

# Response to the Comment on “Exhaustive Generation of Organic Isomers. 5. Unsaturated Optical and Geometrical Stereoisomers and a New CIP Subrule”

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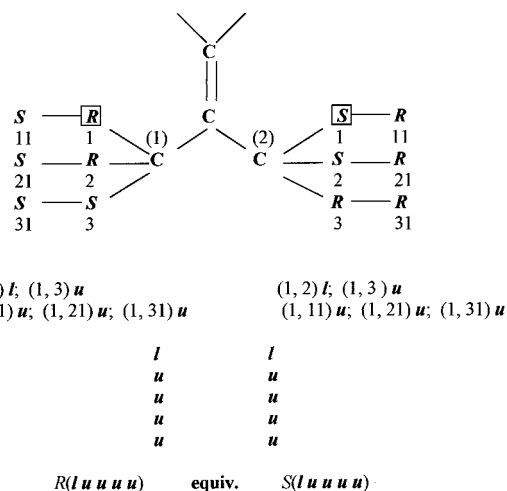
The proposition of a new criterion for ranking different ligand structures but equivalent to each other according to Cahn–Ingold–Prelog (CIP) rules was done within the development of a stereoisomer generation program.<sup>1</sup> The new criterion is applied one step after CIP rules, and only if the analysis of ligands according to those rules gives, as a result, no precedence to any one of them. Ligands containing the same topology and stereogenic units are the targets considered.

Let us analyze the application of CIP rules for molecule A (Figure 1). This molecule has two ligands with identical composition that cannot be ranked according to CIP rules; they have a priority equivalence and hence no precedence between them. Note that carbon atoms 1 and 2 are achiral. For a better understanding a detailed analysis for this example is presented.

Known CIP procedure establishes an exhaustive and sequential application of five rules for ranking ligands.<sup>2</sup> In the present case rule 1 (a higher atomic number precedes a lower atomic number) gives no precedence. Rules 2 and 3 related to atomic mass number and to ligands which differ in cis–trans isomerism are not applicable. Rule 4 related to ligands that contain chiral stereogenic units and different descriptor pairs establishes that the first-chosen *like* descriptor pair (*RR*, *SS*) precedes the corresponding *unlike* descriptor pair (*RS*, *SR*). The methodology for pairing descriptors uses as reference the highest ranked descriptor which is paired with all the remaining descriptors. Pairs of descriptors are formed and compared until any difference is encountered or all pairs are compared.

In molecule A the ligand 1 highest ranked descriptor is *R* because it occurs twice<sup>2</sup> in the highest ranked triad of this ligand structure. For the same reason the highest ranked descriptor of ligand 2 is *S*.

The pairing descriptor procedure for each ligand is carried out in an established ranking order as shown in Figure 1: for the first triad comparisons (1, 2) and (1, 3) are carried out first and then for the next sphere comparisons (1, 11), (1, 21), and (1, 31). Results show that both ligands are equivalent because *R(luuuu)* is equivalent to *S(luuuu)*. Comparisons carried out with the second highest-ranked descriptors, through the same procedure (comparing in the



**Figure 1.** Molecule A and application of CIP rules for ranking ligands 1 and 2.

order (2, 3), (2, 1), (2, 21), (2, 31), and (2, 11)), give *R(uluuu)* equivalent with *S(uluuu)*. Even comparison of ligands using as reference the descriptors with the lowest rank (in the order (3, 1), (3, 2), (3, 31), (3, 11), and (3, 21)) gives the same result because *S(uulll)* is equivalent to *R(uulll)*.

Finally, rule 5 (which establishes that *R* precedes *S*; and *M* precedes *P*) should be applied. As it is known,<sup>2</sup> this rule is used to determine reflection-invariant descriptors *r* or *s* characterizing “pseudoasymmetric” stereogenic units. A special case is that of stereogenic units with ligands that differ only by the presence of two different pseudoasymmetric stereogenic atoms. The CIP system recognizes such chirality elements only after all the other stereogenic atoms have been specified by applying rules 1–5. There are many examples where subrule of rule 4, *r* precedes *s*, can be applied only after rule 5 has been used for determining descriptors *r* or *s*. Also some examples show that after assignment of these descriptors, *r* or *s*, further analysis could allow for the appearance of pairs of reflection variant descriptors *R* or *S*. In this case subsequent reapplication of rule 4 has to be done (see for instance Figure 21b of ref 2). What is important to keep in mind is that rule 5 is applied to determine descriptors *r* or *s* for pseudoasymmetric stereogenic atoms. Molecule A has no such elements on it. When pairs of reflection-variant descriptors *R* or *S* are involved, then rule 4 has to be used. As it was shown application of this rule led to equivalent ligands. So, CIP rules do not allow ranking of ligands 1 and 2 of molecule A.

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At this point application of our proposition<sup>1</sup> is made. For doing that, a numerical value of 1 is given to the *S* configuration and a value of 2 to the *R* configuration. Then, the sum of numerical descriptor values for sons coming from the same father are in turn considered. The first pair of sons of ligand 1 is *R*–*S*, and its numerical descriptor value is 3. The same happens for the second pair. The third pair in this case is *S*–*S*, and its numerical descriptor value is 2. The ordering of these numbers gives a sublevel chiral value of 233 for ligand 1. By applying the same procedure to ligand 2, a final sublevel chiral value of 334 is obtained. From these two values it is concluded that ligand 2 precedes ligand 1 according to our proposition because 334 > 233.

In relation to the Comment by Brecher, the molecule in Figure 1 of Brecher's Comment is not the best example for showing the applicability of the new criterion explained before because of the arguments given in the Comment. However, it should remain clear that the purpose of the paper was not to do any modification on existing CIP rules nor on

its application procedure, and in this way it is not correct to ensure that molecule ligands in Figure 2 of Brecher's Comment could be ranked according to our point of view. That molecule is clearly ranked according to CIP rules,<sup>2</sup> and it does not need any further criteria for assigning proper ligand precedences.

A proper and careful application of CIP rules, as was shown before, indicates that the new subrule proposed by us remains entirely valid, and therefore it can give a remedy for cases (as shown in Figure 1) where CIP rules do not offer a definitive solution.

#### REFERENCES AND NOTES

- (1) Contreras, M. L.; Trevisiol, G. M.; Alvarez, J.; Arias, G.; Rozas, R. Exhaustive Generation of Organic Isomers. 5. Unsaturated Optical and Geometrical Stereoisomers and a New CIP Subrule. *J. Chem. Inf. Comput. Sci.* **1999**, 39, 475–482.
- (2) Prelog, V.; Helmchen, G. Basic Principles of the CIP-System and Proposals for a Revision. *Angew. Chem., Int. Ed Engl.* **1982**, 21, 567–583.

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