

CORRESPONDENCE

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

J. Brecher

CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge, Massachusetts 02140

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In a recent paper,¹ Contreras et al. reported a type of structure (Figure 1) that they described as unrankable according to preestablished rules for determining stereochemical priority in the Cahn–Ingold–Prelog (CIP) system. They then proposed a new CIP subrule to rank the problematic structure. In fact, however, this particular case is already treated unambiguously by the existing CIP rules.^{2,3} Thus, the new subrule proposed by Contreras et al. serves only to complicate the existing CIP rule set, and leads to stereochemical designations different from those defined in earlier works. Let us examine the case more closely.

Contreras et al. state that the CIP rules involve “recursively comparing total summation of atomic numbers by levels until a difference arises”. Thus, in Figure 1, they state that ligands *i* and *j* are identical:

level	ligand <i>i</i>	ligand <i>j</i>	analysis
1	C1	C2	equivalent
2	C3; C4; C5	C6; C7; C8	equivalent
3	C9, H, H; C10, H, H, C11, C12, C13	C14, H, H; C15, C16, H; C17, C18, H	equivalent
4	5 × HCIF	5 × HCIF	equivalent

Unfortunately, while a per-level summing of atomic numbers is one part of the CIP rules, it is one part only. Prelog and Helmchen address this precise misconception.² According to Contreras et al., the structure in Figure 2 (Figure 15 in ref 2) would be ranked with C1' > C1 (hydrogens omitted for clarity):

level	left (unprimed)	right (primed)	analysis
1	Cl	Cl'	equivalent
2	C2, C6	C2', C6'	equivalent
3	C3, C5, F	C3', C5', F	equivalent
4	C4, C4, Cl, Br	C4', C4', Cl, I	primed > unprimed because I > Br

In reality, the CIP rules rank Figure 2 with C1 > C1'. In addition to the comparison of atomic numbers at a given level, the CIP rules also mandate that “a rank established for a sphere nearer to the core remains valid with respect to atoms in more distant spheres.”² Thus, in this case, C2 > C6 and C2' > C6' because F > H. Once this ranking is specified at level 2, then only the children of C2 and C2' should be evaluated when the lower levels are examined. This compound is actually ranked with C1 > C1' because Br > Cl (the highest-ranking descendants of C2 and C2' at their first difference).

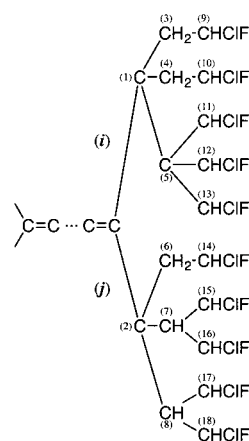


Figure 1. Example provided by Contreras et al. illustrating a perceived limitation of the existing CIP rule set. Note that while the total summation of atom types is identical for ligands *i* and *j* at each level, the absolute connectivity of each ligand is not.

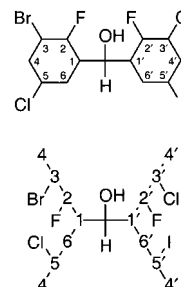


Figure 2. Example provided by Prelog and Helmchen to show that the CIP rules do not simply compare the total summation of atom types at each level.

The same logic can be applied to the compound in Figure 1. Proceeding down the tree, levels 1 (C1 and C2) and 2 (C2, C4, C5 and C6, C7, C8) are constitutionally equivalent. The differences appear at the next level, and C5 > C4 because (C11, C12, C13) > (C10, H, H). This comparison of children is the same procedure used in Figure 2 to determine which branch (C2 or C6 in that figure) to follow for subsequent analyses. Completing the analysis at level 2, C7 > C6 because (C15, C16, H) > (C14, H, H), while C8 = C7 and C4 = C3. It is now clear that, while the immediate children of C1 and C2 are constitutionally equivalent (three carbons in each case), they can be differentiated by their own respective children. Thus, C1 > C2 because (C5 (C, C), C3 (C, H, H), C4 (C, H, H)) > (C7 (C, C, H), C8 (C, C, H), C6 (C, H, H)). Or, in other words, C1 > C2 because the

highest-ranking child of C1 outranks the highest-ranking child of C2. So $i > j$ according to existing rules.

The five rules of the CIP system contain many subtleties, and can be extremely difficult to interpret, particularly for ligands that differ only by their own internal stereochemistries. There are no ambiguities, however, when considering acyclic ligands that differ in the gross connectivity of their atoms. Such is the case in the example provided by Contreras et al., and the existing CIP rules are fully adequate for ranking those ligands. Consequently, the interpretation published by Contreras et al. is at variance with established practice. No new subrule is needed or should be considered.

REFERENCES AND NOTES

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