Organic and Biological Chemistry

Applications of the Sequence Rule. I. Naming the Paired Ligands g,g at a Tetrahedral Atom Xggij. II. Naming the Two Faces of a Trigonal Atom Yghi

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Abstract: The *R/S* system of Cahn, Ingold, and Prelog for specifying absolute configurations is extended in two ways. I. The *pro-R/pro-S* System. Rules are provided for naming the paired ligands g,g at tetrahedral atoms Xggij, *e.g.*, the two hydrogens at the methylene carbon of ethanol. A new geometrical concept, that of *prochirality*, is defined, and atoms of the type Xggij are said to be prochiral. The symbols used in naming the paired ligands are *pro-R* and *pro-S* or, in certain circumstances, *pro-r* and *pro-s*. II. The *re/si* System. Rules are provided for naming the two faces of a trigonal atom Yghi, *e.g.*, the faces of the carbonyl carbon of acetaldehyde. The symbols used in naming the two faces are *re* and *si*. The naming of the two faces of isolated double bonds and mesomeric systems is also discussed. Examples are given of the way in which the *R/S*, *pro-R/pro-S*, and *re/si* systems, when used in conjunction with standard chemical nomenclature, may serve to transmit stereochemical information in a brief and unambiguous manner without the use of projection or structural formulas. The systems are of value in discussing the stereochemistry of enzyme reactions.

In recent years increasing numbers of investigations have been concerned with the stereochemistry of enzyme-catalyzed reactions in which like groups or atoms attached to the same carbon atom behave differently. (The two hydrogen atoms of the methylene group of ethanol, for example, may be differentiated by an enzyme.[1]) Stereospecific additions to carbonyl groups, and to carbon–carbon double bonds, are also commonplace to the biochemist. These biochemical reactions are limiting cases of stereoselective reactions frequently encountered in organic chemistry. There is a need for a single convention that allows the stereochemistry of all such reactions to be discussed in unambiguous terms. The convention must be suitable for use in abstracts, summaries, and reviews where it is necessary to state results without the aid of projection or structural formulas.

During the last 14 years a system for specifying absolute configurations of organic compounds has been developed by Cahn, Ingold, and Prelog.[2-5] The internal consistency of the method, which will be referred to here as the *R/S* system, has been extensively tested by it originators, and by the editors of the third supplement of Beilstein's "Handbuch der organischen Chemie." It has been found to be of practical use in chemical and biochemical discourse, and in indexing. In the present paper two extentions of the *R/S* system are set forth. In part I (the *pro-R/pro-S* system), problems related to the naming of the identical but distinguishable ligands g,g at a tetrahedral atom Xggij are considered.[6] Part II (the *re/si* system) is concerned in the first place with the naming of the two faces of a trigonal atom Yghi, *i.e.*, with naming the two sides of the plane where the plane contains Y and the first atoms of the three ligands g, h, and i. The first of these two topics has already been discussed by Hirschmann.[7] His proposals are compared in section 1.6 with those advocated here.

Summary of the *R/S* System. The language of the present paper is that of the revised system;[5] thus three-dimensional objects that may exist in enantiomeric forms are said to be *chiral* (Greek: of or pertaining to the hand). Such objects may have one or multifold axes of symmetry. An object is said to be *asymmetric* only if it has the trivial property of a onefold axis of symmetry and no other symmetry element (point group C_1).

The following statements summarize those aspects of the *R/S* system required for understanding the present paper. The objects to be examined in applying the system are three-dimensional molecular models in which each atom is assigned an integral atomic number and mass number. The model is first examined to establish the type and position of each chiral feature: centers of chirality, including centers which are pseudo-asymmetric, axes of chirality, planes of chirality, and if conformations are to be specified, axes of helicity.

(1) F. A. Loewus, F. H. Westheimer, and B. Vennesland, *J. Am. Chem. Soc.*, 75, 5018 (1953).

(2) Paper I on the sequence rule: R. S. Cahn, and C. K. Ingold, *J. Chem. Soc.*, 612 (1951).

(3) Paper II: R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(4) An introduction to paper III: R. S. Cahn, *J. Chem. Educ.*, 41, 116, erratum 508 (1964).

(5) Paper III: R. S. Cahn, Sir C. Ingold, and V. Prelog, *Angew. Chem.*, 78, 413 (1966); *Angew. Chem. Intern. Ed. Engl.*, 5, 385 (1966).

(6) The term ligand is used in this paper in the most general sense of "that which is bound," whatever the chemical nature of the binding. An *n*-dentate ligand, in the normal chemical sense, is examined by the sequence rule *n* times, once from each point of binding, and so in the present paper it is represented by *n* single letters and treated as *n* separate ligands. Specifically, bidenticity is discussed as involving two distinct, but linked, ligands. The letters g,h,i,j are used to represent ligands when the priority order is indeterminate (*i.e.*, g > h and h > g are both allowed, etc.). This usage is of particular value in discussing geometrical principles. A definite priority order is indicated by the sequence a > b > c > d.

(7) H. Hirschmann, *J. Biol. Chem.*, 235, 2762 (1960).

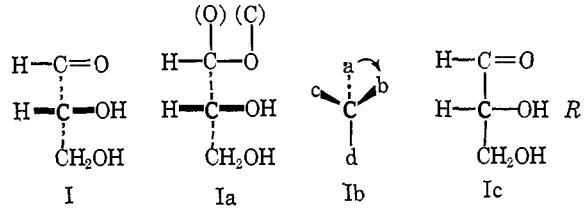
This process is termed *factorization*, and the centers, axes, and planes of chirality are *chiral elements*. The only chiral centers discussed in the present paper are tetrahedral carbon atoms of the type Cghij; chiral axes will be considered, but octahedral centers and chiral planes will receive only passing mention. Molecular conformations are not discussed.

The *sequence rules* prescribe the method for exploring the ligands about an element of chirality and the ordering of these ligands. The *standard sequence subrules* required for examining chiral centers of the type Xghij and chiral axes are

(0) nearer end of axis precedes further (axial chirality only)
(1) higher atomic number precedes lower
(2) higher mass number precedes lower
(3) *seqcis* groups precede *seqtrans*
(4) like pair *R,R* or *S,S* precedes unlike *R,S* or *S,R;* also *r* precedes *s*
(5) *R* chirality precedes *S*

(The reasons for transferring the mass-number rule from position 4 to position 2 and introducing a new subrule are given in paper III.[5]) If two ligands cannot be distinguished by one subrule then the next subrule is applied, and so on, until a decision is reached or all the subrules have been applied. Where multiple bonds occur it is necessary to expand the ligands at their unsaturated atoms by *replica atoms* before the subrules are applied. The valences of the replica atoms are completed by *phantom atoms* of zero atomic number and mass. In certain cases involving heteroatoms in conjugated ring systems replica atoms with fractional atomic numbers are employed.

The *chirality rules* prescribe the methods for examining chiral elements with their ordered ligands and arriving at decisions as to the chirality of the elements. The chirality symbols *R* or *S*, or in the case of pseudo-asymmetry *r* or *s*, are first assigned to the chiral centers, then *aR* or *aS*, or *ar* or *as*, to the chiral axes, then *pR* or *pS* to the chiral planes.



I Ia Ib Ic

The *R/S* system may be used to specify the absolute configurations of molecular models and equivalent molecular species, of "pure" chemical compounds with their natural distribution of isotopes, and of isotopically labeled compounds. Isotopic labeling is considered in section 1.4. The procedure for chemical compounds may be illustrated by considering a simple example: that of D-(+)-glyceraldehyde. The model to be examined is represented by the projection formula I (heavy bonds above, and dotted bonds below the plane of the paper). In such a model one must either assign specific "normal" mass numbers to the various atoms, or rule that all atoms with the same atomic number have the same mass number. In either case the essential fact is preserved that the chirality arising from the natural statistical distribution of isotopes in a chemical compound cancels out. The analysis of the model proceeds as follows. (i) Factorization. The model has a single tetrahedral chiral center (boldface type). Of the four ligands, no two ligands can be selected that differ only in that they are enantiomeric, *i.e.*, the center is asymmetric rather than pseudo-asymmetric. The chirality symbol to be assigned to the center is therefore *R* or *S* rather than *r* or *s*. (ii) The sequence rule. The multiple linkage of the aldehyde group is first expanded with the replica atoms (O) and (C) to give formula Ia. Subrule 0 does not apply. By Subrule 1, OH > CHO > CH_2OH > H. All ligands being ordered the procedure stops. (iii) The chirality rule. The assigned sequence is represented in Ib by a > b > c > d.[6] The rule prescribes that the tetrahedral assembly Ib be viewed from the side *remote* from the ligand of lowest precedence (d). Starting from the ligand of highest precedence a path a → b → c may be traced which is clockwise (right handed) and the chirality of the center is therefore *R* (*rectus*). Had the path been anticlockwise (left handed) the chirality would have been *S* (*sinister*). The chirality symbol assigned to the model is then applied to the chemical compound and may be used as part of its chemical name.

Fischer Projections. Unless heavy and dotted bonds are used, projection formulas are shown in this paper according to the convention proposed by Emil Fischer, *i.e.*, horizontal bonds above the plane of the paper and vertical bonds below (compare Ic and I). A word of caution is appropriate. This method is not universally adopted. In both carbohydrate and amino acid nomenclature it is permissible to reverse the convention and write formulas horizontally with C-1 to the right. The standard presentation in terms of the Fischer convention is achieved by rotating such formulae through 90° so that C-1 is at the top, as in Ic.[8]

I. The *pro-R/pro-S* System. Naming the Paired Ligands g,g at a Tetrahedral Atom Xggij

1.1. Prochirality and Chirality. Before providing rules for examining molecular models it is desirable to introduce a new geometrical concept, that of prochirality. To this end the term *point ligand* is employed. Point ligands have only two properties: (i) any two point ligands may be identical or non identical, and (ii) two point ligands may not occupy the same position in space. They have no intrinsic order (symbols g,h,i,j), but they may be arranged in some specified order (symbols a > b > c > d). Although the term is new the concept is implicit in the *R/S* system and in discussions of stereochemistry from the time of van't Hoff and Le Bel.

If, in D of Figure 1, one of the identical point ligands g is replaced by h (h is not already represented in the assembly), then either E or F is produced. The two identical point ligands of D may be distinguished by this procedure, but the identical ligands of A, B, and C

(8) "Rules of Carbohydrate Nomenclature" (British and American Chemical Societies), *J. Org. Chem.*, **28**, 281 (1963); "Definitive Amino Acid Rules" (IUPAC), *J. Am. Chem. Soc.* **82**, 5575 (1960); Special PublicationNo.14, The Chemical Society, London, 1960, p 48; see also *J. Org. Chem.*, **28**, 291 (1963), and *Chem. Eng. News*, **30**, 4522 (1952).

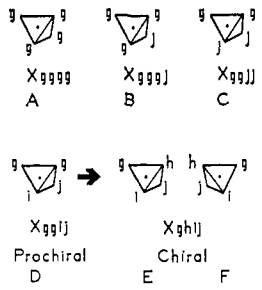


Figure 1. Centers defined by assemblies of tetrahedrally arranged point ligands.[6] A prochiral center in a molecular model corresponds to the reference assembly D. As the paired ligands may have highest, middle, or lowest sequence rule priority, there are three subtypes of prochiral assembly: Xbbcd, Xaccd, and Xabdd. A chiral center in a moleclar model corresponds to either E or F. When ordered ligands are under consideration the center is defined as Xabcd (*e.g.*, Ib).

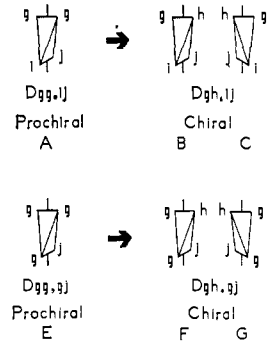


Figure 2. Prochiral and chiral axes defined by assemblies of point ligands arranged at the corners of disphenoids.[6] Assemblies of the type Dgj,gj (not shown) are chiral. The transformations indicated by arrows result from the replacement of one of the g,g point ligands on the short edge of the disphenoid by a point ligand not already represented in the assembly. Because of subrule 0, the final reference assembly for a prochiral axis in a molecular model is either Dbb,cd or Dab,dd (Dad,cc is eliminated from A) and that for a chiral axis Dab,cd (Dac,bd is eliminated from B and C). Cases B, F, and G, and assemblies of the type Dgj,gj are also eliminated by subrule 0.

cannot be so distinguished. Assembly D therefore stands in a special relationship to the chiral assemblies E and F. As D comes before E and F in the operation, it is convenient to apply the adjective *prochiral* to D (*Greek*, *pro-*: before in time or place, as in prolog or proscenium). In the same way that g,h,i,j in E and F define chiral centers, g,g,i,j define a *prochiral center* which may also be called a *prochiral tetrahedral center.*

In Figure 2 the two possible types of prochiral axis are shown (A and E). Each axis is defined by four point ligands at the corner of a disphenoid (an elongated tetrahedron). The point ligands g,g on a short edge of the disphenoid may be distinguished by reference to an appropriate enantiomeric pair of chiral disphenoids. In the transformations shown, one or other of the identical point ligands is replaced by a point ligand not already represented in the assembly. If replacements are made with point ligands, such as j, that are already represented, then A is related to an enantiomeric pair Dgj,ij (equivalent to F and G) and B to a pair of the type Dgj,gj (not shown).

The above examples are sufficient for the material discussed in this paper. It may be desirable in the future to define prochiral octahedral complexes (there are six types) and planar prochirality. A general *definition of prochirality* may be given thus. *If a chiral assembly is obtained when a point ligand in a finite nonchiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral.* It follows that for every point ligand that can be replaced to give a chiral assembly, there is at least one other point ligand that can be replaced to give an enantiomeric assembly. Not all replacements of such point ligands lead to chirality (see Figure 1), but replacement by a point ligand not already represented in the assembly necessarily gives a chiral assembly. A nonchiral assembly must have at least one mirror plane, or a center of symmetry, or at least one $2n$-fold alternating axis of symmetry where n is even. Individually all of these symmetry elements are compatible with prochirality. For tetrahedral, octahedral, and disphenoidal prochiral assemblies, only mirror planes are encountered. It remains to be determined which combinations of symmetry elements, *i.e.*, which point groups, are compatible with prochirality.

1.2. Prochirality and Molecular Models. Molecular models may be said to be chiral or nonchiral. Models are nonchiral if they can adopt a nonchiral conformation or can adopt with equal probability conformations of opposite chirality. It would be possible to describe certain nonchiral molecules as prochiral, but this course will not be followed since it would serve no practical purpose. We shall, however, speak of a model being *factorized* into both *chiral* and *prochiral elements.*

In defining chiral and prochiral elements, the sequence rule is used to reduce a complex of material and stereochemical information concerning a molecular model to the simple geometrical relationship of an ordered assembly of point ligands. One may thus speak of a *prochiral center* in a model, of a prochiral atom, or, more specifically, of a *prochiral carbon atom* Cggij in the same way that one speaks of a chiral center or a chiral carbon atom Cghij, even though the chirality or prochirality in the two cases is, strictly speaking, that defined by the tetrahedral *reference assembly* (*e.g.*, Ib). In some circumstances it may be convenient to speak of a *prochiral methylene group.* One may also speak of a *prochiral axis* in a model in the same way that one speaks of a chiral axis. The identical ligands to be distinguished at a prochiral center or axis cannot be ordered by subrules 0 to 5. It is convenient to speak of these as *paired ligands*, or when appropriate, as paired groups, substituents, or atoms.

In factorizing a model into chiral and prochiral elements, it is usually possible to identify these elements by inspection.[9] The sequence rule is only applied in detail in order to assign chirality symbols to the chiral elements and to name the paired ligands at the prochiral elements. The names for the paired ligands are derived from the word prochirality, and the appropriate chirality symbols are shown in Table I. The symbols *pro-r* and *pro-s*, or *pro-ar* and *pro-as* are employed when the nonpaired ligands are enantiomeric.

(9) If the concept of a prochiral center is extended to permit assignments to be made for octahedral complexes, then care will be needed to avoid treating as prochiral certain types of chiral complex in which the chirality depends upon the polydenticity of the ligands. This problem does not arise in the case of tetrahedral centers or disphenoidal axes. It is shown in paper III[5] that polydenticity may cause centers of the type Cggii, Cgggj, and Cgggg to be chiral.

Table I

	Chirality symbols	Prochirality symbols	Subscripts designating paired ligands
Centers	*R*, *S*	*pro-R*, *pro-S*	$-H_R$, $-H_S$
	r, *s*	*pro-r*, *pro-s*	$-H_r$, $-H_s$
Axes	*aR*, *aS*	*pro-aR*, *pro-aS*	$-H_{aR}$, $-H_{aS}$
	ar, *as*	*pro-ar*, *pro-as*	$-H_{ar}$, $-H_{as}$

The molecule having been factorized, chirality symbols are first assigned to the chiral elements by the chirality rule and then prochirality symbols are assigned at the prochiral elements by the prochirality rule. This order is necessary, as prochirality assignments may depend upon chirality assignments. The reader may find it helpful in considering the following rule to refer to the first example in section 1.3. Before applying the prochirality rule the three types of ligand at the prochiral center or axis must first be ordered by the sequence rule.

The Prochirality Rule (in note form). **If elevation in the sequence gives** *R*, **then** *pro-R;* **if** *r*, **then** *pro-r;* **if** *aR*, **then** *pro-aR;* **if** *ar*, **then** *pro-ar*, **etc.**

In detail this may be stated as follows. At a prochiral center, arbitrarily select one of the paired ligands and give this priority over the other ligand of the pair. (The arbitrary priority given to the chosen ligand must not be such as to disturb its priority relative to the unpaired ligands.) Examine the derived center Xabcd as prescribed by the chirality rule. If the observed sequence a → b → c is clockwise when the tetrahedral assembly is viewed from the side opposite to d (*R* or *r* chirality), then the selected ligand is the *pro-R* or *pro-r* ligand, and the other ligand is the *pro-S* or *pro-s* ligand.

The *pro-R* ligand may be said to be in the *pro-R* position, or *pro-R* to the prochiral atom. Similar statements apply to *pro-S*, *pro-r*, and *pro-s* ligands. It is permissible in formulas or in a text, where it is clear that chirality is not implied, to use *R* and *S*, or *r* and *s*, as subscripts in order to distinguish the ligands.

Apply the same procedure to *prochiral axes* but employ the symbols *pro-pR*, etc.

(It should be noted that, strictly speaking, it is the reference assembly Xggij which is transformed into the assembly Xghij and not the prochiral atom of the molecular model which is transformed into a chiral atom. The note form of the rule should thus be regarded as an aid to memory and not a formal statement.)

Cyclic Systems. The above rule is sufficient for all cases in which the paired ligands of a prochiral element do not constitute the atoms of one and the same ring. The following *supplementary rules* are required for such cyclic systems. Although the rules are stated for prochiral centers, analogous rules apply when prochiral axes are under consideration. The rules are placed here for convenience of reference. The reader is advised to turn to the simple examples of the use of the prochirality rule given in the next section before returning to the more specialized cases covered by the following. Supplementary rules a and b state how atoms or groups of atoms may be specified with reference to a particular prochiral ring atom. Supplementary rules c and d may be applied if the atoms of a ring constitute the paired ligands of two, and only two, prochiral atoms X_1 and X_2.[10] The contracted prochirality names defined in these rules provide an alternative to supplementary rule b.

Edges (definition). The two edges of a ring relative to a particular ring atom X are composed of the two chains of ring atoms leading from the atom X and terminating with atoms attached to the second ring atom (even-membered rings), or with atoms linked to each other (odd-membered rings). The number of atoms in the two edges are equal.

Supplementary Rules. (a) If the atoms of a ring constitute the paired ligands of a single prochiral atom Xggij, then the two edges of the ring are the *pro-R* edge and the *pro-S* edge, or the *pro-r* edge and the *pro-s* edge. The atoms of the *pro-R* edge are said to be *pro-R* to the prochiral atom X, etc.

(b) If the atoms of a ring constitute the paired ligands of more than one prochiral atom then one may speak of a particular atom of the ring as being *pro-R* to a particular prochiral atom, or of an edge *pro-R* to a particular atom etc.

(c) If the same edge of the ring is *pro-R* to both X_1 and X_2, this edge is the *pro-R–R* edge. The other edge is the *pro-S–S* edge. In like manner one may define a *pro-r–r*, *pro-R–r*, or *pro-r–R* edge, etc. (for order of citation *R* and *r* see below).

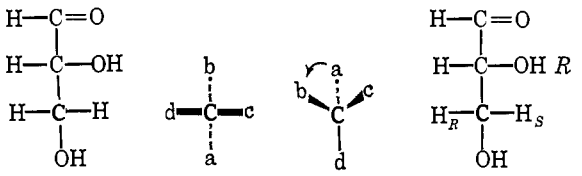
(d) If the same edge of the ring is *pro-R* with respect to X_1 and *pro-S* with respect to X_2, then the edges of the ring are the *pro-R–S* and *pro-S–R* edges. In like manner one may define a *pro-r–s* and a *pro-s–r* edge, a *pro-R–s* and a *pro-S–r* or a *pro-r–S* and *pro-s–R* edge.

To establish which name applies to which edge, assign priorities by sequence subrules 1 to 5 to the four ligands at X_1 and X_2 which do not form the ring. Cite first the edge relative to the atom bearing the highest priority ligand, or, if both atoms carry identical highest priority ligands, cite first the edge relative to the atom bearing the next highest priority ligand. If these also are identical, cite first the edge relative to the atom with the highest priority by sequence subrules 1 and 2. No decision can be reached if the two prochiral atoms are geometrically indistinguishable and the pairs of nonidentical ligand are *cis* oriented. Supplementary rule b, however, may still be applied.

1.3. Examples. The above procedure may be illustrated by again considering the chemical compound D-(+)-glyceraldehyde. As we are not here concerned with isotopic labeling, we assume that all atoms with the same atomic number have the same mass number and examine the model represented in Fischer projection as II. (i) Factorization. The model has both a tetrahedral chiral center and a tetrahedral prochiral center (boldface type). The chiral carbon atom is not pseudo-asymmetric and the chiral center has thus either *R* or *S* chirality. Similarly, the nonpaired ligands at the prochiral carbon atom are not enantiomeric and therefore the paired ligands (the hydrogen atoms) are to be named *pro-R* and *pro-S*. (ii) The chiral center. As before, the chirality at this center is *R*. (iii) The prochiral center and the prochirality rule.

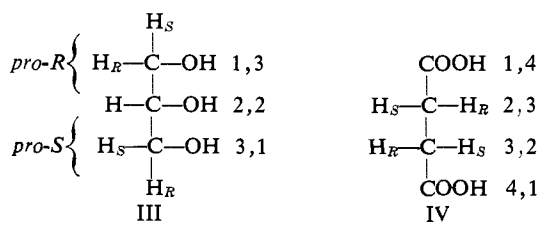
(10) Baeyer was much intrigued by this type of system and spoke of X_1 and X_2 as having relative asymmetry: A. Bayer, *Ann.*, **245**, 103, 128 (1888).

The ligands are ordered as follows: sequence subrule 0 does not apply. By subrule 1, OH > CHOHCHO > H and H. The ligands H and H cannot be ordered by subrules 2 to 5. As all the subrules have been applied the examination stops. If the hydrogen to the right is selected for naming, then this hydrogen is given priority in the sequence over the other hydrogen. By this operation the sequence a > b > d = d becomes the sequence a > b > c > d shown as the reference assembly IIa, equivalent to IIb. Viewed from the side opposite to d the sequence is anticlockwise and the hydrogen selected is therefore the *pro-S* hydrogen; the other is the *pro-R* hydrogen. The results of the analysis are summarized in IIc with the aid of the subscript notation.



It is necessary to employ the prochirality and chirality symbols in conjunction with standard chemical nomenclature. The exact way in which this is done will depend upon the topic under discussion and the practices acceptable to the journal or abstracting system in which the material is to be printed. Cahn, Ingold, and Prelog recommend that where adequate "local systems" have been developed, such as those for the carbohydrates, amino acids, and steroids, the *R*/*S* system should be used to supplement rather than to replace. Cumbersome, ambiguous, or controversial extensions of local systems may be avoided by use of the *R* and *S* symbols. In like manner the prochirality names may be used in conjunction with local systems, and one may speak of the *pro-R* hydrogen at C-3 (or H_R at C-3) of D-glyceraldehyde. As there is only one prochiral center it is permissible to omit the C-3 from the specification. It would be equally correct to speak of the hydrogen *pro-R* to C-3 of (2*R*)-2,3-dihydroxypropane-1-aldehyde. In many cases the systematic name will be the only one available. In steroid nomenclature, the symbols α and β provide a satisfactory means for naming paired hydrogens or methyl groups. In this field, therefore, the *pro-R*, *pro-S* terms will be required only for special cases.

The task of specifying a particular ligand at a particular prochiral center is a simple one for compounds with a single such center (*e.g.*, ethanol, D-glyceraldehyde, L-malic acid) and for compounds in which the various prochiral centers can be numbered in an obvious and unambiguous way (*e.g.*, unbranched fatty acids). Complications arise where alternative numbering or alphabetizing schemes are possible, or the symmetry of the molecule is such that two prochiral carbon atoms are geometrically indistinguishable.

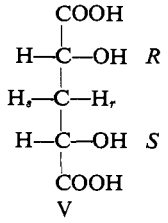


Formula III shows the assignments for glycerol (the case of citric acid XXX is equivalent). There are three prochiral centers and the three types of ligand at each center are ordered by subrule 1. The carbon chain may be numbered so that either the *pro-R* or *pro-S* ligand at C-2 has lower numbering. The phrases "the *pro-R* hydrogen of the *pro-R* CH_2OH group" or "H_R of the $(CH_2OH)_R$ group" avoid all question of numbering. The phrase "H_R at C-1 (*pro-R* to C-2)" avoids ambiguity by defining the numbering employed. "H_R at C-3 (*pro-R* to C-2)" would convey the same information, but the use of the lower numbering is to be preferred. The same problem arises for 4-methylheptane, but in this case the use of numbering cannot easily be avoided as the two prochiral methylene groups in each of the paired propyl groups must be distinguished.

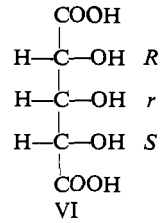
The situation in which two prochiral carbon atoms are geometrically indistinguishable may be illustrated by succinic acid (IV). In inspecting a model, there is no way in which we may again identify one of the two carboxyl groups, one of the α-carbon atoms, one of the *pro-R* hydrogen atoms, or one of the *pro-S* hydrogen atoms. It is desirable to phrase statements about such a molecule in a manner that emphasizes this limitation of knowledge; thus it is better to write "one of the two equivalent *pro-R* hydrogen atoms" than "H_R at C-2." With a longer carbon chain the use of arbitrary numbering becomes unavoidable: for hexane one may speak of "one of the two equivalent atoms specified as H_R at C-3," and of "one of the two equivalent pairs of atoms specified as H_R at C-3, H_S at C-4." It is instructive to compare the case of succinic acid with that of (2*R*,3*R*)-(+)-tartaric acid: here the two chiral centers are geometrically indistinguishable.

So far we have only considered cases in which the three types of ligand at a prochiral center may be ordered by subrule 1. The question of isotopic substitution (subrule 2) and isotopic labeling will be discussed in section 1.4. Cases involving subrules 3 and 4 require no special comment, but the connection between the use of the *pro-r*, *pro-s* terms and subrule 5 requires exposition.

Consider the model represented by V. On factorization there are seen to be two chiral centers (asymmetric carbon atoms) and one prochiral center. The nonpaired ligands at the prochiral center are enantiomeric and therefore the terms *pro-r* and *pro-s* are to be used in naming the paired ligands. The chirality assignments are made in the usual way. For the prochiral center subrule 0 does not apply, subrule 1 gives CHOHCOOH (*R*) and CHOHCOOH (*S*) > H and H. Subrules 2, 3, and 4 do not apply. Subrule 5 (*R* precedes *S*) leads to the sequence CHOHCOOH (*R*) > CHOHCOOH (*S*) > H and H. All subrules having been applied the procedure stops and the prochirality assignments are determined as before. The close similarity of V to compound VI, in which there are two asymmetric centers and one pseudoasymmetric center, will be apparent. Both are *meso* compounds. Not all cases in which subrule 5 is employed in making chirality or prochirality assignments are *meso* compounds. Thus if the paired ligands in V are replaced by $CHClCH_3$ (*R* chirality) these ligands are differentiated as *pro-r* and *pro-s*.

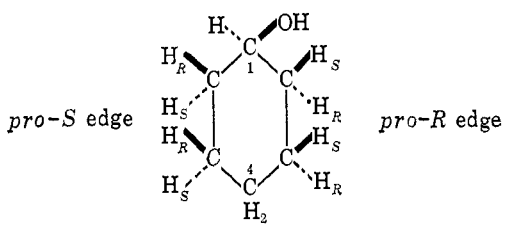


V



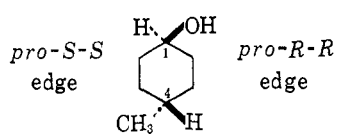
VI

Cyclic systems. An example of the use of the terms *pro-R* edge and *pro-S* edge is provided by cyclohexanol (VII). There are five prochiral carbon atoms. The paired ligands at C-1 constitute the atoms of the ring as do the unpaired ligands of four of the five methylene groups. Although the two hydrogens at C-4 can be distinguished by their *cis* or *trans* relationship to the hydroxyl group, C-4 is not, by the present rules, a prochiral atom but is of the type Cggii. In making the assignments shown, all ligands are ordered by subrule 1. To specify a particular ligand at a particular prochiral center either the *pro-R* or the *pro-S* edge carbon atoms may be given lower numbering. The phrase "H_R at C-3 (edge *pro-R* to C-1)" or, as there is only one *pro-R* edge in the model, the phrase "H_R at C-3 (*pro-R* edge)" uniquely specifies a particular atom. The arbitrary choice of numbering is indicated in the statement. It would, of course, be possible to say that a particular hydrogen is *cis* or *trans* to the hydroxyl group and to specify the carbon atom to which the hydrogen is attached with the aid of a prochirality symbol.

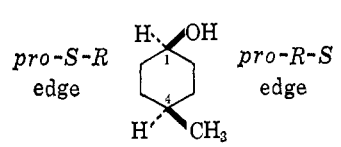


VII

Formulas VIII to XI illustrate the situation in which the atoms of a ring constitute the paired ligands of two prochiral carbon atoms.[10] The prochiral methylene groups in each ring are not shown. For VIII either the *pro-R–R* edge or the *pro-S–S* edge may be given lower numbering. The phrase "H_R at C-2 (edge *pro-R* to C-1)," or "H_R at C-2 (*pro-R–R* edge)," specifies a particular hydrogen atom. Case IX may be handled in a similar manner.

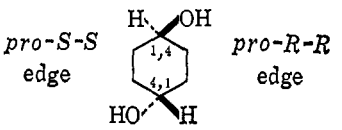


VIII

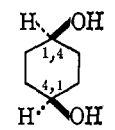


IX

Cases X and XI resemble that of succinic acid (IV) in that various pairs of atoms are geometrically indistinguishable. Having selected one of two equivalent atoms as C-1 then either the edge *pro-R* to C-1 or that *pro-S* to C-1 may be given lower numbering. For X one may speak of "one of the two equivalent atoms specified as H_R at C-2 (*pro-R–R* edge)." For both X and XI "H_R at C-2 (edge *pro-R* to C-1)" specifies two equivalent atoms.



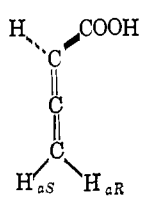
X



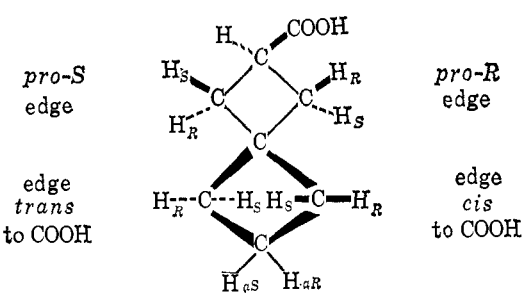
XI

Models in which the atoms of a ring constitute the identical ligands of more than two prochiral atoms can be constructed. By the present rules the paired ligands of all six atoms of the ring of *cis*- or *trans*-inositol are classified as prochiral rather than as pseudo-asymmetric atoms of indeterminant chirality. The symmetry of the cyclitols is discussed in paper II on the *R/S* system.[3] Important revisions in the treatment of these compounds appear in paper III.[5]

Axial Prochirality. On factorizing XII only one prochiral axis is observed. The nonpaired ligands COOH and H are not enantiomeric and the paired ligands (hydrogen atoms) are therefore to be named *pro-aR* and *pro-aS*. (If instead of COOH and H at one end of the axis we had CHOHCOOH (*R*) and CHOHCOOH (*S*) as in V, then the terms *pro-ar* and *pro-as* would apply.) In order to assign prochirality symbols to the model an arbitrary choice must be made. We may view the model from either end of the axis without affecting the final result. If XII is viewed from the COOH-bearing end, subrule 0 prescribes that COOH and near H > far H and far H. Subrule 1 then decrees that COOH > near H. Combining the two results gives near COOH > near H > far H and far H. Subrules 2, 3, 4, and 5 do not further order the ligands.



XII

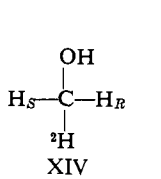


XIII

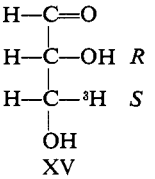
If we now select for naming the hydrogen of the paired hydrogens that is to the right in the printed formula, we may construct a disphenoidal reference assembly of the type Dab,cd (see legend to Figure 2). When viewed from the side remote from the point ligand of lowest precedence (d), the sequence a → b → c is clockwise and the ligand selected is therefore the *pro-aR* ligand.

The spiro compound XIII illustrates the way in which a model may be factorized into prochiral centers and a prochiral axis. The spiro atom itself is of the type Cggii and as such is neither chiral nor prochiral.

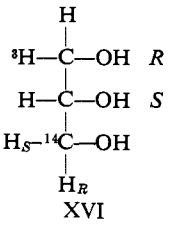
1.4. Isotopic Substitution and Isotopic Labeling. The models considered above were constructed so that all the atoms of a given element had the same mass number. If such a restriction is not made, then isotopic differences must be taken into account when considering the symmetry of the model, and subrule 2 must be included when chirality and prochirality assignments are made. In the following formulas the isotopes ^{1}H, ^{12}C, and ^{16}O are adopted as "normal" and only their replacements are shown (^{2}H, ^{3}H, ^{14}C, ^{18}O). Formula XIV illustrates the way in which isotopic *substitution* may produce a prochiral center. Formulas XV, XVI, and XVII illustrate the results of isotopic substitution in formulas II, III, and V, respectively. It should be noted that for XVII, unlike V, the nonpaired ligands are not enantiomeric and therefore the assignments are *pro-R* and *pro-S* rather than *pro-r* and *pro-s;* also that the ligands are ordered $CHOH^{14}COOH$ (*S*) > $CHOH^{12}COOH$ (*R*) by subrule 2.



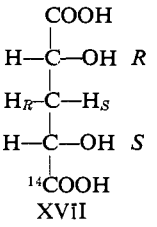
XIV



XV



XVI



XVII

Although the *R*/*S* system is not a genetic system, and each molecular model must be treated on its own merits, the prochirality rule has been stated in such a way that certain generalizations may be made about the change from prochirality to chirality produced by isotopic substitution.

Corollary 1 (in note form). **If the paired ligands are protium, then isotopic substitution at the *pro-R* ligand gives *R* chirality, etc.** In detail this would be as follows. If at a prochiral center or axis the paired ligands are protium (^{1}H), and if a chiral center or axis is derived by subsituting deuterium or tritium for protium, then the derived chirality is that specified as part of the prochirality name of the substituted atom (*pro-R* gives *R*, *pro-r* gives *r*, *pro-aR* gives *aR*, etc.), except for a molecule of the type $RC^{1}H_{2}{}^{2}H$ where substitution of the *pro-R* protium by tritium gives *S* chirality.

Corollary 2 (in note form). **If subrule 1 orders the ligands, then substitution by a heavy isotope in the *pro-R* ligand gives *R* chirality, etc.** In detail this would be as follows. If the four ligands at the various chiral centers (and axes) and the three types of ligand at the various prochiral centers (and axes) can be ordered by sequence subrule 1 (or subrules 0 and 1 for axes), then introducing a single heavy isotope into a *pro-R* substituent or edge of a ring gives *R* chirality etc. (similarly *pro-aR* gives *aR* chirality, etc.). Substitution into the edge of a ring that is formed from the paired ligands of two prochiral centers leads to the appropriate chirality at each center, *i.e.*, substitution in a *pro-R–R* edge gives *R* chirality at both centers, etc.

(This corollary is applicable to the majority of compounds encountered by the chemist and biochemist. It covers many cases also covered by corollary 1.)

Corollary 3 (in note form). **Sum of *pro* terms gives sum of chiral centers produced.** In detail this would be as follows. The sum of the *pro-R*, *pro-r*, *pro-S*, and *pro-s* (or *pro-aR*, etc.) terms employed to specify a particular atom in a compound that is not isotopically substituted corresponds to the sum of the chiral centers (or axes) produced when the atom in question is isotopically substituted (the condensed terms *pro-R–R*, etc., count as two terms), except that, when the atoms of a ring constitute the paired ligands of more than two prochiral atoms, then a single isotopic substitution will give rise to two additional chiral centers if the ring is even membered, and one if odd.

The application of these corollaries may be tested by considering formulas XV and XVI. It should be noted that the rules apply to the introduction of a single isotopic substituent and not to multiple substitution.

The corollaries apply to molecular models and to equivalent molecular species. Chemists and biochemists are, however, normally concerned with *labeled compounds*. In such compounds there is both a natural distribution of isotopes and a preponderance, at certain positions, of a labeling isotope. (In the case of labeling by deuterium, replacement by deuterium may be essentially 100%.) Cahn, Ingold, and Prelog recommend that, in naming an isotopically labeled compound, the chirality symbols employed should be those appropriate to a model in which a labeling isotope (^{2}H, ^{3}H, ^{14}C, ^{18}O, etc.) is substituted for a conventional normal isotope (^{1}H, ^{12}C, ^{16}O, etc.) at all of the positions in the compound that are labeled. (In these instances the labeling is achieved with heavy isotopes, but there is no requirement that this should always be the case.) If the above convention is borne in mind, then the corollaries may be used when the relationship of unlabeled compounds to labeled compounds is under discussion.

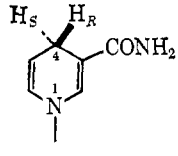
Biochemical Examples. The following examples illustrate the importance of the link between prochirality and isotopic labeling.[11] In each case experiments involving isotopic chirality lead directly to generalizations that are stated in terms of prochirality.

(11) The precise way in which an isotopically labeled compound is named will depend upon the practices of the journal or abstracting system in which the name is printed. The system used in this paper follows from that adopted by the editors of the British Chemical and Biochemical Societies (*J. Chem. Soc.*, 4203 (1953); S. L. Thomas, and H. S. Turner, *Quart. Rev.* (London), 7, 407 (1953)) and more recently by the editors of *Biochemistry*. The *R,S* symbols apply to a model with full isotopic substitution. Clearly they must be added to the name of the labeled compound, not inserted inside the square brackets as if isotopic chirality could be treated by itself.

(i) It may be shown[1,12-14] that the enzyme alcohol: NAD oxidoreductase (EC 1.1.1.1)[15] catalyzes the reaction

$$(2R)\text{-}[2\text{-}^2\text{H}]\text{ethanol} + \text{NAD}^+ \rightleftharpoons \text{acetaldehyde} + (4R)\text{-}[4\text{-}^2\text{H}]\text{NADH} + \text{H}^+$$

where NAD^+ stands for the coenzyme nicotinamide adenine dinucleotide, NADH (+ H^+) for its reduced form, and the 4 indicates C-4 of the reduced nicotinamide ring (partial formula XVIII).[16] (The Enzyme Commission's nomenclature would also permit this labeled form of the reduced coenzyme to be written as (4*R*)-[4-^{2}H]reduced-NAD.) It follows that the *pro-R* hydrogen of ethanol is transferred in the presence of the enzyme and becomes the *pro-R* hydrogen at C-4 of reduced-NAD.



XVIII

(ii) Tritium is lost to water when (2*R*,3*R*)-[2-^{3}H]-citrate is treated with citrate (isocitrate) hydro-lyase (EC 4.2.1.3), an enzyme better known by the name aconitase.[18] It follows that the *pro-R* hydrogen of the *pro-R* CH_2COOH group of citrate is eliminated, along with the C-3 hydroxyl group, when *cis*-aconitate is formed in the presence of the enzyme (citric acid, see formula XXX; *cis*-aconitic acid, *cis*-1-propene-1,2,3-tricarboxylic acid). In both of these examples corollary 2 leads directly from the experiment to the inference.

1.5. Stereoselective Reactions. Prochiral and chiral centers and axes may be classified in terms of the symmetry properties of the model in which they occur. The classification of prochiral elements is of importance in considering stereoselective reactions.

Three classes of prochiral center may be distinguished: class 1, in which the model can be oriented so that a mirror plane passes, or may be said to pass, through the prochiral atom and the nonpaired ligands; class 2, in which a mirror plane cannot be associated with such an atom; class 3, in which the model can be oriented so that a mirror plane passes, or may be said to pass, through the prochiral atom and between the nonpaired ligands. The phrase "may be said to pass" is introduced to cover situations in which the required orientation is only achieved when bond angles are seriously distorted. Such a limitation may be the result of steric hindrance or of the presence of a ring system. In all cases involving a true or a fictional mirror plane, there is for every chiral conformation of the molecule an equally probable mirror image conformation.

The three classes of prochiral centers may be exemplified as follows: class 1 by the methylene carbon of ethanol, C-2 of glycerol (III), or C-3 of citric acid (XXX); class 2 by C-3 of D-glyceraldehyde (II), the terminal carbons of glycerol, or C-2 and C-4 of citric acid (arbitrary numbering); class 3 by C-3 of (2*R*,4*S*)-2,4-dihydroxyglutaric acid (V). The paired ligands for all compounds containing class 3 atoms are *meso* compounds. Certain cases in which *pro-r* and *pro-s* are used, however, belong to class 2 (see discussion of compound V).

A molecule containing a prochiral element may be attacked by a reagent which is either chiral or nonchiral. All arrangements of a chiral object and a second object which is not its enantiomer, are, when the two objects are considered together, chiral. It follows that, for all classes of prochiral element, a chiral reagent may, in principle, be found that reacts in a stereoselective manner with the paired ligands. For class 3 prochiral elements the unpaired ligands, which differ only in their chirality, also react differently with a chiral reagent. In such reactions unequal amounts of enantiomers or diastereoisomers are produced. The nonpaired ligands for classes 1 and 2 are structurally distinct and are necessarily differentiated.

A nonchiral reagent may react with the paired and nonpaired ligands at a prochiral element in various ways. Following Hirschmann,[7] the potential reactivity of the ligands may be tabulated as follows, where √ indicates simple structural differentiation, + indicates stereoselectivity, and − indicates equivalent reactivity.

Class	Mirror plane	Selection between ligands g,g	h,i
1	Through center and h,i	−	√
2	None	+	√
3	Through center and g,g	+	−

Only for class 1 prochiral elements is it necessary to employ a chiral reagent to distinguish between paired ligands. This important generalization was first noted by Schwartz and Carter.[19] They demonstrated that a chiral reagent would, indeed, react in a stereoselective manner with the paired ligands at a class 1 prochiral atom by treating β-phenylglutaric anhydride with an optically active amine.

Trigonal atoms of the type Yghi and certain atoms of the type Ykki (see part II) may be classified in a similar manner. For all three classes a chiral reagent may react in a stereoselective manner with the two faces of the trigonal atom. For nonchiral reagents the reactivity of the two faces corresponds to the reactivity of the paired ligands at a prochiral atom.

The above generalizations are subject to the following caveat. It is impossible to differentiate chemically between atoms or faces which are geometrically indistinguishable.[7] Thus in succinic acid (IV), the two class 1 prochiral atoms are geometrically equivalent.

(12) R. U. Lemieux, and J. Howard, *Can. J. Chem.*, **41**, 308 (1963).
(13) H. R. Levy and B. Vennesland, *J. Biol. Chem.*, **228**, 85 (1957).
(14) J. W. Cornforth, G. Ryback, G. Popjak, C. Donninger, and G. Schroepfer, Jr., *Biochem. Biophys. Res. Commun.*, **9**, 371 (1962); J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popjak, G. Ryback, and G. J. Schroepfer, Jr., *Proc. Roy. Soc.* (London), **B163**, 439 (1965).
(15) Here and elsewhere the numbers and systematic or trivial names assigned by the Enzyme Commission of the International Union of Biochemistry are employed ("1964 Recommendations," Elsevier Publishing Co., Amsterdam, 1965). In line with the Commission's usage and the practice advocated by de la Mare and Klyne, *Progr. Stereochem.*, **3**, 301 (1962), ionizable acids, where they are regarded as enzyme substrates, are referred to as anions, but are shown in formulas in their un-ionized forms.
(16) As the absolute stereospecificity of this and various other NAD or NADP oxidoreductases is now known,[14] it may be desirable that the arbitrary designations[17] *A* and *B* (or α and β) should be replaced by stereochemically meaningful names. In terms of the *pro-R*/*pro-S* system an enzyme with *A* specificity shows *pro-R* specificity toward the reduced coenzyme
(17) H. R. Levy, P. Talalay, and B. Vennesland, *Progr. Stereochem.*, **3**, 299 (1962).
(18) K. R. Hanson, and I. A. Rose, *Proc. Natl. Acad. Sci. U. S.*, **50**, 981 (1963).
(19) P. Schwartz and H. A. Carter, *ibid.*, **40**, 499 (1954).

Even a chiral reagent cannot distinguish between the two *pro-R* hydrogens or between the two *pro-S* hydrogens (see also formulas X, XI, XXII, and XXIII).

As all enzymatic reactions involve a chiral reagent (the enzyme) the properties of the three classes of prochiral element or trigonal atom are only of secondary interest to the biochemist. Stereospecificity is commonplace and the lack of stereospecificity may be taken as evidence for a reaction step in an enzymatic reaction which is not enzyme catalyzed. The fact that the paired ligands at a class 1 prochiral atom can only be differentiated by a chiral reagent is of importance, however, in discussing the history of biochemistry; notably the observation that the biosynthesis and further metabolism of citric acid is stereospecific.[18-21]

meso **Atoms.** Schwartz and Carter, in discussing the stereochemical properties of citric acid, introduced the phrase "*meso*-carbon atom" and applied it to class 1 prochiral carbon atoms (*e.g.*, C-3 of citric acid) and to class 1 trigonal atoms.[19] As class 3 prochiral atoms are present in *meso* compounds whereas class 1 prochiral atoms may or may not be present, this usage is somewhat confusing. Also, the intentions of Schwartz and Carter have been little understood so that it is common practice[17] to use the term *meso*-carbon atom in the way that prochiral carbon atom is used in this paper. It seems better to use the class terminology rather than to try to rehabilitate this unsatisfactory name and to find other names for the other classes.

1.6. Comparison with the Hirschmann Convention. The convention described in the present paper is related to that put forward by Hirschmann.[7] In this earlier proposal, which in part is derived from paper II on the *R/S* system,[3] the symbols (*A*) and (*P*) were used to distinguish the hydrogen atoms at a prochiral methylene group and stereospecific numbering was used to distinguish the atoms of paired ligands other than hydrogen. Hirschmann's convention may be restated in terms of the revised order of sequence subrules and the procedures used here. (a) Examine a molecular model of the unlabeled compound in which all atoms of a given atomic number have the same mass number. If at a prochiral center the paired ligands are hydrogen, then the *pro-R* or *pro-r* ligand is in the (*P*) position (*post*) and the *pro-S* or *pro-s* ligand in the (*A*) position (*ante*). If the paired ligands are other than hydrogen, then the *pro-S* or *pro-s* ligand or edge of a ring has lower numbering. (b) Specify the chirality of a labeled compound in terms of the stereochemical relationships of the unlabeled compound. Thus, the labeled compound (1*R*,2*R*)-[1-^{3}H]glycerol may be named glycerol-3(*P*)-^{3}H. Clearly there is no sense in which the earlier approach is wrong and the present approach right; the proposals set forth in this paper must be regarded as revisions of Hirschmann's treatment made in the light of paper III on the *R/S* system.[5]

Certain minor disadvantages in the Hirschmann convention have arisen which emphasize the difficulty of selecting suitable symbols. The symbol *P* has been appropriated by Cahn, *et al.*,[5] as a helicity symbol (*P* for plus, *M* for minus). Also, now that the absolute stereochemistry of the NAD and NADP oxidoreductases has been established,[14] it appears that the *A*-stereospecific enzymes[17] transfer not the (*A*) but the (*P*) hydrogen.

The major advantages of the present approach are as follows. (i) The treatment offers a unified system for specifying chirality and prochirality and provides a convenient name for all centers of the type Xggij. Although the concepts of chirality and prochirality were implicit in papers I and II on the *R/S* system, and in Hirschmann's proposal, the clear separation of these concepts from that of symmetry should facilitate the analysis of stereochemical problems. (ii) The *R/S* system is retained for specifying isotopic chirality. This ensures maximum understanding between chemists and biochemists in an area where such understanding is of critical importance. If the *R/S* system becomes firmly established as the primary stereochemical reference language, then the use of as few additional systems as possible is to be preferred. The advantages of using the *R/S* system outweigh the disadvantages arising from a lack of complete correspondence between the prochirality names and the chirality produced by isotopic substitution. (iii) The basic distinction between structural and stereochemical information is maintained. Numbering is used to convey structural information, and the *pro-R* and *pro-S* symbols, like the *R* and *S* symbols, convey only stereochemical information. This approach avoids the danger that stereochemical facts will be read into statements where no such facts are implied, and, conversely, prevents stereochemical information being lost though a failure to recognize the use of stereospecific numbering. Although stereospecific numbering is of established or potential value as part of certain local systems (*e.g.*, the cyclitols, quinic acid, and glycerol) its use in a general system would involve a major departure from accepted principles of systematic nomenclature.

II. The *re/si* System. Naming the Two Faces of a Trigonal Atom Yghi

2.1. Reference Assemblies. In describing reactions involving unsaturated systems it is frequently desirable to specify the orientation of an attacking group relative to the attacked molecule, or to specify the binding of the system to some other molecule, *e.g.*, a metal ion or an enzyme surface. It may be required to specify a particular face of a trigonal atom, of a double bond, or of an aromatic ring. The rules put forward in this paper are concerned, in the first place, with naming the two faces of trigonal atoms of the type Yghi, *i.e.*, with naming the two sides of the plane containing Y and the first atoms of the ligands g,h,i. Once the faces of individual trigonal atoms are named, then the faces of the larger planar systems may be specified if they are geometrically distinguishable. The present rules are not concerned with the chirality of the products of any reaction involving a trigonal atom, but only with the topology of the molecular model containing such an atom.

The faces of the two types of trigonal atom shown in Figure 3 may be distinguished. The reference assembly for the first type consists of three point ligands g,h,i at the corner of a triangle whose center is the atom Y.

(20) A. G. Ogston, *Nature*, **162**, 963 (1948).
(21) V. R. Potter and C. Heidelberger, *ibid.*, **164**, 180 (1949).

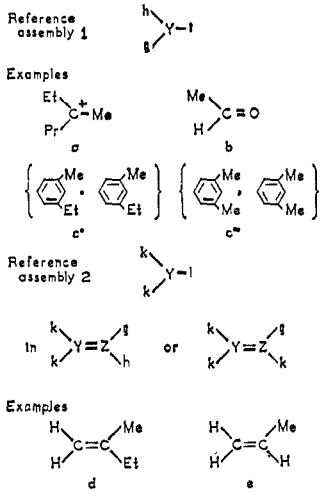


Figure 3. Reference assemblies defining two types of trigonal atom. The two faces of such atoms may be distinguished and named by trigonal atom rules 1 (assembly 1) and 2 (assembly 2).

At least three types of molecular model may be associated with this assembly: (a) in which the three substituents at Y are joined to Y each by a single bond, (b) in which Y is linked by a double bond to another atom which may, or may not, be a trigonal atom, and (c) in which Y, linked to two other trigonal atoms, is part of a mesomeric system. (In example c′ there are six Yghi atoms, in c″ two pairs of geometrically equivalent Yghi atoms.) All of these cases may be treated in the same way provided that the models are first expanded, where necessary, with the aid of replica atoms. This expansion is assumed not to alter the configuration about Y or to create new chiral centers. The three expanded ligands at Y may then be ordered by the sequence rule, and the complex properties of the ligands reduced to the simple properties of the three ordered point ligands in the reference assembly.

In general the two faces of a trigonal atom Ykki are indistinguishable (*e.g.*, the faces of the carbonyl carbon of formaldehyde), but if Y is linked to a second trigonal atom Z by a double bond, and if the two faces at Z are distinguishable, then the faces at Y may be specified by reference to Z. The two possible situations are defined in Figure 3 by reference assembly 2.

For certain other trigonal atoms of the type Ykki in which the identical ligands form the atoms of one and the same ring, the two faces of Y may be distinguished. Thus a reagent attacking the carbonyl carbon of 4-hydroxycyclohexanone is either *cis* or *trans* to the hydroxyl at C-4. The rules given below do not apply to this type of situation, just as the *pro-R*/*pro-S* system does not provide names for the hydrogens at C-4 of cyclohexanol (VII). The *cis–trans* terminology is likely to be adequate for such special cases.

The symbols *re* and *si* used in naming the faces of a trigonal atom are derived from *rectus* and *sinister*. These terms avoid the necessity of learning new words in order to imply clockwise and anticlockwise arrangements of point ligands. The alternatives ρ and σ were eliminated on the grounds that π and σ are already employed in connection with the electronic orbitals of a double bond. The special term "face" is used in preference to "side of the plane," or "side of the double bond," as it may not always be clear in statements which plane and which side is intended, and whether side implies the space bounded by the plane or the surface of the plane.

2.2. Trigonal Atom Rules. Rule 1 specifies how the faces of the trigonal atom Yghi are to be named, and may be stated in note form: *re* **face, sequence clockwise;** *si* **face, anticlockwise.** In detail this would be as follows. Expand all the multiple bonds in the molecular model with replica atoms. Disregard any replica atom attached to the trigonal atom Yghi and assign priorities by sequence subrules 1 to 4 to the three ligands attached to Y. Arbitrarily select for inspection one side of the plane containing Y and the first atoms of the ligands g,h,i. If the priority sequence of the ligands, starting from the ligand of highest priority, is seen to be clockwise, then the *re* face of the trigonal atom is observed. If the sequence is anticlockwise, then the *si* face is observed. It is permissible to speak of *re* attack, or *si* attack, by a reagent on Y.

Rule 2 specifies how the faces of the trigonal atom Ykki in the system kkY = Zgh, or the system kkY = Zgk are to be named and may be stated in note form: **the faces at Y correspond to the faces at Z.** In detail this would be as follows. Name the faces of the trigonal atom Z by rule 1, then name the faces of the trigonal atom Y so that the *re* face at Y and the *re* face at Z are one and the same side of the plane containing Y, Z, and the first atoms of the ligands k,k,g,h or k,k,g,k.

Rule 3 specifies how reference may be made to the two faces associated with a *fixed double bond* or with a *mesomeric system*. The faces of a fixed double bond or of a mesomeric system may be specified by reference to the *re* or *si* faces of particular trigonal atoms, *e.g.*, "the face *re* at C-2," or "the face *re* at the carbonyl carbon"; alternatively the faces at the several trigonal atoms may be specified, *e.g.*, "the 2*re*,3*si* face" of a double bond.

The following **supplementary rules** may be used to name the faces of a *fixed double bond*. These rules correspond to the supplementary prochirality rules c and d for naming the edges of a ring whose atoms are the paired ligands of two prochiral atoms.

(3a) If the face of the double bond is *re* at both the trigonal atoms of the double bond, then this side is the *re–re* face. The other is the *si–si* face. These names necessarily apply if rule 2 applies.

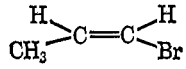
(3b) If the face of the double bond is *re* at one and *si* at the other trigonal atom, then the two sides of the plane are the *re–si* and *si–re* faces.

To establish which name applies to which face, disregard the double bond between the two trigonal atoms and assign priorities to the four singly bonded ligands by sequence subrules 1 to 5. Cite first the side of the plane at the trigonal atom bearing the highest priority ligand or, if both atoms carry identical highest priority ligands, cite first the side at the atom bearing the next highest priority ligand. If these also are identical cite first the side at the atom with the highest priority by sequence subrules 1 and 2. No decision can be reached if the two trigonal atoms are geometrically indistinguishable and the pairs of singly bonded ligands are *cis* oriented.

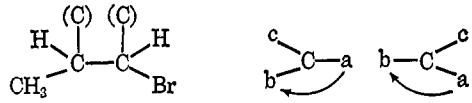
2.3. Examples. In formulas XIX to XXX the plane containing each trigonal atom and its ligating atoms

coincides with that of the paper. *The attached re, si symbols apply to the faces of the trigonal atoms and double bonds viewed by the reader.* It is assumed that all atoms with the same atomic number have the same mass number. The models are thus appropriate for discussing the topology of "pure" chemical compounds. Isotopically labeled compounds are treated as described in section 1.4.

The steps in specifying the faces of the two trigonal atoms of XIX are shown. In XIXa the double bonds are expanded with replica atoms, and in XIXb the priority order of the three ligands at both of the trigonal atoms of the carbon–carbon double bond is indicated. The face of the double bond viewed by the reader is the 1*re*,2*re* face, or simply the *re–re* face.

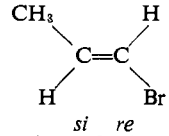


re re
(*re–re* face)
XIX

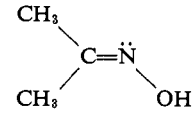


XIXa XIXb

In XX the faces of the trigonal atoms are named as before. The faces of the double bond may be specified as 1*re*,2*si* and 1*si*,2*re*. Alternatively the substituents Br, H, CH_3, and H are examined. As bromine has the highest priority, the side of the plane viewed by the reader is the *re–si* face. In XXI the lone pair of electrons on the nitrogen atom is treated as a phantom atom of zero atomic number and mass, and the faces of the trigonal carbon atom are named with the aid of rule 2.

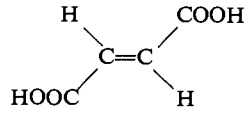


si re
(*re–si* face)
XX

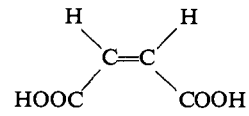


re re
(*re–re* face)
XXI

Fumaric acid (XXII) and maleic acid (XXIII) are examples of molecules with unusual symmetry properties. The faces of each trigonal atom of the carbon–carbon double bond can be named, but in both cases these trigonal atoms are geometrically indistinguishable. Only in the former case can the faces of the double bond be distinguished (*cf.* X and XI; also see ref 10).

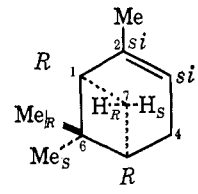


si si
(*si–si* face)
XXII

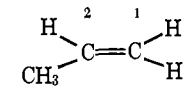


si re
XXIII

2.4. Practical Examples. Steric Hindrance. The *pro-R* methyl group at C-6 and H_S at C-7 of (1*R*,5*R*)-2-pinene[22] (XXIV) are equivalently placed with respect to the double bond, but the smaller bulk of the proton permits readier access to the *re–re* face, *i.e.*, the rear face as we see it in the model. The advantages of this type of statement, as compared to more descriptive statements in terms of *cis* and *trans* or *exo* and *endo* relationships, increase as the stereochemical complexity of the molecule increases.



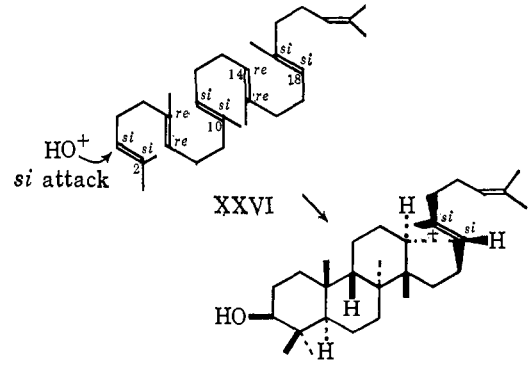
XXIV



re re
XXV

Tactic Polymerization.[23,24] An *isotactic* polymer is formed from 1-propene (XXV) by $-CH_2^-$ carbanion propagation in the *trans* sequence (C-1 *re* to C′-2 *si*)$_n$, a *syndiotactic* polymer by the *trans* sequence (C-1 *re* to C′-2 *re*, C′-1 *si* to C″-2 *si*)$_n$, where C′ belongs to the second molecule and C″ to the third molecule in the repeating polymerization sequence.

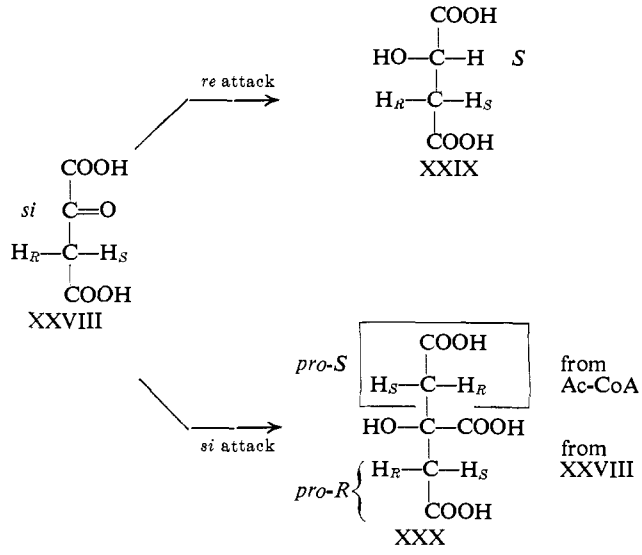
Enzymatic Polymerization. Squalene is converted to lanosterol by the enzyme squalene hydroxylase (EC 1.14.1.3). A mechanism for the reaction has been proposed by Eschenmoser, *et al.*[25] If one end of the squalene chain is arbitrarily selected for numbering, then the first stage of the proposed mechanism (XXVI to XXVII) may be specified as follows. Carbonium ion propagation, HO^+ to C-3 *si*, C-2 *re* to C-7 *re*, C-6 *si* to C-11 *re*, C-10 *si* to C-15 *si*, C-14 *re* to form a *synartetic* (fastened together) carbonium ion[26] with the *si–si* face of the C-18, C-19 double bond (an all-*trans* series of reactions). The reaction is completed by two transformations of the synartetic ion, by a series of hydride and methide shifts, and finally by the loss of H^+. If the carbon numbering of squalene is retained throughout, these transformations may readily be specified. The *re,si* symbols should prove valuable when it is desired to discuss the biosynthesis of a series of isoprenoid compounds in terms of polymerization sequences that differ in one or more points. (It is also possible to specify the absolute configuration of a synartetic ion, or of a metal-coordinated double bond, by the *R/S* system. The preferred method of description will depend upon the context, and the ideas which it is desired to emphasize.)



XXVII

(22) IUPAC 1957 Definitive Rules, A72, *J. Am. Chem. Soc.*, **82**, 5545 (1960); Special Publication No. 14, The Chemical Society, London, 1960, p 48.

(23) G. Natta and F. Dunusso, *J. Polymer Sci.*, **34**, 3 (1959).
(24) C. L. Arcus, *Progr. Stereochem.*, **3**, 264 (1962).
(25) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).
(26) C. K. Ingold, *J. Chem. Soc.*, 2845 (1953).



Other Enzymatic Reactions. The *re* and *si* symbols may be employed to describe additions to, or reductions of, carbonyl groups and carbon–carbon double bonds. Although unknown intermediates may be involved in such reactions, the over-all stereochemistry of the process may be specified. Thus malate dehydrogenase (EC 1.1.1.37) catalyzes the transfer of H_R from C-4 of the nicotinamide ring of reduced-NAD (XVIII) to the *re* face of the carbonyl carbon of oxaloacetate (XXVIII) to form L-malate[27] (XXIX), whereas citrate synthase (EC 4.1.3.7) catalyzes the interaction of acetyl-CoA and the *si* face of this same carbon atom, to form the *pro-S* CH_2COOH group of citrate (XXX).[18]

These examples, and the examples of part I, show how the *re*/*si*, *pro-R*/*pro-S*, and *R*/*S* systems, when used in conjunction with standard chemical nomenclature, may serve to transmit stereochemical information without the use of projection or structural formulas. The symbolism is both brief and unambiguous, and as such is suited for use in summaries and abstracts, and in indexing.

Acknowledgment. The writer is greatly indebted to Dr. R. S. Cahn, Professor Sir Christopher Ingold, and Professor V. Prelog for their helpful suggestions and criticisms at all stages in the preparation of this manuscript; also to Drs. H. Hirschmann and H. B. Vickery and to many other colleagues for their valuable comments on drafts of the paper.

(27) J. L. Graves, B. Vennesland, M. F. Utter, and R. J. Pennington, *J. Biol. Chem.*, **223**, 551 (1956).

The Direct and Sensitized Irradiation of Acyclic Dienes[1-3]

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Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received February 3, 1966*

Abstract: Both the direct and acetophenone-sensitized reaction of 1,1′-bicyclohexenyl (**1**) yielded the valence isomeric cyclobutene **4** as the major product. Myrcene upon direct irradiation yielded mainly the cyclobutene **6** with less than 5% of the bicyclo[2.1.1]hexane isomer **5** which is the sole product of the sensitized reaction. No valence isomerization occurred when 2,3-dimethyl-1,3-butadiene was photosensitized. A possible explanation for this latter result is given. A mechanism for the direct photolysis reaction, based upon the electrocyclization concept of Woodward and Hoffmann, is presented.

The ultraviolet irradiation of cyclic dienes is now a well-established synthetic route to bicyclic compounds containing a cyclobutene ring.[6] Until recently it was not known whether acyclic dienes could similarly be converted into a cyclobutene derivative. The extension of this photochemical reaction to open-chain compounds has been realized in the work of Srinivasan[7] and of Crowley.[8] Parallel studies conducted in this laboratory with 1,1′-bicyclohexenyl (**1**), myrcene (**2**), and 2,3-dimethyl-1,3-butadiene (**3**) yielded similar results which need not be elaborated. In addition, the use of a sensitizer for bringing about the valence isomerization was evaluated.

The direct irradiation of 1,1′-bicyclohexenyl (**1**) formed the valence isomeric cyclobutene **4** and, as was also found by Crowley,[8] at least two other products were formed.[9] Careful fractional distillation gave **4**

1 **4**

in about 90% purity, and in order to obtain pure material the distillate had to be purified by tedious,

(1) For the previous paper in this series, see W. G. Dauben, 13th Council of Chemistry, International Institute of Chemistry (Solvay), Interscience Press, New York, N. Y., in press.

(2) A preliminary report of a portion of this work has appeared in *Pure Appl. Chem.*, **9**, 539 (1964).

(3) This work was supported in part by Public Health Service Grant No. 00709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(4) National Science Foundation Cooperative Fellow, 1960–1963.

(5) National Science Foundation Postdoctoral Fellow, 1964.

(6) For reviews of this reaction see W. G. Dauben and R. M. Coates, *J. Am. Chem. Soc.*, **86**, 2490 (1964), and ref 2.

(7) R. Srinivasan, *ibid.*, **84**, 4141 (1962); R. Srinivasan, *ibid.*, **85**, 4045 (1963).

(8) K. J. Crowley, *Tetrahedron*, **21**, 1001 (1964).

(9) On the basis of spectral data the major of the two side products has been assigned the structure of 1,3′-bicyclohexenyl. This product as well as a more extensive study of the sensitized equilibration of **1** and **4** will be the subject of a future communication (W. G. Dauben and J. Saltiel, unpublished results).