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The CIP Sequence Rules: Analysis and Proposal for a Revision

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Abstract: In spite of their value and wide usage the Cahn, Ingold and Prelog (CIP) Sequence Rules have some deficiencies. In particular incompleteness, inconsistency and ambiguity can arise in their application to complex molecules. Therefore, a complete analysis of the CIP Sequence Rules has been made and modified rules are proposed.

INTRODUCTION

The CIP (Cahn, Ingold and Prelog) System[1-5] is a set of conventions through which the absolute configuration of molecules containing stereogenic units can be described compactly enough to allow its inclusion in the name of the compound. The system has been widely accepted by chemists due to its compactness and applicability to most of the molecules.

The procedure to derive a CIP descriptor can be summarised in the followings three steps:
i) Factorisation of the complex stereomodel assigned to the molecule into stereogenic units[6];
ii) Determination of the ranking of the ligands around each stereogenic unit;
iii) Determination of a descriptor for each stereogenic unit.

The basis of the system is provided by the conventions proposed in the first publication[1], in 1951, and several modifications and extensions have been made since then to achieve greater generality[2, 4, 5].

An analysis of the evolution of the CIP System shows that most of this development was made in a pragmatic way, that is proposing rules to cover all known cases and devising modifications or extensions to overcome the deficiencies pointed out in the light of experience.

Accumulated experience, and particularly the work carried out on the adaptation of the CIP System to computer use, demonstrated the need for a revision and showed that it was necessary to deal in a systematic way with questions which earlier had been answered on a pragmatic basis only. This revision resulted in a new version of the CIP System (1982 version)[5] of which the main improvements are the introduction of the concept of hierarchical digraphs and the methodology developed for the analysis of cyclic molecules.

Although the 1982 revision[5] has considerably improved the applicability and clarity of the system, deficiencies have already been identified in some aspects of this revised version, namely in steps *i)* [7] and *ii)* [8]. In the course of the implementation of the CIP System for computer use[9] some limitations of the applicability, consistency with the theory and generality of the 1982 Sequence Rules were also detected by us. The deficiencies encountered will be discussed below and extensions or modifications to the CIP Sequence Rules will be proposed to overcome them.

ORDERING OF THE LIGANDS - THE SEQUENCE RULES

The ordering of the ligands has a fundamental role in the procedure to derive a CIP descriptor and can be considered the most complex step. Although simple molecules are easily treated, for the more complex cases difficulties arise and the general case is extremely intricate.

In the 1982 paper on the CIP system[5] the meaning of the term "ligand" was clarified, even in complex cyclic molecules, by the introduction of hierarchical digraphs. These are equivalent acyclic structures into which monodentate, polydentate and cyclic ligands must be converted for analysis and comparison. A set of rules must be used to convert a stereocenter and its ligands into an hierarchical digraph of the whole stereogenic unit[4,5] without redundancy or ambiguity.

To describe the absolute configuration of a stereogenic unit it is necessary to determine the rank of its ligands, represented by the hierarchical digraphs, by comparing their properties. Since ligands represented by the hierarchical digraphs can differ in several properties and the rank of ligands must be determined by a single property, this requires a clear-cut hierarchy of the relevant properties, an unambiguous order in which they are compared (Fig. 1) and a methodology for their comparison. All these must be contained in the CIP Sequence Rules.

Constitutional (material and topological)	Reflection - invariant
Geometrical (diastereomorphic)	
Topographical (enantiomorphic)	Reflection - variant

Fig. 1. Hierarchical order of ligand properties[5].

Sequence Rules (1982) [5]

1 - Higher atomic number precedes lower;

2 - Higher atomic mass number precedes lower;

3 - When two ligands differ only in that one has an atom or atom-group of higher rank in a *cis*-, and the other in a *trans*-position to the core of the stereogenic unit, then preference is given to the former. (This rule is restricted to ligands which differ in *cis-trans* isomerism of planar tetraligant atoms or double bonds).

4 - When two ligands have different descriptor pairs, then the one with the first-chosen *like* descriptor-pair has priority over one with a corresponding *unlike* descriptor-pair. *Like* descriptor-pairs are: *RR, SS, RRe, SSi, ReRe, SiSi, MM*, and *PP*, and also by corollary *RM, SP, ReM, SiP*. *Unlike* pairs are: *RS, ReSi, SRe, RSi, MP*; and by corollary *PR, SM, ReP*, and *SiM*.
Methodology for pairing descriptors:
For each ligand the descriptor chosen as first (highest ranked descriptor) is paired with all the remaining descriptors, being the hierarchical rank of the descriptor pairs given by the rank of the second descriptor in the pair.

5- a) A ligand with descriptor *R* or *M* has priority over its enantiomorph with descriptor *S* or *P*.
b) A ligand with descriptor *r* has preference over one with descriptor *s*.

A rule was proposed[5] whose rank was not defined:
"Chiral stereogenic units precede pseudoasymmetric stereogenic units and these precede non-stereogenic units."

ANALYSIS OF THE SEQUENCE RULES

In the following section a complete description will be made of the cases, either detected by us or by others, where the CIP Sequence Rules[5] fail and suggestions will be presented for supplements or modifications of the rules to remove these shortcomings.

Sequence Rules 1 and 2

In the majority of cases the relative rank of ligands is established on the basis of material differences, i.e. by application of Rules 1 and 2. In the 1982 revision of the CIP System[5] it was considered that these two rules were the solid basis on which the CIP system rests and there was no reason for revising them. However some examples[8] have already been encountered which show that these rules do not correctly detect all constitutional differences. One of these is presented in Fig. 2.

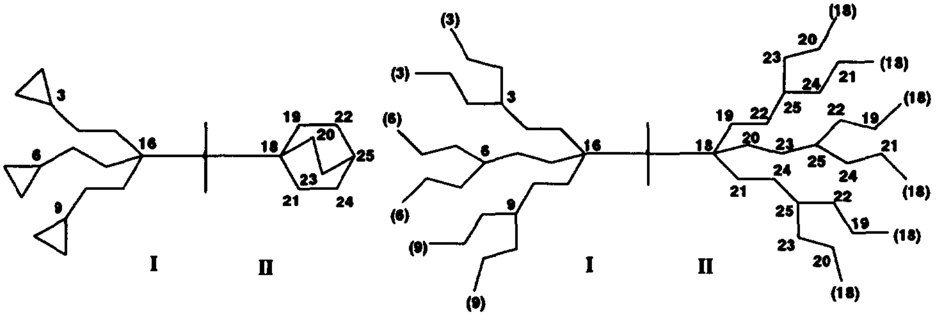


Fig. 2. Two constitutionally different ligands (I and II) whose hierarchical digraphs cannot be distinguished by the 1982 CIP Sequence Rules [8].

A new supplement to Rule 1, based on the comparison of the characteristics of the nodes in the hierarchical digraph, has already been proposed by Custer[8] to guarantee constitutional completeness. This addition states that:

"*A duplicated atom with its predecessor node having the same label closer to the root ranks higher than a duplicated atom with its predecessor node having the same label farther from the root, which rank higher than any non-duplicated-atom-node.*".

Sequence Rule 3

Modification of Rule 3. In the 1982 revision of the CIP System[5] a fundamental modification of this rule was made: the domain of application was restricted to planar tetraligant atoms or double bonds and also the statement was modified in order to cover the case of molecules in which assignment of *seqcis* or *seqtrans*[10] to double bonds in the ligands was not possible, even though these double bonds differ in cis-trans isomerism (Fig. 3). However the same aims could be achieved without this modification of the rule.

If, for a clear analysis of the ligands, they must be converted into hierarchical digraphs, then the comparison of the ligands must always be done considering the hierarchical digraph, and not the real ligand. The concept of auxiliary descriptor[5] was introduced for this purpose for chiral and pseudoasymmetric centres in the 1982 revision of the CIP System. These auxiliary descriptors, usually different from the definitive descriptors, are indispensable when dealing with certain cyclic molecules. This concept can be extended to double bonds, and in this case, molecules such as the one in Fig. 3 could be specified using the 1966 Rule 3[4]. This implies that it was not necessary to change Rule 3, but only to unify the methodology used for the analysis.

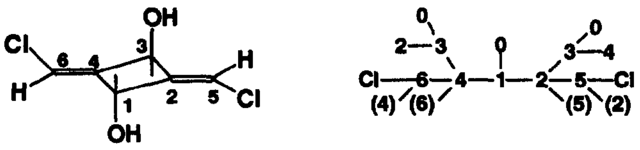
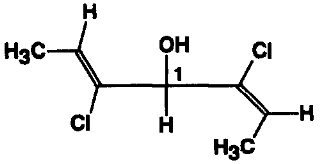


Fig. 3. Centres 1 and 3 have two ligands whose ordering according to Rule 3 of the 1966 version of the CIP System is impossible[5].

While using 1966 Rule 3 for the comparison of the ligands around the stereogenic centre 1 in the molecule in Fig. 3, a problem arises when the ligands on atoms 2 and 4 are compared to specify the double bonds 2=5 and 4=6. If the hierarchical digraph representing the ligands of the stereogenic centre 1 is used in this comparison, the difference between the ligands is quite clear and the auxiliary descriptor *seqcis*$_0$ is assigned to double bond 2=5, *seqtrans*$_0$ to double bond 4=6 and so the descriptor *R* can be assigned to the chiral centre 1.

This method has the advantage of leaving unchanged all the descriptors derived using the 1966 Rule 3 such as the one in Fig. 4, which is considered by Prelog and Helmchen[5] a serious constraint in any kind of revision of the CIP Rules.



1966 Sequence Rules - S
1982 Sequence Rules - R
Our proposal for rule 3 - S

Fig. 4. Stereogenic centre whose specification by the 1966 CIP Rules and by the 1982 revised Rules gives different descriptors [5]. The specification using the methodology proposed in this paper does not change the descriptor assigned by the 1966 Rules.

Thus, it is proposed that the statement of Rule 3 must remain the same as it was in 1966 and the methodology of application must be extended in a way consistent with the methodology used for Rules 4 and 5, as described above. This proposal has several advantages:

i) molecules such as in Fig. 3 can be specified;
ii) all descriptors attributed using the 1966 CIP Rules remain unchanged;
iii) a uniform methodology for applying Rules 3, 4 and 5 is used improving the logical unity of the Sequence Rule procedure.

Comparison of geometrically enantiomorphic double bonds. Stereogenic double bonds can be divided into two different groups: geometrically diastereomorphic double bonds and geometrically enantiomorphic double bonds[5,11,12,13]. In the second group the descriptors assigned in the specification of the double bonds describe the geometric relationship of a preferred ligand to the *R*-ligand of an enantiomorphic pair, as this relationship changes on reflection so do the descriptors assigned to the double bonds, whilst in the first group they remain unchanged on reflection. As pointed out by Hirschmann and Hanson in 1974[11] Rule 3 can only be applied to geometrically diastereomorphic double bonds, and cannot be applied to geometrically enantiomorphic double bonds without resulting in inconsistencies with the theory.

In the molecule in Fig. 5, following the CIP Sequence Rules, the descriptor *S* is attributed to atom 1, a centre lying in a symmetry plane of the molecule. This is inconsistent with the fundamental statement of the CIP System that:

"*Stereogenic units denoted by reflection-variant terms R or S can never lie in a symmetry plane. The latter can only accommodate units with reflection-invariant descriptors r or s.*"[5]

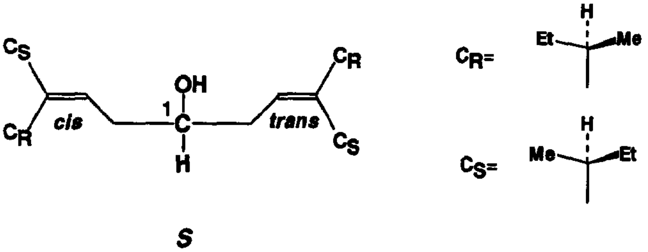


Fig. 5. Stereogenic centre lying in a symmetry plane which is specified, according to the CIP System, by a reflection-variant descriptor. C_R and C_S can be the groups above or any pair of enantiomorphic groups.

Furthermore, in Fig. 6, the same descriptor (*R*) is attributed by the Sequence Rules to the chiral centre 1 in molecule A (which does not lie in a symmetry plane) and to the corresponding chiral centre in the enantiomorphic molecule B, instead of opposite descriptors as prescribed by the theory.

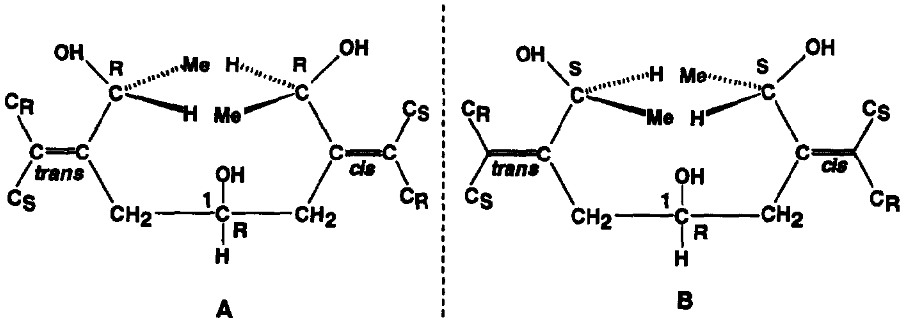


Fig. 6. Chiral centres whose descriptors, as assigned by the 1982 revised CIP System, do not change on reflection[11]. C_R and C_S as in Fig. 5.

In order to deal with these molecules Rule 4 needs to be extended to include additional pairs of *like* and *unlike* descriptors^{11}, specifically the combinations *RseqCis*^{14}, *SseqTrans*, *MseqCis*, *PseqTrans* would constitute new *like* pairs which would have priority over the *unlike* pairs *RseqTrans*, *SseqCis*, *PseqCis*, *MseqTrans*. Also Rule 5 needs to be extended^{11} to contain the additional priority *seqCis>seqTrans*.

Comparison of stereogenic and non-stereogenic units. It is possible to conceive molecules, such as the ones in Fig. 7, in which a double bond that is stereogenic (presenting *cis-trans* isomerism) must be compared with a non stereogenic double bond. These cases are not considered by the 1982 version of the CIP Rules, as Rule 3 does not allow the ordering of the ligands on the basis of this difference. It is possible to order these ligands using other differences: the comparison of other double bonds in the ligands for molecule A (Rule 3) and the relationship between the chiral centres for molecules B and C (Rule 4). However this is not consistent with the philosophy behind the rules, that the ordering must be made by the first difference encountered.

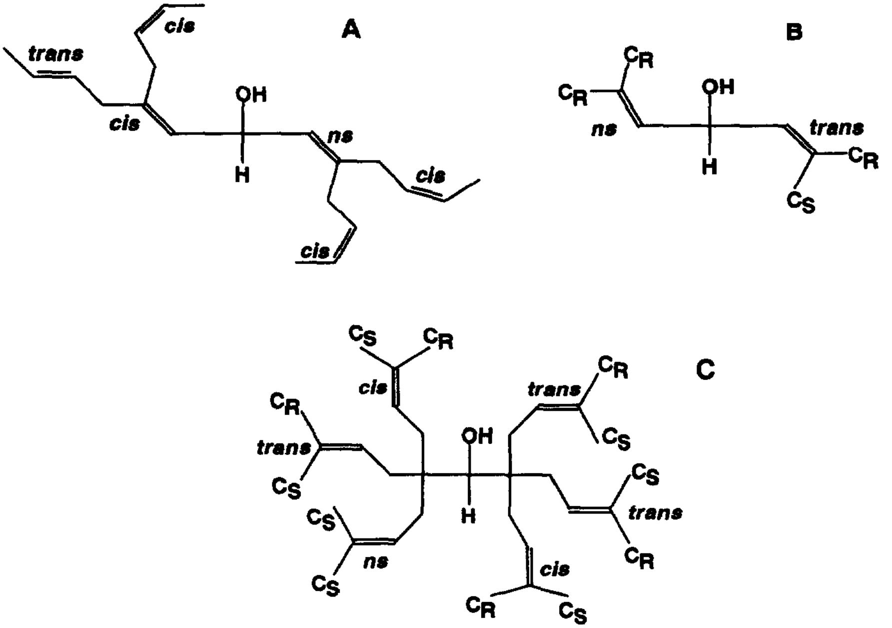


Fig. 7. Stereogenic units whose ligands cannot be ordered by the comparison of the double bonds they contain in spite of the differences between them. ns - non-stereogenic; C_R and C_S as in Fig. 5

If Rule 3 is restricted to the comparison of geometrically diastereomorphic stereogenic units the comparison of cases B and C would have to be done by Rules 4 and 5. In the 1982 revision of the Sequence Rules^{5} a new sub-rule was proposed stating that three-dimensional stereogenic units have preference over three-dimensional non-stereogenic units. This can be considered a first sub-rule of Rule 4 and can be further extended to cover planar stereogenic units, allowing differentiation of ligands in cases such as the molecules in Fig. 7, using the first difference encountered.

Case A requires an extension of Rule 3 to cover comparison of stereogenic and non-stereogenic units, in a way similar to Rule 4 to preserve the logical unity of the Sequence Rules. However, in this case it is not essential to have a separate sub-rule but it is sufficient to extend Rule 3 to achieve the desired aims whilst maintaining the simplicity of the comparison.

Proposal for Rule 3. Considering all the above, the statement proposed for Rule 3 is:

Rule 3 - *seqcis* stereogenic units precede *seqtrans* stereogenic units and these precede non-stereogenic units (*seqcis* > *seqtrans* > non-stereogenic).

The application of this rule is restricted to geometrically diastereomorphic planar tetraligant atoms and double bonds[11], i.e. those in which the ordering of the relevant pairs of ligands for the assignment of auxiliary descriptors can be done by Rules 1 to 4.

Sequence Rules 4 and 5

Comparison of stereogenic and non-stereogenic units. Rules 4 and 5 will be considered simultaneously. However, before starting the discussion of them, it should be noted that in the paper on the 1982 revision of the CIP rules[5] Prelog and Helmchen proposed that chiral stereogenic units should precede pseudoasymmetric stereogenic units and those should precede non stereogenic units. However, in spite of the importance they attach to the order of use of the rules[4,5], they never state explicitly where in the sequence of the application of the rules this comparison should be made. Also this rule is not mentioned at the end of the paper where the new revised rules are presented[5].

In order to avoid any ambiguity in the comparison of the ligands it is essential to establish the hierarchical order for the application of this rule. It is considered, as proposed by other authors[8], that it should be considered the first sub-rule of Rule 4.

This sub-rule must be extended further to cover the comparison of ligands with geometrically enantiomorphic two-dimensional stereogenic units that can be juxtaposed with ligands without a corresponding stereogenic unit. The same precedence should be kept, i.e. stereogenic precedes non-stereogenic. The complete statement proposed in the present paper for this sub-rule 4-a) is:

"Chiral stereogenic units precede pseudoasymmetric stereogenic units and these precede non-stereogenic units. Geometrically enantiomorphic two-dimensional stereogenic units precede two-dimensional non-stereogenic units."

Comparison of pseudoasymmetric stereogenic units. Compare the statement of Rules 4 and 5 in the 1966 version and in the 1982 version of the Sequence Rules:

1966 Version[4]:

Rule 4 - *Like* pair *RR* or *SS* precedes *unlike RS* or *SR*; and *MM* or *PP* precedes *MP* or *PM*; and *RM* or *SP* precedes *RP* or *SM*; and *MR* or *PS* precedes *MS* or *PR*; also *r* precedes *s*.

Rule 5 - *R* precedes *S*; and *M* precedes *P*.

1982 Version[5]:

Rule 4 - When two ligands have different descriptor pairs, then the one with the first-chosen *like* descriptor-pair has priority over one with a corresponding *unlike* descriptor-pair. *Like* descriptor-pairs are: *RR, SS, RRe, SSi, ReRe, SiSi, MM,* and *PP,* and also by corollary *RM, SP, ReM, SiP*. *Unlike* pairs are: *RS, ReSi, SRe, ReSi, MP*; and by corollary *RP, SM, ReP,* and *SiM*.

Rule 5 - A ligand with descriptor *R* or *M* has priority over its enantiomorph with descriptor *S* or *P*. A ligand with descriptor *r* has preference over one with descriptor *s*.

Notice that the sub-rule "*r* precedes *s*" was included in Rule 4 in 1966 and is included in Rule 5 in 1982. The authors justify this [5] by saying that the sub-rule "*r* precedes *s*" can be applied only after Rule 5 has been used to determine descriptors *r* or *s* and that the precept that each rule must be employed exhaustively before proceeding to the next one should be kept.

The rule *r>s* is based on a geometrical difference and the rule *R>S* is based on a topographical difference, in spite of being stated in all papers on the CIP System[1-5], particularly in the last one[5], that it is essential to examine the relevant properties of the ligands in the hierarchical sequence outlined, putting the rule *r>s* as Rule 5-b) the hierarchical sequence is not maintained.

Such a modification is not valid, as it will introduce ambiguity in the specification of stereogenic units (Fig. 8), and also it is not necessary. If a chiral stereogenic unit has some pseudoasymmetric stereogenic units in its ligands and these are responsible for the difference of two or more of the ligands, all the descriptors to be used in Rules 4 and 5 must be derived from the hierarchical digraph as auxiliary descriptors in order to specify the chiral stereogenic unit. In this process feasibility is the sole condition prescribing the ordering which different stereogenic centres are to be assigned [4].

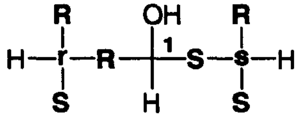


Fig. 8 - Hierarchical digraph corresponding to a molecule in which the specification of centre 1 can be ambiguous using the 1982 version of the Sequence Rules.
How is centre 1 specified using sub-rule R>S or sub-rule r>s (the correct way)?

It is important to keep in mind that the Sequence Rules are used to compare ligands (hierarchical digraphs), and that ligand comparison and the ordering which different stereogenic units are to be assigned are completely different matters that can, and must, be kept independent. It is considered, as by other authors [8], that sub-rule *r>s* must be a sub-rule of Rule 4 as it was before 1982. To be complete this sub-rule must include also *p>m*.

Definition of the like and unlike descriptor pairs. The introduction of the pairs of descriptors *ReRe*, *SiSi*, *ReSi* and *SiRe* in Rule 4 is not clear. Planar diastereomorphic stereogenic units can be considered as a combination of two two-dimensional chiral units and can be classified as a combination of the descriptors *ReRe/SiSi=seqtrans* and *ReSi/SiRe=seqcis*. For practical and historical reasons the existence of a particular rule concerned with the comparison of geometrically diastereomorphic double bonds and planar tetraligant atoms is justified and these double bonds are compared in Rule 3, and exactly in the opposite order. These pairs of descriptors are therefore redundant in Rule 4.

The inclusion of the pairs of descriptors *RRe*, *SSi*, *ReM*, *SiP*, *SRe*, *SSi*, *ReP* and *SiM* in the statement of Rule 4 is also dispensable. These pairs of descriptors can be useful, for example, for the unambiguous specification of the steric course of asymmetric synthesis[15] but not for the comparison of ligands in order to specify stereogenic units. In fact this comparison is made in a three dimensional space in which the two-dimensional chirality is lost, except for:

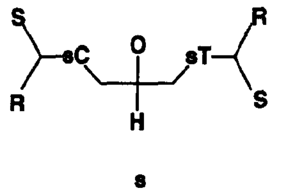
i) the diastereomorphic combinations of these descriptors (referred to in the previous paragraph);

ii) the topic relationships of ligands or half-spaces resulting from the division of the space by the plane containing the molecule, and the consequent distinction of the faces of two-dimensional stereogenic units.
However these last topic relationships are not used to compare ligands[5].

Comparison of geometrically enantiomorphic double bonds. It is necessary to develop a method to compare the pairs formed with the geometrically enantiomorphic double bonds, that is the *like* pairs *seqCisseqCis*, *seqTransseqTrans*, *RseqCis*, *SseqTrans*, *MseqCis* and *PseqTrans* and the *unlike* pairs *seqCisseqTrans*, *RseqTrans*, *SseqCis*, *PseqCis* and *MseqTrans*. It is proposed that the descriptor assigned to the double bonds should be associated in the digraph with the first node corresponding to the atoms involved in the double bond, and then, that the existing methodology should be used to compare nodes to which reflection-variant descriptors have been assigned. Obviously Rule 5 would also include *seqCis*>*seqTrans* and the methodology for comparison would be the same.

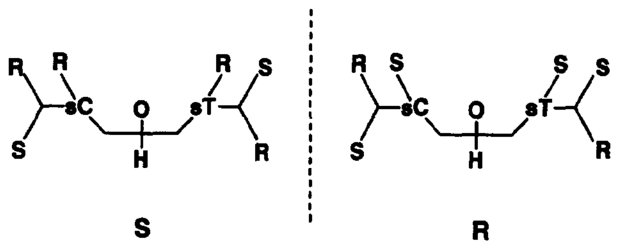
Fig. 9 represents second hierarchical digraphs for molecules in Fig. 5 and 6, derived from the first ones by replacing the specified stereogenic units by the auxiliary descriptors. Considering these hierarchical digraphs and the modified rule that was proposed, the descriptors attributed to the controversial centres of the molecules referred to in Fig. 5 and 6 are now consistent with the theory (*s* for the molecule in Fig. 5 and *R* and *S* for the two enantiomorphic molecules in Fig. 6).

a) Hierarchical digraph corresponding to molecule in Fig. 5



Ordering of the ligands made by rule 5
seqCis > seqTrans

b) Hierarchical digraph corresponding to molecules in Fig. 6



Ordering of the ligands made by rule 4

Fig. 9. Specification of the controversial centres of molecules in Fig. 5 and 6 using the proposed rules and methodology. The descriptors assigned are now consistent with the theory. sT=seqTrans; sC=seqCis

Methodology for the ranking of descriptor pairs. Considering Rule 4 some problems were also pointed out by Custer[8] concerned with the methodology for the comparison of the different pairs of descriptors.

In the methodology proposed by Prelog and Helmchen[5] the hierarchical rank of the descriptors pairs is given by the rank of the second descriptor in the pair. This does not allow the ordering of two pairs of descriptors in which the second descriptors have the same priority. A methodology for the ranking of these cases was proposed[8] which is based on the relationship, in the digraph, between the nodes corresponding to the descriptors. Priority is given to the pair with the lower rank of the least common ancestor in the graph[16].

Proposal for Sequence Rules 4 and 5. Considering all stated above, the following is proposed for Rules 4 and 5:

Rule 4-a) Chiral stereogenic units precede pseudoasymmetric stereogenic units and these precede non-stereogenic units.
Geometrically enantiomorphic two-dimensional stereogenic units precede two-dimensional non-stereogenic units.

b) When two ligands have different descriptor pairs, then the one with the first-chosen *like* descriptor-pair has priority over one with a corresponding *unlike* descriptor-pair. *Like* descriptor-pairs are: *RR, SS, MM, PP, seqCisseqCis, seqTransseqTrans, RseqCis, SseqTrans, MseqCis* and *PseqTrans, RM, SP*. *Unlike* pairs are: *RS, MP, RP, SM, seqCisseqTrans, RseqTrans, SseqCis, PseqCis* and *MseqTrans*.
Methodology for pairing descriptors:
The descriptor assigned to geometrically enantiomorphic double bonds should be associated in the digraph with the first node corresponding to the atoms involved in the double bond.
For each ligand the descriptor chosen as first (highest ranked descriptor) is paired with all the remaining descriptors. The following characteristics determine the hierarchical rank of the pairs of descriptors:
i) Higher rank of the second descriptor in the pair;
ii) Lower rank of the least common ancestor in the graph[8].

c) *r* precedes *s* and *p* precedes *m*.

Rule 5 - A ligand with descriptors *R*, *M* or *seqCis* has priority over its enantiomorph with descriptor *S*, *P* or *seqTrans*.

CONCLUSIONS

The 1982 version of the CIP System[5] allows specification of the great majority of the stereogenic units found in organic chemistry and constitutes a very important improvement of the CIP System. The main successes of this revision are the introduction of the concept of hierarchical digraphs and the methodology developed for the analysis of cyclic molecules. In spite of their wide applicability it is possible to conceive molecules whose specification is impossible, ambiguous or inconsistent with the theory. In the present paper some extensions and modifications to the CIP rules were proposed to solve coherently omissions and ambiguities in the 1982 revised Sequence Rules.

The proposed rules are presented below and for clarity the additions and modifications to the 1982 CIP Sequence Rules appear in bold, and their authors are explicitly referenced.

Proposed revised Sequence Rules:

1 - a) Higher atomic number precedes lower;
b) **A duplicated atom, with its predecessor node having the same label closer to the root, ranks higher than a duplicated atom, with its predecessor node having the same label farther from the root, which ranks higher than any non-duplicated-atom-node.** (Proposed by Custer[8])

2 - Higher atomic mass number precedes lower;

3 - ***seqcis* stereogenic units precede *seqtrans* stereogenic units and these precede non - stereogenic units (*seqcis* > *seqtrans* > *non-stereogenic*).** (Proposed by the authors)
The domain of application of this rule is restricted to **geometrically diastereomorphic** planar tetraligant atoms and double bonds. **All cases involving geometrically diastereomorphic two-dimensional stereogenic units are considered in Rules 4 and 5.** (Proposed by Hirschmann and Hanson [11])

4 - a) **Chiral stereogenic units precede pseudoasymmetric stereogenic units and these precede non-stereogenic units.** (Sub-rule originally proposed by Prelog and Helmchen[5], but their inclusion as first sub-rule of Rule 4 was proposed by Custer [8]).
Geometrically enantiomorphic two-dimensional stereogenic units precede two-dimensional non-stereogenic units. (Proposed by the authors)

b) When two ligands have different descriptor pairs, then the one with the first-chosen *like* descriptor-pair has priority over the one with a corresponding *unlike* descriptor-pair. *Like* descriptor-pairs are: *RR, SS, MM, PP, seqCisseqCis, seqTransseqTrans, RseqCis, SseqTrans, MseqCis* and *PseqTrans, RM, SP*. *Unlike* pairs are: *RS, MP, RP, SM, seqCisseqTrans, RseqTrans, SseqCis, PseqCis* and *MseqTrans*.
(Pairs *RRe, SSi, ReRe, SiSi, ReM, SiP, ReSi, SRe, RSi, ReP* and *SiM* were removed from this rule.) (Proposed by the authors)
Methodology for pairing descriptors:
The descriptor assigned to geometrically enantiomorphic double bonds should be associated in the digraph with the first node corresponding to the atoms involved in the double bond. (Proposed by the authors)
For each ligand the descriptor chosen as first (highest ranked descriptor) is paired with all the remaining descriptors. The following characteristics determine the hierarchical rank of the pairs of descriptors:
i) Higher rank of the second descriptor in the pair;
ii) **Lower rank of the least common ancestor in the graph.** (Proposed by Custer[8])

c) r precedes s and **p precedes m.** (Proposed by the authors)
(The re-inclusion of this sub-rule in Rule 4 was proposed by Custer[8])

5 - A ligand with descriptor R, M or **seqCis** has priority over its enantiomorph with descriptor S, P or **seqTrans.** (Proposed by Hirschmann and Hanson[11]).

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