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PROCHIRAL AND PSEUDOASYMMETRIC CENTERS: IMPLICATIONS OF RECENT DEFINITIONS

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Abstract—New definitions of prochiral and of pseudoasymmetric elements have been proposed by Prelog and Helmchen [*Helv. Chim. Acta* **55**, 2581 (1972)]. The revised definition of prochiral centers would fail to identify many centers bearing like ligands that can be distinguished experimentally. The new definition of the pseudoasymmetric center would cause some that were previously so designated to be considered chiral. Whenever this occurs, concepts like retention and inversion of configuration would no longer have their customary meaning. Concomitant changes in the sequence subrules would not always provide reliable information about the possibilities of stereoisomerism. A modification of the rules is outlined which would avoid this, but secure similar benefits.

In a recent paper entitled, "*Pseudoasymmetrie in der organischen Chemie,*" Prelog and Helmchen[1] set forth some challenging stereochemical ideas which differ in several respects from current practices as codified in the E-rules of IUPAC.[2] The most important of these differences concern the prochiral and the pseudoasymmetric tetrahedral atom. We too have attempted to delineate these categories[3] and find that the new contribution differs from ours not only in the approach but also in some of the conclusions. As the latter affect both practical matters and rather basic concepts it seems appropriate to discuss the proposals.

Prelog and Helmchen[1] start by examining the symmetry properties of certain tetrahedra whose corners are occupied by selected ligands and then use the figures to define the prochiral and the pseudoasymmetric tetrahedral atom. This procedure gives the impression that such definitions have all the force of mathematical necessity. However, these entities as defined by us also can be represented by tetrahedra which have sets of properties in common. When the two proposals[1,3] yield different assignments the differences result from the way a tetrahedron is related to the molecular model, the choice of the figure or figures to be examined, and the superposition test used in the examination. It seems to us that these selections lie outside the realm of geometry. Any preference, therefore, can be justified only by examining how well the resulting concepts serve the purpose of the chemist. These purposes differ from those of workers in allied fields. The spectroscopist and the crystallographer, like the geometer, have singled out from the general class of tetrahedra those distinguished by their symmetry properties. In contrast, the chemist has placed into a special category the carbon atom of bromochlorofluoromethane rather than of carbon tetrachloride.

1. *Prochiral centers.* Prelog and Helmchen use as their model for a tetrahedral prochiral atom a regular tetrahedron whose corners are occupied by the achiral ligands A, A, B, C. This tetrahedron has a plane of symmetry and the two like ligands (A) occupy corresponding positions relative to this plane. The situation was generalized when the enantiotopic[4] relationship between the A ligands was incorporated into the definition of a prochiral atom. If the ligating center is carbon, the definition of the prochiral atom given by Prelog and Helmchen delineates a structure which was called a *meso*-carbon atom by Schwartz and Carter.[5] The latter workers coined the special term, which alludes to the reflective symmetry of the figure, to call attention to the fact that an enzyme or other chiral reagent could distinguish between the like ligands of such a center. Widely studied examples of it are represented by C-1 of ethanol and of C-3 of citric acid. Such steric discrimination, however, is not limited to superposable ligands that lie across a plane of symmetry.[6] It is equally possible if the two superposable ligands, or one or both of the remaining ligands, or all ligands are chiral. To meet

the need for a broader term the concept of a prochiral atom was introduced.[7] It signifies the fact that if discrimination between the two like ligands occurs and one of them is changed to a new ligand, a center of chirality is created that is absent from the original structure. The hydrogens at a methylene carbon of citric acid, or of mevalonic acid, or the CHOHCOOH ligands in chiral trihydroxy glutaric acid are attached to centers which meet this definition of a prochiral atom but none qualifies for this term according to Prelog and Helmchen because at least one of the ligands is chiral and the like ligands occupy diastereotopic positions. Yet we must identify all these ligating centers if we wish to differentiate the distinct positions of their like ligands, *e.g.*, by applying sequence rule procedures.[8] If we thus stress the need for a broader concept of the prochiral atom than is allowed for under the Prelog-Helmchen definition we recognize that there is an important difference between enantiotopic[4] and diastereotopic[4] pairs of ligands: the former can be differentiated by physical observation or chemical transformation only under chiral conditions whereas this circumstance is not essential if the ligands are diastereotopic.[4,9] However, this distinction is already achieved by the terms "enantiotopic" and "diastereotopic." As these are based on an examination of the complete molecular model they serve this purpose better than any subdivision of the original prochiral atoms[3,7] into those that meet the Prelog-Helmchen[1] definition and those that do not.* We conclude that the concept of the prochiral atom now in use serves an essential function; its redefinition, as advocated by Prelog and Helmchen, would therefore create a void as well as a redundancy because the prochiral carbon center, which is by far its most important application, would become a synonym for the *meso*-carbon atom.

2. *Pseudoasymmetric centers.* Prelog and Helmchen[1] derive the pseudoasymmetric atom from their prochiral atom by substituting a pair of enantiomorphic† ligands for the two like ligands of the latter. This transformation retains the plane of symmetry of their prochiral atom. The authors generalize from this model that the enantiomorphic ligands of the pseudoasymmetric atom must always occupy enantiotopic positions and that a center of pseudoasymmetry cannot exist unless it lies in a plane of symmetry of the molecular model.

It is doubtful that this view can be justfied on historical grounds. Prelog and Helmchen have uncovered what appears to be the earliest use of the term "pseudoasymmetry." Landolt[10] used it to characterize the central carbon situated in an open chain and ligated with two constitutionally like chiral ligands and two distinct ligands. Such a center does not lie in a plane of symmetry in all possible isomers. Landolt's presentation was very brief and may not reveal his intent. However, there can be no doubt that subsequent writers of this period[11] subscribed to the view that pseudoasymmetric carbon atoms could exist in chiral compounds. Landolt used the sum of asymmetric and pseudoasymmetric carbon atoms to calculate the total number of possible isomers. The concept of a pseudoasymmetric carbon atom is not essential for this purpose because the sum equals the number of tetrahedral carbon atoms that are centers of stereoisomerism (permutation centers) in all or some of the stereoisomers.

A different and, we believe, more important purpose for distinguishing between asymmetric and pseudoasymmetric centers was suggested when Cahn *et al*[8] stated that the sequence rule symbols of the elements of pseudoasymmetry remain unchanged on reflection of the model. As the spatial distribution of the ligands (configuration) of a typical pseudoasymmetric center such as C-3 of an achiral trihydroxyglutaric acid also remains unchanged on reflection whereas the configuration of a chiral center like C-2 of glyceraldehyde does not, we based our definitions of the chiral and the pseudoasymmetric center on this distinction.‡ A note to Rule E-5·8 of IUPAC[2] evidently tries to express the same idea.

Given this criterion it should be a relatively

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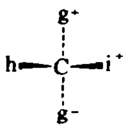
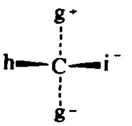
*Groups or atoms that can be differentiated only under chiral conditions are necessarily enantiotopic, but they need not be attached to a common prochiral center or other prochiral element. The pair of hydrogens at C-2 and C-3 of *meso*-tartaric acid illustrates such a case.

†We are following the suggestion[1] of restricting the use of the terms enantiomeric and diastereomeric to comparisons between stereoisomers, and of expressing the same steric relationships between other objects such as ligands by the terms enantiomorphic and diastereomorphic. As will be further explained below, our use of the latter terms will always specify comparisons between *isolated* ligands rather than describe relationships of the ligands within the intact structure of the whole molecule. In extension of this terminology, ligands that in isolation are superposable such as the "like" or "paired"[7] ligands of a prochiral center can be called homomorphic. Except when other work is being quoted, ligands are indicated in the same way as before (ref. 3*a*, footnote 5); e.g., g^+, g^- signifies a pair of enantiomorphic ligands.

‡We have defined a pseudoasymmetric center as a center of stereoisomerism with a configuration that can be specified (without reference to other steric elements in the molecule) only by a chiral descriptor but whose configuration does not change on reflection of the molecular model. More succinctly: a pseudoasymmetric center is graphochiral but not pherochiral. This characterization might be further shortened into "only graphochiral" to contrast the pseudoasymmetric with the chiral center which is both graphochiral and pherochiral, and with the element of the double bond in 5 which is "only pherochiral". For definitions of all terms see ref. 3. Our definition of a pseudoasymmetric center is satisfied by a tetrahedral atom having four different ligands of which two and only two form an enantiomorphic pair.[2]



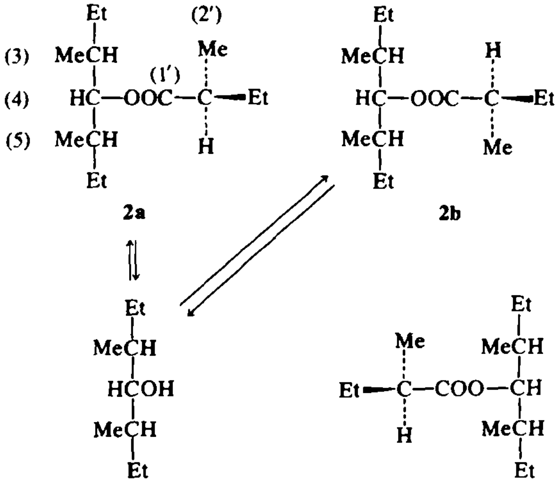
1a



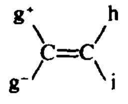
1b

simple matter to decide whether it is appropriate to stipulate that the enantiomorphic ligands of a pseudoasymmetric atom occupy enantiotopic positions. Example **1a** provides a suitable test case. If we simply deduced from the observation that **1a** cannot be superposed on its mirror image **1b** that the configuration of the central carbon atom must have changed, we would have ceased to factorize the chirality of a chiral molecule into its component parts. Our assignments would become trivial because if the whole structure cannot be superposed on its mirror image, it will be equally impossible to superpose *any* of its steric elements and *all* ligands attached thereto on the corresponding structures of the enantiomer. In *cis* ghC = Chi$^+$, *e.g.*, only three of the singly bonded ligands of the double bond can be superposed on the ligands of the enantiomer. If we deduced from this that the configuration of the double bond has changed on reflection, we would have to reach the novel conclusion that in such a compound the double bond represents a chiral element of stereoisomerism in 3-dimensional space.

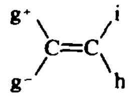
However, we need not give up on factorizing chirality: it is possible to examine each element of stereoisomerism individually.[3]* If we represent C-2 of D-threose by Cghij$^+$ we obtain Cghij$^-$ on reflection. The central carbon atoms and the three ligands common to both representations cannot be superposed. As the distribution of three ligands of a tetrahedral center determines the location of the fourth we can conclude that irrespective of the difference between j$^+$ and j$^-$, the configuration of the central atom must have changed; C-2 is a chiral center. If we reflect **1a** in the plane containing the central atom and the bonds linking it to h and i$^+$ we obtain **1b**. Again three ligands (g$^+$, g$^-$, h) are common to both enantiomers and the 4th is enantiomorphic. However, in contrast to the threose case the spatial distribution of the three common ligands has remained unchanged on reflection. We deduced that the configuration of the central carbon of **1a** had been retained. Evidently Prelog and Helmchen reached the opposite conclusion because they class the atom X in a structure of this type [X(AF$\bar{\text{F}}$L)] as a center of chirality and not of pseudoasymmetry.† They did not explain why there is a change of configuration and we can see only one type of argument which might be used to justify this idea. In a chiral compound like **1a** the disposition of the atoms of the i$^+$ ligand towards g$^-$ and g$^-$ cannot be the same for any thermodynamically unique conformation.[12] If we define the difference between the g ligands by their relationship to the i ligand, we would find that the g$^+$ of **1a** corresponds to the g$^-$ of **1b**. This may become more evident by considering a specific example (**2a**). It depicts a thermodynamically unique conformation which corresponds to the *equally stable* conformation **2b** of the mirror image. It will be seen that the 2′-methyl is directed towards the (*R*)-sec-butyl group of **2a** and towards the (*S*)-group of **2b**. If these relationships towards a third ligand, rather



2a **2b** **3** **4**



5a



5b

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*This reference should be consulted for more complex cases than are discussed in the present paper.

†In discussing a specific example (V of their paper) the authors indicated that the configuration of the central carbon atom changes on reflection, because they described its configuration by a symbol given in a capital letter and modified the sequence sub-rules in such a way that this symbol would change to the inverse one on reflection. Although the symbols derived by the sequence rule ordinarily do not express genetic relationships, this does not seem to apply to structures that are interrelated by symmetry operations of the second kind (reflection, inversion, etc) because great efforts have been made[1,8] to realize a system in which every chiral element would receive the inverse descriptor after a reflection whereas the descriptors of the pseudoasymmetric elements would remain unchanged. *The meaning of these correlations would be obscure and the increased complexity of the system would hardly be justified unless the symbols reflected actual comparisons of configurations between the original compound and its mirror image.*

than their intrinsic characters,* determine which g groups correspond in **1a** and **1b**, we would find that a change of configuration occurred at the central atom on reflection. However, we must question the validity of this form of analysis because one cannot apply it consistently. Reflection of **5a** gives **5b**. If one again defines corresponding g groups before and after reflection by their relationship towards a third group, the g^- (*cis* to h) in **5a** corresponds to g^- (*cis* to h) in **5b**, and similarly g^- (*trans* to h) to g^- in **5b**. Using the same argument as was considered for relating **2a** to **2b** one would have to conclude that the configuration of the double bond has not been altered by the reflection. This, however, is not in keeping with the fact that **5a** and **5b** are stereoisomers differing only in the spatial distribution of the ligands at the double bond.

We encounter other and, we believe, more serious inconsistencies if we regard C-4 of **2a** as a chiral atom which changes configuration on reflection. We can conceive a synthesis of **2a** and **2b** by esterification of **3** with one or the other enantiomer of methylbutanoyl chloride. If the products are held to have opposite configurations at C-4 one conversion would constitute a retention the other an inversion of configuration. Conversely, if **2b** differs from **2a** in the configuration at C-4, **4** must have the same configuration at this center as **2a**. These conclusions would clash with established practices. After Walden's discovery of the inversion that bears his name, the concepts of retention and inversion in substitution reactions at tetrahedral centers have acquired a fixed and universally recognized meaning that has precise geometric implications. One can envisage a reaction cycle which would relate **2a** with its enantiomer **2b** via the parent alcohol. Throughout this cycle three of the ligands[13] of C-4 and the C-O bond to the fourth ligand remain untouched. Therefore, **2a** and **2b** must have the same configuration at this center. It would seem most unfortunate if the results of such a comparison of configurations would depend on the method of comparison: substitution or reflection. The deduction (retention) derived from the former is based on concepts which seem indispensable in stereochemistry and which can hardly be altered. On the other hand, if the enantiomers are compared by reflection the result depends on the classification of the center. As retention of configuration on reflection is a characteristic of the pseudoasymmetric but not of the chiral center, consistent comparisons of the configuration of C-4 are realized only if the center is considered to be pseudoasymmetric.

The restriction that the enantiomorphic ligands of a pseudoasymmetric center must occupy enantiotopic positions seems undesirable even if the molecule is achiral (**6a**). The branched ligands of C-3 can be superposed if detached. They lie across a plane of symmetry of the molecule which bisects C-3 and its H and OH ligands. These facts are in harmony if the old definitions prevail because C-2 and C-4 would be pseudoasymmetric centers which retain their configurations on reflection. However, C-2 and C-4 do not meet the Prelog-Helmchen definition of pseudoasymmetry because their hydroxyethyl ligands are in diastereotopic positions. Consequently if these centers have to be regarded as chiral they ought to change configuration on reflection and C-2 and C-4 would differ in configuration. In spite of this, if we exchange the ligands which contain these centers no new isomer is obtained. C-3 is a prochiral atom.

We find it instructive to compare this example with **7a**. This trihydroxyglutaric acid also is achiral but differs from **6a** in having true chiral centers in the enantiotopic positions C-2 and C-4. In the case of the trihydroxyglutaric acid the ligands which contain these chiral centers cannot be superposed and their exchange produces a new stereoisomer. We encounter the reverse discrepancy if we exchange in **6a** as well as **7a** a pair of ligands at C-2. In both series the resulting isomers (**6b** and **7b**) are chiral but whereas **6b** gives a stereoisomer upon an exchange of ligands at C-3, **7b** does not. Its central carbon atom is prochiral.[3,7]

It is evident that the steric characteristics of **6a** and **6b** are atypical if C-2 and C-4 are regarded as chiral centers. The anomalies were traced to the deduction that C-2 and C-4 of **6a** have *inverse* configurations. This deduction becomes unwarranted and all inconsistencies are removed, as soon as we acknowledge that there is a basic difference between these centers in the isomers of **6** and **7** and classify the centers of **6** as pseudoasymmetric.

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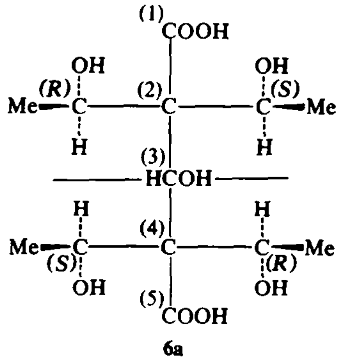
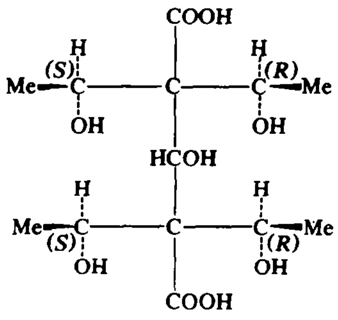
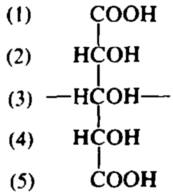
*The phrase (ref. 1, p. 2596), "*Ein enantiomorphes Ligandenpaar wird durch die Anwesenheit eines dritten chiralen Liganden diastereomorph,*" appears to express such a view. We would like to comment on this sentence because we think such terminology needlessly complicates the characterization of ligands. Topic analysis and the ensuing characterization of atoms groups or ligands as homotopic,[12] enantiotopic[4] and diastereotopic is carried out by conducting symmetry operations on the whole molecule. If we used the same form of examination also to classify ligands as homomorphic, enantiomorphic and diastereomorphic, we would have two terminologies for the same relationships but none for the equally essential characterization of *isolated* ligands. The importance of the latter is evident if we recall that the exchange test for the determination of stereoisomerism is an operation conducted with isolated ligands. Actually Prelog and Helmchen have not discontinued the characterization of isolated ligands. Sometimes they stated the conditions of the comparison but often they did not. The first of these practices seems cumbersome and the second is ambiguous. As "morphe" signifies form or shape and "topos" place, the former can be taken as a suitable expression for the characterization of ligands by themselves. Consequently in the example under discussion we would prefer to speak of the diastereotopic relationship or positions of enantiomorphic ligands.



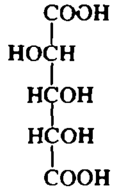
6a



6b

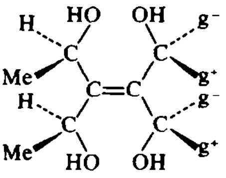


7a

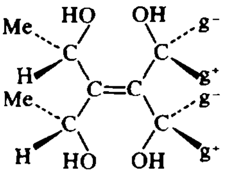


7b

The difference between the two types of centers can also be demonstrated by examination of a single molecule and by an operation conducted on the intact structure: if **8a** is reflected in the plane of the double bond to yield the enantiomer **8b**, the ligands shown on the right are unaltered whereas those on the left are inverted. According to the Prelog-Helmchen view all centers directly linked to the olefinic carbons are chiral and so must be the ligands that contain them. This would obscure a manifest difference between the two pairs of ligands which is important because it can be said that the different reaction of these pairs to reflection is responsible for the chirality of the whole: replacement of either pair of ligands by the type represented by the remaining pair results in an achiral structure.



8a



8b

3. *Sequence subrules*. As already mentioned, Prelog and Helmchen[1] have modified the sequence subrules to achieve an old[8] and desirable goal: Upon reflection of the molecule the descriptors of the chiral elements should always change (*e.g.*, $R \rightleftarrows S$) whereas those of the pseudoasymmetric elements (*e.g.*, *r*) should remain unaltered. This problem was attacked in a bold and ingenious manner. Their proposal included a redefinition of the pseudoasymmetric elements and thereby also of the chiral elements. This aspect of the revision was discussed above. It still remains to inquire whether the altered sequence subrules always serve equally well as the original ones[8] in describing configurations and in distinguishing stereoisomers.

We have examined this question by studying a number of compounds containing two or more centers linked to a pair of enantiomorphic ligands and shall discuss some of the difficulties encountered. Example **6a** presents no problem under the old rules: C-2 and C-4 are both *s*. This is an appropriate result for two reasons: (1) As C-3 is prochiral, the configurations of C-2 and C-4 should be the same; (2) Pseudoasymmetric centers that lie across a plane of symmetry should receive identical configurational descriptors. As discussed above, Prelog and Helmchen have reclassified centers like C-2 and C-4 as chiral. To determine the configuration of C-2 under the revised procedures we must supplement the configurational symbols of its diastereotopic hydroxyethyl ligands by a subscript indicative of a topic relationship. The third of the new rules (1.3) appears to be the one which is applicable to this case because C-2 is bonded to a third chiral ligand containing the "chiral" center C-4. In order to use this rule we need to know the configuration of C-4 which in turn cannot be determined without knowing that of C-2. As the configurations of these chiral centers can only be either *R* or *S* we have tried to break this impass by assigning to C-4 first one and then the other of these descriptors and by testing whether only one of these assumptions can be verified. If we assume

C-4 to be *R*, C-2 is *S* ($R_R > S_R$) which would make C-4 *R* ($S_S > R_S$). If we assume C-4 to be *S*, C-2 is *R* and C-4 is *S*. As both assumptions were verified, no configurations can be deduced for either of these centers by means of Rule 1.3. The new rule 1.2 also deals with diastereotopic relationships. The triangles consisting of C-1, C-3 and either one of the two other atoms ligated to C-2 define two diastereotopic half-spaces which can be characterized by *Re* and *Si* descriptors. However, if we affix these to the conventional configurational symbols of the hydroxyethyl ligands located in these spaces, we obtain R_{Si} and S_{Re} which establishes no priority order under the applicable rule (2.1).

This second failure would leave us only with the possibility of an analysis under rule 1.1 which however does not deal with diastereotopic ligands. Its application to determining the configuration of C-2 in **6a** would have no precedent in the examples given by Prelog and Helmchen who used *Re* and *Si* half-spaces only if the defining atoms were directly linked to the center whose configuration was being determined. According to Rule 1.1, C-2 resides in the *Si* half-space defined by the three other ligands of C-3. If we use this topic descriptor not only to define the position of C-2 (as is undoubtedly proper) but also as a characteristic of its diastereotopic ligands,* C-2 has the *R* configuration ($S_{Si} > R_{Si}$) and C-4 is *S*($R_{Re} > S_{Re}$). Such a set of inverse descriptors for the two branched carbons would be consistent with their new classification as chiral centers, but would result in an anomaly of a novel type to which we already alluded when discussing this example in general terms without reference to the *R*/*S* system of specifying configurations. The groups bonded to C-3 would consist of two constitutionally alike chiral ligands with inverse configurations and two distinct achiral ligands. Such a description would be indistinguishable from the corresponding one for a pseudoasymmetric carbon atom as defined by Prelog and Helmchen. However, C-3 is not pseudoasymmetric because it cannot be isomerized by an exchange of two of its ligands. We would have to conclude that a center (not subject to strain) with four distinctly described ligands need not allow isomerism if two ligands differ in their conventional configurational symbols. The different symbols for C-2 and C-4 which are responsible for this anomaly are the products of two factors, a descriptor of configurations in the traditional sense[8] and a topic descriptor which either preserves (at C-4) or inverts (at C-2) the priority sequence established under the old rules. If both types of description were not fused into a single configurational term, but were stated individually, they would reliably inform about the possibilities of stereoisomerism as well as of steric discrimination.

If we link C-2 and C-4 of **6a** by a second carbinol group as in **9** we encounter a case where we are unable to assign any valid configurational symbols to the ring carbon atoms under the new rules although it is feasible under the old.†

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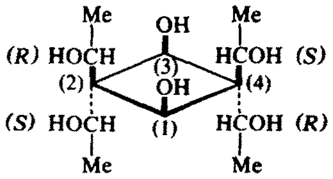
*Clarification of this issue may also be needed for a related problem of much wider concern. Prelog and Helmchen have suggested to distinguish *achiral* ligands in enantiotopic positions by *Re* and *Si* subscripts. As explained in Section 1, if this proposal is limited to enantiotopic ligands, the terminology would be of insufficient scope and therefore be greatly inferior to the *pro-R*/*pro-S* system now in use. Rule 1.2 would seem to allow an extension of *Re*/*Si* designations to diastereotopic ligands and if this is the intent one must always be certain about the identity of the triangle which defines the half-space.

A comprehensive and fully defined *Re*/*Si* system would have similar utility as the *pro-R*/*pro-S* terminology. There is no correspondence between the two types of designations because a *pro-R* may represent a *Re* or a *Si* location. Each system permits certain correlations which will be lost in the other. Unless the revision of the *R*/*S* system advocated by Prelog and Helmchen is adopted by IUPAC we think it best to retain the older terms as these have found wide acceptance.

†Prior to the Prelog–Helmchen paper the centers in the ring had to be classed as pseudoasymmetric because each has a pair of enantiomorphic ligands and two others which are either diastereomorphic or constitutionally distinct.[3a] The configurational assignments under the old rules are made as follows: C-1 and C-3 are determined first. C-1 is *r* because the higher priority ligands (*R*) at C-2 and C-4 are *seqcis* and *seqtrans* respectively, to OH at C-3. Similarly C-3 is *s*. The symbols for C-2 and C-4 follow from $R > S$ and $r > s$. The complete description is *r*, *s*, *s*, *s*, for C-1 to C-4.

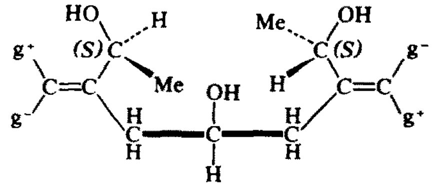
As in **6a** the side chains of C-2 or C-4 of **9** are diastereotopic and require suffixes to determine their priority order under the revised rules. However enantiotopic *Re* and *Si* half-spaces cannot serve this purpose because C-2 and its side chains is now in the *Re* half-space defined by C-4 and by the H and OH ligands of C-3 but in the *Si* half-space of the corresponding ligands of C-1. Alternatively, one may consider it appropriate to derive the suffixes for the chiral ligands at C-2 or C-4 from their geometric relationships to the preferred ligands at C-1 and C-3. This would lead to consistent priorities because both hydroxyl groups are on the same side of the ring. On this basis the preferred ligand at C-2 is R_{cis} and at C-4 S_{cis}. Giving priority to the former, C-1 is *r* and C-3 is *s*. These would lead to an *S* symbol for C-2 ($R_{cis} > S_{trans}$ and $r > s$), and *R* for C-4. At first sight these results seem appropriate because chiral centers across a plane of symmetry should carry inverse descriptors, but closer examination reveals that the assignments for the four ring carbon atoms are mutually contradictory. If one reexamines the configuration of C-1, the first points of difference between its ring ligands are the configurations of C-2 and C-4 and not the configurations in their preferred side chains. As C-2 carries a descriptor (*S*) which is inverse to that of its preferred side chain (R_{cis}) and as the analogous situation exists at C-4, the configurations of C-1 and C-3 have to be reversed. This in turn alters the assignments for C-2 and C-4, and so on. It seems that the configurations of the four ring C atoms have become indeterminate under the new rules.



9

If we have used the new rules as intended by their authors, the revisions have caused some problems which did not exist before. Admittedly, such cases are very rare but so are the anomalies which Prelog and Helmchen wanted to correct. If the elimination of these anomalies is thought to be of sufficient importance to justify a change in the subrules, we believe that this can be achieved without generating new irregularities. In all cases known to us that gave anomalous descriptors under the rules of Cahn *et al.*,[8] the subrule *seqcis* > *seqtrans* was invoked when these terms described the geometric relationship of a preferred ligand to the *R*-ligand of an enantiomorphic pair. Although this relationship changes on reflection, as illustrated by the pair **5a**, **5b**, it was treated as an achiral property under Subrule (3). We would suggest to view it as being of the same type as the *R*/*S* difference from which it is derived and to proceed according to Subrule (4) if the ligands to be compared are diastereomorphic and to use Subrule (5) if they are enantiomorphic.

A typical case is shown in example **10** which we discussed several years ago with Dr. Cahn. (To assign symbols we shall assume that the + superscripts signify (*R*)-configurations). Under the official rules,[2,8] the central atom which is indubitably chiral is *S*(*seqcis* > *seqtrans*) and remains *S* on reflection. The isomerism of the double bonds is of the unusual type discussed above. We suggest indicating this by the new symbols *seqCis* and *seqTrans* which are to express that such symbols interconvert on reflection* and that Subrule (3) does not apply to them.



10

Subrule (4) would be extended to include additional pairs containing the new symbols. Specifically, the combinations *R*, *seqCis* and *S*, *seqTrans* would constitute new like pairs which would have priority over the unlike pairs *R*, *seqTrans* and *S*, *seqCis*. (*SeqCis* and *M* or *seqTrans* and *P* would constitute other like pairs.) Subrule (5), applicable only to enantiomorphic ligands, would contain the additional priority *seqCis* > *seqTrans*. As the unsaturated ligands of **10** are diastereomorphic, Subrule (4) applies. The ligand on the right with two like descriptors, *seqTrans* and *S* (hydroxyethyl group), has priority over the other (*seqCis* and *S*). The central atom, therefore, is *R* and becomes *S* on reflection. If we replace the hydroxyethyl ligand on the right by its (*R*)-enantiomorph, the complete unsaturated ligands are enantiomorphic. In the outward exploration from the center along the bonds, the first steric descriptor reached is that of the double bond. (Although the C-C(O) bond has priority over C=C, only the latter carries a steric descriptor.†) The pseudoasymmetric center, therefore, is *s* (Subrule (5), *seqCis* > *seqTrans*).

This revision would leave the (appropriate) description of **9** (*r*, *s*, *s*, *s*) unchanged and yield (*s*, *r*, *r*, *r*) for the diastereomer that results from inversion at C-1, thus correcting the anomalous description (*s*, *s*, *r*, *r*) derived under the official rules. Our revision would not allow the assignment of configurations to a third diastereomer that results from inversions at both C-1 and C-4 (type **22** of our previous paper[3a]) although it can be described under the Prelog–Helmchen system. We cannot regard our failure as a serious disadvantage relative to their proposals as the latter seem to be inapplicable to **9**.

Our revised rules, therefore, also appear to eliminate the old anomalies but leave the existing definitions of the chiral and pseudoasymmetric center unchanged. As topic differences and descriptors do not enter into the determination of the configurational symbols, no new anomalies would be created and very few descriptions would have to be altered. If these proposals should be favored by the appropriate international body, they would preserve, we believe, much of the simplicity which constituted one of the prime virtues of the original proposals of Cahn *et al.*

Any contribution by Professor Prelog to

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*If the *cis*/*trans* relationship exists between two pairs of chiral ligands (*R*, *S* and *R*′, *S*′), it does not change on reflection and is indicated by *seqcis*/*seqtrans* as before. Example **8a** is not of this type but *seqTrans* (*R trans* to *r*, if g^+ has the (*R*)-configuration). As the symbols used to indicate the *seqcis*/*seqtrans* relationship at ordinary double bonds (*Z* and *E*)[14] are unfortunately written with capital letters and as it is probably too late to change this, some other form of differentiation (perhaps (Z^*) for *seqCis*) might be used if our proposals should be adopted.

†One can conceive of some compounds, where the association of the new descriptors with a bond (or atom) is less obvious. It is not the purpose of this brief outline to give complete specifications of procedure, especially as no instructions are available about solving closely related problems in the application of the existing Subrules (4) and (5).

stereochemical theory has a strong claim for general adoption. We, therefore, thought it important to bring out that, at least in our view, his new proposals constitute not just a minor rephrasing of existing definitions but would require major changes in the ways in which one judges certain steric relationships. Especially as our views on these issues differ from those of Prelog and Helmchen, we want to stress our great indebtedness to Professor Prelog for the stimulation he has given us over many years. His contributions to the sequence rule, his lectures, and his comments expressed in conversations and in correspondence have initiated or modified our own studies in numerous ways.

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Note added in proof:

The full benefits of the modification of the sequence subrules which we have suggested are realized only if the systematic names of enantiomers differ exclusively in the descriptors (such as *R*, Z^*, *M*) that specify the configurations of the pherochiral elements (or units)[3] of stereoisomerism. This requires a numbering system different from the one given in rule E-2.23[2] and further expanded by us.[12] We have, therefore, formulated a new set of numbering rules, which appears to meet the stated objective as well as those of our earlier paper,[12] and shall make copies available on request. The numbering shown in this paper does not always conform to this revised system.

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