

INTERNATIONAL UNION OF  
PURE AND APPLIED CHEMISTRY

ORGANIC CHEMISTRY DIVISION  
COMMISSION ON NOMENCLATURE OF ORGANIC CHEMISTRY

RULES FOR THE NOMENCLATURE  
OF ORGANIC CHEMISTRY

SECTION E: STEREOCHEMISTRY

(RECOMMENDATIONS 1974)

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# IUPAC COMMISSION ON NOMENCLATURE OF ORGANIC CHEMISTRY\*

## RULES FOR THE NOMENCLATURE OF ORGANIC CHEMISTRY

### Section E: Stereochemistry (Recommendations 1974)

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#### INTRODUCTION

This Section of the IUPAC Rules for Nomenclature of Organic Chemistry differs from previous Sections in that it is here necessary to legislate for words that describe concepts as well as for names of compounds.

At the present time, concepts in stereochemistry (that is, chemistry in three-dimensional space) are in the process of rapid expansion, not merely in organic chemistry, but also in biochemistry, inorganic chemistry, and macromolecular chemistry. The aspects of interest for one area of chemistry often differ from those for another, even in respect of the same phenomenon. This rapid evolution and the variety of interests have led to development of specialized vocabularies and definitions that sometimes differ from one group of specialists to another, sometimes even within one area of chemistry.

The Rules in this Section deal only with the main principles of stereochemistry; work on further aspects is under way. The present rules have two objects: to prescribe, for basic concepts, terms that may provide a common language in all areas of stereochemistry; and to define the ways in which these terms may, so far as necessary, be incorporated into the names of individual compounds. Many of these Rules do little more than codify existing practice, often of long standing; however,

These rules may be called the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry. They are issued by the Commission on the Nomenclature of Organic Chemistry of the International Union of Pure and Applied Chemistry. Section A: Hydrocarbons, and Section B: Fundamental Heterocyclic Systems, were published in 1957 (2nd edition, 1966); Section C: Characteristic Groups Containing Carbon, Hydrogen, Oxygen, Nitrogen, Halogen, Sulfur, Selenium, and/or Tellurium, was published in 1965. Section D, which deals with organometallic compounds in general, chains and rings containing heterogeneous atoms, and organic derivatives of phosphorus, arsenic, antimony, bismuth, silicon, and boron, was published in 1973 (as *IUPAC Information Bull.* Appendix 31). Comments of Section E should be addressed to the Secretary of the Commission named in the following footnote.

\*Titular members: N. LOZAC'H (Chairman), S. P. KLESNEY (Secretary, 3609 Boston, Midland, Michigan 48640, U.S.A.), K. BLÁHA, L. C. CROSS, H. GRÜNEWALD, W. KLYNE, K. L. LOENING, J. RIGAUDY. Associate members: K. HIRAYAMA, S. VEIBEL, F. VÖGTLE.

others extend old principles to wider fields, and yet others deal with nomenclatures that are still subject to controversy. The Commission recognizes that specialized nomenclatures are required for local fields; in some cases, such as carbohydrates, amino acids, peptides and proteins, and steroids, international rules already exist; for other fields, study is in progress.

#### RULES

##### Rule E-0

The steric structure of a compound is denoted by an affix or affixes to the name that does not prescribe the stereochemistry; such affixes, being additional, do not change the name or the numbering of the compound. Thus, enantiomers, diastereoisomers, and *cis-trans*-isomers receive names that are distinguished only by means of different stereochemical affixes. The only exceptions are those trivial names that have stereochemical implications (for example, fumaric acid, cholesterol).

*Note:* In some cases (see Rules E-2.2.3 and E-2.3.1) stereochemical relations may be used to decide between alternative numberings that are otherwise permissible.

##### E-1 Types of isomerism

E-1.1. The following non-stereochemical terms are relevant to the stereochemical nomenclature given in the Rules that follow:

(a) The term structure may be used in connexion with any aspect of the organization of matter.

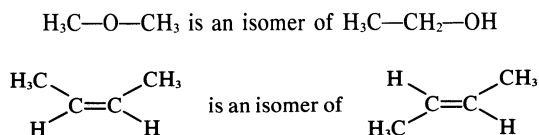
*Hence:* structural (adjectival)

(b) Compounds that have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in arrangement of their atoms in space are termed isomers.

*Hence:* isomeric (adjectival)

isomerism (phenomenological)

*Examples:*



(In this and other Rules a broken line denotes a bond projecting behind the plane of the paper, and a thickened line denotes a bond projecting in front of the plane of the paper. In such cases a line of normal thickness denotes a bond lying in the plane of the paper.)

(c) The constitution of a compound of given molecular formula defines the nature and sequence of bonding of the atoms. Isomers differing in constitution are termed constitutional isomers.

*Hence:* constitutionally isomeric (adjectival)  
constitutional isomerism (phenomenological)

*Example:*

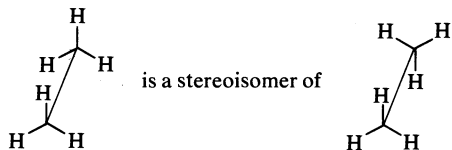
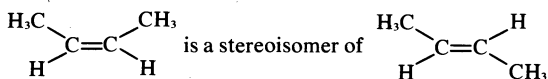
$\text{H}_3\text{C}-\text{O}-\text{CH}_3$  is a constitutional isomer of  
 $\text{H}_3\text{C}-\text{CH}_2-\text{OH}$

*Note:* Use of the term "structural" with the above connotation is abandoned as insufficiently specific.

*E-1.2.* Isomers are termed stereoisomers when they differ only in the arrangement of their atoms in space.

*Hence:* stereoisomeric (adjectival)  
stereoisomerism (phenomenological)

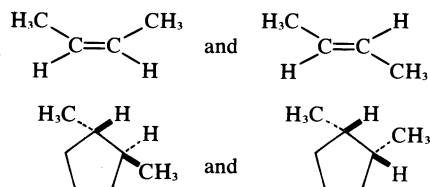
*Examples:*



*E-1.3.* Stereoisomers are termed *cis-trans*-isomers when they differ only in the positions of atoms relative to a specified plane in cases where these atoms are, or are considered as if they were, parts of a rigid structure.

*Hence:* *cis-trans*-isomeric (adjectival)  
*cis-trans*-isomerism (phenomenological)

*Examples:*



*E-1.4.* Various views are current regarding the precise definition of the term "configuration". (a) Classical interpretation: The configuration of a molecule of defined constitution is the arrangement of its atoms in space without regard to arrangements that differ only as after

\*Determination of absolute configuration became possible through work by J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature* **168**, 271 (1951); cf. J. M. Bijvoet, *Proc. Kon. Ned. Akad. Wet., Amsterdam* **52**, 313 (1949).

rotation about one or more single bonds. (b) This definition is now usually limited so that no regard is paid also to rotation about  $\pi$ -bonds or bonds of partial order between one and two. (c) A third view limits the definition further so that no regard is paid to rotation about bonds of any order, including double bonds.

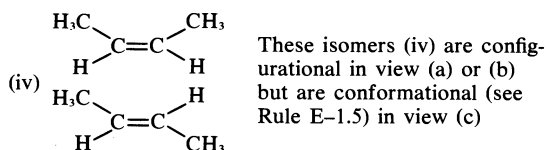
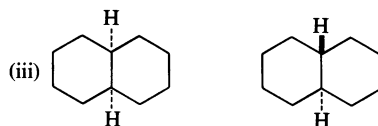
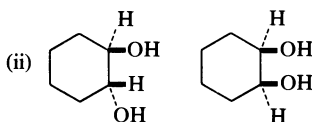
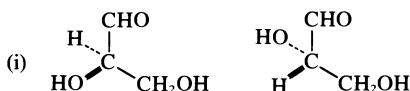
Molecules differing in configuration are termed configurational isomers.

*Hence:* configurational isomerism

*Notes:* (1) Contrast conformation (Rule E-1.5). (2) The phrase "differ only as after rotation" is intended to make the definition independent of any difficulty of rotation, in particular independent of steric hindrance to rotation. (3) For a brief discussion of views (a-c) see Appendix 1.

*Examples:*

The following pairs of compounds differ in configuration:



*E-1.5.* The terms relative stereochemistry and relative configuration are used to describe the positions of substituents on different atoms in a molecule relative to one another.

*E-1.6.* The terms absolute stereochemistry and absolute configuration\* are used to describe the three-dimensional arrangement of substituents around a chiral element. (For a description of chiral element, see Appendix 2.)

*E-1.7.* Various views are current regarding the precise definition of the term "conformation". (a) Classical interpretation: The conformations of a molecule of defined configuration are the various arrangements of its atoms in space that differ only as after rotation about single bonds. (b) This is usually now extended to include rotation about  $\pi$ -bonds or bonds of partial order between one and two. (c) A third view extends the definition further to include also rotation about bonds of any order, including double bonds.

Molecules differing in conformation are termed conformational isomers.

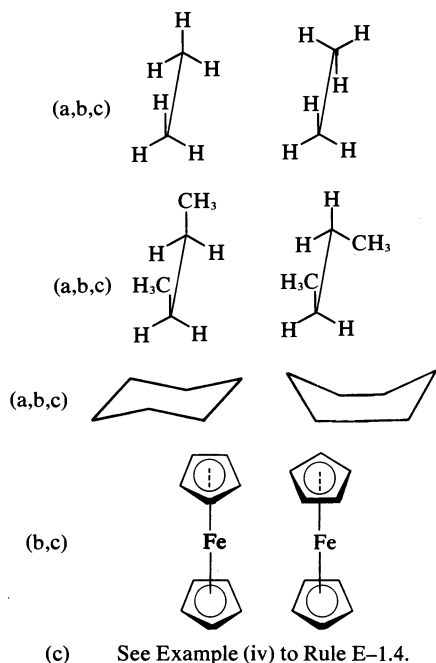
*Hence:* conformational isomerism

*Notes:* All the Notes to Rule E-1.4 apply also to E-1.7.

*Examples:*

Each of the following pairs of formulae represents a

compound in the same configuration but in different conformations.



### E-2 cis-trans-Isomerism\*

#### Preamble:

The prefixes *cis* and *trans* have long been used for describing the relative positions of atoms or groups attached to non-terminal doubly bonded atoms of a chain or attached to a ring that is considered as planar. This practice has been codified for hydrocarbons by IUPAC. There has, however, not been agreement on how to assign *cis* or *trans* at terminal double bonds of chains or at double bonds joining a chain to a ring. An obvious solution was to use *cis* and *trans* where doubly bonded atoms formed the backbone and were non-terminal and to enlist the sequence-rule preferences to decide other cases; however, since the two methods, when generally applied, do not always produce analogous results, it would then be necessary to use different symbols for the two procedures. A study of this combination showed that both types of symbol would often be required in one name and, moreover, it seemed wrong in principle to use two symbolisms for essentially the same phenomenon. Thus it seemed to the Commission wise to use only the sequence-rule system, since this alone was applicable to all cases. The same decision was taken independently by *Chemical Abstracts Service*† who introduced *Z* and *E* to correspond more conveniently to *seqcis* and *seqtrans* of the sequence rule.

It is recommended in the Rules below that these designations *Z* and *E* based on the sequence rule shall be used in names of compounds; but *Z* and *E* do not always

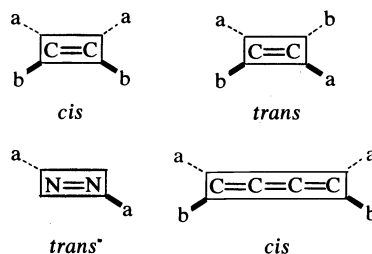
correspond to the classical *cis* and *trans* which show the steric relations of like or similar groups that are often the main point of interest. So the use of *Z* and *E* in names is not intended to hamper the use of *cis* and *trans* in discussions of steric relations of a generic type or of groups of particular interest in a specified case (see Rule E-2.1 and its Examples and Notes, also Rule E-4.11).

It is also not necessary to replace *cis* and *trans* for describing the stereochemistry of substituted monocycles (see Rule E-2.3). For cyclic compounds the main problems are usually different from those around double bonds; for instance, steric relations of substituents on rings can often be described either in terms of chirality (see Subsection E-4) or in terms of *cis-trans*-relationships, and, further, there is usually no single relevant plane of reference in a hydrogenated polycycle. These matters are discussed in the Preambles to Rule E-2.3 and Rule E-3.

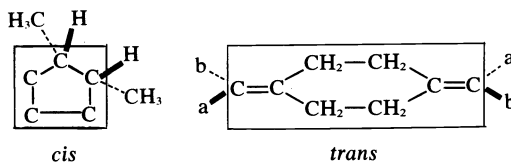
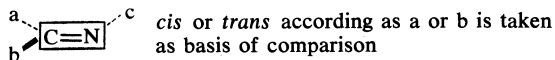
**E-2.1. Definition of cis-trans.** Atoms or groups are termed *cis* or *trans* to one another when they lie respectively on the same or on opposite sides of a reference plane identifiable as common among stereoisomers. The compounds in which such relations occur are termed *cis-trans*-isomers. For compounds containing only doubly bonded atoms the reference plane contains the doubly bonded atoms and is perpendicular to the plane containing these atoms and those directly attached to them. For cyclic compounds the reference plane is that in which the ring skeleton lies or to which it approximates. When qualifying another word or a locant, *cis* or *trans* is followed by a hyphen. When added to a structural formula, *cis* may be abbreviated to *c*, and *trans* to *t* (see also Rule E-2.3.3).

#### Examples:

[Rectangles here denote the reference planes and are considered to lie in the plane of the paper.]



The groups or atoms a,a are the pair selected for designation but are not necessarily identical; b,b are also not necessarily identical but must be different from a,a.

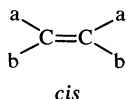


**Notes:** The formulae above are drawn with the reference plane in the plane of the paper, but for doubly bonded compounds it is customary to draw the formulae so that this plane is perpendicular to that of the paper; atoms

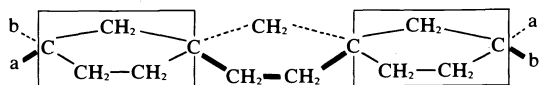
\*These Rules supersede the Tentative Rules for olefinic hydrocarbons published in the *Comptes rendus of the 16th IUPAC Conference*, New York, 1951, pp. 102-103.

†J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca and J. E. Rush, *J. Amer. Chem. Soc.* **90**, 509 (1968); J. E. Blackwood, C. L. Gladys, A. E. Petrarca, W. H. Powell and J. E. Rush, *J. Chem. Docum.* **8**, 30 (1968).

attached directly to the doubly bonded atoms then lie in the plane of the paper and the formulae appear as, for instance:

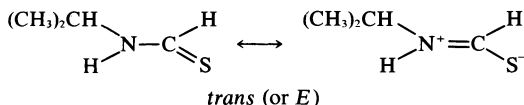


Cyclic structures, however, are customarily drawn with the ring atoms in the plane of the paper, as above. However, care is needed for complex cases, such as:



The central five-membered ring lies (approximately) in a plane perpendicular to the plane of the paper. The two *a* groups are *trans* to one another; so are the *b* groups; the outer cyclopentane rings are *cis* to one another with respect to the plane of the ring.

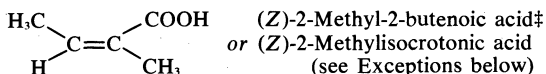
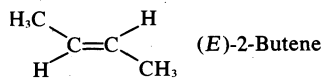
*cis* or *trans* (or *Z* or *E*; see Rule E-2.21) may also be used in cases involving a partial bond order when a limiting structure is of sufficient importance to impose rigidity around the bond of partial order. An example is:



### E-2.2. *cis-trans*-Isomerism around double bonds.

E-2.2.1. In names of compounds steric relations around one double bond are designated by affixes *Z* and/or *E*, assigned as follows. The sequence-rule-preferred\* atom or group attached to one of a doubly bonded pair of atoms is compared with the sequence-rule-preferred atom or group attached to the other of that doubly bonded pair of atoms; if the selected pair are on the same side of the reference plane (see Rule E-2.1) an italic capital letter *Z* prefix is used; if the selected pair are on opposite sides an italic capital letter *E* prefix is used.† These prefixes, placed in parentheses and followed by a hyphen, normally precede the whole name; if the molecule contains several double bonds, then each prefix is immediately preceded by the lower or less primed locant of the relevant double bond.

#### Examples:



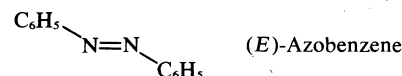
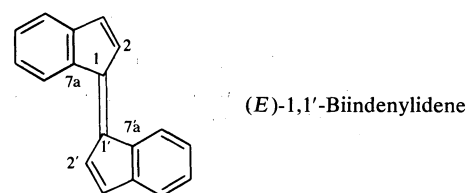
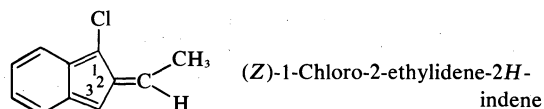
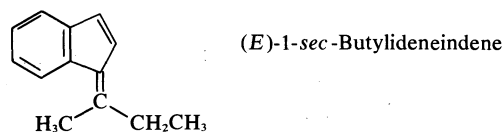
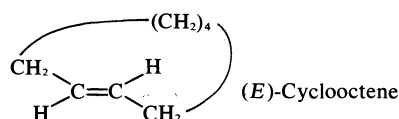
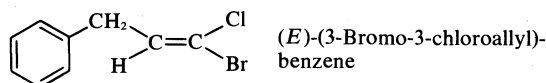
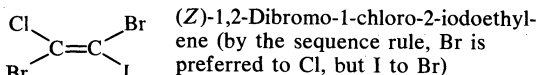
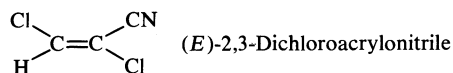
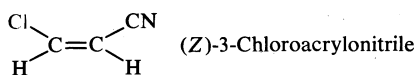
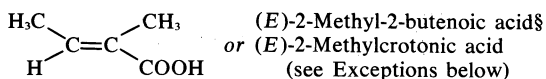
\*For sequence-rule preferences see Appendix 2.

†These prefixes may be rationalized as from the German *zusammen* (together) and *entgegen* (opposite).

‡The name *angelic acid* is abandoned because it has been associated with the designation *trans* with reference to the methyl groups.

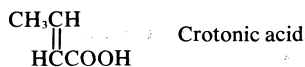
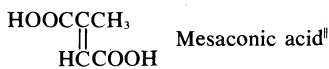
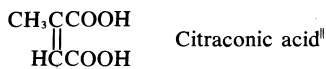
§The name *tiglic acid* is abandoned because it has been associated with the designation *cis* with reference to the methyl groups.

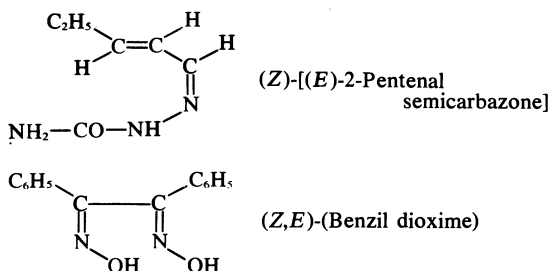
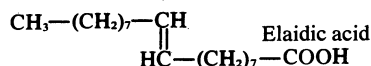
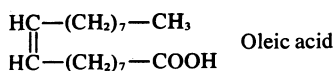
||Systematic names are recommended for derivatives of these compounds formed by substitution on carbon.



#### Exceptions to Rule E-2.2.1:

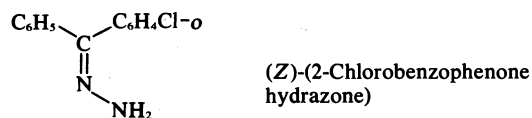
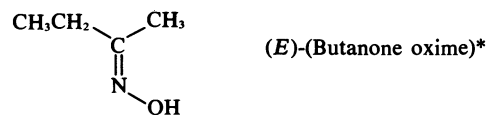
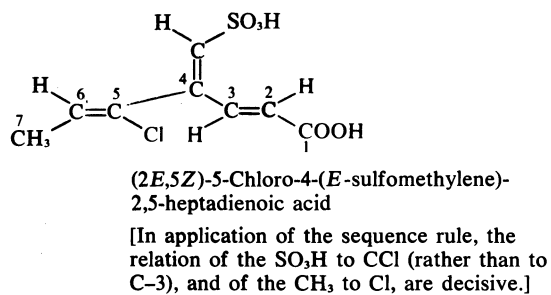
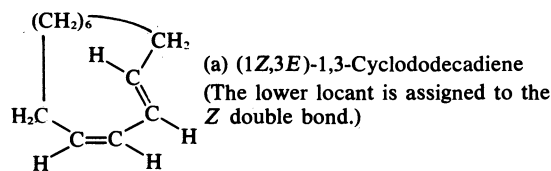
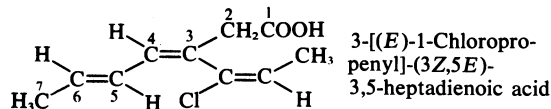
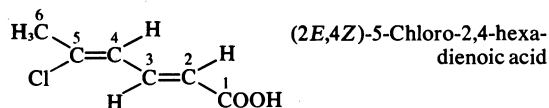
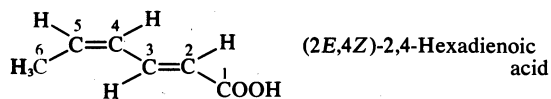
The following are examples of accepted trivial names in which the stereochemistry is prescribed by the name and is not cited by a prefix.





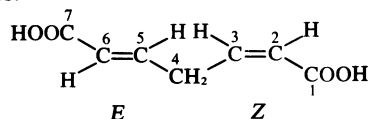
E-2.2.2. (a) When a molecule contains more than one double bond, each *E* or *Z* prefix has associated with it the lower locant of the double bond concerned.

(b) The *E*, *Z* prefixes are given at the beginning of the complete name, unless the prefix is related to a double bond within a substituent; it then forms part of the name of the substituent.

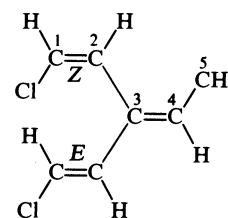


E-2.2.3. When Rule C-13.1 permits alternatives, preference for lower locants and for inclusion in the principal chain is allotted as follows, in the order stated, so far as necessary: *Z* over *E* groups; *cis* over *trans* cyclic groups; if the nature of these groups is not decisive, then the lower locant for such a preferred group at the first point of difference.

Examples:



(2Z,5E)-2,5-Heptadienedioic acid  
[The lower numbers are assigned to the *Z* double bond.]



(1Z,3Z)-1-Chloro-3-[2-chloro-(E)-vinyl]-1,3-pentadiene

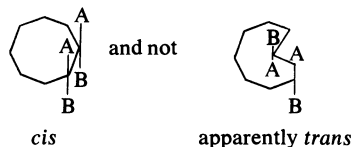
[According to Rule C-13.1 the principal chain must include the C=C-CH<sub>3</sub> group because this gives lower numbers to the double bonds (1,3 rather than 1,4); then the Cl-containing *Z* group is chosen for the remainder of the principal chain in accord with Rule E-2.2.3.]

E-2.3. Relative stereochemistry of substituents in monocyclic compounds†.

Preamble:

*cis*- and *trans*-Prefixes are commonly used to designate the positions of substituents on rings relative to one another; when a ring is, or is considered to be, rigidly planar or approximately so and is placed horizontally, these prefixes define which groups are above and which below the (approximate) plane of the ring. This differentiation is often important, so this classical terminology is retained in Subsection E-2.3; since the difficulties inherent in end-groups do not arise for cyclic compounds it is unnecessary to resort to the less immediately informative *E/Z* symbolism.

When the *cis-trans*-designation of substituents is applied, rings are considered in their most extended form; reentrant angles are not permitted; for example:



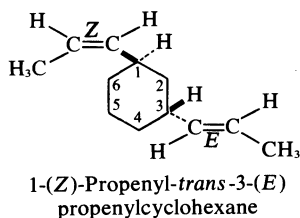
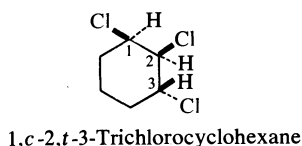
\*The terms *syn*, *anti*, and *amphi* are abandoned for such compounds.

†Formulae in Examples to this Rule denote relative (not absolute) configurations.

The absolute stereochemistry of optically active or racemic derivatives of monocyclic compounds is described by the sequence-rule procedure (see Rule E-4.9 and Appendix 2). The relative stereochemistry may be described by a modification of sequence-rule symbolism as set out in Rule E-4.10. If either of these procedures is adopted, it is then superfluous to use also *cis* or *trans* in the names of individual compounds.

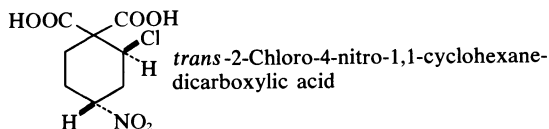
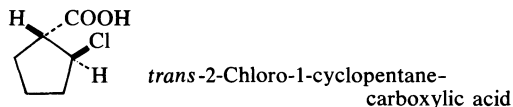
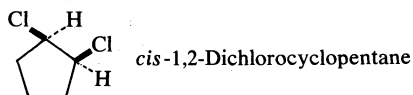
E-2.3.1. When alternative numberings of the ring are permissible according to the Rules of Section C, that numbering is chosen which gives a *cis* attachment at the first point of difference; if that is not decisive, the criteria of Rule E-2.2.3 are applied. *cis*- and *trans*- may be abbreviated to *c*- and *t*-, respectively, in names of compounds when more than one such designation is required.

Examples:



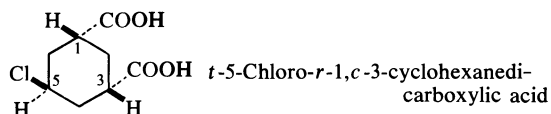
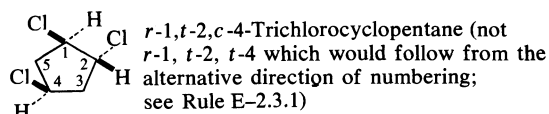
E-2.3.2. When one substituent and one hydrogen atom are attached at each of two positions of a monocycle, the steric relations of the two substituents are expressed as *cis* or *trans*, followed by a hyphen and placed before the name of the compound.

Examples:



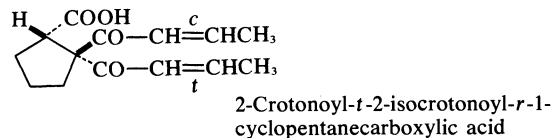
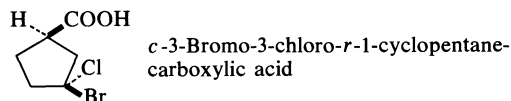
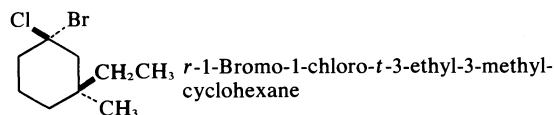
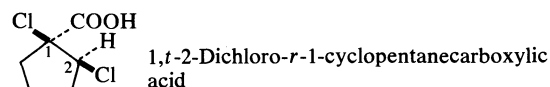
E-2.3.3. When one substituent and one hydrogen atom are attached at each of more than two positions of a monocycle, the steric relations of the substituents are expressed by adding *r* (for *reference* substituent), followed by a hyphen, before the locant of the lowest-numbered of these substituents and *c* or *t* (as appropriate), followed by a hyphen, before the locants of the other substituents to express their relation to the reference substituent.

Examples:



E-2.3.4. When two different substituents are attached at the same position of a monocycle, then the lowest-numbered substituent named as suffix is selected for designation as reference group in accordance with Rule E-2.3.2 or E-2.3.3; or, if none of the substituents is named as suffix, then of the lowest-numbered pair that one preferred by the sequence rule is selected as reference group; and the relation of the sequence-rule preferred group at each other position, relative to the reference group, is cited as *c* or *t* (as appropriate).

Examples:



### E-3 Fused rings

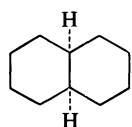
Preamble:

In simple cases the relative stereochemistry of substituted fused-ring systems can be designated by the methods used for monocycles. For the absolute stereochemistry of optically active and racemic compounds the sequence-rule procedure can be used in all cases (see Rule E-4.9 and Appendix 2); for relative configurations of such compounds the procedure of Rule E-4.10 can be applied. Sequence-rule methods are, however, not descriptive of geometrical shape. There is as yet no generally acceptable system for designating in an immediately interpretable manner the configuration of bridged polycyclic compounds (the *endo-exo* nomenclature, which should solve part of the problem, has been used in different ways). These matters will be considered in a later document.

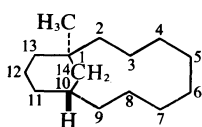
E-3.1. Steric relations at saturated bridgeheads common to two rings are denoted by *cis* or *trans*, followed by a hyphen and placed before the name of the ring system,

according to the relative positions of the exocyclic atoms or groups attached to the bridgeheads. Such rings are said to be *cis*-fused or *trans*-fused.

Examples:



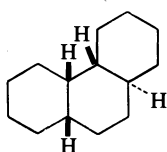
*cis*-Decalin



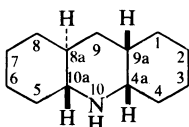
1-Methyl-*trans*-bicyclo[8.3.1]tetradecane

E-3.2. Steric relations at more than one pair of saturated bridgeheads in a polycyclic compound are denoted by *cis* or *trans*, each followed by a hyphen and, when necessary, the corresponding locant of the lower-numbered bridgehead and a second hyphen, all placed before the name of the ring system. Steric relations between the nearest atoms\* of *cis*- or *trans*-bridgehead pairs may be described by affixes *cisoid* or *transoid*, followed by a hyphen and, when necessary, the corresponding locants and a second hyphen, the whole placed between the designations of the *cis*- or *trans*-ring junctions concerned. When a choice remains amongst nearest atoms, the pair containing the lower-numbered atom is selected. *cis* and *trans* are not abbreviated in such cases. In complex cases, however, designation may be more simply effected by the sequence rule procedure (see Appendix 2). Note: the terms *syn* and *anti* were formerly used for *cisoid* and *transoid*.

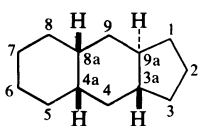
Examples:



*cis*-*cisoid*-*trans*-Perhydrophenanthrene



*cis*-*cisoid*-4a,10a-*trans*-Perhydroacridine or *rel*-(4a*S*,8a*S*,9a*S*,10a*R*)-Perhydroacridine†



*trans*-3a-*cisoid*-3a,4a-*cis*-4a-Perhydrobenz[*f*]indene or *rel*-(3a*R*,4a*S*,8a*R*,9a*R*)-Perhydrobenz[*f*]indene

#### E-4. Chirality

E-4.1. The property of non-identity of an object with its mirror image is termed chirality. An object, such as a molecule in a given configuration or conformation, is termed chiral when it is not identical with its mirror image; it is termed achiral when it is identical with its mirror image.

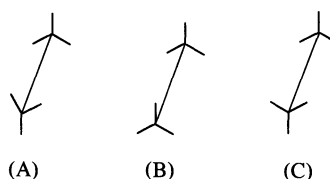
Notes: (1) Chirality is equivalent to handedness, the term

being derived from the Greek  $\chi\epsilon\acute{\iota}\rho$  = hand. Note: The term dissymmetry was formerly used.

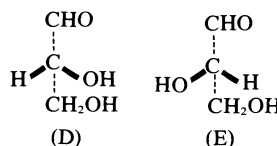
(2) All chiral molecules are molecules of optically active compounds, and molecules of all optically active compounds are chiral. There is a 1:1 correspondence between chirality and optical activity.

(3) In organic chemistry the discussion of chirality usually concerns the individual molecule or, more strictly, a model of the individual molecule. The chirality of an assembly of molecules may differ from that of the component molecules, as in a chiral quartz crystal or in an achiral crystal containing equal numbers of dextrorotatory and laevorotatory tartaric acid molecules.

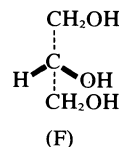
(4) The chirality of a molecule can be discussed only if the configuration or conformation of the molecule is specifically defined or is considered as defined by common usage. In such discussions structures are treated as if they were (at least temporarily) rigid. For instance, ethane is configurationally achiral although many of its conformations, such as (A), are chiral; in fact, a configuration of a mobile molecule is chiral only if all its possible conformations are chiral; and conformations of ethane such as (B) and (C) are achiral.



Examples;



(D) and (E) are mirror images and are not identical, not being superposable. They represent chiral molecules. They represent (D) dextrorotatory and (E) laevorotatory glyceraldehyde.



(F) is identical with its mirror image. It represents an achiral molecule, namely, a molecule of 1,2,3-propanetriol (glycerol).

E-4.2. The term asymmetry denotes absence of any symmetry. An object, such as a molecule in a given configuration or conformation, is termed asymmetric if it has no element of symmetry.

Notes: (1) All asymmetric molecules are chiral, and all compounds composed of them are therefore optically active; however, not all chiral molecules are asymmetric since some molecules having axes of rotation are chiral.

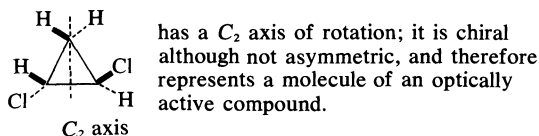
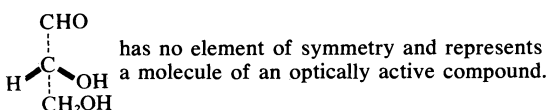
(2) Notes (3) and (4) to Rule E-4.1 apply also in discussions of asymmetry.

\*The term "nearest atoms" denotes those linked together through the smallest number of atoms, irrespective of actual separation in space. For instance, in the second Example to this Rule, the atom 4a is "nearer" to 10a than to 8a.

†For the designation *rel*- see Rule E-4.10.



## Examples:



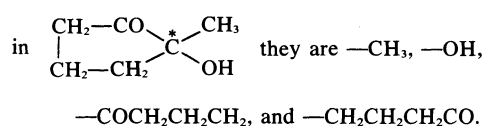
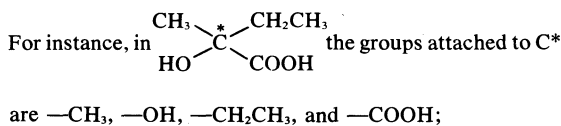
E-4.3. (a) An asymmetric atom is one that is tetrahedrally bonded to four different atoms or groups, none of the groups being the mirror image of any of the others. *Note:* One 'group' may be a lone-pair of electrons, as in sulfoxides.

(b) An asymmetric atom may be said to be at a chiral centre since it lies at the centre of a chiral tetrahedral structure. In a general sense, the term "chiral centre" is not restricted to tetrahedral structures; the structure may, for instance, be based on an octahedron or tetragonal pyramid.

(c) When the atom by which a group is attached to the remainder of a molecule lies at a chiral centre the group may be termed a chiral group.

*Notes:* (1) The term "asymmetric", as applied to a carbon atom in rule E-4.3(a), was chosen by van't Hoff because there is no plane of symmetry through a tetrahedron whose corners are occupied by four atoms or groups that differ in scalar properties. For differences of vector sense between the attached groups see Rule E-4.8.

(2) In Sub-section E-4 the word "group" is used to denote the series of atoms attached to one bond.

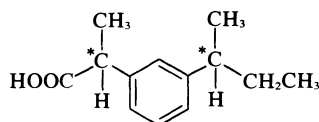


(3) For the chiral axis and chiral plane (which are less common than the chiral centre) see Appendix 2.

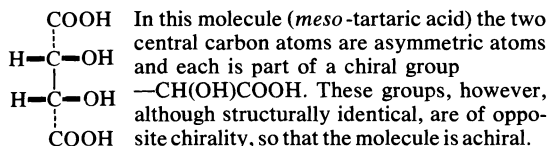
(4) There may be more than one chiral centre in a molecule and these centres may be identical, or structurally different, or structurally identical but of opposite chirality; however, presence of an equal number of structurally identical chiral groups of opposite chirality, and no other chiral group, leads to an achiral molecule. These statements apply also to chiral axes and chiral planes. Identification of the sites and natures of the various factors involved is essential if the overall chirality of a molecule is to be understood.

(5) Although the term "chiral group" is convenient for use in discussions it should be remembered that chirality attaches to molecules and not to groups or atoms. For instance, although the *sec*-butyl group may be termed chiral in dextrorotatory 2-*sec*-butylnaphthalene, it is not chiral in the achiral compound  $(CH_3CH_2)(CH_3)CH-CH_3$ .

## Examples:



In this chiral compound there are two asymmetric carbon atoms, marked  $C^*$ , each lying at a chiral centre. These atoms form parts of different chiral groups, namely,  $-CH(CH_3)COOH$  and  $-CH(CH_3)CH_2CH_3$ .



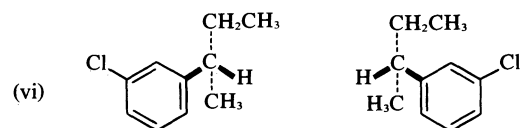
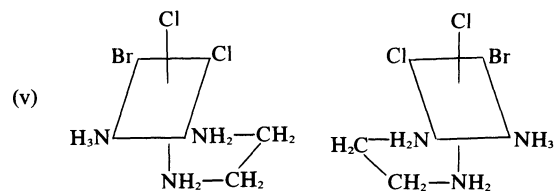
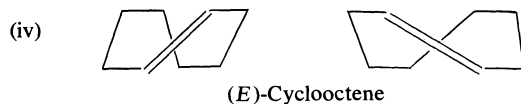
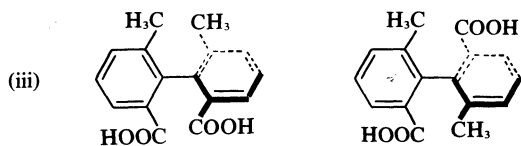
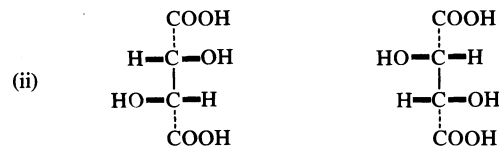
E-4.4. Molecules that are mirror images of one another are termed enantiomers and may be said to be enantiomeric. Chiral groups that are mirror images of one another are termed enantiomeric groups.

*Hence:* enantiomerism (phenomenological)

*Note:* Although the adjective enantiomeric may be applied to groups, enantiomerism strictly applies only to molecules [see Note (5) to Rule E-4.3].

## Examples:

The following pairs of molecules are enantiomeric.



The *sec*-butyl groups in (vi) are enantiomeric.

Enantiomers whose absolute configurations are not known may be differentiated as dextrorotatory (prefix +) or laevorotatory (prefix -) depending on the direction in which, under specified experimental conditions, they rotate the plane of polarized light. The use of *d* instead of + and *l* instead of - is deprecated.

E-4.5. When equal amounts of enantiomeric molecules are present together, the product is termed racemic, independently of whether it is crystalline, liquid, or gaseous. A homogeneous solid phase composed of equimolar amounts of enantiomeric molecules is termed a racemic compound. A mixture of equimolar amounts of enantiomeric molecules present as separate solid phases is termed a racemic mixture. Any homogeneous phase containing equimolar amounts of enantiomeric molecules is termed a racemate.

**Examples:**

The mixture of two kinds of crystal (mirror-image forms) that separate below 28°C from an aqueous solution containing equal amounts of dextrorotatory and laevorotatory sodium ammonium tartrate is a racemic mixture.

The symmetrical crystals that separate from such a solution above 28°C, each containing equal amounts of the two salts, provide a racemic compound.

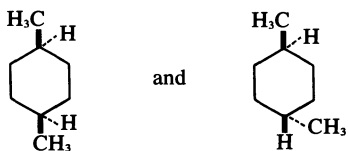
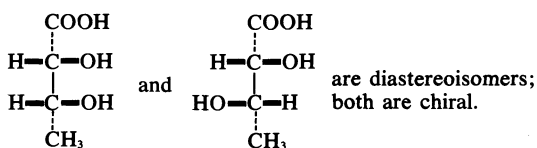
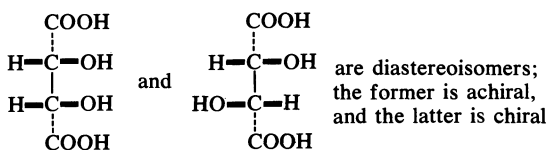
E-4.6. Stereoisomers that are not enantiomeric are termed diastereoisomers.

Hence: diastereoisomeric (adjectival)

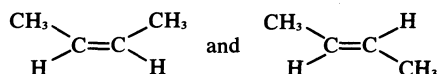
diastereoisomerism (phenomenological)

Note: Diastereoisomers may be chiral or achiral.

**Examples:**



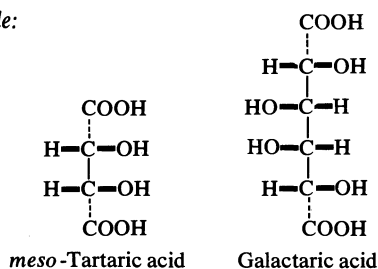
are diastereoisomers and *cis-trans* isomers; both are achiral



are diastereoisomers and *cis-trans* isomers; both are achiral

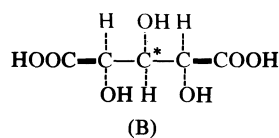
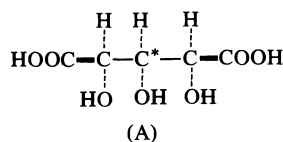
E-4.7. A compound whose individual molecules contain equal numbers of enantiomeric groups, identically linked, but no other chiral group, is termed a *meso*-compound.

**Example:**



E-4.8. An atom is termed pseudoasymmetric when bonded tetrahedrally to one pair of enantiomeric groups (+)-a and (-)-a and also to two atoms or achiral groups b and c that are different from each other.

**Examples:**



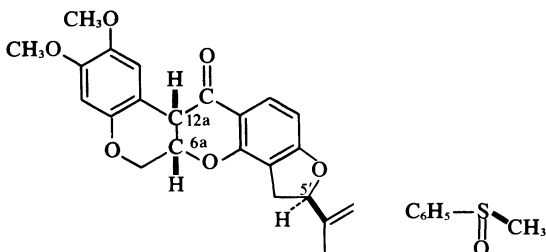
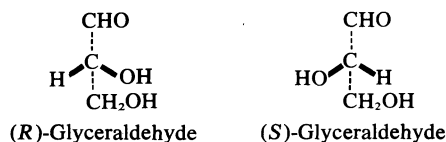
C\* are pseudoasymmetric

Notes: (1) The molecular structure around a pseudoasymmetric atom gives on reflexion an identical (superimposable) structure.

(2) Compounds differing at a pseudo-asymmetric atom belong to the larger class of diastereoisomers. Structures (A) and (B) are interconverted by interchange of the H and OH on C\*. (A) and (B) are achiral diastereoisomers (see Rule E-4.6).

E-4.9. Names of chiral compounds whose absolute configuration is known are differentiated by prefixes *R*, *S*, etc., assigned by the sequence-rule procedure (see Appendix 2), preceded when necessary by the appropriate locants.

**Examples:**



(6a,*S*,12a,*S*,5'*R*)-Rotenone

Methyl phenyl (*R*)-sulfoxide

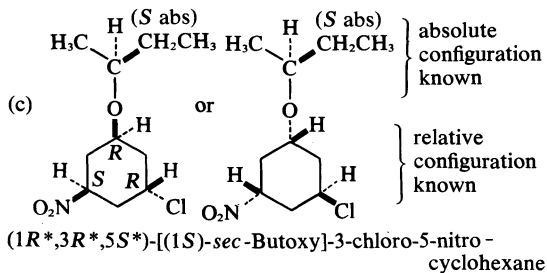
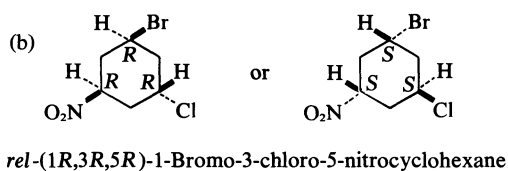
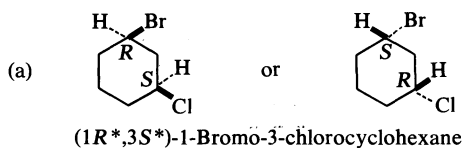
*E-4.10.* (a) Chiral centres, of which the relative but not the absolute configuration is known, may be labelled arbitrarily by prefixes *R\**, *S\** (spoken R star, S star), preceded when necessary by the appropriate locants. These prefixes are assigned by the sequence-rule procedure (see Appendix 2) on the arbitrary assumption that the centre of chirality with the lowest locant has chirality *R*.

(b) In complex cases the stars may be omitted and, instead, the whole name is prefixed by *rel-* (for *relative*).

(c) When a compound contains chiral centres with known absolute configurations and a sterically unrelated set of chiral centres with known relative configurations, then *R\** and *S\** must be used to designate the latter. The prefix *rel-* cannot be used.

This rule (*E-4.10*) does not form part of the Sequence Rule procedure formulated in the original papers (see Appendix 2).

Examples:



*E-4.11.* When it is desired to express relative or absolute configuration with respect to a class of compound, specialized local systems may be used. The sequence rule may, however, be used additionally for positions not amenable to treatment by the local system.

Examples:

*erythro*, *threo*, *arabino*, *gluco*, etc., combined when necessary with D or L, for carbohydrates and their derivatives (see IUPAC/IUB Tentative Rules for Carbohydrate Nomenclature, *IUPAC Information Bull.* Appendix No. 7, 1970).

D, L for amino acids and peptides [see IUPAC/IUB Nomenclature of  $\alpha$ -Amino-acids, Appendix No. 46 (September 1975) to *IUPAC Information Bull.*].

D, L and a series of other prefixes and trivial names for cyclitols and their derivatives [see IUPAC/IUB 1973 Recommendations for the Nomenclature of Cyclitols, *Pure and Applied Chem.* 37, 285-297 (1974)].

$\alpha$ ,  $\beta$ , and a series of trivial names for steroids and related compounds [see IUPAC/IUB, 1971 Recommendations for the Nomenclature of Steroids, *Pure and Applied Chem.* 31, 283-322 (1972)].

The  $\alpha$ ,  $\beta$  system for steroids can be extended to other classes of compound such as terpenes and alkaloids when their absolute configurations are known; it can also be combined with stars or the use of a prefix *rel-* when only the relative configurations are known.

In spite of the Rules of Subsection *E-2*, *cis* and *trans* are used when the arrangement of the atoms constituting an unsaturated backbone is the most important factor, as, for instance, in polymer chemistry and for carotenoids. When a series of double bonds of the same stereochemistry occurs in a backbone, the prefix *all-cis* or *all-trans* may be used.

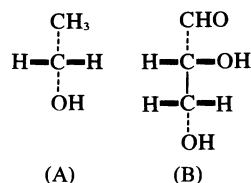
*E-4.12.* (a) An achiral object having at least one pair of features that can be distinguished only by reference to a chiral object or to a chiral reference frame is said to be prochiral, and the property of having such a pair of features is termed prochirality. A consequence is that if one of the features of the pair in a prochiral object is considered to differ from the other feature the resultant object is chiral.

(b) In a molecule an achiral centre or atom is said to be prochiral if it would be held to be chiral when two attached atoms or groups, that taken in isolation are indistinguishable, are considered to differ.

Notes: (1) For a tetrahedrally bonded atom prochirality requires a structure Xabc (where none of the groups a, b, or c is the enantiomer of another).

(2) For a fuller exploration of the concept of prochirality, which is of particular importance to biochemists and spectroscopists, and for its extension to axes, planes, and unsaturated compounds, see K. R. Hanson, *J. Amer. Chem. Soc.* 88, 2731 (1966); H. Hirschmann and K. R. Hanson, *J. Org. Chem.* 36, 3293 (1971); *Europ. J. Biochem.* 22, 301 (1971).

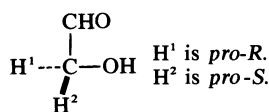
Examples:



In both examples (A) and (B) the methylene carbon atom is prochiral; in both cases it would be held to be a chiral centre if one of the methylene hydrogen atoms were considered to differ from the other. An actual replacement of one of these protium atoms by, say, deuterium would produce an actual chiral centre at the methylene carbon atom; as a result compound (A) would become chiral, and compound (B) would be converted into one of two diastereoisomers.

*E-4.13.* Of the identical pair of atoms or groups in a prochiral compound, that one which leads to an (*R*)-compound when considered to be preferred to the other by the sequence rule (without change in priority with respect to other ligands) is termed *pro-R*, and the other is termed *pro-S*.

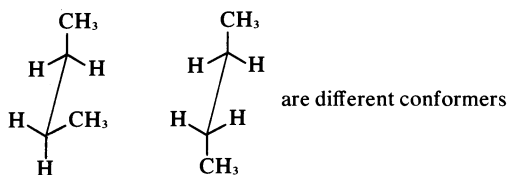
Example:



## E-5. Conformations

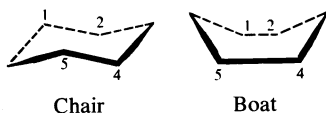
E-5.1. A molecule in a conformation into which its atoms return spontaneously after small displacements is termed a conformer.

## Examples:



E-5.2. (a) When, in a six-membered saturated ring compound, atoms in relative positions 1, 2, 4, and 5 lie in one plane, the molecule is described as in the chair or boat conformation according as the other two atoms lie, respectively, on opposite sides or on the same side of that plane.

## Examples:



Note: These and similar representations are idealized, minor divergences being neglected.

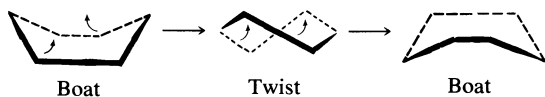
(b) A molecule of a monounsaturated six-membered ring compound is described as being in the half-chair or boat conformation according as the atoms not directly bound to the doubly bonded atoms lie, respectively, on opposite sides or on the same side of the plane containing the other four (adjacent) atoms.

## Examples:



(c) A median conformation through which one boat form passes during conversion into the other boat form is termed a twist conformation. Similar twist conformations are involved in conversion of a chair into a boat form or *vice versa*.

## Example:



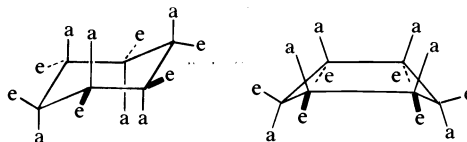
E-5.3. (a) Bonds to a tetrahedral atom in a six-membered ring are termed equatorial or axial according as they or their projections make a small or a large angle, respectively, with the plane containing a majority of the

ring atoms<sup>†</sup>. Atoms or groups attached to such bonds are also said to be equatorial or axial, respectively.

Notes: (1) See, however, pseudo-equatorial and pseudo-axial [Rule E-5.3(b)].

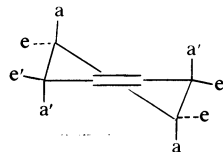
(2) The terms equatorial and axial may be abbreviated to e and a when attached to formulae; these abbreviations may also be used in names of compounds and are there placed in parentheses after the appropriate locants, for example, 1(e)-bromo-4(a)-chlorocyclohexane.

## Examples:



(b) Bonds from atoms directly attached to the doubly bonded atoms in a monounsaturated six-membered ring are termed pseudo-equatorial or pseudo-axial according as the angles that they make with the plane containing the majority of the ring atoms approximate to those made by, respectively, equatorial or axial bonds from a saturated six-membered ring. Pseudo-equatorial and pseudo-axial may be abbreviated to e' and a', respectively, when attached to formulae; these abbreviations may also be used in names, then being placed in parentheses after the appropriate locants.

## Example:



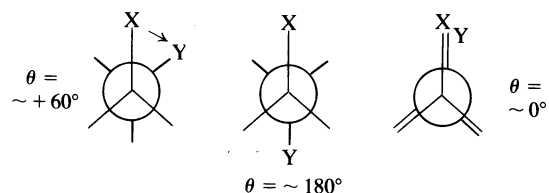
E-5.4. Torsion angle: In an assembly of attached atoms X-A-B-Y, where neither X nor Y is collinear with A and B, the smaller angle subtended by the bonds X-A and Y-B in a plane projection obtained by viewing the assembly along the axis A-B is termed the torsion angle (denoted by the Greek lower-case letter theta  $\theta$  or omega  $\omega$ ). The torsion angle is considered positive or negative according as the bond to the front atom X or Y requires to be rotated to the right or left, respectively, in order that its direction may coincide with that of the bond to the rear selected atom Y or X. The multiplicity of the bonding of the various atoms is irrelevant. A torsion angle also exists if the axis for rotation is formed by a collinear set of more than two atoms directly attached to each other.

Notes: (1) It is immaterial whether the projection be viewed from the front or the rear.

(2) For the use of torsion angles in describing molecules see Rule E-5.6.

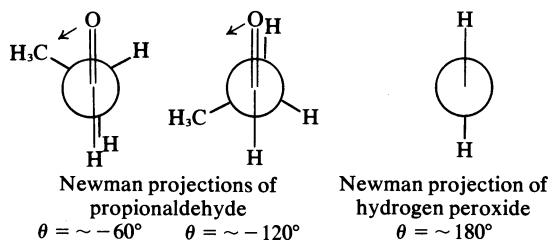
## Examples

(For construction of Newman projections, as here, see Rule E-6.2):



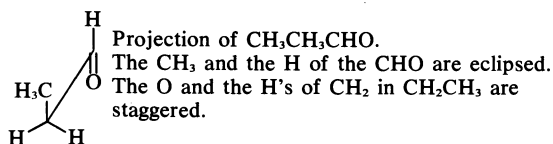
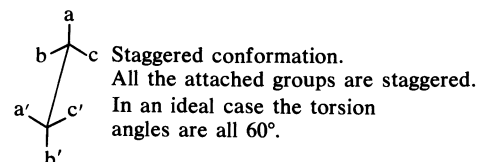
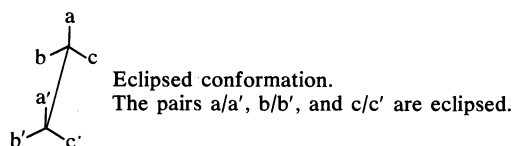
\*The term 'half-boat' has been used here.

<sup>†</sup>The terms axial, equatorial, pseudo-axial, and pseudo-equatorial [see Rule E-5.3(b)] may be used also in connexion with other than six-membered rings if, but only if, their interpretation is then still beyond dispute.



E-5.5. If two atoms or groups attached at opposite ends of a bond appear one directly behind the other when the molecule is viewed along this bond, these atoms or groups are described as eclipsed, and that portion of the molecule is described as being in the eclipsed conformation. If not eclipsed, the atoms or groups and the conformation may be described as staggered.

Examples:



E-5.6. Conformations are described as synperiplanar (*sp*), synclinal (*sc*), anticlinal (*ac*), or antiperiplanar (*ap*) according as the torsion angle is within  $\pm 30^\circ$  of  $0^\circ$ ,  $\pm 60^\circ$ ,  $\pm 120^\circ$ , or  $\pm 180^\circ$ , respectively; the letters in parentheses are the corresponding abbreviations. Atoms or groups are selected from each set to define the torsion angle according to the following criteria: (1) if all the atoms or groups of a set are different, that one of each set that is preferred by the sequence rule; (2) if one of a set is unique, that one; or (3) if all of a set are identical, that one which provides the smallest torsion angle.

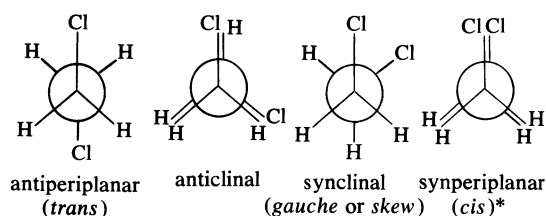
\*The terms *cis*, *gauche*, and *trans* (or their initial letters) have been used, especially in polymer chemistry, to indicate the approximate torsion angles shown below.

<i>cis</i>	c	$0^\circ$
<i>gauche</i>	g	$60^\circ$
<i>trans</i>	t	$180^\circ$

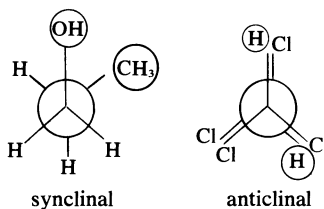
*Gauche* may have + and - signs as superscripts ( $g^+$ ,  $g^-$ ). Since *cis* and *trans* are used in so many other ways, the Commission does not recommend their use in describing conformations. However, '*gauche*' may sometimes be convenient.

†The lone pair of electrons (represented by two dots) on the nitrogen atoms are the unique substituents that decide the description of the conformation (these are the "phantom atoms" of the sequence-rule symbolism).

Examples:

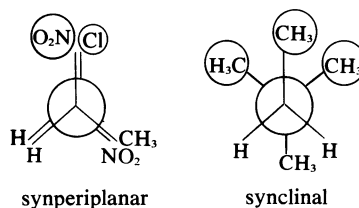


In the above conformations, all  $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$ , the two Cl atoms decide the torsion angle.



Criterion for:  
 rear atom 2  
 front atom 2

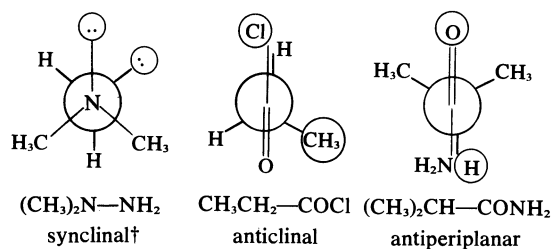
2  
 2



Criterion for:  
 rear atom 1  
 front atom 1

3  
 2

The *ringed* atoms or groups are those used for determining the torsion angles in each case.



Criterion for:  
 rear atom 2  
 front atom 2

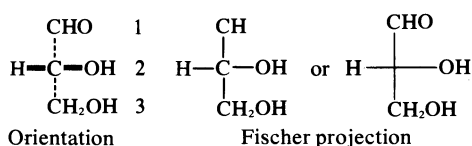
2  
 1

2  
 1

## E-6. Stereoformulae

E-6.1. In a Fischer projection the atoms or groups attached to a tetrahedral centre are projected on to the plane of the paper from such an orientation that atoms or groups appearing above or below the central atom lie behind the plane of the paper and those appearing to left and right of the central atom lie in front of the plane of the paper, and that the principal chain appears vertical with the lowest-numbered chain member at the top.

Example:

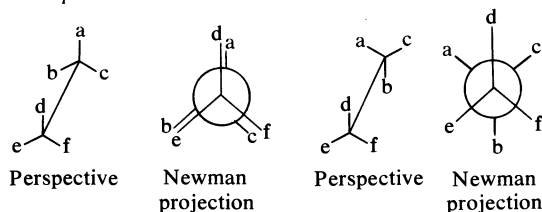


Notes: (1) The first of the two types of Fischer projection should be used whenever convenient.

(2) If a formula in the Fischer projection is rotated through  $180^\circ$  in the plane of the paper, the upward and downward bonds from the central atom still project behind the plane of the paper, and the sideways bonds project in front of that plane. If, however, the formula is rotated through  $90^\circ$  in the plane of the paper, the upward and downward bonds now project in front of the plane of the paper and the sideways bonds project behind that plane. In the latter orientation it is essential to use thickened and dashed lines to avoid confusion.

E-6.2. To prepare a Newman projection a molecule is viewed along the bond between two atoms; a circle is used to represent these atoms, with lines from outside the circle towards its centre to represent bonds to other atoms; the lines that represent bonds to the nearer and the further atom end at, respectively, the centre and the circumference of the circle. When two such bonds would be coincident in the projection, they are drawn at a small angle to each other.\*

Examples:



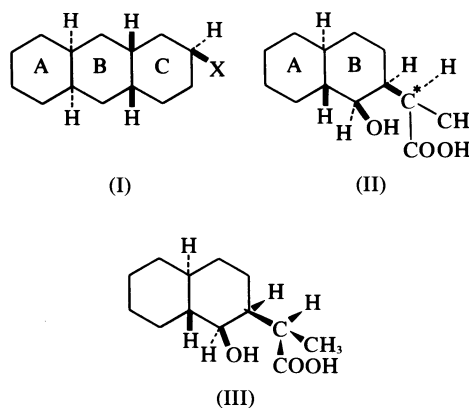
E-6.3. General note. Formulae that display stereochemistry should be prepared with extra care so as to be unambiguous and, whenever possible, self-explanatory. It is inadvisable to try to lay down rules that will cover every case, but the following points should be borne in mind.

A thickened line (—) denotes a bond projecting from the plane of the paper towards an observer, a broken line (---) denotes a bond projecting away from an observer, and, when this convention is used, a full line of normal thickness (—) denotes a bond lying in the plane of the paper. A wavy line (~~~~) may be used to denote a bond whose direction cannot be specified or, if it is explained in the text, a bond whose direction it is not desired to specify in the formula. Dotted lines (.....) should preferably not be used to denote stereochemistry, and never when they are used in the same paper to denote mesomerism, intermediate states, etc. Wedges should not be used as complement to broken lines (but see below). Single large dots have sometimes been used to denote atoms or groups

attached at bridgehead positions and lying above the plane of the paper, with open circles to denote them lying below the plane of the paper, but this practice is strongly deprecated.

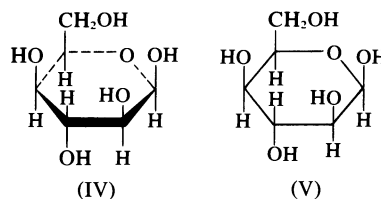
Hydrogen or other atoms or groups attached at sterically designated positions should never be omitted.

In chemical formulae, rings are usually drawn with lines of normal thickness, that is, as if they lay wholly in the plane of the paper even though this may be known not to be the case. In a formula such as (I) it is then clear that the H atoms attached at the A/B ring junction lie further from the observer than these bridgehead atoms, that the H atoms attached at the B/C ring junction lie nearer to the observer than those bridgehead atoms, and that X lies nearer to the observer than the neighbouring atom of ring C.



However, ambiguity can then sometimes arise, particularly when it is necessary to show stereochemistry within a group such as X attached to the rings that are drawn planar. For instance, in formula (II), the atoms O and C\*, lying above the plane of the paper, are attached to ring B by thick bonds; but then, when showing the stereochemistry at C\*, one finds that the bond from C\* to ring B projects away from the observer and so should be a broken line. Such difficulties can be overcome by using wedges in places of lines, the broader end of the wedge being considered nearer to the observer, as in (III).

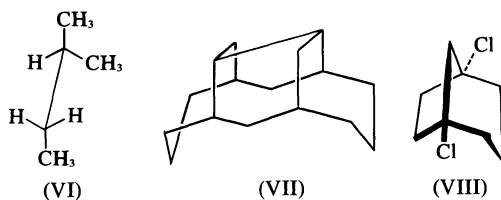
In some fields, notably for carbohydrates, rings are conveniently drawn as if they lay almost perpendicular to the plane of the paper, as shown in (IV); however, conventional formulae such as (V), with the lower bonds considered as the nearer to the observer, are so well established that it is rarely necessary to elaborate this to form (IV).



By a similar convention, in drawings such as (VI) and (VII), the lower sets of bonds are considered to be nearer than the upper to the observer. In (VII), note the gaps in the rear lines to indicate that the bonds crossing them pass in front (and thus obscure sections of the rear bonds). In some cases, when atoms have to be shown as lying in

\*Cf. M. S. Newman, *Chem. Progr. Kreskge-Hooker Sci. Lab. Rep.* 13, 111 (1952); *J. Chem. Educ.* 32, 344 (1955); *Steric Effects in Organic Chemistry*, John Wiley, New York 1956, p. 6. A similar projection was used earlier by J. Böesenken and R. Cohen, *Rec. Trav. chim.* 47, 839 (1928).

several planes, the various conventions may be combined, as in (VIII).



In all cases the overriding aim should be clarity.

#### APPENDIX 1

##### Configuration and Conformation

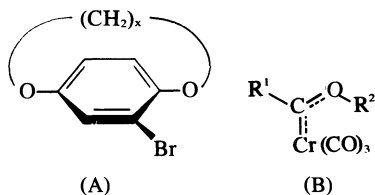
See Rules E-1.4 and E-1.5.

Various definitions have been propounded to differentiate configurations from conformations.

The original usage was to consider as conformations those arrangements of the atoms of a molecule in space that can be interconverted by rotation(s) around a single bond, and as configurations those other arrangements whose interconversion by rotation requires bonds to be broken and then re-formed differently. Interconversion of different configurations will then be associated with substantial energies of activation, and the various species will be separable; but interconversion of different conformations will normally be associated with less activation energy, and the various species, if separable, will normally be more readily interconvertible. These differences in activation energy and stability are often large.

Nevertheless, rigid differentiation on such grounds meets formidable difficulties. Differentiation by energy criteria would require an arbitrary cut in a continuous series of values. Differentiation by stability of isolated species requires arbitrary assumptions about conditions and half-lives. Differentiation on the basis of rotation around single bonds meets difficulties connected both with the concept of rotation and with the selection of single bonds as requisites; and these need more detailed discussion here.

Enantiomeric biaryls are nowadays usually considered to differ in conformation, any difficulty in rotation about the 1,1'-bond due to steric hindrance between the neighbouring groups being considered to be overcome by bond bending and/or bond stretching, even though the movements required must closely approach bond breaking if these substituents are very large. Similar doubts about the possibility of rotation occur with a molecule such as (A), where rotation of the benzene ring around the oxygen-to-ring single bonds affords easy interconversion if  $x$  is large but appears to be physically impossible if  $x$  is small; and no critical size of  $x$  can be reasonably established. For reasons such as these, Rules E-1.4 and E-1.5 are so worded as to be independent of whether rotation appears physically feasible or not (see Note 2 to those Rules).



The second difficulty arises in the many cases where rotation is around a bond of fractional order between one and two, as in the helicenes, crowded aromatic molecules, metallocenes, amides, thioamides, and carbene-metal coordination compounds (such as B). The term conformation is customarily used in these cases and

that appears a reasonable extension of the original conception, though it will be wise to specify the usage if the reader might be in doubt.

When interpreted in these ways, Rules E-1.4 and E-1.5 reflect the most frequent usage of the present day and provide clear distinctions in most situations.

Nevertheless, difficulties remain and a number of other usages have been introduced.

It appears to some workers that, once it is admitted that change of conformation may involve rotation about bonds of fractional order between one and two, it is then illogical to exclude rotation about classical double bonds because interconversion of open-chain *cis-trans*-isomers depends on no fundamentally new principle and is often relatively easy, as for certain alkene derivatives such as stilbenes and for azo compounds, by irradiation. This extension is indeed not excluded by Rules E-1.4 and E-1.5, but if it is applied that fact should be explicitly stated.

A further interpretation is to regard a stereoisomer possessing some degree of stability (that is, one associated with an energy hollow, however shallow) as a configurational isomer, the other arrangements in space being termed conformational isomers; the term conformer (Rule E-5.1) is then superfluous. This definition, however, requires a knowledge of stability (energy relations) that is not always available.

In another view a configurational isomer is any stereoisomer that can be isolated or (for some workers) whose existence can be established (for example, by physical methods); all other arrangements then represent conformational isomers. But it is then impossible to differentiate configuration from conformation without involving experimental efficiency or conditions of observation.

Yet another definition is to regard a conformation as a precise description of a configuration in terms of bond distances, bond angles, and torsion angles.

In none of the above views except the last is attention paid to extension or contraction of the bond to an atom that is attached to only one other atom, such as  $-H$  or  $=O$ . Yet such changes in interatomic distance due to non-bonded interactions may be important, for instance in hydrogen bonding, in differences due to crystal form, in association in solution, and in transition states. This area may repay further consideration.

Owing to the circumstances outlined above, the Rules E-1.4 and E-1.5 have been deliberately made imprecise, so as to permit some alternative interpretations; but they are not compatible with all the definitions mentioned above. The time does not seem ripe to legislate for other than the commoner usages or to choose finally between these.

It is, however, encouraging that no definition in this field has (yet) involved atomic vibrations for which, in all cases, only time-average positions are considered.

Finally it should be noted that an important school of thought uses conformation with the connotation of "a particular geometry of the molecule, i.e. a description of atoms in space in terms of bond distances, bond angles, and dihedral angles", a definition much wider than any discussed above.

#### APPENDIX 2

##### Outline of the Sequence Rule Procedure

The sequence rule procedure is a method of specifying the absolute molecular chirality (handedness) of a compound, that is, a method of specifying in which of two enantiomeric forms each chiral element of a molecule exists. For each chiral element in the molecule it provides a symbol, usually *R* or *S*, which is independent of nomenclature and numbering. These symbols define the chirality of the specific compound considered; they may not be the same for a compound and some of its derivatives, and they are not necessarily constant for chemically similar situations within a chemical or a biogenetic class. The procedure is applied directly to a three-dimensional model of the structure, and not to any two-dimensional projection thereof.

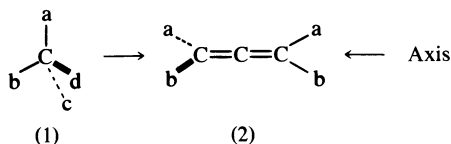
The method has been developed to cover all compounds with ligancy up to 4 and with ligancy 6,\* and for all configurations and conformations of such compounds. The following is an outline confined to the most common situations; it is essential to study the

\*The ligancy of an atom refers to the number of neighbouring atoms bonded to it, irrespective of the nature of the bonds.

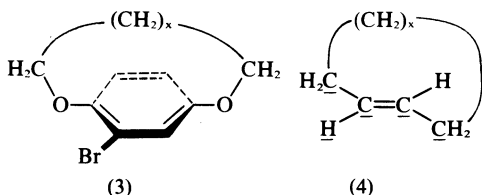
original papers, especially the 1966 paper,<sup>†</sup> before using the sequence rule for other than fairly simple cases.

**General basis.** The sequence rule itself is a method of arranging atoms or groups (including chains and rings) in an order of precedence, often referred to as an order of preference; for discussion this order can conveniently be generalized as  $a > b > c > d$ , where  $>$  denotes "is preferred to".

The first step, however, in considering a model is to identify the nature and position of each chiral element that it contains. There are three types of chiral element, namely, the chiral centre, the chiral axis, and the chiral plane. The chiral centre, which is very much the most commonly met, is exemplified by an asymmetric carbon atom with the tetrahedral arrangement of ligands, as in (1). A chiral axis is present in, for instance, the chiral allenes such as

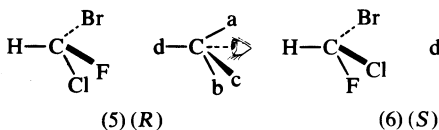


(2) or the chiral biaryl derivatives. A chiral plane is exemplified by the plane containing the benzene ring and the bromine and oxygen atoms in the chiral compound (3), or by the underlined atoms in the cycloalkene (4). Clearly, more than one type of chiral element



may be present in one compound; for instance, group "a" in (2) might be a *sec*-butyl group which contains a chiral centre.

**The chiral centre.** Let us consider first the simplest case, namely, a chiral centre (such as carbon) with four ligands, a, b, c, d which are all different atoms, tetrahedrally arranged, as in CHFCIBr. The four ligands are arranged in order of preference by means of the sequence rule; this contains five sub-rules, which are applied in succession so far as necessary to obtain a decision. The first sub-rule is all that is required in a great majority of actual cases; it states that ligands are arranged in order of decreasing atomic number, in the above case (a) Br > (b) Cl > (c) F > (d) H. There would be two (enantiomeric) forms of the compound and we can write these as (5) and (6). In the sequence-rule procedure

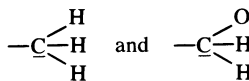


the model is viewed from the side remote from the least-preferred ligand (d), as illustrated. Then, tracing a path from a to b to c in (5) gives a clockwise course, which is symbolized by (R) (Latin *rectus*, right; for right-hand); in (6) it gives an anticlockwise course, symbolized as (S) (Latin *sinister*, left). Thus (5) would be named (R)-bromochlorofluoromethane, and (6) would be named (S)-bromochlorofluoromethane. Here already it may be noted that converting one enantiomer into another changes each R to S, and each S to R, always. It will be seen also that the chirality prefix is

the same whether the alphabetical order is used, as now recommended, for naming the substituents or whether this is done by an order of complexity (giving fluorochlorobromomethane).

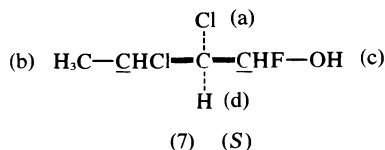
Next, suppose we have  $\text{H}_3\text{C}-\text{CHClF}$ . We deal first with the atoms directly attached to the chiral centre; so the four ligands to be considered are  $\text{Cl} > \text{F} > \text{C}$  (of  $\text{CH}_3$ )  $>$  H. Here the H's of the  $\text{CH}_3$  are not concerned, because we do not need them in order to assign our symbol.

However, atoms directly attached to a centre are often identical, as for example the underlined C's in  $\text{H}_3\text{C}-\text{CHCl}-\text{CH}_2\text{OH}$ . For such a compound we at once establish a preference (a)  $\text{Cl} >$  (b,c)  $\underline{\text{C}} >$  (d) H. Then to decide between the two C's we work outwards, to the atoms to which they in turn are directly attached and we then find:

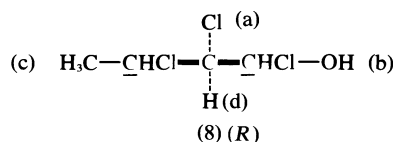


which we can conveniently write as C(H,H,H) and C(O,H,H). We have to compare H,H,H with O,H,H, and since oxygen has a higher atomic number than hydrogen we have  $\text{O} >$  H and thence the complete order  $\text{Cl} > \text{C}$  (of  $\text{CH}_2\text{OH}$ )  $>$  C (of  $\text{CH}_3$ )  $>$  H, so that the chirality symbol can then be determined from the three-dimensional model.

We must next meet the first complication. Suppose that we have a molecule (7):

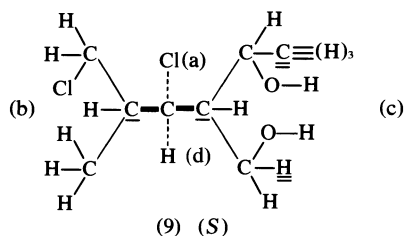
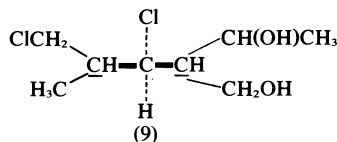


To decide between the two C's we first arrange the atoms attached to them in *their* order of preference, which gives C(Cl,C,H) on the left and C(F,O,H) on the right. Then we compare the preferred atom of one set (namely, Cl) with the preferred atom (F) of the other set; and as  $\text{Cl} >$  F we arrive at the preferences  $a > b > c > d$  shown in (7) and chirality (S). If, however, we had a compound (8):



we should have met C(Cl,C,H) and C(Cl,O,H) and, since the atoms of first preference are identical (Cl) we should have had to make the comparisons with the atoms of second preference, namely,  $\text{O} >$  C, which leads to the different chirality (R) as shown in (8).

Branched ligands are treated similarly. Setting them out in full gives a picture that at first sight looks complex but the treatment is in fact simple. For instance, in compound (9) a first quick glance again shows (a)  $\text{Cl} >$  (b,c)  $\underline{\text{C}} >$  (d) H.



<sup>†</sup>R. S. Cahn, (Sir) Christopher Ingold, V. Prelog, *Angew. Chem. intern. Edit.* 5, 385 (1966) (in English); errata, *ibid.*, p. 511; *Angew. Chem.* 78, 413 (1966) (in German). Earlier papers: R. S. Cahn, C. K. Ingold, *J. Chem. Soc. (London)* 612 (1951); R. S. Cahn, (Sir) Christopher Ingold, V. Prelog, *Experientia* 12, 81 (1956). For a partial, simplified account see R. S. Cahn, *J. Chem. Educ.* 41, 116 (1964).





**Symbolism.** In names of compounds, the *R* and *S* symbols, together with their locants, are placed in parentheses, normally in front of the name, as shown for morphine (10) and sparteine (14); but this may be varied in indexes or in languages other than English. Positions within names are required, however, when more than a single series of numerals is used, as for esters and amines. When relative stereochemistry is more important than absolute stereochemistry, as for steroids or carbohydrates, a local system of stereochemical designation may be more useful and sequence-rule symbols need then be used only for any situations where the local system is insufficient.

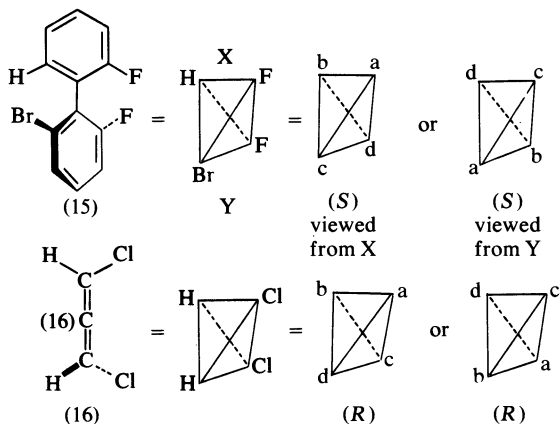
Racemates containing a single centre are labelled (*RS*). If there is more than one centre the first is labelled (*RS*) and the others are (*RS*) or (*SR*) according to whether they are *R* or *S* when the first is *R*. For instance, the 2,4-pentanediols  $\text{CH}_3\text{-CH(OH)-CH}_2\text{-CH(OH)-CH}_3$  are differentiated as:

one chiral form (2*R*,4*R*)-  
 other chiral form (2*S*,4*S*)-  
*meso*-compound (2*R*,4*S*)-  
 racemic compound (2*RS*,4*RS*)-

Finally the principles by which some of the least rare of other situations are treated will be very briefly summarized.

**Pseudoasymmetric atoms.** A sub-rule decrees that *R* groups have preference over *S* groups and this permits pseudoasymmetric atoms, as in Cab(c-*R*)(c-*S*) to be treated in the same way as chiral centres; but as such a molecule is achiral (not optically active) it is given the lower-case symbol *r* or *s*.

**Chiral axis.** The structure is regarded as an elongated tetrahedron and viewed along the axis—it is immaterial from which end it is viewed; the nearer pair of ligands receives the first two positions in the order of preference, as shown in (15) and (16).

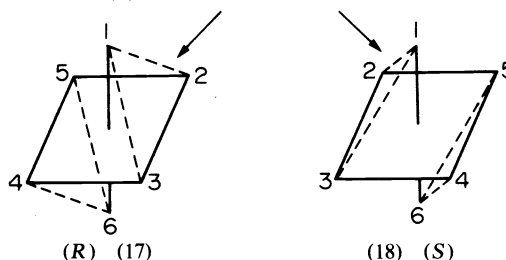


**Chiral plane.** The sequence-rule-preferred atom directly attached to the plane is chosen as "pilot atom". In compound (3)

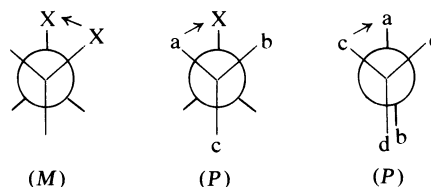
(page 27) this is the C on the left-hand  $\text{CH}_2$  group. Now this is attached to the left-hand oxygen atom in the plane. The sequence-rule-preferred path from this oxygen atom is then explored in the plane until a rotation is traced which is clockwise (*R*) or anticlockwise (*S*) when viewed from the pilot atom. In (3) this path is  $\text{O} \rightarrow \text{C} \rightarrow \text{C}(\text{Br})$  and it is clockwise (*R*).

**Other sub-rules.** Other sub-rules cater for new chirality created by isotopic labelling (higher mass number preferred to lower) and for steric differences in the ligands. Isotopic labelling rarely changes symbols allotted to other centres.

**Octahedral structures.** Extensions of the sequence rule enable ligands arranged octahedrally to be placed in an order of preference, including polydentate ligands, so that a chiral structure can then always be represented as one of the enantiomeric forms (17) and (18). The face 1-2-3 is observed from the side remote from the face 4-5-6 (as marked by arrows), and the path 1→2→3 is observed; in (17) this path is clockwise (*R*), and in (18) it is anticlockwise (*S*).



**Conformations.** The torsion angle between selected bonds from two singly bonded atoms is considered. The selected bond from each of these two atoms is that to a unique ligand, or otherwise to the ligand preferred by the sequence rule. The smaller rotation needed to make the front ligand eclipsed with the rear one is noted (this is the rotatory characteristic of a helix); if this rotation is right-handed it leads to a symbol *P* (plus); if left-handed to *M* (minus). Examples are:



**Details and complications.** For details and complicating factors the original papers should be consulted. They include treatment of compounds with high symmetry or containing repeating units (e.g. cyclitols), also  $\pi$ -bonding (metallocenes, etc.), mesomeric compounds and mesomeric radicals, and helical and other secondary structures.

#### Some common groups in order of sequence-rule preference

Note: ANY alteration to structure, or substitution, etc., may alter the order of preference.

##### A. Alphabetical order: higher number denotes greater preference

64 Acetoxy	75 Bromo	3 Ethyl
36 Acetyl	42 <i>tert</i> -Butoxycarbonyl	46 Ethylamino
48 Acetylamino	5 <i>n</i> -Butyl	68 Fluoro
21 Acetylenyl	16 <i>sec</i> -Butyl	35 Formyl
10 Allyl	19 <i>tert</i> -Butyl	63 Formyloxy
43 Amino	38 Carboxy	62 Glycosyloxy
44 Ammonio $^+\text{H}_3\text{N}$ -	74 Chloro	7 <i>n</i> -Hexyl
37 Benzoyl	17 Cyclohexyl	1 Hydrogen
49 Benzoylamino	52 Diethylamino	57 Hydroxy
65 Benzoyloxy	51 Dimethylamino	76 Iodo
50 Benzoyloxycarbonylamino	34 2,4-Dinitrophenyl	9 Isobutyl
13 Benzyl	28 3,5-Dinitrophenyl	8 Isopentyl
60 Benzyloxy	59 Ethoxy	20 Isopropenyl
41 Benzyloxycarbonyl	40 Ethoxycarbonyl	14 Isopropyl

