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Comparison of Constitutional Properties in the CIP System
The CIP Sequence Rule 1

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Abstract: An analysis of the CIP Sequence Rules was recently published in this journal[1]. However, further work on the implementation of the CIP Rules for computer use suggested that a reformulation of Sequence Rule 1 was required. In this paper this Rule is analyzed and its modification proposed.

INTRODUCTION

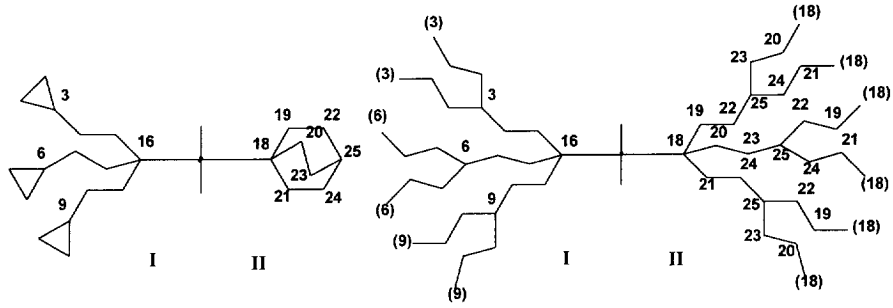
In a recent paper published in this journal[1] an analysis of the 1982 revised CIP Sequence Rules[2] was made and some extensions and modifications to these rules were proposed to solve currently existing omissions and ambiguities.

Some of the deficiencies reported were encountered in the course of the implementation of the CIP Rules for computer use[3]. Others were described in the literature[4,5] along with suggestions for extensions or modifications of the Rules to improve them.

One of the proposed extensions is related to the incompleteness of the original Rule 1[1,4]. However, further work in the implementation of the CIP Rules for computer[6] use suggested that a reformulation of that extension to Sequence Rule 1 was required. In this paper we analyze this sub-rule and propose its modification.

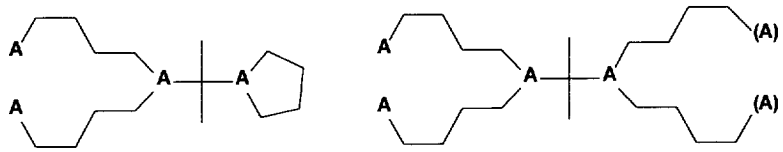
CIP SEQUENCE RULE 1

CIP Sequence Rule 1 deals with the comparison of the constitutional (material and topological) properties of the ligands. In the majority of the cases this comparison is enough to rank the ligands. For a long time it was considered that the original rule (which states that: "higher atomic number precedes lower") was complete enough to detect all the constitutional differences. However, some cases were reported[4] in which ligands constitutionally different cannot be ranked by the original Rule 1 (Figures 1 and 2).



Molecule **Hierarchical Digraph**

Fig. 1. Molecule having constitutionally different ligands that cannot be distinguished by the 1982 CIP Sequence Rules[2].



Molecule **Hierarchical Digraph**

Fig. 2. Another molecule having constitutionally different ligands that cannot be distinguished by the 1982 CIP Sequence Rules[2]. **A** is an hypothetical atom which allows ligancies of 1 and 3 (all single bonds).

An extension to Rule 1[4] was proposed which covers all constitutional differences. The modified Rule 1 is composed of two parts, 1.a) the original rule and 1.b) the extension proposed:

CIP Sequence Rule 1:

1.a) Higher atomic number precedes lower.

1.b) A duplicate atom with its predecessor node having the same label closer to the root, ranks higher than a duplicate atom with its predecessor node having the same label farther from the root, which ranks higher than any non-duplicate-atom-node.

Sub-rule 1.b) should be applied to the digraph if no difference is encountered after an exhaustive comparison of both ligands according to sub-rule 1.a).

Further work in the implementation of sub-rule 1.b)[6] has suggested that its reformulation is desirable. In fact in this sub-rule two different properties associated with a given node are considered: *i)* for corresponding duplicate atom nodes the relationship between the duplicate atom node, its predecessor node with the same label and the root and *ii)* for corresponding nodes the type of node, a duplicate atom node or a real atom node. These properties, being completely distinct, should be considered sequentially in two separate sub-rules as happens in an analogous situation in Rule 4.

This requires the ordering of these rules to be reversed. Analogous to Rule 4, the type of the nodes must be compared (real or duplicate) in the first place. Then, and just if no difference is encountered, the relationship of the duplicate nodes with their predecessor nodes having the same label and the root must be compared.

In our proposal the same properties proposed by Custer are used to rank the ligands. However by considering each one in a separate sub-rule they are sequentially (instead of simultaneously) and exhaustively applied to the entire digraph. This methodology is more logical and consistent with the rest of the CIP Rules than the one proposed by Custer[4]. Such an approach also makes the implementation of these sub-rules more straightforward since at any time only one property associated with each node is considered.

The properties considered in this extension are used only for the ranking of very specific and uncommon molecules. In particular, just an hypothetical case was presented (Figure 2) in which a duplicate node should be compared with a corresponding real node. The considering of these properties in different sub-rules allows the implementation of just one of them and not the other.

According to Custer's proposal a duplicate atom ranks higher than a non-duplicate-atom-node. This convention is inconsistent with the existing rules, and therefore should be revised. Because duplicate atoms can occur only when the corresponding real atom has a valency greater than 1 (except for the hypothetical atom A in Figure 2), the real atom will always have attached real and/or duplicate atoms that take precedence over the phantom atoms attached to the duplicate atom. The precedence of nodes in a hierarchical digraph

representing real atoms over nodes representing duplicate atoms of the same atomic number is also a more natural convention, and thus not only appealing to chemists, but also easier to remember.

Thus our proposal for CIP Sequence Rule 1 is:

CIP Sequence Rule 1:

1.a) Higher atomic number precedes lower.

1.b) A non-duplicate-atom-node ranks higher than a duplicate-atom-node.

1.c) A duplicate-atom-node with its predecessor node having the same label closer to the root ranks higher than a duplicate-atom-node with its predecessor node having the same label farther from the root.

REFERENCES

1. P. Mata, A. M. Lobo, C. Marshall, A. P. Johnson *Tetrahedron: Asymmetry*, **1993**, 4, 657

2. V. Prelog, G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **1982**, 21, 567

3. P. Mata, A. M. Lobo, C. Marshall, A. P. Johnson *J. Chem. Inf. Comput. Sci.*, **1994**, 34, 491

4. R. H. Custer, *Match*, **1986,** 21, 3

5. H. Hirschmann, K. R. Hanson, *Tetrahedron*, **1974**, 30, 3649

6. Nachbar, R. B. unpublished work.

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