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REFLECTION-CONCORDANT STEREOSPECIFIC NUMBERING

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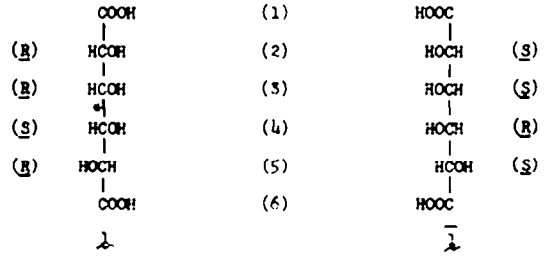
Abstract—If enantiomers are to receive names that agree except for differences in the configurational affixes, it is not sufficient that all descriptors of pherochiral elements are inverted on reflection. It is equally essential that the numbering does not change when the enantiomeric pair is interconverted. A set of rules is suggested which would accomplish this and which would provide for the differentiation by fixed numbering of all the numbered atoms of a molecule that are sterically distinct. As our definition of steric elements that are only graphochiral is basic to the formulation of the numbering rules, we have reaffirmed its appropriateness after considering the recently introduced pseudochirality operations.

The description of racemic mixtures in a generally acceptable manner requires a precise correspondence between the constituting enantiomers: their names must differ in the description of the steric elements or units that change configuration on reflection but agree in all other respects. In particular on comparing a pair of enantiomers, centers that are interconverted by reflection must carry the same number. This view seems to be endorsed by the rules of stereochemical nomenclature promulgated by IUPAC[1a] because the basic rule (E-0) stipulates that the names of enantiomers should differ only in their configurational affixes but not in their numbering. It has become evident, however, that subsidiary rules in the same document can produce names that are at variance with this principle. For example, the numbering rules of IUPAC given in Sections A–C allow two alternative descriptions of compound **1**: 1-(a), 2*R*,3*R*,4*S*,5*R* and 1-(b), 2*R*,3*S*,4*R*,5*R*. Rule E-2.23[1a] eliminated the second of these alternatives by giving priority to *R* over *S* at the first point of difference between the configurational affixes (at C-3 in this case). The same rule when applied to the enantiomer ($\bar{\mathbf{1}}$) would give preference to $\bar{1}$-(a), 2*S*,3*R*,4*S*,5*S*, over $\bar{1}$-(b), 2*S*,3*S*,4*R*,5*S*. The undesirable character of these selections, 2*R*,3*R*,4*S*,5*R* and 2*S*,3*R*,4*S*,5*S*, is clearly evident if they are combined in naming the racemic mixture which would have to be called 2*RS*,3*RR*,4*SS*,5*RS*. This does not have the desired form because the descriptors of center 3 (as well as of 4) are the same. A proper name with inverse descriptors at all chiral centers, 2*RS*,3*RS*,4*SR*,5*RS*, would have resulted if Rule E-2.23 were modified in such a way that in the case of $\bar{\mathbf{1}}$ preference would have to be given to the second alternative listed [$\bar{1}$-(b)]. It is the purpose of this communication to propose such a modification of the rule.†

An analogous problem can arise in cases where the name of the compound is not affected: compound **2**, (2*R*,4*R*)-trihydroxyglutaric acid, allows no choice of the configurational affix. The two chain ligands of C-3 are diastereotopic.[2]‡ They can be distinguished by NMR, by chemical reactions, and by the different descriptors *pro*-3*R* and *pro*-3*S*.[4] For easy reference to individual carbon atoms we thought it desirable to standardize numbering and suggested in analogy to Rule E-2.23 that priority for lower numbering be given to the *pro*-3*R* over

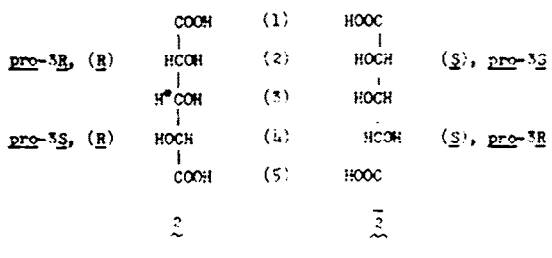


†After this paper was submitted for publication IUPAC published a revision of the E-rules.[1a] The new rule E-2.2.3 which takes the place of E-2.23 no longer specifies that *R* groups should be given preference over *S* groups for lower locants or inclusion in the principal chain. This deletion does not solve the problem posed by the previous rule. In all cases which were governed by it two or more names are now allowed for a single stereoisomer. It, therefore, becomes a matter of individual preferences whether a pair of enantiomers like **1** and $\bar{\mathbf{1}}$ when synthesized in two different laboratories would be named in a compatible or incompatible manner.

‡The following steric terms not defined in the E rules are being used. Morphic analysis (Ref. 3, footnote p. 3650) compares ligands or other partial structures by symmetry and other operations after each part has been separated from the remainder of the molecule whereas topic analysis[3] compares the same partial structures by the same operations in the intact molecule. The respective subdivision for partial structures with the same composition are: homomorphic/heteromorphic [stereoheteromorphic (enantiomorphic/diastereomorphic)/constitutionally heteromorphic]' and homotopic/heterotopic [stereoheterotopic (enantiotopic/diastereotopic)'/constitutionally heterotopic].[4]

Steric descriptors that specify configurations of elements of stereoisomerism or that differentiate homomorphic stereoheterotopic ligands (or other partial structures) by reference to elements of prostereoisomerism are called, respectively, graphochiral or prographochiral if the descriptions are chiral and are called agraphochiral or proagraphochiral if they are not.[5] The same terms are applied to the objects which are being described. These descriptors and their objects are also classified as pherochiral/apherochiral or propherochiral/proapherochiral if the descriptions change/do not change on reflections of the molecule.[5]

More detailed and precise definitions are given in the original publications and more extended summaries in a review.[6]



the *pro*-3*S* ligand.[4] This rule likewise violates the principle that the atoms of enantiomers that are interconverted by reflection should receive the same number in as much as reflection converts the *pro*-3*R* ligand of **2** into the *pro*-3*S* ligand of $\bar{2}$. We have, therefore, modified also our own rules for stereospecific numbering.

If the parts of a structure that have to be compared in selecting the direction of numbering differ in their atomic composition or show constitutional differences, the rules of Sections A-C of IUPAC provide, or at least ought to provide, the criteria for obtaining a unique name. We, therefore, need to concern ourselves with only two possibilities: (a) a center in an open or closed chain is bound to two or more ligands that have identical constitutions and (b) an open or closed chain of atoms can be divided by severance of a bond into two parts with identical constitutions. We shall refer to the ligating center or the midpoint of the severed bond as the *center of exploration*. Such centers (marked by an asterisk) are exemplified by C-3 of compound **2** or by the midpoint of the C-3—C-4 bond in **1**. In closed chain compounds† where alternative centers of exploration could be chosen, ambiguity is resolved by giving preference to the center receiving the lower number, or the midpoint adjacent to the atom receiving the lowest number, e.g. C-1 rather than C-4 is the center of exploration in cyclohexanol or 4-methylcyclohexanol and the midpoint of the C-1—C-2 bond is that for 1,2-cyclohexanediol.

The form and content of the revised rules resulted from two main considerations: (a) The naming of a compound with a unique term requires stereospecific numbering only if the parts or ligands that are constitutionally alike cannot be superposed when viewed in isolation. Such non-superposable ligands are either diastereomorphic or enantiomorphic. If, on the contrary, the ligands or parts are homomorphic, stereospecific numbering is needed only if one wishes to refer by number to individual atoms that can be distinguished experimentally. (b) If the constitutionally alike parts or ligands are diastereotopic (because they cannot be superposed on each other *in situ* by a reflection or a rotation or a combination of both operations), the numbering must stay the same if the original structure is reflected. Conversely, if the parts or ligands are enantiotopic, which is possible only if the compound is achiral, the atoms that are interrelated by a symmetry operation of the second kind must not retain their number. If they did a stereospecific reference to an individual atom would be impossible. Consequently, if the ligands are diastereotopic, numbering must be based on steric descriptors that are invariant to reflection, whereas the numbering of enantiotopic ligands must be based on steric descriptors that change to their opposites on reflection. The following descriptors meet the latter requirement: all pherochiral descriptors (*R*, *M*, *seqCis*,[5] and their opposites) and all propherochiral descriptors (*pro-R*, *pro-M*, *pro-seqCis*, and their opposites). The following are invariant to reflection: descriptors that are apherochiral (*seqcis*, *r*, and their opposites), those that are proapherochiral (*pro-seqcis*, *pro-r*, and their opposites), and the property of two descriptors that are pherochiral, or propherochiral, or one of each, of belonging to the same or different classes. For this characterization we have assigned to the first class all those pherochiral and propherochiral descriptors that are cited above individually and to the second their opposites, and call a pair of descriptors alike if both belong to the same class and unlike if they belong to different classes. As every single pherochiral and propherochiral descriptor is inverted on reflection, a pair that is like or unlike at the outset must remain so after reflection.

As we must have different rules depending on whether the parts or ligands are diastereotopic or enantiotopic and as the purpose of the rules differs if the ligands or parts are homomorphic or not, we have considered separately the five possible combinations of morphic and topic characteristics that are relevant to our problem. Because these five categories are mutually exclusive, there is no required order for applying the rules. There exists a sixth category comprising ligands or parts that are homotopic and, therefore, also homomorphic. We do not, cannot, and should not have rules for the stereospecific numbering of such ligands because they are indistinguishable under any condition.

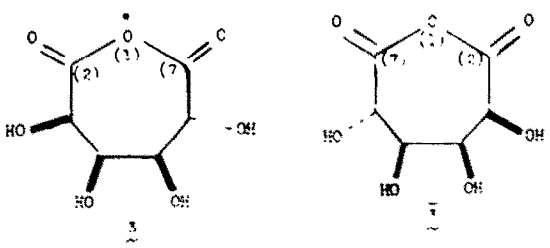
RULES AND SOME EXAMPLES

Among a pair of constitutionally like ligands or parts, inclusion in the principal chain or lower numbering is determined by the priority order given in Rules D, E_D, E_F, H_D and H_F, as follows.

Rule D. This applies if the ligands or parts are *diastereomorphic* and therefore also diastereotopic. Priority is assigned according to the amended[5] sequence Subrules (3) and (4) which are to be applied in this order by outward examination from the center of exploration. [The amended rules may be restated as follows: (3) *seqcis* > *seqtrans*, (4) *r* > *s* or like pair > unlike pair. (Pairs are alike if both descriptors belong to the same class and unlike if they belong to different classes. The first class of pherochiral descriptors consists of *R*,[6] *M*,[6] and *seqCis*;[5] the second of *S*, *P*, and *seqTrans*.)]

Compound **1** provides a simple example. As already stated, cleavage between C-3 and C-4 yields two parts with the same constitution. These parts are diastereomorphic. According to sequence Subrule (4) preference is to be given to the like pair which has the *R*,*R* configurations in **1** and the *S*,*S* configurations in $\bar{1}$. This numbering is shown alongside the structural formulas. It has the desired characteristics: each carbon atom and its counterpart obtained by reflection receive the same number and carbon atoms carrying the same number receive opposing steric descriptors in the enantiomers (**1** and $\bar{1}$). Another example is provided by **3**, the anhydride of **1**. It is standard practice to assign the lowest number to the hetero atom of such a ring. This ring oxygen, rather than the midpoint of the bond between the *R* and *S* centers,

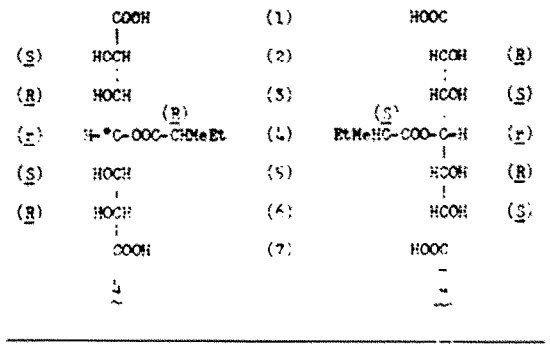
†Ligands are defined as before.[1] Therefore, the bidentate ligand of C-1 of cyclohexanol is considered as two separate factorization ligands with two different proximal atoms. These factorization ligands have an identical constitution. Analogous treatment is assumed for 1,3-cyclohexanediol: each carbinol carbon can be viewed as a distinct atom proximal to the point of cleavage. We, therefore, can compare two parts and again find that their constitutions are the same



therefore, is the center of exploration. As sequence Subrule (3) is considered ahead of (4), priority is derived by *seqcis* > *seqtrans*[8] from the steric relationships of the pairs of hydroxyl groups attached to the ring. This results in the numbering shown for **3** and its enantiomer, $\bar{3}$.

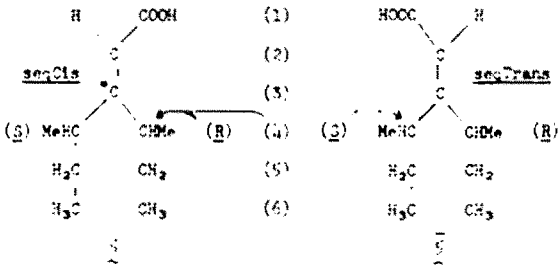
Rule E$_p$. This applies if the ligands are *enantiomorphic and diastereotopic*. Priority is established by the preference like > unlike. The pairs of descriptors to be examined consist of (1) that of the nearest pherochiral element or unit that differentiates the two ligands and (2a) that of the nearest pherochiral element or unit not located in the ligands to be compared that allows a decision. If there is none, the second descriptor (2b) is the prochirality symbol common to both ligands that is derived from the nearest propherochiral element. If there is a choice among the descriptors to be used because two or more in any category are derived from elements or units that are equally close, the one is chosen that is preferred under sequence Subrules (1) to (4) as amended[1] (see above).

Compound **4** illustrates such a case. The two enantiomorphic ligands are attached to C-4, the center of exploration. Both of these ligands contain two chiral centers of which only one, the one closest to C-4, may be used. (It is obvious that no pairs of descriptors that can be contrasted as being like and unlike can be derived solely from a pair of enantiomorphic ligands. In **4**, e.g. the centers are unlike for *both* of these ligands.) As the diastereotopic relationship between the enantiomorphic ligands always results from the presence of a pherochiral or propherochiral element that lies outside of these ligands, the second descriptor must be derived from it. The descriptor of the configuration of C-4 (*r*) is apherochiral and, therefore, cannot be used, but that of the chiral center of the acyl group has the required characteristic of changing on reflection. As its descriptor in **4** (*R*) is the same as that of the carbinol group shown above C-4 but opposite to that of the carbinol group below



C-4, the former receives the lower number. In $\bar{4}$ the like pair is *S* (carbinol group proximal to C-4 and preferred for lower number) and *S* (acyl).

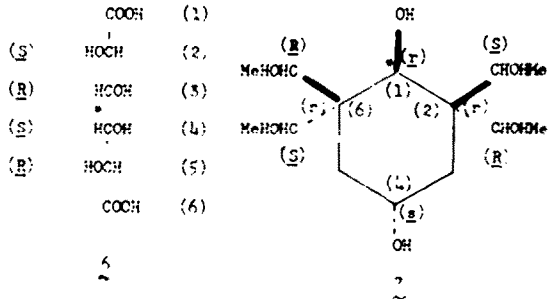
In example **5** which is taken from the IUPAC document,[1a] the carboxyl carbon must be numbered as C-1 regardless of configurations, but an ambiguity exists as to whether the branch containing the (*S*) or the (*R*) center is to be included in the principal chain. The center of exploration is C-3 which bears two enantiomorphic ligands. The pherochiral element outside these ligands is the double bond which is *seqCis* in **5** and *seqTrans* in $\bar{5}$.[†] The descriptors form like pairs, respectively, with the (*R*) center of **5** and the (*S*) center of $\bar{5}$. These chiral centers, therefore, lie in the principal chains. In contrast to the names derived under Rule E-2.23 {(*Z*)-(4*R*)-3[(*S*)-*sec*-butyl]-4-methyl-2-hexenoic acid for **5** and (*E*)-(4*R*)-3[(*S*)-sec-butyl]-4-methyl-2-hexenoic acid for $\bar{5}$}, the new names {(*Z*$^{\Phi}$)-(4*R*)-3-[(*S*)-*sec*-butyl]-4-methyl-2-hexenoic acid for **5** and (*E*$^{\Phi}$)-(4*S*)-3-[(*R*)-*sec*-butyl]-4-methyl-2-hexenoic acid for $\bar{5}$} accomplish the desired changes in the pherochiral descriptors when **5** is reflected into $\bar{5}$. As compound **5** is an example of the "geometrical enantiomorphic isomerism" of Lyle and Lyle[9] it provides an important test for the adequacy of the revised rules.



Rule E$_t$. This applies if the ligands or parts are *enantiomorphic and enantiotopic*. Priority is established under the amended[1] sequence Subrule (5) which provides that *R* > *S*, or *M* > *P*, or *seqCis* > *seqTrans*. These pherochiral elements (or units[1]) are located in the ligands (or parts) which are examined in the outward direction from the center of exploration.

Rule E-2.23[1a] when applied to this class gives results which in most cases are unobjectionable from the theoretical point of view. Nevertheless, we have made two changes: (a) To cover rare situations, *M*/*P* and *seqCis*/*seqTrans* are recognized as pherochiral descriptors. (b) As in all other rules we have dropped the phrase "at the first point of difference" and substituted the distance through the bonds from the center of exploration as the criterion in selecting the decisive pherochiral entity. This principle which is a fundamental idea in the sequence rule was adopted to make our rules as uniform as possible. An example which illustrates this difference between the old[1a] and the present rules is achiral tetrahydroxyhexanedioic acid (**6**). According to Rule E$_t$ it is 2*S*,3*R*,4*S*,5*R* because the lower-numbered center (C-3) closest to the center of exploration should have the preferred configuration (*R*), whereas according to E-2.23 the name is 2*R*,3*S*,4*R*,5*S* because the first point of difference between the two alternatives is C-2 which, therefore, should have the *R* configuration. Compound **7** illustrates numbering based on the use of the priority *seqCis* > *seqTrans*. (The center of exploration is C-1. The *R* side chain at C-2 is *cis*, that at C-6 is *trans* to the

[†] We should like to propose that the terms *seqCis* and *seqTrans* when applied to double bonds be symbolized, respectively, by *Z*$^{\Phi}$ and *E*$^{\Phi}$. The superscript $^{\Phi}$, Greek capital phi, for pherochiral seems more evocative than the superscript $^{\#}$ we had suggested earlier[1]. The new superscript too can be reproduced on a typewriter with standard type (capital O bisected by a slant).

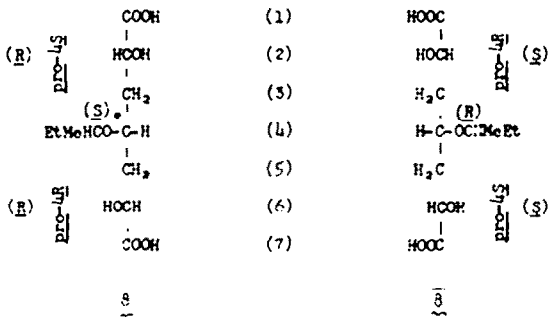


hydroxyl at C-4. This classifies these side chains as *seqCis* and *seqTrans*, respectively, and justifies the numbering shown.)

Rule H_D. This applies if the ligands are *homomorphic and diastereotopic*. Priority is assigned according to the one of the following rules that allows a decision: *pro-seqcis* > *pro-seqtrans* or if inapplicable *pro-r* > *pro-s* or like > unlike. The pairs of descriptors to be compared under this last rule consist (1) of the propherochirality symbol (*pro-R*/*pro-S* or *pro-seqCis*/*pro-seqTrans*) which allows one to differentiate the two ligands and (2a) of the chirality symbol of the nearest preferred (see Rule E_D) pherochiral element or unit. This steric entity which must provide the same symbol for both ligands may be found within or without the ligands to be compared. If there is none the second symbol (2b) is derived from the nearest propherochiral element that yields the same descriptor for the two ligands.

Compound **2** is a simple example. The chain ligands of C-3 can be superposed when detached, but they cannot be superposed in the intact structure by rotation, reflection, or both. They are, therefore, homomorphic and diastereotopic. Each ligand contains a chiral center. Its configuration in both ligands must be the same (*R* in **2** and *S* in **2̄**) because the ligands of each compound are homomorphic. C-3 is a center of prostereoisomerism which permits one to distinguish the ligands as being *pro*-3*R* and *pro*-3*S*. As *pro*-3*R* and *R*, and *pro*-3*S* and *S* constitute like pairs, the numbering is as shown.

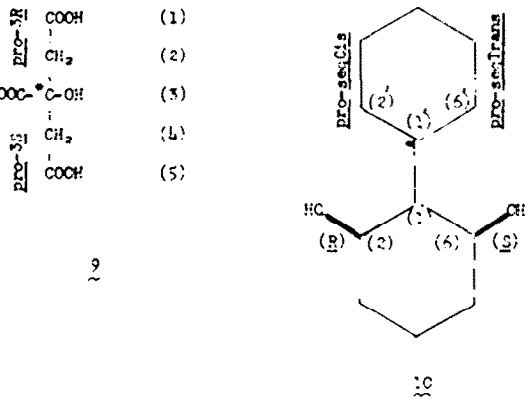
The novel aspect of example **8** lies in the presence of another chiral center which lies outside the pair of homomorphic ligands. It has the same distance (2 bonds) from the center of exploration (C-4) as the chiral centers in the homomorphic ligands (C-2 and C-6). The chiral center of the *sec*-butyl group is given preference because it is reached by a higher priority bond (C–O compared to C–C, sequence Subrule 1). The like pairs, therefore, are *pro*-4*S* and *S* in **8** and *pro*-4*R* and *R* in **8̄**. The numbering would be reversed if the side chain were EtMeHC–H_2C–O–.



Rule H_E. This applies if the ligands are *homomorphic and enantiotopic*. Priority is assigned according to these rules: *pro-R* > *pro-S* or *pro-seqCis* > *pro-seqTrans*.

In most cases the first of these rules will be applicable which is identical with a rule we had proposed before.[4] In citric acid (**9**), e.g. the two CH_2COOH can be superposed if detached. They can also be superposed in the intact structure by a reflection. These two ligands which are, therefore, homomorphic and enantiotopic can be distinguished because one is *pro*-3*R*, the other *pro*-3*S*. This difference accounts for the numbering shown.

Example **10** provides an illustration for the rule *pro-seqCis* > *pro-seqTrans*. The center of exploration for the cyclohexylidene ring is C-1′. The methylene group which is attached to it on the left is *pro-seqCis* (i.e. the ligand which starts with this methylene group is one of a pair of homomorphic ligands and it is *cis* to the *R* ligand of an enantiomorphic pair), the one on the right *pro-seqTrans*. The former methylene, therefore, is to be numbered C-2′. (In the other ring preference is given to *R* over *S* according to Rule E_E).



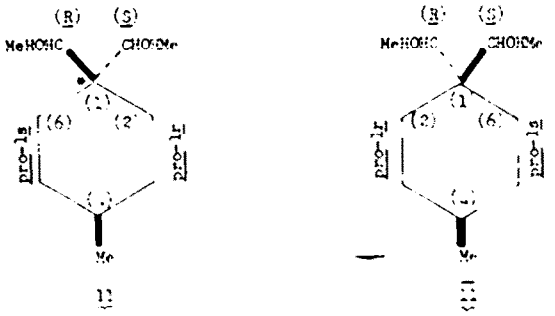
Note—Occasionally ligands are encountered that cannot be distinguished by any criterion given in the sequence rule although these ligands when examined in isolation cannot be superposed. Such ligands have to be treated as if they were homomorphic under rules H_D or H_E as appropriate.

This can happen in even-numbered rings if they are substituted in two positions that lie on a line through the center of the ring. *cis*-4-Methylcyclohexanol (VIII of Ref. 4) is an example. The ring ligands of C-1 are enantiomorphic and enantiotopic but there is no recognized procedure for expressing the morphic differences between the two ring ligands that start with one or the other methylene attached to C-1. They are treated as if they were homomorphic according to Rule H_P which provides that *pro*-1*R* takes precedence over *pro*-1*S*. This analysis of compound VIII is the same as the one given before and the numbering is as shown in Ref. 4 which discusses the use of prochirality symbols derived from such centers of stereoisomerism.

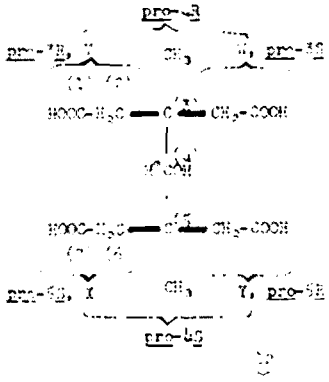
It is equally impossible to distinguish the enantiomorphic ring ligands of C-1 in **11** by accepted descriptors of their morphic differences. Therefore, analysis is carried out under Rule H_D which gives preference to the *pro*-1*r* ligand. Comparison between **11** and **11̄** shows that the carbon atoms retain their numbering when the original structure is reflected into that of the enantiomer. Therefore, in this case too the numbering has the desired characteristics.

FURTHER EXAMPLES

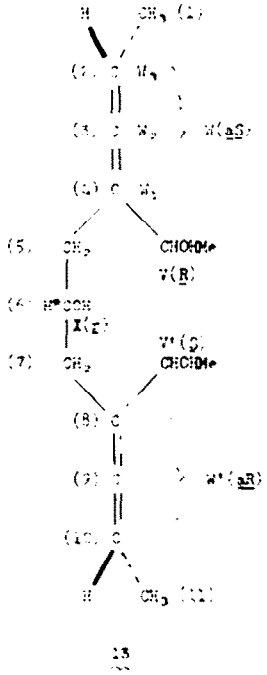
To test the adequacy of these rules we have examined a large number of more challenging examples which included compounds unlikely ever to be encountered in practice. From this survey we shall show only three



further cases which presented special problems. In **12** there are eight possibilities for numbering the principal chain: four for allocating C-1 to one of the carboxyl groups and for every choice we have two further possibilities in locating the end of the chain. The central atom (C-4) meets the criterion for the center of exploration: its branched ligands are homomorphic and enantiotopic. As the ligand above C-4 is *pro*-4*R* and the one below *pro*-4*S*, numbering must commence in the former and end in the latter (Rule H_1). This allows one to allocate C-3 and C-5. Both of these atoms are additional centers of exploration as they also possess a pair of homomorphic ligands. Among the pair attached to C-3 the one marked V is *pro*-3*R* and the other *pro*-3*S*. As the ligand pair V and W is diastereotopic this difference does not suffice for selecting the preferred ligand (Rule H_D). The compound possesses no chiral centers. Therefore, the second symbol must be a second prochirality descriptor that is the same for V and W. Such a descriptor is *pro*-4*R*. It forms a like pair with *pro*-3*R*. Therefore, numbering commences in ligand V. At C-5 the like pair is *pro*-5*S* and *pro*-4*S*. Therefore, ligand X rather than Y is to be included in the principal chain with the result that the two terminal atoms of the chain, C-1 and C-7, occupy enantiotopic positions.

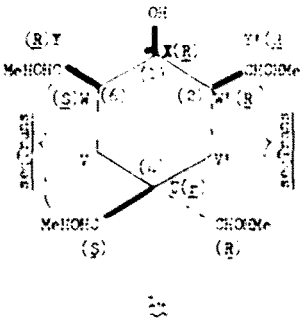


Compound **13** calls for an interpretation of the sequence subrules which appears not to be available. The branched ligands of the pseudoasymmetric center (X) are enantiomorphic. Each one contains two elements of chirality, a center (V) and an axis (W) which are characterized by inverse configurational symbols. (The axis W is *S*, the center V is *R*.) The configuration of X and the direction of numbering depend on whether the configuration of the center or of the axis is decisive for assigning priority to the branched ligands. One may think that centers might be preferred because they are identified first during factorization.[8] However, the phrasing of Subrule (4) indicates otherwise. It states *inter alia* that the



like pairs (*R* and *M*) or (*M* and *R*) have priority over the unlike pairs (*R* and *P*) or (*P* and *R*).[8] If there were a categorical preference for centers over conformations the former should be always cited first. As two separate priorities were stated it can only be because the center and the conformation are treated on a par and one is assumed to be reached ahead of the other during exploration. Consistency requires that we treat a chiral axis the same way as we would a chiral conformation. We, therefore, face the problem of having to decide which atom or bond we wish to associate with the configurational symbol of a chiral axis. We could choose the proximal or the distal end of the axis or a point half-way between them. If we opt for the first W_1 is reached ahead of V and the configuration of the axis determines the configuration of X. If our choice is W_2 or W_3, the preferred path of exploration leads to V and the configuration of the center determines the configuration of X. We think it appropriate to associate the configurational symbol of an element or unit of stereoisomerism with a point half-way between the two terminal atoms of its core.[7] In determining this point we proceed between the two terminal atoms along the bonds by the shortest route and divide the number of bonds traversed by two. (Differences in bond length are ignored.) On this basis we locate the configurational symbol of the chiral axis at W_2. For the reasons stated, the branch with the chiral center having the *R* configuration has priority for lower numbering and for assigning the configuration of X which, therefore, is *r*.

The proposed rule for locating configurational symbols allows us also to analyze compound **14**. Center X has two diastereomorphic ligands. Their priority is determined by Rule D. The first members of the pairs to be classed as like or unlike are the configurations of W (*S*) or W' (*R*); the second descriptors can either be the configurations of Y and Y' which are both *R*, or the configurations of the pherochiral units terminating at W and U and at W' and U which are both *seqTrans*. As the latter are to be located at V and V', Y and Y' are reached first in the exploration from X because a carbinol group has priority over a methylene. Therefore the like pair is *R* (W') and *R* (Y') and



hence the configuration of X and the numbering are as shown.

CONDENSED SUMMARY OF NUMBERING RULES

D: *seqcis* > *seqtrans*//*r* > *s* or like pair > unlike pair;

E_D: like > unlike [(1) pherochirality descriptor differentiating ligands and (2) external pherochirality descriptor//common propherochirality descriptor];

E_E: *R* > *S* or *seqCis* > *seqTrans*;

H_D: *pro-seqcis* > *pro-seqtrans*//*pro-r* > *pro-s* or like > unlike [(1) propherochirality descriptor differentiating ligands and (2) internal or external pherochirality descriptor//common propherochirality descriptor];

H_E: *pro-R* > *pro-S* or *pro-seqCis* > *pro-seqTrans*.

(Choices before // are to be tried first. Other choices are resolved by sequence-rule exploration).

DISCUSSION

The numbering proposed in this communication responds to reflection in the appropriate manner. Therefore, in contrast to Rule E-2.23[10] and some of our own earlier proposals,[4] the new system may be termed reflection-concordant stereospecific numbering. (For ready reference this system could be called the *rcsn*-convention.) We have tested the rules on a wide variety of compounds and observed no anomalous results. Furthermore, unless distinctive numbering is inappropriate because the alternative positions are homotopic, the rules provide for unique numbering if the sequence rule provides the required descriptors as is nearly always the case.† The objectives which have been stated in the introduction, therefore, appear to be met. They were reached in two stages.

In the first we modified the sequence subrules in such a way that only those descriptors of elements or units of stereoisomerism that are pherochiral would change on reflection. The minor change advocated[3] differs from a proposal with the same objective which had been made earlier by Prelog and Helmchen.[12] Both revisions affect only a very small number of compounds. Our proposal is more conservative because it retains a principle of the original sequence rule[8] according to which configurations depend only on morphic differences between ligands. In contrast Prelog and Helmchen used topic properties as well. The disadvantages of this procedure were discussed in an earlier report.[3] This difference in specifying configurations persists at the second stage (numbering), when we too have to use topic characteristics. This sequential application can greatly simplify also the numbering process.‡

The objectives and results of our numbering rules raise a question of fundamental importance. In determining the numbering of **4** and $\bar{\mathbf{4}}$ we considered it appropriate that the atoms of the enantiomeric pair that are interconverted by reflection would receive the same numbers. If such an equivalence is a sound basis for numbering, is it not equally sound to use the same equivalence for deciding whether the configuration of C-4 is being retained or inverted upon reflection? If the ligands that are interconverted by reflection correspond, the configuration of C-4 in **4** differs from that in the enantiomer ($\bar{\mathbf{4}}$) and C-4 should be classed not as a pseudoasymmetric center, as we have done,[13] but as a center of chirality, which is the conclusion reached by Prelog and Helmchen.[12] If such equivalence were a sound principle for distinguishing between retention and inversion on reflection it must either be generally applicable or at least be valid in all cases in which the ligands are diastereotopic as they are in **4**.

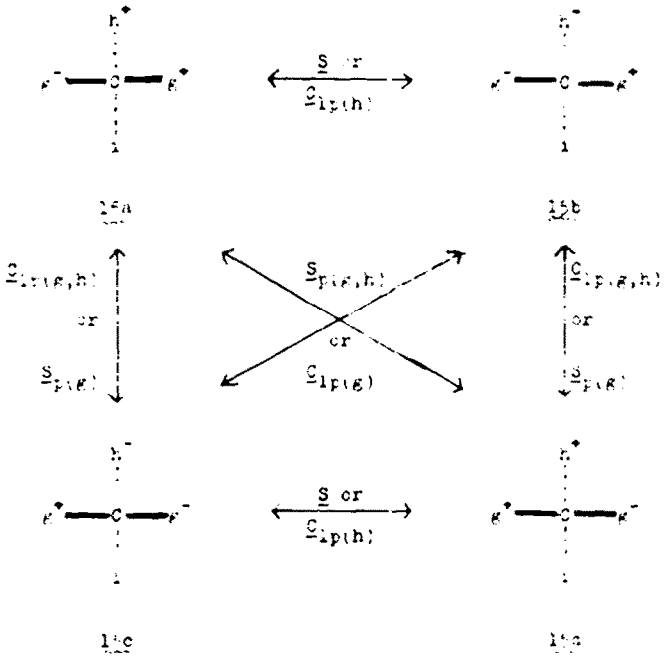
It is important, therefore, to recall[3] that this is not the case. The *R*-ligand of **5** and the *S*-ligand of $\bar{\mathbf{5}}$ are interconverted on reflection. Both are assigned to the principal chain and the numbered atoms retain their numbering on reflection. If it were postulated that these two ligands should also correspond in comparing the configurations of the double bond one would have to conclude by the same reasoning as was tentatively applied to **4** that the double bond retains its configuration on reflection. This is untenable because **5** and $\bar{\mathbf{5}}$ are stereoisomers that can be interconverted by nothing more than an exchange of ligands at the double bond. It is evident that a rule which is useful for numbering has failed in comparing configurations although both applications were made on *identical* structures. Therefore, the idea that ligands of enantiomers necessarily correspond if they are interconverted by a reflection cannot possibly have the status of an axiom for comparing the configurations of enantiomers.

The recent application of group theory to the subject pseudoasymmetry (pseudochirality) also has prompted us to reexamine our definition of an element of stereoisomerism that requires a chiral descriptor but that does not change its configuration on reflection of the molecule. Nourse[11] has introduced two symmetry operations of a new kind, rotation with chirality reversal (C_{nv}) and reflection with chirality reversal (S_{nv}) to define molecular pseudochirality as the attribute of a structure that yields an isomer on C_{nv} as well as S_{nv}. This allows not only an achiral compound (like achiral trihydroxyglutaric acid) but also a chiral one to be pseudochiral.[11]§ A simple example of this is **15a**, the basic structure with a center that has alternatively been considered to be pseudoasymmetric[3] and chiral.[12] It yields isomers on reflection (**15b**) and on both Nourse operations, if the chirality

†For cyclic compounds with high constitutional symmetry like the cyclitols we have used two subsidiary rules, namely that atoms are to be given preference to the midpoints of bonds, as centers of exploration and that all $\alpha\beta$-*cis* relationships are to be considered ahead of $\alpha\gamma$-*cis*. We shall not discuss this in detail as we have no intent to suggest the adoption of our general numbering rules for areas where the needs for unique numbering have been well met by local systems as for example for the cyclitols[10] or glycerol.[11]

‡A striking illustration is provided by C(Cg'g h,Cg g'h,C(i j, Ci i')j) as we can distinguish the diastereomorphic ligands of the center by their *rs* configurations. This determines their priorities for specifying the configuration of the center as well as for numbering. Prelog and Helmchen can ascertain these priorities, if at all, only by exceedingly circuitous routes.

§This concept differs fundamentally from that of Prelog and Helmchen[12] who stressed that pseudoasymmetry can occur only in achiral structures.



reversal is carried out on the g or the g and h ligands (**15c** and **15d**). The structure is therefore both chiral and pseudochiral according to Nourse. He has not defined a center of pseudochirality. Undoubtedly, several definitions can be given which would utilize the Nourse operations. However, the choice is subject to the constraint that a center that yields a pseudoenantiomer on permutation of its ligands and that has no pseudochiral ligands ought to receive the same classification (pseudochiral) as the whole, if the structure contains no other such element. According to this postulate the center of **15a** is pseudochiral.

Solely to allow a comprehensive comparison with our definition of a center to be characterized by *r/s* descriptors we delineated as pseudochiral a center substituted with a pair of enantiomorphic ligands in such a way that the center cannot be superposed upon itself by a symmetry operation with chirality reversal limited to the pair of enantiomorphic ligands attached to the center (e.g. the g ligands of **15**). This description appropriately excludes the center of Cg'g h'h because S_p with respect to the g or the h ligands superposes the center on itself. The definition appears to be equivalent to the one we have given for a center to be described by *r/s*, provided it is tetrahedral. The two definitions can diverge if the center is octahedral or tetragonal, e.g. tetragonal Xg'g h'h yields an isomer on S_p and C_p if the chirality reversal is limited to a single set of the chiral ligands. The structure is, therefore, pseudochiral according to Nourse and so is its center according to the above definition, or any other that is in accord with the Nourse concept of pseudochirality and with the postulate stated above. However, the isomers interconverted by the S_p operation cannot be distinguished by chiral descriptors like *r/s* because any sequence of the ligands that is clockwise when viewed from one side is counterclockwise from the other.

As the different requirements for the classification of the tetragonal center allow no resolution we must conclude that the objective of defining elements of stereoisomerism that can be characterized by the reflection-invariant descriptors *r/s*, and that of establishing symmetry relationships for a large variety of diastereoisomers are distinct problems that require different approaches. Nevertheless, there must be much common ground, because it appears that any center that we would characterize by *r/s* can be classed as pseudochiral according to a definition based on chirality reversal operations (the one stated above). This further supports our contention that the minor revisions of the sequence subrules which we have proposed have a sound theoretical basis and hence that the resulting steric descriptors are appropriate tools for the numbering rules here described.

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REFERENCES

[1a]IUPAC 1968 Tentative Rules, Section E, Fundamental Stereochemistry, *J. Org. Chem.* **35**, 2849 (1970). [1b]IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry *Pure Appl. Chem.* **45**, 13 (1976).
[2]K. Mislow and M. Raban, *Top. Stereochem.* **1**, 1 (1967).
[3]H. Hirschmann and K. R. Hanson, *Tetrahedron* **30**, 3649 (1974).
[4]H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.* **22**, 301 (1971).
[5]H. Hirschmann and K. R. Hanson, *J. Org. Chem.* **37**, 2784 (1972).
[6]K. R. Hanson, *Ann. Rev. Biochem.* **45**, 307 (1976).
[7]H. Hirschmann and K. R. Hanson, *J. Org. Chem.* **36**, 3293 (1971).
[8]R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem.* Int. Ed. **5**, 385, 511 (1966).
[9]R. E. Lyle and G. G. Lyle, *J. Org. Chem.* **24**, 1679 (1959).
[10]IUPAC-IUB, The nomenclature of cyclitols, *Eur. J. Biochem.* **5**, 1 (1968).
[11]IUPAC-IUB, The nomenclature of lipids, *J. Biol. Chem.* **242**, 4845 (1967); **245**, 1511 (1970).
[12]V. Prelog and G. Helmchen, *Helv. Chim. Acta* **55**, 2581 (1972).
[13]J. G. Nourse, *J. Am. Chem. Soc.* **97**, 4594 (1975).