## CORRESPONDENCE

# Comment on "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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In a previous issue of this journal a paper[1] was published proposing a new criterion to rank ligands that, allegedly, could not be differentiated by the CIP sequence rules. We[2] and other authors[3] responded to that paper and demonstrated that the referred ligands could be ranked by the CIP system, and that the need for the new subrule resulted from an oversimplified interpretation of the CIP sequence rules.

In a recent issue of this journal a Contreras et al. answer[4] to the Brecher comment[3] was published. In this answer,[4] the authors recognize that their subrule was not necessary to rank the ligands they originally provided to justify it; however they insist on the need for the subrule in other situations. They also state that the new criterion should be applied one step after the CIP rules, and only if analysis according to those rules gives no precedence to any of the ligands being compared.

It is not our purpose to argue the validity of this criterion and its use to rank ligands in the process of generating stereoisomers in US-CAMEO; however, we can demonstrate that, again, the new pair of ligands presented by Contreras et al.[4] can clearly be ranked by the CIP sequence rules and thus that the proposed criterion is not necessary as a complement to the CIP system. Although Contreras et al. conclude their answer[4] by saying that the validity of the new subrule was demonstrated on the basis of "a proper and careful application of the CIP rules", again in this case there was a misinterpretation of some of the CIP sequence rules as explained below.

(a) Contreras et al. demonstrate that the two ligands in Figure 1 in the paper[4] are identical according to CIP sequence rule 4 (comparison of the relationship between the stereogenic centers in the ligands). We agree with this conclusion. However, to do this, they compare pairs of descriptors and use successively as reference descriptors (the first descriptor in the pairs to be compared) the first, second, and third highest ranked descriptors in each ligand. Although this is not decisive in their demonstration, it is important to make it clear that, according to the CIP system, in this case just one descriptor in each ligand should be used as the reference. Comparison of pairs of descriptors using other descriptors as references is completely irrelevant as the information provided is redundant. Pairs of ligands shown in Figure 1 in the paper[4] are all the relevant information necessary to conclude that ligands are identical according to CIP sequence rule 4.

(b) The main misinterpretation of the CIP rules is related to the application of rule 5 (R precedes S). This rule ranks ligands that are identical according to the previous rules, although they are not superimposable but mirror images of each other (enantiomorphic ligands). To do this, the highest ranked descriptors of chiral centers in the ligands are compared. Thus, rule 5 clearly allows the ranking of the two ligands considered (ligand 1 > ligand 2). Contreras et al., however, did not rank the ligands in this way, justifying this decision by saying that rule 5 is only used to specify pseudoasymmetric stereogenic units, thus to determine reflection-invariant descriptors r and s, and that their molecule did not have any of these units.

We cannot agree with this interpretation. In fact, the procedure to derive a CIP descriptor can be summarized in the following three steps: (i) Factorization of the stereomodel assigned to the molecule into stereogenic units (mainly, identification of potential chiral or pseudoasymmetric centers, planes, and axes and also double bonds); (ii) Determination of the ranking of the ligands around each stereogenic unit (using CIP sequence rules); (iii) Determination of the descriptor for each stereogenic unit (R, S, r, s, P, M, p, m, Z, and E, based on a set of conventions).

In this process, CIP sequence rules are used to rank ligands independently from the stereogenic unit to which they are attached (pseudoasymmetric center or double bond, for example). Sequence rule 5 differentiates ligands, and when ligands can only be differentiated by this rule, one can conclude that they are enantiomorphic (mirror images of each other).

The reasoning in the Contreras paper is valid to identify the type of stereogenic center when the two enantiomorphic ligands are attached to one stereogenic center, but invalid to justify not using rule 5 to rank ligands. In fact this rule is used in a very specific phase of the entire process of deriving a descriptor for a stereogenic unit (step ii) that is completely independent of the stereogenic unit being considered.

A careful reading of the Prelog paper[5] that defines the CIP rules should reveal that its authors also considered a case similar to the one discussed by Contreras et al. in which the enantiomorphic ligands are attached to a double bond (section 6.4 and Figure 31 in ref 5). Other authors have also considered this type of double bond, and new nomenclature

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was even proposed for it.[6]

(c) Another situation described,[4] which we do not consider relevant for what was being demonstrated, is the fact that sometimes the ranking of two ligands by CIP rule 4 requires the use of rule 5 to specify pseudoasymmetric centers contained within these ligands. In a previous publication[7] we already discussed this subject and demonstrated that there is no incongruence in such a situation. In fact, CIP sequence rules are used to compare ligands, and ligand comparison and the ordering in which different stereogenic units are to be assigned are completely different matters that can, and must, be kept independent.

There are computer programs that do not use the CIP system for the identification and specification of stereogenic units:[8−10] they use other conventions considered efficient and more suitable for computer use. In this context the rule proposed by Contreras et al.[1,4] can be valid, if included in a more complete and different set of rules. However, for the reasons previously described[2,3] and also as demonstrated above, we do not consider these new proposed criteria necessary as a complement of the CIP system because the CIP sequence rules allow the ranking of the ligands in the situations described and also in any other we can conceive to which the Contreras et al. subrule could be applied.

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