Logic and Order in Stereochemistry

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Dedicated to Professor Vladimir Prelog on the occasion of his 80th birthday

A framework of concepts, definitions, and classifications is discussed that form a basis for a formalized, computer-oriented approach to stereochemistry. These include constitutional symmetry and constitutionally equivalent atoms, chiral genus and its role in asymmetric syntheses, permutation isomers, the chemical identity group of molecules and ensembles of molecules, set-valued mappings and their stereochemical uses that pertain to the correlation of the stereochemical features of the educts and products in chemical reactions, as well as diverse notions that serve to classify and interpret stereoselectivity. – It is the purpose of this article to point out briefly some simple new tools for better understanding, analyzing, and criticizing current stereochemical results.

1. Introduction

The present article addresses those who are interested in the conceptual and formal aspects of stereochemistry. Only moderate knowledge of elementary stereochemistry will be needed to read this paper. It will lead the reader to the frontiers of modern methods of stereochemical reasoning, and with little effort, the reader's ability to comprehend, scrutinize, classify, and criticize current published work in stereochemistry will be substantially enhanced. Early familiarity with a general system of reference as is presented here well serves any student who seriously strives for knowledge in stereochemistry. It is good practice in oenology to establish a system of orderly storage before the cellar is filled with products of varying vintage and provenance.

In general, many modern chemists cherish new experimental results and techniques more than progress in concepts and understanding. New theories are best appreciated if they are usable in the detailed interpretation and prediction of experimental data, preferably in numerical terms.

In present day stereochemistry abstract concepts and general principles do not seem to be at the focus of interest. Chirality[1] and conservation of orbital symmetry are some of the few exceptions[2].

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More attention seems to focus on recent experimental developments in the area of highly stereoselective reactions and their application to the synthesis of chiral natural products and related compounds[3–8]. This domain includes some of the most spectacular successes of modern organic chemistry. Experimental work on stereoselective reactions is now one of the most fashionable endeavours in chemistry.

However, new ideas, concepts, models, and theories are still, and even increasingly, important for the interpretation of current empirical results and data, as well as for guiding future experimental research. Although computer assistance in chemistry[9] is still a young discipline, computers are already indispensable for many areas of chemistry. Progress in the chemical applications of computers depends largely on qualitative mathematical theories and models of the logical structure of chemistry, as well as on formalized representations of chemical systems and phenomena[10–12]. This is specially true for the solution of chemical problems whose unknowns are a molecular system or a chemical reaction. Note that progress in models and mathematical approaches often requires advances in chemical concepts, but that new theories also may lead to novel ideas. «Chemical distance» is an example[10, 13]. In this article some concepts, relations, principles, definitions, classifications, and formalisms will be presented as parts of the grammar of stereochemistry. Its relationship to the global framework of the logical structure of chemistry[12] will be discussed.

2. Chemical Constitution and Constitutional Symmetry

An up-to-date system for the classification and representation of molecular structures and their essential features is an indispensable foundation of any conceptual progress in chemistry.

The customary hierarchic classification of isomers[14] according to *isomers, constitutional isomers, configurational isomers, and conformational isomers* is useful as a hierarchical system of order. This system corresponds to a hierarchy of the structural features of the molecules and it indicates that the structure of a molecule is primarily determined by its chemical constitution, whereas its stereochemical features are just a molecular «fine structure»[11].

Ivar Ugi: A brief curriculum vitae is found in Chimia 39 (1985) 43. In 1962 the present author began to investigate the mechanism of stereoselective four component condensations. For this a novel mathematical and computer-assisted approach to complex systems of parallel and consecutive reactions was developed in a joint effort with the mathematician Günther Kaufhold of Bayer AG, Leverkusen. This led to Ugi's continued active interest in stereochemistry, and especially its conceptual and mathematical aspects. The theoretical physicist and mathematician Prof. Ernst Ruch (Freie Universität Berlin) cooperated with the author during the years 1965–1969 in the formulation of the stereochemical analogy model for stereoselective reactions that is based on group theory and statistical thermodynamics. Some of the general insights and ideas concerning stereoselective reactions that have evolved from combined experimental and theoretical studies by Ugi and co-authors are portrayed in the present paper. Beginning 1970 the author had an intense collaboration with Prof. James Dugundji, a prominent topologist at the University of Southern California, Los Angeles (Dugundji passed away on January 8, 1985). The first major joint project was the development of the theory of the BE- and R-matrices, a qualitative universal mathematical model of the logical structure of constitutional chemistry. The theory made the computer-assisted deductive solution of various types of chemical problems possible. The «Leitmotiv» of Dugundji's and Ugi's stereochemical endeavours was chemical identity, a notion which affords a unified representation of the logical structure of static and dynamic stereochemistry. From 1976 to 1984 J. Dugundji, Dr. Rosemarie Kopp, the late Prof. Dieter Marquarding, and the author elaborated the theory of chemical identity groups, a qualitative mathematical theory that encompasses all important qualitative stereochemical relationships. It was first published in "Perspectives in Theoretical Stereochemistry", and its essence, together with some additional applications, are presented here, but with minimal use of mathematics.

Recall that the chemical constitution of a molecule is specified by stating for each constituent atom its covalent bonds and the atoms to which it is attached by those bonds.

Frequently the placement of the lone pair valence electrons is included. The chemical constitution is customarily described by a constitutional formula.

In chemical documentation (e.g. by the Chemical Abstracts Service (C.A.S.)) the chemical constitution of a molecule is generally represented by a MORGANized connectivity matrix[15]. For computer assistance in chemistry the chemical constitution of molecules and ensembles of molecules (EM) is advantageously represented by BE-matrices[10, 16]. The atoms in an EM are indexed, and the atomic indices are used as the row/column indices of a BE-matrix. Since n atoms can be indexed in n! distinct ways, an EM of n atoms is representable by up to n! distinct BE-matrices.

When the atoms are indexed by the algorithm CANON[17], the corresponding BE-matrix is called CANONical.

The off-diagonal entries $b_{ij} = b_{ji}$ of a BE-matrix are the formal bond orders of the covalent bonds between the atoms A_i and A_j. The diagonal entries b_{ii} are the numbers of lone valence electrons at the atoms A_i.

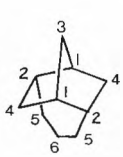
With its diagonal entries a BE-matrix contains more information than a corresponding adjacency or connectivity matrix, and in contrast to the latter, a BE-matrix is not just a table but a genuine mathematical entity with well-defined algebraic properties[10].

If any two atoms in a molecule belong to the same chemical element and all of their covalent connections are superimposable, these atoms are constitutionally equivalent[17a]. This corresponds to a constitutional symmetry, in essence an isomorphism of the labeled molecular graph.

In contrast to the MORGAN algorithm that is primarily based on the unlabeled molecular graph, the algorithm CANON gives equal emphasis to the edges and the labeled nodes of the molecular graph. CANON is thus capable of recognizing the constitutional equivalence classes of atoms, and it assigns atomic equivalence class indices (ECI) to the atoms as well as the atomic indices.

1

2



3

In formulae **1**–**3** the ECI of the carbon atoms indicate the constitutional symmetries that are present. The constitutional equivalence classes of atoms in a molecule determine the constitutional contribution to its NMR spectrum, and accordingly the chemical shift pattern of an NMR spectrum reflects directly the constitutional symmetries that are present.

Recognition of the constitutional equivalence classes of atoms is a prerequisite for computer-assisted representation and documentation of the stereochemical features of molecular structures. For instance, the asymmetric carbon atoms are recognized as those carbon atoms whose covalently bound neighbor atoms have all different ECI. The ECI of the asymmetric carbon atoms also directly indicate which of these are constitutionally equivalent, as in tartaric acid.

The relative CANONical indices of the α-atoms of the ligands at a stereogenic unit, i.e. those atoms of the ligands that are directly attached to the central skeleton may also be used as ligand indices, in analogy to the CIP priorities[18]. Accordingly, the algorithm CANON may be used for complete chemical documentation that covers constitutional as well as stereochemical aspects, and provides an interface between constitutional chemistry and stereochemistry[11c].

3. Stereochemistry and Chirality

Stereoisomers and their distinct observable chemical and physical properties are the topic of stereochemistry.

In classical stereochemistry, the stereoisomers were defined as molecules that have the same chemical constitution, but differ in the relative spatial arrangement of their constituent atoms. Since the majority of molecules studied in modern stereochemistry undergo a variety of internal motions, often there is no chemically meaningful rigid model that expresses the essential features of such a molecule[11].

Accordingly, in order to be generally valid, a definition of stereoisomers is preferable that does not refer to any geometric features of molecules:

Any two molecules are stereoisomers if they have the same chemical constitution, but are not chemically identical. Under given observation conditions, any two molecules are called chemically identical if they interconvert spontaneously and belong to the same chemical compound[11].

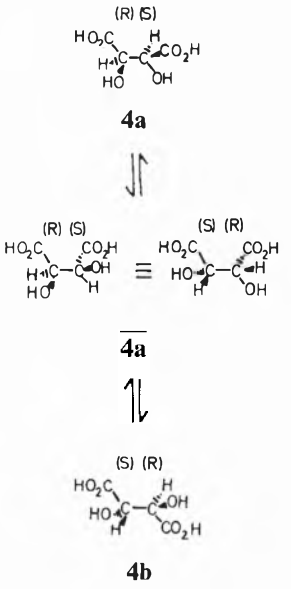
When the solution of a stereochemical problem depends on a single molecular species an entirely geometry-based treatment is feasible, as is provided by the methods of classical stereochemistry, molecular mechanics, and quantum chemistry.

In modern stereochemistry it is, however, often necessary to analyze molecular relations within ensembles and families of stereoisomers and permutation isomers[11], whose geometric features change with time. Thus, there is a need for new ideas beyond geometry in order to cope with the great variety of rigid and nonrigid stereochemical systems.

Prelog recognized that the concept of chirality as defined for geometric objects by *Lord Kelvin*, is much more adequate for stereochemistry than «asymmetry» or «dissymmetry» – in particular, when chiral molecules are considered that are representable by geometric models[1].

There are, however, some nonrigid molecules whose chirality or achirality cannot be interpreted by geometry-based reasoning alone. An example is *meso*-tartaric acid **4** that has no observable chirality. In many textbooks this fact is explained by the cavalier statement that the asymmetric carbon atoms of **4** have opposite configurations, and thus offset each other.

Scheme 1

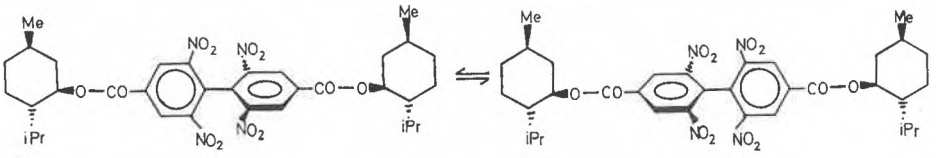


A more satisfactory interpretation of the observable properties of **4** is that the enantiomeric conformations of **4**, e.g. **4a** and $\overline{\mathbf{4a}}$, equilibrate through internal rotations about the central C–C bond. Furthermore, **4** has one staggered conformation **4b** that is achiral because it has a center of inversion.

Mislow[19] designed and investigated the compound **5**. It has no observable chirality, and yet it does not have any single achiral conformation. The explanation is that **5** and its enantiomer $\overline{\mathbf{5}}$ equilibrate by a 90° internal rotation of its biphenyl moiety (Scheme 2).

These examples, and many others, indicate the need to extend the concept of chirality from geometric objects and molecules that are geometrically representable to non-rigid molecules. This is in fact simple to achieve. The replacement of «chirality» by «chemical chirality», of «geometric object» by «molecule», of «mirror image» by «enantiomer» and inclusion of «intramolecular motions that can occur under observation conditions» suffices[20].

Scheme 2



5 $\bar{5}$

This notion of chemical chirality also affords a measure of chirality, the so-called *chiral genus*:

The chiral genus of an ensemble of molecules is one-half the minimal number of cuts of covalent bonds needed to racemize its double by exchanges of molecular parts.

Cuts of endocyclic bonds are permitted if and only if the required conversion cannot be accomplished by any set of non-endocyclic cuts[20].

The double of a given ensemble EM of molecules is the ensemble 2 EM which contains two copies of each molecule of EM. Our measure of the chirality of the ensemble is its chiral genus. We convert the double of EM into the achiral racemic ensemble EM+$\overline{\text{EM}}$ ($\overline{\text{EM}}$ is the enantiomer of EM) by cutting covalent bonds in some or all of the molecules and reassembling the fragments of each cut molecule to form its enantiomer or suitable stereoisomer. The chiral genus of EM will be the smallest number of cuts required to transform 2 EM into the chemically achiral ensemble EM + $\overline{\text{EM}}$.

With the above definition, an ensemble of molecules has chiral genus zero if and only if it is chemically achiral. Applying the defintion to a single molecule, we find that the chiral genus of a single molecule is ½ the number of cuts which are necessary to convert it into its enantiomer. More generally, letting G(EM) denote the chiral genus of any ensemble EM, we have $G(EM) \geqslant 0$ for every EM and $G(EM \cup EM') \leqslant G(EM)+G(EM')$ for any two ensembles EM and EM′. Thus G can be regarded as a finitely subadditive set function on the set of all ensembles of molecules. Observe that the chiral genus of an ensemble need not be equal to the sum of the chiral genera of its members. For example, a chiral molecule has the same (non-zero) chiral genus as its enantiomer, but the racemate (the ensemble consisting of that molecule and its enantiomer) has chiral genus zero.

Two types of quantitative measures of chirality are needed in stereochemistry, which will be illustrated using the following metaphor: One important characteristic of a herd of cattle is the average weight of the animals, and it depends on feeding. The overall number of animals in a herd is independent of feeding, as long as this is adequate, and changes only through death and birth. Both types of data are relevant for the comparison of herds.

The quantitative aspect of chirality which is represented by chirality functions[21b] corresponds to the weight of animals in the above example. The enumeration of chirality elements by chiral genus is that aspect of molecular chirality that is comparable to counting the animals in the herd.

4. Permutation Isomers and the Theory of Chemical Identity Groups

A solid foundation for a completely general and rigorous unified treatment of stereochemistry is provided by the theory of chemical identity groups[11]. In special cases this theory may be more cumbersome to use than the more familiar but less rigorous energetic-geometric methods, but it is more adequate, because it avoids unjustified assumptions, and it considers the geometric/structural and the chemical aspects of molecules simultaneously.

In order to achieve this we need first a precise and universal way to represent any features of molecular structures and their changes that are essential for a given stereochemical question.

We can accomplish all this by regarding the molecule as consisting of a skeleton and a set of ligands, where we call ligands those atoms, or polyatomic groups, that can be permuted, and we call skeletal sites that part of the molecule which remains after all the ligands are removed. To give the broadest scope to our considerations, we take the permissible molecular rearrangements to be all the distinct ways of placing the ligands on the skeletal sites.

Any two molecules obtained by a ligand rearrangement are called permutationally isomeric, and the set of all the molecules obtained in this way is called a family of permutation isomers[11, 22].

An exact description of all these molecules can be obtained by selecting one of them as the reference isomer X. We select one molecular individual E from the isomer X as a characteristic model, the reference model. Then any rearrangement of the given ligands on the skeletal sites is completely described by a permutation of the ligands on the reference model. For example, with the reference model E the permutation (1→2→4→1) of ligands, which we write as (124) in the standard permutational notation, results in the molecule denoted by (124) E.

Scheme 3

E(≡ **6a**) (124)E(≡ **6b**)

As a mathematical operation permutation is as elementary as addition and subtraction, and as easy to execute.

Use of a permutational approach for the study of molecules was initiated by *Polya*[23] in 1936, in his enumeration of certain types of isomers. *Polya*'s counting procedure was significantly extended by *de Bruijn*[24], and modified by *Ruch* et al.[21a] who also use permutations for classification purposes. The general concept and term «permutational isomerism» was first defined in 1970[22], when its distinction from stereoisomerism was also pointed out. *Klemperer*[25] and *Nourse*[26] published interesting contributions to permutation isomerism. The proceedings of a conference on the use of permutations in chemistry and physics[27] provide a review of the recent literature of this field.

In the earlier uses of permutations in chemistry the molecules are conceptually dissected into a set of ligands and a skeleton, and the ligands and the skeletal sites are indexed. A molecular configuration is given by indicating the placement of the ligands at the skeletal sites[22]. Isomerizations through permutations of the ligands and the equivalencies of ligands are expressed by permutations of the ligand indices. Skeletal symmetry operations are expressed by permutations of the skeletal site indices[21, 28].

The traditional uses of permutation groups in stereochemistry[21–28] have been successful in the solution of various stereochemical problems. However, in those approaches a given permutation can represent either a ligand exchange, or a possibly nonexistent skeletal symmetry operation (because of deformations of its skeleton through the different ligands), or an intraskeletal motion, which, as can be expected, generates conceptual difficulties. No universally applicable unified theory of stereochemistry has evolved from those studies, because they are essentially based only on elementary geometry. What all these idealized operations express that are represented by permutations in the traditional approach, are essentially identity-preserving operations. In the present approach the considered ligand permutations are explicitly defined as the operations that preserve chemical identity, regardless of their other meaning, and are represented by permutations of the ligands.

In 1976 seemingly minor progress was achieved by the use of ligand indices only[29]. As we now know, this was, however, an absolutely crucial breakthrough for the development of the theory of chemical identity groups[11], in that the geometric skeletal symmetries and other geometric features of the molecules were replaced by the concept of chemical identity. The concept of chemical identity implicitly embraces molecular geometry and chemistry, and it is also directly applicable to molecules that are not representable by any geometric model.

The concept of permutational isomerism must be carefully distinguished from that of stereoisomerism. There exist permutation isomers which are not stereoisomers, and there are stereoisomers that are not permutation isomers[22]. In the case of permutation isomers with a polycentric skeleton some members of a family of permutation isomers have the same chemical constitution and thus are stereoisomers, while others are constitutional isomers.

If L is the set of ligands, then the set of all permutations of L forms a group SymL, the symmetric group on L objects. With this terminology we provide the following definitions:

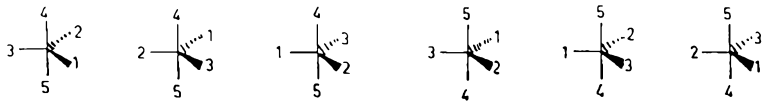
Let X be a given compound and E a reference model for X having a set L of chemically distinguishable ligands. Let S_X be the set of all permutations of the ligands of E that yield models chemically identical with E, all representing X. For reasons based entirely on the nature of chemistry, the set S_X will be a subgroup of SymL. We call S_X the chemical identity group of X, and $J_X(L)$ is the family of permutation isomers with a ligand set L and a reference isomer X.

The chemical identity group is the conceptual basis for our representation of the stereochemistry of molecules, flexible or not. As is well known, groups are frequently used to express geometric symmetries. Our chemical identity group is, however, new in concept and in intent. The chemical identity group does not express geometric symmetries so much as it expresses stereochemical realities. Moreover, even our indexing system[29, 30] is different from those used previously: our approach is based entirely on permutations of indexed ligands on a fixed model, and we do not assign indices to the skeletal sites at all (see e.g. ref.[21]).

Although a particular chemical identity group may be isomorphic to groups representing symmetries of some geometric models or to the Longuet-Higgins group[31] and related groups, the meaning of the corresponding chemical identity groups is entirely different[11]. Their elements never represent any symmetry-related operations that bring some geometric objects into self-coincidence (see Scheme 4 and below).

If all the ligands are chemically distinct, X has exactly $|SymL|:|S_X|$ chemically distinct permutation isomers; all the permutations belonging to a given left coset λS_X of S_X in SymL will generate the same isomer from E. The chemical identity groups of the permutation isomers all belong to the conjugacy class of S_X in SymL. Thus, the family **6** contains $|SymL|:|S_{6a}| = 5!:6 = 20$ permutation isomers that are represented by the cosets λS_{6a} (see Table 1).

Scheme 4



6a$_1$ E | **6a**$_2$ (123)E | **6a**$_3$ (132)E | **6a**$_4$ (12)(45)E | **6a**$_5$ (13)(45)E | **6a**$_6$ (23)(45)E

Under given observation conditions, X has an enantiomer $\overline{X}$ if each geometric arrangement of a molecule from X is the mirror image of some molecule from $\overline{X}$ and conversely. A mixture of equal numbers of molecules from X and $\overline{X}$ is called the racemate of X.

Let X be the reference isomer of a family $J_X(L)$ of permutation isomers with all ligands in the set $L = \{L_1, \ldots L_n\}$ chemically distinguishable. If X has an enantiomer $\overline{X}$ belonging to the same family of permutation isomers, then X and $\overline{X}$ have the same skeleton; we then say that the skeleton of X is achiral. In this case, any permutation of the ligands of X that preserves the chemical identity of X also preserves the chemical identity of $\overline{X}$, so that both X and $\overline{X}$ have the same chemical identity group. The chirality of such isomers must then be due to differences in the placement of the ligands on the skeleton. The set of R_X of all permutations that preserve the chemical identity of X and the set of all permutations that interconvert X with its enantiomer $\overline{X}$, form a union that is the racemate group of X.

It turns out that $S_X \subset R_X$ is a subgroup of order 2 and therefore normal in R_X. The coset $\overline{S_X}$ of S_X in R_X is called the enantiomer coset; any permutation belonging to the enantiomer coset will interchange X and $\overline{X}$ with each other.

A brief discussion of the asymmetric carbon atom will illustrate the differences between earlier uses of permutations in chemistry and the chemical identity approach.

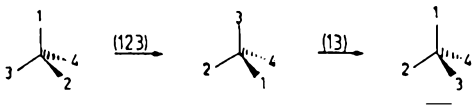
Le Bel and *van't Hoff* based their postulate of the asymmetric carbon atom on the chemical evidence that was available to them[32], namely that all the ways of attaching four chemically distinguishable ligands to a carbon atom give molecules of exactly two distinct enantiomeric compounds. Under the assumption that the carbon atom has a rigid valence skeleton, the only geometric model that is compatible with the known facts is a skeleton with a tetrahedral point group symmetry T_d. With this skeletal symmetry, the central carbon atom is located at the center of a regular tetrahedron whose vertices are occupied by the ligands 1, ..., 4. Then any even permutation of the idealized ligands (i.e. permutation that corresponds to an even number of pairwise ligand exchanges) of a model E leads to a rotated form of E. For example, the even permutation (123) represents a 120° rotation of E = **7a** about an axis passing through the central atom and ligand 4; thus **7a** gives a molecule **7b** (Scheme 5). The odd ligand permutations convert **7** into $\overline{7}$, the enantiomer of **7**.

Table 1. Family of permutation isomers **6** represented by the left cosets of S_{6a} in SymL.

6	Corresponding left coset $\lambda \cdot S_{6a}$
a	e, (123), (132), (12) (45), (13) (45), (23) (45)
ā	(12), (13), (23), (45), (123) (45), (132) (45)
b	(124), (13) (24), (243), (254), (12543), (13254)
b̄	(24), (1243), (1324), (1254), (13) (254), (2543)
c	(125), (13) (25), (253), (245), (12453), (13245)
c̄	(25), (1253), (1325), (1245), (13) (245), (2453)
d	(134), (234), (12) (34), (13542), (354), (12354)
d̄	(34), (1234), (1342), (12) (354), (1354), (2354)
e	(135), (235), (12) (35), (13452), (345), (12345)
ē	(35), (1235), (1352), (12) (345), (1345), (2345)
f	(142), (143), (14) (23), (154), (15423), (15432)
f̄	(14), (1423), (1432), (1542), (1543), (154) (23)
g	(145), (14523), (14532), (152), (153), (15) (23)
ḡ	(15), (1523), (1532), (1452), (1453), (145) (23)
h	(14) (25), (14253), (14325), (15) (24), (15243), (15324)
h̄	(1425), (143) (25), (14) (253), (1524), (153) (24), (15) (243)
i	(14) (35), (14235), (14352). (15342), (15) (34), (15234)
ī	(1435), (14) (235), (142) (35), (152) (34), (1534), (15) (234)
j	(24) (35), (12435), (13524), (12534), (13425), (25) (34)
j̄	(2435), (124) (35), (135) (24), (125) (34), (134) (25), (2534)

The product $\mu \cdot \lambda$ of the permutations λ and μ is given by the sequential action of λ and μ, i.e. the action of λ followed by the action of μ (see e.g. **7a**→**7b**→$\overline{\mathbf{7a}}$).

Scheme 5



7a E | **7b** (123)E | $\overline{\mathbf{7a}}$ (13)(123)E = (23)E

Thus, the chemical identity group of the asymmetric carbon atom is compatible

with the customary geometrical representation of that molecule: both serve to explain the observed chemical behavior.

The simple and extremely attractive idea that the observed chemical behaviour of an asymmetric carbon atom can be explained by a T_d point-group symmetry of the molecular skeleton has a serious logical shortcoming: such a symmetry is rarely found on real molecules. In fact, in an asymmetric carbon atom the bond angles generally deviate from the idealized 109° 33′, due to differences in the interaction of the pairwise different ligands; in addition, the bond lenghts between the central atom and the ligands are also not all the same. For example, for bond angles in CHBrClF we have that HCF < HCCl < HCBr < ClCBr and for bond lengths, C–H < C–F < C–Cl < C–Br.

Thus, although the asymmetric carbon atoms behave as if they had an idealized T_d skeleton, they in fact never have that idealized T_d skeletal symmetry. There is no such thing as an «approximate symmetry». The geometry-based approach has difficulties in justifying the use of symmetry considerations which work flawlessly in practice, but are clearly not in agreement with the known ideal skeletal geometries.

This logical inconsistency is entirely avoided by using the chemical identity approach to stereochemistry. The geometry of the asymmetric carbon atom is of little use in determining its chemical identity group: the basic consideration was the behavior of the chemical identity of the molecule under permutations of the ligands; and it was information from chemistry, rather than from geometry, that enabled us to determine the chemical identity group. By regarding the deformations in bond length and bond angle at the valence skeleton of the central atom as «moving along» with the ligands undergoing permutation, the skeleton and its symmetries can be totally neglected. The asymmetric carbon atom can therefore be interpreted in terms of ligand permutations, obviating idealizations or approximations. The classical interpretation of the asymmetric carbon atom is so successful, although the underlying geometrical ideas are definitely not valid, because the chemical identity group of the asymmetric carbon atom and the rotational symmetry point-group of the idealized tetrahedral skeleton are isomorphic. The usual picture of the asymmetric carbon atom does not depict the reality of the geometrical structure of that atom; it is simply a mnemonic device to indicate whether or not a given ligand permutation will change the chemical identity of the compound; and this is probably the basic reason that the flawed model for the asymmetric carbon atom works so flawlessly in practice.

The most powerful new mathematical devices for the solution of stereochemical problems that the theory of the chemical identity group provides are the chemical identity group of an ensemble of permutation isomers (the other authors of ref.[11] named it the «Dieter group» in memory of the late *Dieter Marquarding* who passed away on July 9, 1982) and above all, the representation of chemical equivalencies through mappings of the partitions and coverings in SymL[11, 30].

The chemical identity group D[Q] of an ensemble Q of permutation isomers contains all permutations that preserve the chemical identity of Q. A ligand permutation preserves the chemical identity of the system Q if its action on any $A_i \in Q$, either preserves the chemical identity of A_i or converts it into some $A_j \in Q$. If Q is the racemate $Q = \{A, \bar{A}\}$, D[Q] is the racemate group of A.

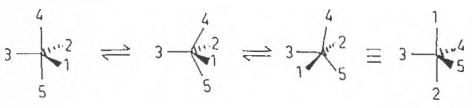
$$D[Q] = \begin{vmatrix} \lambda_1 S_X \lambda_1^{-1} & \lambda_2 S_X \lambda_1^{-1} & \dots & \lambda_n S_X \lambda_1^{-1} \\ \lambda_1 S_X \lambda_2^{-1} & \lambda_2 S_X \lambda_2^{-1} & \dots & \lambda_n S_X \lambda_2^{-1} \\ \dots & \dots & & \dots \\ \lambda_1 S_X \lambda_n^{-1} & \lambda_2 S_X \lambda_n^{-1} & \dots & \lambda_n S_X \lambda_n^{-1} \end{vmatrix}$$

$$Q = \{A_1 \dots A_n\} = \{\lambda_1 S_X, \dots, \lambda_n S_X\}$$

The Dieter group is used to discuss isomerizations. We assume an isomerization $A_1 \rightleftharpoons A_2 \rightleftharpoons \dots \rightleftharpoons A_n$ proceeds through some unknown common intermediate Y or ensemble of intermediates Y, and the problem is to determine the species Y. It is plausible to suppose that, whatever Y may be, any ligand permutation that preserves the chemical identity of all reactants, or which interconverts the members of the system $\{A_1, \dots, A_n\}$, should preserve the chemical identity of X. Since $D[A_1, \dots, A_n] \in S_n$ is precisely the set of ligand permutations doing this, and since it is also a group, we define $D[A_1, \dots, A_n]$ to be the chemical identity group of the intermediate Y. This characterizes the species Y at the level of the chemical identity group; a molecular representation compatible with $D[A_1, \dots, A_n]$ and the chemistry of the set $\{A_1, \dots, A_n\}$ of stereoisomers can then be sought.

Let Q contain **6a** and $\overline{\mathbf{6h}}$:

Scheme 6



6a **8** $\overline{\mathbf{6h}}$

Since $S_{6a} = \{e, (123), (132), (12)(45), (13)(45), (23)(45)\}$
the Dieter group of $Q = \{\mathbf{6a}, \overline{\mathbf{6h}}\}$ is

$$D[\mathbf{6a}, \overline{\mathbf{6h}}] = \begin{vmatrix} S_{6a} & (1524)S_{6a} \\ S_{6a}(1524)^{-1} & (1524)S_{6a}(1524)^{-1} \end{vmatrix}$$

$$= \{e, (12)(45), (1524), (1425)\}$$

An intermediate whose chemical identity group corresponds to $D[\mathbf{6a}, \overline{\mathbf{6h}}]$ is **8**. Thus a Berry pseudorotation[33] (BPR) with ligand 3 as a pivot and the transition state **8** is an interconversion mechanism for the ensemble $Q = \{\mathbf{6a}, \overline{\mathbf{6h}}\}$. The corresponding Dieter group of turnstile rotation[34] (TR) has the order $|D_{TR}| = 6$.

The Dieter group of an ensemble Q can also be used for deciding the existence or non-existence of an intermediate with a non-trivial chemical identity group that belongs to the interconversion of the members of A. Furthermore, the «Dieter group» of an ensemble Q permits to check on whether an assumed ensemble of interconverting permutation isomers is complete.

The solution of many important stereochemical problems involves a decision whether or not some molecular systems are chemically identical, or interconvertible. Such decisions are generally reached through an analysis of the intersections of certain coverings and partitions of SymL. The special cases where the coverings are replaced by partitions are the so-called set-valued mappings[30]. These are particularly important for chemistry.

A covering of SymL is a family of subsets, not necessarily pairwise disjoint, whose union is SymL. If all of the aforementioned subsets are pairwise disjoint, they form a partition.

Within the framework of the theory of chemical identity groups, molecules with some indistinguishable ligands are treated as follows:

In a family of permutation isomers $J_X(L)$ with a set of chemically distinguishable ligands $L = \{1, 2, \dots, n\}$. The permutation isomers of X are represented by the left cosets λS_X of S_X in SymL. When the ligand set L is replaced by a ligand set $L' = I_1 \cup I_2 \cup I_3 \dots \cup I_m$ where the ligands in each I_i are chemically indistinguishable from one another, but chemically distinguishable from any $I_j \neq I_i$, then L′ has m chemically distinct types of ligands. If $\Sigma = \{\sigma \in \text{SymL} | \sigma(I_1 \dots I_m) = (I_1 \dots I_m)\}$ is the set of all permutations that map I_i onto itself, i.e. permute only chemically indistinguishable ligands among themselves, we call $\Sigma \in$ SymL the stabilizer of the ligand substitution $L' \rightarrow L$.

The unions of left cosets λS_X of S_X that intersect with right cosets $\Sigma\lambda$ of Σ are the double cosets that represent the distinct permutation isomers with the ligand set L′.

For example, in the compound **6a**, let us make ligands 1 and 2 chemically indistinguishable, and also ligands 3 and 4 chemically indistinguishable (i.e. $L_1 = L_2$ and $L_3 = L_4$, but $L_1 \neq L_3$). To find the number of chemically distinct isomers of $\hat{\mathbf{6}}$, we will use the stabilizer of this ligand substitution $\Sigma = \{e, (12), (34), (12)(34)\}$.

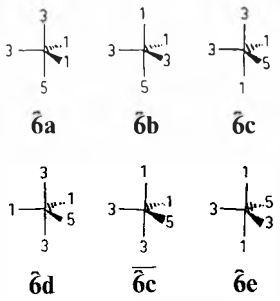
All the permutations λ belonging to a single double coset, and only those permu-

tations, will give models E that belong to the same chemical compound when the ligands are made equivalent according to Σ. In particular, for any model λE, all the models μE with $\mu \in \Sigma\lambda S_{6a}$ will become chemically equivalent. This double coset is easily calculated: multiply Σ by λ and take the union of all the cosets λS_X containing those elements. Thus, for example, if λ = (14), then Σ(14) = {(14), (12) (14), (34) (14), (12) (34) (14)} = {(14), (124), (143), (1243)}, and the cosets in Table 1 that contain these elements make up a single double coset.

The distinct double cosets $\Sigma\lambda S_{6a}$ and the λS_{6a} cosets with which they are constructed are given explicitly in Table 2.

Table 2. Family of permutation isomers $\bar{6}$ represented by the double cosets $\Sigma\lambda S_{6a}$.

Representative right Σ-coset	Member of family **6**	converted into member of family $\bar{6}$
e, (12) (34), (12), (34)	**a**, **d**, $\bar{a}$, $\bar{d}$	**a**
(124), (143), (14), (1243)	**b**, **f**, $\bar{f}$, $\bar{b}$	**b**
(125), (15) (34), (15), (125) (34)	**c**, **i**, $\bar{g}$, $\bar{j}$	**c**
(145), (12435), (1245), (1435)	**g**, **j**, $\bar{c}$, $\bar{i}$	$\bar{c}$
(135), (12435), (1245), (1435)	**e**, $\bar{e}$	**d**
(14) (25), (15243), (1524), (143) (25)	**h**, $\bar{h}$	**e**



A great variety of permutational isomerizations and other chemical reactions can be treated by the set-valued mappings of the left coset spaces of chemical identity groups.

Let E→P be a reference reaction. Then the non-empty intersections of the left cosets λS_E and λS_P in SymL represent the mechanistically similar reactions that involve the permutation isomers of the educt E and the product P.

The interconversion of the permutation isomers of **6a** by BPR, or the resultwise equivalent TR, provides a simple example for the procedure. The interconversion of **6a** ⇌ $\bar{\mathbf{6}}\mathbf{h}$ serves as a reference reaction. The isomer **6a** is the reference isomer on the «educt side». It is represented by its chemical identity group S_E, and its left cosets represent the permutation isomers of the «educt side», whereas $\bar{\mathbf{6}}\mathbf{h}$ (≡ P) with the chemical identity group S_P is the reference isomer of the «product side», and the left cosets of S_P describe the permutation isomers of **P**. The non-empty intersections of the «educt cosets» and the «product cosets» are connected by arrows that indicate the interconversion of the respective permutation isomers; thus graphs of permutational isomerizations are obtained (Scheme 7).

Note that here each intersection of the cosets λS_E and λS_P (λ ∈ SymL) in SymL contains two permutations. Since the order of the groups S_E and S_P is $|S_E| = |S_P| = 6$, each member of the family **6a–j** is directly interconverted with three of its permutation isomers. It also follows that the graph of the BPR/TR is contiguous and consists of 30 edges and 20 nodes of degree three.

The previously published applications of the set-valued mappings were confined to permutation isomers and their interconversions. Recently, however, the range of the applications of the set-valued mappings has been extended to include any chemical reactions that preserve the ligands of the participating molecules.

The treatment of some Diels-Alder reactions may serve to illustrate the versatility and power of this new tool.

The Diels-Alder reaction **9** + **10**→**11** with chemically distinguishable ligands is used as a reference reaction. Note that none of these molecules are permutationally isomeric (Scheme 8). Two questions arise: Which other products can conceivably be formed from **9** + **10** by an analogous reaction? Are there any other educts than **9** + **10** that could also yield **11** through a similar process?

The chemical identity group $S_{9\,10}$ of the ensemble {**9**, **10**} is the direct product* $S_9 \times S_{10}$ of the chemical identity groups S_9 and S_{10} where

S_9 = {e, (12) (34), (13) (24), (14) (23)} of **9** and

S_{10} = {e, (58) (67) (910)} of **10**.

The chemical identity group of **11** is

S_{11} = {e, (14) (23) (57) (68) (910)}.

Since $|S_{9\,10}| = 8$, and $S_{9\,10} \cap S_{11}$ = {e} contains only one element, namely e, $S_{9\,10}$ intersects with the eight left cosets $\lambda \cdot S_{11}$ ($\lambda \in S_{9\,10}$) of S_{11}. Each one of these eight cosets represents a permutation isomer of **11** that can be formed by a Diels-Alder reaction of **9** + **10**.

The left coset {(14) (23) (57) (68) (910)} · $S_{9\,10}$ of $S_{9\,10}$ represents **9** + **12** that is obtained from {**9**, **10**} by the action of the ligand permutation (14) (23) (57) (68) (910). The product **11** can thus also be obtained from **9** + **12**. Here the dienophile **9** must participate, whereas the diene can be replaced by **12**, one of its permutation isomers.

The Diels-Alder reaction of **9** + **13** (Scheme 9) can also yield eight permutationally isomeric adducts, **14** and seven permutation isomers that correspond to the left cosets $\lambda \cdot S_{14}$ ($\lambda \in S_{9\,13} = S_9 \times S_{13}$) of S_{14}. However, **14** can also be produced from **15** + **16** that is represented by the left coset {(17) (28) (35) (46) (910) (1112)} · $S_{9\,13}$. Note that there the educt ensembles {**9**, **13**} and {**15**, **16**} are permutationally isomeric, but not the dienophiles **9** and **15**, nor the dienes **13** and **16**.

S_{13} = {e, (58) (67) (910) (1112)};

S_{14} = {e, (17) (28) (35) (46) (910) (1112)}.

The Diels-Alder reaction of **9** + **17** (Scheme 10) yields **18** and seven of its permutation isomers represented by the left cosets $\lambda \cdot S_{18} = \lambda \cdot \{e\} = \{\lambda\}$ of S_{18} with $\lambda \in S_{9\,17}$, and $S_{9\,17} = S_9 \times S_{17}$. Since S_{18} has only one element, **18** cannot be obtained from any other educts than **9** + **17**.

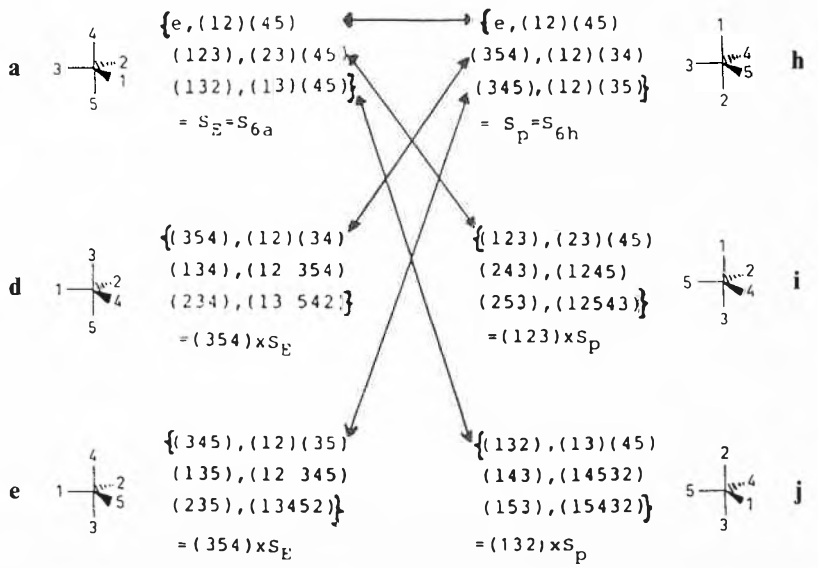
S_{17} = {e, (56) (78)};

S_{18} = {e}.

An analogous analysis of the conceivable educts and products of similar Diels-Alder reactions, in whose dienes and dienophiles some of the ligands 1,...,12 are chemically indistinguishable, requires another set-valued mapping. In such cases the ligand equivalency is represented by a stabilizer group Σ.

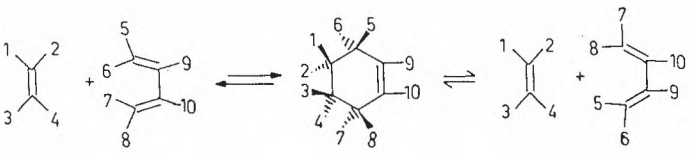
First, unions of the cosets λS_E and λS_P of the chemical identity groups of their educts E and the products P formed according to the intersections of the left cosets λS_E and

Scheme 7



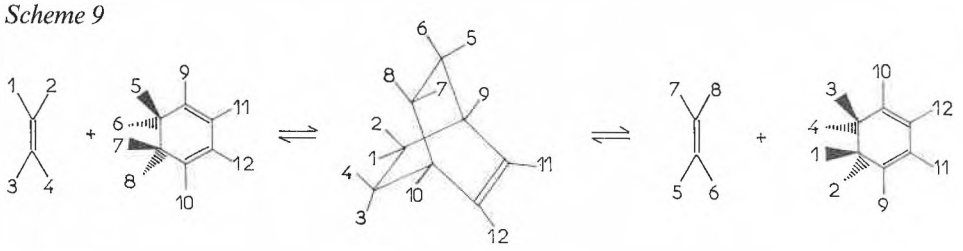
* A group G is the direct product G = N × K of a normal subgroup N ◁G and a normal subgroup K ◁G whenever G = N · K, and N ∩ K = {e}. Each g∈G is representable as a product g = n · k = k · n.

Scheme 8



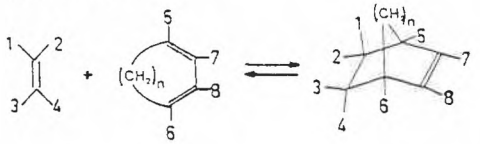
9 **10** **11** **9** **12**

Scheme 9



9 **13** **14** **15** **16**

Scheme 10



9 **17** **18**
(n = 1, or n ≥ 3)

λS_P with the right cosets $\Sigma\lambda$ of Σ. Thus the double cosets $\Sigma\lambda S_E$ and $\Sigma\lambda S_P$ are obtained as representatives of the distinct permutation isomers of the educts E and the products P. Then the set-valued mappings of these double coset spaces are examined for non-empty intersections that indicate conceivable chemical reactions.

Roth et al.[35] confirmed through an elegant isotope labeling experiment that 1,5-hydrogen-shift reaction proceeds indeed in a suprafacial manner, as is predicted by the Woodward-Hoffmann rules[2]. These results were used as an example for the application of Dieter groups[11b] and it was found that besides the three known participating species a fourth isomer must take part in the process. The same result could have been obtained more effectively through the use of a set-valued mapping of the aforementioned type.

Since it is relatively easy to implement computer programs that can generate and manipulate permutation groups and their coset spaces, it is foreseeable that the above qualitative mathematical formalism will become a versatile and effective device in computer-assisted stereochemistry.

5. Stereoselectivity

Selective chemical reactions are systems of competing parallel reactions that produce or destroy preferentially some of the reacting chemical compounds.

Let k_i and k_j be the rate constants of the reactions that affect the compounds P_i and P_j; then $S = |\ln (k_i/k_j)| = \Delta G^{\ddagger}_{ij}/RT$, a linear function of free activation enthalpies $\Delta G^{\ddagger}$ of the competing reactions, expresses the selectivity of the system. If the rate constants for the formation or destruction are equal, then $S = 0$. If, however, only one of the actually, or conceivably competing compounds is completely formed or destroyed, then $S = \infty$. If a selective reacting system discriminates between stereoisomers it is called stereoselective.

In the remainder of this chapter we shall recall known notions, definitions, and classifications, though some in modified form, and a few new concepts and ideas will also be added. They will be useful for the discussion, interpretation, and design of stereoselective reactions.

A stereoselective reaction may be thermodynamically controlled, or it may be kinetically controlled. The concentrations of the competing reactants of a thermodynamically controlled stereoselective reaction are time-independent. The relative concentrations of the reactants depend only on their free enthalpies and the reaction conditions.

In contrast, in kinetically controlled stereoselective reactions the concentrations of the participating compounds are time-dependent[29].

A productive stereoselective reaction[16] is a system of competing reactions whose products P are competitively formed from common educts E (Scheme 11).

Scheme 11

$$P_i \overset{k_i}{\leftarrow} E \overset{k_j}{\rightarrow} P_j$$

In the above simple case, the concentration ratio of the products P_i and P_j is observed, and it is given by the ratio of the rate constants k_i and k_j:

$$p_i : p_j = k_i : k_j$$

In contrast to productive selective reactions, one many also consider destructive selective reactions[36].

A destructive stereoselective reaction is a system of parallel reactions that compete in the destruction of educts E (Scheme 12) whose concentration ratio is observed.

Scheme 12

$$P_i \overset{\bar{k}_i}{\leftarrow} E_i \qquad E_j \overset{\bar{k}_j}{\rightarrow} P_j$$

For a destructive stereoselective reaction the concentration ratio of the educts is a non-linear function of the rate constants k_i, k_j and time t. A destructive system of first order reactions follows:

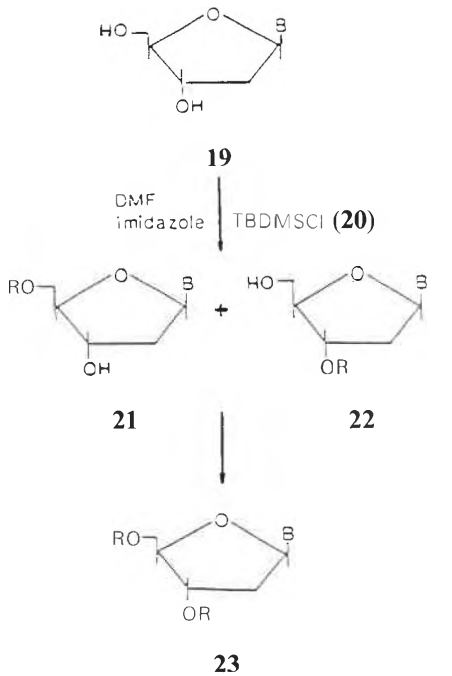
$$(e_i/e_j)_\tau = (e_i/e_j)_0 \cdot 2^{-(\bar{k}_i/\bar{k}_j - 1)\tau}$$

$$\tau = \bar{k}_j \cdot t \cdot \ln 2$$

Efficient selective syntheses can be based on productive selectivity, followed by destructive selectivity if $k_i \gg k_j$ and $\bar{k}_j \gg \bar{k}_i$, or $k_j \gg k_i$ and $\bar{k}_i \gg \bar{k}_j$.

Ogilvie's synthesis of the 5'-protected nucleoside derivatives **21** from **19** and *tert*-butyldimethylsilyl chloride (TBDMSCl) **20** (Scheme 13) can be interpreted as a

Scheme 13



B = A, C, G, T, C(Bz), A(Bz), G(Ac)
R = $Si(CH_3)_2C(CH_3)_3$

combination of evident productive selectivity with evident destructive selectivity. We have $k_{19\to21} : k_{19\to22} \approx k_{22\to23} : k_{21\to23} \approx 10$. When **19** is reacted with 10% excess **20**, practically no **22** is formed, but only **21**, contaminated with the non-isomeric **23**, which can easily be removed[37].

When the two isomeric products P_i and P_j of productive selective reaction are formed via a pair of isomeric transition states $P_i^{\ddagger}$ and $P_j^{\ddagger}$ (see Fig. 1), we have a so-called pair of corresponding reactions[38, 39].

Here E may also be an equilibrium system of chemically distinct educts, provided that the equilibrium is fast enough to be maintained throughout the formation of P_i and P_j, a prerequisite for the applicability of the Curtin-Hammett principle[40].

The relative amounts $p_i : p_j = k_i : k_j = \Delta G_{ij}^{\ddagger}/RT$ of the products of a pair of corresponding reactions are independent of the concentration of the educts E. The selectivity $S = |\ln(k_i/k_j)|$ of a pair of corresponding reactions is a linear function of $1/T$[41–43], as is illustrated by the selectivities of the reactions presented in Scheme 14 (Fig. 2)[42].

Note that a pair of corresponding reactions has a zero selectivity temperature $T_0 = \Delta H_{ij}^{\ddagger}/\Delta S_{ij}^{\ddagger}$ where $S = |\ln(k_i/k_j)| = 0$[45]. At T_0 the algebraic sign of $\ln(k_i/k_j)$ changes, i.e. at $T > T_0$ the one isomer prevails, and at $T < T_0$ the other. With regard to the reaction of Scheme 14 we distinguish between two types of amines. Within the usable temperature range, the reaction has a high degree of selectivity at higher temperatures with amines of typ I, e.g. **25**, R = CH_3, whereas with amines of type II, e.g. **25**, R = $CH(CH_3)_2$, the reaction is more selective at low temperatures. It follows that knowledge of the critical temperature T_0 and the slope $dS/d(1/T)$ of the plot S vs. $1/T$ (cf. Fig. 2) in a given solvent is a prerequisite for any good use of pairs of corresponding reactions in stereoselective syntheses. Pairs of corresponding reactions with non-evident direction of selectivity (see below) cannot be interpreted by geometry-based reasoning, nor by the customary quantum-chemical methods. They require an approach which takes into account the multitude of states that contribute to the outcome of such reactions. When certain requirements are met, the stereochemical analogy model[28], a theory of stereoselectivity that is based on a group-theoretical analysis of partition functions, can be used for the theoretical treatment of pairs of corresponding reactions.

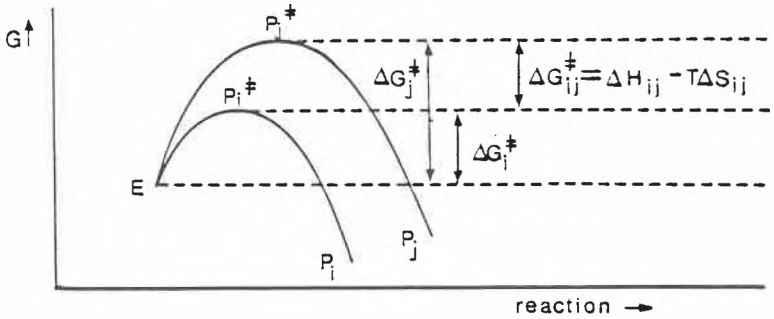


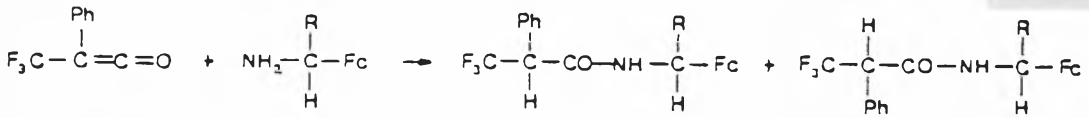
Fig. 1. The selectivity-determining free enthalpies of a pair of corresponding reactions.

There are two distinct categories of stereoselective reactions: the «evident» and the «non-evident» stereoselective reactions[44].

The «evident» stereoselective reactions proceed via a uniform reaction mechanism, i.e. there is a one-to-one correspondence of stereoisomeric transition states $P_i^{\ddagger}$, $P_j^{\ddagger}$, ... and stereoisomeric compounds P_i, P_j, ... that are formed or destroyed. Thus we have a set of corresponding reactions.

In the «evident» category the direction of selectivity is evident from geometry-related physical reasoning, i.e. it is evident which one of the participating chemical compounds will prevail.

Scheme 14



24 **25** **26a** **26b**

Ph = Phenyl
Fc = Ferrocenyl

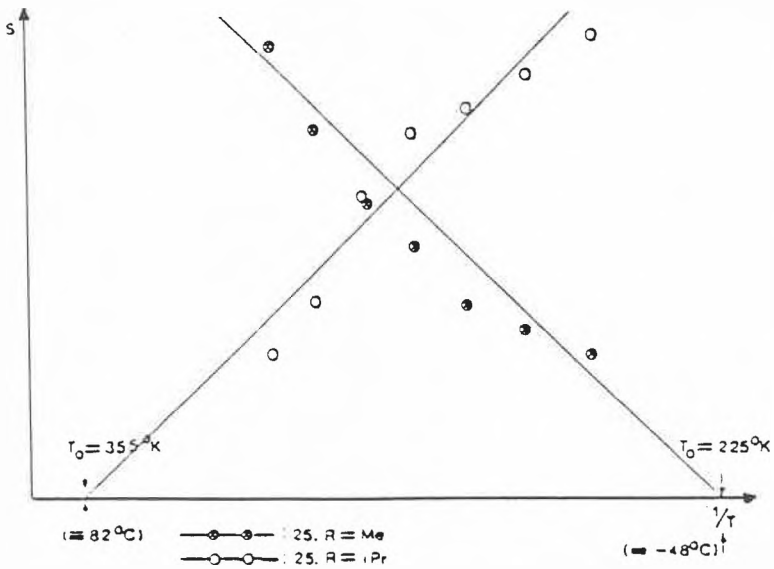


Fig. 2. The temperature dependence of stereoselectivity of the acylation of type I and type II amines **25** *by ketene* **24**.

A stereoselective reaction with such evident direction of selectivity has generally a high relative yield of the preferred product, and this is fairly constant over a wide range of usable conditions. Such reactions are almost ideally suited for stereoselective syntheses and stereorelating syntheses[47].

Stereoselectivity with evident preference is easy to interpret by inspection of suitable geometric molecular models, if the competing processes are obviously affected to differing degrees by strain or steric hindrance in the selectivity-determining molecular species.

The synthesis of penam derivatives by four component condensation (4CC)[48] is an example of evident stereoselectivity. The *trans*-isomers cannot be formed, since the required bicyclic α-adduct would have too much ring strain.

The selective silylation of nucleoside derivatives[37, 43] (Scheme 13) is an example

of selectivity that is based on differences in steric hindrance.

Not so easy to visualize, but still interpretable in a straightforward manner, are the concerted stereoselective reactions whose stereochemical course is determined by transition states that differ with regard to the bonding vs. antibonding parts in their set of orbitals. Through the ingenious contributions of *Woodward* and *Hoffmann, Fukui, Dewar* and *Evans, Longuet-Higgins, Oosterhoff, Schuler*, and many others this class of selective reactions has become one of the well-illuminated showcases of chemistry[2].

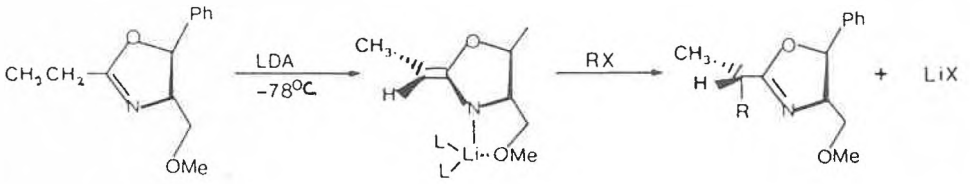
Stereoselective reactions without evident direction of selectivity are not amenable to the aforementioned approaches. The absence of evident qualitative differences in the bond systems and non-bonding interactions of the competing situations is a characteristic feature of this category with a non-evident steric course[44]. The stereoselective reactions of non-rigid molecules and non-rigid transition states belong generally to this category.

As a rule, in the non-evident category the direction of preference and the concentration ratio of the competing reaction products depends appreciably on the reaction conditions. The products are often formed by more than one reaction mechanism, and none of the products is as strongly preferred as is generally encountered in the evident category. There is, however, a great variety of non-evident selective reactions that are systems of various competing reaction mechanisms and consist of more than one pair of corresponding reactions[28, 39, 43].

Before a stereoselective reaction is used preparatively, the evident or non-evident nature of its stereoselectivity must be established. For some reactions this information exists already in the literature, or it follows from mechanistic reasoning in a straightforward manner. For many other reactions the decision whether or not a reaction belongs to the evident category must be based on some experimental investigation. If a reaction is highly stereoselective and the same stereoisomer prevails over a wide range of usable reaction conditions, the reaction generally belongs to the evident category. If however, the degree of stereoselectivity is considerably dependent on the reactants or catalysts, non-evident stereoselectivity is certainly involved.

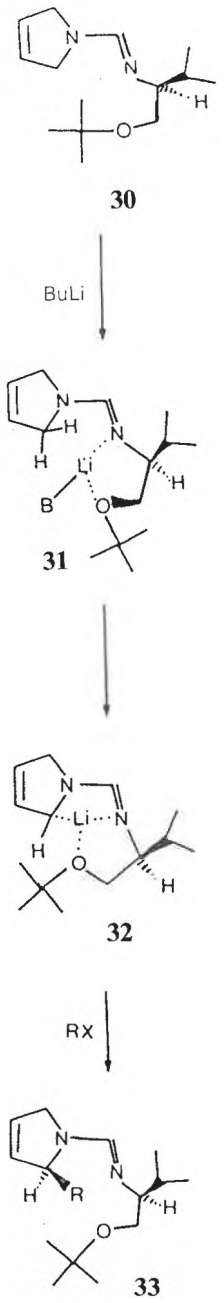
Since non-evident stereoselectivity is less desirable for stereoselective syntheses, one can either avoid the reactions whose stereoselectivity had been found to belong to the non-evident category by proceeding via an alternate synthetic route using reactions with evident selectivity, or one can modify the reaction by reducing the molecular flexibility of some intermediates or transition states through the introduction of chelating auxiliary groups and suitable chelating reagents. Thus by chelate assistance some reactions of entirely non-rigid molecular systems can be converted into reactions of rigid species with evident selectivity[47]. This is a simple general recipe, often garnished by highly sophisticated details, that has led to many of the recent spectacular advances in stereoselectivity[3–8]. The syntheses of the compounds **29** and **33** by *Meyers* et al.[6a–c] illustrate chelate-assisted evident stereoselectivity particularly well.

Scheme 15



27 **28** **29**

Scheme 16



In many cases the preparative use of a reaction with non-evident stereoselectivity cannot be avoided. Then a careful optimization of stereoselectivity is desirable, despite the efficiency of modern separation and purification methods. Although reaction mechanisms need not be known for computer-assisted optimization[49], mechanistic information is often useful when computers are used to optimize reactions.

About 30 years ago *Pracejus* et al.[50] investigated very thoroughly stereoselective acylations by ketenes in the presence of amines. *Pracejus* and his co-workers demonstrated that the observation of stereoselectivity under a single set of reaction conditions is almost worthless, and that a systematic variation of the solvent, the temperature, and the concentrations of reactants, catalysts and additives can yield most valuable information on a stereoselective reaction. Their elucidation of the various competing reaction mechanisms and the complex role of the reaction conditions set an example that is not followed often enough.

If the systematic study of a stereoselective reaction of preparative interest indicates that in a given solvent the observed relative concentrations of the products are independent of the initial concentrations of the reactants, and if furthermore the plot of S vs. $1/T$ (cf. of example Fig. 2) is a straight line, then the reaction represents a single pair of corresponding reactions. Depending on the zero selectivity temperature T_0 and the usable temperature range, one then chooses the temperature at which the combination of stereoselectivity and overall yield is best for preparative purposes. If T_0 and $dS/d(1/T)$ do not suit the purpose, and a variation in the structure of some of the reactants is permissible, a reactant with a more desirable combination of T_0 and $dS/d(1/T)$ can often be found.

Since 1960 stereoselective four component condensations (4CC) have been studied in our laboratory in order to develop syntheses of peptides by stereoselective 4CC[51–54]. It was an early insight that chiral α-ferrocenylalkylamines **25** are the most suitable amine components of such 4CC[52]. It was observed that at low temperature particularly the amines **25**, R = *sec*-alkyl, led to the highest degrees of stereoselectivity[53], but it was also observed that with these amines some undesirable side reactions were seriously competing with the 4CC[54], and, worst of all the low temperature 4CC of these

amines gave results that were hard to reproduce. This lack of reliability seems to be due to the fact that sometimes the reactants form a supersaturated solution in which the 4CC takes place at a low temperature, whereas sometimes the starting materials crystallize out before the 4CC occurs. The components then undergo the 4CC after redissolving when the reaction mixtures are warmed.

Therefore, it seems to be desirable to run the stereoselective 4CC at higher temperatures. Now that we know about the «type I» α-ferrocenylalkylamines, we hope that it will be possible to carry out 4CC with a high degree of stereoselectivity at relatively high temperatures. In order to avoid some of the conceivable side reactions, amines **25** of type I with an electron withdrawing group R look particularly promising. With regard to peptide syntheses by stereoselective 4CC, we are almost back to square one.

If the analysis of stereoselectivity as a function of reaction conditions shows that the given stereoselective reaction is not just a pair of corresponding reactions, but a more complex system of parallel and consecutive reactions, it is advisable to obtain as much mechanistic information as possible from a systematic variation of the reaction conditions, possibly including a computer-assisted analysis of the data, and to exploit this information in a computer-assisted optimization of stereoselectivity and overall yield by factor analysis[55], simplex methods[56], etc.

6. Asymmetric Reactions

A brief discussion of the history of the concept of asymmetric reactions, may illustrate the necessity for the present treatment of the problem.

The notion of asymmetric induction originates with *Emil Fischer*[57] who used it to explain the formation of optically active carbohydrates from CO_2 and water by plants. He conjectured that optically active chlorophyll exerts a stereochemically directing influence upon photosynthesis. After that it was believed for quite some time that «only living organisms with their asymmetric tissues, or asymmetric products of living organisms or the latter themselves with their inherent asymmetry can achieve this. Only asymmetry can create asymmetry».

This prejudice was overcome by the first *in vitro* asymmetric reactions by *Marckwald*[58] and *Mc Kenzie*[59]. *Marckwald* defined asymmetric syntheses as follows: «Asymmetric syntheses are those which produce optically active substances from symmetrically constituted compounds with intermediate use of optically active substances but avoiding any analytical operation».

Owing to conceptual progress in stereochemistry and the discovery of many new types of asymmetric reactions, the definitions of asymmetrically induced syntheses underwent successive modification and extension to yield the currently most widely accepted statement[60] that «in its broadest interpretation, an asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts».

This definition which was given in a monograph by *Mosher* and *Morrison*[60] corresponds to a definition in *Eliel*'s[61] textbook of stereochemistry. It includes cases in which the chiral reference system is part of the same molecule where the new center of chirality is generated. According to *Klabunowski*[62], asymmetric syntheses are confined to the syntheses of optically active compounds from substances «whose molecules are optically inactive before the reaction», with the explicit exclusion of racemates as starting materials.

The facts that there are many definitions of «asymmetric induction» which differ substantially from each other, and that from a present-day view point it seems impossible to define asymmetric reactions in an unambiguous manner on the basis of the traditional stereochemical concepts, point to the need for new concepts to classify the phenomena in this field, leading to the present definition.

Let $A_1,\ldots,A_n$ be any molecules in a balanced stoichiometric equation, and $\{a_1A_1,\ldots,a_nA_n\}$ denote the ensemble of initial reactants that contains a_i copies of A_1, and a_n copies of A_n, analogous considerations apply to the final products $B_1,\ldots,B_k$.

A reaction
$\{a_1A_1+\ldots+a_nA_n\}\rightarrow\{b_1B_1+\ldots+b_kB_k\}$
is called an asymmetric synthesis, if

(a) the reaction is stereoselective, and

(b) $G(\{a_1A_1,\ldots,a_nA_n\}) < G(\{b_1B_1,\ldots,b_kB_k\})$ is valid with stereoselectivity while $G(\{a_1A_1,\ldots,a_nA_n\}) = G(\{b_1B_1,\ldots,b_kB_k\})$ holds for the corresponding reaction without stereoselectivity, and

(c) $G(\{b_1B_1,\ldots,b_kB_k\}) < \sum_{i}^{k} G(\{b_iB_i\})$, in words, the chiral genus of the ensemble of final products must be strictly smaller than the sum of the chiral genera of its individual members.

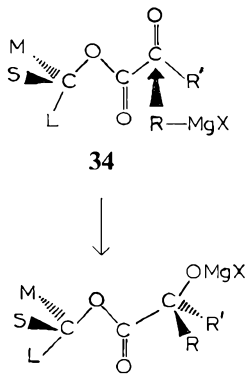
The condition (a) states that unequal amounts of stereoisomers are produced or destroyed by the reaction; together conditions (b) and (c) assure that the increase in chiral genus is due to a stereoselectivity which is caused by chiral influences alone. Condition (a) is an essential part of the definition: it is interrelated with condition (c), and together they restrict the type of chirality-increasing stereoselective reactions that will be called an asymmetric synthesis. In fact, a stereoselective reaction is never «infinitely selective», because this would require an infinite free enthalpy difference of stereoisomers or stereoisomeric transition states, respectively. In the case of idealized destructive selectivity «infinite selectivity» would be reached at infinite reaction time, when none of the considered stereoisomers would be left over[36].

The previous difficulties in defining asymmetric syntheses are mainly due to the lack of an adequate quantitative measure of molecular chirality.

Any definition of asymmetric syntheses must express that these are stereoselective reactions during which an «increase of chirality occurs, caused by chiral influences».

Despite considerable effort that has gone into the study of asymmetric reactions, they remained almost as mysterious as they were at *Emil Fischer*'s time, until *Vladimir Prelog*[63] discovered that in the preferred products of asymmetric reactions there exists a well-defined configurational relation of the initial chiral moieties of the educts and the newly formed chiral parts. The observed direction of selectivity is determined by the relative sizes of the residues. This rule contains the statement: «The addition reactions of carbonyl compounds proceed according to the rule *as if* the attack at the carbonyl group by the reactant would preferentially take place from the less sterically hindered side of a conformation specified by the respective rule»[40c].

Scheme 17



34 **35**

Prelog's rule (steric bulk L > M > S)

Prelog also noticed that the extent of stereoselectivity of asymmetric reactions depends on the relative steric bulk of the ligands at the initial asymmetric carbon atom.

For *Ernst Ruch*[28] and the present author[38], as well as for many others, *Vladimir Prelog*'s insights were the decisive stimulus for their endeavours in stereochemistry.

Received: September 22, 1986 [FR 30]

Acknowledgement: The financial support of the work reviewed here by Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie, Alexander von Humboldt Foundation, and the Stiftung Volkswagenwerk e.V. is gratefully acknowledged. The author wishes to thank Clair Collins and Charles McKenna for valuable suggestions, and Mrs. M. Baumeister, D. Neumeier, and M. Martin for their help in preparing the manuscript.

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