The CIP System Again: Respecting Hierarchies Is Always a Must

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In a recent paper published in this journal, a computational implementation of the Cahn−Ingold−Prelog (CIP) rules was reported and a new subrule was proposed to rank complex ligands containing chiral centers. In this paper, it is demonstrated that this new subrule is unnecessary and its need only results from an oversimplified implementation of the CIP system.

1. INTRODUCTION

The CIP system[1−4] 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 basis of the CIP system is provided by the conventions proposed in the first publication on the subject, in 1951.[1] Since then several modifications and extensions have been made to achieve greater generality.[2−4] Accumulated experience and particularly the work carried out in the implementation of the CIP system for computer use demonstrated the need of further modifications and extensions.[5−7]

The ordering of the ligands has a fundamental role in the specification of a stereogenic unit and is the most complex step in this procedure. Although quite straightforward for simple molecules, for the more complex cases difficulties arise and the general case is extremely intricate. The application of the CIP system and particularly its computational implementation are a nontrivial task.

In a recent paper published in this journal,[8] a new computational implementation of the Cahn−Ingold−Prelog (CIP) rules was reported and a new subrule was proposed to rank complex ligands containing chiral centers. In the present paper, it will be demonstrated that this new subrule is unnecessary and that their need resulted from an oversimplified implementation of the CIP system.

2. CIP SEQUENCE RULES FOR LIGAND RANKING

The meaning of the term ligand can be quite clear in the case of monodentate ligands, but it is not as clear for polydentate and cyclic ligands. This is addressed and rectified in the CIP system by converting the most complex ligands into equivalent acyclic structures—the hierarchical digraphs.[3,4] Since ligands, represented by the hierarchical digraphs, can differ in several properties and the ordering of ligands must be done unambiguously by a single property, an hierarchical ranking of the properties used for the comparison and a methodology for this comparison are required. This is the object of the CIP sequence rules, and the hierarchy of the properties is clearly defined (Figure 1).

As stated by Prelog and Helmchens,[4] "It is essential to examine the relevant properties of ligands in the hierarchical sequence outlined—exhaustively for each type—before proceeding to the next lower rank." This implies that geometrically equivalent ligands must be equivalent topologically but can be different topographically.

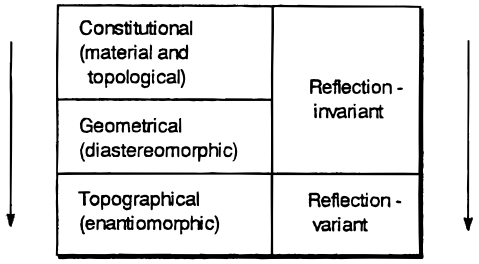

Figure 1. Hierarchical ranking of properties.[4]

The methodology for the comparison of the ligands according to each of the properties is clearly described in the 1966 Cahn et al. paper[3] and further clarified in the paper by Prelog and Helmchen in 1982.[4]

Contreras et al.[8] refer to an example of a molecule whose ligands they consider to be undistinguishable by the CIP system (Figure 2). However, the CIP system can rank the two ligands, and this ranking is made by Rule 1, thus not requiring the comparison of the chiral centers.

In this molecule, and in the majority of the cases, the relative rank of the ligands is established on the basis of material and topological properties, i.e., by the application of Rule 1 that mainly states that higher atomic numbers precede lower ones. In the methodology used for the comparison according to this rule,[3,4] the connectivity of the atoms is fully considered (Table 1).

In the first level, C_1 and C_2 are compared; since there is no difference in their atomic numbers, one should proceed to the next level and consider the atoms connected to C_1 and C_2. In both ligands, these atoms are connected only to carbon atoms; thus, in the second level, there is no difference. In the third level, in ligand i one carbon atom (C_5) is connected to three carbon atoms and the other two (C_3 and C_4) are connected to one carbon atom and two hydrogen atoms. Thus, the branch comprising C_5 has priority over the branches comprising atoms C_3 and C_4. In ligand j, however, there are two carbon atoms (C_7 and C_8) connected to two carbon atoms and one hydrogen atom and one carbon atom (C_6) connected to one carbon atom and two hydrogen atoms. Thus, the

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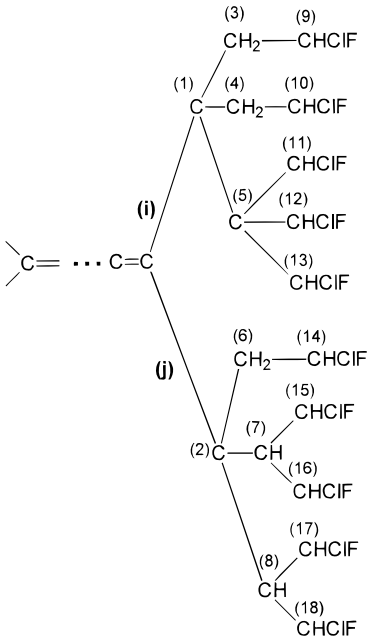

Figure 2. Molecule with ligands considered indistinguishable by the CIP system.[8]

Table 1. Comparison According to CIP Rule 1

level	ligand i	ligand j
1	C1	C2
2	C3, C4, C5	C6, C7, C8
3	(C_{11}, C_{12}, C_{13}) > (C_9,H,H) = (C_{10},H,H)	(C_{15}, C_{16}, H) = (C_{17},C_{18},H) > (C_{14},H,H)

branches containing C_7 and C_8 have priority over the branch containing C_6. A comparison at this level is first made between the higher ranked branches, that is, the branch containing C_5 and a branch containing C_7 or C_8. Thus, we should compare (C,C,C) in ligand i with (C,C,H) in ligand j. This comparison allows us to rank the ligands as (C,C,C) > (C,C,H), and thus, ligand i > ligand j.

The main problems with the US−CAMGEC implementation[8] described are that ligands are not compared exhaustively for each property before proceeding to the next lower rank property and, also, the methodology of comparison is not the one stated for the CIP sequence rules. According to the US−CAMGEC flow diagram presented in the Contreras paper,[8] each atom level (and not each ligand) is compared according to several properties before going to the next level and even this comparison is oversimplified, as in each level topology is not considered but the total summation of atomic numbers by level.

3. CONCLUSIONS

Although quite straightforward for simple molecules, the application of the CIP system for the complex cases can be extremely intricate; thus, its computational implementation is complex. Oversimplification should be avoided, as this usually results in incorrect specifications of stereogenic units.

As demonstrated above, the oversimplification in the described implementation of the CIP system in the US−CAMGEC software[1] does not allow for a correct ranking of the ligands, and therefore, the newly proposed subrule to rank ligands which the authors consider indistinguishable using the CIP system is unnecessary since a correct analysis using the original CIP system can distinguish these ligands using rule 1.

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