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A Tribute to the Centennial of the Fischer Projection. Display of Alkene Geometry and Axial Stereogenicity.

Hubert Maehr

Roche Research Center
Hoffmann - La Roche Inc.
Nutley, N.J. 07110

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Abstract: *The conventions of the Fischer projection have been extended so that the geometry of alkenes can be represented in a standardized manner and axially stereogenic molecules can be shown for the first time in a topographically unequivocal fashion. Similar to the conventional Fischer diagrams, the latter category reveals the Cahn-Ingold-Prelog notation directly and the diagrams of chirally unperturbed allenes reflect the sign of the optical rotation within the confines of the Lowe-Brewster rule. Computer-assisted synthesis design, previously encumbered by pattern recognition of diagrams containing stereodescriptors, now permits the use of Fischer-projected chirons.*

1. Historical background and assignment of *R*/*S* descriptors of stereocenters.

The conception of the tetrahedral geometry at carbon by van't Hoff and Le Bell[1] in 1874 initiated the era of stereochemistry with the concommitant need to describe stereochemistry in a two-dimensional format.[2] The early recognition that the determination of a stereogenic center's chirality sense would be long in coming, allowed the graphic description of stereochemical results to be limited to geometric relationships. Consequently, the first stereodescriptive tool as proposed by van't Hoff was very rudimentary whereby the geometric relationships of stereocenters were arbitrarily registered. The stereocenters 2-5 of glucose (2*R*,3*S*,4*R*,5*R* for the D-isomer), for instance, were denoted as –,+,+,+, and the antipode as +,–,–,–. Gulose, differing from glucose at centers 3 and 4, then received the designation –,–,–,+ or +,+,+,–. This concept of denotation was used by Emil Fischer only until substantial progress in the stereochemical elucidation of carbohydrates required not only a more refined, but also the first *graphic* device for the representation of results.[3]

Fischer's ingenious solution to the problem dates back to the year 1891 and consists of two steps.[4] In the absence of any topographic[5] information, it required first the establishment of a stereogenic reference unit together with an arbitrary but definite topographic commitment. Any other stereocenter would then be compared to this reference, equivalent to the dogmatic assignment of a certain algebraic sign to a coordinate system serving as the stage for the molecule's graphic display. Fischer chose D-tartaric acid as reference with the allocated chirality sense that we regard today as 2*R*,3*R*. There was no need to exercise his option of a reversal as the arbitrary assumption of topography was shown to be fortuitously correct some sixty years later.[6]

Fischer then proceeded to devise an extremely simple, yet universal graphic tool that anchored the stereocenter to a projection plane, henceforth referred to as the Fischer plane, in a unique and topographically binding fashion, so that the resulting projection onto this plane permits the unambiguous reconstruction of the object's chirality sense. Diagrams B and C in Fig. 1 show the position of an sp^3-hybridized carbon atom in the Fischer plane and diagram A illustrates the corresponding Fischer projection.

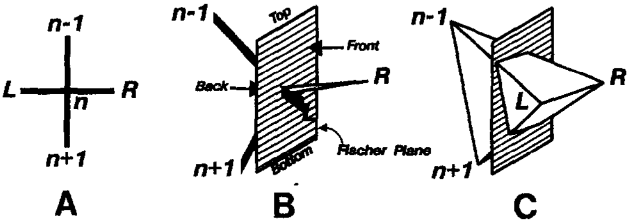


Figure 1

Fischer projection of carbon atom *n* and its substituents (A) and orientations of the corresponding five-point geometric figure (B) and T_d-tetrahedron (C) with respect to the Fischer plane.

This projection is readily extended to multi-center stereogenic systems, as in carbohydrates, and requires first the identification of the "Fischer chain", i.e. the string of connected atoms that includes the stereocenters.[7] The projection process is completed after the consecutive positioning of all chain atoms into theFischer plane. In the course of this process, the atoms of the Fischer chain are positioned into the plane, one at a time and according to B in Fig. 1, while proceeding in one direction from low to high locant number. During each residency of an atom *n* in the Fischer plane the two geminal chain atoms ($n-1$) and ($n+1$) are located below and the two ligands R and L at atom *n* above the plane. Ligands R and L, as well as chain atoms ($n-1$) and ($n+1$) are then projected onto the Fischer plane. By definition, the projection image is observed from a suprafacial position of the viewer with respect to the Fischer plane's front leading to A in Fig. 1.

The topographic integrity of the projected object is not compromised by rotation of the image within the Fischer plane as long as the suprafacial view point is being maintained, i.e. the Fischer projection of a stereocenter is not reflection invariant.

Although vertical projections of molecules with multi-stereocenters are now common,[8] carbohydrates used to be projected from right to left.[9] If a horizontal projection is sought, a projection sequence from left to right, concomitant with the presentation of the locant sequence increasing from left to right, however, is more appropriate.

In the course of the years, supplementary graphic methods were devised for the portrayal of stereochemical information which allow perspective perceptions.[10] After a century of use, nonetheless, the Fischer projection remains as a fundamental graphic aid. This is not surprising, for, *unlike any other, this projection will furnish the same diagram, regardless of the object's complexity and the person who drew it.* For this very reason, a Fischer diagram, by virtue of its non-perspective nature, facilitates stereochemical pattern recognition; it can illustrate more clearly than any other projection the comparative aspects of a molecule's stereocenters as in carbohydrates and other complex natural products[11a,c] and is employed more advantageously as a tool in certain biosynthetic[11b,d] and retrosynthetic studies,[11e] especially for the purpose of screening the content of the so-called "chiral pool". Due to the absence of stereodescriptors, generally used for perspective impressions, computer-aided synthesis design is accomplished most directly with data bases containing Fischer-projected chirons.

A Fischer projection permits the rapid assignment of the *R*/*S* descriptors to a stereocenter without the need to redraw the object or to resort to the inspection of models.[12] The descriptor for atom *n* is obtained by observing its ligands (*n*–1), (*n*+1), L, and R by repositioning the familiar display A (Fig. 2) so that the tetrahedral edge L-R appears as shown in the center of diagram B in the form of a Fischer arrangement. Assuming lowest *Cahn-Ingold-Prelog* (CIP) priority for ligand (*n*–1) reveals the remaining three ligands as a triangle (the "CIP face") which is exposed toward the viewer, or suprafacially. The situation is unchanged if the other Fischer-chain ligand (*n*+1) is of lowest priority. Thus, the corresponding CIP faces III and I, respectively, and hence the priority sequences themselves, are provided by the Fischer projection.

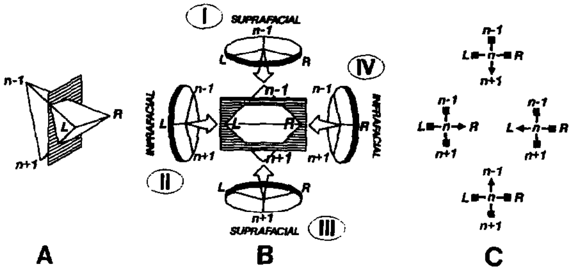


Figure 2

Position of a T_d tetrahedron with respect to the Fischer plane for the assignment of the *R*/*S* descriptors.

If the lowest CIP priority substituent resides in a lateral position in the Fischer projection, however, it is necessary to project from a CIP face in the direction of our view point. The resulting infrafacial dispositions of the CIP faces require a reversal of the *R*/*S* assignments obtained by reading the priority sequence from the *apparent* faces II and IV as furnished by the Fischer projection in diagram B (Fig 2).

In summary, projection in the direction of ligands on the vertical axis in the Fischer projection, as in I and III reveals the CIP sequence directly. Projection in the direction of the laterally disposed ligands as II and IV exposes CIP faces in the Fischer projection whose *apparent* priority sequences have to be reversed to arrive at the correct *R*/*S* assignment. The four corresponding CIP projections are reiterated in diagram C.

Parallel with the evolution of the Fischer projection there was a steady development of nomenclature, a process that is still ongoing and that has led to a unique system, unrelated to the CIP notation, but with the advantage of a direct and immediate correlation between name and stereoformula.[8]

Description of relative configuration. Three sets of stereodescriptors characterize relative arrangements at two, three, and four stereocenters. Derived from the sugar nomenclature, the terms *erythro* and *threo* describe the relative configuration of two stereocenters and imply similar ligands on the same or on the opposite side, respectively, in the Fischer projection. The use of these terms outside of the carbohydrate field has led to some inconsistencies in the definition of "ligand similarity" so that replacement terminology was proposed for non-carbohydrate applications.[13] Two additional sets of descriptors, *ribo*, *arabino*, *xylo*, *lyxo*, and *allo*, *altro*, *gluco*, *manno*, *gulo*, *ido*, *galacto*, *talo* are used exclusively in carbohydrate connotations and describe the geometry of three and four stereocenters, respectively.[14] Sets containing more than 4 stereogenic centers in the Fischer chain are described by a composite of descriptors. 4n+1 descriptors are delineated by *glycero* + n four-center descriptors whereby *glycero* refers to the highest numbered locant and the required number of the others follow in the direction from high to low locant number. Similarly, the description of 4n+2 stereocenters commences with a two-center descriptor and 4n+3 centers are preceded by the appropriate three-center descriptor.

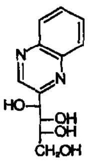
To decribe the stereocenters in non-carbohydrates, the symbols c_F and t_F (*c*is and *t*rans in the *F*ischer projection) after the locant number designate the position of the particular substituent to be on the same or opposite side, respectively, as the *reference* ligand which, in turn, is denoted by the locant suffix r_F as in roxaticin (**3**).

In a complex system which contains a *catenary* extension with stereocenters as part of its structure, the locant that commences the Fischer-chain extension must be identified and receives the suffix cat_F as in **1**, D$_r$-1cat_F-quinoxalin-2-yl-butane-1t_F,2c_F,3r_F,4-tetraol.[8]

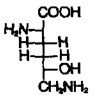
Description of absolute configuration. The letters D and L designate on which side in the Fischer projection the reference ligand is located. The locant numbers on the vertically arranged Fischer chain increase in the direction from top to bottom. The reference ligand is that lateral substituent at the highest numbered stereocenter which assumes the higher priority. Thus, the symbols D and L lend topographic significance to the geometric descriptors mentioned above. D-glucose, for example, implies that the hydroxyl ligand at C5 is located at the right in the Fischer projection while the term *gluco* defines the relative configuration of all four stereocenters. The descriptor "*glycero*" refers to a single stereocenter and receives topographic meaning in connection with the prefixes D or L.

In a further refinement, the symbols D$_g$, D$_s$ and L$_g$, L$_s$ serve in connection with the descriptor *threo*. D$_g$ and L$_g$ are used in the sense of D and L and imply that the *higher* numbered reference ligand is located on the right or left side, respectively, in the Fischer projection. The terms D$_s$ and L$_s$, however, assert that the *lower* numbered reference ligand is on the right or left, respectively, in the Fischer projection. As an example, therefore, D$_g$-threo-5-hydroxylysine (**2a**) and D$_s$-threo-5-hydroxylysine (**2b**) are antipodes whereas the corresponding D$_g$/L$_s$ pair refers to one and the same compound.

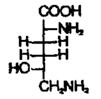
The reference stereocenter in non-carbohydrates (cf. **1**) is designated r_F in the form of a suffix to the highest locant number; the addition of the prefix D$_r$ or L$_r$ to the name assures topographic definition as it determines whether the reference ligand is located on the right or left side, repectively, in the Fischer projection.



1



2a



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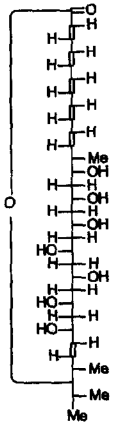


3

The usefulness of the Beilstein nomenclature becomes particularly apparent when compared with the systematic names of more complex molecules such as roxaticin (**3**). The Beilstein name, L_r-13t_F,15t_F,17t_F,19c_F,21t_F,23c_F,25c_F,29r_F-octahydroxy-12t_F,28t_F,30-trimethylhentriaconta-2,4,6,8,10,26-(all-*E*)-hexaenoicacid 1,29-lactone allows ready reconstruction of diagram **3**. To arrive at a structural diagram from the systematic name, [13*S*-(3*E*,5*E*,7*E*,9*E*,11*E*,13*R**,14*S**,16*S**,18*S**,20*R**,22*R**,24*S**,26*S**,27*E*,29*R**,30*R**)]-14,16,18,20,22,24,26-heptahydroxy-13,29-dimethyl-30-(1-methylethyl)-oxacyclotriaconta-3,5,7,9,11,27-hexaen-2-one is a much more laborious task.

2. Stereogenic Planes: Alkene Geometry.

The Fischer projection has now witnessed, virtually unchanged, a century-long evolution of stereochemistry. It is not surprising then, that this projection lacks the endowment to portray certain stereochemical features of complex molecules, most notably alkene geometry and the topography associated with axial stereogenicity. To mention these categories of compounds does not imply our intention to suggest the general use and preference of Fischer projections in favor of other well-established graphic devices. In view of the prevalence of alkenes and allenes in many natural products and as ubiquitous structural units in chirons, we merely direct our concern toward the facility to display these structural features within a Fischer projection's frame work whenever the need arises.

The inability to accommodate stereogenic alkenes within Fischer's convention has been particularly troublesome and led to provisional solutions, such as an interruption of the conventional Fischer projection of stereogenic centers with an alkene's side projection, or the use of a vertical alkene display with explicitly added verbal *E*/*Z* descriptors.[11d,15]

To project an alkene, we thus propose that the double bond be placed in the Fischer plane in such a fashion that the π-orbitals are bisected by that plane as shown in diagram B, Figure 3. Such an arrangement forces the alkene ligands into a plane that is perpendicular to the Fischer plane.

Similar to the treatment of consecutive sp^3 centers, the stereogenic axis n - (n+1), as well as its terminal ligands (n-1) and (n+2) that are Fischer-chain members, are now projected along a straight line that extends from the top to the bottom in the Fischer plane. The ligand pattern of the alkene with respect to the Fischer plane is no longer reflected on the *left* or *right* as encountered in the projection of stereocenters, but rather *below* or *above* the Fischer plane; i.e. the ligands appear superimposed upon the Fischer chain without lateral differentiation from each other.

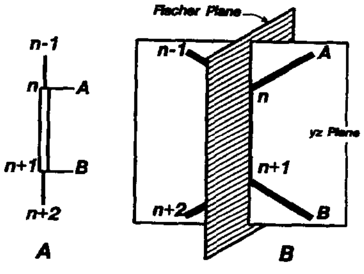


Figure 3

Fischer projection of an alkene (A) and
orientation of the corresponding six-point geometrical figure (B)

Building on this alkene orientation in the Fischer plane, we further propose that ligands at sp^2 centers *above* the Fischer plane are denoted at the *right*, those *below*, on the *left* in the projection. With all alkene substituents in the yz plane, the Fischer-chain ligand (*n*-1) preceding the double bond assembly is positioned, *per conventionem*, below the Fischer plane, as customary for the projections of tetrahedral centers. Consequently, the projection of an alkene will exhibit *cis*-substituents on the right and *trans*-substituents on opposite sides, i.e. all ligands of conjugated *cis*- alkenes will appear on the right, those of conjugated *trans*-alkenes alternatingly on opposite sides with the first one on the right and the last one on the left.[11c] Clearly, the interpretation of these projection diagrams is unchanged after displacements or reflections in the Fischer plane, provided that no stereocenters are present. Other planar molecules, such as a cumulene with an odd number of double bonds, can be projected similarly.

3. Stereogenic Axes: Allenes.

To project axially stereogenic molecules such as allenes, the stereogenic axis is positioned into the Fischer plane in such a fashion, that it extends from top to bottom as exemplified by diagram C1 in Fig. 4. The ligand geometry can then be represented with the aid of two additional short axes, *A*-*B* and *Y*-*Z*, henceforth referred to as the orthogonal axes[16]. For the purpose of a Fischer projection, the molecular assembly can be rotated around the stereogenic axis to assume any position but excluding those two arrangements were one of the two

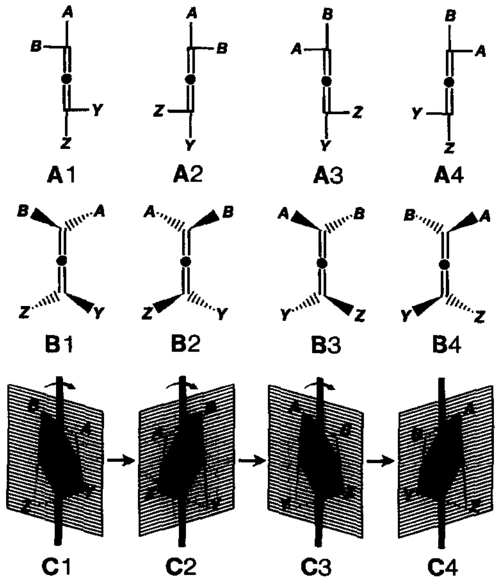
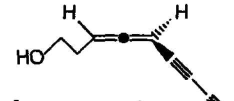


Figure 4

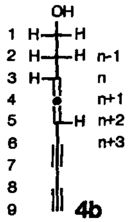
Fischer projections of an allene (A) and orientations of the corresponding six-point geometrical figures (B) and D_{2d}-tetrahedrons (C) with respect to the Fischer plane.

orthogonal axes lies in the Fischer plane. One of the two ligands at each orthogonal axis will then be positioned below the Fischer plane (*A* and *Z* in C1), and become part of the Fischer chain in accord with the traditional convention, while the other two ligands (*B* and *Y* in C1) are located above the plane and are biased laterally. Consequently, the object assumes an orientation with respect to the Fischer plane which permits a projection reminiscent of sp^3-centers (Fig. 1) where the Fischer-chain ligands immediately preceding and succeeding the stereogenic unit lie below the Fischer plane and the remaining two ligands are arrayed laterally. Three successive 90° rotations around the orthogonal axis furnish three additional diagrams (C2-C4), each representing the same object but with a different tetrahedral side as Fischer chain. The corresponding six-point geometrical figures B1-B4 illustrate more clearly the skeletal D_{2d} symmetry and hence the genesis of the resulting Fischer projections A1-A4.[17]

The topography inherent in the resulting Fischer diagram is readily visualized as demonstrated by the projection of marasin (**4a**), a metabolite of *Marasmius ramealis* and *Cornellius berkeleyanus*,[18] as **4b**. The stereogenic axis is defined by atoms *n*, (*n*+1), and (*n*+2). The ligands (*n*−1) and (*n*+3), which precede and succeed the axis, are destined to become Fischer chain members and are chosen to be the hydroxyethyl and diyne ligand, respectively, rather than the hydrogen substituents at *n* and (*n*+2), as shown in **4b**. Thus, the chirality sense of **4a**, described in the form **4c** as a D_{2d} tetrahedron by the Fischer-chain ligands (*n*-1) and (*n*+3) and the laterally biased hydrogen substituents at *n* (H3) and *n*+2 (H5), is reflected unambiguously by **4b**.

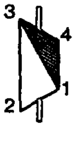


4a: Marasin, $[\alpha]_D$ -385°

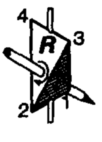


4b

4c



4d



4e

As expected, an allene's Fischer projection can be moved freely within the Fischer plane without loss of topographic fidelity, but, analogous to stereocenters, the projection diagram is not reflection invariant. The Fischer diagram of the enantiomer is produced by interchange of one substituent at a certain orthogonal axis, a process that is equivalent to reflection of the diagram.

The rules for *R*/*S* assignments of sp^3-hybridized carbon from Fischer diagrams are readily extended to axially stereogenic molecules. For this purpose we inspect the stereogenic object, and its relationship to the Fischer plane, from a suprafacial view point as illustrated in the center of Fig. 5. If the substituent *A*, identical with (*n*-1) of the stereocenters, is of lowest priority, the *R*/*S* assignment demands projection in that direction with the obvious advantage of a suprafacially exposed CIP face. This CIP face as well as the direction of projection is redrawn in III (Fig. 5), together with the Fischer projection of the object, where the direction of projection is shown by an arrow and the points describing the CIP face by squares. A comparison of the apparent CIP face at the tetrahedron with the one provided by the Fischer projection reveals congruency so that the Fischer projection can serve directly for this particular *R*/*S* assignment. Exactly the same situation prevails if the lowest priority substituent resides at the opposite end of the Fischer chain as illustrated in I.

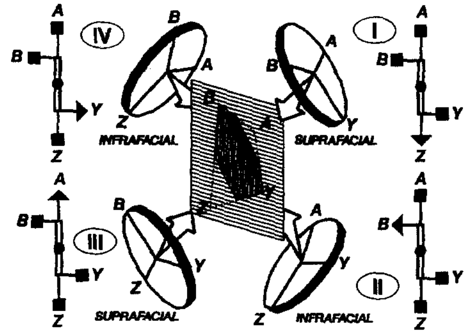
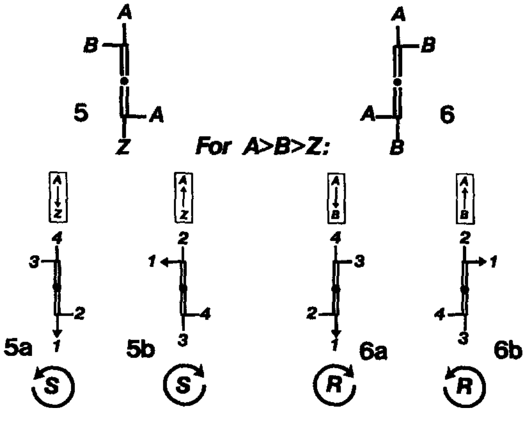


Figure 5

Position of a D_{2d} tetrahedron with respect to the Fischer plane for the assignment of the *R*/*S* descriptors.

Projection in the direction of the laterally designated ligands (II and IV) provides the viewer with an infrafacial exposition of the CIP face, whose apparent priority sequence has to be reversed to arrive at the correct *R*/*S* designation.

The requirement for chirality in a stereogenic assembly described by a D_{2d} tetrahedron is less rigorous as in the T_d case and allows identical ligands to be present as exemplified by asymmetric **5** and dissymmetric **6**. Chirality merely requires different substituents at any of the two orthogonal axes. To accommodate these allenes, a refinement of the rule is required which incorporates the arbitrary ligand prioritization that gives preference to the ligands at the near orthogonal axis over those at the more remote one.[19] To assign the *R*/*S* descriptors to **5**, for instance, we assume a priority sequence A>B>Z so that the priority diagram **5a** results from a view of **5** along the Fischer chain in the direction A to Z. Inspection of **5a** reveals a required projection toward the lowest priority, 1, that is part of the Fischer chain. The direction of the counterclockwise priority arrangement 4-3-2 provided by the Fischer diagram allocates the *S*-configuration to **5**. Assuming a view in the direction Z to A imparts priority to the orthogonal axis A-Z over A-B and leads to **5b**. The apparent clockwise arrangement has to be reversed in view of a projection in a direction which does not coincide with a Fischer chain ligand. Similarly, an inspection of **6** with a view along the Fischer chain in the direction A to B leads



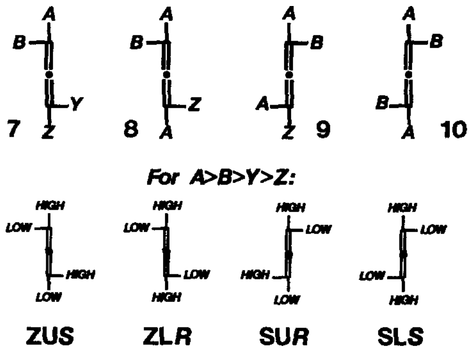
5 **6**

For A>B>Z:

5a **5b** **6a** **6b**

to diagram **6a** which furnishes the *R* notation directly. Diagram **6b** results from a view in the direction *B-A* and conveys the *R* configuration after inversion of the apparent CIP sequence.

These rules for the assignments of the *R/S* descriptors appear to be appropriate in view of their close similarity to those for stereocenters. Nonetheless, it is usually more expeditious to proceed with the *R/S* assignments from Fischer diagrams *without the conventional ligand prioritizations.* For this purpose it is required that the diagram is first placed into one of two possible categories depending whether the lateral substituents are arranged in a geometry similar to the letter "Z" as in **7** and **8**, or in the antipodal geometry as in the letter "S" and exemplified by **9** and **10**. The ligand priorities at each orthogonal axis are given relative assignments regardless of the other orthogonal axis' ligands. Compounds of the "Z"-geometry have the *R*-configuration if the laterally displayed ligands have "like" CIP priorities, (*HIGH/HIGH* or *LOW/LOW*, i.e. **8**). "Unlike" priorities of the lateral ligands are indicative of the *S*-configuration (e.g. *LOW/HIGH* as in **7**). Compounds of the "S"-geometry have the *S*-configuration if the laterally displayed substituents are like (e.g. **10**). Unlike lateral ligand priorities are diagnostic of the *R*-configuration (e.g. **9**).[20]



The optical rotation at the sodium D-line of chirally unperturbed allenes, predictable on the basis of the Lowe-Brewster rule,[21,22] can be ascertained from a Fischer diagram with particular ease. A vista of an asymmetric allene in the direction of the allenic axis reveals four helical components with dihedral angles of 90° each, which can be associated with the Fischer diagram as illustrated in Fig. 6. According to the signs of their dihedral angles, these components can be grouped into two opposing pairs. The positive contributors are designated *AY*, *BZ* in **11a** but as *AZ*, *BY* in the antipode **12a**. The two remaining pairs of helical units on each diagram are the negative ones. Each helical unit describes a quarter turn of a screw pattern whose handedness is defined by its sign. Furnishing the ligands *A*, *B*, *Y*, and *Z* with polarizability parameters, and considering the four helical contributors as their sum, describes the complete turn of a screw whose direction and pitch is linked to the sign and extent, respectively, of the molar rotation, $[\Phi]_D$, of a given allene.[22-24]

Diagrams **11a** and **12a** and their respective Fischer projections **11b** and **12b** (Fig. 6) serve to illustrate left or right handed screw patterns, and hence levo- or dextrorotatory optical behavior, depending upon the preponderance of the sum of the two levo-contributing helical units (*AZ+BY* in **11a**, *AY+BZ* in **12a**) over the dextro-contributors (*AY+BZ* in **11a**, *AZ+BY* in **12a**), or vice versa, respectively. Although the helical units are located along the stereogenic axis, the additivity postulate for the description of the full screw-turn permits the preponderance of the helical pair with the same sign to be ascertained by comparing the polarizability parameters of the ligand pairs at the *termini* of the orthogonal axes as expanded in Fig. 6.

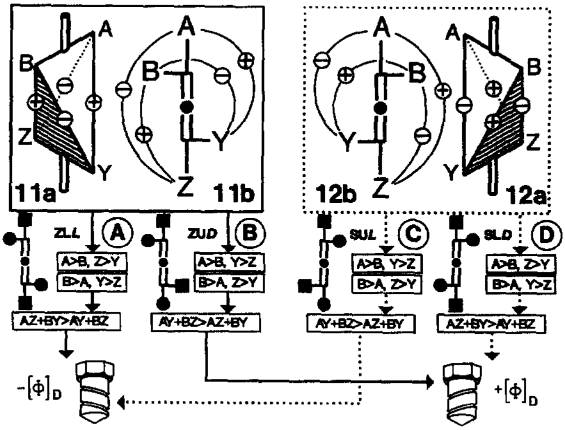


Figure 6

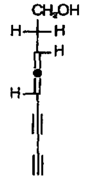
Correlation of Fischer-projected, chiral allenes with the signs of their optical rotations.
11a and **12a**: Signs of the dihedral angles of the four helical components in D_{2d}-tetrahedra.
11b and **12b**: Fischer projections of **11a** and **12b**, respectively.

The diagrammatic layout of the Fischer projection and the inherent topographic order leads to a simple rule for chirally unperturbed allenes. First it is necessary to compare the polarizability parameters of the ligands at each orthogonal axis so that two simple priority statements, *A* versus *B*, and *Y* versus *Z*, are obtained as elaborated in Fig. 6. If the Fischer projection exhibits the lateral ligands in "S" geometry as in **12b** and if these ligands have "like" priorities (*HIGH/HIGH* or *LOW/LOW*, e.g. case D), the molecule is dextrorotatory, if their parameters are "unlike" the molecule is levorotatory (*LOW/HIGH* as in case C). If the arrangement of the lateral substituents is antipodal to the letter "S" as in "Z" and depicted in **11b**, the opposite applies (cases A and B).[25] The lower portion of Fig. 6 illustrates the application of this rule to the Fischer projections **11b** and **12b** in terms of all possible priority statements.

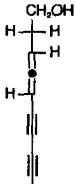
Several examples of naturally occuring allenes shall now serve to demonstrate the value of the Fischer projection in terms of comparative aspects, assignment of *R*/*S* descriptors, and prediction of optical rotation.

The convenience of a Fischer projection is appreciated if the *R*/*S* notation of a formula such as **4a** is sought by the conventional route. Accordingly, the allene topography may be reconstructed in the form of a tetrahedron such as **4c**, followed by the generation of a priority diagram exemplified by **4d** that requires a 90 rotation around the stereogenic axis to arrive at **4e** permitting the *R*-assignment. Employing the Fischer projection for this assignment and proceeding without the conventional ligand prioritization, one will first recognize the "Z" geometry of the lateral ligands and their "like" priorities so that the *R*-configuration can be allocated (ZLR). To predict the optical rotation one will notice again the "Z" geometry of the lateral ligands as well as their "like" polarizability parameters; consequently, **4b** is predicted to be levorotatory (ZLL).

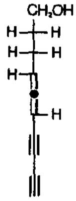
Aleurodiscus roseus produces the enantiomer of marasin[18] (**13**) and, in contrast to **4b**, exhibits the two allenic hydrogen ligands on opposite sides. To arrive at the *R*/*S* notation, one notes the "S"-ligand-geometry with "like" lateral CIP priorities, thus allocating the S-notation (SLS). Further, the two lateral ligands are identical and hence of equal polarizability so that dextrorotation can be predicted (SLD) for **13**.



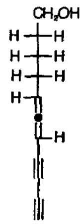
13 *(S)*
SLS
$[\alpha]_D$ +385°
SLD



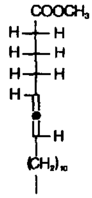
14 *(S)*
SLS
$[\alpha]_D$ +340°
SLD



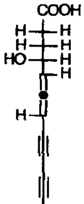
15 *(R)*
ZLR
$[\alpha]_D$ -290°
ZLL



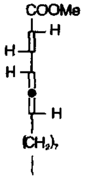
16 *(R)*
ZLR
$[\alpha]_D$ -180°
ZLL



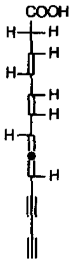
17 *(R)*
ZLR
$[\alpha]_D$ -43.3°
ZLL



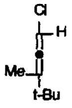
18 *(S)*
SLS
$[\alpha]_D$ +385°
SLD



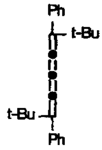
19 *(R)*
ZLR
$[\alpha]_D$ -162°
ZLL



20 *(R)*
ZLR
$[\alpha]_D$ -130°
ZLL



21 *(S)*
SLS
$[\alpha]_D$ -44.25°
SUL



22 *(S)*
SLS
$[\alpha]_D$ +336.6°
SLD

A homolog of **13** was discovered as a metabolite of *Daedalea juniperina* and was identified as **14**. The two additional homologs **15** and **16** of opposite configuration were found as metabolites of *Odontia bicolor* and of *Flammula sapinea*.[18] Fischer projections **15** and **16** reveal *R*-configurations (ZLR) and allow the prediction of levorotation (ZLL). 5,6-Octadecadienoic acid (**17**) is derived from the seed oil of *Leonotis nepetaefolia* (family *Labiatae*) and is known as laballenic acid.[18] In addition to a stereogenic axis, odyssic acid (**18**), isolated from cultures of a *Basidiomycete* species, contains a stereogenic center whose configuration, however, is uncertain.[18,23,24] Interestingly, (*E*)-2,4,5-tetradecatrienoic acid methyl ester (**19**) is the pheromone of the male bean weevil, *Acanthoscelides obtectus*[18] while all predominant structural features encountered in the examples mentioned above are found in the antibiotic mycomycin (**20**). This substance is the first naturally occurring allene to be discovered[26] and is produced by yet another organism, *Nocardia acidophilus*. Diagram **20** demonstrates the display of *E* and *Z* alkenes as well as an allene whose *R* topograpgy and predicted optical levorotation is readily apparent. Compound **21** provides an example of an allene with a heteroatom as ligand. Wheras the assignment of the *S*-configuration is trivial (SLS), the prediction of the sign of optical rotation requires a more profound inspection of the polarizability parameters.[23,24] Consequently, the orthogonal axes Cl–*H* and *Me*–tBu rank LOW-*HIGH* and *LOW*-HIGH, respectively, so that the lateral ligands, indicated in italic print, are classified as "unlike" (*HIGH-LOW*). This assessment allows the prediction of levorotation (SUL). Replacement of Cl by Br in **21** does not alter the *S*-configuration, but changes the predicted sign of rotation in view of a reversal of the polarizability parameters at the upper orthogonal axis from LOW-*HIGH* to HIGH-*LOW*. The lateral ligands then assume the *LOW-LOW* category, which is the criterion for dextrorotation (SLR). These predictions agree with experimental results.[24]

The successful resolution of a cumulenic pentatetraene with C_2 symmetry provides another example of the Fischer projection's inherent information. The Fischer projection of an optically active cumulenic pentaene with C_2 symmetry is exemplified by **22**. This compound has been obtained by resolution[24] and its diagram reveals the *S*-configuration and allows the prediction of dextrorotation.

References and Notes

1. For English translations of the original publications see: "Classics in the Theory of Chemical Combination", O. T. Benfey, Ed., Dover Publications, New York, 1963, pp. 151- 171.
2. Stereoisomeric arguments were invoked by J. Wislicenus (*Ann.* **1873**, *167*, 3) before van't Hoff and Le Bell's advancement of the tetrahedron theory: "Wird einmal die Möglichkeit gleich zusammengesetzter, structur-identischer, aber in ihren Eigenschaften etwas abweichender Molecule zugegeben, so kann dieselbe nicht wohl anders als durch die Annahme erklärt werden, daβ die Verschiedenheit ihren Grund nur in einer verschiedenartigen räumlichen Lagerung der in gleichbleibender Reihenfolge miteinander verbundenen Atome beruhe". Dazzled by the existence of three different forms of lactic acid, Wislicenus recognized the insufficiency of conventional formulas used at that time and goes so far as to suggest the need to represent such "finer isomerisms" in three dimensions with some sort of "model formulas" (*Chem. Ber.* **1869**, *2*, 551).
3. Profound and outstanding as Fischer's contribution to stereochemistry may appear today, his scientific contemporaries built only slowly on his work. The correctness of his findings was not in doubt, but the addition of a third dimension required fundamental readjustments in the perception of chemistry. After he had delivered a lecture on the stereochemistry of sugars, probably in the fall of 1893, Fischer reflected on an episode that is characteristic of that time: [Nach dem Vortrag] "kam Helmholtz zu mir, um seiner Freude Ausdruck zu verleihen, dass die Chemie derartige komplizierte Fragen des molekularen Baues behandeln könne. Selbstverständlich war das Urteil eines solchen Mannes für mich und meine Wissenschaft besonders ehrenvoll. Ich habe zwar gleich gemerkt, daß er die Sache nur halb verstanden hatte, weil ihm die Tatsachen, auf denen die Spekulation beruhte, zu fremd waren, aber mit dem Feingefühl des Genies hatte er doch den grossen Fortschritt erkannt, den die Lehre von van't Hoff und Le Bell und ihre Spezialanwendung auf so komplizierte Gebilde wie die Zucker der Chemie gebracht haben" (taken from: Aus meinem Leben von Emil Fischer, M. Bergmann, Ed., Verlag von J. Springer, Berlin 1922).
4. E. Fischer, *Chem. Ber.* **1891**, *24*, 2683.
5. Prompted by the remarks of a referee who erroneously equated topology and topography, Prelog and Helmchen's comment on the terms *geometry* and *topography* is reiterated: "It follows from [Klein's definition] that the *chirality* (orientability in Euclidean space) of a figure is a *geometric* property, whereas its *chirality sense* (the orientation of that figure and its algebraic sign) is a *topographical* one" (Angew. Chem. Int. Ed. Engl. 1982, 567-583). On the contrary, the science of *topology* deals with those properties of a figure that remain invariant under distortion without tearing or joining. The *conformation* of a figure is therefore a *topological* property, but a variation in shape that involves tearing and joining is not (e.g. a doughnut and a pretzel).
6. J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature* **1951**, *168*, 271.
7. Beilstein refers to the Fischer chain as the principal chain and the connecting bonds as catenary bonds (Latin *catenarius*, fr. *catena* chain); analogously, bonds connecting ligands that are not part of the Fischer chain are termed extracatenary (Beilstein, Drittes und Viertes Ergänzungswerk **18** (1975) XIV.
8. Beilstein, 5th Suppl. Series, vol. 18, p. LIII-LVI.
9. K. Freudenberg, in *Stereochemie*, K. Freudenberg, Ed., Franz Deuticke, Leipzig 1933, pg. 665.
10. H. Maehr, *J. Chem. Educ.* **1985**, *62*, 114.

11. For illustrative examples see: a) A. A. Nagel, W. C. Celmer, M. T. Jefferson, L. A. Vincent, E. B. Whipple, *J. Org. Chem.* **1986**, *51*, 5397; b) W. D. Celmer, *Ann. N. Y. Acad. Sci.* **1986**, *471*, 299; c) H. Maehr, R. Yang, Li-Na Hong, C.-M. Liu, M. Hatada, L. J. Todaro, *J. Org. Chem.* **1989**, *54*, 3816; d) A. Nakagawa and S. Omura, in *Macrolide Antibiotics. Chemistry, Biology, and Practice*; S. Omura, Ed., Academic Press: New York 1984; p 65; e) R. B. Woodward, In *Frontiers in Bioorganic Chemistry and Molecular Biology*, Yu. A. Ovchinnikov, and M. N. Kolosov, Ed.; Elsevier: Amsterdam 1979; p 39-58.
12. a) K. Freudenberg, *Naturwiss.* **1977**, *64*, 338; b) R. A. Dietzel, *J. Chem. Educ.* **1979**, 56, 451; c) H. C. Price, *Biochem. Educ.* **1980**, *8*, 105; d) J. P. Idoux, *J. Chem. Educ.* **1982**, *59*, 553; e) G. A. Epling, *J. Chem Educ.* **1982**, 59, 650; f) Y. Brun, P. Leblanc, *J. Chem Educ.* **1983**, *60*, 403; g) F. O. Ayorinde, *J. Chem. Educ.* **1983**, *60*, 928.
13. See [10] for appropriate references. Ironically, it is the multiplicity of suggested alternatives that has favored the retention of the terms *erythro* and *threo* they were supposed to replace. Alluding to the array of options, Prof. K. N. Houk jokingly proposed two new terms, *elps* (*e*rythro, *l*ike, *p*ref, *s*yn) and *tupa* (*t*hreo, *u*nlike, *p*arf, *a*nti), which actually serve as valuable didactic aids.
14. The names and Fischer projections of 8 hexoses, 4 pentoses and 2 tetroses, i.e. a total of 28 stereoisomers, are easily recalled. A mnemonic for the recapitulation of the hexoses' names has been used for a long time: "*all alt*ruists *gl*adly *ma*ke *gu*m *i*n *ga*llon *ta*nks". This sentence, together with a simple number sequence, will permit the reconstruction of all eight Fischer projections in the D-series, where the numbers (identical with the numbering system of the carbon chain) indicate those locants in a given hexose whose hydroxyl groups are located on the left in the Fischer projection: 0, 2, 3, 2/3, 4, 2/4, 3/4, 2/3/4 (e.g. D-allose has no hydroxyl groups on the left, D-altrose has C2-*OH* on the left, D-glucose has C3-*OH* on the left, etc.). Arranging the eight hexoses into pairs (allose/altrose, glucose/manose, gulose/idose, galactose/talose) and deleting the first stereocenters (H-C2-OH), will furnish the four Fischer projections of the D-pentoses, one from each pair of hexoses, the names of which (*ri*bose, *arab*inose, *x*ylose, *ly*xose) can be obtained from the sentence: "*ri*ch *Arabs* *cross* *Ly*onnesse". Grouping the four pentoses into two pairs and again deleting C2 in each, yields the Fischer projections of the two tetroses, erythrose and threose, in alphabetical order.
15. For examples see: a) S. Masamune, G. S. Bates, J. W. Corcoran, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 585; b) H. Maehr, *Helv. Chim. Acta.* **1974**, *57*, 936.
16. The substituents at the orthogonal axis' termini are identical with the *fiducial* groups, defined by Cahn, Ingold and Prelog as follows: "The fiducial groups shall be the pairs nearest together of groups, directly bonded to atoms on the axis, that lie one pair in each of the planes of atoms that intersect along the axis" (ref. 19, pg. 399).
17. There is, of course, the alternative way to obtain a Fischer projection which utilizes exactly those positions of the D_{2d} tetrahedron where one of the orthogonal axes lies in the Fischer plane. Such an arrangement displays the second orthogonal axis perpendicular to the Fischer plane. Similar to the projection of alkenes, a convention could then be invoked which assigns ligands above the Fischer plane to the right in the Fischer diagram. Consequently, the resulting projections produce Fischer diagrams were the patterns of image and mirror image are not related like "S" and its mirror image "Z" but rather like the symbols "S" and "⊂". From the view point of pattern recognition in CASD the feature of an S/⊂ relationship between antipodes is desirable; the concept of the diagram's reflection

invariance within the Fischer plane (S/Z and ⊂/⊃) and the relationships S/⊂ and Z/⊃ between antipodes, however, which would be the result of such a convention, lack conformity.

18. R. E. Bew; Chapman, J. R; Jones, E. R. H.; Lowe, B. E.; Lowe, G. *J. Chem. Soc. (C)* **1966**, 129.
19. R. S. Cahn, C. Ingold, V. Prelog, *Angew. Chem. Internat. Edit.* **1966**, *5*, 385.
20. The following mnemonic applies for *R/S* assignments: For "S"-ligand-geometry unlike lateral substituent priorities are indicative of the R configuration (SUR as in sure). The remaining three letter combination follow logically, e.g. SLS, ZUS, ZLR.
21. G. Lowe, *J. Chem. Soc. Chem. Commun.* **1965**, 411.
22. J. H. Brewster, *Topics in Stereochemistry* **1967**, 2, 1-72.
23. W. Runge, In "*The Chemistry of the Allenes*", S. R. Landor, Ed.; Academic Press: New York, 1982; vol. 3, p 579-594.
24. W. Runge, In "*The Chemistry of Ketenes, Allenes and Related Compounds*", S. Patai, Ed.; John Wiley and Sons: New York, 1980; Part 1, p 99-154.
25. The following mnemonic applies for the prediction of the optical rotation: For "S" geometry unlike lateral substituent polarizability parameters are indicative of the levorotation (SUL as in sulfur). The remaining three letter combination follow logically, e.g. ZUD, SLD, and ZLL.
26. W. D. Celmer, I. A. Solomons, *J. Am. Chem. Soc.* **1953**, *75*, 1372, 3430.