthesis* and is conceptually related to the problem of the origin of life on Earth associated with the appearance of optically active molecules in nature. First examples of the absolute asymmetric synthesis were also reported in 1930s.[48,49] Considerable interest in this peripheral area of stereochemistry stems from speculative constructions aimed at creating the concept of the occurrence, at least in the accessible region of the Universe, *i.e.*, on Earth, of enantiomerically pure biologically important compounds: amino acids and carbohydrates and, consequently, proteins and nucleic acids.[50]

The first half of the 20th century culminated in the discovery of the possibility to establish absolute configurations of optically active molecules using anomalous X-ray scattering,[51] which was a great event in the stereochemistry. Numerous correlations of relative configurations were provided with the reliable starting point. Thus, it became possible to determine real three-dimensional configurations of (+)- and (−)-enantiomers. By coincidence, the first step on the road to the development of a new *R*/*S* nomenclature[52] was made in the same year (see Section 3).

In the second half of the 20th century, all areas of stereochemistry, which have been worked out in the first half of the century, were progressing and new areas were elaborated due to the syntheses of new structures (particularly, in the field of organometallic chemistry) and in connection with the application of different divisions of mathematics.

Noteworthy is the progress in the techniques of the optical resolution and determination of the enantiomeric purity. Classical methods for the resolution of racemates into enantiomers through the formation of diastereomeric compounds were still most generally employed, but the development of chromatographic methods (gas and liquid) made it possible to detect and employ finer differences between diastereomers in both analysis of mixtures and preparative chemistry.[53,54] The more precise determination of the enantiomeric purity is achieved (compared to results obtained by polarimetry) either with the use of the preliminary conversion of an *enantiomeric compound* into a mixture of diastereomers or by utilizing an optically pure chromatographic phase involved in a diastereomeric interaction with the specimen analyzed. Ligand-exchange chromatography of chiral compounds based on formation of transition metal complexes is an important special case (see the review[55]). Another method for the determination of the enantiomeric purity comparable in accuracy with the chromatographic techniques involves analysis of diastereomeric mixtures by NMR spectroscopy. Methods of kinetic resolution[56] and isotopic dilution[57] are also worthy of note.

The method for the optical resolution of racemates through formation of inclusion compounds with optically active matrices gained some acceptance.[58—59] In particular, this method was used for resolving bromochlorofluoromethane.[60]

In dealing with the stereochemical problems, mechanical molecular models were of considerable utility.

The most helpful models were proposed by Dreiding in the early 1950s. These models have been widely employed before computers came into use.

1. New structural types of optically active molecules

Stereochemical analysis of molecules is traditionally started with a search for asymmetric carbon atoms and, later on, for asymmetric atoms of other four-coordinate elements[61] (silicon, nitrogen, phosphorus, sulfur, *etc.*); it should be noted that one coordination position can be occupied by a free electron pair (tertiary phosphines, arsines, and sulfoxides). Transition metal atoms can serve as asymmetric centers with a pseudotetrahedral coordination where one vertex of the tetrahedron is occupied by the centroid of the planar ligand, as, for instance, in optically active π-cyclopentadienyl complexes of such metals, as manganese[62] or rhenium.[63] An important point was an understanding that the isotopic difference between two substituents is sufficient for a molecule to become optically active and to possess a measurable angle of optical rotation or a CD spectrum. This is particularly true for the hydrogen isotopes characterized by the largest difference in weight (H/D, Me/CD_3, *etc.*).[64] Using all three hydrogen isotopes, one can obtain the chiral methyl group. In this connection, let us mention the syntheses of both enantiomers[65] of acetic acid *CHDT-COOH and optically active hydrocarbons[66] *CHDT-Alk. Since tritium is always present in trace amounts, the enantiomeric purity of such compounds can be estimated only by enzymatic methods. It should be noted that researchers engaged in enzymology are the major purchasers and consumers of isotopic enantiomers. For heavier atoms, the isotopic difference is relatively less significant; however, it is responsible for chirality observed in sulfoxide ($^{12}C/^{13}C$) and sulfone ($^{16}O/^{18}O$) or in the $PhCH_2CH_2—O—S(^{16}O)(^{17}O)(^{18}O)$ [67] and $R—O—P(^{18}O)(^{17}O)(^{16}O)$ anions.[68]

Owing to the chemistry of coordination compounds of transition metals, the concept of an asymmetric atom, which initially referred only to the tetrahedron, was supplemented with the octahedron, but it remained, in principle, unchanged. The noticeable progress was made once the optical activity of molecules without asymmetric atoms was realized first for allenes and then for spiranes (in which a special atoms persists, but it cannot be called asymmetric) and biaryls. In allenes and biaryls, the presence of an important structural axis is clearly evident. Later on, using spiranes as an example,[69] it was demonstrated that the absence of a symmetry plane in the presence of the mirror-rotational axis S_4 does not give rise to optical activity. This provided a deeper insight into the role of symmetry elements. The resolution of *trans*-cyclooctene[70] into enantiomers (through the platinum π-complex) revealed that the presence of a rotation axis (in this case, C_2) without an asymmetric atom does not hinder the manifestation of optical activity. Optically active molecules, which contain neither a special atom nor a special axis, came to be known due to investigations of substituted *para*-cyclophanes[71] and *ansa*-compounds of the aromatic series.[72] These structures, which are very unusual for purely organic molecules, turn out to be typical of transition metal π-complexes containing planar organic ligands from olefins[73] to arenes.[74] The optical activity of organometallic compounds was detailed in the monograph.[75] For lack of a conventional appropriate term, authors dealing with these problems treated the above compounds differently and described this structural type, for example, as "asymmetry of an oriented plane".[76] Helicenes have also attracted attention.[77,78] Due to steric hindrances, these nonplanar aromatic molecules adopt a spiral conformation and can exhibit optical activity. Deprived of functional groups, these compounds were resolved into enantiomers through molecular complexes. Some compounds can exhibit optical activity because, due to steric hindrances, their stable conformers belong to chiral symmetry groups, for example, to $\mathbf{C_3}$ (tri-*o*-thymotide,[79] cyclotriveratryl,[80] or the tris(pentachlorophenyl)methyl radical)[81] or $\mathbf{C_1}$ (the (8-methylnaphthyl)-*p*-biphenylyl carbenium ion).[82]

The syntheses of molecular compounds corresponding to topological figures[83] provided new examples of enantiomeric molecules. Among these is a trefoil knot, whose optical activity has been predicted well before and has even been evaluated by calculations[84] according to the Kirkwood theory. The simplest hydrocarbon knot $(CH_2)_n$ is as yet unavailable, but a complex knot molecule[85] as well as catenanes[86] were synthesized in enantiomerically pure form. Fullerene C_{76}, which represents an ellipsoid with the symmetry $\mathbf{D_2}$ and which was prepared in enantiomerically pure form, is the most recent example of a new type of chiral molecules.[87]

2. Fundamental triad of stereochemistry: conformation, chirality, and configuration

Beginning in the 1950s, the *configurations* of optically active compounds, to be more precise, the *configurations* of asymmetric centers and then of other fragments responsible for optical activity (axis, plane, and helicoid), came to be known. By then abundant data were accumulated, which provided evidence for the internal flexibility of molecules, *viz.*, rotations about bonds, vibrations relative to planes, *etc.* The state of a molecule at a particular moment in time was called the *conformation*. The transformation of one conformation into another is a conformational transition characterized by a particular energy. A molecule is a combination of all accessible conformations, which represent the conformational space of the molecule.[17] The presence of various conformations has no qualitative effect on the configuration, for example, of the carbon atom, but exerts a noticeable quantitative effect on the chiroptical properties. Problems associated with conformational

analysis are beyond the scope of the present review, except for the existence of chiral and achiral conformations (*i.e.*, the relationship between the conformation and the chirality) and their influence on the chiroptical properties. It should be emphasized that an achiral molecule *can* adopt chiral conformations (conformational chirality), but these conformations will be necessarily present as both enantiomers in its conformational space, unless there is a chiral environment. The relationship between chiral and achiral conformations is considered in Section 3.

As a result, the fundamental triad lying at the heart of the system of stereochemistry is formed:[17] conformation, chirality, and configuration. It is in this logical order that a molecule is considered. Thus, a molecule exists as *conformations*, which are classified into two groups by applying the notion of *chirality*. One of these groups (chiral) is characterized by a new specific property, namely, *configuration*, which takes one of two possible values for each enantiomer. Therefore, the *configuration* occupies the highest stage in the stereochemical hierarchy. The precise definition of the stereochemical configuration, which is intuitively quite understandable, presents, however, serious difficulties, and this problem remains to be solved. Within the framework of one of approaches, the *configuration* was determined as an invariant of a chiral molecular topological form constructed in a particular way.[88] The configuration, which can take the *plus* (+) or *minus* (−) sign (for achiral structures, the configuration, is, by definition, characterized by *zero*), is realized only for homochiral structures in the Ruch sense (see Section 12). An optically inactive molecule of the biaryl series containing fragments of D- and L-menthol, which has first been considered by Mislow,[89] was of considerable importance in the understanding of the relationship between the conformation and the configuration. There are no achiral conformations in the conformational space of this molecule (*i.e.*, it is a purely racemic manifold, see Section 12). More recent analysis[90] demonstrated that the symmetry $\mathbf{S_4}$ of an achiral fragment is an essential fact and analogous (although hypothetical) structural models were proposed. The view of the configuration was considered from alternative standpoints as well.[17,91–93]

3. Chirality

Prelog[94] revived the notion of *chirality*, which has been proposed by Kelvin[95] but which has been little used for more than 50 years. The general character of this concept is best suited to stereochemical objects. *Chirality is the property of an object to be non-superimposable with its mirror image*.* Clearly, no mention is made of molecules, and objects can be of any type (although chemists see the description of enantiomers). That is why the concept of chirality, which has first been accepted in chemistry, found use in other branches of natural science and mathematics. The definition of the symmetry conditions of chirality stimulated interest in the molecular symmetry.

The chirality of molecules is associated with particular structural elements, which were called *chirality elements*: a center, an axis, and a plane of chirality (see Sections 6, 7, and 12).

The question of whether chiral or achiral molecules are more commonly occurring is incorrect. Both these subsets are, in principle, infinite. However, it can easily be shown that *any* achiral molecule can generate an *infinite* number of chiral molecules by incorporating a chiral fragment through a single modification event (for example, by the replacement of the hydrogen atom). On the contrary, a chiral molecule can be converted, if at all, into an achiral one by a *single event* using the *only* procedure, *e.g.*, by removing a chiral fragment. Hence it follows that the power of the subset of chiral molecules is higher than that of the achiral subset. This can be illustrated with the simplest example: the enumeration of chiral and achiral isomers of alkanes,[96] which was performed based on the Polya theorem,[97] demonstrated that the number of chiral isomers increases more rapidly and becomes larger than the number of achiral isomers (for C_nH_{2n+2}, starting with $n > 10$; for monosubstituted $C_nH_{2n+1}X$, starting with $n > 6$).

This brings up the question: What molecules are "more" and "less" chiral? In a general way, the question about the existence of the quantitative measure of chirality is considered in Section 12.

Achirality is a notion opposite to chirality; these concepts are mutually exclusive. However, achirality can be further subclassified by determining the "length of the chiralization path" as the minimum number of events of single modifications required for the molecular structure to be converted into the chiral structure.[17,98] Hence, the achirality area assumes a layered structure. The length of the chiralization path equal to unity characterizes *prochiral* molecules. When moving from a depth of the achiral area to its surface, at the instant the "achiral—chiral" boundary is crossed, bifurcation occurs; the final point change of *one* prochiral object gives a *pair* of enantiomers.[99] *Prochirality*[100] is of particular importance in the treatment of the asymmetric synthesis. *Pseudochirality*[14,101] arises when two enantiomeric ligands in a molecule are combined with one chiral fragment. The occurrence of achiral diastereomers was established with these models.[102] The refinement of the terms, which is of no significance in practical use but which is essential to the improvement of the mathematical rigor, is still in progress.[103,104]

In the case that a molecule bears several structurally similar chiral fragments, it can easily happen that the molecule as a whole satisfies the criterion for achirality, *i.e.*, it coincides with its mirror image. The trivial case

* This canonical definition was changed more than once; for example, the expression "through translation and rotation operations" was added.

of the *meso* form, which contains two chiral fragments adopting opposite configurations, is an example. However, it appears that two fragments in the *same* configuration can be coupled to form an achiral object. It was first exemplified by a homochiral dissection of the *Coupe du Roi* apple[105] (which represents a model of the sphere), which revealed the presence of three mutually perpendicular C_2 axes, *i.e.*, the symmetry group $\mathbf{D_2}$. Chemical analogies were described with the use of enzymatic reactions.[106]

Anisochronism (nonequivalence) of magnetic nuclei in particular structures, which is manifested in NMR spectra, was explained within the concept of enantiotopism (diastereotopism)[107] taking into account chirality and prochirality. Owing to this phenomenon, NMR spectroscopy became a powerful tool in revealing and studying the chirality of molecules. An important point is that it is the *chirality* of a molecule rather than the predominance of one of enantiomers that plays a role. This is a rare example of the *chiral* effect in the strict sense of the word.

The syntheses of molecules with topological bonds[108] (knots and catenanes) and Möbius-strip-shaped molecules[109] called for application of the concept of topological chirality.[110] The existence of various sources of chirality gives rise to the chirality hierarchy (as well as to the achirality hierarchy); however, the highest categories in this hierarchy are unlikely to have any meaning other than mathematical.[111]

4. Stereochemical nomenclature and terminology

The rigorous nomenclature establishing an unambiguous correspondence between the name and the structure is required for the adequate description of a molecule. This is of particular importance if a molecule contains many chiral fragments. The Cahn—Ingold—Prelog stereochemical nomenclature (hence abbreviated with CIP),[112] which is closely associated with the new concept of chirality, has a wide application. This nomenclature is also called the *RS* nomenclature because the absolute configurations of chiral centers are denoted by *R* and *S*. The CIP rules proved to be so useful that they received general acceptance. Later on, only several supplementation concerning other chiral fragments were proposed.[113] Noteworthy is also the Framework Group Symmetry system,[114] which provides the unambiguous description of the structures of both chiral an achiral molecules based on available symmetry elements.

Although possessing considerable advantages, the CIP nomenclature assures the description of the morphology of the molecular world, but does not reveal mathematical relations providing its basis. The latter problem was worked out in succeeding years.

The terminology does not reduce to the nomenclature. Related terms, *e.g.*, *achirality*, *prochirality*, *pseudochirality*, and *topological chirality*, were proposed along with the concept of *chirality*. On the contrary, biomolecular chirality (see for example, the paper[115]) is a false term because it means nothing else but usual chirality in molecules of biological origin. *Chiralization* implies a transformation of an achiral object into a chiral one (this term is more strict than desymmetrization because symmetry axes may persist in a chiral object); *dechiralization* means the reverse process. The term *chiroselectivity* combines enantioselectivity with diastereoselectivity for optically active compounds. The stereochemical practice called for other special notions to describe new objects, phenomena, and processes. For example, interrelation of stereochemistry and NMR spectroscopy brought into existence the terms *homotopism — enantiotopism — diastereotopism*.[107] New terms were often received with skepticism. Presently, some of them do not gain general acceptance. It takes long to get accustomed to new terms because the English/Roman-type language massif must be first formed and then the Russian-language terminology should be accepted; however, the progress, though slow, is evident. It should be noted that different interpretations of the terms are not always associated with a misunderstanding. Thus, the term *homochiral* is used in the Ruch sense (see Section 12) and in the routine meaning of "identical configuration". The term *stereogenic*, which is distantly related to the concept of chirality and implies only that a particular structural fragment is a source of optical activity, receives rather wide acceptance.

5. Chemical topology

The geometrical basis of stereochemistry has been evident since the advent of the tetrahedral model of the carbon atom. The development of fundamentals of this branch of science, which has been started with the concept of chirality, was continued by Prelog in his lecture "Problems of Chemical Topology"[94] delivered at the meeting of the Royal Society of Chemistry in 1968. In the brief rigorous style, Prelog presented the view of the role of symmetry elements and symmetry groups in the definition of "chirality — achirality," outlined the notions of the 2D and 3D chirality, achiral simplexes, and procedures for their chiralization (desymmetrization), listed structures corresponding to different point symmetry groups, and exemplified new types of optically active stereoisomers, which have been synthesized based on the preliminary design.

The most characteristic feature common to stereochemistry and topology is the fact that metric relations are of no significance, *e.g.*, the qualitative aspect dominates over the quantitative one. This characteristic feature is of importance in the elucidation of the concept of configuration based on the molecular topological form (see Section 12). The view of chemical topology in its geometric-structural aspect has been proposed earlier.[116] Prelog underlined the aspect associated with the theory of sets and demonstrated that the topological

rather than geometric features are characteristic of stereochemistry. This is evidenced, in particular, by the phenomemon of cyclodiastereoisomerism discovered by Prelog;[117] for this phenomenon, the *direction* of the ring dictated by the structure is of importance. Here, one can readily see the analogy with the topological chirality of oriented catenanes.[14]

6. Symmetry groups and chirality

Analysis of the symmetry based on the theory of groups is of paramount importance for an understanding of chirality.[118] In chemistry, symmetry groups were first employed in analysis of vibrational spectra. It was established that chiral molecules are those possessing only rotation axes, *i.e.*, those belonging to the axial point symmetry groups $\mathbf{C_n}$, $\mathbf{D_n}$, **T**, **O**, or **I**. In other words, the absence of mirror-rotational axes S_n is a necessary condition for chirality to be manifested. All symmetry groups can be arranged as tree graphs using yes-or-no answers to questions about the presence of symmetry elements.[119] The trees differ depending on the character and the sequence of questions. A tree in which chiral symmetry groups were separated from achiral groups already after the first step was constructed.[120]

Within the framework of the concept of chirality, different classes of chiral molecules are characterized by different chirality elements, among which are a center, an axis, and a plane of chirality or, in other words, a chiral center, a chiral axis, and a chiral plane. Correspondingly, molecules are divided into molecules possessing central, axial, or planar chirality. Helicene-type molecules possess helical chirality. A comprehensive idea of chiral elements can be achieved by developing mathematical aspects of stereochemistry within the framework of the geometrical theory of chirality (see Section 12).

7. Chirality of molecular polyhedra

The geometry and stereochemistry of coordination compounds were discussed in monographs[14,121,122] and those of metal clusters were considered in a review.[123] The octahedron was the first (following the tetrahedron) studied polyhedron determining the arrangement of atoms involved in the nearest sphere about the central atom. This polyhedron is most typical of the coordination number of 6, which is common in inorganic complex compounds. The tetrahedron and the planar square are characterized by the coordination number of 4. Examples of compounds with the coordination number of 5 (for example, $Fe(CO)_5$) are also large in number. Later on, it became evident that all possible geometric forms must be considered. In a molecule, the nearest neighbors of each atom form a coordination polyhedron. The chirality of these polyhedra is determined by the number of different types of ligands and their relative positions. All coordination polyhedra actually realized in molecules are achiral. Chiralization of these polyhedra occurs only in the presence of *different* ligands; the dentation of the ligands should be taken into account. For example, in the case of monodentate ligands, the tetrahedron becomes chiral if all four vertices are different, *i.e.*, ligands of four types are required. The minimum number of different types of monodentate ligands (two) can ensure chirality of the trigonal prism.[14] Chiralization of the octahedron occurs in the presence of three symmetrical bidentate ligands.

Several polyhedra correspond to the same coordination number, the mutual transformations of these polyhedra being possible. The dynamic stereochemistry deals with intramolecular isomerizations of polyhedra.[14] Quantum-chemical calculations revealed enantiomeric paths between two stable isomeric species. In particular, one enantiomer of methane (containing four different vertices) can be transformed into another enantiomer bypassing the planar isomer, and this path proved to be energetically favorable.[124]

Coordination polyhedra are virtual geometric figures in the sense that their edges do not exist as chemical bonds; instead, only radial bonds between the vertices and the central atom occur. Because of this, the polyhedra are conformationally labile. Real polyhedral molecules are represented by carboranes (primarily by icosahedral) and fullerenes. The first member of the latter family is the Archimedean polyhedron C_{60} with the symmetry $\mathbf{I_h}$. The surfaces of all fullerenes consist of 12 pentagons and a number of hexagons. Chiral fullerenes were found among higher fullerenes; the first of them is C_{76} with the symmetry $\mathbf{D_2}$ (see Section 6). The chirality of all fullerene derivatives was surveyed in detail in a review.[125]

In the above discussion, it was assumed without mention that all polyhedra are convex. It is self-evident that the criterion for chirality can also be applied to nonconvex polyhedra, which are rarely used in the consideration of molecular structures. Since the chirality is treated as a mathematical phenomenon and, hence, it is extended from the three-dimensional (3D) space to the two-dimensional (2D) space, where a triangle rather than a tetrahedron serves as a simplex, the chirality of polygons, including nonconvex (which are "more" chiral than convex polyhedra[126,127]) can be examined.

8. Chiroptical methods

The angle of rotation of the polarization plane at a specified wavelength remains one of the most important characteristics of optically active compounds. The optical rotatory dispersion reflects the difference between the indices of refraction of right- and left-hand polarized light for an enantiomer in solution, whereas the circular dichroism reflects an analogous difference between the absorption coefficients.[128—131]

The Cotton effects account for optically active electron transitions in molecules, which are often localized in particular functional groups called *chromophores*. A class of dissymmetrical chromophores was distinguished and their optical rotations were calculated using hexahelicene as an example.[132] Symmetrical chromophores make a contribution to the optical rotation due to dissymmetry of the environment. The configuration of the chiral centers adjacent to the chromophore and the conformations of the molecule influence the sign and the value of the Cotton effect. For the purpose of analyzing this effect, the octant rule was first stated for the carbonyl group.[133] Later on, various section rules were stated for other chromophores.[75,134–136] These rules allow the determination of the configuration of the adjacent center from the sign of the Cotton effect. The more isolated is the chromophore, the more precise are the results of analysis, including quantitative data (the determination of the rotational force).[131] For overlapped chromophores, mathematical methods were developed for separating CD curves into regions of the regular Gaussian shape corresponding to individual chromophores.

All methods for the evaluation of the enantiomeric purity are based on the determination of the ratio of diastereomers formed in reactions with enantiomeric partners. The exceptions are polarimetry and circular dichroism spectroscopy, where light with a particular polarization direction serves as an "enantiomeric partner". This accounts for a special place of chiroptical methods of investigation of enantiomeric compounds (and "justifies" the commonly accepted term *optically active*). On the whole, methods of NMR spectroscopy and chromatography using enantiomeric solvents or phases are more sensitive than chiroptical methods. Less common related chiroptical methods are also available. Among them are luminescence circular polarization,[137,138] which is of importance in the case of optically nontransparent materials and films, and nonlinear optical activity, *i.e.*, circular polarization of the second harmonic observed for chiral molecules sorbed at the interface.[115] The last-mentioned method possesses very high sensitivity exceeding that of the conventional circular dichroism method by several orders of magnitude. Oriented achiral molecules were demonstrated[139] to exhibit optical activity (optical rotatory dispersion in the transparent region and circular dichroism in the absorption region).

All molecules exhibit magnetic circular dichroism and magnetic optical rotation, *viz.*, optical activity induced in the magnetic field (Faraday effect). In these methods, interactions with the oriented external magnetic field rather than electron transitions in the molecule located in the asymmetrical environment (due to its enantiomerism) serve as the source. The relation of these methods to stereochemistry has been discussed previously.[14]

9. Theories of optical activity

The aim of a theory of optical activity is to determine the sign of optical rotation or of the Cotton effect from the configuration of the enantiomer (the qualitative aspect) and to calculate its value or the intensity (the quantitative aspect) based on the molecular structure. In some cases, *ab initio* quantum-chemical calculations can be performed starting only from the molecular formula without resorting to the experimental data.[75,132,140] Semiempirical methods are based on the inclusion of experimental data on the optical rotation of a particular basis series of molecules.

Such a method for calculations of the optical rotation, which was proposed by Brewster,[141,142] takes advantageos account of the contribution of the conformational chirality and allows the correct prediction of the configuration of asymmetric atoms (not only carbon) in conformationally labile compounds.[143]

The intensity of the Cotton effect corresponding to an individual chromophore is estimated by the value called the rotational force, which can be calculated from the electric and magnetic moments of the chromophore and compared with the experimental value.

10. Chiral macromolecules

All natural molecules, *e.g.*, proteins, polysaccharides, nucleic acids, *etc.*, are not only chiral, but also enantiomerically pure. Early studies of the chiroptical properties of macromolecules have been devoted to sterically homogeneous simpler poly-L- and poly-D-peptides for which the relationships between the sign and the value of optical rotation, on the one hand, and the configurations of the asymmetric centers, the length of the polypeptide chain, and the nature of the solvent, on the other hand, were revealed.[134] This helped in estimating the contents of helical regions in the analysis of the tertiary structures of proteins.

More recently, optical activities of synthetic homopolymers and copolymers were examined.[144] The helical conformation of the main chain makes the major contribution to the optical rotation. For isotactic polymers in both the solid phase and solutions, this helical conformation can be very stable. Under the appropriate "chiral conditions," *i.e.*, in the presence of an asymmetric catalyst, an optically active polymer, which possesses a single helical direction and, consequently, exhibits high optical rotation, can be obtained from an achiral monomer.[145] Interestingly, the enantioselectivity of polymerization of chiral substrates, *i.e.*, the efficiency of internal induction by a chiral fragment, can be very high. Thus, the mere difference between protium and deuterium in the synthesis of poly-(*R*)-1-deuterio-*n*-hexyl isocyanate gave rise to polyamide with $[\alpha]_D$ −367° and the Cotton effects from the amide chromophore.[146]

A peculiar stereochemical aspect was observed in the chemistry of nucleic acids. Thus, the phosphate phosphorus atom becomes chiral upon replacement of one oxygen atom in its environment by the sulfur atom. Since the carbohydrate portion is enantiomerically pure, phosphonothioate analogs of nucleotides and nucleic acids exist as two diastereomers, which, naturally, differ in behavior.[147] Such analogs find use in biochemical assays of natural oligophosphates, in particular, of ATP.[148]

Finally, high-molecular-weight individual molecules with a peculiar architecture, *viz.*, dendrimers, have recently attract attention.[149,150] Chiral (enantiomeric) fragments can either be attached at the periphery of a dendrimer or be introduced into its core. Interactions of these fragments, provided that their conformational lability is restricted, are of interest and still are not studied at all.

11. Supramolecular chiral structures

Even the simplest molecules without any asymmetry can be packed in *crystals* in an asymmetric fashion. This fact has long been known. For example, urea, which was used for the optical resolution of 2-haloalkanes, crystallizes in the hexagonal lattice.[151] Chiral crystals of such compounds, as glycine or benzil, are also known. The optical activity of molecules in crystals has been discovered prior to that in solutions and, what is a matter of common knowledge, is not necessarily based on chirality of the molecule. Crystals of dialkylamides of phenylglyoxylic acid in which molecules adopt chiral conformations due to rotation about the OC—CO bond (which is confirmed by the observation of the CD spectrum of a suspension of the crystals in Nujol mulls) is an excellent recent example.[152] Irradiation of these crystals with UV light resulted in the asymmetric synthesis of β-lactam. Even higher enantiomeric yield (up to 100%) was observed in the case of enantioselective photocyclization of analogous prochiral molecules incorporated into an optically active matrix and thus forced to adopt a chiral conformation.[153] Toda has performed extensive studies of such inclusion compounds using optically active 1,6-diaryl-1,6-diphenylhexa-2,4-diyne-1,6-diols as a matrix and solid-phase asymmetric photochemical reactions.[154,155]

Spontaneous crystallization of racemic compounds as mixtures of crystals of two enantiomers, which has been known since Pasteur's studies (tartrates provide a classical example), was examined statistically.[156] Interest in the absolute asymmetric synthesis both under the action of polarized radiation and asymmetric crystals was still associated with the problem of the occurrence of optically active compounds in nature. The most essential studies performed in that period of time were surveyed in the monograph.[14]

The occurrence of chiral three-dimensional structures in the *liquid phase* is typical of two classes of liquid crystals,[157] *viz.*, cholesteric and nematic, which are generally formed by optically active molecules (often belonging to steroids). Intermolecular complexes without covalent or coordination bonds of the host—guest type have long been known. If one of the components is optically active, the complex possesses this property as well, chromophores of the optically inactive component exhibiting induced optical activity with characteristic Cotton effects. This phenomenon has been studied in most detail for inclusion compounds in which cyclodextrins, which are natural cyclic oligosaccharides[158] devoid of chromophores beyond the far UV region, serve as a host and various organic or organometallic compounds serve as a guest.[159,160]

12. Mathematical aspects of chiral stereochemistry

Once the geometrical context of stereochemistry has been extended to topological, an important role of other divisions of mathematics, *viz.*, of the theory of graphs, the theory of sets, and the algebra, was brought to light.

One of the main goals in the theoretical analysis of the main concepts of stereochemistry is to realize the meaning of the terms *chirality* and *configuration* (see above) and to use them for constructing a logical system of stereochemistry. A considerable volume of research has been carried out by several groups;[161—172] however, each group generally carried out investigations based on their own views without regard for the results obtained by other groups. Attempts to integrate various concepts into a unified system failed; in part, these concepts were generalized in a number of studies.[14,17,172] The concept of chirality, which has been studied in detail and found widest use in chemistry, is also of importance in allied sciences (in physics and biology, which are located lower and higher than chemistry on the scale of complexity). The chirality is considered as a mathematical phenomenon, including, in particular, the chirality of sets, the chirality of figures, and the chirality of graphs.

The totality of chemical compounds was treated as a complete chemical set, its algebraic properties were examined,[173] and the notion of chiral sets was stated.[174] The latter has extensive applications. Chiral sets were defined based on the main and the only criterion, *e.g.*, the presence of at least one element non-superimposable with its mirror image. The more comprehensive classification gives rise to a set tree[17] including complete, achiral, chiral, enantiomeric, racemic, and empty sets. In the case of more than one parameters, diastereomeric sets occur.

Ruch elaborated the algebraic theory of chirality.[175,176] He proposed the notion of chirality as a function of ligand parameters whose sign characterizes the chirality of the object. For achiral molecules, this function vanishes by definition. Based on the Ruch theorem, a class of molecules, chiroids *a*, was distinguished for which no other (chiral) zeros occur (for example, the tetrahedron and the trigonal bipyramid). For these molecules, the

notions of *homochirality* and configuration series have significance. Another class, chiroids *b* (represented, for example, by a tetragonal pyramid), is characterized by the presence of chiral zeros of the function, *i.e.*, it is possible to go from one enantiomer to another bypassing the achiral point; the homochirality and the configuration series are absent. The examination of the chirality function and the algebraic approaches was continued in a series of studies cited above.

The geometrical theory of chirality[177,178] gave an insight into *n*-dimensional chirality elements as achiral elements of an (*n*+2)-dimensional chiral structure. Therefore, the chirality center is an achiral element of the chiral 2D space (plane) and the chirality axis is an achiral element of the chiral 3D space. Furthermore, the chiral 4D space including a chirality plane as an achiral element was first appeared in the logically substantiated construction.

Any field of science possessing a strict logical basis can, within certain limits, be developed axiomatically. It is also true that complete axiomatization is impossible (let us recall the Hilbert sixths problem — "Axiomatization of physics"). One of the most important postulates of the experiment on axiomatization of stereochemistry[179] saying "*Non-induced enantioselectivity is impossible*" goes back to the Curie principle (1894). In the more modern interpretation proposed by Shubnikov,[180,181] this postulate is phrased in the following way: "*Stationary symmetry of isolated systems can only increase; for dissymmetrization, the system must be extended with disturbance of its isolation*".

There is a direct analogy between the chiral graphs and the enantiomeric reaction pathways. The existence of asymmetric pathways between enantiomers bypassing an achiral intermediate was first established for molecules containing two chiral centers.[10] More recently, other examples, in particular, enantiomerizations of methane were studied.[124] Chiral and achiral pathways were analyzed theoretically in relation to the character of the transition state.[182]

The extremely complex problem of quantitative evaluation of chirality is yet to be solved.[183] Mislow[170] dealt with a simpler case of the 2D chirality of triangles. Kuz'min[171] offered the dissymmetry function for evaluation of the degree of deviation of a chiral structure from achirality,[93] which was determined as the geometric average of the degrees of dissymmetry of a molecule with respect to the symmetry elements S_n, and described some applications of this approach. Avnir proposed the method of continuous symmetry measures for estimating the asymmetry of a molecular object relative to any symmetry element.[92] An attempt was made to generalize these two approaches.[184] Analysis of chiral structures based on chiral simplexes with the use of stereochemical codes, which were developed according to particular rules, was also proposed.[185] The chirality of large random macromolecular structures in relation to stereoselectivity was treated.[186]

13. Chiral recognition

This problem, which has assumed great importance, is directly relevant to interactions of any chiral objects. From the practical standpoint, this problem is associated with separation of enantiomers by chromatographic methods using enantiomeric phases (adsorbents).[187] Chromatography along with NMR spectroscopy is the most sensitive method for enantiomeric analysis. This preparative method has been developed in various versions. The question arises as to the number of contact points required for chiral recognition. In 1952, it was suggested[188] that three simultaneous interactions are necessary (in accordance with the earlier model proposed for enzymes by Ogston[189]). Later on, this view received support;[190] however, another model was also advanced according to which only two points are required.[191] Recent analysis of the relationships between enantioselectivity and chirality allowed the conclusion that the necessary and sufficient number of point contacts is a variable value, which depends on the structures of both partners determining the character of interactions.[192]

Investigations of active centers of enzymes and the optimum arrangement of substrates (docking) have assumed great importance in bioorganic and medical chemistry. These studies are based on the use of stereochemistry in combination with computer simulation, the approach being versatile. An active center in which a substrate is bound, even though the latter is achiral, consists of enantiomeric amino acid residues and the substrate can be forced to adopt a chiral conformation responsible for its further reactivity. This line is one of the most important in investigations of active centers of enzymes and receptors of biologically active molecules.

14. Chiroselective synthesis

In the development of the fine organic synthesis, goals to be sought become more and more complicated. The existence of natural complex compounds challenged creativity of scientists but simultaneously added a competitive element. Thus, record achievements concerning the molecular size (molecular weight) and the number of asymmetric centers were registered in the spirit of the Guinness Book of Records. The directed synthesis of the desired molecule requires ingenuity and acquires traits of art. This line of investigation became very popular in the third quarter of the 20th century marked by creative activities of Woodward and Corey. In particular, reserpine,[193] colchicine,[194] penicillins,[195,196] chlorophyll,[197,198] macrocyclic antibiotics,[199] *etc.* were synthesized. Although more complex molecules were synthesized later on, the ideological peak in this field has been already passed. Apparently, the assurance that *any* molecule can be synthesized (probably, except for only macromolecules) was of decisive importance. Palytoxin, which is a poisonous com-

pound isolated from the marine soft coral, remains the record-breaking molecule as regards the stereochemical complexity. Its overall structure was established in 1981 and its detailed structure was determined in the course of the multistage synthesis. The enantioselective synthesis of this molecule containing 63 chiral centers was carried out starting from eight pre-synthesized blocks[200] at the Harvard University in 1989.

Although the synthesis still attracts considerable attention (because the number of interesting objects increases), it requires a particular additional motivation in deciding on objects. The biochemical trend becomes more noticeable; the special biomimetic line of investigation has been developed[201] whose aim is to simulate reactions under biological conditions (enzymatic reactions). Natural compounds is the original source of all optically active compounds. The diversity of available natural nonracemic compounds suitable for the preparation of new optically active molecules was called the chiral pool. Asymmetric reactions (see Section 15),[202,203] including catalytic processes,[204] acquire increasing practical importance. Although molecules of natural compounds remained the main objects in the organic synthesis, the progress of the molecular design brought forth other targets, which often bear no direct relation to the chiral stereochemistry: molecular polyhedra, topological figures, *etc.* Since the pioneering studies on the retrosynthetic analysis and computer synthesis,[205] this line of investigation becomes increasingly important. Although the enumeration of all synthesized optically active molecules is beyond the scope of this review, let us note several prominent examples: twistane with the symmetry $\mathbf{D_2}$,[206,207] double *para*-cyclophane,[208] helicenes,[209] catenanes,[210] and Möbius-strip-shaped molecules.[108] The recent examples of topological objects in enantiomeric form were obtained in the chemistry of coordination compounds.[211] The stereoselective synthesis of ligands, metal complexes, and organometallic compounds performed in the interests of asymmetric catalysis or simulation of metalloproteins continues to grow in popularity.

The latest innovation in the synthesis is the techniques of combinatorial libraries.[212,213] This techniques represents the ideology of pragmatism* and, in essence, keeps the imaginative element to a minimum replacing it with the screening technology based on the employment of high-performance equipment, which allows the separation of complex mixtures of products produced by numerous analogous competitive reactions.

15. Asymmetric synthesis and catalysis

For a chiral fragment to be introduced in one stage, the starting molecule must be prochiral. Asymmetric reactions are most often performed with the use of such prochiral groups as C=O, C=N, or CX_2, where X is generally H, the formation of simultaneously two chiral centers being possible in the case of C=C. Recently, procedures were developed for cascade (competitive) reactions, which allow the chiroselective formation of several chiral centers (see, for example, the study[214]). The principle of "chiral economy,"[215] which assumes the most complete conversion of a prochiral substrate into the only target enantiomer of the product and the minimum sacrifice of the enantiomeric purity at each stage of the chiroselective synthesis, was proposed as the general strategy.

Asymmetric reactions (as well as other processes) can be performed in either the stoichiometric or catalytic mode. Among the most popular reactions performed in the stoichiometic mode are hydroboration,[216] cyclopropanation,[217] and hydroxylation[218] of olefins, which are often used in laboratory practice. The second group of reactions involves various versions of hydrogenation of the C=C, C=O, and C=N double bonds catalyzed by transition metal complexes[219] and nickel- or palladium- catalyzed cross-coupling.[220] The synthetic scope of this approach is very wide and includes many interesting reactions, for example, the four-component Ugi reaction[221] and the reaction of dialkylzinc with aldehydes catalyzed by optically active aminoalcohols.[222] Examples of chiral phase transfer catalysis were reported.[223] An ingenious aspect of the chiroselective synthesis of substituted α-amino acids consists in the employment of octahedral transition metal complexes for activation of glycine or alanine fragments of ligands (see the review[224]). Chiral complexes of transition metals with *salen*-type ligands were used in the efficient asymmetric catalysis of epoxidation of olefins[225] and in the addition of trimethylsilyl cyanide to aldehydes.[226] An advantageous approach involves the asymmetric synthesis of different classes of enantiomeric compounds based on the common key precursor.[227] In all these reactions, the final products contain a chiral center. Successful attempts to perform the asymmetric synthesis of molecules with non-central chirality are much less in number. Among these are asymmetric cylopalladation involving a series of metallocenes in the course of which the planar chirality is induced by a chiral center of an external catalyst.[228] The reactions relating compounds with different chirality types are of importance in establishing configurations (for example, center—axis[229] and cyclophane—helicene[230]).

Asymmetric catalysis, which has been originated as heterogeneous, was then developed predominantly as homogeneous. Such reactions are carried out predominantly with the use of optically active transition metal complexes containing enantiomeric ligands as catalysts.[231] The simplest and widely used asymmetric hydrogenation reaction was discovered in 1968 for rhodium catalysts containing optically active phosphine

* "Combinatorial chemistry is, in essence, a brute force alternative to the reasoned, intellectual efforts of chemists to design, in a rational manner, compounds for specific purposes".[213]

ligands.[232,233] Later on, the chelating diphosphine ligand DIOP gained popularity. This ligand is rather stable and efficient and is readily accessible in the form of both enantiomers.[234] Many other ligands were also proposed. A search for new ligands is being continued because the enantioselectivity of the reactions involving different substrates depends on the nature of the ligand.

Recently, the integration of conventional approaches used in organic chemistry with biocatalysis has received widespread attention. The use of enzymes in the preparative chiroselective synthesis gained acceptance in the examination of their application as catalysts to artificial substrates. The unjustified assumption that enzymes can be used only in reactions with natural substrates was gradually overcame in subsequent studies of inhibitors and substrate analogs. Organic reactions are often performed with the use of an appropriate growing microorganism rather than an enzyme isolated in pure form. In these cases, culture liquids contained many enzymes possessing different selectivities. Hence, quantitatively different and even qualitatively opposite stereochemical results can be obtained for different, though related, substrates.[235,236] Preparative methods for the enantioselective enzymatic synthesis have been developed. In particular, an interesting procedure involving enzymes in hydrocarbon media was proposed.[237,238] The latest innovation consists in expressing a useful enzyme in yeast using the cloning technique in which recombinant yeast cells act as a biocatalyst. For example, cyclohexanone monooxygenase was introduced into yeast and enantioselective Baeyer—Villiger oxidation of alkyl-substituted cyclohexanones was carried out to obtain seven-membered lactones in high enantiomeric yield.[239] The latter were used as chiral building blocks. Yet another line of investigation associated with bioorganic chemistry involves catalysis with the use of monoclonal antibodies;[240] these processes require functioning of entire organisms. Antibodies are large proteins possessing specificity to a particular compound (hapten); examples of enantioselective catalysis are available.[241]

It is not surprising that a considerable achievement in a particular field of science brings to the fore its practical implementation. Its is well known that the society as a whole and its representatives (government, companies) are interested in practical implementations resulting from fundamental studies. The applied aspect of chiral stereochemistry involves the preparation of chiral compounds in optically active form using the most convenient and economic procedures.[242] That is why the advancement of procedures for the asymmetric synthesis gained popularity in the last decade. The asymmetric synthesis is, in principle, the best approach to the target compounds because it allows the preparation predominantly of one enantiomer of a chiral product immediately from an achiral (more precisely, from a prochiral) precursor; the enantiomeric purity can exceed 99%. Preference given to the asymmetric catalysis (compared to stoichiometirc asymmetric reactions) also results from consideration of economy because it allows one to achieve chemical yields much higher than 100% with respect to the catalysts. In the field of asymmetric reactions, the homogeneous catalysis apparently wins the competition with the heterogeneous variation. The first procedure used industrially involved catalytic hydrogenation of acetamidocinnamic ester in the presence of the rhodium complex of *ortho*-anisylmethylcyclohexylphosphine producing a derivative of optically active phenylalanine.[243] Asymmetric catalytic hydrogenation can be carried out in liquefied gases[244] or in supercritical CO_2.[245]

Of other examples of asymmetric catalysis, hydroformylation have received the most study.[246] Many reactions find use in laboratory practice. In particular, the enantioselective $[4\pi+2\pi+2\pi]$-*cyclo*-addition of norbornadiene to olefins or butadienes, which is catalyzed by cobalt complexes with optically active diphosphines, proceeds with high asymmetric yields.[247] Catalysts (including catalysts of the enantioselective addition and stereoregular polymerization of olefins) belonging to *ansa*-derivatives of titanocene and zirconocene are studied extensively.[248] Enantiomerically pure compounds came into demand in different fields: stereoregular polymeric materials, liquid crystals, materials for nonlinear optics, *etc.* The enantiomeric purity is particularly required of drugs used in present-day medicine to avoid the injurious effect of another enantiomer on the living organism.* Hence, scientists presently struggle to enhance the enantiomeric yield of the target product, no matter how small the improvement may be (one percent or even smaller).** Pharmaceutical companies spend much money on these investigations. This is the only explanation for the fact that many laboratories are conducting extensive studies on the synthesis of more and more analogous ligands for asymmetric catalysis using known procedures. The reason is that a catalytic combination best suited for a particular compound is searched for by the trial-and-error method. Various procedures for the chromatographic separation of racemates into enantiomers are very popular for the same reasons.

16. Stereochemical community

Scientists have organized professional communities, either formal or nonformal, for years and maintain relations by keeping up a correspondence and owing to specialized journals and conferences. It is rather surprising that no regular general conferences devoted to stereo-

* The dramatic history of thalidomide is the most impressive example.[249]

** The conceptual importance of this increase by a small percentage is insignificant, but its practical advantages are apparent.

chemical problems are held, but the proportion of stereochemical investigations presented at congresses on organic, coordination, and organometallic chemistry and on catalysis grows steadily. Famous stereochemical conferences in Bürgenstock (Switzerland),[250] which are held annually beginning with 1965, are very authoritative, but involve a small number of participants. The series "Topics in Stereochemistry" was started in 1967. As for periodicals, journals devoted to chiral stereochemistry have recently founded: Tetrahedron: Asymmetry (1990), Enantiomer (1996), and Chirality (1989). The last-mentioned journal is designed essentially to publish papers devoted to applied problems describing various procedures for the optical resolution of particular molecules, which are predominantly of practical interest.

The achievements of leading researchers concerned with the problems of stereochemistry gained due recognition of the international scientific community: Werner (1914), Barton and Hassel (1969), and Cornforth and Prelog (1975) were winners of the Nobel Prize, which is the most prestige award of the 20th century.

Since Werner, Dreiding, Prelog, and his large research team worked in Zurich, this city played a unique role in the history of stereochemistry and has a rightful claim to the unofficial name "the stereochemical capital of the 20th century." Vladimir (Vlado) Prelog, the Professor of the Swiss Federal Institute of Technology (ETH, Zurich), not only performed a series of experimental research into stereochemistry honored with the Nobel prize, but also proposed the concept of chirality and was a founder of chemical topology, thus taking a decisive step toward the conceptual development of stereochemistry. Owing to his scientific versatility, energy, enormous creativity, pedagogical gift, and bright individuality, Prelog had a great influence on colleagues from different countries and, in my opinion, can be called the main person in the stereochemistry of the 20th century.

Conclusion

I do not like predictions but I have a feeling that the chiral stereochemistry of individual molecules and the construction of the stereochemical system have been in principle completed, except for the mathematical development of some quantitative aspects. The future of this field of science will lie with the stereochemistry of chiral ensembles and supramolecular stereochemistry. However, the applied aspects of stereochemistry will persist: the chiroselective synthesis of new molecules will be carried out and procedures for the enantioselective synthesis will be improved (*i.e.*, the number of the compounds synthesized will be increased ininitely).

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